BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW

Application Type	351(k) BLA
Application Number	BLA 761215
Received Date	12/18/2020
BsUFA Goal Date	12/18/2021
Division/Office	Division of Diabetes, Lipid Disorders, and Obesity/ Office of Cardiology, Hematology, Endocrinology, and Nephrology
Review Completion Date	See DARRTS stamped date
Product Code Name	LY2963016
Proposed Nonproprietary Name[1]	insulin glargine-aglr
Proposed Proprietary Name[1]	REZVOGLAR
Pharmacologic Class	Long-acting human insulin analog
Applicant	Eli Lilly and Company
Applicant Proposed Indication(s)	To improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus Limitations of use: Rezvoglar is not recommended for treating diabetic ketoacidosis
Recommendation on Regulatory Action	Approval as biosimilar to U.S.-licensed Lantus (insulin glargine) (b) (4)

[1]Section 7 of the Biosimilar Multidisciplinary Evaluation and Review discusses the acceptability of the proposed nonproprietary and proprietary names, which are conditionally accepted until such time that the application is approved.

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OBP = Office of Biotechnology Products
OPMA = Office of Pharmaceutical Manufacturing Assessment
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error and Prevention Analysis
DRISK = Division of Risk Management
DPMH = Division of Pediatric and Maternal Health

Glossary

AC	Advisory Committee
ADA	Anti-drug Antibodies
AE	Adverse Event
BLA	Biologics License Application
BMER	Biosimilar Multidisciplinary Evaluation and Review
BMI	Body Mass Index
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Agreements
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence Interval
CMC	Chemistry, Manufacturing, and Controls
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSC	Computational Science Center
CTD	Common Technical Document
CV	Coefficient of Variation
DEPI	Division of Epidemiology
DIA	Division of Inspectional Assessment
DMC	Data Monitoring Committee
DMA	Division of Microbiology Assessment
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DRISK	Division of Risk Management
eCTD	Electronic Common Technical Document
EU-Lantus	European Union-approved Lantus
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
ICH	International Conference on Harmonization
IND	Investigational New Drug
ITT	Intention to Treat
LLOQ	Lower Limit of Quantitation
MAPP	Manual of Policy and Procedure
mITT	Modified Intention to Treat
MOA	Mechanism of Action
NAb	Neutralizing Antibody
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events

NCT	National Clinical Trial
OBP	Office of Biotechnology Products
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
OSIS	Office of Study Integrity and Surveillance
PD	Pharmacodynamics
PeRC	Pediatric Review Committee
PK	Pharmacokinetics
PMC	Postmarketing Commitments
PMR	Postmarketing Requirements
PREA	Pediatric Research Equity Act
PHS	Public Health Service
PLR	Physician Labeling Rule
PLLR	Pregnancy and Lactation Labeling Rule
REMS	Risk Evaluation and Mitigation Strategies
ROA	Route of Administration
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Events
ULOQ	Upper Limit of Quantitation
U.S.- Lantus	U.S.-licensed Lantus
USPI	U.S. Prescribing Information
%SB	Percent specific binding

Signatures

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1. Executive Summary

1.1. Product Introduction

Eli Lilly (hereafter referred to as "the Applicant") has submitted a BLA for LY2963016 under section 351(k) of the PHS Act as a proposed (b) (4) biosimilar to U.S.-Lantus (insulin glargine). The proposed nonproprietary name for LY2963016 is insulin glargine-aglr and the proprietary name is REZVOGLAR. LY2963016 is a long acting insulin analog administered subcutaneously. The primary sequence of insulin glargine-aglr differs from that of human insulin by 3 amino acids: asparagine at position 21 instead of glycine of chain A and 2 arginine residues added to the C-terminus of the B chain. LY2963016 is supplied at 100 units/mL (U-100) available as a 3 mL single-patient-use prefilled pen (PFP) for subcutaneous injection. The Applicant is seeking licensure for the following indication for which U.S.-Lantus has been previously approved: to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus (T1DM) and in adults with type 2 diabetes mellitus (T2DM).

LY2963016 (Basaglar) was originally approved in 2015 (NDA 205692)[2], under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act FDCA).

1.2. Determination Under Section 351(k)(2)(A)(ii) of the Public Health Service (PHS) Act

The Applicant cross-referenced animal studies from BLA 205692 to support its 351(k) application. However, given the absence of detectable differences in the results from the battery of in vitro assays, and given that the results from the euglycemic clamp study support a demonstration of PK similarity, animal studies would not be informative to the evaluation of toxicity (see section 4.1 for additional information). Moreover, as also described in this review, the applicant's comparative analytical and clinical data supports a demonstration that LY2963016 is highly similar to U.S.-licensed Lantus notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between LY2963016 and U.S.-licensed Lantus in terms of safety, purity and potency. Accordingly, FDA has determined that the animal studies are unnecessary in this 351(k) application and therefore, the in vivo animal toxicology studies were not reviewed.

[2] Basaglar NDA 205692 was approved on December 16, 2015 under the 505(b)(2) regulatory pathway. On March 23, 2020, the marketing application ceased to exist as a new drug application and was deemed to be an approved BLA under section 351(a) of the PHS Act (BLA 205692).

1.3. Mechanism of Action, Route of Administration, Dosage Form, Strength, and Conditions of Use Assessment

Insulin and insulin analogues (including U.S.-LANTUS) regulate blood glucose by binding and activating the insulin receptor. Insulin receptor activation lowers blood glucose through enhanced peripheral blood glucose uptake by skeletal muscle and fat and by inhibiting hepatic glucose production, lipolysis and proteolysis.

Comparative analytical testing including multiple orthogonal assays relevant to the mechanim of action of US-Lantus, plus comparative clinical pharmacodynamic data evaluating glucose metabolism, demonstrated that LY2963016 has the same mechanism of action as that of U.S.-LANTUS, to the extent known.

Insulin glargine is a 2-chain protein containing 53 amino acids. Insulin glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and 2 arginines are added to the C-terminus of the B-chain.

LY2963016 is proposed as below:

- ROUTE OF ADMINISTRATION: subcutaneous injection
- DOSAGE FORM: injection
- STRENGTH: LY2963016 is available as a 3 mL single-patient-use prefilled pen (KwikPen) with a concentration of 100 units/mL (U-100). The strength of LY2963016 is the same as U.S.-LANTUS, which is also available as a 3mL single-patient-use prefilled pen (SoloStar) with a concentration of 100 units/mL.
- Additionally, the conditions of use for which the applicant is seeking licensure have been previously approved for U.S.-LANTUS.

1.4. Inspection of Manufacturing Facilities

Adequate descriptions of the facilities, equipment, environmental controls, clearning and contamination strategy were provided by the Applicant for the proposed drug substance and drug product. All proposed manufacturing and testing facilitites are acceptable base on their current CGMP compliance status. The Office of Biotechnology Products (OBP), and the Office of Pharmaceutical Manufacturing Assessment (OPMA) concurred that an on-site inspection of this facility was not necessary.

1.5. Scientific Justification for Use of a Non-U.S.-Licensed Comparator Product

Not applicable. Data generated from studies using EU-approved Lantus were not used to support a demonstration of biosimilarity (b) (4).

1.6. Biosimilarity (b) (4) Assessment

Table 1 Summary of the Assessment of Biosimilarity (b) (4)

Comparative Analytical Studies[3]	
Summary of Evidence	LY2963016 is highly similar to U.S.-licensed Lantus, notwithstanding minor differences in clinically inactive components. The strength of U.S.-Lantus is labeled in units per unit volume (100 units/mL) and is available in 3 mL single-patient use prefilled pens. The Applicant is seeking approval of LY2963016 for this same strength and presentation as U.S.-Lantus. LY2963016 has the same dosage form and route of administration as U.S.-Lantus. Comparative concentration and potency was evaluated at drug product release, stability testing, and during beginning, middle, and end of filling as part of the process validation study. The comparative concentration and manufacturing data support a demonstration that LY2963016 has the same strength as U.S.-Lantus prefilled pen. The Applicant used a comprehensive array of analytical methods suitable to evaluate critical quality attributes (CQA) of LY2963016 to support a demonstration that LY2963016 is highly similar to U.S.-Lantus. A total of 21 independent LY2963016 drug product lots manufactured between 2010 to 2020 were used in the comparative analytical assessment (CAA). All the drug product lots used in the CAA were manufactured using the commercial manufacturing process.The comparative analytical studies included testing for protein concentration, purity, product-related impurities, primary and higher order structure, and functional activities. The methods were adequately validated or qualified to support that the methods were scientifically appropriate and suitable for their intended use.
Assessment of Residual Uncertainties	There are no residual uncertainties from the product quality assessment.
Animal/Nonclinical Studies	

[3]Refer to the Product Quality Review, including the Comparative Analytical Assessment (CAA) Chapter therein for additional information regarding comparative analytical data.

Summary of Evidence	In vitro studies evaluating the insulin receptor and insulin-like growth factor-1 (IGF-1) receptor binding, activation, metabolic activity, and mitogenic activity demonstrated that LY2963016 was similar to U.S.-Lantus. In vitro studies support the demonstration of biosimilarity. FDA determined that animal studies were were not necessary in this 351(k). The animal toxicology studies were therefore not reviewed.
Assessment of Residual Uncertainties	There are no residual uncertainties from the pharmacology and toxicology perspective.
Clinical Studies	
Clinical Pharmacology Studies	
Summary of Evidence	PK and PD similarity between LY2963016 and U.S.-Lantus were demonstrated in healthy subjects (Study ABEO). The least-square geometric mean ratio (GMR) for each PK and PD parameters and 90% CI of all pairwise comparisons were within the prespecified acceptability margin of 80% to 125%. The PK and PD data from Study ABEO add to the totality of evidence to support a demonstration of no clinical meaningful differences between LY2963016 and U.S.-Lantus.
Assessment of Residual Uncertainties	There are no residual uncertainties from a clinical pharmacology perspective.
Additional Clinical Studies	
Summary of Evidence	Not applicable. FDA determined that, based on the information in the application, including the applicant's immunogenicity assessment, a clinical immunogenicity study comparing LY2963016 and U.S.-Lantus is not necessary in this 351(k) application. No clinical data comparing LY2963016 to U.S.-Lantus, other than the euglycemic clamp PK/PD study ABEO were necessary to support a demonstration of biosimilarity of LY2963016 and U.S.-Lantus.

Assessment of Residual Uncertainties	There are no residual uncertainties from the clinical perspective.

(b) (4)

Any Given Patient Evaluation	
Summary of Evidence	The data submitted by the Applicant, including the comparative analytic assessment data and pharmacokinetic and pharmacodynamic data support a scientific conclusion that LY2963016 can be expected to produce the same clinical result as U.S.-Lantus in any given patient.
Assessment of Residual Uncertainties	No residual uncertainties from the clinical perspective.
Extrapolation	

Summary of Evidence	The information submitted in the application, including the comparative analytical data and the PK/PD similarity results (which together demonstrate that the mechanism of action is the same in LY2963016 and U.S.-Lantus, to the extent known) supports a demonstration that LY2963016 and U.S.-Lantus are highly similar notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences in terms of safety, purity, and potency. The information in this BLA also supports a demonstration that LY2963016 can be expected to produce the same clinical result as U.S.-Lantus in any given patient (b) (4) An extrapolation of the finding of PK similarity of LY2963016 and U.S.-Lantus in healthy adults to adult patients with T1D, pediatric patients with T1D and adult patients with T2D is justified because the scientific factors that determine absorption, distribution, metabolism, and elimination are the same in healthy adults and patients with diabetes mellitus. The extrapolation of the finding of PD similarity of LY2963016 and U.S.-Lantus in healthy adults to adult patients with T1D, pediatric patients with T1D and adult patients with T2D is justified because the assessed PD endpoints evince the binding and activation of insulin receptors, which is the pertinent MOA for all conditions of use of U.S. Lantus (to the extent known). No comparison of other factors across the conditions of use were necessary to justify the extrapolation. The extrapolation does not require specific knowledge about the relationship between PK and PD profiles observed in healthy adults and the PK and PD profiles that would be observed in patients with diabetes mellitus. The information submitted by the applicant demonstrates that LY2963016 is biosimilar to U.S.-Lantus for the following indication (including all of the indicated patient populations) for which the Applicant is seeking licensure and for which U.S.-Lantus has been previously approved: to improve glycemic control in

	adults and pediatric patients with T1DM and in adults with T2DM. See also section 1.7.
Assessment of Residual Uncertainties	There are no residual uncertainties from the clinical perspective.

