CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208673Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	(see electronic signature)
From	William H. Chong, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 208673
Applicant	Sanofi-Aventis
Date of Submission	December 21, 2015
PDUFA Goal Date	August 21, 2016 (amended to November 21, 2016 due to major amendment)
Proprietary Name / Non-Proprietary Name	Soliqua 100/33 / insulin glargine and lixisenatide injection
Dosage form(s) / Strength(s)	Solution for subcutaneous injection / 100 U/mL insulin glargine and 33 mcg/mL lixisenatide
Applicant Proposed Indication(s)/Population(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with insulin glargine and lixisenatide is appropriate
Recommendation on Regulatory Action	*Approval, pending agreement on labeling.*
Recommended Indication(s)/Population(s) (if applicable)	*To improve glycemic control in adults with type 2 diabetes mellitus and inadequately controlled on basal insulin (less than 60 units) or lixisenatide.*

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Type 2 diabetes mellitus (T2DM) is a condition of chronic impaired glucose homeostasis that leads to chronic hyperglycemia and increases the risk for vascular complications (both microvascular and macrovascular). Therapies for T2DM have focused on improving glycemic control as assessed by change in hemoglobin A1c (HbA1c). While there are multiple drug products approved both as individual drugs and as fixed combination drug products (FCDP), many patients are unable to achieve glucose targets. Thus, additional therapeutic options are needed to facilitate individualization of therapy.

This FCDP is a combination of a once daily basal insulin (i.e., insulin glargine) and a once daily glucagon-like peptide-1 (GLP-1) receptor agonist (i.e., lixisenatide). The two active pharmaceutical ingredients are combined at a fixed ratio which allows for dosing of both via a single injection. This approach links the doses such that each product cannot be individually titrated.

The contribution of both components to the claimed effect has been demonstrated at the doses achieved in the studies. In each of two phase 3 studies, the insulin glargine and lixisenatide FDCP was found to be statistically superior to either of the individual components in reducing HbA1c at 30 weeks. Whether this is true across the entire range of doses is unknown, with the contribution of lixisenatide in the low dose range being the main concern. Whether patients will achieve doses where it can be concluded that there is a contribution of each component to offset the additional risks incurred with adding a second drug is unknown, though it is likely that patients already treated with one of the components but needing additional glycemic control would reach doses where they are reaping some benefit from both components.

The safety profile of the FCDP is consistent with what would be expected based on combining lixisenatide and insulin glargine. The most common adverse reactions are gastrointestinal adverse reactions (e.g., nausea and vomiting), though the incidence of these was intermediate between what was seen with lixisenatide and insulin glargine separately. There is a potential for an increased risk of hypoglycemia compared to the individual components, though this did not appear to be a dramatic increase in the clinical studies. Combining these two peptide products did not appear to potentiate the risk for allergic/hypersensitivity reactions. The incidence of anti-insulin antibodies appeared to be higher in the group treated with the FCDP compared to that in the group treated with insulin glargine alone, but the significance of these antibodies is not known.

A unique safety concern with the FCDP arises from the proposed presentation. The applicant is proposing to market a pen injector with dosing based on ‘units’ and there is the potential for misinterpretation that the product can be used like other insulin products. The platform for the pen injector is identical to currently marketed insulin pen injectors which may lead to patients and prescribers assuming that the FCDP is another insulin product. This potential for confusion is compounded by the choice of ‘units’ to designate the dose.

The proposed presentation has been studied in Human Factors studies. In those studies, the proposed presentation was shown to be usable by prescribers, other health care providers, and patients. Acknowledging that usability has been shown, I remain uncertain whether the proposed presentation has been optimized to communicate to prescribers, health care providers, and patients, the presence of two different drug substances and that the presentation has been optimized to prevent risks of overdosage and duplication of therapies. Though I would like to see data from evaluations of other approaches before selecting, such an assessment cannot be required in the presence of a successful study.

In summary, the data suggests that each of the components of the FCDP contribute to improving glycemic control at the doses achieved in the studies, but the data are inadequate to conclude that this is true across the entire proposed dose range. However, there is evidence which suggests that there is some additional risk incurred with the use of the FCDP over use of the individual components alone. Thus, I cannot conclude that there is a favorable benefit-risk for all patients. I believe that there is a favorable benefit-risk for patients that will be achieving doses which include > 10 mcg of lixisenatide as the data seem supportive that there is a contribution of the lixisenatide component at or above these doses. While it is impossible to predict who will achieve such a dose, it is reasonable to assume that patients already treated with one of the components but with inadequate glycemic control would achieve these doses. Thus, I would recommend approval for use in a population already treated with basal insulin or with lixisenatide. Though I do not believe that the product presentation has been sufficiently evaluated to identify the optimal presentation and term of measure, I acknowledge that the proposed presentation has been demonstrated to be usable and that there is no regulatory basis for issuing a Complete Response given this. Labeling language can be added to attempt to clearly communicate the presence of two components and to try and mitigate the potential risk of overdosage and duplication of therapy.

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 and the United Kingdom Prospective Diabetes study, 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	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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	control in patients with T2DM. Many of these medications are also approved as fixed combination drug products (FCDPs). • 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.	
Benefit	• The fixed combination drug product of insulin glargine and lixisenatide has demonstrated that the combination results in better glycemic control than the use of the individual components at the doses achieved in the studies. • Though statistically superior to insulin glargine in the phase 3 studies, issues with study design and conduct preclude concluding clinical superiority over insulin glargine alone. • Whether initiating multiple medications at once rather than adding medication sequentially as the need for additional glycemic control becomes apparent results in better clinical outcomes is not known. • It is unknown whether there is a contribution of each component to the claimed effect in the low dose range of the product. • Whether a broad population of patients would achieve doses where the contribution of each component has been demonstrated is unknown. Patients already treated with one of the components seem the most likely to achieve a dose that is adequate to assure that the risk-benefit of using two drugs is favorable. • Whether the approach to combining insulin glargine and lixisenatide into a mixture is better than combining the two approved products as separate therapies is not known.	The insulin glargine and lixisenatide combination drug product has demonstrated that there is a benefit on glycemic control over each of the individual components at the doses achieved in the studies. The benefit of this product would be most relevant to the population of patients with inadequate glycemic control despite treatment with one of the components as this population is the most likely to achieve doses where the contribution of the lixisenatide component has been demonstrated.
Risk	• The risks associated with the fixed combination drug product are consistent with what would be expected by combining the safety profile of the two individual products. • The main safety issues identified were gastrointestinal side effects.	The clinical risks associated with use of the insulin glargine and lixisenatide are what would be expected with use of the two drugs. In itself, the combination of insulin glargine

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• There may be a small increase in the risk for hypoglycemia, though this is consistent with the approved labeling for lixisenatide which states that there may be an increased risk for hypoglycemia when used with insulin or an insulin secretagogue. • The administration of two peptide products does not seem to result in a potentiation in the risk for allergic/hypersensitivity reactions, though the incidence of anti-insulin antibodies may be increased. • The product presentation introduces some additional risks in terms of potential medications errors (e.g., overdosage, duplication of therapy) as a result of a potential misperception that the drug product contains only insulin. • While the proposed product presentation has been demonstrated to be usable in Human Factors studies, whether the final proposed presentation (i.e., naming, labeling, use of 'units' for dosing) is the best approach to communicate the presence of two different components is not clear. • Whether an alternative approach to naming (proprietary and non-proprietary) and the dosing would improve the comprehension that there is an insulin and a non-insulin component to the product is not known.	and lixisenatide does not present any substantial safety concerns. However, the proposed product presentation introduces some unique concerns with respect to potential medication errors. The proposed to-be-marketed device is a pen injector with the dose dialed in 'units'. The use of 'units' may obscure the presence of both components. This, combined with delivery via a product that is designed to look and be used like currently marketed insulin pen devices, raises the possibility that the FCDP could be confused for a basal insulin product and that the limitations on dosing introduced by the non-insulin component may be ignored. It is unknown what is the optimal approach to ensure that patients and prescribers comprehend that there is an insulin and a non-insulin component to the drug product. While the best way to label (e.g., naming, terms for dosing) the drug product has not been assessed, the proposed presentation has been studied in Human Factors studies and found to be usable.
Risk Management	• The adverse reaction profiles associated with use of lixisenatide and insulin glargine can be generally addressed with clear labeling. • While the proposed presentation has been shown to be usable in Human Factors studies, whether the proposed presentation is the best approach to prevent overdosage or duplication of therapy is not known.	The adverse reactions and safety profile of the fixed combination drug product can be adequately labeled to communicate these safety concerns. While the proposed presentation has been shown to be usable in Human Factors studies, it remains unknown whether alternative approaches would be better. Labeling language should emphasize the presence of two drug substances and should include language to minimize the potential for overdose or

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		duplication of therapy.

APPEARS THIS WAY ON ORIGINAL

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 including basal, prandial, and mixed insulin 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, Lixisenatide
Sodium glucose co-transporter-2 (SGLT2) inhibitors	Canagliflozin, Dapagliflozin, Empagliflozin
Amylin analogs	Pramlintide
Bile acid sequestrants	Colesevelam
Dopamine agonists	Bromocriptine

Despite the number of available anti-diabetic drugs, many patients continue to have difficulty achieving the desired degree of glycemic control. Additional alternative therapies are needed.

This New Drug Application (NDA) is for a fixed combination drug product (FCDP) containing a once daily basal insulin (i.e., insulin glargine) and a once daily GLP-1 receptor agonist (i.e., lixisenatide).

Insulin glargine is a long-acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

Lixisenatide is a GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

The applicant is proposing the FCDP (hereafter also referred to as IGlarLixi) for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both insulin glargine and lixisenatide is appropriate. The FCDP is recommended for once daily administration by subcutaneous injection.

The applicant initially proposed to market two different pen injectors, each with a different dosage strength. The first pen injector (hereafter referred to as Pen A) was proposed for lower doses and contained a higher concentration of lixisenatide. The second pen injector (hereafter referred to as Pen B) was proposed for higher doses and contained a lower concentration of lixisenatide. Characteristics of the two pens are described below in Table 2. The sponsor has proposed a recommended dose range for each pen (Table 3).

Table 2: Summary of dose strength of initially proposed pen injectors

Pen ID	Insulin glargine concentration	Lixisenatide concentration	Ratio[1]
Pen A	3.64 mg/mL (100 U/mL)	50 mcg/mL	2:1
Pen B	3.64 mg/mL (100 U/mL)	33 mcg/mL	3:1

[1] units of insulin glargine: mcg of lixisenatide
Source: Adapted from review of Module 3.2.P.1 "Description and Composition of the Drug Product" from NDA 208673

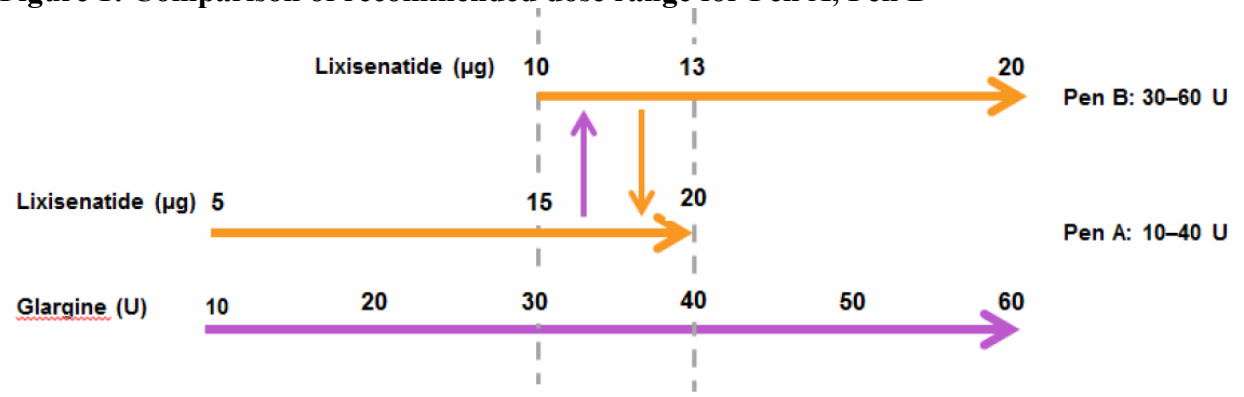
Table 3: Summary of dosing features of proposed pen injectors

Pen	Ratio[1]	Dose Increment[2]	Lowest Selectable Dose[2]	Maximum Selectable Dose[2]	Recommended Range[2]
Pen A	2:1	1 U	1 U	40 U	10 to 40 U
Pen B	3:1	1 U	1 U	60 U	30 to 60 U

[1] units of insulin glargine : µg of lixisenatide; [2] as expressed in units of insulin
Source: Adapted from Figure 1 of Quality Overall Summary: 2.3.P Drug Product from NDA 208673

As a result of the two different ratios, there is an overlap in the recommended dose range for the two pen injectors (Figure 1).

Figure 1: Comparison of recommended dose range for Pen A, Pen B



Source: Excerpted from Figure 2 of the Summary of Clinical Efficacy from NDA 208673

The dose presented on the dial refers to the units of insulin glargine in the volume to be delivered. The corresponding amount of lixisenatide will be delivered with the selected dose of insulin glargine.

For patients previously treated with oral anti-diabetic drugs (OADs), the applicant proposed a starting dose of 10 'units' using Pen A (i.e., 10 units of insulin glargine and 5 mcg of lixisenatide).

For patients previously on basal insulin, the applicant proposed a starting dose based on total daily basal insulin dose (Table 4).

