CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205692Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Jean-Marc Guettier, MD
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	205692
Applicant Name	Eli Lilly and Company
Date of Submission	10/18/2013
PDUFA Goal Date	08/18/2014
Proprietary Name / **Established (USAN) Name**	Basaglar (insulin glargine injection)
Dosage Forms / Strength	Injection / 100 units/mL
Proposed Indication(s)	Improve glycemic control in Type 1 (adults and children) and Type 2 (adults) diabetes mellitus
Action/Recommended Action:	*Tentative Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Lisa Yanoff, MD
Statistical Review	Lee Ping Pian, PhD
Pharmacology Toxicology Review	Miyun Tsai-Turton, PhD
CMC Review/OBP Review	Xavier Ysern, PhD and Muthukumar Ramaswamy, PhD
Microbiology Review	Jessica Cole, PhD
Clinical Pharmacology Review	Manoj Khurana, PhD
DDMAC	Ankur Kalola
DSI	Jong Hoon Lee
CDTL Review	Lisa Yanoff, MD
OSE/DMEPA	Sarah Vee, PharmD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

Eli Lilly and Company submitted a new drug application pursuant to section 505(b)(2) of the Federal Food Drug and Cosmetic Act (FD&C Act) for Basaglar. Basaglar injection is a solution containing 100 units of insulin glargine per mL filled in a 3 mL glass cartridge pre-assembled in an auto-injector pen-device (Basaglar KwikPen). The applicant is seeking to indicate Basaglar to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

2. Background

The applicant relies, in part, on FDA's finding of safety and effectiveness for the listed drug Lantus[1] (insulin glargine [rDNA origin] injection; NDA# 021081) to support approval of Basaglar. The applicant established a "bridge" between Basaglar and Lantus to demonstrate that Basaglar was sufficiently similar to Lantus such that reliance is scientifically justified. These data, together with product-specific data (including product-specific data demonstrating safety and effectiveness), establish Basaglar's safety and effectiveness for its proposed conditions of use.

The composition, strength, and presentation of Basaglar are similar to the composition, strength and presentation of the US-approved listed drug (refer to Drs. Ysern and Ramaswamy's review for details). The applicant, in a series of analytical studies, compared the identity, purity, potency and stability of Basaglar to Lantus. The applicant evaluated the impact of potential differences between the two products on safety and efficacy using toxicology bridging studies, clinical pharmacology bridging studies and clinical studies. These bridging studies support the scientific appropriateness of reliance on FDA's finding of safety and effectiveness for Lantus to support approval of Basaglar, and the clinical studies also provide data on the safety and effectiveness of Basaglar.

The toxicology bridging studies allows for an abbreviated non-clinical development program and provides scientific justification for reliance on FDA's finding of safety for Lantus (as reflected in product labeling that describes, among other things, reproduction and early development, carcinogenicity and chronic toxicology studies) to support approval of Basaglar. Additionally, these toxicology studies qualify, from a toxicological perspective, any differences in impurity/degradant profiles that may result from a difference in manufacturing processes between Basaglar and Lantus.

[1] Note: The applicant refers to Lantus (NDA# 021081) as 'US-approved Lantus' in the application to distinguish it from the Lantus product approved for use in the European Union. In my review Lantus refers to the US-approved listed drug.

The clinical pharmacology bridging study (ABEO) allow for an abbreviated clinical pharmacology program and provides scientific justification for reliance on FDA's finding of safety and effectiveness for Lantus (as reflected in product labeling that describes, among other things, clinical pharmacology studies such as special populations studies, timing of administration studies, drug interaction studies) to support approval of Basaglar.

The clinical studies compared the impact of product-related differences on clinical efficacy outcomes (i.e., HbA1c), provide comparative clinical safety data in the chronic use setting and comparative clinical immunogenicity data after repeated and chronic dosing. In the clinical program, long term safety for Basaglar and Lantus were compared in the two adult populations for whom Lantus is indicated (i.e., type 1 and type 2 diabetes populations). Safety concerns including but not limited to those related to interactions with co-administered drugs, risk of hypoglycemia, risk of immune mediated disorders, risk of weight gain, risk of fluid retention and risk of cardiovascular complications (i.e., heart failure; CVD) are different between the two diseased populations studies and both studies were needed to provide robust comparative safety data relevant to the intended uses.

