Sep 26 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#	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
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Keywords: subgroup analyses

Table of Contents

1 EXECUTIVE SUMMARY

This review examined existing data to assess the treatment effect of lixisenatide on change in HbA1c from baseline within each sex, age, race, and ethnicity subgroup and whether the treatment effect of lixisenatide on change in HbA1c from baseline differs by sex, age, race, or ethnicity. We acknowledge that the analyses provided in this review are exploratory and the trials were not designed to support such investigations. Despite possible statistical limitations, these investigations were undertaken in the interest of transparency and to provide as much information regarding subgroup differences as is possible using the available data.

This review concludes that

- For subgroup analyses by sex,
    - Lixisenatide is superior to placebo with respect to the change in HbA1c from baseline within each sex.
    - Lixisenatide is or is supposed to be (based on similarity in response across subgroups) non-inferior to exenatide BID and insulin glargine QD and TID within each sex.
    - Available data did not give a strong indication that the treatment effect for lixisenatide is larger in one sex than the other.

- For subgroup analyses by age group (< 65, ≥ 65 years of age),
    - Lixisenatide is superior to placebo with respect to the change in HbA1c from baseline within each age group.
    - Lixisenatide is or is supposed to be (based on similarity in response across subgroups) non-inferior to exenatide BID and insulin glargine QD and TID within each age group.
    - Available data did not give a strong indication that the treatment effect for lixisenatide is larger in one age group than the other.

- For subgroup analyses by race,
    - Lixisenatide is superior to placebo with respect to the change in HbA1c from baseline within each race group.
    - Lixisenatide is non-inferior to exenatide BID and insulin glargine QD and TID within white patients. It is not feasible to make conclusions about race subgroups other than white based on the active-controlled studies, since the majority of patients in the two active-controlled studies are white.
    - In the pooled placebo-controlled studies, it appeared that the treatment effect within the Asian subgroup was slightly bigger than that within the white subgroup (-0.66 versus -0.40, p-value=0.003).

- For subgroup analyses by ethnic group (Hispanic, Non-Hispanic),

- Lixisenatide is superior to placebo with respect to the change in HbA1c from baseline within each ethnic group.
- Lixisenatide is or is supposed to be (based on similarity in response across subgroups) non-inferior to exenatide BID and insulin glargine QD and TID within each ethnicity group.
- Available data did not give a strong indication that the treatment effect for lixisenatide is larger in one ethnic group than the other.

2 INTRODUCTION

This document is written as part of a pilot partnership between Division of Biometrics 2 and the Patient Advocacy and Stakeholder Engagement (PASE) group. The objective of this statistical review is to advise PASE in using existing data to understand the effects of lixisenatide within age, sex, racial, and ethnic subgroups and whether these effects differ across subgroups.

3 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

3.1 Available Data

The applicant proposed and the Agency has approved lixisenatide for use to improve glycemic control in adults with Type 2 Diabetes Mellitus (T2DM).

The applicant provided results of eight placebo-controlled and two active-controlled phase 3 trials conducted to evaluate the efficacy of lixisenatide in patients with T2DM.

The placebo-controlled studies were all multinational, multicenter, randomized, double-blind, parallel-group. The active-controlled studies were multinational, multicenter, randomized, open-label, parallel-group. Key features of these studies were summarized in Table 1. In all studies, the efficacy of lixisenatide was evaluated in terms of HbA1c reduction from baseline to the end of the main treatment period. The placebo-controlled studies were designed as superiority studies. Lixisenatide was used as a monotherapy and with a variety of background therapies. The active-controlled studies were designed as non-inferiority studies. The active comparators were exenatide BID, insulin glargine QD and insulin glargine TID respectively. The pre-specified non-inferiority margin was 0.4% for all comparisons. Consistent with product labeling, these ten phase 3 trials are the basis of the efficacy portion of the "drug snapshot" and the evaluation of whether treatment effects vary across subgroups. Comparisons of HbA1c reduction in the lixisenatide group versus the control group in each of the studies is summarized in Table 2.

Table 1 – Study Designs

Study	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 **EFC10743**	Placebo Lixisenatide 2-step Lixisenatide 1-step	162 (80+82) 161 161	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
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.

