CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205692Orig1s000

MEDICAL REVIEW(S)

CDTL MEMO and CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205692
Priority or Standard	S
Submit Date(s)	18 Oct 2013
Received Date(s)	18 Oct 2013
PDUFA Goal Date	18 Aug 2014
Reviewer Name(s)	Lisa B. Yanoff, M.D.
Review Completion Date	Jul 2014
Established Name	Insulin glargine
Trade Name	Basaglar
Therapeutic Class	insulin
Applicant	Lilly Research Laboratories
Formulation(s)	Subcutaneous injection
Dosing Regimen	individualized
Indication(s)	(b) (4) of diabetes mellitus
Intended Population(s)	Adults and children with type 1 and type 2 diabetes mellitus

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1 Recommendations/Risk Benefit Assessment

The current application is for approval of Basaglar, an insulin glargine product. The Sponsor has submitted a 505(b)(2) application that relies, in part, for approval on FDA's finding of safety and effectiveness for the listed drug Lantus (insulin glargine [rDNA origin] injection).

1.1 Recommendation on Regulatory Action

I recommend tentative approval of this NDA pending agreement on labeling. Tentative approval is appropriate because this is a 505(b)(2) application that otherwise meets the requirements for approval under the Federal Food, Drug, and Cosmetic Act (FD&C Act), but cannot be approved until the expiration of a period of patent protection for the listed drug relied upon and the expiration of a 30-month stay of approval.

As noted above, this 505(b)(2) application for Basaglar relies, in part, on FDA's finding of safety and effectiveness for Lantus (insulin glargine [rDNA origin] injection). We are tentatively approving Basaglar with the established name "insulin glargine injection," consistent with current nomenclature practices for products approved under the FD&C Act.[1] The nonproprietary name of Basaglar and Lantus reflects certain scientific characteristics of these products. A deviation from current nonproprietary naming practices for products approved under the FD&C Act is not warranted for Basaglar at this time. We note, however, that nomenclature practices for biological products continue to be under review within FDA, and we will consider this issue again at such time as the Sponsor requests final approval of Basaglar.

1.2 Risk Benefit Assessment

The Sponsor has submitted a 505(b)(2) application that relies, in part, for approval on FDA's finding of safety and effectiveness for the listed drug Lantus. This reviewer concludes that the Sponsor has satisfactorily established that such reliance is scientifically justified. based on comparative physico-chemical tests and bioassay, nonclinical data, pharmacokinetic/pharmacodynamic data, and clinical data (including an assessment of immunogenicity)
Data from a clinical trial in type 1 diabetes patients and data from a double-blind add on to oral antidiabetes medications clinical trial in type 2 diabetes patients show that the safety and efficacy profile of Basaglar is similar to that of Lantus. Immunogenicity data suggest no important differences between Basaglar and Lantus.

The Sponsor included both US-approved Lantus and a non-US-approved insulin glargine product (EU approved Lantus) in comparator groups in these pivotal phase 3 studies. This is acceptable because the Sponsor has provided an adequate scientific bridge between US-approved Lantus and EU-approved Lantus based on CMC, Pharm/Tox and Clinical Pharmacology data. However,

1 Although this proposed product has a name that does not include the source of origin, this difference reflects a change in naming practice from when the previous insulin glargine product was approved (i.e., the listed drug) and is not intended to have any regulatory significance.

for the purposes of labeling the regulatory approval status of the comparator insulin glargine products should be noted, as FDA considers US-approved Lantus and EU-approved Lantus to be distinct products, and EU-approved Lantus is considered an investigational new drug in the U.S.

Nevertheless, the phase 3 studies had sufficient power to analyze the US-approved Lantus subgroups individually, and there were no clinically important differences from the entire study population noted.

1.3 Recommendations for Postmarket Risk Management Activities

None.

There is no current Risk Evaluation and Mitigation Strategy (REMS) for the listed drug Lantus and no safety concern that warrants a REMS for Basaglar.

1.4 Recommendations for Postmarket Studies/Clinical Trials

None.

Note that parenteral insulins are currently exempt from the requirement to conduct cardiovascular safety risk assessment studies.[2]

The Division determined that this application does not trigger the Pediatric Research Equity Act. Therefore, no pediatric studies under PREA are recommended.

2 Introduction and Regulatory Background

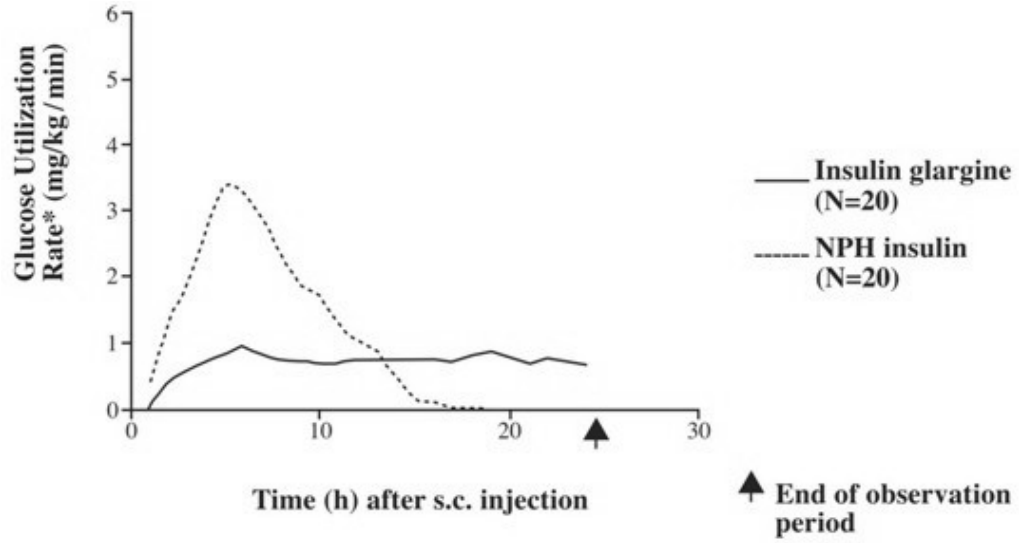
2.1 Product Information

Basaglar (also known as LY296306) is an insulin glargine product that relies, in part, on FDA's finding of safety and effectiveness for Lantus (insulin glargine [rDNA origin] injection), the listed drug produced by Sanofi-Aventis (Lantus is a registered trademark of Sanofi-Aventis). (b) (4) produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of Escherichia coli as the production organism.

Insulin glargine is a recombinant human insulin analog that is a long-acting parenteral blood-glucose-lowering agent. Glargine exhibits a relatively constant glucose-lowering profile over 24 hours that permits once-daily dosing (see figure below).

2 See Guidance for Industry - Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

Activity Profile of Lantus in Patients with Type 1 Diabetes



Insulin glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and two arginines are added to the C-terminus of the B-chain. These intended structural modifications cause a shift in the isoelectric point of the molecule (from a pH of 5.4 to 6.7), rendering it soluble at pH 4 (clear solution in the prescription vial) and significantly decreasing its solubility at physiological pH. Therefore, insulin glargine precipitates in the subcutaneous milieu after injection, stabilizing insulin hexamers, delaying their dissociation and allowing for slow, consistent absorption into the systemic circulation.

2.2 Tables of Currently Available Treatments for Proposed Indications

Patients with type 2 diabetes (T2DM) often undergo an initial trial of diet and exercise. If control is inadequate, a variety of oral agents are available. If adequate blood glucose control is not achieved with oral agents, subcutaneous insulin is often used.

Diabetes Therapies:

- Insulin and insulin analogs
- Sulfonylureas (SU)
- Biguanides
- Meglitinides
- Thiazolidinediones (TZDs)
- Inhibitors of alpha-glucosidase
- Analogues of Glucagon-like Peptide 1 (GLP-1)
- Synthetic analogues of human amylin
- Inhibitors of the enzyme dipeptidyl peptidase 4 (DPP4)
- Bile acid sequestrants
- Dopamine agonists
- SGLT-2 inhibitors

Type 1 diabetes (T1DM) is currently treated almost exclusively with subcutaneously administered insulin, which is available in a variety of formulations and analogs, with a spectrum of time-action profiles. Because Type 1 diabetics have virtually no residual pancreatic islet beta cell function, these patients depend on exogenously administered insulin for survival, and cannot be managed with diet and exercise alone. Patients generally receive one or two subcutaneous injections per day of a long-acting insulin as "basal" insulin, and take a short-acting subcutaneous insulin before each meal (prandial insulin). Continuous subcutaneous infusion via insulin pump of short-acting insulin, with mealtime boluses, is also used.

Pramlintide, an amylin analog, was approved as the first agent other than insulin for treatment of Type 1 diabetes, but pramlintide is an adjunct to mealtime insulin, rather than a substitute for subcutaneous insulin.

2.3 Availability of Proposed Active Ingredient in the United States

Lantus was approved on 20 Apr 2000 for once-daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

2.4 Important Safety Issues With Consideration to Related Drugs

Hypoglycemia is the most common adverse reaction of insulin. The risk of hypoglycemia increases with intensive glycemic control. Severe hypoglycemia can lead to unconsciousness or convulsions and may result in temporary or permanent impairment of brain function or death.

Immunogenicity is also a safety issue with insulins. All insulin products can elicit the formation of insulin antibodies. The presence of such insulin antibodies may increase or decrease the efficacy of insulin and may require adjustment of the insulin dose.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Extensive communication between the Sponsor and FDA occurred prior to the submission of this NDA. One particularly relevant issue is noted below.

Pre-NDA meeting between FDA and Sponsor on 28 Aug 2013
Minutes in DARRTS 27 Sep 2013; Reference ID: 3380666

Discussion: Lilly provided clarification that they used both US-approved Lantus and EU-approved insulin glargine as the active comparator in their clinical trials. Lilly informed FDA that the analysis of the 2 comparative clinical efficacy trials pooled clinical data from patients treated with either US-approved Lantus or EU-approved insulin glargine into one data set against which to compare Lilly's proposed product. Lilly did indicate that they were adequately powered for a non-inferiority margin of 0.4% in both trials for the comparison to US-approved Lantus; however, Lilly intends to provide this information as a subgroup analysis and has conducted their primary analysis against the "full data set" from patients treated with either the US or EU product. Lilly clarified that only US-approved Lantus and EU-approved insulin glargine were

used in the clinical studies. Specifically, only the US-approved Lantus was used in sites based in the US and Puerto Rico; at all other international sites, EU-approved insulin glargine was used in the clinical studies.

FDA reiterated that the advice about providing an adequate scientific bridge to justify the relevance of comparative data with a non-US-approved product in a Phase 3 trial was not intended to support the "pooling" of data regarding US-approved Lantus and EU-approved insulin glargine in a single study arm. FDA stated that based on the clarification provided by Lilly during the meeting that further internal discussion would need to occur before they could provide advice to Lilly on the acceptability of their analysis,

Post Meeting Comment: While the primary analysis may combine the US-approved Lantus and EU-approved insulin glargine data, differences between these two strata (e.g., test vs. reference by US vs. EU interaction) should be evaluated and submitted. The acceptability of Lilly's proposed primary analysis will be a review issue. FDA notes that Lilly's proposed approach involves some risk; for example, in the event that the subgroup analyses trend in different directions. In addition, FDA notes that any discussion of the combined analysis in product labeling, if necessary, would reflect the use of "insulin glargine" and "a non US-approved insulin glargine" in the comparator group.

2.6 Other Relevant Background Information

none

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission quality was acceptable.

Clinical investigator site inspections were conducted at three sites[3]; sites were selected for participation in both studies and large subject enrollment. No findings of regulatory or clinical significance were noted. Both study sites were found to be GCP-compliant; all findings (cited and not cited) were limited to minor isolated deficiencies unlikely to have a significant impact on the study outcome. The data from the inspected study sites appear reliable.

3.2 Compliance with Good Clinical Practices

The Sponsor states that the study was performed in compliance with Good Clinical Practices.

No independent data monitoring committee was appointed.

3 See Clinical Inspections Summary in DARRTS dated 23 Jun 14

There were no substantial protocol amendments for this protocol.

The Sponsor provided listings of protocol deviations. These did not appear to cluster among any one site and did not likely affect overall study integrity.

3.3 Financial Disclosures

There were no important reportable financial interests.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

An important efficacy/safety issue related to other review disciplines is demonstration of sufficient similarity between Basaglar and the listed drug Lantus to scientifically justify reliance, in part, on FDA's finding of safety and effectiveness for Lantus and use of the 505(b)(2) pathway for approval of this NDA. The 505(b)(2) approval pathway may be used for an insulin analog product that is demonstrated to be sufficiently similar to an approved product to permit reliance, where scientifically justified, on certain existing information (including FDA's finding of safety and/or effectiveness for an approved drug product) for approval of an NDA. All review disciplines concluded that Lilly had demonstrated sufficient similarity between Basaglar and US-approved Lantus to support the scientific appropriateness of reliance on FDA's finding of safety and effectiveness for Lantus. The CMC and Office of Clinical Pharmacology reviewers also concluded that the submitted data provide a scientific bridge between Basaglar and EU-approved Lantus, and between US-approved Lantus and EU-approved Lantus, scientifically justifying the appropriateness of using the data generated for EU-approved Lantus in Phase 3 trials to support the US marketing approval of Basaglar.

4.1 Chemistry Manufacturing and Controls

The primary CMC review was conducted by Dr. Ramaswamy (drug product) and Dr. Ysern (drug substance) (ONDQA/DNDQA III/Branch VII).[4]

The 21 Jul review summary states that the applicant resolved all CMC issues satisfactorily and there are no pending specific CMC issues. The CMC review team performed risk assessment on the factors that can impact product quality and concluded that the potential risk to overall product quality is low. The final quality recommendation was to be determined after the recommendation CDRH regarding the pen injector, and OC recommendation for manufacturing and testing facilities.

The final quality recommendation[5] from Dr. Ramaswamy, ONDQA is approval. Specific details are as follows:

4 See review in DARRTS dated 21 Jul 2014
5 See review in DARRTS dated 12 Aug 2014

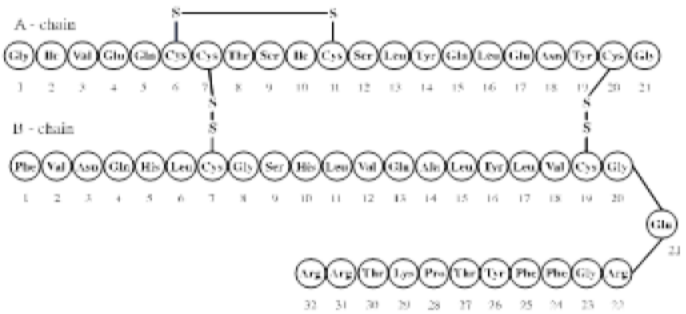
- The Office of Compliance (OC) at CDRH has reassessed the need for inspection of facilities associated with pen injector and based on desk review the OC at CDRH has concluded that no facilities need to be inspected.[6]

- The Office of Compliance (OC) at CDER has determined that the relevant facilities employed for the manufacture and testing of the drug substance, drug product are acceptable.[7]

- CDRH's technical review of the pen injector found no quality-specific deficiency.[8]

Summary of CMC information

Chemically, insulin glargine is 21A-Gly-30Ba-L-Arg-30Bb-L-Arg-human insulin and has the empirical formula C267H404N72O78S6 and a molecular weight of 6063. Insulin glargine has the following structural formula:



The drug substance, LY2963016, is Lilly's insulin glargine obtained by recombinant DNA technology using the production strain E. coli K12 (b) (4).

The drug product [LY296306 (Basaglar™ KwikPen™ 100 U/mL 3 mL)] is a sterile, preserved drug product in a glass cartridge in a pen injector (KwikPen). Each pen contains 300 units (3 mL) of LY2963016 and is intended for use over 28 days.

The CMC reviewer concluded that there is an adequate scientific bridge between US-approved Lantus and EU-approved Lantus, and between both Lantus products and Basaglar. (b) (4) All excipients used in LY2963016 injection are similar to that used in LANTUS except the following minor differences. In LY2963016 Injection, (b) (4).

6 For additional information, please refer to CDRH Office of Compliance memo in DARRTS dated August 12, 2014.
7 A copy of the Establishment Evaluation Request Summary Report from OC is enclosed in the 12 Aug memo
8 For additional information, please refer to memo in DARRTS dated June 12, 2014

The Sponsor states that LY2963016 Injection uses (b) (4) % glycerin instead of (b) (4) % glycerin used in Lantus. (b) (4) The impurity profiles are not identical.

The proposed final formulation is the same as the one used in development and Phase 3 clinical studies.

4.2 Clinical Microbiology

The primary microbiology review was conducted by Dr. Cole. The Clinical Microbiology team recommended approval of this NDA.[9]

According to Dr. Cole, 'this is a preserved, sterile drug product produced (b) (4) at two drug product manufacturing sites. There is adequate information on the preservative effectiveness (b) (4) for this drug product.'

4.3 Preclinical Pharmacology/Toxicology

The primary Pharm/Tox review was conducted by Dr. Tsai-Turton.[10] The Pharm/Tox team recommends approval of this NDA.

Per Dr. Tsai-Turton "The nonclinical development program for LY2963016 focused on demonstrating the similarity of LY2963016 to EU-approved or US-approved Lantus with regards to primary pharmacodynamics, pharmacokinetics, and animal toxicity. The nonclinical development of Y2963016 demonstrated that LY2963016 and Lantuswere similar with respect to in vitro (insulin and insulin life growth factor-1 receptor binding, metabolic potency, and mitogenic potential) and in vivo (PK, glucodynamics, local tolerability, and toxicity profile) characteristics."

