CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208471Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	(see electronic signature)
From	William H. Chong, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 208471
Applicant	Sanofi Aventis US, LLC
Date of Submission	July 27, 2015
PDUFA Goal Date	July 27, 2016
Proprietary Name / Non-Proprietary Name	ADLYXIN / lixisenatide
Dosage form(s) / Strength(s)	Solution for subcutaneous injection (50 µg/mL and 100 µg/mL)
Applicant Proposed Indication(s)/Population(s)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Recommendation on Regulatory Action	*Approval, pending agreement on labeling*
Recommended Indication(s)/Population(s) (if applicable)	*Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.*

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Lixisenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist with a proposed indication for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Type 2 diabetes mellitus is a disease of impaired glucose homeostasis leading to chronic hyperglycemia and an increased risk for microvascular and macrovascular complications. Improving glycemic control as assessed by reduction in HbA1c has been shown to reduce the risk of microvascular complications and has been an accepted endpoint for anti-diabetic agents. While there are multiple approved drug products indicated to improve glycemic control, many patients struggle to achieve glycemic targets. Patients often require multiple therapies to maintain glycemic control and may better respond or tolerate one therapy over another. Additional therapeutic options are needed to allow for individualization of therapy.

Lixisenatide has demonstrated the ability to improve glycemic control as evidenced by findings of superiority in reducing HbA1c compared to placebo in randomized, blinded clinical trials in a variety of clinical use scenarios. Placebo adjusted changes in HbA1c ranged from -0.3 to -0.8%.

The safety profile of lixisenatide is generally consistent with what would be expected for a GLP-1 receptor agonist. Gastrointestinal adverse reactions (i.e., nausea, vomiting) are the most common adverse reactions. The clinical trial data suggests that anti-drug antibody (ADA) formation is higher with lixisenatide, but the impact of these antibodies is unclear. Information on specific sub-types of antibodies is limited, and there is uncertainty with regard to whether these antibodies could cross-react with endogenous GLP-1 or glucagon. There is no data on the presence of neutralizing antibodies, though the clinical data raises concerns that these could be present. Related to the immunogenic potential of lixisenatide is the potential for allergic reactions (including anaphylaxis). Allergic reactions are a concern with all peptide products which include GLP-1 receptor agonists, and there is language in the label discussing this safety concern in all of the approved GLP-1 receptor agonists. The lixisenatide program is differentiated by the fact that a signal for anaphylaxis was seen in the clinical development program, in contrast to other members of the class where the signal for serious hypersensitivity reactions was identified in the postmarketing setting. There are differences between the development programs (such as size, use of an adjudication committee for allergic events) which may have contributed to this. The overall incidence of anaphylaxis is low and does not preclude approval, but there is some residual concern that the incidence may be higher compared to other members of the class.

A cardiovascular outcomes trial has been completed for lixisenatide. There is no evidence of an increased risk for major adverse cardiovascular events with lixisenatide.

Overall, the data submitted for lixisenatide support a favorable benefit-risk profile for use as an adjunct to diet and exercise to improve glycemic

control in adults with type 2 diabetes mellitus. Lixisenatide has demonstrated an ability to improve glycemic control. The safety profile is generally consistent with other members of the class, with the possible exception of immunogenicity/allergic reactions. While these may occur at a higher incidence with lixisenatide compared to other members of the class, the impact of anti-drug antibodies is unclear and the overall incidence of serious allergic reactions (including anaphylaxis) is low. The safety concerns identified with lixisenatide can be adequately communicated with labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Type 2 diabetes mellitus (T2DM) is a condition of chronic impaired glucose homeostasis leading to chronic hyperglycemia and an increased risk for microvascular (e.g., retinopathy, nephropathy) and macrovascular (e.g., myocardial infarction, stroke) complications. The Center for Disease Control estimates that there are over 29 million patients with type 2 diabetes mellitus in the United States.	Type 2 diabetes mellitus is a serious and life threatening condition that if left untreated leads an increased risk for morbidity and mortality.
Current Treatment Options	• Based on the results of the Diabetes Control and Complication Trial (DCCT) and the United Kingdom Prospective Diabetes study (UKPDS), improved glycemic control (as measured using hemoglobin A1c [HbA1c]) is believed to result in improved clinical outcomes (i.e., reduced microvascular complications). • There are currently 12 classes of medications (generally with multiple members in each class), approved to improve glycemic control in patients with T2DM. There are different safety concerns for each class. Metformin is often considered first-line therapy with the choice of subsequent therapies individualized by prescribers based on the patient. • While all of the approved antidiabetic agents have been shown to improve glycemic control, data on the ability of individual agents to improve clinical outcomes is generally not available.	Despite the many available treatment options, many patients continue to have difficulty with achieving the desired degree of glycemic control. Further, T2DM is a progressive disorder and patients typically need additional agents added as the course of the disease progresses. Additional alternative therapies are needed.
Benefit	• The efficacy of lixisenatide has been demonstrated in double-blind, placebo-controlled studies in a range of clinical settings. These include as add-on to diet and exercise, as add-on to metformin, as add-on to sulfonylurea, and as add-on to basal insulin. The placebo-adjusted effect on change from baseline for HbA1c ranges from -0.3	Treatment with lixisenatide has demonstrated improvement in glycemic control in a variety of clinical settings compared to treatment with placebo. The Division has accepted improvement in glycemic control as measured

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	to -0.8%. • Though the clinical pharmacology data suggest that twice daily (BID) administration may be more effective and better tolerated, lixisenatide was studied at a dose of 20 µg once daily. • Reduction from baseline of hemoglobin A1c (HbA1c) has been the accepted surrogate endpoint for antidiabetic agents.	using HbA1c as a surrogate for improved clinical outcomes. While clinical pharmacology data suggest that BID dosing may be more effective and better tolerated, the phase 3 studies have demonstrated the efficacy of once daily dosing.
Risk	• The safety profile is generally consistent with the class. Treatment with lixisenatide is associated with nausea/vomiting, an increased risk for hypoglycemia when used in combination with insulin and secretagogues, and allergic reactions. • The high rate of immunogenicity and a signal for anaphylaxis are concerning. The impact of ADAs is unclear, and there is limited information on sub-types of antibodies. Acknowledging that the overall incidence of anaphylaxis is low (0.2%), it remains unknown whether the observed incidence in the clinical trials will translate into a higher incidence in the postmarketing setting. • The completed cardiovascular outcomes trial does not suggest an increased risk for cardiovascular events with lixisenatide.	The safety profile of lixisenatide has been generally well characterized. Findings from the development program suggest that the safety profile is generally consistent with other members of the GLP-1 receptor agonist class. A signal for an increased risk for anaphylaxis was seen in the development program, but the overall incidence of anaphylaxis is low. The risk of major adverse cardiovascular events is not increased with lixisenatide.
Risk Management	• There is uncertainty with respect to the impact of the high incidence of anti-drug antibodies with lixisenatide treatment. Whether these antibodies can neutralize lixisenatide, cross-react with endogenous GLP-1 or glucagon is not known. This will need to be studied further. • The signal for anaphylaxis seen in the development program is unique to lixisenatide when compared to the other GLP-1 receptor agonists. Whether this is due to differences in the size and rigor of assessment is unclear. Given that the overall incidence is low, this risk can likely be adequately communicated with labeling.	The risks associated with lixisenatide can be handled with adequate labeling. The concern for anaphylaxis and serious allergic reactions should be made more prominent in section 5 of the label. The uncertainties with respect to the anti-drug antibodies will need to be further assessed, but this can be accomplished in the postmarketing setting.

2. Background

Diabetes mellitus is a disease of impaired glucose homeostasis that results in chronic hyperglycemia. There are two main types of diabetes mellitus: type 1 diabetes mellitus (T1DM; characterized by autoimmune destruction of pancreatic β-cells and loss of insulin secretion) and type 2 diabetes mellitus (T2DM; characterized by resistance to insulin activity with inadequate insulin production to maintain euglycemia). As a result of chronic hyperglycemia, patients with diabetes mellitus are at an increased risk for microvascular (e.g., retinopathy, nephropathy) and macrovascular (e.g., myocardial infarction, stroke) complications. Based on the results of the Diabetes Control and Complication Trial (DCCT) and the United Kingdom Prospective Diabetes study (UKPDS), improved glycemic control (as measured using hemoglobin A1c [HbA1c]) is believed to result in improved clinical outcomes.

The development of therapies to treat T2DM has focused on developing agents that can improve glycemic control as assessed by the ability to reduce HbA1c. Currently there are 12 FDA approved drug classes with each class generally having multiple drug products (Table 1). Some of these drug products are also available in combination with other drug products.

Table 1: Summary of FDA approved drugs to improve glycemic control in diabetes

Drug Class	Drug Products
Insulin	Multiple products
Biguanides	Metformin(as an immediate release and an extended-release formulation)
Sulfonylureas	Chlorpropamide Glimepiride Glipizide Glyburide
Thiazolidinediones	Rosiglitazone Pioglitazone
Meglitinides	Repaglinide Nateglinide
Alpha-glucosidase inhibitors	Acarbose Miglitol
Dipeptidyl peptidase-4 (DPP-4) inhibitors	Sitagliptin Saxagliptin Alogliptin Linagliptin
Glucagon-like peptide-1 (GLP-1) receptor agonists	Exenatide (as a twice daily and as a once weekly) Liraglutide Albiglutide Dulaglutide
Sodium glucose co-transporter-2 (SGLT2) inhibitors	Canagliflozin Dapagliflozin Empagliflozin
Amylin analogs	Pramlintide
Bile acid sequestrants	Colesevelam
Dopamine agonists	Bromocriptine

This New Drug Application (NDA) is for a new GLP-1 receptor agonist. Lixisenatide would be

the sixth member of the GLP-1 receptor agonist class of drug products. An NDA for lixisenatide was previously submitted to the FDA in 2012 but it was withdrawn prior to the action date. Lixisenatide is currently approved in over 50 countries worldwide.

The applicant is proposing that lixisenatide be indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The applicant is proposing to market lixisenatide in two strengths (i.e. a 0.05 mg/mL strength to be used for initiation and titration and a 0.1 mg/mL strength to be used for maintenance). The product presentation will be a disposable pen-injector. Two pens (one for each strength) will be marketed. One will deliver a 10 µg lixisenatide dose (0.2 mL of 0.05 mg/mL solution) and the other will deliver a 20 µg lixisenatide dose (0.2 mL of 0.1 mg/mL solution). The proposed starting dose of lixisenatide is 10 µg once daily for 14 days (titration dose), followed by an increase to the maintenance dose of 20 µg once daily (therapeutic dose).

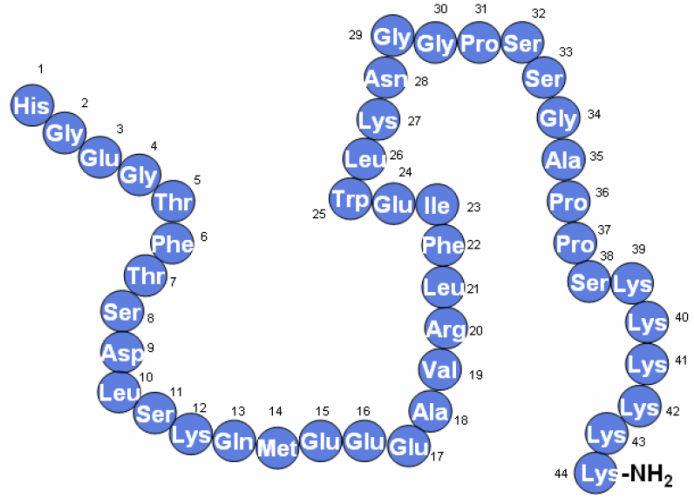
3. Product Quality

The overall recommendation from the Product Quality perspective is approval.

a. Drug Substance

Lixisenatide is a synthetic peptide containing 44 amino acids with six lysine residues at the C-terminal to prevent physiological degradation by dipeptidyl peptidase-4 (Figure 1). It has a molecular formula of $C_{215}H_{347}N_{61}O_{65}S$ and an average molecular mass of 4858.5.

Figure 1: Structural formula of lixisenatide



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

The final drug substance is a white to off-white (b) (4) powder. The manufacturing process for lixisenatide is divided into four operations:

(b) (4)

(b) (4)

The manufacturing process, proposed specifications, and stability data have been reviewed by Dr. Joseph Leginus. Impurities and degradation products have been adequately qualified. No approvability issues with respect to the drug substance were identified.