The two clinical studies allow for an abbreviated clinical development program and provide the scientific justification needed to allow reliance on FDA's finding of safety and effectiveness for Lantus to support approval of Basaglar across different patient populations (adult and pediatric patients with type 1 diabetes mellitus and type 2 diabetes mellitus, patients with type 2 diabetes at high risk of cardiovascular events) and across multiple clinical use scenarios (e.g., as basal bolus therapy, as basal therapy added to background oral anti-diabetic agents).

To support approval of a completely novel insulin molecule (i.e., a new analog) clinical data to establish efficacy and safety of the new product across the two distinct adult patient populations (type 1 and type 2 diabetes) and across the most common clinical use scenarios (basal bolus regimen, added to background oral drugs) generally is required. In general, at least two clinical studies in type 1 diabetes and two clinical studies in type 2 diabetes are used to support an adult indication for each of these two diseases. Additional studies could be required pre-marketing to qualify the clinical impact of a novel identified risk or to assess the efficacy and safety of a novel dosing regimen if this is proposed by the applicant. We also would need to consider whether pediatric clinical studies would be required to support a pediatric indication for patients with type 1 diabetes and type 2 diabetes.

In phase 3 clinical trials, the applicant also compares Basaglar to European Union approved Lantus (EU-approved Lantus); the applicant included sites in phase 3 trials outside the US. The applicant provides analytical data, toxicology data and clinical pharmacology data comparing Lantus to EU-approved Lantus that provide an adequate scientific bridge to the U.S.-approved listed drug and justify the relevance of this supportive comparative data. Studies that were used for this bridging purpose will not be discussed in this review and are detailed in individual reviews and in Dr. Yanoff's CDTL memorandum.

3. CMC/Device

CMC data were reviewed by Drs. Ysern and Ramaswamy and summarized in Dr. Yanoff's CDTL memorandum. The applicant characterized the chemistry, manufacturing processes and controls for the drug substance, excipients and drug product in Basaglar.

The drug substance in Basaglar is manufactured by recombinant DNA technology using a specific *E.Coli* production strain. (b) (4)

The composition, strength, and presentation of Basaglar are similar to the composition, strength and presentation of the listed drug (refer to Drs. Ysern and Ramaswamy's review for details).

Basaglar is a sterile, clear, and colorless aqueous solution containing 600 nmol[2] of insulin glargine, 17 mg of glycerol[3], 2.7 mg of metacresol[4], 30.0 µg of zinc[5] and water for injection. Hydrochloric acid or sodium hydroxide is added to adjust the product pH to a final desired pH of approximately 4.0. The strength of the proposed formulation is 100 Units/mL. Dr. Ramaswamy notes that excipients used in Basaglar injection are similar to those used in Lantus except for the following minor differences. (b) (4)

The application contains analytical data comparing the identity, purity, potency and stability of Basaglar to Lantus. Comparative studies included structural characterization to assess the primary, secondary, tertiary and quaternary protein structure (e.g., intact and reduced mass, peptide mapping, amino acid analysis, N-terminal sequencing, IEF, Far UV, tertiary near-UV, 2D-NMR and light scattering techniques), physicochemical characterization, biological potency characterization (e.g., in vitro receptor binding and functional assays), impurity profile characterization, and stability testing comparisons using multiple batches of Lantus and Basaglar.

Two minor differences between Basaglar and Lantus were noted. Basaglar contains (b) (4) (b) (4) process-related impurity not found to be present in Lantus. A slightly higher content of (b) (4) were observed in Basaglar compared to Lantus in accelerated stability studies. Dr. Ramaswamy states that this may not translate into significant difference during actual long-term storage condition. The Applicant suggests that

[2] Drug product concentration of 600 nmol = 3.6378 mg of insulin glargine per mL of product

(b) (4)

the presence of (b) (4) in the Lantus formulation (b) (4) Basaglar does not contain (b) (4) and the acceptance criteria set in the product specification for these impurities were found to be acceptable.