The CDRH consult request response identified potential leachables from the drug cartridge that they stated in their review may need review by Pharm/Tox. This was identified as a concern at the late cycle meeting.

This issue was satisfactorily addressed by the CMC review: ONDQA included a review of the leachables, impurities and degradants in their review which indicates that the profile is in accordance with ICHQ3 and the levels observed do not require further qualification based on their compliance with the guidance.

4.4 Clinical Pharmacology

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCPII) has reviewed the clinical pharmacology data submitted under NDA 205692 and recommends approval for Basaglar.[11]

9 See the review in DARRTS dated 28 Feb 2014 by Dr. Cole.
10 See review in DARRTS dated 21 Jul 2014 for details.

Clinical pharmacology of LY2963016 under this 505(b)(2) submission was supported by 3 clinical studies including two definitive PK/PD similarity studies (ABEO and ABEN). These two PK/PD similarity studies (ABEO and ABEN) were deemed pivotal for approval.

The Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections of the clinical and analytical portions of the following bioequivalence (ABEO) and comparative bioavailability (ABEN) studies.[12] The results from the clinical and bioanalytical portions of studies ABEN and ABEO were deemed acceptable for Agency review.

4.4.1 Mechanism of Action

Insulin and its analogs, e.g. Basaglar and Lantus, lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis and proteolysis, and enhances protein synthesis.

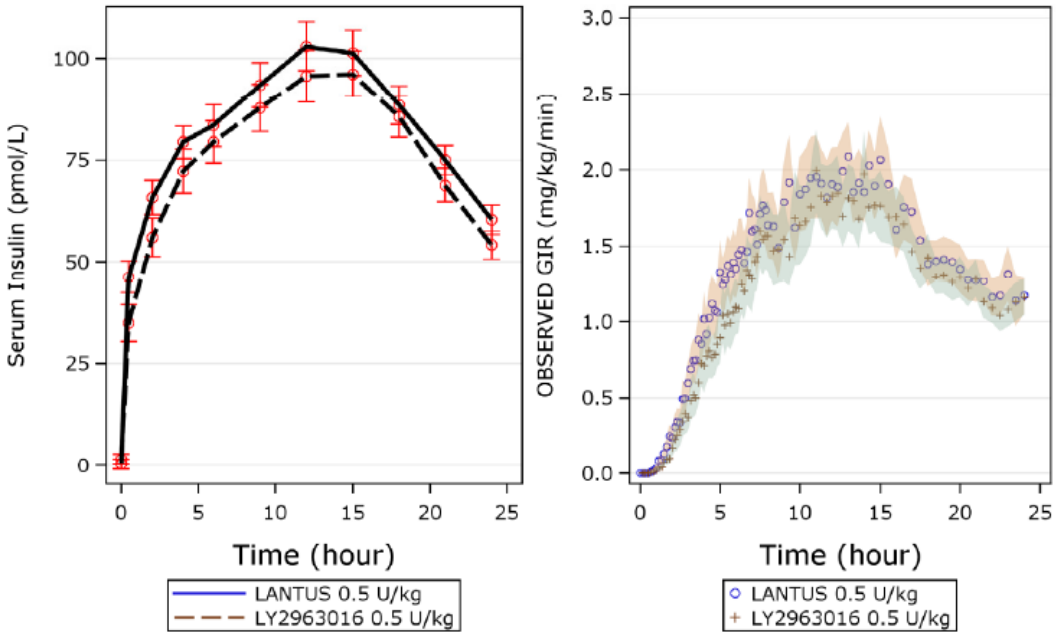
4.4.2 Pharmacodynamics

The PK and PD similarity of Basaglar to Lantus were assessed in healthy volunteers in study ABEO. Study ABEO administered a single subcutaneous dose of 0.5 U/kg Basaglar or US-approved Lantus and showed that the time action profile of Basaglar is similar to US-approved Lantus.

The figure below from the OCP review shows the mean insulin glargine concentrations (left panel) and mean glucose infusion rate (right panel) time plots in study ABEO.

11 See the OCP/DCPII review in DARRTS dated 21 Jul 2014 for details.
12 See memo dated 18 Jul 2014.

Mean baseline-adjusted serum insulin glargine, glucose infusion rate (GIR) from single SC dose of Basaglar or US-Approved Lantus (ABEO)



The major PK/PD parameters of Basaglar vs. Lantus are shown in the table below from the Office of Clinical Pharmacology review.

Type	Parameter	0.5 U/kg LY2963016 Mean (%CV)	0.5 U/kg US-Lantus® Mean (%CV)
PK	C_{max} (pmol/L)	110.5 (37)	116.7 (37)
	AUC_{0-24h} (pmol*h/L)	1850 (36)	1989 (31)
	T_{max} (h)*	12.0 (2.0 – 21.0)	12.0 (2.0 – 24.0)
PD	GIR_{max} (mg/kg/min)#	3.18 (53)	3.44 (49)
	$GIRAUC_{0-24h}$ (mg/kg)#	1935.94 (58)	2155.64 (57)
	$T_{GIR,max}$ (h)*	11.1 (1.9 – 23.5)	11.9 (2.2 – 23.9)

*Median (Range); #Reported as Rmax and Gtot, respectively in the sponsor's reports

Source: OCP review

Results of comparative analyses showed that geometric mean ratios and confidence intervals for both PK and PD parameters were within the pre-specified limits of 0.80 – 1.25, i.e. PK/PD parameters for Basaglar are similar to Lantus.

Type	Parameter	GMR (90%CI)*
PK	C_{max} (pmol/L)	0.92 (0.87 – 0.97)
	AUC_{0-24h} (pmol*h/L)	0.90 (0.85 – 0.96)
PD	GIR_{max} (mg/kg/min)	0.92 (0.87 – 0.98)
	$GIRAUC_{0-24h}$ (mg/kg)	0.91 (0.84 – 0.97)

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

There also appears to be no significant difference in the duration of action.

Statistical analysis of duration of action

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)		

Source: OCP review

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 Basaglar and EU-approved Lantus, and between EU-approved Lantus and US-approved Lantus, respectively. As noted in the OCP review, data from ABEA and ABEN provide a scientific bridge between Basaglar and EU-approved Lantus, or between US-approved Lantus and EU-approved Lantus, scientifically justifying the appropriateness of using the data generated for EU-approved Lantus in Phase 3 trials to support the US marketing approval of Basaglar.

Note that this comparative PK/PD data is used to support the appropriateness of a 505(b)(2) applicant's reliance on FDA's finding of safety and effectiveness for a listed drug and that such comparative data is not generally included in drug product labeling.

4.4.3 Pharmacokinetics

See combined PK/PD discussion in section 4.4.2 above.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

In sum, the efficacy and safety data include two phase 3 studies, one in patients with T1DM and one in patients with T2DM, and five phase 1 clinical pharmacology studies in healthy subjects

and one phase 1 clinical pharmacology study in patients with T1DM (Table 1). Clinical pharmacology studies are discussed in section 4 above. The two Phase 3 clinical studies used both US-approved Lantus (US and Puerto Rico sites) and EU-approved Lantus (all other sites, European Union, Mexico and Japan).

Given that the Sponsor is relying, in part, on FDA's finding of safety and effectiveness for the listed drug Lantus, the clinical program is abbreviated compared with that of insulins applying for marketing authorization under the 505(b)(1) pathway. The clinical pharmacology studies listed in Table 1 were, in general, conducted to characterize the PK/PD profile of Basaglar and to provide an adequate scientific bridge between Basaglar and Lantus. Further, because the Sponsor included EU-approved Lantus as the comparator drug in the phase 3 clinical trials the Sponsor was advised at the pre-NDA meeting to provide an adequate scientific bridge to justify the relevance of comparative data with a non-US-approved insulin glargine product in phase 3 trials.

Note that the Sponsor was advised by the Division to conduct a three-way cross-over PK/PD study, as to directly compare head-to-head their product versus US-approved Lantus and EU-approved Lantus. This approach would allow for pivotal PK/PD bridging of Basaglar to US-approved Lantus, in addition to providing data to justify the relevance of clinical trial data comparing Basaglar to EU-approved insulin glargine to support, in part, a demonstration of sufficient similarity to US-approved Lantus. However, Sponsor chose to conduct three separate studies, ABEO, ABEA, and ABEN which was determined to be acceptable by OCP and the Division.

Two pivotal phase 3 trials were required to support the Sponsor's reliance, in part, on FDA's finding of safety and effectiveness for the listed drug Lantus for this application. The Division's reasoning was primarily related to the issue of potential immunogenicity with insulin products. All insulin products can elicit the formation of insulin antibodies. The presence of such insulin antibodies, theoretically, may increase or decrease the efficacy of insulin and may require adjustment of the insulin dose. The presence of antibodies could also, theoretically, increase the likelihood of hypoglycemia, a major safety concern with insulin products, or result in other adverse events. Differences in manufacturing of the insulin glargine could potentially lead to differences in immunogenicity potential. Therefore, the Sponsor was required to conduct two large phase 3 studies (one in each diabetes type because immunogenicity potential is different in each type) to assess the safety and efficacy of Basaglar. These two trials were considered necessary for approval. The total patient exposure in phase 3 studies is reduced from what would have been required from a stand-alone application.

Table 1 - Table of Clinical Studies

Study name	Study Description	Population
Phase 1		
ABEO	Single-center, randomized, double-blind, single-dose (0.5 U/kg), 2-treatment, 4-period crossover, replicate, euglycemic clamp study to compare the PK and PD of BASAGLAR to US-approved LANTUS	Healthy volunteers
ABEA	Single-center, randomized, double-blind, single-dose (0.5 U/kg), 2-treatment, 4-period crossover, replicate, euglycemic clamp study to compare the PK and PD of BASAGLAR to EU-approved LANTUS	Healthy volunteers
ABEI	Single-center, randomized, open-label, single-dose (0.5 U/kg), 2-	Healthy volunteers

	treatment, 2-period crossover euglycemic clamp study to evaluate the relative bioavailability and PD response of BASAGLAR to EU-approved LANTUS	
ABEM	Single-center, randomized, subject- and investigator-blind, 4-treatment, 4-period, crossover euglycemic clamp study to compare the PK and PD of BASAGLAR to EU-approved LANTUS following single-dose administration at 2 different dose levels (0.3 U/kg and 0.6 U/kg)	Healthy volunteers
ABEE	Single-center, randomized, subject- and investigator-blind, single-dose (0.3 U/kg), 2-period crossover, 42-hour postdose euglycemic clamp study to compare the PK and PD of BASAGLAR to EU-approved LANTUS	Type 1 diabetes patients
ABEN	Single-center, randomized, subject- and investigator-blind, single-dose (0.5 U/kg), 2- treatment, 4-period crossover, replicate, euglycemic clamp study to compare the PK and PD of EU-approved LANTUS to US-approved LANTUS	Healthy volunteers
Phase 3		
ABEB	Phase 3, randomized, multinational, multicenter, 2-arm, active-control, open-label, parallel, 24-week treatment study with a 28-week active-controlled extension and 4-week post-treatment follow-up to compare BASAGLAR and LANTUS when each was used in combination with mealtime insulin lispro.	Adults with type 1 diabetes
ABEC	Phase 3, randomized, multinational, multicenter, 2-arm, active-control, double-blind, parallel, 24-week treatment study with a 4-week post-treatment follow-up to compare BASAGLAR and LANTUS when used in combination with at least 2 OAMs, in adult patients with T2DM.	Adults with type 2 diabetes
Abbreviations: EU = European Union; PD = pharmacodynamics; PK = pharmacokinetics; US = United States, OAM=oral antidiabetic medications		

5.2 Review Strategy

The content of this review critically evaluates the safety and efficacy findings from the phase 3 studies listed in section 5.1.

A separate primary efficacy review for biostatistics has been conducted by Dr. Lee Pian.

5.3 Discussion of Individual Studies/Clinical Trials

In this section the two pivotal studies to support the indication are described.

Type 1 Diabetes Trial

Study Title:

ABEB - A ProspEctive, Randomized, Open-LabEl CoMparison of a Long-Acting Basal Insulin Analog LY2963016 to LANTUS® in Combination with Mealtime Insulin Lispro in Adult PatiENTs with Type 1 Diabetes Mellitus: The ELEMENT 1 Study

Study Phase: 3

Primary objective:

The primary objective of this study was to test the hypothesis that Basaglar/LY2963016 (QD) was noninferior to Lantus (QD), as measured by change in HbA1c, from baseline to 24 weeks, when used in combination with pre-meal insulin lispro administered three times a day (TID).

Secondary objectives:

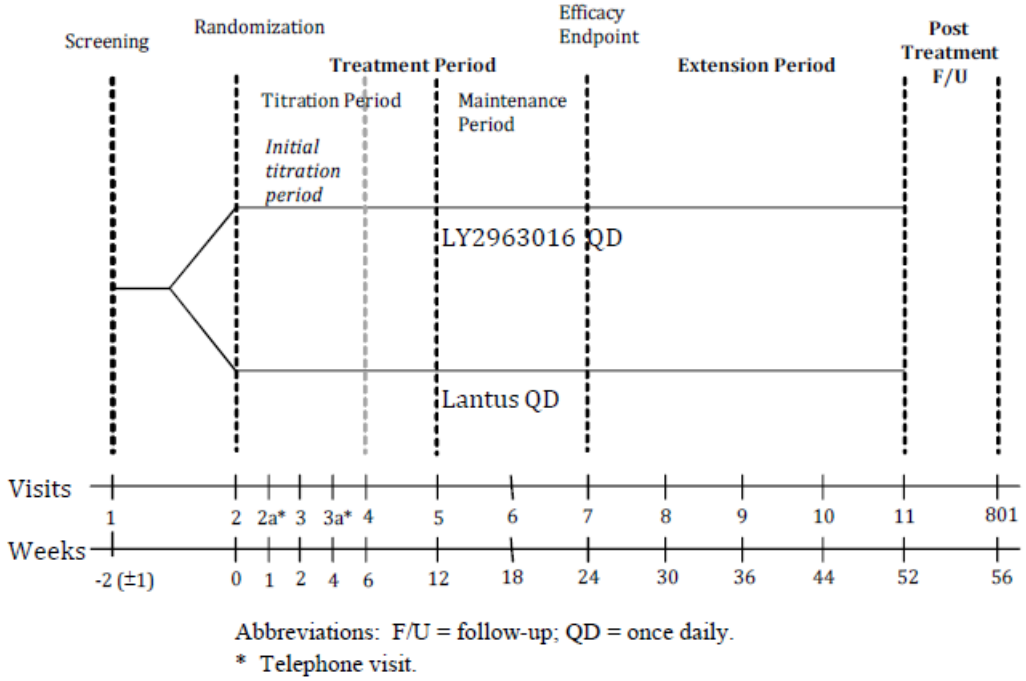
Secondary objectives were to compare Basaglar and Lantus in terms of safety and other efficacy variables.

Study Design:

Study ABEB was a prospective, randomized, multinational, multicenter, 2-arm, active-controlled, open-label, parallel study. The study included a 24-week treatment period, a 28-week active-controlled extension period, and a 4-week post-treatment follow-up. The study was designed to determine noninferiority of LY2963016 to Lantus by change in HbA1c from baseline in patients with T1DM. The design schematic is shown in the figure below.

An open-label design was chosen because the study was to provide efficacy and safety data (including evaluation of antibody data), using the insulin presentation that is comparable to the marketed product (i.e., prefilled pen device). Due to proprietary considerations and distinctiveness of the container closure systems and the pen, double-blinding Study ABEB would have required a double-dummy design, which increases the number of injections. The sponsor attempted to minimize bias by keeping personnel involved in the analysis of the data blinded to drug assignment during the trial.

Study ABEB Design Schematic



Abbreviations: F/U = follow-up; QD = once daily.
* Telephone visit.

Source: Figure ABEB.9.1

Subjects:

Planned were 400 to 550 (200 to 275 per treatment arm); blinded sample size re-estimation was performed and recommended sample size was 400; however, the planned sample size was set to 500 to provide a sufficient number of patients in the safety database as agreed with FDA.

Inclusion Criteria:

- Men or women at least 18 years of age at screening
- Diagnosis of T1DM based on the WHO diagnostic criteria
- Diabetes for at least 1 year at screening
- HbA1c value ≤11.0%
- On basal-bolus insulin therapy for at least 1 year prior to screening. Basal insulin was required to be QD injection of NPH, Lantus, or detemir for at least 3 months (90 days) prior to screening and combined with mealtime injections of human regular insulin, or insulin analog lispro, aspart, or glulisine.
- Body mass index (BMI) ≤35 kg/m2.