Facility inspections for the drug substance as well as for the control testing laboratories have been completed. No issues were identified.

b. Drug Product

Lixisenatide will be manufactured as a sterile solution for subcutaneous injection and packaged in a glass cartridge. The solution contains lixisenatide, glycerol, sodium acetate, methionine, metacresol, and water for injection. Hydrochloric acid and/or sodium hydroxide are added to achieve a target pH (b) (4) The two different dosage strengths differ only in the amount of lixisenatide (i.e., either 10 µg/0.2 mL or 20 µg/0.2 mL).

The primary packaging material consists of a clear, colorless, glass cartridge with a (b) (4) (b) (4) plunger stopper which is in contact with the drug product. The cap also includes a (b) (4) cap. This cartridge is then integrated into a disposable, fixed dose pen injector. The components of the pen injector are (b) (4), and none of these parts come in contact with the drug product.

The manufacturing process previously submitted with NDA 204961 has been modified. The new manufacturing process (b) (4)
(b) (4)

A reanalysis of stability data based upon the modified manufacturing process has changed the proposed shelf-life. In NDA 204961, the proposed shelf-life was (b) (4) months. The new proposed shelf-life is 24 months. This 24 month expiry is acceptable for lixisenatide when stored at 5ºC. For in use stability, the Office of Product Quality recommends 14 days when stored at 30ºC.

Dr. Ravindra Kasliwal has reviewed the drug product, the specifications, the modified manufacturing process, and the proposed 24 month shelf-life and has not identified any approvability issues. Dr. Maria Cruz-Fisher has reviewed the microbiology risk of the drug product manufacturing and has not identified any approvability issues.

The drug product manufacturing facility has been inspected. No issues were identified.

c. Pen Injector Device

The lixisenatide pen-injector is a disposable device combining a glass cartridge with an injector device designed to deliver a fixed dose of lixisenatide. A priming step is required with the first use, but not necessary for subsequent doses. A new needle is attached prior to each dose. The dose is dispensed as a result of manual pressure by the user.

Each pen injector will be able to dispense 14 doses, with each dose consisting of 0.2 mL of the respective lixisenatide solution. The two different dosage strengths will be presented in different color pen injectors: green for the 10 μg/0.2 mL and burgundy for the 20 μg/0.2 mL. Additionally, there are tactile features to assist in differentiation: lines for the green pen and circles for the burgundy pen.

The review of the device was completed by Dr. Lana Shiu. Biocompatability of the device was completed by Dr. Bifeng Qian. Additional information on the testing performed on the device was requested by Dr. Shiu and Dr. Qian. The responses to these requests adequately addressed their concerns. Both Dr. Shiu and Dr. Qian recommend approval of the device.

CDR Alan Stevens had residual concerns with regard to dose accuracy given that a priming step is only required with the initial dose of the pen injector and not with subsequent doses. As needles were not changed during the design verification studies it is unclear whether the absence of priming before each dose could negatively impact dosing. The applicant indicated that they believe capillary action will fill the space when a new needle is applied, and that any residual volume loss would be negligible given the size of the needle. CDR Stevens reviewed these responses and found them acceptable. No further concerns with the dose accuracy were expressed.

Overall, no product quality issues were identified which would preclude approval of lixisenatide.

4. Nonclinical Pharmacology/Toxicology

The nonclinical studies include 19 primary pharmacology studies, 4 secondary pharmacology studies, 8 safety pharmacology studies, 26 general toxicology studies, 7 genetic toxicology studies, 2 carcinogenicity studies, 12 developmental, reproductive and juvenile toxicology studies, and 3 local tolerability studies. Additionally, the applicant performed 13 nonclinical studies to evaluate the potential for thyroid C-cell proliferation.

In vitro studies show that lixisenatide has a binding affinity to the human GLP-1 receptor that is approximately 4x greater than that of endogenous human GLP-1. Combined with findings that lixisenatide has a low affinity for a wide range of other receptors leads to the conclusion that lixisenatide is a selective agonist for the GLP-1 receptor. In animal models, lixisenatide was shown to improve oral glucose tolerance, fasting blood glucose, and HbA1c. As with other GLP-1 receptor agonists, lixisenatide enhanced glucose-stimulated insulin secretion in a glucose-dependent manner.

Treatment with lixisenatide resulted in bodyweight loss or decreased weight gain that correlated

with decreased food and water consumption. This is consistent with the GLP-1 receptor agonist class. These effects tended to diminish with treatment duration.

The primary target organs after repeated dosing were the testes and the injection site. In a 6 month repeat dose study in rats, an increased incidence and severity of microscopic findings in the testes (e.g., seminiferous tubule atrophy and necrosis, spermatid stasis, mineralization), seminal vesicle (e.g., atrophy), and epididymis (oligospermia, aspermia, lymphocytic infiltrate). These were found to be mostly reversible after a 1 month recovery period. In a 12 month repeat dose study in dogs, similar microscopic findings were observed in the epididymis and testes, including hypospermatogenesis in seminiferous tubules and epididymal dilation, degeneration, oligospermia, or aspermia. This occurred at doses ≥ 200 μg/kg BID (equivalent to 4,062x the expected clinical human exposure). Similar findings were seen in an 8-month dog juvenile toxicology study at dose ≥ 5 μg/kg BID (equivalent to 7x the expected clinical human exposure). As with the rats, these findings were reversible following a 2 month treatment free period.

Additional studies were performed to further evaluate this signal. Expression of the GLP-1 receptor is higher in dog testes than in humans (3-10x). This suggests that dogs are more sensitive to lixisenatide inhibition of spermatogenesis due to increased GLP-1 receptor expression. A clinical study (study TDR11215) was performed which examined the effect of lixisenatide 20 μg once daily for 6 months in obese men on human spermatogenesis. This study did not find any clinically significant effects on human spermatogenesis (i.e., total sperm count, motility, or morphology) or on reproductive hormones, suggesting that these nonclinical findings are not relevant to humans.

Treatment of pregnant rats resulted in delayed fetal growth with visceral and skeletal malformations. Cases of fetal malformations were observed at all doses studied. These included thorocogastroschisis, amelia of forelimbs, absent bones, malformed bones, spina bifida, malposition of main arterial vessels, absence of organs, exencephaly, and omphalocele. Maternal rats displayed decreased motor activity, sleepiness, decreased reactivity, piloerection, reduced food consumption, and decrease in body weight. It is unclear whether the fetal malformation can be completely attributed to the reduced food consumption of the maternal rat.

Carcinogenicity studies were performed in mice and in rats. In the 2-year mouse carcinogenicity study, thyroid C-cell adenomas were seen in the male mice treated with lixisenatide (n=1 at 40 μg/kg BID, n=1 at 200 μg/kg BID, and n=4 at 1000 μg/kg BID) compared to none in the control groups (Table 2). Thyroid C-cell hyperplasia was also slightly increased in the 200 μg/kg BID group. In female animals, only one animal was found to have thyroid C-cell adenomas and that animal was in the 1000 μg/kg BID treatment group.

In the 2-year rat carcinogenicity study, thyroid C-cell adenomas were noted in all of the lixisenatide treated groups compared to none in the control group (Table 2). Thyroid C-cell carcinomas were observed in the mid- and high-dose groups compared to none in the control group. A "no observed effect level" was not identified for thyroid C-cell adenomas.

Table 2: Estimated safety margins for GLP-1 receptor agonist effects on thyroid C-cells

GLP-1 Receptor Agonist	Carc Dosing Regimen	Clinical Dosing Regimen	Gender	Multiple of Human Exposure at LOEL			Exposure Margins of Carc Study Doses†
				C-Cell Carcinoma	C-Cell Adenoma	C-Cell Hyperplasia	
RATS							
Exenatide (Byetta)	QD	BID	M	-	-	22X	5, 22, 130X
			F	-	<5X#	22X	
Liraglutide (Victoza)	QD	QD	M	<1X	2X	<1X	0.5, 2, 8X
			F	2X	<1X	2X	
Exenatide QW (Bydureon)	Q2W	QW	M	10X	<2X	<2X	1-2, 10, 25X
			F	25X#	<1X	<1X	
Lixisenatide	BID	QD	M	340X#	<90X	<90X*	90, 340, 1120X
			F	340X#	<90X	<90X*	
MICE							
Exenatide (Byetta)	QD	BID	M	-	-	-	7, 26, 95X
			F	-	-	-	
Liraglutide (Victoza)	QD	QD	M	-	10X	2X	0.2, 2, 10, 45X
			F	45X#	10X	2X	
Exenatide QW (Bydureon)	NA	QW	M	NOT TESTED			NA
			F				
Lixisenatide	BID	QD	M	-	1045X	165X	37, 165, 1045X
			F	-	-	1045X	

BID = twice daily dosing; carc = carcinogenicity; F = female; LOEL = lowest observed effect level; M = male; NA = not applicable; QD = once daily dosing; QW = once weekly dosing; Q2W = dosing every other week.
#nonstatistically significant numerical increase vs. control
*Slight numerical increase vs. control
†Values represent the mean of both genders combined
Source: Excerpted from Dr. B. Timothy Hummer's Pharmacology/Toxicology review for NDA 204961, submitted to NDA 208471 by Dr. Todd Bourcier

Overall, the nonclinical data do not raise any concerns that would preclude approval. Findings in terms of effects on the epididymis and testes do not appear to be relevant to humans. The effect on thyroid C-cells appears more consistent with exenatide BID than with the long-acting GLP-1 receptor agonist. Though there is some residual uncertainty in terms of the effect on fetal development, the findings may be a result of maternal effects rather than direct teratogenic effects of lixisenatide. I believe that this concern can be adequately communicated with adequate labelling.

For a detailed discussion of the nonclinical findings, see the Pharmacology/Toxicology review from Dr. B. Timothy Hummer, submitted to NDA 208471 by Dr. Todd Bourcier.

5. Clinical Pharmacology

The pharmacokinetic properties of lixisenatide are summarized in Table 1 of Dr. Suryanarayana Sista's Clinical Pharmacology review (excerpted below).

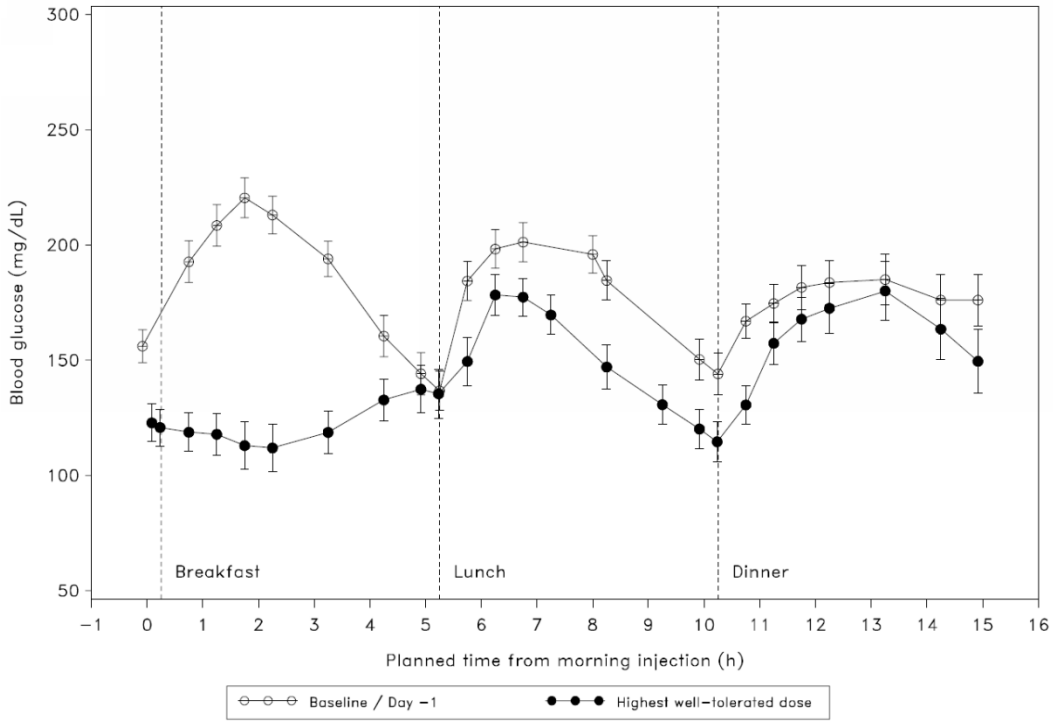
Table 1 Highlights of Pharmacokinetics

Proposed dose	• Starting dose of 10 µg for 14 days; • Maintenance dose of 20 µg from Day 15
Absorption	• Median T_{max} – 1-3.5 h in patients with type 2 diabetes • Dose-proportional PK in the 10 µg-20 µg dose range • Absolute bioavailability reported to be about 32% • Unchanged lixisenatide is the main drug-related component in plasma
Distribution	• Approximately 55% bound to human plasma protein • Mean Vz/F: Approximately 100L following subcutaneous administration, indicating extensive tissue distribution
Metabolism and Elimination	• Lixisenatide, being a peptide, is eliminated through glomerular filtration, followed by tubular reabsorption and subsequent metabolic degradation, resulting in smaller peptides and amino acids, which are reintroduced in the protein metabolism. • Apparent terminal half-life: Approximately 3 hours after multiple-dose administration • Apparent clearance (CL/F) is about 35 L/h

Pharmacodynamic effects of lixisenatide include blunting of postprandial glucose excursions, and delayed gastric emptying. The effect on postprandial glucose is most notable in the first meal after injection, and is attenuated with subsequent meals (Figure 2). With twice daily administration, the reduction in postprandial glucose excursions is seen most clearly in the meal after each injection (Figure 3).