Table 4: Proposed initiating dose for patients already on basal insulin

Total daily basal insulin dose being discontinued	<25 units	25 units to ≤40 units	>40 units to ≤60 units
Pen used for initiation	**Pen A**	**Pen A**	**Pen B**
Initiation dose	**10 'units'**	**20 'units'**	**30 'units'**

Pen A contains a ratio of 2 units of insulin glargine: 1 mcg lixisenatide; Pen B contains a ratio of 3 units of insulin: 1 mcg lixisenatide
Source: Adapted from Module 1.14.1.3 "Proposed Prescribing Information" from NDA 208673

The dose would then be titrated based on the patient's need for additional glycemic control.

Following the Advisory Committee meeting held on May 25, 2016 and further discussion with the Agency, the proposed product presentation was changed on August 11, 2016 to a single pen injector with the 3:1 ratio of insulin glargine: lixisenatide. The proposed dose range would be from 15 to 60 'units'. The dial would not include doses between 2 and 15 'units', with the '2' identifying the priming dose. With this updated presentation, the applicant has proposed a new starting dose (b) (4) for patients previously treated with basal insulin (see below, excerpted from Prescribing Information submitted to NDA 208673 on August 11, 2016).

(b) (4)

(b) (4)

---

3. Product Quality

The proposed formulation of IGlarLixi is based on the commercially available insulin glargine injection and lixisenatide injection. The two dosage strengths (b) (4) (50 mcg/mL for Pen A and 33 mcg/mL for Pen B; see Table 1 and Table 2 of Module 3.2.P.1 "Description and composition of the drug product" from NDA 208673, excerpted below).

(b) (4)

Table 2 - Composition of insulin glargine / lixisenatide solution for injection 100 U/mL insulin glargine with 33 µg/mL lixisenatide

Components [a]	Composition			Function	Reference to standards [b]
	Percentage [%]	Per mL [mg]	Per unit (3 mL cartridge) [mg]		
Insulin glargine *[equivalent to U of insulin glargine]*	0.36	3.6378 *[100]*	10.9134 *[300]*	Drug substance	Ph. Eur., USP
Lixisenatide	0.003	0.033	0.099	Drug substance	In-house
Glycerol (b) (4) per cent)	2.0	20.0	60.0	(b) (4)	Ph. Eur.
Methionine	0.3	3.0	9.0		Ph. Eur., USP
Metacresol [c]	0.27	2.7	8.1		Ph. Eur., USP
Zinc (b) (4)	(b) (4)				Ph. Eur., USP
Hydrochloric acid, (b) (4) (b) (4)					Ph. Eur., NF
Sodium hydroxide					Ph. Eur., NF
Water for injection					Ph. Eur., USP
(b) (4)					

a Components are listed according to their pharmacopoeial names, if available. If more than one monograph exists, other names are given in brackets, along with the compendial origin.
b Reference is made to the current edition of the Pharmacopoeia.
c For metacresol, the common chemical name "m-cresol" is also used within this document.
d (b) (4)
e The amount of zinc (b) (4)

Source: Excerpted from Module 3.2.P.1 "Description and composition of the drug product" from NDA 208673

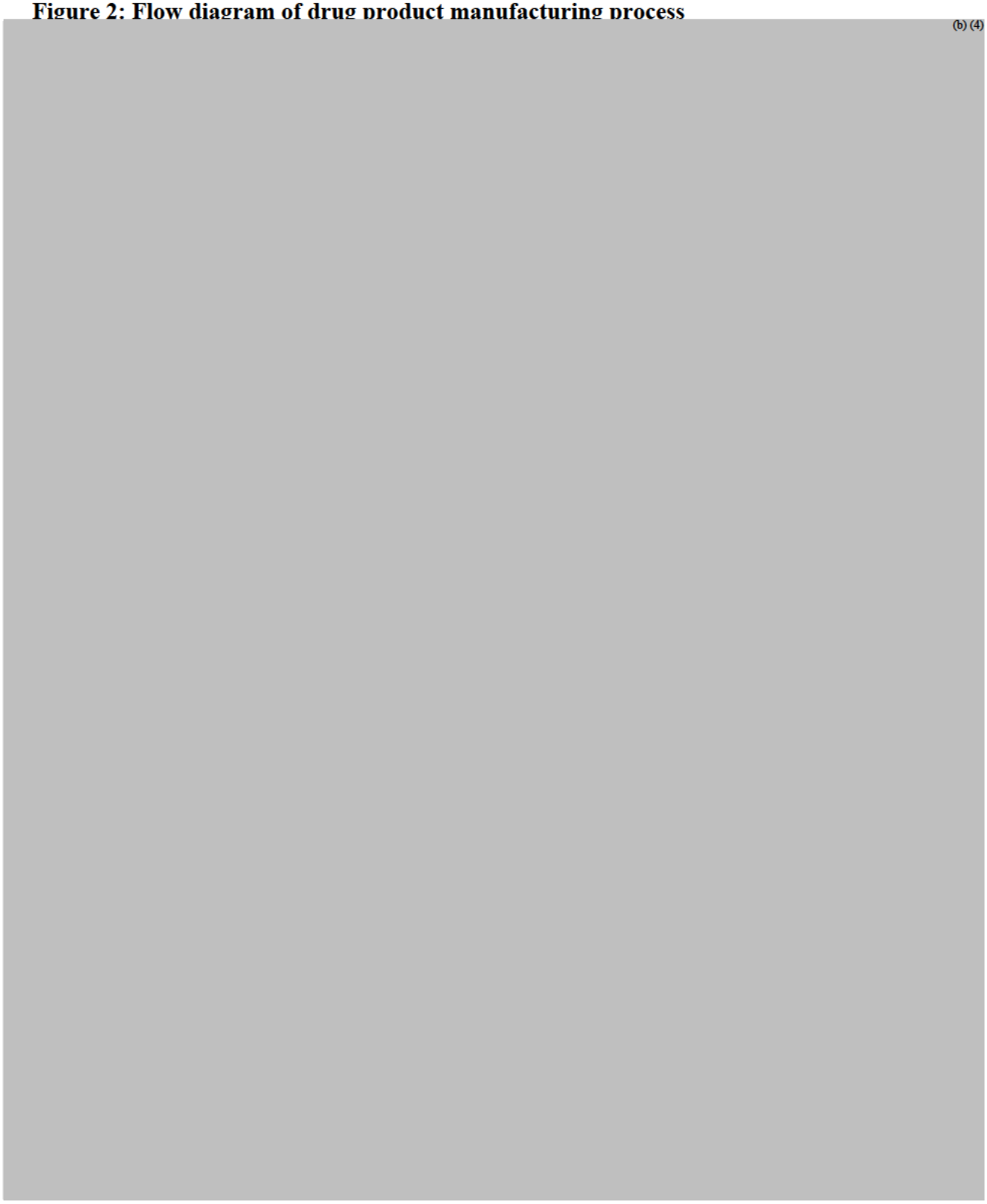
Study of the active pharmaceutical ingredients (i.e., lixisenatide and insulin glargine) found them to be compatible with each other and there was no evidence of interaction between the two. In study of possible formulations, it was observed (b) (4) The proposed final to-be-marketed formulation does not contain (b) (4). No compatibility issues were noted with the proposed excipients.

The primary container closure for the drug substance consists of a 3 mL glass cartridge sealed with a (b) (4) rubber plunger on one end (b) (4)

A summary of the manufacturing process is provided below (Figure 2). In brief, (b) (4) (b) (4)

Figure 2: Flow diagram of drug product manufacturing process

(b) (4)



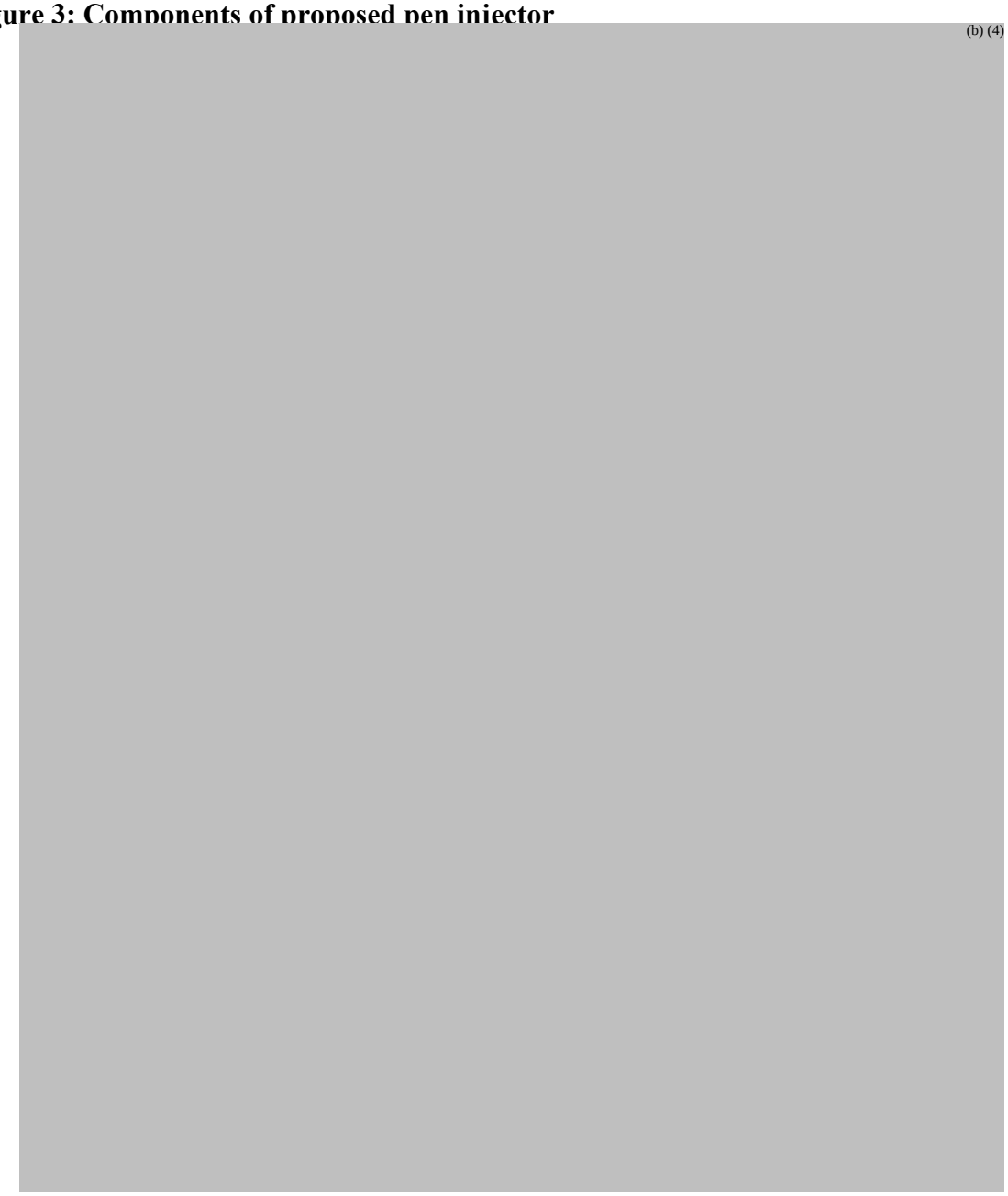
The manufacturing process was found to be acceptable. Stability studies support a shelf-life of 18 months and a 14 day in-use period for the product.

The Office of Product Quality (OPQ) has recommended approval of the FCDP. Facilities inspections have been completed and no manufacturing deficiencies were identified. See Dr. Muthukumar Ramaswamy's Drug Product review, Dr. Yuesheng Ye's Process review, and Dr. Maria Cruz-Fisher's Microbiology review for a detailed discussion.

The to-be-marketed pen injector is based on the already marketed SoloStar pen injector platform utilized by the applicant's approved insulin glargine product. The primary container closure is incorporated into the pen injector. The components of the pen injector are shown in Figure 3.

Figure 3: Components of proposed pen injector

(b) (4)



No biocompatibility issues were identified for the pen injector materials. While the to-be-marketed device differed from the devices used in the clinical studies in terms of color (pen injectors were gray in clinical studies), the numbering of the dial (doses below recommended dose range were not displayed in pen injectors used in clinical studies vs. (b) (4) , and the addition of a maximum dose stop (no maximum dose stop was built into the pen injectors used in studies), the Center for Devices and Radiologic Health (CDRH) consultant did not consider these to be significant changes.

The CDRH consultant also reviewed the performance characteristics and requirements of the pen injector. This included force needed to remove the cap, force needed to dial/select the desired dose, force needed to administer dose, and dose accuracy. No issues were identified for any of these attributes. The CDRH consultant has recommended approval of the FCDP. See Mr. John McMichael's consult review for a detailed discussion.

The OPQ reviewers and the CDRH consultants have recommended a post-marketing commitment for ongoing stability analyses. I agree with this recommendation.

4. Nonclinical Pharmacology/Toxicology

Nonclinical studies performed to support IGlarLixi include *in vitro* studies to assess potential cross-receptor binding and activation, *in vitro* studies of effects on thyroid and pancreas, *in vivo* studies of the pharmacokinetic (PK) and pharmacodynamic (PD) profile compared to the individual components, and local tolerance tests.

The *in vitro* studies did not find evidence that lixisenatide and insulin glargine cross-react with the other's receptor. There was also no evidence that administration of the combination resulted in additional effects on the thyroid or pancreas at doses relevant to clinical doses.

The *in vivo* studies did not suggest a PK interaction between lixisenatide and insulin glargine when administered in combination, though the half-life of lixisenatide appeared slightly reduced. Reductions in glucose (both fasting and postprandial [during oral glucose tolerance test]) were seen with each component and with the combination. In the fasting state, the combination was statistically significantly better in reducing glucose than insulin glargine at all timepoints. In the oral glucose tolerance test (OGTT), the combination was better than both insulin glargine alone and lixisenatide alone in terms of glucose excursion at 60 and 90 minutes.

