

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205692Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY REVIEW**

---

<b>NDA: 205692</b>	Submission Date(s): 10/18/2013
<b>Brand Name</b>	BASAGLAR™
<b>Generic Name</b>	Insulin Glargine (LY2963016)
<b>Reviewer</b>	Manoj Khurana, Ph.D.
<b>Team Leader</b>	Lokesh Jain, Ph.D.
<b>OCP Division</b>	Division of Clinical Pharmacology II
<b>OND division</b>	Metabolism and Endocrinology Products
<b>Sponsor</b>	Eli Lilly and Company
<b>Submission Type; Code</b>	NDA 505(b)(2); Standard
<b>Formulation; Strength(s)</b>	100 units/mL (U-100) solution for subcutaneous (SC) injection, 3 mL BASAGLAR™ KwikPen™(prefilled)
<b>Proposed Indication</b>	Long-acting human insulin analog indicated to improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

**LIST OF FIGURES..... 2**

**LIST OF TABLES..... 2**

**1 EXECUTIVE SUMMARY ..... 3**

**1.1 RECOMMENDATION..... 3**

**1.2 PHASE IV COMMITMENTS ..... 3**

**1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS..... 3**

**2 QUESTION-BASED REVIEW (QBR)..... 5**

**2.1 GENERAL ATTRIBUTES ..... 5**

**2.1.1 What is the relevance and importance of the clinical pharmacology data in establishing similarity of proposed insulin product to a reference insulin product in the context of the current 505(b)(2) application? ..... 5**

**2.1.2 What are the important design features of the clinical pharmacology studies and the analyses used to support the current application?..... 7**

**2.1.3 What is the composition of to be marketed formulation of LY2963016? ..... 11**

**2.2 KEY CLINICAL PHARMACOLOGY ISSUES ..... 12**

**2.2.1 Does the PK and PD data from the clinical pharmacology studies support the similarity claim for the to-be-marketed formulation of LY2963016 in reference to US-Lantus®? ..... 12**

**2.2.2 How do the PK and PD profiles compare between LY2963016 and EU sourced Insulin Glargine or between US-Lantus and EU-sourced Insulin Glargine and how does this information support the PK and PD similarity assessment for LY2963016 versus US-Lantus?. 13**

**2.2.3 How do the PK and PD profiles (duration of action) compare between LY2963016 and EU sourced Insulin Glargine in Type 1 diabetes patients and how does this information support the PK and PD similarity assessment for LY2963016 versus US-Lantus? ..... 15**

**2.2.4 How are the results of PKPD studies of LY2963016 related to the efficacy comparison of LY2963016 versus US-Lantus or EU-sourced Insulin Glargine? ..... 18**

2.3	ANALYTICAL	22
2.3.1	Are the analytical methods appropriately validated?	22
3	PRELIMINARY LABELING COMMENTS	26
4	APPENDIX	29
4.1	INDIVIDUAL STUDY SYNOPSES AS REPORTED	29
4.1.1	PKPD Study ABEO (LY2963016 versus US-Lantus)	29
4.1.2	PKPD Study ABEA (LY2963016 versus EU-Glargine)	36
4.1.3	PKPD Study ABEN (EU-Glargine versus US-Lantus)	41
4.1.4	PKPD Study ABEM (Dose-response of LY2963016 versus EU-Glargine)	46
4.1.5	PKPD Study ABEE (Duration of action: US-Lantus versus EU-Glargine)	52
4.2	OCP FILING MEMO	56

## List of Figures

---

Figure 1	Mean baseline-adjusted serum insulin glargine, glucose infusion rate (GIR) and plasma glucose-time profiles from single SC dose of LY2963016 or US-Lantus formulations (ABEO)	4
Figure 2	Differences in insulin time-action profile (partial GIRAUC) translate in to the clinical use in relation to the meal-time (Based on data from NDA 21-629 Clinical Pharmacology Review)	7
Figure 2	Schematic of PK and PD comparisons in healthy subjects (Study ABEO, ABEN, and ABEA)	8
Figure 4	Schematic of euglycemic clamp study for PK and PD evaluation to characterize insulin time-action profile in healthy subjects (Study ABEO, ABEN, and ABEA)	10
Figure 5	Summary of statistical analysis of PK and PD parameters from supportive studies (ABEA, ABEN, and ABEM)	14
Figure 6	Mean PD response ( $GIR_{max}$ and $AUC_{GIR0-24h}$ ) versus insulin SC dose for LY2963016 or EU sourced Insulin Glargine	15
Figure 7	Mean (90% confidence interval) glucose infusion rate versus time profiles (upper), the corresponding Super GL glucose levels (lower) following a single subcutaneous administration of LY2963016 (0.3 U/kg) or Lantus® (0.3 U/kg)	16
Figure 8	Time-to-event (survival) plot of duration of action (hours), all subjects	17
Figure 9	Overall mean (95% CI) basal (left panel) and prandial (right panel) insulin dose (U/kg) versus time profile by treatment in Type 1 Diabetes Population (ABEB)	19
Figure 10	Mean (95% CI; shown as bands) insulin dose (U/kg) over time profile by region (EU and US) treatment in Type 1 Diabetes Population (ABEB)	20
Figure 11	Mean (95% CI; shown as bands) insulin dose (U/kg) over time profile by region (EU and US) treatment in Type 2 Diabetes Population (ABEC)	21

## List of Tables

---

Table 1	Overview of clinical studies	9
Table 2	Quantitative Composition of LY2963016	12
Table 3	Summary statistics for primary PK and PD parameters	12
Table 4	Statistical analysis results for primary PK and PD parameters	13
Table 5	Statistical analysis of duration of action, proportional hazard estimates	17
Table 6	Summary of Treatments Administered	18
Table 7	Summary of the Performance Characteristics of Insulin Glargine Assay	23

## **1 Executive Summary**

Eli Lilly and Co. (the sponsor) is seeking approval of Basaglar™ (LY2963016) under the provisions of Section 505(b)(2) for the following proposed indication:

*“Long-acting human insulin analog indicated to improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.”*

The sponsor is relying upon the Agency’s previous findings of safety and effectiveness for the reference listed drug (RLD), US-Lantus® (Insulin Glargine Recombinant; NDA 21-081, Sanofi Aventis US). Basaglar™ is proposed as a 100 units/mL (U-100) solution of LY2963016 for SC injection, and will be made available in a 3 mL cartridge sealed in a prefilled pen injector (KwikPen™).

Clinical pharmacology of LY2963016 under this 505(b)(2) submission was supported by 3 clinical studies including two definitive PKPD similarity studies (ABEO and ABEN). In addition, the sponsor conducted two randomized, double-blind, placebo-controlled, parallel-group, non-inferiority phase 3 trials in patients with type 1 diabetes (T1DM; ABEC) and type 2 diabetes (T2DM; ABEB) to assess the relative safety and efficacy of LY2963016 compared to US-Lantus. Two PKPD similarity studies (ABEO and ABEN) were deemed pivotal for approval.

### **1.1 Recommendation**

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the clinical pharmacology data submitted under NDA 205692 and recommends approval for Basaglar™ (Insulin Glargine; LY2963016).

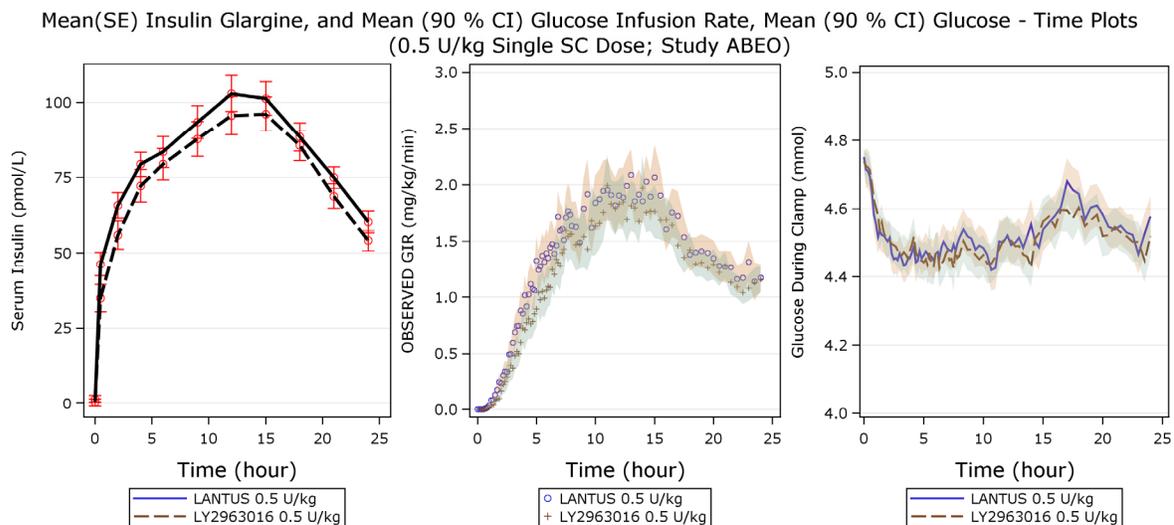
### **1.2 Phase IV Commitments**

None

### **1.3 Summary of Important Clinical Pharmacology Findings**

The PK and PD similarity was adequately demonstrated. The evidence presented by the PKPD study ABEO supports that PK and PD (time-action) profile of LY2963016 is similar to US-Lantus®.

Mean PK and PD profile by treatment is presented in Figure 1 below.



**Figure 1 Mean baseline-adjusted serum insulin glargine, glucose infusion rate (GIR) and plasma glucose-time profiles from single SC dose of LY2963016 or US-Lantus formulations (ABEO)**

The results show that geometric mean ratios and confidence intervals for both PK and PD parameters were within the pre-specified limits of 0.80 – 1.25. In addition, median difference in time to peak plasma insulin concentration ( $T_{max}$ ) was 0.50 hours (95% CI: -0.76, 1.25) [p-value=0.48] using Hodges-Lehmann method. No statistically significant difference was noted in the time to peak glucose lowering effect ( $T_{GIR,max}$ ) when compared using the ANOVA on rank sum test (Mann-Whitney). Estimated median (25<sup>th</sup> – 75<sup>th</sup> %ile)  $T_{GIR,max}$  was 11.1 (7.9 – 14.1) hours for LY29630163 and 11.9 (8.0 – 15.0) hours for US-Lantus, respectively.

The results from PK and PD studies ABEA and ABEN in healthy subjects showed that insulin PK and PD profile did not differ significantly between LY2963016 and EU-Glargine, and between EU-Glargine and US-Lantus, respectively. Collectively, data from ABEA and ABEN provides a scientific bridge between LY2963016 and EU-Glargine, or between US-Lantus and EU-Glargine, justifying the appropriateness of using the data generated for EU-Glargine in Phase 3 trials to support the US marketing approval of LY2963016. The bridging also supports the reliance on dose-response and duration of action comparison in clinical pharmacology studies ABEM and ABEE, respectively, conducted with EU-Glargine. However, this scientific bridging must not be interpreted as Agency’s conclusion of the “similarity” between US-Lantus and EU-Glargine with respect to PK and PD parameters.

The duration of action did not significantly differ between LY2963016 and EU-Glargine.

While the non-inferiority claim for LY29630163 was confirmed in the statistical review<sup>1</sup>, there were regional (US versus non-US) differences in the dose utilization as well as HbA1c response. However, based on total data (i.e., not sub-grouped based on regions), the dose utilization for basal insulin component was similar between LY2963016 and reference insulin glargine, which was in agreement with the observed similarity in the PD response ( $GIR_{max}$  and  $AUC_{GIR0-24h}$ ) from PKPD studies. In other words, the assumption that LY2963016 has same unit dose definition as US-Lantus and therefore formulated in the same strength as US-Lantus (i.e., as 100 IU/mL) was substantiated by the similar PD response for the same unit dose (0.5 U/kg) of LY2963016 and US-Lantus in the PK/PD study. The assumption of same unit dose definition for LY2963016 and reference insulin glargine was further confirmed by similar dose utilization for test and reference in Phase 3 trials showing non-inferior HbA1c response. Therefore, PKPD results corroborated the Phase 3 efficacy results with regards to the unit dose definition.

## 2 Question-Based Review (QBR)

### 2.1 General Attributes

#### 2.1.1 What is the relevance and importance of the clinical pharmacology data in establishing similarity of a proposed insulin product to a reference product in the context of current 505(b)(2) submission?

The clinical pharmacology data on comparative PK and PD profile is the fundamental basis of assessing similarity between insulin products with respect to efficacy. The importance of information generated in the PK and PD experiments in the context of a 505(b)(2) proposal rests on two pivotal concepts:

1. *The molar dose ratio for insulin products is determined based on PK/PD studies:* As per WHO and the American Diabetes Association (ADA) standards, 1 unit (U) of regular human insulin (formulated as 100 U/mL) equals 6 nmol<sup>2</sup> of human insulin. To claim that a test insulin has similar unit dose (equipotent) to a reference insulin (e.g. regular human insulin (RHI)) on a molar basis, the new insulin drug product, when formulated as 100 U/mL or 600 nmol/mL and given as the same U/kg SC dose (same injection volume), must demonstrate a similar glucose lowering effect. Similarity of glucose lowering effect is evaluated based on the comparison of PD profiles (i.e., glucose infusion rate) from euglycemic clamp studies. In the clamp studies, glucose lowering effect is typically measured as the glucose utilization per unit insulin dose and presented as AUCGIR.
2. *Time-action profile drives method of clinical use for insulin products:* The PK and PD profiles (time to onset, peak action, and duration of action – collectively regarded as *time-action profile*) forms the fundamental principal in defining the

<sup>1</sup> Statistical Review by Dr. Lee Ping Pian dated 05/29/2014.

<sup>2</sup> Table 1—Système International (SI) units for plasma, serum, or blood concentrations, Diabetes Care December 1997 20:1931.

safe and effective use of an insulin product. For instance, RHI is clinically safe and effective when administered 30 minutes prior to meal<sup>3</sup>, and insulin lispro (Humalog®) is clinically safe and effective when administered 15 minutes prior to or immediately after consuming a meal<sup>4</sup>. For each insulin product, this recommendation is informed by the respective time-action profile. The time of administration with respect to meal is determined such that the time to peak insulin action approximately matches with the time of post-prandial glucose excursion.

Therefore, demonstration of similarity of PK and PD profiles between test and reference insulin ensures that test insulin has same unit dose definition and clinical use profile.

Among the rapid-acting insulin products, insulin lispro, insulin aspart (data not shown here), and insulin glulisine have comparable overall PD response ( $AUC_{0-clamp\_end}$  for glucose infusion rate over time profile in Figure 2); therefore, they have same unit dose definition (i.e., all are formulated as 100 U/mL or 600 nmol/mL). However, PD effect observed during the initial 1 to 2 hours post-dose varies among these products, which supported a unique time of administration (with respect to meal) for these products (See Figure 2) that was different from RHI.

Among the basal insulin products, both Neutral Protamine Hagedorn (or NPH) insulin and Insulin Glargine are formulated as 600 nmol/mL (100 U/mL), which is supported by comparable PD effect to RHI and NPH, respectively for a given unit dose. However, what differed between NPH and RHI or NPH and Insulin Glargine was the magnitude of peak effect (typically measured as  $GIR_{max}$  in PKPD study), time to peak action (typically measured as  $T_{GIR,max}$  in PKPD study), and duration of action. These differences supported an alternative clinical use for the same insulin molecule (NPH as basal insulin versus RHI as prandial insulin). Further structural modifications were carried out (Insulin glargine versus NPH) to closely mimic the basal insulin secretion profile.

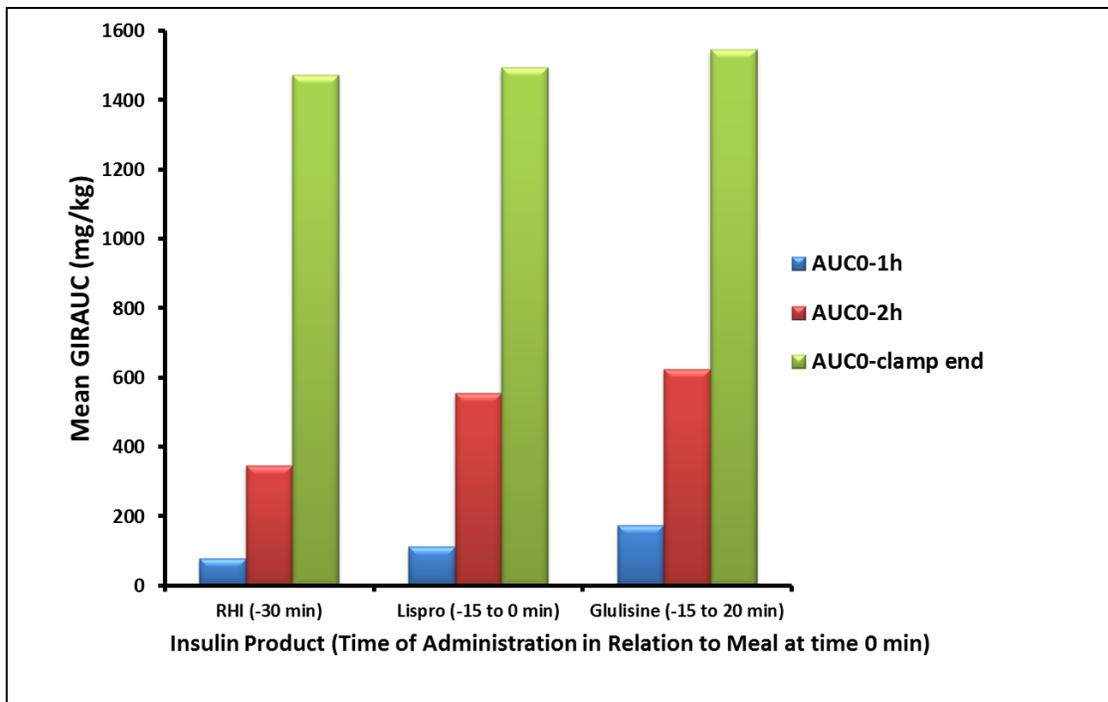
The description above shows that PKPD studies are reliable in establishing the unit dose definition (in vivo potency) for insulin products, and are sensitive in capturing the differences in time-action profile that have led to different methods of clinical use.

Therefore, the demonstration of PK and PD similarity (time – concentration/action profile and net PD effect) between a test and reference insulin product presents the evidence that a test insulin product has the same unit dose, time to onset of action, peak action, and duration of action as the reference, and will be equally effective, if used in a similar manner to the reference insulin product. In other words the method of clinical use for test insulin will not differ from the reference insulin product.

---

<sup>3</sup> Humulin R U-100 (NDA 018780) Label available at:  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/018780s132lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/018780s132lbl.pdf)

<sup>4</sup> Humalog (NDA 020563) Label available at:  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/020563s115lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020563s115lbl.pdf)



**Figure 2 Differences in insulin time-action profile (partial GIRAUC) translate in to the clinical use in relation to the meal-time (Based on data from NDA 21-629 Clinical Pharmacology Review<sup>5</sup>)**

The concept of utilizing PK and PD similarity in its entirety is not new considering that PKPD evaluations, along with the efficacy and safety evaluation, were relied upon during the transition from porcine insulin to semisynthetic insulin, and then to recombinant human insulin. It is worth noting that the current clinical pharmacology evaluations for insulin PKPD as well as efficacy/safety evaluations have become far more rigorous over time. This has happened due to advancements in experimental technology and scientific understanding of challenges in therapeutic management of Type 1 and Type 2 diabetes.

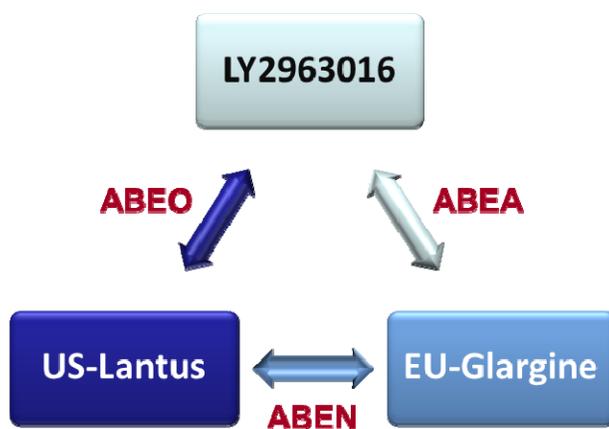
**2.1.2 What are the important design features of the clinical pharmacology studies and the analyses used to support the current application?**

The sponsor has claimed that the data and results from the LY2963016 development program demonstrate the similarity of LY2963016 to US-Lantus® with respect to structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and Phase 3 clinical safety and effectiveness. Further, these data demonstrate that there are no meaningful differences in the safety and efficacy of LY2963016 as compared to US-Lantus®.

<sup>5</sup> NDA 21-629 Clinical Pharmacology Review available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2004/21-629\\_Apidra\\_BioPharmr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-629_Apidra_BioPharmr.pdf)

Clinical pharmacology of LY2963016 under this 505(b)(2) submission was supported by 5 PKPD studies including three PK and PD similarity studies (ABEO, ABEA, and ABEN), out of which two were deemed pivotal for this application (see Table 1).

These three studies including the pivotal PKPD studies namely, ABEO (PK and PD similarity of LY2963016 versus US-Lantus) and ABEN (bridging PK and PD of Phase 3 study reference treatments: US-Lantus versus EU-Glargine) were euglycemic clamp studies conducted in healthy subjects using a replicate cross-over design. Concentrations of insulin glargine (PK), C-peptide (baseline correction for PK), glucose infusion rate (GIR; Primary PD), and plasma glucose (clamp integrity; supportive PD) were measured at baseline and over the 24 hour clamp duration.



**Figure 3 Schematic of PK and PD comparisons in healthy subjects (Study ABEO, ABEN, and ABEA)**

These three studies were homogenous with respect to the basic design factors.

- All of them were conducted in a replicate cross-over fashion in healthy subjects at 0.5 U/kg doses of test and reference treatments.
- The clamp duration was 24 hours.
- While PK sampling was discrete with samples at 30 min, 0 min (pre-dose), 0.5, 2, 4, 6, 9, 12, 15, 18, 21, and 24 h post-dose, the PD measurements (GIR) were performed every minute. Plasma glucose was assessed at -30, -20, -10, 0 min; followed by every 10 min to 480 min; then every 20 min to 900 min; then every 30 min to the end of clamp.
- When applicable, the baseline correction for plasma insulin concentrations was performed as:  
$$[\text{Exogenous Insulin}] = [\text{Total Insulin}] - F \times [\text{C\_peptide}]$$

Where, F is the average of the ratios of (immunoreactive LY2963016 or immunoreactive US-Lantus®) concentrations to C-peptide concentration at baselines (-30 and 0 minutes).

- A locally weighted scatterplot smoothing (LOESS) function was applied to all individual GIR versus time profiles in each treatment group. The fitted data for each subject were used to calculate the primary PD parameters, peak GIR effect ( $R_{max}$  or  $GIR_{max}$ ) and total GIR effect ( $G_{tot}$  or  $AUC_{GIR0-t}$ ,  $t=24$  h or 42 h depending upon study).
- Pre-defined criteria to conclude PK and PD similarity was less than  $\pm 20\%$  difference is PK and PD parameters between test and reference products, which was to be concluded if the least-square (LS) geometric mean ratios and 90% confidence intervals (CI) for comparison of test and reference parameters fall within the pre-specified range of 0.80 to 1.25, inclusive. These ratios were evaluated for PK parameters (peak plasma concentration ( $C_{max}$ ), area under the curve ( $AUC_{0-24h}$  for baseline adjusted insulin concentrations) and PD parameters [ $GIR_{max}$  (or  $R_{max}$ ),  $AUC_{GIR,0-24h}$  (or  $G_{tot}$ )].

The Table 1 below presents the overview of clinical development plan for LY2963016.

**Table 1 Overview of clinical studies**

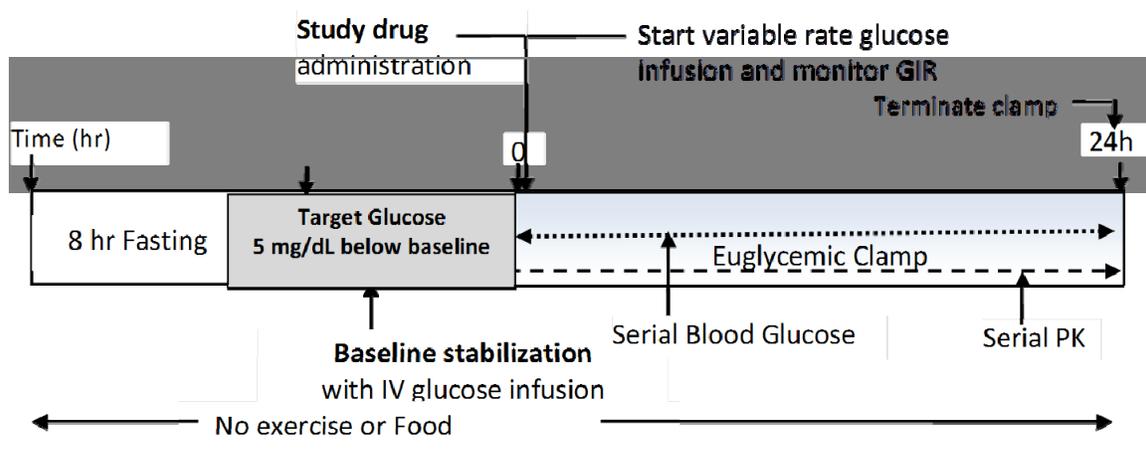
Study	Objective	Study Population	Number of Subjects Randomized
<b>Phase 1 Studies</b>			
ABEO	Comparison of the PK and PD of LY2963016 and US-approved LANTUS	Healthy subjects	91
ABEA	Comparison of the PK and PD of LY2963016 and EU-sourced insulin glargine	Healthy subjects	80
ABEN	Comparison of the PK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

Abbreviations: EU = European Union; HbA1c = hemoglobin A1c; OAM = oral antihyperglycemic medication; PD= pharmacodynamics; PK = pharmacokinetic; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; US = United States.

### Overview of the euglycemic clamp method used for PK/PD assessment of LY2963016

Insulin PKPD studies are commonly conducted using the euglycemic (*means “same glucose”*) clamp technique where, insulin is injected into subjects and glucose is infused to prevent the expected decrease in blood glucose concentration, thus “clamping” blood glucose to a predetermined basal level. The rate of glucose infusion and total amount of glucose infused approximates the rate of glucose disappearance and net PD effect (i.e., glucose-lowering effect) of the tested insulin (typically the resulting sum of the suppression of hepatic glucose production and the stimulation in glucose utilization)<sup>6</sup>.

The study schematic including the euglycemic clamp procedure used by the sponsor for evaluating PK and PD of LY2963016 in healthy subjects is shown in Figure 4 below:



**Figure 4 Schematic of euglycemic clamp study for PK and PD evaluation to characterize insulin time-action profile in healthy subjects (Study ABEO, ABEN, and ABEA)**

In all PKPD studies conducted in healthy subjects, the clamp procedures were performed using a manual technique, wherein, the GIR was manually adjusted based upon blood glucose measurements taken at regular intervals. The clamp procedure was performed the morning after an overnight fast of approximately 8 hours. The time of insulin dosing was defined as time zero, and the study insulin was administered by SC injection into the abdominal wall by trained site personnel at approximately the same time of day in each treatment period. Following dosing, glucose was infused intravenously at a variable rate to maintain or ‘clamp’ blood glucose concentrations within approximately  $\pm 5\%$  to  $10\%$  of the subjects’ glucose target. For individual subjects, a mean pre-dose blood glucose value was calculated from up to 4 pre-dose blood glucose measurements, and the subject’s blood glucose target was defined as 5 mg/dL (0.3 mmol/L) below this mean pre-dose value. Throughout the 24-hour clamp procedure, the GIR required to maintain

<sup>6</sup> Pharmacokinetics and Pharmacodynamics of Basal Insulins. Francesca Porcellati, M.D., Ph.D., Geremia B. Bolli, M.D., and Carmine G. Fanelli., *Diabetes Technology & Therapeutics* Volume 13, Supplement 1, 2011.

euglycemia and blood glucose concentrations were documented, and samples were collected simultaneously for pharmacokinetic (PK) and C-peptide analyses. The clamp was discontinued if the GIR fell to zero for at least 30 to 60 minutes after the clamp had been underway for at least 4 to 8 hours. Unless the investigator judged a meal necessary for safety reasons, subjects did not receive meals until the last PK sample had been collected at the end of the 24-hour period.