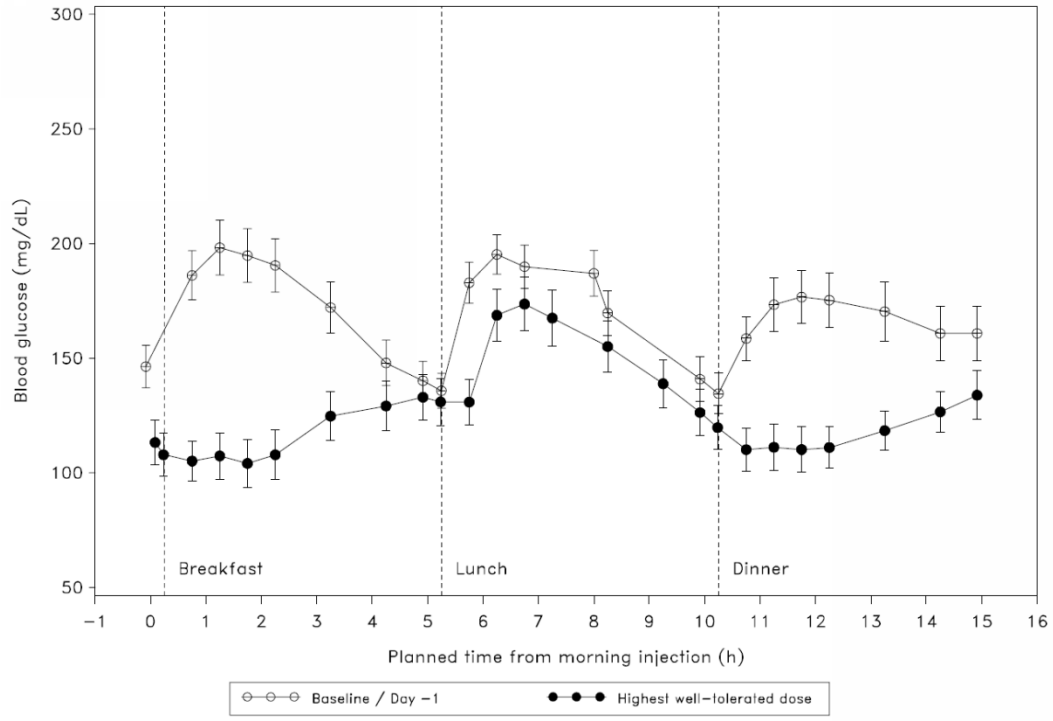
While GLP-1 receptor agonists are generally considered to also result in a glucose-dependent increase in insulin secretion, the clinical pharmacology studies did not demonstrate such an effect. Whether there are effects on insulin secretion is unclear, and the predominant effect appears to be on delayed gastric emptying.

Figure 2: Mean blood glucose values with lixisenatide once daily in study ACT6011



Source: Excerpted from Figure 6 of the study report for study ACT6011 from NDA 208471

Figure 3: Mean blood glucose values with lixisenatide twice daily in study ACT6011



Source: Excerpted from Figure 7 of the study report for study ACT6011 from NDA 208471

Due to the effect on gastric emptying, administration of oral drugs following injection with

lixisenatide can result in delayed absorption and alterations in maximum concentration (C_{max}), time to C_{max} (t_{max}), and area under the curve (AUC). Drug-drug interaction (DDI) studies showed that the altered gastric emptying after administration of lixisenatide does alter the pharmacokinetic characteristics of some oral medications. Administration of acetaminophen 1 to 4 hours after a 10 µg dose of lixisenatide resulted in a reduction in C_{max} of 29 to 31% and a delay in t_{max} of 1.75 to 2 hours, though the AUC was not changed. Similar findings were seen with oral contraceptives, atorvastatin, warfarin, and digoxin where the C_{max} was decreased and the t_{max} was delayed without a change in AUC. Based on these findings, Dr. Sista has recommended that oral medication with threshold concentration for efficacy, such as antibiotics, be taken at least 1 hour before lixisenatide. Similarly, though the implication of a reduced peak exposure of the components of oral contraceptives is unknown Dr. Sista also recommends advising patients to take oral contraceptives at least 1 hour before, or 11 hours after lixisenatide.

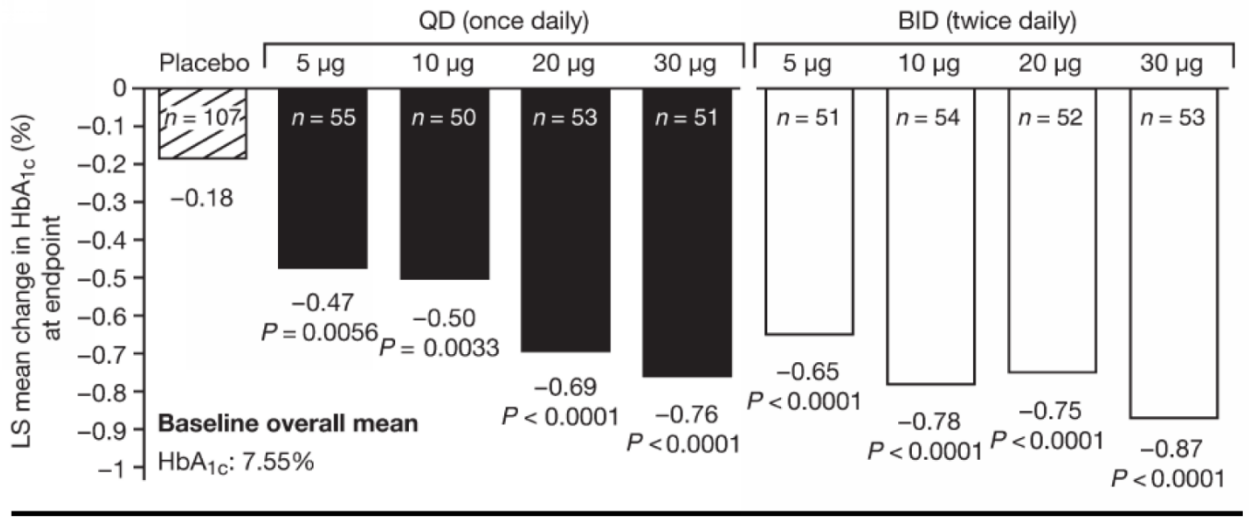
Intrinsic factors assessed for an influence on exposure included age, gender, race, and renal function. Exposure was somewhat higher in elderly subjects compared to young subjects. This may be due to lower creatinine clearance. Female subjects had a slightly higher exposure than male subjects, but this correlated with a lower average body weight and smaller volume of distribution in the females. The observed difference is more likely due to difference in body weight rather than to gender differences. Race did not influence the pharmacokinetic characteristics. Lixisenatide exposures increased as creatinine clearance decreases. The impact of this on efficacy and safety was considered. There was no apparent impact on glycemic efficacy. The incidence of hypoglycemia and nausea and vomiting was slightly increased in subjects with renal impairment. No dose adjustment is recommended for age, gender, or race. Dr. Sista also does not recommend a dose adjustment for patients with moderate renal impairment, but recommends that lixisenatide be used with caution due to concerns for dehydration resulting in acute kidney injury with the GLP-1 receptor agonist class, and for an increased incidence in selected adverse reactions. In patients with severe renal impairment, Dr. Sista recommends limiting the dose to 10 µg based on exposure matching. For those patients with severe renal impairment tolerating lixisenatide and requiring additional glycemic control, the dose could be increased to 20 µg. The applicant has not proposed a dose adjustment, but simply proposes to state that there is limited clinical experience in patients with severe renal impairment.

No studies of the impact of hepatic impairment on the pharmacokinetic profile of lixisenatide were performed. However, Dr. Sista does not expect hepatic dysfunction to affect the pharmacokinetic characteristics to any meaningful degree as lixisenatide is primarily cleared by the kidney. No dose adjustment is recommended.

A thorough QT study was performed for lixisenatide. No concern for QT prolongation was identified from this study.

In a 13-week dose ranging study, lixisenatide was studied in a range of doses and administered once daily and twice daily. For the same total daily dose, twice daily administration resulted in a numerically greater reduction in HbA1c from baseline (Figure 4). The percentage of patients with an HbA1c < 7% was similar between once daily and twice daily administration (Figure 5).

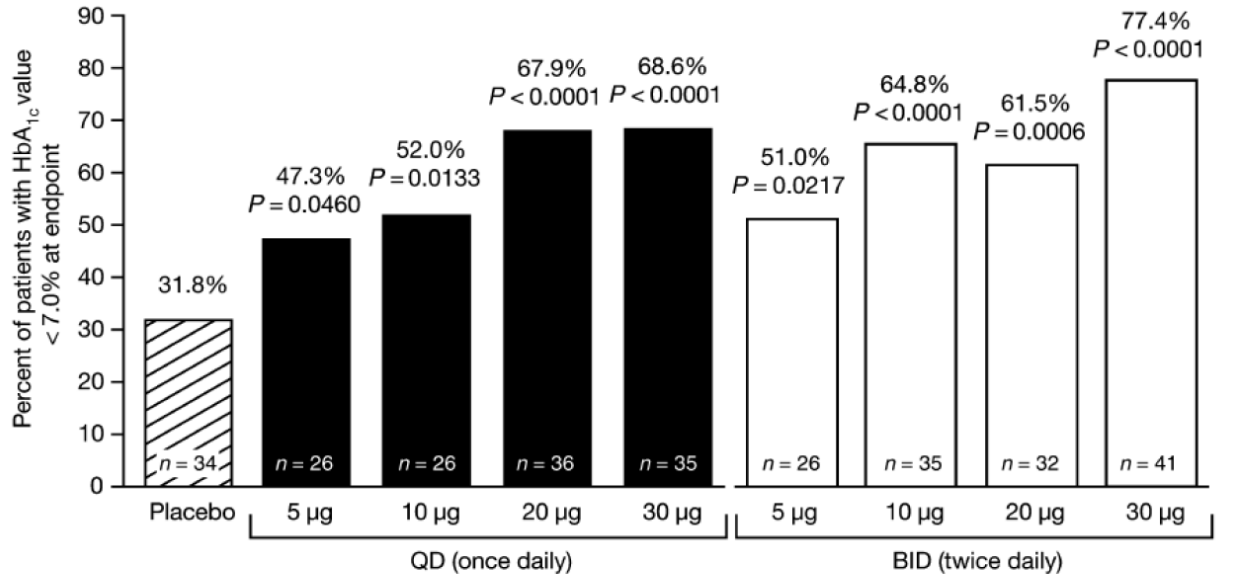
Figure 4: Mean change in HbA1c after 13 weeks in study DRI6012



BID = twice daily; HbA1c = glycosylated hemoglobin; ITT = intent-to-treat; LS = least square; *n* = number of patients; QD = once daily

Source: Excerpted from Figure 10 of the Summary of Clinical Efficacy from NDA 208471

Figure 5: Percentage of subjects with HbA1c < 7% after 13 weeks in study DRI6012



BID = twice daily; HbA1c = glycosylated hemoglobin; ITT = intent-to-treat; *n* = number of patients; QD = once daily

Source: Excerpted from Figure 11 of the Summary of Clinical Efficacy from NDA 208471

Review of the adverse event profile from study DRI6012 suggested better gastrointestinal (GI) tolerability with twice daily administration compared to once daily administration (Table 3). While 10 µg BID had more injection site reactions than 20 µg QD, the observation of more injection site reactions with BID administration compared to QD administration was not consistently seen.

