CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208471Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Jean-Marc Guettier, MD
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	NDA 208471
Applicant Name	Sanofi Aventis US, LLC
Date of Submission	July 27, 2015
PDUFA Goal Date	July 27, 2016
Proprietary Name / **Established (USAN) Name**	Adlyxin/lixisenatide
Dosage Forms / Strength **/Presentation**	Solution for subcutaneous injection (50 mcg/mL and 100 mcg/mL)
Proposed Indication(s)	1. As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Suchitra Balakrishnan, MD PhD
Statistical Review	Wei Liu, PhD; Jiwei He, PhD; Yueqin Zhao, PhD
Pharmacology Toxicology Review	Timothy Hummer, PhD; Feleke Eshete, PhD
CMC Review	Joseph Leginus, PhD; Ravindra Kasliwal, PhD
Microbiology Review	Maria Cruz-Fisher, PhD
Clinical Pharmacology Review	Sista Suryanarayana, PhD
OPDP	Charuni Shah, PharmD
DSI	Cynthia Kleppinger, MD
CDTL Review	Bill Chong, MD
OSE/DMEPA	Sara Vee, PharmD
OSE/DDRE	Debra Ryan, PharmD
OSE/DRISK	Naomi Redd, PharmD

OND=Office of New Drugs
OPDP= Office of Prescription Drug Promotion
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

1. Introduction

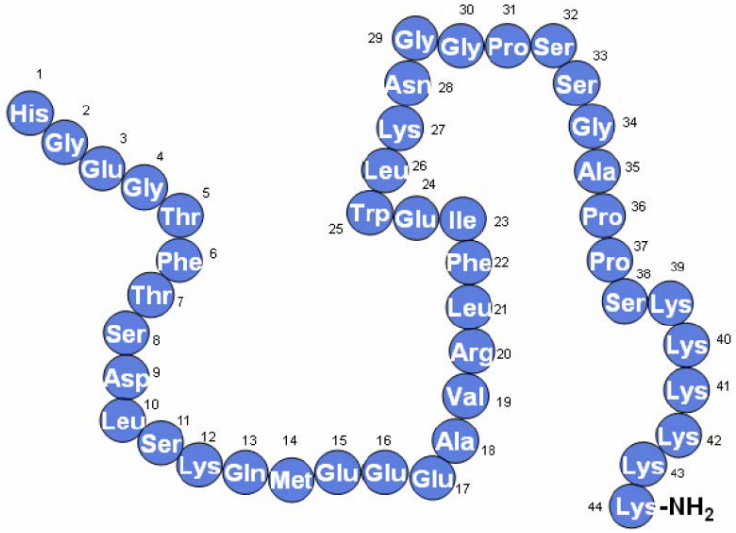
On July 27, 2015 Sanofi Aventis US LLC submitted a New Drug Application (NDA) for Adlyxin under section 505(b)(1) of the Federal Food Drug and Cosmetic Act. The applicant is seeking to indicate Adlyxin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Adlyxin is a solution for injection containing either; 50 mcg/mL and 100 mcg/mL of lixisenatide [i.e., a glucagon-like peptide 1 (GLP-1) receptor agonist]. Adlyxin is to be administered by subcutaneous injection at once daily intervals. Once approved, Adlyxin will be the sixth GLP-1 agonist indicated for use in the management of patients with type 2 diabetes mellitus in the United States.

This document serves as the division director's memorandum for the application.

2. Background

The drug substance in Adlyxin is lixisenatide. Lixisenatide is a synthetic peptide derived from the exendin-4 hormone. It is made up of 44 amino acids and includes six lysine residues at the C-terminal end of the molecule which were added to prevent degradation of the peptide by dipeptidyl peptidase-4 and increase the peptide's residence time in circulation.

Figure 1: Structural formula of lixisenatide



Source: Excerpted from Table 2 of Quality Overall Summary: 2.3.S. Drug Substance from NDA 208471

Lixisenatide was demonstrated to bind to and activate the GLP-1 receptor. The biological effects of endogenous GLP-1 on glucose homeostasis include augmentation of glucose stimulated insulin secretion, inhibition of glucagon release, and delay of gastric emptying. These effects are, in concert, believed to be responsible for the glucose lowering effect of exogenously administered GLP-1 agonists.

Serious labelled risks for GLP-1 therapies include: The theoretical risk of thyroid C-cell tumors including medullary thyroid carcinoma specifically for longer acting GLP-1 receptor agonists, the risk of acute pancreatitis, the risk of worsening renal function precipitated by dehydration, the risk of hypoglycemia when used with drugs known to cause hypoglycemia (i.e., sulfonylurea or insulin), and the risks of immunogenicity, hypersensitivity and injection site reactions.

Common adverse reactions reported for this class of antidiabetic drugs include gastrointestinal tolerability issues and increased heart rate.

The lixisenatide application has had a complex regulatory history including withdrawal of a previously submitted NDA (#204961). The regulatory history is summarized in the clinical reviews by Dr. Balakrishnan under NDA 204961 and in this current NDA (#208471). See these reviews for relevant details of pre-submission activities. Included in this NDA is the study report for the completed cardiovascular outcomes trial, ELIXA, which is used to establish that use of lixisenatide in adult patients with type 2 diabetes is not associated with a 30% excess risk of atherosclerotic cardiovascular disease.

3. CMC/Device

The lixisenatide drug substance is manufactured by chemical synthesis. The lixisenatide drug product, Adlyxin, will be supplied as a sterile solution for injection in two product strengths: a 50 mcg/mL strength for the 10 mcg dose recommended for titration and 100 mcg/mL strength for the 20 mcg maintenance dose.

