CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208673Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 208673
Drug Name:	Fixed-Ratio Combination of Insulin Glargine with Lixisenatide
Indication(s):	Treatment of Patients with Type 2 Diabetes Mellitus
Applicant:	Sanofi
Date(s):	Date submitted: December 21, 2015 Review due date: July 24, 2016 PDUFA due date: August 21, 2016
Review Priority:	Priority
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Keywords: NDA review, Clinical studies

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1. Executive Summary

1.1 Conclusion and recommendations

Sanofi proposes the fixed ratio combination (FRC) of insulin glargine (100 U/mL) and lixisenatide for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) when treatment with both insulin glargine and lixisenatide is appropriate. Lixisenatide is a new molecular entity Glucagon-like peptide-1 (GLP-1) receptor agonist. Insulin glargine (Lantus) has been approved in the US and Europe since 2000. Based on the results in change in HbA1c from baseline, the sponsor claims the FRC is effective in improving glycemic control in adults with T2DM. My review of the statistical evidence suggests support for the claim.

An advisory committee meeting was held on May 25, 2016 for this application. The voting question was: Based on data in the briefing materials and presentations at today's meeting do you recommend approval of the lixisenatide/glargine fixed-combination drug delivered using the proposed pen devices for the treatment of adult patients with type-2 diabetes mellitus?

The vote was 12 Yes and 2 No.

1.2 Brief overview of clinical studies

This review focuses on two Phase 3 studies. Both were randomized, 30-week, active-controlled, open-label, parallel-group, multinational studies that enrolled patients with T2DM diagnosed for at least 1 year at the time of screening. The primary efficacy endpoint in both studies was change in HbA1c from baseline to Week 30.

Study EFC12404 was a 3-arm study comparing the FRC to insulin glargine and lixisenatide respectively in insulin naïve patients uncontrolled on metformin ± a second OAD. Study EFC12405 was a 2-arm study comparing the FRC to insulin glargine in patients uncontrolled on basal insulin ± OADs. The daily dose of FRC and of insulin glargine as stand-alone treatment was titrated once weekly to a fasting SMPG target. The dose of lixisenatide in the lixisenatide alone arm was 20 µg.

1.3 Statistical issues and findings

The primary analysis results were summarized in **Table 1**. The FRC demonstrated superiority to both insulin glargine and lixisenatide in terms of change in HbA1c from baseline to Week 30 in the sponsor's Phase 3 studies.

Table 1 Mean change in HbA1c (%) from baseline to Week 30 in Phase 3 studies[1]

Study	Treatment Arms	Number of Subjects Analyzed	Mean Baseline HbA1c	LS Mean Change from Baseline	LS Mean Treatment Difference of FRC vs. (95% CI)	P-value
Add-on to Met alone **EFC12404**	FRC	467	8.08	-1.63		
	Insulin Glargine	464	8.08	-1.34	-0.29 [-0.38, -0.19]	<0.0001
	Lixisenatide	233	8.13	-0.85	-0.78 [-0.90, -0.67]	<0.0001
With or without Met **EFC12405**	FRC	364	8.07	-1.13		
	Insulin Glargine	364	8.08	-0.62	-0.52 [-0.63, -0.40]	<0.0001

[1] Using mixed effect model with repeated measures (MMRM) with all available post-baseline observations up to the main treatment period

Statistical issues from the review of the FRC application include:

- **Difficulty in interpreting sponsor's exploratory analysis by final dose**: Final insulin dose is a post-randomization variable and is affected by assigned treatment. Differences between the FRC and insulin glargine alone groups within each final insulin dose category no longer represent treatment effect. Therefore, the differences cannot be used to make inference about the contribution of lixisenatide in the FRC. The contribution of low doses of lixisenatide to the effect of the FRC on HbA1c change is not clear. More details can be found in Section 3.2.3.

- **External validity of the results to the practice of the treatment of T2DM:** In both Phase 3 studies, insulin glargine was capped at 60 U in the insulin glargine alone arm to match the maximum insulin glargine dose in the FRC arm. This cap, together with the limitations of the insulin titration algorithm, raised concerns that the treatment difference observed in the Phase 3 studies may not reflect actual treatment difference in practice.

- **Missing data not impactful**: In each study, the percent of patients with missing data for the primary endpoint was quite low, around 5%, and was similar between treatment groups. The results from the sensitivity analysis were very close to those from the primary analysis. In order to tip the statistical significance of the results, unrealistic assumptions about the missing data need to be made. Therefore, missing data did not appear to have much impact in this application. More details can be found in Sections 3.2.1 and 3.2.2.

- The open-label design in the Phase 3 studies was not an optimal study design, as bias can be introduced.

- The efficacy analysis population in this application was all randomized patients who had both a baseline assessment and at least 1 postbaseline assessment of any primary or secondary efficacy endpoints, irrespective of compliance with study protocol and

procedures. As having a post-baseline measurement is post-randomization and may be related to treatment, the analysis population should include all randomized patients with a baseline assessment. Considering the small amount of missing in this application, this issue was not impactful.

2. Introduction

2.1 Overview

2.1.1 Class and Indication

The FRC of insulin glargine (100 U/mL) with lixisenatide is intended for use as an adjunct to diet and exercise to improve glycemic control in the treatment of adults with T2DM when treatment with both insulin glargine and lixisenatide is appropriate. Insulin glargine is intended to provide fasting glycemic control. Lixisenatide, a GLP-1 receptor agonist, is intended to provide complementary prandial glycemic control.

The combination has been formulated as 2 different fixed-ratios that can be delivered once-daily in a fixed ratio pen-injector. A dose range of 10 to 60 U of insulin glargine and 5 to 20 µg lixisenatide can be delivered according to each patient's individual needs. It should be administered subcutaneously once a day within the hour prior to the first meal of the day (b) (4)

2.1.2 History of drug development

Both insulin glargine and lixisenatide were developed by Sanofi. Insulin glargine (Lantus) was approved in the US (NDA021081) and Europe in 2000 and has been marketed worldwide. NDA204961 for lixisenatide was submitted in December 2012 and was subsequently withdrawn in September 2013 pending results from the cardiovascular outcome trial (CVOT) ELIXA. That study has been completed and a new NDA for lixisenatide (NDA208471) was submitted on 27 July 2015 and is currently under review. Effect of lixisenatide was studied for 20 µg maintenance dose in the Phase 3 lixisenatide clinical program.

The insulin glargine/lixisenatide FRC IND105157 was initiated in April 2009. Statistical comments on Phase 3 protocols were conveyed to the sponsor on 7 February 2014 and 12 June 2014:

- The agency stated that a non-inferiority comparison is not appropriate for an efficacy claim when the experimental arm consists of a drug/biology added to the control therapy. In such cases, a superiority comparison is required.
- The agency recommended that the primary analysis uses all available HbA1c measurements irrespective of whether discontinued randomized therapy or used rescue

medication, and that the primary analysis represents the subjects with missing data based on adherence to therapy.

A pre-NDA meeting was held on 28 September 2015. The clinical team raised concerns that "it is unclear whether the available data supports that there is a contribution of each component to the observed effect over the proposed range of the proposed drug product". The sponsor proposed to perform benefit-risk evaluations of the Phase 3 efficacy results according to final insulin and lixisenatide dose levels.

2.1.3 Specific studies reviewed

This review focuses on the 2 Phase 3 efficacy studies. Both studies were randomized, 30-week, active-controlled, open-label, parallel-group, multinational studies that enrolled patients with T2DM diagnosed for at least 1 year at the time of screening. Study EFC12404 enrolled insulin naïve patients, whereas Study EFC12405 enrolled patients uncontrolled on basal insulin. Table 2 summarized trial specification for these studies.

Table 2 Trial Specification for Phase 3 Efficacy Trials

Study[1]	**Antidiabetic Treatment at Screening**	**HbA1c (%) at Screening**	**Treatment Arms**	**# of Subjects Randomized**
Add-on to Met alone **EFC12404**	Met ± a 2nd OAD	≥7 to ≤9 if on 2nd OADs and ≥7.5 to ≤10 if on Met alone	FRC Insulin Glargine Lixisenatide	469 467 234
With or without Met **EFC12405**	Basal insulin ± 1 to 2 OADs	≥7.5 to ≤10	FRC Insulin Glargine	366 365

[1]Met = Metformin.

2.2 Data sources

The sponsor submitted this NDA including the study data to the FDA CDER Electronic Document Room (EDR) with the link \\CDSESUB1\EVSPROD\NDA208673\208673.enx. The information needed for this review was contained in Module 1 FDA Regional Information (cover letter, meeting correspondence, and labeling), Module 2.5 Clinical Overview, Module 2.7 Clinical Summary, and Module 5 Clinical Study Report.

3. Statistical evaluation

3.1 Data and analysis quality

This submission is in electronic common technical document (eCTD) format with xml backbone. The sponsor submitted the datasets and annotated SAS code for all the primary and supportive analyses. Study datasets are provided as SAS XPORT transport files version 5. All required documents that are necessary for statistical review are submitted.

