CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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 208471
Supplement #:	Not Applicable
Drug Name:	Lixisenatide injection (AVE0010), 10 µg to 20 µg once daily (QD).
Indication(s):	For the treatment of adults with Type 2 diabetes mellitus to achieve glycemic control as an adjunct to diet and exercise.
Applicant:	Sanofi
Date(s):	Date submitted: 07/27/2015 PDUFA due date: 07/27/2016
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Keywords:	Cardiovascular outcome trial; Safety assessment; Survival analysis; MACE; MACE+; all-cause mortality

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1 EXECUTIVE SUMMARY

This statistical review evaluates cardiovascular safety of lixisenatide using evidence submitted in NDA 208471 to support marketing of this drug. The sought indication for lixisenatide injection once a day is as add-on therapy to standard of care for glycemic control in type 2 diabetic patients.

1.1 Conclusions and Recommendations

The cardiovascular safety of lixisenatide was evaluated based on the final results of the ELIXA trial. The pre-specified primary endpoint for the trial was the time until first major adverse cardiovascular event (MACE+), defined as any of the following adjudicated events: cardiovascular (CV) death, non-fatal myocardial infarction (MI), non-fatal ischemic stroke and hospitalization for unstable angina. In addition to the primary MACE+ endpoint, two secondary endpoints – time to first secondary MACE event (defined as CV death, non-fatal MI and non-fatal stroke) and time to all-cause mortality – were also evaluated. All events included in the primary and secondary endpoints were adjudicated by an independent Cardiovascular Adjudication Committee (CAC).

The study was designed to test the primary MACE+ endpoint against the 1.3 risk margin specified by the 2008 FDA guidance, "Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes" to establish the cardiovascular safety of lixisenatide.

Of the 6068 randomized subjects, approximately 96.5% completed the study in both groups. Treatment exposure was similar in both study groups; median exposure was 679 days for lixisenatide and 701 days for placebo. Vital status was available for 99% of subjects.

In the 6068 randomized subjects, a total of 805 primary MACE+ events were included in the pre-specified final analysis on the intention-to-treat (ITT) population that included all MACE+ observed in the trial, 406 events in the 3034 subjects randomized to the lixisenatide group, and 399 events in the in 3034 subjects randomized to the placebo group. The pre-specified Cox proportional hazards model-based hazard ratio estimate for MACE+ was 1.02 with an associated 95% confidence interval of (0.89, 1.17). The upper bound of 1.17 ruled out the risk margin of 1.3 in accordance with the 2008 FDA Diabetes Guidance. No component of the primary MACE+ endpoint raised any statistical concerns, nor did any additional sensitivity analyses performed by the FDA for this endpoint.

There were 792 secondary MACE events observed in the study for the ITT population, 400 in the lixisenatide group and 392 in the placebo group. The pre-specified Cox proportional hazards analysis resulted in a hazard ratio estimate of 1.02 with an associated 95% confidence interval of (0.89, 1.17). The upper bound of this analysis, 1.17, was less than 1.3, and was thus supportive of the findings for the MACE endpoint. Additional sensitivity analyses found similar results.

There were a total of 211 all-cause mortalities in the lixisenatide group and 223 in the placebo group. The pre-specified Cox proportional hazards model, yielded a hazard ratio estimate of 0.94

and 95% confidence interval of (0.78, 1.13) which covers unity. Additional sensitivity analyses found similar results.

One can conclude on the basis of the ELIXA trial that the criteria for ruling out excess CV risk, i.e., the 1.3 risk margin for cardiovascular events specified by the 2008 FDA Diabetes Guidance, was met.

An assessment of the malignancy risks for thyroid, lung, colorectal, breast (female) and prostate (male), a time-to-event analysis using ELIXA trial (**Appendix B1**) and a meta-analysis using a selected list of controlled Phase III trials (**Appendix B2**) were conducted. These analyses were not pre-specified and were conducted for exploratory purpose only. It was found that the event rates in the ELIXA trial and in the integrated analysis of all trials were low and did not provide sufficient evidence to support that there were any increased malignancy risks in the lixisenatide group.

1.2 Statistical Issues and Findings

ELIXA was a multinational, randomized, parallel and balanced design trial comparing lixisenatide to placebo as an add-on therapy to standard of care (lifestyle and diet therapy, or other non GLP-1 receptor agonist or non DPP-IV inhibitors). The study population is type 2 diabetic subjects who experienced a cardiovascular event at most 180 days before start of study. A total 6068 subjects were randomized to lixisenatide (3034) or placebo (3034). The trial was generally well-conducted and there were no significant statistical issues about trial design or conduct. The primary endpoint for cardiovascular events is MACE+, a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and hospitalization for unstable angina. These cardiovascular events were adjudicated by a cardiovascular adjudication committee (CAC) blinded to treatment assignment.

The primary analysis was time to first on study event using a Cox proportional hazard model with treatment and region as factors. The objective of ELIXA was to rule out an excess hazard ratio of 1.3 of lixisenatide compared to placebo. The analysis was conducted when 805 MACE+ were observed and tested at a two-sided alpha=0.05 significance level.

A total of 7,719 patients were screened in 828 study centers across 49 countries worldwide; of these, 6,068 patients were randomized 1:1 to double-blind treatment: 3,034 to placebo and 3,034 to lixisenatide. **Table 1** shows results that were obtained from the pre-specified final analysis of the primary MACE+ endpoint on the ITT population that includes all the 805 MACE+ events observed during the trial. There were 406 in the lixisenatide group and 399 in the placebo group. Using the pre-specified Cox proportional hazards model, the hazard ratio estimate and associated 95% confidence interval is 1.017 (0.886, 1.168).

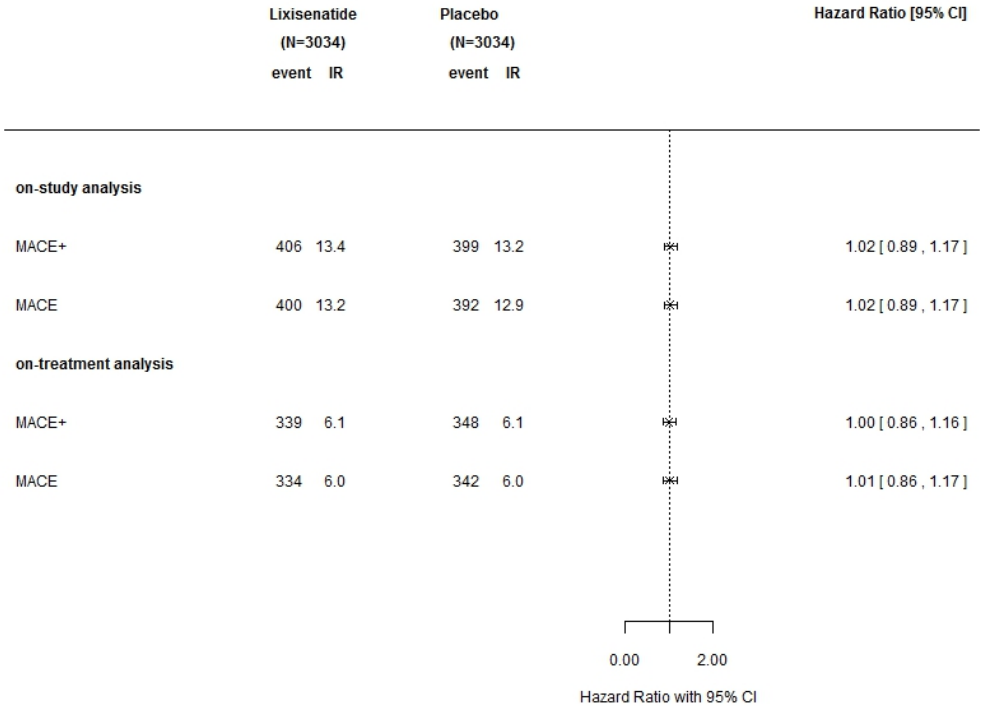
Table 1: Pre-specified Analysis of Primary MACE+ Endpoint

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

Source: Created by the reviewer. Same results were also provided in Clinical Report (page 90).

The pre-specified analysis on the ITT population for MACE+ and sensitivity analyses of MACE+ and MACE (a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) during the on-study and on-treatment period are presented in **Figure 1**. This figure shows a consistent finding of ELIXA ruling out the 1.3 risk margin.

Figure 1: Hazard Ratios of the MACE+ and MACE Endpoint (On-study and On-treatment Analysis)



Source: Created by the reviewer.

In ELIXA, a total of 434 deaths were observed: 223 (7.4%) in the placebo group and 211 (7.0%) in the lixisenatide group for the ITT population. The pre-specified Cox proportional hazards

model for time to on-study all-cause mortality resulted in a hazard ratio estimate of 0.94 for lixisenatide versus placebo with a two-sided 95% confidence interval of 0.78 to 1.13 (**Table 2**). The results are similar for on-treatment analysis.

Table 2: Analysis of All-cause Mortality

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

Source: Created by the reviewer using adsl.xpt, adtte.xpt and adtte30.xpt.

2 INTRODUCTION

This statistical review evaluates cardiovascular risk and the risk of malignancy associated with the use of lixisenatide based upon data submitted in NDA 208471 to support marketing of this drug. In this introduction, an overview of the application objectives and regulatory background are provided along with the material reviewed and a brief summary of the studies used in the evaluation.

2.1 Overview

This NDA seeks the approval of lixisenatide solution for subcutaneous injection, 20μg once a day (QD), to be indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Lixisenatide is a once-daily glucagon-like peptide-1 (GLP-1) receptor agonist for the treatment of Type 2 diabetic mellitus. The primary data cut-off date for the 2015 US CTD was March 2nd, 2015, which is the EFC11319 (ELIXA) database lock date. By the primary data cut-off date, there were 24 Phase 2/3 trials. Of these, 20 trials had been completed and 4 are ongoing at the time of the primary data cutoff date (2 March 2015). The 20 completed trials include:

- three Phase 2 placebo-controlled, double blind trials,
- two Phase 2 active-controlled, open-label trials,
- nine Phase 3 placebo-controlled, double-blind trials,
- one Phase 3 placebo-controlled cardiovascular outcome trial (CVOT), referred to as the ELIXA trial,
- three Phase 3 active-controlled trials,
- one Phase 3 lixisenatide-controlled trial, and
- one Phase 3 uncontrolled trial.

The evaluation of cardiovascular safety is based on the cardiovascular outcome trial (CVOT), titled "A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate cardiovascular outcomes during treatment with lixisenatide in type 2 diabetic (T2DM) patients after an Acute Coronary Syndrome event" (Trial ID: EFC11319, also referred to as the ELIXA trial). ELIXA was designed and powered to assess the cardiovascular risks related to the product lixisenatide with the objective of ruling out the 1.3 risk margin as stipulated in the 2008 FDA Guidance[1].

A planned interim analysis from ELIXA was performed after 263 patients had experienced a primary outcome event with the objective of ruling out the 1.8 risk margin as stipulated in the 2008 FDA Guidance. Results from this planned interim analysis were submitted under NDA 204961 on 12/20/2012. The submission was subsequently withdrawn by the applicant on 9/11/2013. The interim analysis results from ELIXA were reviewed by Dr. Rima Izem (see statistical review signed on 9/6/2013).

[1] 2008 FDA Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes.

The ELIXA trial was completed on 2/11/2015. Findings from the completed ELIXA trial form the basis of assessing cardiovascular risk.

In reviewing the ELIXA trial, it was found that there were numerical differences for malignancy events in favor of placebo compared to the lixisenatide. For a comprehensive assessment of the malignancy risks for thyroid, lung, colorectal, breast (female) and prostate (male), a time-to-event analysis using ELIXA trial (**Appendix B1**) and a meta-analysis using a selected list of controlled Phase III trials (**Appendix B2**) were conducted. These analyses were not pre-specified and were conducted for exploratory purposes only.

2.2 Data Sources

The material submitted by the applicant and considered in this statistical review included two parts. The first part is the applicant's datasets and documents from the cardiovascular outcome trial, ELIXA (EFC11319). This part forms the primary evaluation of cardiovascular safety for lixisenatide. The second part is the report and datasets for the integrated summary of safety. This part forms the evaluation of malignancy outcomes for lixisenatide using ELIXA trials and other controlled Phase III trials.

Links to material reviewed in the evaluation of ELIXA (EFC 11319) are the following.

- Clinical Report as well as protocol and statistical analysis plan: \\cdsesub1\evsprod\NDA208471\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5351-stud-rep-contr\efc11319
- Safety analyses datasets from ELIXA: \\cdsesub1\evsprod\NDA208471\0000\m5\datasets\efc11319
- Data sets utilized in the review are the following:
    - Demographic variables: addm.xpt
    - Subject characteristics: adsl.xpt
    - Disposition variables: adds.xpt
    - Time to event variables: adtte.xpt
    - Time to event variables for on-treatment analysis: adtte30.xpt
    - Exposure variables: adex.xpt
    - Comorbidity variables: adcm.xpt
    - Medical history variables: addm.xpt

SAS code for the primary analysis of MACE+ was submitted.

3 STATISTICAL EVALUATION

The primary statistical evaluation of cardiovascular safety for lixisenatide is based upon the cardiovascular outcome trial ELIXA. This review covers the data and analysis quality in Section 3.1 and findings from the ELIXA trial in Section 3.3.

3.1 Data and Analysis Quality

The data and reports of this submission were submitted electronically. The data and analysis quality were deemed to be adequate as it allowed for reproduction of key safety findings and conduction of additional analyses. The datasets were well documented in the define.pdf files. Spot checks on the key variables found that the analysis datasets (ADS) were consistent with the SDTM datasets.

3.2 Evaluation of Efficacy

For a statistical evaluation of efficacy for this supplement, please refer to the review by Dr. Jiwei He.

3.3 Evaluation of Safety

In this section, cardiovascular safety is assessed using information from the completed cardiovascular outcome trial, ELIXA. ELIXA is a double-blind, placebo-controlled, 1:1 randomized, 2-arm, parallel-group, multinational Phase III trial, to evaluate the effect of lixisenatide on the composite cardiovascular endpoint (cardiovascular (CV) death, non-fatal myocardial infarction (MI), non-fatal stroke, and hospitalization for unstable angina) in patients with type 2 diabetes mellitus who recently experienced a spontaneous biomarker-positive acute coronary syndrome (ACS) event within 180 days of enrollment.

The primary safety objective was to rule out a relative excess cardiovascular risk of 30% for lixisenatide versus placebo. The safety objective would be considered to be met if the upper bound of the 2-sided 95% confidence interval of the hazard ratio was <1.3, as stipulated in the 2008 FDA Guidance.[1] The applicant also intended to seek a CV superiority claim if the upper bound of the 2-sided 95% confidence interval (CI) of the hazard ratio was less than 1.0.

The secondary objectives are:

- To demonstrate that when compared to placebo, lixisenatide can reduce (i.e. superiority claim):
  - Composite endpoint of cardiovascular death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or hospitalization for heart failure,
  - Composite endpoint of cardiovascular death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, hospitalization for heart failure, or coronary revascularization procedure,
  - Urinary albumin excretion (based on the urinary albumin/creatinine ratio) at 108 weeks (ie, approximately 2 years),
- To assess the safety and tolerability of lixisenatide.

3.3.1 Study Design

The trial was planned to recruit approximately 6000 patients, over an estimated 37 months enrollment period and estimated 10 months follow up period, in order to obtain 844 positively-adjudicated events for the primary cardiovascular endpoint based on the assumption of 10% yearly event rate for the first year and 7% yearly rate afterwards. The number of total events was expected to provide 96% power to rule out a relative excess cardiovascular risk of 30% for lixisenatide versus placebo at the 2-sided 5% level of significance.

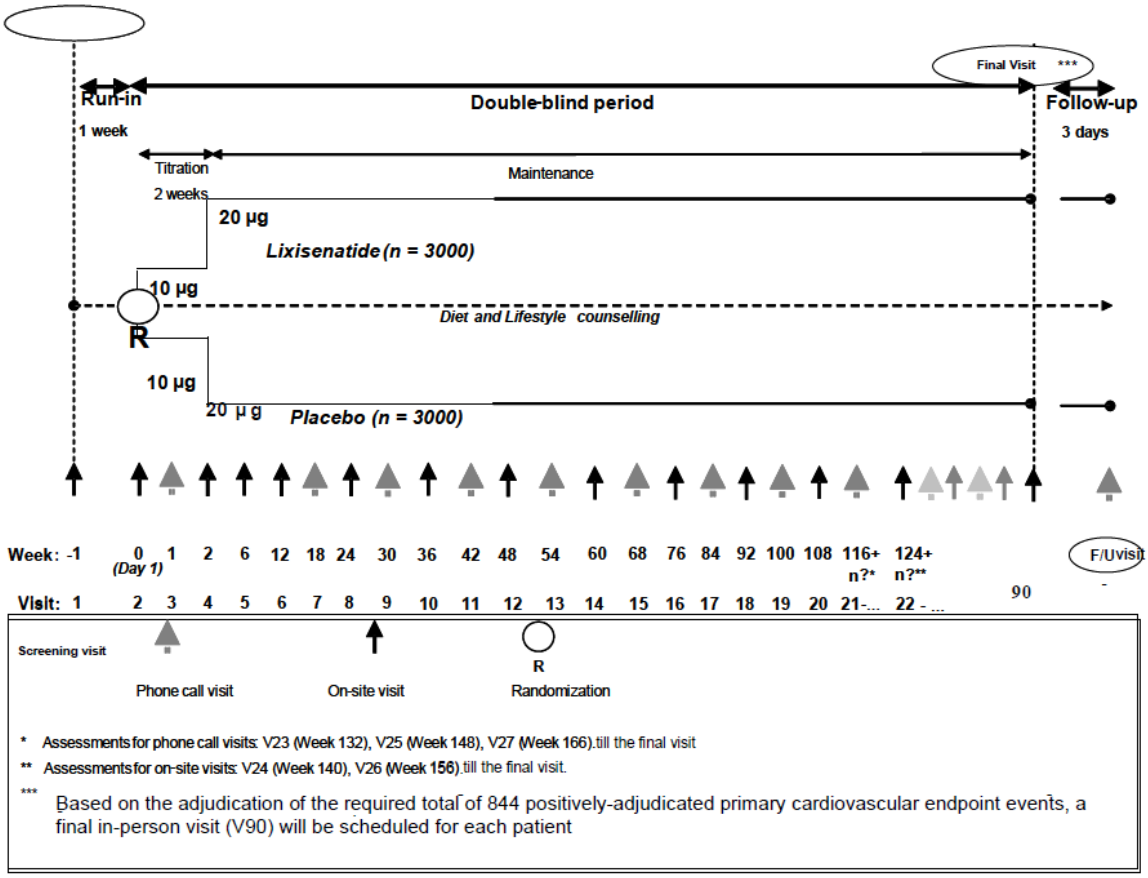
The main criteria for inclusion in the trial are to have T2DM and to have experienced a spontaneous acute coronary syndrome (ACS) event within 180 days of enrollment. For subjects newly diagnosed with T2DM, the diagnosis was based on World Health Organization criteria. That is, either a fasting venous plasma glucose concentration of ≥ 7.0 mmol/L or 2-hour post glucose load venous plasma glucose ≥ 11.1 mmol/L confirmed on 2 occasions. Acute coronary syndrome is defined as a ST-segment elevation myocardial infarction or non-ST segment elevation myocardial infarction or unstable angina.

No background antidiabetic medications were specified, and subjects were eligible for enrollment regardless of whether or not they were receiving pharmacologic treatment for T2DM. During the double-blind treatment period, subjects were allowed to continue lifestyle and diet therapy and take other antidiabetic treatment except other GLP-1 receptor agonists or DPP-IV inhibitors. The investigational product –lixisenatide– is investigated as an add-on treatment on top of lifestyle and diet therapy and/or other antidiabetic treatment.

Figure 2 shows the design of the trial and the sequence of treatment periods. The trial design has three periods: run-in period of one week, treatment period of estimated maximum duration of 203 weeks, and follow up period of 3 days.

The lixisenatide treatment in this trial consists of one injection every day within 1 hour prior to breakfast. The starting dose for lixisenatide is 10µg. This dose included a one-step increase at two weeks to 20µg. The higher 20µg dose was maintained by investigators until the end of the trial if subjects tolerated it. If a subject did not tolerate the drug, a down titration to 10µg together with an up titration later in the trial was planned.

Figure 2: Flowchart of Trial Design for ELIXA.



Source: Clinical Study Report, page 24.

The 6000 subjects were planned to be recruited from 1000 sites worldwide. By the end of the trial, 6068 subjects were randomized in 828 centers across 49 countries. The intent to treat (ITT) population includes 6068 subjects with 3034 subjects randomized to the lixisenatide group and 3034 randomized to the placebo group. Subjects in both lixisenatide and placebo groups were allowed to continue lifestyle and diet therapy taken before the randomization and take antidiabetic medications other than GLP-1 receptor agonists or DPP-IV inhibitors.

3.3.2 Trial Endpoints

The following trial endpoints were pre-specified in the protocol to evaluate cardiovascular risk.

Primary endpoint: Time to first occurrence, from randomization to the end of trial, of any of the following positively adjudicated events: cardiovascular (CV) death, non-fatal myocardial infarction (MI), non-fatal stroke, and hospitalization for unstable angina.

Reviewer's comment*: The primary endpoint is referred to in this review as MACE+. The last element in this composite: hospitalization for unstable angina has the potential to show more geographic variability than the other elements of the composite which may introduce more noise*

in assessing cardiovascular outcomes. Thus, in addition to the assessment of MACE+, the applicant was requested to also investigate MACE, a composite endpoint defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke, as adjudicated by the cardiovascular events adjudication committee (CAC).

Secondary endpoints include alternate composites of cardiovascular outcomes, MACE and all-cause mortality, and other exploratory endpoints.

3.3.3 Statistical Methodologies

Statistical methodologies and analysis details used by the applicant and any additional analyses performed in this statistical review are discussed below. All analyses described below were pre-specified in the protocol unless otherwise noted.

The primary analysis population is intent to treat (ITT) and the events considered are on study. ITT is defined as all randomized subjects, that have a subject number and a treatment kit number allocated to them based on the randomization scheme. Using an on study analysis, cardiovascular events contributing to the analysis include those occurring from randomization to the common study end date, even if a subject has discontinued randomized treatment.

3.3.3.1 Analyses of primary endpoint

The analysis for the primary safety endpoint (the time to the first occurrence of the primary composite cardiovascular event, MACE+) was performed using a Cox proportional hazards model with treatment (lixisenatide, placebo) and region (North America, South and Central America, Western Europe, Eastern Europe, Africa/Near East, and Asia/pacific) as the covariates to estimate the hazard ratio between lixisenatide and placebo and the associated two-sided 95% confidence interval.

The safety objective (i.e. ruling out a relative excess risk of 30%) would be considered to be met if the upper bound of the 2-sided 95% CI of the hazard ratio is less than the 1.3 risk margin. If the 1.3 risk margin was ruled out, the superiority of lixisenatide over placebo was planned and would be claimed if the upper bound of the 2-sided 95% CI of the hazard ratio is less than1.

Sensitivity analyses

The time to the first occurrence of the primary composite cardiovascular event occurring during the on-treatment period was also analyzed using a Cox proportional hazards model with treatment (lixisenatide, placebo), and region as the factors. The on-treatment period for CV endpoints is defined as the time from randomization up to 30 days after the last injection of randomized product.

3.3.3.2 Analyses of secondary endpoints

The time to the first occurrence of time-to-event secondary endpoints were analyzed using a similar Cox proportional hazards model as the primary analysis which includes treatment and

region as the covariates. The hazard ratios between lixisenatide and placebo were estimated along with the associated 2-sided 95% confidence intervals.

3.3.3.3 Multiplicity adjustment

A step-down procedure was planned for multiplicity adjustment between the primary and secondary endpoints in order to control the overall familywise type I error rate. If the primary objective, ruling out a relative excess risk of 30%, was met, the primary composite endpoint was tested for superiority. If the primary composite CV endpoint was statistically significant at α=0.025 (one-sided) for superiority, then the step-down procedure used the following prioritized order:

- Time to the first occurrence of any of the following clinical events positively adjudicated by the CAC: cardiovascular death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or hospitalization for heart failure;
- Percent change in the urinary albumin/creatinine ratio from baseline to 108 weeks (ie, approximately 2 years);
- Time to the first occurrence of any of the following clinical events positively adjudicated by the CAC: cardiovascular death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, hospitalization for heart failure, or coronary revascularization procedure.

The testing procedure was planned to be stopped as soon as an endpoint was found not statistically significant for superiority at the one-sided α=0.025 level. No multiplicity adjustments were made on other secondary outcomes that are not mentioned above.

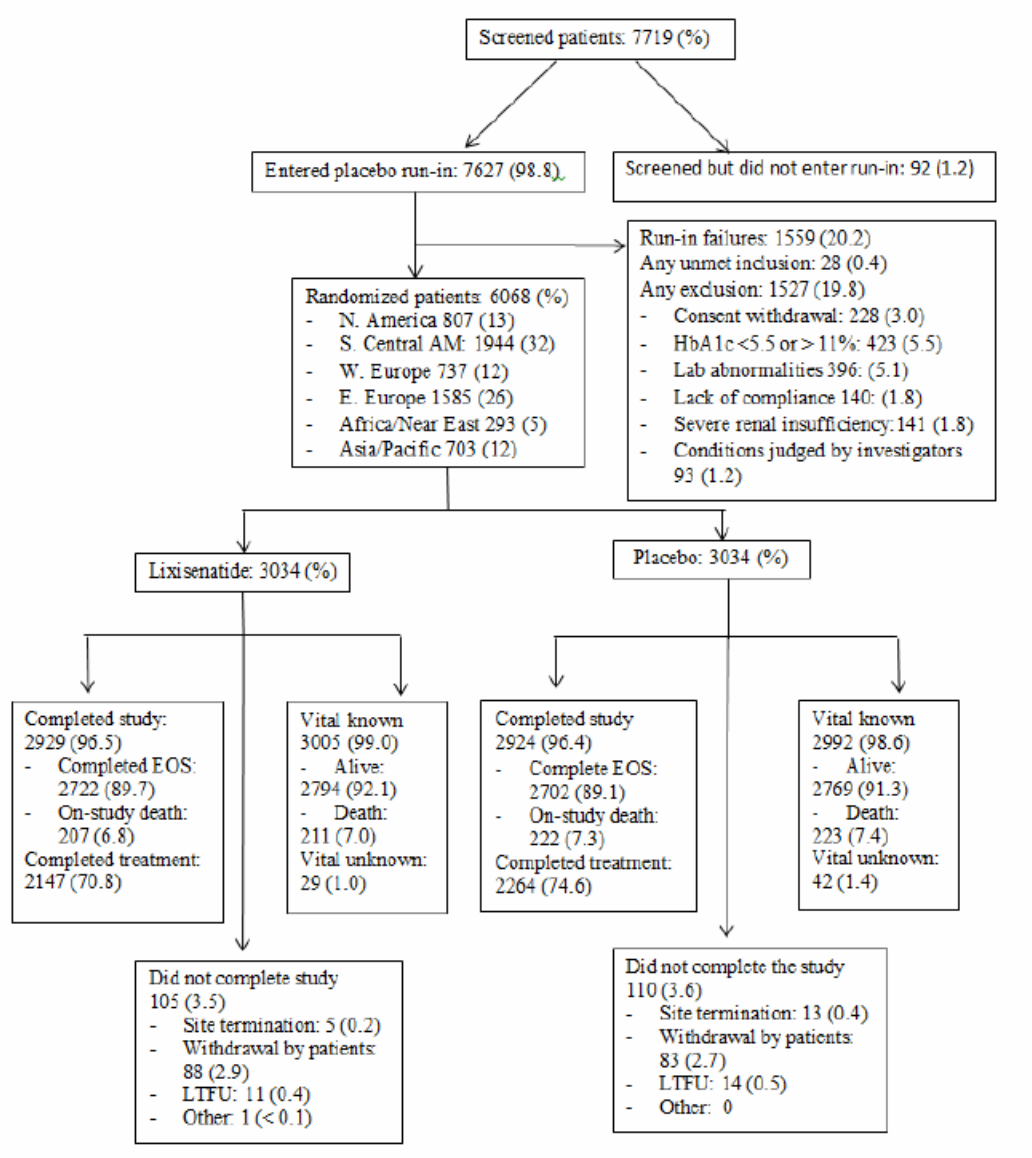
3.3.3.4 Interim analyses

While there were interim analyses planned for ruling out an 80% relative increase in CV risk (i.e. a test of the 1.8 risk margin), there were no planned interim analyses to rule out the 1.3 risk margin. As such, the analysis of ruling out a relative excess risk of 30%, is conducted at the two-sided α=0.05 level.

3.3.3.5 Patient Disposition, Demographic and Baseline Characteristics

The patient disposition is shown in **Figure 3**. We see in the figure that the ITT population included 3034 subjects in the placebo group and 3034 subjects in the lixisenatide group. A similar percent of subjects completed the trial: 96.5% in the lixisenatide group and 96.4% in the placebo group. Of those subjects that withdrew from trial, the majority of discontinuations were due to subject request (2.9% in lixisenatide group and 2.7% in placebo group). There was a similar rate of deaths in the lixisenatide group (7.0%) compared to the placebo group (7.4%).

Figure 3: Patient Disposition



Source: Clinical Report (page 68); results reproduced by the reviewer.

The baseline characteristics of subjects in the lixisenatide group are comparable to those in the placebo group as shown in **Table 3**. The median age is 60 years in both treatment groups. More male and Caucasian patients were enrolled in the study. The majority of subjects were either obese or overweight with a median BMI of 29.4 kg/m^2. The regional distribution of subjects is similar in the two treatment groups. The two regions with the largest contributions of subjects in the study are South and Central America (32%) and Eastern Europe (25.6-26.7%). The two regions with medium contribution of subjects in the study are North America (13.3%) and Western Europe (11.7-12.4%). The two regions with smallest contributions are Asia Pacific (10.8-12.3%) and Africa (4.7-5.1%).

Table 3: Demographics and Subject Characteristics at Baseline

Demographic and regional characteristics	Lixisenatide (N=3034)	Placebo (N=3034)
Age		
Number	3034	3034
Mean (SD)	59.9 (9.7)	60.6 (9.6)
Age Group (years), n(%)		
Number	3034	3034
< 50	464 (15.3%)	377 (12.4%)
>= 50 to < 65	1567 (51.6%)	1617 (53.3%)
>= 65 to < 75	805 (26.5%)	792 (26.1%)
>= 75	198 (6.5%)	248 (8.2%)
Sex, n(%)		
Number	3034	3034
Female	923 (30.4%)	938 (30.9%)
Male	2111 (69.6%)	2096 (69.1%)
Race, n(%)		
Number	3034	3034
Caucasian	2258 (74.4%)	2318 (76.4%)
African American	118 (3.9%)	103 (3.4%)
Asian	404 (13.3%)	367 (12.1%)
Other	254 (8.4%)	246 (8.1%)
Ethnicity, n(%)		
Number	3034	3034
Hispanic	865 (28.5%)	903 (29.8%)
Non-hispanic	2169 (71.5%)	2131 (70.2%)
Baseline BMI (kg/m^2)		
Number	3033	3032
Mean (SD)	30.1 (5.6)	30.2 (5.8)
Region, n(%)		
Number	3034	3034
North America	404 (13.3%)	403 (13.3%)
South and Central America	972 (32.0%)	972 (32.0%)
Western Europe	354 (11.7%)	377 (12.4%)
Eastern Europe	776 (25.6%)	811 (26.7%)
Africa/Near East	154 (5.1%)	142 (4.7%)
Asia Pacific	374 (12.3%)	329 (10.8%)

Source: Created by the reviewer. Similar results were also provided in Clinical Report (page 74 and 75).

The medical history of subjects in both lixisenatide and placebo groups are similar, as shown in **Table 4**. Average age at onset of diabetes is 51 years in both placebo group and lixisenatide group, and average duration of type 2 diabetes since diagnosis is around 9 years. Baseline HbA1c mean in both treatment groups is 7.5%. Average baseline fasting blood glucose is between 8.2-8.3, also larger than the entry criteria 7mmol/L defining diabetes, as expected. Time

since ACS events, one of the main inclusion criteria into the study, has similar distribution in the two treatment groups. The majority of subjects (>70%) in both treatment groups had a qualifying ACS within 90 days prior to randomization. The most common type of qualifying ACS in both treatment groups was ST-segment elevation MI followed by non ST-segment elevation MI.

Table 4: Disease Characteristics at Screening or Baseline

Medical history	**Lixisenatide (N=3034)**	**Placebo (N=3034)**
Duration of diabetes (years)		
Number	3031	3034
Mean (SD)	9.2 (8.2)	9.4 (8.3)
Duration of diabetes (years), n(%)		
Number	3031	3034
<10	1828 (60.3%)	1789 (59.0%)
≥10	1203 (39.7%)	1245 (41.0%)
Age at onset of diabetes		
Number	3031	3034
Mean (SD)	50.8 (10.7)	51.3 (10.7)
Baseline HbA1c (%)		
Number	3034	3033
Mean (SD)	7.7 (1.3)	7.6 (1.3)
Baseline FPG (mmol/L)		
Number	2954	2947
Mean (SD)	8.3 (2.8)	8.2 (2.9)
Baseline FPG (mg/dL)		
Number	2954	2947
Mean (SD)	148.9 (50.9)	147.8 (52.3)
Duration (days) btw Qualifying ACS and Randomization, n(%)		
Number	3033	3031
< 30 days	397 (13.1%)	399 (13.2%)
>= 30 - < 60 days	1086 (35.8%)	1099 (36.3%)
>= 60 - < 90 days	722 (23.8%)	675 (22.3%)
>= 90 days	828 (27.3%)	858 (28.3%)
Qualifying ACS Event, n(%)		
Number	3028	3028
Non-ST segment elevation MI	1165 (38.4%)	1183 (39.0%)
ST segment elevation MI	1349 (44.5%)	1317 (43.4%)
Unstable angina	514 (16.9%)	528 (17.4%)

Source: Created by the reviewer. Similar results were also provided in Clinical Report (page 77 and 78).

The medication use at baseline is comparable in both lixisenatide and placebo groups, as shown in **Table 5**. Among all the subjects, about 39% had used insulin, 26.5% had used ARB, about 60% used ACE inhibitors and 92-93% used statin.

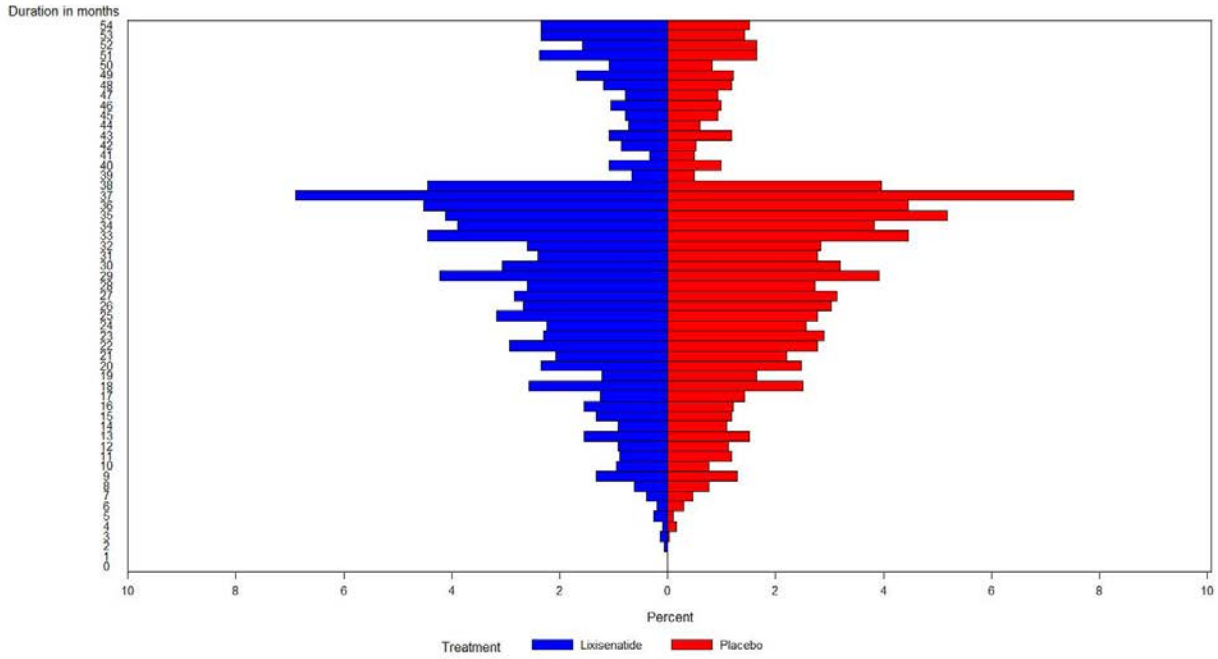
Table 5: Concomitant Medication Use at Baseline

Concomitant medication use at baseline	Lixisenatide (N=3034)	Placebo (N=3034)
Insulin, n(%)	1190 (39.2%)	1184 (39.0%)
Angiotensin II antagnonists, n(%)	804 (26.5%)	804 (26.5%)
ACE inhibitors, n(%)	1833 (60.4%)	1827 (60.2%)
Statin, n(%)	2831 (93.3%)	2796 (92.2%)

Source: Created by the reviewer. Similar results were also provided in Clinical Report (page 86).

The histogram in **Figure 4** shows the treatment exposure for the ITT population. The median treatment exposure time was 679 days for Lixisenatide and 701 days for placebo. Overall, the distribution of treatment exposure was similar across both groups.

Figure 4: Distribution of Treatment Exposure (ITT population).



Source: Created by the reviewer, using adex.xpt.

3.3.4 Results and Conclusions

3.3.4.1 Primary analyses of MACE+

By the end of the trial, there were 805 subjects (399 in placebo and 406 in lixisenatide) with at least one positively adjudicated primary CV endpoint event, as shown in **Table 6**. The incidence rates are 6.34 and 6.39 per 1000 person-year for placebo and lixisenatide, respectively. We see in

this table that most MACE+ events were non-fatal myocardial infarctions and there were very few hospitalizations for unstable angina events (~0.3%).

Using the pre-specified Cox proportional hazards model, the hazard ratio estimate and associated 95% confidence interval is 1.02 (0.89, 1.17). The upper bound of the 95% confidence interval for the hazard ratio is significantly lower than 1.3 at the two-sided alpha=0.05 significance level. A graphical check (**Figure 14** in **Appendix A**) shows that the assumption of proportional hazards appears reasonable for the MACE+ analysis.

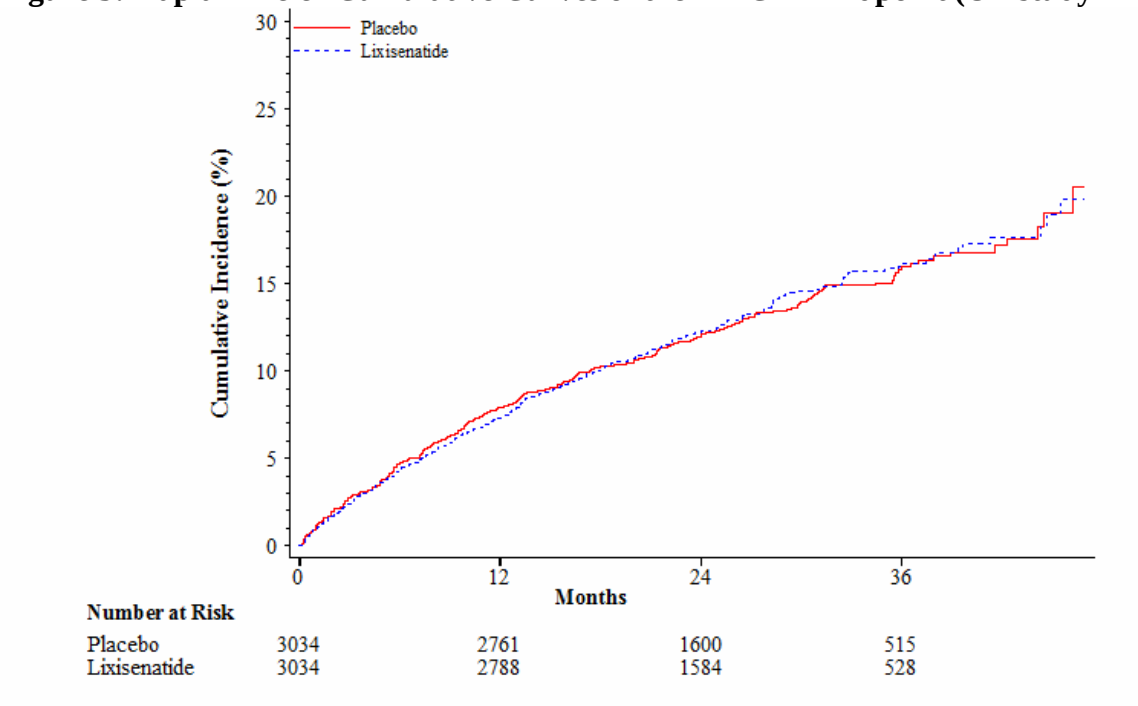
Table 6: Analysis of the Primary CV endpoint (On-study Analysis)

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

Source: Created by the reviewer. Same results were also provided in Clinical Report (page 90).

Kaplan-Meier cumulative curves of time from randomization to the first primary CV endpoint event for lixisenatide and placebo were superimposed for the majority of the study period (**Figure 5**).

Figure 5: Kaplan-Meier Cumulative Curves of the MACE+ Endpoint (On-study Analysis)



Source: The applicant's study report, page 91.

3.3.4.2 Sensitivity Analyses of MACE+

The results of planned sensitivity analyses of MACE+ during the on-treatment period also show similar results as the primary analysis (**Table 7**). The 95% confidence interval of hazard ratio is (0.86, 1.17) with a point estimate of 1.01. The on-treatment period for CV endpoints is defined as the time from randomization up to 30 days after the last injection of lixisenatide.

Table 7: Analysis of the Primary CV Endpoint (On-treatment Analysis)

	Placebo (N=3034)	Lixisenatide (N=3034)	Hazard ratio (95% CI)[c]
Composite of CV death, non-fatal MI, or non-fatal stroke*			1.005 (0.864, 1.169)
Number of patients with event (%)	342 (11.3%)	334 (11.0%)	-
Total patient years for the event[a]	5730.4	5550.9	-
Incidence rate per 100 patient years[b]	5.97	6.02	-

CV: cardiovascular, MI: myocardial infarction, CI: confidence interval.
* Only CAC positively adjudicated events are included.
a Calculated as time from randomization date to the first event date or censoring date (the earlier date of end of study date and treatment discontinuation plus 30 days) for patients who had no events.
b Calculated as number of patients with an event divided by total patient years for the event and multiplied by 100.
c Hazard ratio of lixisenatide versus placebo estimated using Cox proportional hazards model based on ITT population, with treatment (lixisenatide, placebo), and region (North America, South and Central America, Western Europe, Eastern Europe, Africa/Near East, and Asia/Pacific) as covariates, and the associated two-sided 95% CI.

Source: Clinical Report (page 94); results reproduced by the reviewer.

3.3.4.3 Analyses of MACE

ITT analyses (on-study and on-treatment) of MACE, defined as cardiovascular death, non-fatal MI, and non-fatal stroke, are consistent with those of MACE+ (**Table 8**). The reason for the similarity is that only 0.3% of subjects in the ITT population experienced hospitalization for unstable angina. For ITT analysis 792 MACE events were observed, 392 and 400 in placebo and lixisenatide group, respectively. The 95% confidence interval for the hazard ratio is (0.887, 1.172) with a point estimate of 1.02. The results of on-treatment analysis of MACE are similar. A graphical check (**Figure 15** in **Appendix A**) shows that the assumption of proportional hazards appears reasonable for the MACE analysis.

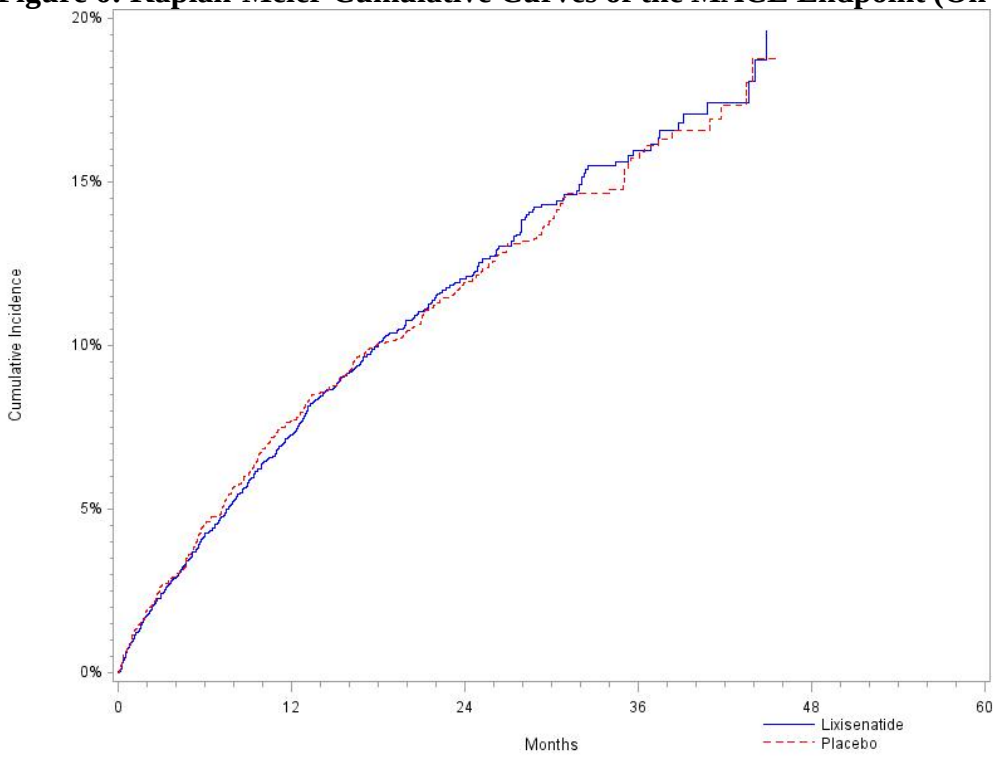
Table 8: Analysis of the MACE Endpoint

	Placebo (N=3,034)	Lixisenatide (N=3,034)	Hazard ratio (95% CI)
MACE endpoint (on-study)			1.02 (0.89, 1.18)
No. of patients with event (%)	392 (12.9%)	400 (13.2%)	
Total Person Year	6340.2	6368.7	
Incidence Rate	6.18	6.28	
MACE endpoint (on-treatment)			1.01 (0.87, 1.17)
No. of patients with event (%)	342 (11.3%)	334 (11.0%)	
Total Person Year	5730.4	5550.9	
Incidence Rate	5.97	6.02	

Source: Created by the reviewer.

Figure 6 shows the Kaplan-Meier Curve of cumulative incidence of MACE over time in both groups. The median time to MACE event is around 26 months for both groups. The incidences were superimposed for the majority of the trial.

Figure 6: Kaplan-Meier Cumulative Curves of the MACE Endpoint (On-study Analysis)



Source: Created by the reviewer, using adtte.xpt.

3.3.4.4 Analyses of All-cause Mortality

In ELIXA, a total of 434 deaths were observed with 223 (7.4%) in the placebo group and 211 (7.0%) in the lixisenatide group for the ITT population. Vital status was available for 99% of the randomized subjects as shown in Section 3.3.1.5; only 71 subjects lacked vital status follow-up – 42 in the placebo group and 29 in the lixisenatide group.

The pre-specified Cox proportional hazards model for time to on-study all-cause mortality resulted in a hazard ratio estimate of 0.94 for lixisenatide versus placebo with two-sided 95% confidence interval of 0.78 to 1.13 (**Table 9**). When only the death during treatment is investigated, the results are similar.

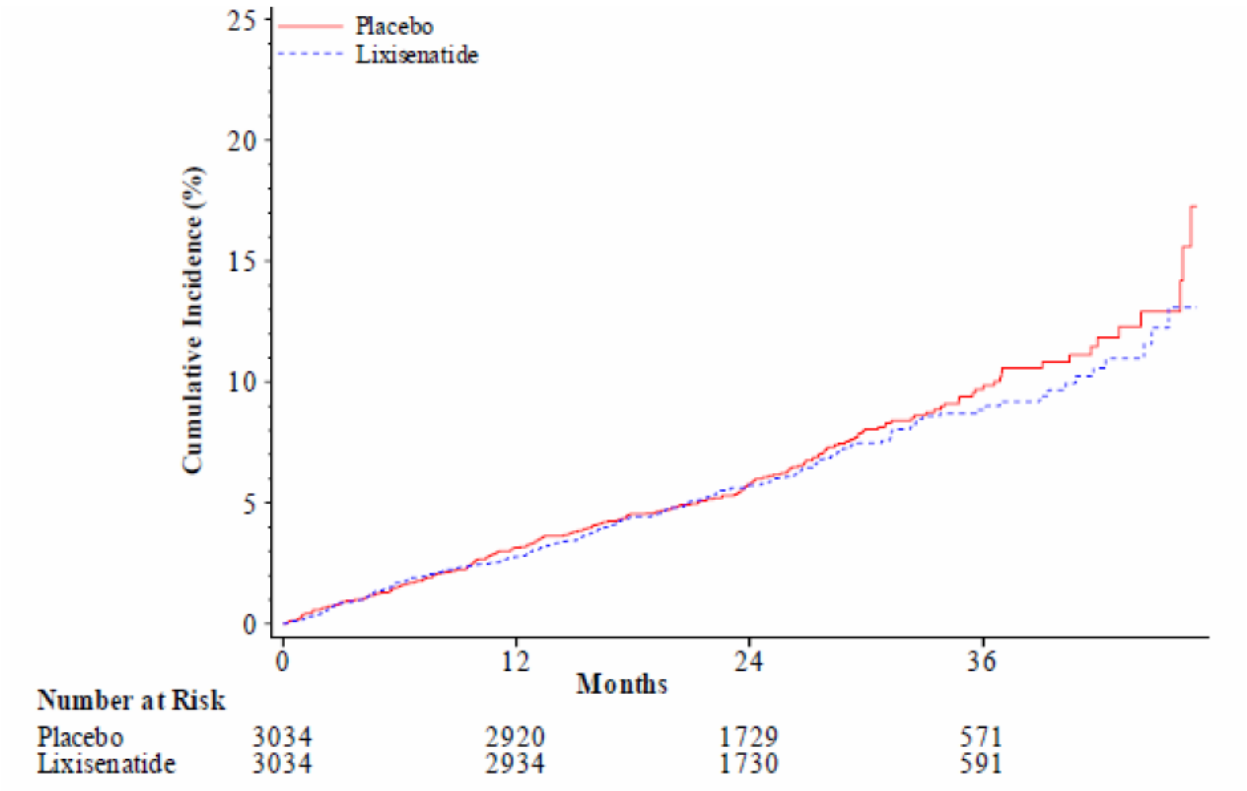
Table 9: Analyses of All-cause Mortality

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

Source: Created by the reviewer using adsl.xpt, adtte.xpt and adtte30.xpt.

Kaplan-Meier curves of time from randomization to death from any cause for lixisenatide and placebo were superimposed for a large part of the study period (**Figure 7**).

Figure 7: Kaplan-Meier Cumulative Curves for All-cause Mortality (On-study Analysis)



Source: Clinical Report (page 101); results reproduced by the reviewer.

A graphical check (**Figure 16** in **Appendix A**) shows that the assumption of proportional hazards appears reasonable for the all-cause mortality analysis.

4 FINDINGS IN SUBGROUP ANALYSES

This section presents subgroup analyses for the primary MACE+ and all-cause mortality endpoints. Because there were very few unstable angina events reported in the study, the subgroup analyses for MACE were not conducted. Subgroups presented here were pre-specified in the statistical analysis plan and defined by baseline demographic factors, medical history and medications taken at the baseline. Note that these subgroup analyses were for exploratory purposes only; as such, statistical findings are based on the two-sided nominal alpha level of 0.05. Analyses of subgroups were based upon a Cox proportional hazards model with treatment and region as factors.

Subgroups analyzed are

- Gender,
- Age group (<65 and ≥65 years of age),
- Race (Caucasian, Black, Asian/Oriental, and Other),
- Region (North America, South and Central America, Western Europe, Eastern Europe, Africa/Near East, and Asia/Pacific),
- Categories of duration of diabetes (<10 years, ≥10 years),
- Index ACS event (ST-segment elevation MI, non ST-segment elevation MI and unstable angina),
- Duration between qualifying ACS and randomization (<30, ≥30 -<60, ≥60 - < 90, ≥90 days),
- Percutaneous coronary intervention (PCI) after ACS and prior to screening (yes, no),
- Baseline HbA1c (< 7.5%, ≥ 7.5%),
- Baseline BMI (< 30, ≥ 30 kg/m^2),
- Intake of Angiotensin Converting Enzyme (ACE) Inhibitors or Angiotensin II Receptor Blockers (ARB) at baseline (yes, no), and
- Intake of statin at baseline (yes, no).

The hazard ratios and the corresponding 95% CIs for each subgroup category were estimated through the Cox model, and the results are shown in forest plots (**Figure 8** to **Figure 13**). A hazard ratio of one is indicative of equivalent rates between lixisenatide and placebo, a hazard ratio greater than one is indicative of a higher rate in lixisenatide compared to placebo and vice versa for a hazard ratio less than one.

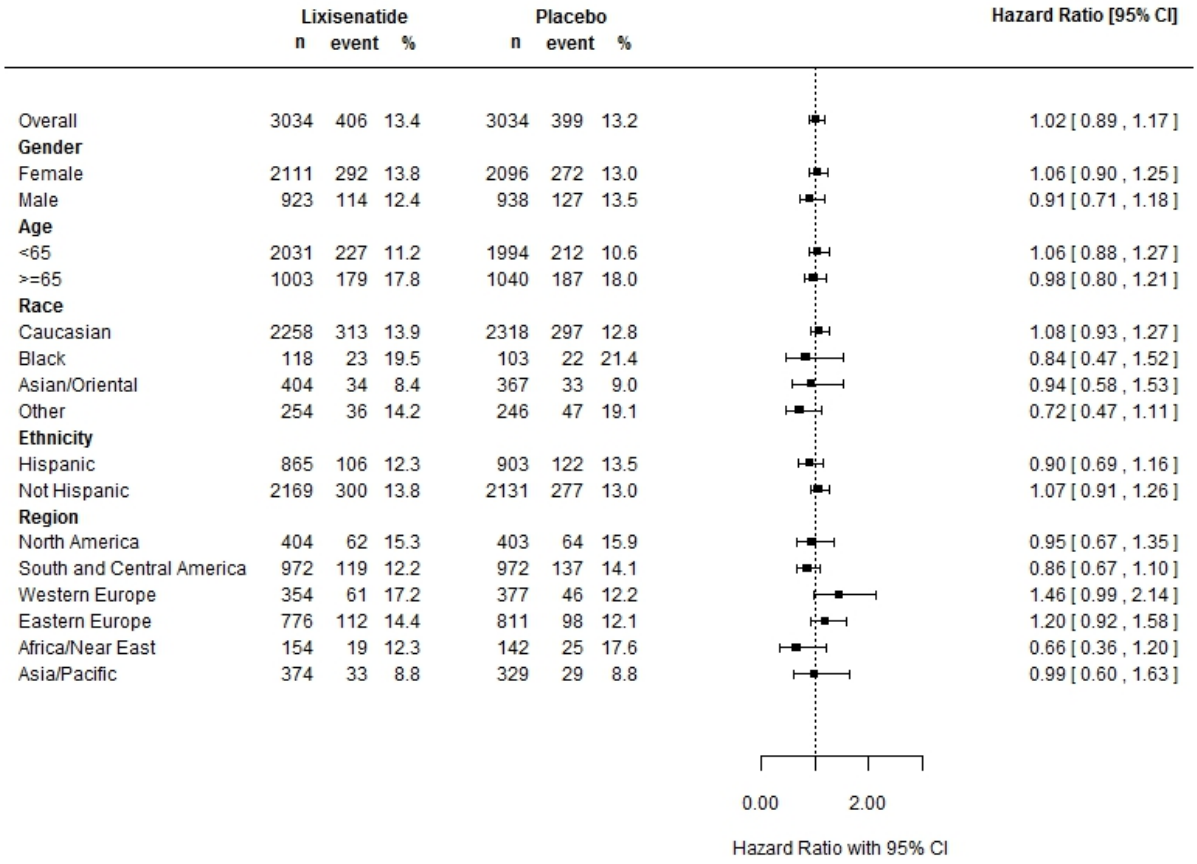
4.1 Subgroup Analyses for MACE+

4.1.1 Demographic Characteristics and Geographical Region

The treatment effect is consistent across demographic variables and geographic location as shown in **Figure 8**. Event rates are similar in males and females (12%-14%) and in both treatment groups. The MACE+ rate for those 65 years old or higher is around 18% in both groups, which is higher than those younger than 65 years old (around 11%). Event rates for

Caucasians are similar to the overall population (around 13%). The smaller subgroups of Asian and Black or African American show a different trend with wide confidence intervals. Event rates are similar in Hispanic and non-Hispanic groups and in both treatment groups. Event rates for North America and Asia/Pacific are similar between two treatment groups, though Asia Pacific has lower rates (8.8%) than overall rates with wide confidence intervals. MACE+ rates for the regions of Western and Eastern Europe are higher for lixisenatide group (14.4-17.2%) than the placebo group (12.1-12.2%) with wide confidence intervals. The regions of South and Central America and Africa/Near East have lower events rates in lixisenatide groups than the placebo groups.