In the duration of action Study ABEE conducted in subjects with type 1 diabetes mellitus (T1DM), euglycemic clamp procedures were performed using an automated procedure, wherein, blood glucose was measured continuously, and the GIR was adjusted using a computerized feedback algorithm (Biostator). The clamp procedure was performed the morning after an overnight fast of approximately 8 hours. Subjects were connected to a Biostator and began the clamp run-in period. A variable intravenous infusion of insulin lispro and/or glucose was initiated to obtain and maintain a target blood glucose level of 100 mg/dL (5.5 mmol/L) ( $\pm$  20%) continuously for at least 1 hour before dosing. The time of insulin dosing was defined as time zero, and the study insulin was administered in the abdominal wall by trained site personnel at approximately the same time of day in each treatment period. Once an effect of the study insulin was observed, indicated by a decrease in blood glucose of approximately 5 mg/dL (0.3 mmol/L), the insulin lispro infusion (if any) was terminated. Thereafter, the Biostator was programmed to maintain blood glucose concentration at approximately 100 mg/dL (5.5 mmol/L). The Biostator were recalibrated at regular intervals (at least every 30 minutes) by external blood glucose measurements performed with a laboratory method (Super GL Glucose Analyzer). The clamp continued for 42 hours after dosing, unless the blood glucose level reached 250 mg/dL (13.8 mmol/L) before this time. Throughout the 42-hour clamp procedure, the GIR required to maintain euglycemia and blood glucose concentrations were documented, and samples for PK analyses were collected. Even if the clamp was discontinued before 42 hours, patients did not receive meals until the last PK sample had been collected at the end of the 42-hour period unless the investigator judged a meal necessary for safety reasons.

### **2.1.3 What is the composition of to be marketed formulation of LY2963016?**

Same LY2963016 formulation was for all clinical studies, which is same as the to-be-marketed formulation. All drug substance lots were manufactured in Lilly Indianapolis. The drug product cartridge presentation was manufactured in Lilly France; the drug product vial presentation was manufactured in Lilly Indianapolis. Both drug product presentations used the commercial formulation, which was filled into 3 mL glass cartridges ((b) (4) batch size), (b) (4). Readers should refer to the review by the ONDQA/CMC reviewer for further details on acceptability of the drug product in this regard.

The quantitative composition of the to-be-marketed LY2963016 formulations is presented in Table 2 below.

**Table 2 Quantitative Composition of LY2963016**

Ingredient	Quantity/mL
LY2963016	100 Units (3.6378 mg)
Glycerin	17 mg
Metacresol	2.7 mg
Zinc Oxide	(b) (4)
Water for Injection	q.s. to 1 mL

Abbreviations: q.s. = quantity sufficient

## 2.2 Key Clinical Pharmacology Issues

### 2.2.1 Does the PK and PD data from the clinical pharmacology studies support the similarity claim for the to-be-marketed formulation of LY2963016 in reference to US-Lantus®?

Yes, the evidence presented by the PKPD study ABEO supports that PK and PD profile of LY2963016 is similar to US-Lantus®.

Summary statistics of insulin PK (based baseline adjusted data) and PD parameters is presented in Table 3 below.

**Table 3 Summary statistics for primary PK and PD parameters**

Type	Parameter	0.5 U/kg LY2963016 Mean (%CV)	0.5 U/kg US-Lantus® Mean (%CV)
PK	C <sub>max</sub> (pmol/L)	110.5 (37)	116.7 (37)
	AUC <sub>0-24h</sub> (pmol*h/L)	1850 (36)	1989 (31)
	T <sub>max</sub> (h)*	12.0 (2.0 – 21.0)	12.0 (2.0 – 24.0)
PD	GIR <sub>max</sub> (mg/kg/min) <sup>#</sup>	3.18 (53)	3.44 (49)
	GIR AUC <sub>0-24h</sub> (mg/kg) <sup>#</sup>	1935.94 (58)	2155.64 (57)
	T <sub>GIR,max</sub> (h)*	11.1 (1.9 – 23.5)	11.9 (2.2 – 23.9)

\*Median (Range); <sup>#</sup>Reported as R<sub>max</sub> and G<sub>tot</sub>, respectively in the sponsor's reports

The results of the statistical analysis for the pre-specified PK and PD metrics are presented in Table 4 below.

**Table 4 Statistical analysis results for primary PK and PD parameters**

Type	Parameter	GMR (90%CI)*
PK	C <sub>max</sub> (pmol/L)	0.92 (0.87 – 0.97)
	AUC <sub>0-24h</sub> (pmol*h/L)	0.90 (0.85 – 0.96)
PD	GIR <sub>max</sub> (mg/kg/min)	0.92 (0.87 – 0.98)
	GIRAU <sub>C</sub> <sub>0-24h</sub> (mg/kg)	0.91 (0.84 – 0.97)

**\*Based on post-hoc analysis by FDA after excluding confounded data**

The results show that geometric mean ratios and confidence intervals for both PK and PD parameters were within the pre-specified limits of 0.80 – 1.25. In addition, median difference (95% CI) [p-value] in T<sub>max</sub> was 0.50 (-0.76, 1.25) [0.48] using Hodges-Lehmann method. The T<sub>GIR,max</sub> when compared using the ANOVA on rank sum test (Mann-Whitney in SigmaPlot® platform) revealed no statistically significant differences. Estimated median (25<sup>th</sup> – 75<sup>th</sup> %ile) T<sub>GIR,max</sub> was 11.1 (7.9 – 14.1) hours for LY2963016 and 11.9 (8.0 – 15.0) hours for US-Lantus, respectively. Note that since GIR was continuously assessed (every minute), T<sub>GIR,max</sub> assessment is not prone to the ascertainment bias introduced by the usual method of discrete sampling times.

Therefore, based on the statistical analysis results:

- The PK profile of LY2963016 is similar to US-Lantus® with regards to baseline adjusted exogenous insulin C<sub>max</sub> and AUC<sub>0-24h</sub>. The pre-defined criteria of geometric mean ratios and 90% CI to fall within 0.8 to 1.25 were met for both PK parameters. In addition, time of peak insulin concentration (T<sub>max</sub>) was also similar between LY2963016 and US-Lantus®.
- The PD profile of LY2963016 is similar to US-Lantus® with regards to GIR<sub>max</sub> and GIRAUC<sub>0-24h</sub> (computed from loess smoothed data). The pre-defined criteria of geometric mean ratios and 90% CI to fall within 0.8 to 1.25 were met for both PD parameters. In addition, time of peak insulin action T<sub>GIR,max</sub> was also similar between LY2963016 and US-Lantus®.

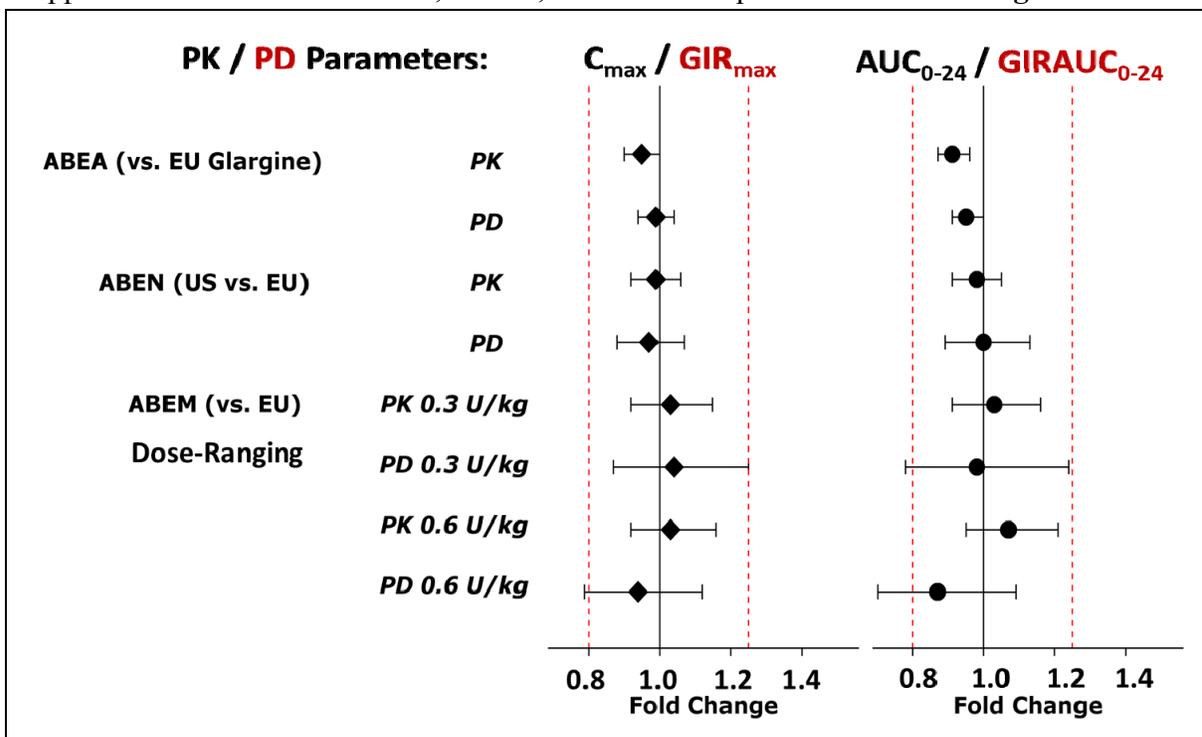
### **2.2.2 How do the PK and PD profiles compare between LY2963016 and EU sourced Insulin Glargine or between US-Lantus and EU-Glargine, and how does this information support the PK and PD similarity assessment for LY2963016 versus US-Lantus?**

The results from PK and PD studies ABEA and ABEN in healthy subjects showed that insulin PK and PD profile did not differ significantly between LY2963016 and EU-Glargine, and between EU-Glargine and US-Lantus, respectively. Collectively, data from

ABEA and ABEN also provides a scientific bridge between LY2963016 and EU-Glargine, or between US-Lantus and EU-Glargine LY2963016 and EU-Glargine, and between US-Lantus and EU-Glargine.

The scientific bridge between US-Lantus and EU-Glargine justifies the appropriateness of using the data generated for EU-Glargine in Phase 3 trials to support the marketing approval of LY2963016 in the USA. The bridging also supports the reliance on dose-response and duration of action comparison in clinical pharmacology studies ABEM and ABEE, respectively, conducted with EU-Glargine. However, this must not be interpreted as Agency’s conclusion of the “similarity” between US-Lantus and EU-Glargine with respect to PK and PD parameters.

The summary of the statistical analysis for primary PK and PD parameters from the supportive PKPD studies ABEA, ABEN, and ABEM is presented below in **Figure 5**.

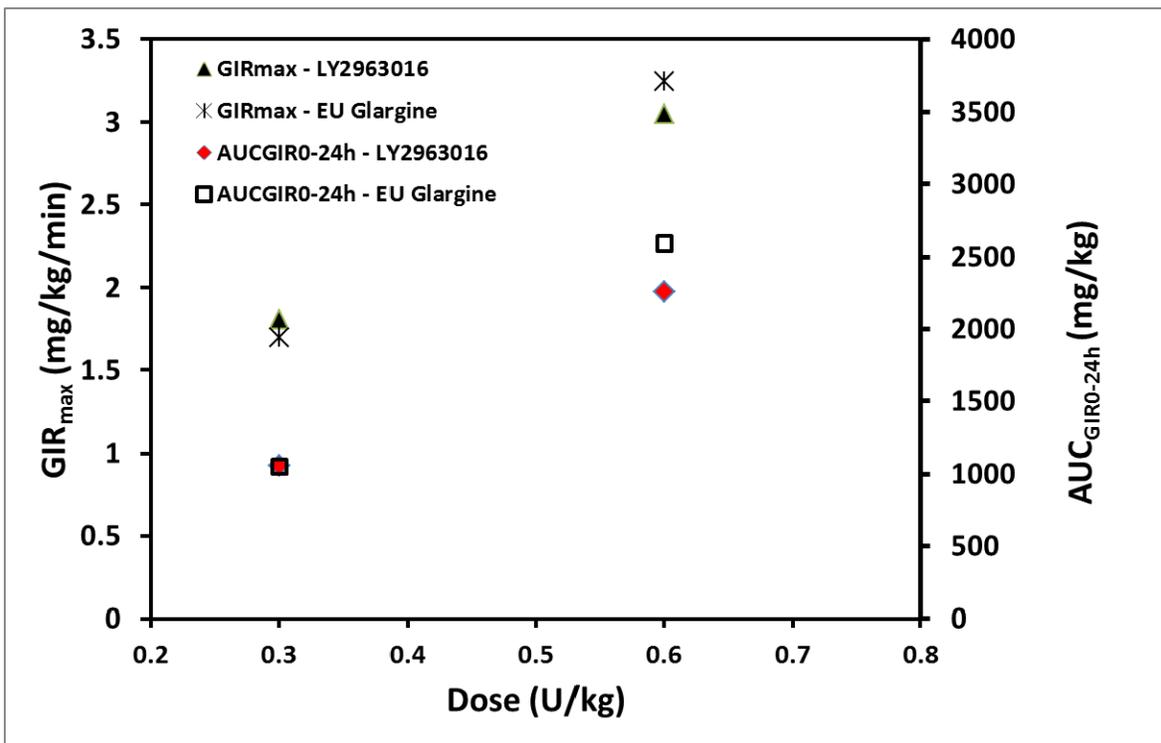


**Figure 5 Summary of statistical analysis of PK and PD parameters from supportive studies (ABEA, ABEN, and ABEM)**

Based on statistical analysis of PK and PD parameters from studies ABEA and ABEN, geometric mean ratios and 90% CIs for PK ( $C_{max}$  and  $AUC_{0-24h}$ ) and PD parameters ( $GIR_{max}$  and  $AUC_{GIR,0-24h}$ ) were contained within the pre-specified bounds of 0.80 – 1.25.

Further, the comparison of PK and PD data between LY2963016 and EU-Glargine treatments at two dose levels (0.3 U/kg and 0.6 U/kg) showed that PD response increased in a dose-dependent manner and the response was overlapping between the two

treatments. Although, in comparison to the EU sourced Insulin Glargine, on average, the response was 13% lower for LY2963016 at 0.6 U/kg dose (Figure 6).



**Figure 6 Mean PD response ( $GIR_{max}$  and  $AUC_{GIR0-24h}$ ) versus insulin SC dose for LY2963016 or EU sourced Insulin Glargine**

The overall conclusions are as follows:

- PK and PD profile did not differ significantly between LY2963016 and EU-Glargine, and between EU-Glargine and US-Lantus.
- LY2963016 and EU-Glargine did not differ with regards to dose response at 0.3 and 0.6 U/kg dose levels (covers the range of doses utilized in Phase 3 trials).

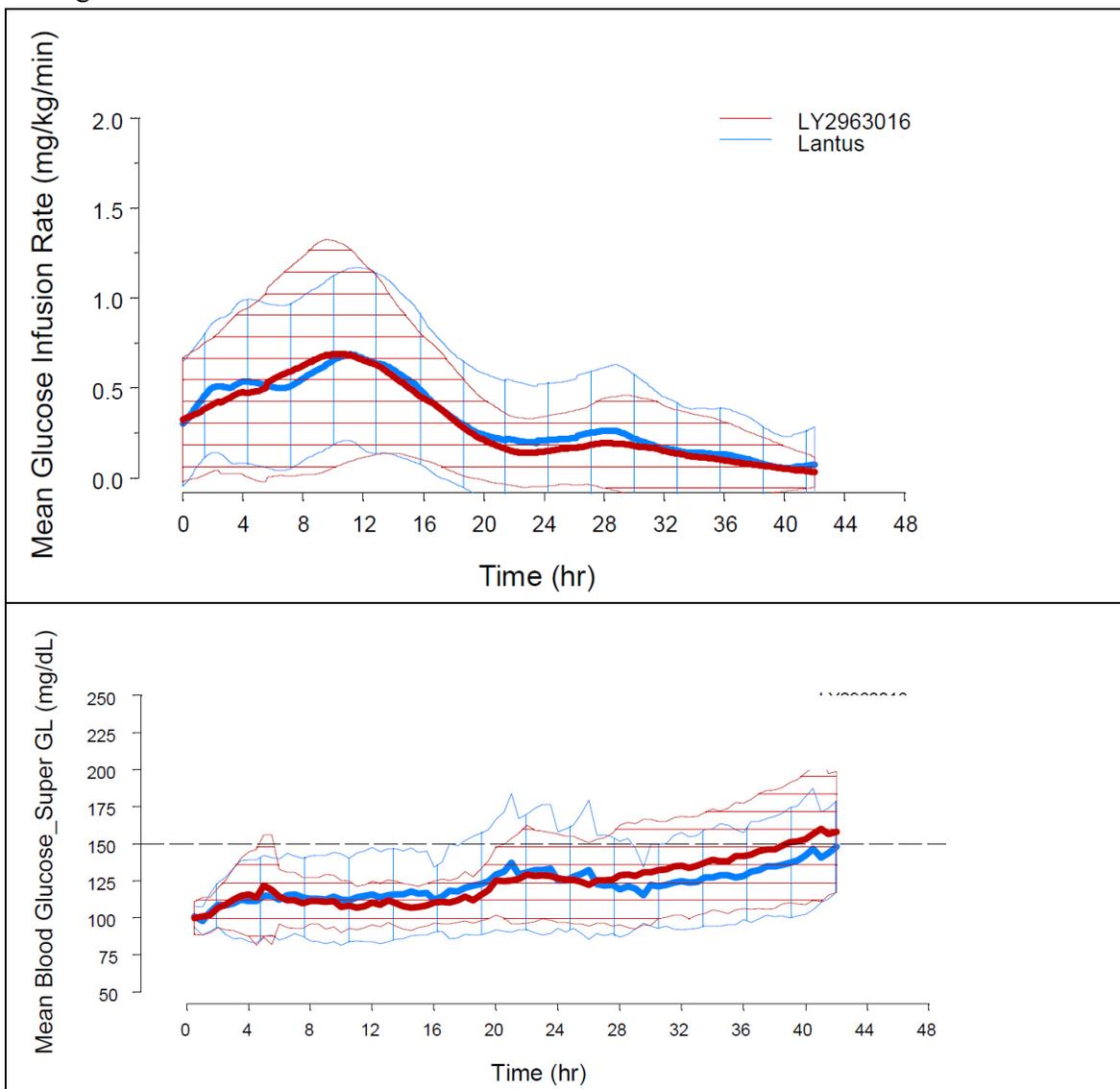
### 2.2.3 How do the PK and PD profiles (duration of action) compare between LY2963016 and EU sourced Insulin Glargine in Type 1 diabetes patients, and how does this information support the PK and PD similarity assessment for LY2963016 versus US-Lantus?

Duration of action of LY2963016 was compared to EU-Glargine in study ABEE at 0.3 U/kg doses, which was a 42 hour euglycemic clamp study.

The PK data was only collected till 24 hour in this trial, limiting the utility in assessing the relationship with 42 hour PD response. Although, since this study was conducted in T1DM patients, there are no reasons to doubt the PD profile beyond 24 hours due to absence of endogenous insulin. This is also substantiated by the glucose values monitored

during the clamp, which are highly sensitive to changes due to GIR, when the exogenous insulin is nearing the baseline (glucose will escape the clamp target quickly).

Mean (90% confidence interval) glucose infusion rate versus time profiles (upper panel) and the corresponding glucose levels (lower panel) following a single subcutaneous administration of LY2963016 (0.3 U/kg) or EU-Glargine (0.3 U/kg) are presented below in Figure 7.

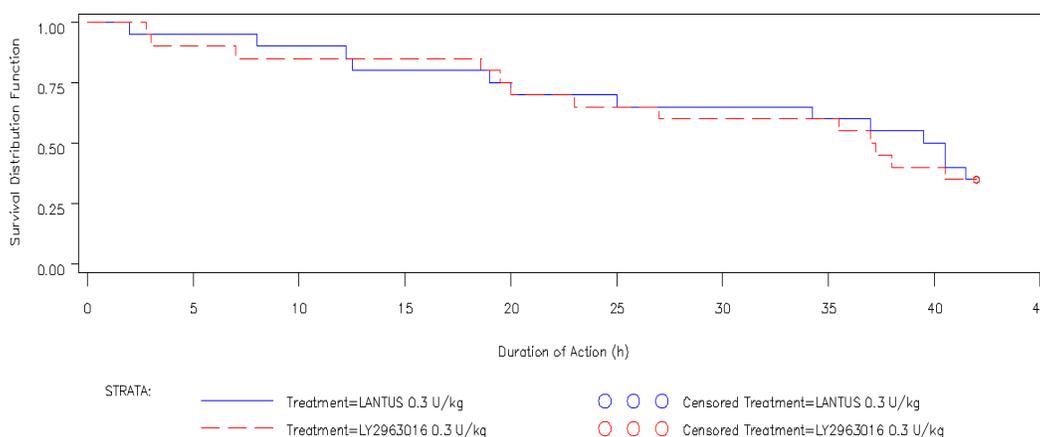


**Figure 7 Mean (90% confidence interval) glucose infusion rate versus time profiles (upper), the corresponding Super GL glucose levels (lower) following a single subcutaneous administration of LY2963016 (0.3 U/kg) or Lantus® (0.3 U/kg)**

Sponsor used the survival analysis to assess the duration of action. Survival is defined as failure of subject's blood glucose to rise to certain pre-specified target during clamp. The use of survival analysis method for assessment of duration of action, defined as the time

period between the dose and the end of action is unique but not new to the Agency as it has been utilized by other sponsors of Insulin applications. Regardless, it is important to mention that glucose during clamp duration as a metric is physiologically relevant and highly sensitive. Blood/plasma glucose during clamp is the net effect of insulin response and counterbalancing effect of GIR, and thus provides the information clamp integrity (over or under infusion of glucose) and end of action (time when glucose escapes a pre-specified set point (typically the clamp target glucose + 5%). End of action was pre-specified by the sponsor as the time when the subject’s BG was consistently >150 mg/dL (8.3 mmol/L) without any glucose infusion. Each end of action observation was considered an ‘event’ and if a subject did not achieve end of action within the 42-hour clamp period the clamp was terminated at 42 hours and declared a censored event.

The results of duration of action comparison are presented in Figure 8 and Table 5 below.



**Figure 8 Time-to-event (survival) plot of duration of action (hours), all subjects.**

**Table 5 Statistical analysis of duration of action, proportional hazard estimates**

Treatment (dose) / N=20	Hazard Ratio LY2963016/EU-Glargine (90% CI)	p-value
LY2963016 (0.3 U/kg)	1.063 (0.489, 2.312)	0.877
EU-approved LANTUS® (0.3 U/kg)		

The use of such statistical analysis is not common in the PKPD studies, and therefore, its interpretation is essential. For time based comparisons, the hazard ratio is equivalent to the odds that a subject in the group with the higher hazard reaches the endpoint first<sup>7</sup>. Thus, in PKPD study examining time to end-of-action, the hazard ratio represents the

<sup>7</sup> Hazard Ratio in Clinical Trials. ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2004, 2787–2792.

odds that a treated patient will have end-of-action (glucose escaping 150 mg/dL) before a control patient.

A secondary analysis, the duration of action following the LY2963016 dose was compared with that following EU-Glargine using a linear mixed-effects model. The mean duration for LY2963016 was estimated to be 0.45 hour shorter than for EU-Glargine, with a 95% CI of (-10.45, 9.55).

The overall conclusions are as follows:

- The duration of action did not significantly differ between LY2963016 and EU-Glargine.

#### **2.2.4 How are the results of PKPD studies of LY2963016 related to the efficacy comparison of LY2963016 versus US-Lantus or EU-Glargine?**

The sponsor conducted two randomized, active-control, Phase 3, global clinical studies, intended to support efficacy of LY2963016 compared to Lantus® in patients with T1DM (Study ABEB) and T2DM (Study ABEC). While readers are referred to the Clinical Review by Dr. Lisa Yanoff and Statistical Review by Dr. Lee Ping Pian for detailed assessment of efficacy/safety, some aspects of the results relevant to the clinical pharmacology are described here along with brief descriptions of these studies.

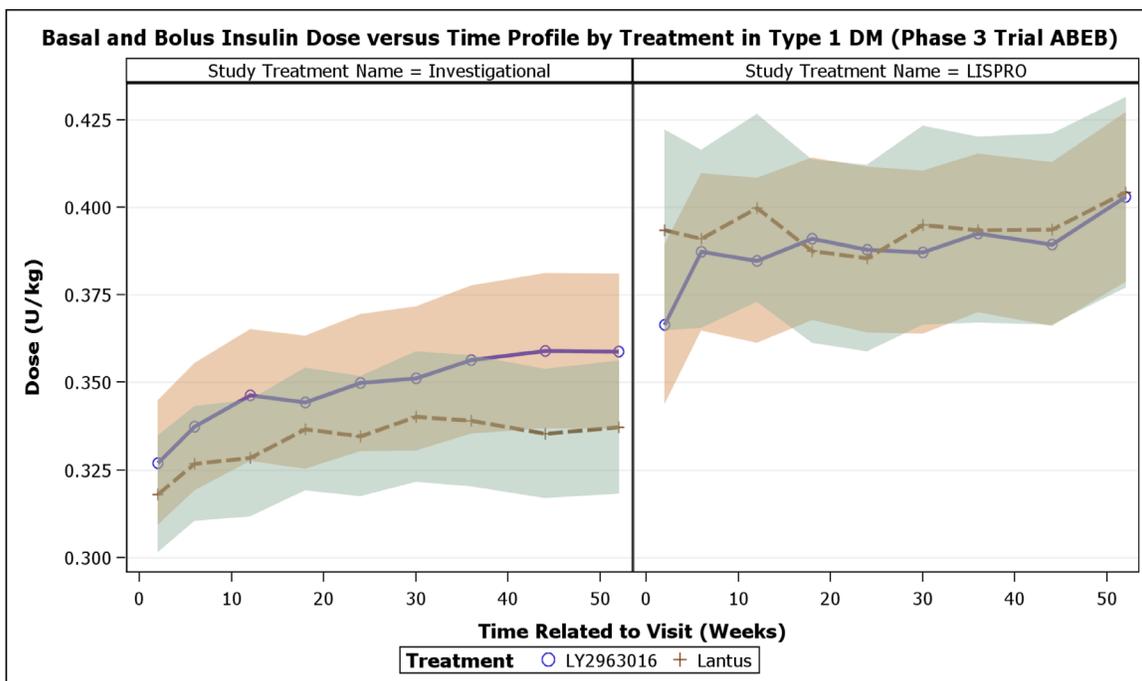
The primary objective of both Phase 3 studies (ABEB and ABEC) was to test the hypothesis that LY2963016 (once daily [QD]) is non-inferior to Lantus® (QD) based on change in HbA1c from baseline to the 24-week endpoint. The summary of study designs is presented below in Table 6.