Dr. Ramaswamy concludes that Basaglar is similar to Lantus with respect to product composition, strength, presentation, physicochemical, structural, biological properties, and stability profile under long term storage.

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug substance and drug product. Manufacturing site inspections were acceptable. Stability testing supports a shelf-life of 24 months when the pre-filled pen is stored at (b) (4) away from excessive light. In-use stability data support an in-use period of 28 days at up to 30°C.

4. Nonclinical Pharmacology/Toxicology

Dr. Tsai-Turton notes that no biologically important differences between Basaglar and Lantus were detected on receptor binding assays or receptor functional assays at either the insulin or IGF-1 receptors (refer to Study No DBT93 and Study No DBT149). Data from these studies demonstrate that both products contain potent, functional, insulin molecules and suggest in vitro insulin receptor or IGF-1 receptor affinity and potency are similar between Basaglar and Lantus products.

The applicant conducted a 4 week toxicity study using Basaglar and Lantus (Study No 8229488). This study did not identify major differences in pharmacokinetic, glucodynamics, local tolerability, and toxicity profile between Basaglar and Lantus, and supports the scientific appropriateness of reliance on FDA's finding of safety for Lantus.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology study ABEO allows for an abbreviated clinical pharmacology program and contributes to the scientific justification for reliance on FDA's finding of safety and effectiveness for Lantus to support marketing approval of Basaglar. This study was a comparative PK/PD, single-dose (0.5 U/kg), 24-hour, glucose clamp study carried out in healthy volunteers. To measure serum glargine levels following drug administration, the applicant relied on a validated radioimmunoassay with cross-reactivity to endogenous insulin. Slightly lower maximum and overall serum insulin exposure were observed after a single dose of Basaglar compared to a single dose of Lantus. However the results of the study support a conclusion that maximum (i.e.., C_{max}) and overall exposure (AUC_{0-24h}) to serum insulin were

sufficiently similar. The 90% confidence interval for the geometric mean ratios for C_{max} and $AUC_{0\text{-}24h}$ were within 0.8 and 1.25 between Basaglar and Lantus. Dr. Khurana also notes in his review that time to achievement of maximum insulin concentration was similar between Basaglar and Lantus. The study results also support a conclusion that maximum glucose lowering after a single dose (Glucose Infusion $Rate_{max}$) and overall glucose lowering after a single dose (Glucose Infusion Rate $AUC_{0\text{-}24h}$) were similar between Basaglar and Lantus; the 90% confidence interval for the geometric mean ratios for the two PD parameters were within 0.8 and 1.25. Refer to Table 4 in Dr. Khurana's review.

Dr. Yanoff has summarized all clinical pharmacology studies submitted with the Basaglar new drug application in Table 1 of her review. It is important to note that studies ABEE, ABEI and ABEA in the Table were neither required to support Basaglar approval in the US nor used to establish a scientific bridge to justify the appropriateness of reliance on FDA's finding of safety and effectiveness for Lantus. Studies ABEM (i.e., Basaglar versus EU-approved Lantus single dose PK/PD dose response study) and ABEN (Lantus versus EU-approved Lantus single dose PK/PD comparative study) provide supportive data and a PK/PD bridge between the EU-approved Lantus and the U.S.-approved listed drug (Lantus) to justify the relevance of this supportive comparative data in the application.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics review team that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

In this section, I summarize the pivotal efficacy findings for the Basaglar program. For full details on efficacy analyses refer to Drs. Pian and Yanoff's reviews.

A clinical study in type 1 diabetes (Study ABEB) and another in type 2 diabetes (study ABEC) provide the scientific justification needed to allow reliance on FDA's finding of effectiveness for Lantus to support an indication of Basaglar for the treatment of type 1 diabetes mellitus and the treatment of type-2 diabetes mellitus (refer to Background Section).