Local tolerance tests showed that injection of the combination was generally well tolerated.

No toxicity studies, carcinogenicity studies, or reproductive toxicology studies were performed with the combination of lixisenatide and insulin glargine.

Dr. Feleke Eshete recommends approval based on the nonclinical findings. For detailed discussion of the pharmacology/toxicology data submitted in support of IGlarLixi, see Dr. Eshete's Pharmacology/Toxicology review.

5. Clinical Pharmacology

The Clinical Pharmacology review considered both the general clinical pharmacology of the FCDP and examined information available to address efficacy questions that remained unanswered. The discussion in this section will be limited to the general clinical pharmacology data. The clinical pharmacology assessment of the available data to address outstanding efficacy questions will be discussed in "Clinical/Statistical- Efficacy".

The effect of mixing lixisenatide and insulin glargine in a single solution was assessed as part of the clinical pharmacology development program.

The relative bioavailability of lixisenatide when administered with insulin glargine was assessed in a study with healthy volunteers (study BDR12547). In this study, different ratios were used, and this did not impact lixisenatide concentrations.

In a second relative bioavailability study (study BDR10880), the pharmacokinetic and pharmacodynamic characteristics of separate simultaneous injections vs. with injection of a pre-mixed formulation were compared in patients with type 1 diabetes mellitus during a euglycemic clamp procedure. Two different strengths were used for the pre-mixed formulation and are described below:

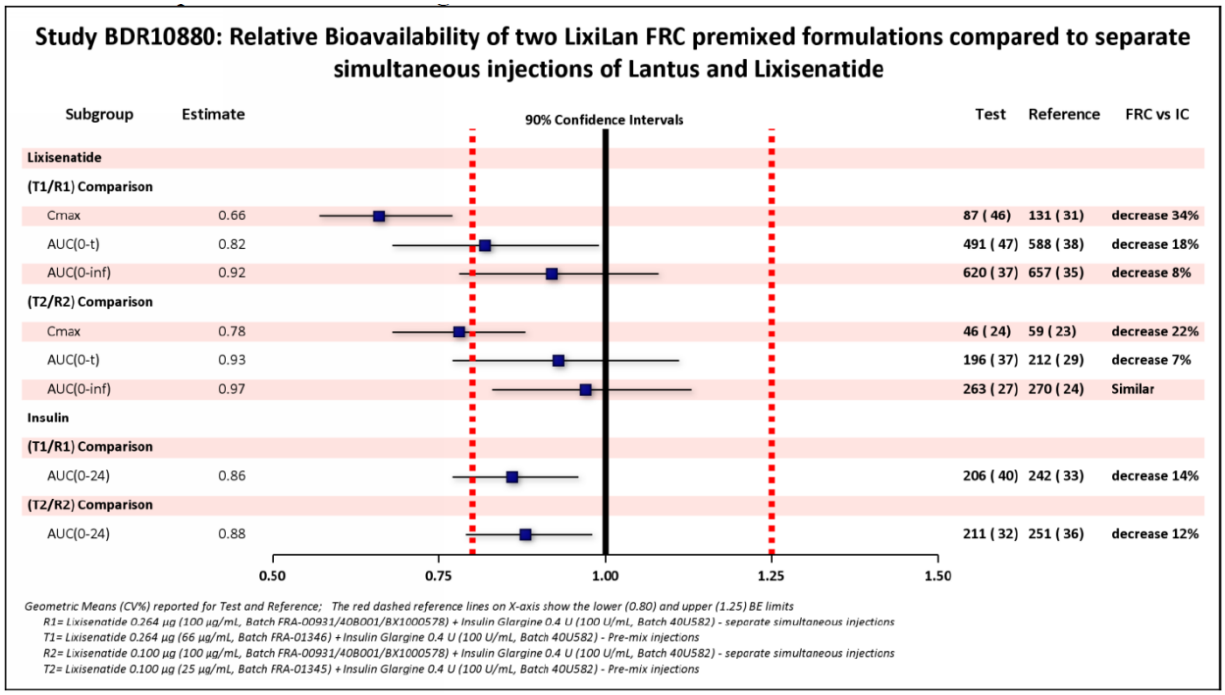
Test 1 (T1): mixture of insulin glargine 100 U/mL and lixisenatide 66 mcg/mL
Test 2 (T2): mixture of insulin glargine 100 U/mL and lixisenatide 25 mcg/mL

With T1, subjects received 0.4 U/kg of insulin glargine and 0.264 mcg/kg of lixisenatide. The comparator (R1) was separate simultaneous injections of insulin glargine 0.4 U/kg and lixisenatide 0.264 mcg/kg.

With T2, subjects received 0.4 U/kg of insulin glargine and 0.1 mcg/kg of lixisenatide. The comparator (R2) was separate simultaneous injections of insulin glargine 0.4 U/kg and lixisenatide 0.1 mcg/kg.

The maximum concentration of lixisenatide was reduced when administered in the premixed formulation with insulin glargine compared to that achieved when lixisenatide was administered separately (Figure 4). The exposure to insulin glargine based on area under the concentration curve was also slightly reduced when administered in the premixed formulation compared to separate administration of insulin glargine.

Figure 4: Relative bioavailability of IGlarLixi comparedto separate simultaneous injections in patients with type 1 diabetes (Study BDR10880)



Source: Excerpted from Figure 12 of the Clinical Pharmacology review

Though there were some differences observed in the pharmacokinetic profiles of lixisenatide and insulin glargine when administered as a pre-mixed formulation, these differences did not appear to translate into notable differences in the pharmacodynamic profiles. Based on review of the blood glucose curves and glucose infusion rate curves, the clinical pharmacology reviewer has concluded that the pharmacodynamic activity (as assessed by glucose infusion rate area under the curve from 0 to 24 hours) of the mixed formulation is comparable to separate simultaneous injection (for the comparison of T1 to R1), but that it was slightly lower with T2 compared to R2 (Table 5).

Table 5: Summary of comparison of pharmacodynamic activity of pre-mixed formulation compared to simultaneous separate administration of the components

T1/R1 (90% CI):	0.95 (0.76, 1.18)
T2/R2 (90% CI):	0.83 (0.61, 1.12)

T1 = injection of insulin glargine 0.4U/kg and lixisenatide 0.264 mcg/kg as pre-mixed formulation containing insulin glargine 100 U/mL and lixisenatide 66 mcg/mL
R1 = separate simultaneous injection of insulin glargine 0.4 U/kg and lixisenatide 0.264 mcg/kg
T2 = injection of insulin glargine 0.4U/kg and lixisenatide 0.1 mcg/kg as pre-mixed formulation containing insulin glargine 100 U/mL and lixisenatide 25 mcg/mL
R2 = separate simultaneous injection of insulin glargine 0.4U/kg and lixisenatide 0.1 mcg/kg
Source: Adapted from 3.3.4.b of the Clinical Pharmacology review

No dedicated drug-drug or food-drug interaction studies were performed for the IGlarLixi FCDP. Information on drug-drug interactions for labeling will be based on the approved insulin glargine and lixisenatide labels.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The clinical program for the FCDP consisted of a supportive phase 2 study (study ACT12374) and two phase 3 studies (study EFC12404 and study EFC12405).

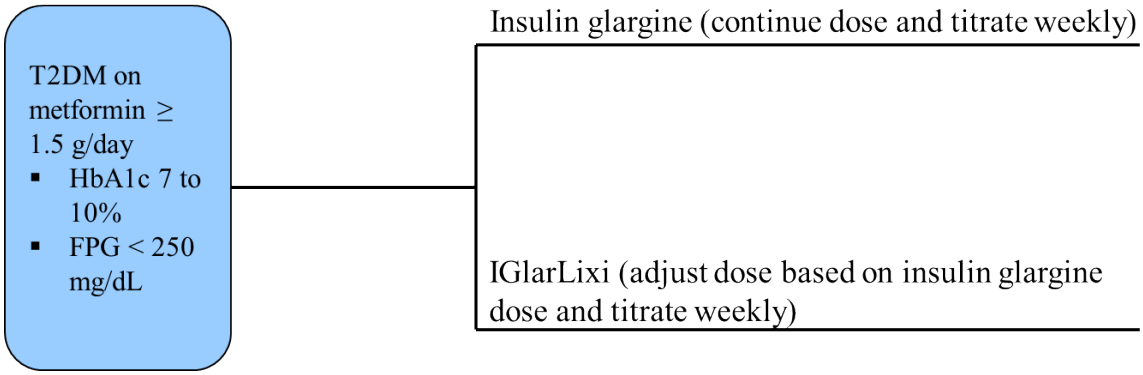
Study Design:

Study ACT12374:

Study ACT12374 was a phase 2 proof of concept study designed as a 24-week, open-label, active-controlled study of patients with inadequate glycemic control despite metformin therapy. The primary endpoint was change in HbA1c from baseline to week 24.

Subjects were randomized to receive insulin glargine titrated to effect, or IGlarLixi titrated to effect (Figure 5). Subjects randomized to insulin glargine were started at 10 units once daily. Subjects randomized to IGlarLixi were started at 10 'units' once daily (i.e., 10 units of insulin glargine and 5 mcg of lixisenatide). The dose of insulin glargine or IGlarLixi was adjusted once a week during the study with a goal of achieving a fasting glucose between 80 to 100 mg/dL (Table 6). The ratio utilized for the IGlarLixi arm was 2 U insulin glargine: 1 mcg lixisenatide and the dose was capped at 60 'units' (equivalent to 60 units insulin glargine and 30 mcg lixisenatide). The insulin glargine arm had no cap on dose.

Figure 5: Schematic of study design for Study ACT12374



Source: Reviewer generated based on review of protocol for study ACT12374

Table 6: Titration algorithm for Study ACT12374

Median fasting SMPG from last 3 days	Dose change[1]
> 140 mg/dL	+6
> 120 and ≤ 140 mg/dL	+4
> 100 and ≤ 120 mg/dL	+2
80 to 100 mg/dL	No change
≥ 60 to < 80 mg/dL	-2
< 60 mg/dL or occurrence of ≥ 2 symptomatic hypoglycemia or one severe hypoglycemia in preceding week	-2 or -4 at the discretion of the investigator

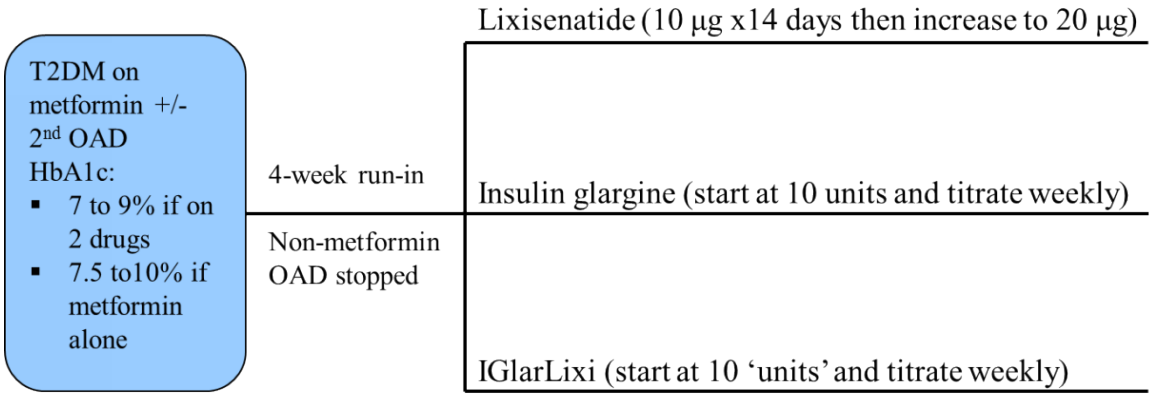
[1] in units per day or 'units' per day
SMPG = self-monitored plasma glucose
Source: Adapted from Table 1 of the protocol for study ACT12374

Study EFC12404:

Study EFC12404 was a 30-week, open-label, active-controlled study of patients with inadequate glycemic control despite oral anti-diabetic drugs. The primary efficacy endpoint was change in HbA1c from baseline to week 30.

Subjects were randomized to receive lixisenatide 20 mcg, insulin glargine titrated to effect, or IGlarLixi titrated to effect (Figure 6). All three were administered once daily. Subjects randomized to insulin glargine were started at 10 units once daily. Subjects randomized to IGlarLixi were started at 10 'units' once daily (i.e., 10 units of insulin glargine and 5 mcg of lixisenatide). The dose of insulin glargine or IGlarLixi was adjusted once a week during the study with a goal of achieving a fasting glucose between 80 to 100 mg/dL (Table 7). The dose was capped at 60 units for insulin glargine and 60 'units' for IGlarLixi.