This review covers datasets from 2 Phase 3 efficacy studies, including adsl.xpt, adeff.xpt, ades.xpt. For the individual trials, both tabulation and analysis datasets are provided. The tabulation and analysis datasets are joinable by the unique record identifier (USUBJID). No pooled dataset for efficacy was used for this application.

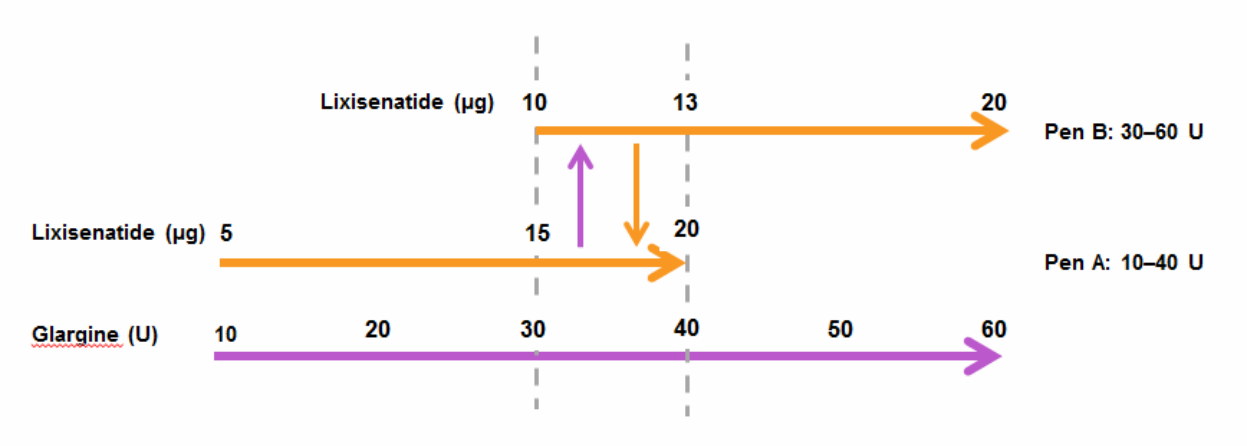
The datasets are in good organization. Variables in study datasets are consistently named and used across trials, with clear description in the Define.pdf file. The reported analysis results are in good quality. I was able to reproduce the sponsor's results for the primary and all key secondary endpoints.

3.2 Evaluation of efficacy

Both studies EFC12404 and EFC12405 were randomized, 30-week, active-controlled, open-label, parallel-group, multinational Phase 3 studies that enrolled patients with T2DM diagnosed for at least 1 year at the time of screening. According to the sponsor, these studies were open-label because of the differences in the type and number of pens used to administered the FRC, insulin glargine, and lixisenatide. The populations assessed were those either insulin naïve patients uncontrolled on metformin ± a second OAD (Study EFC12404) or patients uncontrolled on basal insulin ± OADs (Study EFC12405). Patients currently using basal plus prandial insulin were excluded from the trials.

In order to cover the range of 10 to 60 U of insulin glargine while maintaining the maximum lixisenatide dose to 20 µg, two pens with two different fixed ratios and dose-ranges were used in the Phase 3 studies as shown in Figure 1. The daily maintenance dose of lixisenatide, per the globally approved label and proposed in the US, is 20 µg. The sponsor selected 5 µg as the lower end of lixisenatide based on the Phase 2 dose-ranging Study DRI6012 in NDA208471. The daily dose of FRC and of insulin glargine as stand-alone treatment was titrated once weekly to a fasting SMPG target. During titration, the choice of a pen for FRC was based on the patient's current insulin glargine requirement.

Figure 1 Fixed ratio recombination of lixisenatide and insulin glargine in two pens of different ratios and ranges



Source: Sponsor's Summary of Clinical Efficacy Figure 2

The primary efficacy endpoint in the Phase 3 studies was change in HbA1c from baseline to Week 30.

Key secondary efficacy endpoints include 2h-glucose excursion, body weight, fasting plasma glucose (FPG), 7-point average SMPG and % of patients reaching HbA1c <7% with no body weight gain.

Efficacy analysis sets were defined by the sponsor as the following:

- Randomized: The randomized population consisted of all patients who had signed informed consent, with a randomized open-label treatment kit allocated and recorded in the IVRS/IWRS database, regardless of whether the treatment kit was used or not.
- Modified intent-to-treat (mITT): All randomized patients who had both a baseline assessment and at least 1 postbaseline assessment of any primary or secondary efficacy endpoints, irrespective of compliance with the study protocol and procedures.
- Completers: A patient is defined as a study completer if the patient completes the treatment per eCRF, or Visit 20 is performed on Day 195 (relative to the date of randomization) or later.

All efficacy analyses were based on the mITT analysis set. **The primary analysis** is a mixed-effect model with repeated measures (MMRM) analysis using all postbaseline observations regardless of treatment discontinuation or initiation of rescue therapy.

MMRM assumes missing data are missing at random (MAR). To examine the impact of missing data, the sponsor conducted a **sensitivity analysis** for the primary endpoint. Missing HbA1c values at Week 30 were imputed using multiple imputation for patients who permanently discontinued the study using data from patients in the same treatment group and the same randomization strata who permanently discontinued the study treatment but had Week 30 measurements (retrieved dropouts). Patients who completed study treatment but had no Week 30 measurements were assumed to be MAR. Their missing values were imputed using multiple imputation based on MCMC method. The completed data were analyzed using an ANCOVA model. For Study EFC12405, the sponsor stated the number of retrieved dropouts was not sufficient to build a reliable imputation model.

Lixisenatide in the FRC ranges from 5 to 20 µg. FDA raised concern about the contribution of each component, in particular low doses of lixisenatide, to the effect of the FRC. To address this concern, the sponsor evaluated key efficacy endpoints by final insulin and lixisenatide dose category subgroups to support the use of the product across the entirety of the dose range of the FRC.

3.2.1 Study EFC12404

3.2.1.1 Study Design and Endpoints

Study EFC12404 is a 30-week, open-label, active-controlled, 2: 2: 1 randomized, 3-arm parallel group, multi-national, multi-center Phase 3 study. The patient population was T2DM patients who were insulin-naïve and not adequately controlled on metformin ± a second OAD.

In the lixisenatide arm, lixisenatide had an initiation dose of 10 µg and was escalated to and maintained at 20 µg. In the FRC and insulin glargine arms, doses were adjusted according to individual patients' need. In the insulin glargine alone arm, insulin glargine was capped at 60 U to match the maximum insulin glargine dose in the FRC. HbA1c measurement was made at baseline, 8, 12, 24 and 30 weeks.

The primary objectives were to demonstrate the superiority of the FRC to lixisenatide in HbA1c change from baseline to Week 30, and to demonstrate the noninferiority of the FRC to insulin glargine in HbA1c change from baseline to Week 30. Superiority of the FRC compared to insulin glargine on HbA1c change from baseline to Week 30 was a pre-specified secondary endpoint in the testing hierarchy.

The primary analysis was an MMRM analysis with treatment groups (FRC, insulin glargine alone, lixisenatide alone), randomization strata of HbA1c (<8.0%, ≥ 8.0%) at Visit 4 (Week -1), randomization strata of second OAD use at screening (Yes, No), visit (Week 8, 12, 24, and 30), treatment-by-visit interaction, and country as fixed effects, and baseline HbA1c value-by-visit interaction as a covariate. The analyses for continuous key secondary endpoints used MMRM

similar to the primary analysis. The analyses for categorical key secondary endpoints used Cochran Mantel Haenszel (CMH) test adjusting for randomization strata.

The sample size was based on the primary efficacy endpoint, with the following assumptions:

- A common standard deviation (SD) of 1.1%
- A true difference between FRC and insulin glargine alone of 0 and a noninferiority margin of 0.3%
- A 0.4% mean difference between FRC and lixisenatide alone in change from baseline in HbA1c

A sample size of 1125 patients (FRC: 450; insulin glargine: 450; lixisenatide: 225) ensured at least 95% power for a 1-sided t-test with 2.5% significance level.

3.2.1.2 Patient disposition, demographic and baseline characteristics (EFC12404)

A description of the patient disposition is shown in Table 3. The lixisenatide group showed more discontinued treatment due to adverse events compared to the other two treatment groups. The actual percent of patients missing the HbA1c measurement at Week 30 was around 5% in each treatment group.