Study ABEB; Type 1 Diabetes Mellitus; Basal-Bolus Use

Study ABEB was a randomized (1:1) multinational, multicenter, active-controlled, open-label, 24-week trial in patients with type 1 diabetes mellitus (T1DM). Patients in this trial were adult patients diagnosed with type-1 diabetes for at least one year, inadequately controlled

on an insulin regimen that included a 'basal' insulin and a 'meal time' insulin. Patients were randomized to Basaglar or Comparator (Lantus or EU-approved Lantus depending on region). The intervention period was divided into a titration phase where insulin doses were adjusted to target HbA1c, fasting plasma glucose and post prandial glucose levels and a maintenance phase where insulin doses were to be relatively stable.

Demographic and disease characteristics across the two intervention groups and across the US and European regions were similar (refer to Tables 6 and 7 in Dr. Pian's review). Patients in the US region were on average older, more overweight per BMI criteria, and had had diabetes for longer than patients randomized in the European region. More subjects randomized to Basaglar in the US-region were male (~68%) compared to the overall (58%) or European region (~55%) respectively.

The primary efficacy endpoint was the difference in the change in HbA1c from baseline between intervention groups at Week 24. The study was powered to exclude the possibility that glycemic control, captured using HbA1c change from baseline to Week 24, on Basaglar was worse by 0.4%[8] or more (non-inferiority margin) compared to the glycemic control observed on comparator (Lantus + EU-Lantus). A non-inferiority trial design using a non-inferiority margin of 0.4% was regarded as an appropriate design to compare the glucose lowering efficacy of the two products and establish the efficacy of Basaglar in this setting.

The primary efficacy results from Study ABEB are shown below. The applicant demonstrates that the glucose lowering efficacy of Basaglar co-administered with insulin Lispro at the end of 24 weeks is similar to the glucose lowering efficacy of Lantus + EU-approved Lantus co-administered with insulin Lispro in patients with type 1 diabetes.

Table 1: Primary Efficacy Results Type 1 DM Trial-Study ABEB

Treatment Arm	**n***	**Baseline HbA1c [% (±SEM)]**	**Adjusted Mean Change From Baseline HbA1c [% (±SEM)]**	**Adjusted Between Group† Difference in HbA1c Change from Baseline [% (95% CI)]**
Basaglar	267	7.9 (0.09)	-0.35 (0.05)	**+0.11 (-0.002, 0.22)** *(p-value = 0.055)*
Lantus and EU-approved Lantus	267	7.9 (0.09)	-0.46 (0.05)	

Source: Table 9 in Dr. Pian's Review.
*Subjects randomized with at least one post-baseline HbA1c value.
†Primary comparison on the full analysis set population with data up to time of discontinuation used and missing data imputed using LOCF. Estimates are based on 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.

[8] A non-inferiority margin of 0.4% is routinely used to compare the relative efficacy of two insulin products in situations where a placebo-control trial would be unethical. For ABEB the applicant calculated the sample size [refer to the applicant's statistical analysis plan (SAP)] for two non-inferiority margin's (i.e., 0.4% and 0.3%). In the SAP, the number to be randomized was calculated based on the number of completers (N=384) needed to exclude an NI margin of 0.4% with 90% power and the number of completers (N=432) needed to exclude an NI margin of 0.3% with 90% power. Both assume no difference in effect, a .05 two-sided alpha and a 15% discontinuation rate. In the end, the applicant randomized more patients than required for efficacy objectives (N=536) which provides additional exposure to assess for rarer safety outcomes.

Results for subgroup analyses by regions separating US-/Puerto Rico sites (Lantus comparator) from non- US sites (EU-approved Lantus comparator) are shown below.

Table 2: Primary Efficacy Results Type 1 DM Trial (Study ABEB) by Regional Subgroups comparing US/Puerto Rico sites (Lantus used as comparator) versus Non-US sites (EU-Lantus used as comparator).

Treatment Arm	n*	Baseline HbA1c [% (±SEM)]	Adjusted Mean Change From Baseline HbA1c [% (±SEM)]	Adjusted Between Group† Difference in HbA1c Change from Baseline [% (95% CI)]
Basaglar	98	7.8 (0.12)	-0.22 (0.06)	**+0.19 (0.02, 0.36)**
Lantus†	96	7.7 (0.12)	-0.41 (0.06)	*(p-value = 0.028)*
Basaglar	169	7.9 (0.11)	-0.46 (0.07)	**+0.07 (-0.08, 0.21)**
EU-approved Lantus	171	7.9 (0.12)	-0.53 (0.08)	*(p-value = 0.345)*

Source: Table 9 in Dr. Pian's Review.
*Subjects randomized with at least one post-baseline HbA1c value.