Key Exclusion Criteria:

- Exposed to a biosimilar[13] insulin glargine

13 This clinical trial was conducted at multiple study sites in the United States and outside the United States. Currently, Lantus is the only insulin glargine product approved in the United States, and it was approved under the FD&C Act. In the United States, "biosimilar" refers to a biological product licensed under section 351(k) of the Public Health Service Act (PHS Act). The 351(k) pathway is only available for a proposed biological product that

- Excessive insulin resistance at entry into the study (total daily insulin dose ≥1.5 U/kg)
- More than 1 episode of severe hypoglycemia within 6 months of screening
- More than 1 episode of diabetic ketoacidosis or emergency room visits for uncontrolled diabetes leading to hospitalization within 6 months prior to screening
- Known hypersensitivity or allergy to any of the study insulins (insulin glargine or insulin lispro) or to excipients of the study insulins
- Liver disease, renal transplant, or on renal dialysis
- Clinically significant cardiac disease
- Presence or history of cancer within previous 5 years (except basal-cell cancer or carcinoma in situ)
- Clinically significant gastrointestinal disease
- Blood transfusion or severe blood loss within 3 months prior to screening, or known hemoglobinopathy, hemolytic anemia, or sickle cell anemia
- Receiving chronic (lasting longer than 14 consecutive days) systemic glucocorticoid therapy at pharmacological doses (excluding topical, intra-articular, intraocular, or inhaled preparations and physiologic replacement doses for adrenal deficiency) or had received such therapy within 4 weeks preceding screening
- Taken oral antihyperglycemic medications or received treatment with pramlintide or continuous subcutaneous insulin infusion within 3 months prior to screening
- Used twice daily (BID) insulin glargine within 6 months prior to screening
- Breastfeeding, pregnant, or intended to become pregnant during the course of the study, or were sexually active women of childbearing potential not actively practicing birth control using a method deemed to be medically acceptable by the investigator

Treatments Administered:

Basal Insulins
Basal insulins were the open-label Basaglar or Lantus. Both were administered via prefilled pen-injector. The Basaglar formulation used was the to-be-marketed formulation. Patients assigned to Lantus at sites in the US and Puerto Rico received US-approved Lantus, and all other patients assigned to Lantus received EU-approved Lantus.

- Dosing and Administration
  - Starting Dose: At the start of the study, the dose of basal insulin (LY2963016 or Lantus) was equivalent to the dose of the individual patient's pre-study QD basal insulin that was discontinued, and administered subcutaneously QD at the same time every day, consistent with the Lantus label.

  - Dose Titration: The dose of LY2963016 or Lantus was titrated by patients using self-monitored glucose values (minimum 4 times daily) primarily based on FPG with treat-to-target titration algorithms and glycemic goal guidelines. The guidelines are complex and are not reproduced here, but they can be found in attachment 4 of the study protocol. The

demonstrates biosimilarity to a "reference product" licensed under section 351(a) of the PHS Act. Thus, the term "biosimilar" used in the protocol would not describe an insulin glargine product in the United States.

titration plan appears reasonable and is based on published literature. The same guidelines were applied across treatment arms.

Target glycemic goals were the same for all patients (HbA1c <7%, FPG ≤6.0 mmol/L [≤108 mg/dL]), other preprandial capillary BGs 70-130 mg/dL ([3.9-7.2 mmol/L], without incurring hypoglycemia).

The treatment period was composed of a titration period (12 weeks) and a maintenance period
(12 weeks). To ensure that the HbA1c by Week 24 reflected glycemic control on the patient's insulin regimen, it was expected that most of the basal (and bolus) insulin adjustments would occur during the initial titration period (Weeks 0 through 6). However, titration could have been extended up to Week 12 for patients who needed more intensification to achieve glycemic targets.

Bolus insulin
The study participants' pre-meal insulin during the study was insulin lispro, which was also provided at the day of randomization.

- Dosing and Administration
  - Starting Dose: Dosing of lispro was started at a dose based on a unit-to-unit conversion of their pre-study mealtime insulin dose of regular insulin, aspart, glulisine, or lispro, with appropriate dose optimization to achieve glycemic targets.
  - Dose Titration: Titration of prandial insulin was also guided by the plan outlined in attachment 4 of the protocol.

Efficacy Assessments:

Primary Efficacy Endpoint:
Change in HbA1c at 24 weeks or last post-baseline observation carried forward (LOCF)

Secondary Efficacy Endpoints:
Secondary efficacy variables included change in HbA1c from baseline to 6, 12, 24, 36, and 52 weeks, 7-point SMBG, percentage of patients reaching glycemic goals, daily basal insulin dose, Lispro insulin dose, total daily insulin dose (basal plus lispro bolus doses), weight and body mass index (BMI).

Safety Assessments:

Adverse events (AEs) including treatment-emergent adverse events (TEAEs) (all and related to study drug, disease, and procedures), serious adverse events (SAEs), discontinuations due to AEs, allergic events, injection-site events, hypoglycemic events (total, severe, nocturnal, non-nocturnal, documented symptomatic, asymptomatic, probable symptomatic, relative, unspecified); laboratory measures including insulin antibodies (% binding); and vital signs.

Statistical Methods:

The noninferiority margin of 0.4% was selected because of historical precedent this is the usual margin used in insulin non-inferiority trials.

As summarized in Dr. Pian's review,

- the primary analysis model was an analysis of covariance model (ANCOVA) with treatment, country, time of basal insulin injection (daytime, evening/bedtime) as fixed effects and baseline HbA1c as a covariate;
- the proportions of patients achieving HbA1c target values (HbA1c<7.0% and ≤ 6.5%) were analyzed using Fisher's Exact test;
- the analysis of the continuous secondary efficacy variables used the same ANCOVA model as the primary efficacy endpoint;
- Missing data was imputed by the LOCF methodology.

At the pre NDA meeting the Sponsor was given the following advice: *We note that the Last Observation Carried Forward (LOCF) technique is your primary imputation method as stated in the protocols submitted in May 12, 2011. This was accepted by the Agency at that time. However, the Division is reconsidering this LOCF approach following the publication in 2010 of a report on missing data by the National Academy of Sciences (NAS). Therefore, please amend your primary imputation method and specify a primary statistical analysis which does not rely on LOCF and which is in line with NAS recommendations.*

The sponsor stated that since they were planning to submit their NDA soon after the preNDA meeting, they would still like to submit the results based on the LOCF method for missing data and retain this method as their primary analysis, but will provide additional analyses such as mixed model repeated measures as sensitivity analyses. The Division reiterated the current position regarding missing data handling, but agreed with the sponsor's proposal at this time since the data were already unblinded and analyzed, and the dropout rate was not high.

Type 2 Diabetes Trial

Study Title: ABEC - A Prospective, Randomized, Double-Blind Comparison of a Long-Acting Basal Insulin Analog LY2963016 to LANTUS® in Adult Patients with Type 2 Diabetes Mellitus: The ELEMENT 2 Study

Study Phase: 3

Primary objective:

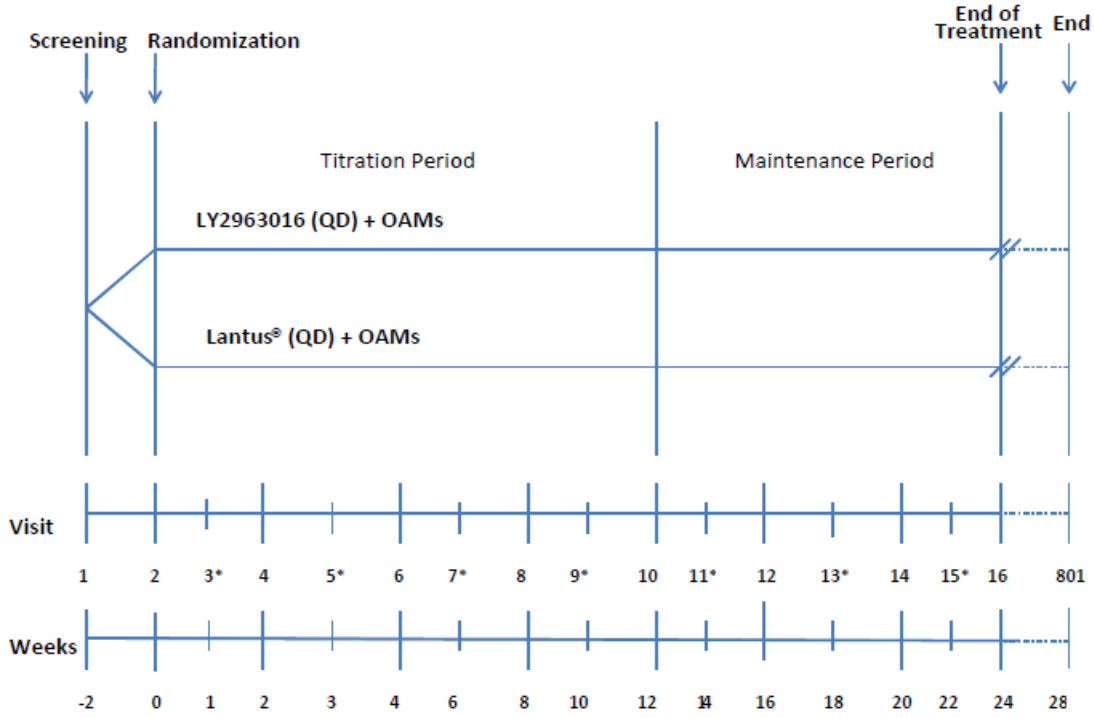
The primary objective of this study was to test the hypothesis that LY2963016 administered once daily (QD) was noninferior to Lantus administered QD, as measured by change in HbA1c from baseline to 24 weeks, when used in combination with oral antihyperglycemic medications (OAMs).

Secondary objectives:

Secondary objectives were to compare Basaglar and Lantus in terms of safety and other efficacy variables.

Study Design:

Study I4L-MC-ABEC was a Phase 3, prospective, randomized, multinational, multicenter, 2-arm, active-controlled, double-blind, parallel, 24-week study with a 4-week post-treatment follow-up in patients with T2DM. The study was designed to determine noninferiority of LY2963016 to Lantus in change in HbA1c from baseline when used to initiate insulin therapy in patients with T2DM who were either insulin naïve and had failed to achieve adequate glycemic control on at least 2 OAMs, or were already administering Lantus along with at least 2 OAMs with adequate or inadequate glycemic control. The design schematic is shown in the figure below.



Abbreviations: OAM = oral antihyperglycemic medication; QD = once daily;
* = telephone visit.

Source: Figure ABEC.9.1

Subjects:

Planned were 606 to 792 (303 to 396 per treatment arm); blinded sample size re-estimation was performed and recommendation was to enroll up to, but not exceed the maximum sample size of 792 patients.

Inclusion Criteria:

- Men or women at least 18 years of age at screening
- Diagnosis of T2DM based on WHO diagnostic criteria
- Receiving 2 or more OAMs at stable doses for the 12 weeks prior to screening, with or without Lantus. The use and dose of oral agents in combination with insulin had to be in accordance with the local product label.
    - Patients taking metformin who were found to have a contraindicated serum creatinine level (≥1.4 mg/dL for females, ≥1.5 mg/dL for males, or based on country-specific label) had to discontinue use of metformin at randomization.
    - If the patient was on 2 OAMs at study entry and there was a need to discontinue 1 OAM due to country labeling requirements or clinical parameters, that patient was not eligible.
- HbA1c ≥7.0% and ≤11.0% if insulin naïve; had an HbA1c ≤11.0% if previously on Lantus
- Body mass index (BMI) ≤45 kg/m2

Key Exclusion Criteria:

- Used any other insulin except Lantus within the previous 30 days
- Exposed to a biosimilar[14] insulin glargine within the previous 90 days
- History of taking basal bolus therapy or, in the investigator's opinion, required mealtime insulin to achieve target control
- Used glucagon-like peptide 1 (GLP-1) agonist within the previous 90 days
- Used pramlintide within the previous 30 days
- Excessive insulin resistance at study entry (total insulin dose ≥1.5 U/kg)
- More than 1 episode of severe hypoglycemia within 6 months prior to study entry
- Known hypersensitivity or allergy to Lantus or its excipients
- Receiving chronic (lasting longer than 14 consecutive days) systemic glucocorticoid therapy at pharmacological doses (excluding topical, intra-articular, intra-ocular, or inhaled preparations and physiologic replacement doses for adrenal deficiency) or had received such therapy within 4 weeks preceding screening
- Liver disease, renal transplant, or on renal dialysis
- Significant cardiac or gastrointestinal disease
- Active cancer or personal history of cancer within previous 5 years (with the exception of basal cell carcinoma or carcinoma in situ)
- Blood transfusion or severe blood loss within 3 months prior to screening, or known hemoglobinopathy, hemolytic anemia, or sickle cell anemia
- Breastfeeding, pregnant, or intended to become pregnant during the course of the study, or were sexually active women of childbearing potential not actively practicing birth control using a method deemed to be medically acceptable by the investigator

Treatments Administered:

Patients were to continue on their pre-study OAMs throughout the study.

Basal Insulins
Basal insulins were the double-blind Basaglar or Lantus. The Basaglar formulation used was the to-be-marketed formulation. Basaglar or Lantus were provided in covered insulin vials (for blinding purposes) and syringes during the study. Patients assigned to Lantus at sites in the US and Puerto Rico received US-approved Lantus, and all other patients assigned to Lantus received EU-approved Lantus.

- Dosing and Administration
  - Starting Dose: Patients previously on Lantus started Lantus or Basaglar QD at the same dose as prestudy Lantus. Insulin naïve patients had a starting dose of 10 U QD.

  - Dose Titration: All patients followed a patient-driven dosing algorithm while being supervised by investigators through the course of the study to maintain the fasting blood glucose (FBG) ≤100 mg/dL (5.6 mmol/L) while avoiding hypoglycemia.

Efficacy Assessments:

14 See footnote above regarding the term biosimilar

Similar to trial ABEB

Primary Efficacy Endpoint: Change in HbA1c from baseline to Week 24 or last post-baseline observation carried forward (LOCF)

Secondary Efficacy Endpoints: 7-point SMBG (plasma-equivalent glucose values obtained before each meal, after morning and midday meals, at bedtime, and 3 am); intrapatient variability as measured by the standard deviation (SD) of the FBG; change in HbA1c from baseline to 4, 8, 12, 16, 20 and 24 weeks, or LOCF; percentage of patients achieving HbA1c targets (<7%, ≤6.5%); basal insulin dose at end of study; and body weight.

Safety Assessments:
Similar to trial ABEB

Statistical Methods:

Similar to trial ABEB

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The intended indication of Basaglar is as follows: Basaglar is a long-acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. It is intended that the indication be the same as that for Lantus.

6.1.1 Methods

The efficacy evaluation came from the two pivotal phase 3 studies.

6.1.2 Demographics

Subject demographics for study ABEB are shown in table 2. The overall mean age was 41.16 years; there were few patients that were at least 65 years of age (25 [4.7%]). The majority of patients were White (74.5%), and more than half of the patients were male (57.9%). The United States enrolled the greatest number of patients.

The FDA statistician presented the demographic data for the US-approved and non-US-approved Lantus subgroups separately. Patient demographics were generally similar between treatment groups.

Table 2– Subject Demographics – full analysis set Study ABEB

Variable	LY2963016 (N=268)	Lantus (N=267)	Total (N=535)
Age in years			
Number of Patients	268	267	535
Mean	40.96	41.37	41.16
SD	13.65	13.25	13.44
SE	0.83	0.81	0.58
Minimum	18.28	19.46	18.28
Median	39.84	40.46	40.28
Maximum	81.35	71.46	81.35
Age Group in years (< 65, >= 65); n (%)			
Number of Patients	268	267	535
< 65	254 (94.8)	256 (95.9)	510 (95.3)
>= 65	14 (5.2)	11 (4.1)	25 (4.7)
Age Group in years (< 75, >= 75); n (%)			
Number of Patients	268	267	535
< 75	266 (99.3)	267(100.0)	533 (99.6)
>= 75	2 (0.7)	0 (0.0)	2 (0.4)
Gender; n (%)			
Number of Patients	268	267	535
Male	155 (57.8)	155 (58.1)	310 (57.9)
Female	113 (42.2)	112 (41.9)	225 (42.1)
Ethnicity; n (%)			
Number of Patients	268	266	534
Hispanic or Latino	11 (4.1)	10 (3.8)	21 (3.9)
Not Hispanic or Latino	177 (66.0)	170 (63.9)	347 (65.0)
Not Applicable	80 (29.9)	86 (32.3)	166 (31.1)
Race; n (%)			
Number of Patients	267	267	534
American Indian or Alaska Native	11 (4.1)	12 (4.5)	23 (4.3)
Asian	49 (18.4)	51 (19.1)	100 (18.7)
Black or African American	9 (3.4)	2 (0.7)	11 (2.1)
Multiple	1 (0.4)	1 (0.4)	2 (0.4)
White	197 (73.8)	201 (75.3)	398 (74.5)
Country; n (%)			
Number of Patients	268	267	535
Belgium	12 (4.5)	11 (4.1)	23 (4.3)
Germany	26 (9.7)	28 (10.5)	54 (10.1)
Greece	15 (5.6)	13 (4.9)	28 (5.2)
Hungary	14 (5.2)	16 (6.0)	30 (5.6)
Japan	49 (18.3)	51 (19.1)	100 (18.7)
Mexico	17 (6.3)	19 (7.1)	36 (6.7)
Poland	18 (6.7)	17 (6.4)	35 (6.5)
Romania	18 (6.7)	16 (6.0)	34 (6.4)
United States	99 (36.9)	96 (36.0)	195 (36.4)
Region-Approved Lantus; n (%)			
Number of Patients	268	267	535
US-approved	99 (36.9)	96 (36.0)	195 (36.4)
EU-approved	169 (63.1)	171 (64.0)	340 (63.6)

Source: Table ABEB.11.1

Other patient characteristics in study ABEB are shown in Table 3. Characteristics are similar across treatment groups.