Figure 8: Subgroup Analyses for MACE+ by Demographic Characteristics (On-study Analyses)



Source: Created by the reviewer, using adsl.xpt and adtte.xpt. Similar results were also provided in Clinical Report (page 95).

4.1.2 Medical History

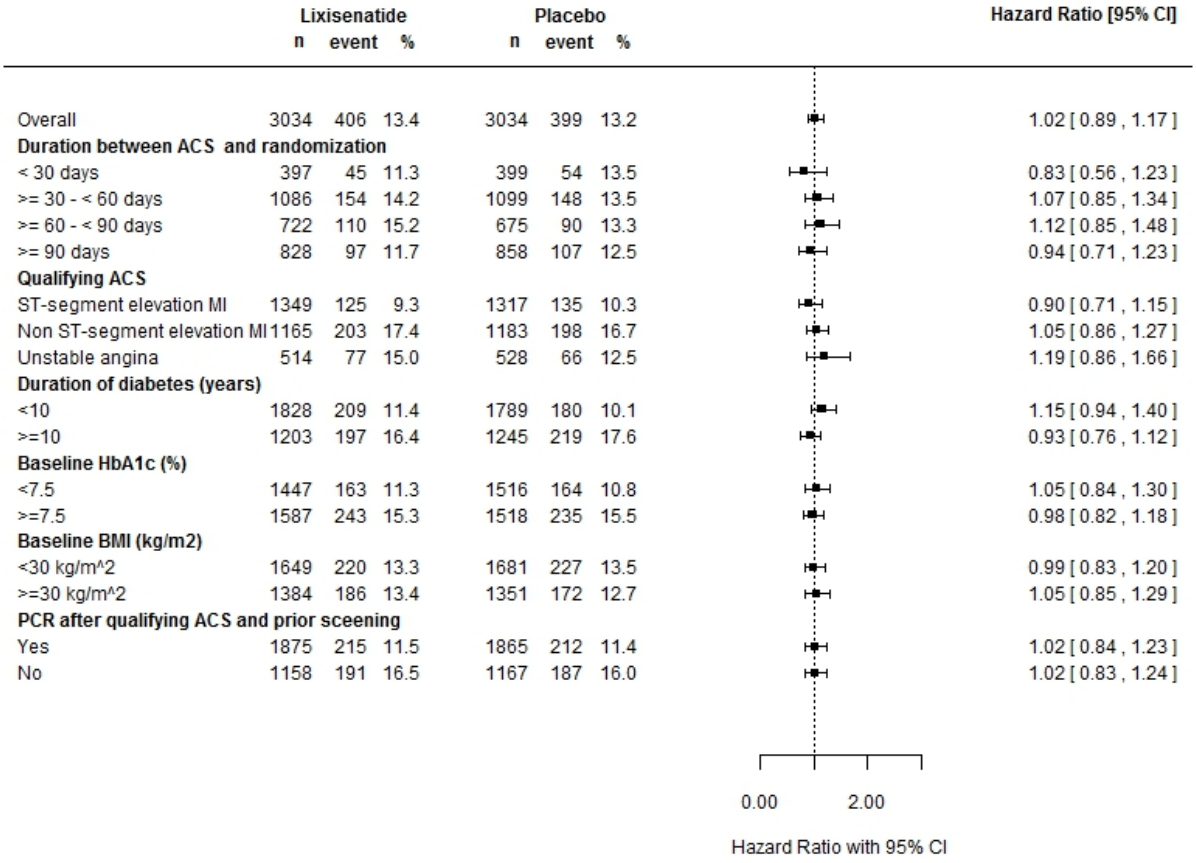
Figure 9 shows the MACE+ event rates, hazard ratios and 95% CIs for the medical history subgroups: time since qualifying ACS event at baseline, qualifying ACS event at baseline, duration of diabetes, HbA1c, BMI and PCI after qualifying ACE and prior screening.

In the lixisenatide group, the event rates is lower (around 11%) for those with the duration between ACS event and randomization shorter than 30 days or longer than 90 days, and higher (around 14-15%) for those with the duration between 30 to 90 days. The event rates in the placebo group are similar to the overall event rates, regardless of the duration between ACS and randomization.

The event rates are higher for those with non ST-segment elevation MI as qualifying ACS and lower for those with ST-segment elevation MI as qualifying ACS. The event rates for those with unstable angina as qualifying ACS is higher in the lixisenatide group than in the placebo group, however it is a relatively small subgroup and the confidence interval for the HR is wide and includes 1.

The event rates are higher for those with a longer diabetes history (16%-17%) than those with shorter history (10%-11%). For the baseline HbA1c, BMI and PCI subgroups, the MACE+ event rates are similar between two treatment groups. Subjects with HbA1c level≥7.5%, BMI<30kg/m^2, or not having PCI after qualifying ACS and prior screening, are found with higher MACE+ events rates, compared to others.

Figure 9: Subgroup Analyses for MACE+ by Medical Conditions at Baseline (On-study Analyses)



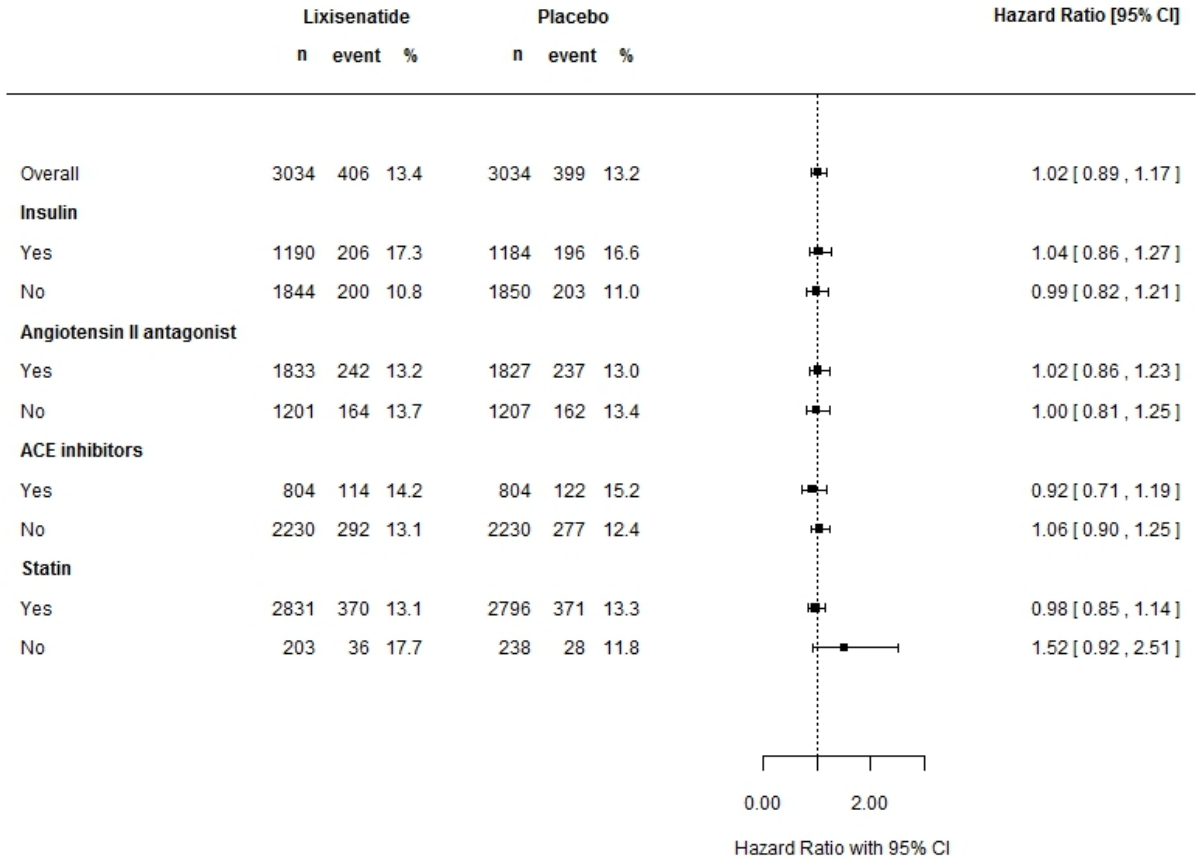
Source: Created by the reviewer, using adsl.xpt and adtte.xpt. Similar results were also provided in Clinical Report (page 96).

4.1.3 Concomitant Medications

The treatment effect is consistent across baseline concomitant medication subgroups as shown in **Figure 10**. This figure shows MACE+ results for those taking or not taking the following drugs at baseline: insulin, Angiotensin II receptor blockers (ARBs), angiotensin-converting-enzyme (ACE) inhibitors or statin. The event rates are higher in insulin users (16%-17%) than in insulin non-users (10-11%), and similar between treatment groups.

For the subgroups of ARB and ACE inhibitors, the results are consistent with overall results, with similar event rates in each subgroup and treatment. Within the statin users, the event rates are similar between treatment groups, similar to the overall incidence rate; and within statin non-users, the event rate is higher in lixisenatide group (17.7%) than in placebo group (11.8%) with a wide confidence interval.

Figure 10: Subgroup Analyses for MACE+ by Concomitant Medication at Baseline (On-study Analyses)



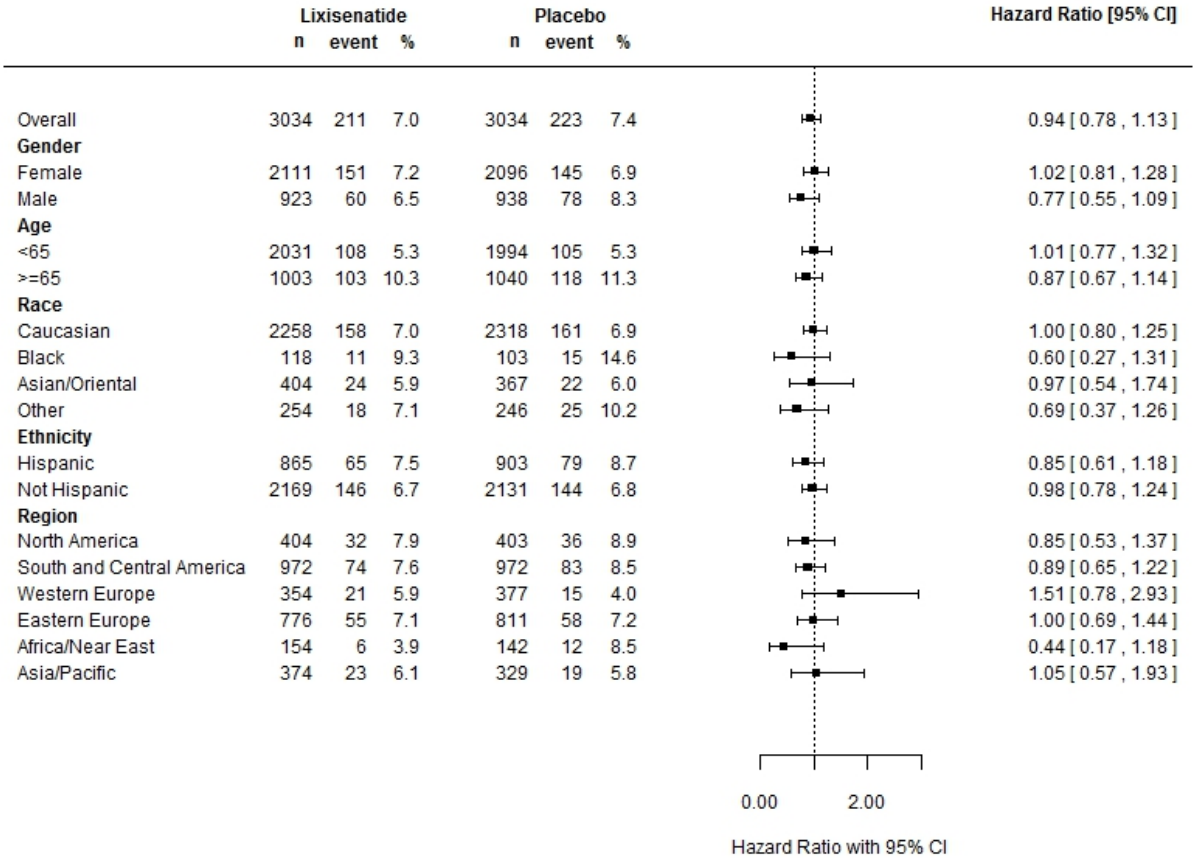
Source: Created by the reviewer, using adsl.xpt and adtte.xpt.

4.2 Subgroup Analyses for All-cause Mortality

4.2.1 Demographic Characteristics and Geographic Region

The treatment effect for mortality is consistent across demographic variables and geographic location as shown in **Figure 11**. Event rates are similar in males and females (6%-8%) and in both treatment groups. The mortality rate for those 65 years old or higher is around 11% in both groups, which is higher than those younger than 65 years old (5.3%). Mortality rates for Caucasians are similar to the overall population (around 7%). The smaller subgroups of Asian and Black or African American show a different trend with wide confidence intervals. Mortality rates in Hispanics (7.5-8.7%) are higher than non-Hispanics (6.7-6.8%) for both treatment groups. In the regions of North America, South America, and Africa/Near East, the mortality rates in the lixisenatide group are lower than those in the placebo group. In the regions of Eastern Europe and Asia/Pacific, the mortality rates are similar between two treatment groups. In the region of Western Europe, the mortality rates are higher for the lixisenatide group (5.9%) than the placebo group (4.0%) with wide confidence intervals.

Figure 11: Subgroup Analyses for All-cause Mortality by Demographic Characteristics (On-study Analyses)



Source: Created by the reviewer, using adsl.xpt and adtte.xpt.

4.2.2 Medical History

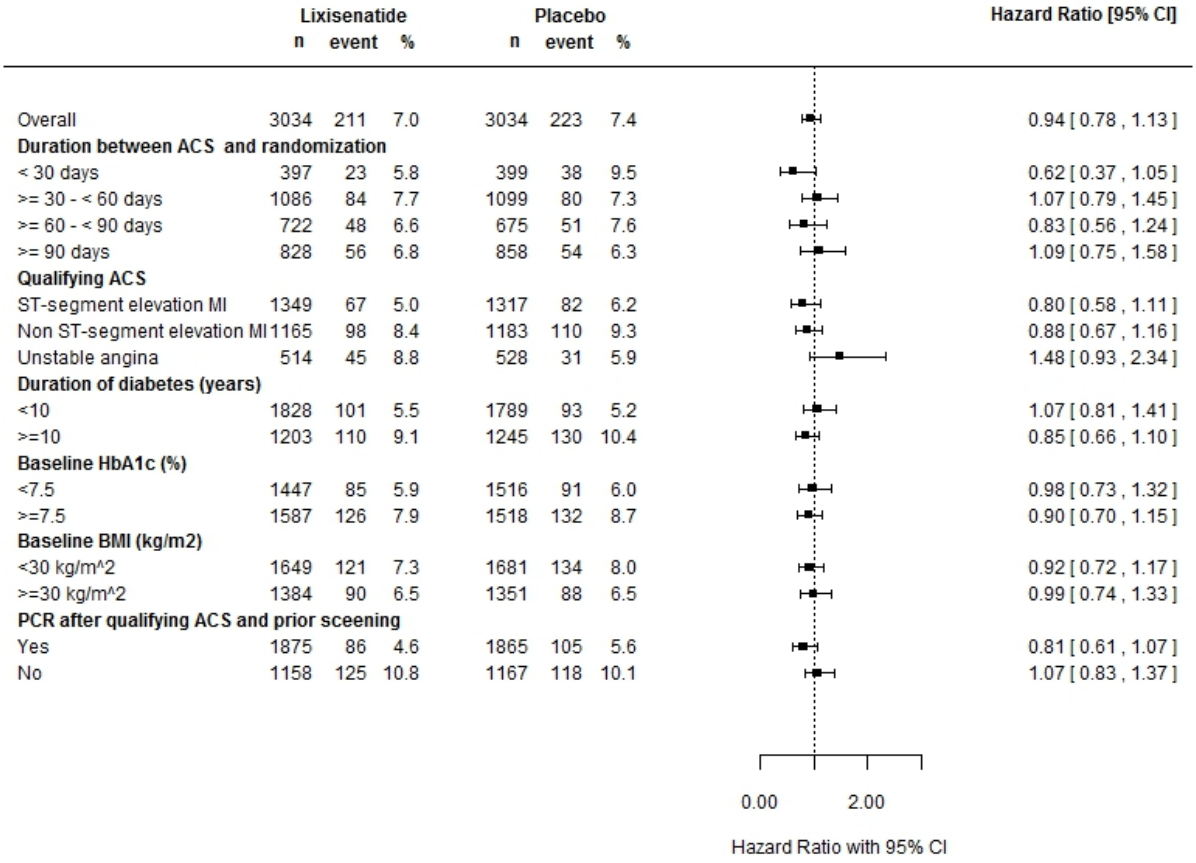
Figure 12 shows the mortality rates, hazard ratios and 95% CIs for the medical history subgroups.

For the duration between ACS event and randomization, if this duration is shorter than 30 days, the lixisenatide group has a mortality rate (5.8%) lower than the overall rate, while the placebo group has a mortality rate (9.5%) higher than the overall rate. The mortality rates for those with the duration longer than 30 days are similar in both treatment groups, which are also similar to overall rates.

The mortality rates are higher (8-9%) for those with non ST-segment elevation MI as qualifying ACS and lower (5-6%) for those with ST-segment elevation MI as qualifying ACS. The mortality rates for those with unstable angina as qualifying ACS is higher in the lixisenatide group (8.8%) than those in the placebo group (5.9%), however it is a relatively small subgroup and the confidence interval for the HR is wide and includes 1.

The mortality rates are higher for those with longer diabetes history (9%-10%) than those with shorter history (around 5%). For the baseline HbA1c, BMI and PCI subgroups, the mortality rates are similar between two treatment groups. Subjects with HbA1c level≥7.5%, baseline BMI<30kg/m^2, or not having PCI after qualifying ACS and prior screening, are found with higher mortality rates, compared to those with lower HbA1c, higher BMI or having PCI after ACS, respectively.

Figure 12: Subgroup Analyses for All-cause Mortality by Medical Conditions at Baseline (On-study Analyses)



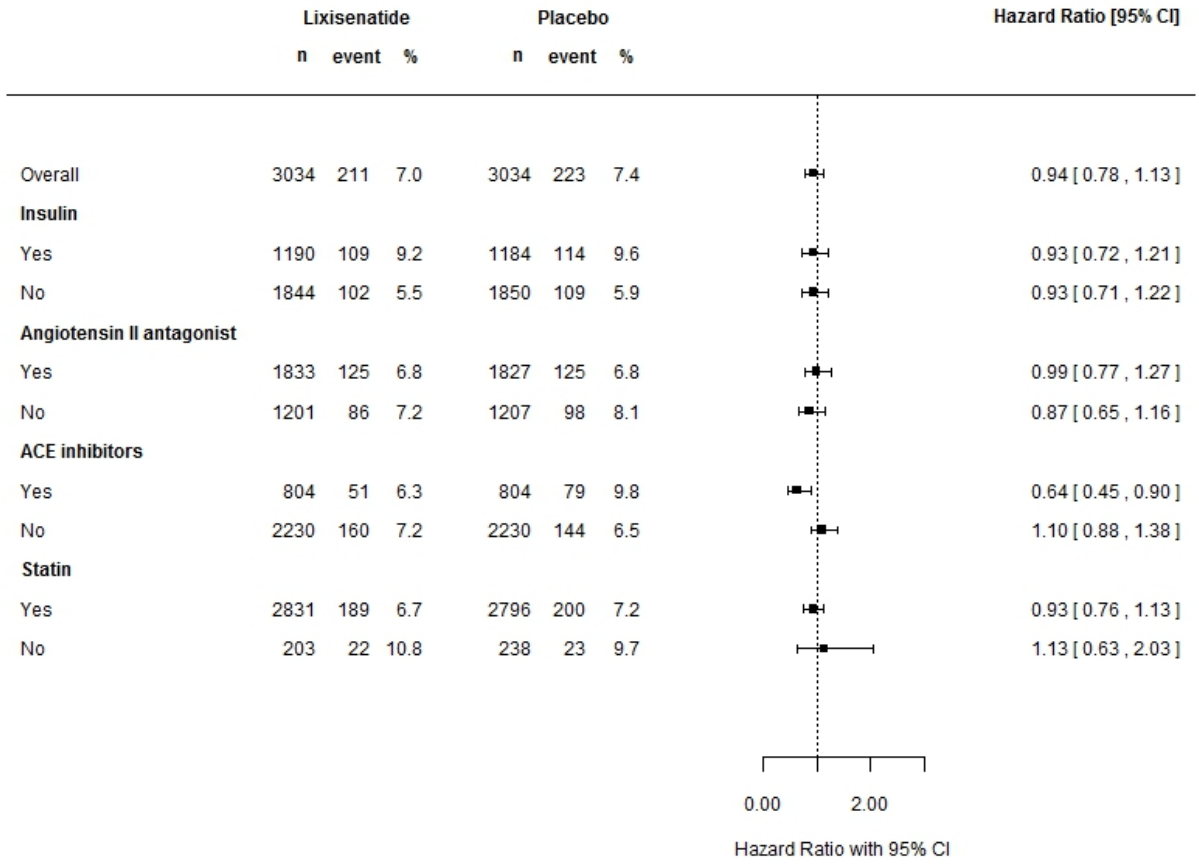
Source: Created by the reviewer, using adsl.xpt and adtte.xpt.

4.2.3 Concomitant Medications

The treatment effect is consistent across baseline concomitant medication subgroups as shown in **Figure 13**. This figure shows mortality results for those taking or not taking the following drugs at baseline: insulin, ARBs, ACE inhibitors or statin. The mortality rates are higher in insulin users (around 9%) than in insulin non-users (around 5%), and similar between treatment groups.

For the subgroups of ARB users, the mortality rates are similar between treatment groups; and for the non-ARB users, the lixisenatide group has a mortality rate similar to the overall rate while the placebo group has a higher mortality rate (8.1%). For the subgroups of ACE inhibitor users, the mortality rates in the lixisenatide group is lower than the placebo group; and for the non-ACE users, the lixisenatide group has a mortality rate similar to the overall rate, while the placebo group has a lower mortality rate (6.5%). Within the statin users, the event rates are similar between treatment groups, similar to the overall incidence rate; and within statin non-users, the event rate is higher in the lixisenatide group (10.8%) than in the placebo group (9.7%).

Figure 13: Subgroup Analyses for All-cause Mortality by Concomitant Medication at Baseline (On-study Analyses)



Source: Created by the reviewer, using adsl.xpt and adtte.xpt.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The ELIXA trial was a well-conducted double-blind, placebo-controlled, randomized clinical trial. The primary endpoint is MACE+ (cardiovascular death, non-fatal myocardial infarction, non-fatal ischemic stroke, and hospitalization for unstable angina), and the secondary endpoints

are composite CV endpoints and all-cause mortality. The primary time-to-event analyses were based upon a Cox proportional model adjusted by treatment and region for the ITT population that includes all events observed during the trial (i.e. this analysis is based on all randomized subjects and includes all events that occur either on or off treatment). The proposed testing strategy and plan to rule out a risk margin of 1.3 are in-line with the 2008 FDA Guidance "Diabetes Mellitus – Evaluating Cardiovascular Risk in New Anti-diabetic Therapies to Treat Type 2 Diabetes." There are no statistical concerns on the design, conduct, and analysis of the primary and secondary endpoints.

5.2 Collective Evidence

The ELIXA trial was a randomized, double-blind, placebo-controlled cardiovascular outcome trial designed to assess the cardiovascular safety of lixisenatide. A total of 6068 randomized subjects were included in the intent-to-treat population. The analysis of ELIXA was planned to rule out a hazard ratio of 1.3 or above for lixisenatide compared to placebo.

Pre-specified endpoints included a primary MACE+ endpoint, secondary CV endpoints, and all-cause mortality. Cardiovascular events were adjudicated by a committee of specialists, blinded to treatment assignment. The primary analysis was time to first event using a Cox proportional hazard model with treatment and regions as factors. The adjudication of events and analyses used in ELIXA are appropriate.

The analysis of the ELIXA trial ruled out a hazard ratio risk margin of 1.3 or above of lixisenatide compared to placebo. By the end of the study, there were 805 MACE+ events, 406 in the lixisenatide group and 399 in the placebo group. The 95% confidence level for MACE+ is 1.02 (0.89, 1.17).

Sensitivity analyses planned by the applicant or conducted by the reviewer supported the same conclusion of ruling out a hazard ratio of 1.3 or above of lixisenatide compared to placebo. This holds true for on treatment MACE+, and on study or on-treatment MACE. All subgroup analyses were consistent with the treatment observed in overall population except for some small subgroups. Analyses of all-cause mortality found no increased risk of subjects randomized to the lixisenatide group compared to the placebo group.

An assessment of the malignancy risks for thyroid, lung, colorectal, breast (female) and prostate (male), a time-to-event analysis using ELIXA trial (**Appendix B1**) and a meta-analysis using a selected list of controlled Phase III trials (**Appendix B2**) were conducted. These analyses were not pre-specified and were conducted for exploratory purpose only. It was found that the event rates in the ELIXA trial and in the integrated analysis of all trials were low and did not provide sufficient evidence to support that there were any increased malignancy risks in the lixisenatide group.

5.3 Conclusions and Recommendations

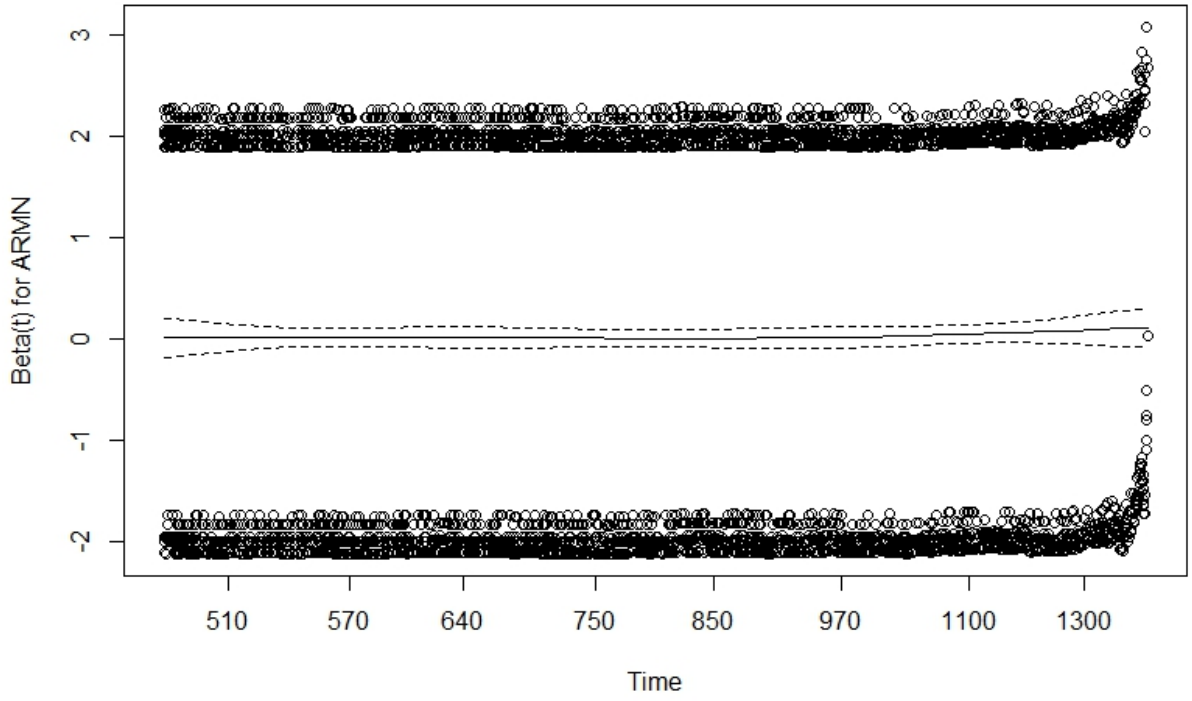
The applicant evaluated cardiovascular safety of lixisenatide through the ELIXA cardiovascular outcomes trial. The pre-specified Cox proportional hazards model for the primary MACE+

endpoint (cardiovascular death, non-fatal myocardial infarction, and non-fatal ischemic stroke, and hospitalization for unstable angina) estimated a hazard ratio of 1.02 with an associated 95% confidence interval of (0.89, 1.17). The upper bound of this confidence interval was smaller than 1.3 and therefore met the hazard ratio risk margin specified by the 2008 FDA Guidance on establishing cardiovascular safety of a new antidiabetic product.

APPENDICES

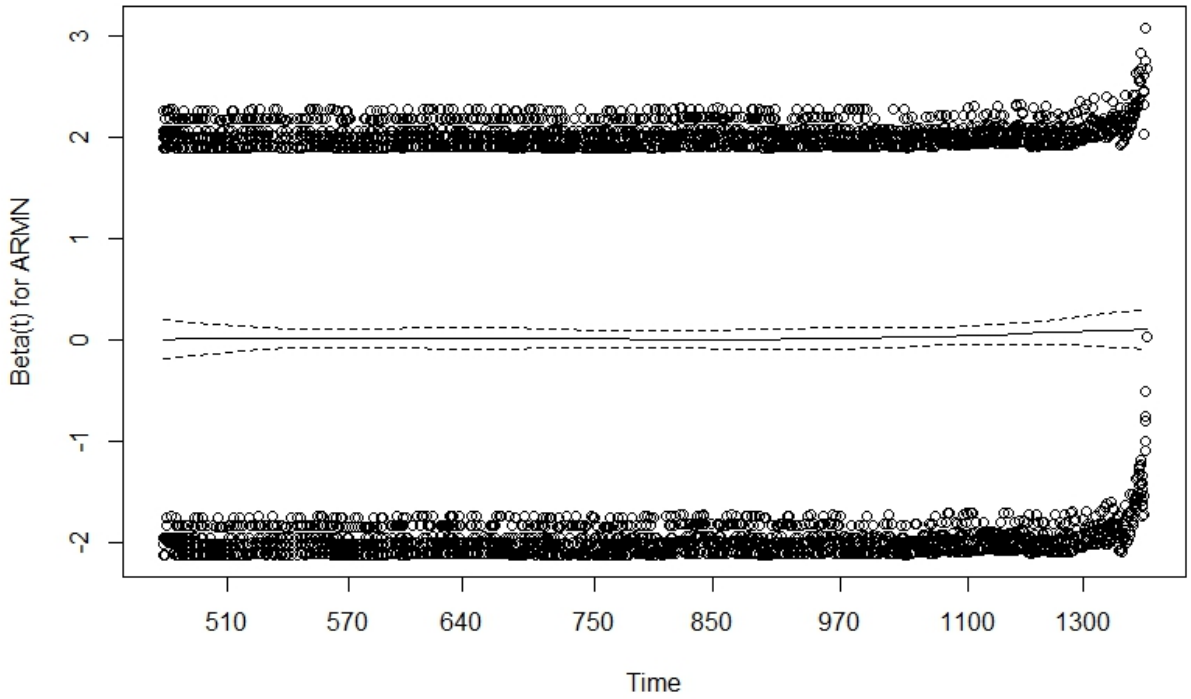
Appendix A: Evaluation of the Cox Proportional Hazard Model Assumptions

Figure 14: Assessment of Proportional Hazards Assumption for Primary MACE+ Analysis



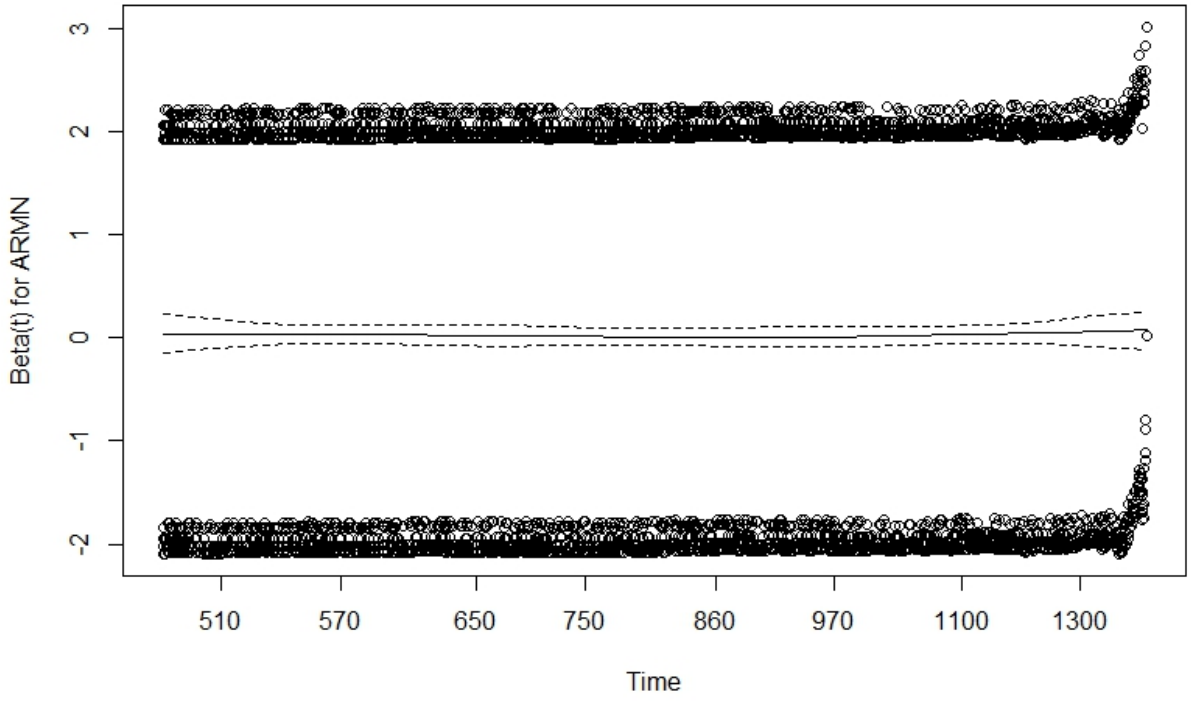
The primary MACE+ analysis used a Cox proportional hazards model to estimate hazard ratio and associated confidence intervals. To assess the proportional hazards assumption, Scaled Schoenfeld residuals were plotted in **Figure 14**. It included residuals from both the lixisenatide and placebo groups. In the plot, deviations from the horizontal line of the fitted line indicated potential violation of the proportional hazards assumption. The fitted line did not show evidence of a non-zero slope. Hence the proportional hazards assumption was reasonable for the Cox proportional hazards model fit to the primary MACE+ Cox analysis.

Figure 15: Assessment of Proportional Hazards Assumption for On-study MACE Analysis



The on-study MACE analysis used a Cox proportional hazards model to estimate the hazard ratio and associated confidence intervals. To assess the proportional hazards assumption, Scaled Schoenfeld residuals were plotted in **Figure 15**. It included residuals from both the lixisenatide and placebo groups. In the plot, deviations from the horizontal line of the fitted line indicated potential violation of the proportional hazards assumption. The fitted line did not show evidence of a non-zero slope. Hence the proportional hazards assumption was reasonable for the Cox proportional hazards model fit to the on-study MACE Cox analysis.

Figure 16: Assessment of Proportional Hazards Assumption for On-study All-cause Mortality Analysis



The on-study all-cause mortality analysis used a Cox proportional hazards model to estimate the hazard ratio and associated confidence intervals. To assess the proportional hazards assumption, Scaled Schoenfeld residuals were plotted in **Figure 16**. It included residuals from both the lixisenatide and placebo groups. In the plot, deviations from the horizontal line of the fitted line indicated potential violation of the proportional hazards assumption. The fitted line did not show evidence of a non-zero slope. Hence the proportional hazards assumption was reasonable for the Cox proportional hazards model fit to the on-study all-cause mortality Cox analysis.

Appendix B: Malignancy Risks

In the review of the ELIXA trial, more malignancy events (thyroid, lung, colorectal, breast (female) and prostate (male)) were observed in lixisenatide subjects compared to placebo subjects. To investigate the risk of malignancy (thyroid, lung, colorectal, breast [female] and prostate [male]) in lixisenatide compared to placebo, a time-event analysis of malignancy events in the ELIXA trial was conducted in **Appendix B1**. In addition, an exploratory meta-analysis was conducted for a select list of controlled and completed Phase 3 studies in **Appendix B2**. Statistical methodologies and analysis details used below were only for exploratory purpose.

Appendix B1: Time-to-event Analysis of Malignancy Risks in ELIXA

In this section, a time-event analysis of malignancy events was conducted using information from the ELIXA trial.

Design and Analysis Methods

The analysis population is the safety population, ie, all randomized patients who received at least one dose of double-blind lixisenatide or placebo drug. The events considered are on-study. Using an on-study analysis, malignancy events contributing to the analysis include those occurring from randomization to the common study end date, even if a subject has discontinued randomized treatment.

Malignancy was defined by Medical Dictionary for Regulatory Activities (MedDRA) Standardized MedDRA Queries (SMQ) of malignant tumors #20000091[2]. Additional classifications by subcategory (thyroid, lung, colorectal, breast, prostate, and other) were done based on this SMQ.

The analysis for the malignancy outcomes (thyroid, lung, colorectal, breast [female] and prostate [male]) was performed using a Cox proportional hazards model with treatment (lixisenatide, placebo) and region (North America, South and Central America, Western Europe, Eastern Europe, Africa/Near East, and Asia/pacific) as the covariates to estimate the hazard ratio between lixisenatide and placebo and the associated two-sided 95% confidence interval.

Study Results

For each site-specific malignancy, the results are presented in **Table 10** for number of events, person-years within each group, the estimated hazard ratio between lixisenatide and placebo and the associated two-sided 95% confidence interval.

Thyroid Cancer

By the end of the study, there were 20 subjects (8 in placebo and 11 in lixisenatide) with at least one thyroid malignancy event. The incidence rates were 1.2 and 1.6 per 1000 person-years for

[2] Refer to for a definition of the Malignancies SMQ (pg. 159):
http://www.meddra.org/sites/default/files/guidance/file/smq_intguide_16_0_english.pdf

placebo and lixisenatide, respectively. Using the Cox proportional hazards model, the hazard ratio estimate and associated 95% confidence interval is 1.38 (0.55, 3.43) which includes unity.

Lung Cancer
By the end of the study, there were 20 subjects (12 in placebo and 8 in lixisenatide) with at least one lung malignancy event. The incidence rates were 1.8 and 1.2 per 1000 person-years for placebo and lixisenatide, respectively. Using the Cox proportional hazards model, the hazard ratio estimate and associated 95% confidence interval is 0.66 (0.27, 1.61) which includes unity.

Colorectal Cancer
By the end of the study, there were 28 subjects (11 in placebo and 17 in lixisenatide) with at least one colorectal malignancy event. The incidence rates were 1.6 and 2.5 per 1000 person-years for placebo and lixisenatide, respectively. Using the Cox proportional hazards model, the hazard ratio estimate and associated 95% confidence interval is 1.55 (0.73, 3.31) which includes unity.

Breast Cancer (Female)
By the end of the study, there were 6 female subjects (3 in placebo and 3 in lixisenatide) with at least one breast malignancy event. The incidence rates were 1.4 and 1.5 per 1000 person-years for placebo and lixisenatide, respectively. Using the Cox proportional hazards model, the hazard ratio estimate and associated 95% confidence interval is 1.03 (0.21, 5.13) which includes unity.

Prostate Cancer (Male)
By the end of the study, there were 22 male subjects (8 in placebo and 14 in lixisenatide) with at least one prostate malignancy event. The incidence rates were 1.8 and 3.0 per 1000 person-years for placebo and lixisenatide, respectively. Using the Cox proportional hazards model, the hazard ratio estimate and associated 95% confidence interval is 1.75 (0.73, 4.16) which includes unity.

Table 10: Analysis of Malignancy Outcomes (ELIXA, Safety Population, On-study Analysis)

	Placebo (N=3,032)	Lixisenatide (N=3,031)	Hazard ratio (95% CI)
Thyroid			1.38 (0.55, 3.43)
No. of patients	3,032	3,031	
No. of patients with event (%)	8 (0.3%)	11 (0.4%)	
Total Person Year	6680.6	6708.1	
Incidence Rate (per 1000 PY)	1.2	1.6	
Lung			0.66 (0.27, 1.61)
No. of patients	3,032	3,031	
No. of patients with event (%)	12 (0.4%)	8 (0.3%)	
Total Person Year	6678.2	6719.7	
Incidence Rate (per 1000 PY)	1.8	1.2	
Colorectal			1.55 (0.73, 3.31)
No. of patients	3,032	3,031	
No. of patients with event (%)	11 (0.4%)	17 (0.6%)	
Total Person Year	6673.7	6705.0	
Incidence Rate (per 1000 PY)	1.7	2.5	
Breast (female)			
No. of patients	937	920	1.03 (0.21, 5.13)
No. of patients with event (%)	3 (0.3%)	3 (0.3%)	
Total Person Year	2094.4	2032.4	
Incidence Rate (per 1000 PY)	1.4	1.5	
Prostate (male)			
No. of patients	2,095	2,111	1.75 (0.73, 4.16)
No. of patients with event (%)	8 (0.4%)	14 (0.7%)	
Total Person Year	4579.2	4669.9	
Incidence Rate (per 1000 PY)	1.8	3.0	

Source: Created by the reviewer using adsl.xpt, adtte.xpt and adae.xpt from ELIXA trial.

Appendix B2: Meta-analysis of Malignancy Risks

In this section, an exploratory meta-analysis of a selected list of trials was conducted to further investigate malignancy risks (thyroid, lung, colorectal, breast [female] and prostate [male]) in lixisenatide exposed subjects.

Among all Phase 2 and Phase 3 clinical trials that study the efficacy of lixisenatide on glycemic control (HbA1c) over 24 weeks, the meta-analysis was conducted using the subset of trials that:

- had a treatment duration of at least 76 weeks, and
- had a randomized placebo group or active control group.

The meta-analysis studied the safety population in all the qualified trials. The safety population is defined as all randomized patients who actually received at least one dose of investigational product (lixisenatide or control drug).

Malignancy was defined by MedDRA SMQ of Malignant tumors #20000091. Additional classifications by subcategory (thyroid, lung, colorectal, breast, prostate, and other) were done based on this SMQ.

Data Source

The material submitted by the applicant and considered in this section are the study report and datasets for the integrated summary of safety as well as the study report and datasets for ELIXA which have previously been discussed in the main body of the review (see Section 3 and 4).

Links to material about malignancy outcomes from the ISS are the following.

- Integrated Summary Safety Report: \\cdsesub1\evsprod\nda208471\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5353-rep-analys-data-more-one-stud\iss\iss.pdf
- Datasets for Integrated Summary Safety Report: \\cdsesub1\evsprod\NDA208471\0000\m5\datasets\iss\analysis\legacy\datasets

In addition to the ELIXA datasets, datasets utilized in this section are the following:

- Demographic variables in Integrated Safety Summary (ISS) datasets: addm.xpt
- Subject-level variables in ISS datasets: adsl.xpt
- Exposure variables in ISS datasets: adex.xpt
- Adverse event variables in ISS datasets: adex.xpt

Analysis Methods

The odds ratio (OR) and 95% confidence interval (CI) were calculated for each study, and results were compared through the use of a fixed effect model via one step Peto's method.

Trial Similarities and Differences

As of March 2nd, 2015 there were 20 completed Phase 2 and Phase 3 clinical trials. By applying the inclusion criteria of 1) Treatment period ≥76 weeks and 2) placebo or active drug controlled, this meta-analysis of malignancy included six pivotal trials and the ELIXA trial.

The studies have similar main design elements and a few differences, summarized in **Table 11**. Trial sample size varied from 482 subjects in the EFC10743 trial to 6063 subjects in the ELIXA trial. Overall, the trials included a total of 5405 subjects randomized to lixisenatide and 4292 subjects randomized to comparator.

All trials were multinational randomized trials in type 2 diabetic subjects with treatment durations of at least 76 weeks. The trials were different in several aspects. First, the six pivotal trials enrolled subjects diagnosed with T2DM, and the ELIXA trial enrolled subjects diagnosed with T2DM and also experienced a spontaneous ACS event within 180 days of enrollment. Second, the EFC6019 trial was open-label, and all the other trials were double-blinded trials. Third, the background therapies were different among all the trials. Lastly, the lixisenatide dosage and titration was not the same. All the six pivotal trials considered a therapy with two-step titration from 10 μg to 15 μg to a maintenance dose of 20μg whereas the ELIXA trial considered one-step titration from 10 μg to 20 μg.

Table 11: Summary of Trials Included in Meta-analysis of Malignancy Events

Studies % of subjects in US	Treatment Duration and titration	Design	Number of subjects per treatment group in Safety Population	Background therapy for T2D patients
Pivotal Trials				
EFC6014	≥76 weeks (2-step titration)	Multinational, randomized, parallel-group, double-blind, 4-arm, unbalanced design	Placebo=170 Lixisenatide=510	Metformin
EFC6015	≥76 weeks (2-step titration)	Multinational, randomized, parallel-group, double-blind, 2-arm, unbalanced design	Placebo=286 Lixisenatide=573	Sulfonylurea with or without metformin
EFC6016	≥76 weeks (2-step titration)	Multinational, randomized, parallel-group, double-blind, 2-arm, unbalanced design	Placebo=167 Lixisenatide=328	Basal insulin with or without metformin
EFC6017	≥76 weeks (2-step titration)	Multinational, randomized, parallel-group, double-blind, 4-arm, unbalanced design	Placebo=161 Lixisenatide=323	Pioglitazone with or without metformin
EFC6019	≥76 weeks (2-step titration)	Multinational, randomized, parallel-group, 2-arm, open-label, balanced design	Exenatide=316 Lixisenatide=318	Exenatide
EFC10743	≥76 weeks (2-step titration)	Multinational, randomized, parallel-group, double-blind, 4-arm, unbalanced design	Placebo=160 Lixisenatide=322	Metformin
CVOT Trial				
EFC11319	≥76 weeks (1-step titration)	Multinational, randomized, parallel-group, double-blind, 2-arm, balanced design	Placebo=3032 Lixisenatide=3031	Metformin, sulfonylureas, thiazolidinediones, insulin, and others.

Differences in study designs have contributed to some between study heterogeneity of baseline characteristics and could contribute to between study heterogeneity of results in malignancy event outcomes. The objective for this meta-analysis was to detect safety signals of malignancy using the clinical trial data. Because the six pivotal trials have more similarity in trial designs, they were pooled together to compare with the ELIXA trial.

Table 12 shows the demographics characteristics of the subjects in all the trials. In each treatment group the mean age was 56-60 years. The sex ratio was fairly balanced in the six pivotal trials, and there were more males than females in the ELIXA trial. The study population was about three quarters Caucasian and 12-17% Asian.

Table 13 shows the baseline medical condition. In each treatment group, the mean age at first diagnosis of T2DM was 48-52 years, and the mean duration of type 2 diabetes was around 8 years for the subjects in the six pivotal trials and 9 years for the ELIXA trial. In addition, the mean baseline BMI was around 32 for the subjects in six pivotal trials and 30 for ELIXA trial, the mean baseline HbA1c was around 8.1 for the subjects in six pivotal trials and 7.6 for ELIXA trial. There were around 20% former smokers in the six pivotal trials, and around 45% in the ELIXA trial.

Table 12: Subject's demographic characteristics in studies in the meta-analysis, by treatment

Treatment groups	Pivotal trials		ELIXA	
	Lixisenatide	All comparators	Lixisenatide	Placebo
Total sample size, N	2374	1260	3031	3032
Age (years)				
mean (sd)	56.2(9.6)	57.0(10.0)	59.9(9.7)	60.6(9.6)
median (min, max)	57(23, 87)	57(20, 83)	60(30, 93)	61(30, 89)
Sex, n (%)				
Female	1266(53)	606(48)	920(30)	937(31)
Male	1108(47)	654(52)	2111(70)	2095(69)
Race, n (%)				
White	1856(78)	1008(80)	2255(74)	2317(76)
Asian	395(17)	188(15)	404(13)	366(12)
Black or African American	69(3)	39(3)	118(4)	103(3)
Other	54(2)	25(2)	254(8)	246(8)

Source: Created by the reviewer, using iss/adsl.xpt dataset.

Table 13: Subject's medical history at baseline in studies in the meta-analysis, by treatment

Treatment groups	Pivotal trials		ELIXA	
	Lixisenatide	All comparators	Lixisenatide	Placebo
Age at onset of type 2 diabetes (years)				
Number	2374	1260	3030	3032
mean (sd)	48.1(9.4)	48.8(9.9)	50.8(10.7)	51.3(10.7)
median (min, max)	48(12, 80)	49(14, 77)	51(17, 91)	51(13, 87)
Duration of type 2 diabetes (years)				
Number	2374	1260	3030	3032
mean (sd)	8.1(6.0)	8.2(5.9)	9.2(8.2)	9.4(8.3)
median (min, max)	6.8(0.5, 52.1)	6.8(0.6, 40.0)	7.4(0.0, 50.0)	7.4(0.0, 54.7)
Baseline BMI (kg/m^2)				
Number	2374	1260	3031	3030
mean (sd)	32.2(6.4)	32.6(6.6)	30.1(5.6)	30.2(5.8)
median (min, max)	31.4(19.0, 64.4)	31.6(19.5, 69.3)	29.4(17.1, 68.9)	29.3(16.9, 59.3)
Baseline HbA1c (%)				
Number	2374	1260	3031	3031
mean (sd)	8.1(0.9)	8.1(0.8)	7.7(1.3)	7.6(1.3)
median (min, max)	8.0(5.3, 12.7)	8.0(6.1, 10.8)	7.5(4.9, 13.3)	7.5(5.0, 11.5)
Smoking Status at baseline				
Number	2360	1248	3031	3032
Current smoker	321(14)	162(13)	355(12)	353(12)
Former smoker	465(20)	258(21)	1390(46)	1356(45)
Never smoker	1574(67)	828(66)	1286(42)	1323(44)

Source: Created by the reviewer, using iss/adsl.xpt dataset.

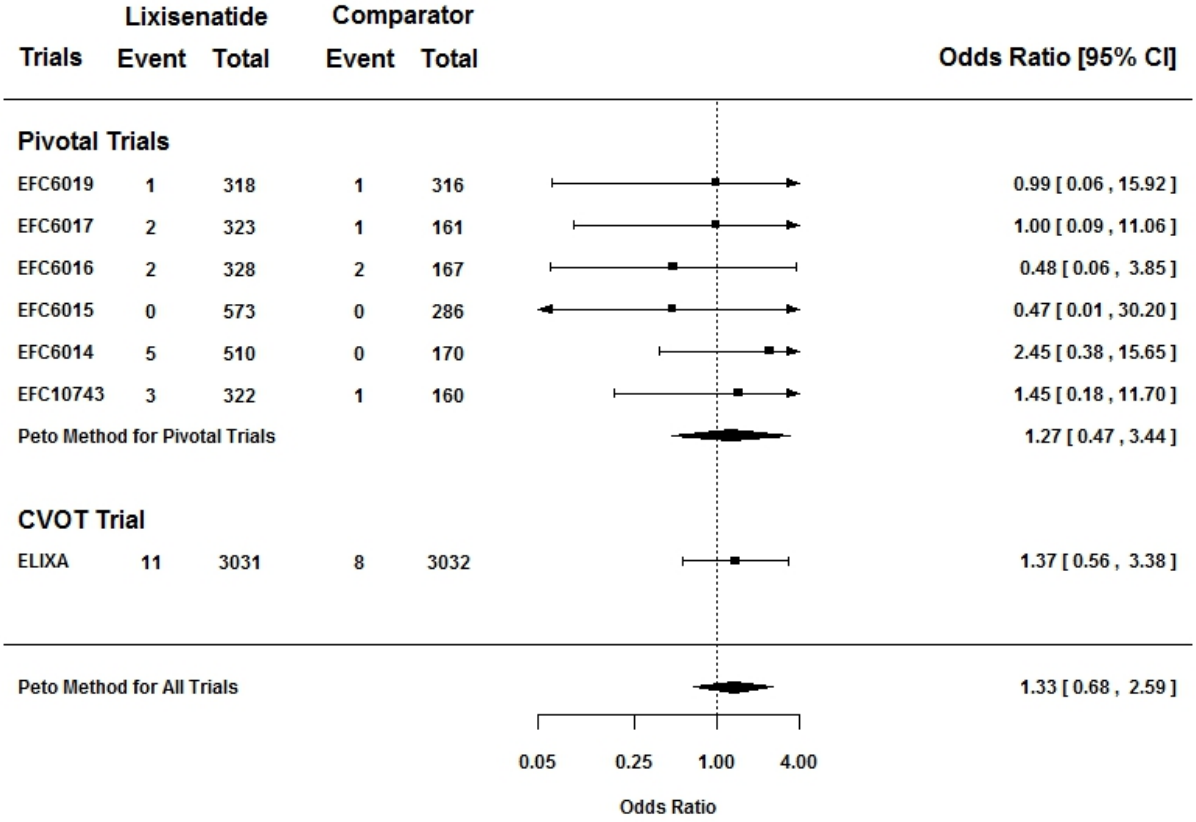
Meta-analysis Results

This section summarizes the results of meta-analysis findings for thyroid, lung, colorectal, breast (female) and prostate (male) malignancies.

Thyroid Cancer

There were a total of 38 thyroid cancer events from the 7 trials, 25 events in the lixisenatide group and 13 events in the all comparators group. Most trials had a low number of events and numerically favor comparator over lixisenatide. The forest plot in **Figure 17** shows the number of events, the event rate and the estimate of the odds ratio of lixisenatide compared to comparators. There were fewer or equal to 4 events in each treatment group in most trials, 20 events were contributed by the ELIXA trial and 5 events were contributed by the EFC 6014 trial. By pooling all the six pivotal trials together, the odds ratio was estimated at 1.27 with a 95% confidence interval of (0.47, 3.44). From the ELIXA trial, the odds ratio was estimated at 1.37 with a 95% confidence interval of (0.56, 3.38). The overall estimate of the thyroid odds ratio that includes all six pivotal trials and ELIXA was 1.33 with a 95% confidence interval of (0.68, 2.59).