Comparison are based on the full analysis set population with data up to time of discontinuation used and missing data imputed using LOCF. Estimates are based on 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 results of these analyses are consistent with the overall analysis and based on these analyses one would conclude that Basaglar is effective. These results also support a conclusion that Basaglar is sufficiently similar to Lantus from a glucose lowering standpoint in type 1 diabetes to justify reliance, in part, on FDA's finding of effectiveness for Lantus in this disease (as reflected in product labeling that describes, among other things, efficacy studies performed in type 1 diabetes). Minor differences in effect size across subgroups are likely the result of chance, small sample size, or minor differences in trial conduct across the two regions rather than due to differences in comparator response driven by product-related differences between Lantus and EU-approved Lantus. This is supported by the fact that differences across regions appear predominantly driven by differences in Basaglar response between the two regions (same drug across the two regions) and not by large differences in comparator response across the two regions. Potential differences in trial conduct across the two regions is supported by the observation of a somewhat lower completion rate in the US region (refer to Table 5 in Dr. Pian's review) and the fact that patients randomized to Basaglar in the US region, on average, had a comparatively larger decrease in their baseline short acting co-administered insulin dose (i.e., lispro insulin) immediately following randomization compared to patients randomized to Basaglar in Europe or randomized to Lantus and EU-approved Lantus (refer to figure 9 in Dr. Pian's review). Finally, subgroup analyses across regions in the type 2 diabetes trial (ABEC) did not confirm the presence of a difference between Basaglar/Lantus and Basaglar/EU-approved Lantus comparisons and this trial, in contrast to trial ABEB, is better suited to detect differences due to comparator products because it does not have the issue of confounding by a co-administered short-acting insulin product.

Results for supportive secondary outcomes (i.e., Self-monitored blood glucose, HbA1c responder rates, and insulin dose)[9] were consistent with results based on HbA1c and support a conclusion that Basaglar is effective in type 1 diabetes mellitus.

Study ABEC; Type 2 Diabetes Mellitus; Basal added to Oral Anti-Diabetic Use

Study ABEC was a randomized (1:1) multinational, multicenter, active-controlled, double-blind, 24-week trial in patients with type 2 diabetes mellitus (T2DM). Patients in this trial were adult patients diagnosed with type-2 diabetes, inadequately controlled on two or more oral anti-diabetic agents on a stable dose for at least 12-weeks prior to screening. Patients were randomized to Basaglar or Comparator (Lantus or EU-approved Lantus depending on region). The intervention phase was divided into a titration phase where intervention insulin doses were adjusted to target a fasting plasma glucose of 100 mg/dL and a maintenance phase where insulin doses were to have remained relatively stable.

Demographic and disease characteristics across the two intervention groups and across the US and European regions were similar (refer to Tables 18 and 19 in Dr. Pian's review).

The primary objective and efficacy endpoint were similar to those of trial ABEB described (i.e, excluding a non-inferiority margin of 0.3%-0.4%). Results for the primary analysis across the entire trial population and subgrouped by regions are shown in Tables 3 and 4.

Table 3: Primary Efficacy Results Type 2 DM Trial-Study ABEC

Treatment Arm	**n***	**Baseline HbA1c [% (±SEM)]**	**Adjusted Mean Change From Baseline HbA1c [% (±SEM)]**	**Adjusted Between Group† Difference in HbA1c Change from Baseline [% (95% CI)]**
Basaglar	369	8.3 (0.08)	-1.29 (0.06)	**+0.05 (-0.07, 0.17)** *(p-value = 0.40)*
Lantus and EU-approved Lantus	375	8.3 (0.08)	-1.34 (0.06)	

Source: Table 21 in Dr. Pian's Review.
*Subjects randomized with at least one post-baseline HbA1c value.
†Primary comparison on the full analysis set population with data up to time of discontinuation used and missing data imputed using LOCF. Estimates are based on an analysis of covariance model (ANCOVA) with treatment, country, sulfonylurea use, time of basal insulin injection (daytime, evening/bedtime) as fixed effects and baseline HbA1c as a covariate.