The compositions of the two strengths differ only in the amount of active pharmaceutical ingredient (i.e., lixisenatide drug substance). The solution contains the following excipients; 85% glycerol (b) (4) sodium acetate trihydrate (b) (4) methionine (b) (4), metacresol (b) (4) and water for injection. Hydrochloric acid and/or sodium hydroxide is added to adjust the pH to a pH of 4.5. All excipients comply with compendial requirements.

The primary packaging material consists of clear, colorless 3 mL cartridges (b) (4) closed with plunger stoppers (b) (4) on one side and (b) (4) on the opposite end. The cartridge is (b) (4) integrated into a fixed dose disposable pen-injector.

The lixisenatide pen-injector is a manual, pressure operated, injector device designed to deliver a fixed volumetric dose of lixisenatide (0.2 mL). Each pen injector dispenses up to 14 doses. A new needle is attached prior to each dose and a priming step is required with the first use. The two different product strengths will be presented as different color pen

injectors; a green pen for the 0.05 mg/mL strength and burgundy pen for the 0.1 mg/mL strength.

The review of the devices was completed by Dr. Lana Shiu. Biocompatability of the device was completed by Dr. Bifeng Qian. Both Drs. Shiu and Qian recommend approval.

The drug substance and product manufacturing processes and (b) (4) controls were reviewed in details by Drs. Joseph Leginus, Ravindra Kasliwal, Yuesheng Ye, and no issues precluding approval were identified. Dr. Vipulchandra Dholakia assessed the proposed drug substance and drug product manufacturing facilities. No concerns that would impact approvability of Adlyxin were identified in this assessment and sites involved in drug substance and product manufacturing were deemed acceptable.

I concur with the conclusions reached by the product quality review team that the identity, potency as well as chemical and microbial purity of Adlyxin will be assured in manufacturing. Stability testing supports an expiration date of 24 months for the drug product (both 0.1 mg/mL and 0.05 mg/mL strengths) when stored between 2 to 8°C. In use stability testing supports use of the product for up to 14 days when stored at 30°C. There are no outstanding CMC/Device issues.

4. Nonclinical Pharmacology/Toxicology

Drs. Hummer and Eshete have reviewed nonclinical pharmacology and toxicology studies in details. Dr. Bourcier has summarized the main nonclinical toxicology findings in the application and key findings excerpted from Dr. Bourcier's assessment are repeated here for convenience.

In-vitro pharmacology studies confirm that lixisenatide is a selective GLP-1 receptor agonist that binds this receptor with high affinity (i.e., nanomolar range affinity).

General toxicity to support chronic clinical use was evaluated in a one year dog study and a six month rat study. Assessment of carcinogenic potential was assessed in a two year study in rats and a two year study in mice. Embryofetal and post-natal developmental toxicity were assessed in studies performed in rats and rabbits and juvenile toxicity studies were performed in rats and dogs. Juvenile toxicology studies were conducted in rats and in dogs.

The most prominent toxicology findings observed in the nonclinical studies with lixisenatide related to gastrointestinal effects which manifested as dose-related reduction in food intake and variable reductions in weight gain. These gastrointestinal effects of lixisenatide were deemed consistent with the toxicity profile observed with other marketed GLP-1 receptor agonists and would be expected to present clinically as gastrointestinal side effects and weight loss.

Other toxicological findings noted in chronic toxicity studies were effects at the injection site and testes. The relevance of the testicular findings to humans was evaluated with additional non-clinical and clinical testing. The results of this testing suggested the findings were specific to the non-clinical species used in the toxicity studies and of little relevance to humans. See Dr. Chong's CDTL memorandum for a review of these data. These will not be further discussed.

Consistent with other investigational and marketed GLP-1 receptor agonists (Egan et al, NEJM 2014; 370:794-797), there were no findings of adverse histological changes or signs of drug-related neoplasms in pancreatic tissue in mice or rats receiving lixisenatide for up to 2 years, or in dogs for up to 1 year at high multiples of the clinical exposure.

The GLP-1 mimetic drug class is associated with proliferative or neoplastic changes affecting the parafollicular C-cells of the thyroid in 2-year rodent carcinogenicity studies. 'Short-acting' agonists yield a weak response at high doses and 'long-acting' agonists provoke a more robust neoplastic response at markedly lower doses, the difference likely being related in part to the degree and persistence of GLP-1 receptor activation. Lixisenatide increased the incidence of thyroid C-cell adenomas in mice and in rats with statistical significance, and numerically increased thyroid C-cell carcinomas in rats; however, these responses occurred at excessively high doses (≥1000-times) relative to the 20 mcg/day clinical dose, based on plasma drug exposure. In terms of receptor potency, half-life, and exposure/response for tumor outcome in the rodent studies, the thyroid tumor risk profile more closely resembles that of the short-acting GLP-1 receptor agonists.

Lixisenatide administration during the period of organogenesis was associated with increased incidences of skeletal and visceral malformations, including closure defects, at doses that sharply reduced food intake and weight gain for the first days of exposure. This brief interruption of nutritional status in the dams may have resulted in the adverse skeletal findings, but its contribution to the occurrence of rare closure defects, including micro- and anophthalmia, diaphragmatic hernia, thoracogastroschisis, and spina bifida, is less obvious. While the very low placental transfer of lixisenatide (0.1% in rats, ≤0.5% rabbits) argues for a more prominent role of maternal factors in the adverse outcome, a direct adverse effect of lixisenatide on developing fetuses cannot be entirely excluded. The risk summary in the product label will disclose that visceral and skeletal defects were observed in embryofetal development studies at doses that decreased nutritional intake and weight gain during gestation, and that appropriate alternative therapies should be considered to control diabetes during pregnancy.

The toxicology profile in juvenile rats and dogs is consistent with observations made in adult rats and dogs, and is adequate to inform safety for the planned pediatric clinical studies.