**Table 6 Summary of Treatments Administered**

<b>Type 1 Diabetes Mellitus (T1DM)</b>	
Study I4L-MC-ABEB (ABEB)	Phase 3, prospective, randomized, multinational, multicenter, 2-arm, active-control, open-label, parallel, 24-week treatment study with an 28-week active-control, open-label extension, and a 4-week posttreatment follow up to compare LY2963016 and LANTUS® when each is used in combination with mealtime insulin lispro in adult patients with T1DM. LY2963016 was initiated at the same dose as the patient's prestudy once-daily basal insulin. Insulin lispro was administered with meals at the same dose as the patient's prestudy mealtime insulin dose while avoiding hypoglycemia. Investigators recommended basal and bolus insulin dose adjustments to achieve glycemic targets.
<b>Type 2 Diabetes Mellitus (T2DM)</b>	
Study I4L-MC-ABEC (ABEC)	Phase 3, prospective, randomized, multinational, multicenter, 2-arm, active-control, double-blind, parallel, 24-week treatment study with a 4-week posttreatment follow-up to compare LY2963016 and LANTUS® when each is used in combination with at least 2 oral antihyperglycemic medications in adult patients with T2DM. Patients were either insulin-naïve or already administering once-daily (QD) LANTUS®. If the patient was insulin-naïve, the starting dose for LY2963016 was 10 units (U) QD. If the patient was already taking LANTUS®, LY2963016 was initiated at the same dose as the patient's prestudy LANTUS® dose. All patients were to then follow a patient-driven dosing algorithm under investigator supervision throughout the study.

In these studies, patients who were in the control arm received either US-Lantus or EU-Glargine (randomly), depending on the location of the study site; patients at sites in the EU, Mexico, Japan, South Korea, and Taiwan received EU-Glargine, and patients at sites in the US and Puerto Rico received US-Lantus®. In Study ABEB, a total of 535 randomized patients received study drug and were included in the full analysis set (FAS) population (LY2963016: 268; Lantus®: 267); 171 patients received EU-Glargine (compared to 96 patients who received US-approved Lantus®). In Study ABEC, a total of 756 randomized patients received study drug and were included in the FAS population (LY2963016: 376, US-Lantus®: 380); 165 patients received EU-Glargine (compared to 215 patients who received US-Lantus®).

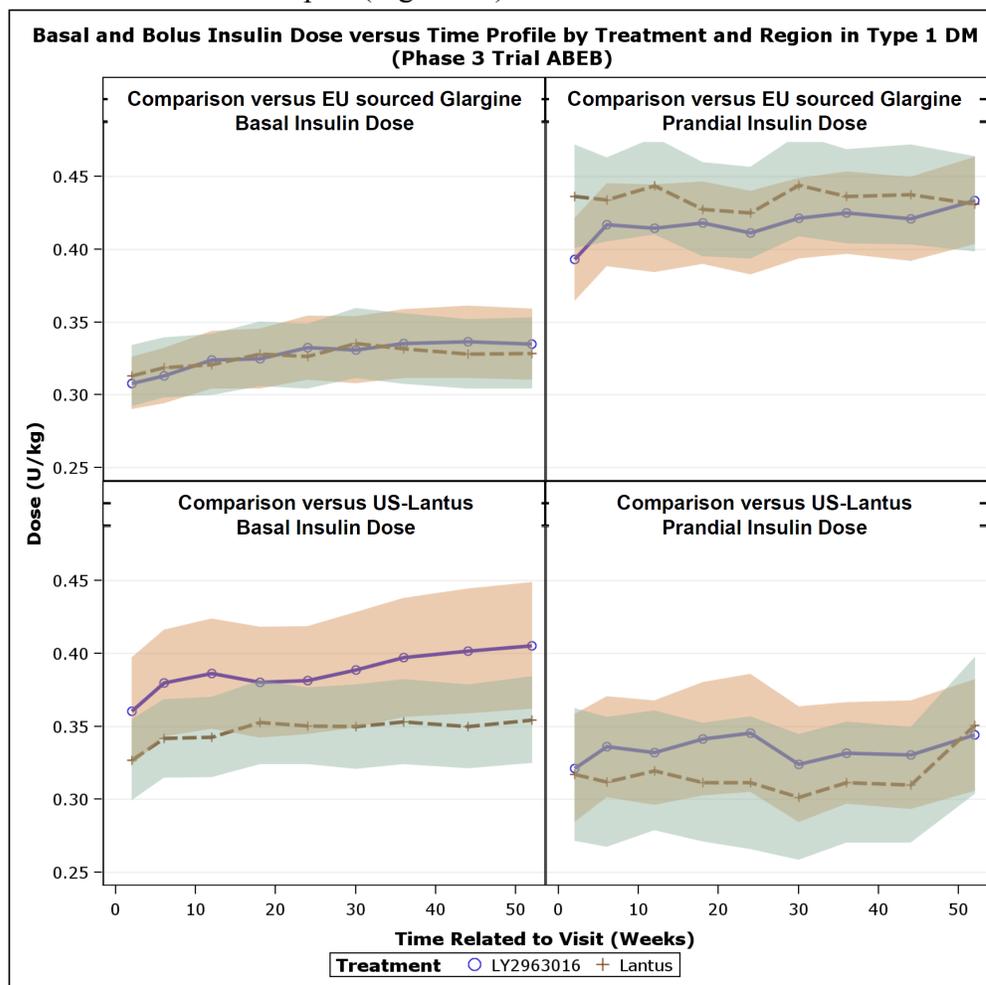
The non-inferiority comparison in the clinical efficacy studies assumes similar unit dose definition for test and reference products, which is determined based on PKPD similarity (specifically the AUCGIR0-24h or Gtotal similarity). However, this assumption is penalized and reveals as either higher or lower insulin dose utilization in the clinical testing, if there are significant differences in the response/unit dose. To evaluate this aspect the unit dose utilization versus time profile were compared between treatments in the two efficacy/safety trials. The overall and by region mean (95% CI) insulin dose (U/kg) over time profile by treatment and insulin type are presented below in Figures 9 and 10, respectively.



**Figure 9 Overall mean (95% CI) basal (left panel) and prandial (right panel) insulin dose (U/kg) versus time profile by treatment in Type 1 Diabetes Population (ABEB).**

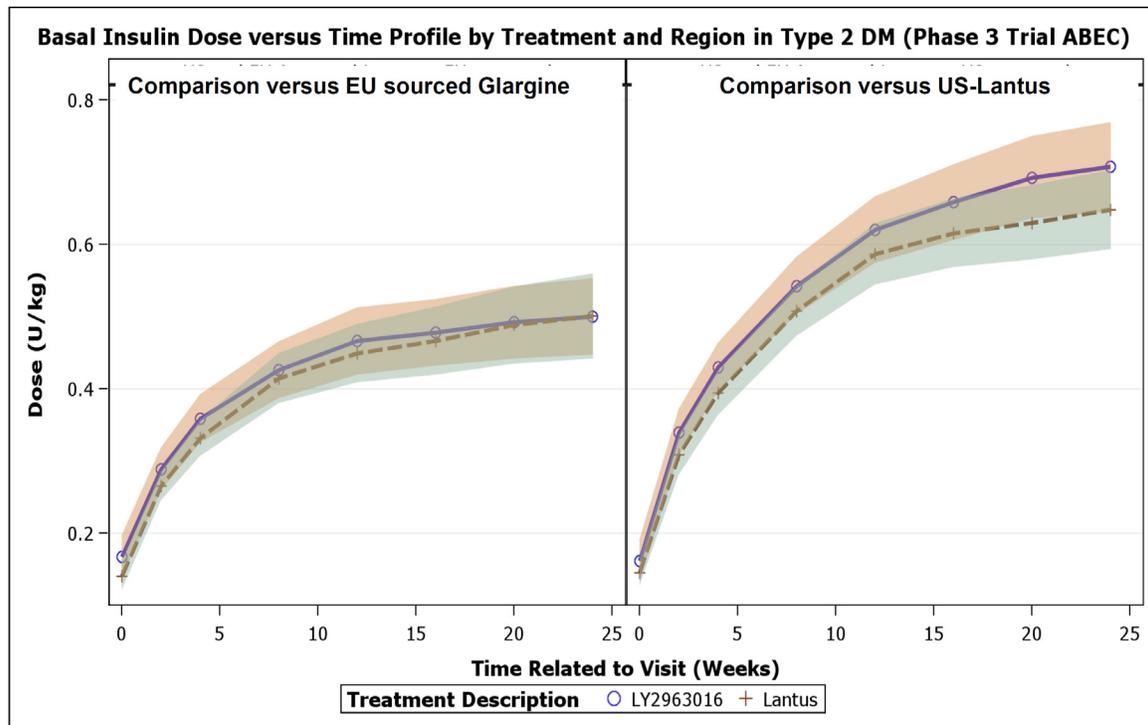
Based on overall dose-time profile for the basal and prandial insulin components utilized in the trial, on average the basal dose utilization was higher for the LY2963016 treatment arm (Figure 9). This was in agreement with the PKPD result showing that on average response/Unit dose was slightly lower, but not statistically different, for LY2963016 treatment arm compared to US-Lantus arm at 0.5 U/kg. The doses evaluated in the PKPD similarity study were also similar to the average basal insulin dose utilized in the efficacy/safety trials.

Regional differences are somewhat difficult to explain. There was statistically significant difference in HbA1c response (See review by Dr. Lee Ping Pian in DAARTS dated 05/29/2014) between LY2963016 and US-Lantus (with lower response for LY2963016), while the HbA1c response was similar between LY2963016 and EU-Glargine. The comparison of basal and prandial doses between US and EU regions shows that the prandial insulin doses used in the EU part of the trial were significantly higher compared to doses used in the US part (Figure 10).



**Figure 10 Mean (95% CI; shown as bands) insulin dose (U/kg) over time profile by region (EU and US) treatment in Type 1 Diabetes Population (ABEB)**

Notably, the dose-time profiles in Type 2 DM patients (ABEC) did not differ between LY2963016 and US-Lantus or between LY2963016 and EU-Glargine (Figure 11). Although, some differences were noted in the amount of doses utilized over trial duration between US and EU regions, the +0.01 [-0.15, +0.18] between treatment difference [95% CI] in HbA1c change from baseline to week 24 showed that LY2963016 was non-inferior to Lantus in patients with T2DM (*see review by Dr. Lee Ping Pian in DAARTS dated 05/29/2014*).



**Figure 11 Mean (95% CI; shown as bands) insulin dose (U/kg) over time profile by region (EU and US) treatment in Type 2 Diabetes Population (ABEC)**

Overall, the unit dose utilization for basal insulin component was similar between LY2963016 and reference insulin glargine, which was in agreement with the assessment of similarity in the PD response ( $GIR_{max}$  and  $AUC_{GIR0-24h}$ ) from PKPD studies. In other words, the assumption that LY2963016 has same unit dose definition as US-Lantus and therefore formulated in the same strength as US-Lantus (i.e., as 100 IU/mL) was substantiated by the similar PD response for the same unit dose (0.5 U/kg) of LY2963016 and US-Lantus in the PK/PD study. The assumption of same unit dose definition for LY2963016 and reference insulin glargine was further confirmed by similar dose utilization for test and reference in Phase 3 trials showing non-inferior HbA1c response. Therefore, PKPD results corroborated the Phase 3 efficacy results with regards to the unit dose definition.

## 2.3 Analytical

### 2.7.1 Are the analytical methods appropriately validated?

An RIA method ( (b)(4) report 8225343) for the measurement of immunoreactive insulin glargine concentrations in serum samples was validated at (b)(4)

Samples were pretreated with polyethylene glycol (PEG) precipitation to remove any antibody/insulin glargine complexes, so the measured concentrations represent “free” immunoreactive insulin glargine. The antibody employed in the RIA was generated against despentapeptide human insulin. As a consequence, the RIA demonstrated full cross-reactivity with both insulin glargine and native human insulin. The PKPD study samples collected after dosing either LY2963016 or LANTUS® were analyzed with the same RIA method (8225343) for measuring the serum concentrations of immunoreactive insulin glargine.

The range of quantification for immunoreactive insulin glargine is from 50 to 2000 pM. Serum samples with concentrations higher than 2000 pM were diluted up to 1:256 prior to analysis. Both precision and accuracy, as expressed by the inter-assay coefficient of variation (%CV) and the inter-assay relative error (%RE), respectively, were  $\leq 16.0\%$  for the measurement of immunoreactive insulin glargine in human serum. Quality control samples across the standard curve range were included in each sample analysis batch. Incurred samples for reanalysis (ISR) were assayed in comparative PK and PD Studies ABEO, ABEA and ABEN and met predefined acceptance criteria.

The RIA for measurement of insulin glargine in human serum is a competitive radioimmunoassay. The assay format involved incubating calibrators, controls and samples with 25% PEG solution in tubes, followed by incubation and then centrifugation.

After centrifugation, the 25% PEG-treated standards, controls and samples were then diluted 1:1 with assay buffer in tubes. Hydrated  $^{125}\text{I}$ -Insulin tracer and anti-DPI antibody were then added to the tubes and the solution was allowed to incubate overnight. After incubation, Precipitating Reagent was added, followed by vortex and centrifugation. Immediately following centrifugation, the tubes were decanted and counts were read in a gamma counter.

The summary of the performance characteristics of insulin glargine assay are presented in Table 7 below.

**Table 7 Summary of the Performance Characteristics of Insulin Glargine Assay**

Validation Parameters	Target Specifications	Target Specifications Met (Yes/No)
<b>System Suitability</b>	AR: 80 to 120% of the nominal concentration CV≤20%  At LLOQ and ULOQ AR: 75 to 125% of the nominal concentration CV≤25%	<b>Yes</b> AR: 87.9-106.1% CV≤14.8%
<b>Accuracy and Precision/Range of Quantitation</b>	<b>Accuracy (expressed as mean bias or percent relative error [RE])</b> RE: ±20% RE: ±25% at LLOQ and ULOQ  <b>Precision</b> CV≤20% CV≤25% at LLOQ and ULOQ  <b>Total error</b> (absolute RE + interbatch precision): should not exceed 30%; 40% for LLOQ and ULOQ	<b>Yes</b> <b>Inter-assay</b> RE: ±18.7% CV≤17.0% TE≤27.9%, ≤35.7% for LLOQ1 and LLOQ2  <b>No</b> <b>Intra-assay</b> RE: ±18.2% ULOQ-LQC with the exception of run 027 at the LQC level. RE: ±34.3% for LLOQ1 RE: ±27.4% and LLOQ2 CV≤15.0% Note: LLOQ will be set at 50pM
<b>Comparability of LY2963016 (BIV) to Glargine</b>	<b>Accuracy (expressed as mean bias or percent relative error [RE])</b> RE: ±20% RE: ±25% at LLOQ and ULOQ  <b>Precision</b> CV≤20% CV≤25% at LLOQ and ULOQ	<b>Yes</b> <b>Inter-assay</b> RE: ±9.7% CV≤16.3% <b>Intra-assay</b> RE: ±15.7, 22.0% at LLOQ CV≤9.0%

Validation Parameters	Target Specifications	Target Specifications Met (Yes/No)
<b>Comparability of Glargine to Insulin</b>	<b>Accuracy (expressed as mean bias or percent relative error [RE])</b> RE: $\pm 20\%$ RE: $\pm 25\%$ at LLOQ and ULOQ <b>Precision</b> CV $\leq 20\%$ CV $\leq 25\%$ at LLOQ and ULOQ	<b>Yes</b> RE: $\pm 22.5\%$ CV $\leq 9.4\%$
<b>Dilution Linearity</b>	AR: 80 to 120% of the corresponding nominal concentration in at least 67% of the dilution samples between and including the LLOQ and the ULOQ	<b>Yes</b> AR: 93.2-100.5% of the corresponding nominal concentration in 100% samples within the quantitative range
<b>Method Selectivity</b>	75 to 125% recovery of the expected final concentration as determined by the spiked concentration plus endogenous concentration (unspiked)  Criteria must be met in at least 80% of samples tested.  If the targeted criteria are not met, refer to Appendix 2.	<b>Yes</b> Criteria met in 100% of samples
<b>Freeze/Thaw (F/T) Stability</b>	Stability is acceptable if the measured concentrations of analyte in $\geq 67\%$ of all stability samples, with $\geq 50\%$ at each level, meet the following criteria (unless otherwise established by A&P data): AR: 80 to 120% of the baseline concentration CV $\leq 20\%$	<b>Yes</b> Freeze/Thaw stability was established up to 5 freeze/thaws AR: 82.5-101.46% CV $\leq 8.2\%$

Validation Parameters	Target Specifications	Target Specifications Met (Yes/No)
<b>Bench Top Stability at ART</b>	Stability is acceptable if the measured concentrations of analyte in $\geq 67\%$ of all stability samples, with $\geq 50\%$ at each level, meet the following criteria (unless otherwise established by A&P data): AR: 80 to 120% of the baseline concentration CV $\leq 20\%$	<b>Yes</b> Bench top stability was established up to 24 hrs. AR to baseline: 87.5-98.8% CV $\leq 6.0\%$
<b>Refrigerator Stability</b>	Stability is acceptable if the measured concentrations of analyte in $\geq 67\%$ of all stability samples, with $\geq 50\%$ at each level, meet the following criteria (unless otherwise established by A&P data): AR: 80 to 120% of the baseline concentration CV $\leq 20\%$	<b>Yes</b> Refrigerator stability was established up to 72 hrs. AR: 92.6-101.7% CV $\leq 11.2\%$
<b>Long Term Stability (LTS)</b>	Stability is acceptable if the measured concentrations of analyte in $\geq 67\%$ of all stability samples, $\geq 50\%$ at each level, meet the following criteria (unless otherwise established by A&P data): AR of 80 to 120% of the baseline concentration CV $\leq 20\%$	Long term stability will be added by amendment to the final report.

The assay methods were adequately validated and covered the observed concentrations ranges of insulin glargine in the clinical pharmacology studies.

Based on internal e-mail communication dated 07/18/14, Office of Scientific Investigation (OSI) inspection of bioanalytical and clinical conduct of the pivotal PKPD studies ABEO and ABEN were satisfactory and did not reveal any eclipsing issues (OSI review is pending in DAARTS).

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

***FDA Recommendation:***

*Recommend deleting this and describe this in Section 8 as follows:*

**8.6 Hepatic Impairment**

The effect of hepatic impairment on the pharmacokinetics of BASAGLAR has not been studied. Frequent glucose monitoring and dose adjustment may be necessary for BASAGLAR in patients with hepatic impairment [see Warnings and Precautions (5.3)].

**8.7 Renal Impairment**

The effect of renal impairment on the pharmacokinetics of BASAGLAR has not been studied. Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. Frequent glucose monitoring and dose adjustment may be necessary for BASAGLAR in patients with renal impairment [see Warnings and Precautions (5.3)].

## 4 Appendix

### 4.1 Individual Study Synopses as Reported

#### 4.1.1 PKPD Study ABEO (LY2963016 versus US-Lantus)

### Clinical Study Report Synopsis: Study I4L-MC-ABEO

<b>Title of Study:</b> Comparative Pharmacokinetics and Pharmacodynamics of LY2963016 and US-Approved LANTUS® after Single-Dose Subcutaneous Administration to Healthy Subjects	
<b>Number of Investigators:</b> This single-center study included 1 principal investigator.	
<b>Study Center:</b> This study was conducted at 1 study center in 1 country.	
<b>Publications Based on the Study:</b> None at this time.	
<b>Length of Study:</b> Date of first subject entered (signed informed consent): 20 September 2012 Date of last subject completed: 14 February 2013	<b>Phase of Development:</b> 1
<b>Objectives:</b> <u>Primary objective:</u> To evaluate the pharmacokinetic (PK) similarity of LY2963016 (test) to United States (US)-approved LANTUS® (reference) following subcutaneous (SC) administration of a single 0.5-U/kg dose to healthy subjects. <u>Secondary objective:</u> To demonstrate the pharmacodynamic (PD) similarity of LY2963016 to US-approved LANTUS® following SC administration of a single 0.5-U/kg dose to healthy subjects.  Note: LANTUS® is the registered trademark of Sanofi Aventis®.	
<b>Study Design:</b> This was a randomized, double-blind, single-dose, 2-treatment, 4-period, crossover, replicate-treatment, euglycemic clamp study. Subjects were randomly assigned to 1 of 2 dosing sequences and received 0.5 U/kg LANTUS on 2 occasions and 0.5 U/kg LY2963016 on 2 occasions.	
<b>Number of Subjects:</b> Planned: Up to 105 subjects to ensure 78 subjects complete the study Randomized and treated (at least 1 dose): 91 subjects Completed: 82 subjects	
<b>Diagnosis and Main Criteria for Inclusion:</b> Subjects were required to be overtly healthy males or females, with no history of first-degree relatives known to have diabetes mellitus, and between the ages of 21 and 65 years, with a body mass index between 18.5 and 29.9 kg/m <sup>2</sup> .	
<b>Study Drug, Dose, and Mode of Administration:</b> LY2963016 was supplied as 100-U/mL solution in 3-mL prefilled pens from lot number CT575489. LY2963016 was administered SC as a 0.5-U/kg dose using a 30 gauge × 8 mm needle.	
<b>Reference Therapy, Dose, and Mode of Administration:</b> US-approved LANTUS® was supplied as 100-U/mL solution in 3-mL prefilled pens from lot number 1F638A. LANTUS® was administered SC as a 0.5-U/kg dose using a 30 gauge × 8 mm needle.	
<b>Duration of Treatment:</b> Subjects were admitted to the clinical research unit on the night before each treatment (Day -1, Periods 1 through 4). On Day 1 of each period, subjects underwent a euglycemic clamp procedure until approximately 24 hours postdose. Subjects were discharged on Day 2 of each period. There was a minimum washout period of 7 days between study periods. Subjects were required to return to the clinical research unit between 5 and 14 days after the end of the last study period for a poststudy follow-up assessment.	

**Variables:**

**Pharmacokinetic:** During each treatment visit, venous blood samples were collected predose and up to 24 hours postdose to determine the serum concentrations of immunoreactive LY2963016 or immunoreactive LANTUS<sup>®</sup>. The bioanalytical assay detects both insulin glargine (LY2963016 or LANTUS<sup>®</sup>) and endogenous insulin. To allow for correction of serum immunoreactive LY2963016 and immunoreactive LANTUS<sup>®</sup> 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.

**Pharmacodynamic:** The PD measurements were derived from the euglycemic clamp procedure, where the glucose infusion rate (GIR) over time was used as a measure of insulin effect.

**Safety:** Safety was assessed by recording of adverse events (AEs), concomitant medications monitoring, physical examinations, clinical laboratory tests, electrocardiograms (ECGs), and vital signs measurements.

**Evaluation Methods:**

**Bioanalytical:** Serum concentrations of immunoreactive LY2963016 or immunoreactive LANTUS<sup>®</sup> were determined using a validated radioimmunoassay method following dosing with LY2963016 or LANTUS<sup>®</sup>.

**Pharmacokinetic:** For the primary analysis, serum concentrations of immunoreactive LY2963016 or immunoreactive LANTUS<sup>®</sup> were corrected using C-peptide data. Pharmacokinetic parameter estimates for LY2963016 and LANTUS<sup>®</sup> were calculated by standard non-compartmental methods of analysis. The primary parameters for PK analysis for LY2963016 and LANTUS<sup>®</sup> were area under the concentration versus time curve (AUC) from time zero to 24 hours (AUC[0-24]) and maximum observed drug concentration ( $C_{max}$ ). Secondary PK parameters included the AUC from time zero to time t, where t is the last time point with a measurable concentration (AUC[0- $t_{last}$ ]), and AUC from zero to infinity (AUC[0- $\infty$ ]). The AUC values were calculated by the linear/log trapezoidal method, where the linear trapezoidal method was employed up to the time of  $C_{max}$  ( $t_{max}$ ) and the log trapezoidal rule was used for concentrations beyond  $t_{max}$ . Other PK parameters that were estimated included  $t_{max}$ , apparent total body clearance of drug calculated after extra-vascular administration (CL/F), half-life associated with the terminal rate constant in non-compartmental analysis ( $t_{1/2}$ ), and apparent volume of distribution during the terminal phase after extra-vascular administration ( $V_z/F$ ).

**Pharmacodynamic:** A locally weighted scatterplot smoothing (LOESS) function was applied to all individual GIR versus time profiles in each treatment group using TIBCO Spotfire S+<sup>®</sup> 8.2 for Windows<sup>®</sup>. The fitted data for each subject were used to calculate the primary PD parameters, maximum glucose infusion rate ( $R_{max}$ ) and total glucose infusion over the clamp duration ( $G_{tot}$ ), over the duration of the clamp procedure. A secondary PD parameter, the time of  $R_{max}$  ( $TR_{max}$ ), was calculated using the LOESS function. Raw (that is, observed) GIR values from each clamp procedure were used to calculate the other secondary PD parameters, such as the time of first change of GIR postdose ( $T_{onset}$ ), the time of last measurable GIR ( $T_{last}$ ), time to 50% maximal GIR before  $TR_{max}$  (early  $TR_{max50\%}$ ), time to 50% maximal GIR after  $TR_{max}$  (late  $TR_{max50\%}$ ), time to 75% maximal GIR after  $TR_{max}$  (late  $TR_{max75\%}$ ), and the value of the last measurable GIR ( $GIR_{last}$ ).

**Safety:** Adverse events were listed and summarized by the Medical Dictionary for Regulatory Activities (MedDRA; Version 15.0) system organ class and preferred term.

**Pharmacokinetic statistical analyses:** The primary PK parameters, AUC(0-24) and  $C_{max}$ , were log transformed prior to analysis. A linear mixed-effects model was fitted to the data. The model included subject as a random effect with period, sequence, and treatment as fixed effects. For each PK parameter, the difference in least squares (LS) means along with the 90% confidence intervals (CIs) were back transformed to produce the ratio of geometric means and the CI comparing LY2963016 to LANTUS<sup>®</sup>. Similarity was to be concluded if the 90% CIs for both AUC(0-24) and  $C_{max}$  were contained within the interval of 0.80 to 1.25. Within- and between-subject variability were reported for each PK parameter. An analogous statistical analysis was performed for the log-transformed secondary PK parameters AUC(0- $t_{last}$ ) and AUC(0- $\infty$ ). A nonparametric approach was taken to evaluate  $t_{max}$  using the Wilcoxon signed-rank test. The difference in median  $t_{max}$  between treatments and the 95% CIs for the differences were presented.

An additional analysis was performed for the primary PK parameters, AUC(0-24) and  $C_{max}$ , as well as the secondary parameters, to include only the PK data obtained from subjects who completed all 4 periods of the study and who had evaluable PK data in those periods. The model used for this analysis included period, sequence, treatment, and subject nested within sequence as fixed effects; no random effects were included.

**Pharmacodynamic statistical analyses:** The primary PD parameters,  $R_{max}$  and  $G_{tot}$ , were log transformed prior to analysis. A linear mixed-effects model was fitted to the data. The model included subject as a random effect with period, sequence, and treatment as fixed effects. For each PD parameter, the difference in LS means along with the 90% CIs were back transformed to produce the ratio of geometric means and the CI comparing LY2963016 to LANTUS<sup>®</sup>. Pharmacodynamic similarity was concluded if the 90% CI was contained within the interval of 0.80 to 1.25. The analysis was repeated using the same model with a corresponding 95% CI. Within- and between-subject variability were reported for each PD parameter. An additional analysis was performed for the primary PD parameters,  $G_{tot}$  and  $R_{max}$ , to include only the data obtained from subjects who completed all 4 periods of the study. The model used for this analysis included period, sequence, treatment, and subject nested within sequence as fixed effects; no random effects were included.