Table 3 – Subject Characteristics – full analysis set Study ABEB

Duration of Diabetes in years			
Number of Patients	268	267	535
Mean	16.23	16.56	16.39
SD	11.00	10.83	10.91
SE	0.67	0.66	0.47
Minimum	1.00	1.13	1.00
Median	14.26	15.21	14.52
Maximum	54.31	55.20	55.20

Baseline BMI in kg/m2			
Number of Patients	268	267	535
Mean	25.65	25.42	25.54
SD	4.18	3.70	3.94
SE	0.26	0.23	0.17
Minimum	16.90	18.50	16.90
Median	25.30	25.20	25.20
Maximum	38.00	35.50	38.00
Baseline HbA1c (%)			
Number of Patients	268	267	535
Mean	7.75	7.79	7.77
SD	1.13	1.03	1.08
SE	0.07	0.06	0.05
Minimum	4.80	5.20	4.80
Median	7.70	7.70	7.70
Maximum	11.50	10.30	11.50
Entry Basal Insulin (Lantus, other); n (%)			
Number of Patients	268	267	535
Lantus	218 (81.3)	234 (87.6)	452 (84.5)
Other	50 (18.7)	33 (12.4)	83 (15.5)
Entry Short-Acting Insulin (Insulin Lispro, other); n (%)			
Number of Patients	267	267	534
Insulin Lispro	124 (46.4)	121 (45.3)	245 (45.9)
Other	143 (53.6)	146 (54.7)	289 (54.1)
Time of basal insulin injection; n (%)			
Number of Patients	268	267	535
Daytime	51 (19.0)	48 (18.0)	99 (18.5)
Evening/Bedtime	217 (81.0)	219 (82.0)	436 (81.5)
Stages of Kidney Disease; n (%)			
Number of Patients	268	267	535
Normal or increased GFR (>90 mL/min/1.73 m2)	196 (73.1)	197 (73.8)	393 (73.5)
Mild reduction in GFR (60-89 mL/min/1.73 m2)	61 (22.8)	64 (24.0)	125 (23.4)
Moderate reduction in GFR (30-59 mL/min/1.73 m2)	11 (4.1)	6 (2.2)	17 (3.2)

Source: Table ABEB.11.1

Subject demographics for study ABEC are shown in table 4. The age of patients was similar across treatment groups, with an overall mean age of 59 years; there were few patients that were at least 75 years of age (34 [4.5%]). The majority of patients were White (78.4%) and 50.0% of the patients were male. The US enrolled the greatest number of patients.

Table 4– Subject Demographics – full analysis set Study ABEC

Variable	LY2963016 (N=376)	Lantus (N=380)	Total (N=756)
Age in years			
Number of Patients	376	380	756
Mean	58.98	58.67	58.82
SD	10.17	10.02	10.09
SE	0.52	0.51	0.37
Minimum	23.40	26.48	23.40
Median	59.51	59.31	59.40
Maximum	84.34	82.42	84.34
Age Group in years (< 65, >= 65); n (%)			
Number of Patients	376	380	756
< 65	264 (70.2)	278 (73.2)	542 (71.7)
>= 65	112 (29.8)	102 (26.8)	214 (28.3)
Age Group in years (< 75, >= 75); n (%)			
Number of Patients	376	380	756
< 75	355 (94.4)	367 (96.6)	722 (95.5)
>= 75	21 (5.6)	13 (3.4)	34 (4.5)

Gender; n (%)			
Number of Patients	376	380	756
Male	179 (47.6)	199 (52.4)	378 (50.0)
Female	197 (52.4)	181 (47.6)	378 (50.0)
Race; n (%)			
Number of Patients	376	380	756
American Indian or Alaska Native	17 (4.5)	21 (5.5)	38 (5.0)
Asian	29 (7.7)	35 (9.2)	64 (8.5)
Black or African American	26 (6.9)	32 (8.4)	58 (7.7)
Multiple	2 (0.5)	1 (0.3)	3 (0.4)
White	302 (80.3)	291 (76.6)	593 (78.4)
Country; n (%)			
Number of Patients	376	380	756
Czech Republic	18 (4.8)	18 (4.7)	36 (4.8)
France	8 (2.1)	8 (2.1)	16 (2.1)
Germany	15 (4.0)	13 (3.4)	28 (3.7)
Greece	10 (2.7)	12 (3.2)	22 (2.9)
Hungary	32 (8.5)	30 (7.9)	62 (8.2)
Italy	6 (1.6)	5 (1.3)	11 (1.5)
Korea, Republic Of	17 (4.5)	15 (3.9)	32 (4.2)
Mexico	29 (7.7)	29 (7.6)	58 (7.7)
Poland	12 (3.2)	11 (2.9)	23 (3.0)
Puerto Rico	39 (10.4)	31 (8.2)	70 (9.3)
Spain	10 (2.7)	12 (3.2)	22 (2.9)
Taiwan	9 (2.4)	12 (3.2)	21 (2.8)
United States	171 (45.5)	184 (48.4)	355 (47.0)
Region-Approved Lantus; n (%)			
Number of Patients	376	380	756
US-approved	210 (55.9)	215 (56.6)	425 (56.2)
EU-approved	166 (44.1)	165 (43.4)	331 (43.8)

Source: Table ABEC.11.1

Other patient characteristics in study ABEC are shown in Table 5. Characteristics are similar across treatment groups.

Table 5 – Subject Characteristics – full analysis set Study ABEC

Duration of Diabetes in years			
Number of Patients	376	380	756
Mean	11.66	11.24	11.45
SD	6.79	6.82	6.80
SE	0.35	0.35	0.25
Minimum	0.52	0.44	0.44
Median	10.78	10.24	10.49
Maximum	40.44	33.45	40.44
BMI in kg/m2			
Number of Patients	376	380	756
Mean	31.92	31.88	31.90
SD	5.50	5.43	5.46
SE	0.28	0.28	0.20
Minimum	20.00	19.60	19.60
Median	31.50	31.45	31.50
Maximum	45.50	45.70	45.70
Baseline HbA1c (%)			
Number of Patients	376	380	756
Mean	8.34	8.31	8.33
SD	1.09	1.06	1.08
SE	0.06	0.05	0.04
Minimum	4.90	5.90	4.90
Median	8.25	8.15	8.20
Maximum	11.30	11.20	11.30
Sulfonylurea Use; n (%)			
Number of Patients	376	380	756
Yes	315 (83.8)	315 (82.9)	630 (83.3)
No	61 (16.2)	65 (17.1)	126 (16.7)
Time of Basal Insulin Injection; n (%)			
Number of Patients	376	380	756
Daytime	187 (49.7)	188 (49.5)	375 (49.6)
Evening/Bedtime	189 (50.3)	192 (50.5)	381 (50.4)

Stage of Kidney Disease at Study Entry; n (%)			
Number of Patients	376	380	756
Kidney damage with normal or increased GFR (>90 mL/min/1.73 m2)	252 (67.0)	258 (67.9)	510 (67.5)
Mild reduction in GFR (60-89 mL/min/1.73 m2)	98 (26.1)	102 (26.8)	200 (26.5)
Moderate reduction in GFR (30-59 mL/min/1.73 m2)	26 (6.9)	18 (4.7)	44 (5.8)
Severe reduction in GFR (15-29 mL/min/1.73 m2)	0 (0.0)	2 (0.5)	2 (0.3)
Entry Basal Insulin (Lantus, None); n (%)			
Number of Patients	376	380	756
Lantus	155 (41.2)	144 (37.9)	299 (39.6)
None	221 (58.8)	236 (62.1)	457 (60.4)

Source: Table ABEC.11.1

6.1.3 Subject Disposition

Table 6 shows patient disposition for study ABEB from the Sponsor's study report. The dropout rate appears low and there are no important differences between the study groups.

Table 6 – Patient Disposition, Full analysis set, Study ABEB

Patient Disposition	LY2963016 (N=268) n (%)	Lantus (N=267) n (%)	Total (N=535) n (%)
Completed	245 (91.4)	245 (91.8)	490 (91.6)
Discontinued	23 (8.6)	22 (8.2)	45 (8.4)
Adverse Event	2 (0.7)	5 (1.9)	7 (1.3)
Death	0 (0.0)	1 (0.4)	1 (0.2)
Lost To Follow-Up	3 (1.1)	6 (2.2)	9 (1.7)
Physician Decision	3 (1.1)	2 (0.7)	5 (0.9)
Withdrawal By Subject	15 (5.6)	8 (3.0)	23 (4.3)

Source: Table ABEB.10.1

The following table from Dr. Pian's statistical review shows patient disposition by source of Lantus. It is apparent that there is a higher discontinuation rate among patients treated with US-approved Lantus, but there still do not appear to be any important differences between Basaglar and Lantus treatment groups.

	US-approved Lantus		EU-approved Lantus		ABEB	
	LY	Lantus	LY	Lantus	LY	Lantus
n	100	96	169	171	269	267
Completed	82 (82%)	82 (85%)	159 (94%)	161 (94%)	241 (90%)	243 (91%)
Discontinued	18 (18%)	14 (15%)	10 (6%)	10 (6%)	28 (10%)	24 (9%)
Adverse Event	1 (1%)	1 (1%)	1 (0.6%)	4 (2.3%)	2 (0.7%)	5 (1.9%)
Death	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
Entry Criteria Not Met	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lost To Follow-Up	5 (5%)	5 (5.2%)	2 (1.2%)	3 (1.8%)	7 (2.6%)	8 (3%)
Physician Decision	2 (2%)	0 (0%)	1 (0.6%)	2 (1.2%)	3 (1.1%)	2 (0.7%)
Withdrawal By Subject	10 (10%)	7 (7.3%)	6 (3.6%)	1 (0.6%)	16 (5.9%)	8 (3%)

Source: Dr. Pian's review

Table 7 shows patient disposition for study ABEC from the Sponsor's study report. The dropout rate appears low and there are no important differences between the study groups that are concerning for Basaglar, i.e. the dropout rate due to adverse events was higher in the Lantus group compared to Basaglar.

Table 7 - Patient Disposition, Full analysis set, Study ABEC

Patient Disposition	LY2963016 (N=376) n (%)	Lantus (N=380) n (%)	Total (N=756) n (%)
Completed	334 (88.8)	328 (86.3)	662 (87.6)
Discontinued	42 (11.2)	52 (13.7)	94 (12.4)
Adverse Event	5 (1.3)	10 (2.6)	15 (2.0)
Death	1 (0.3)	1 (0.3)	2 (0.3)
Lack of Efficacy	1 (0.3)	2 (0.5)	3 (0.4)
Lost To Follow-Up	7 (1.9)	9 (2.4)	16 (2.1)
Physician Decision	9 (2.4)	9 (2.4)	18 (2.4)
Protocol Violation	8 (2.1)	5 (1.3)	13 (1.7)
Subject Decision	11 (2.9)	16 (4.2)	27 (3.6)

Source: Table ABEC.10.1

Dr. Pian's review showed that there still do not appear to be any important differences between Basaglar and Lantus treatment groups when examined by subgroups, although again, there is a higher dropout rate among US-approved Lantus treated subjects.

	US-approved Lantus		EU-approved Lantus		ABEC	
	LY2963016	Lantus	LY2963016	Lantus	LY2963016	Lantus
n	213	215	166	165	379	380
Completed	180 (85%)	176 (82%)	149 (90%)	151 (92%)	329 (87%)	327 (86%)
Discontinued	33 (15%)	39 (18%)	17 (10%)	14 (8%)	50 (13%)	53 (14%)
Adverse Event	4 (1.9%)	9 (4.2%)	2 (1.2%)	1 (0.6%)	6 (1.6%)	10 (2.6%)
Death	0 (0%)	0 (0%)	1 (0.6%)	1 (0.6%)	1 (0.3%)	1 (0.3%)
Entry Criteria Not Met	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lack of Efficacy	1 (0.5%)	2 (0.9%)	0 (0%)	0 (0%)	1 (0.3%)	2 (0.5%)
Lost To Follow-Up	12 (5.6%)	7 (3.3%)	1 (0.6%)	3 (1.8%)	13 (3.4%)	10 (2.6%)
Physician Decision	6 (2.8%)	6 (2.8%)	3 (1.8%)	3 (1.8%)	9 (2.4%)	9 (2.4%)
Protocol Violation	5 (2.3%)	4 (1.9%)	3 (1.8%)	1 (0.6%)	8 (2.1%)	5 (1.3%)
Sponsor Decision	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Subject Decision	5 (2.3%)	11 (5.1%)	7 (4.2%)	5 (3%)	12 (3.2%)	16 (4.2%)

Source: Dr. Pian's review

6.1.4 Analysis of Primary Endpoint(s)

For purposes of drug approval and labeling, final demonstration of efficacy should be based on reduction in HbA1c (i.e., HbA1c is the primary endpoint of choice, albeit a surrogate), which will support an indication of glycemic control.[15] For the current application, in both phase 3 trials the primary endpoint was change in HbA1c from baseline to 24 weeks.

Noninferiority of Basaglar to Lantus was to be concluded if the upper limit of the 95% CI for the treatment difference was <0.4%. If the 0.4% noninferiority margin was met, the upper limit of the 95% CI was compared with the 0.3% noninferiority margin.

Type 1 diabetes trial

15 See Guidance for Industry Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention

Table 8 shows the primary efficacy analysis for study ABEB conducted by the FDA statistician. Results from ANCOVA showed that treatment difference in HbA1c change from baseline to week 24 was +0.11% with an upper 95% CI of +0.22% (<0.4% and <0.3% margins).

Table 8 – ANCOVA of Change in HbA1c from Baseline to Week 24 (LOCF) Study ABEB

	ABEB T1DM		US subgroup		EU subgroup	
Treatment n	**LY2963016 n=267**	**Lantus n=267**	**LY2963016 n=98**	**US Lantus n=96**	**LY2963016 n=169**	**EU Lantus n=171**
LSM Baseline (SE)	7.86 (0.09)	7.90 (0.09)	7.76 (0.12)	7.73 (0.12)	7.85 (0.11)	7.93 (0.12)
LSM Change (SE)	-0.35 (0.05)	-0.46 (0.05)	-0.22 (0.06)	-0.41 (0.06)	-0.46 (0.07)	-0.53 (0.08)
Treatment difference [95% CI], p-value[a]	**+0.11 [-0.002, +0.22] p=0.055**		**+0.19 [+0.02, +0.36] p=0.028**		**+0.07 [-0.08, +0.21] p=0.345**	

ANCOVA Model includes treatment, country and time of baseline basal insulin injection (daytime or evening/bedtime) as fixed effects and baseline HbA1c as covariate
[a] p-values are for testing for a difference
Source: Dr. Pian's review

Because large phase 3 trials were required to assess immunogenicity and other safety endpoints, the phase 3 studies were actually 'overpowered' for efficacy. The FDA statistician noted that there was sufficient power to perform efficacy analyses for the US-approved Lantus and non-US approved Lantus subgroups separately. For the US-approved Lantus subgroup, the +0.36% upper 95% CI was <0.4% meeting the non-inferiority margin. However, the criteria of 'statistically worse' for the comparison of Basaglar to US-approved Lantus was met due to the +0.02% lower 95% CI excluding 0 (p=0.028). For the EU-approved Lantus subgroup, Basaglar was non-inferior and not statistically worse than EU-approved Lantus.

It is unclear why Basaglar had lesser efficacy than Lantus in the US-approved Lantus subgroup analysis; however, this is not concerning for approval because 1) the primary objective of non-inferiority for the overall population was met 2) the Sponsor has provided an adequate scientific bridge between US-approved Lantus and EU-approved Lantus based on CMC, Pharm/Tox and Clinical Pharmacology data 3) even for the US-approved Lantus subgroup, the criteria for non-inferiority was still met.

In this non-inferiority design, it is important to know that the active control had its expected effect in the study. This is critical to knowing that the trial had 'assay sensitivity' (i.e., could have distinguished an effective from an ineffective drug).[16] The trial should also have good study quality, including adequate and comparable titration of insulins in study groups. In this trial, insulins appear to have been adequately titrated and the trial appears to have adequate assay sensitivity. Further, missing data are not a major concern for interpretability of the trial results. Therefore, this reviewer concludes that the study results are reliable.

As reported in the Clinical Study Report, the Sponsor showed the same results as the FDA analysis but interpreted them differently. The Sponsor concluded Basaglar was noninferior to

16 See Guidance for Industry Non-Inferiority Clinical Trials

Lantus in the primary treatment comparison that tested for noninferiority with 0.4% and 0.3% noninferiority margins in a gated approach. Also, Lantus was noninferior to Basaglar in the secondary treatment comparison; "therefore, Basaglar and Lantus were considered to have equivalent efficacy."

According to the Guidance for Industry Non-Inferiority Clinical Trials, in most cases a successful non-inferiority study supports effectiveness of the test drug, but it only rarely will support a conclusion that the drug is "equivalent" or "similar" to the active control. Based on the data, this reviewer does not agree with the Sponsor that the drugs have equivalent efficacy. This reviewer recommends that only a claim of non-inferiority be included in labeling.