Figure 6: Schematic of study design for study EFC12404



Source: Reviewer generated based on review of protocol for study EFC12404

Table 7: Titration algorithm

Median fasting SMPG from last 3 days	Dose change[1]
> 140 mg/dL	+4
> 100 and ≤ 140 mg/dL	+2
80 to 100 mg/dL	No change
≥ 60 to < 80 mg/dL	-2
< 60 mg/dL or occurrence of ≥ 2 symptomatic hypoglycemia or one severe hypoglycemia in preceding week	-2 to -4 at the discretion of the investigator

[1] in units per day or 'units' per day
SMPG = self-monitored plasma glucose
Source: Adapted from Table 1 of the protocol for study EFC12404

Study EFC12405:

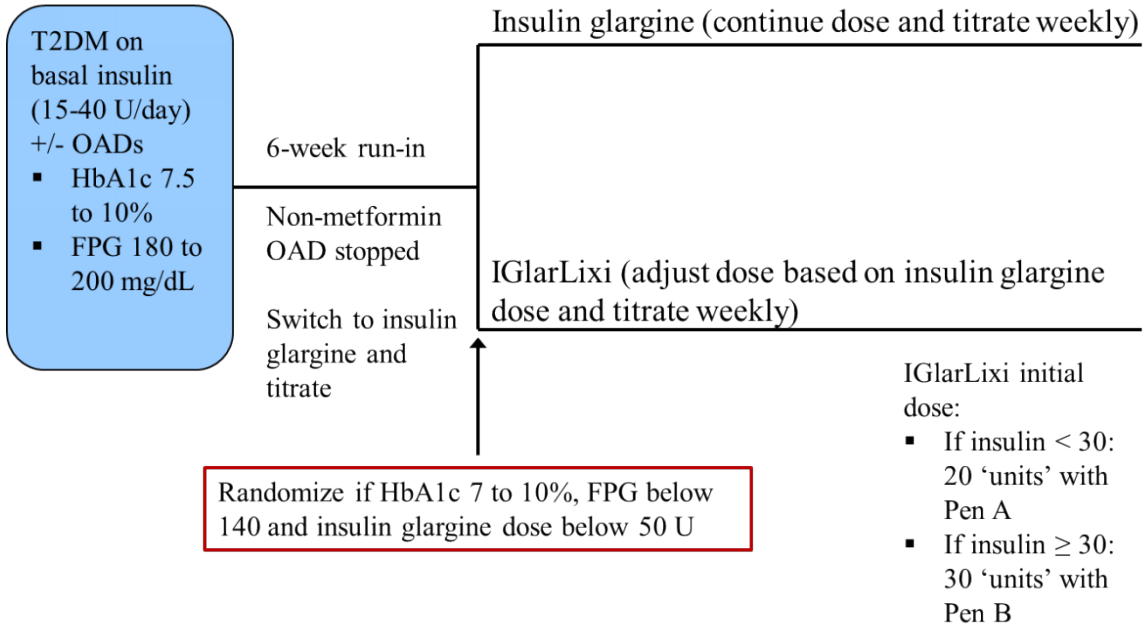
Study EFC12405 was a 30-week, open-label, active-controlled study of patients with inadequate glycemic control despite treatment with basal insulin. The primary efficacy endpoint was change in HbA1c from baseline to week 30.

In study EFC12405 subjects were to receive either insulin glargine or IGlarLixi once daily, both titrated to effect. Subjects randomized to insulin glargine continued the same dose of insulin glargine. Subjects randomized to IGlarLixi were switched to the appropriate FCDP pen injector based upon the insulin dose at randomization as follows:

- If insulin glargine dose was < 30 units, Pen A was used and the starting dose was 20 'units' of IGlarLixi (i.e., 20 units of insulin glargine and 10 mcg of lixisenatide)
- If insulin glargine dose was ≥ 30 units, Pen B was used and the starting dose was 30 'units' of IGlarLixi (i.e., 30 units of insulin glargine and 10 mcg of lixisenatide)

In both studies, the dose of insulin glargine or IGlarLixi was adjusted once a week during the study with a goal of achieving a mean fasting glucose between 80 to 100 mg/dL (Table 7). The dose was capped at 60 units for insulin glargine and 60 'units' for IGlarLixi.

Figure 7: Schematic of study design for study EFC12405



Source: Reviewer generated based on review of protocol for study EFC12405

The focus of the efficacy discussion will be the two phase 3 studies (i.e., study EFC12404 and study EFC12405) as study ACT12374 was a proof-of-concept phase 2 study.

Study Results:

The mean final dose of IGlarLixi in study EFC12404 was 39.8 'units' compared to a mean final dose of insulin glargine of 40.5 units. The mean final dose of lixisenatide in the IGlarLixi subjects was 15.5 mcg.

The mean final dose of IGlarLixi in study EFC12405 was 46.7 'units' compared to a mean final dose of insulin glargine of 46.7 units. The mean final dose of lixisenatide in the IGlarLixi subjects was 16.9 mcg.

IGlarLixi demonstrated statistical superiority for change in HbA1c from baseline to each of the active comparators in the phase 3 studies (Table 8). Subgroup analyses for the primary endpoint did not demonstrate any apparent effect of gender, race or ethnicity.

Table 8: Results for primary endpoint in study EFC12404 and study EFC12405

Study EFC12404 –IGlarLixi vs. lixisenatide and vs. insulin glargine in subjects not previously treated GLP-1 receptor agonist or insulin			
	Lixisenatide N=233	Insulin glargine N=464	IGlarLixi N=467
HbA1c (%)			
- Baseline	8.13	8.08	8.08
- LS mean change from baseline (SE)	-0.85 (0.05)	-1.34 (0.04)	-1.63 (0.04)

Study EFC12404 –IGlarLixi vs. lixisenatide and vs. insulin glargine in subjects not previously treated GLP-1 receptor agonist or insulin			
	Lixisenatide N=233	Insulin glargine N=464	IGlarLixi N=467
- LS mean difference of IGlarLixi vs. (95% CI)	-0.78 (-0.90, -0.66)	-0.29 (-0.38, -0.19)	---
- p-value	< 0.0001	< 0.0001	---
Study EFC12405 –IGlarLixi vs. insulin glargine in subjects previously treated with basal insulin			
		Insulin glargine N=364	IGlarLixi N=364
HbA1c (%)			
- Baseline		8.08	8.07
- LS mean change from baseline (SE)		-0.62 (0.06)	-1.13 (0.06)
- LS mean difference of IGlarLixi vs. (95% CI)		-0.52 (-0.63, -0.40)	---
- p-value		< 0.0001	---

Source: Adapted from Table 5 and Table 9 of Dr. Jiwei He's Statistical review from NDA 208673

Secondary endpoints included 2 hour glucose excursion following a standardized meal, change in body weight, and change in fasting glucose (Table 9). In considering the known effects of GLP-1 receptor agonists and of insulin the effects seen with IGlarLixi for these endpoints predictably fall somewhere in between the two. There is a greater effect on fasting plasma glucose than that seen with lixisenatide alone, but not much difference compared to insulin glargine alone. IGlarLixi was associated with a greater effect on post-prandial glucose and less weight gain than seen with insulin glargine alone. Compared to lixisenatide alone, IGlarLixi was associated with weight gain and was less effective on controlling post-prandial glucose. The clinical relevance of these endpoints is not entirely clear given the small differences between treatment arms.

Table 9: Results for selected secondary endpoints in study EFC12404 and study EFC12405

Study EFC12404 –IGlarLixi vs. lixisenatide and vs. insulin glargine in subjects not previously treated GLP-1 receptor agonist or insulin			
	Lixisenatide	Insulin glargine	IGlarLixi
2 hour glucose excursion (mmol/L)[1]	N=192	N=425	N=428
- LS mean difference of IGlarLixi vs. (95% CI)	0.91 (0.45, 1.38)	-2.13 (-2.5, -1.77)	---
Body weight (kg)	N=233	N=465	N=467
- LS mean difference of IGlarLixi vs. (95% CI)	2.01 (1.4, 2.61)	-1.4 (-1.89, -0.91)	---
Fasting plasma glucose (mmol/L)[1]	N=232	N=465	N=465
- LS mean difference of IGlarLixi vs. (95% CI)	-1.96 (-2.25, -1.68)	-0.19 (-0.42, 0.04)	---
Study EFC12405 –IGlarLixi vs. insulin glargine in subjects previously treated with basal insulin			
		Insulin glargine	IGlarLixi
2 hour glucose excursion (mmol/L)[1]		N=365	N=365
- LS mean difference of IGlarLixi vs. (95% CI)		-3.43 (-3.92, -2.94)	---
Body weight (kg)		N=365	N=365
- LS mean difference of IGlarLixi vs. (95% CI)		-1.37 (-1.81, -0.93)	---

APPEARS THIS WAY ON ORIGINAL

Fasting plasma glucose (mmol/L)[1]		N=364	N=364
- LS mean difference of IGlarLixi vs. (95% CI)		0.11 (-0.21, 0.43)	---

[1]Glucose values are presented in mmol/L. To convert to mg/dL, multiply by 18
Source: Adapted from Table 5 and Table 9 of Dr. Jiwei He's Statistical review from NDA 208673

From the review of the efficacy data, Dr. He concludes that the use of IGlarLixi results in a greater improvement in glycemic control compared to use of either of the components alone.

Dr. He did note some issues with regard to the efficacy conclusions. The first is the external validity of the study results. In both studies, the dose of insulin glargine was capped. This would not be the case in practice. Further the titration algorithm used may not reflect how insulin glargine is titrated in practice. As a result, the observed treatment difference may not reflect the actual treatment difference in practice. The second is the open-label design. Such a design could have introduced bias.

For additional discussion of the statistical efficacy analyses, see Dr. He's Statistical review.

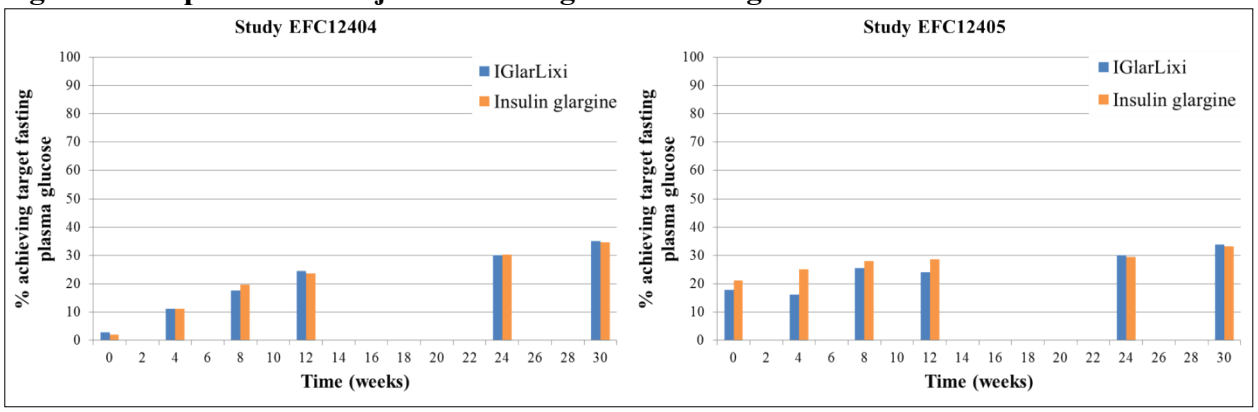
Discussion of Efficacy:

I agree with Dr. He that the conducted studies demonstrate that the IGLarLixi product demonstrated statistical superiority to both of the individual components for change in HbA1c at 30 weeks. However, I have some reservations with concluding clinical superiority of IGlarLixi over insulin glargine. As noted in Dr. He's review, there are study design features that raise question to the external validity of the study results.

Both of the phase 3 studies used a titration algorithm to direct dose adjustments. The titration algorithm was based on fasting glucose values and, in general, fasting glucose reflects the adequacy of the basal insulin dose (which in this case was insulin glargine). The titration algorithm limited dose increases to no more than 4 units (or 'units') per week.

Despite having a titration algorithm in place, the proportion of subjects achieving the intended fasting plasma glucose targets (a measure of adequacy of insulin glargine dosing) was less than 40% (Figure 8). It is unclear why treatment targets were not achieved in a higher proportion of subjects. Whether a more aggressive titration algorithm would have led to more subjects achieving targets is unknown.

Figure 8: Proportion of subjects achieving titration targets



Source: Reviewer generated based on data in February 2, 2016 response to Information Request from NDA 208673

The cap on the dose of insulin glargine raises further concerns that the observed effect from the insulin glargine arm may not reflect the full treatment effect of insulin glargine. In both studies, more subjects were at the dose limit in the insulin glargine arm than in the IGlarLixi arm. Of note, these subjects were not at titration targets.

Table 10: Subjects at 60 unit/'unit' limit for insulin glargine and IGlarLixi

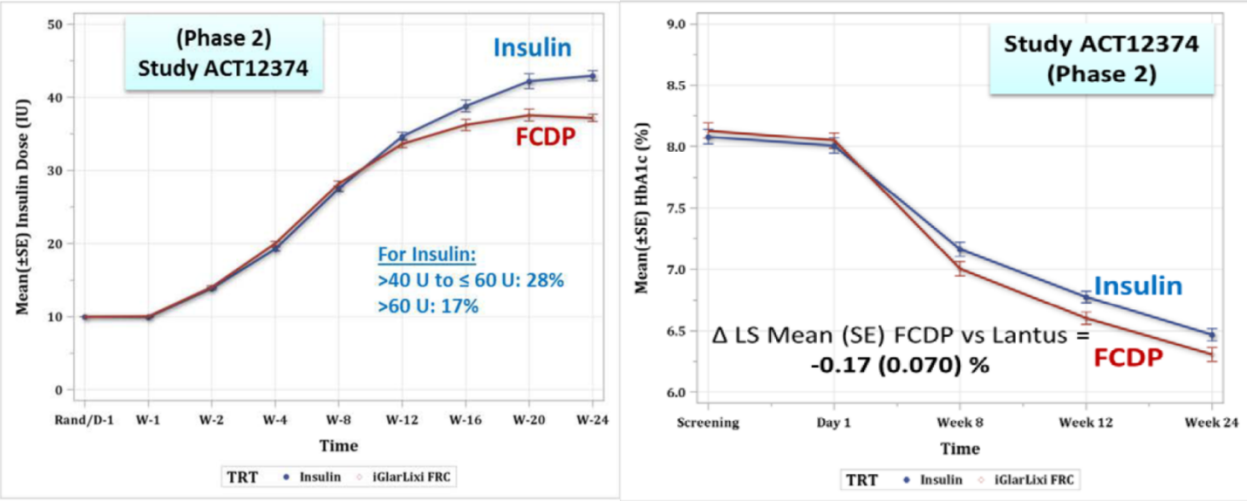
	IGlarLixi	Insulin Glargine
Study EFC12404		
- % of subjects at 60 Units	16%	20%
- Mean fasting glucose (mg/dL)	129.4	133.4
Study EFC12405		
- % of subjects at 60 Units	27%	31%
- Mean fasting glucose (mg/dL)	130.2	132.6

Source: Adapted from Table 16 of Dr. Balakrishnan's Clinical review for NDA 208673

These two issues bring into question whether the observed insulin glargine effect reflects the full treatment effect. This in turn raises concerns as to whether the comparison between IGlarLixi and insulin glargine is unbiased and whether the observed study findings are generalizable to the clinical care setting.