I concur with the conclusions reached by the pharmacology/toxicology review team that the toxicity profile is consistent with what is known for this drug class and that there are no outstanding pharmacology/toxicology issues that preclude approval of Adlyxin.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by Dr. Suryanarayana Sista the clinical pharmacology/biopharmaceutics reviewer for the application that there are no outstanding clinical pharmacology issues that preclude approval.

During review, the Office of Clinical Pharmacology noted that phase-2 data suggested the benefit-risk balance could have been possibly more favorable had a twice daily administration schedule been selected for evaluation in the phase 3 program. Indeed, greater HbA1c reduction and less GI tolerability issues for 10 mcg twice daily compared to 20 mcg once daily were observed in the phase 2 dose finding study #DRI6012 (reviewed in Dr. Chong's and Sista's memoranda). The applicant opted not to evaluate this administration schedule in phase 3 stating that the advantages of a twice daily schedule would be outweighed more injection site reactions and potentially loss of adherence with a twice daily regimen. The application contained insufficient data to robustly establish the safety and efficacy of a twice daily dosing schedule and the dosing schedule to be recommended is the dosing regimen evaluated in phase 3 and established to be safe and effective, that is, a once daily subcutaneous injection of 20 mcg per day of Adlyxin.

The exposure to lixisenatide was observed to increase dose proportionally with doses of 10 mcg and 20 mcg. Lixisenatide was observed to have a terminal half-life of approximately 3 hours. Elimination occurs through renal excretion and protein catabolism. Subcutaneous administration of Adlyxin in the abdomen, thigh, or upper arm results in similar exposure and Adlyxin can be administered at all three sites.

The impact of the following intrinsic factors on drug pharmacokinetics was evaluated: body weight, age, sex, race, ethnicity, and renal impairment. The only factor noted to affect pharmacokinetics was renal impairment. Increases in exposure to circulating lixisenatide were noted in subjects with mild, to moderate renal impairment. Exploratory safety analyses suggested that greater exposure appeared to track with an increased incidence of hypoglycemia and gastro-intestinal product-related adverse reactions in these patients (refer to figures 30 and 31 in Dr. Sista's). There are insufficient clinical data in this application to truly inform whether benefits would outweigh risks in patients with severely impaired patients. The absence of evidence to inform this question will be communicated in labeling and is consistent with the approach taken for the other members of the class. No dose adjustment based on intrinsic factor will be recommended and mitigation strategies consisting of enhanced monitoring for renal consequences of product-related adverse reactions will be communicated in labeling. Several drug-drug interactions studies were conducted. The findings and labeling recommendations made based on these studies are summarized in the Dr. Sista's review.

6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewers (Drs. Jessica Cole and Maria Cruz-Fisher) that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

The data establishing that Adlyxin 20 mcg subcutaneously once daily improves glycemic control in adult patients with type 2 diabetes mellitus, whose disease is not controlled by diet and exercise, is derived from 11 clinical trials.

Two other phase 3 trials that were not directly relevant to the indication were also submitted. One trial evaluated weight changes compared to sitaglipitn (Trial EFC10780) and the other compared Adlyxin injection in the evening to Adlyxin injection with the main meal of the day (Trial EFC12261). These trials were reviewed and are discussed in the clinical and statistical memoranda but will not be discussed here as they were not primarily designed to address the claimed indication.

Finally, another trial was a cardiovascular safety trial (ELIXA) which will be briefly discussed in the safety section of this memorandum.

The eleven trials that form the basis of the efficacy claim were multi-center, multi-national, multi-arm, and randomized. The trial schedule included a screening period, a single blind run-in period, a 24 week treatment period (+/- and extension) and a four weeks post-treatment follow-up period. Nine trials were double-blind and placebo-controlled, and two trials were open-labeled and active-controlled.

The primary objective of these 11 trials was to evaluate the effect of Adlyxin and comparators on the change in HbA1c between baseline and trial end. The trials aimed to establish the glucose lowering effectiveness and the safety of Adlyxin in, distinct, clinically relevant use settings over three to six months. This included evaluating use of Adlyxin as the sole glucose lowering drug (monotherapy setting) in patients whose disease was not controlled by diet and exercise and evaluating use of adding Adlyxin to one or more commonly used antidiabetic drug in patients whose disease was not adequately controlled at baseline on one or more of these drug(s). Specifically, studies evaluating use of Adlyxin in combination with maximally effective doses of metformin (add-on to metformin setting), sulfonylurea (add-on to sulfonylurea setting), piogligtazone (add-on to ppar[1]-gamma setting) and basal insulin (add-on to basal insulin setting) were carried out. Three of the 11 trials also included an evaluation of different Adlyxin dosing regimens (i.e., titration steps and time of day) and two

[1] Peroxisome proliferator-activated receptor

of the 11 trials were carried out to meet the requirements of other health regulatory bodies (i.e., trials performed exclusively in Asian populations). The efficacy assessment was carried out at 24 weeks for 10 trials and 12-weeks for one trial. The main trial descriptions are summarized in Drs. Liu's and Balakrishnan's reviews and in Dr. Chong's CDTL memorandum. Key characteristics of the trial are repeated here for convenience.

Table 1: Phase 2-3 Trials Used to Establish the Effectiveness of Adlyxin for the Type 2 Diabetes Indication (Adapted from Tables 4 and 5 in Dr. Chong's CDTL memorandum).