Table 3: Selected treatment emergent adverse events from study DRI6012

High Level Term	Placebo N=109	Lixisenatide once daily				Lixisenatide twice daily			
		5 µg QD N=55	10 µg QD N=52	20 µg QD N=55	30 µg QD N=54	5 µg BID N=53	10 µg BID N=56	20 µg BID N=54	30 µg BID N=54
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Nausea and vomiting symptoms	5 (4.6)	5 (9.1)	9 (17.3)	15 (27.3)	21 (38.9)	7 (13.2)	10 (17.9)	14 (25.9)	18 (33.3)
Injection and infusion site reactions	2 (1.8)	2 (3.6)	4 (7.7)	2 (3.6)	9 (16.7)	3 (5.7)	6 (10.7)	6 (11.1)	8 (14.8)

QD = once daily; BID = twice daily
Source: Based on review of ADAE.xpt for study DRI6012 from NDA 208471

Though splitting the dose of lixisenatide (i.e., twice daily administration) resulted in a numerically greater reduction in HbA1c with better GI tolerability compared to once daily administration, the applicant elected to study a 20 µg QD dose in phase 3. The reasons for selecting this dose include practical considerations with regard to administration of oral medications due to delayed gastric emptying, and a higher incidence of nausea and vomiting at doses > 20 µg a day.

For detailed discussion of the Clinical Pharmacology findings, see Dr. Sista's review.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The efficacy of lixisenatide was assessed in 9 placebo-controlled studies and in 4 active-controlled studies. Two different approaches to titration were used in these studies. In a 1-step titration, lixisenatide was initiated at 10 µg QD then increased to 20 µg QD after 2 weeks. In a 2-step titration, lixisenatide was initiated at 10 µg QD, increased to 15 µg after 1 week, and then increased to 20 µg QD after another week. A brief summary of the studies is shown below:

Table 4: Summary of placebo-controlled studies

Study ID	Description	Treatment arms	Primary endpoint
EFC6018	Randomized, double-blind, placebo-controlled study as add-on to diet and exercise	Lixisenatide 1-step Lixisenatide 2-step Placebo	12 weeks
EFC10743	Randomized, double-blind, placebo-controlled study as add-on to metformin	Lixisenatide 1-step Lixisenatide 2-step Placebo	24 weeks
EFC6015	Randomized, double-blind, placebo-controlled study as add-on to sulfonylurea +/- metformin	Lixisenatide Placebo	24 weeks
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 +/- pioglitazone	Lixisenatide Placebo	24 weeks

Study ID	Description	Treatment arms	Primary endpoint
EFC10887	Randomized, double-blind, placebo-controlled study in Asian patients as add-on to basal insulin +/- sulfonylurea	Lixisenatide Placebo	24 weeks
EFC11321	Randomized, double-blind, placebo controlled study in Asian patients as add-on to metformin +/- sulfonylurea	Lixisenatide Placebo	24 weeks
EFC6014	Randomized, placebo-controlled study as add-on to metformin	Lixisenatide in AM Lixisenatide in PM Placebo	24 weeks
EFC6017	Randomized, placebo-controlled study as add-on to pioglitazone +/- metformin	Lixisenatide Placebo	24 weeks
EFC11319 (ELIXA)	Randomized, placebo-controlled study in patients with acute coronary syndrome within 180 days as add-on to local standard of care	Lixisenatide Placebo	Time to event

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

Table 5: Summary of active-controlled studies

Study ID	Description	Treatment arms	Primary endpoint
EFC10780	Randomized, double-blind, active-controlled study of obese patients with type 2 diabetes, < 50 years old as add-on to metformin	Lixisenatide Sitagliptin	24 weeks
EFC6019	Randomized, open-label, active-controlled study as add-on to metformin	Lixisenatide Exenatide BID	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
EFC12261	Randomized, open-label, active-controlled study as add-on to metformin	Lixisenatide prior to breakfast Lixisenatide prior to main meal of the day	24 weeks.

BID = twice daily; QD = once daily; TID = three times a day
Source: Adapted from module 5.2 Tabular Listing of Clinical Studies for NDA 208471

The primary endpoint in most studies was change from baseline for HbA1c. The two exceptions were study EFC10780 where the primary endpoint was a composite of percentage of patients with HbA1c < 7% AND weight loss of at least 5%, and study EFC11319 which was the cardiovascular outcomes trial.

The primary analysis utilized by the applicant was analysis of covariance (ANCOVA) with missing data imputed via last observation carried forward (LOCF). The LOCF approach is no long recommended by the Division. Supportive analyses using the mixed effect model repeat measurement (MMRM) approach were performed by the applicant. Unless otherwise noted, the MMRM results are used in the discussion of the primary endpoint.

The findings for change from baseline in HbA1c for the placebo controlled studies are shown below in Table 6.

Table 6: Results for HbA1c from placebo controlled studies of lixisenatide

Study	Arms (N)	LS mean change from baseline	LS mean treatment difference vs. placebo (95% CI)	p-value
EFC6018 (add-on to diet and exercise)	Placebo (116)	-0.14		
	Lixi 2-step (117)	-0.66	-0.52 (-.0761, -0.285)	< 0.0001
	Lixi 1-step (118)	-0.79	-0.65 (-0.891, -0.418)	< 0.0001
EFC10743 (add-on to met)	Placebo (157)	-0.42		
	Lixi 2-step (154)	-0.84	-0.42 (-0.598, -0.245)	< 0.0001
	Lixi 1-step (155)	-0.9	-0.48 (-0.662, -0.306)	< 0.0001
EFC6015 (add-on to SU +/- met)	Placebo (273)	-0.23		
	Lixi (545)	-0.91	-0.69 (-0.811, -0.56)	< 0.0001
EFC6016 (add-on to basal insulin)	Placebo (157)	-0.25		
	Lixi (303)	-0.68	-0.43 (-0.629, -0.236)	< 0.0001
EFC10781 (add-on to insulin glargine + met)	Placebo (219)	-0.37		
	Lixi (213)	-0.67	-0.3 (-0.447, -0.147	0.0001
EFC10887 (add-on to basal insulin +/- SU)	Placebo (156)	0.08		
	Lixi (153)	-0.72	-0.79 (1.032, -0.552)	< 0.0001
EFC11321 (add-on to met +/- SU)	Placebo (188)	-0.59		
	Lixi (190)	-0.88	-0.3 (-0.473, -0.118)	0.0012
EFC6014 (add-on to met)	Placebo (166)	-0.47		
	Lixi AM (245)	-0.88	-0.41 (-0.58, -0.234)	< 0.0001
	Lixi PM (245)	-0.72	-0.25 (-0.425, -0.078)	0.0046
EFC6017 (add-on to pio +/- met)	Placebo (157)	-0.44		
	Lixi (307)	-0.97	-0.53 (-0.692, -0.372)	< 0.0001

Lixi = 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; 1-step: lixisenatide initiated at 10 µg QD then increased to 20 µg QD after 2 weeks; met = metformin; SU = sulfonylurea; pio = pioglitazone
Source: Adapted from Table 8 of Dr. Jiwei He's Statistical Review from NDA 208471

The results of these studies support a conclusion that lixisenatide is superior to placebo with regard to improving glycemic control as assessed by change in HbA1c.

The findings for change from baseline in HbA1c for the placebo controlled studies are shown below in Table 7.

Table 7: Results for HbA1c from active controlled studies of lixisenatide

Study	Arms (N)	LS mean change from baseline	LS mean treatment difference vs. comparator (95% CI)	p-value[1]
EFC6019[2] (add-on to met)	Exenatide BID (293)	-1.03		
	Lixi (302)	-0.85	0.18 (0.046, 0.307)	0.0083

Study	Arms (N)	LS mean change from baseline	LS mean treatment difference vs. comparator (95% CI)	p-value[1]
EFC12626[2] (add-on to insulin glargine +/- met)	Insulin glulisine QD (290)	-0.57		
	Insulin glulisine TID (291)	-0.84		
	Lixi (284)	-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
EFC12261[2] (add-on to met)	Lixi breakfast (220)	0.79		
	Lixi main meal (218)	-0.71		
	- Lixi breakfast vs. Lixi main meal		0.08 (-0.076, 0.235)	0.316
EFC10780[3] (add-on to met)	Sitagliptin (160)	-0.74		
	Lixi (153)	-0.7	0.04 (-0.198, 0.288)	

[1] p-value for superiority; [2] primary analysis was for non-inferiority with a pre-specified non-inferiority margin of 0.4 ; [3] change from baseline for HbA1c was not primary endpoint
met = metformin; BID = twice daily; Lixi = lixisenatide; QD = once daily; TID = three times daily
Source: Adapted from Table 8 of Dr. Jiwei He's Statistical Review from NDA 208471

Non-inferiority was demonstrated based upon a pre-specified non-inferiority margin of 0.4%. While change from baseline in HbA1c was not the primary endpoint[1] for study EFC10780, lixisenatide also appears to be non-inferior to sitagliptin. Lixisenatide was also statistically inferior to exenatide BID and insulin glulisine TID.

Data after treatment discontinuation or initiation of rescue therapy was not collected. As a result, 5% to 16% of subjects did not have an HbA1c measurement at the primary endpoint. Additional analyses were performed to consider the impact of this missing data. These analyses did not result in changing the conclusions with the exception of the comparison of lixisenatide to insulin glulisine TID in study EFC12626. Using multiple imputation for missing values, the non-inferiority margin of 0.4% was no longer excluded (LS mean treatment difference [95% CI]: 0.28 [0.157, 0.408]).

For a detailed discussion of the efficacy of lixisenatide in improving glycemic control, see Dr. Jiwei He's Statistical Review from NDA 208471 and Dr. Wei Liu's Statistical Review from NDA-204961.

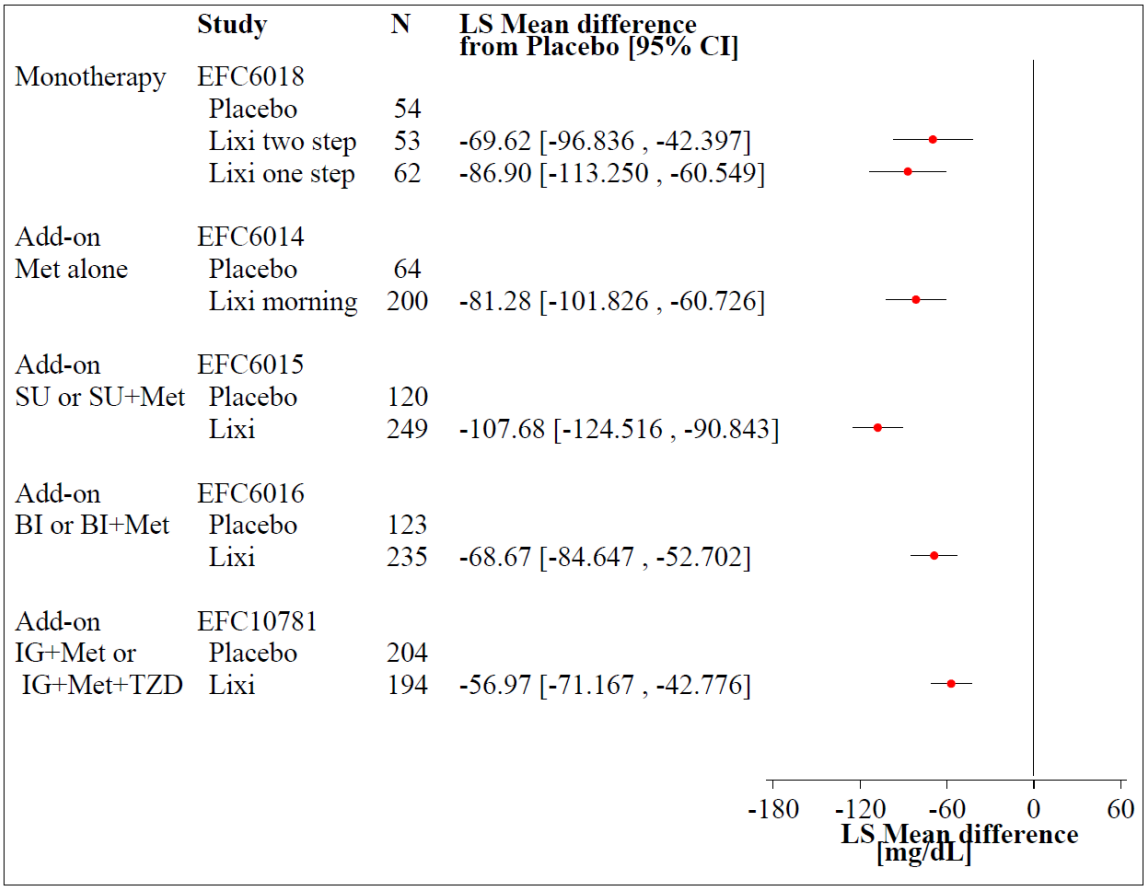
Other endpoints assessed by the applicant included ability to achieve a target HbA1c, change in 2-hour postprandial glucose during a standardized meal, change in fasting plasma glucose, and change in body weight.