Table 3 Summary of patient dispositions in Study EFC12404

	FRC	**Insulin Glulisine**	**Lixisenatide**
Randomized, n	469	467	234
Randomized and Treated, n(%)	469 (100%)	467 (100%)	233 (99.6%)
mITT, n(%)	468 (99.8%)	466 (99.8%)	233 (99.6%)
Completed 30-Week Treatment, n(%)	440 (93.8%)	440 (94.2%)	205 (87.6%)
Discontinued Treatment, n(%)	29 (6.2%)	27 (5.8%)	28 (12.0%)
Adverse event	12 (2.6%)	9 (1.9%)	21 (9.0%)
Lack of efficacy	1 (0.2%)	0	3 (1.3%)
Poor compliance to protocol	8 (1.7%)	9 (1.9%)	4 (1.7%)
Others	8 (1.7%)	9 (1.9%)	0
Had HbA1c measurement at Week 30, n(%)	444 (94.7%)	446 (95.5%)	222 (94.9%)
Missed HbA1c measurement at Week 30, n(%)	25 (5.3%)	21 (4.5%)	12 (5.1%)

A description of the patient demographics is shown in Table 4. The overall population was balanced by sex and was predominantly white.

Table 4 Summary of patient demographic information in Study EFC12404

	FRC	Insulin Glulisine	Lixisenatide
Sex, n(%) males	222 (47.3%)	237 (50.7%)	133 (56.8%)
Age, years			
Mean (SD)	58.2 (9.5)	58.3 (9.4)	58.7 (8.7)
Range	18 : 79	25 : 82	31 : 80
n %) ≥65	133 (28.4%)	114 (24.4%)	59 (25.2%)
Race, n (%)			
White	417 (88.9%)	421 (90.1%)	216 (92.3%)
Black	33 (7.0%)	33 (7.1%)	12 (5.1%)
Asian/Oriental	8 (1.7%)	7 (1.5%)	3 (1.3%)
Other	11 (2.3%)	6 (1.3%)	3 (1.3%)
Ethnicity, n(%) Hispanic	85 (18.1%)	87 (18.6%)	51 (21.8%)
Country, n(%) US	133 (28.4%)	150 (32.1%)	79 (33.8%)
HbA1c at Week-1, n(%) <8%	207 (44.1%)	207 (44.3%)	103 (44.0%)
Baseline BMI, n(%) <30 kg/m^2	174 (37.1%)	179 (38.3%)	75 (32.1%)
Screening creatinine clearance (mL/min), n(%)			
30 to <60	4 (0.9%)	3 (0.7%)	3 (1.3%)
60 to <90	117 (25.2%)	128 (27.6%)	44 (19.0%)
≥ 90	344 (74.0%)	333 (71.8%)	185 (79.7%)

Source: Sponsor's Clinical Study Report for Study EFC12404 Table 11

3.2.1.3 Results and Conclusions (EFC12404)

I verified the sponsor's primary and key secondary analyses and the results were shown in Table 5. These results are supportive to the superiority of FRC to both insulin glulisine and lixisenatide in terms of change in HbA1c from baseline to Week 30 (p-value < .0001 for both comparisons). Although the primary objective was to demonstrate the superiority of the FRC to lixisenatide and the non-inferiority of the FRC to insulin glargine, superiority of the FRC to insulin glargine was also demonstrated based on the pre-specified testing hierarchy. The following secondary endpoints were also confirmed based on the pre-specified testing hierarchy:

- Superiority of FRC to insulin glargine in terms of 2h-glucose excursion (p-value < .0001)
- Superiority of FRC to insulin glargine in terms of body weight (p-value < .0001)
- Superiority of FRC to lixisenatide in terms of FPG (p-value < .0001)
- Superiority of FRC to both lixisenatide (p-value < .0001) and insulin glargine (p-value < .0001) in terms of 7-point average SMPG
- Superiority of FRC to insulin glargine in terms of % of patients reaching HbA1c < 7% with no body weight gain (p-value < .0001)

The results from the sponsor's sensitivity analysis using multiple imputations for missing values were shown in Table 6. Because of the small percentage of missing data (~5%), results from the sensitivity analysis were similar to those from the primary analysis.

Table 5 Primary and key secondary endpoints at Week 30 for FRC, insulin gargline and lixisenatide - Study EFC12404

Endpoint	**FRC**	**Insulin Glargine**	**Lixisenatide**
HbA1c %	N=467	N=464	N=233
Mean baseline LS mean change from baseline (SE) LS mean difference of FRC vs. [95% CI] p-value	8.08 -1.63 (0.04)	8.08 -1.34 (0.04) -0.29 [-0.38, -0.19] <.0001	8.13 -0.85 (0.05) -0.78 [-0.90, -0.66] <.0001
2h Glucose Excursion (mmol/L)[1]	N=428	N=425	N=192
Mean baseline LS mean change from baseline (SE) LS mean difference of FRC vs. [95% CI] p-value	5.31 -2.31 (0.15)	5.02 -0.18 (0.16) -2.13 [-2.50, -1.77] <.0001	5.07 -3.23 (0.22) 0.91 [0.45, 1.38]
Body Weight (kg)	N=467	N=465	N=233
Mean baseline LS mean change from baseline (SE) LS mean difference of FRC vs. [95% CI] p-value	89.44 -0.29 (0.18)	89.75 1.11 (0.18) -1.40 [-1.89, -0.91] <.0001	90.79 -2.30 (0.26) 2.01 [1.40, 2.61]
FPG (mmol/L)	N=465	N=465	N=232
Mean baseline LS mean change from baseline (SE) LS mean difference of FRC vs. [95% CI] p-value	9.88 -3.46 (0.09)	9.75 -3.27 (0.09) -0.19 [-0.42, 0.04] 0.102	9.79 -1.50 (0.12) -1.96 [-2.25, -1.68] <.0001
7-Point Average SMPG (mmol/L)	N=421	N=411	N=204
Mean baseline LS mean change from baseline (SE) LS mean difference of FRC vs. [95% CI] p-value	10.47 -3.35 (0.08)	10.31 -2.66 (0.08) -0.69 [-0.89, -0.50] <.0001	10.41 -1.95 (0.11) -1.40 [-1.64, -1.16] <.0001
% of Patients Reaching HbA1c < 7% with No Body Weight Gain[2]	N=469	N=466	N=233
Number of responders, n(%) p-value for comparison of FRC vs.	202 (43.2%)	117 (25.1%) <.0001	65 (27.9%)

Source: Sponsor's Clinical Study Report for Study EFC12404 Tables 15, 19, 21, 22, 23, 24

[1] ANCOVA with LOCF

[2] CMH test adjusting for randomization strata

Table 6 Sensitivity analysis: change in HbA1c (%) from baseline to Week 30 using ANCOVA[1] with multiple imputation for missing values at Week 30 - Study EFC12404

	FRC (N=468)	**Insulin Glargine** (N=466)	**Lixisenatide** (N=233)
Mean baseline	8.08	8.08	8.13
LS mean change from baseline (SE)	-1.65 (0.04)	-1.34 (0.04)	-0.88 (0.06)
LS mean difference of FRC vs. [95% CI]		-0.31 [-0.41, -0.21]	-0.78 [-0.90, -0.65]
p-value		<.0001	<.0001

Source: Sponsor's Table 16.2.6.1.6 in Appendix 16.2.6 Efficacy response data Study EFC12404

[1] ANCOVA model includes treatment groups, randomization strata, and country as fixed effects and baseline HbA1c value as a covariate

3.2.2 Study EFC12405

3.2.2.1 Study Design and Endpoints

Study EFC12405 is a 30-week, open-label, 1: 1 randomized, active-controlled, 2-arm parallel group, multi-national, multi-center study. The patient population was T2DM patients who were not adequately controlled on basal insulin with or without 1 to 2 OADs.

In both arms, doses were adjusted according to individual patients' need. In the insulin glargine alone arm, insulin glargine was capped at 60 U to match the maximum insulin glargine dose in the FRC. HbA1c measurement was made at baseline, 8, 12, 24 and 30 weeks.

The primary objective was to demonstrate the superiority of the FRC to insulin glargine in HbA1c change from baseline to Week 30.

The primary analysis was MMRM with treatment groups (FRC and insulin glargine), randomization strata of HbA1c (<8.0%, ≥ 8.0%) at Visit 5 (Week -1), randomization strata of metformin use at screening (Yes, No), visit (Week 8, 12, 24, and 30), treatment-by-visit interaction, and country as fixed effects, and baseline HbA1c value-by-visit interaction as covariates. The analyses for continuous key secondary endpoints used MMRM similar to the primary analysis. The analyses for categorical key secondary endpoints used CMH test adjusting for randomization strata.

The sample size was based on the primary efficacy endpoint, with the following assumptions:

- A common standard deviation (SD) of 1.1%
- A 0.4% mean difference between the FRC and insulin glargine in change in HbA1c from baseline to Week 30

A sample size of 350 per group ensured at least 95% power for a 2-sided t-test with 5% significance level.

3.2.2.2 Patient disposition, demographic and baseline characteristics (EFC12405)

A description of the patient disposition in the review is shown in Table 7. The FRC group showed more discontinued treatment due to adverse event compared to the insulin glargine group. The low percentage of treatment discontinuation in the insulin glargine group was probably due to fact that the patients in Study 12405 were already on basal insulin at the time of enrolment. The actual percent of patients missing the HbA1c measurement at Week 30 was around 5% in each treatment group.