[9] Refer to Tables 10 and 11 in Dr. Yanoff's CDTL memorandum.

Table 4: Primary Efficacy Results Type 2 DM Trial (Study ABEC) by Regional Subgroups comparing US/Puerto Rico sites (Lantus used as comparator) versus Non-US sites (EU-approved Lantus used as comparator).

Treatment Arm	n*	Baseline HbA1c [% (±SEM)]	Adjusted Mean Change From Baseline HbA1c [% (±SEM)]	Adjusted Between Group† Difference in HbA1c Change from Baseline [% (95% CI)]
Basaglar	205	8.4 (0.10)	-1.29 (0.06)	**+0.01 (-0.15, 0.18)**
Lantus	213	8.3 (0.10)	-1.30 (0.06)	*(p-value = 0.88)*
Basaglar	164	8.3 (0.10)	-1.25 (0.07)	**+0.11 (-0.07, 0.29)**
EU-approved Lantus	162	8.3 (0.10)	-1.36 (0.08)	*(p-value = 0.23)*

Source: Table 21 in Dr. Pian's Review.
*Subjects randomized with at least one post-baseline HbA1c value.
Comparison are based on the full analysis set population with data up to time of discontinuation used and missing data imputed using LOCF.
Estimates are based on 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 results establish that Basaglar administered daily over 24 weeks is effective in patients with type 2 diabetes inadequately controlled on two oral agents at baseline compared to comparator (Lantus or EU-approved Lantus), Lantus alone, and EU-approved Lantus alone. These results also support that Basaglar is sufficiently similar to Lantus from a glucose lowering standpoint in type 2 diabetes to justify reliance, in part, on FDA's finding of effectiveness for Lantus in this disease (as reflected in product labeling that describes, among other things, efficacy studies performed in type 2 diabetes).

Results for supportive secondary outcomes (i.e., self-monitored blood glucose, HbA1c responder rates, and insulin dose[10]) were consistent with results based on HbA1c and further support a conclusion that Basaglar is effective patients with type 2 diabetes mellitus.

8. Safety

The main safety dataset comprises all subjects who participated in trials ABEB and ABEC. In these two trials, 644 subjects were exposed to Basaglar and the mean exposure time to Basaglar was ~ 34 weeks (i.e., 7.8 months). Five hundred subjects were exposed to Basaglar for six months or greater. Relatively few patients were exposed to Basaglar for ≥ 12 months and ≥ 18 months. Although the diabetes guidance recommends that ~1300-1500 patients and 300-500 patients be exposed to a novel insulin product for ≥ 12 months and ≥ 18 months respectively, the size of the population exposed to Basaglar and exposure duration to Basaglar was regarded as adequate to provide product specific safety and justify reliance, in part, on FDA's finding of safety for Lantus as reflected in product labeling.

The applicant presents comparative safety data in three ways. The main safety analyses compare safety data generated for all patients exposed to Basaglar to safety data generated

[10] Refer to Tables 25, 26, 27 in Dr. Pian's review.

in all patients exposed to comparator (Lantus and EU-approved Lantus) across the two trials. Supportive analyses compare specific safety data generated for the subgroup of patients exposed to Basaglar in the US region to safety data generated in patients exposed to Lantus. A third supportive analyses compares specific safety data generated for the subgroup of patients exposed to Basaglar in the EU region to safety data generated in patients exposed to EU-approved Lantus. Dr. Yanoff has reviewed safety data across the three safety groupings and the three analyses groupings are sufficiently granular to establish Basaglar's safety.

Deaths, Serious Adverse Events, Discontinuations due to Adverse Events and Common Adverse Events

There were three deaths in the program, one on Basaglar (lung adenocarcinoma after 5 months of exposure) and two on Lantus or EU-approved Lantus (hypertrophic cardiomyopathy and myocardial infarction). The three deaths were not judged to be product related due to the presence of known pre-existing risk factors in the case histories and in the case of the lung adenocarcinoma the relatively short exposure to product prior to the cancer diagnosis.