#### **Summary:**

##### **Demographics and Disposition:**

A total of 91 healthy subjects (85 males and 6 females) aged 22 to 62 years, inclusive, participated in the study. Of the 91 subjects who entered the study, 82 subjects completed the study in accordance with the protocol. Nine subjects did not complete the study: 3 subjects were withdrawn due to subject decision, 2 subjects were withdrawn due to physician decision, 3 subjects were withdrawn due to sponsor decision, and 1 subject was withdrawn due to an AE (lethargy) that was not considered to be related to study treatment.

##### **Pharmacokinetics:**

Following SC administration of a single dose, the serum concentration profiles were similar between LY2963016 and LANTUS<sup>®</sup>, with peak concentration reached at 12 hours (median) for both treatments. Based on statistical comparisons of AUC(0-24) and  $C_{max}$ , the primary PK parameters were demonstrated to be similar between LY2963016 and LANTUS<sup>®</sup>. The ratios of LS geometric means were 0.90 and 0.92 for AUC(0-24) and  $C_{max}$ , respectively, with the 90% CIs for the ratios contained within the prespecified interval of 0.80 to 1.25. An additional analysis was performed to meet the requirements of the European Medicines Agency (EMA) 2010 guidance, in which only data from subjects who completed all 4 periods of the study and had evaluable PK data for all 4 periods were included. The conclusion of similarity was confirmed for the primary parameters AUC(0-24) and  $C_{max}$ , with the 90% CIs contained within the interval 0.80 to 1.25. Similar mean serum C-peptide profiles were observed following administration of LY2963016 or LANTUS<sup>®</sup>, suggesting a similar degree of suppression of the endogenous insulin following administration of either drug.

**Pharmacodynamics:**

Following a single SC administration of 0.5 U/kg LY2963016 or LANTUS®, the mean and 90% CI band of the smoothed mean GIR versus time profiles and the corresponding glucose levels were essentially overlapping. The statistical comparisons of  $G_{tot}$  and  $R_{max}$  demonstrated similarity in PD between LY2963016 and LANTUS®. The ratios of LS geometric means were 0.91 and 0.93, respectively, for  $G_{tot}$  and  $R_{max}$ , with the 90% CIs for the ratios contained within the prespecified interval of 0.80 to 1.25. An additional analysis was performed to meet the requirements specified for PD in the EMA 2010 guidance, in which only data from subjects who completed all 4 periods of the study were included. The conclusion of similarity was confirmed for the primary parameters,  $G_{tot}$  and  $R_{max}$ , with the 90% CIs contained within the interval of 0.80 to 1.25.

**Safety:**

A total of 67 (73.6%) subjects reported a total of 145 treatment-emergent AEs (TEAEs), of which 144 TEAEs were considered to be unrelated to study treatment by the investigator. All reported TEAEs were mild (143 AEs) or moderate (2 AEs) in severity.

One TEAE, an episode of dizziness that was mild in severity, was considered to be related to study treatment. This AE occurred after dosing with 0.5 U/kg LY2963016.

Of the 144 TEAEs that were not considered by the investigator to be treatment-related, 92 (63.9%) TEAEs were considered by the investigator to be related to study procedures; the remaining non-treatment related TEAEs were considered to be related to "other medical condition." The most common TEAEs (experienced by more than 10% of subjects) were catheter site haematoma (22 AEs in 18 subjects), catheter site swelling (17 AEs in 16 subjects), and catheter site pain (11 AEs in 10 subjects).

One subject was withdrawn from the study after completing Period 1, due to an AE of lethargy that was not considered by the investigator to be related to study treatment. The subject reported being uncomfortable with the AE and requested to be withdrawn from the study. The AE was considered by the investigator to be moderate in severity and to be related to study procedures.

There were no changes in the clinical chemistry, hematology, urinalysis, supine pulse rate, supine systolic blood pressure, supine diastolic blood pressure, or ECG parameter data for individual subjects during the study that were considered clinically significant by the investigator.

**Conclusions:**

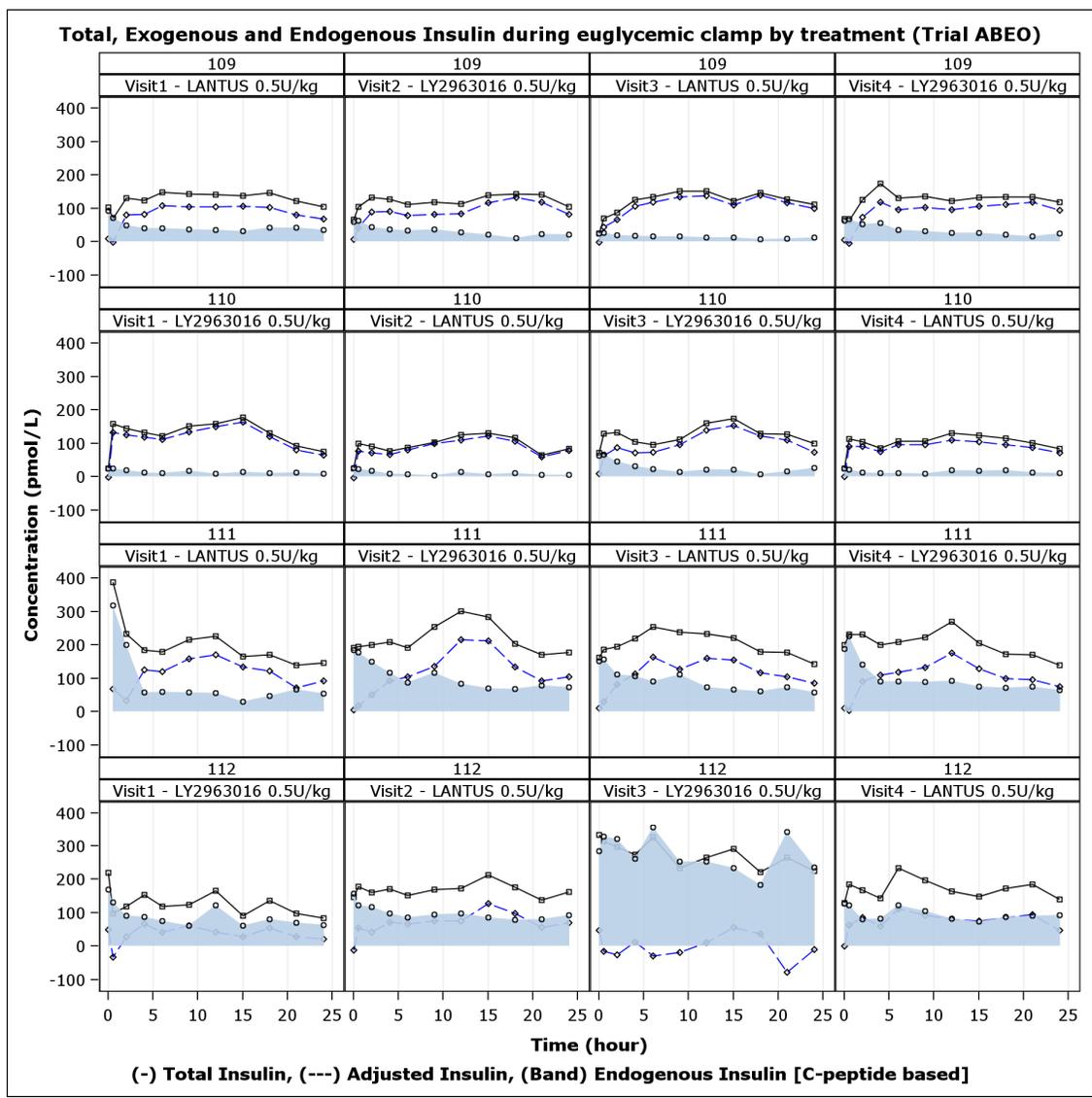
- The primary PK parameters, AUC(0-24) and  $C_{max}$ , of LY2963016 were demonstrated to be similar to those of LANTUS®, with the 90% CIs of the ratios of geometric means of the 2 treatments contained within the prespecified interval of 0.80 to 1.25.
- The PD of LY2963016 was demonstrated to be similar to that of LANTUS®, with the 90% CIs for the ratios of geometric means of the 2 treatments contained within the prespecified interval of 0.80 to 1.25.
- The safety profiles of LY2963016 and LANTUS® were comparable with regard to AEs, and there were no changes in the clinical laboratory, vital signs, or ECG parameters during the study that were considered clinically significant by the investigator.

**Reviewer's Analysis and Comments:**

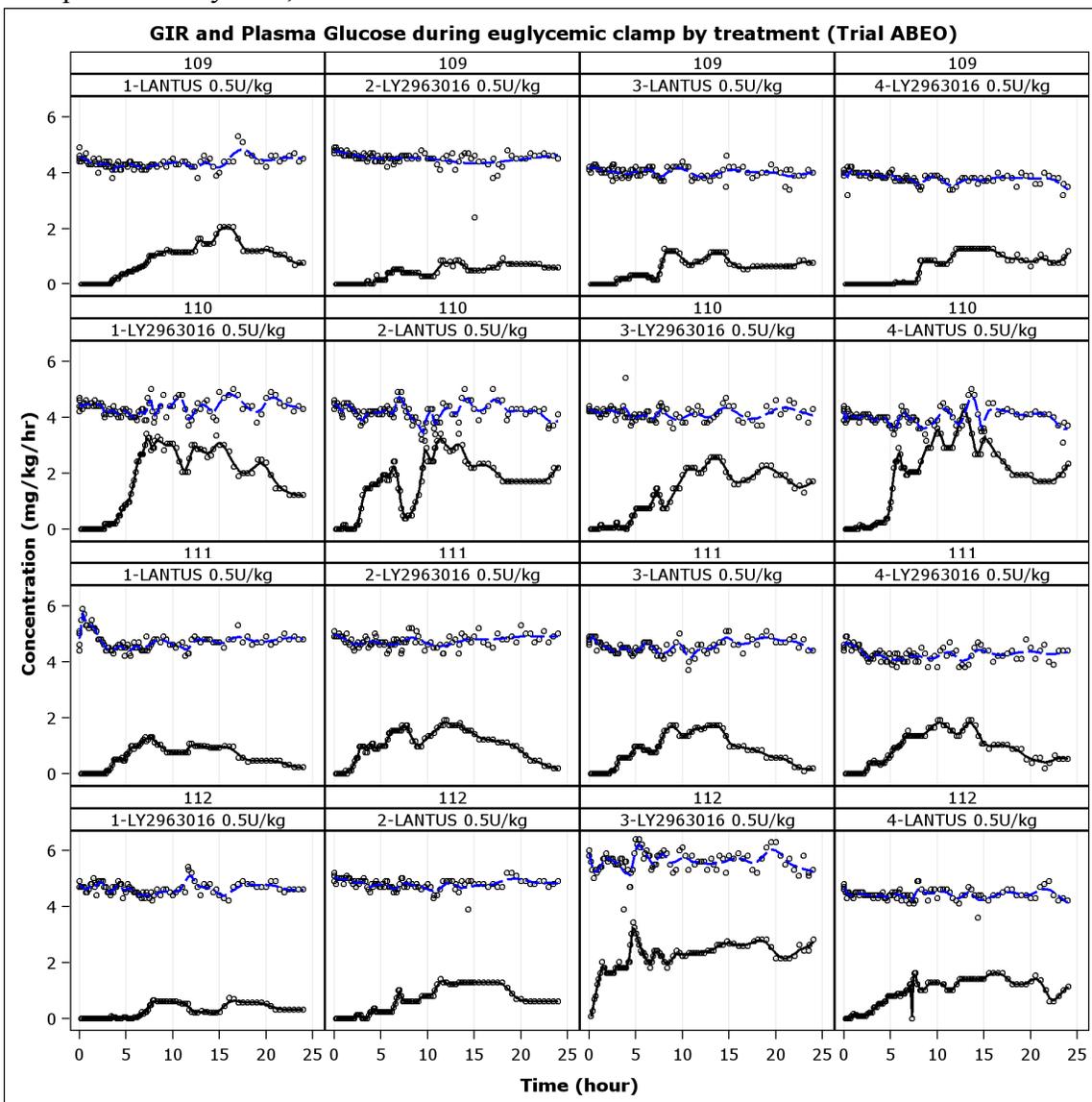
The study was reasonable in design and conduct to meet the intended objective. Replicate-crossover design allows for assessment of inter-individual and intra-individual variability assessment besides enabling the bioequivalence assessment for PK and PD parameters with relatively small number of subjects. Considering the current study design was replicate cross-over, the study seemed overpowered with a sample size of ~91. There were 3 noteworthy protocol deviations during the study. All 3 resulted in early termination of study participation for the affected subjects (due to un-evaluable PK and/or PD data). Subject 0157 received the incorrect dose of LY2963016 in Period 2. As the dose was lower than prescribed by the protocol, there was no overdose or immediate safety concern. Subject 0158 received an incorrect amount of intravenous glucose during the first 10 hours of his clamp procedure in Period 2. The investigator did not consider

the error to be a safety concern, and the subject completed the clamp uneventfully. Subject 0185 received intravenous glucose at an incorrect infusion rate for 9 minutes during his clamp in Period 1. As the subject received more glucose than required for a short period, this was judged by the investigator as a non-safety concern. The exclusion of these subjects was justified.

However, considering the nature of independent comparison of PK and PD parameters from insulin PKPD studies to assess similarity, it is highly important and desirable to include PK and PD data that has minimum confounding factors and has mutual support from each other (i.e., both PK and PD are available from same patient). Therefore, the individual level PK and PD data was evaluated graphically to identify any confounded data. A representative figure presenting individual level PK data on total insulin (solid line with squares), baseline corrected insulin (blue dash line with diamonds), and endogenous insulin (band) versus time, by visit, in select subjects is shown below.



A representative figure presenting corresponding individual level PD data; glucose infusion rate (solid black line with circle) and blood glucose (blue dashed line) over clamp duration by visit, is shown below.



For instance, Visit 2-Lantus and Visit 3-LY2963016 for subject 112 were confounded as the corrected insulin concentrations were nearly 0. However, GIR data looked similar to the visits where reasonable increase in insulin concentration above baseline was observed. The total and endogenous profile revealed that there was minimal exogenous insulin on board but since the endogenous concentrations were high, the glucose infusion profile is likely driven through endogenous insulin secretion. This behavior is difficult to catch during the experiment. However, simultaneous evaluation of PK and PD profiles can reveal such discrepancy. Under such circumstances, exclusion of PK data alone, based on negligible insulin concentrations is not justified and the corresponding PD data

should also be excluded from statistical evaluation. The statistical analysis plan should also be prospectively defined to keep a provision in tackling such data.

The results from the reviewer's analysis of PK and PD data after excluding confounded data (ID-Visit: 157-102, 158-102, 185-101, 112-103, 154-102, 157-101, 178-102, 181-102, 183-101, 188-101) confirmed that PK similarity conclusions for baseline corrected and PD similarity conclusions for AUC<sub>GIR0-24h</sub> did not change from original analysis. In addition, total insulin and endogenous (suppression effect) were also similar between LY2963016 and US-Lantus.

**Statistical Comparison of Insulin PK Parameters (Study ABEO)**

Comparison	PK Parameter	Units	Ratio(%)	90% CI
LY2963016-0.5 U/kg vs. Lantus-0.5 U/kg	Total Insulin AUC0-t	pmol.hr/L	92.74	89.61 - 95.97
	Total Insulin Cmax	pmol/L	93.46	90.07 - 96.98
	Endogenous Insulin AUC0-t	pmol.hr/L	95.74	90.05 - 101.79
	Endogenous Insulin Cmax	pmol/L	98.81	93.34 - 104.59
	Baseline Adjusted Insulin AUC0-t	pmol.hr/L	90.34	85.41 - 95.55
	Baseline Adjusted Insulin Cmax	pmol/L	92.04	87.41 - 96.92

**Statistical Comparison of Insulin PD Parameters (Study ABEO)**

Comparison	PD Parameter	Units	Ratio(%)	90% CI
LY2963016-0.5 U/kg vs. Lantus-0.5 U/kg	Observed GIR AUC0-t	mg/kg	90.56	84.17 - 97.43
	Observed GIR AUC0-12h	mg/kg	82.52	74.67 - 91.2
	Observed GIRmax	mg/kg/min	92.73	87.5 - 98.26
	Smoothed GIR AUC0-t	mg/kg	90.52	84.17 - 97.35
	Smoothed GIR AUC0-12h	mg/kg	82.5	74.68 - 91.15
	Smoothed GIRmax	mg/kg/min	92.42	87.39 - 97.74

#### 4.1.2 PKPD Study ABEA (LY2963016 versus EU-Glargine)

<b>Title of Study:</b> Bioequivalence Study Comparing the Pharmacokinetics and Pharmacodynamics of LY2963016 with Insulin Glargine in Healthy Volunteers	
<b>Number of Investigators:</b> This single-centre study included 1 principal investigator.	
<b>Study Centre:</b> This study was conducted at 1 study centre in 1 country.	
<b>Publications Based on the Study:</b> None at this time.	
<b>Length of Study:</b> Date of first subject visit: 09 November 2011 Date of last subject visit: 06 July 2012	<b>Phase of Development:</b> 1
<b>Objectives:</b> The <b>primary objective</b> of this study was to evaluate the pharmacokinetic (PK) equivalence of LY2963016 (test) to LANTUS® (insulin glargine) (reference) following subcutaneous (SC) administration of a single dose (0.5 U/kg) to healthy subjects.  <b>Secondary objectives</b> were to (i) demonstrate the pharmacodynamic (PD) comparability of LY2963016 (test) to LANTUS® (reference) following SC administration of a single dose (0.5 U/kg) to healthy subjects, and (ii) assess the safety and tolerability of LY2963016 when administered to healthy subjects.  Note: Although advice from United States Food and Drug Administration suggested changing study wording from “equivalence” or “comparability” to “similarity,” it was elected to maintain the wording in the primary and first secondary objectives in order to align with the protocol.	
<b>Study Design:</b> This Phase 1 study was a single centre, randomized, double-blind, single-dose (0.5 U/kg), 2-treatment, 4-period, crossover, replicate, euglycaemic clamp study in healthy subjects. Subjects were admitted to the Clinical Research Unit for dosing and the 24-hour clamp procedure.	
<b>Number of Subjects:</b> Planned: Up to 98 healthy subjects enrolled to have at least 78 subjects complete the study. Randomized and treated: 80 subjects received at least 1 dose of LY2963016 and LANTUS® Completed: 78 subjects completed LY2963016 and LANTUS® dosing	
<b>Diagnosis and Main Criteria for Inclusion:</b> Healthy males or females, aged between 18 and 60 years, inclusive, with a screening body mass index of 18.5 to 32.0 kg/m <sup>2</sup> (inclusive) were eligible for this study. Subjects who were allergic to heparin, insulin glargine, or related compounds were excluded.	
<b>Study Drug, Dose, and Mode of Administration:</b> LY2963016, 0.5 U/kg, administered SC during 2 of 4 study periods according to a randomised sequence; supplied from package lot CT565119.	
<b>Reference Therapy, Dose, and Mode of Administration:</b> LANTUS®, 0.5 U/kg, administered SC during 2 of 4 study periods according to a randomised sequence; supplied from package lot 1F156A.	
<b>Duration of Treatment:</b> Each subject received LY2963016 or LANTUS® in a total of 4 periods. Each period was approximately 36 hours in duration. There was a minimum washout interval of 7 days between study periods. A follow-up visit occurred within 5 to 14 days of the end of the last study period.	

**Variables:**

**Safety:** Adverse events (AEs), vital signs, electrocardiograms (ECGs), clinical laboratory tests, and medical assessments.

**Bioanalytical:** Blood samples were collected to determine the serum concentrations of immunoreactive LY2963016 or immunoreactive LANTUS® after administration of LY2963016 or LANTUS®.

**Pharmacokinetic:** Serum concentrations of LY2963016 and LANTUS® were used to determine primary PK parameters of area under the serum insulin glargine concentration-time curve (AUC) from zero to 24 hours (AUC[0-24]) and maximum serum insulin glargine concentration ( $C_{max}$ ). Secondary PK parameters included the AUC from time zero to last measured concentration value (AUC[0- $t_{last}$ ]) and AUC from time zero to infinity (AUC[0- $\infty$ ]). Other PK parameters that were estimated include time of maximum serum insulin glargine concentration ( $T_{max}$ ), total body clearance of drug calculated after extravenous administration (CL/F), half-life associated with the terminal rate constant ( $t_{1/2}$ ), and apparent volume of distribution during the terminal phase after extravenous administration (Vz/F).

**Pharmacodynamic:** PD measurements were derived from the euglycaemic clamp procedure, where the glucose infusion rate (GIR) over time was used as a measure of insulin effect. The primary parameters were the maximum GIR ( $R_{max}$ ) and the total amount of glucose infused ( $G_{tot}$ ) over the duration of the clamp procedure.

**Statistical or Other Evaluation Methods:**

**Statistical:** The sample size was based on the PK within-subject variability of LANTUS® observed in a PK/PD variability clamp study.

**Safety:** Safety analyses was conducted for all enrolled subjects. All study drug and protocol procedure AEs were listed, and if the frequency of events allowed, safety data was summarised using descriptive methodology. Clinical laboratory parameters, vital signs, and ECG parameters were listed and summarised using standard descriptive statistics.

**Pharmacokinetic:** PK parameter estimates for LY2963016 and LANTUS® were calculated by standard noncompartmental methods of analysis. The primary PK parameters ( $C_{max}$  and AUC) were log-transformed prior to analysis. A linear mixed-effects model was fitted to the data. The model included subject as a random effect, with period, sequence, and treatment as fixed effects. For each PK parameter, the difference in least-square means along with the 90% confidence interval (CI) was back transformed to produce the ratio of geometric means and the CI comparing LY2963016 to LANTUS®. PK equivalence was to be concluded if the 90% CI was completely contained within the interval of 0.80 to 1.25.

**Pharmacodynamic:** The primary PD parameters ( $R_{max}$  and  $G_{tot}$ ) were log-transformed prior to analysis. A linear mixed-effects model was fitted to the data. The model included subject as a random effect, with period, sequence, and treatment as fixed effects. For each PD parameter, the difference in least-square means along with the 90% CI was back transformed to produce the ratio of geometric means and the CI comparing LY2963016 to LANTUS®. PD comparability was concluded if the 90% CI was completely contained within the interval of 0.80 to 1.25.

**Summary:**

A total of 80 healthy subjects, 56 male and 24 female, between the ages of 18 and 60 years (inclusive) participated in this study. Of the 80 subjects who entered the study, all were randomly assigned to treatment, all received at least 1 dose of study drug, 78 completed the study, and 2 did not complete the study. The 2 subjects who did not complete the study discontinued due to subject decision (job related) and were replaced.

Similarity was demonstrated for PK between LY2963016 and LANTUS® with the ratios of least-square geometric means for AUC(0-24) and  $C_{max}$  of 0.91 and 0.95, respectively, with the 90% CIs for the ratios contained within the interval of 0.8 to 1.25 for these primary parameters. Moreover, the statistical comparisons of  $G_{tot}$  and  $R_{max}$  demonstrated PD similarity between the 2 treatments, with the ratios of least-square geometric means of 0.95 and 0.99, respectively, and the 90% CIs of the ratios contained within the 0.8 to 1.25 range. In addition, the

concentration-time profiles of C-peptide appear similar between LY2963016 and LANTUS®, suggesting a similar degree of suppression of endogenous insulin by the 2 treatments.

The PK and PD profiles of LANTUS® observed in this study are generally consistent with what was previously reported for LANTUS® following SC administration of a single dose of 0.5 U/kg. Variability of both the PK and PD are consistent with previously reported studies.

Given that the study was conducted in healthy subjects and the insulin glargine assay used demonstrates cross-reactivity to endogenous insulin, the PK of insulin glargine was corrected for the endogenous insulin levels through the use of C-peptide concentration data. Specifically, the concentrations of endogenous insulin at each sampling time point was estimated from the corresponding C-peptide concentrations using the Owens methods (Owens 1986). This C-peptide correction method is considered the gold standard for the estimation of endogenous insulin based on C-peptide data and has been widely used (Scholtz et al. 2005). Therefore, the estimation of exogenous insulin (drug insulin) by means of C-peptide correction was considered reasonable and reliable. Concentrations of immunoreactive LY2963016 and immunoreactive LANTUS®, uncorrected for endogenous insulin, were also compared and were demonstrated to be similar.

The serum concentrations of LY2963016 and LANTUS® were generally sustained beyond 24 hours. A PK sampling duration longer than 24 hours to capture the entire concentration-time profile would be ideal but was not feasible in the current study design. Therefore, a PK sampling duration of 24 hours was applied and AUC(0-24) was used as the primary PK parameter. As expected, the extrapolated area for AUC(0-∞) is relatively high for some subjects, making the estimation of AUC(0-∞) unreliable for those subjects. Nevertheless, the mean extrapolated area for AUC(0-∞) is 26% and is the same for LY2963016 and LANTUS® based on the PK analysis.

Of the 80 subjects who received 1 or more doses of LY2963016 or LANTUS®, 11 (13.8%) reported 16 LY2963016-related AEs and 14 (17.5%) reported 16 LANTUS®-related AEs. The most common adverse events for both LY2963016 and LANTUS® were injection site pain, injection site erythema, and hypoglycaemia. All other events were reported in 1 subject each. All AEs were of mild or moderate severity. No serious AEs were reported.

Six subjects experienced treatment-related hypoglycaemic episodes, with 1 event being considered as a moderate AE and the remaining as mild AEs. These events were evenly divided between subjects receiving LY2963016 and those receiving LANTUS®. All episodes of hypoglycaemia occurred during the glucose clamp procedure and, because the clamp procedure required that subjects have an intravenous line, all subjects were treated with intravenous glucose. Upon examination of these events, there was no apparent relationship to study treatment, site of injection (upper vs lower abdominal quadrant), or body mass index. Of note, 4 of 6 of these subjects had unusually high PK concentrations during the time corresponding to the hypoglycaemic episodes compared to other subjects in the study at similar time points; moreover, 4 of the hypoglycaemia episodes occurred 15 minutes postdose. This may indicate that the hypoglycaemia events were possibly caused by injection of the study drugs into or close to the intravascular space. Although high concentrations were not evident in the PK profiles for the other 2 subjects, it was possible that the high concentrations fell between the PK sampling time points and were not captured.

#### **Conclusions:**

- The PK of LY2963016 was demonstrated to be similar to that of LANTUS®, with the 90% CIs of the ratio of geometric means of the 2 treatments contained within the prespecified interval of (0.8, 1.25).

- The PD of LY2963016 was demonstrated to be similar to that of LANTUS®, with the 90% CIs for the ratio of geometric means of the 2 treatments contained within the prespecified interval of (0.8, 1.25).
- Overall, AE rates were similar between LY2963016 and LANTUS®.
- LY2963016, when administered as a single dose of 0.5 U/kg SC, was well tolerated, with no clinically significant findings observed with respect to AEs, vital signs, ECGs, and clinical laboratory evaluations.

#### References:

Owens DR. Human insulin: clinical pharmacological studies in normal man. New York: Springer Publishing; 1986.