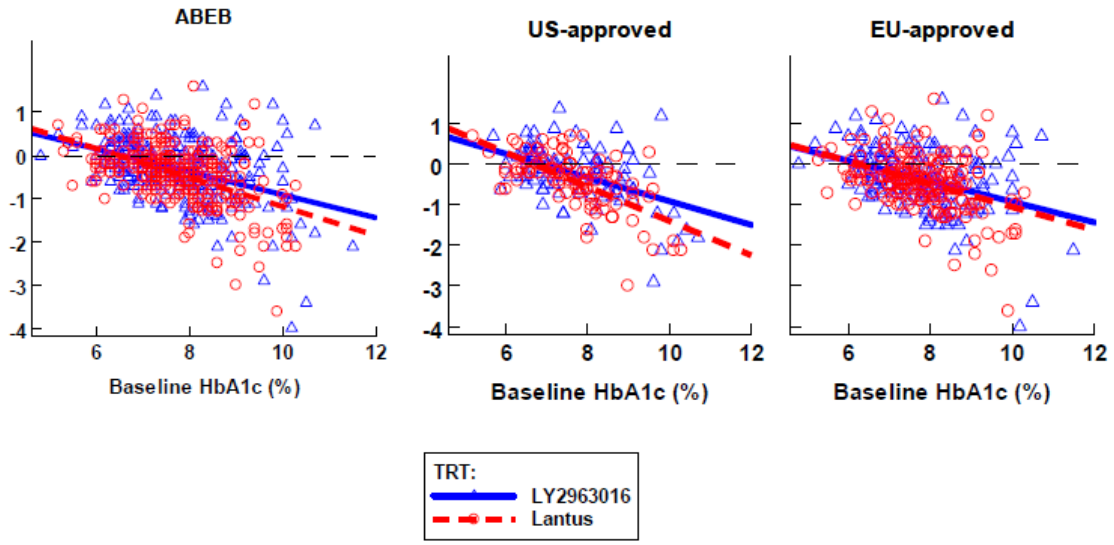
Sensitivity analyses: the mixed model repeated measure (MMRM) analysis results conducted by Dr. Pian are similar to the ANCOVA (LOCF) results.

Subgroup analyses

For all subgroups analyzed for change in HbA1c from baseline to 52-week endpoint (LOCF), including entry HbA1c levels, basal insulin treatment at entry, entry BMI, age at entry, time of basal insulin injection, sites with US-approved Lantus versus sites with EU-approved Lantus, patients in Japan versus other sites, gender, country, and race, in the Sponsor's analyses there were no statistically significant treatment-by-subgroup interactions, indicating no significant differential treatment effects on the change in HbA1c across levels of a subgroup.

The FDA statistical reviewer examined whether efficacy varied by subgroups for study ABEB, and confirmed the Sponsor's analyses. The overall treatment-by-baseline HbA1c interaction was not significant (p=0.22) and was also not significant for US-approved and non-US-approved Lantus subgroups analyzed separately. As discussed in Dr. Pian's review, this interaction test examines whether the difference in treatment effects of Basaglar and Lantus depends on baseline HbA1c. This test does not provide information on whether the treatment effect of Basaglar relative to placebo depends on baseline HbA1c.

The following figures from Dr. Pian's review show regression analysis of change in HbA1c from baseline by baseline HbA1c. It is interesting that for the US-approved Lantus subgroup, the treatment effect of Lantus appears to be greater for a higher baseline HbA1c, i.e. compared with the EU-approved Lantus subgroup.



Type 2 diabetes trial

Table 9 shows the primary efficacy analysis results conducted by the FDA statistical reviewer. ANCOVA results showed that treatment difference (Basaglar-Lantus) in HbA1c change from baseline to week 24 was +0.05% with an upper 95% CI of +0.17% meeting the non-inferiority margin. It is concluded that Basaglar was noninferior to Lantus in patients with T2DM. The results by subgroup were similar.

Table 9 - ANCOVA of Change in HbA1c from Baseline to Week 24 (LOCF) Study ABEC

	ABEC		US subgroup		EU subgroup	
Treatment n	**LY n=369**	**Lantus n=375**	**LY n=205**	**US Lantus n=213**	**LY n=164**	**EU Lantus n=162**
LSM Baseline (SE)	8.32 (0.08)	8.28 (0.08)	8.43 (0.10)	8.30 (0.10)	8.26 (0.10)	8.32 (0.10)
LSM Change (SE)	-1.29 (0.06)	-1.34 (0.06)	-1.29 (0.08)	-1.30 (0.08)	-1.25 (0.09)	-1.36 (0.09)
Treatment difference [95% CI], p-value	**+0.05 [-0.07, +0.17] p=0.40**		**+0.01 [-0.15, +0.18] p=0.88**		**+0.11 [-0.07, +0.29] p=0.23**	

*Model includes treatment, country, sulfonylurea use and time of baseline basal insulin injection (daytime or evening/bedtime) as fixed effects and baseline HbA1c as covariate

Source: Dr. Pian's review

Sensitivity analyses: the mixed model repeated measure (MMRM) analysis results conducted by Dr. Pian are similar to the ANCOVA (LOCF) results.

Subgroup analyses

Dr. Pian confirmed the Sponsor's analyses that there were no significant treatment by subgroup interactions.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary endpoints were change in HbA1c from baseline to 6, 12, 24, 36, and 52 weeks, 7-point SMBG, percentage of patients reaching glycemic goals, daily basal insulin dose, lispro insulin dose for trial ABEB, total daily insulin dose, weight and body mass index (BMI).

Not all secondary endpoints are reviewed here, only those considered important for the risk/benefit assessment.

Note that Dr. Pian's review includes an analysis of SMBG results. She did not report any notable findings. This review does not consider SMBG results because endpoints derived from home glucometers are less reliable than centrally measured glucose values. Not only are they subject to reporting bias, but glucometer readings are often unreliable in the extreme glucose ranges, i.e. high or low. There was no centrally measured fasting plasma glucose endpoint.

Type 1 diabetes trial

Proportion of patients reaching glycemic target of less than 7%

Proportion of patients reaching the American Diabetes Association target HbA1c of less than 7% at week 24 and the Fisher's exact test results for study ABEB are shown in Table 10. There was no statistically significant difference in the proportion of patients reaching target between the treatment groups. Treatment-by subgroup interaction was not significant (p=0.28).

Table 10 – Proportion of patients achieving HbA1c < 7% at Week 24 Study ABEB

	LY n=267	Lantus n=267	Treatment Difference	p-value
US-approved Lantus	30/98 (31%)	30/96 (31%)	-0.6% [-14%, +12%]	0.92
EU-approved Lantus	62/169 (37%)	56/171 (33%)	+4% [-6%, +14%]	0.45
Study ABEB	92 (34%)	86 (32%)	+2% [-6%, +10%]	0.58

Source: Dr. Pian's review

Analyses of insulin doses

As this was a trial in type 1 diabetes patients, all were on insulin therapy prior to study enrollment. In this type of study it is important to examine the comparative change from baseline in insulin dose between study groups as insulin is a titratable drug and efficacy parameters depend on insulin doses achieved.

In Dr. Pian's analysis (table 11) there was no statistically significant difference in change in basal, prandial, or total insulin dose from baseline to week 24 between treatment groups, whether examining the entire study population or by US-approved/non-US-approved Lantus subgroups.

Table 11–ANCOVA for insulin (U/day) dose change at week 24 (LOCF) Study ABEB

Basal Insulin

	US-approved		EU-approved		ABEB	
LSmeans	LY2963016 n=99	Lantus n=96	LY2963016 n=169	Lantus n=170	LY2963016 n=268	Lantus n=266
Baseline (SE)	30.7 (1.53)	27.7 (1.55)	24.9 (0.96)	23.9 (0.99)	25.7 (0.91)	24.0 (0.93)
Change (SE)	2.1 (0.79)	2.2 (0.80)	-1.03 (1.24)	-2.01 (1.27)	2.0 (0.51)	2.0 (0.52)
Trt diff [95% CI] p-value	-0.07 [-2.18, +2.04] p=0.95		+0.02 [-1.15, +1.19] p=0.98		-0.01 [-1.07, +1.06] p=0.99	

Lispro (prandial insulin)

	US-approved		EU-approved		ABEB	
LSmeans	LY2963016 n=96	Lantus n=96	LY2963016 n=168	Lantus n=170	LY2963016 n=264	Lantus n=266
Baseline (SE)	29.3 (2.0)	25.0 (2.0)	27.6 (1.6)	28.4 (1.7)	27.6 (1.34)	26.5 (1.35)
Change (SE)	-2.38 (1.70)	-1.09 (1.70)	-1.03 (1.24)	-2.01 (1.27)	-1.28 (1.07)	-1.44 (1.09)
Trt diff [95% CI] p-value	-1.3 [-5.8, +3.2] p=0.573		+0.98 [-1.43, 3.39] p=0.43		+0.16 [-2.1, +2.4] p=0.888	

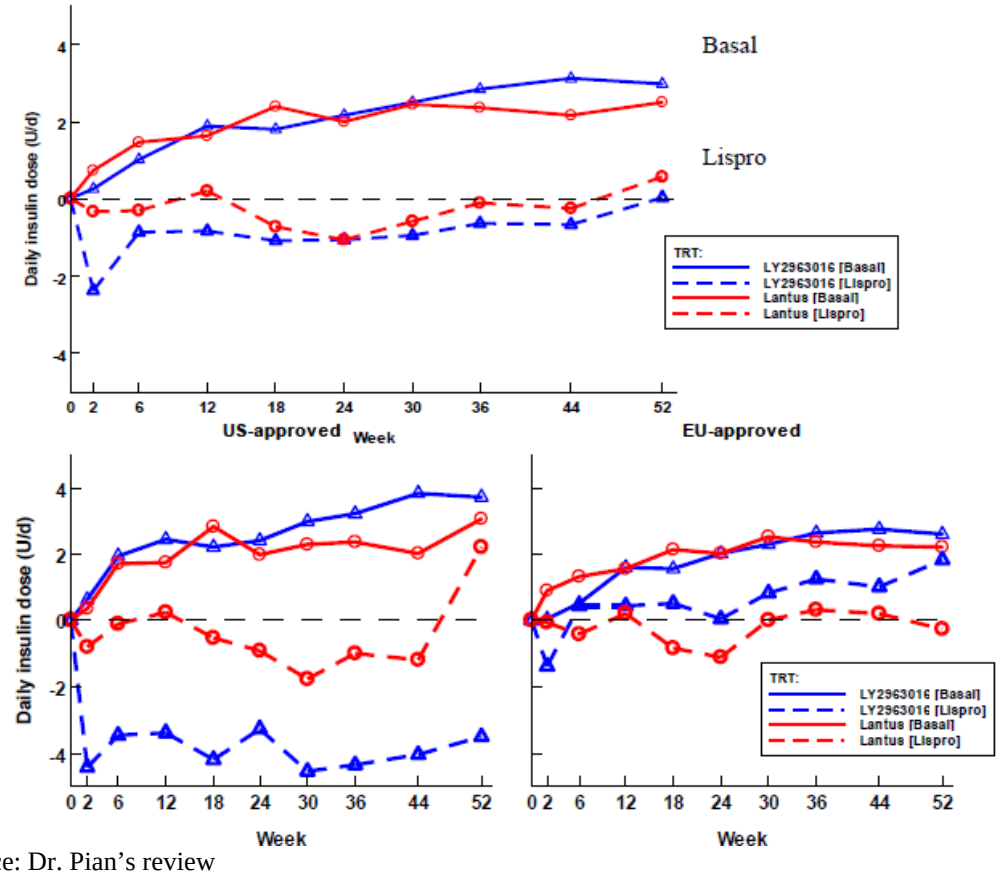
Total insulin (basal plus prandial)

	US-approved		EU-approved		ABEB	
LSmeans	LY2963016 n=96	Lantus n=96	LY2963016 n=168	Lantus n=170	LY2963016 n=264	Lantus n=266
Baseline (SE)	59.7 (3.1)	52.7 (3.1)	52.7 (2.2)	52.4 (2.2)	53.4 (1.9)	50.5 (1.9)
Change (SE)	-0.13 (1.93)	+1.08 (1.93)	+1.31 (1.44)	+0.33 (1.47)	0.75 (1.23)	0.55(1.24)
Trt diff [95% CI] p-value	-1.21 [-6.29, +3.88] p=0.64		+0.98 [-1.82, +3.77] p=0.49		+0.20 [-2.36, +2.75] p=0.88	

Source: Dr. Pian's review

Insulin doses were also plotted over time in the figures below. Note that the figures show data out to week 52, although the primary efficacy endpoint was at week 24. For the overall group the doses appear relatively similar, but for the US-approved Lantus subgroup, it appears that the Basaglar arm received less prandial insulin compared to the Lantus arm. It is possible that this difference contributed to the efficacy finding of a worse HbA1c response in the Basaglar arm for the US-approved Lantus subgroup analysis.

Mean change from baseline in daily insulin dose (U/day) study ABEB



Source: Dr. Pian's review

Body weight

The Sponsor analyzed body weight changes from baseline to study endpoint between treatment groups. The LS mean increases from baseline to the 24-week endpoint (LOCF) were 0.66 kg and 0.42 kg in the Basaglar and Lantus groups, respectively; increases at the 52-week endpoint (LOCF) were 0.93 kg and 0.59 kg, respectively. Similar results were observed for BMI There were no statistically significant differences between treatment groups for actual mean body weight or change in body weight or BMI from baseline at any visit or endpoints (LOCF) based on ANCOVA analyses.

For labeling purposes it would be acceptable to note that changes in body weight were not clinically significant and there was no difference between treatment groups.

Type 2 diabetes trial

Proportion of patients reaching glycemic target of less than 7%
Treatment difference in the proportion of patients with HbA1c<7% was not statistically significant (Table 12). No treatment-by-subgroup interaction was detected (p=0.27) by Dr. Pian. It is notable however, that the proportion of patients reaching the glycemic target was numerically lower for Basaglar in the Basaglar vs. US approved Lantus comparison.

Table 12 – Proportion of patients achieving HbA1c < 7% at Week 24 Study ABEC

	LY2963016	Lantus	Treatment Difference	p-value
US-approved Lantus	87/205 (41%)	110/213 (52%)	-9.2% [-19%, +0.3%]	0.06
EU-approved Lantus	93/164 (57%)	87/162 (54%)	+3% [-8%, +14%]	0.59
Study ABEB	180/369 (49%)	197/375 (53%)	-4% [-11%, +3%]	0.31

Analyses of insulin doses

Treatment difference in basal insulin change (U/d) from baseline to week 24 was not statistically significant for both the entire study population and for the subgroup analyses of US-approved Lantus and non-US-approved Lantus (Table 13).

Table 13–ANCOVA for insulin (U/day) dose change at week 24 (LOCF) Study ABEC

	ABEC		US-approved Lantus		EU-approved Lantus	
LSmeans (SE)	LY2963016 n=374	Lantus n=379	LY2963016 n=209	Lantus n=214	LY2963016 n=165	Lantus n=165
Baseline (SE)	15.4 (1.2)	12.0 (1.2)	19.2 (2.5)	13.3 (2.5)	11.0 (1.55)	9.6 (1.54)
Change (SE)	32.3 (2.5)	32.6 (2.5)	51.2 (3.57)	49.9 (3.62)	28.5 (2.45)	31.0 (2.44)
Trt difference [95% CI] p-value	-0.27 [-0.51, +4.60) p=0.913		+1.3 [-6.34, +9.00] p=0.736		-2.48 [-7.68, +2.71] p=0.347	

ANCOVA model included treatment, country and time of baseline basal insulin injection (Daytime or Evening/Bedtime) as fixed effects and baseline HbA1c as covariate

Source: Dr. Pian's review

Body weight

The Sponsor analyzed body weight changes from baseline to study endpoint between treatment groups. Change from baseline was approximately +2 kg in both treatment groups.

For labeling purposes it would be acceptable to note that changes in body weight were not clinically significant and there was no difference between treatment groups.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety data comes from the Phase 3 studies ABEB and ABEC. Data from phase 2 studies were to be included if appropriate, i.e. for deaths or rare events.

7.1.2 Categorization of Adverse Events

A treatment emergent adverse event (TEAE) was defined as an event that was newly reported or worsened in severity after randomization and categorized using MedDRA Version 15.1.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The two pivotal phase 3 studies were pooled to estimate and compare incidence of deaths, serious adverse events, events leading to dropout, and other rare events because this larger pool allows for better examination of any differences between Basaglar and comparator for less common events.

Hypoglycemia, common adverse events, and immunogenicity are analyzed separately for the two diabetes types because the two diseases are distinct and the rates of these safety issues are not expected to be similar between the two diabetes populations.

For safety assessments, the data presented below are 'pooled' in terms of the US-approved Lantus patients and the non-US-approved Lantus patients. This reviewer agrees with the Sponsor's conclusion that safety findings were not different across the two subgroups. This review presents data using the entire safety population because there were no differences in safety outcomes between the subgroups.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The overall exposure to Basaglar adheres to agreements made between FDA and the Sponsor at presubmission meetings. FDA recommended roughly 500 patients per trial, in two trials (Table 14).

Table 14 - Exposure to BASAGLAR and Lantus in Phase 3 Studies

Variable	LY2963016 (N=644)	Lantus (N=647)	Total (N=1291)
Exposure Duration in Years			
Mean	0.64	0.64	0.64
Standard Deviation	0.29	0.30	0.29
Minimum	0.00	0.00	0.00
Median	0.47	0.47	0.47
Maximum	1.08	1.07	1.08
Total Patient- Years	414.61	416.60	831.21

Source: Table 2.7.4.4 ISS

Subject characteristics of the safety database were as follows: The overall mean age of patients was 51.5 years, with a total of 239 patients that were at least 65 years of age (Basaglar: 126 patients [19.6%]; Lantus: 113 patients [17.5%]), and 36 patients that were at least 75 years of age (Basaglar: 23 patients [3.6%]; Lantus: 13 patients [2.0%]). Most patients were White (76.8%) and approximately half of the patients were male (53.3%). Mean baseline HbA1c was 8.10% in both treatment groups.