No imbalance in non-fatal serious adverse events between Basaglar (5.4%) and Lantus or EU-approved Lantus (6.5%) were noted (refer to Table 15 in Dr. Yanoff's review). No large imbalance in any specific adverse event terms was noted across system organ class to suggest a Basaglar related issue. Hypoglycemia (2.3%) coronary artery disease (~0.3%) and cellulitis (~0.2%) accounted for the majority of events in both groups.

Discontinuations due to adverse events were infrequent (<3%) but more subjects randomized to Lantus or EU-approved Lantus discontinued due to an adverse event (1.2% versus 2.6% for Basaglar versus Lantus comparators). Review of individual adverse events preferred terms do not raise concern with regard to a product specific issue related to Basaglar (Refer to Table 16 in Dr. Yanoff's review).

The proportion of patients reporting at least one common adverse event was similar between Basaglar and Lantus or EU-approved Lantus (refer to Table 20 in Dr. Yanoff's review). Imbalances in specific events were in general due to small differences between groups (i.e., 2-7 additional cases responsible for any specific imbalance). Imbalances for adverse event terms denoting similar issues were on a whole balanced. For example abnormal weight gain events were reported more frequently in Basaglar treated patients (10 cases versus 3) but the terms adverse events of weight increased and oedema peripheral were reported more frequently in the Lantus or EU-approved Lantus groups. Analyses based on directly measured weight did not reveal a difference between Basaglar and Lantus or EU-approved Lantus. No imbalance in the proportion of reported events for any one specific adverse event term raises a concern that would suggest an issue related to Basaglar.

Hypoglycemia

Drs. Yanoff and Pian have reviewed comparative data for severe hypoglycemia across the main pool and across the two regional subgroup pools for the Type 1 diabetes trial (ABEB) and the Type 2 Diabetes (ABEC) trial individually. In the type 1 diabetes trial, no differences in the rate of severe hypoglycemia was observed between Basaglar and Lantus and EU-approved Lantus, Basaglar and Lantus in the US-region, and Basaglar and EU-approved Lantus in the EU-region (Refer to Table 28 in Dr. Pian's review). In the type 2 diabetes trial, no differences in the rate of severe hypoglycemia was observed between Basaglar and Lantus and EU-approved Lantus, Basaglar and Lantus in the US-region, and Basaglar and EU-approved Lantus in the EU-region (Refer to Table 29 in Dr. Pian's review).

Analyses based on severe hypoglycemia are clinically important and informative because these events compare the occurrence of specific life-threatening events between interventions. These analyses are limited however by the infrequent occurrence of these events in clinical trials. To provide supportive data for analyses based on severe events, analyses based on less specific but more frequent hypoglycemic events were also carried out. These analyses were based on various definitions of 'hypoglycemia' (e.g., defined for example by the presence of a self-measured blood glucose < 54 mg/dL and presence of symptoms compatible with hypoglycemia) and the results of these analyses were consistent with analyses based on severe hypoglycemic events (refer to Table 17 in Dr. Yanoff's review) and did not suggest a difference in the risk of hypoglycemia between Basaglar and Lantus.

Immunogenicity

Immunogenicity data were reviewed by Drs. Sheikh (Office of Biotechnology Products) and Yanoff. No significant differences in immune response between Basaglar and Lantus or EU-approved Lantus in either the type 1 diabetes or type 2 diabetes patient populations were noted with respect to anti-body development at any visit. The applicant reviewed the impact of developing 'treatment emergent antibodies' on specific efficacy (HbA1c response, insulin dose) and safety outcomes (hypoglycemia) across the entire safety dataset and in the regional Lantus subgroup datasets (refer to Summary of Clinical Safety pages 71-80). Overall, development of treatment emergent antibodies in either the Basaglar, Lantus or EU-approved Lantus groups did not impact these efficacy or safety outcomes (Source: figure 2.7.4.2 in the summary of clinical safety).