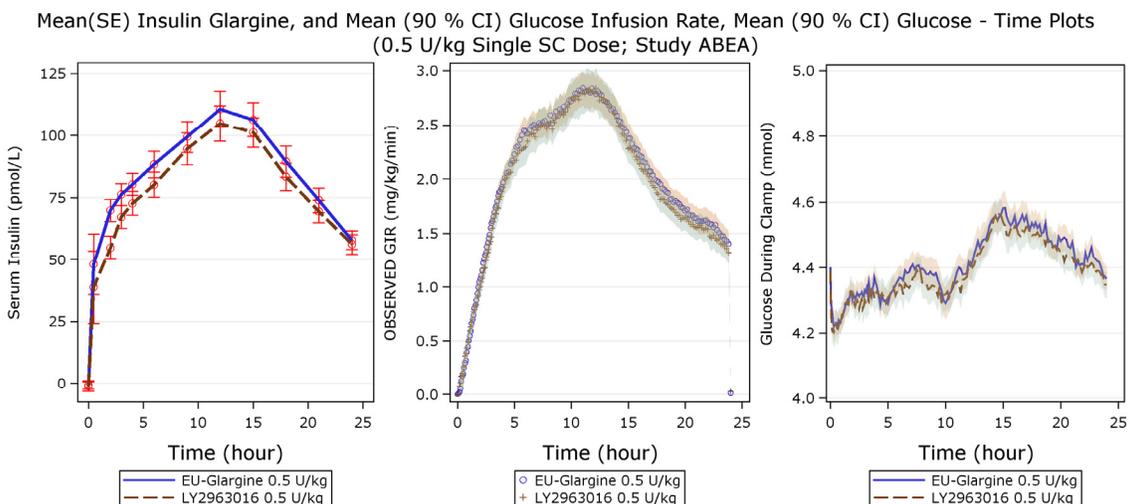
Scholtz HE, Pretorius SG, Wessels DH, Becker RH. Pharmacokinetic and glucodynamic variability: assessment of insulin glargine, NPH insulin and insulin ultralente in healthy volunteers using a euglycaemic clamp technique. *Diabetologia*. 2005;48(10):1988-1995.

#### Reviewer's Analysis and Comments:

The study was reasonable in design and conduct to meet the intended objective. There were no noteworthy protocol deviations during the study.

However, considering the nature of independent comparison of PK and PD parameters from insulin PKPD studies, it is highly important and desirable to include PK and PD data that has minimum confounding factors and has mutual support from each other (i.e., both PK and PD are available from same patient).

Therefore, the individual level PK and PD profiles were evaluated graphically to identify any confounded data. After ensuring the absence of any confounded data, the results from the reviewer's analysis of PK and PD data confirmed the PK similarity conclusions for baseline corrected data ( $C_{max}$  and  $AUC_{0-24h}$ ) and PD similarity conclusions ( $GIR_{max}$  and  $AUC_{GIR0-24h}$ ) in reference to the sponsor's analysis. In addition, total insulin and endogenous insulin (suppression effect) were also similar between LY2963016 and EU-glargine.



**Statistical Comparison of Insulin PK Parameters (Study ABEA)**

Comparison	PK Parameter	Units	Ratio(%)	90% CI
LY2963016 0.5 U/kg vs. EU-Glargine 0.5U/kg	Total Insulin AUC0-t	pmol.hr/L	94.8	91.83 - 97.88
	Total Insulin Cmax	pmol/L	96.23	92.8 - 99.79
	Endogenous Insulin AUC0-t	pmol.hr/L	99.5	93.51 - 105.88
	Endogenous Insulin Cmax	pmol/L	97.92	92.55 - 103.61
	Baseline Adjusted Insulin AUC0-t	pmol.hr/L	91.7	86.99 - 96.67
	Baseline Adjusted Insulin Cmax	pmol/L	96.02	90.05 - 102.39

**Statistical Comparison of Insulin PD Parameters (Study ABEA)**

Comparison	PD Parameter	Units	Ratio(%)	90% CI
LY2963016 0.5 U/kg vs. EU-Glargine 0.5 U/kg	Observed GIR AUC0-t	mg/kg	103.54	98.4 - 108.95
	Observed GIR AUC0-12h	mg/kg	103.7	98.25 - 109.45
	Observed GIRmax	mg/kg/hr	99.56	94.32 - 105.09
	Smoothed GIR AUC0-t	mg/kg	103.54	98.4 - 108.95
	Smoothed GIR AUC0-12h	mg/kg	103.7	98.25 - 109.45
	Smoothed GIRmax	mg/kg/hr	99.56	94.32 - 105.09

### 4.1.3 PKPD Study ABEN (EU-Glargine versus US-Lantus)

<b>Title of Study:</b> Bioequivalence of US LANTUS® to EU LANTUS® after Single-Dose Subcutaneous Administration to Healthy Subjects	
<b>Number of Investigators:</b> This single-center study included 1 principal investigator, Dr (b) (4)	
<b>Study Center:</b> This study was conducted at 1 study center in 1 country.	
<b>Publications Based on the Study:</b> None at this time.	
<b>Length of Study:</b> First subject entered (signed informed consent): 19 April 2012 Last subject completed: 22 August 2012	<b>Phase of Development:</b> 1
<p><b>Objectives:</b></p> <p>The primary objective of the study was to evaluate the pharmacokinetic (PK) equivalence of European Union-sourced insulin glargine (EU-approved LANTUS®; test) to United States-sourced insulin glargine (US-approved LANTUS®; reference) following subcutaneous (SC) administration of a single 0.5 U/kg dose to healthy subjects.</p> <p>The secondary objective of the study was to demonstrate the pharmacodynamic (PD) comparability of EU insulin glargine (EU-approved LANTUS®) to US insulin glargine (US-approved LANTUS®) following SC administration of a single 0.5 U/kg dose to healthy subjects.</p> <p>Note: Global trials have used both EU-approved LANTUS® (EU-approved insulin glargine) and US-approved LANTUS® (US-approved insulin glargine) as the comparator product. The investigational product is marketed under the trade name LANTUS® in the EU and the US. For the purposes of this report, the investigational product will be referred to as LANTUS® except where necessary to distinguish between the source of the drug.</p> <p>Note: Advice from US Food and Drug Administration (FDA) suggested changing the wording in the study title and primary and secondary objectives from 'equivalence' or 'comparability' to 'similarity.' However, since the protocol had already been finalized using the original language, it was elected to maintain the wording in order to align with the protocol. This change in wording is reflected in the remainder of the study report.</p>	
<p><b>Study Design:</b></p> <p>This was a randomized, subject- and investigator-blind, single-dose, 2-treatment, 4-period, crossover, replicate, euglycemic clamp study. Subjects were randomly assigned to 1 of 2 dosing sequences. Each subject was administered 0.5 U/kg of the reference treatment, US-approved LANTUS®, on 2 occasions and the same dose of the test treatment, EU-approved LANTUS®, on 2 occasions.</p>	
<p><b>Number of Subjects:</b></p> <p>Planned: Up to 48 subjects with a minimum of 33 subjects to complete the study Randomized and treated (at least 1 dose): 40 subjects Completed: 34 subjects</p>	
<p><b>Diagnosis and Main Criteria for Inclusion:</b></p> <p>Subjects were required to be between the ages of 21 and 65 years, inclusive, with a body mass index between 18.5 and 29.9 kg/m<sup>2</sup>, inclusive.</p>	
<p><b>Study Drug, Dose, and Mode of Administration:</b></p> <p>EU-approved LANTUS® was supplied by Lilly as 3 mL SoloStar® prefilled pens at 100 units/mL from lot number 1F094A. The insulin was drawn from the cartridge located in the pen device by means of a conventional needle and syringe and was administered SC as 0.5 U/kg doses using a 30 gauge × 8 mm needle. For all study periods, doses were calculated using the subjects' body weight as measured on Day -1 of Period 1.</p>	

**Reference Therapy, Dose, and Mode of Administration:**

US-approved LANTUS® was supplied by Lilly as 3 mL SoloStar prefilled pens at 100 units/mL from lot number 1F805A. The insulin was drawn from the cartridge located in the pen device by means of a conventional needle and syringe and was administered SC as 0.5 U/kg doses using a 30 gauge × 8 mm needle. For all study periods, doses were calculated using the subjects' body weight as measured on Day -1 of Period 1.

**Duration of Treatment:**

Subjects were admitted to the clinical research unit (CRU) on Day -1 and remained resident for the duration of the euglycemic clamp procedure, which began on Day 1 and was maintained for up to 24 hours postdose. Subjects remained in the CRU until the post-clamp safety evaluation had been performed on Day 2. A minimum washout interval of 7 days occurred between study periods. Subjects were required to return to the CRU for a post study follow-up assessment 5 to 14 days after the end of the last study period.

**Variables:**

**Pharmacokinetic:** At each treatment visit, venous blood samples were collected prior to dosing and up to 24 hours postdose for the determination of serum concentrations of immunoreactive LANTUS®. To allow for correction of serum immunoreactive LANTUS® concentrations for endogenous insulin, each subject had samples taken for the analysis of C-peptide concentrations at the same time points as the PK samples.

**Pharmacodynamic:** The PD measurements were derived from the euglycemic clamp procedure, where the glucose infusion rate (GIR) over time is used as a measure of insulin effect.

**Safety:** Adverse events (AEs), concomitant medication monitoring, physical examinations, clinical laboratory tests, electrocardiograms (ECGs), body weight, and vital signs assessments.

**Evaluation Methods:**

**Bioanalytical:** Serum concentrations of immunoreactive LANTUS® were determined using a validated radioimmunoassay method.

**Pharmacokinetic:** For the primary analysis, serum concentrations of immunoreactive LANTUS® were corrected using C-peptide data. Specifically, LANTUS® serum concentrations were calculated as the difference between immunoreactive LANTUS® and endogenous insulin. The term “immunoreactive LANTUS®” refers to the uncorrected concentration of LANTUS® (i.e. the raw data obtained from the bioanalytical assay). Note that for brevity, concentrations of immunoreactive LANTUS® are subsequently referred as “insulin” concentrations in this report. All PK analyses and plots presented in this report are based on insulin concentrations that have been corrected for endogenous insulin, unless clearly stated otherwise.

Pharmacokinetic parameter estimates for EU- and US-approved LANTUS® were calculated by standard noncompartmental methods of analysis. The primary parameters for PK analysis for both EU- and US-approved LANTUS® were area under the concentration versus time curve (AUC) from time zero to 24 hours (AUC[0-24]) and maximum observed drug concentration ( $C_{max}$ ). Secondary PK parameters included AUC from time zero to time t, where t is the last time point with a measurable concentration (AUC[0- $t_{last}$ ]) and AUC from zero to infinity (AUC[0- $\infty$ ]). Other PK parameters that were estimated include: time of  $C_{max}$  ( $t_{max}$ ), apparent total body clearance of drug calculated after extra-vascular administration (CL/F), half-life associated with the terminal rate constant in noncompartmental analysis ( $t_{1/2}$ ), and volume of distribution during the terminal phase after extra-vascular administration ( $V_z/F$ ).

**Pharmacodynamic:** A locally weighted scatterplot smoothing (LOESS) function was applied to all individual GIR versus time profiles in each treatment group using TIBCO Spotfire S+® 8.2 for Windows software. The fitted data for each subject were used to calculate the primary PD parameters: maximum GIR ( $R_{max}$ ) and total amount of glucose infused ( $G_{tot}$ ). A secondary PD parameter, the time of  $R_{max}$  ( $TR_{max}$ ), was calculated using the LOESS function. Raw (that is, observed) GIR values from each clamp procedure were used to calculate the other secondary PD parameters, such as the time of first change of GIR postdose ( $T_{onset}$ ), the time of last measurable GIR ( $T_{last}$ ), and the value of last measurable GIR ( $GIR_{last}$ ).

**Safety:** Adverse events, clinical laboratory parameters, and vital signs were summarized using standard descriptive statistics.

**Pharmacokinetic statistical analysis:** Log-transformed AUC(0-24) and  $C_{max}$  were evaluated with a linear mixed effects model including subject as a random effect with period, sequence, and treatment as fixed effects. For each PK parameter, the difference in least squares (LS) means along with the 90% confidence interval (CI) were back transformed to produce the ratio of geometric means and the CI comparing EU-approved LANTUS® to US-approved LANTUS®. Pharmacokinetic similarity was to be concluded if the 90% CIs for both AUC(0-24) and  $C_{max}$  were completely contained within the interval of 0.80 to 1.25. Within- and between-subject variability were reported for each PK parameter. Similar statistical analyses of log-transformed secondary PK parameters AUC(0-∞) and AUC(0- $t_{last}$ ) were conducted. A nonparametric approach was taken to evaluate  $t_{max}$ , using the Wilcoxon signed-rank test. The difference in median  $t_{max}$  between treatments and the 95% CIs for the differences were presented.

An additional analysis was performed for the primary PK parameters, AUC(0-24) and  $C_{max}$ , as well as the secondary parameters, which included only the PK data obtained from subjects who completed all 4 periods of the study and had evaluable PK in those periods. The model used for this analysis included period, sequence, treatment, and subject nested within sequence as fixed effects; no random effects were included.

**Pharmacodynamic statistical analysis:** Log-transformed  $R_{max}$  and  $G_{tot}$  estimates were evaluated with a linear mixed effects model including subject as a random effect and period, sequence, and treatment as fixed effects. For all PD parameters, the difference in LS means along with the 90% CI were back transformed to produce the ratio of geometric means and the CI comparing EU-approved LANTUS® to US-approved LANTUS®.

Pharmacodynamic comparability was to be concluded if the 90% CI was contained completely within the interval of 0.80 to 1.25. The analysis was repeated using the same model with a corresponding 95% CI.

Within- and between- subject variability were reported for each PD parameter. An additional analysis was performed for the primary PD parameters,  $G_{tot}$  and  $R_{max}$ , to include only the data obtained from subjects who completed all 4 periods of the study. The model used for this analysis included period, sequence, treatment, and subject nested within sequence as fixed effects; no random effects were included.

**Summary:**

**Disposition:**

Of the 40 subjects who entered the study, 34 subjects completed the study in accordance with the protocol. Six subjects did not complete the study: 2 subjects (Subjects 0115 and 0124) were withdrawn due to subject decision, and 4 subjects (Subjects 0116, 0121, 0122, and 0140) were withdrawn due to physician decision.

**Pharmacokinetics:**

Following SC administration of a single 0.5 U/kg dose, the C-peptide corrected serum insulin concentration profiles were similar between EU-approved LANTUS® and US-approved LANTUS®, with peak concentration reached at 12 hours (median) for both treatments. Based on statistical comparisons of AUCs and  $C_{max}$ , the PK was demonstrated to be similar between EU-approved LANTUS® and US-approved LANTUS®, with ratios of LS geometric means of 0.98 and 0.99 for AUC(0-24) and  $C_{max}$ , respectively. The 90% CIs for these parameters were completely contained within the prespecified interval 0.8 to 1.25, confirming similarity in the PK between EU-approved LANTUS® and US-approved LANTUS®. Results for the secondary PK parameters AUC(0-∞) and AUC(0- $t_{last}$ ) also support the conclusion of similarity.

An additional analysis was performed to meet the requirements of European Medicines Agency (EMA) guidance, in which only data from subjects who completed all 4 periods of the study and had evaluable PK data for all 4 periods were included. The conclusion of similarity is confirmed for the primary parameters AUC(0-24) and  $C_{max}$ , with the 90% CIs completely contained within the interval 0.8 to 1.25. Results for the secondary parameters confirm the conclusion of similarity.

**Pharmacodynamics:**

Following single SC injections of 0.5 U/kg EU-approved LANTUS® and US-approved LANTUS®, the mean and 90% CI band of the smoothed mean GIR versus time profiles and the corresponding glucose levels were essentially overlapping. The statistical comparisons of  $G_{tot}$  and  $R_{max}$  demonstrated similarity in the PD between EU-approved LANTUS® and US-approved LANTUS® with the ratios of LS geometric means of 1.00 and 0.97, respectively. The 90% CIs for the primary parameters were completely contained within the prespecified interval 0.8 to 1.25, confirming similarity in the PD parameters between EU-approved LANTUS® and US-approved LANTUS®.

An additional analysis was performed in which only data from subjects who completed all 4 periods of the study were included. The conclusion of similarity is confirmed for the primary parameters  $G_{tot}$  and  $R_{max}$ , with the 90% CIs completely contained within the interval 0.8 to 1.25.

**Safety:**

No AEs were considered to be related to the study drug by the investigator. A total of 98 treatment-emergent AEs were reported during the study. All treatment-emergent AEs were considered by the investigator to be unrelated to study drug, with 69 (70.4%) related to study procedures and 29 (29.6%) related to “other medical condition.” All reported AEs were mild in severity and were mostly procedural complications.

There were no changes in the clinical chemistry, hematology, urinalysis, or ECG data for individual subjects during the study that were considered clinically significant by the investigator.

There were no changes in supine pulse rate, systolic blood pressure, or diastolic blood pressure during the study that were considered clinically significant by the investigator. Fluctuations in systolic blood pressure and pulse rate were noted during the study, but these were consistent with those expected due to clamp procedures and natural diurnal variation.

**Conclusions:**

- The PK of EU-approved LANTUS® was demonstrated to be similar to that of US-approved LANTUS®, with the 90% CIs of the ratio of geometric means of the 2 treatments contained within the prespecified interval of (0.8, 1.25).
- The PD of EU-approved LANTUS® was demonstrated to be similar to that of US-approved LANTUS®, with the 90% CIs for the ratio of geometric means of the 2 treatments contained within the prespecified interval of (0.8, 1.25).
- The safety profiles of EU-approved LANTUS® and US-approved LANTUS® were comparable with regard to AEs, and there were no changes in the clinical laboratory, vital signs, or ECG parameters during the study that were considered clinically significant by the investigator.

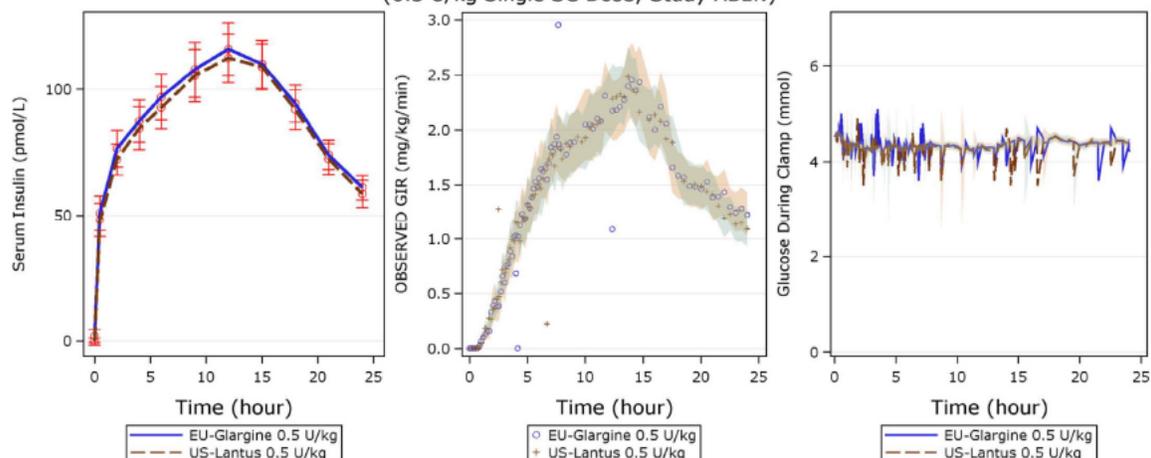
**Reviewer’s Analysis and Comments:**

The study was reasonable in design and conduct to meet the intended objective. There were no noteworthy protocol deviations during the study.

However, considering the nature of independent comparison of PK and PD parameters from insulin PKPD studies, it is highly important and desirable to include PK and PD data that has minimum confounding factors and has mutual support from each other (i.e., both PK and PD are available from same patient).

Therefore, the individual level PK and PD profiles were evaluated graphically to identify any confounded data. After ensuring the absence of any confounded data, the results from the reviewer’s analysis of PK and PD data confirmed the PK similarity conclusions for baseline corrected data ( $C_{max}$  and  $AUC_{0-24h}$ ) and PD similarity conclusions ( $GIR_{max}$  and  $AUC_{GIR0-24h}$ ) in reference to the sponsor’s analysis. In addition, total insulin and endogenous (suppression effect) were also similar between EU-Glargine and US-Lantus.

Mean(SE) Insulin Glargine, and Mean (90 % CI) Glucose Infusion Rate, Mean (90 % CI) Glucose - Time Plots (0.5 U/kg Single SC Dose; Study ABEN)



**Statistical Comparison of Insulin PK Parameters (Study ABEN)**

Comparison	PK Parameter	Units	Ratio(%)	90% CI
US-Lantus 0.5U/kg vs. EU-Glargine 0.5U/kg	Total Insulin AUC0-t	pmol.hr/L	100.57	93.86 - 107.76
	Total Insulin Cmax	pmol/L	100.77	94.11 - 107.91
	Endogenous Insulin AUC0-t	pmol.hr/L	105.93	94.87 - 118.29
	Endogenous Insulin Cmax	pmol/L	108.22	99.34 - 117.9
	Baseline Adjusted Insulin AUC0-t	pmol.hr/L	99.26	91.42 - 107.77
	Baseline Adjusted Insulin Cmax	pmol/L	98.61	90.89 - 106.98

**Statistical Comparison of Insulin PD Parameters (Study ABEN)**

Comparison	PD Parameter	Units	Ratio(%)	90% CI
EU-Glargine 0.5 U/kg vs. Lantus-0.5 U/kg	Observed GIR AUC0-t	mg/kg	105.88	91.42 - 122.62
	Observed GIR AUC0-12h	mg/kg	92.34	74.41 - 114.58
	Observed GIRmax	mg/kg/hr	106.23	94.95 - 118.86
	Smoothed GIR AUC0-t	mg/kg	105.88	91.42 - 122.62
	Smoothed GIR AUC0-12h	mg/kg	92.34	74.41 - 114.58
	Smoothed GIRmax	mg/kg/hr	106.23	94.95 - 118.86

#### 4.1.4 PKPD Study ABEM (Dose-response of LY2963016 versus EU-Glargine)

<b>Title of Study:</b> Pharmacokinetics and Pharmacodynamics of LY2963016 Compared to LANTUS® in Healthy Subjects following Two Single Subcutaneous Doses	
<b>Number of Investigators:</b> This single-center study included 1 principal investigator.	
<b>Study Center:</b> This study was conducted at 1 study center in 1 country.	
<b>Publications Based on the Study:</b> None at this time.	
<b>Length of Study:</b> Date of first subject visit: 09 July 2012 Date of last subject completed: 21 September 2012	<b>Phase of Development:</b> 1
<p><b>Objectives:</b> The primary objective of the study was:</p> <ul style="list-style-type: none"> <li>To compare the pharmacokinetics (PK) of LY2963016 and LANTUS® in healthy subjects following administration of single subcutaneous (SC) doses of 0.3 and 0.6 U/kg.</li> </ul> <p>The secondary objectives of the study were:</p> <ul style="list-style-type: none"> <li>To compare the pharmacodynamics (PD) of LY2963016 and LANTUS® in healthy subjects following the administration of single SC doses of 0.3 and 0.6 U/kg.</li> <li>To assess the safety and tolerability of LY2963016 when administered to healthy subjects.</li> </ul> <p>Note: LANTUS® is the registered trademark of Sanofi Aventis. The comparator product is marketed under the trade name LANTUS® in the European Union (EU) and the United States. In this study, the comparator was EU-approved LANTUS® (EU-approved insulin glargine). For the purposes of this report, the comparator product will be referred to as LANTUS®.</p>	
<b>Study Design:</b> This was a randomized, subject- and investigator-blind, 4-treatment, 4-period, crossover, euglycemic clamp study. Subjects were randomly assigned to 1 of 4 dosing sequences and received a total of 2 doses (0.3 and 0.6 U/kg) each of LY2963016 and LANTUS® on 1 occasion each.	
<p><b>Number of Subjects:</b> Planned: Up to 28 subjects to ensure 20 subjects completed the study Randomized and treated (at least 1 dose): 24 subjects Completed: 23 subjects</p>	
<b>Diagnosis and Main Criteria for Inclusion:</b> Subjects were required to be overtly healthy, with no history of first-degree relatives known to have diabetes mellitus, and between the ages of 21 and 65 years, inclusive, with a body mass index between 18.5 and 29.9 kg/m <sup>2</sup> , inclusive, at screening.	
<b>Study Drug, Dose, and Mode of Administration:</b> LY2963016 was supplied as 100-U/mL solution in a cartridge (lot number CT573598). LY2963016 U-100 was administered SC as 0.3- and 0.6-U/kg doses using a 30 gauge × 8 mm needle.	
<b>Reference Therapy, Dose, and Mode of Administration:</b> European Union-approved LANTUS® was supplied as 100-U/mL solution in a cartridge (lot number CT574589). LANTUS® U-100 was administered SC as 0.3- and 0.6-U/kg doses using a 30 gauge × 8 mm needle.	

**Pharmacokinetic statistical analyses:** Log-transformed AUC(0-24) and  $C_{max}$  estimates were analyzed using a linear mixed effects model with period, sequence, and treatment as fixed effects and subject as a random effect. For each PK parameter, the difference in least squares (LS) means along with the 90% confidence interval (CI) was back transformed to produce the ratio of geometric means and the CI comparing LY2963016 to LANTUS<sup>®</sup> at 0.3 U/kg and at 0.6 U/kg. Within-subject coefficient of variation (CV%) for each insulin was reported. A similar statistical analysis was performed for log-transformed secondary PK parameters AUC(0-∞) and AUC(0-t<sub>last</sub>). A nonparametric approach was taken to evaluate t<sub>max</sub>. Medians were presented along with the median difference between LY2963016 and LANTUS<sup>®</sup>. The approximate 90% CI for the median difference was also presented. The calculations were made using the SAS procedure PROC UNIVARIATE. The dose relationship was examined using a power model for LY2963016 and LANTUS<sup>®</sup> separately. The results were expressed as a ratio of dose-normalized means with 90% CIs.

**Pharmacodynamic statistical analyses:** Log-transformed R<sub>max</sub> and G<sub>tot</sub> were analyzed using a linear mixed effects model with period, sequence, and treatment as fixed effects and subject as a random effect. For each PD parameter, the difference in LS means along with the 90% CI was back transformed to produce the ratio of geometric means and the CI comparing LY2963016 to LANTUS<sup>®</sup> at 0.3 U/kg and at 0.6 U/kg. Within-subject CV% for each insulin was reported. Exploratory analyses for other PD parameters, including TR<sub>max</sub>, T<sub>onset</sub>, and T<sub>last</sub>, were also performed using a nonparametric approach. Medians were presented along with the median difference between LY2963016 and LANTUS<sup>®</sup>. The approximate 90% CI for the median difference was also presented. The calculations were made using the SAS procedure PROC UNIVARIATE. The dose relationship of R<sub>max</sub> and G<sub>tot</sub> was examined using a power model. The results were expressed as a ratio of dose-normalized means with 90% CIs.

**Summary:**

**Disposition:**

A total of 24 healthy subjects (20 males and 4 females) aged 23 to 52 years participated in the study. Of the 24 subjects who entered the study, 23 subjects received all 4 doses of study drug (LY2963016 and LANTUS<sup>®</sup>) and completed the study as planned. One subject (Subject 0118) withdrew from the study due to subject decision. She received 1 dose of 0.6 U/kg (37 IU) LY2963016 and 1 dose of 0.6 U/kg (37 IU) LANTUS<sup>®</sup> in Periods 1 and 2, respectively, before withdrawing. Of note, this subject was subsequently found to have anaemia, which resulted in hospitalization and was therefore documented as a serious AE (SAE).

**Pharmacokinetics:**

Following SC administration of a single dose, the mean C-peptide corrected insulin concentration versus time profiles were similar between LY2963016 and LANTUS<sup>®</sup> at each dose level (0.3 and 0.6 U/kg), with peak concentration reached at 9 to 12 hours (median) postdose for both treatments at both doses. The ratios of geometric LS means for the primary PK parameters, AUC(0-24) and  $C_{max}$ , following administration of LY2963016 versus LANTUS<sup>®</sup> were 1.03 for both parameters following a 0.3-U/kg dose, and 1.07 and 1.03, respectively, following a 0.6-U/kg dose. All the corresponding 90% CIs spanned 1 and were contained within the interval of (0.8, 1.25). Results for the secondary PK parameters, AUC(0-∞) and AUC(0-t<sub>last</sub>), were similar.