1.7. Conclusions on Approvability

In considering the totality of the evidence submitted in the application, including the comparative analytical data, the PK/PD results and the justification why a comparative immunogenicity assessment is unnecessary, the data and information submitted by the Applicant demonstrate that LY2963016 is highly similar to U.S.-Lantus notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between LY2963016 and U.S.-LANTUS in terms of the safety, purity, and potency of the product. The information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that LY2963016 is biosimilar to U.S.-LANTUS for each of the following indications for which U.S.-LANTUS has been previously approved and for which the Applicant is seeking licensure of LY2963016: to improve glycemic control in adults and pediatric patientswith type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

The data and information provided by the Applicant are sufficient to support a scientific conclusion that LY2963016 can be expected to produce the same clinical result as the reference product in any given patient (b) (4)

Therefore, the information submitted by the Applicant demonstrates that LY2963016 is biosimilar to US- Lantus for the following indication, for which US-licensed Lantus has been previously approved and for which the Applicant is seeking licensure: to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

This application was submitted under section 351(k) (b) (4)
(b) (4)
(b) (4) Therefore, at this time, our recommendation is approval of LY2963016 as a

biosimilar to U.S.-Lantus [redacted].

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2. Introduction and Regulatory Background

2.1. Summary of Presubmission Regulatory History Related to Submission

The following section summarizes the regulatory history of LY2963016 under Pre-IND (PIND) 140889 prior to the Applicant's submission of this 351(k) BLA.

In October 2018 the Applicant requested a type 2 Biological Product Development (BPD) meeting to discuss development of LY2963016 as [redacted] biosimilar to US-Lantus, and a PIND file was opened for the product. Below is a summary of the key regulatory interactions and agreements between the Agency and the Applicant under PIND 140889.

- **<u>January 8, 2019 BPD Type 2 Meeting:</u>**

[redacted]

(b) (4)

- The Agency agreed that it may be possible for the Applicant to leverage analytical data generated previously and submitted as part of the Applicant's 505(b)(2) application for Basaglar (under NDA 205692), but noted that the lots of US-Lantus used as comparators in the original 505(b)(2) application were collected between 2012-2014. The Agency recommended that current lots of US-Lantus be included in the analytical similarity assessment for this 351(k) submission to account for any manufacturing changes in US-Lantus.

- **November 25, 2019 Advice Letter:**
  - The Agency informed the Applicant of our updated scientific thinking on issues that had been discussed at the January 8, 2019 BPD type 2 meeting. FDA referenced the draft guidance for industry, *Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products* (November 2019)[4] (hereafter referred to as the "*Insulin Immunogenicity Guidance*").
  - Consistent with this draft guidance, the Agency clarified that a comparative clinical immunogenicity study generally would be considered unnecessary to support a demonstration of biosimilarity (b) (4) for the Applicant's proposed insulin product if the comparative analytical assessment adequately supported a demonstration of highly similar as part of a demonstration of biosimilarity.
  - FDA still expected a clinical pharmacology study or studies, such as a comparative PK/PD study.
  - FDA also noted that a comparative clinical immunogenicity study may still be necessary as a scientific matter to support licensure, for example, if there were differences in certain impurities or novel excipients that gave rise to questions or residual uncertainty related to immunogenicity of the Applicant's proposed insulin product.
  - FDA stated that if the Applicant intended to pursue licensure of LY2963016 as a biosimilar to U.S.-Lantus under Section 351(k) of the PHS Act and the Applicant believed that data from a comparative clinical immunogenicity study may not be necessary, FDA recommended that the submission include an immunogenicity assessment justifying why a comparative clinical study to assess immunogenicity is not necessary to support a demonstration of biosimilarity for their proposed product.
  - In addition, FDA stated its scientific thinking that if the Applicant demonstrates biosimilarity between LY2963016 and U.S.-Lantus without conducting a comparative clinical immunogenicity study, (b) (4)

[4] Food and Drug Administration. Draft guidance for industry: Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products, November 2019, accessed from: https://www.fda.gov/media/133014/download

- **April 29, 2020 BPD Type 2 Meeting:**
  - The Agency agreed that the quality attributes included in the Applicant's comparative analytical assessment appeared sufficient to support a demonstration that LY2963016 is highly similar to US-Lantus, but the determination of "highly similar" will be made based on the totality of evidence from analytical studies in the BLA at the time of BLA review.
  - The Applicant proposed to use the existing comparative analytical data originally submitted to the Basaglar BLA205692, to support a new 351(k) BLA for LY2963016, based on their position that no change in product quality has been observed for either the LY2963016 product or US-Lantus since the initial 505(b)(2) submission. The Agency requested that the Applicant submit additional data in the 351(k) application to support this approach, including justification for providing analytical data derived from 8 product batches of US-Lantus rather than 10 reference product lots (i.e., the minimum number of reference product lots recommended in the Guidance for Industry, *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations* (May 2019). The Agency did not agree with the Applicant's proposal to pool data derived from lots of US-Lantus and EU-Lantus.
  - In a post-meeting comment, the Agency clarified that additional comparative analytical data are needed derived from contemporary lots of US-Lantus and the proposed (current) LY2963016 product, in order to confirm that the previously generated comparative analytical data are consistent with the products' current product quality profiles. The Agency noted that comparative analytical data derived from the historical lots and contemporary lots could potentially be combined to support the demonstration of biosimilarity, provided the historical and contemporary analytical data are consistent.
  - The Agency stated that the BLA should include a description of manufacturing process differences between historical and contemporary lots of LY2963016.
  - (b) (4)
  - The Agency acknowledged the Applicant's intention to submit comparative PK/PD data as their clinical data package for the 351(k) submission, along with a justification as to why a comparative clinical

study to assess immunogenicity is not necessary to support a demonstration of biosimilarity. The Agency noted that this plan was acceptable but a comparative clinical immunogenicity study may be necessary if residual uncertainties or deficiencies are identified during review of the 351(k) application.
  - The Agency clarified the required nonclinical data package to support the demonstration of biosimilarity in the 351(k) submission. The Agency also stated the Applicant should include a justification as to why animal studies are unnecessary in the application.
  - In a post-meeting comment the Agency agreed that a pediatric assessment for LY2963016 would not be expected to include pediatric studies and a waiver need not be requested.

- **<u>September 8, 2020 BPD Type 4 Meeting:</u>**
  - The Applicant clarified that they plan to request (b) (4) , employed at their Indianapolis (b) (4) manufacturing facility, in the 351(k) BLA submission.
  - The Agency acknowledged the Applicant's planned threshold analysis submission and stated we would provide a written response regarding whether a comparative use human factors study would be needed.
  - (b) (4)
  - The Agency agreed that the justification for why a comparative clinical study to assess immunogenicity is unnecessary could be placed in the Clinical Overview (Module 2.5).

- **<u>November 24, 2020 Agreed Initial Pediatric Study Plan Agreement Letter:</u>**
  - The Agency agreed that the Applicant can fulfill requirements for pediatric assessments under the Pediatric Research Equity Act (PREA) via extrapolation from the adult population to the pediatric population and from Lantus to LY2963016, based on demonstrating biosimilarity between US-Lantus and LY2963016 and providing an adequate justification under the BCPI Act for extrapolation.
  - No pediatric waivered or deferrals were requested and no studies in pediatric patients are planned.

2.2. Studies Submitted by the Applicant

Refer to the Product Quality review, including the Comparative Analytical Assessment (CAA) Chapter for information regarding comparative analytical studies provided to support a demonstration of biosimilarity. Refer to Section 13.3Nonclinical Appendices for information regarding additional comparative in vitro pharmacology studies.

Table 2. Listing of All Submitted Clinical Studies

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
PK Similarity Study					
Study I4L-MC-ABEO	NCT01688635	To compare the relative PK and PD properties of LY2963016 and US-Lantus	Single-center, randomized, double blind, single-dose (0.5 U/kg), 2-treatment, 4-period, crossover, replicate, euglycemic clamp; active control (US-Lantus)	Healthy Subjects	91 randomized 82 completed all 4 treatment periods LY2963016: 88 US-Lantus: 89
Study I4L-MC-ABEA	NCT01476345	To compare the relative PK and PD properties of LY2963016 and EU-Lantus	Single-center, randomized, double blind, single-dose (0.5 U/kg), 2-treatment, 4-period, crossover, replicate, euglycemic clamp; active control (EU-Lantus)	Healthy Subjects	80 randomized 78 completed all 4 treatment periods LY2963016: 80 US-Lantus: 80
Study I4L-MC-ABEN		To compare the relative PK and PD properties of US-Lantus and EU-Lantus	Single-center, randomized, double blind, single-dose (0.5 U/kg), 2-treatment, 4-period, crossover, replicate, euglycemic clamp; active control (US-Lantus)	Healthy Subjects	40 randomized 34 completed all 4 treatment periods US-Lantus: 34 EU-Lantus: 34

The applicant submitted the clinical studies listed in Table 2 above to the 351(k) BLA. All

of these clinical studies were also submitted to NDA 205692 (Basaglar) and reviewed by FDA under that NDA. Study I4L-MC-ABEO (hereafter referred to as "Study ABEO") compared the PK and PD profiles of LY2963016 and U.S.-Lantus after a single subcutaneous dose of 0.5 unit/kg in a euglycemic clamp study. The study results were acceptable to establish PK and PD similarity between LY2963016 and U.S.-Lantus.

The applicant also submitted PK/PD Studies I4L-MC-ABEA and I4L-MC-ABEN to the 351(k) BLA, which compared the PK and PD profiles of LY2963016 and E.U.-Lantus, and the PK and PD profiles of U.S.-Lantus and E.U.-Lantus, respectively. These two studies are not described further in this review because FDA is not relying on them to support a demonstration of biosimilarity. To support this determination FDA is relying on, among other data, the data from PK/PD Study ABEO, described in this review.

On review of BLA 761215 and consistent with the *Insulin Immunogenicity Guidance*, FDA determined that no additional clinical data other than the data from the comparative clinical pharmacology study ABEO were necessary to support a demonstration that LY2963016 is biosimilar to U.S.-Lantus.

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3. Summary of Conclusions of Other Review Disciplines

3.1. Office of Pharmaceutical Quality (OPQ)

The OPQ review team concluded that the LY2963016 manufacturing process and control strategy are sufficient and lead to a drug product of acceptable quality to ensure drug safety and effectiveness for patients. All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

A comparative analytical assessment (CAA) was conducted to assess the similarity of LY2963016 drug product (DP) to U.S.-Lantus in terms of physiochemical characteristics and functional assessments. The CAA included:

- Batch analyses (e.g., comparisons of DP lot release data, product-related impurities)
- Characterization studies (e.g., primary and higher order structure, in vitro precipitation, biological potency)
- Stability studies
- Forced degration studies

The OPQ review concluded that the analytical comparison of LY2963016 and U.S.-Lantus supports a demonstration that LY2963016 is highly similar to U.S.-Lantus. A total of 21 independent LY2963016 drug product (DP) lots manufactured between 2010 to 2020 were used in the comparative analytical assessment (CAA). All the DP lots were manufactured using the commercial manufacturing process. The age of DP lots used at the time of analytical testing allows for a meaningful comparison to support the CAA. All U.S.-Lantus lots were tested before their expiration dates. LY2963016 lots selected for the CAA are within and span across 24 months shelf life.