Compared to placebo, lixisenatide was nominally statistically superior for the percentage of subjects that achieved an HbA1c < 7%. This is consistent with the statistically superior reduction in HbA1c demonstrated in these studies. Similarly, lixisenatide was statistically superior to placebo for change in 2-hour postprandial glucose (Figure 6). This endpoint was assessed by administering a standardized meal immediately after administration of lixisenatide at baseline and at the time of the primary endpoint. The relevance of this endpoint is unclear, and whether a reduction in postprandial glucose persists with other meal is unknown. Based on the phase 2 studies, continued reduction in postprandial glucose beyond the first meal after injection

[1] The primary endpoint of this study was a composite of percentage of subjects with HbA1c <7% AND weight loss of ≥ 5%. There was no statistically significant difference between treatment arms.

seems unlikely (Figure 2).

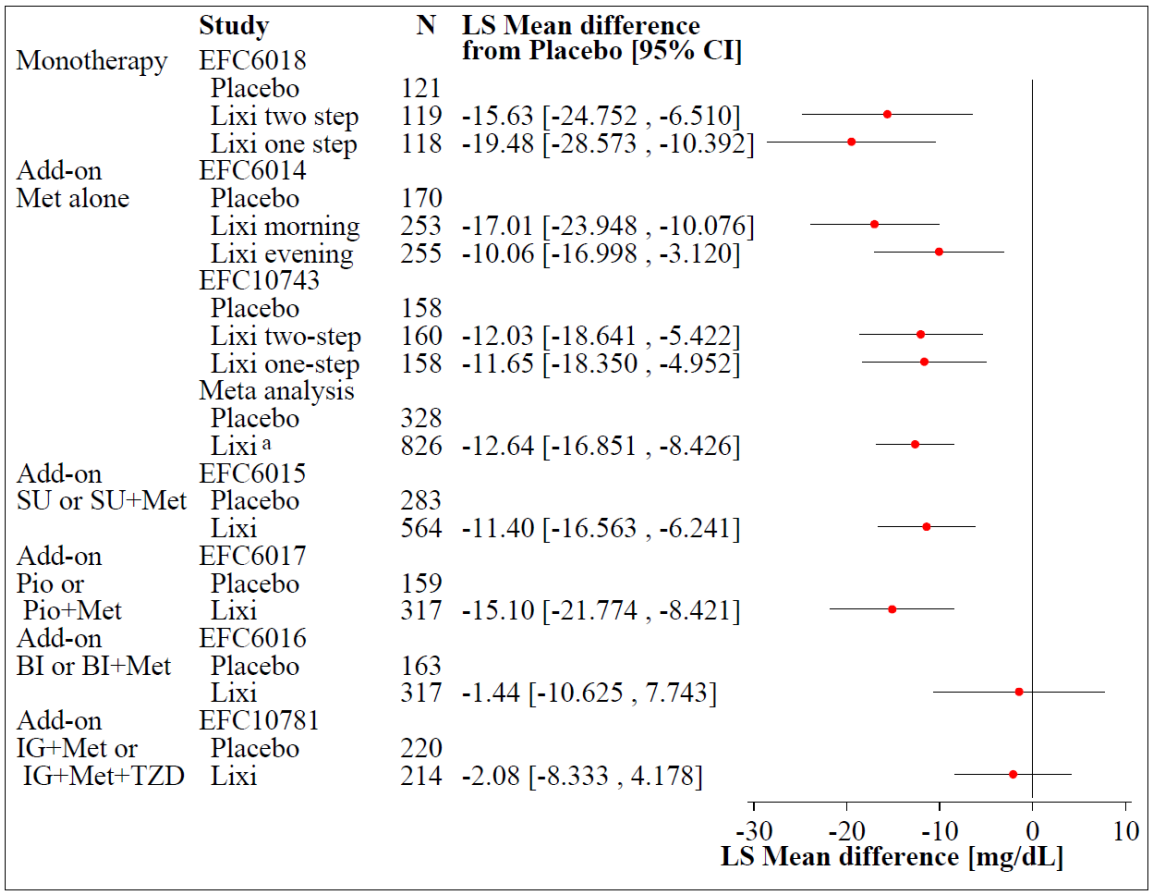
Figure 6: Forest plot of difference between lixisenatide and placebo for change in 2-hour postprandial glucose (mg/dL)



Lixi = lixisenatide; Met = metformin; SU = sulfonylurea; BI = basal insulin; IG = insulin glargine; TZD = thiazolidinedione
Source: Excerpted from Figure 4 of the Clinical Summary of Efficacy from NDA 208471

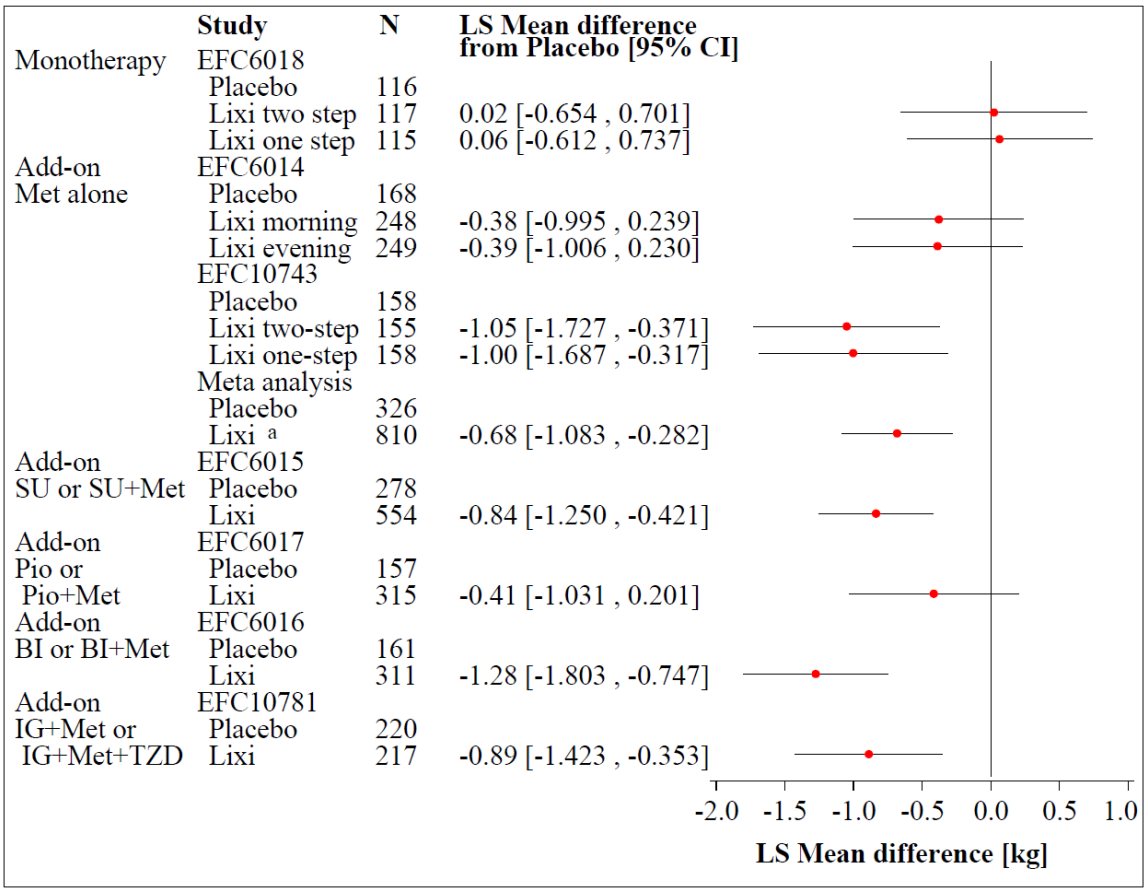
The results for change in fasting plasma glucose and for change in body weight were less consistently demonstrated (Figure 7, Figure 8). While lixisenatide was generally statistically superior to placebo for change in fasting plasma glucose, no apparent difference was seen in two of the placebo-controlled studies (study EFC6016 and study EFC10781). Notably, these two studies were on a background of basal insulin. With regard to change in body weight, lixisenatide was not statistically superior to placebo in three of the placebo-controlled studies (study EFC6018, study EFC6014, study EFC6017). Even in those studies where lixisenatide was statistically superior to placebo on change in weight, the magnitude of the difference between treatment arms was small (ranging from -1.28 kg to -0.84 kg). The clinical relevance of this small difference in weight is unclear. The studies were not designed to demonstrate that these small differences in weight either improve clinical outcomes or improve quality of life for patients.

Figure 7: Forest plot of difference between lixisenatide and placebo for change in fasting plasma glucose (mg/dL)



Lixi = lixisenatide; Met = metformin; SU = sulfonylurea; BI = basal insulin; IG = insulin glargine; TZD = thiazolidinedione
Source: Excerpted from Figure 6 of the Clinical Summary of Efficacy for NDA 208471

Figure 8: Forest plot of difference between lixisenatide and placebo for change in body weight (kg)



Lixi = lixisenatide; Met = metformin; SU = sulfonylurea; BI = basal insulin; IG = insulin glargine; TZD = thiazolidinedione
Source: Excerpted from Figure 8 of the Clinical Summary of Efficacy for NDA 208471

For additional discussion of the secondary endpoints, see Dr. Jiwei He's Statistical Review and Dr. Suchitra Balakrishnan's Clinical Review for NDA 208471.

Conclusions on Efficacy:

Lixisenatide has demonstrated the ability to improve glycemic control compared to placebo. Though the active comparator studies suggest that lixisenatide may be inferior to some other approved therapies in terms of glycemic control that does not preclude approval of lixisenatide.

8. Safety

The safety database included 7,874 subjects exposed to lixisenatide with a total of 10,035.9 patient-years. A total of 20 studies make up this database which includes the cardiovascular outcomes trial (CVOT). Nearly half of the subjects (3,031 exposed to lixisenatide with 5,732.2 patient-years) came from the CVOT (i.e., study EFC11319 [ELIXA]).

For the assessment of safety, Dr. Balakrishnan reviewed three sources of data. The first was a pool of the phase 3 placebo controlled studies (Datapool 1). This pool was used to assess the common adverse events, and both a main treatment period (i.e., up to primary endpoint) and an entire treatment period (i.e., to study end) were considered. The second pool was a pool of phase 2/3 studies (including ELIXA) which covered the entire safety database (Datapool 2). This pool was used to assess rare adverse events. The final source was the ELIXA database. This study was analyzed separately as it is comprised of a population at high cardiovascular risk, thus potentially also at high risk for other adverse events.

Table 8: Summary of safety databases

	Lixisenatide	Placebo	Active comparator
Datapool 1 - Placebo-controlled phase 3 glycemic control studies	2869	1639	---
Datapool 2 - Pool of phase 2/3 studies	7874	4842	1237
ELIXA - Cardiovascular outcomes trial	3031	3032	---

Source: Adapted from section 7.2.1 of Dr. Balakrishnan's Clinical Review from NDA 208471

The safety database appears adequate. I will focus on Datapool 1 as this provides the clearest understanding of the safety profile of lixisenatide. I will use Datapool 2 to inform the incidence of rare adverse events of interest. The findings from ELIXA will be discussed separately.

Death:

There was no evidence of an increase in the incidence of death with lixisenatide (Table 9). There were no clear imbalances in the reported reasons for death.