**Pharmacodynamics:**

Following single SC injections of LY2963016 and LANTUS<sup>®</sup>, the mean and 90% CI band of the smoothed mean GIR versus time profiles and the corresponding glucose levels were comparable at each dose level. The PD of LY2963016 was comparable to that of LANTUS<sup>®</sup>. The ratios of the geometric means for the primary PD parameters (R<sub>max</sub> and G<sub>tot</sub>) following administration of LY2963016 versus LANTUS<sup>®</sup> were 1.04 and 0.98, respectively, following a 0.3-U/kg dose, and 0.94 and 0.87, respectively, following a 0.6-U/kg dose. All the associated 90% CIs contained 1. In addition, statistical analysis of PD time parameters indicated no statistically significant differences between LY2963016 and LANTUS<sup>®</sup>, with the 90% CIs for the median differences of the secondary PD parameters – T<sub>onset</sub>, TR<sub>max</sub>, and T<sub>last</sub> – including 0 at each dose level.

**Safety:**

One SAE of anaemia was reported during the study, which was not considered by the investigator to be related to study treatment. A total of 58 treatment-emergent AEs were reported by a total of 20 (83.3%) subjects, of which 16 AEs in 5 (20.8%) subjects were considered by the investigator to be related to study treatment. Of the 42 treatment-emergent AEs that were not considered by the investigator to be drug-related, 27 (64.3%) were considered by the investigator to be related to study procedures (e.g. procedural pain [8 AEs in 6 subjects], application site haematoma [7 AEs in 6 subjects], and post procedural swelling [7 AEs in 6 subjects]). All AEs reported as drug-related were considered by the investigator to be mild in severity. The most common AEs considered related to study drug by the investigator were vomiting (5 events in 2 subjects) and dizziness (2 events in 2 subjects).

The total number of AEs considered to be drug-related by the investigator reported across all dose levels was similar following treatment with LY2963016 compared with LANTUS®, although small differences between the dose levels of LY2963016 were observed.

There were no changes in the clinical chemistry, hematology, or urinalysis data for individual subjects during the study that were considered clinically significant by the investigator, with the exception of 1 subject (Subject 0118) who experienced an SAE of anaemia. During her early discontinuation assessments, Subject 0118 was found to have values below the lower limit of the reference range for erythrocyte count (RBC) and hemoglobin. This was recorded as an SAE of anaemia (considered secondary to menorrhagia) and was not considered by the investigator to be related to study drug. The anaemia resolved after approximately 44 days.

There were no changes in supine pulse rate, systolic blood pressure, or diastolic blood pressure values during the study that were considered clinically significant by the investigator. Fluctuations in systolic blood pressure and pulse rate were noted during the study, but these were consistent with those expected due to clamp procedures and natural diurnal variation. There were no changes in ECG parameters for individual subjects during the study that resulted in AEs.

**Conclusions:**

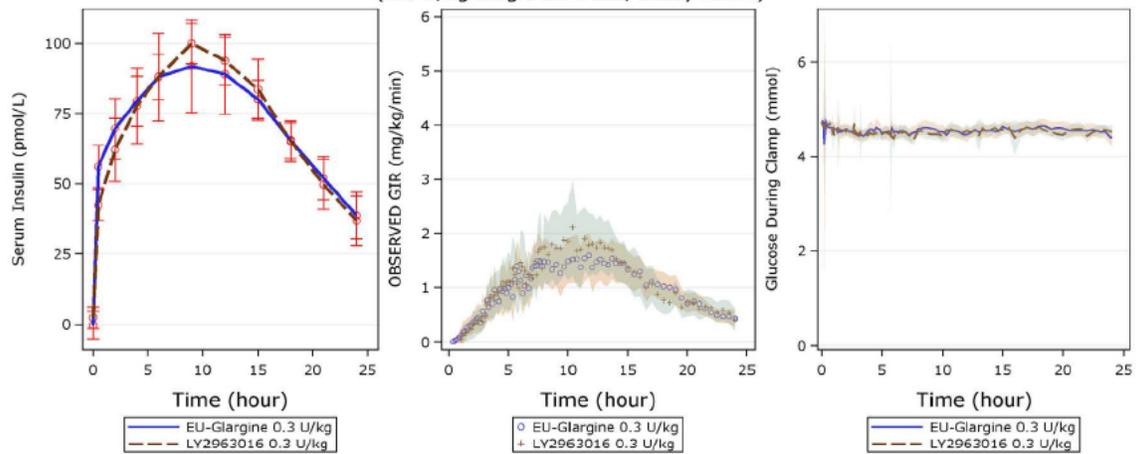
- The PK of LY2963016 was demonstrated to be similar to that of LANTUS® at both 0.3 and 0.6 U/kg. The ratios of the geometric means for the primary PK parameters, AUC(0-24) and C<sub>max</sub>, ranged from 1.03 to 1.07. No statistically significant differences in PK between LY2963016 and LANTUS® were detected.
- The PD of LY2963016 was demonstrated to be similar to that of LANTUS® at both 0.3 and 0.6 U/kg. The ratios of the geometric means for the primary PD parameters, R<sub>max</sub> and G<sub>tot</sub>, ranged from 0.87 to 1.04. No statistically significant differences in PD between LY2963016 and LANTUS® were detected.
- Single doses of 0.3 and 0.6 U/kg LY2963016 and LANTUS® were well tolerated by the healthy subjects in this study and no safety concerns were identified.

**Reviewer's Analysis and Comments:**

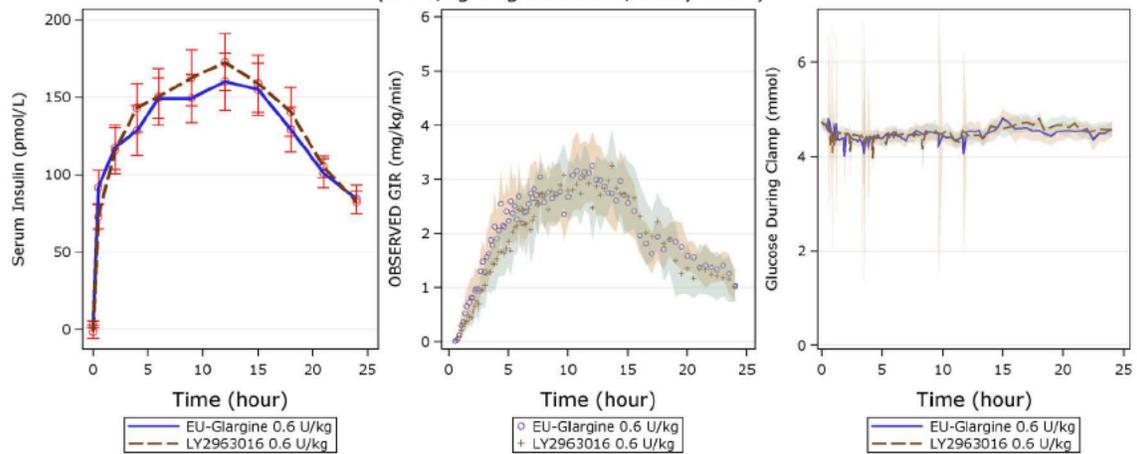
The study was reasonable in design and conduct to meet the intended objective. The protocol deviations during the study did not impact the study results. Due to human error, some of the investigational product retention samples (LY2963016 and LANTUS®) were exposed to temperatures of -6.1°C to -5.5°C and -3.3°C to -3.0°C, respectively, for a duration of 30 minutes during packaging of the samples for transit shipment. According to the protocol these were supposed to be stored under refrigeration (2°C to 8°C) and any LY2963016 or LANTUS® that has been allowed to freeze must be discarded. Accordingly, these samples were destroyed.

The results from the reviewer's analysis of PK and PD data confirmed the PK conclusions for baseline corrected data (C<sub>max</sub> and AUC<sub>0-24h</sub>) and PD conclusions for GIR<sub>max</sub> and AUC<sub>GIR0-24h</sub> in reference to the sponsor's analysis.

Mean(SE) Insulin Glargine, and Mean (90 % CI) Glucose Infusion Rate, Mean (90 % CI) Glucose - Time Plots (0.3 U/kg Single SC Dose; Study ABEM)



Mean(SE) Insulin Glargine, and Mean (90 % CI) Glucose Infusion Rate, Mean (90 % CI) Glucose - Time Plots (0.6 U/kg Single SC Dose; Study ABEM)



**Statistical Comparison of Insulin PK Parameters (Study ABEM)**

<b>Comparison</b>	<b>PK Parameter</b>	<b>Units</b>	<b>Ratio(%)</b>	<b>90% CI</b>
LY2963016-0.3 U/kg vs. Lantus-0.3 U/kg	Total Insulin AUC0-t	pmol.hr/L	103.77	94.95 - 113.42
	Total Insulin Cmax	pmol/L	105.72	94.39 - 118.41
	Endogenous Insulin AUC0-t	pmol.hr/L	111.19	95.8 - 129.06
	Endogenous Insulin Cmax	pmol/L	110.49	95.69 - 127.58
	Baseline Adjusted Insulin AUC0-t	pmol.hr/L	104.1	94.83 - 114.27
	Baseline Adjusted Insulin Cmax	pmol/L	102.88	90.93 - 116.4
LY2963016-0.6 U/kg vs. LY2963016-0.3 U/kg	Total Insulin AUC0-t	pmol.hr/L	159.67	149.04 - 171.07
	Total Insulin Cmax	pmol/L	147.93	131.77 - 166.06
	Endogenous Insulin AUC0-t	pmol.hr/L	96.39	82.2 - 113.02
	Endogenous Insulin Cmax	pmol/L	104.31	88.79 - 122.53
	Baseline Adjusted Insulin AUC0-t	pmol.hr/L	181.38	168.9 - 194.77
	Baseline Adjusted Insulin Cmax	pmol/L	166.59	148.24 - 187.21
LY2963016-0.6 U/kg vs. Lantus-0.6 U/kg	Total Insulin AUC0-t	pmol.hr/L	107.6	95.45 - 121.3
	Total Insulin Cmax	pmol/L	106.26	95.5 - 118.24
	Endogenous Insulin AUC0-t	pmol.hr/L	119.1	101.17 - 140.21
	Endogenous Insulin Cmax	pmol/L	115.83	100.81 - 133.09
	Baseline Adjusted Insulin AUC0-t	pmol.hr/L	107	93.61 - 122.31
	Baseline Adjusted Insulin Cmax	pmol/L	103.5	91.77 - 116.73
Lantus-0.6 U/kg vs. Lantus-0.3 U/kg	Total Insulin AUC0-t	pmol.hr/L	153.99	130.95 - 181.09
	Total Insulin Cmax	pmol/L	147.16	121.68 - 177.98
	Endogenous Insulin AUC0-t	pmol.hr/L	89.99	73.05 - 110.87
	Endogenous Insulin Cmax	pmol/L	99.49	84.79 - 116.74
	Baseline Adjusted Insulin AUC0-t	pmol.hr/L	176.45	148.74 - 209.33
	Baseline Adjusted Insulin Cmax	pmol/L	165.59	134.6 - 203.72

**Statistical Comparison of Insulin PD Parameters (Study ABEM)**

<b>Comparison</b>	<b>PD Parameter</b>	<b>Units</b>	<b>Ratio(%)</b>	<b>90% CI</b>
LY2963016-0.3 U/kg vs. Lantus-0.3 U/kg	Observed GIR AUC0-t	mg/kg	103.45	64.82 - 165.09
	Observed GIR AUC0-12h	mg/kg	138.01	61.56 - 309.42
	Observed GIRmax	mg/kg/min	108.48	76.51 - 153.79
	Smoothed GIR AUC0-t	mg/kg	103.34	64.8 - 164.81
	Smoothed GIR AUC0-12h	mg/kg	138.04	61.52 - 309.73
	Smoothed GIRmax	mg/kg/min	107.14	74.88 - 153.29
LY2963016-0.6 U/kg vs. LY2963016-0.3 U/kg	Observed GIR AUC0-t	mg/kg	203.4	130.4 - 317.26
	Observed GIR AUC0-12h	mg/kg	205.17	113.04 - 372.37
	Observed GIRmax	mg/kg/min	161.23	116.24 - 223.62
	Smoothed GIR AUC0-t	mg/kg	203.42	130.51 - 317.07
	Smoothed GIR AUC0-12h	mg/kg	205.25	113.24 - 372.03
	Smoothed GIRmax	mg/kg/min	164.21	117.81 - 228.88
LY2963016-0.6 U/kg vs. Lantus-0.6 U/kg	Observed GIR AUC0-t	mg/kg	86.95	62.84 - 120.3
	Observed GIR AUC0-12h	mg/kg	82.43	53.7 - 126.53
	Observed GIRmax	mg/kg/min	93.22	71 - 122.38
	Smoothed GIR AUC0-t	mg/kg	87.02	62.9 - 120.38
	Smoothed GIR AUC0-12h	mg/kg	82.55	53.81 - 126.63
	Smoothed GIRmax	mg/kg/min	93.97	71.7 - 123.18
Lantus-0.6 U/kg vs. Lantus-0.3 U/kg	Observed GIR AUC0-t	mg/kg	242	169.33 - 345.86
	Observed GIR AUC0-12h	mg/kg	343.53	170.66 - 691.5
	Observed GIRmax	mg/kg/min	187.62	139.11 - 253.05
	Smoothed GIR AUC0-t	mg/kg	241.58	169.06 - 345.2
	Smoothed GIR AUC0-12h	mg/kg	343.22	170.22 - 692.04
	Smoothed GIRmax	mg/kg/min	187.22	138.24 - 253.55

#### 4.1.5 PKPD Study ABEE (Duration of action: US-Lantus versus EU-Glargine)

<b>Title of Study:</b> Pharmacodynamics of LY2963016 Compared to LANTUS® in Subjects with Type 1 Diabetes Mellitus	
<b>Number of Investigators:</b> This single-center study included 1 principal investigator.	
<b>Study Center:</b> This study was conducted at 1 study center in 1 country.	
<b>Publications Based on the Study:</b> None at this time.	
<b>Length of Study:</b> Date of first subject visit: 23 May 2012 Date of last subject completed: 18 July 2012	<b>Phase of Development:</b> 1
<p><b>Objectives:</b> The primary objective of the study was:</p> <ul style="list-style-type: none"> <li>To assess the duration of action of LY2963016 compared to LANTUS® in subjects with type 1 diabetes mellitus (T1DM).</li> </ul> <p>The secondary objectives of this study were:</p> <ul style="list-style-type: none"> <li>To compare the pharmacokinetics (PK) of LY2963016 and LANTUS® in subjects with T1DM.</li> <li>To compare additional glucodynamic parameters of LY2963016 to LANTUS® in subjects with T1DM.</li> </ul> <p>Note: The comparator product is marketed under the trade name LANTUS® in the European Union (EU) and the United States. In this study, the comparator was EU-approved LANTUS® (EU-approved insulin glargine). For the purposes of this report, the comparator product will be referred to as LANTUS®.</p>	
<p><b>Study Design:</b> This was a randomized, investigator- and subject-blind, single-dose, 2-period, 2-sequence, crossover, 42-hour euglycemic clamp study in subjects with T1DM. A single 0.3 U/kg subcutaneous (SC) dose of either LY2963016 or LANTUS® was administered during each period according to a randomly allocated treatment sequence.</p>	
<p><b>Number of Subjects:</b> Planned: 20 subjects to ensure that at least 16 subjects completed the study Randomized and treated (at least 1 dose): 20 subjects Completed: 20 subjects</p>	
<p><b>Diagnosis and Main Criteria for Inclusion:</b> Subjects were required to be males or females between the ages of 18 and 60 years, inclusive, with a body mass index <math>\leq 29</math> kg/m<sup>2</sup> who had been diagnosed with T1DM for <math>\geq 1</math> year prior to screening. Subjects were also required to have a hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) value <math>\leq 10.0\%</math> and a fasting C-peptide value <math>\leq 0.3</math> nmol/L at screening.</p>	
<p><b>Study Drug, Dose, and Mode of Administration:</b> LY2963016 was supplied as 100-U/mL solution in a cartridge (lot number CT571839). LY2963016 was administered SC as a 0.3-U/kg dose using a 30 gauge <math>\times</math> 8 mm needle.</p>	
<p><b>Reference Therapy, Dose, and Mode of Administration:</b> EU-approved LANTUS® was supplied as 100-U/mL solution in a cartridge (lot number 0F050A). LANTUS® was administered SC as a 0.3-U/kg dose using a 30 gauge <math>\times</math> 8 mm needle.</p>	

**Duration of Treatment:**

Subjects were admitted to the clinical research unit (CRU) on Day 1 of each period. On Day 1 of each study period, subjects underwent a euglycemic clamp procedure up to 6 hours prior to LY2963016 or LANTUS® dosing and continued this procedure up to 42 hours postdose. Following completion of the clamp procedure on Day 3, subjects remained in the CRU until a post-clamp safety evaluation was performed. There was a 7- to 21-day washout between each study period. Subjects returned for a follow-up visit 7 to 14 days after the end of Period 2.

**Variables:**

Pharmacokinetic: Venous blood samples were collected predose and up to 42 hours postdose to determine the serum concentrations of immunoreactive LY2963016 and immunoreactive LANTUS®, and up to 15 hours postdose to determine serum concentrations of insulin lispro.

Pharmacodynamic: The pharmacodynamic (PD) parameters were derived from the euglycemic clamp procedure, where the glucose infusion rate (GIR) over time was used as a measure of insulin effect.

Safety: Safety was assessed by recording of adverse events (AEs), concomitant medications monitoring, physical examinations, clinical laboratory tests, electrocardiograms (ECGs), body weight, and vital signs measurements.

**Evaluation Methods:**

Bioanalytical: Serum concentrations of immunoreactive LY2963016 or immunoreactive LANTUS® were determined using a validated radioimmunoassay (RIA) method. Serum concentrations of insulin lispro were also determined using a validated RIA method.

Pharmacokinetic: Insufficient concentration data were available for PK analysis due to multiple serum concentrations being below the quantifiable lower limit of the assay (BQL; lower limit of quantification of 50 pM) for immunoreactive LY2963016 or immunoreactive LANTUS®. Serum concentration data available were summarized with concentration versus time plots for LY2963016 and LANTUS® at the mean level and for each individual. Given the possible confounding effect of lispro on the PK of LY2963016 and LANTUS® at the early time points (due to inconsistent cross-reactivity of the RIA with insulin lispro), mean concentration-time plots with and without correction for the lispro concentrations were generated and compared.

Pharmacodynamic: The time profiles of GIR and blood glucose concentration were recorded during each clamp for each individual following administration of LY2963016 or LANTUS®. The primary variable of interest was the duration of action, which was defined as the period of time elapsed between dose administration and the time at which the subject's blood glucose was >150 mg/dL (8.3 mmol/L) without any glucose infusion for 5 consecutive glucose readings (end of action). The blood glucose measurements of the Biostator (for the automatic clamps) were recalibrated at regular intervals (at least every 30 minutes) by external blood glucose measurements performed with a laboratory method (Super GL Glucose Analyzer, (b) (4)). Blood glucose profiles determined by the Super GL Glucose Analyzer were considered more reliable and less variable and were therefore used for the estimation of end of action for each subject. A locally weighted scatterplot smoothing function (with a smoothing factor that ranged from 0.075 to 0.2) was applied to all individual GIR versus time profiles in each treatment group using TIBCO Spotfire S+® software (Version 8.2, Insightful Corp., Seattle, WA, USA). The fitted GIR-time profiles were used to calculate several other PD parameters, including total glucose infusion over the clamp duration ( $G_{tot}$ ), maximum glucose infusion rate ( $R_{max}$ ), time of  $R_{max}$  ( $TR_{max}$ ), time to 50% maximal GIR before  $TR_{max}$  (early  $TR_{max50\%}$ ), time to 75% maximal GIR after  $TR_{max}$  (late  $TR_{max75\%}$ ), and time to 50% maximal GIR after  $TR_{max}$  (late  $TR_{max50\%}$ ). Time of last measurable GIR ( $T_{last}$ ) and value of last measurable GIR ( $GIR_{last}$ ) were estimated from the raw (unfitted) GIR profiles.

Safety: Adverse events were listed and summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Concomitant medications, clinical laboratory data, vital signs, ECG data, and body weight were listed.

profiles summarized with data corrected for the lispro concentrations and the uncorrected profiles, suggesting the impact of lispro on the LY2963016 and LANTUS® concentration profiles was low.

#### **Pharmacodynamics:**

Following single SC injections of 0.3 U/kg, the mean and 90% CI band of the smoothed GIR profiles and the corresponding blood glucose profiles were comparable between LY2963016 and LANTUS® over the 42-hour clamps.

To address the primary objective of the study, a linear mixed-effects model and a time-to-event (survival) analysis that allows for censored observations were applied. As expected, some subjects did not reach the end of action by the end of their 42-hour clamps. Specifically, 7 subjects in the LY2963016 treatment period and 7 subjects in the LANTUS® treatment period did not reach the end of action. Among them, 4 subjects did not reach the end of action for either treatment. There was a substantial number (35%) of clamps that were terminated at 42 hours, before the end of action was reached. The summary of the duration of action events showed similar durations between LY2963016 and LANTUS®. The median duration of action was estimated to be 37.1 and 40.0 hours for LY2963016 and LANTUS®, respectively, while mean duration of action was 23.8 and 25.5 hours for LY2963016 and LANTUS®, respectively.

The survival curves for LY2963016 and LANTUS® appear to be similar over the 42-hour clamp interval (log-rank test of equality with p-value = 0.859), where ‘survival’ means the subject’s blood glucose did not rise to 150 mg/dL (8.3 mmol/L). For the primary endpoint (duration of action), the hazard ratio (LY2963016/LANTUS®) was 1.063 with a p-value = 0.8777, supporting the earlier finding that there does not appear to be a difference in the duration of action between LY2963016 and LANTUS®. In a secondary analysis, the duration of action following the LY2963016 dose was compared with that following LANTUS® using a linear mixed-effects model. The mean duration for LY2963016 was estimated to be 0.45 hour shorter than for LANTUS®, with a 95% CI of (-10.45, 9.55). Statistical analysis of key PD parameters ( $G_{tot}$  and  $R_{max}$ ) generated ratios of geometric means for LY2963016 versus LANTUS® (90% CI) of 0.77 (0.46, 1.30) and 0.91 (0.52, 1.61), respectively.

#### **Safety:**

A total of 5 subjects reported a total of 9 treatment-emergent AEs (TEAEs), all of which were considered to be unrelated to study drug by the investigator. All reported TEAEs were mild (7 AEs) or moderate (2 AEs) in severity. There were no changes in the clinical laboratory parameters or ECG data for individual subjects during the study that were considered clinically significant by the investigator.

There were no changes in supine pulse rate, systolic blood pressure, or diastolic blood pressure values during the study that were considered clinically significant by the investigator.

One subject experienced a hypoglycemic event (defined as a blood glucose reading of  $\leq 63$  mg/dL [3.5 mmol/L]) after dosing in Period 2. The subject received 0.3 U/kg LANTUS® in Period 2. Approximately 2 days later (after completion of the clamp procedure), between bedtime and breakfast, a blood glucose value of 30 mg/dL (1.7 mmol/L) was recorded for the subject. The event was not considered by the investigator to be severe, and the subject was unaware he was hypoglycemic. Although the subject was capable of treating himself, because he was still resident in the CRU and he still had a venous catheter in place from the clamp procedure at the time of the event, the investigator chose for convenience to infuse intravenous glucose to treat the event. The subject did not have any AEs associated with this event.

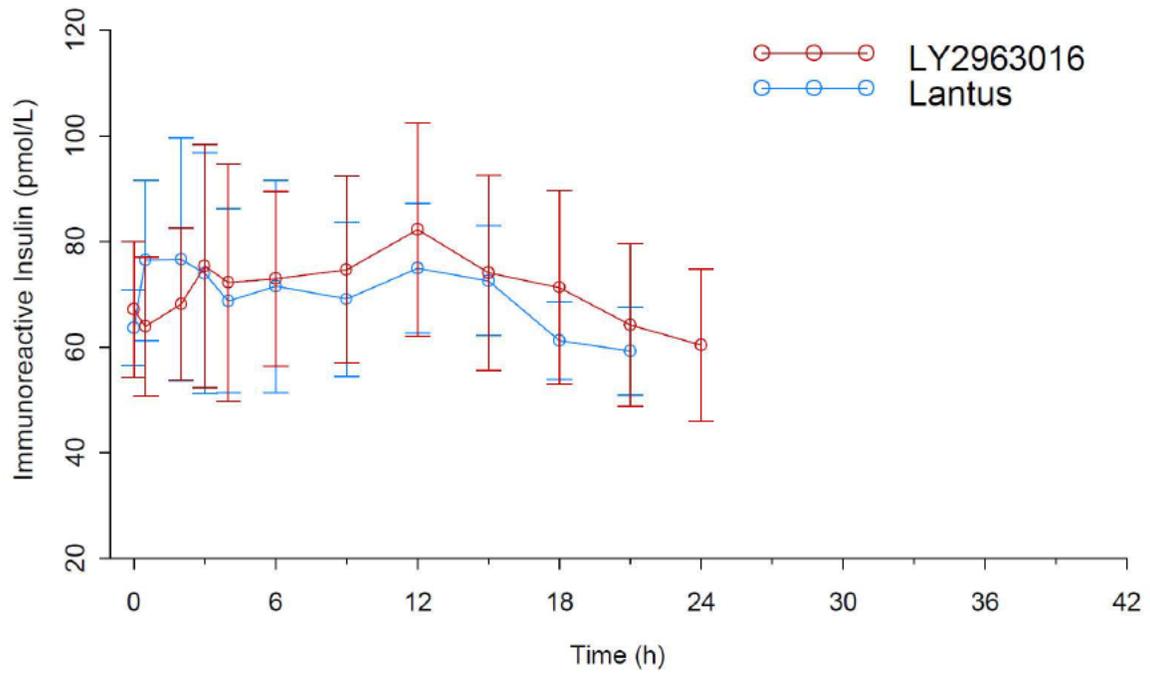
#### **Conclusions:**

- A similar duration of action was demonstrated following a single 0.3 U/kg dose in subjects with T1DM; the median duration of action was 37.1 and 40.0 hours for LY2963016 and LANTUS®, respectively.
- During a 42-hour glucose clamp procedure,  $R_{max}$  and  $G_{tot}$  appeared comparable between LY2963016 and LANTUS® following a single 0.3 U/kg dose in subjects with T1DM.
- Pharmacokinetic profiles appeared to be comparable between LY2963016 and LANTUS® based on visual comparison of the available PK data at a single dose of 0.3 U/kg in subjects with T1DM.