The OPQ review made the following determinations:

- The comparative analytical studies were performed using appropriate orthogonal analytical methods for each quality attribute, which included testing for protein concentration, purity, product-related impurities, primary and higher order structure, and functional activities. The methods were adequately validated or qualified to support that the methods were scientifically appropriate and suitable for their intended use.
- Comparative forced degradation studies were performed using an appropriate variety of forced degradation conditions, including thermal, high and low pH, light, oxygen, freeze/thaw, and chemical stresses (hydrogen peroxide and metals).
- Stability studies were conducted to compare the rates and pathways of degradation for LY2963016 and U.S.-Lantus under both long-term (5˚C) and accelerated (30˚C) stability storage conditions.
- The applicant used quality ranges defined by mean ±1.5 x the standard deviation observed for U.S.-Lantus as acceptance criteria for quality range attributes; appropriate justification was provided for the proposed approach. Attributes assessed by visual comparison of results were appropriately justified.
- The comparisons of process-related impurities, such as host cell protein (HCP), host cell DNA (HCD), (b) (4) were not included as part of the CAA because the manufacturing process of LY2963016 was demonstrated to have a robust capacity to consistently remove these process related impurities to acceptable ranges. This approach is appropriately justified.
- The strength of U.S.-Lantus is labeled in units per unit volume (100 units/mL) and is available in 3 mL single-patient use prefilled pens. The Applicant is seeking approval of LY2963016 for the same strength and presentation as U.S.-Lantus. LY2963016 has the same route of administration, and dosage form as U.S.-Lantus. Comparative concentration and potency was evaluated as part of the CAA, at DP release and stability testing, and during beginning, middle, and end of filling as part of process validation study. The comparative concentration and manufacturing data support a demonstration that LY2963016 has the same strength as U.S-Lantus prefilled pen.

3.2. Devices

3.2.1. Center for Devices and Radiological Health (CDRH)

CDRH's Division of Drug Delivery, General Hospital, and Human Factors (DHT3C) reviewed the device component of the pre-filled pen evaluating the:

- Device description
- Labeling
- Design controls
- Risk analysis
- Design verification
- Facilities and quality systems

All components of the review were deemed satisfactory by CDRH, who concluded that the device constituent parts of the combination product are approvable for the proposed indication.

3.2.2. Division of Medication Error Prevention and Analysis (DMEPA)

In an April 24, 2020 written response to a BPD type 2 Meeting request, the Applicant was advised to submit a comparative task analysis, labeling comparison, and physical comparison between their proposed (b) (4) biosimilar product, LY2963016 and US-licensed Lantus SoloStar. (b) (4)

DMEPA reviewed the comparative threshold analysis for LY2963016 to determine whether the Applicant needed to submit the results of a comparative use human factors study to support their 351(k) application seeking licensure of the LY2963016 pre-filled pen as (b) (4) biosimilar with U.S.-licensed Lantus. The Applicant submitted a physical comparison, comparative task analysis, and labeling comparison of the proposed LY2963016 multidose prefilled pen device to U.S.-licensed Lantus SoloStar. DMEPA identified minor and other than minor design differences between the proposed LY2963016 prefilled pen injector device and U.S.-licensed Lantus SoloStar that do not impact the performance of critical tasks in a meaningful way. DMEPA therefore concluded that the Applicant did not need to submit data from a comparative use human factors study to support the 351(k) application of LY2963016 as a proposed

(b) (4) biosimilar with U.S.-licensed Lantus.[5]

DMEPA reviewed side-by-side comparisons of the proposed labels and labeling for LY2963016 and U.S.-Lantus. DMEPA performed a review of the proposed prescribing information (PI) and IFU to identify areas of vulnerability that may lead to medication errors. DMEPA determined that the proposed PI and IFU submitted by the Applicant were acceptable from a medication error perspective.

Notwithstanding DMEPA's determination that the proposed PI, PPI, and IFU submitted by the Applicant were acceptable from a medication error perspective, language and positional differences in comparison to the U.S.-Lantus IFU were noted. FDA sent the applicant an information request (IR) on November 18, 2021, advising, among other things, that FDA draft Guidance (b) (4) In the Labeling for Biosimilar Products guidance, it recommends that the IFU for the proposed biosimilar product should incorporate relevant information from the IFU for the refence product and present the information in a similar manner. The Applicant subsequently submitted revised labeling. DMEPA had no further comment on the revised PI, PPI, and IFU.

DMEPA also reviewed the proposed container labels and carton labeling and provided recommendations to minimize the risk of medication errors, including changes to the format for the expiration date, proposals to improve the consistency of the presentation of storage information between the PI and the carton labeling, and requested that the Applicant review the guidance on product identifiers required under the Drug Supply Chain Security Act to determine if the product identifier (e.g., 2D data barcode) requirements apply to the product's labeling.[6]

3.3. Office of Study Integrity and Surveillance (OSIS)

Refer to Section 3.4 below for details.

3.4. Office of Scientific Investigations (OSI)

The Applicant had no new clinical studies and therefore no new clinical inspections were

[5] The review deferred review of the applicant's proposal (b) (4) The applicant subsequently removed (b) (4) from its proposed labeling.

[6] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. June 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers

necessary. The Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections of the clinical and bioanalytical portions of study I4L-MC-ABEO, "Comparative Pharmacokinetics of of LY2963016 and US-Approved LANTUS® after Single-Dose Subcutaneous Administration to Healthy Subjects" as part of the original approval for Basaglar. The clinical study inspection was conducted by ORA at Lilly-NUS Centre for Clinical Pharmacology Pte. Ltd., at the National University of Singapore, in Singapore, from May 26 to May 30, 2014. There were no objectionable findings during the inspection and Form FDA-483 was not issued. The inspection of the bioanalytical portions of the studies was conducted by ORA and DBGLPC at (b) (4) . The bioanalyses at (b) (4) were limited to measurement of total insulin (insulin glargine plus endogenous insulin). The results from the clinical and bioanalytical portions of I4L-MC-ABEO were deemed acceptable for Agency review.

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4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

4.1. Nonclinical Executive Summary and Recommendation

Insulins and insulin analogs bind to and activate two isoforms of the insulin receptor formed by alternative splicing of the mRNA: insulin receptor A (IR-A) and insulin receptor B (IR-B). IR-B primarily exerts the metabolic actions of insulin, while IR-A activation serves a developmental function and, as evidenced by its expression in cancer cells, mediates mitogenic and proliferative actions. Mitogenicity of insulin and insulin analogs is also mediated through the insulin-like growth factor-1 (IGF-1) receptor. Comparative analytical data, including in vitro studies evaluating receptor binding, receptor activation, metabolic activity, and mitogenic activity, were submitted to support a demonstration of biosimilarity of LY2963016 to U.S.-Lantus.

In vitro assays compared the IR-A and IR-B binding kinetics (association rate [ka] and dissociation rate [kd]) of LY2963016 and U.S.-Lantus, as well as the activation of these receptors via IR-A and IR-B phosphorylation in cells overexpressing either IR-B or IR-A. The assays demonstrated that the binding kinetics of LY2963016 to IR-A and IR-B and its ability to activate these insulin receptors were similar to those of U.S.-Lantus. The in vitro binding kinetics of LY2963016 and U.S.-Lantus at the IGF-1 receptor were also similar. The ability of LY2963016 and U.S.-Lantus to potentiate mitogenesis was further evaluated in IGF-1 receptor-dependent (Saos2 cells) and IR-dependent (H4IIE cells) mitogenic assays, in which the mitogenic potential of LY2963016 in the two assays was

similar to that of U.S.-Lantus. Lastly, the in vitro metabolic activities of LY2963016 and U.S.-Lantus as assessed by de novo lipogenesis of triglycerides were similar.

The results of the in vitro studies support a demonstration of biosimilarity between LY2963016 and U.S.-Lantus.

From a nonclinical perspective, because the toxicity of insulin glargine products, barring differences in clinical pharmacokinetic (PK) parameters, is a direct function of their affinity and activity at insulin and IGF-1 receptors, the comprehensive battery of in vitro cell-free and cell-based studies are considered more sensitive than animal studies in detecting functional differences and toxicities, should they exist, between LY2963016 and U.S.-Lantus. Similar characteristics in the battery of in vitro tests are thus considered adequate to support an assessment of biosimilarity. The battery of in vitro assays did not detect differences between LY2963016 and U.S.-Lantus, and PK similarity was evaluated in an euglycemic clamp study in healthy subjects. In the absence of specific pharmacokinetic, physicochemical, or other identifiable concerns, in vivo assays are not anticipated to provide additional meaningful information to inform the evaluation of toxicity.

Accordingly, although animal studies from BLA 205692 were cross-referenced, these studies were not reviewed.

4.1.1. Nonclinical Residual Uncertainties Assessment

There were no nonclinical residual uncertainties.

4.2. Product Information

Product Formulation

The LY2963016 drug product is a sterile, clear, and colorless solution at a pH of 4.0 that contains 100 Units/mL of LY2963016 drug substance. The table below lists the quantitative and qualitative composition of the LY2963016 drug product on a per-unit basis. The drug product is supplied in a 3 mL glass cartridge with (b) (4) seal and plunger for administration via subcutaneous injection.

Unit Formulation for LY2963016 Injection, 3 mL Cartridges.

Ingredient	Quantity/mL	Function
Active Ingredient		
LY2963016	100 Units (3.6378 mg-)	Active
Other Ingredients		
Glycerin	17 mg	(b) (4)
Metacresol	2.7 mg	
Zinc Oxide[1]	q.s. to provide Zn^{2+} content of 0.03 mg	
Hydrochloric Acid Solution 10%	q.s	Adjust pH
Sodium Hydroxide Solution 10%	q.s	Adjust pH
Water for Injection	q.s. to 1 mL	(b) (4)

Source: BLA 761215, Module 3.2.P.1, Table 3.2.P.1.1

Comments on Excipients

There are no novel excipients. All excipients have been used in similar amounts in US listed drugs based on the Inactive Ingredients Database (IID).

Comments on Impurities of Concern

There are no impurities or degradants of toxicological concern.

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5. Clinical Pharmacology Evaluation and Recommendations

5.1. Clinical Pharmacology Executive Summary and Recommendation

The Applicant conducted study ABEO that compared the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of LY2963016 in cartridges (formulation intended for pen presentations) compared to U.S.- Lantus to support a demonstration of no clinically meaningful differences between LY2963016 and U.S.-licensed Lantus in terms of safety, purity and potency. The study was performed in healthy subjects. The study results provided an adequate time-concentration profile and time-action profile for each product based on reliable measures of systemic exposure and glucose response (glucose infusion rate), using a euglycemic clamp procedure.

The scientific basis for relying on the comparative PK and PD data between LY2963016 and U.S.- Lantus (in conjunction with the data and information from the comparative analytical analysis (CAA), including nonclinical *in vitro* assays), to support a demonstration of the biosimilarity (b) (4) of LY2963016 with U.S.- Lantus in this submission, is as follows:

- Demonstration that the molar dose ratio for LY2963016 (test insulin product) is similar to U.S.- Lantus (reference product) as determined based on similarity in peak concentration (Cmax), total exposure (AUC0-24h), the corresponding peak (GIRmax) and net glucose lowering effect (AUCGIR; from PD profiles (i.e., glucose infusion rate over time) from euglycemic clamp studies) when given as the same unit/kg SC dose (i.e. same injection volume for a unit dose).
- Demonstration of similarity in the time-action profile between LY2963016 and U.S.- Lantus is on a unit to unit basis, i.e. LY2963016 has the same unit dose definition, time to peak action and duration, which supports that LY2963016 will be equally effective as U.S.- Lantus.

The similarity data from the randomized, crossover design PK/PD study conducted for LY2963016 and U.S.- Lantus supports a conclusion about whether there are no clinically meaningful differences between the treatments. In this submission, the demonstration of PK/PD similarity using the concept of average equivalence assessment for PK and PD parameters provides sufficient sensitivity for detecting clinically meaningful differences, should they exist, between LY2963016 and U.S.- Lantus.

Table 3. Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments

Pharmacokinetics	• PK similarity between LY2963016 and U.S.-Lantus was demonstrated in healthy subjects (Study ABEO). • PK data from Study ABEO supports a demonstration of no clinical meaningful differences between LY2963016 and US-Lantus.
Pharmacodynamics	• PD similarity between LY2963016 and U.S.-Lantus was demonstrated in healthy subjects (Study ABEO). • PD data from Study ABEO supports a demonstration of no clinical meaningful differences between LY2963016 and U.S.-Lantus.
Immunogenicity	• Not applicable; The single dose cross-over design of euglycemic clamp studies is appropriate for assessing PK/PD similarity, but not for evaluating immunogenicity.