Figure 17: Meta-analysis Results of Thyroid Malignancies

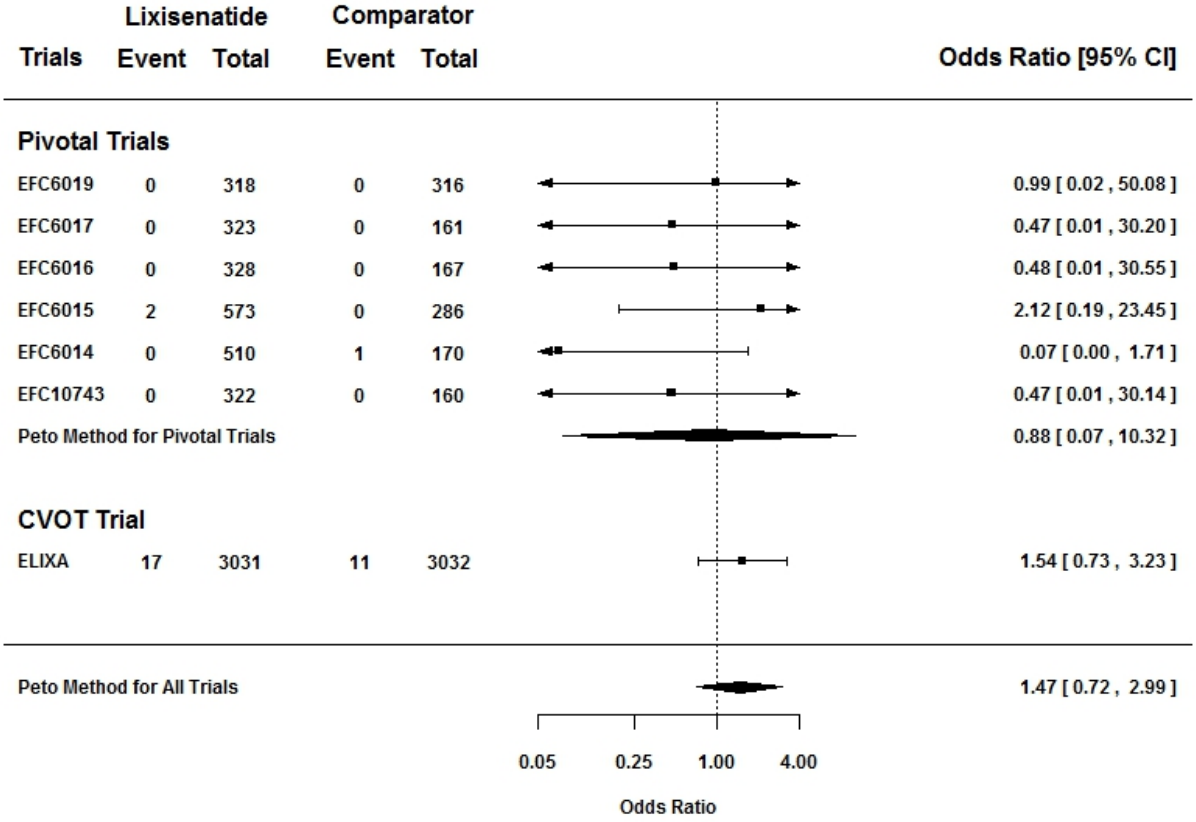


Source: Created by the reviewer using iss\addm.xpt and iss\adae.xpt.

Colorectal Cancer

There were a total of 31 colorectal cancer events, 19 events in the lixisenatide group and 12 events in the all comparators group. Most trials have no events, except EFC 6014, EFC 6015 and EFC 11319. 28 events were contributed by the ELIXA trial. The forest plot in **Figure 18** shows the number of events, the event rate and the estimate of the odds ratio of lixisenatide compared to comparators. By pooling all the six pivotal trials together, the odds ratio was estimated at 0.88 with a 95% confidence interval of (0.07, 10.32). From the ELIXA trial, the odds ratio was estimated at 1.54 with a 95% confidence interval of (0.73, 3.23). The overall estimate of the colorectal cancer odds ratio that includes all six pivotal trials and ELIXA was 1.47 with a 95% confidence interval of (0.72, 2.99).

Figure 18: Meta-analysis Results of Colorectal Malignancies

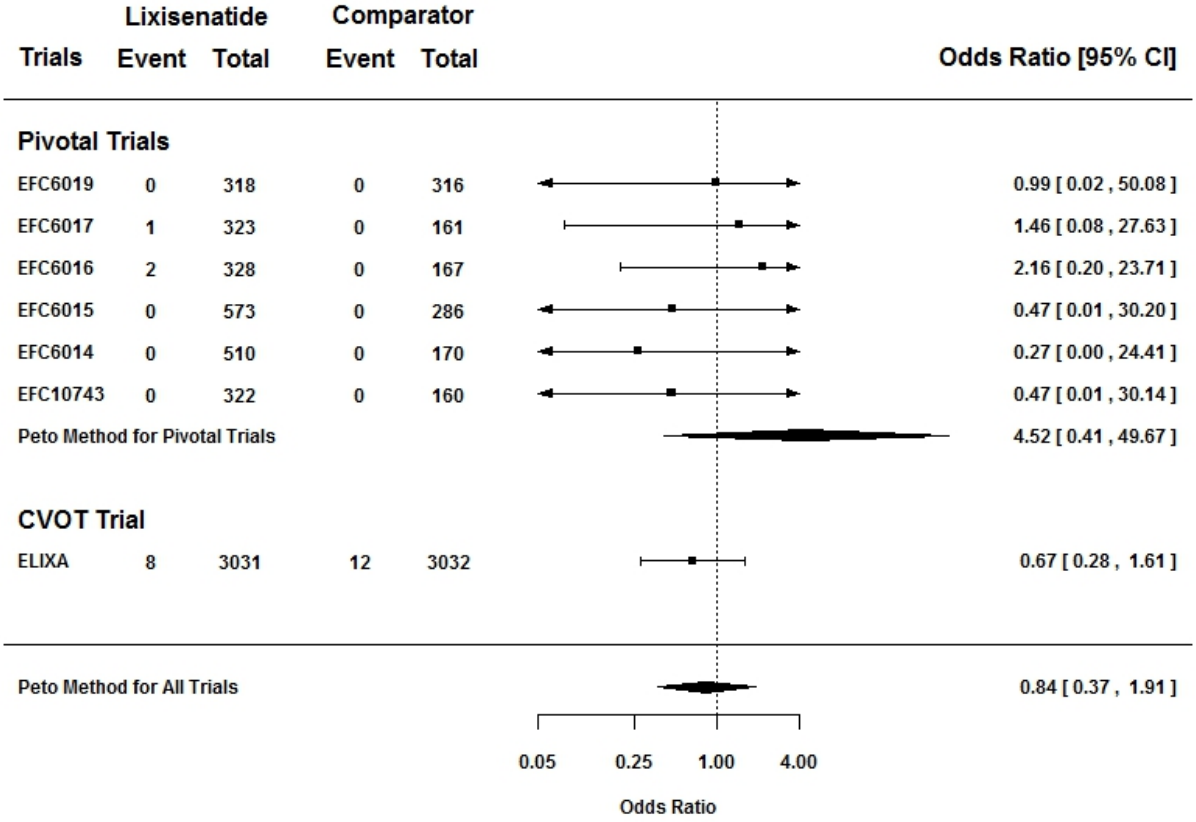


Source: Created by the reviewer using iss\addm.xpt and iss\adae.xpt.

Lung Cancer

There were 23 lung cancer events overall, 11 events in the lixisenatide group and 12 events in the all comparators group. Most trials have no events, except EFC 6016, EFC 6017 and EFC 11319. 20 events were contributed by the ELIXA trial. The forest plot in **Figure 19** shows the number of events, the event rate and the estimate of the odds ratio of lixisenatide compared to comparators. By pooling all the six pivotal trials together, the odds ratio was estimated at 4.52 with a 95% confidence interval of (0.41, 49.67). From the ELIXA trial, the odds ratio was estimated at 0.67 with a 95% confidence interval of (0.28, 1.61). The overall estimate of the lung cancer odds ratio that includes all six pivotal trials and ELIXA was 0.84 with a 95% confidence interval of (0.37, 1.91).

Figure 19: Meta-analysis Results of Lung Malignancies

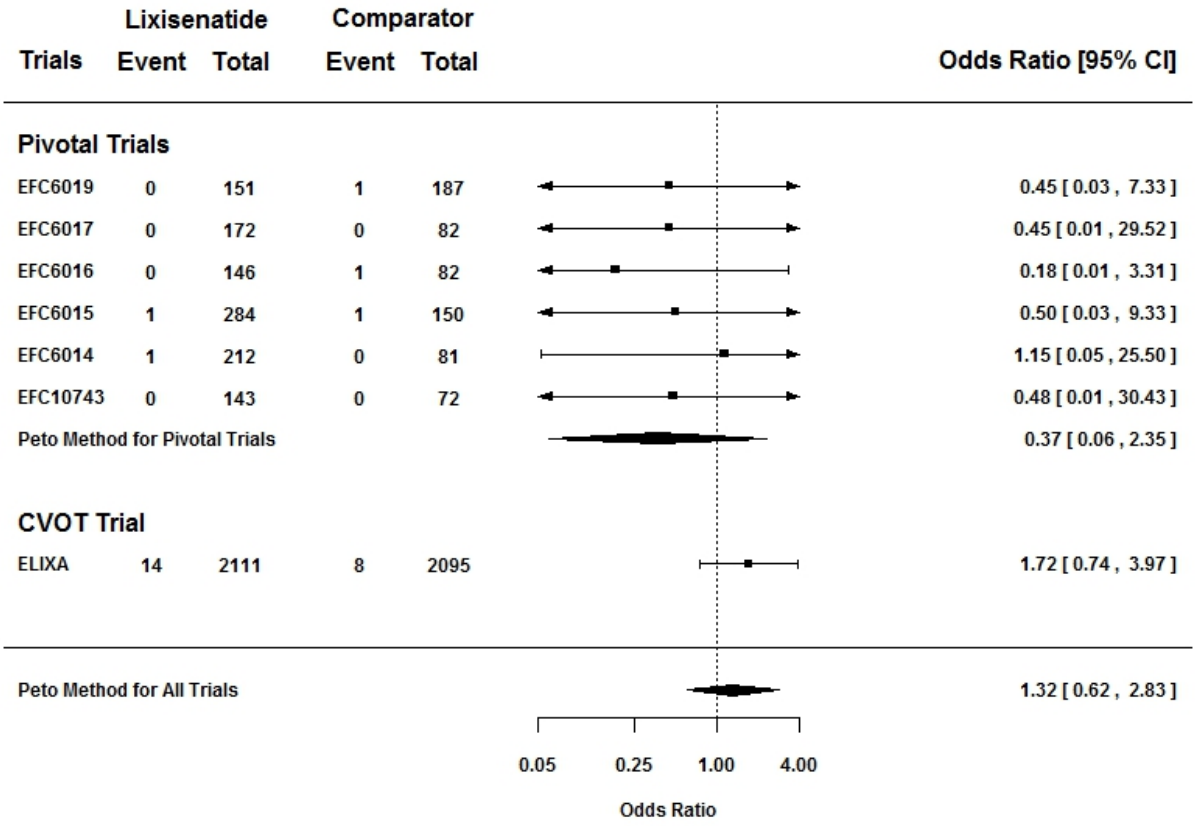


Source: Created by the reviewer using iss\addm.xpt and iss\adae.xpt.

Prostate Cancer

There were 27 prostate cancer events overall, 16 events in the lixisenatide group and 11 events in the all comparators group. Most trials have low number of events and numerically favor comparator over lixisenatide. The forest plot in **Figure 20** shows the number of events, the event rate and the estimate of the odds ratio of lixisenatide compared to comparators. There were fewer or equal to 2 events in most trials, and 22 events were contributed by the ELIXA trial. By pooling all the six pivotal trials together, the odds ratio was estimated at 0.37 with a 95% confidence interval of (0.06, 2.35). From the ELIXA trial, the odds ratio was estimated at 1.72 with a 95% confidence interval of (0.74, 3.97). The overall estimate of the prostate cancer odds ratio that includes all six pivotal trials and ELIXA was 1.32 with a 95% confidence interval of (0.62, 2.83).

Figure 20: Meta-analysis Results of Prostate Malignancies in Males



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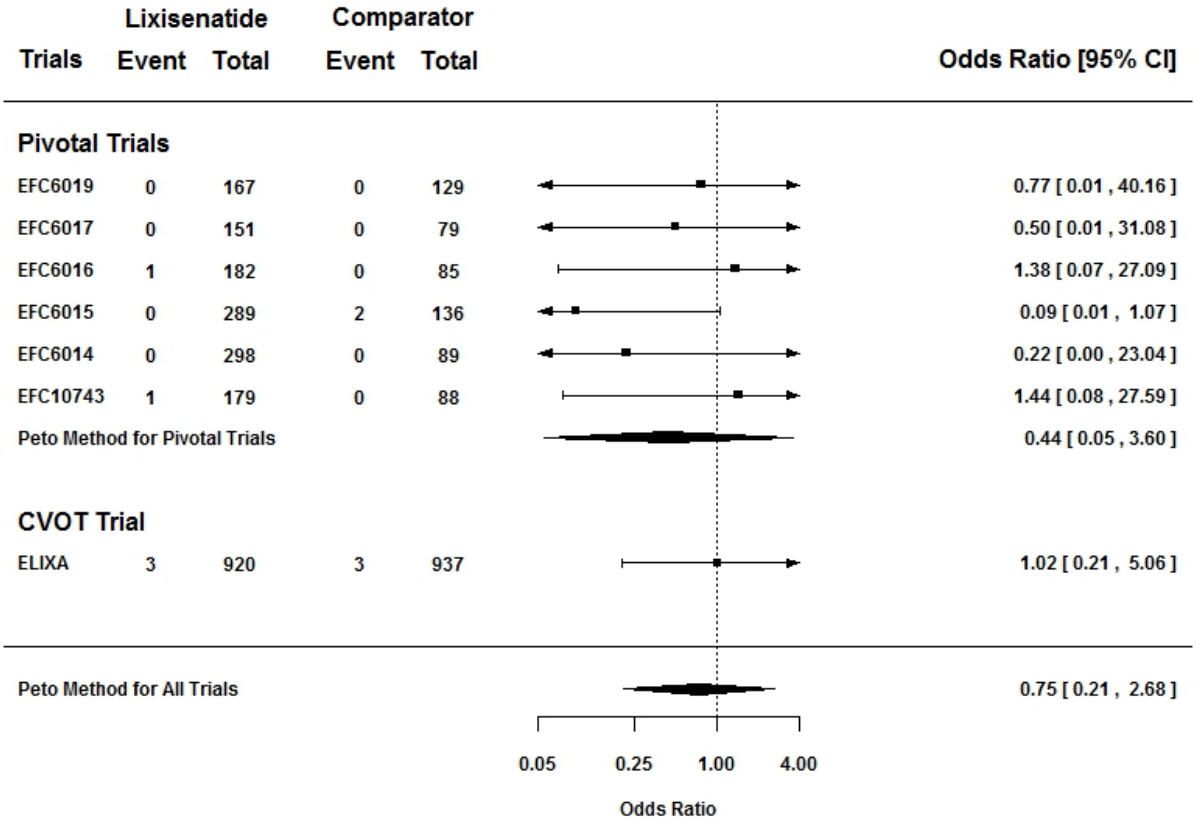
Breast Cancer

There were 10 breast cancer events overall, 5 events in the lixisenatide group and 5 events in the all comparators group. The forest plot in **Figure 21** shows the number of events, the event rate and the estimate of the odds ratio of lixisenatide compared to all comparators. There were fewer or equal to 2 events in most trials, and 6 events were contributed by the ELIXA trial. By pooling all the six pivotal trials together, the odds ratio was estimated at 0.44 with a 95% confidence interval of (0.05, 3.60). From the ELIXA trial, the odds ratio was estimated at 1.02 with a 95% confidence interval of (0.21, 5.06). The overall estimate of the breast cancer odds ratio that includes all six pivotal trials and ELIXA was 0.75 with a 95% confidence interval of (0.21, 2.68).

Figure 21: Meta-analysis Results of Breast Malignancies in Females



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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 208471
Drug Name:	Lixisenatide Injection
Indication(s):	Improve Glycemic Control in Adults with Type 2 Diabetes Mellitus
Applicant:	Sanofi
Date(s):	Date submitted: July 27, 2015 Review due date: April 2, 2016 PDUFA due date: July 27, 2016
Review Priority:	Standard (10-month)
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Jiwei He, Ph.D.
Concurring Reviewers:	Mark D. Rothmann, Ph.D. (Team Leader)
Medical Division:	Metabolism and Endocrinology Products (DMEP)
Clinical Team:	Suchitra Balakrishnan, M.D. William Chong, M.D. (Team Leader) Jean-Marc Guettier, M.D. (Division Director)
Project Manager:	Martin White, M.S.

Keywords: NDA review, Clinical studies

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1. Executive Summary

Sanofi proposed lixisenatide for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Lixisenatide is a short-acting Glucagon-like peptide-1 (GLP-1) receptor agonist. It is administered once daily using two disposable fixed-dose pen injectors: 10 μg for dose initiation and 20 μg for maintenance dose. Based on the results in change in HbA1c from baseline, the sponsor claims lixisenatide is effective in improving glycemic control in adults with T2DM. My review of the statistical evidence suggests lixisenatide was superior to placebo in terms of change in HbA1c from baseline. This NDA is approvable from statistical point of view.

An NDA for lixisenatide (NDA 204961) was originally submitted on 20 December 2012 but was subsequently withdrawn on 10 September 2013 pending results from the cardiovascular outcomes trial EFC11319 (ELIXA). The original submission contained 11 Phase 3 efficacy studies and was reviewed by Dr. Wei Liu. This is a resubmission with the completed ELIXA trial and two additional Phase 3 efficacy studies.

This review covers all the 13 Phase 3 efficacy studies (summarized in Table 1) with a focus on the two additional efficacy studies EFC12626 and EFC12261 submitted in this cycle. Please refer to Dr. Wei Liu's review for details on the studies in the previous submission. Among the 13 studies, 9 are double-blinded, placebo-controlled studies supporting the efficacy of Lixisenatide as monotherapy, in combination with metformin, sulfonylurea, metformin and sulfonylurea, pioglitazone, metformin and pioglitazone, basal insulin, basal insulin and metformin, basal insulin and sulphonyurea, and in combination with (insulin glargine and metformin) or (insulin glargine and thiazolidinediones). EFC6019 and EFC12626 are open-label, active-controlled studies comparing the efficacy of lixisenatide QD to exenatide BID, insulin glargine QD or insulin glargine TID respectively. EFC10780 is a double-blinded, double-dummy, active-controlled study comparing the efficacy of lixisenatide QD to sitagliptin QD. EFC12261 is an open-label, active-controlled meal-time study comparing the efficacy of lixisenatide administered prior to main meal to lixisenatide administered prior to breakfast.

The primary efficacy endpoint in 12 of the Phase 3 efficacy studies (except EFC10780) was change in HbA1c from baseline after 24 weeks of treatments (12 weeks for EFC6018 and 26 weeks for EFC12626). In Study EFC12626, change in body weight from baseline at Week 26 was a co-primary endpoint. The pre-specified non-inferiority margin in all the active-controlled studies was 0.4%. The pre-specified primary analysis is an analysis of covariance (ANCOVA) model using the last observation carried forward method (LOCF) for missing observations. Since the Division no longer recommends LOCF as the approach for dealing with missing data, the sponsor also performed post-hoc MMRM analysis using all available post-baseline observations regardless of treatment discontinuation or initiation of rescue therapy. Currently we think this analysis is more appropriate for labeling.

Based on the results from MMRM analysis using all available observations (summarized in Table 8), lixisenatide demonstrated superiority to placebo in terms of HbA1c change from baseline at the primary efficacy time point in all placebo-controlled Phase 3 efficacy studies, as monotherapy or in combination

with other antidiabetic drugs. Lixisenatide demonstrated non-inferiority to exenatide, insulin glulisine QD and TID based on a noninferiority margin of 0.4%. However, Lixisenatide was significantly worse than exenatide (LS mean for treatment difference was 0.18; 95% CI: 0.046, 0.307; p-value =0.0083) and insulin glargine TID (LS mean for treatment difference was 0.21; 95% CI: 0.094, 0.331; p-value = 0.0005). No significant difference was observed between lixisenatide and sitagliptin (LS mean for treatment difference was 0.04%; 95% CI: -0.198, 0.288; p-value =0.717).

In the study design, the sponsor did not intend to continue measuring HbA1c after treatment discontinuation or initiation of rescue therapy. There was considerable amount (>10%) of missing data in some of the Phase 3 studies. MMRM assumes data are missing at random (MAR). The conclusions from the MMRM analysis may be subject to bias due to violation of the MAR assumption. Upon request, the sponsor performed post-hoc sensitivity analyses to examine the impact of violation of the MAR assumption. The post-hoc sensitivity analyses confirmed most of the conclusions from the MMRM analysis using all available post-baseline observations. They suggest there is a possibility that lixisenatide did not achieve noninferiority versus insulin glargine TID based on a non-inferiority margin of 0.4% (LS mean treatment difference was 0.28%; 95% CI: 0.157, 0.408). However, considering that the imputation approach is very conservative and that the upper bound of the 95% CI for the treatment difference is just a little over 0.4%, this possibility is not very high.

In the mealtime study EFC12261, lixisenatide main meal achieved non-inferiority to lixisenatide breakfast based on a non-inferiority margin of 0.4% in both the MMRM analysis and the sensitivity analysis. However, the pre-specified non-inferiority margin is too big for this scenario. A more appropriate margin (less than or equal to 0.346%) should be used and the sensitivity analysis should be conducted based on the revised margin (See Section 5.1.1 for more details).

2. Introduction

2.1 Overview

2.1.1 Class and Indication

GLP-1 is an incretin hormone that is secreted from the enteroendocrine L-cells of the gastrointestinal tract following ingestion of a meal. Its main effects include stimulation of insulin release, suppression of glucagon release and delaying gastric emptying. Lixisenatide is a short-acting GLP-1 receptor agonist. Supplied as a solution for injection, it is intended for use as an adjunct to diet and exercise to improve glycemic control in the treatment of adults with type 2 diabetes mellitus (T2DM). Human physiologic GLP-1 has a very short half-life in circulation (90 to 120 seconds) because of N-terminal cleavage by endogenous proteases such as dipeptidyl peptidase 4 (DPP-4). Lixisenatide is resistant to cleavage by DPP-4. It results in a longer duration of action making it possible to be administered once daily (QD) for therapeutic purposes.

Lixisenatide is subcutaneously administered once daily, within the hour prior to the first meal of the day [redacted]. Two disposable fixed-dose pen injectors are proposed: 10 µg for dose initiation and 20 µg for maintenance dose.

(b) (4)

2.1.2 History of drug development

An NDA for lixisenatide (NDA 204961) was originally submitted on 20 December 2012 but was subsequently withdrawn on 10 September 2013 following discussions with the Agency regarding the proposed process for review of the interim data from the cardiovascular outcomes trial ELIXA. The sponsor thought that the FDA's evaluation of lixisenatide should be based on the complete results of the ELIXA study rather than interim data.

A meeting was held on 15 October 2013 to gain FDA feedback on major deficiencies and issues found during the 1st review cycle. Statistics comments included: "Study EFC6019 had an open-label design. Therefore, the results may be subject to bias. We prefer a double-blind trial comparing lixisenatide to exenatide." The sponsor stated that a double-blind design would be very difficult, due to the pen presentations of the two products and other logistical issues.

The original submission contains 11 Phase 3 efficacy studies. This is a resubmission with the completed ELIXA trial and two additional Phase 3 efficacy studies. A pre-NDA meeting request (written response) was sent on 9 April 2015. It contained questions about the ELIXA study which were addressed by Division of Biometrics VII.

2.1.3 Specific studies reviewed

This submission contains

- 9 placebo-controlled Phase 3 efficacy studies
- 4 active-controlled Phase 3 efficacy studies (including the supportive study EFC10780)
- 1 cardiovascular outcomes trial ELIXA (EFC11319)

This review covers all the 13 Phase 3 efficacy studies. Table 1 summarized trial specification for these studies. All the studies are randomized and parallel group. The 11 Phase 3 studies in the original submission have been reviewed by Dr. Wei Liu. Among them, the 9 double-blinded placebo-controlled studies support the efficacy of Lixisenatide as monotherapy, in combination with metformin, sulfonylurea, metformin and sulfonylurea, pioglitazone, metformin and pioglitazone, basal insulin, basal insulin and metformin, basal insulin and sulphonyurea, and in combination with (insulin glargine and metformin) or (insulin glargine and thiazolidinediones). The active-controlled study EFC6019 compares the efficacy of lixisenatide QD to exenatide BID. The active-controlled study EFC10780 compares the efficacy of lixisenatide QD to sitagliptin QD. Please refer to Dr. Wei Liu's review for details about these studies. This review focuses on the two additional efficacy studies submitted in this cycle:

- **EFC12626** is a randomized, open-label, active-controlled, 26-week study to compare efficacy and safety of lixisenatide vs insulin glargine QD and insulin glargine 3 times daily (TID) in T2DM patients insufficiently controlled with insulin gargline with or without metformin,

- **EFC12261** is a 24-week, open-label, randomized study to compare efficacy and safety of lixisenatide injected prior to the main meal of the day vs lixisenatide injected prior to breakfast in T2DM patients not adequately controlled on metformin.

This review also focuses on the additional supportive and sensitivity analyses submitted in this review cycle.

Table 1 Trial Specification for Phase 3 Efficacy Trials[1]

Study[2]	**Treatment Arms**	**Number of Subjects Randomized**	**HbA1c Measurement in Main Treatment Period (Week)**
Placebo-controlled, Double-blinded			
Monotherapy **EFC6018**	Placebo Lixisenatide 2-step Lixisenatide 1-step	122 (61+61) 120 119	8, 12
Add-on to Met alone **EFC6014** **EFC10743**	Placebo Lixisenatide morning Lixisenatide evening Placebo Lixisenatide 2-step Lixisenatide 1-step	170 (85+85) 255 255 162 (80+82) 161 161	8, 12, 24 8, 12, 24
Add-on to SU or SU+Met **EFC6015**	Placebo Lixisenatide	286 573	8, 12, 24
Add-on to Pio or PIO+Met **EFC6017**	Placebo Lixisenatide	161 323	8, 12, 24
Add-on to BI or BI+Met **EFC6016**	Placebo Lixisenatide	167 329	8, 12, 24
Add-on IG+Met or IG+Met+TZD **EFC10781**	Placebo Lixisenatide	223 223	8, 12, 24
Add-on to BI or BI+SU **EFC10887**	Placebo Lixisenatide	157 154	8, 12, 24
Add-on to Met or Met+SU **EFC11321**	Placebo Lixisenatide	195 196	8, 12, 24
Active-controlled, Open-label			
Add-on to Met alone **EFC6019**	Exenatide Lixisenatide	319 320	8, 12, 24
Add-on to IG or IG+Met			

EFC12626	Insulin glargine QD Insulin glargine TID Lixisenatide	298 298 298	12, 20, 26
Add-on to Met alone **EFC12261**	Lixisenatide breakfast Lixisenatide main meal	226 225	8, 12, 16, 24
Active-controlled, Double-blind, Double-dummy			
Add-on to Met alone **EFC10780**[3]	Sitagliptin Lixisenatide	161 158	4, 8, 12, 16, 24

[1] Modified from Dr. Wei Liu's review Table 2.1

[2]In all studies, the study population was with HbA1c (%) ≥7 to ≤10 at screening; lixisenatide dose was 20 µg QD. Met = Metformin, SU = Sulfonylurea, Pio = Pioglitazone, BI = Basal insulin, IG = Insulin glargine, TZD = Thiazolidinediones.

[3]Supportive study. The primary efficacy endpoint in the study is the percentage of patients with HbA1c < 7% at week 24 and a weight loss of at least 5% of baseline body weight at week 24. Results from this study are not in the label.

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\NDA208471\208471.enx. Study data were submitted in SAS Xport transport format.

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. This review covers datasets from 13 Phase 3 efficacy studies. We requested some additional sensitivity analyses for these studies to explore the impact of missing data. The sponsor conducted those analyses as instructed and submitted the results in February 2016. This review also covers one integrated summary of efficacy (ISE) which pooled data from 8 placebo-controlled 24-week Phase 3 studies.

For the individual trials, both tabulation and analysis datasets are provided. The tabulation and analysis datasets are joinable by the unique record identifier (USUBJID). The ISE dataset is primarily stacking of the individual trial analysis datasets for selected variables. They are mainly used for subgroup analysis on HbA1c in this review.

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 from the primary analysis as well as the post-hoc supportive analysis using MMRM with all available post-baseline observations.

3.2 Evaluation of efficacy

The primary efficacy endpoint in the Phase 3 efficacy studies (except Study EFC10780) was the change from baseline in HbA1c at the end of the main treatment period. **The primary objective** was to demonstrate the superiority of lixisenatide in the placebo-controlled studies and noninferiority in active-controlled studies in terms of reduction in HbA1c at the end of the main treatment period.

The key secondary efficacy endpoints include 2-hour post prandial glucose (PPG), fasting plasma glucose (FPG) and body weight.

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

- Intent-to-treat (ITT): All randomized patients who received at least 1 dose of double-blind (or open-label for studies EFC6019, EFC12626 and EFC12261) investigational product and who had a baseline assessment.
- Modified intent-to-treat (mITT): All randomized patients who received at least 1 dose of double-blind (or open-label for studies EFC6019, EFC12626 and EFC12261) investigational product and who had both a baseline assessment and at least one post-baseline assessment of the primary or secondary efficacy variables, irrespective of compliance with the study protocol and procedures.
- Completers: The 24-week (12-week in EFC6018 and 26-week in EFC12626 and EFC12626) completer's population was defined as all patients who had completed the main treatment period and who had not been rescued during this main treatment period.

All efficacy analyses were based on mITT analysis set. **The primary analysis** is ANCOVA model using LOCF for missing observations. It is based on mITT analysis set. No formal statistical testing was performed for all secondary endpoints in the 3 active controlled studies EFC6019, EFC12626 and EFC12261.

The LOCF approach for handling missing data is no longer recommended by the Division. The sponsor also performed **post-hoc supportive analyses** for all Phase 3 efficacy studies in this resubmission, including mixed-effect model with repeated measures (MMRM) using on-treatment data which excluded data after treatment discontinuation or initiation of rescue therapy and MMRM using all postbaseline observations regardless of adherence to assigned treatment.

MMRM assumes missing data are MAR. Upon our request, the sponsor performed post-hoc sensitivity analyses to examine the impact of violation of the MAR assumption in the Phase 3 studies.

3.2.1 Study EFC12626

3.2.1.1 Study Design and Endpoints

Study EFC12626 is a 26-week, open-label, active-controlled, 1: 1: 1 randomized, 3-arm parallel group, multi-national, multi-center study. **The primary objective** was to demonstrate in patients with T2DM not adequately controlled on insulin glargine ± metformin:

- The non-inferiority of lixisenatide versus insulin glulisine QD (Basal Plus regimen) on HbA1c reduction at Week 26
- The non-inferiority of lixisenatide versus insulin glulisine TID (Basal Bolus regimen) on HbA1c reduction or superiority on body weight change at Week 26.

The co-primary endpoints were change in HbA1c from baseline at Week 26 and change in body weight from baseline at Week 26. The primary analysis was based on the following co-primary comparisons in patients with insulin glargine ± metformin:

1. Non-inferiority of lixisenatide versus insulin glulisine QD on HbA1c change from baseline to Week 26

2a. Non-inferiority of lixisenatide versus insulin glulisine TID on HbA1c change from baseline to Week 26

2b. Superiority of lixisenatide versus insulin glulisine TID on body weight change from baseline to Week 26

The study was to be declared positive if both 1 and 2 (at least one of 2a or 2b) were met. Both 1 and 2 (either 2a or 2b) were assessed separately at α=0.025 (1-sided). For the co-primary endpoint 2, Hochberg procedure was used for 2a and 2b. Both 1 and 2a were assessed at a non-inferiority margin of 0.4%. For 1 and 2a, if the non-inferiority was met, then the superiority over insulin glulisine QD or insulin glulisine T1D on HbA1c change from baseline was to be checked respectively.

The primary analysis was an ANCOVA model with treatment (lixisenatide, insulin glulisine QD, and insulin glulisine TID), stratum of HbA1c at Visit 7 (Week -1) (<8%, ≥8%), randomization stratum of metformin use (yes, no), and country as fixed effects and using the corresponding baseline value as a covariate.

As a post-hoc supportive analysis, a MMRM was performed for HbA1c and body weight respectively using all available post-baseline observations. The MMRM model included all factors in the ANCOVA model as well as visit (Week 12, 20, 26 for HbA1c and Week 2, 6, 12, 20, 26 for body weight), treatment-by-visit interaction, and baseline-by-visit interaction. The same MMRM was also performed using on-treatment data.

All secondary endpoints analyses in this study were exploratory. No multiplicity adjustment was made for secondary endpoints.

A sample size of 285 patients per arm ensured:

- At least 94% power for the non-inferiority test 1 assuming a common standard deviation of 1.2%, a true difference of 0 in change from baseline in HbA1c and a 20% dropout rate,
- At least 90% power for the noninferiority test 2a assuming a common standard deviation of 1.2%, a true difference of 0 in change from baseline in HbA1c and a 20% dropout rate,
- At least 90% power for the superiority test 2b assuming a common standard deviation of 2.75 kg and a true difference of 1 kg in change from baseline in body weight.

The study was slightly overpowered, since the standard deviation was estimated to be 1.0% and the sample size was 298 per arm with a dropout rate ≤ 10%.

3.2.1.2 Patient disposition, demographic and baseline characteristics (EFC12626)

A description of the patient disposition in the review is shown in Table 2. Completers were the subjects who completed the study treatment period. No rescue therapy was planned for the study, instead discontinuation was recommended if HbA1c was above 8.5% at Week 12 or later on, and if appropriate corrective action failed and the repeated HbA1c 4 weeks later remained above 8.5%.

Table 2 Summary of patient dispositions in Study EFC12626

	Lixisenatide	**Insulin Glulisine QD**	**Insulin Glulisine TID**
Randomized, n	298	298	298*
mITT, n(%)	297 (99.7%)	298 (100%)	295 (99.0%)
Completer, n(%)	268 (89.9%)	281 (94.3%)	285 (95.6%)
Discontinued Treatment, n(%)	30 (10.1%)**	17 (5.7%)	13 (4.4%)
Adverse event	14 (4.7%)	2 (0.7%)	5 (1.7%)
Lack of efficacy	6 (2.0%)	4 (1.3%)	0
Poor compliance to protocol	0	3 (1.0%)	2 (0.7%)
Others	9 (3.0%)	8 (2.7%)	6 (2.0%)
Had HbA1c measurement at Week 26, n%	263 (88.3%)	275 (92.3%)	283 (95.0%)

Source: modified from Study EFC12626 clinical study report Table 4

*: One patient in the insulin glulisine TID group was not treated

**: One patient in the lixisenatide group was diagnosed with breast cancer soon after randomization and was discontinued from study

Subject demographic information for Study EFC12626 was summarized in Table 3. One patient in the insulin glulisine TID group who was randomized but not treated had missing baseline HbA1c and BMI information. The three treatment groups were roughly balanced for all the demographic factors.

Table 3 Summary of patient demographic information in Study EFC12626

	Lixisenatide	**Insulin Glulisine QD**	**Insulin Glulisine TID**
Gender, n(%) males	138 (46.3%)	135 (45.3%)	132 (44.3%)
Age, years			
Mean (SD)	59.8 (8.6)	60.2 (8.6)	59.4 (9.5)
Range	35 : 79	35 : 78	32 : 87
n(%) ≥65	89 (29.9%)	93 (31.2%)	96 (32.2%)
Race, n (%)			
White	276 (92.6%)	280 (94.0%)	272 (91.3%)
Black	13 (4.4%)	11 (3.7%)	12 (4.0%)
Asian/Oriental	9 (3.0%)	7 (2.3%)	13 (4.4%)
Other	0	0	1 (0.0%)
Ethnicity, n(%) Hispanic	63 (21.1%)	58 (19.5%)	68 (22.8%)
Country, n(%) US	47 (15.8%)	43 (14.4%)	48 (16.1%)
Baseline HbA1c, n(%) <8%	195 (65.4%)	192 (64.4%)	186 (62.6%)
Baseline BMI, n(%) <30 kg/m^2	97 (32.6%)	118 (39.6%)	97 (32.7%)
Screening creatinine clearance (mL/min)			
30 to <60 (moderate decrease in GFR)	17 (5.7%)	18 (6.1%)	15 (5.1%)
60 to ≤90 (mild decrease in GFR)	78 (26.2%)	71 (24.0%)	80 (26.9%)
≥90 (normal)	203 (68.1%)	207 (69.9%)	202 (68.0%)

Source: Study EFC12626 clinical study report Table 7

3.2.1.3 Results and Conclusions (EFC12626)

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I verified the sponsor's primary analyses and the results were shown in **Error! Reference source not found.**. I obtained slightly different LS mean change from baseline but the same LS mean difference as the sponsor. These results are supportive to the noninferiority of lixisenatide to both insulin glulisine QD and insulin glulisine TID in terms of mean change in HbA1c from baseline as the upper bound of the 2-sided 95% CI was below the noninferiority margin of 0.4%. However, lixisenatide did not achieve superiority over insulin glulisine QD or insulin glulisine TID in terms of mean change in HbA1c from baseline. In fact, lixisenatide was significantly worse than insulin glulisine TID (p-value = 0.0005). Lixisenatide also demonstrated superiority to both insulin glulisine QD and insulin glulisine TID in terms of mean change in body weight from baseline (p-value < 0.0001 for both comparisons). Results from MMRM using all available observations were consistent with those from the primary analysis.

Table 4 HbA1c (%) and body weight at Week 26 for Lixisenatide and Insulin Glulisine QD and TID in Patients with T2DM in Study EFC12626

Endpoint	**Lixisenatide**		**Insulin Glulisine QD**		**Insulin Glulisine TID**	
HbA1c %	N		N		N	

LS mean change from baseline						
LOCF[1]	292	-0.63	292	-0.58	295	-0.84
MMRM on-treatment	284	-0.63	289	-0.57	291	-0.84
MMRM all available observations	284	-0.63	290	-0.57	291	-0.84
LS mean difference (SE) of Lixisenatide vs.						
LOCF				-0.05 (0.059)		0.21 (0.059)
MMRM on-treatment				-0.06 (0.061)		0.21 (0.060)
MMRM all available observations				-0.06 (0.061)		0.21 (0.060)
95% CI						
LOCF				(-0.170 to 0.064)		(0.095 to 0.328)
MMRM on-treatment				(-0.180 to 0.058)		(0.094 to 0.331)
MMRM all available observations				(-0.176 to 0.061)		(0.094 to 0.331)
Body weight	N		N		N	
LS mean change from baseline						
LOCF	292	-0.63	292	1.03	295	1.37
MMRM on-treatment	295	-0.65	295	1.03	294	1.38
MMRM all available observations	297	-0.68	297	0.99	294	1.35
LS mean difference (SE) of Lixisenatide vs.						
LOCF				-1.66 (0.305)		-1.99 (0.305)
MMRM on-treatment				-1.68 (0.319)		-2.03 (0.318)
MMRM all available observations				-1.67 (0.318)		-2.03 (0.317)
95% CI						
LOCF				(-2.257 to -1.062)		(-2.593 to -1.396)
MMRM on-treatment				(-2.306 to -1.054)		(-2.655 to -1.406)
MMRM all available observations				(-2.297 to -1.050)		(-2.651 to -1.407)

Source: Study EFC12626 clinical study report Table 13, Table 14, ISE Table 1.4.1.9 and Table 1.4.1.14

[1] Numbers are slightly different from the sponsor's.

3.2.2 Study EFC12261

3.2.2.1 Study Design and Endpoints

Study EFC12261 is a 24-week, open-label, 1: 1 randomized, active-controlled, 2-arm parallel group, multi-national, multi-center study. **The primary objective** was to demonstrate non-inferiority of lixisenatide injected prior to the main meal of the day versus lixisenatide injected prior to breakfast in terms of HbA1c reduction from baseline at week 24, in T2DM patients not adequately controlled on metformin.

The primary efficacy endpoint was change in HbA1c from baseline at Week 24. **The primary analysis** was an ANCOVA model with treatment (lixisenatide main meal, Lixisenatide breakfast), randomization stratum of screening HbA1c (<8%, ≥8%), randomization stratum of main meal of the day (breakfast, lunch or dinner), and country as fixed effects and using the baseline HbA1c value as a covariate.

Non-inferiority was demonstrated if the upper bound of the two-sided 95% CI of the difference between lixisenatide injected prior to the main meal of the day and lixisenatide injected prior to breakfast on mITT population was ⩽0.4%. If non-inferiority was established, then a corresponding check of statistical superiority of lixisenatide injected prior to the main meal of the day over lixisenatide injected prior to breakfast was performed for the primary endpoint.

As a supportive analysis, a MMRM was performed using all available post-baseline observations. The MMRM model included all factors in the ANCOVA model as well as visit (Week 8, 12, 16, 24), treatment-by-visit interaction, and baseline-by-visit interaction. The same MMRM was also performed using on-treatment data.

All secondary endpoints analyses in this study were exploratory. No multiplicity adjustment was made for secondary endpoints.

A sample size of 400 patients (200 per arm) ensured at least 90% power for the non-inferiority test with 0.4% margin, assuming a common standard deviation of 1.2% and a true difference in HbA1c between the 2 lixisenatide regimes of 0.

3.2.2.2 Patient disposition, demographic and baseline characteristics (EFC12261)

A description of the patient disposition is shown in Table 5. No rescue therapy was planned for the study, instead discontinuation was recommended if FPG/HbA1c values are above pre-defined threshold values, and no reason can be found for insufficient glucose control.

Table 5 Summary of patient dispositions in Study EFC12261

	Lixisenatide Main Meal	**Lixisenatide Breakfast**
Randomized, n	225	226
mITT, n(%)	224 (99.6%)	226 (100%)
Completer, n(%)	189 (84.0%)	202 (89.4)
Discontinued Treatment, n(%)	36 (16.0%)	24 (10.6%)
Adverse event	10 (4.4%)	11 (4.9%)
Lack of efficacy	10 (4.4%)	5 (2.2%)
Poor compliance to protocol	8 (3.6%)	3 (1.3%)
Others	8 (3.6%)	5 (2.2%)
Had HbA1c measurement at Week 26, n%	36 (16.0%)	25 (11.1%)

Source: Study EFC12261 clinical study report Table 4

Subject demographic information for Study EFC12261 was summarized in **Table 6**. The two treatment groups were roughly balanced for all the demographic factors.

Table 6 Summary of patient demographic information in Study EFC12261

	Lixisenatide Main Meal	Lixisenatide Breakfast
Gender, n(%) males	101 (44.9%)	97 (42.9%)
Age, years		
Mean (SD)	56.3 (10.6)	57.5 (9.7)
Range	23: 82	21: 76
n(%) ≥65	52 (23.1%)	57 (25.2%)
Race, n (%)		
White	211 (93.8%)	211 (93.4%)
Black	4 (1.8%)	8 (3.5%)
Asian/Oriental	10 (4.4%)	7 (3.1%)
Ethnicity, n(%) Hispanic	11 (4.9%)	12 (5.3%)
Country, n(%) US	36 (16.0%)	38 (16.8%)
Baseline HbA1c, n(%) <8%	141 (62.7%)	127 (56.2%)
Baseline BMI, n(%) <30 kg/m^2	51 (22.7%)	60 (26.6%)
Screening creatinine clearance (mL/min)		
50 to ≤80	21 (9.3%)	21 (9.3%)
>80	204 (90.7%)	205 (90.7%)

Source: Study EFC12261 clinical study report Table 7

3.2.2.3 Results and Conclusions (EFC12261)

I verified the sponsor's primary analyses and the results were shown in Table 7. I obtained slightly different LS mean change from baseline but the same LS mean difference as the sponsor. These results are supportive to the noninferiority of lixisenatide main meal to lixisenatide breakfast in terms of mean change in HbA1c from baseline as the upper bound of the 2-sided 95% CI was below the noninferiority margin of 0.4%. However, superiority of lixisenatide main meal to lixisenatide breakfast was not achieved. Results from MMRM using all available observations were consistent with those from the primary analysis.

Table 7 HbA1c (%) at Week 24 for Lixisenatide main meal and Lixisenatide breakfast in Patients with T2DM in Study EFC12261

Endpoint	Lixisenatide Main Meal		Lixisenatide Breakfast	
HbA1c %	N		N	
LS mean change from baseline				
LOCF[1]	222	-0.65	218	-0.74
MMRM on-treatment	215	-0.71	219	-0.79
MMRM all available observations	218	-0.71	220	-0.79
LS mean difference (SE) of Lixisenatide Main vs.				
LOCF				0.09 (0.079)
MMRM on-treatment				0.08 (0.080)
MMRM all available observations				0.08 (0.079)
95% CI				
LOCF				(-0.067 to 0.242)
MMRM on-treatment				(-0.076 to 0.237)

MMRM all available observations				(-0.076 to 0.235)

Source: Study EFC12261 clinical study report Table 11, ISE Table and Table 1.4.1.10 and 1.4.1.15

[1] Numbers are slightly different from the sponsor's.

3.2.3 Post-hoc Supportive Analyses

Dr. Wei Liu and I have verified the results of the sponsor's primary analysis using ANCOVA with LOCF. Since the LOCF approach for handling missing data is no longer recommended by the Division, the sponsor also performed a post-hoc supportive analyses using MMRM with all available post-baseline observations regardless of treatment discontinuation or initiation of rescue therapy. Currently we think this analysis is more appropriate for labeling. I verified the sponsor's results for this analysis. The results were presented in Table 8.

Results from the supportive analyses using MMRM with all available post-baseline observations were consistent with those from the primary analysis using ANCOVA with LOCF. In the 9 place-controlled studies, the mean reduction in HbA1c from baseline was significantly greater with lixisenatide treatment than the placebo. In the active-controlled studies, Lixisenatide achieved non-inferiority to exenatide, insulin glulisine QD and TID in terms of mean reduction in HbA1c from baseline and based on a pre-specified noninferiority margin of 0.4%. However, lixisenatide was significantly worse than exenatide (LS mean for treatment difference was 0.18; 95% CI: 0.046, 0.307; p-value =0.0083) and insulin glargine TID (LS mean for treatment difference was 0.21; 95% CI: 0.094, 0.331; p-value = 0.0005). In the mealtime study EFC12261, lixisenatide main meal achieved non-inferiority to lixisenatide breakfast based on a non-inferiority margin of 0.4%. However, the pre-specified non-inferiority margin is questionable and is likely too big for this scenario (See Section 5.1.1). I also verified the sponsor's HbA1c results in Study EFC10780. There was no significant difference between lixisenatide and sitagliptin in terms of HbA1c change from baseline (LS mean for treatment difference was 0.04; 95% CI: -0.198, 0.288; p-value =0.717).

Table 8 Mean change in HbA1c (%) from baseline using MMRM with all available post-baseline observations up to the main treatment period

Study	**Treatment Arms**	**Number of Subjects Analyzed**	**LS Mean Change from Baseline**	**LS Mean Treatment Difference vs. Control (95% CI)**	**P-value[3]**
Placebo-controlled, double-blind					
Monotherapy **EFC6018**	Placebo Lixisenatide 2-step Lixisenatide 1-step	116 (57+59) 117 118	-0.14 -0.66 -0.79	 -0.52 [-0.761, -0.285] -0.65 [-0.891, -0.418]	 <0.0001 <0.0001
Add-on to Met alone **EFC6014**	Placebo Lixisenatide morning	166 (83+83) 245	-0.47 -0.88	 -0.41 [-0.580, -0.234]	 <0.0001

EFC10743[1]	Lixisenatide evening	245	-0.72	-0.25 [-0.425, -0.078]	0.0046
	Placebo	157 (79+78)	-0.42		
	Lixisenatide 2-step	154	-0.84	-0.42 [-0.598, -0.245]	<0.0001
	Lixisenatide 1-step	155	-0.90	-0.48 [-0.662, -0.306]	<0.0001
Add-on to SU or SU+Met **EFC6015**	Placebo	273	-0.23		
	Lixisenatide	545	-0.91	-0.69 [-0.811, -0.560]	<0.0001
Add-on to Pio or PIO+Met **EFC6017**	Placebo	157	-0.44		
	Lixisenatide	307	-0.97	-0.53 [-0.692, -0.372]	<0.0001
Add-on to BI or BI+Met **EFC6016**	Placebo	157	-0.25		
	Lixisenatide	303	-0.68	-0.43 [-0.629, -0.236]	<0.0001
Add-on IG+Met or IG+Met+TZD **EFC10781**	Placebo	219	-0.37		
	Lixisenatide	213	-0.67	-0.30 [-0.447, -0.147]	0.0001
Add-on to BI or BI+SU **EFC10887**	Placebo	156	0.08		
	Lixisenatide	153	-0.72	-0.79 [-1.032, -0.552]	<0.0001
Add-on to Met or Met+SU **EFC11321**[2]	Placebo	188	-0.59		
	Lixisenatide	190	-0.88	-0.30 [-0.473, -0.118]	0.0012
Active-controlled, Open-label					
Add-on to Met alone **EFC6019**	Exenatide	293	-1.03		
	Lixisenatide	302	-0.85	0.18 [0.046, 0.307]	0.0083
Add-on to IG or IG+Met **EFC12626**	Insulin glargine QD	290	-0.57	-0.06 [-0.176, 0.061]	0.341
	Insulin glargine TID	291	-0.84	0.21 [0.094, 0.331]	0.0005
	Lixisenatide	284	-0.63		
Add-on to Met alone **EFC12261**	Lixisenatide breakfast	220	-0.79		
	Lixisenatide main meal	218	-0.71	0.08 [-0.076, 0.235]	0.316
Active-controlled, Double-blind, Double-dummy					
Add-on to Met alone **EFC10780**	Sitagliptin	160	-0.74		
	Lixisenatide	153	-0.70	0.04 [-0.198, 0.288]	0.717

Source: Integrated Summary of Efficacy Tables 1.4.1.12, 1.4.1.13, 1.4.1.14, 1.4.1.15

[1.] In SAS Proc Mixed procedure, the sponsor set singular=1e-11, otherwise the likelihood was infinite and there there was no output.

[2.] In the MMRM model, country was pooled as China and other countries.

[3.] For active-controlled studies, p-value is associated with a superiority test with null hypothesis of zero treatment difference.

3.2.4 Post-hoc Sensitivity Analyses

In the study design, the sponsor did not intend to collect data after treatment discontinuation or initiation of rescue therapy. There remained 5%-16% patients who did not have HbA1c measurement at the primary efficacy time point (Table 9). The percentage of patients who missed HbA1c measurement at the primary efficacy time point was similar to the percentage of patients who discontinued treatment during the main treatment period in most of the Phase 3 studies. In some studies, the Lixisenatide arm had more missing data than the placebo arm (e.g. EFC10743, EFC10781, EFC12626, and EFC12261). <1% - 13% patients took rescue therapy in the 11 Phase 3 studies that allowed rescue therapy (except EFC12626 and EFC12261). In some placebo-controlled studies, the placebo arm received more rescued therapy than the Lixisenatide arm(s) (11% versus 3% and 4% in Study EFC6014, 13% versus 4% in EFC6015, 11% versus 4% in EFC6017).

Table 9 n% of subjects who missed HbA1c (%) measurement at the primary efficacy time point, did not complete treatment for the main treatment period, required rescue therapy during the main treatment period

Study	**Treatment Arms**	**Randomized**	**Had missing HbA1c measurement,** n%	**Discontinued Treatment**, n%	**Rescue Therapy**, n%
Placebo-controlled, double-blind					
Monotherapy					
EFC6018	Placebo	122 (61+61)	12 (9.8%)	9 (7.4%)	3 (2.5%)
	Lixisenatide 2-step	120	13 (10.8%)	10 (8.3%)	2 (1.7%)
	Lixisenatide 1-step	119	12 (10.1%)	11 (9.2%)	1 (0.8%)
Add-on to Met alone					
EFC6014	Placebo	170 (85+85)	15 (8.8%)	12 (7.1%)	18 (10.6%)
	Lixisenatide morning	255	22 (8.6%)	22 (8.6%)	7 (2.7%)
	Lixisenatide evening	255	28 (11.0%)	31 (12.2%)	10 (3.9%)
	Placebo	162 (82+80)	9 (5.6%)	11 (5.6%)	7 (4.4%)
EFC10743[1]	Lixisenatide 2-step	161	15 (9.3%)	17 (10.6%)	5 (3.1%)
	Lixisenatide 1-step	161	18 (11.2%)	14 (8.7%)	2 (1.3%)
Add-on to SU or SU+Met					
EFC6015	Placebo	286	36 (12.6%)	31 (10.8%)	36 (12.6%)
	Lixisenatide	573	75 (13.1%)	74 (12.9%)	23 (4.0%)
Add-on to Pio or PIO+Met					
EFC6017	Placebo	161	19 (11.8%)	24 (14.9%)	18 (11.3%)
	Lixisenatide	323	30 (9.3%)	35 (10.8%)	12 (3.8%)
Add-on to BI or BI+Met					
EFC6016	Placebo	167	22 (13.2%)	20 (12.0%)	12 (7.2%)
	Lixisenatide	329	54 (16.4%)	54 (16.4%)	19 (5.8%)
Add-on IG+Met or IG+Met+TZD					
EFC10781	Placebo	223	10 (4.5%)	12 (5.4%)	1 (0.4%)
	Lixisenatide	223	19 (8.5%)	29 (13.0%)	1 (0.4%)
Add-on to BI or BI+SU					
EFC10887	Placebo	157	10 (6.4%)	13 (8.3%)	5 (3.2%)
	Lixisenatide	154	13 (8.4%)	21 (13.6%)	2 (1.3%)

Add-on to Met or Met+SU **EFC11321**	Placebo Lixisenatide	195 196	11 (5.6%) 14 (7.1%)	11 (5.6%) 17 (8.7%)	13 (6.7%) 7 (3.6%)
Active-controlled, Open-label					
Add-on to Met alone **EFC6019**	Exenatide Lixisenatide	316 318	45 (14.2%) 43 (13.5%)	45 (14.2%) 41 (12.9%)	12 (3.8%) 8 (2.5%)
Add-on to IG or IG+Met **EFC12626**	Insulin glargine QD Insulin glargine TID Lixisenatide	298 298 298	23 (7.7%) 15 (5.0%) 35 (11.7%)	17 (5.7%) 12 (4.0%) 30 (10.1%)	NA
Add-on to Met alone **EFC12261**	Lixisenatide breakfast Lixisenatide main meal	226 225	25 (11.1%) 36 (16.0%)	24 (10.6%) 36 (16.0%)	NA
Active-controlled, Double-blind, Double-dummy					
Add-on to Met alone **EFC10780**	Sitagliptin Lixisenatide	161 158	9 (5.6%) 15 (9.5%)	11 (6.8%) 16 (10.1%)	11 (6.8%) 15 (9.5%)

MMRM assumes missing data are MAR. Considering that there was considerable amount of missing data and that there was evidence that data were not MAR in some of the Phase 3 studies, we sent information request to the sponsor on 1 January 2016 for additional sensitivity analyses to examine the impact of violation of the MAR assumption. The sponsor performed the analyses for all 13 Phase 3 studies.

In these analyses, the imputation was under the null hypothesis and all observed cases of HbA1c change from baseline at the primary efficacy time point were treated as non-missing.

- For the placebo-controlled studies, missing values at the primary efficacy time point in the placebo arm were imputed based on the MAR assumption. The regression model contained terms for baseline HbA1c values and randomization strata. Missing values in the lixisenatide arm were imputed using the baseline HbA1c values, randomization strata and parameters from the imputation model for the placebo group plus an error.

- For the active-controlled studies, the missing values at the primary efficacy time point were imputed as equal to their baseline plus an error in the control group and equal to their baseline plus 0.4% plus an error in the lixisenatide group.

The error was normally distributed with mean zero and a standard deviation set equal to the estimated pooled standard deviation. Missing HbA1c values at the primary efficacy time point were imputed 100 times to generate 100 datasets with complete HbA1c values at the primary efficacy time point. Each of the complete dataset was analyzed by the same ANCOVA model as done for the primary analysis.

Table 10 **Sensitivity Analysis: mean change in HbA1c (%) from baseline at the primary efficacy time point using ANCOVA with multiple imputation for missing values in Phase 3 efficacy studies[1]** summarized the results of these analyses. The difference in the estimate for treatment difference between the sensitivity analysis and the MMRM analysis in Table 8 was less than 0.10 except for Study EFC6015 where the difference was 0.11. In most of the sensitivity analyses, the conclusion on the efficacy of lixisenatide did not change. Lixisenatide achieved superiority over placebo in all the placebo-controlled studies. Lixisenatide achieved non-inferiority to exenatide and insulin glargine QD based on a non-inferiority margin of 0.4%. However, lixisenatide failed not achieve non-inferiority to insulin glargine TID in Study EFC12626 based on a non-inferiority margin of 0.4% (LS mean treatment difference was 0.28%; 95% CI: 0.157, 0.408). Like in the MMRM analysis, even though lixisenatide main meal achieved non-inferiority to lixisenatide breakfast in Study EFC12261 based on a non-inferiority margin of 0.4% (LS mean treatment difference was 0.14%; 95% CI: -0.039, 0.318), the pre-specified non-inferiority margin is questionable and is likely too big for this scenario (See Section 5.1.1). Like in the MMRM analysis, there was no significant difference between lixisenatide and sitagliptin in the mean change in HbA1c in Study EFC10780 (LS mean treatment difference was 0.10%; 95% CI: -0.157, 0.359).