The mean body mass index (BMI) of patients was similar across treatment groups (Basaglar: 29.31 kg/m^2; Lantus: 29.22 kg/m^2).

Slightly less than half of the patients in both treatment groups were enrolled at sites in the US-approved-Lantus region (US and Puerto Rico) (Basaglar: 48.0%; Lantus 48.1%) and approximately 63% of patients injected their insulin in the evening/bedtime.

The majority of patients in both treatment groups had normal renal function (Basaglar: 448 patients [69.6%]; Lantus: 455 patients [70.3%]); the remaining patients had mild to severe renal impairment, and were similarly distributed between treatment groups.

The safety population appears adequately representative of the US diabetes population in order to reliably apply the safety findings of this review to the risk/benefit assessment of Basaglar.

7.2.2 Explorations for Dose Response

Insulins in this trial were titrated to glycemic goals; explorations for dose response are not applicable.

7.2.3 Special Animal and/or In Vitro Testing

None

7.2.4 Routine Clinical Testing

Routine clinical testing included the safety assessments described in section 5 of this review

7.2.5 Metabolic, Clearance, and Interaction Workup

See section 4 – Clinical Pharmacology

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Hypoglycemia is the major adverse event associate with insulin use. Hypoglycemia is reviewed in sections 6 and 7.3.4.

Immune reactions are also potential adverse events associated with insulin use. Immunogenicity was assessed by antibody measurements and is discussed in section 7.4.6.

7.3 Major Safety Results

Note: data tables in this section are sourced from the Integrated Summary of Safety in the submission.

7.3.1 Deaths

There were a total of 3 deaths in the Phase 3 studies (Basaglar: 1 patient; Lantus: 2 patients).

Patient 6007 (Study ABEC, BASAGLAR), a 68-year-old female, insulin-naïve patient with a medical history that included hypertonia, hyperlipoproteinemia, and diabetes mellitus, experienced an SAE of lung adenocarcinoma with a fatal outcome approximately 7 months after initiating study drug (duration of treatment with study drug was approximately 5 months).

Patient 9709 (Study ABEB, LANTUS), a 48-year-old female using Lantus prior to study entry, had a medical history that included cardiomyopathy and hyperlipidemia. The patient experienced an SAE of hypertrophic cardiomyopathy with a fatal outcome approximately 6 months after initiating study drug. The actual date of the last dose of study drug was unknown.

Patient 3505 (Study ABEC, LANTUS), a 67-year-old male using Lantus prior to study entry, had a medical history that included arrhythmia, hypertension, hyperlipoproteinemia, and diabetes mellitus. The patient experienced an SAE of myocardial infarction with a fatal outcome approximately 1 month after initiating study drug.

Reviewer's comment: There is no imbalance in deaths. Further, the deaths are not from unusual causes for a population of diabetes patients. This reviewer has no safety concerns regarding these data.

7.3.2 Nonfatal Serious Adverse Events

There was no apparent difference in the incidence of SAEs in the Phase 3 studies (BASAGLAR: 35 patients [5.4%]; LANTUS: 42 patients [6.5%]). (Table 15)

The most frequently reported SAE in the Phase 3 studies was hypoglycemia, occurring in 15 patients (2.3%) in each treatment group. Additional SAEs reported by more than 1 patient included coronary artery disease (BASAGLAR: 1 patient [0.2%]; LANTUS: 3 patients 0.5%]), cellulitis (BASAGLAR: 2 patients [0.3%]; LANTUS: 1 patient [0.2%]), bronchitis (BASAGLAR: 1 patient [0.2%]; LANTUS: 1 patient [0.2%]), chest pain (BASAGLAR: 1

patient [0.2%]; LANTUS: 1 patient [0.2%]), pregnancy (BASAGLAR: 0 patients; LANTUS: 2 patients [0.3%]), and suicidal ideation (BASAGLAR: patients [0.3%]; LANTUS: 0 patients). For every other preferred term, SAEs occurred in 1 patient only.

Table 15 –Serious Adverse Events – Safety Population

Preferred Term	LY2963016 (N=644) n	(%)	Lantus (N=647) n	(%)
Patients with >= 1 SAE	35	(5.4)	42	(6.5)
Hypoglycaemia	15	(2.3)	15	(2.3)
Coronary artery disease	1	(0.2)	3	(0.5)
Cellulitis	2	(0.3)	1	(0.2)
Bronchitis	1	(0.2)	1	(0.2)
Chest pain	1	(0.2)	1	(0.2)
Pregnancy	0	(0.0)	2	(0.3)
Suicidal ideation	2	(0.3)	0	(0.0)
Acute tonsillitis	0	(0.0)	1	(0.2)
Alcohol poisoning	1	(0.2)	0	(0.0)
Asthma	1	(0.2)	0	(0.0)
Bladder cancer	0	(0.0)	1	(0.2)
Cardiac failure congestive	1	(0.2)	0	(0.0)
Cardiac operation	0	(0.0)	1	(0.2)
Carotid arteriosclerosis	0	(0.0)	1	(0.2)
Cerebral ischaemia	0	(0.0)	1	(0.2)
Cerebrovascular accident	1	(0.2)	0	(0.0)
Cholecystitis	1	(0.2)	0	(0.0)
Clostridial infection	1	(0.2)	0	(0.0)
Coeliac disease	1	(0.2)	0	(0.0)
Constipation	0	(0.0)	1	(0.2)
Convulsion	0	(0.0)	1	(0.2)
Deep vein thrombosis	1	(0.2)	0	(0.0)
Dehydration	1	(0.2)	0	(0.0)
Diverticulitis	0	(0.0)	1	(0.2)
Exostosis of jaw	0	(0.0)	1	(0.2)
Femoral artery occlusion	1	(0.2)	0	(0.0)
Fistula	1	(0.2)	0	(0.0)
Gangrene	1	(0.2)	0	(0.0)
Gastroenteritis	0	(0.0)	1	(0.2)
Gliomatosis cerebri	0	(0.0)	1	(0.2)
Hypertension	1	(0.2)	0	(0.0)
Hypertensive crisis	1	(0.2)	0	(0.0)
Hypertrophic cardiomyopathy	0	(0.0)	1	(0.2)
Hypotension	0	(0.0)	1	(0.2)
Intestinal obstruction	1	(0.2)	0	(0.0)
Ketoacidosis	0	(0.0)	1	(0.2)
Lung adenocarcinoma	1	(0.2)	0	(0.0)
Lung carcinoma cell type unspecified recurrent	1	(0.2)	0	(0.0)

Lung infection	1	(0.2)	0	(0.0)
Maternal exposure during pregnancy	0	(0.0)	1	(0.2)
Myocardial infarction	0	(0.0)	1	(0.2)
Nasal septum deviation	0	(0.0)	1	(0.2)
Open wound	0	(0.0)	1	(0.2)
Pancytopenia	0	(0.0)	1	(0.2)
Pneumonia bacterial	1	(0.2)	0	(0.0)
Psychotic disorder	1	(0.2)	0	(0.0)
Pulmonary embolism	1	(0.2)	0	(0.0)
Pulmonary oedema	0	(0.0)	1	(0.2)
Subclavian artery occlusion	0	(0.0)	1	(0.2)
Suicide attempt	0	(0.0)	1	(0.2)
Syncope	0	(0.0)	1	(0.2)
Toxicity to various agents	1	(0.2)	0	(0.0)
Trigeminal neuralgia	1	(0.2)	0	(0.0)
Upper limb fracture	0	(0.0)	1	(0.2)

Source: Table 2.7.4.9 ISS

Reviewer's comment: The data regarding serious adverse events do not suggest a safety signal for Basaglar. The serious adverse events appear to be related to diabetes itself (i.e. coronary artery disease) or events likely unrelated to insulin glargine use (i.e. bronchitis).

7.3.3 Dropouts and/or Discontinuations

Dropouts due to adverse events were less frequent among Basaglar-treated patients compared to the Lantus–treated patients (Table 16). There did not appear to be a clustering of preferred terms reported as reasons for discontinuation.

Reviewer's comment: the data regarding dropouts due to adverse events do not suggest a safety signal for Basaglar. The events span multiple system organ classes and preferred terms. Moreover, injection site reactions are not an important reason for discontinuation, and a similar number of patients discontinued due to injection site reactions between treatment groups (one in Basaglar and two in Lantus).

Table 16 - Adverse Events Leading to Discontinuation Summary by Preferred Term

Preferred Term	LY2963016 (N=644) n (%)	LANTUS® (N=647) n (%)	Total (N=1291) n (%)
Patients with ≥1 discontinuation due to AE	8 (1.2)	17 (2.6)	25 (1.9)
Injection site pain	1 (0.2)	1 (0.2)	2 (0.2)
Maternal exposure during pregnancy	1 (0.2)	1 (0.2)	2 (0.2)
Anxiety	0 (0.0)	1 (0.2)	1 (0.1)
Cardiac operation	0 (0.0)	1 (0.2)	1 (0.1)
Coronary artery disease	0 (0.0)	1 (0.2)	1 (0.1)
Fatigue	0 (0.0)	1 (0.2)	1 (0.1)
Fluid retention	0 (0.0)	1 (0.2)	1 (0.1)
Gliomatosis cerebri	0 (0.0)	1 (0.2)	1 (0.1)
Hypertrophic cardiomyopathy	0 (0.0)	1 (0.2)	1 (0.1)
Hypoglycemia	0 (0.0)	1 (0.2)	1 (0.1)
Hypotension	0 (0.0)	1 (0.2)	1 (0.1)
Injection site mass	0 (0.0)	1 (0.2)	1 (0.1)
Intestinal obstruction	1 (0.2)	0 (0.0)	1 (0.1)
Lung adenocarcinoma	1 (0.2)	0 (0.0)	1 (0.1)
Lung carcinoma cell type unspecified recurrent	1 (0.2)	0 (0.0)	1 (0.1)
Myocardial infarction	0 (0.0)	1 (0.2)	1 (0.1)
Paraesthesia oral	0 (0.0)	1 (0.2)	1 (0.1)
Pregnancy	0 (0.0)	1 (0.2)	1 (0.1)
Psychotic disorder	1 (0.2)	0 (0.0)	1 (0.1)
Refractory cytopenia with unilineage dysplasia	0 (0.0)	1 (0.2)	1 (0.1)
Suicidal ideation	1 (0.2)	0 (0.0)	1 (0.1)
Suicide attempt	0 (0.0)	1 (0.2)	1 (0.1)
Tension headache	1 (0.2)	0 (0.0)	1 (0.1)

Abbreviations: AE = adverse event; N = total number of patients in specified treatment group; n = number of patients in specified category.
Sources: ABEB Final CSR (Table ABEB.14.42); ABEC CSR (Table ABEC.14.40).
Source: Table 2.7.4.10 ISS

7.3.4 Significant Adverse Events

Hypoglycemia is a significant adverse event associated with all insulin products. The aim of this review was to determine if the incidence of hypoglycemia was similar between Basaglar and Lantus, rather than focusing on the actual incidence which can vary depending on the population studied and the level of glycemia control achieved.

In the Phase 3 studies, hypoglycemic events were categorized as the following:

- Total hypoglycemia—any event that met the criteria for documented symptomatic hypoglycemia, asymptomatic hypoglycemia, and unspecified hypoglycemia, all with a threshold of blood glucose (BG) ≤70 mg/dL, if available. Events meeting the criteria for probable symptomatic hypoglycemia and severe hypoglycemia, as defined below, were also included. Total hypoglycemia using a BG threshold of <54 mg/dL, if available, was also evaluated.

- Severe hypoglycemia—any event that required the assistance of another person to actively administer carbohydrate, glucagons, or other resuscitative actions. These events may have been associated with sufficient neuroglycopenia to induce seizure or coma. Blood glucose measurements may not have been available during such an event, but neurological recovery attributable to the restoration of BG to normal was considered sufficient evidence that the event was induced by low BG.

Severe hypoglycemia was further divided into the following 4 additional subcategories:

- Severe hypoglycemia with a BG <54 mg/dL (major hypoglycemic event)
- Severe hypoglycemia with BG ≤70 mg/dL
- Severe hypoglycemia not biochemically confirmed because the BG was missing: no BG was obtained prior to administration of treatment or at the time of neuroglycopenic symptoms
- Severe hypoglycemia not biochemically confirmed because the BG was not aligned with severe symptoms: the event was reported/confirmed by the investigator as a severe hypoglycemia event associated with neuroglycopenic symptoms or cognitive impairment that required assistance for active administration of glucose or glucagon for recovery, but a BG >70 mg/dL was reported on the case report form (CRF) that could not be resolved through queries.

Reviewer's comment: In the Lantus label 'severe symptomatic hypoglycemia' was defined as an event with symptoms consistent with hypoglycemia requiring the assistance of another person and associated with either a blood glucose below 50 mg/dL (≤56 mg/dL in the 5-year trial) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration. This definition is slightly different than the definition used in the Basaglar program. Therefore the Basaglar label should include a notation that specifies the definition of severe hypoglycemia used.

Other definitions of hypoglycemia used in the study:

- Nocturnal hypoglycemia—any event that occurred between bedtime and waking, with a BG threshold ≤70 mg/dL. These events were also evaluated using a BG threshold of <54 mg/dL.
- Non-nocturnal hypoglycemia—any event that occurred between waking and bedtime, with a BG threshold ≤70 mg/dL or <54 mg/dL.
- Documented symptomatic hypoglycemia—any event during which typical symptoms of hypoglycemia were accompanied by a measured BG concentration ≤70 mg/dL or <54 mg/dL.
- Asymptomatic hypoglycemia—any event not accompanied by typical symptoms of hypoglycemia but with a measured BG concentration ≤70 mg/dL or BG <54 mg/dL.
- Probable symptomatic hypoglycemia—any event during which symptoms of hypoglycemia were not accompanied by a BG measurement, but the event was presumably caused by a low BG concentration.

- Relative hypoglycemia—any event during which the patient with diabetes reported any of the typical symptoms of hypoglycemia and interpreted those as indicative of hypoglycemia but with a measured BG concentration >70 mg/dL or ≥54 mg/dL.
- Unspecified hypoglycemia—any event during which BG concentration was ≤70 mg/dL or BG <54 mg/dL, but no information relative to symptoms of hypoglycemia was recorded.

Reviewer's comment: The Sponsor's table of comparative incidence of hypoglycemia is shown below. However, it is noted that the most specific definition of hypoglycemia (the definition as a whole, not the subcategories) is the 'severe' definition. This is the definition that this reviewer recommends for labeling. Analyses using the rest of the definitions should be considered supportive, because they rely on subjective reporting of symptoms and data derived from point of care blood glucose monitor which is often inaccurate at the lower range.

Summaries of the overall incidence and rate of each category/subcategory of hypoglycemia are presented by individual study rather than pooled due to the different patient populations (T1DM and T2DM) and the disparity in the incidence and rate of hypoglycemia in these 2 patient populations. This approach was agreed upon at the pre-NDA meeting with the Agency.

There were no significant differences between treatment groups for the overall incidence of each category/subcategory of hypoglycemia in Study ABEB and Study ABEC (Table 17).

Table 17 - Incidence of Hypoglycemia

	ABEB (T1DM)					ABEC (T2DM)				
	LY2963016 (N=268)		LANTUS® (N=267)			LY2963016 (N=376)		LANTUS® (N=380)		
Category/Subcategory	n (%)	Events	n (%)	Events	p-value[a]	n (%)	Events	n (%)	Events	p-value[a]
Total hypoglycemia										
BG ≤70 mg/dL, if available	256 (95.5)	19,541	259 (97.0)	20,852	.495	296 (79.4)	3564	292 (77.7)	3845	.594
BG <54 mg/dL, if available	236 (88.1)	6098	238 (89.1)	6594	.786	158 (42.4)	580	163 (43.4)	689	.825
Severe hypoglycemia	10 (3.7)	13	11 (4.1)	16	.828	2 (0.5)	7	2 (0.5)	2	
BG ≤70 mg/dL	6 (2.2)	6	6 (2.2)	9	>.999	1 (0.3)	6	2 (0.5)	2	
BG <54 mg/dL	5 (1.9)	5	6 (2.2)	9	.772	1 (0.3)	2	1 (0.3)	1	
BG missing	4 (1.5)	7	7 (2.6)	7	.382	1 (0.3)	1	0 (0.0)	0	
BG not aligned with severe symptoms	0 (0.0)	0	0 (0.0)	0		0 (0.0)	0	0 (0.0)	0	
Nocturnal hypoglycemia										
BG ≤70 mg/dL	231 (86.2)	4105	235 (88.0)	4485	.606	212 (56.8)	1248	203 (54.0)	1386	.462
BG <54 mg/dL	187 (69.8)	1584	194 (72.7)	1605	.504	98 (26.3)	250	98 (26.1)	267	>.999
Non-nocturnal hypoglycemia										
BG ≤70 mg/dL	252 (94.0)	15,184	257 (96.3)	16,140	.315	269 (72.1)	2289	265 (70.5)	2451	.629
BG <54 mg/dL	228 (85.1)	4446	226 (84.6)	4943	.905	118 (31.6)	326	122 (32.4)	422	.815
Documented symptomatic hypoglycemia										
BG ≤70 mg/dL	238 (88.8)	11,853	240 (89.9)	13,581	.780	221 (59.2)	1819	221 (58.8)	1825	.941
BG <54 mg/dL	210 (78.4)	4239	214 (80.1)	4888	.670	116 (31.1)	384	120 (31.9)	400	.814
Asymptomatic hypoglycemia										
BG ≤70 mg/dL	216 (80.6)	7021	219 (82.0)	6555	.740	241 (64.6)	1603	246 (65.4)	1856	.819
BG <54 mg/dL	126 (47.0)	1473	123 (46.1)	1309	.863	53 (14.2)	119	68 (18.1)	197	.165

Probable symptomatic hypoglycemia	71 (26.5)	297	71 (26.6)	297	>.999	43 (11.5)	64	39 (10.4)	80	.641
Relative hypoglycemia										
BG >70 mg/dL	14 (5.2)	40	9 (3.4)	11	.394	36 (9.7)	76	29 (7.7)	57	.366
BG ≥54 mg/dL	225 (84.0)	7654	227 (85.0)	8704	.811	214 (57.4)	1511	219 (58.2)	1482	.825
Unspecified hypoglycemia										
BG ≤70 mg/dL	31 (11.6)	370	29 (10.9)	419	.891	27 (7.2)	78	26 (6.9)	84	.888
BG <54 mg/dL	16 (6.0)	88	19 (7.1)	100	.605	6 (1.6)	9	8 (2.1)	11	.789

Abbreviations: BG = blood glucose; N = total number of patients; n = number of patients in the specified category; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

[a] Treatment comparison was analyzed using the Fisher's Exact test or Pearson's Chi-square test. To avoid computational problems for p-value calculation, a maximum computation time = 5 minutes was programmed into the analysis for Fisher's Exact test. If it did not converge in this time, then Pearson's Chi-square test was used.