Under this 351(k) BLA submission, LY2963016 is being proposed as an (b) (4) biosimilar biological product to U.S.- Lantus. To demonstrate that LY2963016 is biosimilar to (b) (4) U.S.-Lantus, the applicant submitted three clinical pharmacology studies, ABEO, ABEA and ABEN. All three studies had been reviewed by the clinical pharmacology team under NDA 205692. This Clinical Pharmacology review focuses on comparison of LY2963016 to U.S.- Lantus from study ABEO for this BLA.

Study ABEO is a randomized, double-blind, single-dose, 2-treatment, 4-period, cross-over, euglycemic glucose clamp study in healthy subjects designed to compare the PK and PD (i.e., glucose infusion rate [GIR]) profile of LY2963016 and US-Lantus following a single 0.5 Unit/kg bodyweight subcutaneous (SC) dose. The least-square geometric mean ratio (GMR) of the PK and PD parameters along with the 90% confidence intervals (CI) of all pairwise comparisons were within the prespecified acceptability margin of 80% to 125%. The results of the study established the PK and PD similarity between LY2963016 and US-Lantus based on the primary PK endpoints of C_{max} and $AUC_{0\text{-}24h}$, and PD endpoints of GIR_{max} and $AUC_{GIR0\text{-}24h}$.

Overall, the results from ABEO supports the demonstration of no clinically meaningful differences between LY2963016 and US-Lantus, which add to the totality of the evidence to support a demonstration that LY2963016 is biosimilarity to US Lantus.

Table 4. Summary of statistical analyses for assessment of PK and PD similarity (Study ABEO)

Primary Parameter	**Study ABEO - Geometric LS Mean Ratio (90% CI)**

	LY2963016 vs. US-Lantus
PK:	
$AUC_{0\text{-}24h}$ (pmol·hr /L)	0.90 (0.86, 0.94)
C_{max} (pmol/L)	0.92 (0.87, 0.96)
PD:	
$AUC_{GIR0\text{-}24h}$ (mg/kg)	0.91 (0.85, 0.98)
GIR_{max} (mg/kg/min)	0.93 (0.88, 0.98)

* Source: Reviewer's analysis

5.1.1. Clinical Pharmacology Residual Uncertainties Assessment

The clinical pharmacology study adequately demonstrated PK and PD similarity of LY2963016 with US-Lantus. There are no residual uncertainties from the clinical pharmacology assessment.

5.2. Clinical Pharmacology Studies to Support the Use of a Non-U.S.-Licensed Comparator Product

Not Applicable.

5.3. Human Pharmacokinetic and Pharmacodynamic Studies

To demonstrate that LY2963016 is biosimilar to (b) (4) US-Lantus, the applicant submitted three clinical pharmacology studies, ABEO, ABEA and ABEN. The clinical pharmacology review focused on study ABEO which provided comparative pharmacokinetics and pharmacodynamics of LY2963016 and U.S.-Lantus after single-dose subcutaneous administration to healthy subjects.

5.3.1. STUDY ABEO

Clinical Pharmacology Study Design Features

Study ABEO was a randomized, double-blind, single-dose, two-treatment, four period, fully replicated crossover design euglycemic glucose clamp study in healthy subjects. The PK and PD of LY2963016 were compared to U.S.- Lantus.

The study consisted of six study visits (Figure 1): a Screening Visit (Visit 1), four Dosing Periods (Visits 2-5) during the Treatment Period, and a Follow-up Visit (Visit 6). There was a minimum 7-day washout period between each of the Dosing Periods. Each Dosing Period included one 24-hour euglycemic glucose clamp and was identical in procedure. PK, PD, and safety endpoints were assessed. The preparation (LY2963016 or U.S.- Lantus) was administered as a 0.5-Unit/kg single SC dose on Day 1 of each

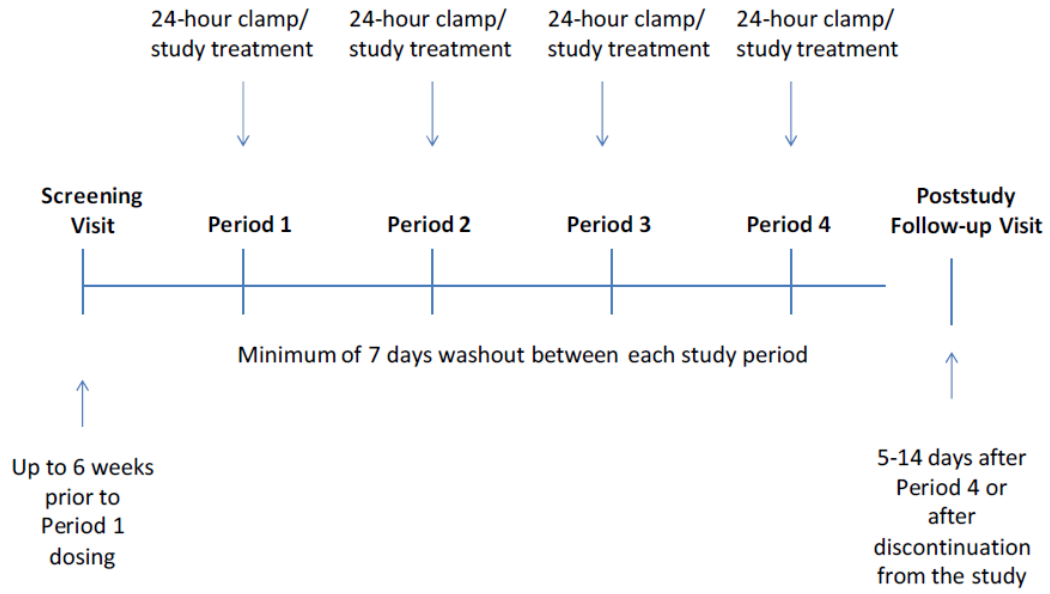
study period. The study drug was drawn from the cartridge located in the pen device by means of a conventional needle and syringe in order to maintain blinding. All insulin injections were administered SC in the CRU by means of a 30 gauge × 8 mm needle. The injections were alternated between 4 sites on the abdominal wall, below and approximately 5 cm from the umbilicus, for each dose. To allow for correction of serum immunoreactive LY2963016 and immunoreactive US-LANTUS concentrations for endogenous insulin, each subject had blood samples taken for the measurement of C-peptide concentrations at the same time points as the PK samples.

A total of 91 subjects were randomized, and 82 subjects (90.1%) completed all 4 treament periods of the study. All of the enrolled subjects (N = 91) who received at least 1 dose of study drug and who had evaluable data were included in the full analysis set (FAS) and the Safety Analysis Set. Three subjects were excluded from the per-protocol population (PPP, N = 88), which included all subjects in the FAS who completed at least 1 periods of the study without any major protocol deviation. All 3 excluded subjects had early termination of study participation due to un-evaluable PK and/or PD data. Subject (b) (6) received the incorrect dose in Period 2. Subject (b) (6) received an incorrect amount of intravenous glucose during the first 10 hours of his clamp procedure in Period 2. Subject (b) (6) received intravenous glucose at an incorrect infusion rate for 9 minutes during his clamp in Period 1. The exclusion of these subjects was justified. All subjects in the PPP were included in the PK/PD analysis with the following exceptions:

- For PK analysis, all serum concentration versus time data from completed study periods were included in the PK evaluation with the following exceptions: Subject (b) (6) in period 1 with outlier identified, Subject (b) (6) period 3, Subject (b) (6) period 2, Subject (b) (6) periods 1 and 2, Subject (b) (6) period 2, Subject (b) (6) period 2, Subject (b) (6) period 1, and Subject (b) (6) period 1 due to insufficient samples for PK evaluation.

- For PD analysis: none.

Figure 1. Schematic overview of the chronological structure of Study ABEO



Clinical Pharmacology Study Endpoints

In Study ABEO, the primary PK endpoints were area under the insulin concentration curve from 0 to 24 hours ($AUC_{0\text{-}24h}$) and maximum observed insulin concentration (C_{max}). The primary PD endpoints were total glucose infusion over the clamp duration from 0 to 24 hours (G_{tot}) and maximum glucose infusion rate (GIR_{max}).

To demonstrate similarity for PK and PD endpoints, the 90% CI of the geometric LS mean ratios needs to fall within 80-125%.

PK Bioanalytical Method and Performance

The bioanalytical method ([redacted] (b) (4) report 8225343) for measurement of immunoreactive study drug concentrations in serum samples in Study ABEO employed an radioimmunoassay (RIA) method. Samples were pretreated with polyethylene glycol (PEG) precipitation to remove any antibody/study drug complexes, so the measured concentrations represent "free" immunoreactive study drug. The antibody employed in the RIA was generated against despentapeptide human insulin. As a consequence, the RIA demonstrated full cross-reactivity with both study drugs and native human (i.e., endogenous) insulin. The endogenous insulin was estimated from the C-peptide concentration data using the Owens method (Owens 1986). Concentrations of LY2963016 or US-LANTUS in the serum were calculated using the following equation:

[LY2963016 or US-LANTUS] = [immunoreactive LY2963016 or immunoreactive US-LANTUS] – F*[C-peptide]

in which F is the average of the ratios of immunoreactive LY2963016 or immunoreactive US-LANTUS to C-peptide at baselines (-30 and 0 minutes).

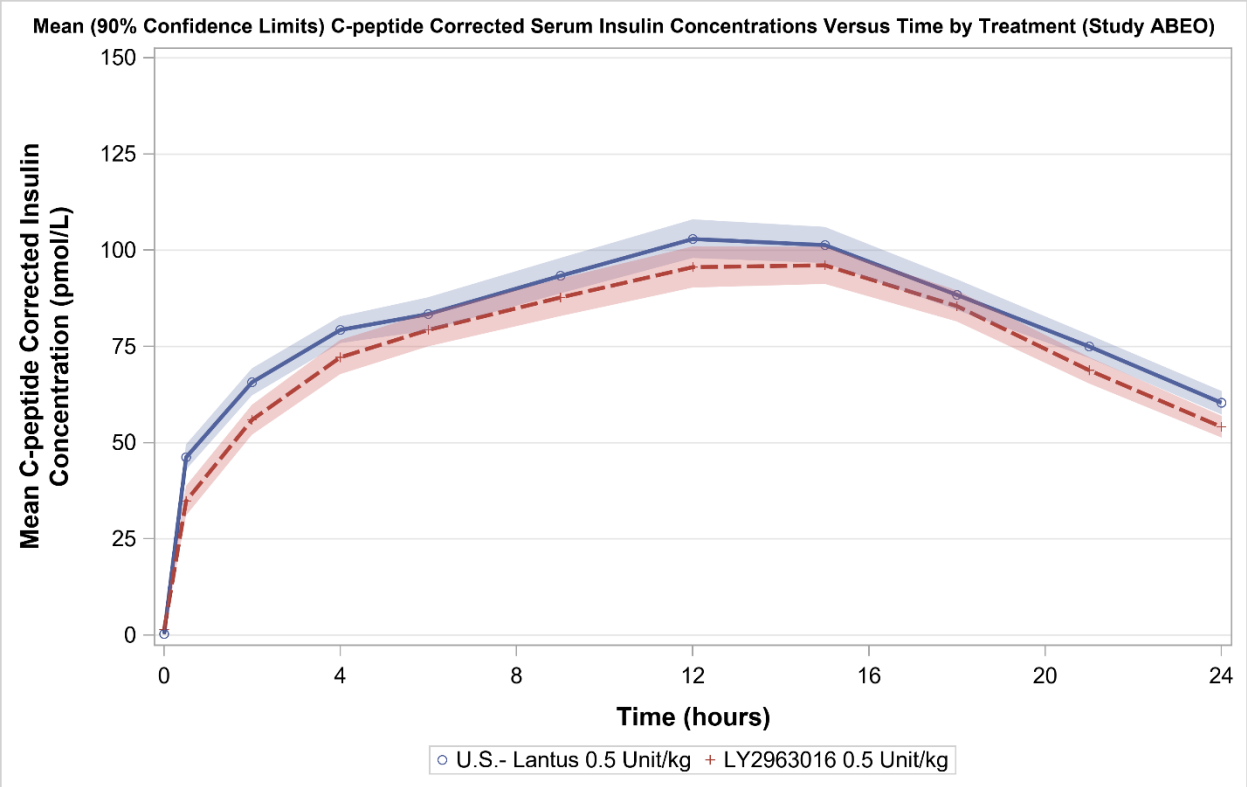
The method was validated over a range of 50 to 2000 pM for study drug. Method GIA3HPP was fully validated in accordance with the Bioanalytical Method Validation guidance from the agency.