Study ID	Description	Treatment arms	Primary endpoint
Monotherapy			
EFC6018	Randomized, double-blind, placebo-controlled study as add-on to diet and exercise	Lixisenatide 1-step Lixisenatide 2-step Placebo	12 weeks
Add-on to metformin			
EFC10743	Randomized, double-blind, placebo-controlled study as add-on to metformin	Lixisenatide 1-step Lixisenatide 2-step Placebo	24 weeks
EFC6014	Randomized, placebo-controlled study as add-on to metformin	Lixisenatide in AM Lixisenatide in PM Placebo	24 weeks
EFC6019	Randomized, open-label, **active-controlled** study as add-on to metformin	Lixisenatide **Exenatide BID**	24 weeks
EFC11321	Randomized, double-blind, placebo controlled study in **Asian** patients as add-on to metformin +/- sulfonylurea	Lixisenatide Placebo	24 weeks
Add-on to sulfonylurea			
EFC6015	Randomized, double-blind, placebo-controlled study as add-on to sulfonylurea +/- metformin	Lixisenatide Placebo	24 weeks
Add-on to PPAR-gamma			
EFC6017	Randomized, placebo-controlled study as add-on to pioglitazone +/- metformin	Lixisenatide Placebo	24 weeks
Add-on to basal insulin			
EFC6016	Randomized, double-blind, placebo-controlled study as add-on to basal insulin	Lixisenatide Placebo	24 weeks
EFC10781	Randomized, double-blind, placebo-controlled study as add-on to insulin glargine and metformin	Lixisenatide Placebo	24 weeks
EFC10887	Randomized, double-blind, placebo-controlled study in **Asian** patients as add-on to basal insulin +/- sulfonylurea	Lixisenatide Placebo	24 weeks
EFC12626	Randomized, open-label**, active-controlled** study as add-on to basal insulin +/- oral anti-diabetic drugs	Lixisenatide Insulin **glulisine QD** Insulin **glulisine TID**	26 weeks

Lixisenatide 1-step: lixisenatide initiated at 10 µg QD then increased to 20 µg QD after 2 weeks; Lixisenatide 2-step: lixisenatide initiated at 10 µg QD, increased to 15 µg after 1 week, and then increased to 20 µg QD after another week
Source: Adapted from module 5.2 Tabular Listing of Clinical Studies for NDA-208471

The population of participants across the trials varied somewhat with respect to age, race, BMI, country of origin, background antidiabetic therapies at baseline, duration of disease at baseline and level glycemic control at baseline and other disease characteristics (e.g., level of renal function at baseline). Patient with type-1 diabetes, clinically relevant gastro-intestinal disease (e.g., gastroparesis, pancreatitis, nausea and vomiting etc.), cardiovascular disease in the past six months, poorly controlled hypertension, known liver disease, and end-stage renal disease were excluded from the studies. See Drs. Balakrishnan and Liu's review for a detailed description of the study population across studies.

The applicant had pre-specified the primary efficacy assessment to be the change in hemoglobin A1c (i.e., HbA1c) from baseline to the end of the main treatment period (i.e., the landmark visit), designated as either 24/26 weeks or 12 weeks depending on the trial. The primary analysis was to be performed on the mITT population (all subjects who had received at least one dose of the investigational agent) and relies on an ANCOVA model with terms for treatment, and randomization strata for HbA1c, country, background antidiabetic drug(s), and BMI as fixed effects and baseline HbA1c value as covariate.

In reality, the primary analysis was not strictly speaking based on the change in HbA1c from baseline to the landmark visit but reflected the change from baseline to either the landmark visit, the onset of rescue (for subjects rescued) or the last on study visit (for subjects who discontinued prior to the landmark visit). The amount of missing data at the landmark visit ranged from 5% to 16% across the phase 3 trials and missing data were handled in the sponsor's original analyses by carrying forward the last available on-treatment observation (LOCF method). Assumptions made in handling missing data in this way are unlikely to be valid and the Agency has been recommending since 2009 that applicants use methods to handle missing values that are based on a set of more plausible and valid assumptions. The sponsor repeated the analyses using a mixed effect model repeated measure (MMRM model) using all available data (including data obtained post-rescue or retrieved). Dr. He performed a sensitivity analysis for missing data that relied on a method that also used all available data but did make the assumption that data were missing at random (i.e., an ANCOVA model using multiple imputations for missing values). While Dr. He's analyses changed the estimates of efficacy somewhat; overall conclusions for 10 of the 11 studies were not altered. Missing data handling in this way did however affect the conclusion of study EFC12626, the study comparing lixisenatide to insulin glulisine TID. Using a multiple imputation for missing values model, a conclusion of non-inferiority of lixisenatide to glulisine TID (using a NI margin of 0.4%) could no longer be made (LS mean treatment difference [95% CI]: 0.28 [0.157, 0.408]) calling into question the persuasiveness of the reported results based on the sponsor's MMRM analysis. Overall the statistical group viewed estimates of efficacy using the MMRM analyses to be reasonably reflective of the effect of Adlyxin and recommended that these be used to reflect Adlyxin efficacy in the final product label. It will be emphasized that Adlyxin was not as effective as insulin glulisine TID in the product label.

The main efficacy results for the 11 trials, adapted from Table 8 in Dr. He's review and Tables 6 and 7 in Dr. Chong's CDTL memorandum, are shown below.