Dr. Yanoff reviewed data for outliers (defined as patients with a percent binding antibodies of >20%). Three patients met this definition in the Basaglar group and two in the Lantus or EU-approved Lantus group. The presence of > 20% binding antibodies did not appear to correlate to HbA1c response, insulin dose or risk of hypoglycemia.

These data establish the immunogenicity profile of Basaglar and support a conclusion that Basaglar has an acceptable immunogenicity profile.

Allergic and Injection Site Reactions

Allergic reactions were captured using a list of preferred terms (Refer to Table APP 2.7.4.7.13 in the summary of clinical safety appendix). No differences in the occurrence of allergic reactions were noted (41 cases in Basaglar versus 38 cases for Lantus + EU-approved Lantus). The most frequently reported terms across the entire safety pool were arthralgia (1.6% versus 2.0% for Basaglar versus Lantus + EU-approved Lantus respectively), pruritus (1.1% versus 0.8% for Basaglar versus Lantus + EU-approved Lantus respectively), injection site reaction (0.9% versus 0.8% for Basaglar versus Lantus + EU-approved Lantus respectively) and rash (0.8% and 0.8% for Basaglar versus Lantus + EU-approved Lantus respectively). Imbalances between groups were due to small numerical differences. These data do not reveal large differences between Basaglar and Lantus with regard to occurrence of allergic reactions and establish that Basaglar has an acceptable safety profile with regard to occurrence of allergic reactions.

Adverse events related to the administration site (e.g., injection site reactions, induration, pruritus, nodule, local swelling) were more frequently reported in the Basaglar group (n=11 or 1.7%) compared to the Lantus + EU-approved Lantus group (n=6 or 0.9%). Differences in specific terms are shown in Table 18 in Dr. Yanoff's review. Overall imbalances were driven by numerically few cases. Small differences in reported incident injection site reactions, did not lead to more frequent discontinuation or translate to clinically important differences in efficacy. These data establish that Basaglar has an acceptable safety profile with regard to occurrence of administration site reactions.

Vital Signs, Laboratory and ECG Abnormalities:

Dr. Yanoff has reviewed these outcomes and notes that no clinically significant differences across these safety parameters between Basaglar and Lantus in the safety pool were observed (refer to Section 7.4.2-7.4.4 in her review).

The results of these safety analyses establish the safety Basaglar administered daily over ≥ 24 weeks in patients with type 1 and type 2 diabetes mellitus and provide scientific justification for reliance, in part, on FDA's finding of safety for Lantus (as reflected in product labeling that describes, among other things safety outcomes from clinical studies performed in type 1 and type 2 diabetes).

9. Advisory Committee Meeting

No new efficacy or safety issue rose to the level of requiring the input from an advisory panel. Therefore no advisory committee was convened.

10. Labeling

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. 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 Lilly requests final approval of Basaglar. Refer to Dr. Yanoff's review for additional comments regarding labeling.

11. Decision/Action/Risk Benefit Assessment

- Regulatory Action

I recommend a tentative approval.

- Risk Benefit Assessment

In this application Eli Lilly, established the efficacy and safety of Basaglar in adults with type 1 and type 2 diabetes in two clinical trials (i.e., ABEB, ABEC). Use of Basaglar was shown to be effective at improving glycemic control in adults with type 1 and type 2 diabetes. Basaglar specific risks were consistent with known risks for the product class (i.e., insulin) and no novel risks were identified in safety analyses across the two disease populations. The impact of potential product related differences between Basaglar and Lantus on safety and efficacy was evaluated using a toxicology bridging study, a clinical pharmacology bridging study (ABEO) and the two pivotal clinical studies (ABEB, ABEC). These studies were used to support a determination of 'sufficient similarity' between Basaglar and Lantus to justify reliance, in part, on FDA's finding of safety and effectiveness for Lantus (as reflected in specifics of product labeling that describe, non-clinical studies, clinical pharmacology studies and clinical efficacy studies and clinical safety studies).

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

No new safety findings from this clinical development program prompt the need for a postmarketing risk evaluation and management strategies.

- Recommendation for other Postmarketing Requirements and Commitments

No new safety findings from this clinical development program prompt the need for a postmarketing requirements and commitments.

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/s/

JEAN-MARC P GUETTIER
08/18/2014