Although the RIA is a non-specific method that detected both study drugs and endogenous insulin, this method is acceptable since we recognize that M1 (21A-Gly-insulin) is major circulating moiety in the serum compared to other moieties (e.g., insulin glargine, M2, and endogenous insulin) that may be interacting with the antibody (anti-des-pentapeptide human Insulin) in the RIA assay. The availability of C-pepetide data and endogenous insulin concentrations facilitated appropriate assessment of exogenous insulin concentrations in this cross-over study.

PK Similarity Assessment

For the primary PK parameters (AUC_{0-24h} and C_{max}) of the study drugs, the similarity criterion (90% CI of the geometric least-square mean ratio for test/reference within the limits 80.00% and 125.00%) was met in all the comparisons (Table 4 and Table 6).

Figure 2. Mean C-peptide corrected serum study drug concentration versus time profiles by treatment in Study ABEO



Source: Reviewer's Analysis using PPP excluding Subject (b) (6) in Period 1, Subject (b) (6) Period 3, Subject (b) (6) Period 2, Subject (b) (6) Periods 1 and 2, Subject (b) (6) Period 2, Subject (b) (6) Period 2, Subject (b) (6) Period 1, and Subject (b) (6) Period 1.

Table 5. Summary statistics of Geometric Mean (Coefficient of Variation) Pharmacokinetic Parameter Estimates for C-Peptide Corrected LY2963016 and U.S.- Lantus after a Single 0.5 unit/kg Subcutaneous Dose in Study ABEO

Treatment	Parameter	Units	No of observations	Mean	CV(%)	SD	Median	Min	Max
LY2963016	AUC0-24h	pmol·hr/L	165	1847.4	35.8	662.1	1784.3	272.4	4485.8
	Cmax	pmol/L	167	110.5	36.8	40.7	101.8	20.4	245.6
	Tmax	Hr	167	12.2	35.9	4.4	12.0	2.0	21.0
US-LANTUS	AUC0-24h	pmol·hr/L	167	2009.0	31.9	640.6	1950.6	520.7	4381.4
	Cmax	pmol/L	169	117. 6	32.1	37.8	114.2	43.1	276.7
	Tmax	hr	169	12.1	38.2	4.6	12.0	2.0	24.0

Source: Reviewer's Analysis using PPP excluding Subject (b) (6) in Period 1, Subject (b) (6) Period 3, Subject (b) (6) Period 2, Subject (b) (6) Periods 1 and 2, Subject (b) (6) Period 2, Subject (b) (6) Period 2, Subject (b) (6) Period 1, and Subject (b) (6) Period 1.

Table 6. Summary of statistical comparison of primary PK parameters (baseline adjusted) between LY2963016 and U.S.- Lantus after a single 0.5 unit/kg subcutaneous dose in study ABEO

Comparison	PK Parameters	Units	Geometric LS Means LY2963016	Geometric LS Means US-Lantus	Ratio (%)	90% CI
LY2963016 and U.S.- Lantus	AUC0-t	pmol.hr/L	1718.4	1901.7	90.3	85.4 – 95.5
	Cmax	pmol/L	103.0	111.5	92.4	87.4 – 96.9

Source: Reviewer's Analysis using PPP excluding Subject (b) (6) in Period 1, Subject (b) (6) Period 3, Subject (b) (6) Period 2, Subject (b) (6) Periods 1 and 2, Subject (b) (6) Period 2, Subject (b) (6) Period 2, Subject (b) (6) Period 1, and Subject (b) (6) Period 1.

PD Bioanalytical Method and Performance

The euglycemic clamp technique was used to measure PD response of study drugs. In this technique glucose is administered intravenously as to counter the glucose lowering effect of insulin in order to maintain the plasma glucose (thus the name euglycemia). The temporal profile of glucose-ifusion rate over time serves as the PD response measure for insulin.

On Day 1 of each period in study ABEO, subjects underwent a euglycemic clamp procedure until approximately 24 hours postdose. Each clamp includes a 60-minute stabilization period and target glucose value of 81 mg/dL (4.45 mmol/L). Blood samples

were collected during the 24-hour clamp procedure to determine glucose levels for PD evaluations

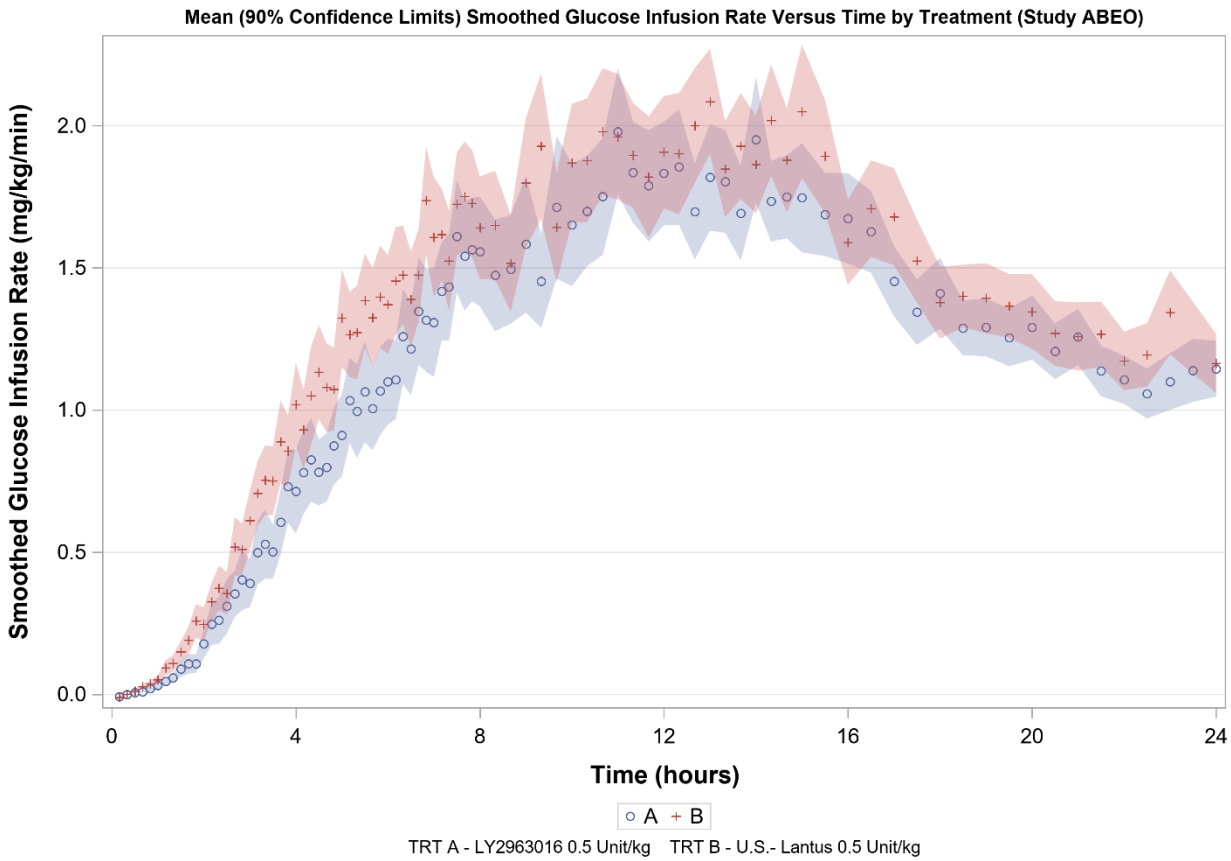
C-peptide concentrations in serum samples from Study ABEO were measured by an accredited CLIA/CAP lab. Serum concentrations of C-peptide were determined using a validated assay.

We found the overall clamp methodology acceptable based on the glucose control data included with the study results.

PD Similarity Assessment

Figure 3 below shows the mean (90%CI) GIR versus time profile by treatment. On average, the PD response as assessed by GIR over time was consistent between LY2963016 and US-Lantus.

Figure 3. Mean GIR versus time profile by treatment in Study ABEO



Source: Reviewer's analysis using PPP.

Table 7. Summary statistics PD parameters in Study ABEO

Treatment	Parameter	Units	Num of Obs	Mean	CV%	Median	Minimum	Maximum
LY2963016	GIRAUC0-24h	mg/kg	171	1938.7	56.57	1905	19	6670
	GIRmax	mg/kg/min	171	2.4	54.1	2.3	0.386	7.86
	TGIRmax	hr	171	12.7	36.4	12.9	3.3	24
U.S.-Lantus	GIRAUC0-24h	mg/kg	170	2156.5	56.5	1905	19	6670
	GIRmax	mg/kg/min	170	2.6	54.1	2.265	0.386	7.86
	TGIRmax	hr	170	12.3	36.4	12.9	3.3	24

Source: Reviewer's Analysis using PPP.

For the PD parameters, the equivalence criterion (90% CI of the ratio test/reference within the limits 80.00% and 125.00%) was met in both comparisons for the primary PD parameters (AUCGIR0-24h and GIRmax) (Table 8).

Table 8. Treatment comparisons of primary PD parameters in Study (b) (4)

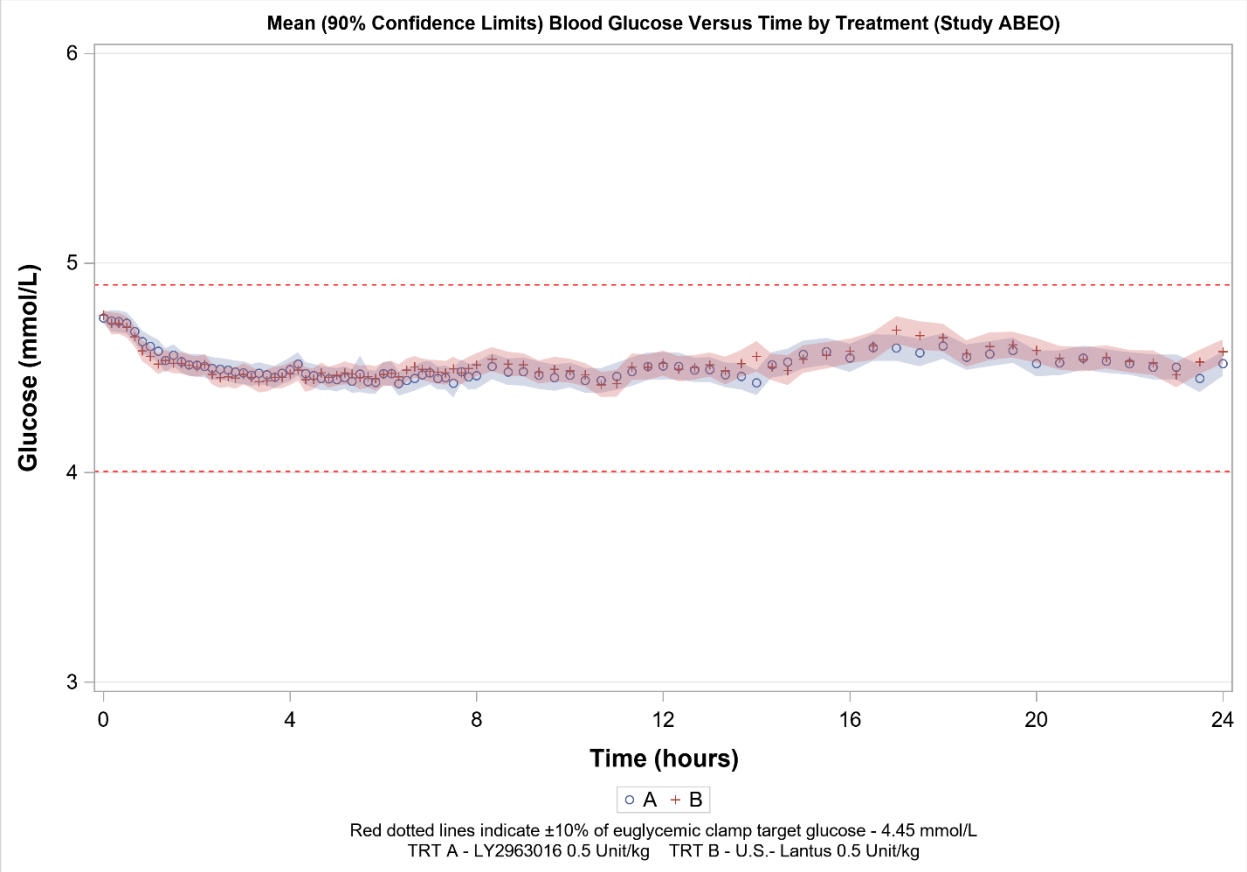
Comparison	PD Parameters	Units	Ratio (%)	90% CI
LY2963016 vs. US-LANTUS	$GIR_{0\text{-}24h}$	mg/kg	92.9	86.2 - 100.0
	GIR_{max}	mg/kg/min	93.4	88.4 - 98.7

Source: Reviewer's Analysis using PPP.