Table 2: Mean change in HbA1c (%) from baseline using MMRM with all available post-baseline observations up to the main treatment period (Adapted from Tables in Drs. Chong and He's reviews)

Study	Arms (n)	Baseline HbA1c	LS mean change in HbA1c from baseline	LS mean treatment difference vs. placebo (95% CI)	p-value for superiority
Monotherapy					
EFC6018	Placebo (116)	7.97	-0.14		
	Lixi 2-step (117)	8.06	-0.66	-0.52 (-.0761, -0.285)	< 0.0001
	Lixi 1-step (118)	8.07	-0.79	-0.65 (-0.891, -0.418)	< 0.0001
Add-on to metformin					
EFC10743	Placebo (157)	8.12	-0.42		
	Lixi 2-step (154)	7.99	-0.84	-0.42 (-0.598, -0.245)	< 0.0001
	Lixi 1-step (155)	8.03	-0.9	-0.48 (-0.662, -0.306)	< 0.0001
EFC6014	Placebo (166)	8.07	-0.47		
	Lixi AM (245)	8.07	-0.88	-0.41 (-0.580, -0.234)	< 0.0001
	Lixi PM (245)	8.02	-0.72	-0.25 (-0.425, -0.078)	0.0046
EFC6019	Exenatide BID (293)	7.97	-1.03		
	Lixi (302)	7.96	-0.85	+0.18 (0.046, 0.307)	0.0083
EFC11321 +/- sulfonylurea	Placebo (188)	7.95	-0.59		
	Lixi (190)	7.83	-0.88	-0.3 (-0.473, -0.118)	0.0012
Add-on to sulfonylurea					
EFC6015 +/- metformin	Placebo (273)	8.28	-0.23		
	Lixi (545)	8.22	-0.91	-0.69 (-0.811, -0.56)	< 0.0001
Add-on to PPAR-gamma					
EFC6017 +/- metformin	Placebo (157)	8.08	-0.44		
	Lixi (307)	8.05	-0.97	-0.53 (-0.692, -0.372)	< 0.0001
Add-on to basal insulin					
EFC6016 +/- metformin	Placebo (157)	8.39	-0.25		
	Lixi (303)	8.38	-0.68	-0.43 (-0.629, -0.236)	< 0.0001
EFC10781 +/- met or met and ppar-gamma	Placebo (219)	7.56	-0.37		
	Lixi (213)	7.60	-0.67	-0.3 (-0.447, -0.147)	0.0001
EFC10887 +/- sulfonylurea	Placebo (156)	8.53	0.08		
	Lixi (153)	8.53	-0.72	-0.79 (1.032, -0.552)	< 0.0001
EFC12626 +/- metformin	Insulin glulisine QD (290)	7.73	-0.57		
	Insulin glulisine TID (291)	7.79	-0.84		
	Lixi (284)	7.77	-0.63		
	Lixi vs. insulin glulisine QD			-0.06 (-0.176, 0.061)	0.341
	Lixi vs. insulin glulisine TID			+0.21 (0.094, 0.331)	0.0005

Drs. Chong and Balakrishnan have reviewed analyses for secondary glycemic endpoints (i.e., fasting plasma glucose and 2-hour post-prandial glucose etc). The results of these analyses are for the most part consistent with the HbA1c analyses and with glucose lowering effects expected based on the relatively short-lived pharmacokinetic profile of the drug (i.e., greatest glucose lowering effect is closest to time of injection).

The overall results are consistent with a conclusion that Adlyxin improves glycemic control in adult patients with type 2 diabetes inadequately controlled on diet and exercise alone or when used in combination with commonly used antidiabetic drugs. The efficacy of Adlyxin is modest. At the proposed maximally effective dose of 20 mcg per day it reduces Hba1c by ~ 0.5 to 0.6% from a baseline of ~ 8.0% after six month of use. Adlyxin appears less effective than Byetta twice daily and insulin glulisine three times daily at improving glycemic control. Of note, the efficacy against glulisine should be interpreted in light of the fact that glulisine dose titration may have been suboptimal, dose increase was limited in time and that the maximally effective dose of glulisine was not used (insulin has no cap on its glucose lowering effect and the meaningfulness of comparative efficacy to insulin in a short term trial is questionable).

Analyses of HbA1c response by subgroups defined by gender, race (White, Black, Asian), age (< 65 years, ≥ 65 years), ethnicity (Hispanic, non-hispanic), region (US, non-US), baseline HbA1c (< 8.5%, ≥ 8.0%), baseline BMI (≤ 30, > 30), duration of diabetes, creatinine clearance positive or negative antibody status did not reveal notable differences in Lixisenatide's effect across these subgroups. Refer to the reviews by Drs. Chong, Liu and He for details. Dr. Liu also explored additional subgroups defined by anti-lixisenatide antibody status (positive versus negative) and concentration in Table 4.1 of his review. Participants with the highest concentration of anti-lixisenatide antibody (>100 nmol/L; ~ 2% of the population) appeared to exhibit less glucose lowering than those with lower or undetectable concentration (a decrease in HbA1c of 0.2% versus 0.5%). While these results are interesting in that they suggest an effect of anti-lixisenatide antibody on efficacy of the product they are subject to the limitations of subgroup analyses defined on the basis of a post-randomization event.

The applicant evaluated effects of Adlyxin on body weight in secondary analyses (see figure 8 in Dr. Chong's CDTL memorandum). Adlyxin does not cause weight gain or loss when used alone and appears to cause a small amount (≤1 kg) of weight loss over 6 months when added to metformin. Statistical differences in body weight between Adlyxin and placebo favoring Adlyxin were also observed when Adlyxin was used in combination with drugs known to cause a modest amount of weight gain (basal insulin, and sulfonylurea). This may have been due, in part, to differential use of these co-administered drugs in the trial. For example, randomization to Adlyxin could have led to a reduction in the dose of the co-administered drug(s) in that arm (i.e., removal of a drug that causes weight gain). Alternatively, increases in the dose of the co-administered drug(s) in the placebo arm to address worsening glucose control could have also contributed to the observed difference. These possibilities were not looked into in the reviews. Overall, the magnitude of the placebo-adjusted weight difference observed in the phase 3 studies was small and of unclear significance from a clinical perspective.

8. Safety

Drs. Chong and Balakrishnan have summarized the general safety findings in the application and Dr. Zhao the cardiovascular risk analyses specifically. Two major data pools and the large randomized placebo-controlled cardiovascular outcomes trial (ELIXA) were used to characterize risks associated with Adlyxin use.