Table 9: Incidence of death in lixisenatide development program

	Lixisenatide	Placebo	Active Comparator
Incidence of death in Datapool 1	0.5%	0.7%	---
Incidence of death in Datapool 2	2.9%	4.8%	0.5%
Incidence of death in ELIXA	7%	7.4%	---

Source: Adapted from Table 13 and Table 14 of Dr. Balakrishnan's Clinical Review from NDA 208471

Serious adverse events:

There was no evidence for an increase in the incidence of nonfatal serious adverse events with lixisenatide (Table 10). While there were some types of serious adverse events (SAEs) that were seen more commonly with lixisenatide, there was no marked difference to placebo (Table 11). A similar finding was observed when looking at ELIXA (Table 12).

Table 10: Incidence of nonfatal serious adverse events in lixisenatide development program

	Lixisenatide	Placebo	Active Comparator
Incidence of nonfatal SAE in Datapool 1	8.5%	7.8%	---
Incidence of nonfatal SAE in Datapool 2	11.9%	16.5%	4.1%
Incidence of nonfatal SAE in ELIXA	20.6%	22.1%	---

SAE = serious adverse event
Source: Adapted from review of section 3.4 and Appendix 1.4.4.3 and 1.4.4.4 of the Summary of Clinical Safety for NDA 208471

Table 11: Treatment emergent serious adverse events from Datapool 1 occurring in ≥ 0.2% of subjects and with higher incidence (by high level term) in lixisenatide

System organ class - High level term	Lixi N=2869 n (%)	Placebo N=1639 n (%)
Infections and infestations	41 (1.4)	20 (1.2)
- Abdominal and gastrointestinal infections	5 (0.2)	0
Injury, poisoning and procedural complications	38 (1.3)	15 (0.9)
- Non-site specific injuries NEC	7 (0.2)	2 (0.1)
- Upper limb fractures and dislocations	5 (0.2)	2 (0.1)
Musculoskeletal and connective tissue disorders	35 (1.2)	20 (1.2)
- Osteoarthropathies	7 (0.2)	2 (0.1)
- Upper limb fractures	5 (0.2)	2 (0.1)
Nervous system disorders	45 (1.6)	16 (1.0)
- Central nervous system hemorrhages and cerebrovascular accidents	16 (0.6)	7 (0.4)
- Transient cerebrovascular events	5 (0.2)	1 (0.1)
Renal and urinary disorders	15 (0.5)	10 (0.6)
- Genitourinary tract infections and inflammations NEC	6 (0.2)	2 (0.1)
Respiratory, thoracic and mediastinal disorders	36 (1.3)	24 (1.5)
- Respiratory signs and symptoms NEC	8 (0.3)	2 (0.1)
Vascular disorders	91 (3.2)	44 (2.7)
– Cerebrovascular and spinal necrosis and vascular insufficiency	21 (0.7)	6 (0.4)
– Ocular hemorrhagic disorders	5 (0.2)	1 (0.1)

Lixi = lixisenatide; NEC = not elsewhere classified
Source: Based on review of ADAE.xpt submitted with the Integrated Summary of Safety in module 5.3.5.3 from NDA 208471

Table 12: Treatment emergent serious adverse events from ELIXA occurring in ≥ 0.2% of subjects and with higher incidence (by high level term) in lixisenatide

System organ class – High level term	Lixi N=3031 n (%)	Placebo N=3032 n (%)
Cardiac disorders	145 (4.8)	151 (5.0)
– Ventricular arrhythmias and cardiac arrest	24 (0.8)	17 (0.6)
– Dyspneas	11 (0.4)	8 (0.3)
Endocrine disorders	53 (1.7)	67 (2.2)
– Diabetic complications dermal	14 (0.5)	4 (0.1)
Gastrointestinal disorders	150 (4.9)	146 (4.8)
– Gastric and gastroenteric infections	23 (0.8)	12 (0.4)
– Malignant intestinal neoplasms	15 (0.5)	10 (0.3)
– Intestinal infections	7 (0.2)	4 (0.1)
– Nausea and vomiting symptoms	7 (0.2)	4 (0.1)
– Gastrointestinal infections, site unspecified	6 (0.2)	4 (0.1)
– Inguinal hernias	5 (0.2)	3 (0.1)

System organ class – High level term	Lixi N=3031 n (%)	Placebo N=3032 n (%)
General disorders and administration site conditions	93 (3.1)	84 (2.8)
– Pain and discomfort NEC	59 (1.9)	51 (1.7)
– Death and sudden death	15 (0.5)	11 (0.4)
Hepatobiliary disorders	46 (1.5)	46 (1.5)
– Cholecystitis and cholelithiasis	33 (1.1)	25 (0.8)
– Malignant hepatobiliary neoplasms	6 (0.2)	3 (0.1)
Immune system disorders	17 (0.6)	16 (0.5)
– Allergic conditions NEC	6 (0.2)	4 (0.1)
Infections and infestations	207 (6.8)	231 (7.6)
– Abdominal and gastrointestinal infections	30 (1.0)	21 (0.7)
– Infections NEC	26 (0.9)	22 (0.7)
– Skin structures and soft tissue infections	9 (0.3)	6 (0.2)
– Viral infections NEC	6 (0.2)	3 (0.1)
– Upper respiratory tract infections	5 (0.2)	4 (0.1)
Injury, poisoning and procedural complications	72 (2.4)	78 (2.6)
– Non-site specific injuries NEC	17 (0.6)	16 (0.5)
– Non-site specific procedural complications	12 (0.4)	10 (0.3)
– Bone and joint injuries NEC	5 (0.2)	3 (0.1)
Metabolism and nutrition disorders	80 (2.6)	94 (3.1)
– Diabetic complications dermal	14 (0.5)	4 (0.1)
– Respiratory acidoses	8 (0.3)	5 (0.2)
– Total fluid volume decreased	7 (0.2)	4 (0.1)
– Sodium imbalance	5 (0.2)	4 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	98 (3.2)	81 (2.7)
– Colorectal neoplasms malignant	17 (0.6)	10 (0.3)
– Prostatic neoplasms malignant	14 (0.5)	8 (0.3)
Nervous system disorders	85 (2.8)	91 (3.0)
– Chronic polyneuropathies	15 (0.5)	5 (0.2)
– Neurological signs and symptoms NEC	6 (0.2)	2 (0.1)
Reproductive system and breast disorders	37 (1.2)	19 (0.6)
– Prostatic neoplasms and hypertrophy	20 (0.7)	11 (0.4)
– Ovarian and fallopian tube cysts and neoplasms	5 (0.2)	1 (< 0.1)
Respiratory, thoracic and mediastinal disorders	195 (6.4)	193 (6.4)
– Respiratory signs and symptoms NEC	58 (1.9)	49 (1.6)
– Bronchospasm and obstruction	27 (0.9)	25 (0.8)
– Respiratory tract infections NEC	7 (0.2)	4 (0.1)
– Bacterial lower respiratory tract infections	5 (0.2)	3 (0.1)
– Thoracic musculoskeletal disorders	5 (0.2)	4 (0.1)
– Upper respiratory tract infections NEC	5 (0.2)	4 (0.1)
Vascular disorders	210 (6.9)	238 (7.8)
– Accelerated and malignant hypertension	24 (0.8)	17 (0.6)

Lixi = lixisenatide; NEC = not elsewhere classified
Source: Based on review of ADAE.xpt submitted with the Integrated Summary of Safety in module 5.3.5.3 from NDA 208471

Discontinuations:

Discontinuation of study drug due to an adverse event was more common in the subjects treated with lixisenatide than in those treated with placebo (Datapool 1: 7.2% with lixisenatide vs. 3.2% with placebo during main treatment period, 9.3% with lixisenatide vs. 4.8% with placebo over the entire treatment period).

In looking at the terms associated with the adverse events leading to discontinuation (Table 13), they are consistent with the pharmacodynamic action of antidiabetic drugs (e.g., 'hypoglycemia') or consistent with the known safety profile of GLP-1 receptor agonists (e.g., 'nausea', 'vomiting').

Table 13: Discontinuation due to treatment emergent adverse events occurring in ≥ 0.2% of subjects in the main treatment period of Datapool 1 and more commonly with lixisenatide

Preferred Term	Lixi N=2869	Placebo N=1639
	n (%)	n (%)
Nausea	80 (2.8)	0
Vomiting	35 (1.2)	0
Dizziness	16 (0.6)	1 (0.1)
Diarrhea	12 (0.4)	1 (0.1)
Hypoglycemia	9 (0.3)	0
Asthenia	6 (0.2)	0
Decreased appetite	5 (0.2)	1 (0.1)
Dyspepsia	5 (0.2)	0
Headache	5 (0.2)	1 (0.1)

Lixi = lixisenatide
Source: Based on review of ADAE.xpt submitted with the Integrated Summary of Safety in module 5.3.5.3 from NDA 208471

Similar findings were seen in ELIXA where 11.4% of lixisenatide treated subjects discontinued study drug compared to 7.2% of placebo treated subjects. Again, the terms showing an imbalance (Table 14) were consistent with what might be expected from an antidiabetic agent (e.g., 'hypoglycemia') or from a member of the GLP-1 receptor agonist class (e.g., 'nausea', 'vomiting').

Table 14: Discontinuation due to treatment emergent adverse events occurring in ≥ 0.2% of subjects from ELIXA and more commonly with lixisenatide

Preferred Term	Lixi N=3031	Placebo N=3032
	n (%)	n (%)
Nausea	91 (3.0)	11 (0.4)
Vomiting	33 (1.1)	5 (0.2)
Myocardial infarction	23 (0.8)	23 (0.8)
Sudden cardiac death	8 (0.3)	3 (0.1)
Diarrhea	7 (0.2)	3 (0.1)
Dizziness	7 (0.2)	3 (0.1)
Lipase increased	6 (0.2)	4 (0.1)
Decreased appetite	6 (0.2)	0
Asthenia	5 (0.2)	2 (0.1)
Hypoglycemia	5 (0.2)	2 (0.1)
Malaise	5 (0.2)	1 (< 0.1)
Abdominal discomfort	5 (0.2)	0
Cardiac failure acute	5 (0.2)	0

Lixi = lixisenatide
Source: Based on review of ADAE.xpt submitted with the Integrated Summary of Safety in module 5.3.5.3 from NDA 208471

Cardiovascular Safety:

The assessment of the cardiovascular safety of lixisenatide was based on the results of a single, large cardiovascular outcomes trial, ELIXA. The main findings are discussed below. For detailed discussion, see Dr. Yueqin Zhao's Statistical Review.

The ELIXA study enrolled a population of patients with type 2 diabetes and a recent biomarker acute coronary syndrome (ACS). This was defined as:

Men and women with a history of T2DM who experienced a spontaneous ACS (i.e., ST-elevation myocardial infarction [STEMI], non-ST-elevation myocardial infarction [NSTEMI], or unstable angina) that satisfied the following requirements:

- Documented elevation above the normal reference range of a cardiac biomarker (e.g., troponin, creatine kinase-MB), AND
- Presentation consistent with ACS leading to admission to an acute care facility (e.g., emergency room, coronary care unit, catetherization laboratory, hospital). If the ACS event occurred after a revascularization procedure, it must be > 15 days after percutaneous coronary intervention or > 45 days after coronary artery bypass graft, AND
- Screening within 180 days of admission for the qualifying ACS event

Study subjects were then randomized to receive either lixisenatide 20 μg once daily or placebo once daily. Dosing was initiated at a dose of 10 μg once daily. After two week, the dose was increased to 20 μg once daily (i.e., therapeutic/maintenance dose). All other therapies (including additions or changes in anti-diabetic agents) were to be prescribed during the course of the study at the investigator's discretion to be consistent with local standard of care. The only exception was that GLP-1 agonists or DPP-4 inhibitors could not be used.

The primary endpoint of this study was time to first occurrence of a composite endpoint. This composite outcome (hereafter referred to as MACE+) consisted of:

1) cardiovascular death,
2) non-fatal myocardial infarction,
3) non-fatal stroke, and
4) hospitalization for unstable angina.

An additional composite endpoint was considered (hereafter referred to as MACE) and consisted of:

1) cardiovascular death,
2) non-fatal myocardial infarction, and
3) non-fatal stroke.

An adjudication committee reviewed potential events to determine whether and what type of an

event occurred. Adjudication was performed by a blinded, independent cardiovascular adjudication committee (CAC).

The treatment arms were generally balanced in terms of baseline characteristics. While the mean age was similar between arms, a larger proportion of subjects were ≥ 75 years old in the placebo arm compared to the lixisenatide arm (8.2% vs. 6.5%). South/Central America and Eastern Europe provided the highest proportion of subjects, with more than 50% of subjects coming from these two regions.