Table 10 Sensitivity Analysis: mean change in HbA1c (%) from baseline at the primary efficacy time point using ANCOVA with multiple imputation for missing values in Phase 3 efficacy studies[1]

Study	Treatment Arms	N	LS Mean (SE)	LS Mean Treatment Difference (SE)	95% CI	P-value
Placebo-controlled, double-blind						
Monotherapy						
EFC6018	Placebo	122	-0.18 (0.128)			
	Lixisenatide 2-step	120	-0.64 (0.124)	-0.45 (0.130)	[-0.709, -0.199]	0.0005
	Lixisenatide 1-step	119	-0.83 (0.127)	-0.65 (0.129)	[-0.903, -0.399]	<.0001
Add-on to Met alone						
	Placebo	170	-0.49 (0.076)			
EFC6014	Lixisenatide morning	255	-0.87 (0.065)	-0.39 (0.090)	[-0.564, -0.212]	<.0001
	Lixisenatide evening	255	-0.71 (0.067)	-0.22 (0.090)	[-0.399, -0.045]	0.0141
EFC10743	Placebo	160	-0.26 (0.112)			
	Lixisenatide 2-step	161	-0.65 (0.112)	-0.39 (0.090)	[-0.567, -0.215]	<.0001
	Lixisenatide 1-step	161	-0.72 (0.115)	-0.46 (0.092)	[-0.640, -0.279]	<.0001
Add-on to SU or SU+Met						
	Placebo	286	-0.18 (0.078)			
EFC6015	Lixisenatide	573	-0.77 (0.068)	-0.58 (0.067)	[-0.715, -0.453]	<.0001
Add-on to Pio or PIO+Met						
	Placebo	161	-0.43 (0.094)			
EFC6017	Lixisenatide	323	-0.91 (0.083)	-0.48 (0.084)	[-0.647, -0.318]	<.0001
Add-on to BI or BI+Met						
	Placebo	167	-0.34 (0.106)			
EFC6016	Lixisenatide	328	-0.71 (0.092)	-0.36 (0.099)	[-0.557, -0.170]	0.0002

Add-on IG+Met or IG+Met+TZD **EFC10781**	Placebo Lixisenatide	223 223	-0.42 (0.099) -0.70 (0.098)	-0.28 (0.079)	[-0.434, -0.123]	0.0005
Add-on to BI or BI+SU **EFC10887**	Placebo Lixisenatide	157 154	0.07 (0.141) -0.70 (0.146)	-0.76 (0.125)	[-1.005, -0.516]	<.0001
Add-on to Met or Met+SU **EFC11321**	Placebo Lixisenatide	194 196	-0.57 (0.095) -0.84 (0.095)	-0.27 (0.091)	[-0.447, -0.090]	0.0032
Active-controlled, Open-label						
Add-on to Met alone **EFC6019**	Exenatide Lixisenatide	316 318	-0.91(0.062) -0.68(0.061)	0.22(0.076)	[0.073, 0.372]	
Add-on to IG or IG+Met **EFC12626**	Insulin glargine QD Insulin glargine TID Lixisenatide	298 297 298	-0.52(0.058) -0.80(0.057) -0.52(0.060)	0.01(0.064) 0.28(0.064)	[-0.120, 0.131] [0.157, 0.408]	
Add-on to Met alone **EFC12261**	Lixisenatide breakfast Lixisenatide main meal	226 225	-0.67(0.087) -0.53(0.090)	0.14(0.091)	[-0.039, 0.318]	
Active-controlled, Double-blind, Double-dummy						
Add-on to Met alone **EFC10780**	Sitagliptin Lixisenatide	161 158	-0.71(0.104) -0.61(0.101)	0.10(0.132)	[-0.157, 0.359]	

Source: Sponsor's response to information request 21 January 2016 Tables 4, 5, 6, 7, 8

[1]Results were not verified by this reviewer

3.3 Evaluation of safety

Analyses on safety events were reviewed by Dr. Yueqing Zhao from Division of Biometrics VII. These include results from the CVOT study ELIXA.

4. Findings in special/subgroup populations

Dr. Wei Liu has conducted subgroup analyses of the primary endpoint at Week 24 using data pooled from 8 placebo-controlled studies (except Study EFC6018 with the primary endpoint at Week 12). Please refer to his review for the results on these analyses. I performed subgroup analyses for studies EFC12626 and EFC12261 submitted in this cycle.

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 using MMRM, similar to the one used for the post-hoc supportive analyses, with additional covariate on the subgroups being analyzed and 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 11 for Study EFC12626 and Table 12 for Study EFC12261. The sponsor's forest plots for treatment difference within subgroups were presented in Appendices.

In Study EFC12626, the difference in treatment effect of lixisenatide versus insulin glargine TID between Hispanic and Non-Hispanic subjects was statistically significant at alpha = 0.10 (p-value = 0.083). However, the difference was small (LS mean = 0.250%, SE=0.144). It was not considered clinically relevant.

In Study EFC12261, no statistically significant difference in treatment effect between subgroups was found.

Table 11 Subgroup analysis on mean HbA1c (%) change from baseline in Study EFC12626

	Treatment Difference Lixisenatide - Insulin Glulisine QD [95% CI]	**P-value at Week 26[1]**	**Treatment Difference Lixisenatide - Insulin Glulisine TID [95% CI]**	**P-value at Week 26[1]**
Sex				
Male	0.001 [-0.175, 0.177]	0.387	0.196 [0.020, 0.372]	0.801
Female	-0.104 [-0.266, 0.058]		0.227 [0.066, 0.388]	
Age				
<65	-0.031 [-0.173, 0.111]	0.499	0.211 [0.069, 0.354]	0.997
≥65	-0.121 [-0.340, 0.097]		0.211 [-0.005, 0.427]	
Race				
White	-0.051 [-0.173, 0.071]	0.372	0.237 [0.114, 0.360]	0.609
Black	-0.480 [-1.151, 0.191]		-0.072 [-0.679, 0.534]	
Asian and Other	0.197 [-0.552, 0.945]		0.282 [-0.369, 0.934]	
Ethnicity				
Hispanic	-0.105 [-0.367, 0.156]	0.703	0.404 [0.156, 0.653]	0.083
Non-Hispanic	-0.048 [-0.181, 0.085]		0.154 [0.020, 0.289]	
Country				
US	-0.039 [-0.352, 0.274]	0.867	0.250 [-0.051, 0.551]	0.810
Non-US	-0.068 [-0.197, 0.062]		0.210 [0.081, 0.340]	

[1.] F-test for difference in treatment difference between subgroups at Week 26

Table 12 Subgroup analysis on mean HbA1c (%) change from baseline in Study EFC12261

	Treatment Difference Lixisenatide - Insulin Glulisine QD [95% CI]	P-value at Week 24[1]
Sex		
Male	-0.041 [-0.275, 0.192]	0.170
Female	0.176 [-0.030, 0.383]	
Age		
<65	0.050 [-0.127, 0.227]	0.562
≥65	0.159 [-0.165, 0.482]	
Race		
White	0.071 [-0.088, 0.231]	0.550
Black	0.052 [-1.061, 1.166]	
Asian	0.531 [-0.280, 1.341]	
Ethnicity		
Hispanic	0.031 [-0.708, 0.770]	0.897
Non-Hispanic	0.081 [-0.078, 0.240]	
Country		
US	0.190 [-0.211, 0.590]	0.552
Non-US	0.059 [-0.108, 0.226]	

1. F-test for difference in treatment difference between subgroups at Week 24

4.2 Other Special/Subgroup Populations (optional)

Please refer to the sponsor's forest plots in Appendices.

5. Summary and conclusions

5.1 Statistical Issues

5.1.1 Non-inferiority Margin

We sent information request to the sponsor for justification of the non-inferiority margin in Study EFC12261 (0.4%) and Study EFC6019 (0.4%). The non-inferiority margin in Study EFC12261 (0.4%) should be based on the effect on HbA1c at 24 weeks of lixisenatide prior to breakfast with a background of metformin versus metformin alone. The non-inferiority margin in Study EFC6019 should be based on the effect of HbA1c at 24 weeks of exenatide with a background of metformin versus metformin alone. The sponsor evaluated the margins post-hoc using a fixed margin method and the 95%-95% method.

- For Study EFC12261, the sponsor evaluated the treatment effect of lixisenatide injection prior to breakfast add-on to metformin alone using 2 placebo-controlled studies in the same application: EFC6014 (lixisenatide breakfast arm) and EFC10743 (lixisenatide breakfast with 1-step or 2-step increase). The difference between lixisenatide breakfast and placebo from the pooled data was estimated as -0.46% [-0.576% to -0.346%] using the inverse of variance weighted average. The

sponsor did not provide details about the weighting method. Based on this result, the non-inferiority margin should be at most 0.346%. The pre-specified 0.4% margin is too big. The difference between lixisenatide main meal and lixisenatide breakfast was estimated as 0.08% [-0.076% to 0.235%] in the post-hoc MMRM analyses. It was estimated as 0.14% [-0.039% to 0.318%] in the post-hoc sensitivity analyses. Both achieved non-inferiority based on the M_1 margin 0.346%, although the appropriate margin is likely less than 0.346%. The M_1 margin assures that the test drug had an effect greater than zero. This may not be sufficient to assure that the test drug had a clinically meaningfully effect.

- For Study EFC6019, the sponsor evaluated the treatment effect of exenatide add-on to metformin using two historical placebo-controlled 30-week studies: exenatide 10µg add-on to metformin alone and exenatide 10 µg add-on to metformin + sulfonylurea. The difference between exenatide and placebo in the study with add-on to metformin alone was estimated as -0.9% [-1.1% to -0.6%]. The difference between exenatide and placebo from the pooled data was estimated as -1.0% [-1.1% to -0.8%]. The pre-specified non-inferiority margin (0.4%) is half of the upper bound of 95% CI from the pooled data (0.8%). We think the pre-specified margin for Study EFC6019 is acceptable. From a labeling perspective, the results from Study EFC6019 were not presented the proposed label.

5.1.2 Missing Data

In the study design, the sponsor did not intend to collect data after treatment discontinuation or initiation of rescue therapy. There remained 5%-16% patients who did not have HbA1c measurement at the end of the main treatment period. MMRM assumes missing data are MAR. Considering that there was considerable amount of missing data and that there was evidence that data were not MAR in some of the Phase 3 studies, the results from the MMRM analysis using all available post-baseline observations in Table 8 may be subject to bias.

We requested additional sensitivity analyses from the sponsor to examine the impact of the violation in the MAR assumption. The sponsor's results for the post-hoc sensitivity analyses did not change most of the conclusions from the MMRM analysis using all available post-baseline observations. The maximum difference between the sensitivity analysis and the MMRM analysis in the estimate for treatment difference was 0.11 (Study EFC6015). In the sensitivity analysis for Study EFC12626, lixisenatide did not achieve non-inferiority versus insulin glargine TID based on a non-inferiority margin of 0.4% (LS mean treatment difference was 0.28%; 95% CI: 0.157, 0.408). The LS mean treatment difference in the MMRM analysis was 0.21% (95% CI: 0.094, 0.331).

5.2 Collective Evidence

Currently we think the MMRM analysis using all available post-baseline observations is more appropriate for labeling. Based on the results from this analysis, lixisenatide demonstrated superiority to placebo in terms of HbA1c change from baseline at the primary efficacy time point in all placebo-controlled Phase 3 efficacy studies, as monotherapy or in combination with other antidiabetic drugs.

Lixisenatide demonstrated non-inferiority to exenatide, insulin glulisine QD and TID based on a noninferiority margin of 0.4%. However, Lixisenatide was significantly worse than exenatide (LS mean for treatment difference was 0.18; 95% CI: 0.046, 0.307; p-value =0.0083) and insulin glargine TID (LS mean for treatment difference was 0.21; 95% CI: 0.094, 0.331; p-value = 0.0005). No significant difference was observed between lixisenatide and sitagliptin (LS mean for treatment difference was 0.04%; 95% CI: -0.198, 0.288; p-value =0.717). However, these conclusions may be subject to bias due to violation of the MAR assumption.

The post-hoc sensitivity analyses confirmed most of the conclusions from the MMRM analysis using all available post-baseline observations. They suggest there is a possibility that lixisenatide did not achieve noninferiority versus insulin glargine TID based on a non-inferiority margin of 0.4% (LS mean treatment difference was 0.28%; 95% CI: 0.157, 0.408). However, considering that the imputation approach is very conservative and that the upper bound of the 95% CI for the treatment difference is just a little over 0.4%, this possibility is not very high.

In the mealtime study EFC12261, lixisenatide main meal achieved non-inferiority to lixisenatide breakfast based on a non-inferiority margin of 0.4% in both the MMRM analysis and the sensitivity analysis. However, the pre-specified non-inferiority margin is too big for this scenario. A more appropriate margin (less than or equal to 0.346%) should be used and the sensitivity analysis should be conducted based on the revised margin.

Subgroups analyses of HbA1c were conducted based on pooled patient populations from the 8 Phase 3 placebo-controlled studies with the primary endpoint at Week 24. The HbA1c difference between lixisenatide and placebo are similar across subgroups defined by sex, age, race, country, baseline BMI, duration of diabetes, baseline level of creatinine clearance, antilixsenatide antibody status, and anti-lixisenatide antibody concentration except for the baseline HbA1c level. Significant treatment-baseline HbA1c levels interactions were observed at alpha=0.10 ($p<0.001$) level that lixisenatide was better for patients with higher HbA1c baseline level than those with lower level.

5.3 Conclusions and Recommendations

Lixisenatide QD demonstrated superiority to placebo in terms of HbA1c change from baseline, as monotherapy or in combination with other antidiabetic drugs. Its effect size appeared to be comparable to insulin glargine QD and sitagliptin QD but smaller than insulin glargine TID and exenatide BID.

The conclusion from the mealtime study EFC12261 is not clear. The pre-specified non-inferiority margin of 0.4% is too big for this scenario. A more appropriate margin (less than or equal to 0.346%) should be used and the sensitivity analysis should be conducted based on the revised margin.

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

5.4 Labeling recommendations

The proposed product label contains results from all the 9 placebo-controlled studies (monotherapy study EFC6018, add-to to basal insulin alone or in combination with oral antidiabetics EFC6016, EFC10887, EFC10781, add-on to metformin alone or in combination with sulfonylurea EFC10743, EFC6014, EFC11321, add-on to sulfonylurea alone or in combination with metformin EFC6015, add-on to Pioglitazone alone or in combination with metformin EFC6017), 2 active-controlled studies (insulin glargine as active comparator EFC12626, meal time study EFC12261) and the ELIXA cardiovascular outcome study.

1. The results in the label are based on the primary analysis using ANCOVA with LOCF. The LOCF approach is no longer recommended by the Division. These results should be replaced with those from the post-hoc supportive analyses using MMRM with all available post-baseline observations. Each table should include a footnote providing the percentage of subjects with missing HbA1c measurement at the end of the main treatment period.

2. In overall, the secondary 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).

3. The percentage of patients achieving HbA1c < 7.0% was not in the pre-specified hierarchy of hypothesis testing but appears in the label.

4. Change in insulin glargine dose is not an appropriate efficacy endpoint and should be removed from the results tables in section 14.

Appendices

Figure 1 Sponsor's forest plot of mean change in HbA1c (%) from baseline to Week 24 by baseline factor – Study EFC12626 lixisenatide versus insulin glargine QD

Characteristic	Diff	[95% CI]
Race		
Caucasian	-0.05	(-0.165 to 0.073)
Black	-0.41	(-1.048 to 0.234)
Asian/Oriental	0.12	(-0.610 to 0.846)
Ethnicity		
Hispanic	-0.09	(-0.343 to 0.170)
Non Hispanic	-0.05	(-0.177 to 0.085)
Age		
< 50	0.06	(-0.274 to 0.397)
≥50 to < 65	-0.05	(-0.208 to 0.102)
≥65	-0.11	(-0.319 to 0.103)
Gender		
Male	-0.02	(-0.192 to 0.153)
Female	-0.08	(-0.236 to 0.080)
Baseline BMI (kg/m²)		
<30	0.06	(-0.132 to 0.255)
≥30	-0.11	(-0.254 to 0.040)
Baseline HbA1c (%)		
<8.0	-0.04	(-0.188 to 0.100)
≥8.0	-0.07	(-0.267 to 0.132)
Actual metformin use		
Yes	-0.04	(-0.167 to 0.082)
No	-0.12	(-0.451 to 0.208)
Duration of diabetes at screening (Years		
<10	-0.13	(-0.316 to 0.053)
≥10	-0.00	(-0.151 to 0.149)
Daily total glargine dose at baseline(U)		
<45	0.01	(-0.214 to 0.229)
≥45	-0.08	(-0.213 to 0.062)
Duration of basal insulin treatment (Yea		
<3	-0.08	(-0.225 to 0.068)
≥3	0.01	(-0.183 to 0.201)

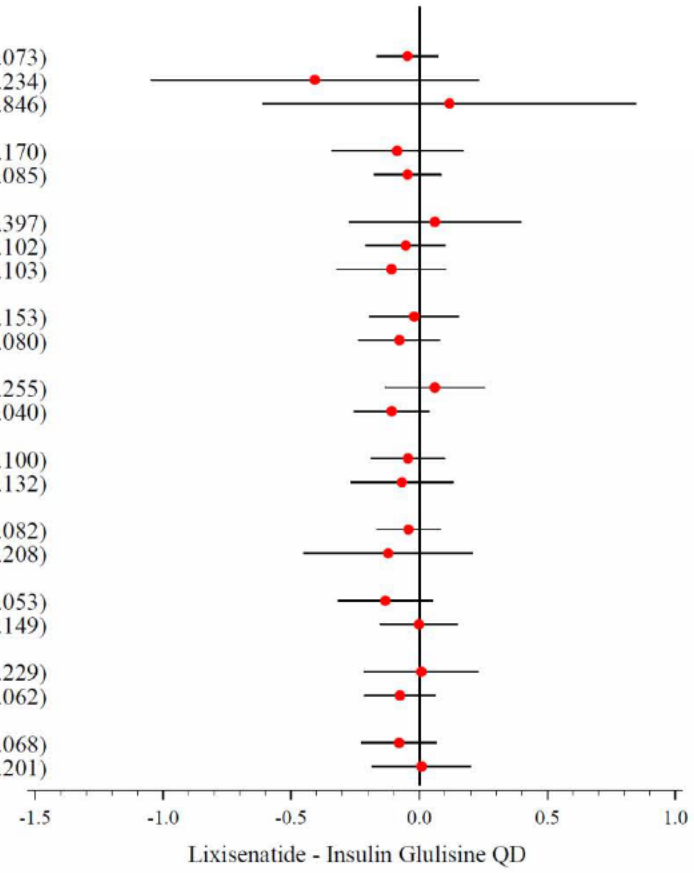


Figure 2 Sponsor's forest plot of mean change in HbA1c (%) from baseline to Week 24 by baseline factor – Study EFC12626 lixisenatide versus insulin glargine TID

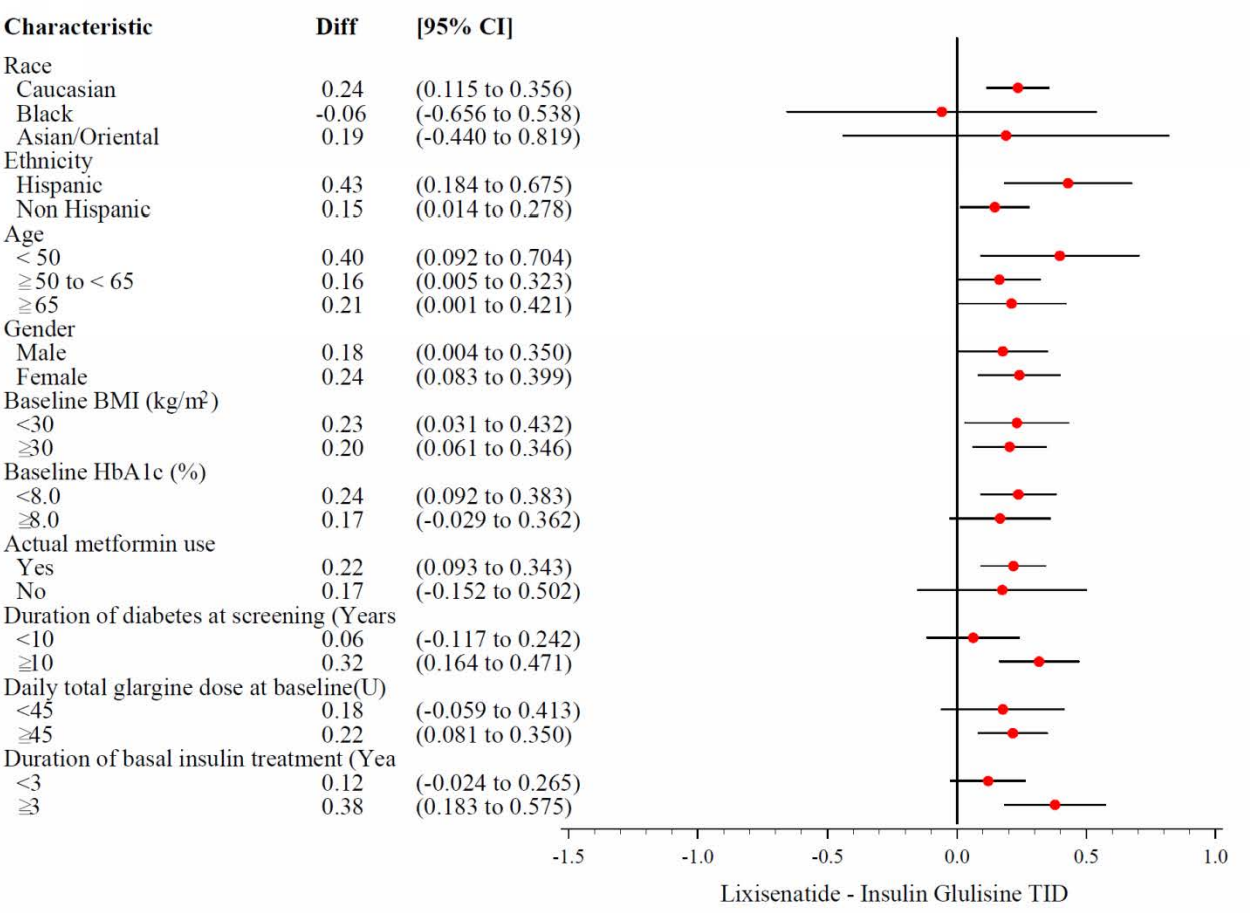


Figure 3 Sponsor's forest plot of mean change in HbA1c (%) from baseline to Week 24 by country – Study EFC12626 lixisenatide versus insulin glargine QD

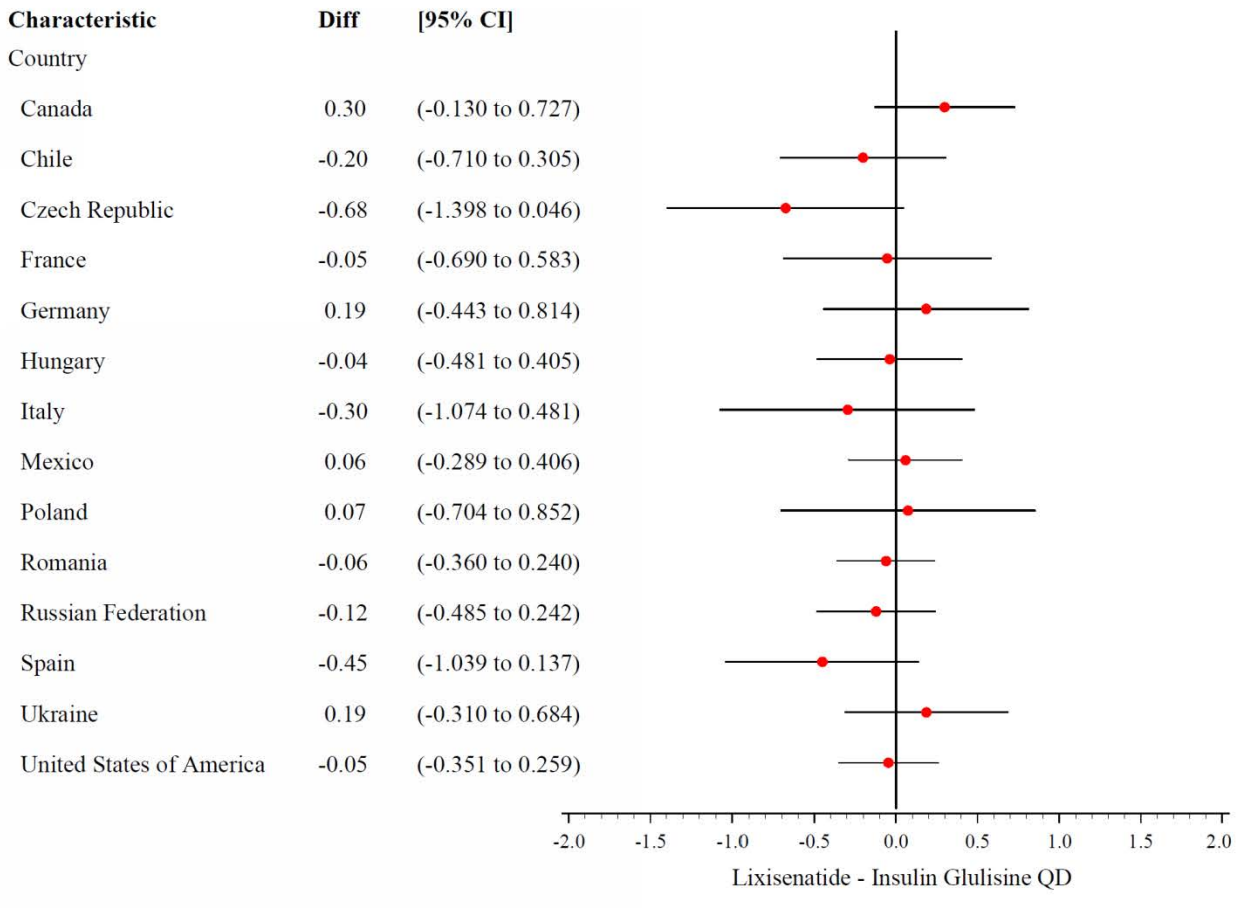


Figure 4 Sponsor's forest plot of mean change in HbA1c (%) from baseline to Week 24 by country – Study EFC12626 lixisenatide versus insulin glargine TID

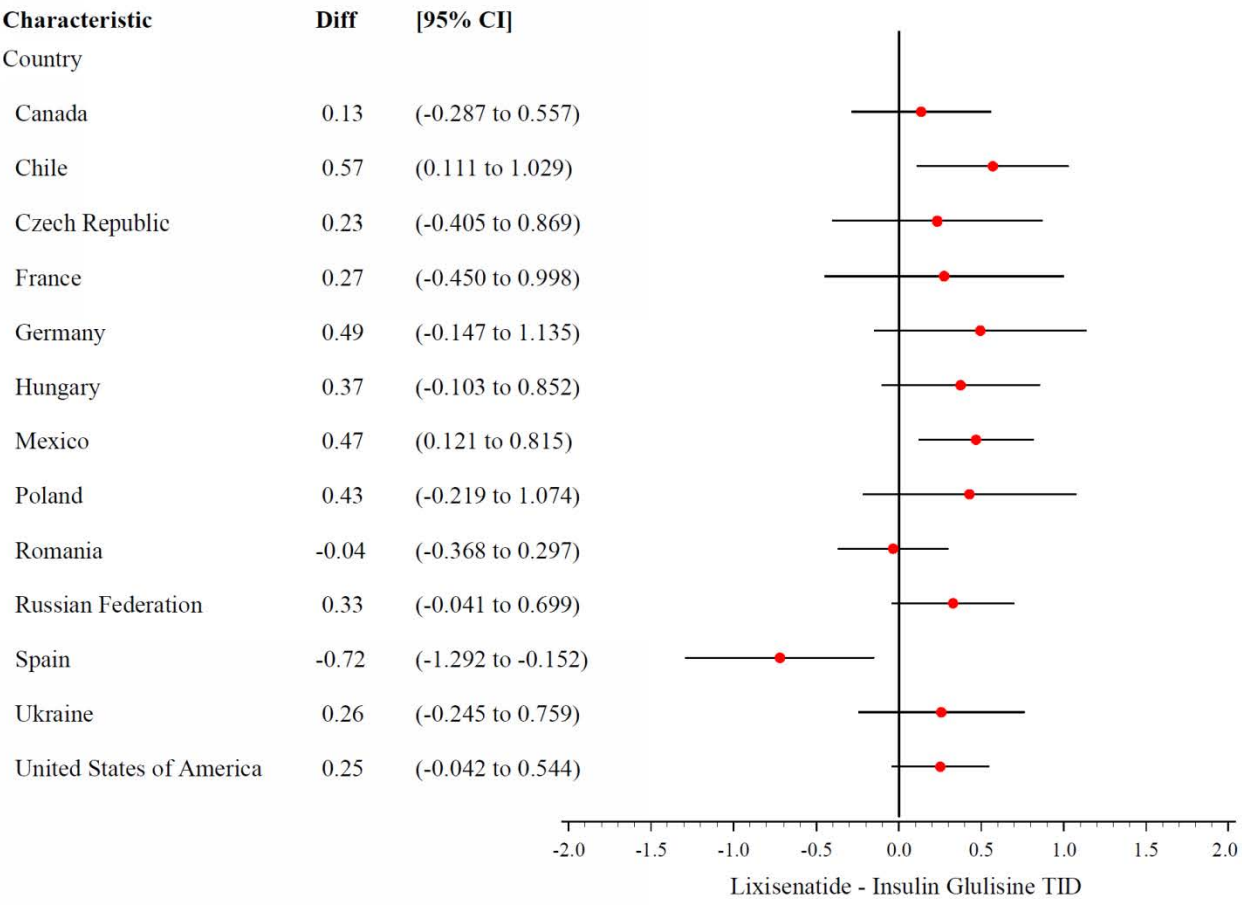


Figure 5 Sponsor's forest plot of mean change in HbA1c (%) from baseline to Week 24 by baseline factor – Study EFC12261

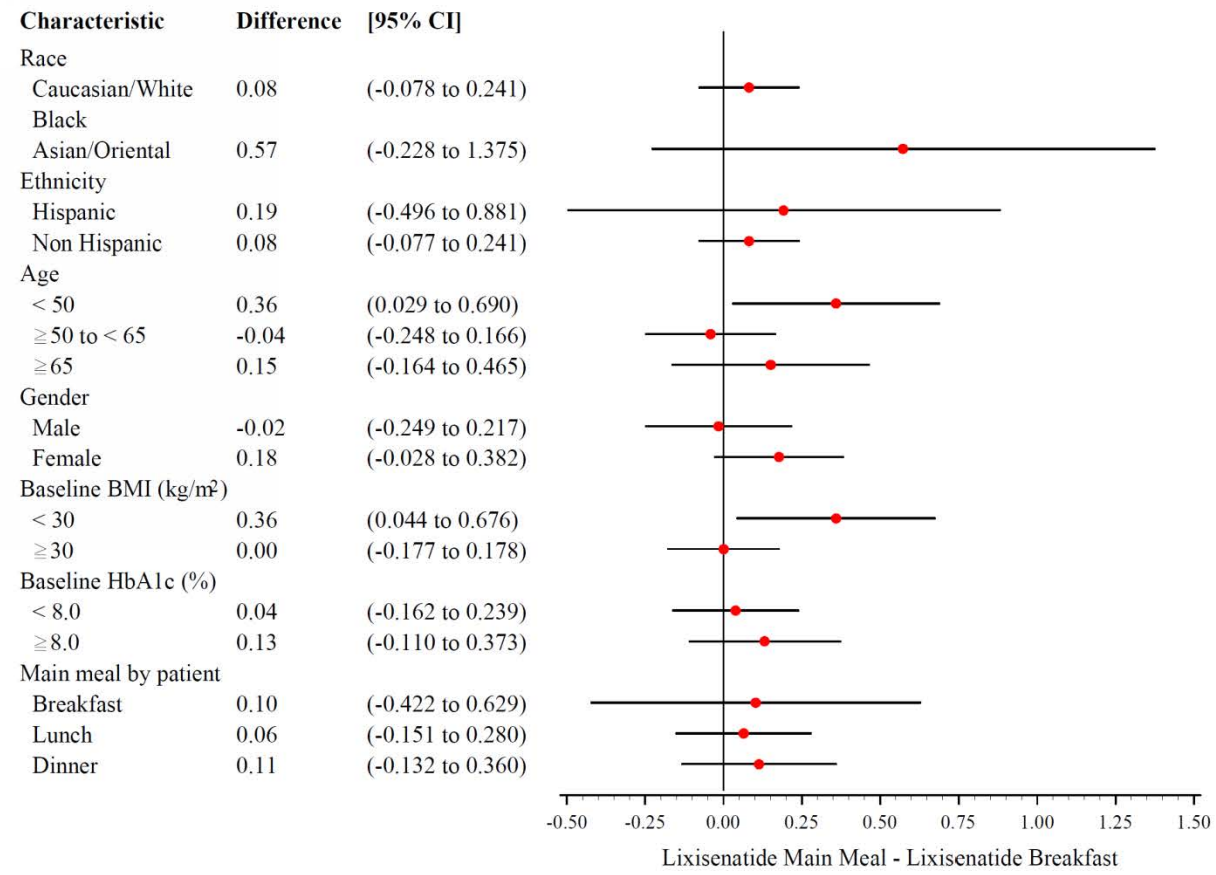
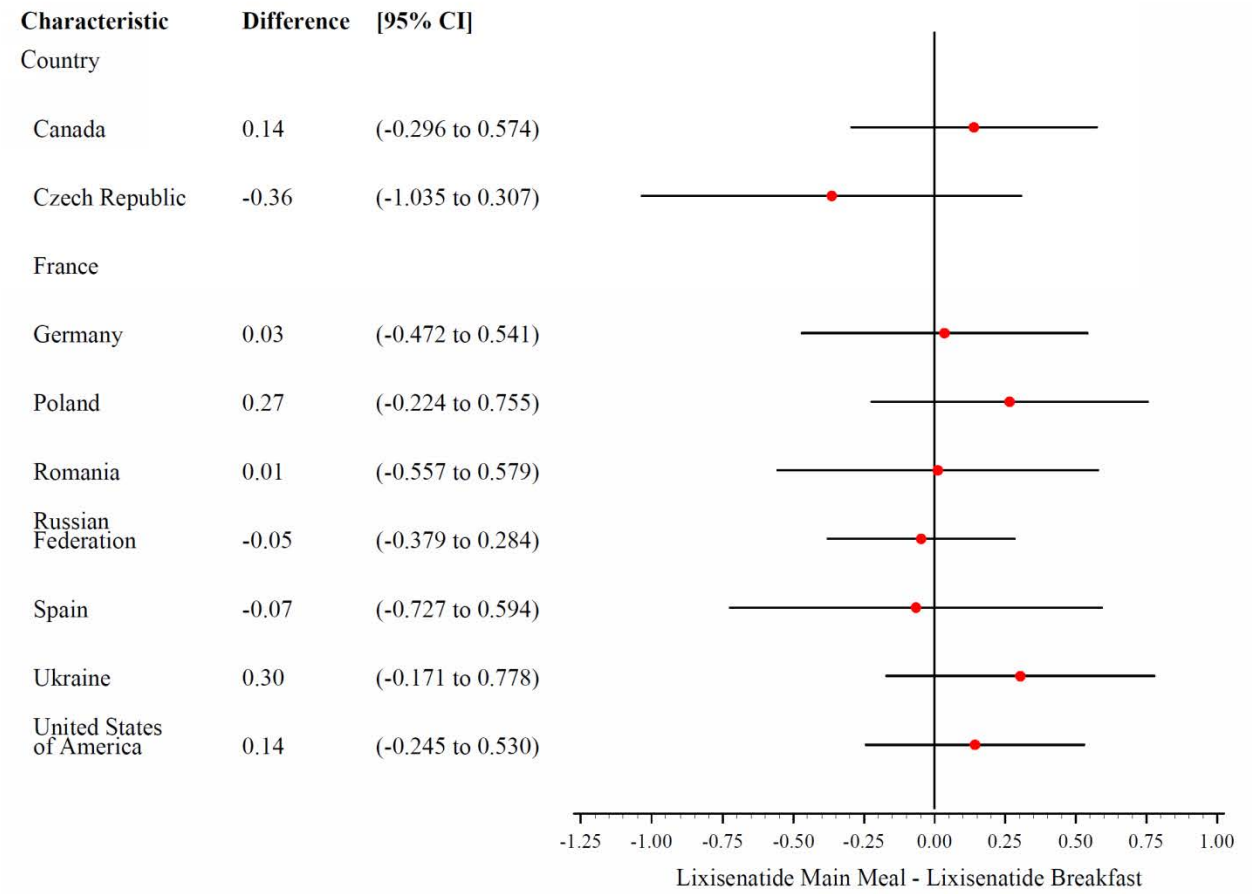


Figure 6 Sponsor's forest plot of mean change in HbA1c (%) from baseline to Week 24 by country - Study EFC12261



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/s/

JIWEI HE
03/21/2016

MARK D ROTHMANN
03/21/2016
I concur

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 208471 **Applicant: Sanofi** **Stamp Date: July 27 2015**

Drug Name: Lixisenatide **NDA/BLA Type: Standard Review**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	*			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	*			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	*			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	*			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?
Yes.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comments
Designs utilized are appropriate for the indications requested.				The active-controlled trials were open-label.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	*			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			*	
Appropriate references for novel statistical methodology (if present) are included.			*	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	*			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.				The results were based on LOCF as the primary method accounting for missing data. Analyses using MMRM were consistent with the primary results using

				LOCF. The sponsor included several other sensitivity analyses.

Comments:

The Division is reconsidering the use of the LOCF approach to handle missing data following a publication in 2010 by the National Academy of Sciences (NAS), *The Prevention and Treatment of Missing Data in Clinical Trials*. We do not think the use of LOCF especially in the primary analysis is appropriate because it relies on the strong, untestable, and implausible assumption that outcomes remain constant after patients drop out, and as a single-imputation approach, it does not take into account the statistical uncertainty in the imputation process.

Supportive and sensitivity analyses will be important for evaluating the treatment effect in this application. In addition to the MMRM analysis with all HbA1c data regardless of treatment discontinuation or initiation of rescue therapy that was already included in the application, we would like subjects with missing values who do not adhere to therapy to have their missing values represented by those subjects on the same treatment arm who were similarly non-adherent to therapy and were measured for the endpoint, when possible.

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/s/

JIWEI HE
09/23/2015

MARK D ROTHMANN
09/24/2015
Concur

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	NDA 208471
Supplement #:	Not Applicable
Related IND #:	IND 062724
Product Name:	Lixisenatide injection (AVE0010), 10 µg to 20 µg once daily (QD).
Indication(s):	For the treatment of adults with Type 2 diabetes mellitus to achieve glycemic control as an adjunct to diet and exercise.
Applicant:	Sanofi
Dates:	Date submitted: 07/27/2015 PDUFA due date: 07/27/2016 Filing meeting date: 09/10/2015
Review Priority:	Standard
Biometrics Division:	Biometrics Division VII
Statistical Reviewer:	Yueqin Zhao, Ph.D.
Concurring Reviewers:	Mat Soukup, Ph.D.
Medical Division:	OND/ODEII/DMEP
Clinical Team:	Ondina Lungu, M.D., Primary Reviewer William Chong, M.D., Team Leader Jean-Marc Guettier, M.D., Division Director
Project Manager:	Martin White

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

Lixisenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist. The Applicant seeks the following indication for this biologic: "indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus". This statistical review will focus on the trial "A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate cardiovascular outcomes during treatment with lixisenatide in type 2 diabetic patients after an Acute Coronary Syndrome event" (Trial ID: EFC11319, also referred to as the ELIXA trial). This is a trial designed to assess the cardiovascular risks related to the product lixisenatide with the objective of ruling out the 1.3 risk margin as stipulated in the 2008 FDA Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. A summary of the trial EFC11319 (ELIXA) is provided in Table 1.

Table 1: Summary of Trial EFC11319 (ELIXA) to be Assessed in the Statistical Review

Design	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
Randomized, Double-blind, placebo-controlled, 1:1 randomized, 2-arm, parallel-group, multinational Phase III study	Planned: 6000 Randomized : 6068 Treated: 6063 Completed the study: 5853 ITT population: Lixisenatide: 3034 Placebo: 3034	**Primary**: Time to the first occurrence of any of the following events[1]: cardiovascular (CV) death, non-fatal myocardial infarction (MI), non-fatal stroke, hospitalization for unstable angina. **Key Secondary**: - Time to the first occurrence of any of the following events[1]: CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or hospitalization for heart failure - Time to the first occurrence of any of the following events[1]: CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, hospitalization for heart failure, or coronary revascularization procedure - Percent change in the urinary albumin/creatinine ratio (UACR) from baseline to Week 108 (approximately 2 years) **Analysis methods**: Cox Proportional Hazards Model	The study found 805 positively adjudicated CV events. The hazard ratio for the ITT analysis of the primary endpoint for lixisenatide compared to placebo is 1.02 with a 95% confidence interval of (0.89, 1.17). **Table 1.1: Analysis of the primary CV endpoint – ITT population** Placebo (N=3034) / Lixisenatide (N=3034) Primary CV endpoint No. of patients with event (%): 399 (13.2%) / 406 (13.4%) Total Person Year: 6328.2 / 6356.8 Incidence Rate: 6.31 / 6.39 Component of CV events CV death: 93 (3.1%) / 88 (2.9%) Non-fatal MI: 247 (8.1%) / 255 (8.4%) Non-fatal stroke: 49 (1.6%) / 54 (1.8%) Hospitalization for unstable angina: 10 (0.3%) / 9 (0.3%)

[1] Events were positivily adjudicated by a Cardiovascular Events Adjudication Committee (CAC)

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	Yes
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	Yes
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	Two interim analyses were planned in the protocol. As pre-specified, one interim analysis was reported to FDA in 2012, and the other one was to be performed only if the 1.8 criterion was not met at the first interim analysis. DSMB meeting minutes are provided.
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	Yes
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	Yes

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\CDSESUB1\evsprod\NDA208471\0000\m5\datasets\efc11319\analysis\legacy\datasets
Dataset structure (e.g., SDTM or ADaM)	ADaM
List the dataset(s) that contains the primary endpoint(s)	ADTTE: Time to event ADEFCV: CV related efficacy data
Are the define files sufficiently detailed?	Yes
Based on the *analysis datasets*, can results of the primary endpoint(s) be reproduced?	Yes, the reviewer was able to reproduce the results of the primary endpoints.
Are there any concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	No
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	Not Applicable. The evaluation of CV risk is based upon a single trial –

Content Parameter	Response/Comments
	ELIXA.

4. Filing Issues

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	**X**			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	**X**			
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	**X**			
Data sets in EDR are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	**X**			
Application is free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements	**X**			

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE? Yes. Based on our initial review, the Applicant has submitted necessary documents and datasets for this NDA application

5. Comments to be Conveyed to the Applicant

We have no comments to convey to the Applicant at this time.

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/s/

YUEQIN ZHAO
09/21/2015

MATTHEW J SOUKUP
09/21/2015
Concur

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 204961/0000
Supplement #:	NA
Drug Name:	Lixisenatide Injection (proposed tradename (b) (4))
Indication(s):	Treatment of patients with type 2 diabetes mellitus
Applicant:	Sanofi
Date(s):	December 20, 2012
Review Priority:	Standard (10-month)
Biometrics Division:	Division of Biometrics 2 (HFD-715)
Statistical Reviewer:	Wei Liu, Ph.D.
Concurring Reviewers:	Mark D. Rothmann, Ph.D. (Team Leader)
Medical Division:	Metabolism and Endocrinological Products (HFD-510, DMEP)
Clinical Team:	Suchitra Balakrishnan, M.D. Karen Mahoney, M.D. (Team Leader)
Project Manager:	Pooja Dharia

Keywords: NDA review, clinical studies

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1. EXECUTIVE SUMMARY

The applicant seeks the indication of lixisenatide tablets for the treatment of patients with type 2 diabetes mellitus.

Confirmation of efficacy:
All superiority comparisons of lixisenatide vs placebo in HbA1c change from baseline, the primary efficacy endpoint, were statistically significant in all studies. The analyses were based on last observation carried forward method (LOCF) as the primary method for accounting for missing data. Analyses using MMRM were consistent with the primary results with LOCF.

The primary efficacy findings by this reviewer are shown in Table 1.

Table 1. Primary Efficacy Results (HbA1c) for Lixisenatide in Patients with Type 2 Diabetes (Phase 3 Studies) (mITT/LOCF)

Study (Weeks)	Treatment arm	n	Baseline Mean ± SE	LSMean change ± SE	Lixi minus control (95% CI)	p-value
Monotherapy						
EFC6018 (12)	Lixi 2-step inc Lixi 1-step inc Placebo	113 114 112	7.97 ± 0.09 8.06 ± 0.08 8.07 ± 0.09	-0.73 ± 0.12 -0.85 ± 0.12 -0.19 ± 0.12	-0.54 (-0.78, -0.30) -0.66 (-0.90, -0.42)	<.0001 <.0001
Add-on to Metformin alone						
EFC6014 (24)	Lixi, morning Lixi, evening Placebo	244 239 164	8.07 ± 0.06 8.07 ± 0.06 8.02 ± 0.07	-0.87 ± 0.07 -0.75 ± 0.07 -0.38 ± 0.08	-0.48 (-0.66,-0.31) -0.37 (-0.54,-0.19)	<.0001 <.0001
EFC10743 (24)	Lixi 2-step inc Lixi 1-step inc Placebo	152 156 158	8.12 ± 0.07 7.99 ± 0.07 8.03 ± 0.07	-0.83 ± 0.10 -0.92 ± 0.10 -0.42 ± 0.10	-0.41 (-0.58, -0.23) -0.49 (-0.67, -0.32)	<.0001 <.0001
EFC6019[1] (24)	Lixisenatide Exenatide	295 297	7.97 ± 0.05 7.96 ± 0.04	-0.79 ± 0.05 -0.96 ± 0.05	0.17 (0.03, 0.30)	0.0143
Add-on to Sulfonylurea or (Sulfonylurea + Metformin)						
EFC6015 (24)	Lixisenatide Placebo	544 274	8.28 ± 0.04 8.22 ± 0.05	-0.85 ± 0.06 -0.10 ± 0.07	-0.74 (-0.87, -0.62)	<.0001
Add-on to Pioglitazone or (Pioglitazone + Metformin)						
EFC6017 (24)	Lixisenatide Placebo	308 148	8.08 ± 0.05 8.05 ± 0.06	-0.90 ± 0.09 -0.34 ± 0.10	-0.56 (-0.73, -0.39)	<.0001
Add-on to Basal Insulin or (Basal Insulin + Metformin)						
EFC6016 (24)	Lixisenatide Placebo	304 158	8.39 ± 0.05 8.38 ± 0.07	-0.74 ± 0.09 -0.38 ± 0.11	-0.36 (-0.55, -0.17)	0.0002
Add-on to (Insulin glargine + Metformin) or (Insulin glargine + Metformin + Thiazolidinediones)						
EFC10781 (24)	Lixisenatide Placebo	215 221	7.56 ± 0.04 7.60 ± 0.04	-0.71 ± 0.09 -0.40 ± 0.09	-0.32 (-0.46, -0.17)	<.0001

Add-on to Basal Insulin or (Basal Insulin + Sulfonylurea)						
EFC10887 (24)	Lixisenatide Placebo	146 154	8.53 ± 0.06 8.53 ± 0.06	-0.77 ± 0.14 0.11 ± 0.13	-0.88 (-1.12, -0.65)	<.0001
Add-on to Metformin or (Metformin + Sulfonylurea)						
EFC11321 (24)	Lixisenatide Placebo	185 188	7.95 ± 0.06 7.83 ± 0.05	-0.83 ± 0.10 -0.47 ± 0.10	-0.36 (-0.55, -0.16)	0.0004

[1] Lixisenatide QD versus Exenatide **BID**

Lixisenatide QD was shown to be non-inferior to exenatide BID in reducing the mean HbA1c from baseline to Week 24 in Study EFC6019 using a pre-specified non-inferiority margin of 0.4%. However, the non-inferiority was no longer preserved after 36 weeks of treatment. At Week 36, the treatment difference from exenatide based on the changes of HbA1c from baselines was 0.30 (95% CI: 0.17 to 0.44); at Weeks 52 and 76, the difference was 0.27 (95% CI: 0.13 to 0.42) and 0.29 (95% CI: 0.12 to 0.46), respectively. The study also showed that lixisenatide was statistically worse than exenatide during the entire treatment period, with the mean treatment difference was 0.17% at Week 24 and 0.29 at Week 76, respectively.

Subgroups analyses of HbA1c were conducted based on pooled patient populations from the 8 Phase 3 placebo-controlled studies with the primary endpoint at Week 24. The HbA1c difference between lixisenatide and placebo are similar across subgroups defined by sex, age, race, country, baseline BMI, duration of diabetes, baseline level of creatinine clearance, anti-lixsenatide antibody status, and anti-lixsenatide antibody concentration except for the baseline HbA1c level. Significant treatment-baseline HbA1c level interaction was observed at alpha=0.10 ($p<0.001$) level that the difference of lixisenatide – placebo was larger for patients with higher HbA1c baseline level than those with lower level.

Considerations that may limit the efficacy:

1. The multiplicity procedure shown in sponsor's EFC6018 SAP Figure 1 does not control the overall type 1 error rate at level 0.05 for secondary endpoints in the parallel 1-step and 2-step increase arms.

2. There was one active-controlled and open-label pivotal study EFC6019 in which the efficacy of lixisenatide was compared to Exenatide. To reduce the bias, we suggested earlier that the sponsor should ideally use double-blinded technique in this non-inferiority trial instead of an open-label design. However, the sponsor did not explain why it is not possible to blind this trial.

3. There were patients who were under rescue medication prior to the end of main treatment period but who were labeled as completers in the submitted datasets.

Recommendations:
Recommendations for the proposed label are included in part 5.4.

2. INTRODUCTION

2.1 Overview

Glucagon-like peptide-1 (GLP-1) is an incretin hormone that is secreted by specialized intestinal L-cells of the small and large intestine following ingestion of a carbohydrate- or fat-containing meal. It regulates nutrient metabolism by improving pancreatic responsiveness to high glucose, stimulating insulin secretion and reducing glucagon secretion, and thereby improving glucose tolerance, fasting blood glucose levels, and overall metabolic control. In nonclinical studies, GLP-1 induced ß-cell proliferation and increased pancreatic ß-cell mass. Additional non-pancreatic GLP-1 effects include inhibition of gastric emptying, which contributes to decrease glycemic excursion and consequently, reduced glucose-stimulated insulin secretion. Moreover GLP-1 increases satiety and reduces food intake, which contributes to a decrease in body weight. Native GLP-1 is rapidly degraded by dipeptidyl peptidase-4 (DPP-4), resulting in a half-life of only 1 to 2 minutes, which limits its therapeutic usefulness (4).

Lixisenatide (AVE0010) is a short-acting GLP-1 receptor agonist that was developed for the treatment of patients with type 2 diabetes mellitus (T2DM). It has structural similarities to exendin-4 and is resistant to enzymatic cleavage by DPP-4. It has demonstrated beneficial effects on glucose control and body weight reduction in nonclinical and Phase 1 clinical studies. Lixisenatide results in a longer duration of action making it possible for lixisenatide to be administered once daily (QD) for therapeutic purposes.

The sponsor, Sanofi (hereafter referred to as the sponsor) submitted NDA 204961 on December 20, 2012 for the use of lixisenatide (proposed tradename (b) (4)) 20 µg QD injection in adult patients with type 2 diabetes (T2DM) as an adjunct to diet and exercise to improve glycemic control.

The sponsor submitted data of 10 phase 3 pivotal studies. There were 9 double-blind placebo-controlled studies (EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887 and EFC11321) for supporting the efficacy of lixisenatide as monotherapy, in combination with metformin, sulfonylurea, metformin and sulfonylurea, pioglitazone, metformin and pioglitazone, basal insulin, basal insulin and metformin, basal insulin and sulphonyurea, and in combination with (insulin glargine and metformin) or (insulin glargine and thiazolidinediones). There was one active-controlled pivotal study EFC6019 in which the efficacy of lixisenatide QD was compared to Exenatide BID. All pivotal phase 3 studies evaluated a dose of 20 µg once daily (QD) as the maintenance dose. Table 2.1 presents the overview of these Phase 3 clinical studies. These pivotal studies were reviewed by this reviewer.

Note that there were 85% of non-US patients and only 3.5% black patients, which is not reflective of the population in the US with diabetes.

Table 2.1. Phase 3 Trials Overview

Study[1]	Design[2]	Main Treatment Period	Extension	# of Subjects per Arm (randomized)
Monotherapy				
EFC6018	R,DB,PC, PG	12weeks	NA	Placebo 122 (61+61) Lixisenatide 2-step 120 Lixisenatide 1-step 119
Add-on to Met alone				
EFC6014 (Table 7)	R,DB,PC,PG	24weeks	≥ 52 weeks	Placebo 170 (85+85) Lixisenatide morning 255 Lixisenatide evening 255
EFC10743 (Table 7)	R,DB,PC,PG	24 weeks	≥ 52 weeks	Placebo 162 (80+82) Lixisenatide 2-step 161 Lixisenatide 1-step 161
EFC6019 (NI)[3]	R,OL,AC, PG	24 weeks	≥ 52 weeks	Exenatide 319 Lixisenatide 320
Add-on to SU or SU+Met				
EFC6015 (Table 9)	R,DB,PC, PG	24 weeks	≥ 52 weeks	Placebo 286 Lixisenatide 573
Add-on to Pio or PIO+Met				
EFC6017 (Table 10)	R,DB,PC, PG	24 weeks	≥ 52 weeks	Placebo 161 Lixisenatide 323
Add-on to BI or BI+Met				
EFC6016 (Table 5)	R,DB,PC,PG	24 weeks	≥ 52 weeks	Placebo 167 Lixisenatide 329
Add-on IG+Met or IG+Met+TZD				
EFC10781 (Table 6)	R,DB,PC, PG	24 weeks	NA	Placebo 223 Lixisenatide 223
Add-on to BI or BI+SU				
EFC10887 (Table 5)	R,DB,PC,PG	24 weeks	NA	Placebo 157 Lixisenatide 154
Add-on to Met or Met+SU				
EFC11321 (Table 8)	R,DB,PC, PG	24 weeks	NA	Placebo 195 Lixisenatide 196

[1] In all studies, the study population was with HbA1c (%) ≥7 to ≤**10 at screening; lixisenatide dose was 20 µg QD.**
Met = Metformin, SU = Sulfonylurea, Pio = Pioglitazone, BI = Basal insulin, IG = Insulin glargine, TZD = Thiazolidinediones.
[2] R: randomized; DB: double-blind; PC: placebo-controlled; PG: parallel-group; AC: active-controlled. OL: open-label;
[3] Five patients from one site were randomized and treated but excluded from all analyses due to significant noncompliance to the protocol.

2.2 Data Sources

The sponsor submitted this NDA including the study data to the FDA CDER Electronic Document Room (EDR) with the link shown below. Study data were submitted in SAS Xport transport format.

Application:	NDA 204961/0000
Company	Sanofi
Drug	Lixisenatide
CDER EDR link	\\CDSESUB1\EVSPROD\NDA204961\0000
Letter date	12/20/2012

All graphs and tables in the review were created by this reviewer unless otherwise noted.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Review the quality and integrity of the submitted data. Relevant issues include:

- It is possible to reproduce the primary analysis dataset from tabulation or "raw" datasets.
- It is possible to trace how the primary endpoint was derived from the original data source (e.g., case report form).
- It is possible to verify the randomized treatment assignments.

3.2 Evaluation of Efficacy

The primary objective of the 10 pivotal Phase 3 studies was to demonstrate the efficacy of lixisenatide on glycemic control as evaluated by the reduction in HbA1c at Week 12 as monotherapy in Study EFC6018 or at Week 24 as add-on treatment in the other studies. The aim was to demonstrate the superiority of lixisenatide in the placebo-controlled studies (Studies EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887 and EFC11321) and non-inferiority in active-controlled Study EFC6019.

This section provides efficacy evaluations of the 10 pivotal phase 3 studies designed to establish the efficacy and safety of lixisenatide in the trials of monotherapy and add-on to other anti-hyperglycemic agent.

The primary efficacy endpoint in pivotal Phase 3 studies was the change from baseline in HbA1c at the end of the main treatment period (Week 12 in Study EFC6018 or Week 24 in the rest studies). The percentage of patients with HbA1c <7% at the end of the main treatment period was also assessed in all Phase 3 controlled studies.