The results of the phase 2 study (Study ACT12374) provide some insight to the potential impact of the titration algorithm and the dose cap. In this study, a more aggressive titration algorithm was used, and there was no upper cap on the dose of insulin glargine. As a result of these two differences, the insulin glargine arm achieved higher doses of insulin and the treatment difference was reduced (Figure 9). In this study 16.7% of insulin glargine subjects were using a dose > 60 U.

Figure 9: Insulin dose and HbA1c over time from study ACT12374



Source: Adapted from Figure 1 and Figure 2 of the Clinical Pharmacology review

From these results, it does appear that the selected titration algorithm and cap on insulin dose may have biased the superiority conclusion of the phase 3 studies. The applicant was asked to assess the impact of different dosing schemes on the results of the phase 3 studies using modeling and simulation. Details of the model and the simulations are discussed in 4.2.1 of the Clinical Pharmacology review.

Based on the results of the simulations, the applicant concludes for study EFC12404 that higher insulin doses could have been achieved if either there was no cap on insulin dose or there was no cap on insulin dose combined with a more aggressive titration algorithm (i.e., the algorithm used in study ACT12374). However, the sponsor concludes that in both of these scenarios, the impact on self-monitored blood glucose and on HbA1c is minimal.

The results of the modeling and simulation have been reviewed and considered by the Office of Clinical Pharmacology. In considering the results of the modeling and simulation, several issues that limit the applicability of this model are noted. The pharmacometric reviewer comments are reproduced below:

Reviewer's Comments:

Although, the developed longitudinal dose-response model for fasting SMPG has shown to describe the observed SMPG data reasonably well, there are certain issues that limit the applicability of this model to predict the effect of different titration algorithms on clinically relevant endpoint (HbA1c reduction) in insulin naïve patients:

1. *For the simulations, the strategies used to account for the deviation between protocol defined insulin dose adjustments vs. actual dose adjustment were not patient specific and can't really capture the range of reasons for the titrations to slow down.*
2. *It is worth noting that the ED50 and Emax for the longitudinal dose-SMPG model (**Table 10** [1]) between the ACT12374 and EFC12404 population are similar.*

However, the HbA1c profiles for insulin arm in the two studies are not similar, as seen with the blue lines in ***Figure 13*** [2]*. Therefore, it is reasonable to conclude that it is not possible to explain the difference between the two studies in terms of HbA1c, using the developed model.*

3. *In addition, due to the sparse sampling of HbA1c, linear regression was conducted to develop a relationship between SMPG and HbA1c which is not an adequate strategy to link SMPG to HbA1C as these effects are not directly related. Therefore, uncertainty exists whether or not the predicted HbA1C profiles demonstrate the expected difference between the titration scenarios. The simulated results therefore may not represent the true effect of insulin dose capping and titration scheme.*

Source: Excerpted from section 4.2.1 of the Clinical Pharmacology review

While the applicant concludes that IGlarLixi is superior to insulin glargine in terms of HbA1c, a more appropriate conclusion might be that a contribution of each component to the effect has been demonstrated at the doses achieved.

A separate efficacy issue has to do with the low dose range of the proposed FCDP. The Code of Federal Regulations (21 CFR 300.50) stipulates that "[t]wo or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects […]". The design of the studies does not allow for an assessment of the contribution of each component across the proposed dose range, specifically for the lower dose range.

There are limited data to inform the contribution of lixisenatide to HbA1c reduction for the low part of the FCDP dosing range as lixisenatide 20 mcg once daily (the approved dose) was the only dose studied in phase 3 for the lixisenatide product (NDA 208471). The phase 3 data for the FCDP also provides only a limited amount of data to consider as the dose was titrated.

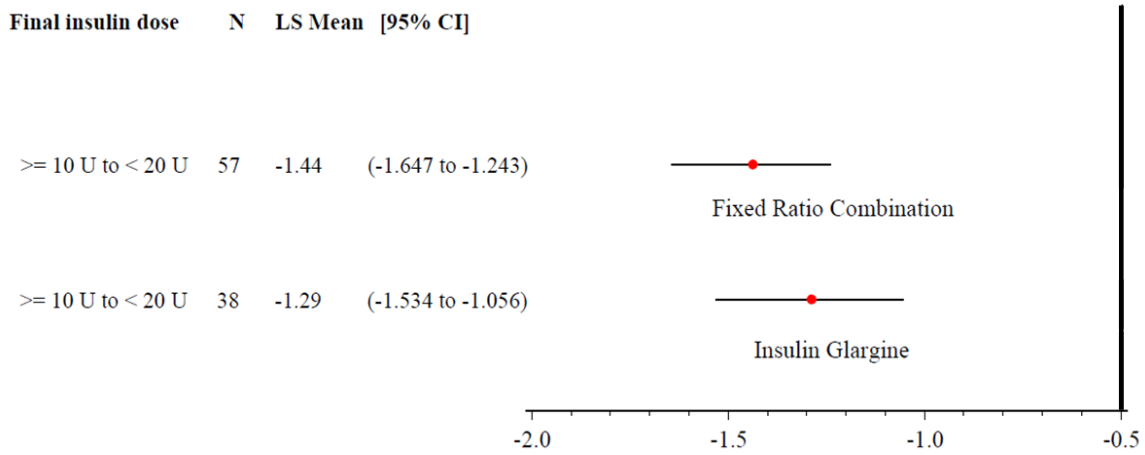
In study EFC12404, 12.4% of the IGlarLixi subjects were on a dose that coincided with a lixisenatide dose < 10 mcg at week 30. In study EFC12405, 0.8% of the IGlarLixi subjects were on a dose that coincided with a lixisenatide dose < 10 mcg. As a result, study EFC12405 is not informative with regard to the contribution of lixisenatide in the low dose range. While it could be argued that data to support a contribution of each component in the low dose range is not necessary as the proportion of subjects in this range (i.e., 12.4% in study EFC12404 and 0.8% in study EFC12405) was low, it is worth noting that study subjects discontinued non-metformin OADs prior to randomization. It is possible that there would be more subjects in the low dose range had this not occurred.

In post-hoc exploratory analyses examining the sub-group of subjects with final insulin glargine doses between 10 units and 20 units from study EFC12404 (which corresponds to lixisenatide 5 mcg to 10 mcg in the IGlarLixi population), no discernible differences between treatment arms were observed (Figure 10). Recognizing the inherent limitations of this

[1] Referenced table not shown here. See the Clinical Pharmacology review.
[2] Referenced figure not shown here. See the Clinical Pharmacology review.

analysis, the observation, at a minimum, does not further inform the question of whether both components contribute to the claimed effect at the low end of the range.

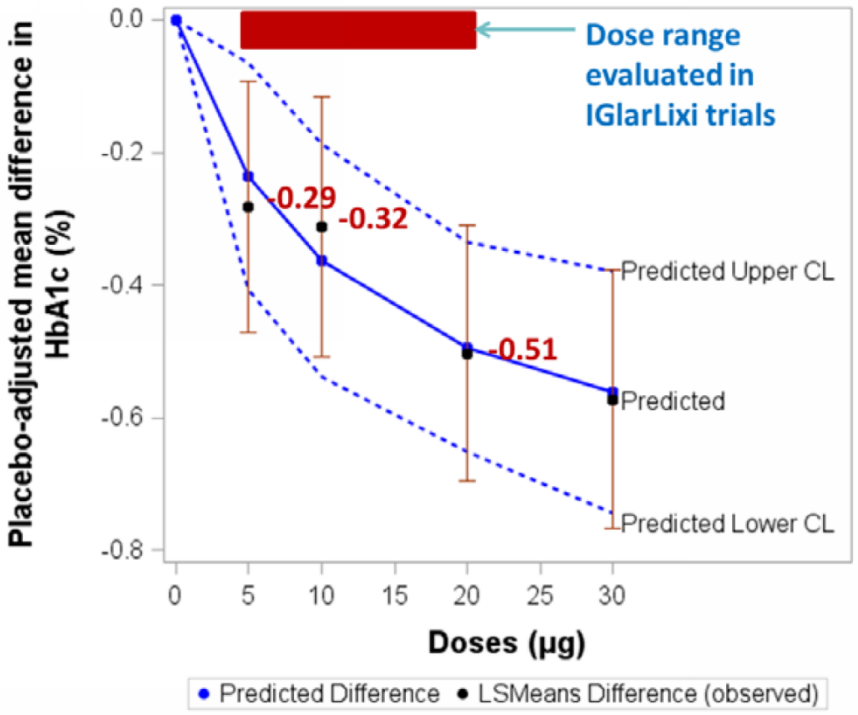
Figure 10: Mean HbA1c change from baseline at 30 weeks for subjects using 10 to 20 units of insulin glargine (corresponding to 5 to 10 mcg of lixisenatide) in study EFC12404



Source: Adapted from section 16.2.6.6.2.2 and 16.2.6.6.2.3 of the Appendix to the study report for study EFC12404 from NDA 208673

Data from the lixisenatide development programs was also reviewed in an attempt to address this concern. While the dose-response of lixisenatide suggested some glycemic lowering effect of doses of lixisenatide as low as 5 mcg (Figure 11), it is not known whether this data would accurately reflect the effect seen when used in combination with insulin.

Figure 11: Dose response of lixisenatide from study DRI6012 (NDA 208471)



Source: Excerpted from Figure 5 of the Clinical Pharmacology review

Prior experience with fixed combination drug products suggests that the additional effect seen with initiating two drug products at once is not additive, rather that the net effect is less than the sum of the two individual components (see example below).

Table 6 Glycemic Parameters at 24 Weeks in a Study Comparing JARDIANCE and Metformin to the Individual Components as Initial Therapy

	JARDIANCE 10 mg + Metformin 1000 mg[a] N=161	JARDIANCE 10 mg + Metformin 2000 mg[a] N=167	JARDIANCE 25 mg + Metformin 1000 mg[a] N=165	JARDIANCE 25 mg + Metformin 2000 mg[a] N=169	JARDIANCE 10 mg N=169	JARDIANCE 25 mg N=163	Metformin 1000 mg[a] N=167	Metformin 2000 mg[a] N=162
HbA1c (%)								
Baseline (mean)	8.7	8.7	8.8	8.7	8.6	8.9	8.7	8.6
Change from baseline (adjusted mean)	-2.0	-2.1	-1.9	-2.1	-1.4	-1.4	-1.2	-1.8
Comparison vs JARDIANCE (adjusted mean) (95% CI)	-0.6[b] (-0.9, -0.4)	-0.7[b] (-1.0, -0.5)	-0.6[c] (-0.8, -0.3)	-0.7[c] (-1.0, -0.5)	--	--	--	--
Comparison vs metformin (adjusted mean) (95% CI)	-0.8[b] (-1.0, -0.6)	-0.3[b] (-0.6, -0.1)	-0.8[c] (-1.0, -0.5)	-0.3[c] (-0.6, -0.1)	--	--	--	--

[a]Metformin total daily dose, administered in two equally divided doses per day.
[b]p-value ≤0.0062 (modified intent to treat population [observed case] MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA1c).
[c]p-value ≤0.0056 (modified intent to treat population [observed case] MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA1c).

Source: Excerpted from Table 6 of the label approved on March 18, 2015 for empagliflozin (NDA 204629)

Based on this example if the contribution of each component when initiated simultaneously is additive, initiating metformin 2000 mg with empagliflozin 10 mg should result in a reduction in HbA1c of -3.2%. Instead, the treatment arm where this occurs demonstrated a reduction of only -2.1%. Thus, it would be imprudent to assume that the -0.29% reduction in HbA1c seen

with lixisenatide 5 mcg in study DRI6012 (NDA 208471) can be added on top of the expected reduction from using insulin glargine. How much this contribution would be attenuated is unclear. Given that the treatment effect of lixisenatide 5 mcg appears to be relatively small any attenuation raises concerns that there may not be a contribution of low dose lixisenatide to glycemic control in the FCDP.

Given the uncertain contribution of lixisenatide to the claimed effect in the low dose range, it is worth considering whether the low doses of lixisenatide carry any additional risk over the use of insulin glargine alone. To explore this, the safety profiles of the FCDP, glargine alone and lixisenatide alone in the first 28 days of study EFC12404 were examined as in this period subjects randomized to IGlarLixi would be expected to be receiving between 5 to 10 mcg of lixisenatide. Adverse events from this early study period demonstrate that risks specific to the lixisenatide component (nausea, vomiting, diarrhea) were more frequent in subjects receiving IGlarLixi then in subjects receiving glargine (Table 11). Whether the small doses of lixisenatide would increase the risk of serious non-dose related adverse events (e.g., anaphylaxis) is not known, but it seems unlikely that lowering the dose would alter the occurrence of these events.