The pre-specified primary analysis was time for first on study event using a Cox proportional hazard model with treatment and region as factors. The final analysis was conducted after 805 MACE+ were observed.

In total, 399 MACE+ were observed in placebo-treated subjects compared to 406 MACE+ in lixisenatide treated subjects (Table 15). Non-fatal myocardial infarction provided the majority of events in both arms. The findings were generally similar when considering the MACE composite (Table 16). For both composite endpoints, the 1.3 risk margin was excluded.

Table 15: Results of pre-specified primary analysis for MACE+ from ELIXA

	Placebo (N=3,034)	Lixisenatide (N=3,034)	Hazard ratio (95% CI)
Primary CV endpoint			1.02 (0.89, 1.17)
No. of patients with event (%)	399 (13.2%)	406 (13.4%)	
Total Person Year	6328.2	6356.8	
Incidence Rate	6.31	6.39	
Component CV event			
CV death	93 (3.1%)	88 (2.9%)	
Non-fatal MI	247 (8.1%)	255 (8.4%)	
Non-fatal stroke	49 (1.6%)	54 (1.8%)	
Hospitalization for unstable angina	10 (0.3%)	9 (0.3%)	

Source: Excerpted from Table 1 of Dr. Yueqin Zhao's Statistical Review from NDA 208471

Table 16: Results of analysis for MACE from ELIXA

	Placebo (N=3,034)	Lixisenatide (N=3,034)	Hazard ratio (95% CI)
MACE endpoint (on-study)			1.02 (0.89, 1.18)
No. of patients with event (%)	392 (12.9%)	400 (13.2%)	
Total Person Year	6340.2	6368.7	
Incidence Rate	6.18	6.28	

Source: Excerpted from Table 8 of Dr. Yueqin Zhao's Statistical Review from NDA 208471

Dr. Zhao also performed analyses of the risk of death in ELIXA (Table 17). A total of 434 deaths occurred in the study (223 in placebo-treated subjects and 211 in lixisenatide treated subjects). Similar to what was seen for MACE and MACE+, there was no evidence of increased

risk of death with lixisenatide compared to placebo.

Table 17: All-cause mortality from ELIXA

	Placebo (N=3,034)	Lixisenatide (N=3,034)	Hazard ratio (95% CI)
Death from any cause (on-study analysis)			0.94 (0.78, 1.13)
Number of patient with event (%)	223 (7.4%)	211 (7.0%)	
Total patient years for the event	6692.0	6735.3	
Incidence rate per 100 patient years	3.33	3.13	
Death from any cause (on-treatment analysis)			0.95 (0.75, 1.21)
Number of patient with event (%)	138 (4.5%)	128 (4.2%)	
Total patient years for the event	5997.5	5820.2	
Incidence rate per 100 patient years	2.30	2.20	

Source: Excerpted from Table 2 of Dr. Yueqin Zhao's Statistical Review from NDA 208471

Overall, the findings from ELIXA do not raise concerns for increased cardiovascular risk or mortality with lixisenatide.

Adverse events of interest:

Due to concerns identified with the GLP-1 receptor agonist class or as a result of findings of the development program, selected safety concerns were analyzed in greater detail as part of the NDA review. These events of interest were:

a. Immunogenicity and allergic reactions
b. Hypoglycemia
c. Pancreatitis
d. Malignancies (particularly thyroid tumors and pancreatic tumors)
e. Effects on spermatogenesis

With the possible exception of immunogenicity and allergic reactions, the findings for lixisenatide were generally consistent with what is known for GLP-1 receptor agonists. I will discuss the findings related to immunogenicity and allergic reactions then briefly discuss each of the other events of interest. A more detailed discussion of these events can be found in Dr. Balakrishnan's Clinical Review.

Immunogenicity and Allergic Reactions:

a. Immunogenicity

Like other peptide products, lixisenatide has the potential to induce an immune reaction which can have serious consequences including loss of efficacy, inactivation of endogenous proteins, and safety concerns such as anaphylaxis. The assessment of the immunogenicity of lixisenatide included both an analysis of the proportion of anti-drug antibody (ADA) positive subjects and an analysis of categorization by ADA concentration.

Lixisenatide treated subjects were more likely to be ADA positive. By week 24, approximately 70% of lixisenatide treated subjects were ADA positive compared to < 8% for the placebo treated subjects. While comparing the immunogenicity of products should be undertaken with caution as multiple factors can impact the rate of ADA detection (including the sensitivity and specificity of the assay, timing of sampling, concomitant medications, and underlying disease) this incidence is notable in that it is higher than what has been reported for other GLP-1 receptor agonists (Table 18).

Table 18: Summary of incidence of anti-drug antibodies with other GLP-1 receptor agonists

	Reported incidence of ADA formation[1]
Exenatide	20-38%
Liraglutide	8.6%
Exenatide LAR	49%
Albiglutide	5.5%
Dulaglutide	1.6%

[1] based on approved drug labels

In addition to reporting antibody status, antibody concentrations were measured when sufficient samples were available. As would be expected, lixisenatide treated subjects had higher concentrations of ADAs compared to the placebo treated subjects (Table 19). Almost all placebo-treated subjects that were positive for ADAs had concentrations below the lower limit of quantification (LLOQ). For the lixisenatide-treated subjects, the proportion with measurable concentrations of ADA increased over time.

Table 19: Summary of anti-drug antibody concentration categories in placebo-controlled phase 3 studies for lixisenatide

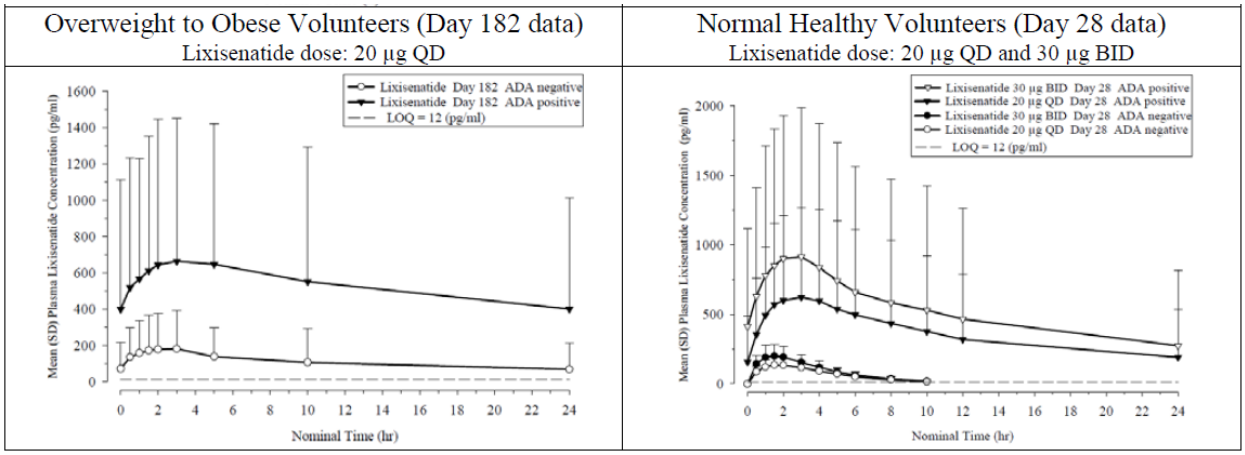
	Placebo			Lixisenatide		
	n	N	%	n	N	%
Baseline						
≤ LLOQ	28	29	96.6	59	65	90.8
≥ LLOQ						
• ≤ 100 nmol/L	1	29	3.4	6	65	9.2
• > 100 nmol/L	0	0	0	0	0	0
Week 12						
≤ LLOQ	2	2	100	38	93	40.9
≥ LLOQ						
• ≤ 100 nmol/L	0	0	0	55	93	59.1
• > 100 nmol/L	0	0	0	2	93	2.2
Week 24						
≤ LLOQ	88	89	98.9	885	1309	67.6
≥ LLOQ						
• ≤ 100 nmol/L	1	89	1.1	384	1309	29.3
• > 100 nmol/L	0	0	0	40	1309	3.1

	Placebo			Lixisenatide		
	n	N	%	n	N	%
Week 76						
≤ LLOQ	27	29	93.1	502	907	55.3
≥ LLOQ						
• ≤ 100 nmol/L	2	29	6.9	365	907	40.2
• > 100 nmol/L	0	0	0	40	907	4.4

LLOQ = lower limit of quantification
Source: Adapted from Table 87 of 5.3.5.3 Integrated Summary of Safety from NDA 208471

One consequence of ADA formation is that the presence of ADAs increased overall exposure and variability in derived pharmacokinetic parameters (Figure 9). The significance of this is unclear.

Figure 9: Mean plasma concentration time profile of lixisenatide after multiple subcutaneous doses of 10 µg, 20 µg, or 30 µg



Source: Excerpted from Figure 4 of Dr. Suryanarayana Sista's Clinical Pharmacology Review for NDA 204961

Due to the high degree of homology of lixisenatide to endogenous GLP-1 and endogenous glucagon (Figure 10), ADAs to lixisenatide could cross-react with endogenous GLP-1 and endogenous glucagon with potential safety and efficacy implications. Additionally, the ADAs could be neutralizing antibodies which could impact efficacy.

Figure 10: Comparison of amino acid sequence for lixisenatide to endogenous GLP-1 and to endogenous glucagon

Lixisenatide: HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPS(K)$_6$
Exenatide: HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS
Human GLP-1: HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRG
Glucagon: HSQGTFTSDYSKYLDSRRAQDFVQWLMNT

Source: Excerpted from Figure 1 of Dr. Farukh Sheikh's Office of Biotechnology Products Consult from NDA 208471

The assessment for cross-reactive antibodies is limited. There was no assessment for neutralizing antibodies.

The relevance of ADA formation was explored both for efficacy and for safety. Due to the limited information on specific sub-types of antibodies, these analyses were based on overall antibody status and antibody concentration.

A pool of eight placebo-controlled studies [2] was used to examine the impact of antibodies on reduction in HbA1c at 24 weeks (Table 20). These studies were selected because antibody data were collected in these studies and there was efficacy data at 24 weeks. In a meta-analysis of the change from baseline for HbA1c, there was no apparent difference between antibody positive and antibody negative subjects. However, it is notable that high titer subjects had a smaller reduction in HbA1c. Reasons for this are unclear.

Table 20: Mean change from baseline for HbA1c at 24 weeks for lixisenatide treated subjects in a pool of 8 placebo-controlled studies by antibody status and titer

	n/N	LS mean change	SE	95% CI
Ab negative	621/1954	-0.83	0.044	-0.92, -0.746
Ab positive	1333/1954	-0.82	0.036	-0.895, -0.755
– < LLOQ	854/1890	-0.88	0.043	-0.963, -0.796
– ≥ LLOQ to ≤ 100 nmol/L	370/1890	-0.63	0.05	-0.732, -0.534
– > 100 nmol/L	45/1890	-0.16	0.131	-0.418, 0.096

SE = standard error; LLOQ = lower limit of quantification
Source: Adapted from Table 23 of the Summary of Clinical Efficacy for NDA 208471

From this data, it appears that the presence of ADAs (particularly at high concentrations) may adversely impact the efficacy of lixisenatide. Taking into consideration that the presence of ADAs appears to increase exposure to lixisenatide, this data raises the possibility of ADAs that neutralize lixisenatide.

In examining the incidence of adverse events by ADA status, lixisenatide ADA positive subjects had a higher overall incidence of adverse events compared to lixisenatide ADA negative subjects (Table 21). Hypoglycemia, asthenic conditions, and injection site reactions occurred more commonly in the ADA positive subjects.