The results of the sensitivity analysis of PD data by excluding Subject (b) (6) in Period 1, Subject (b) (6) Period 3, Subject (b) (6) Period 2, Subject (b) (6) Periods 1 and 2, Subject (b) (6) Period 2, Subject (b) (6) Period 2, Subject (b) (6) Period 1, and Subject (b) (6) Period 1 confirmed that PD similarity conclusions for AUCGIR0-24h did not change from the original analysis.

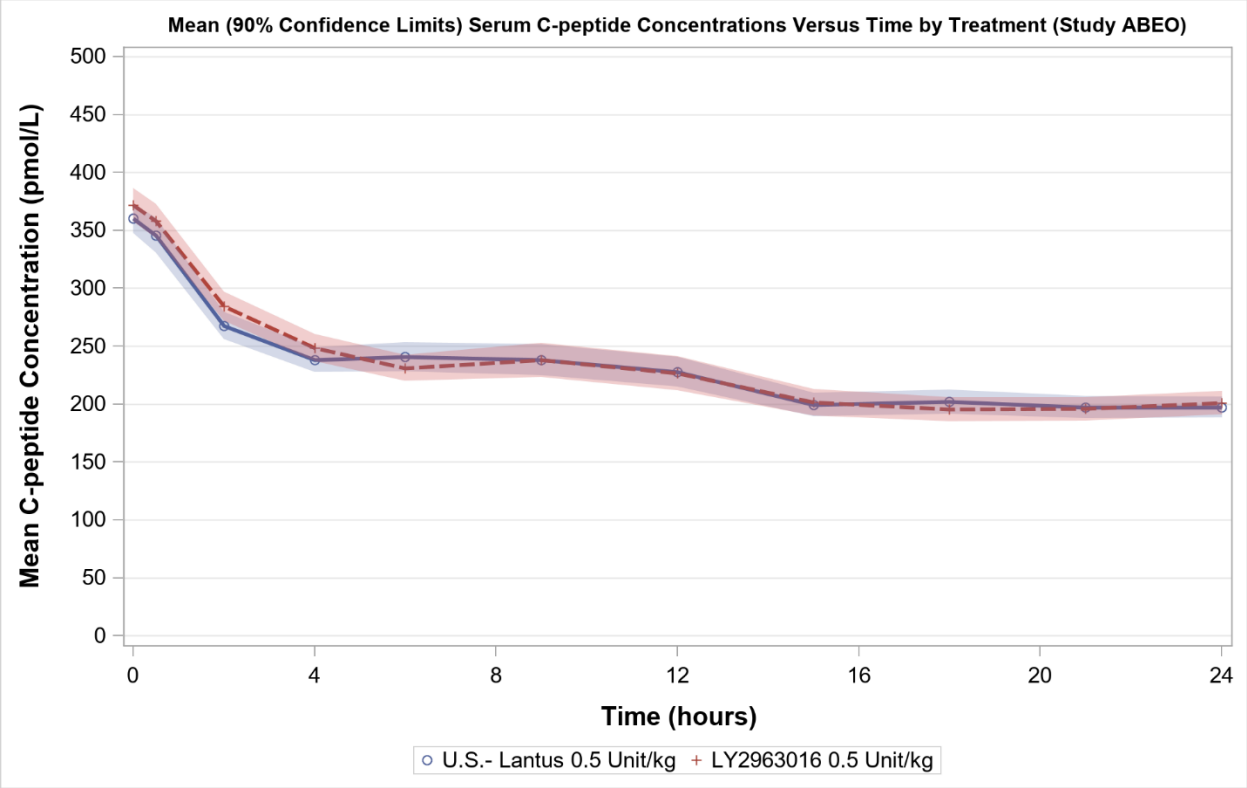
The euglycemic clamp quality were assessed through assessment of coefficient of variation of blood glucose during clamp and percent deviation from the target glucose data. **Error! Reference source not found.** below presents the graphical comparison of clamp quality metrics using blood glucose during clamp duration, which shows that the blood glucose values were consistently within ±10% of the euglycemic target for both treatments. In addition, C-peptide (i.e., a breakdown product of endogenous pro-insulin) was also similarly suppressed during the clamp duration among treatment groups (Figure 5) indicating minimal confounding of the PD response by endogenous insulin.

Figure 4. Mean blood glucose concentrations during clamp by treatment in Study ABEO.



Source: Reviewer's Analysis

Figure 5. Mean C-peptide concentrations during clamp by treatment in Study ABEO.



Source: Reviewer's Analysis

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6. Statistical and Clinical Evaluation and Recommendations

6.1. Statistical and Clinical Executive Summary and Recommendation

The information submitted in the application, including the comparative analytical data and the PK/PD results (which together demonstrate that the MOA is the same for LY2963016 and U.S.-Lantus, to the extent known), supports a demonstration that LY2963016 and U.S.-Lantus are highly similar, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences in terms of safety, purity, and potency.

FDA updated its scientific thinking regarding whether and when comparative clinical

immunogenicity studies may be needed to support licensure of proposed biosimilar (b) (4) insulin products. FDA's updated thinking was outlined in the November 2019 *Insulin Immunogenicity Guidance*. This draft guidance stated a comparative clinical immunogenicity study generally would be considered unnecessary to support a demonstration of biosimilarity in a 351(k) BLA for a proposed insulin product seeking licensure as a biosimilar (b) (4) if the BLA contains a robust and comprehensive comparative analytical assessment demonstrating that the proposed insulin product is "highly similar" to its proposed reference product with very low residual uncertainty regarding immunogenicity and the application otherwise meets the standards for licensure under section 351(k) of the PHS Act. The guidance recommended that a 351(k) BLA for a biosimilar (b) (4) insulin product contain, among other things, an immunogenicity assessment justifying why a comparative clinical study to assess immunogenicity is not necessary to support a demonstration of biosimilarity.

Consistent with the *Insulin Immunogenicity Guidance*, the Applicant performed a comprehensive and robust comparative analytical assessment of LY2963016 and U.S.-Lantus and submitted an immunogenicity assessment justifying why a comparative clinical study to assess immunogenicity was not necessary to support a demonstration of biosimilarity. The former adequately supported a demonstration that LY2963016 is highly similar to U.S.-Lantus, notwithstanding minor differences in clinically inactive components. The results are summarized in Section 3.1. The latter adequately justified why a comparative clinical study to assess immunogenicity is not necessary to support a demonstration of biosimilarity. The assessment is discussed in Section 6.4. Based on the comparative analytical assessment findings and adequate immunogenicity assessment, FDA has determined that there is no residual uncertainty regarding immunogenicity of LY2963016.

Overall, the immunogenicity assessment submitted in this application contributes to the totality of evidence supporting a demonstration of no clinically meaningful differences between LY2963016 and U.S.-Lantus in terms of safety, purity, and potency.

6.1.1. Statistical and Clinical Residual Uncertainties Assessment

There are no residual uncertainties based on the clinical analyses that would affect a demonstration of biosimilarity (b) (4) between LY2963016 and U.S.-Lantus

6.2. Review of Comparative Clinical Studies with Statistical Endpoints

No comparative clinical studies with statistical endpoints were necessary or submitted to this 351(k) application to support a conclusion that LY2963016 is biosimilar to U.S.-Lantus.

6.3. Review of Safety Data

Study ABEO was a euglycemic clamp PK/PD similarity study conducted in healthy volunteers; the design of the studies is presented in Section 5.3.1. Euglycemic clamp studies provide time-concentration profiles and time-action profiles based on reliable measures of systemic exposure and glucose response. Study ABEO collected a limited amount of safety data during its conduct, but the safety data collected were not necessary to the demonstration of biosimilarity between LY2963016 and U.S.-Lantus. The comparative analytical data and the results of Study ABEO demonstrating PK and PD similarity between LY2963016 and U.S.-Lantus support a demonstration of no clinically meaningful differences between LY2963016 and U.S.-Lantus in terms of safety, purity, and potency, without reliance on safety data generated by Study ABEO. The limited amount of safety data that were collected during the conduct of Study ABEO were inspected only to ensure that these data did not conflict with the conclusion of biosimilarity based on the analysis of the comparative analytical data and the finding of PK and PD similarity between LY2963016 and U.S.-Lantus. Review of these limited safety data collected did not suggest any differences in the safety profiles of LY2963016 and U.S.-Lantus.

6.4. Clinical Conclusions on Immunogenicity

Consistent with the *Insulin Immunogenicity Guidance*, the Applicant submitted an immunogenicity assessment justifying why a comparative clinical immunogenicity study was not necessary to support a demonstration of biosimilarity for LY2963016.

The OPQ review concluded that the data provided by the Applicant, including the comparative analytical assessment, are adequate to support the conclusion that the manufacture of LY2963016 is well-controlled and leads to a product that is safe, pure, and potent, and supported a demonstration that LY2963016 is highly similar to U.S.-Lantus, notwithstanding minor differences in clinically inactive components.

In the immunogenicity assessment, the Applicant referenced the results of their clinical program including the three submitted PK/PD studies (as summarized in Table 2), and data from phase 3 clinical studies ABEB and ABEC conducted in patients with type 1 and type 2 Diabetes Mellitus, respectively, previously submitted and reviewed under NDA 205692. The assessment included a summary of the results from the immunogenicity analyses from studies ABEB and ABEC, including a summary of the results from analyses using a treatment emergent antibody response (TEAR) approach, and a reference to the efficacy and safety findings from the studies.

While the Agency does not agree with all of the arguments presented in the applicant's immunogenicity assessment, the applicant does present information that comprises an adequate justification for why a comparative clinical study to assess immunogenicity is not necessary to support a demonstration of biosimilarity for LY2963016. The Applicant's comparative analytical assessment demonstrates that LY2963016 is highly similar to U.S.-Lantus, notwithstanding minor differences in clinically inactive

components. In addition, the FDA review of PK/PD study ABEO concluded that the applicant was able to demonstrate PK and PD similarity between LY2963016 and U.S.-Lantus. In conjunction with the CAA, these results support a demonstration that there are no clinically meaningful differences between LY2963016 and U.S.-Lantus. Finally, although the results from phase 3 clinical studies ABEB and ABEC were unnecessary to demonstrate that there are no clinically meaningful differences between [redacted] (b) (4) and U.S.-Lantus, the results from these studies do not preclude or conflict with that conclusion. Therefore, there is no residual uncertainty regarding immunogenicity from the clinical perspective.

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6.5. Risk in Terms of Safety or Diminished Efficacy [redacted] (b) (4)

The Applicant has developed LY2963016 as a proposed [redacted] (b) (4) biosimilar to U.S.-Lantus and is seeking licensure of LY2963016 for the same indication, same dosage form, strength, and route of administration as U.S.-Lantus.