The key secondary efficacy endpoints in all these 10 pivotal studies are changes from baseline in FPG, body weight, and percentage of patients requiring rescue therapy at the end of the main treatment period (Week 12 in Study EFC6018 or Week 24 in the other studies). Change in 2-hour PPG was also assessed after a standardized breakfast in Studies EFC6014, EFC6015,

EFC6016, EFC6018, EFC10781, EFC10887 and EFC11321. Additional selected secondary efficacy endpoints to further elucidate the effect of lixisenatide were specified in each study.

The sample sizes were determined by sponsor for the 9 pivotal Phase 3 placebo-controlled studies to ensure at least 90% power to detect differences of 0.5% in the change in HbA1c from baseline to Week 24 (Week 12 for Study EFC6018) between lixisenatide and placebo. This calculation assumed a common standard deviation of 1.3% (1.2% at Week 12 for Study EFC6018) with a 2-sided test at the 5% significance level. In Study EFC6019, the sample size was calculated to ensure that the upper limit of the 2-sided 95% confidence interval (CI) for the adjusted mean difference between lixisenatide and exenatide for the mean change in HbA1c from baseline to Week 24 would not exceed 0.4% with 96% power assuming the true difference between lixisenatide and exenatide was zero in HbA1c and a common standard deviation of 1.3% with a 1-sided test at the 2.5% significance level. The predefined non-inferiority margin was 0.4%.

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

- Intent-to-treat (ITT): All randomized patients who received at least 1 dose of double-blind (or open-label for Study EFC6019) investigational product and who had a baseline assessment.
- Modified intent-to-treat (mITT): All randomized patients who received at least 1 dose of double-blind (or open-label for Study EFC6019) investigational product and who had both a baseline assessment and at least one post-baseline assessment of the primary or secondary efficacy variables, irrespective of compliance with the study protocol and procedures.
- Completers: The 24-week (12-week in EFC6018) completer's population was defined as all patients who had completed the main 24-week (12-week in EFC6018) double-blind treatment period and who had not been rescued during this main 24-week treatment period.

All efficacy analyses were based on mITT analysis set.

Primary Analysis was pre-specified by the sponsor: an analysis of covariance (ANCOVA) model using the last observation carried forward method (LOCF) for missing observations. In general, the ANCOVA model included terms for treatment, randomization strata of screening HbA1c (<8.0, =8.0%), country, and randomization strata of either screening anti-diabetic drug use (Yes, No) or screening BMI (<30, ≥30 kg/m^2) as fixed effects and the corresponding baseline HbA1c value as covariate.

In addition to verify the sponsor's primary analysis, I performed two sensitivity analyses in order to investigate if the data are supportive to the efficacy claim using alternative methods to deal with the missing data issue. The first analysis was an ANCOVA using the completers population. The second analysis, change from baseline in HbA1c was analyzed using mixed model repeated measures (MMRM) in observed patients who were not initiated on rescue therapy prior to the visit for the primary endpoint. In addition to the sponsor's ANCOVA model, the MMRM analysis included visit and treatment-by-visit interaction as fixed effects.

In the non-inferiority study (EFC6019), a non-inferiority margin of 0.4% was used for comparing lixisenatide QD to exenatide BID after 24 weeks of treatment. Non-inferiority will be demonstrated if the upper bound of the 2-sided 95% confidence interval of the difference in the adjusted mean change in HbA1c from baseline to Week 24 between lixisenatide QD and

exenatide BID on mITT population is <0.4%. If non-inferiority is established, then a corresponding check of statistical superiority would be performed for the primary endpoint.

To control the family-wise type 1 error rate at 5%, in each Phase 3 study, a sequential testing procedure by the sponsor was pre-specified for testing the treatment differences of the primary and major secondary efficacy endpoints. In the 9 placebo-controlled studies, a prespecified order of priority, for the secondary efficacy endpoints selected in each study, was used in a step-down procedure described by Hochberg and Tamhane (1987) to control the type I error:

- 2-hour PPG (mmol/L)
- FPG (mmol/L)
- Body weight (kg)
- 7-point SMPG (mmol/L)
- β -cell (HOMA- β)
- % of patients requiring rescue therapy
- FPI (pmol/L)
- Total insulin/basal insulin dose

No formal statistical test was performed for all secondary efficacy endpoints in the active-controlled study EFC6019.

In addition to the sponsor's method for the primary analysis, this reviewer used the completers' data for longitudinal graphs.

Sponsor's analysis of major secondary efficacy endpoints was performed using the mITT analysis set. All continuous secondary efficacy variables at Week 24 will be analyzed using a similar ANCOVA model as described for the primary analysis. The categorical secondary efficacy variables were analyzed using a Cochran-Mantel-Haenszel (CMH) method stratified on randomization strata.

The FDA medical officer requested to verify the sponsor's statement "Research activities were terminated at 5 sites due to ongoing noncompliance with the clinical protocol and violations of Good Clinical Practice (GCP) in 3 pivotal Phase 3 studies: Study EFC6016 (Site No. 840-608), Study EFC6019 (Sites No. 276-905, 840-910, and 630-924 [this site also participated in Study EFC6016 as Site No. 630-625 and was also closed in this study]), and Study EFC6017 (Site No. 840-726). It was decided prior to database lock to exclude data for 5 patients from Study EFC6019 (Site No. 276-905) from all efficacy and safety analyses in the clinical study report (CSR). For the other sites mentioned above all subjects treated were included in the analyses, a sensitivity analysis was performed for the primary efficacy endpoint (HbA1c change from baseline to Week 24) excluding these sites." This was done in this review as shown in the corresponding individual study review. In addition, the results of sensitivity analyses including values collected after rescue therapy conducted by the sponsor (section 3.2.3-SCE) were also verified by this reviewer.

3.2.1 Monotherapy Trial

3.2.1.1 Study EFC6018

The study EFC6018 was a randomized, double-blind, placebo-controlled, parallel-group, multicenter 12-week study assessing the efficacy and safety of LIXISENATIDE in patients with type 2 diabetes not treated with antidiabetic agents.

A total of 361 subjects in 61 centers in 12 countries were randomized to receive either placebo or lixisenatide, using a randomization ratio of 2:1:2:1 (2-step lixisenatide titration regimen:2-step placebo titration regimen: 1-step lixisenatide titration regimen: 1-step placebo titration regimen): 120 in the lixisenatide 2-step titration arm, 61 in the placebo 2-step titration arm, 119 in the lixisenatide 1-step titration arm, and 61 in the placebo 1-step titration arm. The patients were stratified by screening values of HbA1c (<8%, ≥ 8%) and Body Mass Index (BMI <30 kg/m^2, ≥ 30 kg/m^2).

For more information about the study design see Appendix 1.1.

3.2.1.1.1 Patient Disposition, Demographic and Baseline Characteristics (EFC6018)

A description of the patient populations in the review is shown in Table 3.2.1.1.1.

Table 3.2.1.1.1. Patient disposition and demographic information in Study EFC6018

	Placebo	Lixisenatide	
		Two-step Titration	One-step Titration
Randomized	122 (100%)	120 (100%)	119 (100%)
ITT	121 (99%)	120 (100%)	118 (99%)
Completers	113 (93%)	110 (92%)	108 (91%)
Rescued	3 (2%)	2 (2%)	1 (1%)
Age (years)			
Mean (SE)	54.1 (1.0)	53.3 (0.9)	53.8 (1.0)
Range	20 - 82	31 - 85	21 - 78
≥ 65	18 (15%)	12 (10%)	16 (13%)
Gender: % males	60 (49%)	63 (53%)	63 (53%)
Race:			
% White	90 (74%)	88 (73%)	85 (71%)
% Black	3 (3%)	0 (0%)	3 (3%)
Country: % U.S.	20 (16%)	13 (11%)	17 (14%)
Baseline HbA1c: <8%	60 (49%)	60 (50%)	58 (49%)
Baseline BMI: <30 kg/m^2	52 (43%)	53 (44%)	49 (41%)

Baseline creatinine clearance (mL/min)			
<30 (severe renal impairment)	1 (1%)	0 (0%)	0 (0%)
30 to <50 (moderate renal impairment)	0 (0%)	1 (1%)	2 (2%)
50 to ≤80 (mild renal impairment)	15 (12%)	13 (11%)	17 (14%)
≥80 (normal)	106 (87%)	106 (88%)	100 (84%)

The Kaplan-Meier Plot of Time to dropout is in Appendix Figure 1.1.

3.2.1.1.2 Results and Conclusions

The sponsor's results of primary and secondary analyses were verified by this reviewer as shown in Table 3.2.1.1.2. These results are supportive to the superiority of lixisenatide on both two-step and one-step titrations over placebo except for the secondary endpoint body weight change from baseline at week 24. There was an observed larger reduction in HbA1c from baseline between lixisenatide and placebo at Week 12 using the one-step titration as compared to that using the two-step titration.

Table 3.2.1.1.2. Glycemic Parameters at Week 12 for Lixisenatide (Two-step and One-step) and Placebo in Patients with Type 2 Diabetes (Study EFC6018, mITT)

Endpoint	**Placebo**		**Lixisenatide**			
			Two-step Titration		**One-step Titration**	
	n		n		n	
Baseline mean ± SE	112	8.07 ± 0.09	113	7.97 ± 0.09	114	8.06 ± 0.08
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	112	-0.19 ± 0.12	113	-0.73 ± 0.12	114	-0.85 ± 0.12
MMRM	111	-0.16 ± 0.11	108	-0.72 ± 0.10	109	-0.83 ± 0.11
Completers	108	-0.18 ± 0.12	104	-0.77 ± 0.12	105	-0.87 ± 0.12
Lixisenatide−P, adj. LS Mean (95% CI)						
LOCF* (by sponsor)				-0.54(-0.78,-0. 30)[1]		-0.66(-0.90, -0.42)[1]
MMRM				-0.56 (-0.78, -0.34)[1]		-0.67 (-0.89,-0.44)[1]
Completers				-0.59 (-0.83, -0.35)[1]		-0.69 (-0.93,-0.45)[1]
Patients (%) achieving HbA1c <7						
Completers	112	29 (26%)	113	56 (50%)	114	52 (46%)
sponsor's results* (LOCF)	112	30 (27%)	113	59 (52%)	114	53(46%)
2-hour PPG (mmol/L)	n		n		n	
Baseline mean ± SE	54	13.99± 0.65	53	14.67 ± 0.52	62	14.55 ± 0.43
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	54	-0.65± 0.56	53	-4.51 ± 0.57	62	-5.47 ± 0.55
Completers	53	-0.68 ± 0.57	53	-4.44 ± 0.57	62	-5.42 ± 0.55
Lixisenatide−P, adj. LS Mean (95% CI)						
LOCF* (by sponsor)				-3.86 (-5.47, -2.35)[2]		-4.82 (-6.29,-3.36)[1]
Completers				-3.77 (-5.29, -2.25)[3]		-4.74 (-6.21,-3.37)[1]

FPG (mmol/L)	n		n		n	
Baseline mean ± SE	121	8.91 ± 0.20	119	9.17 ± 0.18	118	9.02 ± 0.18
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	121	0.19 ± 0.26	119	-0.68 ± 0.25	118	-0.89 ± 0.25
Completers	111	0.18± 0.27	107	-0.79 ± 0.27	107	-0.97 ± 0.27
Lixisenatide−P, adj. LS Mean (95% CI)						
LOCF* (by sponsor)				-0.87 (-1.37, -0.36)		-1.08 (-1.59, -0.58)
Completers				-0.96 (-1.50, -0.43)		-1.15 (-1.68, -0.62)
Body Weight (kg)						
Baseline mean ± SE	116	85.75 ±2.05	117	89.13 ± 2.05	115	87.14 ± 1.95
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	116	-1.99 ± 0.34	117	-1.97 ± 0.33	115	-1.93 ± 0.34
Completers	112	-2.00 ± 0.36	107	-1.91 ± 0.35	107	-1.90 ± 0.36
Lixisenatide−P, adj. LS Mean (95% CI)						
LOCF* (by sponsor)				-0.02 (-0.65, 0.70) [4]		0.06 (-0.61, 0.74) [5]
Completers				0.09 (-0.62, 0.80) [6]		0.10 (-0.60, 0.79) [7]

* This reviewer obtained the same results as the sponsor

[1] p-value<0.0001; [2] p-value=0.0008; [3] p-value=0.0006; [4] p-value=0.9462; [5] p-value=0.8549; [6] p-value=0.8013; [7] p-value=0.7884

Note: Since the tests of body weight not significant at 0.05 level, both body weight and FPG should not be labeled based on the sponsor's step-down testing procedure as seen in Appendix 1, Figure 1.

The time course of the completer's HbA1c difference from baseline over time is shown in Appendix Figures 1.2. There were data available only at two time points after treatment (day 1), week 8 and week 12. At both time points lixisenatide with either 1-step or 2-step increase was superior over placebo with the 1-step lixisenatide increase numerically better in HbA1c reduction than that of the 2-step lixisenatide increase.

This reviewer studied the relationship between the baseline HbA1c and the treatment effect of lixisenatide on the change in HbA1c from baseline to Week 12. Figure 1.3 in the Appendix 1 is a scatterplot of the baseline HbA1c and the change in HbA1c from baseline to Week 12 (LOCF). Values for subjects in the placebo and lixisenatide groups are shown in black, blue and red, respectively. For each treatment the regression line is provided. A treatment by baseline interaction (differing slopes) is significant at alpha = 0.10 level between lixisenatide 1-step increase and placebo (p=0.0806) arms, but not significant between lixisenatide 2-step increase and placebo arms (p=0.4604).

3.2.2 Add-on to Basal Insulin (alone or in combination with oral antidiabetics)

3.2.2.1 EFC6016

Study EFC6016 was entitled "A randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week main treatment period and an extension assessing the efficacy and safety of LIXISENATIDE in patients with Type 2 diabetes insufficiently controlled with basal insulin."

A total of 496 adult subjects were randomized across 111 centers in 15 countries to receive either placebo or lixisenatide, using a randomization ratio of a 1:2 (placebo: lixisenatide). There were

329 patients and 167 patients in the lixisenatide and placebo treatment groups, respectively. Randomization was stratified by HbA1c (<8 %, ≥ 8 %) and metformin use (Yes, No) at screening.

For more information about the study design see Appendix 2.1.

3.2.2.1.1 Patient Disposition, Demographic and Baseline Characteristics

A description of the patient populations in the review is shown in Table 3.2.2.1.1.

Table 3.2.2.1.1. Patient disposition and demographic information in Study EFC6016

	Placebo	Lixisenatide
Randomized	167 (100%)	328 (100%)
ITT	166 (99%)	327 (99%)
Completers*	147 (88%)	275 (84%)
Rescued*	12 (7%)	19 (6%)
Age (years)		
Mean(SE)	56.9 (0.8)	57.4 (0.5)
Range	29 - 81	34 - 80
≥ 65	36 (22%)	70 (21%)
Gender: % males	82 (49%)	146 (45%)
Race:		
% White	130 (78%)	255 (78%)
% Black	6 (4%)	14 (4%)
Country: % U.S.	41 (25%)	88 (27%)
Baseline HbA1c: <8%	51 (31%)	98 (30%)
Baseline BMI: <30 kg/m^2	61 (37%)	138 (42%)
Metformin use at screening: % yes	131 (78%)	262 (80%)
Baseline creatinine clearance (mL/min)		
<30 (severe renal impairment)	1 (1%)	0 (0%)
30 to <50 (moderate renal impairment)	2 (1%)	4 (1%)
50 to ≤80 (mild renal impairment)	22 (13%)	51 (16%)
≥80 (normal)	142 (85%)	271 (83%)

* At week 24

The Kaplan-Meier Plot of Time to dropout is shown in Appendix Figure 2.1. The cumulative dropout's rate in the lixisenatide arm is consistently higher than that of the placebo arm with time increase starting from Week 1 to the end of the main treatment period.

3.2.2.1.2 Results and Conclusions

The sponsor's results of primary and secondary analyses were verified by this reviewer as shown in Table 3.2.2.2. The results based on the primary endpoint and the secondary endpoint 2-hour post prandial glucose (PPG) are supportive to the superiority of lixisenatide over placebo.

Table 3.2.2.2. Glycemic Parameters at Week 24 for Lixisenatide and Placebo in Patients with Type 2 Diabetes (Study EFC6016)

Endpoint	Placebo		Lixisenatide	
HbA1c (%)	n		n	
Baseline mean ± SE	158	8.38 ± 0.07	304	8.39 ± 0.05
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	158	-0.38 ± 0.11	304	-0.74 ± 0.09
MMRM	146	-0.29 ± 0.10	282	-0.68 ± 0.08
Completers	137	-0.39 ± 0.12	259	-0.82 ± 0.11
Lixisenatide−P, adjusted LS Mean (95% CI), p				
LOCF *(by sponsor)				-0.36 (-0.55, -0.17), p=0.0002
MMRM				-0.42 (-0.63, -0.21), p<.0001
Completers				-0.43 (-0.64, -0.22), p<.0001
Patients (%) achieving HbA1c <7				
Completers	158	19 (12%)	304	77 (25%)
sponsor's results* (LOCF)	158	19 (12%)	304	86 (28%)
2h-Post Prandial Glucose (PPG) (mmol/L)	n		n	
Baseline mean ± SE	123	15.85± 0.33	235	16.44 ± 0.28
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	123	-1.72 ± 0.54	235	-5.54 ± 0.47
Completers	123	-1.57 ± 0.55	232	-5.46 ± 0.48
Lixisenatide−P, adjusted LS Mean (95% CI)				
LOCF* (by sponsor)				-3.81 (-4.70, -2.92), p<.0001
Completers				-3.90 (-4.78, -3.01) , p<.0001
FPG (mmol/L)				
Baseline mean ± SE	163	8.03 ± 0.21	317	8.11 ± 0.16
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	163	-0.55 ± 0.28	317	-0.63 ± 0.23
Completers	136	-0.54 ± 0.34	264	-0.62± 0.30
Lixisenatide−P, adjusted LS Mean (95% CI)				
LOCF* (by sponsor)				-0.08 (-0.59, 0.43), p=0.7579
Completers				-0.07(-0.61, 0.46), p=0.8534
Body Weight (kg)				
Baseline mean ± SE	161	89.11 ± 1.65	311	87.39 ± 1.13
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	161	-0.52 ± 0.29	311	-1.80 ± 0.25
Completers	138	-0.52 ± 0.34	257	-1.82 ± 0.29
Lixisenatide−P, adjusted LS Mean (95% CI)				
LOCF* (by sponsor)				-1.28 (-1.80, -0.75)

Completers				-1.30 (-1.90, -0.70)

* This reviewer obtained the same results as the sponsor
Note: Since the tests of FPG not significant at level 0.05, both body weight and FPG should not be labeled based on the sponsor's step-down testing procedure as seen in Appendix 2.

The time course of the completer's HbA1c difference from baseline over time is shown in Appendix Figures 2.2.

This reviewer studied the relationship between the baseline HbA1c and the treatment effect of lixisenatide on the change in HbA1c from baseline to Week 24. Figure 2.3 in the Appendix 2 is a scatterplot of the baseline HbA1c and the change in HbA1c from baseline to Week 24 (LOCF). Values for subjects in the placebo and lixisenatide groups are shown in blue and red, respectively. For each treatment the regression line is provided. A treatment by baseline interaction (differing slopes) is not significant at alpha = 0.10 level (p = 0.2026).

FDA medical reviewer requested to verify the sponsor's sensitivity analysis of HbA_{1c} at Week 24, by excluding data from center 840-608 (Investigator ID=106031) (n=6, 5 in lixi arm and 1 in placebo) due to protocol noncompliance. This reviewer did not find the sensitivity analysis by the sponsor in their study report for the primary efficacy endpoint (HbA1c change from baseline to Week 24) excluding these sites. This reviewer performed such a sensitivity analysis of HbA1c from baseline at Week 24 and the treatment difference from placebo was -0.36 (95% CI: -0.55 to -0.17, p-value=0.0002, n=299 in lixi arm and n=157 in placebo arm) which is similar to that including the two sites.

3.2.2.2 EFC10887

The study EFC10887 was a randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week treatment period assessing the efficacy and safety of LIXISENATIDE in patients with Type 2 diabetes insufficiently controlled with basal insulin with or without sulfonylurea.

A total of 311 patients were randomized in 57 centers in 4 countries (Japan, South Korea, Taiwan, and Philippines) to receive either lixisenatide or placebo, using a randomization ratio of 1:1 (lixisenatide:placebo). Randomization was stratified by HbA1c (<8 %, ≥8 %) and sulfonylurea use (Yes, No) at screening. There were 154 patients in the lixisenatide group and 157 in the placebo group.

For more information about the study design see Appendix 3.1.

3.2.2.2.1 Patient Disposition, Demographic and Baseline Characteristics

A description of the patient populations in the review is shown in Table 3.2.2.2.1.

Table 3.2.2.2.1. Patient disposition and demographic information in Study DEFC10887

	Placebo	**Lixisenatide**

Randomized	157 (100%)	154 (100%)
ITT	157 (100%)	154 (100%)
Completers	144 (92%)	133 (86%)
Rescued	5 (0.4%)	2 (11%)
Age (years)		
Mean(SE)	58.0 (0.8)	58.7 (0.8)
Range	29 - 81	25 - 81
≥ 65	44 (28%)	44 (29%)
Gender: % males	80 (51%)	69 (45%)
Baseline HbA1c: <8%	36 (23%)	35 (23%)
Baseline BMI: <30 kg/m^2	140 (89%)	141 (92%)
Sulfonylurea use at screening: % yes	111 (71%)	108 (70%)
Baseline creatinine clearance (mL/min)		
<30 (severe renal impairment)	1 (1%)	1 (1%)
30 to <50 (moderate renal impairment)	10 (6%)	11 (7%)
50 to ≤80 (mild renal impairment)	55 (35%)	59 (38%)
≥80 (normal)	91 (58%)	83 (54%)

The Kaplan-Meier Plot of Time to dropout is in Appendix Figure 3.1. The dropout rate in the lixisenatide arm is consistently higher than that of the placebo arm throughout the main treatment period.

3.2.2.2.2 Results and Conclusions

The sponsor's results of primary and secondary analyses were verified by this reviewer as shown in Table 3.2.2.2.2. These results are supportive to lixisenatide over placebo.

Table 3.2.2.2.2 Glycemic Parameters at Week 24 for Lixisenatide and Placebo in Patients with Type 2 Diabetes (Study EFC10887)

Endpoint	**Placebo**		**Lixisenatide**	
HbA1c (%)	n		n	
Baseline mean ± SE	154	8.53 ± 0.06	146	8.53 ± 0.06
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	154	0.11 ± 0.13	146	-0.77 ± 0.14
MMRM	150	0.01 ± 0.10	140	-0.82 ± 0.11
Completers	138	0.07 ± 0.12	132	-0.86 ± 0.13
Lixisenatide−P, adjusted LS Mean (95% CI)				
LOCF *(by sponsor)				-0.88 (-1.12, -0.65) , p<.0001
MMRM				-0.83 (-1.06, -0.60) , p<.0001

Completers				-0. 93(-1.16, -0.71), p<.0001
Patients (%) achieving HbA1c <7				
Completers	154	7 (5%)	146	48 (33%)
sponsor's results* (LOCF)	154	8 (5%)	146	52 (36%)
2h-Post Prandial Glucose (PPG) (mmol/L)	n		n	
Baseline mean ± SE	142	17.99 ± 0.31	131	17.88 ± 0.29
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	142	-0.14 ± 0.56	131	-7.96 ± 0.60
Completers	138	-0.08 ± 0.57	129	-7.97 ± 0.61
Lixisenatide−P, adjusted LS Mean (95% CI)				
LOCF* (by sponsor)				-7.83 (-8.89, -6.77) , p<.0001
Completers				-7.89 (-8.97, -6.81) , p<.0001
FPG (mmol/L)				
Baseline mean ± SE	157	7.75 ± 0.18	148	7.64 ± 0.19
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	157	0.25± 0.30	148	-0.42 ± 0.31
Completers	139	0.15 ± 0.29	132	-0.38 ± 0.31
Lixisenatide−P, adjusted LS Mean (95% CI)				
LOCF* (by sponsor)				-0.67 (-1.23, -0.11), p=0.0187
Completers				-0.53 (-1.08, 0.02), p=0.0585
Body Weight (kg)				
Baseline mean ± SE	157	65.60 ± 1.00	150	65.99 ± 1.06
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	157	0.06 ± 0.27	150	-0.38 ± 0.28
Completers	139	-0.01 ± 0.29	132	-0.36 ± 0.31
Lixisenatide−P, adjusted LS Mean (95% CI)				
LOCF* (by sponsor)				-0.43 (-0.93, 0.06), p=0.0857
Completers				-0.35 (-0.89, 0.19), p=0.2053
Change in basal insulin dose (U)				
Baseline mean ± SE	157	23.78 ± 1.15	150	24.70 ± 1.14
(sponpor)	(157)	(24.11 ±)	(151)	(24.87 ±)
Adj. Mean Change from baseline±SE				
LOCF (by sponsor)	157	0.11 ± 0.44		1.39 ± 0.46
LOCF	157	0.18 ± 0.50	151	1.32 ± 0.52
Completers	139	0.20 ± 0.54	150	1.46 ± 0.57
Lixisenatide−P, adjusted LS Mean (95% CI)			132	
LOCF (by sponsor)				-12.9 (-2.10, -0.48), p=0.0019
LOCF				-1.50 (-2.42, -0.58), p=0.0015
Completers				-1.65 (-2.67, -0.64), p=0.0015

* This reviewer obtained the same results as the sponsor

Note: Since the tests of body weight not significant at level 0.05, both body weight and FPG should not be labeled based on the sponsor's step-down testing procedure as seen in Appendix 3 Multiplicity Adjustment. In addition, change in basal insulin dose should not be in the label because this endpoint was not pre-specified with multiplicity adjustment.

The time course plot is in Appendix Figure 3.2, showing significantly more reduction in HbA1c in the lixisenatide arm than in the placebo arm at least as early as being treated for one week with available data. This reviewer studied the relationship between the baseline HbA1c and the treatment effect of lixisenatide on the change in HbA1c from baseline to Week 24. Figure 3.3 in the Appendix 3 is a scatterplot of the baseline HbA1c and the change in HbA1c from baseline to Week 24 (LOCF). Values for subjects in the placebo and lixisenatide groups are shown in blue and red, respectively. For each treatment the regression line is provided. A treatment by baseline interaction (differing slopes) is significant at alpha = 0.10 level (p-value=0.0453).

3.2.2.3 EFC10781

Study EFC10781 was a randomized, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week double-blind treatment period assessing the efficacy and safety of lixisenatide in patients with Type 2 diabetes insufficiently controlled with insulin glargine and metformin.

A total of 446 subjects were randomized and treated in 140 centers in 25 countries with 223 patients in each treatment group. Randomization was stratified by HbA1c (<8 %, ≥ 8 %) and thiazolidinediones (TZDs) use (yes, no) at screening.

For more information about the study design see Appendix 4.1.

3.2.2.3.1 Patient Disposition, Demographic and Baseline Characteristics

A description of the patient populations in the review is shown in Table 3.2.2.3.1.

Table 3.2.2.3.1. Patient disposition and demographic information in Study EFC10781

	Placebo	**Lixisenatide**
Randomized	223 (100%)	223 (100%)
ITT	223 (100%)	223 (100%)
Completers	211 (95%)	194 (87%)
Rescued	1 (0.4%)	1 (0.4%)
Age (years) Mean(SE) Range ≥ 65	 56.1 (0.7) 25 - 81 43 (19%)	 56.4 (0.6) 33 - 80 47 (21%)
Gender: % males	113 (51%)	109 (49%)
Race: % White % Black	 167 (75%) 11 (5%)	 165 (74%) 9 (4%)
Country: % U.S.	24 (11%)	22 (10%)

Baseline HbA1c: <8%	162 (73%)	171 (77%)
Baseline BMI: <30 kg/m^2	103 (46%)	103 (46%)
Thiazolidinediones use at screening: % yes	32 (14%)	40 (18%)
Baseline creatinine clearance (mL/min)		
<30 (severe renal impairment)	0 (0%)	0 (0%)
30 to <50 (moderate renal impairment)	1 (0.4%)	3 (1%)
50 to ≤80 (mild renal impairment)	30 (13%)	41 (18%)
≥80 (normal)	192 (86%)	179 (80%)

The Kaplan-Meier plot of time to dropout is in Appendix Figure 4.1. The dropout rate in lixisenatide arm is consistently higher than that in placebo arm throughout the main treatment period with the difference getting larger with time.

3.2.2.3.2 Results and Conclusions

The sponsor's results of primary and secondary analyses were verified by this reviewer as shown in Table 3.2.2.3.2. The results of primary analyses are supportive to the superiority of lixisenatide over placebo; however, the results of the secondary endpoints are not.

Table 3.2.2.3.2. Glycemic Parameters at Week 24 for Lixisenatide and Placebo in Patients with Type 2 Diabetes (Study EFC10781)

A: Primary Endpoint

Endpoint	**Placebo**		**Lixisenatide**	
HbA1c (%)	n		n	
Baseline mean ± SE	221	7.60 ± 0.04	215	7.56 ± 0.04
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	221	-0.40 ± 0.09	215	-0.71 ± 0.09
MMRM^	210	-0.35 ± 0.08	205	-0.70 ± 0.08
Completers	208	-0.41 ± 0.10	189	-0.73 ± 0.10
Lixisenatide−P, adjusted LS Mean (95% CI)				
LOCF *(by sponsor)				-0.32 (-0.46, -0.17), p<0.0001
MMRM				-0.32 (-0.44, -0.19), p<0.0001
Completers				-0.32 (-0.47, -0.16), p<0.0001
Patients (%) achieving HbA1c <7				
Completers	221	83 (38%)	215	107 (50%)
sponsor's results* (LOCF)	221	85 (38%)	215	121 (56%)
2h-Post Prandial Glucose (PPG) (mmol/L)	n		n	
Baseline mean ± SE	204	12.85 ± 0.26	194	13.02 ± 0.27
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	204	0.08 ± 0.48	194	-3.09 ± 0.48
Completers	202	0.33 ± 0.50	185	-2.90 ± 0.50

Lixisenatide−P, adjusted LS Mean (95% CI)				
LOCF* (by sponsor)				-3.16 (-3.95, -2.37), p<0.0001
Completers				-3.22 (-4.03, -2.42), p<0.0001
FPG (mmol/L)				
Baseline mean ± SE	220	6.69 ± 0.13	214	6.56 ± 0.12
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	220	0.46 ± 0.21	214	0.34 ± 0.21
Completers	208	0.38 ± 0.23	191	0.33 ± 0.23
Lixisenatide−P, adjusted LS Mean (95% CI)				
LOCF* (by sponsor)				-0.12 (-0.46, 0.23), p=0.5142
Completers				-0.05 (-0.41, 0.31), p=0.6003
Body Weight (kg)				
Baseline mean ± SE	220	86.74 ± 1.38	217	87.47 ± 1.49
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	220	1.16 ± 0.33	217	0.28 ± 0.33
Completers	209	1.34 ± 0.36	192	0.34 ± 0.36
Lixisenatide−P, adjusted LS Mean (95% CI)				
LOCF* (by sponsor)				-0.89 (-1.42, -0.35), p=0.0012
Completers				-0.99 (-1.57, -0.42), p=0.0009
Change in insulin glargine dose (U)				
Baseline mean ± SE	223	44.24 ± 1.33	222	43.41 ± 1.27
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	223	5.34 ± 1.26	222	3.10 ± 1.26
Completers	210	4.86 ± 0.1.38	193	2.90 ± 1.37
Lixisenatide−P, adjusted LS Mean (95% CI)				
LOCF* (by sponsor)				-2.24 (-4.26, -0.22), p=0.03
Completers				-1.96 (-4.15, 0.24), p=0.0887

* This reviewer obtained the same results as the sponsor
^ type=cs
Note: Since the test of FPG not significant at level 0.05, FPG should not be labeled.

The sponsor's results of the change in 7-point SMPG (the first secondary endpoint in the sequential tests) from baseline between treatments was significant at alpha=0.05 level, so the significant levels of the secondary endpoints in above table could be in the label except for FPG.

The time course of the completer's HbA1c difference from baseline over time is shown in Appendix Figures 4.2, showing significantly more reduction in HbA1c in the lixisenatide arm than in the placebo arm at least as early as being treated for 8 weeks with available data. The changes of HbA1c from baseline in both arms appear elevated with time during the treatment period of week 8 to week 24.

This reviewer studied the relationship between the baseline HbA1c and the treatment effect of lixisenatide on the change in HbA1c from baseline to Week 24. Figure 4.3 in the Appendix 4 is a scatterplot of the baseline HbA1c and the change in HbA1c from baseline to Week 24 (LOCF). Values for subjects in the placebo and lixisenatide groups are shown in blue and red,

respectively. For each treatment the regression line is provided. A treatment by baseline interaction (differing slopes) is not significant at alpha = 0.10 level (p=0.8887).

3.2.3 Add-on combination therapy to metformin (alone or in combination with sulfonylurea)

Placebo-controlled studies

3.2.3.1 EFC6014

Study EFC6014 was a randomized, double-blind, placebo-controlled, parallel-group, multicenter 24-week study followed by an extension assessing the efficacy and safety of lixisenatide on top of metformin in patients with type 2 diabetes not adequately controlled with metformin.

A total of 680 patients were randomized to receive either lixisenatide or placebo, using a randomization ratio of 3:1:3:1 (morning injection lixisenatide:morning injection placebo:evening injection lixisenatide:evening injection placebo) in 133 centers in 16 countries. The randomization was stratified by screening values of HbA1c (<8%, ≥ 8%) and BMI (<30 kg/m^2, ≥ 30 kg/m^2).

For more information about the study design see Appendix 5.1.

3.2.3.1.1 Patient Disposition, Demographic and Baseline Characteristics

A description of the patient populations in the review is shown in Table 3.2.3.1.1.

Table 3.2.3.1.1. Patient disposition and demographic information in Study EFC6014

		Lixisenatide	
	Placebo	**Morning Injection**	**Evening Injection**
Randomized	170 (100%)	255 (100%)	255 (100%)
ITT	170 (99%)	255 (100%)	255 (99%)
Completers*	158 (93%)	233 (91%)	224 (88%)
Rescued*	18 (11%)	7 (3%)	10 (4%)
Age (years)			
Mean(SE)	55.0 (0.7)	54.5 (0.6)	54.8 (0.6)
Range	25 - 76	33 - 81	23 - 87
≥ 65	28 (16%)	30 (12%)	42 (16%)
Gender: % males	81 (48%)	98 (38%)	114 (45%)
Race:			
% White	155 (91%)	221 (87%)	228 (89%)

% Black	4 (2%)	7 (3%)	6 (2%)
Country: % U.S.	7 (4%)	12 (5%)	20 (8%)
Baseline HbA1c: <8%	84 (49%)	126 (49%)	126 (49%)
Baseline BMI: <30 kg/m^2	59 (35%)	95 (37%)	93 (36%)
Baseline creatinine clearance (mL/min)			
<30 (severe renal impairment)	0 (0%)	0 (0%)	0 (0%)
30 to <50 (moderate renal impairment)	0 (0%)	1 (0.4%)	1 (0.4%)
50 to ≤80 (mild renal impairment)	13 (8%)	21 (8%)	30 (12%)
≥80 (normal)	157 (92%)	232 (91%)	224 (88%)

* Week 24

The Kaplan-Meier plot of time to dropout is in Appendix Figure 5.1. The dropout rate of the placebo arm is the lowest among the three arms while that of the lixisenatide morning arm being the highest.

3.2.3.1.2 Results and Conclusions

The sponsor's results of primary and secondary analyses were verified by this reviewer as shown in Table 3.2.3.1.2. These results are supportive to the superiority of lixisenatide (both the morning and evening injections) over placebo except for the secondary endpoint body weight. There was a larger reduction in HbA1c from baseline between lixisenatide and placebo at Week 24 with the morning injection as compared to that with the evening injection.

Table 3.2.3.1.2. Glycemic Parameters at Week 24 for Lixisenatide and Placebo in Patients with Type 2 Diabetes (Study EFC6014)

A: Primary Endpoint

Endpoint	**Placebo**		**Lixisenatide**			
			Morning Injection		**Evening Injection**	
	n		n		n	
Baseline mean ± SE	164	8.02 ± 0.07	244	8.07 ± 0.06	239	8.07 ± 0.06
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	164	-0.38 ± 0.08	244	-0.87 ± 0.07	239	-0.75 ± 0.07
MMRM	157	-0.37 ± 0.07	238	-0.83 ± 0.06	232	-0.71 ± 0.06
Completers	139	-0.45 ± 0.08	224	-0.79 ± 0.07	212	-0.89 ± 0.06
Lixisenatide−P, adj. LS Mean (95% CI)						
LOCF* (by sponsor)				-0.48(-0.66, -0. 31) [1]		-0.37 (-0.54, -0.19)[1]
MMRM				-0.46 (-0.64, -0.29) [1]		-0.34 (-0.52, -0.17) [1]
Completers				-0.34 (-0.52, -0.17) [1]		-0.44 (-0.62, -0.27) [1]
Patients (%) achieving HbA1c <7						
Completers	164	35 (21%)	244	102 (42%)	239	91(38%)
sponsor's results*(LOCF,by sponsor)	164	36 (22%)	244	105 (43%)	239	97 (41%)
2-hour PPG (mmol/L)	n		n		n	

Baseline mean ± SE	64	15.46 ± 0.49	200	15.81 ± 0.30	NA	NA
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	64		200	-5.92 ± 0.42		
Completers	64	-1.41± 0.59	199	-5.94 ± 0.41		
Lixisenatide−P, adjusted LS Mean (95% CI)		-1.61 ± 0.57				
LOCF* (by sponsor)				-4.51 (-5.65, -3.37) [1]		
Completers				-4.54 (-5.68, -3.41) [1]		
FPG (mmol/L)	n		n		n	
Baseline mean ± SE	170	9.51 ± 0.17	253	9.46 ± 0.14	255	9.28 ± 0.14
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	170	-0.25 ± 0.17	253	-1.19 ± 0.15	255	-0.81 ± 0.15
Completers	140	-0.37± 0.18	222	-1.23 ± 0.16	211	-0.84 ± 0.16
Lixisenatide−P, adj. LS Mean (95% CI)						
LOCF* (by sponsor)				-0.94 (-1.33, -0.56) [1]		-0.56 (-0.94, -0.17) [2]
Completers				-0.86 (-1.27, -0.46) [1]		-0.47 (-0.88, -0.06) [3]
Body Weight (kg)						
Baseline mean ± SE	168	90.40 ±1.55	248	90.14 ± 1.34	249	89.01 ± 1.31
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	168	-1.64 ± 0.27	248	-2.01 ± 0.23	249	-2.02 ± 0.24
Completers	142	-2.04 ± 0.32	226	-2.18 ± 0.27	214	-2.29 ± 0.28
Lixisenatide−P, adj. LS Mean (95% CI)						
LOCF* (by sponsor)				-0.38 (-0.99, 0.24) [4]		-0.39 (-1.01, 0.23) [5]
Completers				-0.14 (-0.87, 0.59) [6]		-0.25 (-0.99, 0.49) [7]

* This reviewer obtained the same results as the sponsor
[1] p-value<0.0001; [2] p=0.0056; [3] p=0.0244; [4] p=0.2293; [5] p=0.2181; [6] p=0.7059; [7] p=0.5091
Note: Since the test of body weight not significant at level 0.05, body weight should not be labeled based on the sponsor's step-down testing procedure as seen in Appendix 5 Figure 1.

The time course of the completer's HbA1c difference from baseline over time is shown in Appendix Figures 5.3, showing both lixisenatide injections persisting better than the placebo arm.

This reviewer studied the relationship between the baseline HbA1c and the treatment effect of lixisenatide on the change in HbA1c from baseline to Week 24. Figure 5.3 in the Appendix 5 is a scatterplot of the baseline HbA1c and the change in HbA1c from baseline to Week 24 (LOCF). Values for subjects in the placebo and lixisenatide groups are shown in black, blue and red, respectively. For each treatment the regression line is provided. A treatment by baseline interaction (differing slopes) is significant at alpha = 0.10 level between each dose of lixisenatide and placebo (both p<=0.01).

3.2.3.2 EFC10743

Study EFC10743 was a randomized, double-blind, placebo-controlled, parallel-group, multicenter, 24-week study followed by an extension assessing the efficacy and safety of LIXISENATIDE in two titration regimens on top of metformin in patients with type 2 diabetes not adequately controlled with metformin.

A total of 484 subjects were randominzed in 75 centers in 15 countries in a 2:2:1:1 ratio to 1 of the 4 treatment groups (161 in the lixisenatide 2-step titration group, 161 in the lixisenatide 1-

step titration group, 80 in the placebo 2-step titration group, and 82 in the placebo 1-step titration group,). Randomization was stratified by screening values of HbA1c (<8%, ≥ 8%) and Body Mass Index (BMI <30 kg/m^2, ≥ 30 kg/m^2).
For more information about the study design see Appendix 6.1.

3.2.3.2.1 Patient Disposition, Demographic and Baseline Characteristics

A description of the patient populations in the review is shown in Table 3.2.3.2.1.

Table 3.2.3.2.1. Patient disposition and demographic information in Study EFC10743

		Lixisenatide	
	Placebo	**Two-step Titration**	**One-step Titration**
Randomized	162 (100%)	161 (100%)	161 (100%)
ITT	159 (98%)	160 (99%)	160 (99%)
Completers*	151 (93%)	144 (89%)	147 (91%)
Rescued*	7 (4%)	5 (3%)	2 (1%)
Age (years)			
Mean(SE)	58.0 (0.8)	54.6 (0.7)	55.4 (0.7)
Range	29 – 79	24 - 73	34 - 73
≥ 65	44 (28%)	14 (9%)	20 (12%)
Gender: % males	73 (45%)	72 (45%)	71 (44%)
Race:			
% White	150 (93%)	146 (91%)	141 (88%)
% Black	1 (1%)	2 (1%)	1 (1%)
Country: % U.S.	0 (0%)	0 (0%)	1 (26%)
Baseline HbA1c: <8%	78 (48%)	77 (48%)	78 (48%)
Baseline BMI: <30 kg/m^2	60 (37%)	59 (37%)	57 (35%)
Baseline creatinine clearance (mL/min)			
<30 (severe renal impairment)	0 (0%)	0 (0%)	0 (0%)
30 to <50 (moderate renal impairment)	1 (1%)	1 (1%)	1 (1%)
50 to ≤80 (mild renal impairment)	21 (13%)	21 (13%)	12 (8%)
≥80 (normal)	140 (86%)	138 (86%)	146 (91%)

* At week 24

The Kaplan-Meier plot of time to dropout is in Appendix Figure 6.1. The dropout rate of the placebo arm is the highest among the three arms while that of the lixisenatide one-step increase arm being the lowest.

3.2.3.2.2. Results and Conclusions

The sponsor's results of primary and secondary analyses were verified by this reviewer as shown in Table 3.2.3.2.2. These results are supportive to the superiority of lixisenatide (both the morning and evening injections) over placebo. There was a slightly larger reduction in HbA1c from baseline between lixisenatide and placebo at Week 24 using the one-step titration as compared to that using the two-step titration, consistent with the finding from EFC6018 at Week 12.

Table 3.2.3.2.2. Glycemic Parameters at Week 24 for Lixisenatide and Placebo in Patients with Type 2 Diabetes (Study EFC10743)

A: Primary Endpoint

Endpoint	**Placebo**		**Lixisenatide**			
			Two-step Titration		**One-step Titration**	
	n		n		n	
Baseline mean ± SE	158	8.03 ± 0.07	152	8.12 ± 0.07	156	7.99 ± 0.07
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	158	-0.42 ± 0.10	152	-0.83 ± 0.10	156	-0.92 ± 0.10
MMRM	156	-0.41 ± 0.11	146	-0.87 ± 0.11	153	-0.93 ± 0.12
Completers	146	-0.45 ± 0.07	138	-0.85 ± 0.07	141	-0.95 ± 0.07
Lixisenatide−P, adj. LS Mean (95% CI)						
LOCF* (by sponsor)				-0.41(-0.58, -0.23) [1]		-0.49 (-0.67, -0.32) [1]
MMRM				-0.46 (-0.69, -0.23) [1]		-0.52 (-0.76, -0.29) [1]
Completers				-0.40 (-0.57, -0.22) [1]		-0.49 (-0.67, -0.32) [1]
Patients (%) achieving HbA1c <7						
Completers	158	36 (23%)	152	61 (40%)	156	70 (45%)
sponsor's results* (LOCF)	158	38 (24%)	152	64 (42%)	156	74 (47%)
FPG (mmol/L)	n		n		n	
Baseline mean ± SE	158	9.46 ± 0.16	160	9.52 ± 0.20	158	9.55 ± 0.16
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	158	0.11 ± 0.21	160	-0.56 ± 0.21	158	-0.53 ± 0.21
Completers	147	-0.45± 0.15	139	-1.10± 0.16	143	-1.14 ± 0.15
Lixisenatide−P, adj. LS Mean (95% CI)						
LOCF* (by sponsor)				-0.67 (-1.04, -0.30) [2]		-0.65 (-1.02, -0.27) [3]
Completers				-0.66 (-1.04, -0.28) [3]		-0.69 (-1.07, -0.31) [2]
Body Weight (kg)						
Baseline mean ± SE	158	87.86 ±1.38	155	88.08 ± 1.35	158	90.30 ± 1.51
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	158	-1.63 ± 0.39	155	-2.68 ± 0.39	158	-2.63 ± 0.39
Completers	147	-1.65 ± 0.29	139	-2.71 ± 0.29	143	-2.77 ± 0.28
Lixisenatide−P, adj. LS Mean (95% CI)						
LOCF* (by sponsor)				-1.06 (-1.76, -0.36) [4]		1.00 (-1.69, -0.32) [5]
Completers				-1.06 (-1.83, -0.42) [4]		-1.13 (-1.84. -0.42) [6]

* This reviewer obtained the same results as the sponsor
[1] p-value<0.0001; [2] p=0.0004; [3] p=0.0007; [4] p=0.0031; [5] p=0.0042; [6] p=0.0019

The time course of the completer's HbA1c difference from baseline over time is shown in Appendix Figures 6.2, showing the efficacy persisting till Week 76.

This reviewer studied the relationship between the baseline HbA1c and the treatment effect of lixisenatide on the change in HbA1c from baseline to Week 24. Figure 6.3 in the Appendix 6 is a scatterplot of the baseline HbA1c and the change in HbA1c from baseline to Week 24 (LOCF). Values for subjects in the placebo and lixisenatide groups are shown in black, blue and red, respectively. For each treatment the regression line is provided. A treatment by baseline interaction (differing slopes) is significant at alpha = 0.10 level for both one-step titration (p=0.0343) and two-step titration (p=0.0544).

3.2.3.3 EFC11321

Study EFC11321 was entitled: "Efficacy and safety of lixisenatide in patients with type 2 diabetes mellitus insufficiently controlled by metformin (with or without sulfonylurea): a multicenter, randomized, double-blind, parallel-group, placebo-controlled study with 24-week treatment period."

A total of 391 subjects were randomized in 35 centers in 4 countries or areas (China, Hong Kong, Malaysia, and Thailand) in a 1:1 ratio to 1 of 2 treatment groups (196 patients and 195 patients in the lixisenatide and placebo treatment groups, respectively). Randomization was stratified by HbA1c (< 8%, ≥ 8%) and sulfonylurea use (Yes, No) at screening, number of patients in each of the sulfonylurea stratum (with sulfonylurea, without sulfonylurea) was balanced.

For more information about the study design see Appendix 7.1.

3.2.3.3.1 Patient Disposition, Demographic and Baseline Characteristics

A description of the patient populations in the review is shown in Table 3.2.3.3.1.

Table 3.2.3.3.1. Patient disposition and demographic information in Study EFC11321

	Placebo	Lixisenatide
Randomized	195 (100%)	196 (100%)
ITT	193 (99%)	195 (99%)
Completers	184 (94%)	179 (91%)
Rescued	13 (7%)	7 (4%)
Age (years)		

Mean(SE) Range ≥ 65	55.2 (0.8) 21 - 83 37 (19%)	54.5 (0.7) 18 - 75 33 (17%)
Gender: % males	91 (47%)	101 (52%)
Race: % White % Black	 0 (0%) 0 (0%)	 0 (0%) 0 (0%)
Country: % U.S.	0 (0%)	0 (0%)
Baseline HbA1c: <8%	101 (52%)	101 (52%)
Baseline BMI: <30 kg/m^2	158 (82%)	161 (83%)
Sulfonylurea use at screening: % yes	93 (48%)	82 (42%)
Baseline creatinine clearance (mL/min) <30 (severe renal impairment) 30 to <50 (moderate renal impairment) 50 to ≤80 (mild renal impairment) ≥80 (normal)	 0 (0%) 0 (0%) 27 (14%) 168 (86%)	 0 (0%) 3 (2%) 26 (13%) 167 (85%)

The Kaplan-Meier plot of time to dropout is in Appendix Figure 7.1, the discontinuation rate is in the lixisenatide arm is consistently higher than that of the placebo arm throughout the main treatment period.

3.2.3.3.2 Results and Conclusions

The sponsor's results of primary and secondary analyses were verified by this reviewer as shown in Table 3.2.3.3.2. These results are supportive the superiority of lixisenatide over placebo.

Table 3.2.3.3.2. Glycemic Parameters at Week 24 for Lixisenatide and Placebo in Patients with Type 2 Diabetes (Study EFC11321)

Endpoint	**Placebo**		**Lixisenatide**	
HbA1c (%)	n		n	
Baseline mean ± SE	188	7.83 ± 0.05	185	7.95 ± 0.06
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	188	-0.47 ± 0.10	185	-0.83 ± 0.10
MMRM	185	-0.72 ± 0.15	182	-1.08 ± 0.16
Completers	169	-0.82 ± 0.24	169	-1.11 ± 0.24
Lixisenatide−P, adjusted LS Mean (95% CI)				
LOCF *(by sponsor)				-0.36 (-0.55, -0.16), p=0.0004
MMRM				-0.30 (-0.46, -0.14) , p=0.0002
Completers				-0.29 (-0.48, -0.11) , p=0.0006

Patients (%) achieving HbA1c <7				
Completers	188	70 (37%)	185	91 (49%)
sponsor's results* (LOCF)	188	73 (39%)	185	98 (53%)
2h-Post Prandial Glucose (PPG) (mmol/L)	n		n	
Baseline mean ± SE	116	17.34 ± 0.	107	16.27 ± 0.
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	116	-1.33 ± 0.38	107	-5.61 ± 0.39
Completers	111	-1.33 ± 0.39	103	-5.64 ± 0.40
Lixisenatide−P, adjusted LS Mean (95% CI)				
LOCF* (by sponsor)				-4.28 (-5.36, -3.20) , p<0.0001
Completers				-4.31 (-5.43, -3.20) , p<0.0001
FPG (mmol/L)				
Baseline mean ± SE	191	8.75 ± 0.13	190	8.83 ± 0.15
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	191	-0.21 ± 0.20	190	-0.69 ± 0.20
Completers	167	-0.22 ± 0.20	167	- 0.68 ± 0.20
Lixisenatide−P, adjusted LS Mean (95% CI)				
LOCF* (by sponsor)				-0.48 (-0.84, -0.11) , p=0.0109
Completers				-0.46 (-0.84, -0.08) , p=0.017
Body Weight (kg)				
Baseline mean ± SE	191	72.94 ± 0.98	188	73.57 ± 1.02
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	191		188	-1.50 ± 0.27
Completers	169	-1.24 ± 0.27	171	-1.58 ± 0.28
Lixisenatide−P, adjusted LS Mean (95% CI)		-1.25 ± 0.28		
LOCF* (by sponsor)				-0.27 (-0.78, 0.24) , p=0.296
Completers				-0.33 (-0.85, 0.19) , p=0.2134

* This reviewer obtained the same results as the sponsor
Note: Since the test of body weight not significant at level 0.05, body weight should not be labeled based on the sponsor's step-down testing procedure as seen in Appendix 7.

The time course of the completer's HbA1c difference from baseline over time is shown in Appendix Figures 7.2, showing significantly more reduction in HbA1c in the lixisenatide arm than that in the placebo arm as early as being treated for 8 weeks with available data..

This reviewer studied the relationship between the baseline HbA1c and the treatment effect of lixisenatide on the change in HbA1c from baseline to Week 24. Figure 7.3 in the Appendix 7 is a scatterplot of the baseline HbA1c and the change in HbA1c from baseline to Week 24 (LOCF). Values for subjects in the placebo and lixisenatide groups are shown in blue and red, respectively. For each treatment the regression line is provided. A treatment by baseline interaction (differing slopes) is not significant at alpha = 0.10 level (p=0.8902).

Active-controlled study versus exenatide

3.2.3.4 EFC6019

Study EFC6019 was a randomized, open-label, active-controlled, 2-arm parallel-group, multicenter 24-week study followed by an extension assessing the efficacy and safety of lixisenatide QD versus exenatide BID on top of metformin in patients with type 2 diabetes not adequately controlled with metformin.

The approximate minimum study duration per patient was 78 weeks (up to 2 weeks screening + 24 weeks main open-label treatment + variable extension + 3 days follow-up).

A total of 639 patients were randomized in 122 centers in 18 countries in a 1:1 ratio to 1 of 2 treatment groups. The randomization was stratified by screening HbA1c (<8.0%, ≥8.0%) and Body Mass Index (BMI) (<30 kg/m², ≥ 30 kg/m²). One site in Germany (Site No. 276-905), which randomized 5 patients, was found to be significantly noncompliant with the protocol. Prior to database lock, it was decided to exclude these 5 patients from all efficacy and safety analyses due to the seriousness of the noncompliance of the German site.

We asked the sponsor when reviewing the protocol of this study that we preferred the double-blind design and asked the sponsor why it was not possible to double-blind the patients. However, there was no response received from the sponsor.

For more information about the study design see Appendix 8.1.

3.2.3.4.1 Patient Disposition, Demographic and Baseline Characteristics

A description of the patient populations in the review is shown in Table 3.2.3.4.1.

Table 3.2.3.4.1. Patient disposition and demographic information in Study EFC6019

	Lixisenatide, QD	**Exenatide,** BID
Randomized	318 (100%)	316 (100%)
ITT	315 (99%)	315 (100%)
Completers	277 (87%)	271 (86%)
Rescued	8 (3%)	12 (4%)
Age (years) Mean(SE) Range ≥ 65	 57.3 (0.5) 29 - 84 68 (21%)	 57.6 (0.6) 21 - 83 77 (24%)
Gender: % males	151 (47%)	187 (59%)
Race: % White % Black	 296 (93%) 8 (3%)	 292 (92%) 10 (3%)
Country: % U.S.	49 (15%)	67 (21%)
Baseline HbA1c: <8%	169 (53%)	169 (53%)

Baseline BMI: <30 kg/m^2	102 (32%)	109 (34%)
Baseline creatinine clearance (mL/min)		
<30 (severe renal impairment)	0 (0%)	0 (0%)
30 to <50 (moderate renal impairment)	3 (1%)	4 (1%)
50 to ≤80 (mild renal impairment)	30 (9%)	35 (11%)
≥80 (normal)	285 (90%)	277 (88%)

The Kaplan-Meier plot of time to dropout is in Appendix Figure 8.1. The dropout rate in the lixisenatide arm is consistently lower than that of the exenatide arm throughout the main treatment period.

3.2.3.4.2 Results and Conclusions

The sponsor's results of primary and secondary analyses were verified by this reviewer as shown in Table 3.2.3.4.2. Lixisenatide is statistically worse than exenatide at a significance level of 0.05. Lixisenatide QD was shown to be non-inferior with respect to exenatide BID (based on a two-sided 95% confidence interval with a non-inferiority margin of 0.4%) after 24 weeks of treatment. FDA medical reviewer requested to check if the non-inferiority still preserved regarding long-term efficacy at 76 weeks. This reviewer performed the analysis of HbA1c from baseline at several time points beyond Week 24 (up to Week 76) based on observed data and found that non-inferiority no longer held after 36 weeks. At Week 36, the treatment mean difference from exenatide was 0.30 (LOCF, 95% CI: 0.16 to 0.43, p<0.0001). Similar results were obtained by MMRM analysis (Week 36, diff=0.30 with 95% CI 0.17 to 0.43, p<0.0001; Week 52, diff=0.32 with 95% CI 0.19 to 0.45, p<0.0001; Week 76, diff=0.35 with 95% CI 0.20 to 0.49, p<0.0001). The time course of the completer's HbA1c difference from baseline over time is shown in Appendix Figures 8.2.