Table 7 Summary of patient dispositions in Study EFC12405

	FRC	**Insulin Glulisine**
Randomized, n	367	369
Randomized and Treated, n(%)	365 (99.5%)	365 (98.9%)
mITT, n(%)	366 (99.7%)	365 (98.9%)
Completed 30-Week Treatment, n(%)	336 (91.6%)	355 (96.2%)
Discontinued Treatment, n(%)	29 (7.9%)	10 (2.7%)
Adverse event	12 (3.3%)	3 (0.8%)
Lack of efficacy	0	0
Poor compliance to protocol	4 (1.1%)	1 (0.3%)
Others	13 (3.5%)	6 (1.6%)
Had HbA1c measurement at Week 30, n(%)	346 (94.3%)	355 (96.2%)
Missed HbA1c measurement at Week 30, n(%)	21 (5.7%)	14 (3.8%)

A description of the patient demographics in the review is shown in Table 8. The overall population was balanced by sex and was predominantly white.

Table 8 Summary of patient demographic information in Study EFC12405

	FRC	**Insulin Glulisine**
Sex, n(%) males	165 (45.0%)	179 (48.5%)
Age, years		
Mean (SD)	59.6 (9.4)	60.3 (8.7)
Range	36 : 85	32 : 80
n(%) ≥65	110 (30.0%)	120 (32.5%)
Race, n (%)	337 (91.8%)	338 (91.6%)
White	17 (4.6%)	21 (5.7%)
Black	12 (3.3%)	8 (2.2%)

Asian/Oriental Other	1 (0.3%)	2 (0.5%)
Ethnicity, n(%) Hispanic	66 (18.0%)	66 (17.9%)
Country, n(%) US	90 (24.5%)	85 (23.0%)
HbA1c at Week-1, n(%) <8%	140 (38.1%)	142 (38.5%)
Baseline BMI, n(%) <30 kg/m^2	156 (42.5%)	158 (42.8%)
Screening creatinine clearance (mL/min), n(%) 30 to <60 60 to <90 ≥ 90	 18 (4.9%) 104 (28.4%) 244 (66.7%)	 9 (2.5%) 117 (31.9%) 241 (65.7%)

Source: Sponsor's Clinical Study Report for Study EFC12405 Table 11

3.2.2.3 Results and Conclusions (EFC12405)

I verified the sponsor's primary and key secondary analyses. The results were shown in Table 9. These results are supportive to the superiority of FRC to insulin glargine in terms of change in HbA1c from baseline to Week 30 (p-value < .0001). The following secondary endpoints were also confirmed based on the pre-specified testing hierarchy:

- Superiority of FRC to insulin glargine in terms of 2h-glucose excursion (p-value < .0001)
- Superiority of FRC to insulin glargine in terms of body weight (p-value < .0001)
- Superiority of FRC to insulin glargine in terms of 7-point average SMPG (p-value < .0001)
- Superiority of FRC to insulin glargine in terms of % of patients reaching HbA1c < 7% with no body weight gain (p-value < .0001)

The sponsor stated that the sensitivity analysis for the primary endpoint based on retrieved dropouts could not be conducted because the number of retrieved dropouts was not sufficient to build a reliable imputation model.

Table 9 Primary and key secondary endpoints at Week 30 for FRC, insulin gargline and lixisenatide in patients with T2DM in Study EFC12405

Endpoint	**FRC**	**Insulin Glargine**
HbA1c %	N=364	N=364
Mean baseline LS mean change from baseline (SE) LS mean difference of FRC vs. [95% CI] p-value	8.07 -1.13 (0.06)	8.08 -0.62 (0.06) -0.52 [-0.63, -0.40] <.0001
2h Glucose Excursion (mmol/L)[1]	N=329	N=336

Mean baseline LS mean change from baseline (SE) LS mean difference of FRC vs. [95% CI] p-value	7.01 -3.90 (0.28)	7.14 -0.47 (0.27) -3.43 [-3.92, -2.94] <.0001
Body Weight (kg)	N=365	N=365
Mean baseline LS mean change from baseline (SE) LS mean difference of FRC vs. [95% CI] p-value	87.81 -0.67 (0.18)	87.09 0.70 (0.18) -1.37 [-1.81, -0.93] <.0001
7-Point Average SMPG (mmol/L)	N=323	N=320
Mean baseline LS mean change from baseline (SE) LS mean difference of FRC vs. [95% CI] p-value	9.22 -1.50 (0.14)	9.05 -0.60 (0.13) -0.90 [-1.15, -0.64] <.0001
% of Patients Reaching HbA1c < 7% with No Body Weight Gain[2]	N=366	N=365
Response rate, n% p-value of comparison between FRC vs.	125 (34.2%)	49 (13.4%) <.0001
FPG (mmol/L)	N=364	N=364
Mean baseline LS mean change from baseline (SE) LS mean difference of FRC vs. [95% CI] p-value	7.33 -0.35 (0.14)	7.32 -0.46 (0.14) 0.11 [-0.21, 0.43] 0.495

Source: Sponsor's Clinical Study Report for Study EFC12405 Tables 16, 20, 22, 23, 24

[1] ANCOVA with LOCF

[2] CMH test adjusting for randomization strata

3.2.3 Subgroup Analyses by Final Dose

The sponsor evaluated change in HbA1c from baseline by final dose categories of insulin glargine and lixisenatide respectively.

Table 10 and Table 11 showed the number of patients in each final dose category in Study EFC12404. The number of patients in each final insulin dose category in the FRC and insulin glargine arms was roughly the same (Table 10), suggesting the two groups took roughly the same amount of insulin glargine. 58(12.4%) subjects received lixisenatide at doses below 10 µg.

Table 12 and Table 13 showed the number of patients in each final dose category in Study EFC12405. Again the number of patients in each final insulin dose category in the FRC and insulin glargine arms was roughly the same (Table 12). Due to the design of the study, few (<1%) subjects received lixisenatide at doses below 10 µg.

Table 10 Number (%) of patients by final insulin dose category at the end of the treatment period in mITT population-Study EFC12404

Final Insulin Dose	Fixed Ratio Combination (N=468)	Insulin Glargine (N=466)
<10 U	0	3 (0.6%)
≥10 U to <20 U	58 (12.4%)	39 (8.4%)
≥20 U to <30 U	76 (16.2%)	96 (20.6%)
≥30 U to ≤40 U	126 (26.9%)	117 (25.1%)
>40 U to ≤60 U	208 (44.4%)	209 (44.8%)
>60 U	0	2 (0.4%)

Source: Sponsor's Table 16.2.6.6.1.1 in Appendix 16.2.6 Efficacy response data

Table 11 Number (%) of patients by final lixisenatide dose category at the end of the treatment period in mITT population-Study EFC12404

Final Lixisenatide Dose	Fixed Ratio Combination (N=468)
<5 µg	0
≥5 µg to <10 µg	58 (12.4%)
≥10 µg to <15 µg	131 (28.0%)
≥15 µg to ≤20 µg	275 (58.8%)
>20 µg	2 (0.4%)

Source: Sponsor's Table 16.2.6.6.1.2 in Appendix 16.2.6 Efficacy response data

Table 12 Number (%) of patients by final insulin dose category at the end of the treatment period in mITT population-Study EFC12405

Final Insulin Dose	Fixed Ratio Combination (N=366)	Insulin Glargine (N=365)
<10 U	0	0
≥10 U to <20 U	2 (0.5%)	3 (0.8%)
≥20 U to <30 U	44 (12.0%)	39 (10.7%)
≥30 U to ≤40 U	97 (26.5%)	87 (23.8%)
>40 U to ≤60 U	222 (60.7%)	236 (64.7%)
>60 U	0	0

Source: Sponsor's Table 16.2.6.6.1.1 in Appendix 16.2.6 Efficacy response data

Table 13 Number (%) of patients by final lixisenatide dose category at the end of the treatment period in mITT population-Study EFC12405

Final Lixisenatide Dose	Fixed Ratio Combination (N=366)
<5 µg	0
≥5 µg to <10 µg	3 (0.8%)