Table 11: Selected treatment emergent adverse events in the first 28 days of study EFC12404

High Level Term	Lixi 20 mcg N=233		Insulin glargine N=464		IGlarLixi N=467	
	N	%	N	%	N	%
Nausea and vomiting symptoms	46	19.7	9	1.9	26	5.6
Diarrhea (excl infective)	9	3.9	9	1.9	15	3.2
Headaches NEC	11	4.7	8	1.7	13	2.8
Neurological signs and symptoms NEC [1]	4	1.7	4	0.9	12	2.6
Cardiac signs and symptoms NEC [1]	5	2.1	5	1.1	11	2.4
Circulatory collapse and shock [1]	4	1.7	5	1.1	11	2.4

[1] Primarily preferred term of 'dizziness'
Source: Based on review of ADAE.xpt for study EFC12404 from NDA 208673

Efficacy Conclusions:

Based on my review of the primary reviews and submitted information, I believe that the applicant has demonstrated that each of the components of the IGlarLixi product contributes to the effect of glycemic control at the doses achieved in the studies. I have reservations with regard to concluding clinical superiority of this product over insulin glargine alone, and do not believe that there is sufficient information to conclude that there is a contribution of each component in the low dose range (i.e., below 10 mcg of the lixisenatide component).

It is unclear whether the risk-benefit assessment would be favorable at low doses of the FCDP as there is uncertainty in terms of the contribution of low doses of lixisenatide and clear evidence of increased risks. As a result, I believe that this product would be most appropriate for patients where the dose would quickly reach a point where there is more certainty that both components contribute to the glycemic lowering effect (e.g., a lixisenatide dose of ~15 mcg which is what was achieved at the end of the phase 3 studies). Based on the final doses achieved in study EFC12404, I do not have enough confidence that patients not already treated

with a GLP-1 receptor agonist or with insulin would quickly achieve meaningful doses of lixisenatide with the FCDP. I have more confidence that patients needing additional glycemic control despite therapy with a basal insulin or with lixisenatide will quickly achieve meaningful doses of lixisenatide with the FCDP. I would recommend indicating this product for this population.

8. Safety

The discussion of safety will be divided into a discussion of the safety findings from the clinical development program and a discussion of concerns for medication errors.

Safety findings from development program:

Safety concerns described in the label for insulin glargine include hypoglycemia and hypersensitivity reactions. The labeled safety concerns for lixisenatide include anaphylaxis/hypersensitivity reactions, injection site reactions, immunogenicity, pancreatitis, nausea, vomiting, and hypoglycemia.

As the proposed FCDP product is a combination of these two pharmaceutical ingredients, it would be expected that it would carry the combined risks. That is indeed what is seen.

As the clinical development program for the FCDP is relatively small, limited conclusions can be made with regard to anything other than common adverse events. No notable differences were seen between treatments from the pool of phase 2/3 studies (i.e., study ACT12374, study EFC12404, and study EFC12405) in terms of deaths or nonfatal serious adverse events. Discontinuation of study drug occurred more commonly with lixisenatide than with other study treatments (9% lixisenatide vs. 1.2% insulin glargine vs. 2.8% IGlarLixi). For a more detailed discussion of deaths, serious adverse events, and discontinuations due to adverse events, see Dr. Suchitra Balakrishnan's Clinical review.

In terms of common adverse events (AEs), the incidence seen in subjects treated with IGlarLixi generally fell in between that of lixisenatide treated subjects and insulin glargine treated subjects (Table 12; see Table 19 in the Appendix for the full list of high level terms reported in ≥ 3% of subjects in any treatment arm). Nausea and vomiting were more common with lixisenatide. The incidence with IGlarLixi was lower than lixisenatide alone but higher than insulin glargine alone. A similar pattern was seen for diarrhea, headache, dizziness, and injection site reactions.

Table 12: Incidence of selected high level terms reported in ≥ 3% of subjects in any treatment arm and selected preferred terms reported in ≥ 2% of subjects from the pool of phase 2/3 studies

High level term ▪ Preferred term[1]	Lixisenatide 20 mcg N=234		Insulin glargine N=998		IGlarLixi N=997	
	N	%	N	%	N	%
Nausea and vomiting symptoms	*61*	*(26.1)*	*26*	*(2.6)*	*106*	*(10.6)*
▪ Nausea	56	(23.9)	19	(1.9)	95	(9.5)
▪ Vomiting	15	(6.4)	10	(1.0)	33	(3.3)
Diarrhea (excl infective)	*21*	*(9.0)*	*36*	*(3.6)*	*63*	*(6.3)*
▪ Diarrhea	21	(9.0)	36	(3.6)	63	(6.3)
Headaches NEC	*18*	*(7.7)*	*37*	*(3.7)*	*54*	*(5.4)*
▪ Headache	18	(7.7)	37	(3.7)	53	(5.3)
Musculoskeletal and connective tissue pain and discomfort	*19*	*(8.1)*	*36*	*(3.6)*	*49*	*(4.9)*
▪ Back pain	8	(3.4)	17	(1.7)	28	(2.8)
▪ Pain in extremity	5	(2.1)	10	(1.0)	18	(1.8)
Cardiac signs and symptoms NEC	*8*	*(3.4)*	*18*	*(1.8)*	*30*	*(3.0)*
▪ Dizziness	7	(3.0)	13	(1.3)	27	(2.7)
Circulatory collapse and shock	*7*	*(3.0)*	*17*	*(1.7)*	*29*	*(2.9)*
▪ Dizziness	7	(3.0)	13	(1.3)	27	(2.7)
Neurological signs and symptoms NEC	*7*	*(3.0)*	*15*	*(1.5)*	*27*	*(2.7)*
▪ Dizziness	7	(3.0)	13	(1.3)	27	(2.7)
Gastric and gastroenteric infections	*8*	*(3.4)*	*11*	*(1.1)*	*26*	*(2.6)*
▪ Gastroenteritis	5	(2.1)	7	(0.7)	15	(1.5)
Asthenic conditions	*8*	*(3.4)*	*13*	*(1.3)*	*21*	*(2.1)*
▪ Fatigue	5	(2.1)	7	(0.7)	12	(1.2)
Injection site reactions	*7*	*(3.0)*	*11*	*(1.1)*	*17*	*(1.7)*

[1] if preferred terms are shown
NEC = not elsewhere classified
Source: Based on review of ADAE.xpt from module 5.3.5.3 ISS of NDA 208673

Hypoglycemia was considered separate from the analysis of adverse events. It was analyzed using three categories:

1. **Documented symptomatic:** An event with typical symptoms of hypoglycemia and a measured glucose concentration ≤ 70 mg/dL
2. **Severe symptomatic:** An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. There is not glucose threshold. Glucose concentrations do not have to be available, but in instances of neuroglycopenia recovery of neurologic status following treatment to normalize plasma glucose is considered sufficient evidence that the event was due to low glucose.
3. **Probable symptomatic:** An event with typical symptoms but without a measured glucose concentration.

As the clinical relevance of "probable symptomatic" hypoglycemic events is not clear, I will be focusing on the first two categories.

In study ACT12374, the incidence of hypoglycemia was similar between treatment arms (Table 13).

Table 13: Summary of hypoglycemia in study ACT12374

	Insulin glargine N=162	IGlarLixi N=161
Documented symptomatic		
• N (%)	37 (22.8)	35 (21.7%)
• Events per pt-year	0.49	0.48
Severe symptomatic		
• N (%)	0	0
• Events per pt-year	0	0

Source: Adapted from Table 21 of the study report for Study ACXT12374 from NDA 208673

In study EFC12404, the incidence of hypoglycemia was lowest in the lixisenatide arm (Table 14). There were numerically fewer events in the insulin glargine arm, though the incidence was similar to that of the IGlarLixi arm. There was only one event of 'severe symptomatic' hypoglycemia, and that occurred in an insulin glargine treated subject.

Table 14: Summary of hypoglycemia in study EFC12404

	Lixisenatide 20 mcg N=233	Insulin Glargine N=467	IGlarLixi N=469
Documented symptomatic			
• N (%)	15 (6.4)	119 (25.5)	128 (27.3)
• Events per pt-year	0.37	1.29	1.55
Severe symptomatic			
• N (%)	0	1 (0.2)	0
• Events per pt-year	0	< 0.01	0

Source: Adapted from Table 37 of the study report for Study EFC12404 from NDA 208673

In study EFC12405, the overall incidence of hypoglycemia was higher than in study EFC12404. In comparing the insulin glargine arm with the IGlarLixi arm, the incidence of "documented symptomatic" hypoglycemia was similar between treatment arms (Table 15). While there were few "severe symptomatic" hypoglycemic events, it is notable that more occurred in the IGlarLixi arm as these events are likely the most clinically significant.

Table 15: Summary of hypoglycemia in study EFC12405

	Insulin glargine N=365	IGlarLixi N=365
Documented symptomatic		
• N (%)	155 (42.5)	146 (40)
• Events per pt-year	4.22	3.03
Severe symptomatic		
• N (%)	1 (0.3)	4 (1.1)
• Events per pt-year	< 0.01	0.02

Source: Adapted from Table 37 of the study report for Study EFC12405 from NDA 208673

Allergic reactions were also reviewed as the fixed combination drug product combines two peptide products, each carrying a risk for development of antibodies and hypersensitivity or allergic reactions. An adjudication committee (Allergic Reaction Assessment Committee [ARAC]) was used to evaluate potential allergic events. Potential events were reviewed and determined to either be an allergic event or not an allergic event. The committee also assigned the event to one of five categories: (1) urticaria (hives), (2) angioedema, (3) anaphylactic reaction, (4) anaphylactic shock, and (5) other allergic reaction. Events were also assessed for possible relationship to study drug. See Table 16 for a summary of adjudicated allergic events from the phase 2/3 studies.

Table 16: Summary of positively adjudicated allergic events from the phase 2/3 studies conducted to support NDA 208673

	Lixisenatide N (%)	Insulin glargine N (%)	IGlarLixi N (%)
ACT12374	N = 0	N = 162	N = 161
ARAC positively adjudicated allergic event	0	1 (0.6)	1 (0.6)
- Other allergic reaction[1]	0	1 (0.6)	1 (0.6)
EFC12404	N = 233	N = 467	N = 469
ARAC positively adjudicated allergic event	2 (0.9)	3 (0.6)	6 (1.3)
- Urticaria	1 (0.4)	1 (0.2)	3 (0.6)
- Angioedema	0	0	3 (0.6)
- Anaphlyactic reaction	1 (0.4)	0	0
- Other allergic reaction	0	3 (0.6)	0
EFC12405	N = 0	N = 365	N = 365
ARAC positively adjudicated allergic event	0	1 (0.3)	0
- Other allergic reaction	0	1 (0.3)	0

[1] Other allergic reactions includes events such as allergic conjunctivitis, allergic rhinitis
ARAC = Allergic Reaction Assessment Committee
Source: Adapted from Table 27 of the study report for study ACT12374, Table 45 of the study report for study EFC12404, and from Table 7 of Appendix 15.3.1 of the study report for study EFC12405 from NDA 208673

Overall, there was not a dramatic difference between treatment arms for allergic events. There were more events with the FCDP in EFC12404 than either lixisenatide or insulin glargine alone, however the ARAC only assessed 3 (0.6%) of the events (all 'urticaria') as 'possibly related' to study drug with IGlarLixi and 2 (0.9%) events (one 'urticaria', one 'anaphylactic reaction') as 'possibly related' to study drug with lixisenatide. None of the events occurring in the insulin glargine arm were assessed as 'possibly related'. The three cases of 'angioedema' stand out as a difference with the FCDP compared to the comparators, but none of these were assessed as 'possibly related' by the ARAC. I have reviewed these three cases, and agree that these are likely due to other causes. All three had a potential alternative etiology. Two of the cases continued study drug and one discontinued but reinitiated study drug without further event.

Antibodies were also assessed as part of the development program. Testing was done both for anti-lixisenatide antibodies and for anti-insulin antibodies.

There did not appear to be an impact of the development of anti-lixisenatide antibodies from combining lixisenatide and insulin glargine (Table 17). Subjects treated with lixisenatide had a baseline incidence of being positive for anti-lixisenatide antibodies of 5.1%. At week 30, the

incidence of being positive for anti-lixisenatide antibodies was 56.8%. Subjects treated with IGlarLixi had a baseline incidence of being positive for lixisenatide antibodes was 4% with a week 30 incidence of 42.8%.

Table 17: Incidence of positive anti-lixisenatide antibodies from pooled IGlarLixi subjects in studies EFC12404 and EFC12405 and lixisenatide subjects in study EFC12404

	IGlarLixi		Lixisenatide	
	n/N	%	n/N	%
Baseline	30/752	4	11/215	5.1
Week 30	321/750	42.8	113/199	56.8
Incidence of conversion from negative at baseline to positive	271/750	36.1	96/199	48.2

Source: Adapted from Table 42 of the Summary of Clinical Safety for NDA 208673

For subjects not previously treated with insulin, combining lixisenatide and insulin glargine appeared to increase the development of anti-insulin antibodies (Table 18). Subjects who had not previously been treated with insulin (i.e., those from study EFC12404) and randomized to IGlarLixi had a baseline incidence of being positive for anti-insulin antibodies of 0.5% with a week 30 incidence of 21%. Subjects who had not previously been treated with insulin and randomized to insulin glargine had a baseline incidence of being positive for anti-insulin antibodies of 0.2% and a week 30 incidence of 8.9%. In subjects previously treated with insulin (i.e., those from study EFC12405), combining lixisenatide and insulin glargine did not appear to appreciably increase the incidence of anti-insulin antibodies compared to subjects previously treated with insulin and randomized to insulin glargine (12.4% at baseline to 26.2% at week 30 for subjects randomized to IGlarLixi compared to 15% at baseline to 24.8% at week 30 for subjects randomized to insulin glargine).