Table 2 – Efficacy Results for HbA1c (% change from baseline)

Study	Primary Hypothesis	Treatment Groups	Treatment Difference (Lixisenatide– Control)	
			LS Mean	95% CI
Placebo-controlled, Double-blinded				
Monotherapy **EFC6018**	superiority	Placebo Lixisenatide[1]	-0.65	(-0.903, -0.399)
Add-on to Met alone **EFC10743**	superiority	Placebo Lixisenatide[1]	-0.46	(-0.640, -0.279)
Add-on to SU or SU+Met **EFC6015**	superiority	Placebo Lixisenatide	-0.58	(-0.715, -0.453)
Add-on to Pio or PIO+Met **EFC6017**	superiority	Placebo Lixisenatide	-0.48	(-0.647, -0.318)
Add-on to BI or BI+Met **EFC6016**	superiority	Placebo Lixisenatide	-0.36	(-0.557, -0.170)
Add-on IG+Met or IG+Met+TZD **EFC10781**	superiority	Placebo Lixisenatide	-0.28	(-0.434, -0.123)
Add-on to BI or BI+SU **EFC10887**	superiority	Placebo Lixisenatide	-0.76	(-1.005, -0.516)
Add-on to Met or Met+SU **EFC11321**	superiority	Placebo Lixisenatide	-0.27	(-0.447, -0.090)
Active-controlled, Open-label				
Add-on to Met alone **EFC6019**	Non-inferiority	Exenatide Lixisenatide	0.17	(0.030 to 0.314)
Add-on to IG or IG+Met **EFC12626**	Non-inferiority	Insulin glargine QD Insulin glargine TID Lixisenatide	-0.04 0.23	(-0.161 to 0.080) (0.112 to 0.352)
1. Only the results from 1-step regime were included in Section 14 of the product label.				

Met = Metformin, SU = Sulfonylurea, Pio = Pioglitazone, BI = Basal insulin, IG = Insulin glargine, TZD = Thiazolidinediones.

3.2 Statistical Methods for Assessing Differences in Treatment Effect across Subgroups

In planning analyses to assess differences in treatment effect across subgroups, the merits of combining studies to provide increased power for small subgroups were weighed against the merits of analyzing all studies separately so as not to miss possible clinical settings where differences in treatment effect across subgroups differ for different populations, dosing styles or background therapy. While we acknowledge that differences in the treatment effect across differing populations, dosing styles, or background therapies are possible, even likely, we note that consistency in the treatment effect across studies is not needed to justify combining studies for the purpose of identifying subgroups where the treatment effect differs. The objective of this review and these analyses is different from assessing the overall efficacy of the product. It is to characterize the differences in treatment effect across subgroups. The important assumption of this type of combined analysis is that if there are differences in the treatment effect between certain subgroups these differences by subgroup should be similar in studies with different populations, dosing styles or background therapy. For example if the treatment effect for lixisenatide in males is larger than that of females in patients with metformin alone, combining this study with a study of patients with a different background therapy is more agreeable if the treatment effect for lixisenatide is also larger for males than females in patients with the different background therapy. We believe that in general this type of assumption is much more likely to be true than the assumption that the overall treatment effect is similar across different populations, dosing styles or background therapy.

As a result of the afore-mentioned considerations, subgroup analyses will be performed on pooled data from all eight placebo-controlled studies. For EFC6018 and EFC10743, only one-step lixisenatide titration arm was included in the analyses consistent with Section 14 of the product label. In addition, subgroup analyses will be performed on the two active-controlled studies individually, since it is not suitable to pool studies with different control groups. These analyses were requested from and provided by the applicant.

In the original application, the treatment effect of lixisenatide (difference in LS mean change from baseline in HbA1c between treatment groups) for the individual trials was estimated from an ANCOVA model with randomization strata, treatment and country as fixed factors, and baseline HbA1c as covariates. Superiority was considered confirmed if the upper bound of the two-sided 95% confidence interval was below 0%. Non-inferiority was considered confirmed if the upper bound of the two-sided 95% confidence interval was below or equal to 0.4%.

Subgroup analyses were conducted for the following factors:

- Sex (Male, Female);

- Age group (< 65, ≥ 65 years of age);
- Race (Caucasian/White, Black, Asian/Oriental, Other);
- Ethnicity (Hispanic, Non-Hispanic);

1. For the individual active-controlled studies (EFC6019 and EFC12626):
   The treatment effect of lixisenatide relative to the active comparator within subgroups was estimated by fitting the ANCOVA model for each subgroup separately. The difference in treatment effect between subgroups was tested by a treatment-by-subgroup interaction. When performing the test for treatment by sub-group interaction, the ANCOVA model was extended with the factor subgroup and a term for treatment by subgroup interaction.

2. All placebo-controlled efficacy studies in Section 14 of the product label combined (8 studies):
   First, for each individual study the treatment effect of lixisenatide relative to placebo within subgroups was estimated by fitting the ANCOVA model for each subgroup separately. The overall treatment effect of lixisenatide relative to placebo within subgroups was estimated by combining the estimates from the individual studies inversely weighted by their variances. The test for treatment by subgroup interaction was performed using the same model and approach as described for the individual trials with the exception that the model was extended with interaction terms with study for each factor and covariate as used in the model for individual trials (e.g. including subgroup by study interaction, treatment-by-study interaction, and baseline HbA1c-by-study interaction).
   Since Studies EFC10887 and EFC11321 were conducted in Asia (ie, Asian patients only), the subgroup analyses by race or ethnicity were performed based on the pooled data of other 6 global studies.