Table 3.2.3.4.2. Glycemic Parameters at Week 24 for Lixisenatide and Exenatide in Patients with Type 2 Diabetes (Study EFC6019)

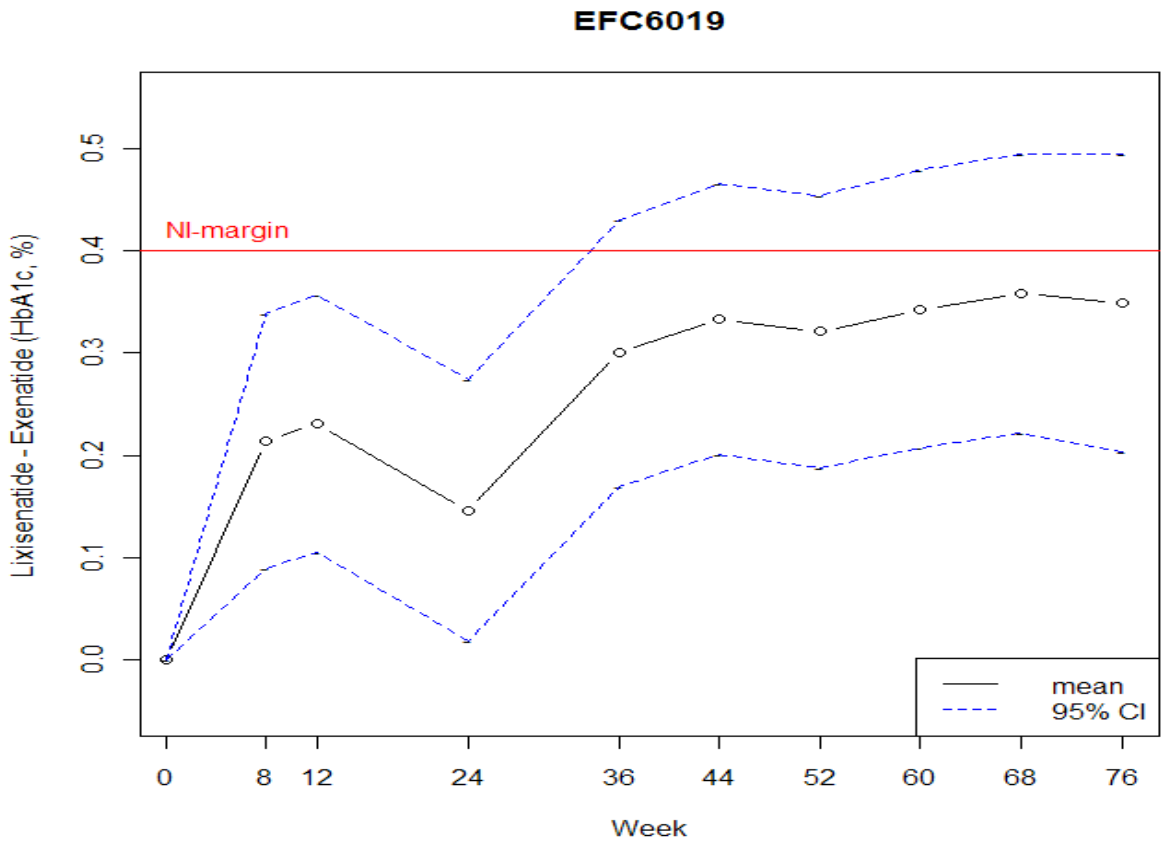
Endpoint	**Lixisenatide, QD**		**Exenatide, BID**	
HbA1c (%)	n		n	
Baseline mean ± SE	295	7.97 ± 0.05	297	7.96 ± 0.04
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	295	-0.79 ± 0.05	297	-0.96 ± 0.05
MMRM	284	-0.80 ± 0.05	285	-0.95 ± 0.05
Completers (at Week 24)	266	-0.84 ± 0.06	258	-1.02 ± 0.06
Observed at Week 52	208	-0.77 ± 0.06	202	-1.05 ± 0.06
Observed at Week 76	139	-0.87 ± 0.08	138	-1.17 ± 0.08
Lixisenatide−Exenatide, adj. LS Mean (95% CI)				
LOCF *(by sponsor)				0.17 (0.03, 0.30), p=0.0143
MMRM				0.15 (0.02, 0.27), p=0.0249
Completers (at Week 24)				0.18 (0.04, 0.32), p=0.0138
Observed at Week 52				0.27 (0.13, 0.42), p=0.0002

Observed at Week 76				0.29 (0.12, 0.46), p=0.0008
Patients (%) achieving HbA1c <7				
Completers	295	134 (45%)	297	137 (46%)
sponsor's results* (LOCF)	295	143 (48%)	297	148 (50%)
FPG (mmol/L)				
Baseline mean ± SE	310	9.72 ± 0.12	301	9.68 ± 0.13
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	310	-1.22 ± 0.12	301	-1.45 ± 0.12
Completers	267	-1.27 ± 0.13	258	-1.50 ± 0.13
Lixisenatide− Exenatide, adjusted LS Mean (95% CI)				
LOCF* (by sponsor)				0.23 (-0.05, 0.52), p=0.1086
Completers				0.24 (-0.07, 0.55), p=0.1366
Body Weight (kg)				
Baseline mean ± SE	295	94.51 ± 1.13	296	96.69 ± 1.33
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	295	-2.96 ± 0.23	296	-3.98 ± 0.23
Completers	268	-3.04± 0.24	259	-4.20 ± 0.24
Lixisenatide− Exenatide, adjusted LS Mean (95% CI)				
LOCF* (by sponsor)				1.02 0.46, 1.58), p=0.0004
Completers				1.17 (0.58 1.76), p=0.0001

* This reviewer obtained the same results as the sponsor

The plot of adjusted difference (lixisenatide – exenatide) in HbA1c change from baseline over time is shown in Figure 3.1 based on MMRM analysis, showing lixisenatide QD is non-inferior to exenatide BID for up to week-24 of treatment but is inferior to exenatide BID after week-36.

Figure 3.1. The Time Course of (Lixisenatide – Exenatide) in HbA1c Changes from Baseline (MMRM).



This reviewer studied the relationship between the baseline HbA1c and the treatment effect of lixisenatide on the change in HbA1c from baseline to Week 24. Figure 8.3 in the Appendix 8 is a scatterplot of the baseline HbA1c and the change in HbA1c from baseline to Week 24 (LOCF). Values for subjects in the placebo and lixisenatide groups are shown in blue and red, respectively. For each treatment the regression line is provided. A treatment by baseline interaction (differing slopes) is not significant at alpha = 0.10 level (p=0.3379).

FDA medical reviewer requested to verify the sponsor's sensitivity analysis of HbA1c at Week 24. This sensitivity analysis is the primary analysis excluding data from 3 centers (1 center in the Germany [Site No. 276-905, investigator ID=86230, patients were not in ITT population], 1 center in the USA [Site No. 840-910, investigator ID=45605, n=4 in LIXI arm and n=1 in Ex arm] and 1 center in Puerto Rico [Site No. 630-924, investigator ID=54301, n=4 in LIXI arm and n=3 in EX arm]) due to their protocol noncompliance. This reviewer did not find the sensitivity analysis by the sponsor in their study report. This reviewer performed such a sensitivity analysis of HbA1c from baseline at Week 24 and the treatment difference from exenatide was 0.16 (95% CI: 0.03 to 0.29, p=0.0191, n=287 in lixisenatide QD arm and n=293 in exenatide BID arm), remaining the non-inferiority of lixisenatide to exenatide at Week 24. There were no subjects from Site 276-905 in the efficacy set.

3.2.4. Add-on combination therapy to a sulfonylurea (alone or in combination with metformin)

3.2.4.1 EFC6015

Study EFC6015 was a randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter 24-week study followed by an extension assessing the efficacy and safety of lixisenatide on top of a sulfonylurea in patients with type 2 diabetes not adequately controlled with sulfonylurea.

A total of 859 patients were randomized in 136 centers in 16 countries in a 2:1 ratio to 1 of 2 treatment groups (573 patients in the lixisenatide group and 286 patients in the placebo group). Randomization of patients was stratified by screening values of HbA1c (<8 %, ≥8%) and metformin use (Yes, No). All 859 randomized patients were exposed to the study treatment.

For more information about the study design see Appendix 9.1.

3.2.4.1.1 Patient Disposition, Demographic and Baseline Characteristics

A description of the patient populations in the review is shown in Table 3.2.4.1.1.

Table 3.2.4.1.1. Patient disposition and demographic information in Study EFC6015.

	Placebo	**Lixisenatide**
Randomized	286 (100%)	573 (100%)
ITT	286 (100%)	570 (99%)
Completers	255 (88%)	499 (87%)
Rescued	36 (13%)	25 (4%)
Age (years) Mean(SE) Range ≥ 65	 57.8 (0.6) 20 - 78 74 (26%)	 57.0 (0.4) 25 - 79 131 (23%)
Gender: % males	150 (53%)	284 (50%)
Race: % White % Black	 151 (53%) 9 (3%)	 297 (52%) 17 (3%)
Country: % U.S.	46 (16%)	94 (16%)
Baseline HbA1c: <8%	101 (35%)	202(35%)
Baseline BMI: <30 kg/m^2	153 (53%)	324 (57%)
Metformin used at screening: % yes	240 (84%)	485 (85%)
Baseline creatinine clearance (mL/min)		

<30 (severe renal impairment)	0 (0%)	0 (0%)
30 to <50 (moderate renal impairment)	4 (1%)	7 (1%)
50 to ≤80 (mild renal impairment)	66 (23%)	113 (20%)
≥80 (normal)	216 (76%)	452 (79%)

The Kaplan-Meier plot of time to dropout is in Appendix Figure 9.1, the dropout rate is higher in the lixisenatide arm than that in the placebo arm after 8 weeks treatment.

3.2.4.1.2 Results and Conclusions

The sponsor's results of primary and secondary analyses were verified by this reviewer as shown in Table 3.2.4.1.2. These results are supportive to the superiority of lixisenatide over placebo.

Table 3.2.4.1.2. Glycemic Parameters at Week 24 for Lixisenatide and Placebo in Patients with Type 2 Diabetes (Study EFC6015)

Endpoint	**Placebo**		**Lixisenatide**	
HbA1c (%)	n		n	
Baseline mean ± SE	274	8.22 ± 0.05	544	8.28 ± 0.04
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	274	-0.10 ± 0.07	544	-0.85 ± 0.06
MMRM	257	-0.22 ± 0.07	520	-0.92 ± 0.06
Completers	212	-0.17 ± 0.08	465	-0.85 ± 0.07
Lixisenatide−P, adjusted LS Mean (95% CI)				
LOCF *(by sponsor)				-0.74 (-0.87, -0.62), p < 0.0001
MMRM				-0.70 (-0.83, -0.57), p < 0.0001
Completers				-0.68 (-0.82, -0.54), p < 0.0001
Patients (%) achieving HbA1c <7				
Completers	274	36 (13%)	544	177 (33%)
sponsor's results *(LOCF)	274	37 (14%)	544	198 (36%)
2h-Post Prandial Glucose (PPG) (mmol/L)	n		n	
Baseline mean ± SE	120	16.55 ± 0.34	249	16.61 ± 0.26
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	120	-0.21 ± 0.49	249	-6.19 ± 0.41
Completers	103	-0.12 ± 0.51	234	-6.16 ± 0.43
Lixisenatide−P, adjusted LS Mean (95% CI)				
LOCF* (by sponsor)				-5.98 (-6.91, -5.04) , p < 0.0001
Completers				-6.04 (-7.00, -5.10) , p < 0.0001
FPG (mmol/L)				
Baseline mean ± SE	283	9.29 ± 0.14	564	9.67 ± 0.09
Adj. Mean Change from baseline±SE				

LOCF* (by sponsor)	283	-0.36 ± 0.16	564	-0.99 ± 0.14
Completers	217	-0.40 ± 0.18	475	-1.02 ± 0.16
Lixisenatide−P, adjusted LS Mean (95% CI)				
LOCF* (by sponsor)				-0.63 (-0.92, -0.35) , p < 0.0001
Completers				-0.63 (-0.93, -0.32) , p < 0.0001
Body Weight (kg)				
Baseline mean ± SE	278	84.52 ± 1..37	554	82.58 ± 0.93
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	278	-0.93 ± 0.23	554	-1.76 ± 0.20
Completers	217	-0.87 ± 0.27	475	-1.74 ± 0.24
Lixisenatide−P, adjusted LS Mean (95% CI)				
LOCF* (by sponsor)				-0.84 (-1.25, -0.42) , p < 0.0001
Completers				-0.87 (-1.32, -0.42) , p = 0.0002

* This reviewer obtained the same results as the sponsor

The time course of the completer's HbA1c difference from baseline over time is shown in Appendix Figures 9.2. There is significantly more reduction in HbA1c in the lixisenatide arm than that in the placebo arm after 8 weeks of treatment and persisting up to 76 weeks.

This reviewer studied the relationship between the baseline HbA1c and the treatment effect of lixisenatide on the change in HbA1c from baseline to Week 24. Figure 9.3 in the Appendix 9 is a scatterplot of the baseline HbA1c and the change in HbA1c from baseline to Week 24 (LOCF). Values for subjects in the placebo and lixisenatide groups are shown in blue and red, respectively. For each treatment the regression line is provided. A treatment by baseline interaction (differing slopes) is significant at alpha=0.10 level (p<0.0001).

3.2.5. Add-on treatment to pioglitazone (alone or in combination with metformin)

3.2.5.1 EFC6017

This was a randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week main treatment period and an extension assessing the efficacy and safety of lixisenatide on top of pioglitazone in patients with type 2 diabetes not adequately controlled with pioglitazone.

A total of 484 patients were randomized in 150 centers in 13 countries to 1 of 2 treatment groups (323 patients and 161 patients in the lixisenatide and placebo treatment groups, respectively). Randomization was stratified by HbA1c (<8 %, ≥ 8 %) and metformin use (Yes, No) at screening. Of the 484 randomized patients, all were exposed to study treatment.

For more information about the study design see Appendix 10.1.

3.2.5.1.1 Patient Disposition, Demographic and Baseline Characteristics

A description of the patient populations in the review is shown in Table 3.2.5.1.1.

Table 3.2.5.1.1. Patient disposition and demographic information in Study EFC6017

	Placebo	Lixisenatide
Randomized	161 (100%)	323 (100%)
ITT	159 (99%)	320 (99%)
Completers	137 (85%)	288 (89%)
Rescued	18 (11%)	12 (4%)
Age (years)		
Mean(SE)	55.3(0.7)	56.0 (0.5)
Range	28 - 77	26 - 82
≥ 65	30 (18%)	58 (19%)
Gender: % males	82 (51%)	172 (53%)
Race:		
% White	132 (82%)	273 (85%)
% Black	9 (6%)	14 (4%)
Country: % U.S.	67 (42%)	135 (42%)
Baseline HbA1c: <8%	79 (49%)	160 (50%)
Baseline BMI: <30 kg/m^2	51 (32%)	106 (33%)
Metformin use at screening: % Yes	131 (81%)	261 (81%)
Baseline creatinine clearance (mL/min)		
<30 (severe renal impairment)	0 (0%)	0 (0%)
30 to <50 (moderate renal impairment)	1 (1%)	5 (2%)
50 to ≤80 (mild renal impairment)	15 (10%)	28 (9%)
≥80 (normal)	142 (90%)	276 (89%)

The Kaplan-Meier plot of time to dropout is in Appendix Figure 10.1, showing the dropout rate in the lixisenatide arm is lower than that in the placebo arm after about 11 weeks of treatment.

3.2.4.4.2 Results and Conclusions

The sponsor's results of primary and secondary analyses were verified by this reviewer as shown in Table 3.2.4.4.2. These results are supportive of the superiority of lixisenatide over placebo except for the secondary endpoint body weight.

Table 3.2.4.4.2. Glycemic Parameters at Week 24 for Lixisenatide and Placebo in Patients with Type 2 Diabetes (Study EFC6017)

Endpoint	Placebo	Lixisenatide

HbA1c (%)	n		n	
Baseline mean ± SE	148	8.05 ± 0.06	308	8.08 ± 0.05
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	148	-0.34 ± 0.10	308	-0.90 ± 0.09
MMRM	144	-0.36 ± 0.09	290	-0.95 ± 0.07
Completers	123	-0.45 ± 0.09	276	-1.00 ± 0.08
Lixisenatide−P, adjusted LS Mean (95% CI)				
LOCF *(by sponsor)				-0.56 (-0.73, -0.39) , p < 0.0001
MMRM				-0.59 (-0.75, -0.43) , p < 0.0001
Completers				-0.55 (-0.72, -0.39) , p < 0.0001
Patients (%) achieving HbA1c <7				
Completers	148	37 (25%)	308	155 (50%)
sponsor's results (LOCF)	148	39 (26%)	308	161 (52%)
FPG (mmol/L)				
Baseline mean ± SE	159	9.12 ± 0.17	317	9.14 ± 0.12
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	159	-0.32 ± 0.22	317	-1.16 ± 0.19
Completers	123	-0.61 ± 0.18	275	-1.35 ± 0.16
Lixisenatide−P, adjusted LS Mean (95% CI)				
LOCF* (by sponsor)				-0.84 (-1.21, -0.47) , p < 0.0001
Completers				-0.74 (-1.06, -0.43) , p < 0.0001
Body Weight (kg)				
Baseline mean ± SE	157	97.0 ± 2.06	315	92.8 ± 1.30
Adj. Mean Change from baseline±SE				
LOCF* (by sponsor)	157	0.21 ± 0.36	315	-0.21 ± 0.32
Completers	123	0.16 ± 0.41	277	-0.22 ± 0.36
Lixisenatide−P, adjusted LS Mean (95% CI)				
LOCF* (by sponsor)				-0.41 (-1.03, 0.20) , p = 0.1864
Completers				-0.39(-1.10, 0.33) , p = 0.2933

* This reviewer obtained the same results as the sponsor
Note: Since the test of body weight not significant at level 0.05, body weight should not be labeled based on the sponsor's step-down testing procedure as seen in Appendix 10 Multiplicity issues.

The time course of the completer's HbA1c difference from baseline over time is shown in Appendix Figures 10.2, showing significantly more reduction in HbA1c change from baseline in the lixisenatide arm than that in the placebo arm during week 8 to week 76.

This reviewer studied the relationship between the baseline HbA1c and the treatment effect of lixisenatide on the change in HbA1c from baseline to Week 24. Figure 10.3 in the Appendix 10 is a scatterplot of the baseline HbA1c and the change in HbA1c from baseline to Week 24 (LOCF). Values for subjects in the placebo and lixisenatide groups are shown in blue and red, respectively. For each treatment the regression line is provided. A treatment by baseline interaction (differing slopes) is not significant at alpha = 0.10 level (p=0.5131).

FDA medical reviewer requested to verify the sponsor's sensitivity analysis of HbA_{1c} at Week 24, by excluding data from center 840-726 (1 subject only, Patient No. 840726008 in lixisenatide

arm) due to its protocol noncompliance. This reviewer did not find the sensitivity analysis by the sponsor in their study report. This reviewer performed such a sensitivity analysis of HbA1c from baseline at Week 24 and the treatment difference from placebo was -0.56 (95% CI: -0.73 to -0.39, p<0.0001).

3.2.5 Integrated and Sensitivity Analyses

3.2.5.1 Integrated Analysis of HbA1c in Patients with Insulin Use

FDA medical reviewer requested to perform efficacy analyses with respect to pooled studies where insulin was used (EFC6016, EFC10781 with and without the Asian study-EFC10887). Analyses were stratified by study. This reviewer performed the analyses as shown in Table 3.2.5.1. There appears no marketable difference in efficacy based on HbA1c values whether the Asian study EFC10887 was included. The efficacy result (based on HbA1c values) of pooled 8 phase 3 placebo-controlled studies (PC) (except study EFC6018 with treatment period 12 weeks) after 24 weeks of treatment is also shown in Table 3.2.5.1.

Table 3.2.5.1. HbA1c Results After 24 Weeks of Treatment in Pooled Placebo-Controlled Studies for Lixisenatide in Patients with Type 2 Diabetes (mITT/LOCF)

Endpoint	**Placebo**		**Lixisenatide**	
HbA1c (%)	n		n	
All PC (without EFC6018)				
Baseline mean ± SE	1465	8.07 ± 0.02	2493	8.13 ± 0.02
Adj. Mean Change from baseline±SE		-0.29 ± 0.02		-0.81 ± 0.02
Lixisenatide−P, adjusted LS Mean (95% CI)				-0.52 (-0.58, -0.46), p < 0.0001
Insulin use (EFC6016, EFC10781, EFC10887)				
Baseline mean ± SE	533	8.10 ± 0.04	665	8.15 ± 0.03
Adj. Mean Change from baseline±SE	533	-0.18 ± 0.04	655	-0.67 ± 0.04
Lixisenatide−P, adjusted LS Mean (95% CI)				-0.49 (-0.60, -0.39), p < 0.0001
Insulin use (EFC6016, EFC10781)				
Baseline mean ± SE	379	7.92 ± 0.04	519	8.05 ± 0.04
Adj. Mean Change from baseline±SE		-0.28 ± 0.05		-0.62 ± 0.04
Lixisenatide−P, adjusted LS Mean (95% CI)				-0.35 (-0.47, -0.23), p < 0.0001

3.2.5.2 Sensitivity Analysis of HbA1c Data Collected after Rescue Therapy in All Patients in Placebo-Controlled Studies

FDA medical reviewer requested to verify the sponsor's sensitivity analysis including values collected after rescue therapy (section 3.2.3-SCE). This reviewer performed the analyses and verified the sponsor's results as shown in Table 3.2.5.2. These results are similar to that of the data before rescue.

Table 3.2.5.2. HbA1c Results for Lixisenatide from Baseline to Week-24 Adjusted by Days on Concomitant Rescue Medication in Patients with Type 2 Diabetes in Phase 3 Placebo-Controlled Studies

Study^	N*	LS Mean ± se	Lixisenatide−P ± se	95% CI	p-value
Monotherapy					
EFC6018					
Placebo 122 (61+61)	112	-0.13 ± 0.11			
Lixisenatide 2-step 120	108	-0.67 ± 0.11	-0.54 ± 0.12	[-0.78, -0.29]	<.0001
Lixisenatide 1-step 119	110	-0.80 ± 0.11	-0.67 ± 0.12	[-0.91, -0.43]	<.0001
Add-on to Met alone					
EFC6014 (Table 7)					
Placebo 170 (85+85)	163	-0.40 ± 0.08			
Lixisenatide morning 255	238	-0.88 ± 0.07	-0.49 ± 0.10	[-0.68, -0.29]	<.0001
Lixisenatide evening 255	235	-0.73 ± 0.07	-0.33 ± 0.10	[-0.53, -0.14]	0.0008
EFC10743 (Table 7)					
Placebo 162 (80+82)	156	-0.44 ± 0.09			
Lixisenatide 2-step 161	149	-0.82 ± 0.09	-0.38 ± 0.11	[-0.58, -0.16]	0.0001
Lixisenatide 1-step 16	153	-0.91 ± 0.09	-0.47 ± 0.11	[-0.68, -0.26]	<.0001
Add-on to SU or SU+Met					
EFC6015 (Table 9)					
Placebo 286	262	-0.16 ± 0.07			
Lixisenatide 57	525	-0.90 ± 0.06	-0.74 ± 0.07	[-0.88, -0.59]	<.0001
Add-on to Pio or PIO+Met					
EFC6017 (Table 10)					
Placebo 161	149	-0.40 ± 0.10			
Lixisenatide 323	295	-0.93 ± 0.08	-0.53 ± 0.09	[-0.72, -0.35]	<.0001
Add-on to BI or BI+Met					
EFC6016 (Table 5)					
Placebo 167	148	-0.17 ± 0.12			
Lixisenatide 329	286	-0.60 ± 0.09	-0.43 ± 0.12	[-0.66, -0.19]	0.0004
Add-on IG+Met or IG+Met+TZD					
EFC10781 (Table 6)					
Placebo 223	210	-0.37 ± 0.08			
Lixisenatide 223	205	-0.68 ± 0.08	-0.31 ± 0.08	[-0.47, -0.16]	<.0001
Add-on to BI or BI+SU					
EFC10887 (Table 5)					
Placebo 157	151	0.12 ± 0.12			
Lixisenatide 154	140	-0.75 ± 0.13	-0.87 ± 0.14	[-1.14, -0.60]	<.0001
Add-on to Met or M+SU					
EFC11321 (Table 8)					
Placebo 195	186	-0.53 ± 0.21			
Lixisenatide 196	184	-0.84 ± 0.22	-0.31 ± 0.14	[-0.54, -0.09]	0.0066

* N=the number of patients in this analysis at a single visit which is either Week 8, 12, or 24 visit. This number is slightly different from that of section 3.2.3-SCE by the sponsor

3.3 Evaluation of Safety

An evaluation of the safety of lixisenatide presented in this submission is included in the clinical review by Dr.Suchitra Balakrishnan.

3.4 Benefit:Risk Assessment (Optional)

See the clinical reviewer's review for a risk-benefit assessment.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

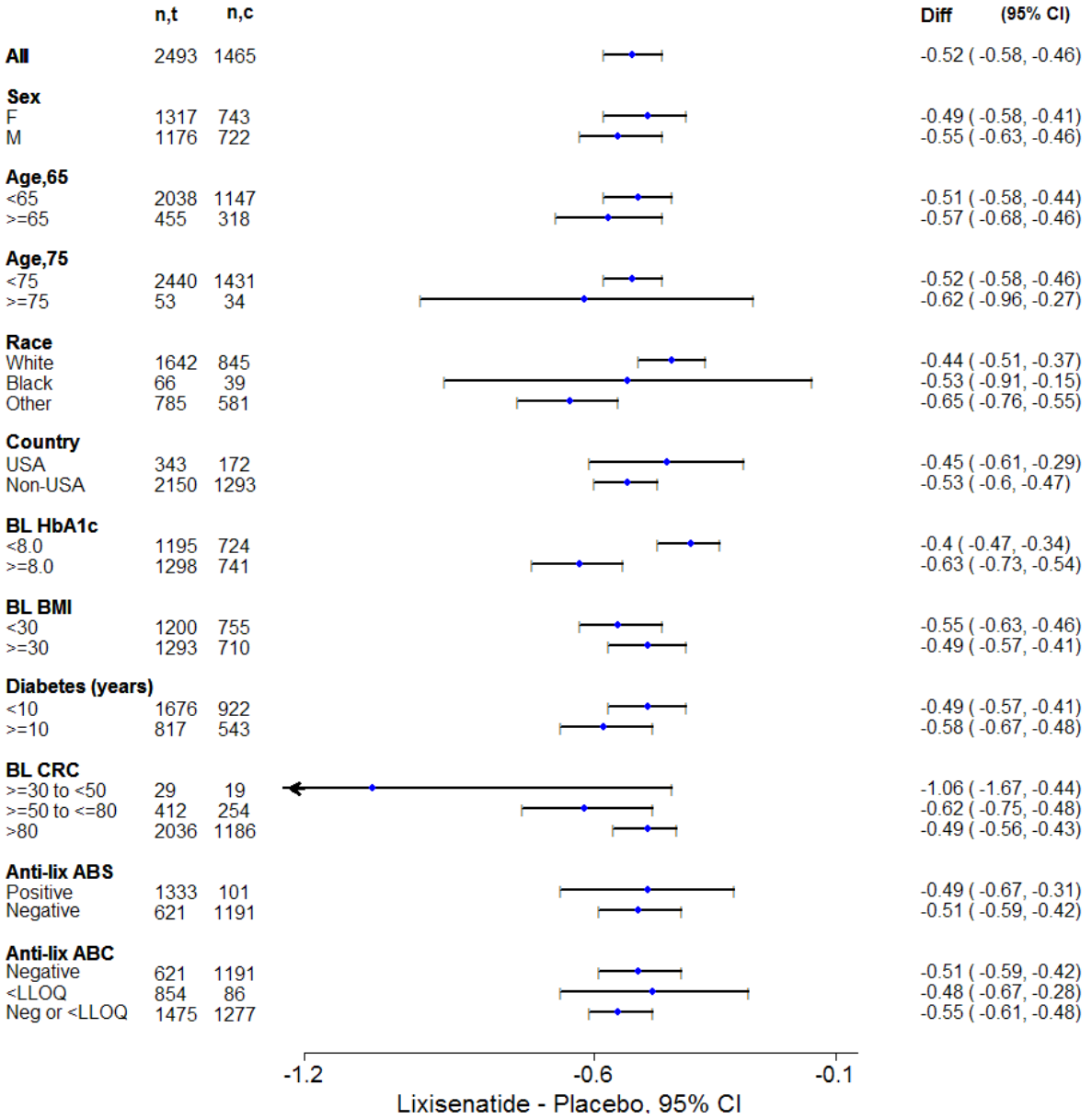
4.1 Gender, Race, Age, and Geographic Region

Meta analysis of the primary endpoint (at Week 24) of the eight placebo-controlled studies was performed across subgroups defined by sex, age (<65 years, ≥65 years; and (<75 years, ≥75 years), race (white, black, others), country (USA, non-USA), baseline HbA1c level (<8.0%, ≥8.0%), baseline BMI (<30 Kg/m^2, ≥30 Kg/m^2), duration of diabetes (<10 years, ≥10 years), baseline level of creatinine clearance (moderate renal impairment: ≥30 to **<**50 ml/min, mild renal impairment: ≥50 to ≤80 ml/min, and normal: >80 ml/min), anti-lixsenatide antibody status (positive, negative), and anti-lixsenatide antibody concentration (antibody negative, <3.21 nmol/L, and either above). The results were taken from ANCOVA analyses (stratified by study) using LOCF method for dealing with missing values.

The results are shown in the forest plots between treatments (see Figure 4.1). They are similar to the sponsor's results (Summary of Clinical Efficacy Table 17) based on the nine placebo-controlled studies, including EFC6018 of which the primary endpoint was at Week 12.

The HbA1c difference between lixisenatide and placebo are similar across subgroups except for the baseline HbA1c level. Significant treatment-baseline HbA1c levels interactions were observed at alpha=0.10 ($p<0.001$) level that lixisenatide was better for patients with higher HbA1c baseline level than those with lower level.

Figure 4.1. The Forest Plot of HbA1c Changes from Baseline to Week 24 between Lixisenatide and placebo Treatments Based on the Pooled Data of 8 Phase 3 Placebo-Controlled Studies (mITT, LOCF).



CRC: Creatinine clearance (ml/min)
Anti-lix ABS: Anti-lixisenatide antibody status
Anti-lix ABC: Anti-lixisenatide antibody concentration; LLOQ: lower limit of quantification (3.21 nmol/L); Neg: negative

4.2 Other Special/Subgroup Populations

FDA medical reviewer requested to verify the sponsor's subgroup analysis of lixisenatide antibody status (Summary of Clinical Efficacy Table 19). Meta analysis of the primary endpoint (at Week 24) of the eight placebo-controlled studies was performed across subgroups based on anti-lixisenatide antibody status and concentration as shown in Table 4.2.1. The results are similar to the sponsor's results.

Table 4.1. Change in HbA1c (%) from Baseline to Week 24 by Anti-lixisenatide Antibody Status and Concentration based on Pooled 8 Placebo-Controlled Studies Results in Patients with Type 2 Diabetes (mITT, LOCF)

Endpoint: HbA1c (%)	**Placebo**		**Lixisenatide**	
	n/N	HbA1c (%)	n/N	HbA1C (%)
Anti-lixisenatide antibody status Positive	101/1292 (8%)		1333/1954 (68%)	
Baseline mean ± SE Adj. Mean Change from baseline±SE (95%CI) Sponsor's result Lixisenatide−P, adjusted LS Mean (95% CI)		8.03 ± 0.09 -0.34 ± 0.09		8.09 ± 0.02 -0.83± 0.03 (-0.88, -0.78) -0.82 ± 0.04 (-0.89, -0.76) -0.49(-0.67, -0.31)
Anti-lixisenatide antibody status Negasitive	1191/1292 (92%)		621/1954 (32%)	
Baseline mean ± SE Adj. Mean Change from baseline±SE (95%CI) Sponsor's result Lixisenatide−P, adjusted LS Mean (95% CI)		8.06 ± 0.02 -0.32 ± 0.03		8.14 ± 0.04 -0.82 ± 0.04 (-0.89, -0.75) -0.83 ± 0.04 (-0.92, -0.75) -0.51 (-0.59, -0.42)
Anti-lixisenatide antibody concentration Negasitive	1191/1278		621/1890 (33%)	
Anti-lixisenatide antibody concentration < LLOQ (<3.21 nmol/L)	86/1278		854/1890 (45%)	
Baseline mean ± SE Adj. Mean Change from baseline±SE (95%CI) Sponsor's result Lixisenatide−P, adjusted LS Mean (95% CI)		7.98 ± 0.09 -0.42 ± 0.10		8.11 ± 0.03 -0.90± 0.03 (-0.92, -0.84) -0.88 ± 0.04 (-0.96, -0.80) -0.48 (-0.67, -0.28)
Anti-lixisenatide antibody concentration Negasitive or < LLOQ	1277/1278		1475/1890 (78%)	
Baseline mean ± SE Adj. Mean Change from baseline±SE (95%CI) Sponsor's result Lixisenatide−P, adjusted LS Mean (95% CI)		8.06 ± 0.02 -0.32 ± 0.03		8.12 ± 0.02 -0.87± 0.02 (-0.91, -0.82) -0.86 ± 0.04 (-0.93, -0.79) -0.55(-0.61, -0.48)
Anti-lixisenatide antibody concentration ≥ LLOQ	1/1278		415/1890 (22%)	
Baseline mean ± SE Adj. Mean Change from baseline±SE (95%CI) Sponsor's result				8.04 ± 0.04 () -0.66± 0.05 (-0.75, -0.57) -0.63 ± 0.05 (-0.73, -0.53)
Anti-lixisenatide antibody concentration ≥ LLOQ and ≤ 100 nmol/L	1/1278		370/1890 (20%)	
Baseline mean ± SE Adj. Mean Change from baseline±SE (95%CI) Sponsor's result				8.04 ± 0.04 -0.72± 0.05 (-0.81, -0.62) -0.64 ± 0.06 (-0.75, -0.53)
Anti-lixisenatide antibody concentration ≥ LLOQ and > 100 nmol/L	0/1278		45/1890 (2%)	

Baseline mean ± SE Adj. Mean Change from baseline±SE (95%CI) Sponsor's result				8.10 ± 0.01 -0.17± 0.15 (-0.48, 0.14) -0.16 ± 0.13 (-0.42, 0.10)

LLOQ: lower limit of quantification (3.21 nmol/L)

Note that there were 8% of patients in the placebo arm found as "Positive" to the anti-lixisenatide antibody status as compared to the 68% in the lixisenatide arm. The differences between treatments for the change in HbA1c from baseline are similar between the "Positive" and "Negative" status.

No additional subgroups were analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

1. The sponsor's multiplicity procedure shown in Appendix Figure 1 (EFC6018) does not control the overall type 1 error rate at level 0.05 for secondary endpoints in the parallel 1-step and 2-step increase arms.
2. There was one active-controlled and open-label pivotal study EFC6019 in which the efficacy of lixisenatide QD was compared to Exenatide BID. To reduce the bias, we suggested when reviewing the protocol that the sponsor should ideally use double-blinded technique in this non-inferiority trial instead of an open-label design. However, the sponsor did not explain why it is not possible to blind this trial.
3. There were patients who were under rescue medication prior to the end of main treatment period but who were labeled as completers in the submitted datasets.

5.2 Collective Evidence

Both the monotherapy (study EFC6018) and add-on to metformin (study EFC10743) studies show that lixisenatide 1-step increase is numerically better than the 2-step increase based on HbA1c reduction from baseline to Week 12 or Week 24 between treatments of lixisenatide and placebo. Similarly, a larger difference in HbA1c change from baseline to Week 24 between lixisenatide and placebo was observed in morning injection than that in evening injection in study EFC6014.

All superiority comparisons of lixisenatide vs placebo in HbA1c change from baseline to week 24, the primary efficacy endpoint, were significant in all studies. The results were based on LOCF as the primary method for accounting for missing data. Analyses using MMRM were consistent with the primary results using LOCF.

Lixisenatide QD was shown to be non-inferior to exenatide BID in reducing the mean HbA1c from baseline to Week 24 in Study EFC6019 using a pre-specified non-inferiority margins of 0.4%. However, non-inferiority was no longer preserved after 36 weeks of treatment. At Week 36, the treatment difference from exenatide based on the changes of HbA1c from baselines was 0.30 (95% CI: 0.17 to 0.44). At Weeks 52 and 76, the treatment difference from exenatide based on the changes of HbA1c from baselines was 0.27 (95% CI: 0.13 to 0.42) and 0.29 (95% CI: 0.12 to 0.46), respectively. In Study EFC6019, lixisenatide was also shown to be statistically

worse than exenatide during the entire treatment period, with the mean treatment difference was 0.17% at Week 24 and 0.29 at Week 76, respectively.

As a collective evidence to support the efficacy of lixisenatide, this reviewer verified the sponsor's results of study EFC10780 (active comparator was sitagliptin, change in HbA1C from baseline was not the primary endpoint in this study). There is no statistical difference at significant level of 0.05 between lixisenatide and sitagliptin in treatment for T2DM patients based on HbA1c reduction from baseline at Week 24 which was not the primary endpoints of the Study EFC10780, with a small mean treatment difference 0.06% (95% CI: -0.18 to 0.31, p=0.6042).

Subgroups analyses of HbA1c were conducted based on pooled patient populations from the 8 Phase 3 placebo-controlled studies with the primary endpoint at Week 24. The HbA1c difference between lixisenatide and placebo are similar across subgroups defined by sex, age, race, country, baseline BMI, duration of diabetes, baseline level of creatinine clearance, anti-lixsenatide antibody status, and anti-lixsenatide antibody concentration except for the baseline HbA1c level. Significant treatment-baseline HbA1c levels interactions were observed at alpha=0.10 ($p<0.001$) level that lixisenatide was better for patients with higher HbA1c baseline level than those with lower level.

5.3 Conclusions and Recommendations

All superiority comparisons of lixisenatide vs placebo in HbA1c change from baseline to week 24, the primary efficacy endpoint, were significant in all studies. The results were based on LOCF as the primary method for accounting for missing data. Analyses using MMRM were consistent with the primary results with LOCF.

Lixisenatide QD was shown to be non-inferior to exenatide BID in reducing the mean HbA1c from baseline to Week 24 in Study EFC6019 using a pre-specified non-inferiority margins of 0.4%. Non-inferiority was shown nominally at the primary time point (Week 24) but does not hold throughout the extension phase. Non-inferiority (evaluated using the same margin, 0.4% in HbA1c) fails at each time point of the extension period. At Week 36, the treatment difference from exenatide based on the changes of HbA1c from baselines was 0.30 (LOCF, 95% CI: 0.17 to 0.44). At Weeks 52 and 76 using LOCF, the treatment difference from exenatide based on the changes of HbA1c from baselines was 0.27 (95% CI: 0.13 to 0.42) and 0.29 (95% CI: 0.12 to 0.46), respectively. The inferiority of lixisenatide versus exenatide during the extension phase was also supported using the MMRM analysis. In Study EFC6019, lixisenatide was also shown to be statistically worse than exenatide during the entire treatment period, with the mean treatment difference was 0.17% at Week 24 and 0.29% at Week 76,

Subgroups analyses of HbA1c were conducted based on pooled patient populations from the 8 Phase 3 placebo-controlled studies with the primary endpoint at Week 24. The HbA1c difference between lixisenatide and placebo are similar across subgroups defined by sex, age, race, country, baseline BMI, duration of diabetes, baseline level of creatinine clearance, anti-lixsenatide antibody status, and anti-lixsenatide antibody concentration except for the baseline HbA1c level. Significant treatment-baseline HbA1c levels interactions were observed at alpha=0.10 ($p<0.001$) level that lixisenatide was better for patients with higher HbA1c baseline level than those with lower level.

5.4 Labeling Recommendations

The statistical review addresses statements in the label (section 14) concerning:

1. The multiplicity procedure shown in sponsor's EFC6018 SAP (Figure 1) does not control the overall type 1 error rate at level 0.05 for secondary endpoints in the parallel 1-step and 2-step increase arms. Moreover, the difference between lixisenatide and placebo in body weight was not significant at 0.05 level for both the 1-step (p=0.9462) and 2-step increase (p=0.8549). Therefore, the significant levels in FPG and body weight should not be included in section 14.1 of the product label.
2. Since the difference between lixisenatide and placebo in FPG was not significant at 0.05 level (p=0.7579) (study EFC6016), the significant levels in FPG, body weight, and basal insulin glargine dose should not be in Table 5 "With basal insulin +/- metformin".
3. Since the difference between lixisenatide and placebo in body weight was not significant at 0.05 level (p=0.0857) (study EFC10887), the significant levels in body weight and FPG should not be reported in Table 5 "With basal insulin +/- sulfonylurea". In addition, basal insulin glargine dose was not adjusted based on the sponsor's multiplicity adjustment, so the results should not be in Table 5 "With basal insulin +/- sulfonylurea".
4. Since the difference between lixisenatide and placebo in FPG was not significant at 0.05 level (p=0.5142) (study EFC10781), the significant levels in FPG should not be in Table 6.
5. Since the difference between lixisenatide and placebo in body weight was not significant at 0.05 level for both the morning injection (p=0.2181) or evening injection (p=0.2293) (study EFC6014), the corresponding significant levels in body weight should not be in Table 7.
6. Since the difference between lixisenatide and placebo in body weight was not significant at 0.05 level (p=0.296) (study EFC11321), the significant level in body weight should not be in Table 8.
7. Since the difference between lixisenatide and placebo in body weight was not significant at 0.05 level (p=0.1864) (study EFC6017), the significant level in body weight should not be in Table 10.
8. The description of "Active-controlled study versus exenatide" should add the information that the design was "open-label" with an extension phase.

APPENDICES

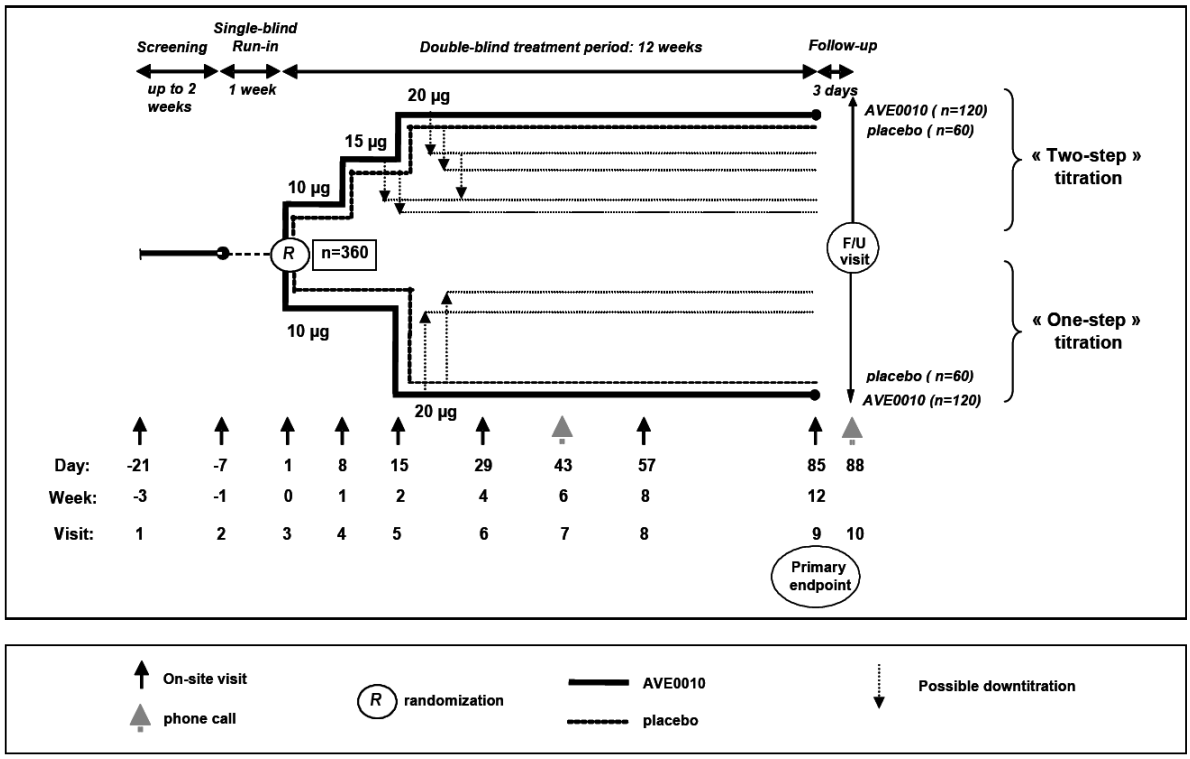
Appendix 1. Monotherapy: EFC6018

Appendix 1.1. Additional study design information (EFC6018)

Study EFC6018 was a randomized, double-blind, placebo-controlled, parallel-group, multicenter 12-week study assessing the efficacy and safety of LIXISENATIDE in patients with type 2 diabetes not treated with antidiabetic agents.

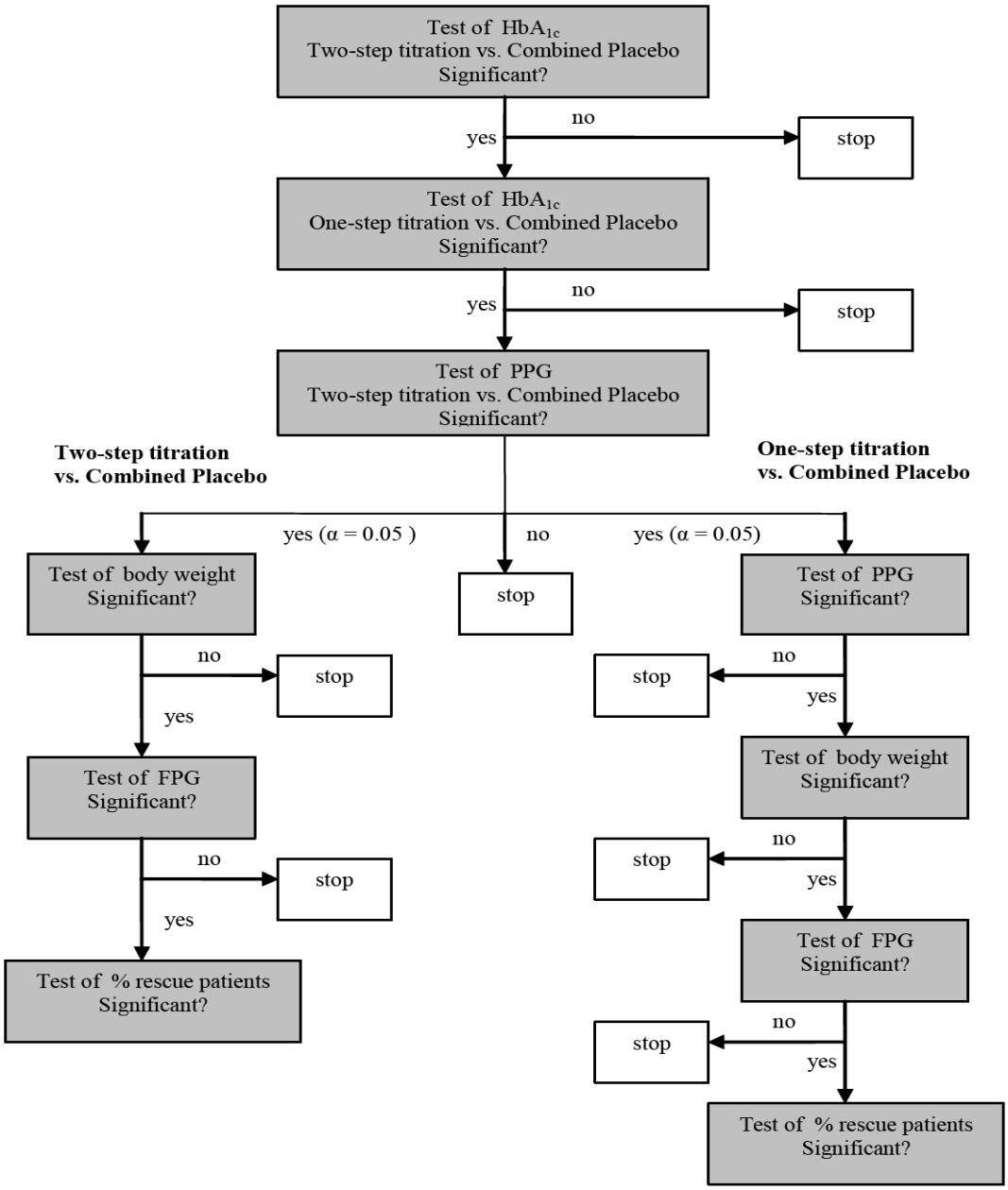
Overall, 361 patients were randomized in 61 centers in 12 countries, using a ratio of 2:1:2:1 (2-step lixisenatide titration regimen: 2-step placebo titration regimen: 1-step lixisenatide titration regimen: 1-step placebo titration regimen): 120 in the lixisenatide 2-step titration arm, 61 in the placebo 2-step titration arm, 119 in the lixisenatide 1-step titration arm, and 61 in the placebo 1-step titration arm. The patients were stratified by screening values of HbA1c (<8%, ≥ 8%) and Body Mass Index (BMI <30 kg/m2, ≥ 30 kg/m2).

The primary efficacy endpoint (change in HbA1c from Baseline to Week 12) was analyzed using an analysis of covariance (ANCOVA) model with treatment groups (2-step titration lixisenatide and placebo arms, 1-step titration lixisenatide and placebo arms), randomization strata of screening HbA1c (<8.0, =8.0%), randomization strata of screening BMI (<30, =30 kg/m2) values, and country as fixed effects and using the baseline HbA1c values as a covariate. In the ANCOVA model, the 2 titration placebo arms were included as separate treatment levels, but they were combined as 1 group when making comparisons using appropriate contrast (eg, [-0.5, -0.5, 0, +1] in the order of 1-step titration placebo arm, 2-step titration placebo arm, 1-step titration lixisenatide arm, and 2-step titration lixisenatide arm to compare 2-step titration lixisenatide arm with the combined placebo group). The statistical testing was 2-sided at a significance level of α=0.05. The primary analysis of efficacy variables at Week 12 was performed based on measurements obtained during the 12-week on-treatment treatment period. The last observation carried forward (LOCF) procedure was used by taking the last available post-baseline on treatment efficacy measurement (before the initiation of the new medication in the event of rescue therapy) as the efficacy value in question at Week 12.



A stepwise testing procedure was applied in order to ensure control of type 1 error using a prespecified order of priority was used in a step-down procedure described by Hochberg and Tamhane to control the type I error (Hochberg and Tamhane, Multiple comparison procedures. New York: John Wiley & Sons. 1987.). First the 2-step titration lixisenatide arm was compared with the combined placebo group. If the test was statistically significant, then the 1-step titration lixisenatide arm could be compared with the combined placebo group. The full stepwise testing procedure indicating how secondary endpoints are accounted for is described in Section 2.5.4.3 of the statistical analysis plan.

Figure 1 - The overall step-down testing procedure

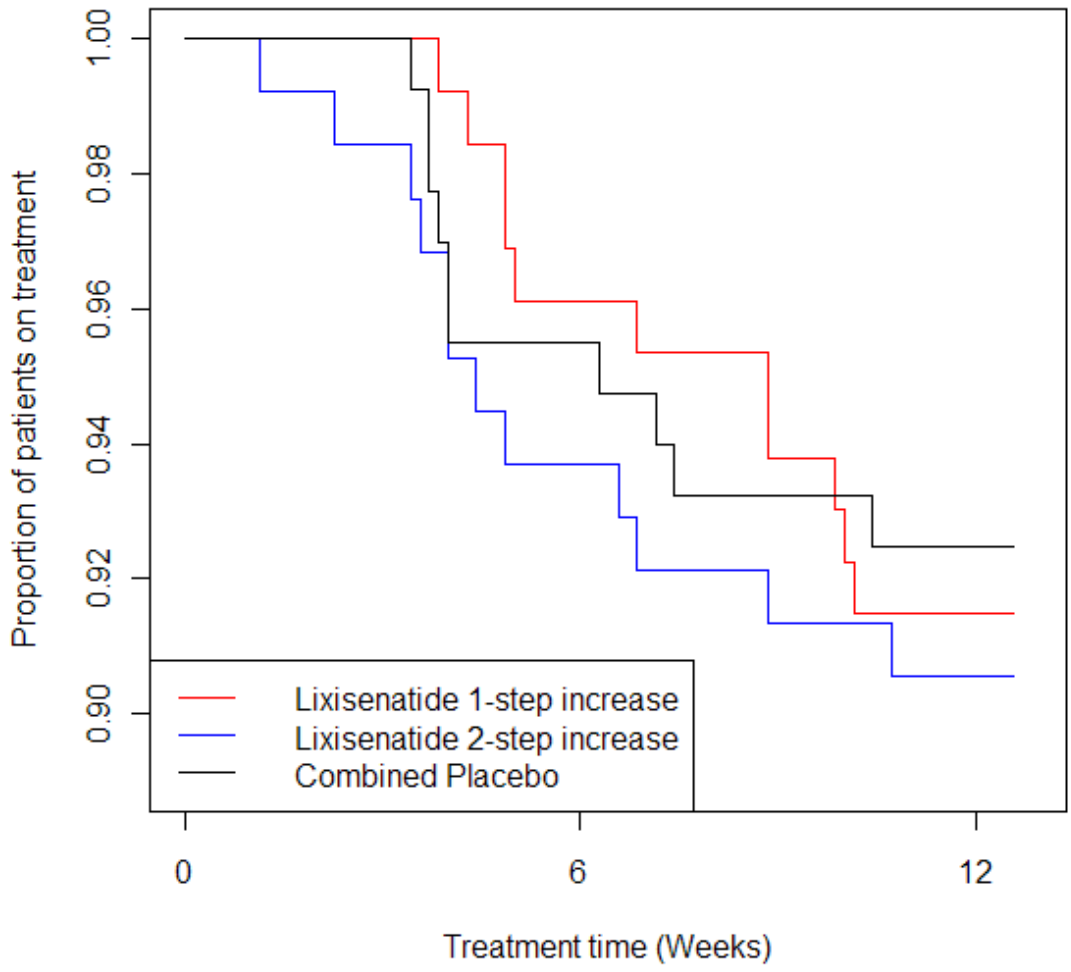


subgroups:

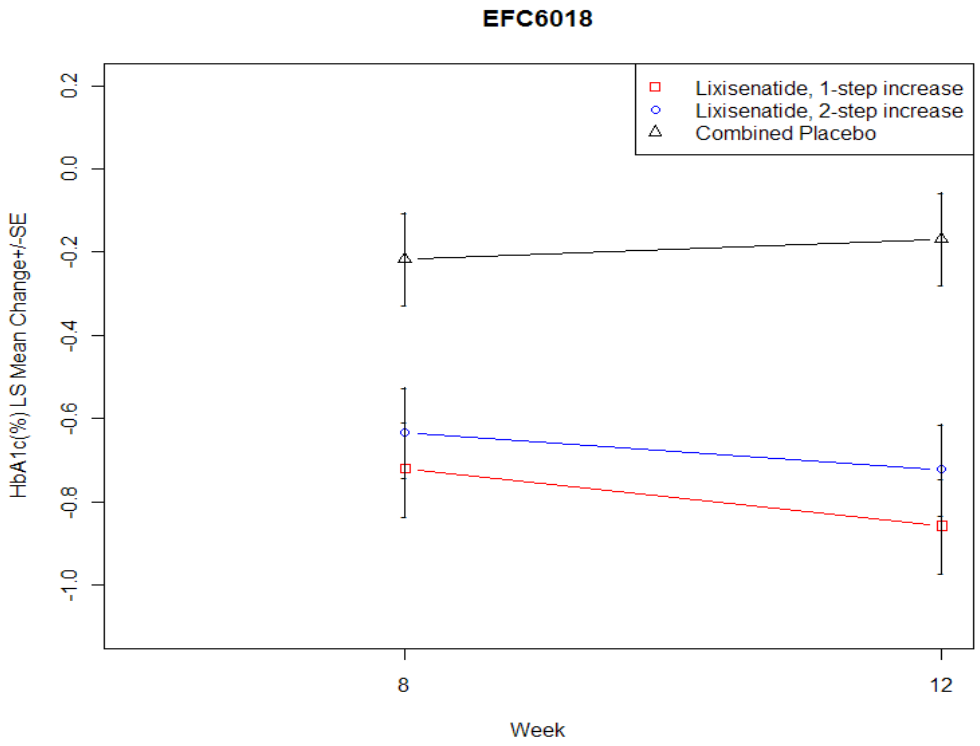
- Race (Caucasian/White/Black/Asian/Oriental/other)

- Ethnicity (Hispanic, not Hispanic)
- Age group (<50, ≥50-<65, ≥65 years of age)
- Gender
- Baseline BMI (<30, ≥30 kg/m2)
- Baseline HbA_{1c} (<8.0, ≥8.0%)

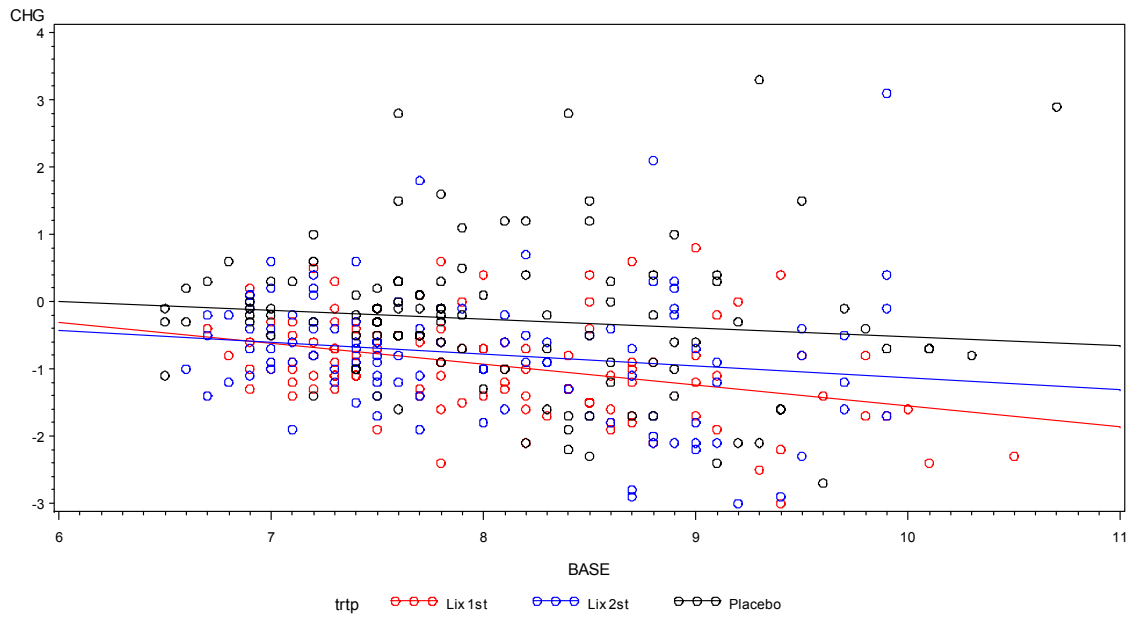
Appendix Figure 1.1. Comparing Time to Dropout during the Treatment Period between Treatment Groups (mITT population, Study EFC6018).