One data pool, referred to in Dr. Balakrishnan's review as Data Pool 1, combined safety information collected in the main treatment period and extension from nine[2] Phase 2 and 3 randomized, double-blind, placebo-controlled trials. This grouping was used to characterize Adlyxin-related adverse reactions and in particular common adverse reactions. Another grouping, referred to as data pool 2, pooled safety information collected from 20[3] completed Phase 2 and 3 controlled trials across the Adlyxin program (includes ELIXA). This grouping was used in analyses of rare adverse events, including serious hypersensitivity reactions, pancreatitis, hepatotoxicity, acute renal failure, medullary thyroid cancer and other malignancies.

The number of participants exposed and the duration of exposure to Adlyxin in the application were adequate to characterize safety. Exposure numbers and duration by categories for the ELIXA trial and the pool of placebo-controlled trials is shown in the two tables below.

Table 2: Number of Subjects Exposed to Adlyxin 20mcg by Defined Duration of Exposure in the ELIXA trial (Source: Table 8 in Dr. Balakrishnan's review)

	Adlyxin	Placebo
≥ 1 day	3031 (100%)	3032 (100%)
≥ 6 months	2679 (88.4%)	2771 (91.4%)
≥ 12 months	2513 (82.9%)	2606 (85.9%)
≥ 18 months	2021 (66.7%)	2105 (69.4%)
≥ 24 months	1376 (45.4%)	1425 (47.0%)
≥ 36 months	828 (27.3%)	860 (28.4%)

Table 2: Number of Subjects Exposed to Adlyxin 20mcg by Defined Duration of Exposure in data pool 1 (Source: Table 9 in Dr. Balakrishnan's review)

	Adlyxin	Placebo
≥ 1 day	2869 (100%)	1639 (100%)

[2] Studies EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887, and EFC11321. Pool 1a refers to safety data accrued in the main treatment period only (i.e., without extension).

[3] Studies EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887, EFC11321, EFC6019, EFC10780, EFC12626, EFC11319, LTS10888, EFC12261, ACT6011, PDY10931, PDY12625, DRI6012, and PDY6797

≥ 3 months	2622 (91.4%)	1533 (93.5%)
≥ 6 months	2248 (78.4%)	1306 (79.7%)
≥ 12 months	1653 (57.6%)	759 (46.3%)
≥ 18 months	1260 (43.9%)	586 (35.8%)
≥ 24 months	272 (9.5%)	111 (6.8%)

Deaths
Overall slightly more deaths were seen on comparators than Adlyxin (refer to Table 13 in Dr. Balakrishnan's review) and Dr. Balakrishnan did not note an imbalance for any one particular cause of death in participants randomized to Adlyxin in the ELIXA trial or across the different pools. See ELIXA trial discussion below for all-cause mortality analyses.

Serious Adverse Events
The incidence for serious adverse events were generally balanced in both the ELIXA trial (22% versus 21% for placebo and Adlyxin respectively) and data pool 1 (8% versus 9% for placebo and Adlyxin respectively). More frequent serious adverse events of nausea, vomiting, and pancreatic enzyme elevation were seen in data pool 1. These adverse reactions are seen with other members of the GLP-1 receptor agonist class. In ELIXA specifically, more serious adverse events related to gall bladder disorders (i.e., cholelithiasis and cholycystitis) were observed (0.6% versus 1.1% for placebo versus Adlyxin respectively). This again was deemed likely related to drug in light of the known effect Adlyxin's on gall bladder contractility (refer to mechanistic study PDY11431). In the ELIXA trial more patients randomized to Adlyxin experienced a serious adverse event of onychomycosis (0.2% versus 0.6%), Tinea Pedis (0.2% versus 0.6%) and paronychia (0.1% versus 0.3%). It is unclear whether this represents a real or a chance finding.

Common Adverse Reactions
The most common Adlyxin-related adverse reaction in the Phase 3 placebo-controlled studies were: nausea (6% versus 25%), vomiting (2% versus 10%), diarrhea (6% versus 8%), dyspepsia (0.2% versus 3.2%), constipation (1.8% versus 2.8%), abdominal distension (0.9% versus 2.2%), abdominal pain upper (0.9% versus 2.2%), and abdominal pain (1.5% versus 2.0%). These adverse reactions are consistent with adverse reactions observed for other members of the GLP-1 receptor agonist class.

Specific issues reviewed in details in Dr. Chong's CDTL memorandum include: immunogenicity, hypersensitivity reactions, pancreatitis, renal adverse reactions, and hypoglycemia. Drs. Chong and Balakrishnan have reviewed pancreatitis, renal adverse reactions, and hypoglycemia and these will not be reviewed here. The findings for these reactions are consistent with what is known for the class.

Immunogenicity
Adlyxin appears to be highly immunogenic. Approximately 70% of clinical subjects tested positive for lixisenatide anti-drug antibodies (ADA) after treatment with lixisenatide for 24

weeks or more. In a meta-analysis of phase 3 data, lixisenatide treated subjects with ADA concentrations of greater than 100 nmol/L appeared to have lesser HbA1c reduction (lower efficacy) when compared to patients with low ADA levels or no antibodies in subgroup analyses (this and limitations of these data are discussed in the Efficacy Section above). In retrospective safety analyses, subjects with ADA were numerically more likely to have reported at least one event of injection site reactions, hypoglycemia and asthenic conditions (refer to Table 20 in Dr. Chong's CDTL memorandum). The incidence of allergic reactions appeared correlated with ADA concentration (refer to Section 7.3.5.5 in Dr. Balakrishnan's review).