Note: If the number of patients with a hypoglycemic event was ≤10, then no analysis was performed.

A Total Hypoglycemic Event was an event which was either a documented symptomatic, asymptomatic, or unspecified hypoglycemia with a BG ≤70 mg/dL or <54 mg/dL, a probable symptomatic hypoglycemic event, or a severe hypoglycemic event.

Hypoglycemia analyses using the same definitions, but analyzing event rates also showed no differences between study groups for either the T1DM trial or the T2DM trial.

Reviewer's comment: the overall data show clearly that there is no difference in hypoglycemia risk between the two insulins. The consistent findings across all definitions of hypoglycemia are reassuring that the data are reliable.

Comparative hypoglycemia data should not be included in labeling. Although generally considered a safety endpoint, hypoglycemia is often regarded as an efficacy endpoint, in that reduction of hypoglycemia rates are sought after properties for any new insulin product. A labeling claim of a reduction in hypoglycemia should require a rigorous assessment with a trial designed and powered for this endpoint. The current phase 3 trials were not designed as such. Further the numerically worse HbA1c response for Basaglar may make a comparative hypoglycemia claim, albeit of similarity, misleading.

7.3.5 Submission Specific Primary Safety Concerns

Allergic and injection site reactions

Allergic events and injection site reactions were examined by an initial blinded review of preferred terms by SOC in order to allow identification of all possible cases of allergic events. As an initial reference for the blinded review, the Sponsor considered a list of prespecified MedDRA allergic preferred terms.

Table 18 shows frequencies of adverse events related to allergic and injection site reactions.

Table 18 – Adverse Events of Allergic or Injection Site Reactions

System Organ Class Preferred Term	LY2963016 (N=644) n	 (%)	Lantus (N=647) n	 (%)
Patients with >= 1 TEAE	41	(6.4)	38	(5.9)
Skin and subcutaneous tissue disorders	15	(2.3)	16	(2.5)
Pruritus	7	(1.1)	5	(0.8)
Rash	5	(0.8)	5	(0.8)
Dermatitis	1	(0.2)	2	(0.3)
Angioedema	1	(0.2)	0	(0.0)
Dermatitis allergic	1	(0.2)	0	(0.0)
Photosensitivity reaction	1	(0.2)	0	(0.0)
Rash macular	0	(0.0)	1	(0.2)
Rash papular	0	(0.0)	1	(0.2)
Rash pruritic	0	(0.0)	1	(0.2)
Rash vesicular	0	(0.0)	1	(0.2)
Urticaria	0	(0.0)	1	(0.2)
Musculoskeletal and connective tissue disorders	11	(1.7)	14	(2.2)
Arthralgia	10	(1.6)	13	(2.0)
Arthritis	1	(0.2)	0	(0.0)
Periarthritis	0	(0.0)	1	(0.2)
General disorders and administration site conditions	11	(1.7)	6	(0.9)
Injection site reaction	6	(0.9)	5	(0.8)
Injection site induration	2	(0.3)	0	(0.0)
Injection site pruritus	1	(0.2)	1	(0.2)
Injection site nodule	1	(0.2)	0	(0.0)
Local swelling	1	(0.2)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	5	(0.8)	5	(0.8)
Asthma	3	(0.5)	5	(0.8)
Allergic respiratory symptom	1	(0.2)	0	(0.0)
Nasal oedema	1	(0.2)	0	(0.0)
Immune system disorders	1	(0.2)	1	(0.2)
Drug hypersensitivity	1	(0.2)	0	(0.0)
Hypersensitivity	0	(0.0)	1	(0.2)

Reviewer's comment: The only area of possible concern from the above data is injection site reactions which, when grouping the preferred terms of 'injection site reaction', 'injection site induration', injection site pruritis' and 'injection site nodule' shows a small imbalance not favoring Basaglar. In addition, it is unclear if any of the events in the SOC of skin and subcutaneous tissue disorders occurred in relation to an injection.

The Sponsor reported that each time an injection site AE occurred, 2 questionnaires, the Skin Evaluation Questionnaire (SKE) and Insulin Questionnaire-Injection Sites (IQIS) were to be completed. The questionnaires recorded an evaluation of the pain, pruritus, and rash associated with the injection along with the characteristics of the injection site (i.e., abscess, nodule, lipoatrophy, lipohypertrophy, or induration). A total of 3 patients (BASAGLAR: 2 patients; LANTUS: 1 patient) in the Phase 3 studies did not complete the SKE and IQIS after reporting injection site AEs; thus, further details regarding their injection site AEs are not included in the summary table below.

The data recorded by these questionnaires suggests that the slight imbalance in injection site reactions not favoring Basaglar is driven primarily by pain associated with injection. There was one case of skin abscess formation in the Basaglar group (Table 19).

Table 19 - Comparison of Injection Site Reactions based on Questionnaire Data

	LY2963016 (N=644) n (%)	Lantus (N=647) n (%)
Patients with >=1 Injection Site Adverse Event	20 (3.1)	14 (2.2)
Patients having pain associated with injection	16 (2.5)	7 (1.1)
Patients having pruritus associated with injection	6 (0.9)	5 (0.8)
Patients having rash associated with injection	5 (0.8)	4 (0.6)
Characteristics of the injection site		
Patients having episode of skin abscess formation	1 (0.2)	0 (0.0)
Patients having site related subcutaneous nodules	3 (0.5)	3 (0.5)
Patients having site related lipoatrophy	0 (0.0)	0 (0.0)
Patients having site related lipohypertrophy	1 (0.2)	1 (0.2)
Degree of induration		
<1 cm	1 (0.2)	2 (0.3)
>= 1 cm	3 (0.5)	1 (0.2)

Reviewer's comment: There are few events limiting conclusions, but there does not appear to be a safety signal for serious allergic or injection site reactions because the imbalance seems to be primarily drive by injection site pain.

Major Cardiac Adverse Events

As noted in section 1, parenteral insulins are currently exempt from the requirement to conduct cardiovascular safety risk assessment studies. Nevertheless, the listed drug Lantus conducted a cardiovascular outcomes trial (ORIGIN) that was reviewed by FDA and included in labeling for Lantus. ORIGIN was an open-label, randomized, 2-by-2, factorial design study. One intervention in ORIGIN compared the effect of Lantus to standard care on major adverse cardiovascular outcomes in 12,537 participants ≥50 years of age with abnormal glucose levels [i.e., impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT)] or early type 2 diabetes mellitus and established cardiovascular (i.e., CV) disease or CV risk factors at baseline. ORIGIN ruled out an excess cardiovascular risk for Lantus based on major cardiac adverse events (MACE) defined as a composite of CV death, nonfatal myocardial infarction and nonfatal stroke.

Based on the demonstration of sufficient similarity between Basaglar and Lantus, this reviewer recommends relying on FDA's findings of cardiovascular safety for Lantus in order to support

approval of Basaglar. Further the available data for Basaglar, although limited, at least do not suggest a cardiovascular safety signal.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the Phase 3 studies, the SOCs with the greatest incidence of total patients reporting AEs were infections and infestations (BASAGLAR: 30.7%; LANTUS: 30.1%), gastrointestinal disorders (BASAGLAR: 11.5%; LANTUS: 11.4%), musculoskeletal and connective tissue disorders (BASAGLAR: 9.3%; LANTUS: 8.5%), and respiratory, thoracic and mediastinal disorders (BASAGLAR: 9.0%; LANTUS: 8.2%) (Table 20).

Table 20 - Adverse Events (AEs) Occurring in ≥1% in Either Treatment Group by Preferred Term – T1DM and T2DM Patients Combined

Preferred Term	LY2963016 (N=644) n	(%)	Lantus (N=647) n	(%)
Patients with >= 1 TEAE	363	(56.4)	350	(54.1)
Nasopharyngitis	64	(9.9)	67	(10.4)
Upper respiratory tract infection	41	(6.4)	36	(5.6)
Diarrhoea	21	(3.3)	24	(3.7)
Back pain	19	(3.0)	19	(2.9)
Influenza	12	(1.9)	20	(3.1)
Cough	14	(2.2)	16	(2.5)
Hypoglycaemia	15	(2.3)	15	(2.3)
Headache	15	(2.3)	13	(2.0)
Sinusitis	15	(2.3)	11	(1.7)
Bronchitis	10	(1.6)	15	(2.3)
Hypertension	17	(2.6)	8	(1.2)
Arthralgia	10	(1.6)	13	(2.0)
Urinary tract infection	11	(1.7)	12	(1.9)
Gastroenteritis	10	(1.6)	12	(1.9)
Gastroenteritis viral	12	(1.9)	9	(1.4)

Nausea	9	(1.4)	11	(1.7)
Sinus congestion	11	(1.7)	9	(1.4)
Oropharyngeal pain	11	(1.7)	8	(1.2)
Vomiting	11	(1.7)	8	(1.2)
Dizziness	12	(1.9)	5	(0.8)
Weight increased	7	(1.1)	8	(1.2)
Oedema peripheral	6	(0.9)	8	(1.2)
Pain in extremity	7	(1.1)	7	(1.1)
Abdominal pain upper	4	(0.6)	9	(1.4)
Abnormal weight gain	10	(1.6)	3	(0.5)
Gastrooesophageal reflux disease	5	(0.8)	7	(1.1)
Pruritus	7	(1.1)	5	(0.8)
Musculoskeletal pain	4	(0.6)	7	(1.1)
Toothache	7	(1.1)	3	(0.5)

The incidence of AEs of dizziness was more than 2 times higher in the BASAGLAR group compared to the LANTUS group (BASAGLAR: 12 patients [1.9%]; LANTUS: 5 patients [0.8%]; p=.086). None of the events of dizziness were severe.

Reviewer's comment: The significance of this small imbalance in events of dizziness is unclear. This reviewer considers that it is likely due to chance because with this sample size, small imbalances are possible. (see also the imbalance in 'abdominal pain upper' and 'toothache' events).

There is also a higher incidence of 'abnormal weight gain' reported in the Basaglar group.

Reviewer's comment: There was no difference in body weight change between treatment groups in either of the two phase 3 trials; greater weight should be placed on the objective body weight data rather than adverse event reporting.

AEs for which the incidence is higher in the Basaglar group compared to the Lantus group and incidence is at least 2%

These events are shown in Table 21. Upper respiratory tract infection, back pain, headache, and sinusitis are common adverse events reported in clinical trials. However, hypertension is not a commonly reported adverse event.

Reviewer's comment: The reported adverse reactions are unlikely related to insulin therapy, but are common clinical events.

There was no difference in blood pressure change between treatment groups in either of the two phase 3 trials; greater weight should be placed on the objective data rather than adverse event reporting.

Table 21 – Adverse Reactions Occurring with Incidence at Least 2%

Adverse Reaction	Basaglar (N=644) %	Lantus (US-approved and non-US approved combined) (N=647)

		%
Upper respiratory tract infection	6.4	5.6
Back pain	3.0	2.9
Headache	2.3	2.0
Sinusitis	2.3	1.7
Hypertension	2.6	1.2

For labeling the Sponsor proposes presenting adverse reactions for the T1DM trial and the T2DM trial separately, with frequency at least 5%. This approach would be consistent with the listed drug label (Lantus) and is reasonable because the two diseases are distinct. The tables below are recommended for labeling by this reviewer.

Adverse Reactions in 52 Week Trial of Adults with Type 1 Diabetes (Adverse Events with overall incidence >5% and same or greater frequency in Basaglar group)

	Basaglar, % (n=268)	**Another insulin glargine product or non-US-approved insulin glargine product, % (n=267)**
Upper respiratory tract infection	22 (8.2%)	21 (7.9%)
Infection[a]	63 (23.5%)	64 (24.0%)

Adverse Reactions in 24 Week Trial of Adults with Type 2 Diabetes (Adverse Events with overall incidence >5% and occurring at same or greater frequency with Basaglar)

	Basaglar, % (n=376)	**Another insulin glargine product or non-US-approved insulin glargine product, % (n=380)**
Upper respiratory tract infection	19 (5.1%)	15 (3.9%)
Infection[a]	63 (16.8%)	59 (15.5%)

Note that in these tables adverse reactions are shown if they occur with a frequency 5% or greater and occur with greater frequency in the Basaglar arm. The Division's approach to labeling is to define adverse reactions as adverse events that occurred more commonly with the study drug.

7.4.2 Laboratory Findings

There were no notable findings with regard to chemistry (including liver-related) or hematology laboratory findings. There are no known safety signals for Lantus with regard to laboratory findings and the data submitted for Basaglar similarly suggest no safety signal.

7.4.3 Vital Signs

In the safety population (i.e. the two trials combined), systolic blood pressure decreased by an LS mean value of 1.28 mm Hg in the Basaglar group and increased by 0.42 mm Hg in the Lantus group (LS mean difference [SE]: -1.70 mm Hg [0.81]); p=0.04). The LS mean DBP values decreased in both treatment groups from baseline to endpoint (LOCF) (Basaglar: -0.89 mm Hg; Lantus: -0.35 mm Hg; p=0.3), and LS mean HR values increased very slightly in both groups

(Basaglar: 0.05 bpm; Lantus: 0.50 bpm; p=0.4). Note that p-values are provided for reference only; the trials were not powered to detect differences in these endpoints, and no adjustment for multiplicity was performed.

For the safety population, there was not a statistically significant treatment difference in the LS mean increase in body weight from baseline to endpoint (LOCF) (Basaglar: 1.60 kg; Lantus: 1.61 kg; p=1.0.) Similar results were observed for BMI. Results of the integrated analyses for weight and BMI were generally consistent with those observed in Study ABEB and Study ABEC.

Body weight and BMI are also discussed in section 6 – Efficacy.

7.4.4 Electrocardiograms (ECGs)

In the Phase 3 studies, electrocardiogram (ECG) measurements were performed only at Visit 1 to screen for eligibility. No routine follow-up ECGs were performed; thus, changes from baseline were not assessed. This is acceptable because there is no ECG-related safety signal with the listed drug Lantus, and no expected signal with Basaglar given its similarity to Lantus.

7.4.5 Special Safety Studies/Clinical Trials

See Immunogenicity 7.4.6

7.4.6 Immunogenicity

Please see the consult review from the Office of Biotechnology Products (OBP), Division of Therapeutic Proteins for a detailed discussion of immunogenicity. The primary review was completed by Faruk Sheikh, Ph.D.[17]

Dr. Sheikh recommended approval and concluded that there appeared to have no significant differences in immune response between Basaglar and Lantus treatment for the patients (T1DM and T2DM) with respect to detectable antibodies and cross-reactivity at any visit. The immunogenicity profile was similar with Basaglar and Lantus. (b) (4) .

To assess immunogenicity the Sponsor measured antibodies to insulin glargine/anti-drug antibodies (ADA) in the two pivotal phase 3 studies. Note that the Sponsor included both US and EU approved Lantus in their study, but the immunogenicity results were not available separately for US and EU products.

More than 80% of patients entering Study ABEB were already on Lantus at enrollment, and all had prior exposure to insulin. Approximately 40% of patients entering Study ABEC were on Lantus (60% of the patients enrolled in Study ABEC were insulin-naïve).

17 See review in DARRTS dated 10 Jul 2014

A brief summary of the ADA analysis follows (from the OBP consult report):
In the type 1 trial ABEB, 17% of the patients treated with LY2963016 were baseline positive for the presence of antibodies to insulin, compared to 20% baseline positive patients treated with Lantus. The total number of patients with detectable antibodies to Basaglar and to Lantus were similar (n=113 of 269 and n=113 of 267) for an overall rate of 42%. In patients that received Basaglar, 73 of 113 ADA+ patients remained ADA positive at the end of the study (week 52), compared to 59 of 113 patients who were treated with Lantus. Binding antibody levels among those that were ADA+ at visit 11 (last visit) was low (<1% total binding by RIP) for 37(51%) and 31 (52%) patients respectively. The fraction of ADA+ samples that cross-reacted with insulin was similar for both treatment groups (n=53 and 51 for Basaglar and Lantus respectively).