Appendix Figure 1.2. The Time Course of HbA1c Changes from Baseline for Treatment Groups (mITT population) in Study EFC6018 to Week 12.



Appendix Figure 1.3. The Plot of HbA1c Changes from Baseline versus Baseline Levels in Treatments in Study EFC6018 at Week12.



Appendix 2. EFC6016

Appendix 1.1. Additional study design information (EFC6016)

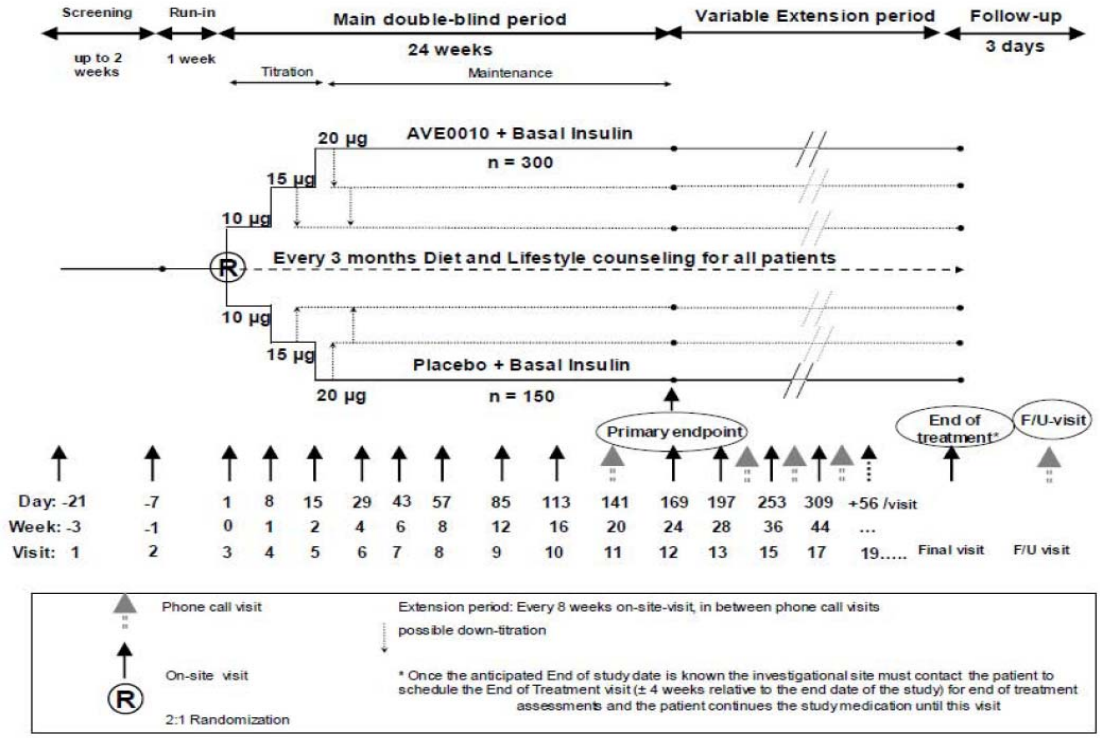
14.2 Add-on to basal insulin (alone or in combination with oral antidiabetics)

2.1. **EFC6016**: A randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week main treatment period and an extension assessing the efficacy and safety of LIXISENATIDE in patients with Type 2 diabetes insufficiently controlled with basal insulin. The main treatment period was 24 weeks.

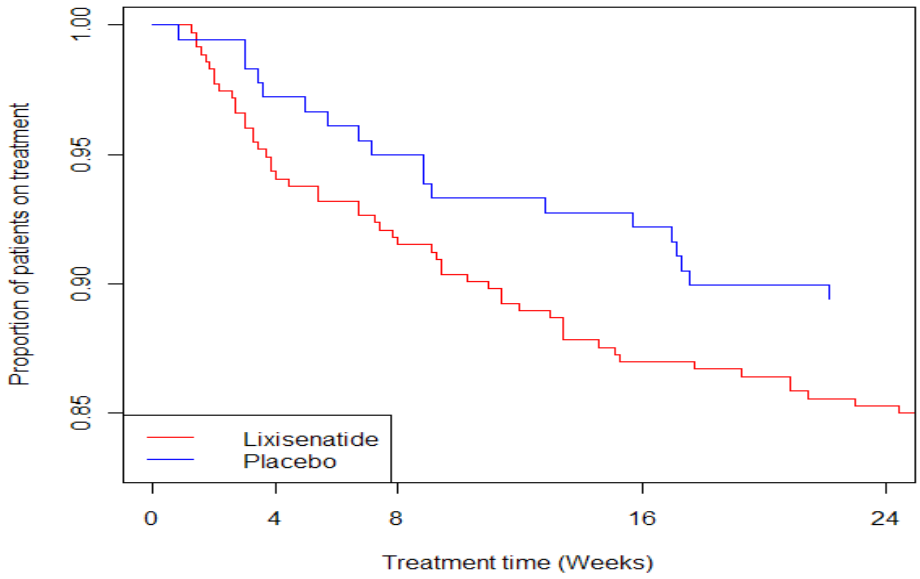
Patients are stratified by HbA1c (<8 %, ≥ 8 %) and metformin use (Yes, No) at screening.

The primary efficacy endpoint (the absolute change in HbA1c from baseline to Week 24) was analyzed using an analysis of covariance (ANCOVA) model with treatment groups (lixisenatide and placebo), randomization strata (screening HbA1c [<8.0%, =8.0%] and metformin use at screening [yes, no]), and country as fixed effects, and using the baseline HbA1c as a covariate.

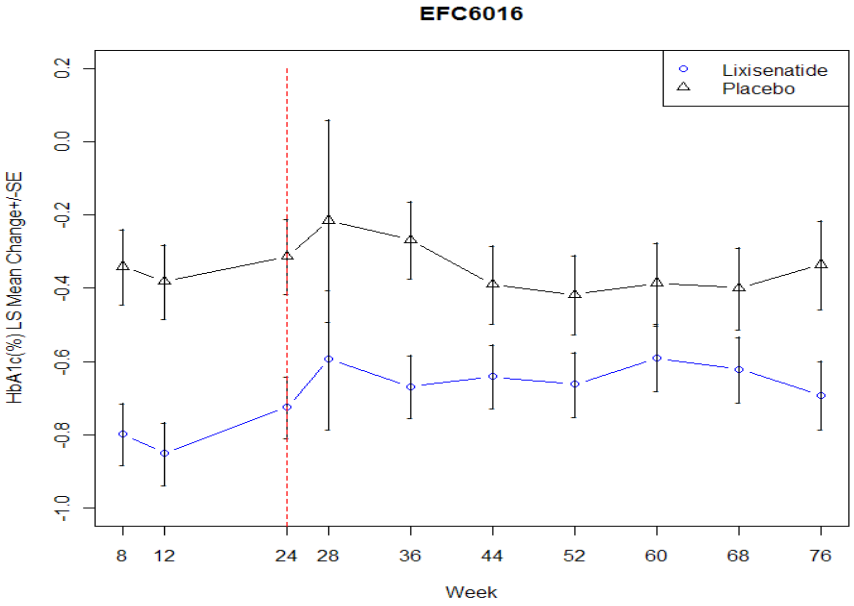
A stepwise testing procedure was applied in order to ensure control of type 1 error. Provided the primary endpoint was shown to be statistically significant at a = 0.05, the testing procedure was performed to test the secondary efficacy variables (change in 2-hour PPG after a standardized meal from baseline to Week 24; change in the average of the 7-point SMPG, FPG, and body weight from baseline to Week 24; and the percentage of patients requiring rescue therapy during the main 24-week double-blind treatment period). The tests stopped as soon as an endpoint was found not statistically significant at a = 0.05. No multiplicity adjustment was made on the other secondary efficacy variables, which are not mentioned above.



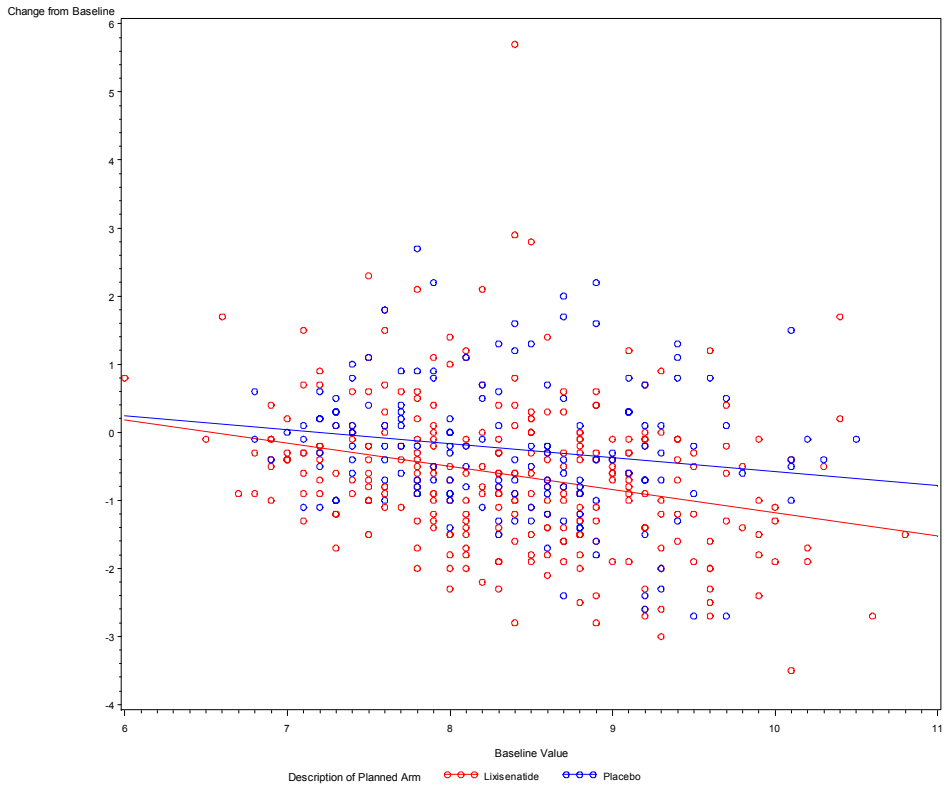
Appendix Figure 2.1. Comparing Time to Dropout during the Treatment Period between Treatment Groups (mITT population, Study EFC6016).



Appendix Figure 2.2. The Time Course of HbA1c Changes from Baseline for Treatment Groups (mITT population) in Study EFC6016 to Week 76.



Appendix Figure 2.3. The Plot of HbA1c Changes from Baseline versus Baseline Levels in Treatments in Study EFC6016 at Week 24.




```
Regression equation :  CHG(ARM:Lixisenatide) =  2.224717 - 0.340381*BASE.
Regression equation :  CHG(ARM:Placebo) =  1.464688 - 0.203824*BASE.
```

Appendix 3. EFC10887

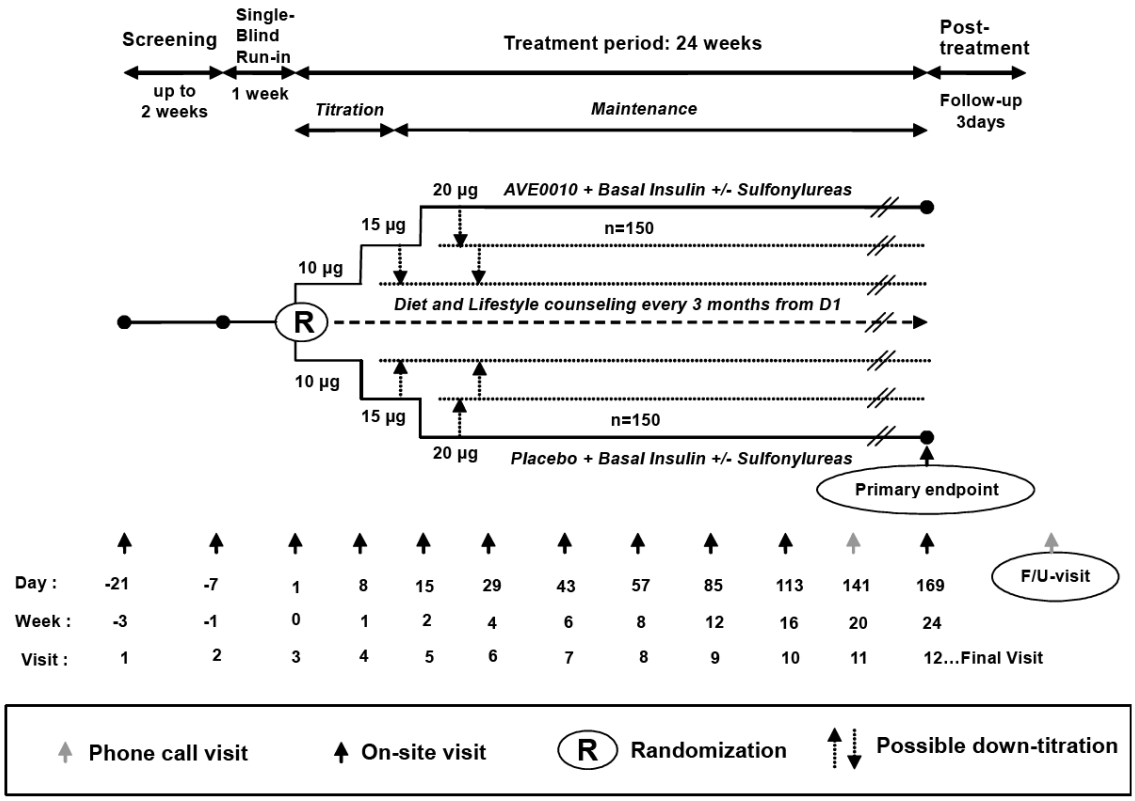
Appendix 3.1. Additional study design information (EFC10887)

2.2. **EFC10887**: A randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week treatment period assessing the efficacy and safety of LIXISENATIDE in patients with Type 2 diabetes insufficiently controlled with basal insulin with or without sulfonylurea. The main treatment period was 24 weeks. Patients are stratified by HbA1c (<8 %, ≥8 %) and sulfonylurea use (Yes, No) at screening.

The primary endpoint, absolute change from baseline to week 24 in HbA1c, will be analyzed an ANCOVA model with treatment (LIXISENATIDE or placebo), randomization strata of screening HbA1c (<8.0, =8.0 %), randomization strata of screening sulfonylurea use (Yes, No), and as fixed effects and using the baseline value as a covariate. Both means and adjusted means will be provided as well as 95 % confidence intervals (CI) constructed for adjusted mean differences between LIXISENATIDE and placebo.

Primary analysis will be performed using the mITT population and excluding HbA1c values obtained after the addition of rescue medication and/or after the treatment cessation plus 3 days.

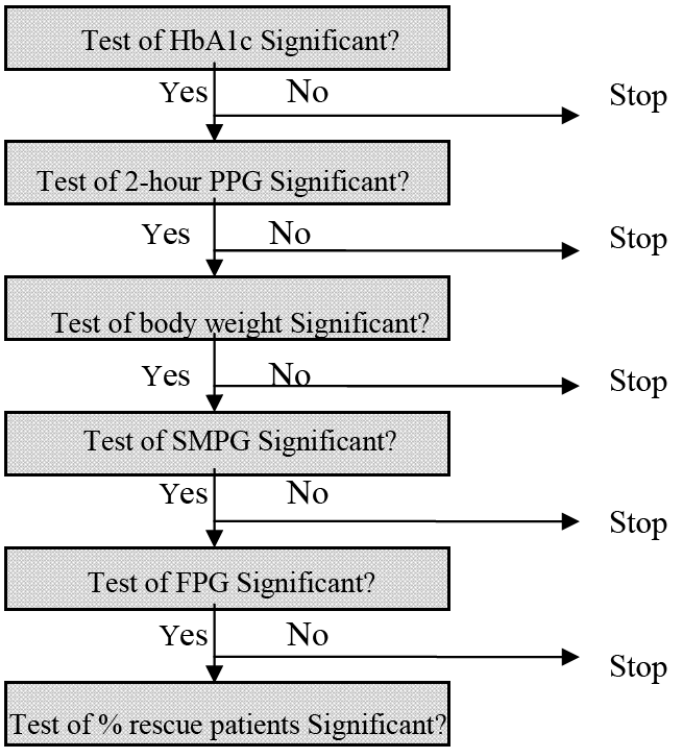
In case of discontinuation of investigational product before week 24, HbA1c will be assessed at time of discontinuation. The LOCF procedure will be used by taking this last available post-baseline on-treatment HbA1c measurement (before the rescue medication is taken in the event of rescue therapy) as the HbA1c value at week 24.



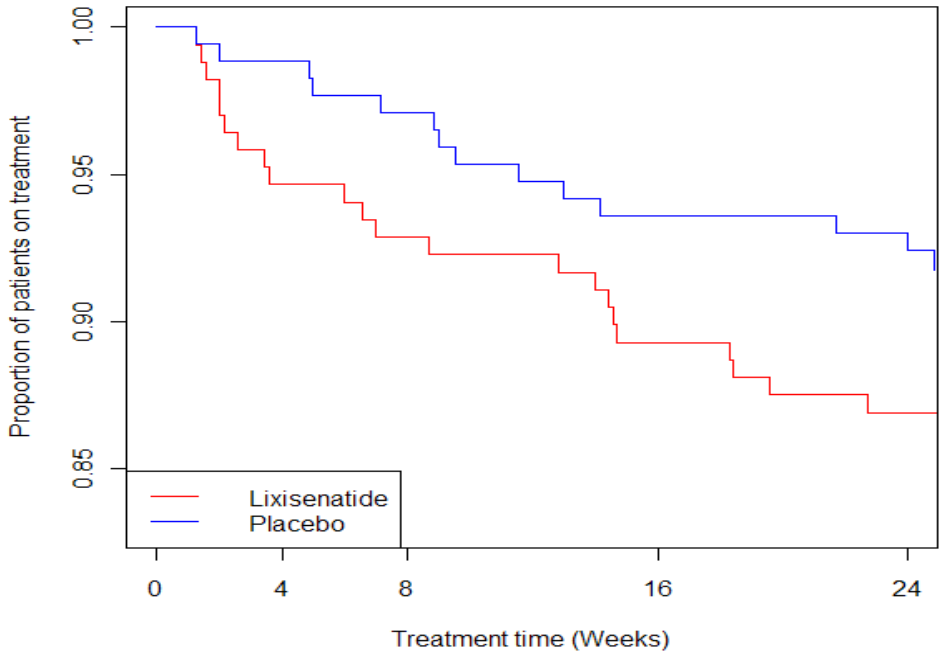
Descriptive analyses will be performed on the primary endpoint to summarize the treatment effects across subpopulations defined by the following or screening factors:

- Country,
- Age group,
- Gender,
- Screening BMI level (< 25, = 25 to <30, =30 kg/m²).

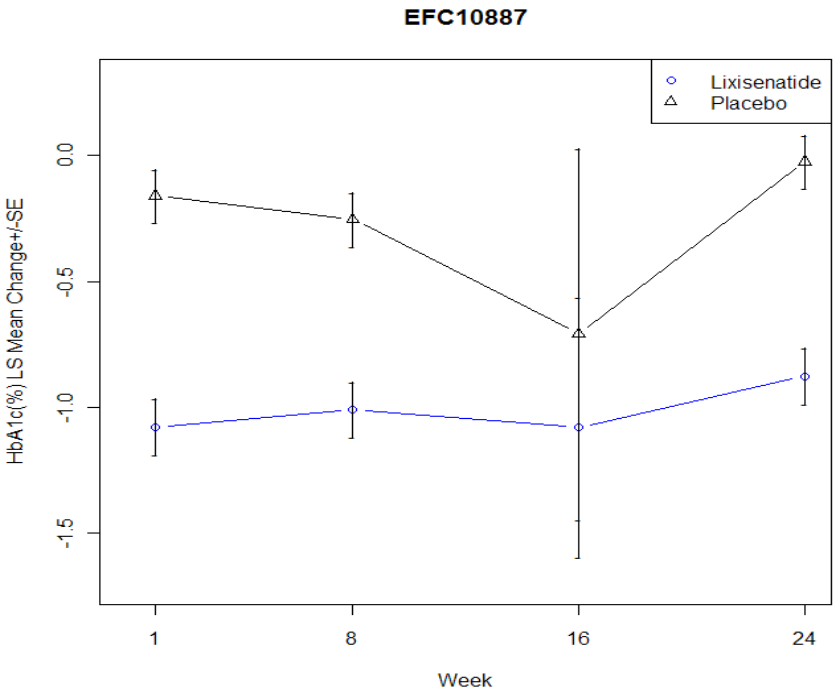
Multiplicity Adjustment



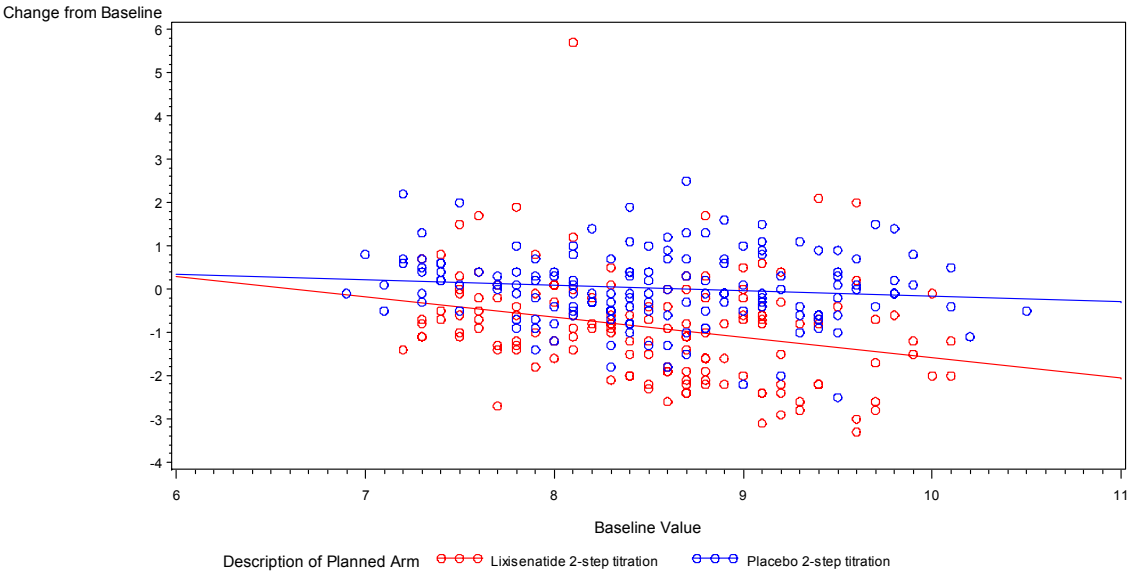
Appendix Figure 3.1. Comparing Time to Dropout during the Treatment Period between Treatment Groups (mITT population, Study EFC10887).



Appendix Figure 3.2. The Time Course of HbA1c Changes from Baseline for Treatment Groups (mITT population) in Study EFC10887 to Week 24.



Appendix Figure 3.3. The Plot of HbA1c Changes from Baseline versus Baseline Levels in Treatments in Study EFC10887 at Week 24.



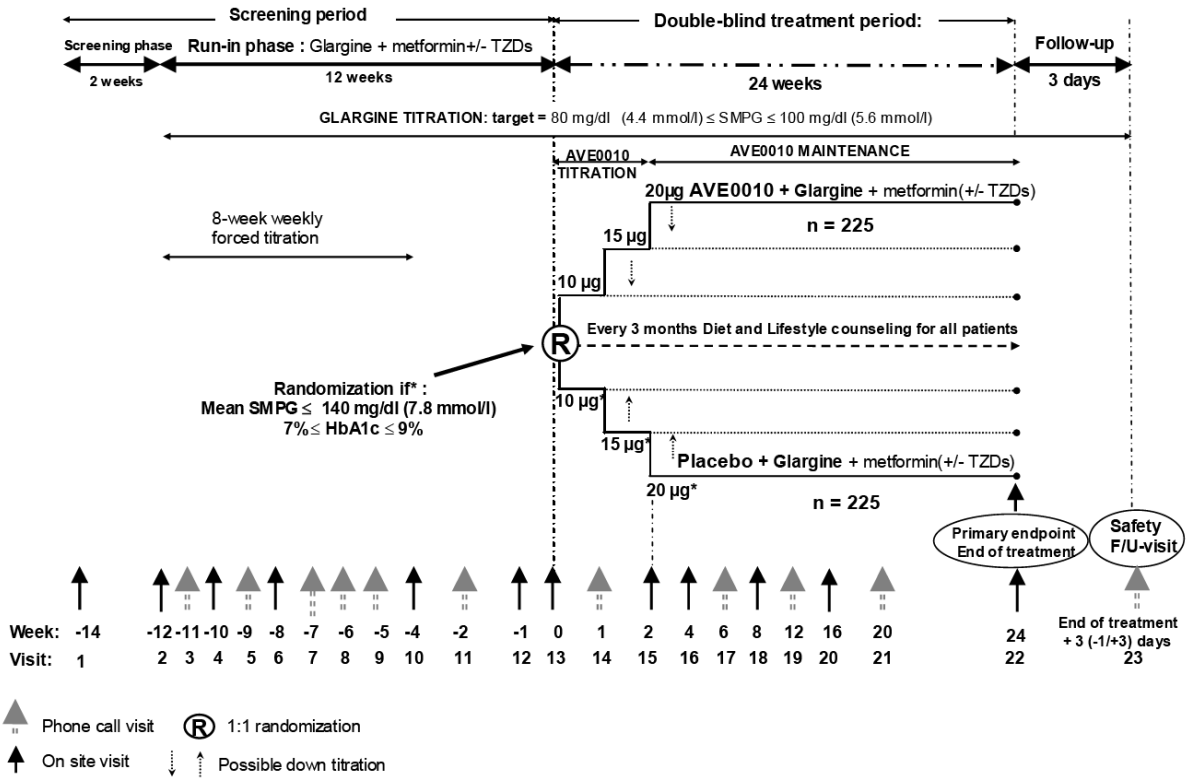

```
Regression equation :  CHG(ARM:Lixisenatide 2-step titration) = 3.083828 - 0.466281*BASE.
Regression equation :  CHG(ARM:Placebo 2-step titration) =  1.067567 - 0.122406*BASE.
```

Appendix 4. EFC10781

Appendix 4.1. Additional study design information (EFC10781)

3. **EFC10781**: A randomized, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week double-blind treatment period assessing the efficacy and safety of lixisenatide in patients with Type 2 diabetes insufficiently controlled with insulin glargine and metformin. The main treatment period was 24 weeks.
This is a double-blind, 1:1 randomized, placebo-controlled, 2-arm parallelgroup study. The study is double-blind with regard to active and placebo treatments. The study drug volume (i.e. dose of active drug or matching placebo) is not blinded. Patients are stratified by HbA1c (<8 %, ≥ 8 %) and thiazolidinediones (TZDs) use (yes, no).

The primary endpoint, change in HbA1c from baseline to week 24 will be analyzed using an ANCOVA model with treatments, randomization strata of V12 HbA1c (<8.0, ≥8.0 %), randomization strata of screening TZDs use (Yes, No), and country as fixed effects and using the baseline HbA1c value as a covariate. Both means and adjusted means will be provided as well as 95% confidence intervals (CI) constructed for adjusted mean differences between lixisenatide and placebo.



For the run-in phase a visit window of ±3 days is acceptable using the date of visit 2 as reference. During the randomized double-blind treatment period a visit window of ±3 days up to visit 15 (week 2) and ± 5 days after visit 15 is acceptable, using the day of visit 13 as reference. A visit window of -1 day or + 3 days is acceptable for the post-treatment follow-up visit using the day of visit 22 as reference.

* Volume matched placebo

2.4.4.3 Multiplicity issues
To control the Type I error, a step-down testing procedure described by Hochberg and Tamhane will be applied (3).

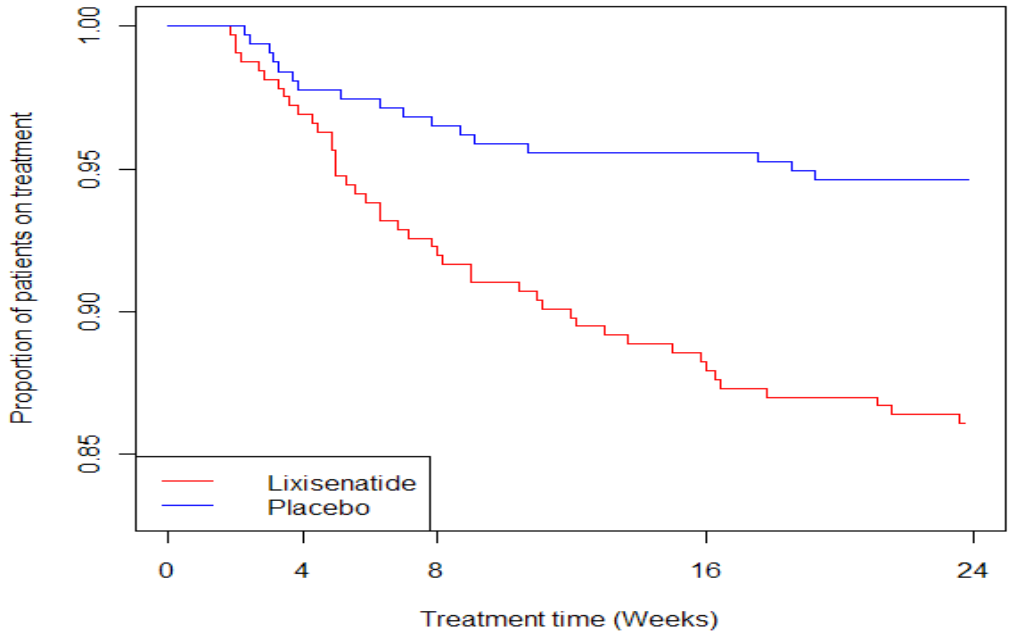
For the primary variable (change from baseline to Week 24 in HbA1c), no multiplicity adjustment is needed to control the Type I error since only one comparison of lixisenatide versus placebo will be performed.

If the primary variable is statistically significant at the 5% level, a hierarchical testing procedure will be performed to test the following secondary efficacy variables in the following prioritized order. Testing will stop when an endpoint is found not to be statistically significant at the 5% level:

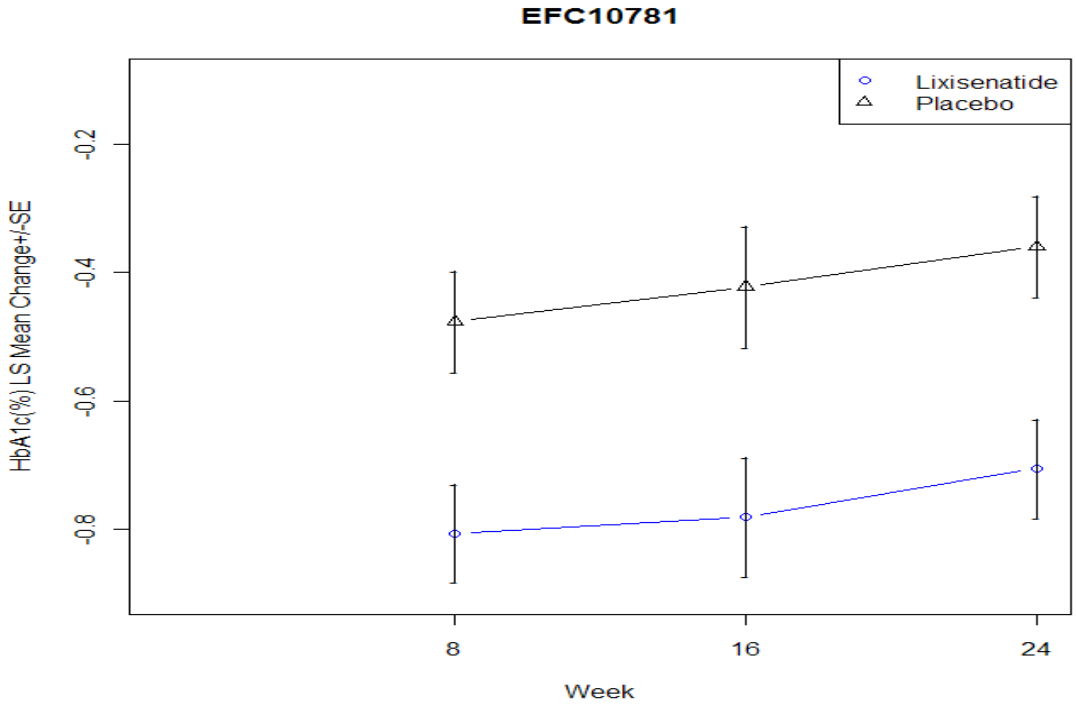
1. Change in 2-hour PPG (mmol/L) after the standardized meal test from baseline to Week 24,
2. Change in the daily average of the 7-point SMPG from baseline to Week 24,
3. Change in body weight (kg) from baseline to Week 24,
4. Change in average daily insulin glargine dose (U) from baseline to Week 24,
5. Change in FPG (mmol/L) from baseline to Week 24, and
6. Percentage of patients requiring rescue therapy during the on-treatment period.

Multiplicity adjustment will not be performed on the secondary efficacy variables that are not included in the above list.

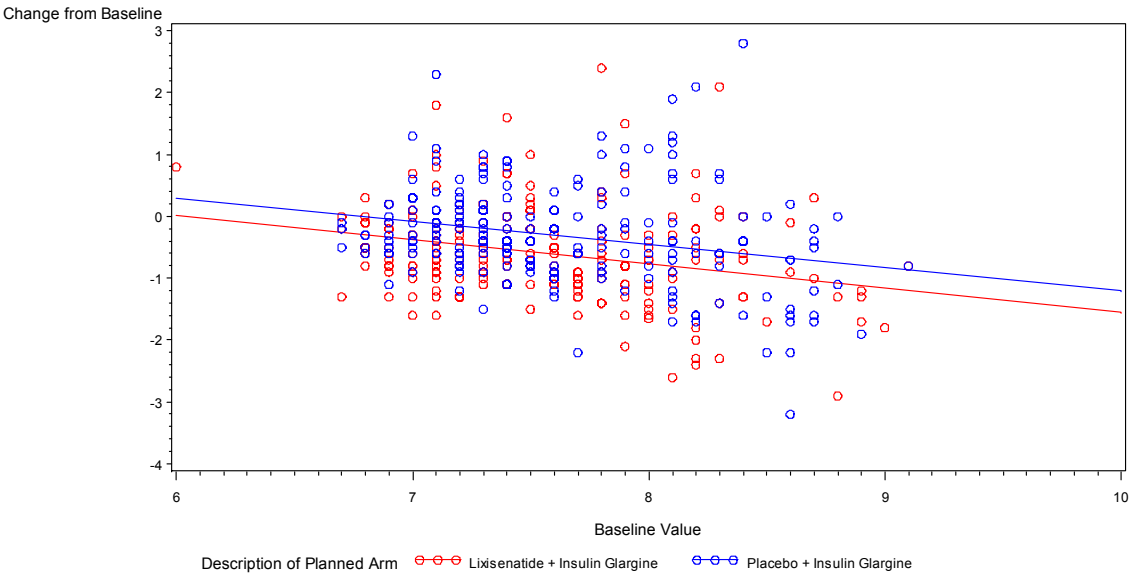
Appendix Figure 4.1. Comparing Time to Dropout during the Treatment Period between Treatment Groups (mITT population, Study EFC10781).



Appendix Figure 4.2. The Time Course of HbA1c Changes from Baseline for Treatment Groups (mITT population) in Study EFC10781 to Week 24.



Appendix Figure 4.3. The Plot of HbA1c Changes from Baseline versus Baseline Levels in Treatments in Study EFC10781 at Week24.



Regression equation : CHG(ARM:Lixisenatide + Insulin Glargine) = 2.357591-0.391011*BASE.
Regression equation : CHG(ARM:Placebo + Insulin Glargine) = 2.521347 - 0.371395*BASE.

Appendix 5. EFC6014

Appendix 4.1. Additional study design information (EFC6014)

14.3 Add-on combination therapy to metformin (alone or in combination with sulfonylurea)

4.1. **EFC6014**: A randomized, double-blind, placebo-controlled, parallel-group, multicenter 24-week study followed by an extension assessing the efficacy and safety of LIXISENATIDE on top of metformin in patients with type 2 diabetes not adequately controlled with metformin. The main treatment period was 24 weeks.

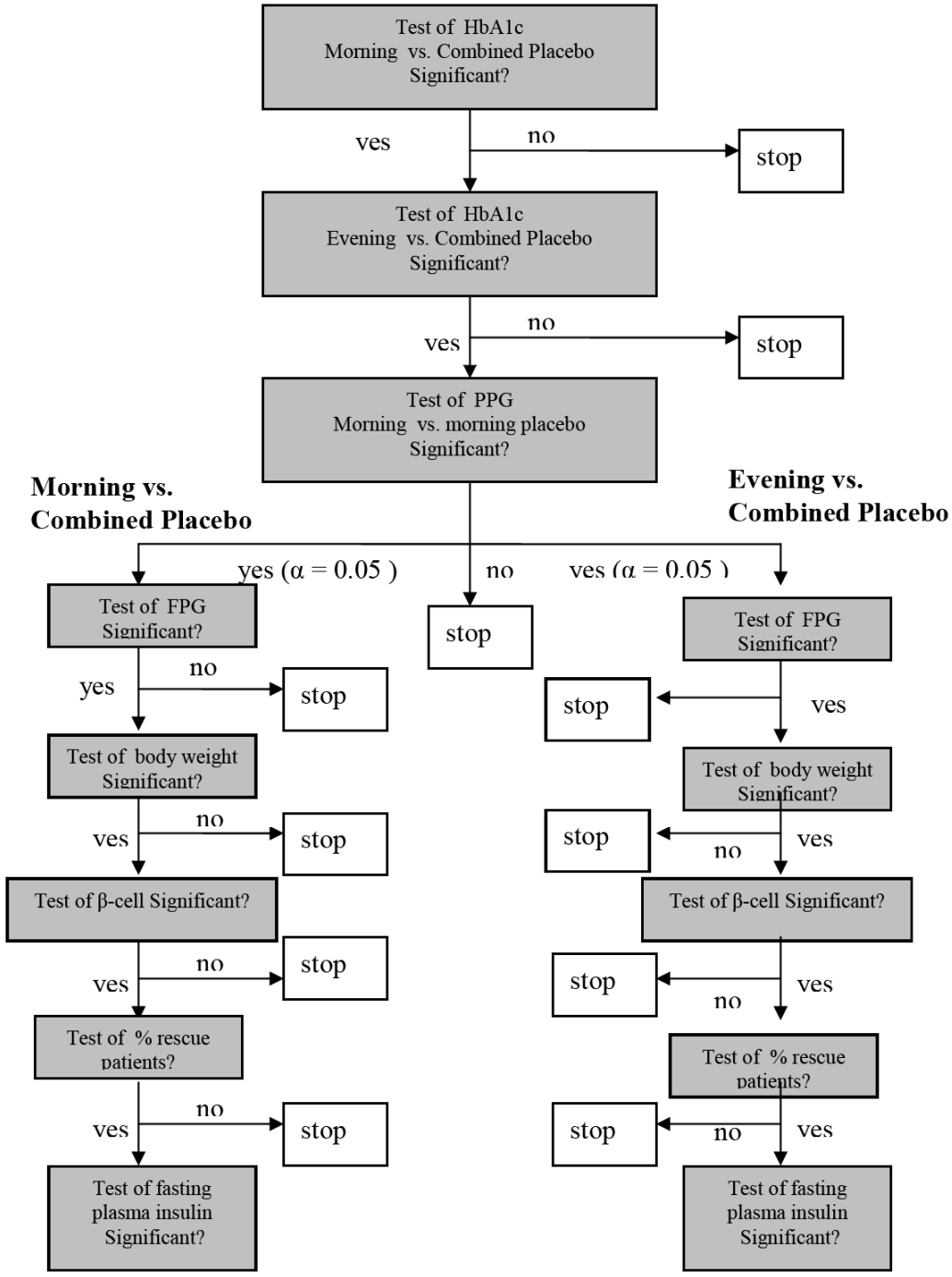
The randomization is stratified according to screening HbA_{1c} (<8, ≥ 8%) and BMI (<30 kg/m_2, ≥ 30 kg/m_2) values. The patients are stratified by screening values of HbA1c (<8%, ≥ 8%) and BMI (<30 kg/m2, ≥ 30 kg/m2).

The primary endpoint, absolute change from baseline to week 24 in HbA1c, will be analyzed using an ANCOVA model with treatment (LIXISENATIDE morning injection and placebo arms, LIXISENATIDE evening injection and placebo arms), randomization strata of screening HbA1c (<8.0, ≥8.0 %), randomization strata of screening BMI (<30 kg/m2, ≥ 30 kg/m2) values, and country as fixed effects and using the baseline value as a covariate. Both means and adjusted means for each LIXISENATIDE arm and the combined placebo group will be provided as well as 95 % confidence intervals (CI) constructed for adjusted mean differences between each LIXISENATIDE arm and combined placebo group.

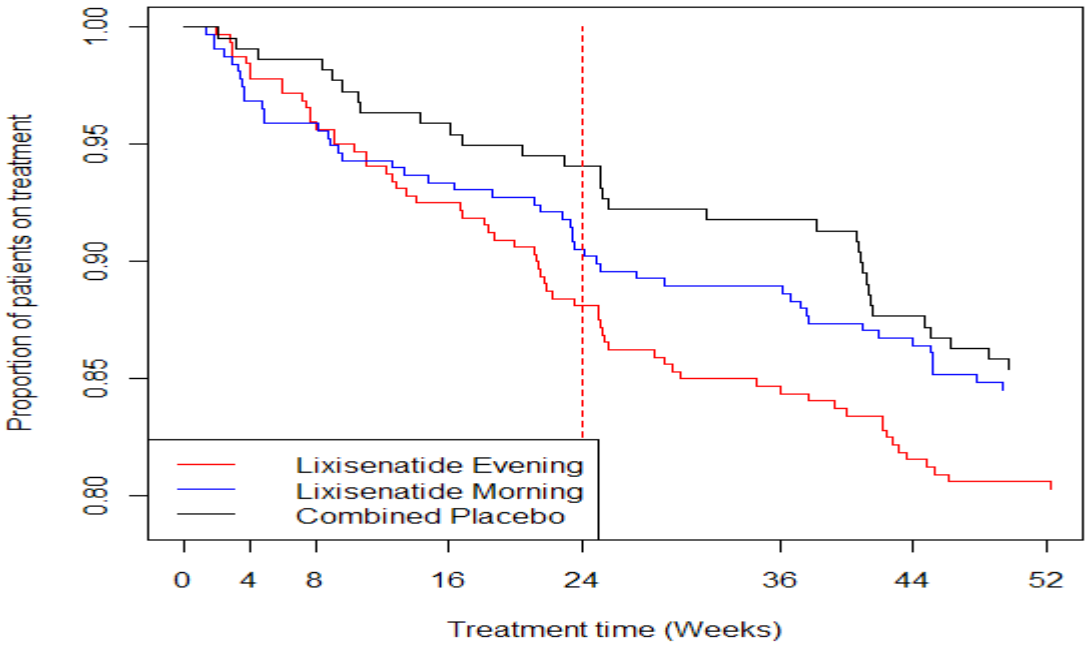
A stepwise testing procedure will be applied to the analysis of the primary efficacy variable to ensure type I error control. First, morning injection LIXISENATIDE arm will be compared with the combined placebo arm. If the test is statistically significant, then evening injection LIXISENATIDE arm will be compared with the combined placebo group. Note: The Figure 1 step-down testing procedure was from the sponsor's original SAP where "ves" should be "Yes".

The statistical test for the primary efficacy variable will be two-sided at alpha level of 0.05.

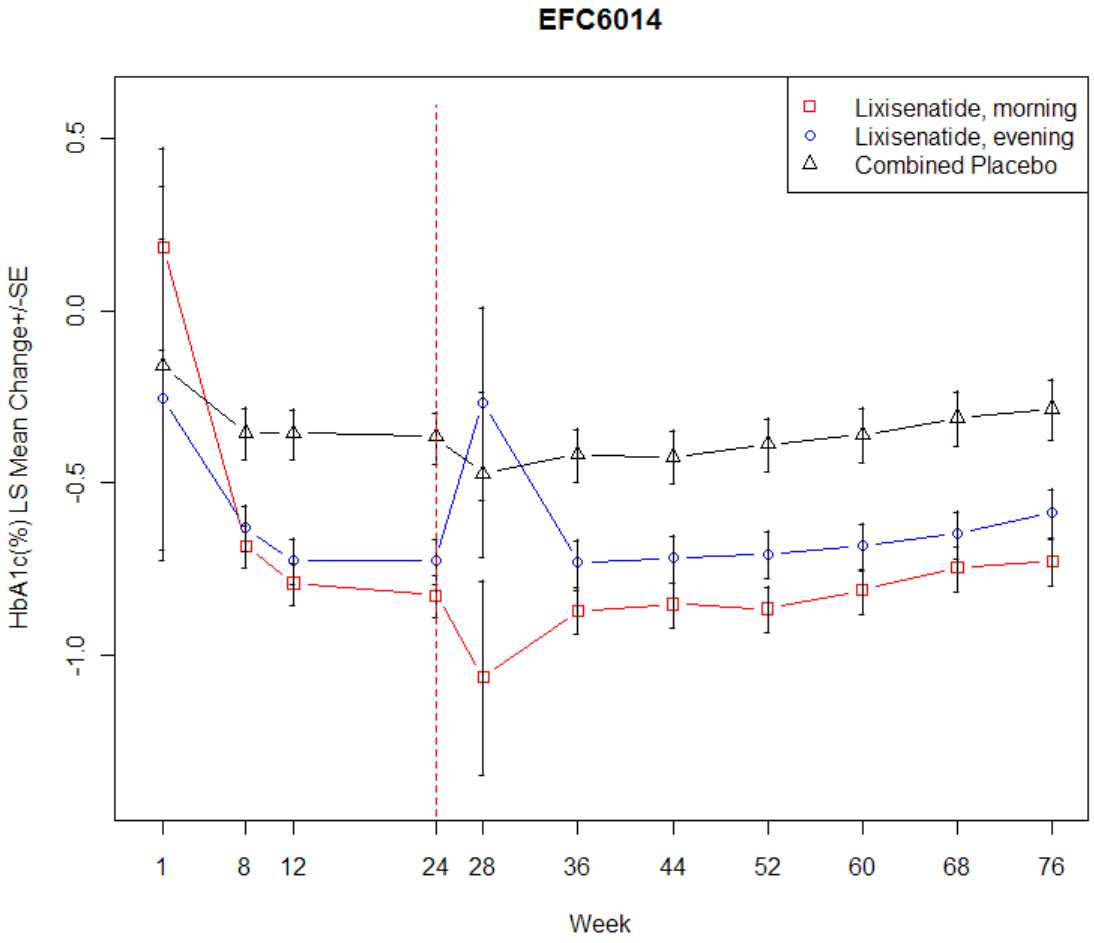
Figure 1 - Step-down testing procedure



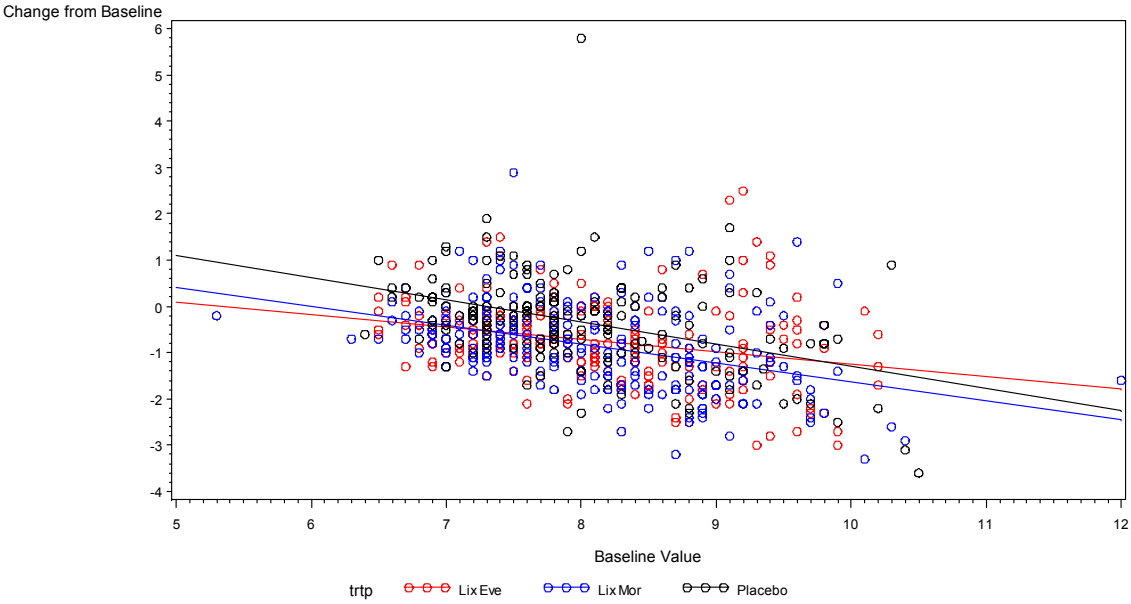
Appendix Figure 5.1. Comparing Time to Dropout during the Treatment Period between Treatment Groups (mITT population, Study EFC6014).



Appendix Figure 5.2. The Time Course of HbA1c Changes from Baseline for Treatment Groups (mITT population) in Study EFC6014 to Week 76.



Appendix Figure 5.3. The Plot of HbA1c Changes from Baseline versus Baseline Levels in Treatments in Study EFC6014 at Week 24.



Appendix 6. EFC10743

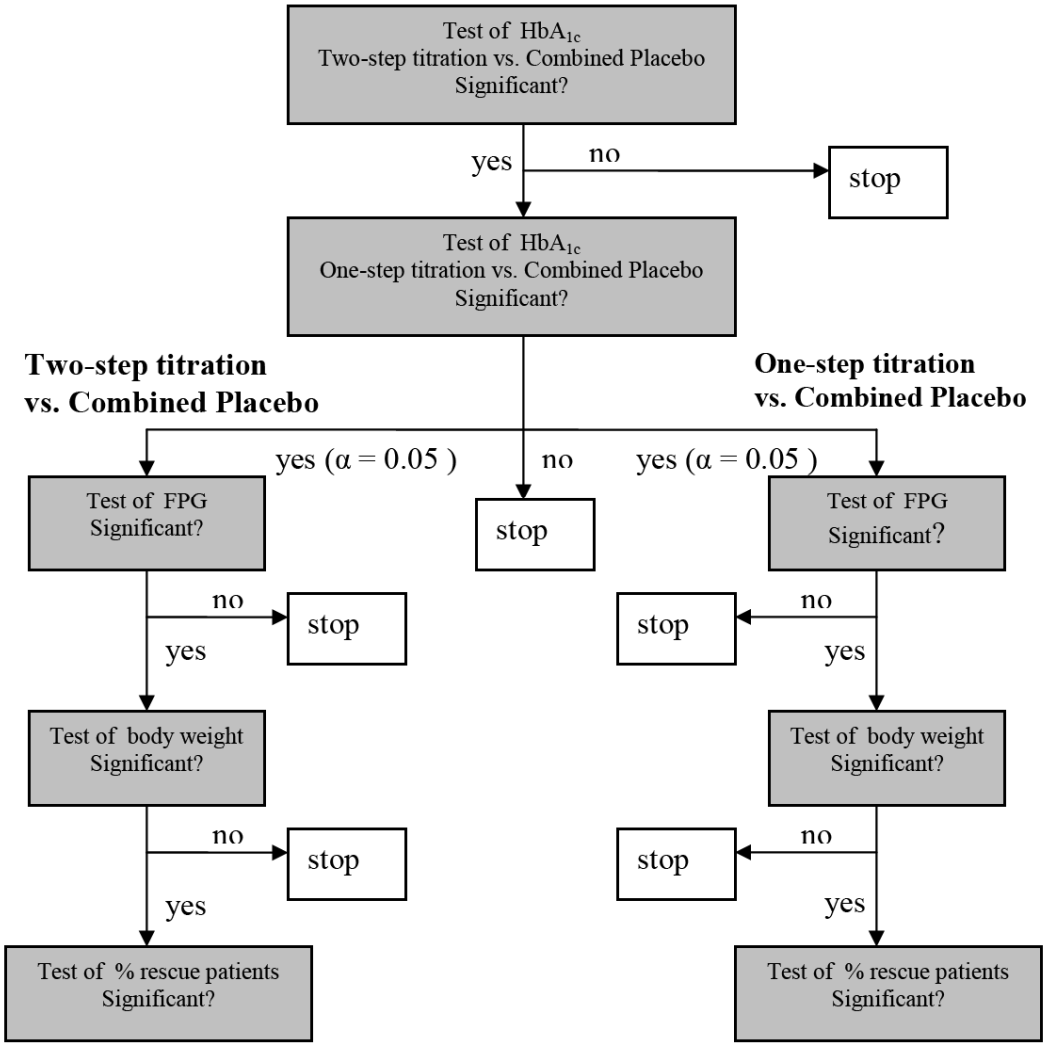
Appendix 6.1. Additional study design information (EFC10743)

4.2. EFC10743: A randomized, double-blind, placebo-controlled, parallel-group, multicenter, 24-week study followed by an extension assessing the efficacy and safety of LIXISENATIDE in two titration regimens on top of metformin in patients with type 2 diabetes not adequately controlled with metformin. The main treatment period was 24 weeks.
The patients are stratified by screening values of HbA1c (<8%, ≥ 8%) and Body Mass Index (BMI <30 kg/m2, ≥ 30 kg/m2).