Twenty eight percent (28%) of participants with anti-drug antibody were found to possess antibodies that cross reacted with endogenous GLP-1 and 4.7% had antibodies that cross-reacted with glucagon. This finding was postulated to be attributable to the overlap in amino acid sequences between lixisenatide, endogenous GLP-1 and endogenous glucagon. Neutralizing ADA could theoretically alter product efficacy and increase drug-related risks through their effects on lixisenatide, endogenous GLP-1 and/or endogenous glucagon. The applicant will be asked to minimize the level of uncertainty around these risks by developing a valid neutralizing antibody assay and specifically determine whether participants with cross-reactive ADA to GLP-1 or glucagon developed antibodies with neutralizing activity against endogenous GLP-1 and endogenous glucagon through a post-marketing requirement.

Hypersensitivity/Allergic Reactions

The applicant prospectively adjudicated all treatment emergent adverse events that could have signaled that an allergic reaction occurred across the majority of Phase 2 and 3 trials. Other GLP-1 receptor agonist drug development programs did not use standardized definitions or prospective adjudication or to evaluate allergic reactions and this application's assessment of allergic reactions was more robust in comparison. Allergic reactions were classified by the adjudication committee as; urticaria, angioedema, anaphylactic reaction, anaphylactic shock (evidence of hypotension in narrative), or other [entered as free text (i.e., allergic rhinitis)]. Use of Adlyxin was associated with a slight increase in the incidence of overall allergic reactions (Refer to Table 21 in Dr. Balakrishnan's first cycle NDA review and Table 22 in Dr. Chong's review).

Dr. Chin from the Division of Pulmonary, Allergy and Rheumatology Products reviewed cases denoting severe hypersensitivity reactions (e.g., anaphylaxis) in participants exposed to Adlyxin. To categorize cases as a severe, potentially life-threatening, allergic reaction, Dr. Chin used a clinical definition based on the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) criteria[4]. A severe, potentially life-threatening allergic reaction was diagnosed if the following conditions in the case were met;

[4] Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NJ, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol. 2006; 117:391-7

Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue- uvula), and at least one of the following:

a) *Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)*
b) *Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia (collapse), syncope, incontinence)*

This case definition is a case definition used by DPARP to detect severe allergic reaction across drug development programs. Using this case definition, eight participants exposed to Adlyxin out of 7874 total participants (0.10%) developed a treatment emergent, severe, allergic reaction that could not be attributed to an alternative etiology (i.e., bee sting, food) or drug and were deemed related to Adlyxin. All members of the GLP-1 class, including Adlyxin, can cause severe, potentially life-threatening, allergic reactions. Absent head to head comparative data, it not to possible to determine with any degree of certainty whether Adlyxin causes more, the same or less of these reactions.

Cardiovascular Risk

To meet the requirements outlined in the Guidance to Industry: *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*, the applicant carried out a randomized, multinational, double-blind, placebo controlled, parallel group, time to event cardiovascular outcomes trial (ELIXA). The statistical analysis plan for the CV-risk assessment was finalized in 2012 and included an analyses to exclude a relative risk margin of 1.8 (i.e., an 80% excess risk) and a final analysis to exclude a relative risk margin of 1.3 (a 30% excess risk). There was no interim analysis planned for 1.3 and the final analysis was carried out using a two sided alpha level of 0.05.

In ELIXA, a total of 6068 adults with type 2 diabetes who had experienced an acute coronary syndrome (ACS) event within 180 days of enrollment were randomized to placebo (N=3034) or lixisenatide (N=3034) in a 1:1 to fashion. Baseline demographic and disease characteristics were balanced. Most participants were Male (70%), White (74%), and were recruited from Eastern Europe and Central or South America (60%). Approximately 13% of participants were recruited from North America. The mean age was 60 year, the mean BMI was 30 kg/m^2, the mean duration of diabetes was 9 years, and the mean baseline HbA1c was 7.7%. Most participants were recruited on the basis of having had a qualifying ACS event of non-ST segment elevation MI (39%) or ST segment elevation MI (~45%) greater than 30 days before randomization (87% of total participants). Medications at baseline were also balanced; 40% used insulin, 65% used metformin and 33% used sulfonylureas alone or in combination to control their diabetes. With regard to atherosclerotic therapies, 97% used an antiplatelet agent, 93% used statins, 85% used a beta-blocker and 85% were on an Angiotensin Converting Enzyme inhibitor or ARB. The mean baseline LDL was ~70 mg/dL.

Approximately 97% of individuals randomized completed the trial and vital status was known for 99% of individuals randomized. The median duration of follow-up was ~ 2 years and similar in both groups.

The primary endpoint in the ELIXA trial was the time to a first major adverse cardiovascular event (MACE) of CV-death, non-fatal myocardial infarction, non-fatal stroke or biomarker positive unstable angina. A total of 805 adjudicated first MACE event were observed in ELIXA (406 [13.4%] in Adlyxin-treated patients and 399 [13.2%] in placebo-treated patients). The estimated hazard ratio for MACE was 1.02 and the upper limit of risk defined by using the upper 95% confidence interval around the estimated hazard ratio was 1.17. Analysis for MACE yielded similar results (see Table 1 of Dr. Zhao's review). The results of this analysis do not suggest that Adlyxin-use is associated with excess CV-risk. Evaluations of hazard ratio across subgroups defined by baseline characteristics were consistent with overall results (Refer to Figure 8 in Dr. Zhao's review). Sensitivity analyses relying on the three component MACE endpoint (CV-death, non-fatal MI and non-fatal stroke) or only "on-treatment" MACE+ were consistent with the results of the primary analysis. There were 434 deaths in ELIXA. Analyses examining all-cause mortality did not suggest either benefit or harm of using Adlyxin in this population. The hazard Ratio (95% CI) for time to all-cause death in the on-study population was 0.94 (0.78, 1.13).