The Applicant submitted data and information from a comprehensive and robust comparative analytical assessment between LY2963016 and U.S.-Lantus demonstrating that LY2963016 is highly similar to U.S.-Lantus, notwithstanding minor differences in clinically inactive components. Additionally, Study ABEO was conducted in healthy subjects that provided time-concentration profile and time-action profile over the duration of LY2963016 and U.S.-Lantus based on reliable measures of systemic exposure and glucose response using a euglycemic clamp procedure. Study ABEO demonstrated PK and PD similarity between LY2963016 and U.S.-Lantus. Given the foregoing as well as the determination described above that the immunogenicity assessment was adequate, and consistent with the principles in the Insulin Immunogenicity Guidance, a comparative clinical immunogenicity study is not necessary [redacted] (b) (4)

As explained above, the known and potential mechanisms of action of insulin products, including U.S.-Lantus, include the regulation of glucose metabolism. Insulin and insulin analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Comparative analytical testing, including multiple orthogonal assays relevant to the mechanism of action of U.S.-Lantus, plus comparative clinical pharmacodynamic data evaluating glucose metabolism, demonstrated that LY2963016 has the same mechanism(s) of action as that of U.S.-Lantus, to the extent known. Healthy subjects comprise an adequately sensitive population in which to evaluate PK and PD similarity via a

euglycemic clamp experiment (which allows the measurement of insulin pharmacokinetics and pharmacodynamic response without risk of hypoglycemia.

U.S.-Lantus has two presentations: a 10 mL multiple-dose vial and a 3 mL single-patient-use pre-filled pen (PFP), and the Applicant is seeking licensure of the 3 mL PFP. There are no residual uncertainties from a device or medication error perspective (b) (4)

The totality of the evidence, including the results of the comparative analytical assessment and pharmacokinetic and pharmacodynamic similarity study ABEO, demonstrates that LY2963016 is biosimilar to US-Lantus. In addition, the totality of the evidence submitted in the application sufficiently demonstrates that LY2963016 can be expected to product the same clinical result as that of U.S.-Lantus in any given patient (b) (4)

6.6. Extrapolation

6.6.1. Division of Diabetes, Lipid Disorders, and Obesity

The information submitted in the application, including the comparative analytical data and the PK/PD results (which together demonstrate that the mechanism of action is the same for LY2963016 and U.S.-Lantus, to the extent known) supports a demonstration that LY2963016 and U.S.-Lantus are highly similar notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences in terms of safety, purity, and potency. An extrapolation of the finding of PK similarity of LY2963016 and U.S.-Lantus in healthy adults to adult patients with T1DM, pediatric patients with T1DM, and adult patients with T2DM is justified because the same scientific factors that determine absorption, distribution, metabolism, and elimination in healthy adults also determine absorption, distribution, metabolism, and elimination in patients with diabetes mellitus. The extrapolation of the finding of PD similarity of LY2963016 and U.S.-Lantus in healthy adults to adult patients with T1DM, pediatric patients with T1DM and adult patients with T2DM is justified because the assessed PD endpoints evince the binding and activation of insulin receptors, which is the pertinent MOA for all conditions of use of U.S. Lantus (to the extent known). No comparison of any other scientific factors across the conditions of use were necessary to justify the extrapolation. The extrapolation does not require specific knowledge about the relationship between the PK and PD profiles observed in healthy adults and the PK and PD profiles that would be observed in patients with diabetes mellitus. The data and information in the application, including comparative pharmacokinetic and pharmacodynamic data demonstrating no meaningful differences in time-concentration profile and time-action profile over the duration of action of each product, from Study ABEO, supports licensure for the conditions of use for which U.S.-Lantus has been previously approved and for which the applicant is seeking licensure.

The information submitted by the applicant demonstrates that LY2963016 is biosimilar to U.S.-Lantus for the following indication (including all of the indicated patient populations) for which the applicant is seeking licensure and for which U.S.-Lantus has been previously approved: to improve glycemic control in adults and pediatric patients with T1DM and in adults with T2DM.

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7. Labeling Recommendations

7.1. Nonproprietary Name

The Applicant's proposed nonproprietary name, insulin glargine-aglr, was found to be conditionally accepted by the Agency (DMEPA review dated September 3, 2021).

7.2. Proprietary Name

The proposed proprietary name for LY2963016 is conditionally approved as REZVOGLAR. This name has been reviewed by DMEPA, who concluded the name was acceptable.

7.3. Other Labeling Recommendations

It was determined that the proposed labeling is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), is consistent with CDER/OND best labeling practices and policies, is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

The Applicant is seeking licensure for the same indications for which U.S.-Lantus is currently approved: to improve glycemic control in adult and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. The proposed LY2963016 labeling incorporated relevant data and information from U.S.-Lantus labeling, with appropriate modifications.

There are multiple approved 351(a) BLAs that have the proper name insulin glargine. Consistent with the Guidance for Industry, Labeling for Biosimilar Products (b) (4) and the biosimilarity statement in the HIGHLIGHTS section of the prescribing information, references to "insulin glargine" in the labeling for LY2963016 are to U.S.-Lantus.

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8. Human Subjects Protections/Clinical Site and other Good Clinical Practice (GCP) Inspections/Financial Disclosure

The data quality and integrity of the studies were acceptable. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

Documented approval was obtained from institutional review boards (IRBs) and independent ethics committees (IECs) prior to study initiation. All protocol modifications were made after IRB/IEC approval. The studies were conducted in accordance with good clinical practice (GCP), code of federal regulations (CFR), and the Declaration of Helsinki.

The Applicant has adequately disclosed financial interests and arrangements with the investigators. Form 3454 is noted in Section 13.2 and verifies that no compensation is linked to study outcome. The Principal Investigators (PIs) did not disclose any proprietary interest to the sponsor.

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9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee was held for this biosimilar application, as it was determined that there were no issues where the Agency needed input from the Committee.

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10. Pediatrics

Under the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric

assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. (b) (4)

In the Applicant's amended pediatric study plan (PSP), dated October 28, 2020, the Applicant noted that LY2963016 was being developed as (b) (4) biosimilar with the same licensed indications as U.S.-licensed Lantus. The Applicant stated that it intended to fulfill PREA requirements by demonstrating biosimilarity between U.S.-Lantus and LY2963016 and providing an adequate scientific justification under the BPCI Act for extrapolation for pediatric patients with type 1 diabetes mellitus, for which US-Lantus is licensed. The Agency confirmed with the Applicant that for the pediatric populations for which US-Lantus is not approved there that there were no pending PREA PMR requirements. No waivers or deferrals were requested. Therefore, as described by the Applicant, no specific studies of LY2963016 in the pediatric population are planned or necessary.

The Pediatric Review Committee (PeRC) meeting was held on April 27, 2021 to review the Applicant's PSP, and the PeRC agreed with this plan.

(b) (4) Based on the information above—including that the Applicant is seeking licensure of LY2963016 for the same indications as U.S.-Lantus—at this time, no change is needed to the Applicant's plan for no specific studies of LY2963016 in the pediatric population.

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11. REMS and Postmarketing Requirements and Commitments

11.1. Recommendations for Risk Evaluation and Mitigation Strategies

None.

11.2. Recommendations for Postmarket Requirements and Commitments

None.

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12. Comments to Applicant

(b) (4)

13. Appendices

13.1. References

Not applicable.

13.2. Financial Disclosure

Covered Clinical Study: ABEO

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value		

could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in Sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Nonclinical Appendices

13.3.1. Nonclinical Pharmacology

In vitro studies comparing LY2963016 to U.S.-Lantus evaluated: insulin receptor binding (association and dissociation constants) for insulin receptor-A (IR-A) and insulin receptor-B (IR-B) and the insulin-like growth factor-1 receptor (IGF-1R); insulin receptor activation (via IR-A and IR-B phosphorylation); metabolic activity (via insulin-stimulated glucose uptake, inhibition of lipolysis, and adipogenesis); and, mitogenic activity (via insulin receptor- and IGF-1 receptor-dependent mitogenicity) to demonstrate biosimilarity of the two insulin analog products. Assay results are reviewed below.

Insulin Receptor A Binding Kinetics
The binding kinetics of the LY2963016 (5 batches: 3 batches manufactured in Indianapolis and 2 batches manufactured in Fegersheim, France) to the insulin receptor-A (IR-A) are similar to those of U.S.-Lantus (5 batches). The affinity binding constant (K_i) was determined in a radioligand competition binding assay using receptor membranes prepared from HEK293 cells over-expressing the recombinant human IR-A. The kinetic association and dissociation constants were assessed using Surface Plasmon Resonance after different concentrations of the LY2963016, U.S.-Lantus, or reference controls were flowed over a chip with immobilized soluble IR A.

IR-A Binding Kinetics of LY2963016 and U.S.-Lantus

	Mean K_i(nM)	Mean K_a1 (1/Ms)	Mean K_d1 (1/s)	Mean K_a2 (1/Ms)	Mean K_d2 (1/s)
LY2963016	0.461	29400	0.0290	5550	0.165
U.S.-Lantus	0.484	30600	0.0287	4520	0.142

Abbreviations: K_i = equilibrium dissociation constant or binding affinity, Ka1 = high affinity kinetic association constant, Kd1 = high affinity kinetic dissociation constant, Ka2 = low affinity kinetic association constant, Kd2 = low affinity kinetic dissociation constant, M = molar, s = seconds,

Insulin Receptor B Binding Kinetics

The binding kinetics of the LY2963016 (5 batches: 3 batches manufactured in Indianapolis and 2 batches manufactured in Fegersheim, France) to the insulin receptor-B (IR-B) are similar to those of U.S.-Lantus (5 batches). The affinity binding constant (K_i) was determined in a radioligand competition binding assay using receptor membranes prepared from HEK293 cells over-expressing the recombinant human IR-B. The kinetic association and dissociation constants were assessed using Surface Plasmon Resonance after different concentrations of the LY2963016, U.S.-Lantus, or reference controls were flowed over a chip with immobilized soluble IR B.

IR-B Binding Kinetics of LY2963016 and U.S.-Lantus

	Mean K_i(nM)	Mean K_a1 (1/Ms)	Mean K_d1 (1/s)	Mean K_a2 (1/Ms)	Mean K_d2 (1/s)
LY2963016	0.416	28600	0.0343	4600	0.180
U.S.-Lantus	0.372	28200	0.0339	6600	0.165

Abbreviations: K_i = equilibrium dissociation constant or binding affinity, Ka1 = high affinity kinetic association constant, Kd1 = high affinity kinetic dissociation constant, Ka2 = low affinity kinetic association constant, Kd2 = low affinity kinetic dissociation constant, M = molar, s = seconds,

IGF-1 Receptor Binding Kinetics

The binding kinetics of the LY2963016 (5 batches: 3 batches manufactured in Indianapolis and 2 batches manufactured in Fegersheim, France) to the insulin-like growth factor-1 receptor (IGF-1R) are similar to those of U.S.-Lantus (5 batches). The affinity binding constant (K_i) was determined in a radioligand competition binding assay using receptor membranes prepared from HEK293 cells over-expressing the recombinant human IGF-1R. The kinetic association and dissociation constants were assessed using Surface Plasmon Resonance after different concentrations of the LY2963016, U.S.-Lantus, or reference controls were flowed over a chip with immobilized soluble IGF-1R.

IGF-1R Binding Kinetics of LY2963016 and U.S.-Lantus

	Mean K_i(nM)	Mean K_a1 (1/Ms)	Mean K_d1 (1/s)	Mean K_a2 (1/Ms)	Mean K_d2 (1/s)
LY2963016	21.4	28600	0.0346	7220	0.198
U.S.-Lantus	18.9	27900	0.0326	7200	0.173

Abbreviations: K_i = equilibrium dissociation constant or binding affinity, Ka1 = high affinity kinetic association constant, Kd1 = high affinity kinetic dissociation constant, Ka2 = low affinity kinetic association constant, Kd2 = low affinity kinetic dissociation constant, M = molar, s = seconds,

IR-A and IR-B Phosphorylation

The capacity of the LY2963016 (5 batches: 3 batches manufactured in Indianapolis and 2 batches manufactured in Fegersheim, France) to activate downstream cellular signaling through IR-A and IR-B, as demonstrated by IR-A and IR-B phosphorylation, is similar to that of U.S.-Lantus (5 batches). There was significant difference in IR-A

autophosphorylation potencies between LY2963016 and U.S.-Lantus based on the unadjusted p-value. The Best Range as per the current effective standard test procedure was not used in the data analysis. Comparison adjustments by the Sidak and Holm-Bonferroni methods both show non-significance between the IR-A autophosphorylation potency of LY2963016 and U.S.-Lantus. Nevertheless, the difference is considered not biologically meaningful because there were no differences in receptor binding affinity and mitogenic potential between LY2963016 and U.S.-Lantus.