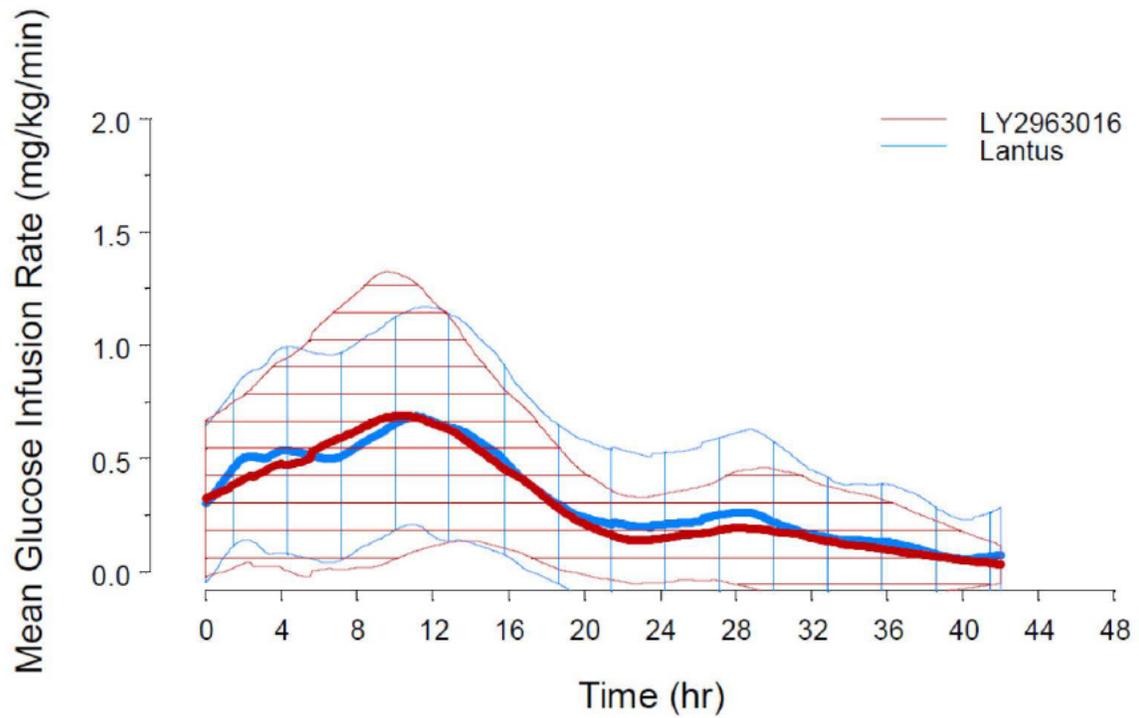
#### **Reviewer’s Analysis and Comments:**

The study was reasonable in design and conduct to meet the intended objective. PK profile comparison over 24 hours limits the utility of PK data in interpreting the 42 hour clamp PD data. In addition, this study was designed as 42 hour clamp in order to capture the complete duration of action of the exogenously administered insulin, and to compare it to reference. There were no protocol deviations during the study.

**PK:**



**PD:**



## 4.2 OCP Filing Memo

<b>Office of Clinical Pharmacology</b>				
<i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
	Information		Information	
NDA/BLA Number	205692		Brand Name	(b) (4)
OCP Division (I, II, III, IV, V)	II		Generic Name	Insulin glargine [rDNA origin]
Medical Division	DMEP		Drug Class	Anti-hyperglycemic
OCP Reviewer	Manoj Khurana, Ph.D.		Indication(s)	To improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus
OCP Team Leader	Lokesh Jain, Ph.D.		Dosage Form	For injection in a disposable delivery device
Pharmacometrics Reviewer	-		Dosing Regimen	Individualized
Date of Submission	10/18/2013		Route of Administration	Sub-cutaneous injection
Estimated Due Date of OCP Review	07/18/2014		Sponsor	Eli Lilly and Company
Medical Division Due Date			Priority Classification	505 (b)(2) Standard
PDUFA Due Date	08/18/2014		Relevant IND	IND 105423
<b>Clinical Pharmacology and Biopharmaceutics Information</b>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Nos./Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
<b>Human Biomaterials:</b>				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I)				
<b>Healthy Volunteers-</b>				
single dose:				
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
<i>in-vivo</i> effects on primary drug:				
<i>in-vivo</i> effects of primary drug:				
<i>in-vitro</i> :				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement

geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD -</b>				
Phase 1:				
Phase 2:				
Phase 3:	X	2		Study ABEB (T1DM) Study ABEC (T2DM)
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:	X	5		LY2963016 vs. US-approved LANTUS® (Study ABEO*). LY2963016 to EU-Insulin Glargine (Study ABEA). US-approved LANTUS® to EU-Insulin Glargine (Study ABEN*). Duration of LY2963016 action compared to EU-Insulin Glargine (Study ABEE). PK/PD response of 2 doses of LY2963016 compared to EU-Insulin Glargine (Study ABEM).
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>				
<b>Bio-waiver request based on BCS</b>				
<b>BCS class</b>				
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		7		

**\*Pivotal PKPD Similarity Studies**

**Note:** For all 5 PKPD studies, electronic raw data and S-plus programs have been submitted.



All drug substance lots were manufactured in Lilly Indianapolis. The drug product cartridge presentation was manufactured in Lilly France; the drug product vial presentation was manufactured in Lilly Indianapolis. Both drug product presentations used the commercial formulation, which was filled into 3 mL glass cartridges ( (b) (4) batch size) (b) (4).

Country of manufacture (of the finished medicinal product) for LANTUS® (insulin glargine [rDNA] injection) or EU-sourced Insulin Glargine used in clinical trials was reportedly, Germany and France (Sponsor’s Table APP.2.7.1.4.7, page 18, Appendix 2.7.1.4 summary-biopharm-app).

**Table 1. Overview of Clinical Studies Supporting US Submission**

Study Alias	Objective	Study Population	Number of Subjects Randomized	Relevance of CP Studies (Regulatory)	
<b>Phase 1 Studies</b>					
ABEO	Comparison of the PK and PD of LY2963016 and US-approved LANTUS®	Healthy subjects	91	Pivotal PKPD Similarity for approval	
ABEA	Comparison of the PK and PD of LY2963016 and EU-approved LANTUS®	Healthy subjects	80		
ABEN <sup>a</sup>	Comparison of the PK and PD of EU- and US-approved LANTUS®	Healthy subjects	40	Pivotal PKPD Similarity for scientific bridge	
ABEI	Relative bioavailability of LY2963016 to EU-approved LANTUS®	Healthy subjects	16		
ABEE	Comparison of the PD of LY2963016 and EU-approved LANTUS®	Patients with T1DM	20	Supportive PKPD	
ABEM	Relative bioavailability of LY2963016 to EU-approved LANTUS®	Healthy subjects	24		
<b>Phase 3 Studies</b>					
ABEB	Comparison of LY2963016 with LANTUS® (EU- and US-approved), as measured by change in HbA1c, when each is used in combination with premeal insulin lispro	Patients with T1DM (open-label)	536		
			LY2963016: 269 LANTUS®: 267 (US-approved: 96/ EU-approved: 171)		
ABEC	Comparison of LY2963016 with LANTUS® (EU- and US-approved), as measured by change in HbA1c, when each is used in combination with OAMs	Patients with T2DM (double-blind)	759		
			LY2963016: 379 LANTUS®: 380 (US-approved: 215/ EU-approved: 165)		
Abbreviations: EU = European Union; HbA1c = hemoglobin A1c; OAM = oral antihyperglycemic medication; PD = pharmacodynamics; PK = pharmacokinetic; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; US = United States.					
<sup>a</sup> Study ABEN was a comparison of EU- and US-approved LANTUS®; no LY2963016 was administered.					
<b>Reviewer’s Comments:</b> As mentioned in the sponsor’s Table above, the sponsor has used the term “EU-approved LANTUS®” in their NDA submission. However, from a regulatory perspective a more appropriate description of “EU-sourced Insulin Glargine or EU-Insulin Glargine” has been used and reflected at various places in this filing review.					

**According to the sponsor:**

- LY2963016 is claimed to be a similar version of LANTUS® (insulin glargine [rDNA origin] injection), the listed reference medicinal product produced by Sanofi-Aventis (LANTUS® is a registered trademark of Sanofi-Aventis). (b) (4)

Based on the structural testing and comparison with published data, Lilly has established that LY2963016 drug product is similar to LANTUS®. Both LY2963016 and LANTUS® are claimed to be similar formulations. LY2963016 is a long-acting insulin analog indicated to improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. LY2963016 is intended to be administered as a subcutaneous injection and will be made available in a 3 mL cartridge sealed in a prefilled pen injector (KwikPen™).

- The data and results from the LY2963016 development program demonstrate the similarity of LY2963016 to LANTUS® with respect to structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and Phase 3 clinical safety and effectiveness. Further, these data demonstrate that there are no meaningful differences in the safety and efficacy of LY2963016 as compared to LANTUS®.

The similarity assessment comprised of the following components as reported by the sponsor:

**Analytical / CMC Assessment (Refer to the CMC Review for more details)**

The starting point for the assessment of similarity was a side-by-side analytical comparison of LY2963016 and LANTUS®. This comparison was made to the active protein molecule (referred to as the drug substance), as well as the formulated drug product, and it included an assessment of physical properties, bioactivity, purity, and product/process-related impurities. Based on the structural testing and comparison with published data, the sponsor claimed that LY2963016 drug substance is similar to insulin glargine. Physicochemical testing, bioassay testing, and stability studies of LY2963016 and LANTUS® also support this claim.

**Nonclinical Assessment (Refer to the Pharm-Tox Review for more details)**

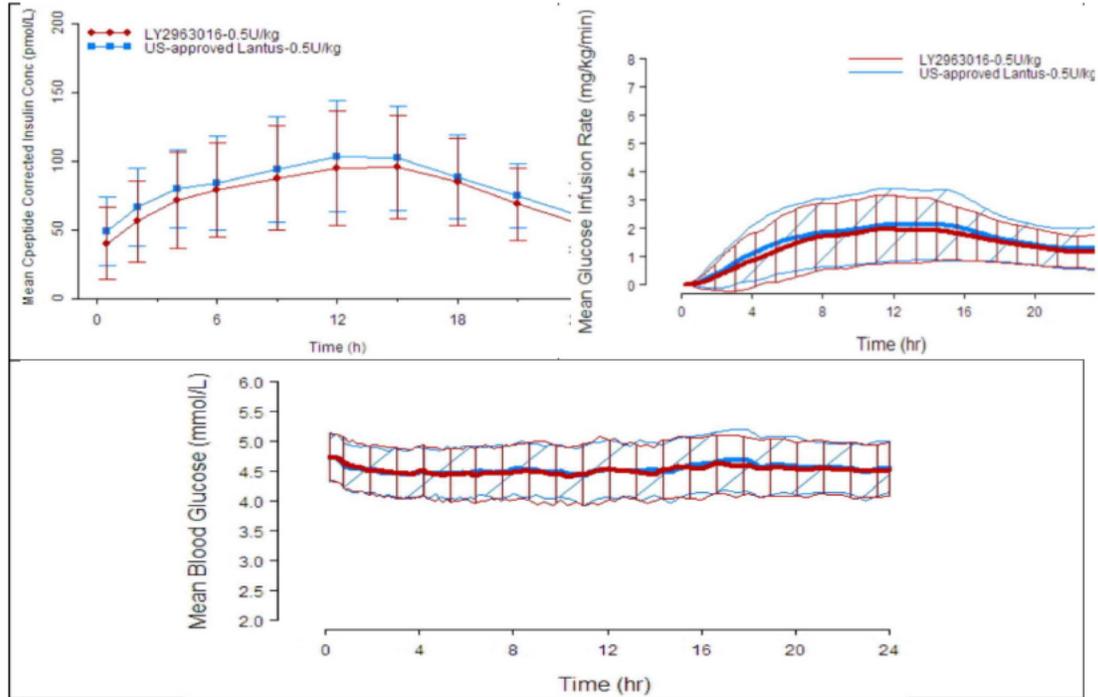
The goal of the nonclinical studies was to determine if LY2963016 and LANTUS® are similar with respect to in vitro (insulin and insulin-like growth factor-1 [IGF-1] receptor binding, metabolic potency and mitogenic potential) and in vivo (PK, glucodynamics, local tolerability, and toxicity profile) characteristics. The in vitro and in vivo evaluations did not identify any biologically meaningful difference between LY2963016 and LANTUS®, therefore sponsor concluded that the nonclinical program supported a finding of similarity.

**Clinical Assessment Tier 1**

The clinical evaluation of LY2963016 included comparative PK/PD, and multinational Phase 3 safety and efficacy information in both patients with T1DM and T2DM. Prior to initiating the comparative PK and PD studies and multinational Phase 3 studies, the sponsor conducted a pilot relative bioavailability (RBA) study (Study I4L-MC-ABEI [ABEI]) as its first administration of LY2963016 to human subjects to assess preliminary safety and tolerability. Results of this study supported further clinical investigation of LY2963016.

A fundamental component of the clinical development program was to establish that LY2963016 has PK and PD properties similar to LANTUS®. To that end, the sponsor conducted 3 comparative PK and PD studies (Study I4L-MC-ABEO [ABEO], I4L-MC-ABEA [ABEA], and I4L-MC-ABEN [ABEN]) to evaluate the PK and PD similarity of LY2963016 and LANTUS®, LY2963016 and EU-approved Insulin Glargine, and US-approved LANTUS® and EU-sourced Insulin Glargine, respectively.

The comparative PKPD results from the pivotal PKPD similarity study (LY2963016 (0.5 U/kg) and US-approved LANTUS® (0.5 U/kg) – Study ABEO) are presented in Figure 1 below:



**Figure 1.** Mean ( $\pm$  standard deviation) C-peptide-corrected serum insulin concentration (top left), mean (and 90% confidence interval) glucose infusion rate versus time profiles (top right) and the corresponding glucose levels (lower panel) following a single subcutaneous administration of LY2963016 (0.5 U/kg) and US-approved LANTUS® (0.5 U/kg) – Study ABEO.

Overview of key PKPD Results is presented below in Tables 2 and 3.

**Table 2. Least-Squares Geometric Mean Ratios and 90% Confidence Intervals for the Primary PK and PD Parameters across Studies ABEO, ABEA, and ABEN**

Study	Dose (U/kg)	Ratio of LS Geometric Means <sup>a,b</sup> (90% Confidence Interval)			
		Pharmacokinetic Parameters		Pharmacodynamic Parameters	
		AUC <sub>(0-24)</sub> (pmol·hr/L)	C <sub>max</sub> (pmol/L)	G <sub>tot</sub> (mg/kg)	R <sub>max</sub> (mg/kg/min)
ABEO	0.5	0.90 (0.86, 0.94)	0.92 (0.87, 0.96)	0.91 (0.85, 0.98)	0.93 (0.88, 0.98)
ABEA		0.91 (0.87, 0.96)	0.95 (0.90, 1.00)	0.95 (0.91, 1.00)	0.99 (0.94, 1.04)
ABEN		0.98 (0.91, 1.05)	0.99 (0.92, 1.06)	1.00 (0.89, 1.13)	0.97 (0.88, 1.07)

Abbreviations: AUC<sub>(0-24)</sub> = area under the serum concentration versus time curve from zero to 24 hours; C<sub>max</sub> = maximum serum concentration; G<sub>tot</sub> = total amount of glucose infused during the clamp procedure; LS = least-squares; PD = pharmacodynamics; PK = pharmacokinetic; R<sub>max</sub> = maximum glucose infusion rate during the clamp procedure.

<sup>a</sup>Ratio is Test/Reference where Test=LY2963016 and Reference=US-approved LANTUS® in Study ABEO; Test=LY2963016 and Reference= EU-sourced Insulin Glargine in Study ABEA; and Test=EU-sourced Insulin Glargine and Reference=US-approved LANTUS® in Study ABEN.

<sup>b</sup>In each study, analyses are based on subjects receiving at least 1 dose of study drug.

**Table 3. Least-Squares Geometric Mean Ratios and 90% Confidence Intervals for the Primary PK and PD Parameters Across Studies ABEI and ABEM**

		Ratio of LS Geometric Means <sup>a</sup> (90% Confidence Interval)			
		Pharmacokinetic Parameters		Pharmacodynamic Parameters	
Study	Dose	AUC <sub>(0-24)</sub> (pmol·hr/L)	C <sub>max</sub> (pmol/L)	G <sub>tot</sub> (mg/kg)	R <sub>max</sub> (mg/kg/min)
ABEI	0.5 U/kg	0.94 (0.83, 1.06)	0.93 (0.83, 1.04)	0.95 (0.74, 1.21)	0.94 (0.73, 1.20)
	0.3 U/kg	1.03 (0.91, 1.16)	1.03 (0.92, 1.15)	0.98 (0.78, 1.24)	1.04 (0.87, 1.25)
ABEM	0.6 U/kg	1.07 (0.95, 1.21)	1.03 (0.92, 1.16)	0.87 (0.70, 1.09)	0.94 (0.79, 1.12)

Abbreviations: AUC<sub>(0-24)</sub> = area under the serum concentration versus time curve from zero to 24 hours; C<sub>max</sub> = maximum serum concentration; G<sub>tot</sub> = total amount of glucose infused during the clamp procedure; LS = least-squares; R<sub>max</sub> = maximum glucose infusion rate during the clamp procedure.

<sup>a</sup>Ratio is Test/Reference where Test=LY2963016 and Reference=EU-sourced Insulin Glargine in studies ABEI and ABEM.

As per the sponsor, comparative PK and PD study results demonstrate similar PK and PD of LY2963016 to LANTUS®. The 90% confidence intervals (CIs) for the ratios of geometric means for PK (area under the serum concentration-time curve from time zero to 24 hours [AUC(0-24)] and maximum serum concentration [C<sub>max</sub>]) and PD (total amount of glucose infused during the euglycemic glucose clamp procedure [G<sub>tot</sub>], maximum glucose infusion rate [R<sub>max</sub>]) parameters in Study ABEO and ABEA were all contained within the predefined acceptance limits of 0.80 to 1.25.

Duration of Action comparison was conducted against EU-sourced Insulin Glargine. The results are summarized in Table 4 below:

**Table 4. Duration of Action Summary Statistics – Study ABEE All Subjects**

	LY2963016	EU-sourced Insulin Glargine
Number of Subjects	20	20
Number (%) of Events <sup>a</sup>	13 (65.0)	13 (65.0)
Number (%) of Censored Events <sup>b</sup>	7 (35.0)	7 (35.0)
<b>Duration of Action (hours)</b>		
Minimum	2.8	2.0
25 <sup>th</sup> Percentile (95% CI)	19.75 (7.00, 37.00)	19.50 (12.23, 39.50)
Median (95% CI)	37.13 (20.00, NA)	40.00 (20.00, NA)
Maximum <sup>c</sup>	40.5	41.5
Mean <sup>c</sup> (SE)	23.78 (3.75)	25.54 (3.91)

Abbreviations: CI = confidence interval; NA = not applicable due to censoring; SE = standard error.

**Note:** The xxth percentile of the survival time (duration of action) is the time beyond which (100-XX)% of the subjects in the treatment group are expected to survive (that is, subject's blood glucose has NOT risen to 150 mg/dL (8.3 mmol/L)).

<sup>a</sup> Each end of action observation was considered an 'event.'

<sup>b</sup> Censored events occurred when a subject's blood glucose did not rise to 150 mg/dL (8.3 mmol/L) within the 42-hour clamp period and the clamp was terminated at 42 hours per the procedures outlined in the protocol.

<sup>c</sup> Based on the 13 uncensored events only.

The mean duration of action for LY2963016 was approximately 0.45 hour shorter than for EU-sourced Insulin Glargine, with a 95% CI of -10.45 to 9.55 hour.

The sponsor's overall clinical pharmacology conclusions were as follows:

- **Pharmacokinetic Characteristics of LY2963016 and LANTUS<sup>®</sup>.** Following single SC doses of LY2963016 and LANTUS<sup>®</sup> in healthy subjects:
  - Serum concentrations increased gradually, indicating a slow, prolonged absorption with median  $t_{max}$  values ranging from 9.0 to 12.0 hours (0.3-, 0.5-, and 0.6-U/kg dose levels). The LY2963016  $t_{max}$  is comparable to that of LANTUS<sup>®</sup>.
  - The serum concentration-time profile was relatively flat and constant over 24 hours with geometric mean  $t_{1/2}$  values ranging from 9.4 to 11.6 hours (0.5- and 0.6-U/kg dose levels). The LY2963016  $t_{1/2}$  is comparable to that of LANTUS<sup>®</sup>.
- **Pharmacodynamic Characteristics of LY2963016 and LANTUS<sup>®</sup>.** Following single SC dose of LY2963016 and LANTUS<sup>®</sup>:
  - The GIR profile is relatively flat, with median  $TR_{max}$  values ranging from 9.1 to 13.6 hours in healthy subjects (0.3-, 0.5-, and 0.6-U/kg dose levels) and from 9.9 to 11.7 hours in subjects with T1DM (0.3-U/kg dose level). The LY2963016  $TR_{max}$  is comparable to that of LANTUS<sup>®</sup>.
  - In subjects with T1DM, both insulins displayed a similar duration of action (0.3-U/kg dose level).

These results, which demonstrate similar PK and PD characteristics for LY2963016 and the reference product LANTUS<sup>®</sup>, contribute to the totality of evidence for LY2963016 being a similar version of LANTUS<sup>®</sup>.

#### **Methodological Aspects and Bioanalytical Method:**

In all clinical pharmacology studies conducted in healthy subjects, the euglycemic clamp procedures were performed using a manual technique, that is, the glucose infusion rate (GIR) was manually adjusted based upon blood glucose measurements taken at regular intervals. In the duration of action Study I4L-MC-ABEE (ABEE) conducted in subjects with type 1 diabetes mellitus (T1DM), clamp procedures were performed using an automated procedure, that is, blood glucose was measured continuously, and the GIR was adjusted using a computerized feedback algorithm (Biostatator).

Bioanalytical portion of the clinical pharmacology studies (Serum Assay for Immunoreactive Insulin Glargine) was conducted at (b) (4). The bioanalytical method 8225343 was validated by (b) (4). The method for the measurement of immunoreactive insulin glargine in human serum is a competitive radioimmunoassay (RIA). This RIA measures "free" immunoreactive insulin glargine (that is, insulin and insulin analogs not bound to endogenous anti-insulin antibodies) in human serum.

The range of quantification is from 50 to 2000 pM. Dilutions up to 256-fold were validated. Calibrator points outside the validation range (15, 30, 4000 pM) were included to serve as anchor points to facilitate curve-fitting. In brief, samples, standards, and controls were extracted with 25% polyethylene glycol (PEG) to remove any pre-existing insulin glargine-antibody complexes. The extract supernatants were then mixed with anti-despentapeptide insulin (DPI) antibody and <sup>125</sup>I-insulin tracer. Immunoreactive insulin glargine in the samples, standards, or controls competed with the <sup>125</sup>I-insulin tracer for binding sites on the DPI antibody. Antibody-antigen complexes were precipitated, and the precipitate was pelleted by centrifugation. After decanting the supernatant, the resulting pellets were counted for radioactivity using a gamma counter. Immunoreactive insulin glargine in study samples was then determined by interpolation from the standard curve.

As expected with the use of a DPI antibody in an RIA assay, Method 8225343 demonstrates cross-reactivity to endogenous human insulin and insulin lispro. Method 8225343 showed similar precision and accuracy in the measurement of immunoreactive insulin glargine against a standard curve prepared using

LANTUS® (insulin glargine) as it did in the measurement of immunoreactive insulin glargine against a standard curve prepared using LY2963016.

An overview of Sites/Vendors used is presented below:

List and Description of OUS Research Facilities used in Study ABEO and ABEN:

Site Number	Primary Investigator Name	Research Facility Name and Address	Description of Research Facility
001	Dr Chew Lan Chong	Lilly-NUS Centre For Clinical Pharmacology Level 6 Clinical Research Centre (MD11) National University of Singapore 10 Medical Drive Singapore 117597	Clinical Research Facility

Abbreviations: NUS = National University of Singapore; OUS = outside the United States.

List and Description of OUS Research Facilities used in Study ABEE (T1DM, DOA):

Site Number	Primary Investigator Name	Research Facility Name and Address	Description of Research Facility
401		(b) (4)	Clinical Research Facility

Abbreviations: OUS = outside the United States.

List and Description of OUS Research Facilities used in Study ABEA:

Site No.	Primary Investigator Name	Research Facility Name and Address	Description of Research Facility
001		(b) (4)	Clinical Research Facility

Abbreviations: No. = number; OUS = outside the United States.

## Clinical Assessment Tier 2

Study ABEN demonstrated similar PK and PD of US-approved LANTUS® and EU-Insulin Glargine. The results of these 3 studies established a rationale and scientific bridge that formed the basis for presenting analyses of clinical efficacy and safety with a single comparator group comprising US-approved LANTUS® and EU-sourced Insulin Glargine for each multinational Phase 3 study.

Two Phase 3 clinical studies (1 double-blind, 24-week treatment study and 1 open-label, 52-week study (24-week treatment period and 28-week extension period) were conducted to evaluate the efficacy and safety profile of LY2963016 compared with LANTUS® and provide direct evidence of safety and efficacy of LY2963016. As mentioned earlier, the LANTUS® treatment arm of both Phase 3 trials included both US-approved and EU-sourced Insulin Glargine.

The support for this approach is based upon the establishment of a “scientific bridge” between US-approved and EU-sourced Insulin Glargine. Data from the two Phase 3 clinical studies provide evidence of equivalent efficacy by meeting the primary test of the non-inferiority of LY2963016 to LANTUS®, as well as the secondary, complementary test of the non-inferiority of LANTUS® to LY2963016 with respect to change in hemoglobin (HbA1c) after 24 weeks in patients with T1DM (Study I4L-MC-ABEB [ABEB]) and T2DM (Study I4L-MC-ABEC [ABEC]); in Study ABEB, the same equivalence criteria were met at the 52-week endpoint. In each of the Phase 3 studies, statistically significant reductions in HbA1c at endpoints were observed in both treatment groups compared with baseline with no significant differences in insulin dose. There were also no statistically significant differences between treatment groups for other secondary measures of efficacy including daily mean BG, fasting BG, and weight.

Clinical safety data from the Phase 3 studies demonstrate a similar safety profile (including immunogenicity, allergic reactions, and hypoglycemia) of LY2963016 relative to LANTUS®. Importantly, the development of anti-insulin glargine antibodies was not associated with any detrimental effect on efficacy and safety outcomes in patients with T1DM or T2DM.