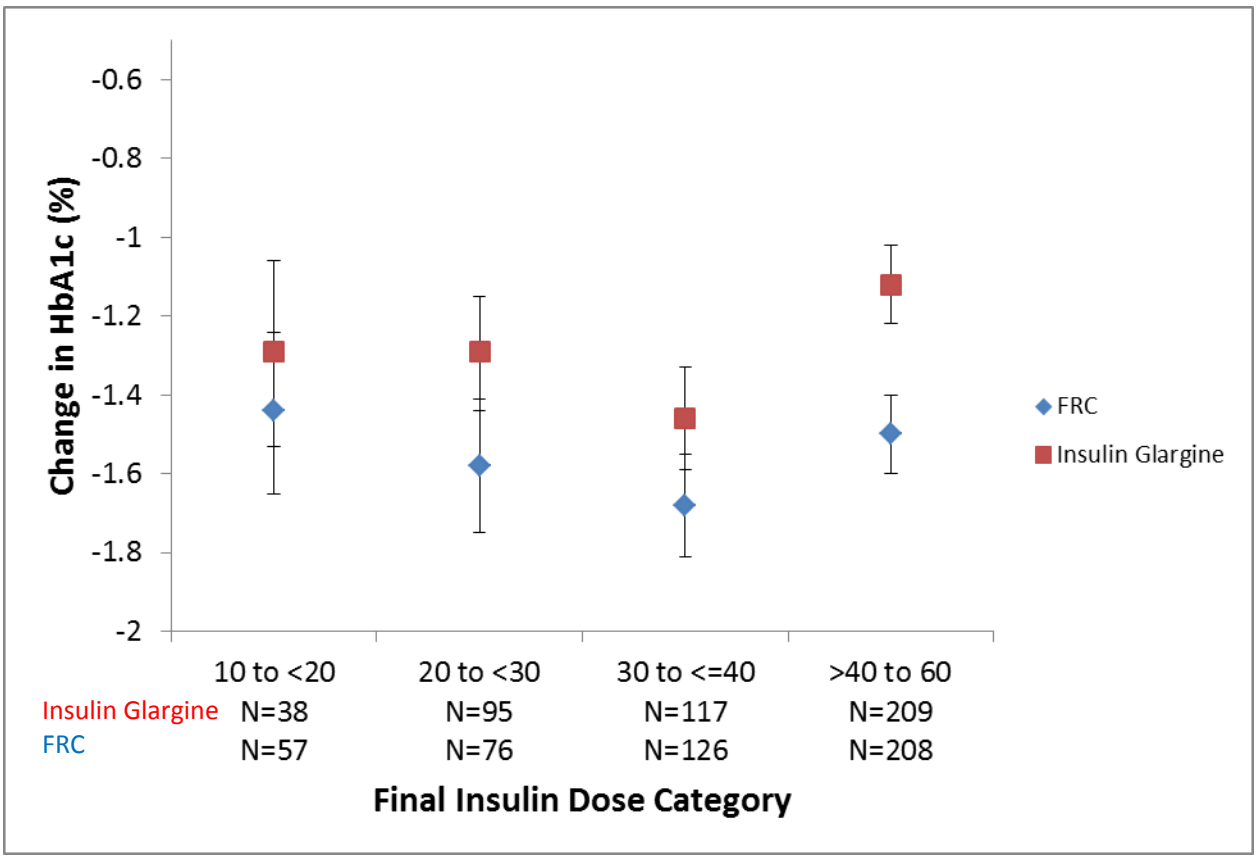
≥10 µg to <15 µg	108 (29.5%)
≥15 µg to ≤20 µg	251 (68.6%)
>20 µg	2 (0.5%)

Source: Sponsor's Table 16.2.6.6.1.2 in Appendix 16.2.6 Efficacy response data

Figure 2 showed LS mean change in HbA1c from baseline to Week 30 by final insulin dose category for the FRC and insulin glargine alone arms in Study EFC12404. The difference between FRC and insulin glargine groups appeared to be very small in the lowest dose category, which corresponds to lixisenatide 5 to 10 µg in the FRC.

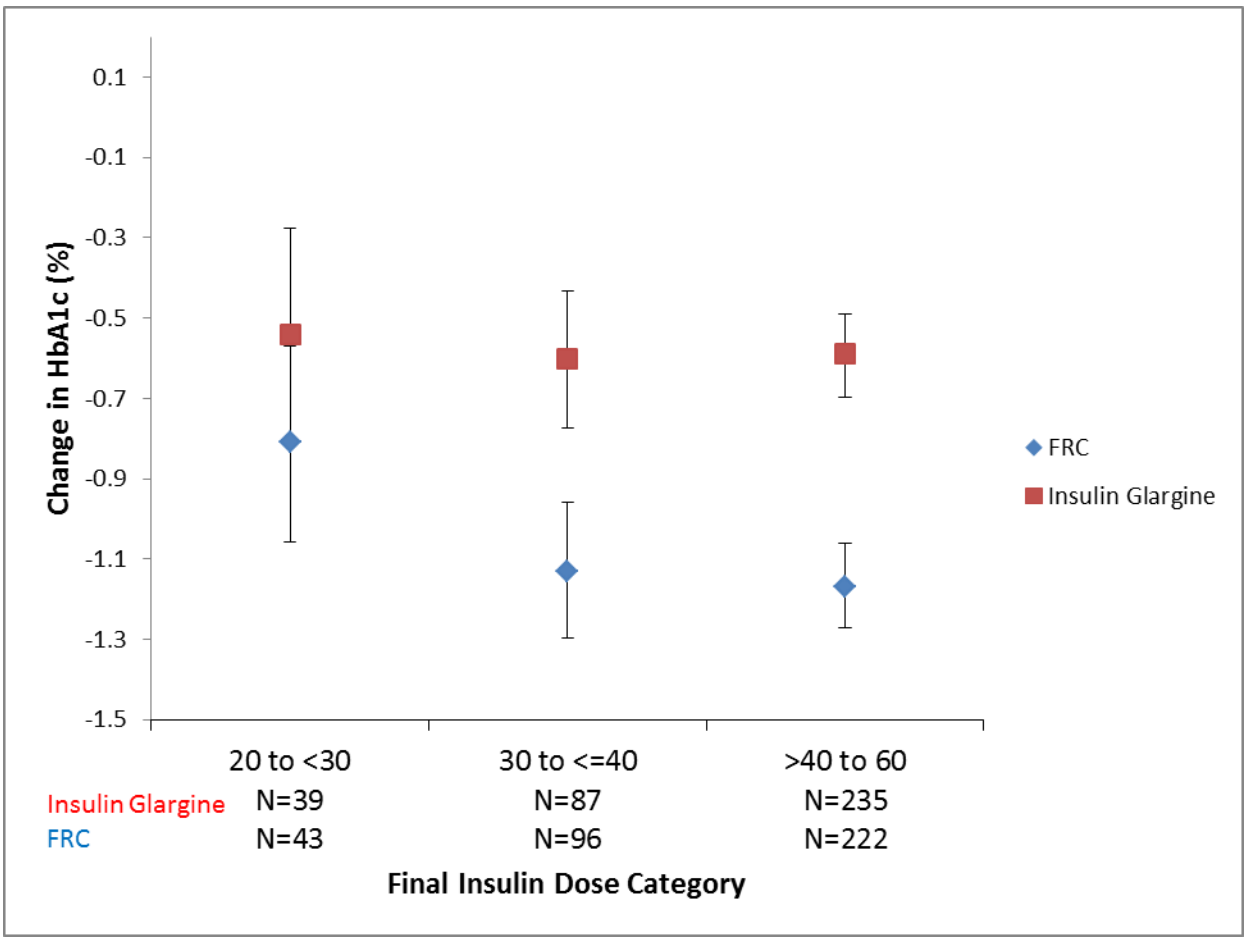
Figure 3 showed LS mean change in HbA1c from baseline to Week 30 by final insulin dose category for the FRC and insulin glargine alone arms in Study EFC12405.

Figure 2 Mean change in HbA1c (%) from baseline to Week 30 by final insulin dose category in mITT population - Study EFC12404



Source: Adapted from sponsor's Figures 16.2.6.6.2.2 and 16.2.6.6.2.3 in Appendix 16.2.6 Efficacy response data for Study EFC12404

Figure 3 Mean change in HbA1c (%) from baseline to Week 30 by final insulin dose category in mITT population - Study EFC12405



Source: Adapted from sponsor's Figures 16.2.6.7.2.2 and 16.2.6.7.2.3 in Appendix 16.2.6 Efficacy response data for Study EFC12404

LS mean change in HbA1c by final lixisenatide dose for the FRC in the two studies was shown in Figure 7 and Figure 8 in Appendix. Based on Figure 7, the contribution of insulin glargine to the effect of the FRC was obvious. The LS mean change in HbA1c for the lixisenatide alone group was only -0.78%, much smaller than that for the FRC in all final dose subgroups (Figure 7).

3.3 Evaluation of safety

Analyses on safety events were reviewed by Dr. Suchitra Balakrishnan.

4. Findings in special/subgroup populations

4.1 Sex, Race, Age, and Geographic Region

The factors considered for subgroup analyses include:

- Age (<65, ≥65)
- Sex
- Race
- Ethnicity
- Geographic Region (US, non-US)

I conducted subgroup analyses on HbA1c change using MMRM, similar to the one used for the primary analysis, with additional covariate on the subgroups being analyzed, treatment-by-subgroup and treatment-by-visit-by-subgroup interactions. The estimates for treatment difference within subgroups and the p-value for testing difference in treatment difference between subgroups were presented in Table 14 for Study EFC12404 and Table 15 for Study EFC12405. The results are consistent with the sponsor's results in Figure 5, Figure 6 and Figure 7 of Appendix.