In the type 2 trial ABEC, the total number of patients that were positive for ADA at least once during the study was 62 for Basaglar and 49 for Lantus treated patients. At baseline, 20 subjects in the Basaglar group were positive for ADA compared to 13 subjects that received Lantus; their antibody levels did not change significantly during the study. Seroconversion rates were similar between groups with 12.6% of Basaglar and 10.7% Lantus- treated patients. At the end of the study (24 weeks), 30 patients remained positive for Basaglar, compared with 26 positives for Lantus.

As noted by Dr. Sheikh, the Sponsor has a validated (by the agency) binding assay for ADA to insulin glargine but does not have a neutralizing antibody assay. To assess the clinical impact of insulin glargine antibodies the Sponsor submitted analyses of the relationship between antibody levels (percent binding) and clinical outcomes, such as HbA1c and hypoglycemia. Correlational analyses did not show any important findings.

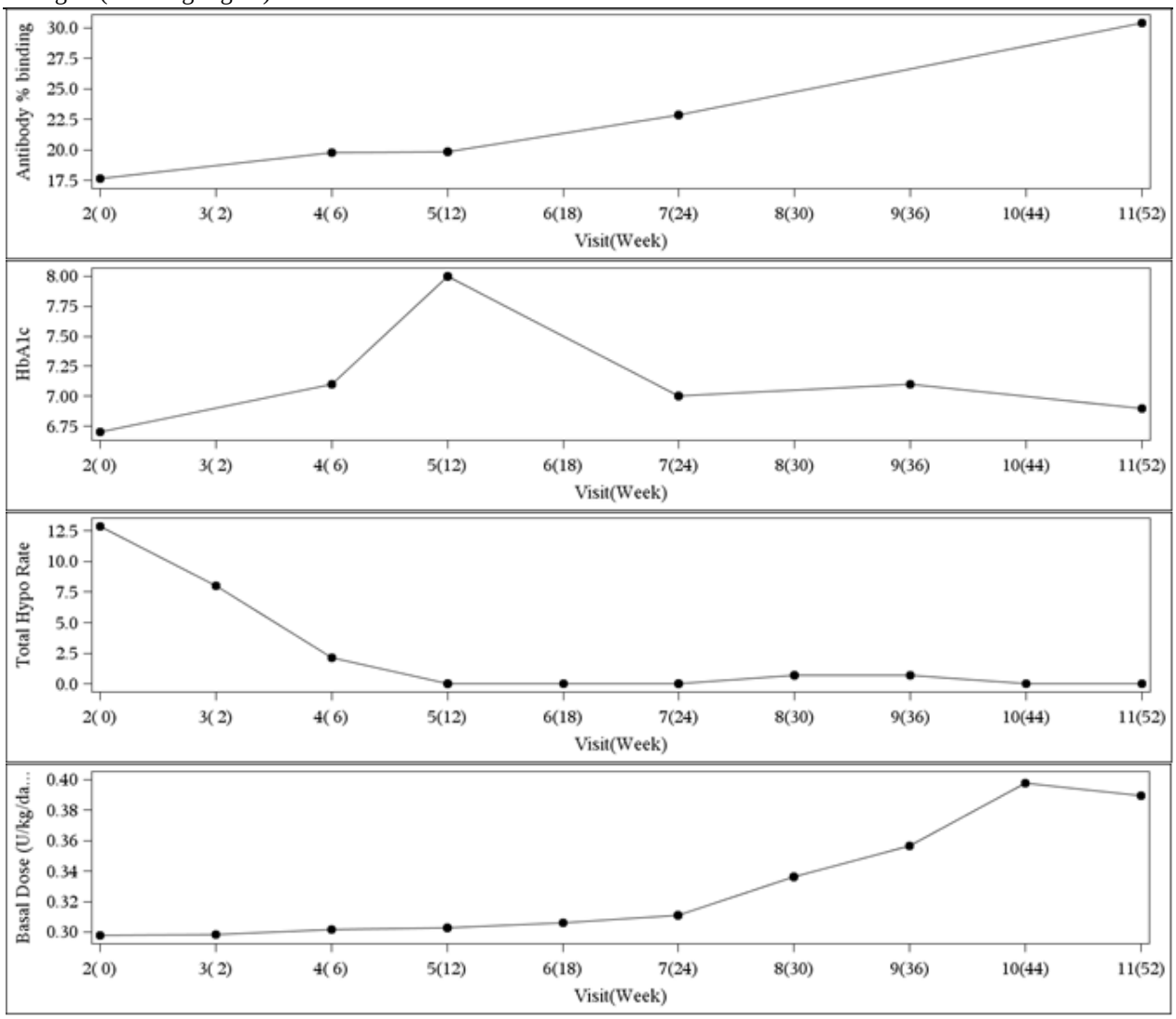
Taken together these data led to the approval recommendation of the OBP consultants. The OBP consult report states “We conclude that there were no statistically or clinically significant differences observed in these studies that would indicate a difference in immunogenicity risk.” Please see the OBP consult for further details.

Outlier analyses: Further analyses were requested by this reviewer from the Sponsor to look at efficacy and safety parameters in patients with particularly high antibody responses, i.e. outliers.[18] Correlational data using the entire antibody positive study group could minimize detection of efficacy and/or safety concerns if these were to occur only in a limited number of patients with a relatively high antibody response.

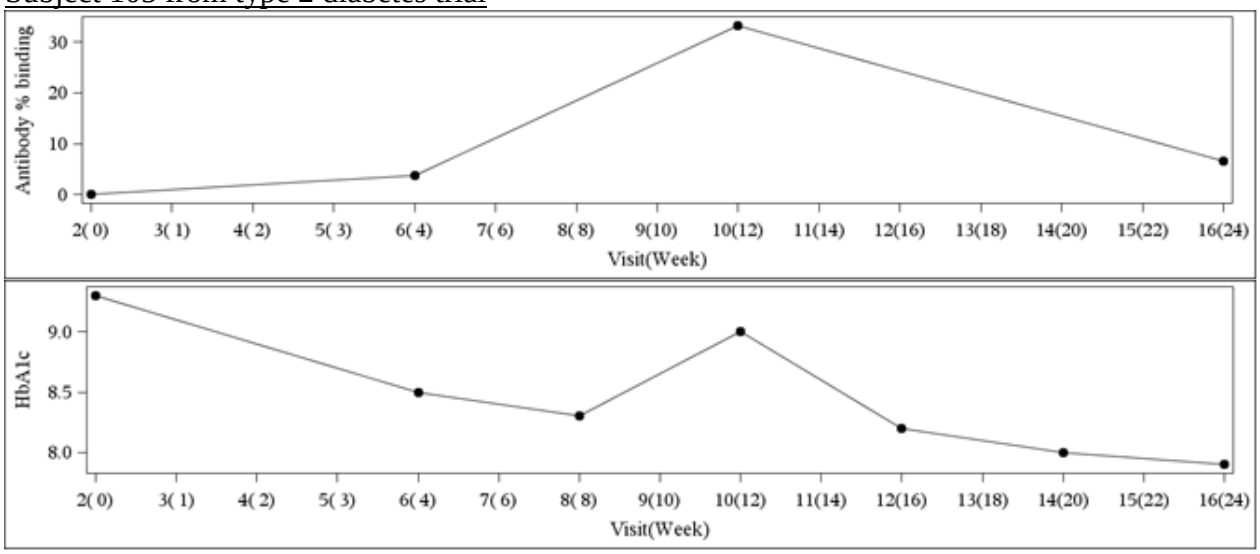
The Sponsor identified 3 patients treated with Basaglar as outliers, defined as % binding greater than 20%. Two outliers treated with Lantus were also identified but their data are not shown here, as Lantus is not the focus of this review and the data did not reveal any significant findings. The antibody binding, HbA1c, hypoglycemia rate, and insulin dose for each Basaglar-treated outlier are shown below.

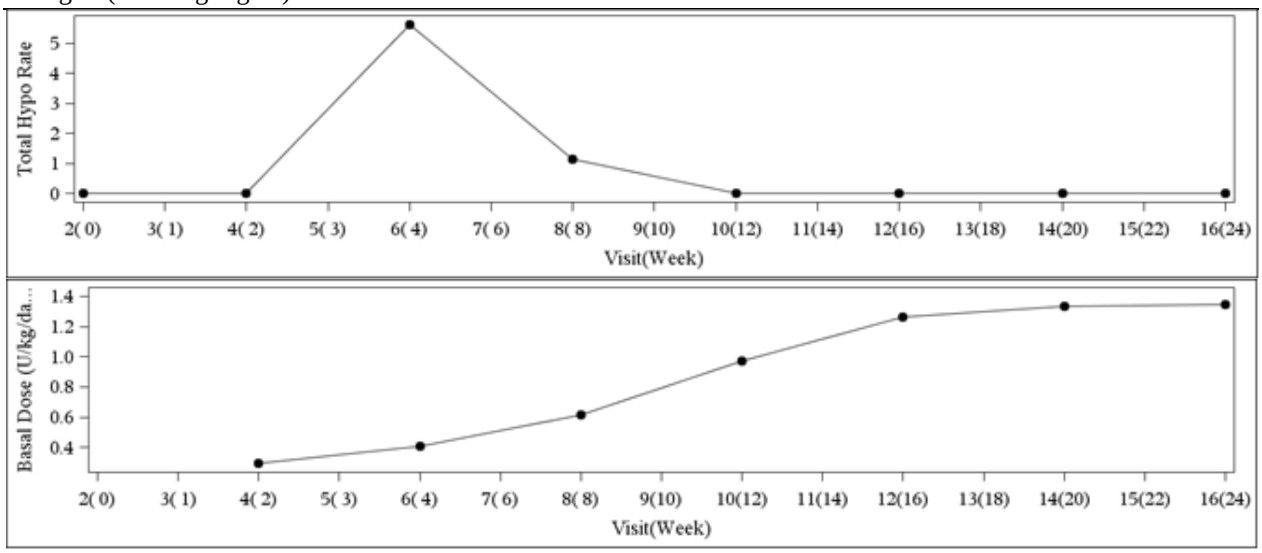
<u>Subject 2009 from type 1 diabetes trial</u>

18 Information requested in an E-mail from the Division to the Sponsor dated 12 Aug 2014

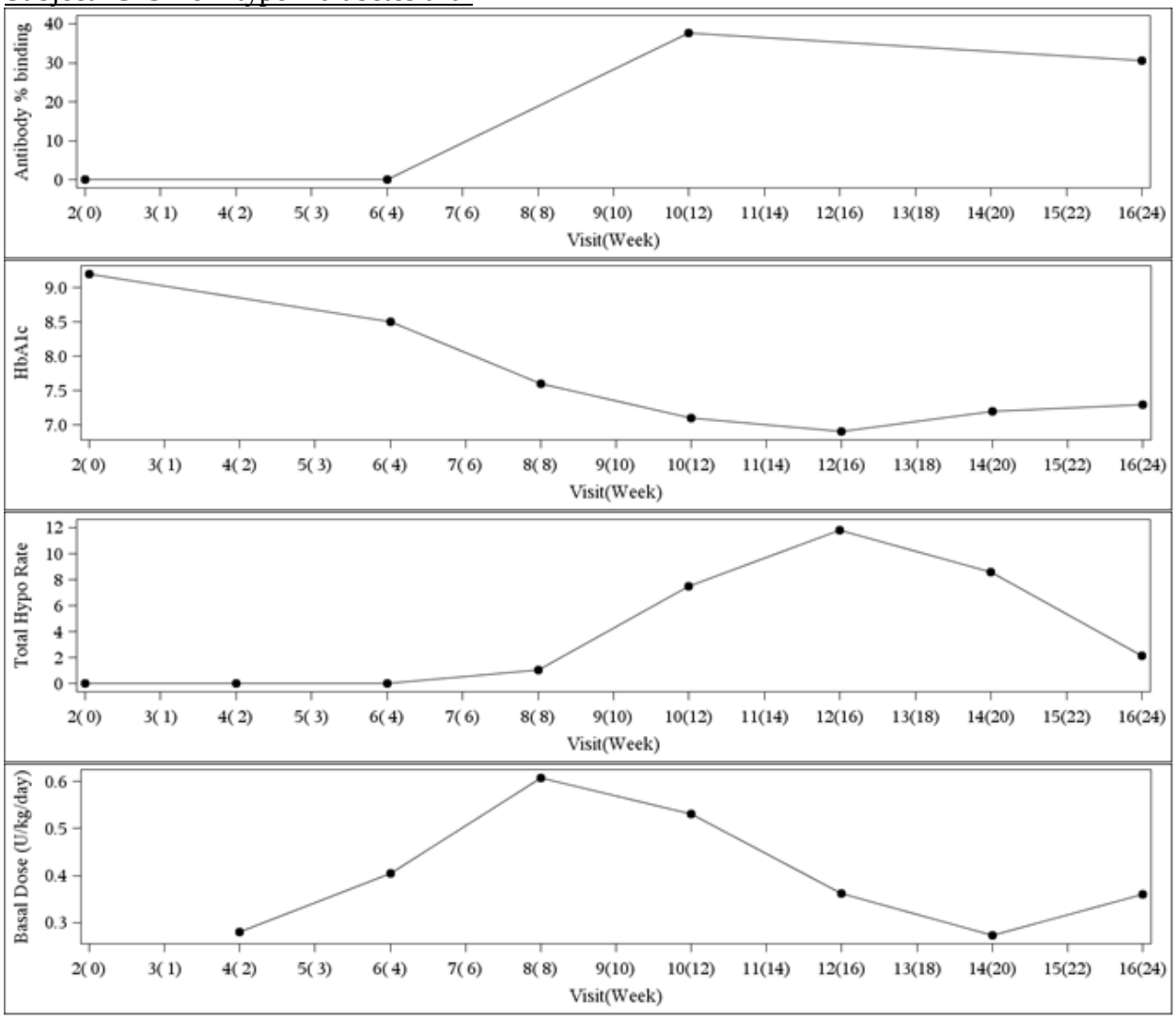


Subject 105 from type 2 diabetes trial





Subject 1313 from type 2 diabetes trial



The data for subject 105 are interesting in that the peak of antibody response seems to correlate with the timing of a rise and peak in HbA1c. However, this pattern is not seen in other patients, and further, HbA1c reflects glycemic control over the previous 2-3 months so it is not clear that the coinciding peaks have any clinical relevance. Overall these data do not suggest an effect of antibody response on efficacy and safety parameters.

For the purposes of labeling note that both OBP and SEALD recommend that comparative data for immunogenicity not be included in labeling, i.e. antibody response data for the Basaglar arms of each trial only be shown. This is the current 'best practices' labeling recommendation. I agree with this recommendation because studies are not powered to detect differences in antibody response and reporting of numerical imbalances could lead to prescribers interpreting differences between products regarding immunogenicity where none may exist.

8 Postmarket Experience

Not applicable

9 Appendices

9.1 Literature Review/References

Allen KV, Frier BM. Nocturnal hypoglycemia: clinical manifestations and therapeutic strategies toward prevention. Endocr Pract. 2003 Nov-Dec;9(6):530-43.

Brunton, Stephen A. Nocturnal Hypoglycemia: Answering the Challenge With Long-acting Insulin Analogs. MedGenMed. 2007; 9(2): 38.

College of American Pathologists. Glycohemoglobin survey. 1999. Northfield, IL: College of American Pathologists; 1999 (Set GH-2).

Goldstein D, Parker K, England J, et al. Clinical application of the glycosylated hemoglobin. Diabetes. 1982; 31: 70-8.

Karges B et al. Management of diabetes mellitus in infants. Nat Rev Endocrinol. 2011 Nov29;8(4)201-11.

Matyka KA. Sweet dreams?--nocturnal hypoglycemia in children with type 1 diabetes. Pediatr Diabetes. 2002 Jun;3(2):74-81.

Nathan DM, Singer DE, Hurxthal K, Goodson JD. The clinical information value of the glycosylated hemoglobin assay. N Engl J Med. 1984; 310: 341-6.

The DCCT Research Group. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. Am J Med. 1991 Apr;90(4):450-9.

9.2 Labeling Recommendations

Labeling recommendations are contained throughout this review.

Labeling recommendations not otherwise discussed in this review:

- The Sponsor proposes for the package insert and patient information to list the distributor address rather than the manufacturer address. This is acceptable. 21 CFR 201.1(a) says that "A drug or drug product (…) in finished package form is misbranded under section… if its label does not bear conspicuously the name and place of business of the manufacturer, packer, or distributor."

- This reviewer is recommending tentative approval. Acceptable draft product labeling is required for a tentative approval. However, an applicant with a tentatively approved application may need to update draft product labeling to incorporate any relevant revisions to the labeling of the listed drug relied upon that were made after the tentative approval or other new safety information.

9.3 Advisory Committee Meeting

Not applicable

APPEARS THIS WAY ON ORIGINAL

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

/s/

LISA B YANOFF
08/18/2014

JEAN-MARC P GUETTIER
08/18/2014
I concur with Dr. Yanoff's assessment. See my summary review for details.