Table 21: Incidence of treatment emergent adverse events by anti-drug antibody status for the main treatment period of Datapool 1

- Occurring in ≥ 2% by High Level Term and more commonly in lixisenatide treated subjects with positive anti-drug antibodies

	Placebo N=1639	Lixisenatide	
		ADA positive N=1765	ADA negative N=995
	N (%)	N (%)	N (%)
Any adverse event	1021 (62.3)	1257 (71.2)	685 (68.8)
High Level Term			
Hypoglycemic conditions NEC	175 (10.7)	254 (14.4)	131 (13.2)

[2] Studies EFC6014, EFC6015, EFC6016, EFC6017, EFC10743, EFC10781, EFC10887,and EFC11321

	Placebo N=1639	Lixisenatide	
		ADA positive N=1765	ADA negative N=995
	N (%)	N (%)	N (%)
Asthenic conditions	55 (3.4)	110 (6.2)	55 (5.5)
Injection site reactions	26 (1.6)	84 (4.8)	19 (1.9)

ADA = anti-drug antibody; NEC = not elsewhere classified
Source: Adapted from Table 89 of the Integrated Summary of Safety from NDA 208471

The Office of Biotechnology Products (OBP) has expressed residual concerns with regard to the impact of cross-reactive antibodies and neutralizing antibodies both in terms of safety and efficacy. As a result, the OBP consult has recommended that the applicant perform additional assessments as a postmarketing requirement. These are:

1. A formal report of the cross-reactivity assay validation and assay standard operating procedures (SOPs)
2. Submission of a neutralixing antibody assay validation and assay SOP
3. An assessment of neutralizing antibody response using the validated neutralizing antibody assay
4. Evaluate whether cross-reactive antibodies are capable of neutralizing endogenous GLP-1 and endogenous glucagon

I agree that there is residual concern with regard to the impact of anti-drug antibody formation. I agree with the recommendation to have the applicant perform a further assessment of this issue (see section 13, below). See Dr. Faruk Sheikh's Review for a detailed discussion of the findings and recommendations from OBP.

b. Allergic reactions

In the lixisenatide development program, the applicant utilized an adjudication committee (Allergic Reactions Adjudication Committee [ARAC]) to evaluate possible allergic adverse events. The ARAC was independent and blinded to treatment. Datapool 2 was used for the assessment of these events.

The ARAC assigned positively adjudicated events to the following categories:

- Urticaria (strictly locate to skin and transitory [< 24 hours])
- Angioedema (mucosal involvement and transitory [< 24 hours])
- Anaphylactic reaction (skin or mucosal lesion of acute onset associated with at least 1 other organ involved [e.g., respiratory, gastrointestinal, vascular])
- Anaphylactic shock (anaphylactic reaction with a drop in blood pressure)
- Other

There was a slight increase in ARAC adjudicated allergic events with lixisenatide (Table 22). Of greater concern was an imbalance in anaphylaxis. Though the overall incidence is low, anaphylaxis is a serious and life-threatening condition. Further, there is a suggestion that the imbalance is a result of treatment with lixisenatide. Acknowledging that anaphylaxis can occur as a result of exposure to many things, it is noteworthy that there were 10 cases from the

lixisenatide subjects that the adjudication committee attributed to study compared to 0 cases from the placebo subjects. This is mirrored in the assessment of the investigators, as 11 cases from the lixisenatide subjects discontinued study drug (which reflects the investigators assessment of possible etiology) compared to 0 cases from placebo.

Table 22: Summary of ARAC adjudication of possible allergic events from Datapool 2

	Lixi N=7874	Placebo N=4842
	n (%)	n (%)
Any ARAC positively adjudicated allergic event	106 (1.5)	45 (1)
ARAC adjudicated 'anaphylaxis'	16 (0.2)	5 (0.1)
ARAC adjudicated 'anaphylaxis' attributed to study drug	10 (0.1)	0
ARAC adjudicated 'anaphylaxis' leading to treatment discontinuation	11 (0.1)	0

ARAC = Allergic Reactions Adjudication Committee
Source: Adapted from Tables 36, 37, and 38 of Dr. Balakrishnan's Clinical Review from NDA 208471

While the approved GLP-1 receptor agonists are labeled with a Warning and Precaution for hypersensitivity reactions, a signal for anaphylaxis is not described in the clinical trial data and references to anaphylaxis and serious hypersensitivity reactions in the currently approved labels are a result of postmarketing data. While this could be due to a greater risk for anaphylaxis and allergic reactions with lixisenatide, it is important to note that differences in the development programs (i.e., size of database) as well as the rigor of identification (i.e., use of an adjudication committee) could have contributed to these differences.

In response to the Division's concerns, the applicant provided some analyses of postmarketing data. An analysis and position paper entitled 'Evaluating Hypersensitivity in the Lixisenatide Development Program' was submitted for consideration. In this paper, the applicant concludes that the risk for hypersensitivity reactions with lixisenatide is comparable to other GLP-1 receptor agonists. The Division of Pharmacovigilance (DPV) and the Division of Epidemiology (DEPI) were consulted to evaluate the included data. Both Dr. Debra Ryan's DPV Consult Review and Dr. Christian Hampp's DEPI Consult Review conclude that these data are limited in utility for drawing conclusions with regard to the risk of anaphylaxis with lixisenatide, particularly compared to other GLP-1 receptor agonists. For a detailed discussion, see Dr. Ryan's and Dr. Hampp's Consult Reviews from NDA 208471.

Acknowledging that the overall incidence of clinical allergic events and anaphylaxis is low, I have residual concerns that the risk for these events may be higher with lixisenatide than with other GLP-1 receptor agonists. This is in part due to the high incidence of ADAs. This is concerning, though what clinical impact they have both in terms of efficacy and safety is unclear. The observed imbalance in anaphylaxis events from the clinical development program is also a concern. While other GLP-1 receptor agonists have hypersensitivity reactions labeled as a safety concern, a signal for serious hypersensitivity reactions such as anaphylaxis were not seen in the development programs.

Hypoglycemia:

The risk for hypoglycemia was increased with lixisenatide when used in subjects already treated with an insulin secretagogue (i.e., a sulfonylurea) and/or basal insulin. This is consistent with

what has been seen with other GLP-1 receptor agonists.

Pancreatitis:

There was no imbalance in clinical events of pancreatitis. Laboratory data did not show a dramatic difference between treatment arms for increases in pancreatic enzymes. This is consistent with other GLP-1 receptor agonists where pancreatitis has not been found to be imbalanced in the development program. However, postmarketing cases of pancreatitis result in this continuing to be a concern for the class.

Malignancies:

The overall incidence of malignancies was similar between treatment arms. No imbalance was seen for pancreatic cancers or for thyroid cancer. There was a single case of medullary thyroid cancer reported in the development program, and that came from a placebo treated subject. No imbalances were observed for other types of malignancies.

In addition to examining clinical events of thyroid tumors, an exploration of changes in serum calcitonin values was done as a potential predictor of risk for thyroid C-cell tumors. Mean serum calcitonin values were not noted to change from baseline to the last on-treatment value, though there were more subjects treated with lixisenatide that had a calcitonin ≥ 50 pg/mL (Table 23).

Table 23: Incidence of calcitonin abnormalities in Datapool 2

	Placebo		**Lixisenatide**		**Other**	
Total	N=4307		N=5580		N=2097	
– > upper limit of reference to < 20 pg/mL	542	12.6	704	11	74	3.5
– ≥ 20 pg/mL to < 50 pg/mL	63	1.5	98	1.5	11	0.5
– ≥ 50 pg/mL	4	< 0.1	22	0.3	0	0
Below upper limit of reference at baseline	N=3268		N=4205		N=695	
– > upper limit of reference to < 20 pg/mL	239	7.3	256	6.1	17	2.4
– ≥ 20 pg/mL to < 50 pg/mL	12	0.4	8	0.2	1	0.1
– ≥ 50 pg/mL	2	< 0.1	9	0.2	0	0

Source: Adapted from Table 97 of the Integrated Summary of Safety from NDA 208471

Considering the clinical data in conjunction with the nonclinical data on thyroid C-cell tumors (see Table 2, above), there does not appear to be an increased risk with lixisenatide.

Spermatogenesis:

Due to findings from nonclinical studies, the applicant conducted a 26 week study in male subjects to assess any potential impact on spermatogenesis (study TDR11215). The Division of Bone, Reproductive and Urologic Products was consulted to review this study. While there was a slightly higher proportion of lixisenatide treated subjects with a > 50% reduction in sperm concentration compared to placebo treated subjects, the difference was not statistically significant, and the pre-specified margin was excluded. The assessment from the consult was:

"Overall, we consider this study to have adequately shown that lixisenatide generally does not

have a clinically significant effect on human spermatogenesis. We are not able to absolutely rule out a drug effect in a small subgroup of men. We do not recommend any additional studies of the effect of lixisenatide on spermatogenesis."

Detailed discussion of these findings can be found in Dr. Donald McNellis' Consult from NDA-204961.

Common Adverse Events:

The discussion of common adverse events will be limited to findings from the main treatment period of Datapool 1. The most common adverse events that occurred more frequently with lixisenatide than placebo are shown in Table 24. This profile is generally consistent with what is known for the GLP-1 receptor agonist class.

Table 24: Adverse events reported in ≥ 5% of subjects and more commonly with lixisenatide than placebo in the main treatment period of Datapool 1

Preferred Term	Lixi N=2869	Placebo N=1639
	n (%)	n (%)
Nausea	724 (25.2)	100 (6.1)
Hypoglycemia	392 (13.7)	174 (10.6)
Vomiting	282 (9.8)	30 (1.8)
Headache	244 (8.5)	99 (6.0)
Diarrhea	221 (7.7)	90 (5.5)
Dizziness	193 (6.7)	71 (4.3)

Lixi = lixisenatide
Source: Based on review of ADAE.xpt submitted with the Integrated Summary of Safety in module 5.3.5.3 from NDA 208471

9. Advisory Committee Meeting

Discussion of lixisenatide was included in an Advisory Committee meeting held on May 25, 2016. While the focus of the meeting was a combination drug product that included lixisenatide, the committee members were presented information on the lixisenatide development program and were asked to opine on any concerns for lixisenatide.

Committee members noted the high incidence of ADAs and the occurrence of a signal for anaphylaxis in the development program. Committee members were of the position that while both of these are of some concern, the significance of the ADAs is unclear and the overall incidence of anaphylaxis is low. Neither of these issues appeared to raise sufficient concern to impact the approvability of lixisenatide, though it was suggested that anaphylaxis could be further assessed in the postmarketing setting. Committee members did not have specific recommendation on how this should be performed.

There was no voting question for lixisenatide.

10. Pediatrics

No pediatric efficacy or safety data were submitted. Postmarketing requirements to perform a multiple dose pharmacokinetic and pharmacodynamic study and to perform an efficacy and safety study in children ages 10 to (b) (4) are planned.

11. Other Relevant Regulatory Issues

Not applicable.

12. Labeling

The applicant has proposed that lixisenatide be used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. I agree that this is an appropriate indication.

The applicant has proposed that lixisenatide be administered once daily with a titration dose of 10 µg for 14 days followed by an increase to a maintenance dose of 20 µg on day 15. While the clinical pharmacology data suggest that lixisenatide may be better suited as a twice daily drug, the clinical efficacy studies only studied once daily administration. These studies demonstrated that once daily lixisenatide improves glycemic control over placebo. The proposed dose and frequency of administration are acceptable.

I agree that a Boxed Warning for the risk of thyroid C-cell tumors is not warranted based on the available data.

Given the residual concerns and uncertainty for anaphylaxis and serious allergic reactions with lixisenatide, this safety concern should be prominently placed in the prescribing information. I recommend that this be the first item in section 6 "Warnings and Precautions".

Much of the information that the applicant has proposed to include in prescribing information is redundant and does not provide for additional meaningful information. This information should be removed. Tables presenting information on hypoglycemia should be limited to the time up to the primary endpoint of the studies and safety findings should be presented as relative to placebo.

Section 14 should limit presentation to those studies evaluating efficacy and should not include (b) (4). Information on (b) (4) should not be presented. (b) (4)

Labeling negotiations are ongoing at the time of completion of this review.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

I do not recommend a REMS.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

Two postmarketing studies will be required under the Pediatric Research Equity Act:

1. A repeat dose pharmacokinetic/pharmacodynamic study of lixisenatide in patients with T2DM ages 10 to 17 years (inclusive)
2. A randomized, placebo-controlled study of the efficacy and safety of lixisenatide in patients with T2DM ages 10 to 17 years (inclusive)

One postmarketing study to further assess the theoretical concerns surrounding the high incidence of ADAs will be required under the Food and Drug Administration Amendments Act:

1. Assessment of neutralizing antibodies and antibodies cross-reactive to endogenous GLP-1 and glucagon. This includes an evaluation of the impact of these antibodies on patient safety as well as the pharmacokinetic/pharmacodynamic parameters and the efficacy of lixisenatide.

14. Recommended Comments to the Applicant

Not applicable.

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

/s/

WILLIAM H CHONG
07/25/2016

JEAN-MARC P GUETTIER
07/25/2016