In Study EFC12404, the difference in treatment effect of FRC versus lixisenatide between US and non-US subjects was statistically significant at alpha = 0.10 (p-value = 0.01). The LS mean difference of US versus non-US was -0.32% (SE=0.13). This result should be viewed with caution due to lack of adjustment for multiplicity. The potential interaction is quantitative rather than qualitative. It implies a larger treatment effect in the US subgroup. Therefore, the difference is not problematic.

In Study EFC12405, no statistically significant difference in treatment effect between subgroups was found.

Table 14 Subgroup analysis on mean HbA1c (%) change from baseline in Study EFC12404

	Treatment Difference FRC - Insulin Glargine [95% CI]	**P-value at Week 30[1]**	**Treatment Difference FRC - Lixisenatide [95% CI]**	**P-value at Week 30[1]**
Sex		0.45		0.41
Male	-0.25 [-0.39, -0.12]		-0.75 [-0.90, -0.59]	
Female	-0.33 [-0.46, -0.20]		-0.84 [-1.02, -0.67]	
Age		0.20		0.45
<65	-0.25 [-0.36, -0.14]		-0.81 [-0.94, -0.67]	
≥65	-0.39 [-0.58, -0.21]		-0.70 [-0.93, -0.47]	

Race		0.34		0.98
White	-0.27 [-0.37, -0.17]		-0.78 [-0.91, -0.66]	
Black	-0.54 [-0.89, -0.19]		-0.74 [-1.22, -0.25]	
Asian and Other	-0.32 [-0.84, 0.21]		-0.79 [-1.50, -0.08]	
Ethnicity		0.99		0.44
Hispanic	-0.29 [-0.51, -0.07]		-0.69 [-0.95, -0.43]	
Non-Hispanic	-0.29 [-0.39, -0.18]		-0.80 [-0.93, -0.67]	
Country		0.46		0.01
US	-0.36 [-0.53, -0.18]		-1.00 [-1.21, -0.78]	
Non-US	-0.28 [-0.39, -0.16]		-0.68 [-0.82, -0.54]	
Baseline HbA1c (%)		0.66		0.09
<8.0%	-0.33 [-0.46, -0.19]		-0.67 [-0.84, -0.50]	
≥8.0%	-0.28 [-0.42, -0.15]		-0.88 [-1.04, -0.72]	
Baseline BMI (30 kg/m^2)		0.14		0.06
<30	-0.40 [-0.55, -0.24]		-0.94 [-1.14, -0.74]	
≥30	-0.25 [-0.37, -0.13]		-0.71 [-0.85, -0.56]	
Screening creatinine clearance (mL/min)		0.62		0.46
30 to <90	-0.27 [-0.45, -0.08]		-0.88 [-1.13, -0.63]	
≥ 90	-0.32 [-0.44, -0.21]		-0.77 [-0.90, -0.64]	

[1] F-test for difference in treatment difference between subgroups at Week 30

Table 15 Subgroup analysis on mean HbA1c (%) change from baseline in Study EFC12405

	Treatment Difference FRC - Insulin Glargine [95% CI]	**P-value at Week 30[1]**
Sex		0.59
Male	-0.48 [-0.65, -0.30]	
Female	-0.54 [-0.70, -0.38]	
Age		0.27
<65	-0.47 [-0.61, -0.33]	
≥65	-0.61 [-0.82, -0.40]	
Race		0.78
White	-0.52 [-0.65, -0.40]	
Black	-0.45 [-0.98, 0.08]	
Asian and Other	-0.29 [-0.98, 0.40]	
Ethnicity		0.97
Hispanic	-0.51 [-0.79, -0.23]	
Non-Hispanic	-0.52 [-0.65, -0.38]	
Country		0.83
US	-0.55 [-0.79, -0.30]	
Non-US	-0.52 [-0.65, -0.38]	
Baseline HbA1c (%)		0.48
<8.0%	-0.47 [-0.65, -0.30]	
≥8.0%	-0.56 [-0.72, -0.40]	
Baseline BMI (30 kg/m^2)	-0.58 [-0.77, -0.40]	0.38
<30	-0.48 [-0.63, -0.32]	

≥30		
Screening creatinine clearance (mL/min)		0.32
30 to <90	-0.61 [-0.81, -0.40]	
≥ 90	-0.48 [-0.63, -0.33]	

[1] F-test for difference in treatment difference between subgroups at Week 30

4.2 Other Special/Subgroup Populations (optional)

I also performed subgroup analyses for the primary endpoint by

- Baseline HbA1c (<8.0% vs ≥8.0%)
- Baseline BMI (<30 kg/m^2 vs ≥30 kg/m^2)
- Creatinine clearance at screening (30 to <90 mL/min vs ≥ 90 mL/min).

The results are also presented in Table 14.

In Study EFC12404, the difference in treatment effect of FRC versus lixisenatide between baseline HbA1c <8.0% and ≥8.0% was statistically significant at alpha = 0.10 (p-value = 0.09). The LS mean difference of baseline HbA1c <8.0% versus ≥8.0% was 0.21% (SE=0.12).

The difference in treatment effect of FRC versus lixisenatide between baseline BMI <30 and ≥30 was statistically significant at alpha = 0.10 (p-value = 0.06). The LS mean difference of baseline BMI <30 versus ≥30 was -0.24% (SE=0.13).

These results should also be viewed with caution because of lack of adjustment for multiplicity. The result for baseline HbA1c subgroups is consistent with previous findings for insulin add-on therapies and therefore may be real.

5. Summary and conclusions

5.1 Statistical Issues

- **Difficulty in interpreting sponsor's exploratory analysis by final dose**: Final insulin dose is a post-randomization variable and is affected by assigned treatment. Differences between the FRC and insulin glargine alone groups within each final insulin dose category no longer represent treatment effect. Even if we disregard this problem and assume the treatment groups were comparable within each final insulin dose category, the differences between treatment groups in the lower dose categories did not appear to be very big, particularly in the lowest dose category which corresponds to lixisenatide 5 to 10 μg in the FRC (Figure 2). The contribution of low doses of lixisenatide to the effect of the FRC on HbA1c change is not clear.

- **External validity of the results to the practice of the treatment of T2DM:** In both Phase 3 studies, insulin glargine was capped at 60 U in the insulin glargine alone arm to match the maximum insulin glargine dose in the FRC arm. However, in real practice insulin glargine is not capped when given alone and can go beyond 60 U. This cap, together with the limitations of the insulin titration algorithm, raised concerns that the treatment difference observed in the Phase 3 studies may not reflect actual treatment difference in practice.

- The open-label design in the Phase 3 studies was not an optimal study design, as bias can be introduced.

5.2 Collective Evidence

The insulin glargine/lixisenatide FRC demonstrated superiority to both insulin glargine and lixisenatide in terms of change in HbA1c from baseline to Week 30 in patients with T2DM in the sponsor's Phase 3 studies. The mean treatment difference of the FRC versus insulin glargine was -0.29% (95% CI: -0.38, -0.19) in insulin naïve patients (EFC12404) and -0.52% (95% CI: -0.63, -0.40) in patients uncontrolled on basal insulin (Study EFC12405). The mean treatment difference of the FRC versus lixisenatide was -0.78% (-0.90, -0.67) in insulin naïve patients.

Overall both components appeared to contribute to the effect of the combination product. There is some uncertainty about the contribution of the low dose lixisenatide to the effect of the FRC, particularly the lixisenatide doses < 10 µg. There is also concern about the external validity of the results to the practice of T2DM.

5.3 Conclusions and Recommendations

The review on efficacy supports the claim of using the FRC for improving glycemic control in patients with T2DM.

The treatment difference of the FRC versus insulin glargine appeared to be larger in patients uncontrolled on basal insulin (Study EFC12405) compared to insulin naïve patients (Study EFC12404). The effect of the FRC versus insulin glargine is modest in insulin naïve patients.