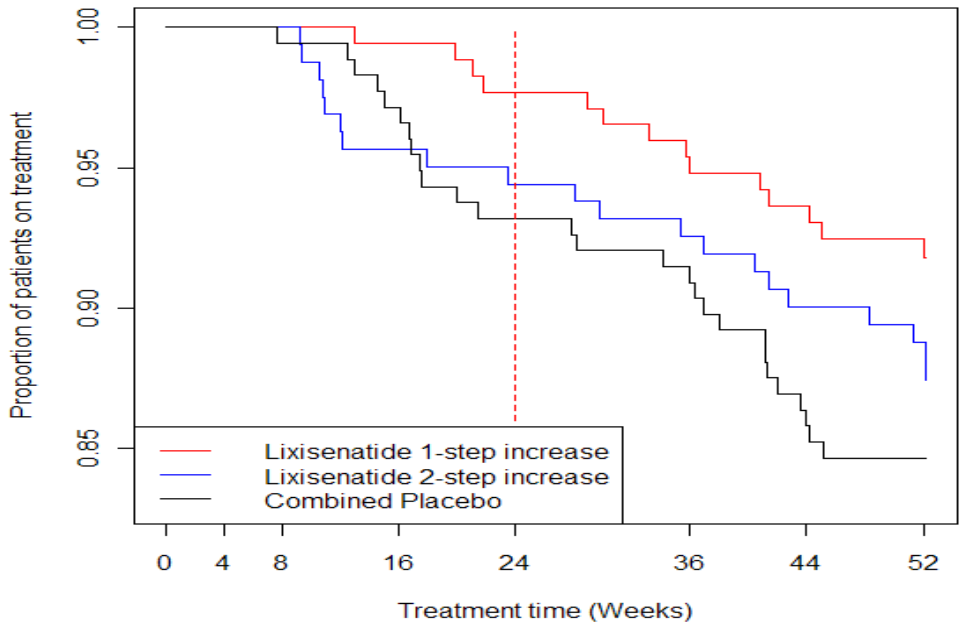
The primary endpoint, absolute change from baseline to week 24 in HbA1c, will be analyzed using an ANCOVA model with treatment groups (two-step titration LIXISENATIDE and placebo arms, one-step titration LIXISENATIDE and placebo arms), randomization strata of screening HbA1c (<8.0, =8.0 %), randomization strata of screening BMI (<30 kg/m2, = 30 kg/m2) values, and country as fixed effects and using the baseline value as a covariate. Both means and adjusted means for each LIXISENATIDE arm and the combined placebo group will be provided as well as 95 % confidence intervals (CI) constructed for adjusted mean differences between each LIXISENATIDE arm and the combined placebo group.

The analysis will be performed using the mITT population and excluding HbA1c values obtained after the addition of rescue medication and/or after the treatment cessation plus 3 days. A stepwise testing procedure will be applied for the primary endpoint in order to control the type I error. First, two-step titration LIXISENATIDE arm will be compared with the combined placebo group. If the test is statistically significant, then one-step titration LIXISENATIDE arm will be compared with the combined placebo group.

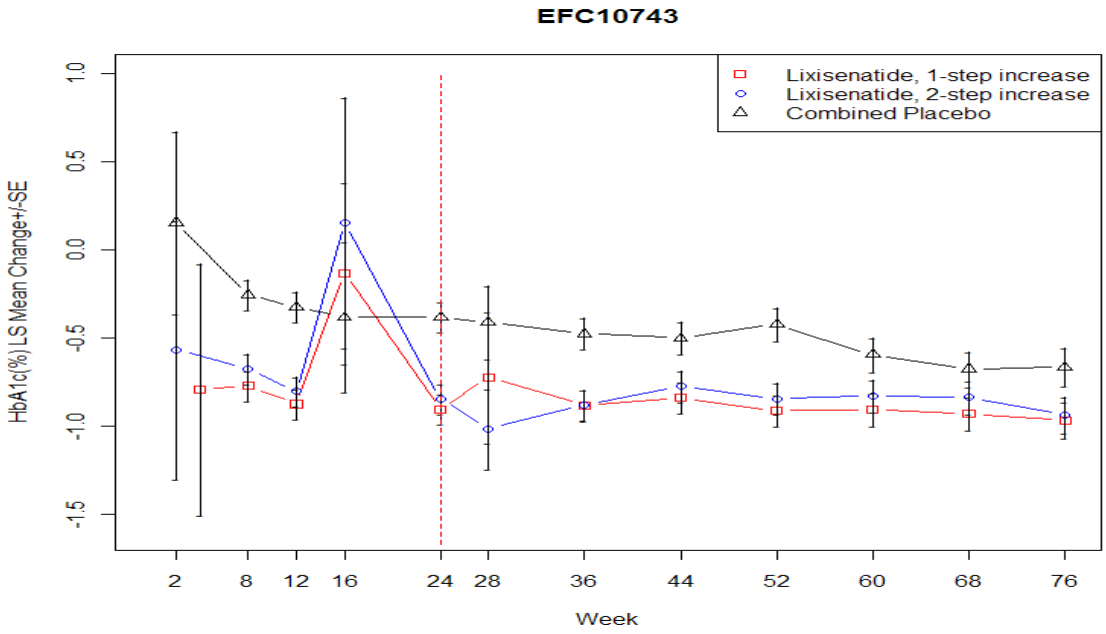
Figure 1 - The overall step-down testing procedure



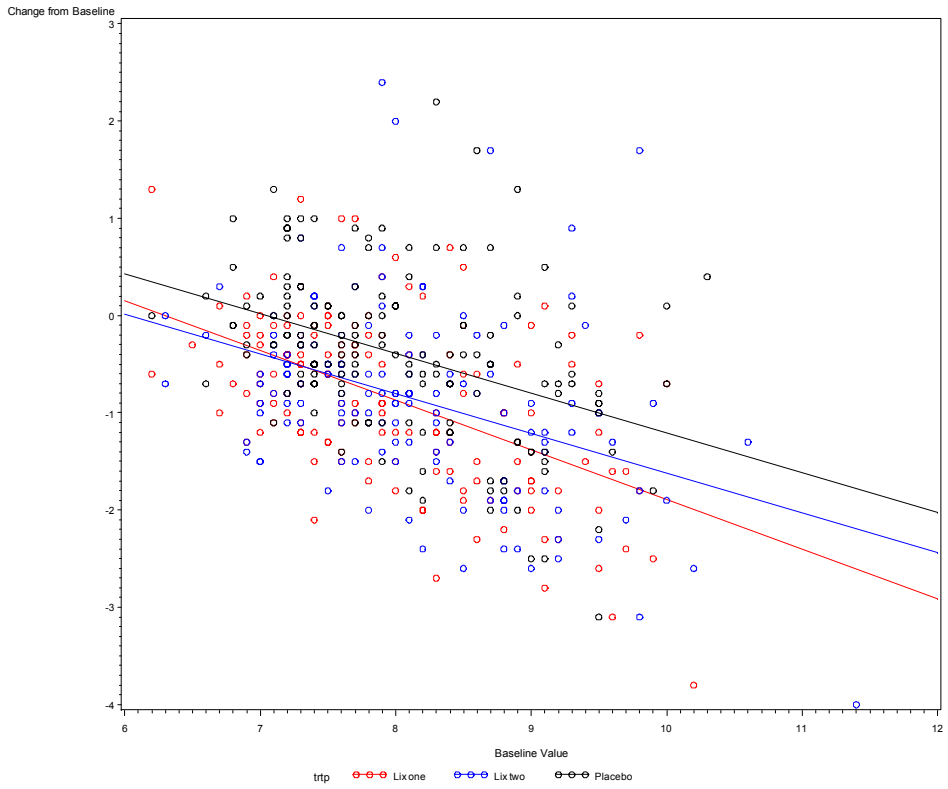
Appendix Figure 6.1. Comparing Time to Dropout during the Treatment Period between Treatment Groups (mITT population, Study EFC10743).



Appendix Figure 6.2. The Time Course of HbA1c Changes from Baseline for Treatment Groups (mITT population) in Study EFC10743 to Week 76.



Appendix Figure 6.3. The Plot of HbA1c Changes from Baseline versus Baseline Levels in Treatments in Study EFC10743 at Week 24 (LOCF).




```
Regression equation :  CHG(trtp:Lix one) =  3.214716 - 0.510428*BASE. (p=0.3575)
Regression equation :  CHG(trtp:Lix two) =  2.471725 - 0.409483*BASE.
Regression equation :  CHG(trtp:Placebo) =  2.87751 - 0.408247*BASE.
```

Appendix 7. EFC11321

Appendix 7.1. Additional study design information (EFC11321)

5. EFC11321: Efficacy and safety of lixisenatide in patients with type 2 diabetes mellitus insufficiently controlled by metformin (with or without sulfonylurea): a multicenter, randomized, double-blind, parallel-group, placebo-controlled study with 24-week treatment period

Patients are stratified by HbA1c (< 8%, ≥ 8%) and sulfonylurea use (Yes, No) at screening, number of patients in each of the sulfonylurea stratum (with sulfonylurea, without sulfonylurea) will be balanced.

The primary efficacy variable (change in HbA1c from baseline to Week 24) will be analyzed using an analysis of covariance (ANCOVA) model with treatment groups (lixisenatide and placebo), randomization strata of screening HbA1c (<8%, =8%), randomization strata of screening sulfonylurea use (Yes, No) and country as fixed effects and using the baseline HbA1c value as a covariate. Both means and adjusted means for lixisenatide and placebo will be provided as well as 95% confidence intervals and p-values for adjusted mean differences between lixisenatide and placebo.

2.4.4.3 Multiplicity issues

To control the type I error, a step-down testing procedure described by Hochberg and Tamhane (3) will be applied.

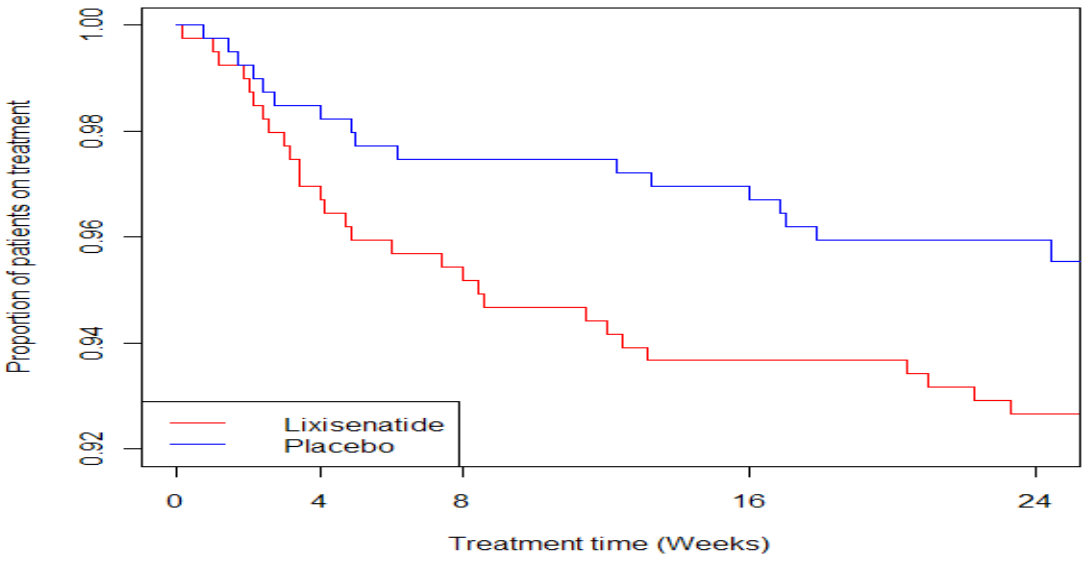
For the primary variable (change from baseline to Week 24 in HbA1c), no multiplicity adjustment is needed to control the type I error since only 1 primary comparison of lixisenatide versus placebo is performed.

Once the primary variable is statistically significant at a=0.05, the testing procedure will be performed to test the following secondary efficacy variables by the following prioritized order. The tests stop as soon as an endpoint is found not statistically significant at a=0.05.
1. Change in 2-hour PPG (mmol/L) after a standardized meal test from baseline to Week 24,
2. Change in FPG (mmol/L) from baseline to Week 24,
3. Change in body weight (kg) from baseline to Week 24,
4. Percentage of patients requiring rescue therapy during the main 24-week double-blind treatment period.

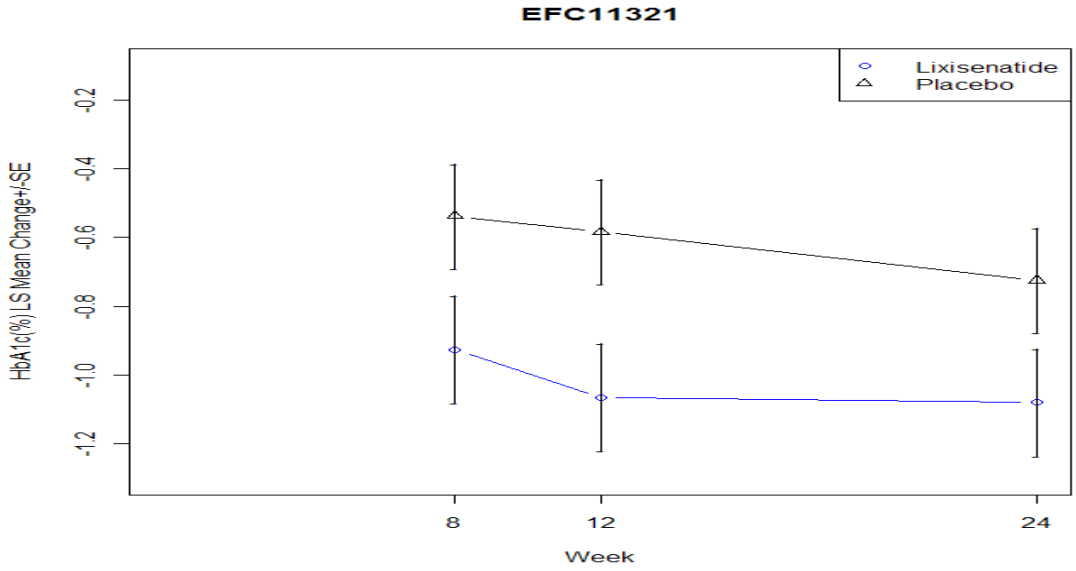
No multiplicity adjustment will be made on other secondary efficacy variables, which are not mentioned above.

Active–controlled study versus exenatide

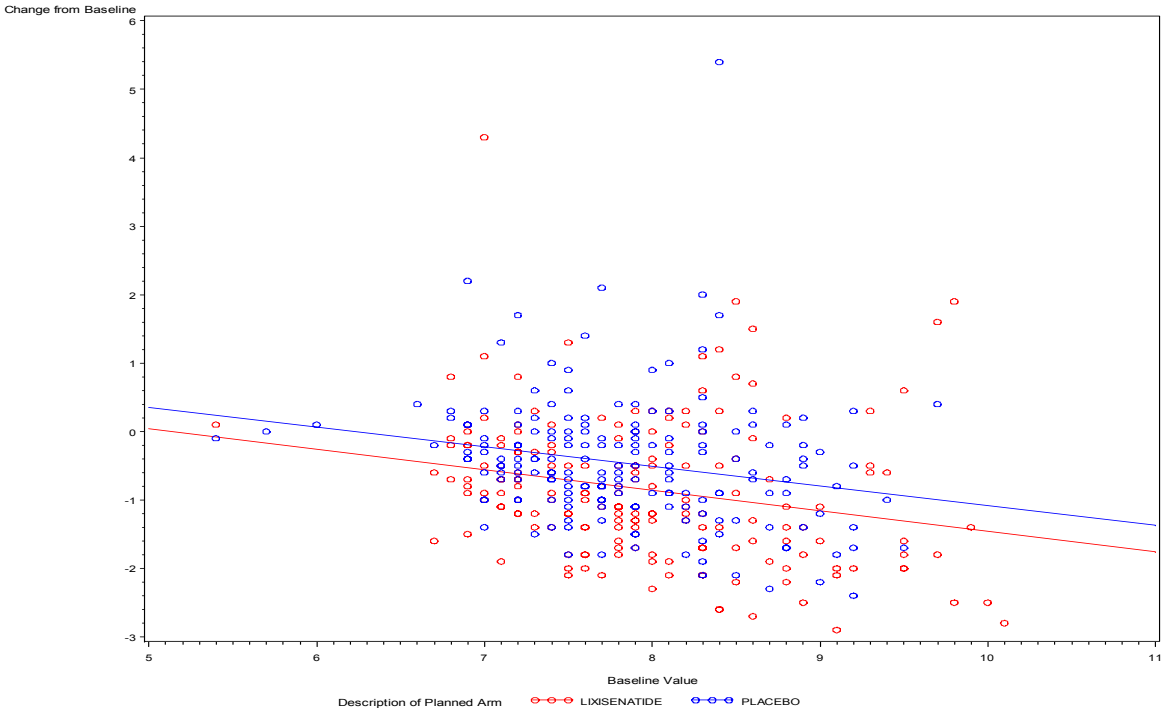
Appendix Figure 7.1. Comparing Time to Dropout during the Treatment Period between Treatment Groups (mITT population, Study EFC11321).



Appendix Figure 7.2. The Time Course of HbA1c Changes from Baseline for Treatment Groups (mITT population) in Study EFC11321 to Week 24.



Appendix Figure 7.3. The Plot of HbA1c Changes from Baseline versus Baseline Levels in Treatments in Study EFC11321 at Week 24.




```
Regression equation :  CHG(ARM:LIXISENATIDE) =  1.53817 - 0.299579*BASE.
Regression equation :  CHG(ARM:PLACEBO) =  1.786111 - 0.286687*BASE.
```

Appendix 8. EFC6019

Appendix 8.1. Additional study design information (EFC6019)

6. **EFC6019**: A randomized, open-label, active-controlled, 2-arm parallel-group, multicenter 24-week study followed by an extension assessing the efficacy and safety of LIXISENATIDE versus exenatide on top of metformin in patients with type 2 diabetes not adequately controlled with metformin. The main treatment period was 24 weeks.

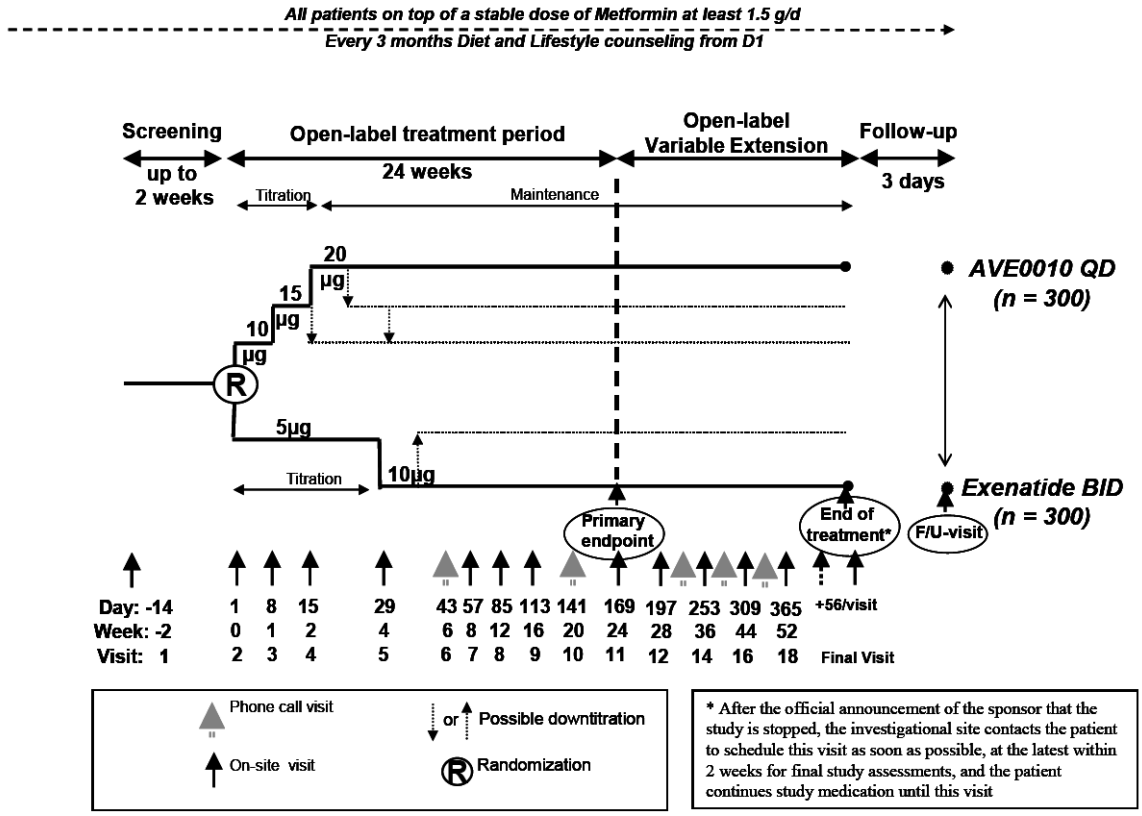
The patients are stratified by screening HbA1c (<8.0%, ≥8.0%) and Body Mass Index (BMI) (<30 kg/m², ≥ 30 kg/m²).

All continuous efficacy parameters including the primary endpoint, change in HbA1c from baseline to Week 24, will be analyzed using an analysis of covariance (ANCOVA) model with treatment, randomization strata of screening HbA1c (<8.0, =8.0%), randomization strata of screening BMI (<30, =30 kg/m²) and country as fixed effects and using the baseline value as a covariate. Differences between lixisenatide and exenatide and 2-sided 95% confidence intervals will be estimated within the framework of ANCOVA.

To assess non-inferiority, the upper bound of the 2-sided 95% confidence interval for the difference in the adjusted mean change in HbA1c from baseline to Week 24 between lixisenatide and exenatide is compared with the predefined non-inferiority margin of 0.4% HbA1c. Non-inferiority will be demonstrated if the upper bound of the 2-sided 95% confidence interval of the difference between lixisenatide and exenatide on mITT population is =0.4%.

In case of discontinuation of study drug before Week 24, HbA1c will be assessed at the time of discontinuation. The LOCF procedure will be used by taking this last available post-baseline on-treatment HbA1c measurement (before the initiation of the new medication in the event of rescue therapy) as the HbA1c value at Week 24. It should be noted that the baseline observation, defined as the last assessment prior to the first injection of the investigational product, is not carried forward to fill in post-baseline missing on-treatment observations.

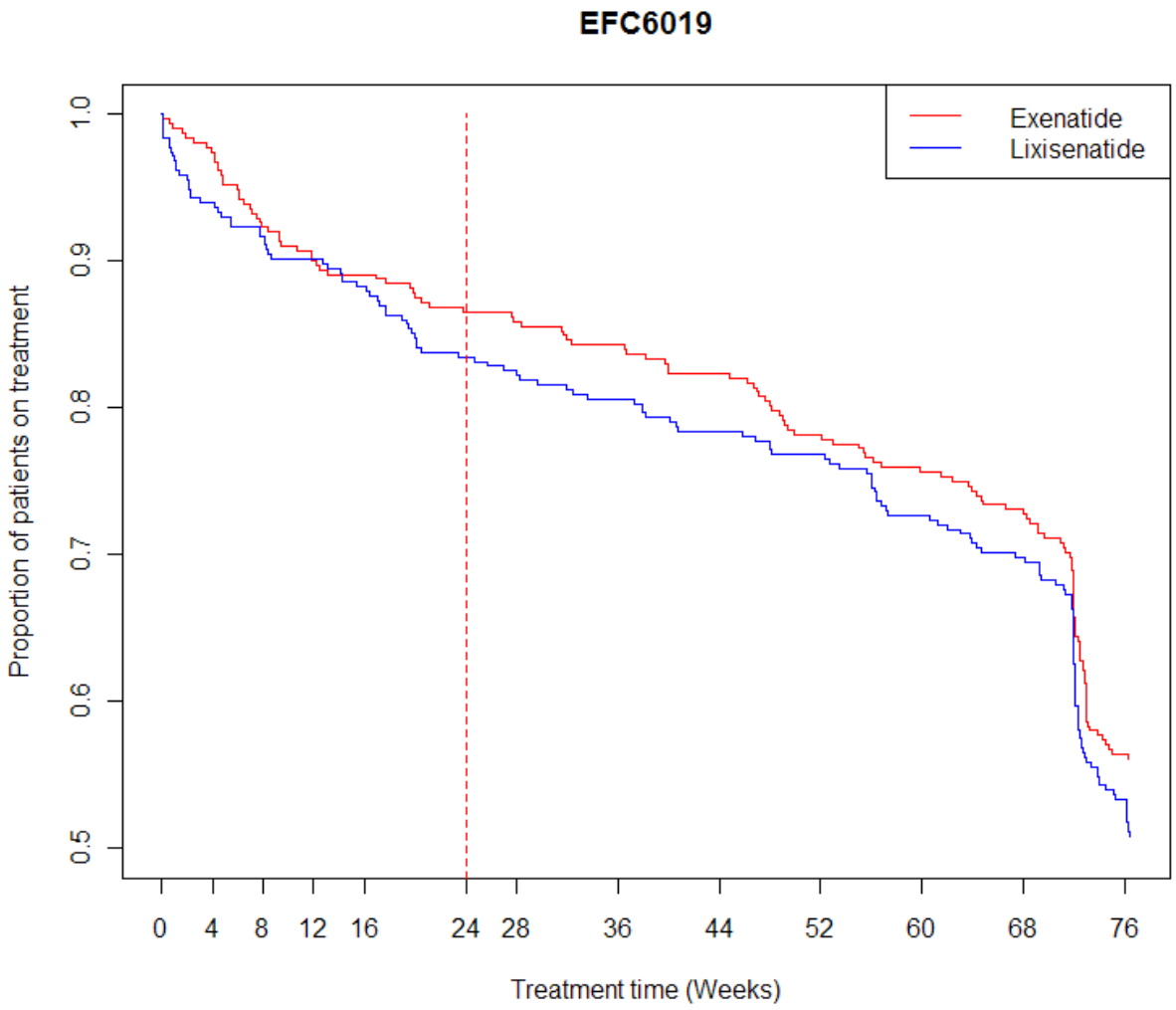
If non-inferiority is established, then a corresponding check of statistical superiority would be performed for primary endpoint.



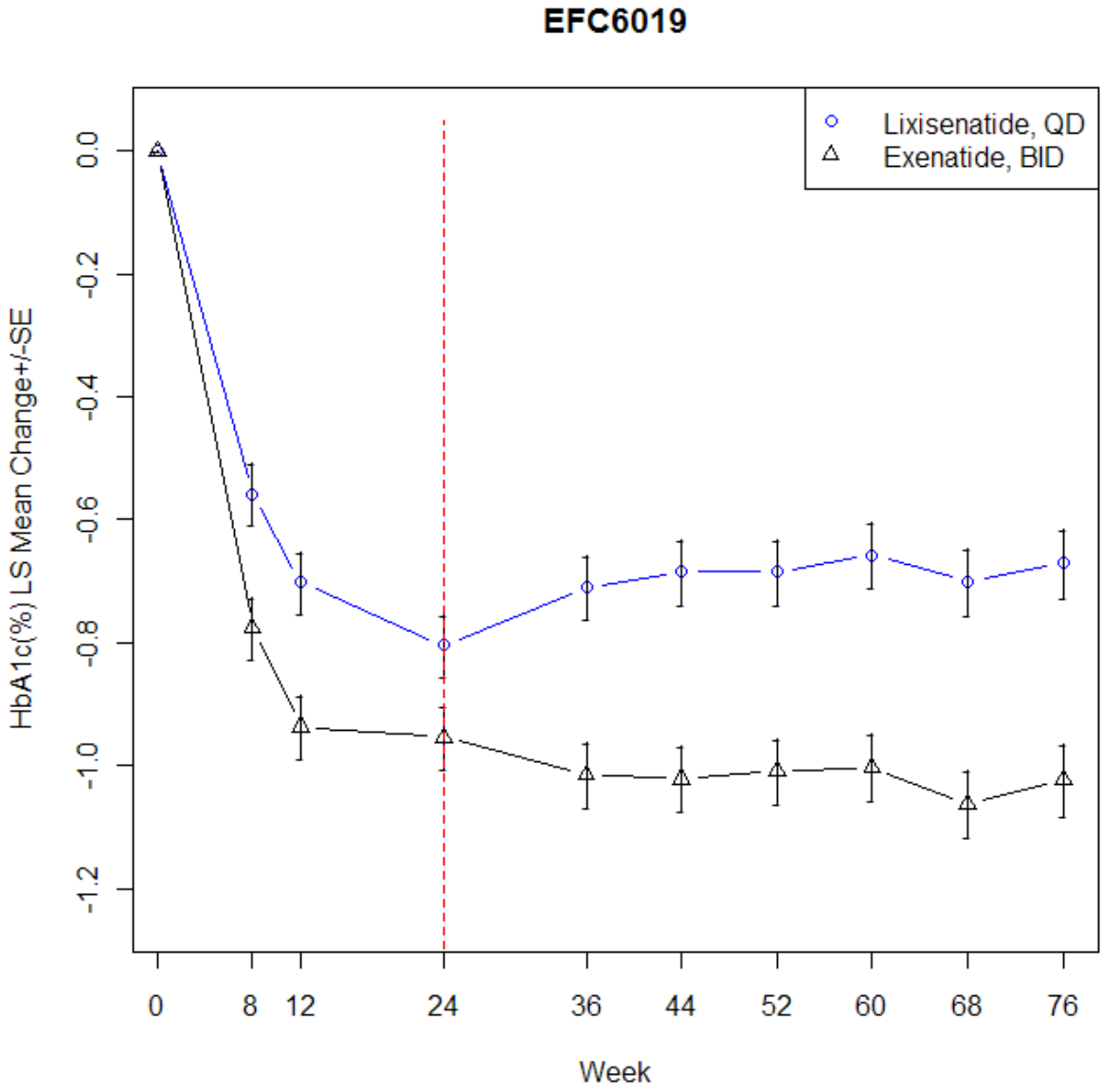
Multiplicity issues

For the primary efficacy variable, the step down procedure will be used by testing the non-inferiority first. Only if non-inferiority is established, then a superiority test will be performed. No formal statistical test will be performed for all secondary efficacy endpoints.

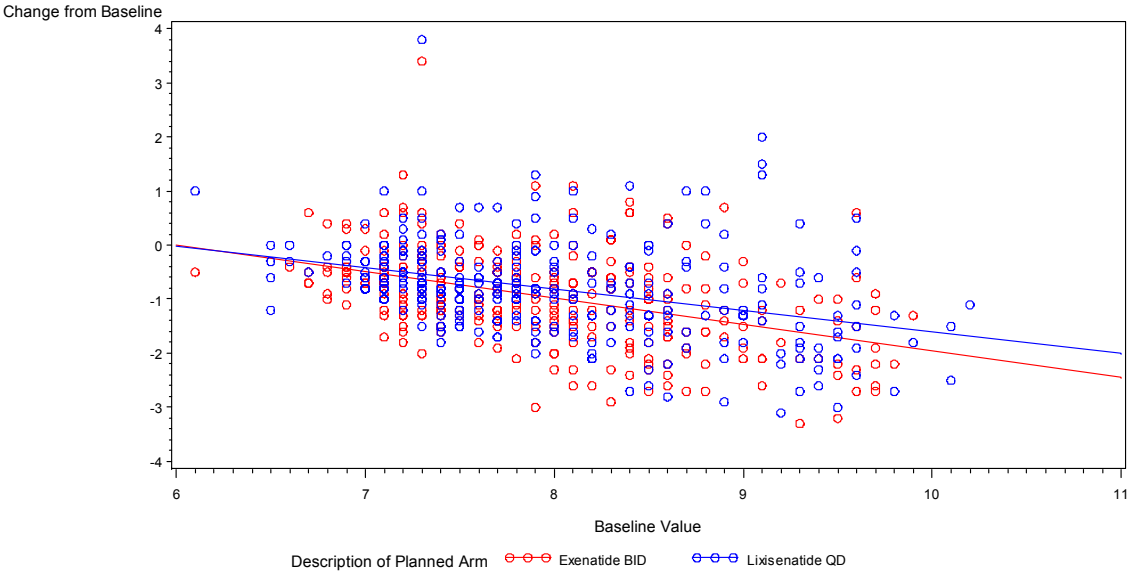
Appendix Figure 8.1. Comparing Time to Dropout during the Treatment Period between Treatment Groups (mITT population, Study EFC6019).



Appendix Figure 8.2. The Time Course of HbA1c Changes from Baseline for Treatment Groups (mITT population) in Study EFC6019 to Week 76.



Appendix Figure 8.3. The Plot of HbA1c Changes from Baseline versus Baseline Levels in Treatments in Study EFC6019 at Week24.




```
Regression equation :  CHG(ARM:Exenatide BID) =  2.92775 - 0.487687*BASE.
Regression equation :  CHG(ARM:Lixisenatide QD) =  2.363923 - 0.396994*BASE
```

Appendix 9. EFC6015

Appendix 9. Additional study design information (EFC6015)

14.4 Add-on combination therapy to a sulfonylurea (alone or in combination with metformin)

7. **EFC6015**: A randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter 24-week study followed by an extension assessing the efficacy and safety of LIXISENATIDE on top of a sulfonylurea in patients with type 2 diabetes not adequately controlled with sulfonylurea. The main treatment period was 24 weeks.

Randomization of patients was stratified by screening values of HbA1c (<8 %, ≥8%) and metformin use (Yes, No).

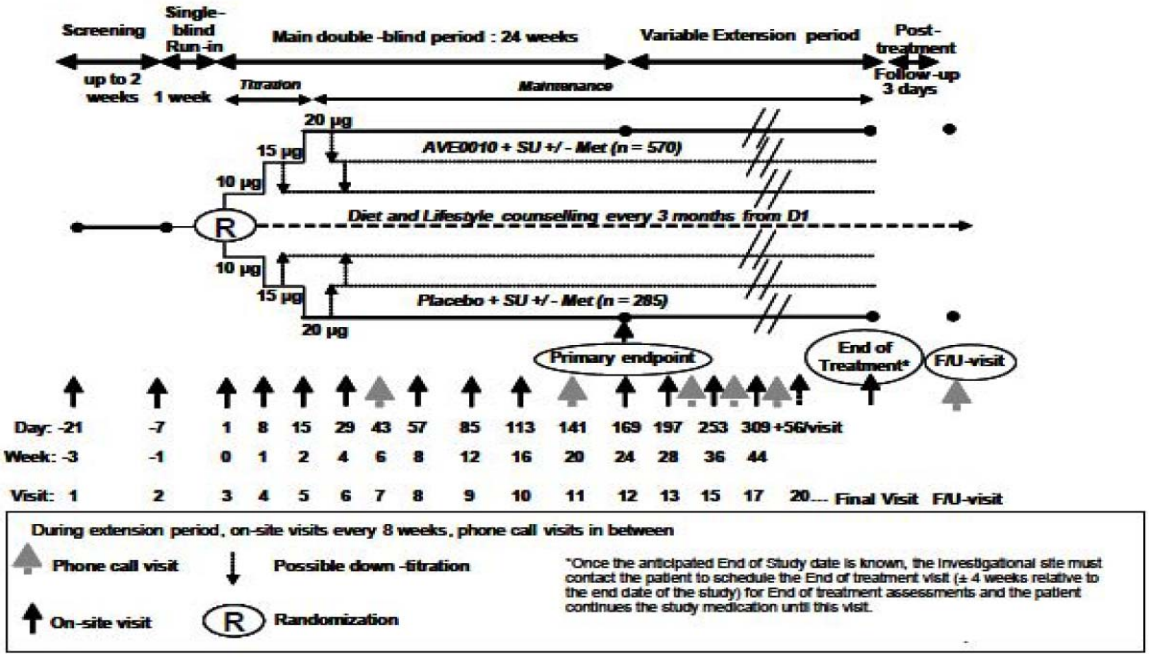
The primary efficacy endpoint (the absolute change in HbA1c from baseline to Week 24) was analyzed using an analysis of covariance (ANCOVA) model with treatment (lixisenatide or placebo), randomization strata (screening HbA1c [<8.0%, =8.0%], and screening metformin use [yes, no]), and country as fixed effects and using the baseline HbA1c as a covariate.

A stepwise testing procedure was applied in order to ensure control of type 1 error.

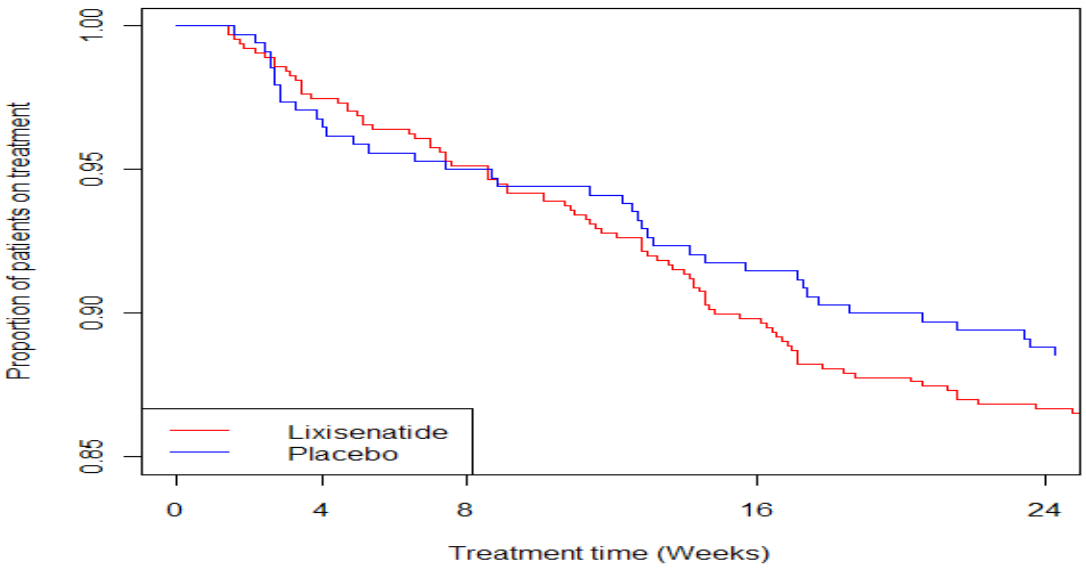
Once the primary variable is statistically significant at a=0.05, the testing procedure will be performed to test the following secondary efficacy variables by the following prioritized order. The tests stop as soon as an endpoint is found not statistically significant at a=0.05.

1. Change in 2-hour postprandial plasma glucose (mmol/L) after a standardized meal test from baseline to Week 24,
2. Change in FPG (mmol/L) from baseline to Week 24,
3. Change in body weight (kg) from baseline to Week 24,
4. Change in ß-cell function assessed by HOMA-ß from baseline to Week 24,
5. Percentage of patients requiring rescue therapy during the main 24-week double-blind treatment period.

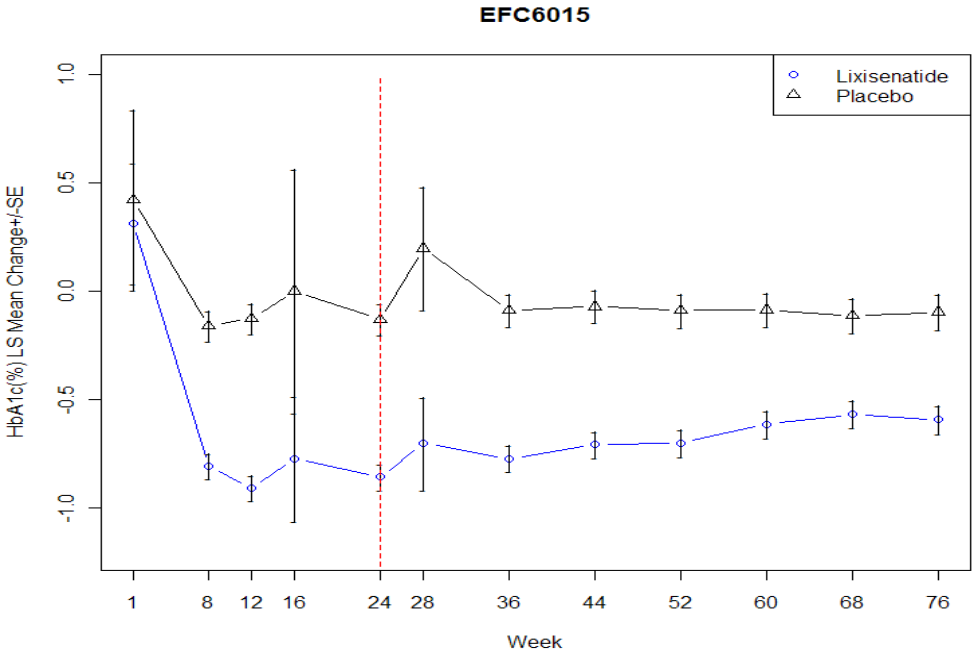
No multiplicity adjustment will be made on other secondary efficacy variables, which are not mentioned above.



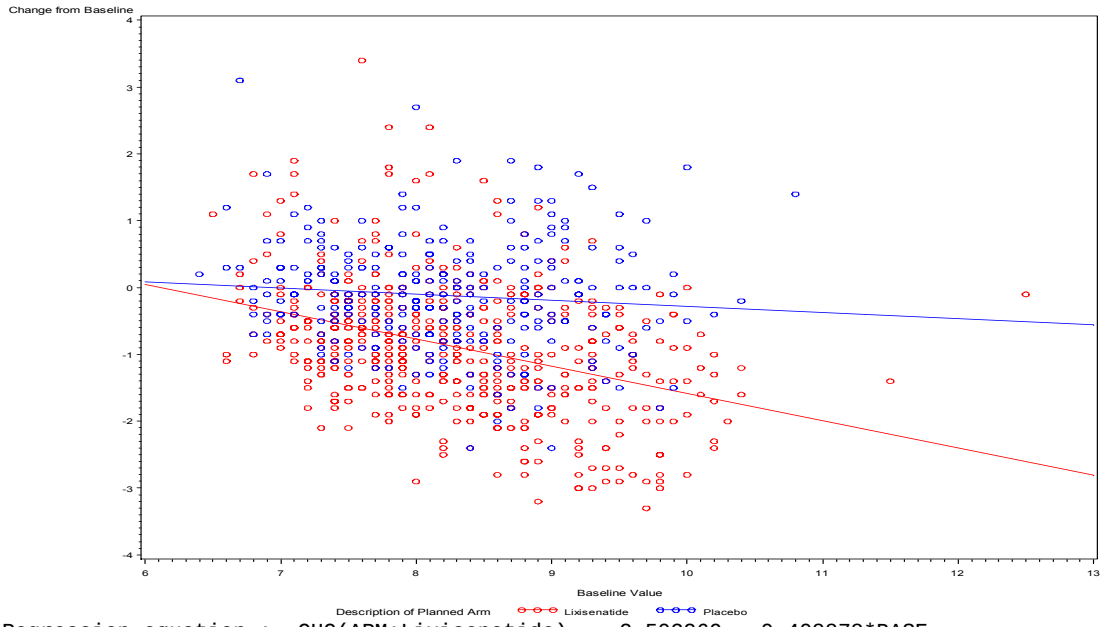
Appendix Figure 9.1. Comparing Time to Dropout during the Treatment Period between Treatment Groups (mITT population, Study EFC6015).



Appendix Figure 9.2. The Time Course of HbA1c Changes from Baseline for Treatment Groups (mITT population) in Study EFC6015 to Week 76.



Appendix Figure 9.3. The Plot of HbA1c Changes from Baseline versus Baseline Levels in Treatments in Study EFC6015 at Week 24.



Regression equation : CHG(ARM:Lixisenatide) = 2.503269 - 0.408878*BASE.
Regression equation : CHG(ARM:Placebo) = 0.641992 - 0.092349*BASE.

Appendix 10. EFC6017

Appendix 7.1. Additional study design information (EFC6017)

14.5 Add-on treatment to pioglitazone (alone or in combination with metformin)

8. **EFC6017**: A randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week main treatment period and an extension assessing the efficacy and safety of LIXISENATIDE on top of pioglitazone in patients with type 2 diabetes not adequately controlled with pioglitazone. The main treatment period was 24 weeks.

Patients are stratified by HbA1c (<8 %, ≥ 8 %) and metformin use (Yes, No) at screening.

The primary efficacy variable (change in HbA1c from baseline to Week 24) will be analyzed using an analysis of covariance (ANCOVA) model with treatment groups (lixisenatide and placebo), randomization strata of screening HbA1c (<8.0, =8.0%), randomization strata of metformin use (Yes, No) at screening, and country as fixed effects and the baseline HbA1c value as a covariate. Both means and adjusted means for lixisenatide and placebo will be provided as well as 95% confidence intervals (CI) constructed for adjusted mean differences between lixisenatide and placebo.

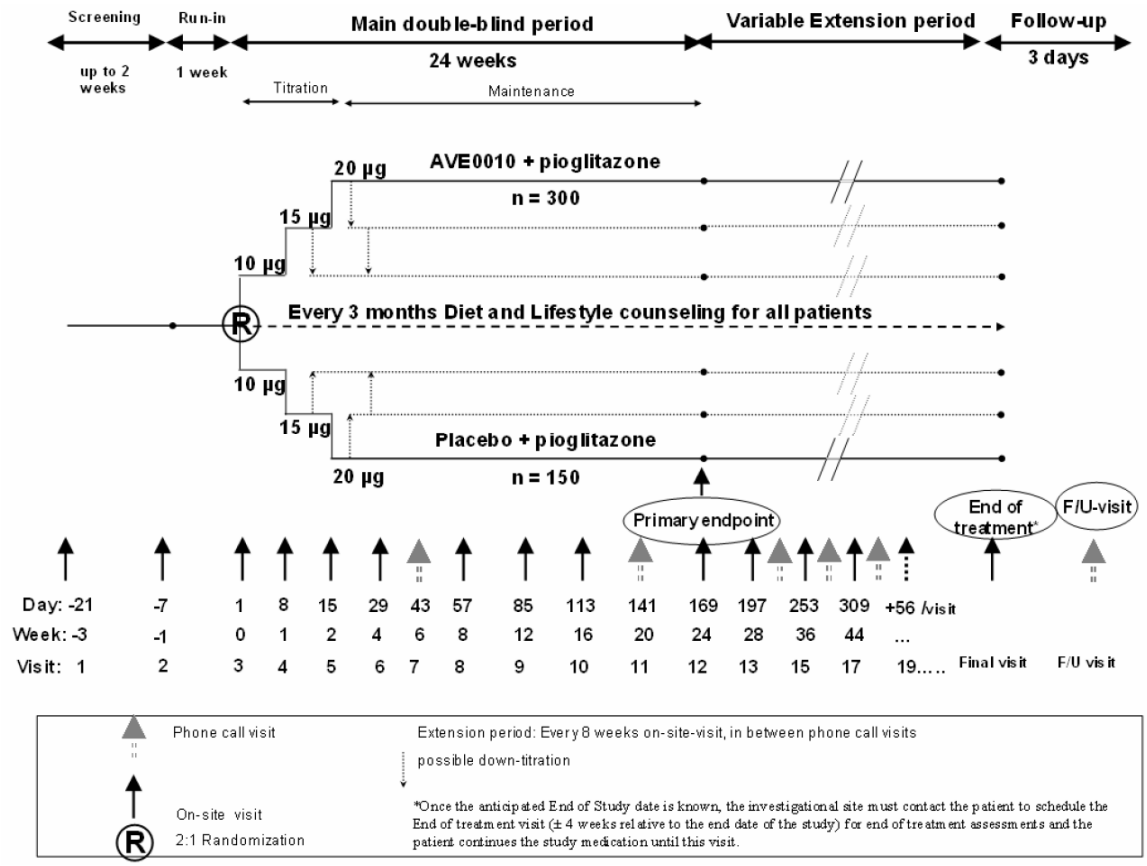
Per a comment from a Health Authority, 2 additional secondary/sensitivity analyses were added: a mixed-effect model with repeated measures (MMRM) under the missing at random frame work, and the 24-week completers analysis for the primary endpoint (HbA1c change from baseline at Week 24).

The MMRM model included the fixed-effect factors for treatment groups, visit, treatment-by-visit interaction, randomization strata of screening HbA1c (<8%, =8%), randomization strata of metformin use at screening (yes, no), country, and baseline HbA1c-by-visit interaction. The factor visit had 3 levels (Visit 8, Visit 9, and Visit 12). The adjusted means of change in HbA1c from baseline to Week 24 for each treatment group were estimated using this model. The 95% CI was constructed for the adjusted mean difference of the lixisenatide treatment group compared with the placebo treatment group. This model was run using SAS Mixed procedure (PROC MIXED®) with an unstructured correlation matrix to model the within-patient errors. Parameters were estimated using a restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom was estimated using a Kenward-Roger approximation by fitting values from all postrandomization visits in the main 24-week double-blind treatment period. This model used all scheduled HbA1c measurements obtained during the main 24-week double-blind treatment period and before the introduction of rescue medication. Any unscheduled measurements were excluded from the analysis.

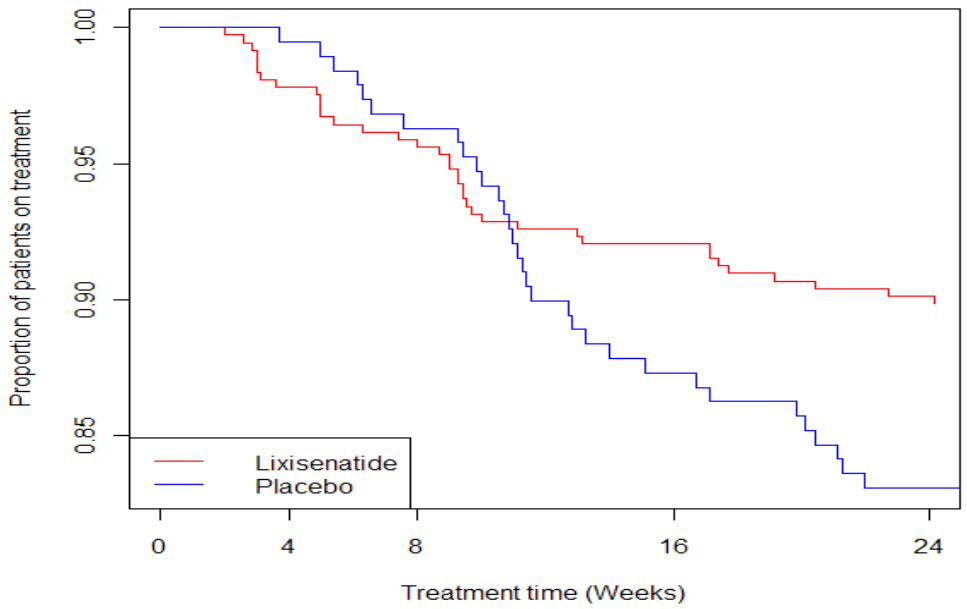
Multiplicity issues

To control the type I error, a step-down testing procedure described by Hochberg and Tamhane (3) will be applied.

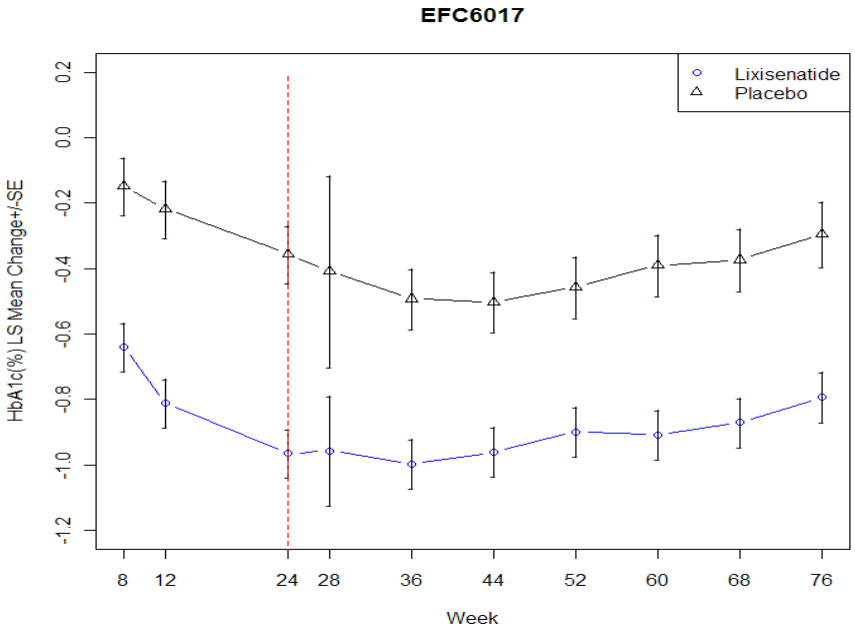
For the primary variable (change from baseline to Week 24 in HbA1c), no multiplicity adjustment is needed to control the type I error since only 1 primary comparison of lixisenatide versus placebo is performed.
Once the primary variable is statistically significant at a=0.05, the testing procedure will be performed to test the following secondary efficacy variables by the following prioritized order.
The tests stop as soon as an endpoint is found not statistically significant at a=0.05.
• Change in FPG (mmol/L) from baseline to Week 24,
• Change in body weight (kg) from baseline to Week 24,
• Change in ß-cell function assessed by HOMA-ß from baseline to Week 24,
• Percentage of patients requiring rescue therapy during the 24-week treatment period,
• Change in FPI (mmol/L) from baseline to Week 24.
No multiplicity adjustment will be made on other secondary efficacy variables than those mentioned above.



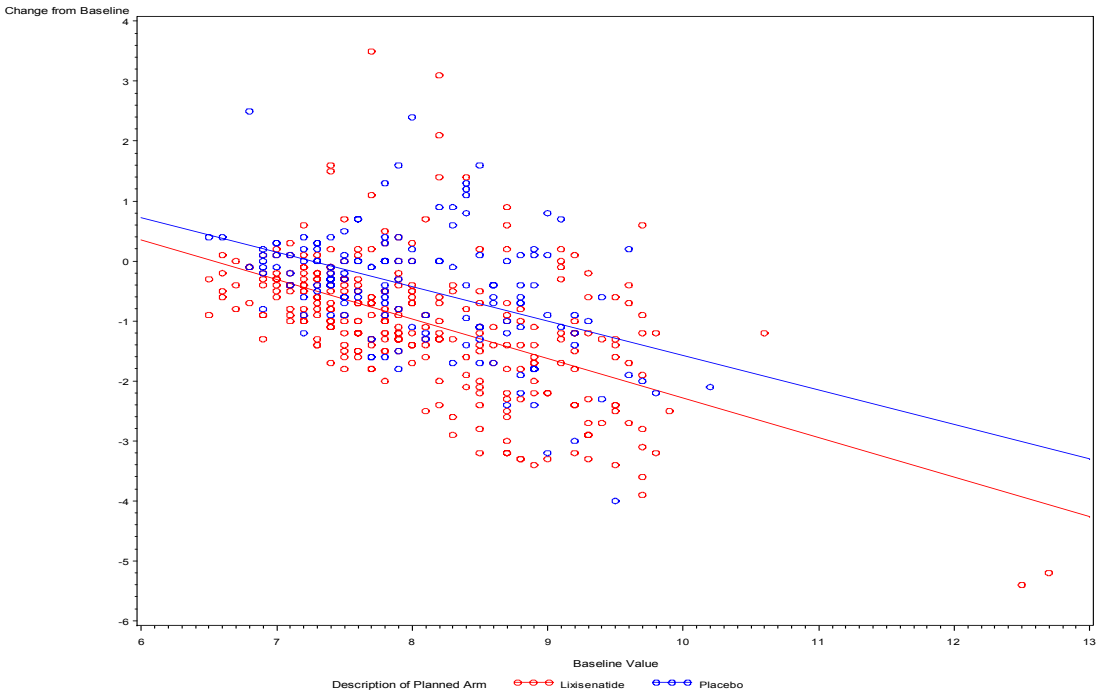
Appendix Figure 10.1. Comparing Time to Dropout during the Treatment Period between Treatment Groups (mITT population, Study EFC6017).



Appendix Figure 10.2. The Time Course of HbA1c Changes from Baseline for Treatment Groups (mITT population) in Study EFC6018 to Week 76.



Appendix Figure 10.3. The Plot of HbA1c Changes from Baseline versus Baseline Levels in Treatments in Study EFC6017 at Week 24.




```
Regression equation :  CHG(ARM:Lixisenatide) =  4.304149 - 0.659237*BASE.
Regression equation :  CHG(ARM:Placebo) =  4.158507 - 0.573452*BASE.
```

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/s/

WEI LIU
08/19/2013

MARK D ROTHMANN
08/19/2013
I concur