Table 18: Incidence of positive anti-insulin antibodies from pooled IGlarLixi subjects and insulin glargine subjects

	IGlarLixi		Insulin glargine	
	n/N	%	n/N	%
EFC12404				
Baseline	2/436	0.5	1/451	0.2
Week 30	90/428	21	38/426	8.9
Incidence of conversion from negative at baseline to positive	81/428	18.9	38/426	8.9
EFC12405				
Baseline	42/339	12.4	51/339	15
Week 30	86/328	26.2	87/351	24.8
Incidence of conversion from negative at baseline to positive	50/328	15.2	40/351	11.4

Source: Adapted from Table 44 of the Summary of Clinical Safety for NDA 208673

The significance of anti-lixisenatide antibodies and/or anti-insulin antibodies is not known. As noted in Dr. Balakrishnan's review, there is a suggestion of a slight reduction in efficacy with the presence of anti-lixisenatide antibodies (see Table 47 of Dr. Balakrishnan's review, excerpted below) but I believe that the data are limited and inconclusive.

Table 47: Mean change from baseline for HbA1c at 30 weeks for FCDP treated subjects in a pool of the 2 phase 3 studies by antibody status and titer

	n/N	LS mean change	SE	95% CI
Ab negative	460/793	-1.57	0.044	-1.656, -1.485
Ab positive	333/793	-1.47	0.049	-1.562, -1.370
– < LLOQ	256/333	-1.55	0.059	-1.665, -1.434
– ≥ LLOQ to ≤ 100 nmol/L	71/333	-1.16	0.095	-1.342, -0.969
– > 100 nmol/L	6/333	--	--	--

Source: Adapted from Table 27 of the Summary of Clinical Efficacy for NDA 208673

From the clinical data, the safety profile of IGlarLixi falls somewhere in between that of lixisenatide and insulin glargine. While the incidence of adverse events consistent with GLP-1 receptor agonists is lower with IGlarLixi compared to lixisenatide, it should be noted that the dose of GLP-1 receptor agonist differed between these two treatment arms. Lixisenatide treated subjects were exposed to the full therapeutic dose of 20 mcg while IGlarLixi subjects generally received a dose of lixisenatide less than 20 mcg. The risk for hypoglycemia did not appear to be increased with the FCDP compared to the individual components, though the results of study EFC12405 suggest that there may be a slight increase in the risk for 'severe hypoglycemia'. Combining the two peptide products did not appear to result in an increase in the risk for hypersensitivity/allergic reactions.

Concerns for medication errors:

The Division of Medication Error Prevention and Analysis (DMEPA) was consulted to review the proposed proprietary name and to review the submitted human factors testing.

The initial proposed proprietary names were 'Soliqua (b) (4) and 'Soliqua (b) (4) In the review of the proprietary name, the DMEPA reviewer did not identify any risks for confusion from use of 'Soliqua'. However the modifiers were not found to be acceptable. The proposed modifiers were found to be unacceptable due to a potential for medication errors. This concern was based on misinterpretation of these modifiers by prescribers and patients in the human factors study.

The human factors study was designed to determine if users were able to perform simulated use tasks. Users were asked to prescribe, dispense, differentiate and comprehend storage. The study included 75 participants (15 prescribers, 15 pharmacists, 15 nurses treating and training patients with diabetes, and 30 patients with diabetes).

The results of the human factors study suggested that physicians were able to follow the prescribing information and prescribe the correct dose and device. In the dispensing task, 14 of 15 pharmacists were able to select the correct package. This was initially attributed to misunderstanding the task, but after clarification of the task the same pharmacist was unable to select the correct product. The root cause of this second error appeared to be due to the overlooking the propietary name modifier. All of the nurses and patients studied in the differentiation task were able to correctly identify the pen. All 15 of the nurses were able to prepare the assigned dose. Of the patients, 14 of 15 prepared the correct dose. The patient that

incorrectly performed the task misinterpreted the modifier as the dose. There were no issues with understanding storage instructions.

The DMEPA review has recommended that the applicant reconsider the proprietary name and modifiers such that they serve to distinguish between the two pens. Even with appropriate modifiers, there is an inherent risk of confusion with the two pens and a one pen presentation may be a better approach. The proposed use of 'units' also raised some concerns. Though the use of 'units' simplifies the expression of the dose, it may be misleading since it references only the insulin component and does not impart the presence of two active ingredients.

Following the May 25, 2016 Advisory Committee meeting the applicant submitted a general correspondence on June 6, 2016 with some proposals to address some of the device related concerns discussed (see "Advisory Committee Meeting" below). This included several proposals for dosage terms and addition of a table in the prescribing information showing the amount of each component with each 'unit'.

After additional internal discussion on the concerns raised by the proposed presentations, it was communicated to the applicant that the FDA believed a single pen presentation to be the most appropriate path forward for the product as it removes the potential for errors with a two pen presentation. A proposed single pen presentation was submitted on August 11, 2016. The new proposed proprietary name is SOLIQUA 100/33.

Discussion of Safety:

In terms of the clinical safety profile of the IGlarLixi FCDP, it is consistent with what would be expected based on what is known about the two active ingredients. The common adverse events suggest that the FCDP falls somewhere in between lixisenatide and insulin glargine, which is consistent with the presence of both drugs and a lower lixisenatide dose in the IGlarLixi arm. The available data suggest that there may be a small increase in the risk for severe hypoglycemia, but the overall incidence in the studies was low. There does not appear to be a potentiating effect of combining these two peptide products on the risk for allergic/hypersensitivity reactions.

The potential for errors as a result of the product presentation is a separate safety concern that warrants further discussion. Among the issues identified by the DMEPA review were issues with the proprietary name (specifically related to the proposed qualfiers used to differentiate the original proposed two pen presentation) and with the choice to market two pen injectors with different ratios of active ingredients. The proposal to market a single pen injector abrogates some the concerns raised in the DMEPA review.

One concern that to my mind has not been fully addressed is communicating that there are two components to this product. The FCDP contains two active ingredients, yet the expression of dose references only one of the components (i.e., use of 'units' references only the insulin glargine component). Given the similarity between the product presentation (i.e., pen injector) and the proposed term for expressing the dose (i.e., 'unit'), it is possible (and very likely) that patients and prescribers will perceive this product as another insulin product. While insulin is

a component, there are considerations in terms of the dosing for the FCDP which require recognition that the product contains more than just insulin. Some of these are:

1. Insulin dosing is on a continuous scale and the dose is only limited by hypoglycemia. In contrast, the IGlarLixi FCDP is limited to a dose of 60 'units' due to the lixisenatide component. Failure to comprehend that there are two components could lead to use of higher than approved doses of lixisenatide. Though the applicant has incorporated an mechanical stop preventing dialing of a dose above 60 'units', there is no way to prevent administration of additional injections.

2. Insulin glargine (though approved for once daily administration) can be, and is, prescribed for twice daily administration. Patients and prescribers that are unaware of the lixisenatide component could administer doses within the recommended dosage range per dose (e.g., 45 'units') but administer them two times in a day resulting in overdosage of the lixisenatide component (e.g., 15 mcg x 2 → 30 mcg).

3. Misinterpreting the product as an insulin only product may result in duplication of therapy. This is a concern particularly for duplication of the GLP-1 receptor agonist component. While different types of insulin (i.e., basal and prandial insulins) are combined to achieve glycemic control there is no situation where one would combine two different GLP-1 receptor agonists.

While this communication could be achieved with appropriate naming and labeling, it is not clear how effective these approaches would be. The potential for medication errors with this product was discussed at the May 25, 2016 Advisory Committee meeting, and concerns were voiced by committee members with respect to the choice to designate the dose in 'units' (see "Advisory Committee Meeting" below). Though the applicant has proposed a variety of terms for dosing, it is not clear that there is any data to support that one approach more clearly communicates the composition of the product better than another. Further, the DMEPA reviewers have raised concerns with respect to the introduction of a new dose term both in terms of confusion and ability to incorporate it into computerized physician order entry systems. Alternative approaches which have not been tested include designating the dose based on lixisenatide (i.e., in mcg). The FCDP could be dosed in 1 mcg intervals with the resulting insulin glargine dose increasing in 3 unit increments.

Alternative approaches to describing the term of measure were considered as part of the review of another FCDP that combines a once daily GLP-1 receptor agonist and a once daily basal insulin (see NDA 208583). The DMEPA reviewers considered the following approaches [3]:

- No terms of measure
- Introducing a novel term (e.g., (b) (4))
- Use of units/mg (or mcg) or mg (or mcg) alone
- Use of units

[3] See Dr. Ariane Conrad's Labeling Review in NDA 208583, submitted on September 28, 2016

Opting for no term of measure was not felt to be viable as there were concerns for miscommunication of dosing information and inability of electronic prescribing systems to support this approach as well as evidence of prescribers assigning a term in the absence of an assigned term. Introduction of a novel term (e.g., (b) (4)) raised concern for confusion as the term does not indicate the product contents and that this novel term would not be supported by electronic prescribing systems. Use of a combined unit (e.g., units/mg [or mcg]) or of mg (or mcg) alone was considered to be confusing for end users and would require redesign of the device/dial as well as additional human factors testing. While the use of units alone may be misleading, the DMEPA reviewers conclude that this approach would be the least problematic as it would not require additional testing, it is a term familiar to health care providers and patients, and it should be easy to integrate into electronic prescribing systems.

Safety Conclusions:

The available safety data for the IGlarLixi FCDP do not raise any significant safety concerns in terms of drug related adverse reactions. The safety profile is essentially what would be expected from combining the safety profile of lixisenatide with the safety profile of insulin glargine. Potential sources for medication errors were identified in the DMEPA review confusion with regard to dosing (due to the initially proposed modifier) and with selecting the correct pen. These are resolved following the applicant's updated proposal to market a single pen injector. The modifier is no longer needed for purposes of differentiating the two pen injectors. Further, it is not possible to select the wrong pen as there will be only one pen injector available.

A potential source of errors that to my mind has not been thoroughly evaluated is describing the dose in 'units'. This approach raises concerns that patients and prescribers may not recognize that there are two active ingredients to this drug product which in turn could lead to overdosage and duplication of therapy. Whether there is a better alternative to the use of 'units' has not been evaluated, however I acknowledge that the Human Factors testing indicated that this approach is serviceable. While my preference would be to have data from studies assessing whether alternative approaches would be better, there is not a regulatory basis to require this testing as the proposed approach has not been shown to be unsafe.

9. Advisory Committee Meeting

An Advisory Committee meeting was held on May 25, 2016 to discuss the IGlarLixi fixed combination drug product. At that meeting, the following discussion topics and voting question were posed to the committee:

1. **DISCUSSION:** Discuss any issues related to the efficacy or safety of lixisenatide for the treatment of patients with type 2 diabetes mellitus. Please comment on whether any of these issues preclude approval of lixisenatide.

2. **DISCUSSION:** Discuss the benefit(s) of starting the fixed-combination drug product containing lixisenatide and insulin glargine in patients with type 2 diabetes mellitus not treated with either a basal insulin or a GLP-1 agonist (i.e., starting two new drugs at once). In your discussion, identify the patient population in whom this use would be particularly

useful, and address why you would select the fixed-combination over use of an available GLP-1 agonist or basal insulin in these patients. Explain your rationale using data from the briefing materials, presentations, or your own clinical experience.

3. **DISCUSSION:** Discuss the benefit(s) of using the fixed-combination drug product containing lixisenatide and insulin glargine in patients with type 2 diabetes previously treated with either a basal insulin or a GLP-1 agonist (i.e., adding a single new drug to an existing regimen). In your answer, identify the patient population in whom use of the fixed-combination drug product in this manner would be particularly useful. Explain your rationale using data from the briefing materials, presentations, or your own clinical experience.

4. **DISCUSSION:** Discuss clinical concerns related to the use of the fixed-combination product which combines a drug that, when used alone, has a wide effective dose range and is titrated to effect on a continuous scale (i.e., insulin glargine) with a drug that, when used alone, has one or two recommended effective dose(s) (i.e., lixisenatide).

   Specifically discuss:
   a. Issues related to loss of dosing flexibility including but not limited to: Use of potentially ineffective doses of one agent in populations with low insulin requirements, inability to dose the two drugs independently with the device presentation proposed, inability to increase the insulin dose beyond 60 units.

   b. Issues related specifically to product presentation/devices including but not limited to: use errors that may occur in the care setting related to a lack of clarity on the amount of each product delivered with each given dose, insufficient understanding that, unlike insulin products, the maximum dose for the combination is capped, inadequate understanding of the role of the two devices.

5. **VOTE:** Based on data in the briefing materials and presentations at today's meeting do you recommend approval of the lixisenetide/glargine fixed-combination drug delivered using the proposed pen devices for the treatment of adult patients with type-2 diabetes mellitus?

   a. If you voted yes, explain your rationale and discuss whether use of the combination should be approved for patients not treated with a basal insulin or a GLP-1, for patients who are inadequately controlled on either a basal insulin or a GLP-1 analog or for both populations. Recommend additional post-approval studies if you think these are needed.

   b. If you voted no, explain your rationale and recommend additional pre-approval studies if you think these are needed.

Comments on the first discussion topic will not be covered in this review as it relates to the lixisenatide product alone.