5.4 Labeling recommendations

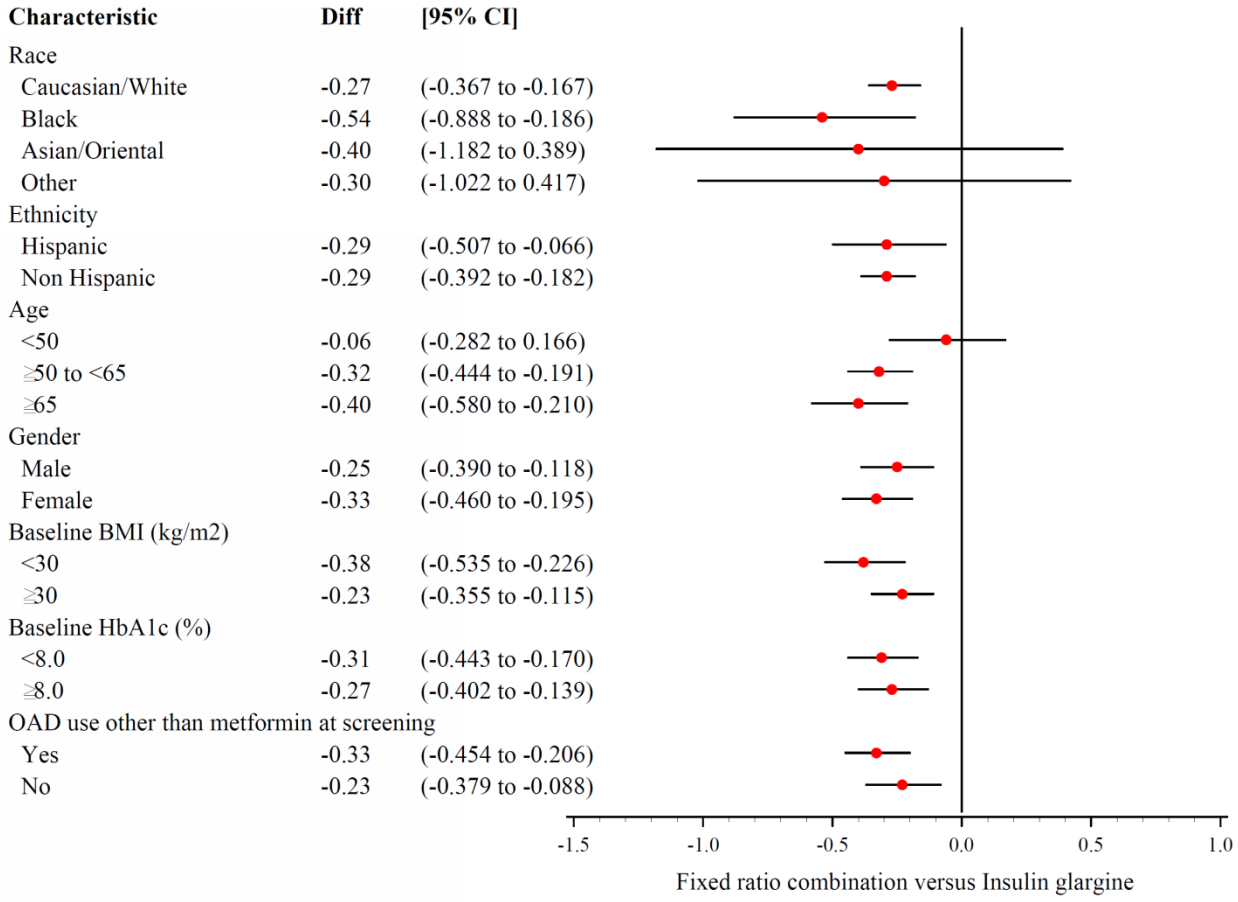
The proposed product label contains results (b) (4)

1. In overall, the primary (b) (4) endpoints in the draft label are consistent with the pre-specified strategy for controlling the type I error stated in the statistical analysis plan (SAP). However, whether they can be included in the label is subject to clinical judgment.

2. [redacted] (b) (4) should be removed from the results tables in section 14.

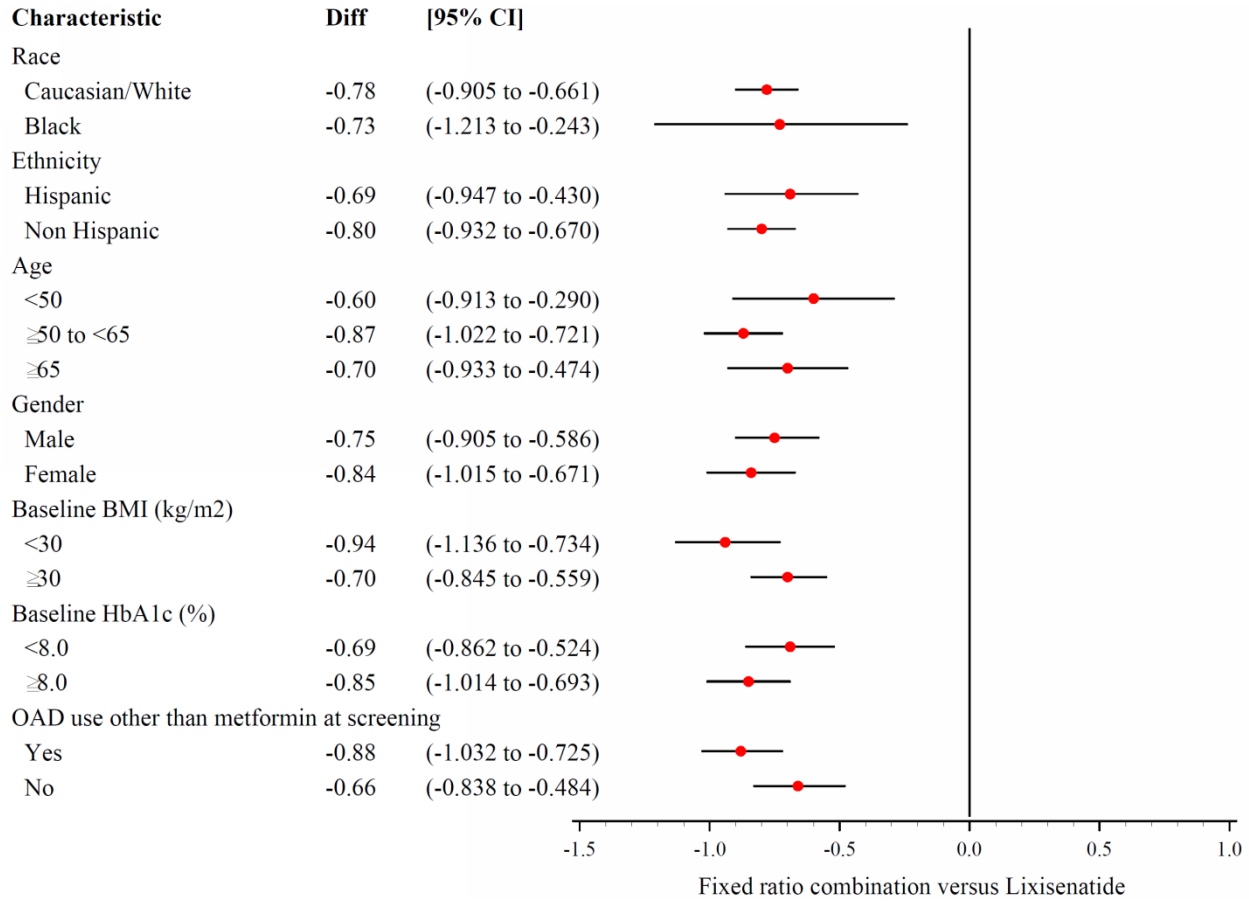
Appendix

Figure 4 Sponsor's forest plot of mean change in HbA1c (%) from baseline to Week 30 by baseline factor – Study EFC12404 FRC versus insulin glargine



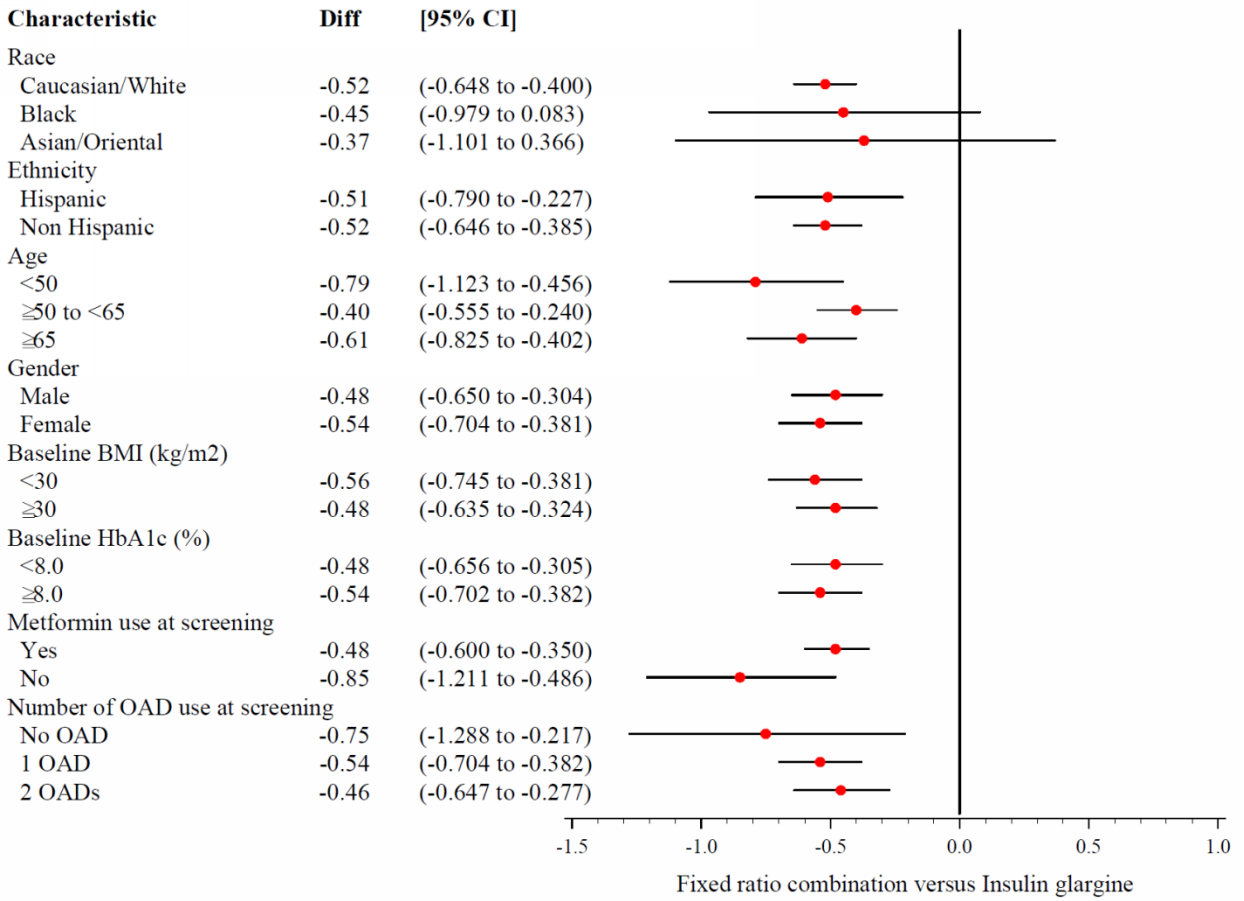
Source: Sponsor's Clinical Study Report for Study EFC12404 Figure 6