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

Content Parameter		Yes	No	N/A	Comment
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

**Comment to Sponsor:**

**We are unable to run the S-Plus scripts for PKPD studies provided with the submission using the datasets indicated within the scripts (Note that we used SAS to read \*.xpt files and export as \*.csv files). For example, the "abee\_pd\_analysis.ssc" script, using the data-set "ABEE\_WNL\_PD\_29JAN2013\_O\_MOD.csv" does not run beyond the initial data read steps. Please recheck the submitted S-plus scripts and data-sets and provide clear instructions on any necessary steps that the reviewer need to follow in order to re-run your analyses.**

Manoj Khurana	19 Dec, 2013
Reviewing Clinical Pharmacologist	Date
Lokesh Jain	19 Dec, 2013
Team Leader/Supervisor	Date

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

MANOJ KHURANA  
07/21/2014

LOKESH JAIN  
07/21/2014

# Office of Clinical Pharmacology

## *New Drug Application Filing and Review Form*

### General Information About the Submission

	Information		Information
NDA/BLA Number	205692	Brand Name	(b) (4)
OCP Division (I, II, III, IV, V)	II	Generic Name	Insulin glargine [rDNA origin]
Medical Division	DMEP	Drug Class	Anti-hyperglycemic
OCP Reviewer	Manoj Khurana, Ph.D.	Indication(s)	To improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus
OCP Team Leader	Lokesh Jain, Ph.D.	Dosage Form	For injection in a disposable delivery device
Pharmacometrics Reviewer	-	Dosing Regimen	Individualized
Date of Submission	10/18/2013	Route of Administration	Sub-cutaneous injection
Estimated Due Date of OCP Review	07/18/2014	Sponsor	Eli Lilly and Company
Medical Division Due Date		Priority Classification	505 (b)(2) Standard
PDUFA Due Date	08/18/2014	Relevant IND	IND 105423

### *Clinical Pharmacology and Biopharmaceutics Information*

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Nos./Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Human Biomaterials:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I)				
<b>Healthy Volunteers-</b>				
single dose:				
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
in-vivo effects on primary drug:				
in-vivo effects of primary drug:				
in-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				

geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD -</b>				
Phase 1:				
Phase 2:				
Phase 3:	X	2		Study ABEB (T1DM) Study ABEC (T2DM)
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:	X	5		LY2963016 vs. US-approved LANTUS® (Study ABEO*). LY2963016 to EU-Insulin Glargine (Study ABEA). US-approved LANTUS® to EU-Insulin Glargine (Study ABEN*). Duration of LY2963016 action compared to EU-Insulin Glargine (Study ABEE). PK/PD response of 2 doses of LY2963016 compared to EU-Insulin Glargine (Study ABEM).
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
<b>III. Other CPB Studies</b>				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
<b>Total Number of Studies</b>		7		

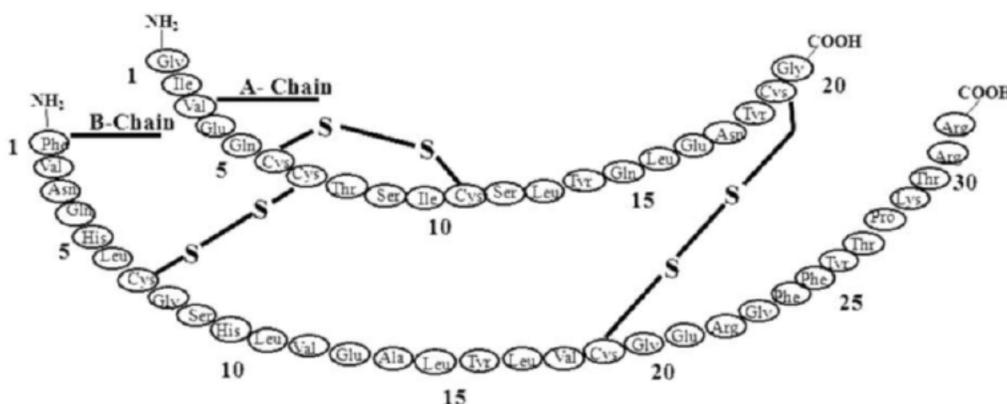
**\*Pivotal PKPD Similarity Studies**

**Note:** For all 5 PKPD studies, electronic raw data and S-plus programs have been submitted.

**Summary of the submission:**

Eli Lilly and Company (Lilly, the sponsor) has submitted this 505(b)(2) NDA 205692 for FDA review for (b) (4) (LY2963016) (b) (4) relying in part on FDA’s previous finding on efficacy and safety of LANTUS® and LANTUS® SoloSTAR® (Insulin Glargine [rDNA origin], NDA 021081).

LY2963016 is a long-acting human insulin analog, claimed to be highly similar in chemical composition to LANTUS® (insulin glargine [recombinant DNA origin] injection). LANTUS® is the registered trademark of Sanofi Aventis®.



**Figure 1. Structure of LY2963016**

LY2963016 is a 2-chain peptide containing 53 amino acids. The A-chain is composed of 21 amino acids and the B-chain is composed of 32 amino acids. LY2963016 has the same primary amino acid sequence as insulin glargine. As in human insulin, LY2963016 contains 2 interchain disulfide bonds and 1 intrachain disulfide bond. LY2963016 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. Due to the characteristics of the amino acid arginine, the isoelectric point of LY2963016 is shifted from 5.4 to approximately 6.8 when compared to human insulin, thus reducing the solubility of LY2963016 at physiological pH.

LY2963016 is presented as a 100-U/mL solution in a 3-mL prefilled pen, and was composed of LY2963016 and the following inactive ingredients: m-cresol, glycerin, zinc oxide, water for injection, hydrochloric acid, and sodium hydroxide. Sponsor mentioned that one LY2963016 formulation was used throughout clinical studies. The composition of the intended commercial formulation is as follows:

**Table 1. Composition of the intended commercial formulation**

Ingredient	Quantity/mL
LY2963016	100 Units (3.6378 mg)
Glycerin	17 mg
Metacresol	2.7 mg
Zinc Oxide	(b) (4)
Water for Injection	q.s. to 1 mL

Abbreviations: q.s. = quantity sufficient

All drug substance lots were manufactured in Lilly Indianapolis. The drug product cartridge presentation was manufactured in Lilly France; the drug product vial presentation was manufactured in Lilly Indianapolis. Both drug product presentations used the commercial formulation, which was filled into 3 mL glass cartridges ( (b) (4) batch size) (b) (4)

Country of manufacture (of the finished medicinal product) for LANTUS® (insulin glargine [rDNA] injection) or EU-sourced Insulin Glargine used in clinical trials was reportedly, Germany and France (Sponsor’s Table APP.2.7.1.4.7, page 18, Appendix 2.7.1.4 summary-biopharm-app).

**Table 1. Overview of Clinical Studies Supporting US Submission**

Study Alias	Objective	Study Population	Number of Subjects Randomized	Relevance of CP Studies (Regulatory)	
<b>Phase 1 Studies</b>					
ABEO	Comparison of the PK and PD of LY2963016 and US-approved LANTUS®	Healthy subjects	91	Pivotal PKPD Similarity for approval	
ABEA	Comparison of the PK and PD of LY2963016 and EU-approved LANTUS®	Healthy subjects	80	Supportive PKPD	
ABEN <sup>a</sup>	Comparison of the PK and PD of EU- and US-approved LANTUS®	Healthy subjects	40	Pivotal PKPD Similarity for scientific bridge	
ABEI	Relative bioavailability of LY2963016 to EU-approved LANTUS®	Healthy subjects	16	Supportive PKPD	
ABEE	Comparison of the PD of LY2963016 and EU-approved LANTUS®	Patients with T1DM	20		
ABEM	Relative bioavailability of LY2963016 to EU-approved LANTUS®	Healthy subjects	24		
<b>Phase 3 Studies</b>					
ABEB	Comparison of LY2963016 with LANTUS® (EU- and US-approved), as measured by change in HbA1c, when each is used in combination with premeal insulin lispro	Patients with T1DM (open-label)	536		
			LY2963016: 269 LANTUS®: 267 (US-approved: 96/ EU-approved: 171)		
ABEC	Comparison of LY2963016 with LANTUS® (EU- and US-approved), as measured by change in HbA1c, when each is used in combination with OAMs	Patients with T2DM (double-blind)	759		
			LY2963016: 379 LANTUS®: 380 (US-approved: 215/ EU-approved: 165)		
Abbreviations: EU = European Union; HbA1c = hemoglobin A1c; OAM = oral antihyperglycemic medication; PD = pharmacodynamics; PK = pharmacokinetic; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; US = United States.					
<sup>a</sup> Study ABEN was a comparison of EU- and US-approved LANTUS®; no LY2963016 was administered.					

**Reviewer’s Comments:** As mentioned in the sponsor’s Table above, the sponsor has used the term “EU-approved LANTUS®” in their NDA submission. However, from a regulatory perspective a more appropriate description of “EU-sourced Insulin Glargine or EU-Insulin Glargine” has been used and reflected at various places in this filing review.

**According to the sponsor:**

- LY2963016 is claimed to be a similar version of LANTUS® (insulin glargine [rDNA origin] injection), the listed reference medicinal product produced by Sanofi-Aventis (LANTUS® is a registered trademark of Sanofi-Aventis). (b) (4)  
Based on the structural testing and comparison with published data, Lilly has established that LY2963016 drug product is similar to LANTUS®. Both LY2963016 and LANTUS® are claimed to be similar formulations. LY2963016 is a long-acting insulin analog indicated to improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. LY2963016 is intended to be administered as a subcutaneous injection and will be made available in a 3 mL cartridge sealed in a prefilled pen injector (KwikPen™).

- The data and results from the LY2963016 development program demonstrate the similarity of LY2963016 to LANTUS® with respect to structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and Phase 3 clinical safety and effectiveness. Further, these data demonstrate that there are no meaningful differences in the safety and efficacy of LY2963016 as compared to LANTUS®.

The similarity assessment comprised of the following components as reported by the sponsor:

**Analytical / CMC Assessment (Refer to the CMC Review for more details)**

The starting point for the assessment of similarity was a side-by-side analytical comparison of LY2963016 and LANTUS®. This comparison was made to the active protein molecule (referred to as the drug substance), as well as the formulated drug product, and it included an assessment of physical properties, bioactivity, purity, and product/process-related impurities. Based on the structural testing and comparison with published data, the sponsor claimed that LY2963016 drug substance is similar to insulin glargine. Physicochemical testing, bioassay testing, and stability studies of LY2963016 and LANTUS® also support this claim.

**Nonclinical Assessment (Refer to the Pharm-Tox Review for more details)**

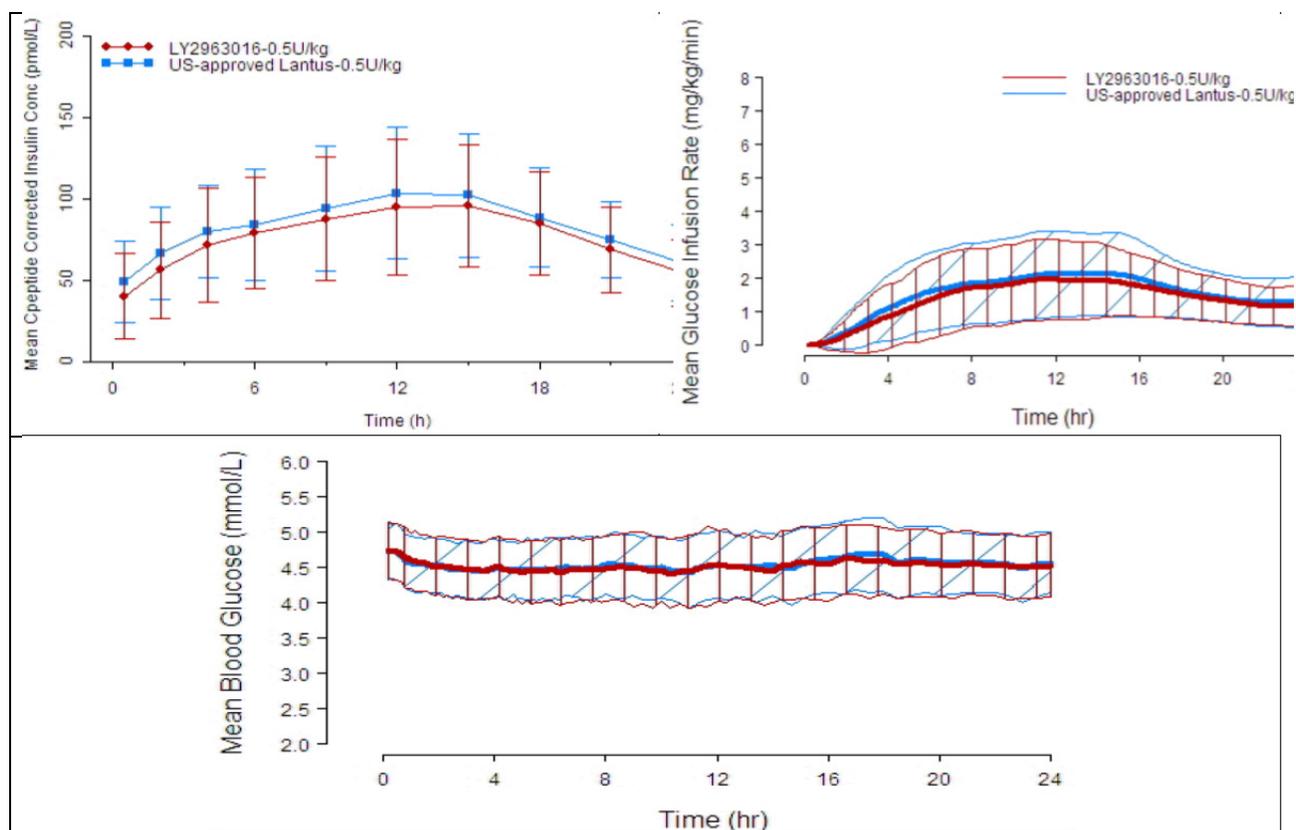
The goal of the nonclinical studies was to determine if LY2963016 and LANTUS® are similar with respect to in vitro (insulin and insulin-like growth factor-1 [IGF-1] receptor binding, metabolic potency and mitogenic potential) and in vivo (PK, glucodynamics, local tolerability, and toxicity profile) characteristics. The in vitro and in vivo evaluations did not identify any biologically meaningful difference between LY2963016 and LANTUS®, therefore sponsor concluded that the nonclinical program supported a finding of similarity.

**Clinical Assessment Tier 1**

The clinical evaluation of LY2963016 included comparative PK/PD, and multinational Phase 3 safety and efficacy information in both patients with T1DM and T2DM. Prior to initiating the comparative PK and PD studies and multinational Phase 3 studies, the sponsor conducted a pilot relative bioavailability (RBA) study (Study I4L-MC-ABEI [ABEI]) as its first administration of LY2963016 to human subjects to assess preliminary safety and tolerability. Results of this study supported further clinical investigation of LY2963016.

A fundamental component of the clinical development program was to establish that LY2963016 has PK and PD properties similar to LANTUS®. To that end, the sponsor conducted 3 comparative PK and PD studies (Study I4L-MC-ABEO [ABEO], I4L-MC-ABEA [ABEA], and I4L-MC-ABEN [ABEN]) to evaluate the PK and PD similarity of LY2963016 and LANTUS®, LY2963016 and EU-approved Insulin Glargine, and US-approved LANTUS® and EU-sourced Insulin Glargine, respectively.

The comparative PKPD results from the pivotal PKPD similarity study (LY2963016 (0.5 U/kg) and US-approved LANTUS® (0.5 U/kg) – Study ABEO) are presented in Figure 1 below:



**Figure 1. Mean ( $\pm$  standard deviation) C-peptide-corrected serum insulin concentration (top left), mean (and 90% confidence interval) glucose infusion rate versus time profiles (top right) and the corresponding glucose levels (lower panel) following a single subcutaneous administration of LY2963016 (0.5 U/kg) and US-approved LANTUS® (0.5 U/kg) – Study ABEO.**

Overview of key PKPD Results is presented below in Tables 2 and 3.

**Table 2. Least-Squares Geometric Mean Ratios and 90% Confidence Intervals for the Primary PK and PD Parameters across Studies ABEO, ABEA, and ABEN**

		Ratio of LS Geometric Means <sup>a,b</sup> (90% Confidence Interval)			
		Pharmacokinetic Parameters		Pharmacodynamic Parameters	
Study	Dose (U/kg)	AUC <sub>(0-24)</sub> (pmol·hr/L)	C <sub>max</sub> (pmol/L)	G <sub>tot</sub> (mg/kg)	R <sub>max</sub> (mg/kg/min)
ABEO	0.5	0.90 (0.86, 0.94)	0.92 (0.87, 0.96)	0.91 (0.85, 0.98)	0.93 (0.88, 0.98)
ABEA		0.91 (0.87, 0.96)	0.95 (0.90, 1.00)	0.95 (0.91, 1.00)	0.99 (0.94, 1.04)
ABEN		0.98 (0.91, 1.05)	0.99 (0.92, 1.06)	1.00 (0.89, 1.13)	0.97 (0.88, 1.07)

Abbreviations: AUC<sub>(0-24)</sub> = area under the serum concentration versus time curve from zero to 24 hours; C<sub>max</sub> = maximum serum concentration; G<sub>tot</sub> = total amount of glucose infused during the clamp procedure; LS = least-squares; PD = pharmacodynamics; PK = pharmacokinetic; R<sub>max</sub> = maximum glucose infusion rate during the clamp procedure.

<sup>a</sup>Ratio is Test/Reference where Test=LY2963016 and Reference=US-approved LANTUS® in Study ABEO; Test=LY2963016 and Reference= EU-sourced Insulin Glargine in Study ABEA; and Test=EU-sourced Insulin Glargine and Reference=US-approved LANTUS® in Study ABEN.

<sup>b</sup>In each study, analyses are based on subjects receiving at least 1 dose of study drug.

**Table 3. Least-Squares Geometric Mean Ratios and 90% Confidence Intervals for the Primary PK and PD Parameters Across Studies ABEI and ABEM**

		Ratio of LS Geometric Means <sup>a</sup> (90% Confidence Interval)			
		Pharmacokinetic Parameters		Pharmacodynamic Parameters	
Study	Dose	AUC <sub>(0-24)</sub> (pmol·hr/L)	C <sub>max</sub> (pmol/L)	G <sub>tot</sub> (mg/kg)	R <sub>max</sub> (mg/kg/min)
ABEI	0.5 U/kg	0.94 (0.83, 1.06)	0.93 (0.83, 1.04)	0.95 (0.74, 1.21)	0.94 (0.73, 1.20)
ABEM	0.3 U/kg	1.03 (0.91, 1.16)	1.03 (0.92, 1.15)	0.98 (0.78, 1.24)	1.04 (0.87, 1.25)
	0.6 U/kg	1.07 (0.95, 1.21)	1.03 (0.92, 1.16)	0.87 (0.70, 1.09)	0.94 (0.79, 1.12)

Abbreviations: AUC<sub>(0-24)</sub> = area under the serum concentration versus time curve from zero to 24 hours; C<sub>max</sub> = maximum serum concentration; G<sub>tot</sub> = total amount of glucose infused during the clamp procedure; LS = least-squares; R<sub>max</sub> = maximum glucose infusion rate during the clamp procedure.

<sup>a</sup>Ratio is Test/Reference where Test=LY2963016 and Reference=EU-sourced Insulin Glargine in studies ABEI and ABEM.

As per the sponsor, comparative PK and PD study results demonstrate similar PK and PD of LY2963016 to LANTUS®. The 90% confidence intervals (CIs) for the ratios of geometric means for PK (area under the serum concentration-time curve from time zero to 24 hours [AUC(0-24)] and maximum serum concentration [C<sub>max</sub>]) and PD (total amount of glucose infused during the euglycemic glucose clamp procedure [G<sub>tot</sub>], maximum glucose infusion rate [R<sub>max</sub>]) parameters in Study ABEO and ABEA were all contained within the predefined acceptance limits of 0.80 to 1.25.

Duration of Action comparison was conducted against EU-sourced Insulin Glargine. The results are summarized in Table 4 below:

**Table 4. Duration of Action Summary Statistics – Study ABEE All Subjects**

	LY2963016	EU-sourced Insulin Glargine
Number of Subjects	20	20
Number (%) of Events <sup>a</sup>	13 (65.0)	13 (65.0)
Number (%) of Censored Events <sup>b</sup>	7 (35.0)	7 (35.0)
<b>Duration of Action (hours)</b>		
Minimum	2.8	2.0
25 <sup>th</sup> Percentile (95% CI)	19.75 (7.00, 37.00)	19.50 (12.23, 39.50)
Median (95% CI)	37.13 (20.00, NA)	40.00 (20.00, NA)
Maximum <sup>c</sup>	40.5	41.5
Mean <sup>c</sup> (SE)	23.78 (3.75)	25.54 (3.91)

Abbreviations: CI = confidence interval; NA = not applicable due to censoring; SE = standard error.

**Note:** The xxth percentile of the survival time (duration of action) is the time beyond which (100-XX)% of the subjects in the treatment group are expected to survive (that is, subject's blood glucose has NOT risen to 150 mg/dL (8.3 mmol/L)).

<sup>a</sup> Each end of action observation was considered an 'event.'

<sup>b</sup> Censored events occurred when a subject's blood glucose did not rise to 150 mg/dL (8.3 mmol/L) within the 42-hour clamp period and the clamp was terminated at 42 hours per the procedures outlined in the protocol.

<sup>c</sup> Based on the 13 uncensored events only.

The mean duration of action for LY2963016 was approximately 0.45 hour shorter than for EU-sourced Insulin Glargine, with a 95% CI of -10.45 to 9.55 hour.

The sponsor's overall clinical pharmacology conclusions were as follows:

- **Pharmacokinetic Characteristics of LY2963016 and LANTUS<sup>®</sup>**. Following single SC doses of LY2963016 and LANTUS<sup>®</sup> in healthy subjects:
  - Serum concentrations increased gradually, indicating a slow, prolonged absorption with median  $t_{max}$  values ranging from 9.0 to 12.0 hours (0.3-, 0.5-, and 0.6-U/kg dose levels). The LY2963016  $t_{max}$  is comparable to that of LANTUS<sup>®</sup>.
  - The serum concentration-time profile was relatively flat and constant over 24 hours with geometric mean  $t_{1/2}$  values ranging from 9.4 to 11.6 hours (0.5- and 0.6-U/kg dose levels). The LY2963016  $t_{1/2}$  is comparable to that of LANTUS<sup>®</sup>.
- **Pharmacodynamic Characteristics of LY2963016 and LANTUS<sup>®</sup>**. Following single SC dose of LY2963016 and LANTUS<sup>®</sup>:
  - The GIR profile is relatively flat, with median  $TR_{max}$  values ranging from 9.1 to 13.6 hours in healthy subjects (0.3-, 0.5-, and 0.6-U/kg dose levels) and from 9.9 to 11.7 hours in subjects with T1DM (0.3-U/kg dose level). The LY2963016  $TR_{max}$  is comparable to that of LANTUS<sup>®</sup>.
  - In subjects with T1DM, both insulins displayed a similar duration of action (0.3-U/kg dose level).

These results, which demonstrate similar PK and PD characteristics for LY2963016 and the reference product LANTUS<sup>®</sup>, contribute to the totality of evidence for LY2963016 being a similar version of LANTUS<sup>®</sup>.

#### **Methodological Aspects and Bioanalytical Method:**

In all clinical pharmacology studies conducted in healthy subjects, the euglycemic clamp procedures were performed using a manual technique, that is, the glucose infusion rate (GIR) was manually adjusted based upon blood glucose measurements taken at regular intervals. In the duration of action Study I4L-MC-ABEE (ABEE) conducted in subjects with type 1 diabetes mellitus (T1DM), clamp procedures were performed using an automated procedure, that is, blood glucose was measured continuously, and the GIR was adjusted using a computerized feedback algorithm (Biostator).

Bioanalytical portion of the clinical pharmacology studies (Serum Assay for Immunoreactive Insulin Glargine) was conducted at (b) (4). The bioanalytical method 8225343 was validated by (b) (4). The method for the measurement of immunoreactive insulin glargine in human serum is a competitive radioimmunoassay (RIA). This RIA measures "free" immunoreactive insulin glargine (that is, insulin and insulin analogs not bound to endogenous anti-insulin antibodies) in human serum.

The range of quantification is from 50 to 2000 pM. Dilutions up to 256-fold were validated. Calibrator points outside the validation range (15, 30, 4000 pM) were included to serve as anchor points to facilitate curve-fitting. In brief, samples, standards, and controls were extracted with 25% polyethylene glycol (PEG) to remove any pre-existing insulin glargine-antibody complexes. The extract supernatants were then mixed with anti-despentapeptide insulin (DPI) antibody and <sup>125</sup>I-insulin tracer. Immunoreactive insulin glargine in the samples, standards, or controls competed with the <sup>125</sup>I-insulin tracer for binding sites on the DPI antibody. Antibody-antigen complexes were precipitated, and the precipitate was pelleted by centrifugation. After decanting the supernatant, the resulting pellets were counted for radioactivity using a gamma counter. Immunoreactive insulin glargine in study samples was then determined by interpolation from the standard curve.

As expected with the use of a DPI antibody in an RIA assay, Method 8225343 demonstrates cross-reactivity to endogenous human insulin and insulin lispro. Method 8225343 showed similar precision and accuracy in the measurement of immunoreactive insulin glargine against a standard curve prepared using

LANTUS® (insulin glargine) as it did in the measurement of immunoreactive insulin glargine against a standard curve prepared using LY2963016.

An overview of Sites/Vendors used is presented below:

List and Description of OUS Research Facilities used in Study ABEO and ABEN:

Site Number	Primary Investigator Name	Research Facility Name and Address	Description of Research Facility
001	Dr Chew Lan Chong	Lilly-NUS Centre For Clinical Pharmacology Level 6 Clinical Research Centre (MD11) National University of Singapore 10 Medical Drive Singapore 117597	Clinical Research Facility

Abbreviations: NUS = National University of Singapore; OUS = outside the United States.

List and Description of OUS Research Facilities used in Study ABEE (T1DM, DOA):

Site Number	Primary Investigator Name	Research Facility Name and Address	Description of Research Facility
401		(b) (4)	Clinical Research Facility

Abbreviations: OUS = outside the United States.

List and Description of OUS Research Facilities used in Study ABEA:

Site No.	Primary Investigator Name	Research Facility Name and Address	Description of Research Facility
001		(b) (4)	Clinical Research Facility

Abbreviations: No. = number; OUS = outside the United States.

**Clinical Assessment Tier 2**

Study ABEN demonstrated similar PK and PD of US-approved LANTUS® and EU-Insulin Glargine. The results of these 3 studies established a rationale and scientific bridge that formed the basis for presenting analyses of clinical efficacy and safety with a single comparator group comprising US-approved LANTUS® and EU-sourced Insulin Glargine for each multinational Phase 3 study.

Two Phase 3 clinical studies (1 double-blind, 24-week treatment study and 1 open-label, 52-week study (24-week treatment period and 28-week extension period) were conducted to evaluate the efficacy and safety profile of LY2963016 compared with LANTUS® and provide direct evidence of safety and efficacy of LY2963016. As mentioned earlier, the LANTUS® treatment arm of both Phase 3 trials included both US-approved and EU-sourced Insulin Glargine.

The support for this approach is based upon the establishment of a “scientific bridge” between US-approved and EU-sourced Insulin Glargine. Data from the two Phase 3 clinical studies provide evidence of equivalent efficacy by meeting the primary test of the non-inferiority of LY2963016 to LANTUS®, as well as the secondary, complementary test of the non-inferiority of LANTUS® to LY2963016 with respect to change in hemoglobin (HbA1c) after 24 weeks in patients with T1DM (Study I4L-MC-ABEB [ABEB]) and T2DM (Study I4L-MC-ABEC [ABEC]); in Study ABEB, the same equivalence criteria were met at the 52-week endpoint. In each of the Phase 3 studies, statistically significant reductions in HbA1c at endpoints were observed in both treatment groups compared with baseline with no significant differences in insulin dose. There were also no statistically significant differences between treatment groups for other secondary measures of efficacy including daily mean BG, fasting BG, and weight. Clinical safety data from the Phase 3 studies demonstrate a similar safety profile (including immunogenicity, allergic reactions, and hypoglycemia) of LY2963016 relative to LANTUS®. Importantly, the development of anti-insulin glargine antibodies was not associated with any detrimental effect on efficacy and safety outcomes in patients with T1DM or T2DM.

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

**Comment to Sponsor:**

**We are unable to run the S-Plus scripts for PKPD studies provided with the submission using the datasets indicated within the scripts (Note that we used SAS to read \*.xpt files and export as \*.csv files). For example, the “abee\_pd\_analysis.ssc” script, using the data-set “ABEE\_WNL\_PD\_29JAN2013\_O\_MOD.csv” does not run beyond the initial data read steps. Please recheck the submitted S-plus scripts and data-sets and provide clear instructions on any necessary steps that the reviewer need to follow in order to re-run your analyses.**

Manoj Khurana

19 Dec, 2013

Reviewing Clinical Pharmacologist

Date

Lokesh Jain

19 Dec, 2013

Team Leader/Supervisor

Date

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

MANOJ KHURANA  
12/20/2013

LOKESH JAIN  
12/20/2013