Dr. Zhao performed several exploratory analyses to address numerical imbalances in specific malignancies which were not favoring Adlyxin in ELIXA. These were; thyroid cancer (20/6068 subjects), colorectal cancer (28/6068 subjects), and prostate cancer (22/4206 male subjects). For these three malginancyies, the imbalance was caused by 3 to 6 excess cases in the Adlyxin arm. I concur with the reviewers, in light of the totality of the evidence and exploratory analyses performed, that these findings likely represent the play of chance and do not suggest a causal association between Adlyxin and these malignancies. Refer to Dr. Zhao's and Balakrishnan's review for details.

The results of ELIXA confirm that use of Adlyxin is not associated with excess cardiovascular risk and the all-cause mortality findings in this trial provide confirmatory evidence to conclude that use of the drug is safe in this population.

9. Advisory Committee Meeting

An Advisory Committee meeting was held on May 25, 2016 to discuss the efficacy and safety findings in the Adlyxin application and in a fixed combination drug product application combining lixisenatide with insulin glargine. The committee members noted that both the anti-drug antibody finding and the risks associated with the rare occurrence of severe allergic reactions was of some concern. The magnitude of the concern was however not sufficient to recommend that products containing lixisenatide not be marketed. See full transcript for details.

10. Pediatrics

This has been reviewed by Drs. Chong and Balakrishnan and the reader is referred to their reviews for details. Pediatric studies for ages less than 10 are waived. Pediatric studies for ages 10-17 were deferred.

11. Other Relevant Regulatory Issues

These have been reviewed by Drs. Chong and Balakrishnan and the reader is referred to their reviews for details. No regulatory issues that would preclude product approval were identified.

12. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

Benefits Assessment: The applicant has established that Adlyxin 20 mcg administered subcutaneously once daily improves glycemic control in adults with type 2 diabetes whose disease is not controlled with diet and exercise. The glucose lowering effect of Adlyxin is modest. At the proposed dose of 20 mcg per day it reduces Hba1c by ~ 0.5 to 0.6% from a baseline of ~ 8.0% at six month of use. The maximum glucose lowering effectiveness occurs early and similar to all other anti-diabetic drugs is expected to wane over time. Adlyxin appears less effective than exenatide (Byetta) twice daily and insulin glulisine three times daily at improving glycemic control in head to head comparisons. The glucose lowering effect of Adlyxin was not associated with weight gain and compared to placebo was not associated with a high risk of hypoglycemia. In contrast, weight gain and hypoglycemia are adverse reactions associated with the insulin and sulfonylurea antidiabetic drug classes.

Risks Assessment: Glucose lowering with Adlyxin is associated with a high risk for gastrointestinal adverse reactions (i.e., mainly nausea and vomiting). The risk of hypoglycemia associated with Adlyxin use is increased when the drug is added to drugs known to cause hypoglycemia (e.g., sulfonylurea and insulin). Some of the serious Adlyxin-related risks identified in the application (i.e., serious allergic reactions, pancreatitis, renal impairment in patients experiencing severe gastrointestinal reactions) are class-related and consistent with safety experience for other marketed products in the class. These risks will be communicated and mitigated through labeling. Common product related adverse reactions were consistent with the drug's pharmacological effect on intestinal motility (gastro-intestinal adverse reactions) or the route of administration (injection site reactions). Use of Adlyxin in patients with type 2 diabetes and established cardiovascular disease was not associated an excess risk of atherosclerotic cardiovascular disease. This will be the first GLP-1 to report the results for a completed CV-risk assessment.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

No 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

FDA is requiring the two following postmarketing studies for Adlyxin ;

A repeat dose, pharmacokinetic/pharmacodynamics (PK/PD) study evaluating Adlyxin (lixisenatide) in patients with type 2 diabetes ages 10 to 17 years (inclusive) that are insufficiently controlled with metformin and/or basal insulin. Subjects will be randomized to lixisenatide or placebo. Titration will occur every 2 weeks increasing the dose from 5 mcg to 10 mcg then to 20 mcg.

A 24-week, randomized, controlled efficacy and safety study comparing Adlyxin (lixisenatide) with placebo in patients with type 2 diabetes ages 10 to 17 years (inclusive), followed by a 28-week double-blind controlled extension. Subjects will be on a background of metformin and/or basal insulin at a stable dose. This trial should not be initiated until the results of the pediatric PK/PD study (PMR 3102-1) have been submitted to and reviewed by the Agency.

Perform immunogenicity testing on anti-drug antibody (ADA)-positive samples from clinical studies of type 2 diabetes patients treated with lixisenatide to determine the incidence of neutralizing antibodies (NAb) and ADA that cross-react with endogenous GLP-1 and glucagon and are capable of neutralizing the effect of these endogenous peptides. Assessments should be performed using assays demonstrated to be suitable for their intended purposes through formal validation studies that have been reviewed by the Agency prior to their use in clinical sample analysis. Samples used for these assessments should be archived under suitable conditions until testing, and should include sufficient quantity to allow for completion of required immunogenicity assessments. Study report(s) submitted to the Agency will include evaluation of the impact of NAb and cross-reactive antibodies on patient safety as well as PK, PD, and efficacy of lixisenatide.

Although not a required post-marketing study or commitment, we will request that for a period of two years, the applicant holder submit all cases of serious hypersensitivity reactions reported with Adlyxin (lixisenatide) injection as 15-day alert reports, and that serious hypersensitivity reactions be considered adverse events of special interest in periodic safety report (i.e., the Periodic Adverse Drug Experience Report [PADER] required under 21 CFR 314.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report [PBRER] format). We expect cumulative data relative to the date of approval of Adlyxin (lixisenatide) injection as well as relative to the prior periodic safety report. Medical literature reviews for case reports/case series of serious hypersensitivity reactions reported with Adlyxin (lixisenatide) injection should also be provided in the periodic safety report.

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/s/

JEAN-MARC P GUETTIER
07/26/2016