Figure 5 Sponsor's forest plot of mean change in HbA1c (%) from baseline to Week 30 by baseline factor - Study EFC12404 FRC versus lixisenatide



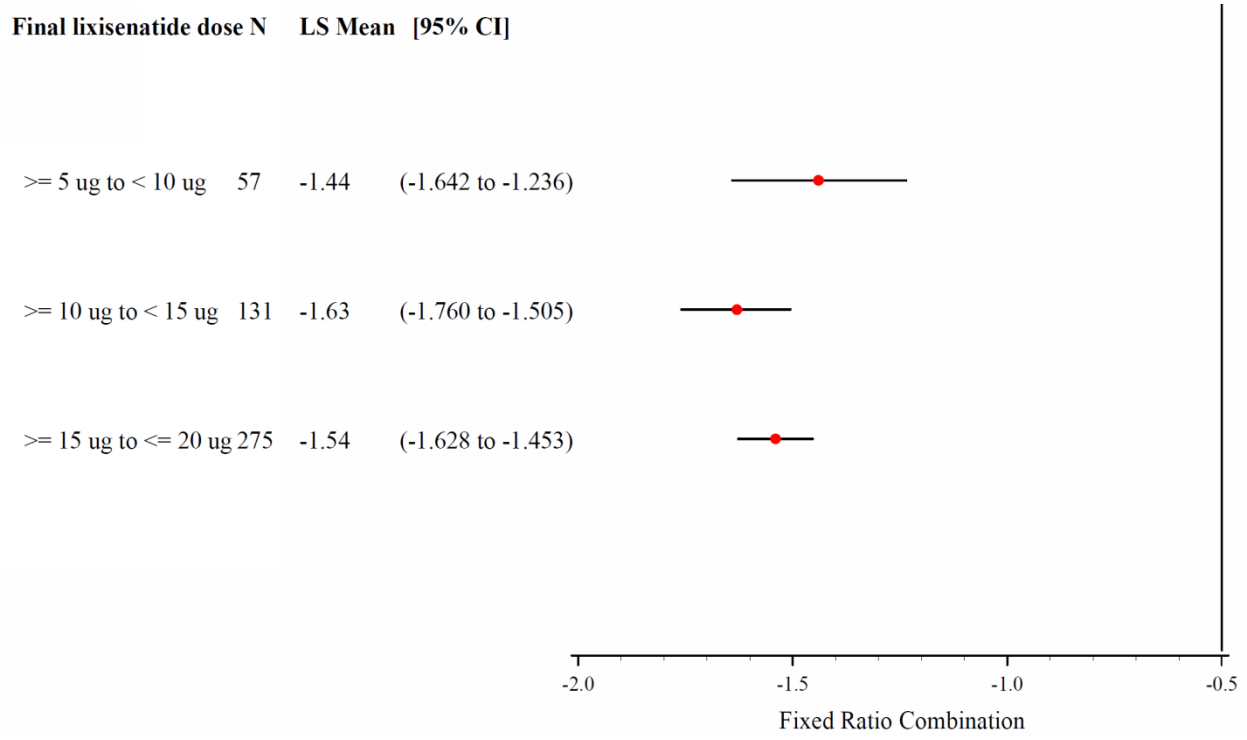
Source: Sponsor's Clinical Study Report for Study EFC12404 Figure 7

Figure 6 Sponsor's forest plot of mean change in HbA1c (%) from baseline to Week 30 by baseline factor - Study EFC12405 FRC versus insulin glargine



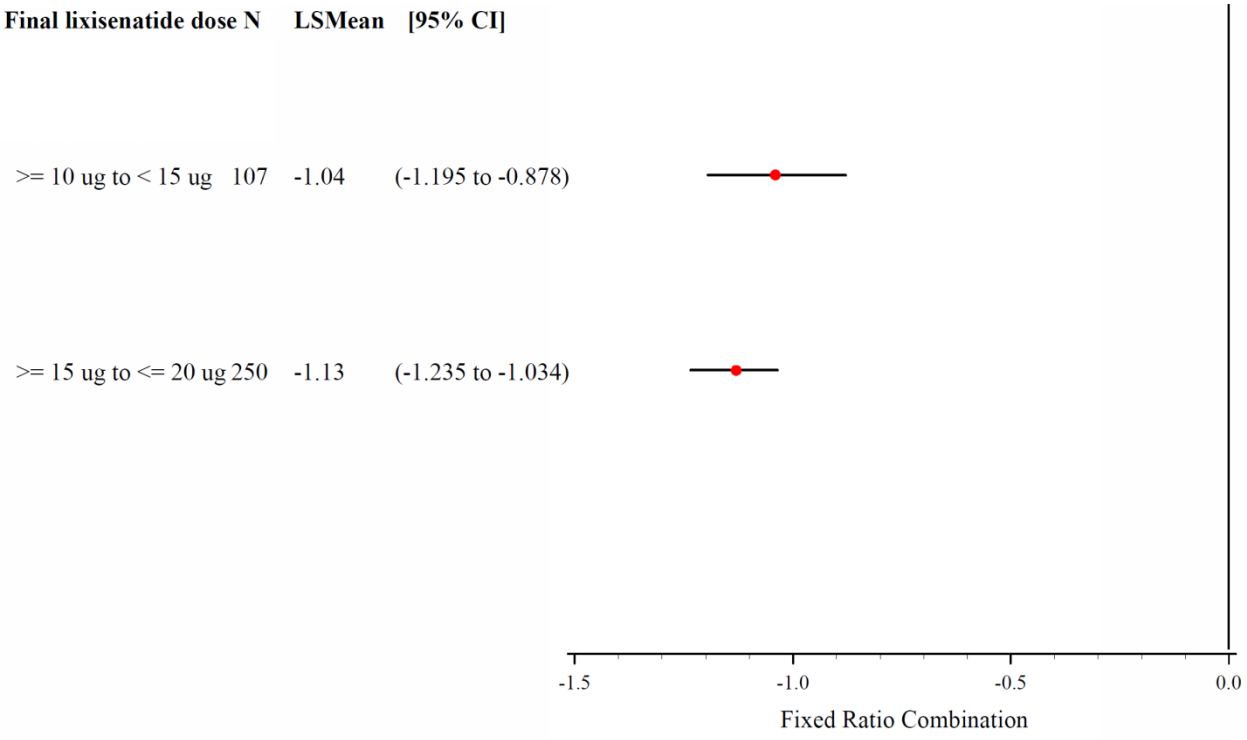
Source: Sponsor's Clinical Study Report for Study EFC12405 Figure 6

Figure 7 Sponsor's forest plot of mean change in HbA1c (%) from baseline to Week 30 by final lixisenatide dose category for the FRC arm in mITT population – Study EFC12404



Source: sponsor's Figures 16.2.6.6.2.7 in Appendix 16.2.6 Efficacy response data for Study EFC12404

Figure 8 Sponsor's forest plot of mean change in HbA1c (%) from baseline to Week 30 by final lixisenatide dose category for the FRC arm in mITT population – Study EFC12405



Source: sponsor's Figures 16.2.6.7.2.7 in Appendix 16.2.6 Efficacy response data for Study EFC12405

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/s/

JIWEI HE
07/21/2016

MARK D ROTHMANN
07/21/2016
I concur