For the second discussion topic (i.e., use of the FCDP in patients not already treated with insulin or a GLP-1 receptor agonist), there were concerns that this population may not reach doses high enough to benefit from both components. It was also expressed that there was uncertainty on how to identify the patient who would need both drugs, as patients may adequately respond to one product and not need the other (either ever or for several years). Additionally, concerns were raised that starting two drugs at once rather than starting one followed by adding the other at a later data may confound the assessment of side effects. Perceived benefits other than glycemic control of using the FCDP included attenuation of weight gain though not all committee members were convinced that the data was sufficient to conclude that there was a weight related benefit with using the FCDP. Other perceived benefits included less GLP-1 receptor agonist related side effects, possibly due to the lower dose of lixisenatide.

For the third discussion topic (i.e., use of the FCDP in patients already treated with a basal insulin or a GLP-1 receptor agonist), the committee viewed the population already treated with one of the components more favorably though it was noted that there was no data in patients with inadequate glycemic control while treated with a GLP-1 receptor agonist. Even for those patients already treated with insulin or a GLP-1 receptor agonist, there was concern raised that the product may not be adequate for some (e.g., those with significant insulin resistance, those with very high body mass index) due to the upper limit on the dose. Again, perceived benefits other than glycemic control were weight related though the ability to administer two drugs with one injection rather than two injections was also viewed as an advantage of this approach. While uncertainty of the efficacy in the lower dose range was noted, most committee members were not concerned as there was evidence of additional efficacy with the doses achieved in the studies.

For the fourth discussion topic (i.e., clinical concerns with product due to design or presentation), committee members acknowledged that there would be some loss of flexibility with the FCDP compared to the use of the individual components separated but whether the sacrifice in flexibility was acceptable should be left to patients and prescribers. With regard to the potential for medication errors, more concerns were voiced by committee members. The proposed presentation raised concerns for selection of the wrong pen and raised questions about whether the naming convention (i.e., insulin glargine first then lixisenatide second) was the best approach. Several committee members voiced concerns that the dose designation should not be strictly in ‘units’. Describing the dose in ‘units’ alone could result in people not recognizing that there are two drugs in the product, which could in turn lead to people not recognizing that the two different pen injectors are different or to duplicate therapies particularly when ordered by someone other than the original prescriber (i.e., re-prescribing during transitions in care). Committee members felt that it was important to clearly communicate that there are two drugs in the FCDP. The ability to dial doses below the approved range also raised concerns for some committee members.

On the voting question (i.e., do you recommend approval) the responses were:

Yes:	12
No:	2

No vote: 1

Committee members voting "yes" were generally supportive of the FCDP in concept commenting that the combination is reasonably safe and effective and that it may be a useful alternative therapy for some patients. In terms of population, the patients most appropriate for this therapy were felt to be those already treated with insulin. Members voiced that patients already treated with a GLP-1 receptor agonist may also be appropriate, but that there was no data to support this population. There were several concerns voiced in terms of the product presentation though the expectation was that the product presentation and labeling issues (e.g., two pens, designation of dose in 'units') could be resolved before approval.

Committee members voting "no" expressed similar sentiments to those voting "yes". In general, the fixed combination drug product appeared to be reasonably safe and effective, but issues with the product presentation and labeling needed to be adequately addressed prior to approval.

The "No vote" was due to a committee member leaving due to schedule issues prior to voting took place.

10. Pediatrics

There are no pediatric data with the IGlarLixi fixed combination drug product. The applicant has requested a full waiver of pediatric studies on the basis of feasibility. I agree that conduct of the appropriate studies to inform pediatric use in type 2 diabetes mellitus would not be feasible due to the size of the appropriate population.

11. Other Relevant Regulatory Issues

Not applicable.

12. Labeling

Labeling negotiations are ongoing at the time of completion of this review. I recommend the following edits to the proposed labeling:

1. The FCDP should be indicated for those patients requiring additional glycemic control despite treatment with basal insulin or lixisenatide.
2. Additional language is needed to clearly communicate that the FCDP contains insulin and a GLP-1 receptor agonist.
3. Only study EFC12405 should be presented in section 14. Presentation should be limited to HbA1c data and data relevant to glycemic control.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

I do not recommend a REMS for this product.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

I do not recommend any PMRs for this product. The applicant has committed to perform ongoing stability analysis to assess maintenance of the essential performance requirements of the final finished combination product through the intended (b) (4) month expiration date. The CDRH reviewer has requested that evidence of completion of these activities be submitted to the NDA in the annual reports. I agree with the request.

14. Recommended Comments to the Applicant

None.

15. Appendix

Table 19: Adverse events reported with an incidence of ≥ 3% by high level term in any treatment arm for the pool of phase 2/3 studies

High level term ▪ Preferred term	Lixisenatide N=234		Insulin glargine N=998		IGlarLixi N=997	
	N	%	N	%	N	%
Asthenic conditions	8	(3.4)	13	(1.3)	21	(2.1)
▪ Fatigue	5	(2.1)	7	(0.7)	12	(1.2)
▪ Asthenia	2	(0.9)	5	(0.5)	9	(0.9)
▪ Lethargy	1	(0.4)	1	(0.1)	0	0
Cardiac signs and symptoms NEC	8	(3.4)	18	(1.8)	30	(3.0)
▪ Dizziness	7	(3.0)	13	(1.3)	27	(2.7)
▪ Palpitations	1	(0.4)	1	(0.1)	2	(0.2)
▪ Syncope	0	0	2	(0.2)	2	(0.2)
▪ Presyncope	0	0	2	(0.2)	0	0
Circulatory collapse and shock	7	(3.0)	17	(1.7)	29	(2.9)
▪ Dizziness	7	(3.0)	13	(1.3)	27	(2.7)
▪ Syncope	0	0	2	(0.2)	2	(0.2)
▪ Presyncope	0	0	2	(0.2)	0	0
Diarrhoea (excl infective)	21	(9.0)	36	(3.6)	63	(6.3)
▪ Diarrhoea	21	(9.0)	36	(3.6)	63	(6.3)
Gastric and gastroenteric infections	8	(3.4)	11	(1.1)	26	(2.6)
▪ Gastroenteritis	5	(2.1)	7	(0.7)	15	(1.5)
▪ Gastroenteritis viral	3	(1.3)	5	(0.5)	11	(1.1)
Headaches NEC	18	(7.7)	37	(3.7)	54	(5.4)
▪ Headache	18	(7.7)	37	(3.7)	53	(5.3)
▪ Post-traumatic headache	0	0	0	0	1	(0.1)
▪ Sinus headache	0	0	2	(0.2)	0	0
▪ Tension headache	0	0	1	(0.1)	0	0
Influenza viral infections	4	(1.7)	28	(2.8)	35	(3.5)
▪ Influenza	4	(1.7)	28	(2.8)	35	(3.5)
Injection site reactions	7	(3.0)	11	(1.1)	17	(1.7)
▪ Injection site pain	3	(1.3)	3	(0.3)	3	(0.3)
▪ Injection site reaction	2	(0.9)	2	(0.2)	2	(0.2)
▪ Injection site erythema	2	(0.9)	0	0	0	0
▪ Injection site bruising	0	0	4	(0.4)	4	(0.4)
▪ Injection site pruritus	0	0	0	0	2	(0.2)
▪ Injection site rash	0	0	0	0	2	(0.2)
▪ Injection site discomfort	0	0	0	0	1	(0.1)
▪ Injection site irritation	0	0	0	0	1	(0.1)
▪ Injection site nodule	0	0	0	0	1	(0.1)
▪ Injection site papule	0	0	0	0	1	(0.1)
▪ Injection site urticaria	0	0	0	0	1	(0.1)
▪ Injection site haemorrhage	0	0	2	(0.2)	0	0
▪ Injection site hypertrophy	0	0	1	(0.1)	0	0
▪ Injection site swelling	0	0	1	(0.1)	0	0
▪ Injection site warmth	0	0	1	(0.1)	0	0
Lower respiratory tract and lung infections	7	(3.0)	26	(2.6)	26	(2.6)
▪ Bronchitis	5	(2.1)	21	(2.1)	20	(2.0)
▪ Pneumonia	1	(0.4)	3	(0.3)	4	(0.4)
▪ Lower respiratory tract infection	1	(0.4)	1	(0.1)	3	(0.3)
▪ Bronchopneumonia	0	0	1	(0.1)	0	0

High level term ▪ Preferred term	Lixisenatide N=234		Insulin glargine N=998		IGlarLixi N=997	
	N	%	N	%	N	%
Lower respiratory tract infections NEC	7	(3.0)	26	(2.6)	26	(2.6)
▪ Bronchitis	5	(2.1)	21	(2.1)	20	(2.0)
▪ Pneumonia	1	(0.4)	3	(0.3)	4	(0.4)
▪ Lower respiratory tract infection	1	(0.4)	1	(0.1)	3	(0.3)
▪ Bronchopneumonia	0	0	1	(0.1)	0	0
Musculoskeletal and connective tissue pain and discomfort	19	(8.1)	36	(3.6)	49	(4.9)
▪ Back pain	8	(3.4)	17	(1.7)	28	(2.8)
▪ Pain in extremity	5	(2.1)	10	(1.0)	18	(1.8)
▪ Musculoskeletal pain	2	(0.9)	7	(0.7)	4	(0.4)
▪ Musculoskeletal discomfort	2	(0.9)	1	(0.1)	1	(0.1)
▪ Neck pain	1	(0.4)	4	(0.4)	3	(0.3)
▪ Flank pain	1	(0.4)	2	(0.2)	0	0
▪ Musculoskeletal chest pain	1	(0.4)	0	0	0	0
▪ Post-traumatic neck syndrome	0	0	2	(0.2)	0	0
Nausea and vomiting symptoms	61	(26.1)	26	(2.6)	106	(10.6)
▪ Nausea	56	(23.9)	19	(1.9)	95	(9.5)
▪ Vomiting	15	(6.4)	10	(1.0)	33	(3.3)
Neurological signs and symptoms NEC	7	(3.0)	15	(1.5)	27	(2.7)
▪ Dizziness	7	(3.0)	13	(1.3)	27	(2.7)
▪ Head discomfort	0	0	0	0	1	(0.1)
▪ Presyncope	0	0	2	(0.2)	0	0
Upper respiratory tract infections	34	(14.5)	150	(15.0)	142	(14.2)
▪ Nasopharyngitis	16	(6.8)	67	(6.7)	67	(6.7)
▪ Upper respiratory tract infection	12	(5.1)	40	(4.0)	49	(4.9)
▪ Pharyngitis	2	(0.9)	13	(1.3)	10	(1.0)
▪ Rhinitis	1	(0.4)	8	(0.8)	10	(1.0)
▪ Sinusitis	1	(0.4)	13	(1.3)	5	(0.5)
▪ Tonsillitis	1	(0.4)	0	0	3	(0.3)
▪ Tracheitis	1	(0.4)	3	(0.3)	0	0
▪ Pharyngotonsillitis	0	0	0	0	4	(0.4)
▪ Acute sinusitis	0	0	2	(0.2)	3	(0.3)
▪ Acute tonsillitis	0	0	5	(0.5)	1	(0.1)
▪ Laryngitis	0	0	3	(0.3)	0	0
▪ Sinobronchitis	0	0	1	(0.1)	0	0
▪ Tracheobronchitis	0	0	2	(0.2)	0	0
Upper respiratory tract infections NEC	34	(14.5)	151	(15.1)	142	(14.2)
▪ Nasopharyngitis	16	(6.8)	67	(6.7)	67	(6.7)
▪ Upper respiratory tract infection	12	(5.1)	40	(4.0)	49	(4.9)
▪ Pharyngitis	2	(0.9)	13	(1.3)	10	(1.0)
▪ Rhinitis	1	(0.4)	8	(0.8)	10	(1.0)
▪ Sinusitis	1	(0.4)	13	(1.3)	5	(0.5)
▪ Tonsillitis	1	(0.4)	0	0	3	(0.3)
▪ Tracheitis	1	(0.4)	3	(0.3)	0	0
▪ Pharyngotonsillitis	0	0	0	0	4	(0.4)
▪ Acute sinusitis	0	0	2	(0.2)	3	(0.3)
▪ Acute tonsillitis	0	0	5	(0.5)	1	(0.1)
▪ Laryngitis	0	0	3	(0.3)	0	0
▪ Oropharyngitis fungal	0	0	1	(0.1)	0	0
▪ Sinobronchitis	0	0	1	(0.1)	0	0
▪ Tracheobronchitis	0	0	2	(0.2)	0	0
Viral infections NEC	7	(3.0)	26	(2.6)	30	(3.0)
▪ Gastroenteritis viral	3	(1.3)	5	(0.5)	11	(1.1)

High level term ▪ Preferred term	Lixisenatide N=234		Insulin glargine N=998		IGlarLixi N=997	
	N	%	N	%	N	%
▪ Respiratory tract infection viral	3	(1.3)	11	(1.1)	10	(1.0)
▪ Gastrointestinal viral infection	1	(0.4)	1	(0.1)	0	0
▪ Viral infection	0	0	4	(0.4)	6	(0.6)
▪ Viral upper respiratory tract infection	0	0	5	(0.5)	4	(0.4)
▪ Viral sinusitis	0	0	0	0	1	(0.1)
▪ Viral rhinitis	0	0	1	(0.1)	0	0
Viral upper respiratory tract infections	4	(1.7)	33	(3.3)	39	(3.9)
▪ Influenza	4	(1.7)	28	(2.8)	35	(3.5)
▪ Viral upper respiratory tract infection	0	0	5	(0.5)	4	(0.4)
▪ Viral sinusitis	0	0	0	0	1	(0.1)
▪ Viral rhinitis	0	0	1	(0.1)	0	0

NEC = not elsewhere classified
Source: Based on review of ADAE.xpt from module 5.3.5.3 ISS of NDA 208673

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
11/21/2016