Using ELISA technique, IR-A and IR-B phosphorylation in cellular lysates from HEK293 cells engineered to over express either IR-A or IR-B were quantified following treatment with different concentrations of LY2963016 , U.S.-Lantus, or a biosynthetic human insulin (BHI) reference. The potencies were reported as the concentration of compound required to elicit a half-maximum response (EC_{50}) relative to a maximally efficacious concentration of a BHI reference standard (1000 nM).

IR-A Autophosphorylation in Response to LY2963016 and U.S-Lantus

	Mean EC_{50}(nM)	Range (nM)
LY2963016	8.66	6.89-9.59
U.S.-Lantus	6.80	6.60-7.47

IR-B Autophosphorylation in Response to LY2963016 and U.S-Lantus

	Mean EC_{50}(nM)	Range (nM)
LY2963016	5.49	4.33-7.54
U.S.-Lantus	5.13	4.46-5.76

In Vitro Metabolic Potential

The metabolic activity, as measured by de novo lipogenesis of triglycerides from [^{3}H]-glucose using differentiated mouse 3T3L1 adipocytes, of LY2963016 (5 batches) is similar to that of U.S.-Lantus (5 batches). The potencies were reported as the concentration of compound required to elicit a half-maximum response (EC_{50}) relative to the response observed with a maximally efficacious concentration of a BHI reference standard (100 nM).

Metabolic Potential, EC_{50}, of LY2963016 and U.S.-Lantus Determined Using Differentiated Mouse 3T3L1 Adipocytes

	Mean EC_{50}(nM)	Range (nM)
LY2963016	5.70	5.42-6.00
U.S.-Lantus	6.12	5.30-7.02

Mitogenicity Assays

The IGF-1 receptor-dependent mitogenic activity of LY2963016 (5 batches) in Saos2 osteosarcoma cells is considered similar to that of U.S.-Lantus (5 batches). The ability to promote the proliferation of Saos2 cells, a human osteosarcoma cell line expressing

IGF-1 receptor, was evaluated following treatment with different concentrations of LY2963016 , U.S.-Lantus, or a BHI reference using a colorimetric method with CellTiter 96 Aqueous One Solution (Promega).

Additionally, LY2963016 (5 batches) and U.S.-Lantus (5 batches) exhibit comparable IR-dependent mitogenic activity in H4IIE cells expressing IR-A. The ability of promote the proliferation of H4IIE cells, a rat hepatoma cell line overexpressing IR-A, was evaluated following treatment with different concentrations of LY2963016, U.S.-Lantus, or a BHI reference using a colorimetric method with CellTiter 96 Aqueous One Solution (Promega).

Mitogenic Potential, EC_{50}, of LY2963016 and U.S.-Lantus in Saos2 IGF-1R Expressing Cells

	Mean EC_{50}(nM)	Range (nM)
LY2963016	0.949	0.735-1.32
U.S.-Lantus	0.827	0.660-1.10

Mitogenic Potential, EC_{50}, of LY2963016 and U.S.-Lantus in H4IIEE IR-A Expressing Cells

	Mean EC_{50}(nM)	Range (nM)
LY2963016	0.181	0.150-0.217
U.S.-Lantus	0.190	0.180-0.204

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13.4. Clinical Pharmacology Appendices

13.4.1. Summary of Bioanalytical Method Validation and Performance

Pharmacokinetics

For the PK similarity study ABEO, serum study drug concentrations of U.S.-Lantus, and LY2963016 measured using a validated RIA method (method RIA-0020) along with the C-peptide assay that was used for endogenous insulin correction were found adequate for the assessment of PK similarity for this submission. Both the method validation entitled “Validation of a Method for the Determination of Insulin Glargine via RIA in Human Serum – report 8225343” and sample analysis for the study were performed at (b) (4). More details are assay validation and performance of the assay methods in (b) (4) are listed in Table 10**Error! Reference source not found.**

Table 9. Summary of the bioanalytical method validation and in-study performance for measurement of LY2963016 and U.S.-Lantus

Bioanalytical Method Validation Report Name and Amendments	Validation of a Method for the Determination of Insulin Glargine via RIA in Human Serum – Report 8225343
Bioanalytical method description	The RIA for measurement of LY2963016 and U.S.-Lantus in human serum is a competitive radioimmunoassay. Samples were pretreated with polyethylene glycol (PEG) precipitation to remove any antibody/study drug complexes, so the measured concentrations represent "free" immunoreactive study drug. The antibody employed in the RIA was generated against despentapeptide human insulin. As a consequence, the RIA demonstrates full cross-reactivity with both study drugs and native human insulin. In addition, to allow for correction of serum immunoreactive LY2963016 and immunoreactive US-LANTUS concentrations for endogenous insulin, each subject had blood samples taken for the measurement of C-peptide concentrations at the same time points as the PK samples C-peptide corrected insulin glargine concentration was calculated based on the following equation: [LY2963016 or US-LANTUS] = [immunoreactive LY2963016 or immunoreactive US-LANTUS] – F*[C-peptide] in which F is the average of the ratios of immunoreactive LY2963016 or immunoreactive US-LANTUS to C-peptide at baselines (-30 and 0 minutes).
Materials used for calibration curve & concentration	Analyte: U.S.-Lantus Tracer molecule: Hydrated 125I-Insulin Antibody: Anti-Des-pentapeptide human Insulin (DPI) Analyte in human serum at the following concentrations: 4000, 2000, 1000, 500, 250, 125, 62.5, 50.0, 30.0, 15.0 pM
Validated assay range	15 pM to 4000 pM
Material used for QCs & concentration	Analyte: U.S.-Lantus and LY2963016 Tracer molecule: Hydrated ^{125}I-Insulin Antibody: Anti-Des-pentapeptide human Insulin (DPI) Concentrations: 30, 50, 100, 240, 1200, 2000 pM

Minimum required dilutions (MRDs)	Serum samples with concentrations higher than 2000 pM were diluted up to 1:256 prior to analysis		
Source & lot of reagents (LBA)	Anti-Des-pentapeptide human insulin (DPI) antibody, supplied by applicant at a 1/5 dilution, Lot# XHP-R42		
Regression model & weighting	Regression Model: 5-Parameter model Weighting factor: 1		
Validation Parameters	**Method Validation Summary**		**Acceptability**
Calibration curve performance during accuracy & precision Per BMV, At least 75% and minimum of 6 non-zero calibrators without anchor points and LBA: ±20% bias (±25% at lower limit of quantitation (LLOQ)), ≤ 20%CV	Number of standard calibrators from LLOQ to upper limit of quantitation (ULOQ)	10	Acceptable
	Cumulative accuracy (%bias) from LLOQ to ULOQ U.S.-Lantus	AR: 87.9-106.1%	Acceptable
	Cumulative precision (%CV) from LLOQ to ULOQ U.S.-Lantus	CV: ≤ 14.8%	Acceptable
QCs performance during accuracy & precision Per BMV, LBA QCs: ±20% bias (±25% at LLOQ), ≤ 20%CV and ≤ 30% total error (≤ 40% at LLOQ)	Cumulative accuracy (%bias) in 6 QCs U.S.-Lantus	Inter-assay Relative error (RE): ±18.7% Intra-assay RE: ±18.2% ULOQ-LQC with the exception of run 027 at the LQC level. RE: ± 34.3% for LLOQ1 (30 pM) RE: ± 27.4% and LLOQ2 (50 pM)	Acceptable Note: The intra-assay accuracy at the LLOQ1 and LLOQ2 levels did not meet the target acceptance criteria of RE within ±25% in several runs. The LLOQ2 (50 pM) did however demonstrate REs within ±30%. While this level fails to meet the target acceptance criteria the results are within reasonable limits and therefore acceptable. The LLOQ for the

			method will be set at 50pM.
	%CV U.S.-Lantus	Inter-batch ≤17.0% Intra-batch ≤15.0%	Acceptable
	Percent total error (TE) U.S.-Lantus	TE≤27.9%, ≤35.7% for LLOQ1 and LLOQ2	Acceptable
	Cumulative accuracy (%bias) in 6 QCs LY2963016	Inter-assay Relative error (RE): ±9.7%	Acceptable
	%CV LY2963016	Inter-batch ≤16.3% Intra-assay ≤9.7%	Acceptable
Selectivity & matrix effect	100% of the samples meet the method selectivity criteria: 75% to 125% recovery of the expected final concentration as determined by the spiked concentration plus endogenous concentration (un-spiked)		Acceptable
Comparability of LY2963016 (BIV) to Glargine	Inter-assay RE: ±9.7% CV≤16.3% Intra-assay RE: ±15.7, 22.0% at LLOQ CV: ≤9.0%		Acceptable
Comparability of Glargine to Insulin	RE: ±22.5% CV: ≤9.4%		
Dilution linearity	AR: 93.2 – 100.5% of the corresponding nominal concentration in 100% samples within the quantitative range		Acceptable
Bench-top/process stability	Bench top stability was established up to 24 hrs. AR to baseline: 87.5 – 98.8% CV ≤ 6.0%		Acceptable
Freeze-Thaw stability	Freeze/thaw stability was established up to 5 freeze/thaws: AR: 82.5% - 101.46% CV: ≤ 8.2%		Acceptable
Refrigerator Stability	Refrigerator stability was established up to 72 hrs. AR: 92.6 – 101.7% CV: ≤ 11.2%		Acceptable

Method Performance in Study ABEO **Report I4L-MC-ABEO provid in Section 5.3.1.4**		
Assay passing rate	Incurred samples (ISR) passed at 90.7%.	Acceptable
Standard curve performance	LLOQ = 50 pM; ULOQ = 2000 pM AR: 97.7% to 104.3% CV: 4.6% to 6.9%	Acceptable
QC performance	QC: 100 pM, 240 pM and 1200 pM Inter-assay RE: 0.9 to 15.0% CV: 7.1% to 16.0%.	Acceptable
Method reproducibility	Incurred samples (ISR) passed at 90.7%.	Acceptable
Study sample analysis/ stability	• LY2963016 and U.S.-Lantus in human serum was stable for up to 12 months when stored at approximately -60 to -80 °C or -15 to 30 °C. • Reconstituted LY2963016 and U.S.-Lantus, when stored at 2 to 8ºC is stable for up to 3 weeks	
C-Peptide Validation		
Bioanalytical method validation report name	C-Peptide on the Siemens ADVIA Centaur XP	
Bioanalytical method description	C-peptide was measured using a validated commercial kit. The ADVIA Centaur® commercial assay, a 2-site sandwich immunoassay using direct chemiluminescent technology, was used to measure C-peptide. Briefly, this C-peptide assay uses constant amounts of 2 antibodies: the first antibody, in the Lite Reagent, is a monoclonal mouse anti-C-peptide antibody labeled with acridinium ester, and the second antibody, in the Solid Phase, is a monoclonal mouse anti-C-peptide antibody. A direct relationship exists between the amount of C-peptide present in the patient sample and the amount of relative light units detected by the system. The ADVIA Centaur® commercial C-peptide assay is FDA approved for in vitro diagnostic use and calibrated in accordance with World Health Organization IS 84/510.	
Calibration	The ADVIA centaur C-Peptide utilizes a two-point calibration	
Intra-assay precision	3.7 – 4.1% CV	
Inter-assay precision	5.1 – 6.2% CV	
Reportable range	0.07 ng/mL to 22 ng/mL, maximum dilution X16 (extending the upper reportable range to 352 ng/mL)	

**Concentration data from impacted samples removed for PK analysis*

Pharmacodynamics

In Study ABEO, the pharmacodynamic effect of the study drugs were assessed using euglycaemic glucose clamp procedure in which glucose infusion rate necessary to maintain blood glucose at predefined level was constantly recored. Subjects had two venous catheters, one for drawing frequent blood samples to monitor the subject's blood glucose continuously and the other one to infuse glucose using a predefined algorithm to keep the subject's blood glucose concentration constant at a pre-determined target level.

The current procedures are in accordance with the US Code of Federal Regulations (see Title 21, Chapter I, Subchapter A, Part 58 Good Laboratory Practice [GLP] for nonclinical laboratory studies) and Federal Register for GLP paragraph 121 ("Proper standards [for calibration] are the responsibility of the management, and these are to be set forth in the standard operating procedures [SOPs]"). All procedures regarding measurements with and QC of the device are regulated by SOPs. Other Clinical Pharmacology Information

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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