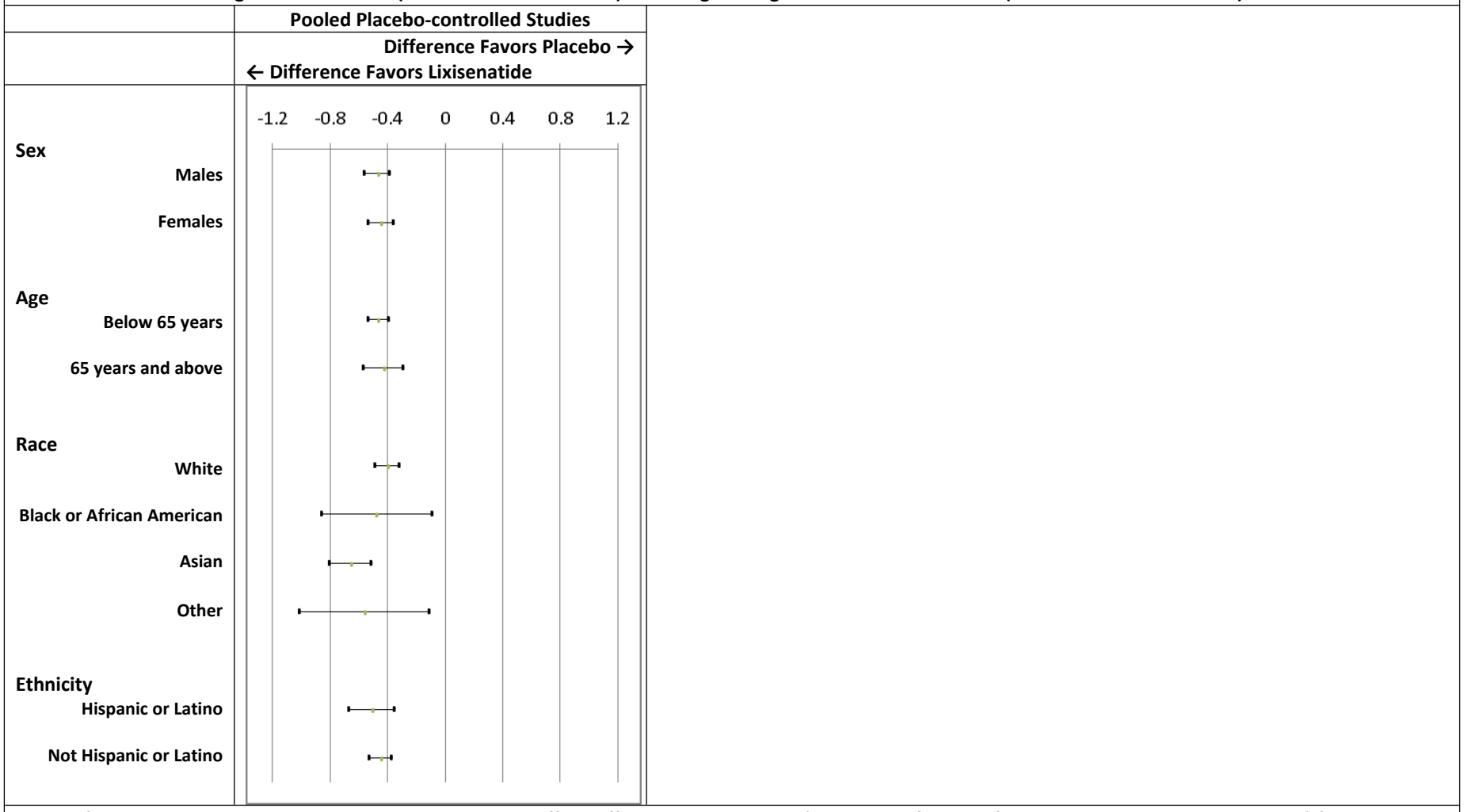
We acknowledge that these analyses are exploratory and the trials were not designed to support such investigations. In general, these comparisons may be limited by multiplicity and low power considerations. Consistency in the differences in treatment effect across subgroups by study is qualitatively examined as a means to minimize (but albeit not eliminate) possible type I errors due to multiple analyses. Despite these possible statistical limitations associated with multiplicity and low power, these investigations are undertaken in the interest of transparency and to provide as much information regarding subgroup differences as is possible using the available data.

3.3 Results by Sex, Race, Age, and Ethnicity

This section provides estimates of the difference between TRESIBA and the active comparators in LSMEAN change from baseline in HbA1c by sex, race, age, and ethnicity subgroups. Approximate 95% confidence intervals for treatment differences within each subgroup were constructed using normal quantiles. Tests for the treatment-by-subgroup interaction are also provided.

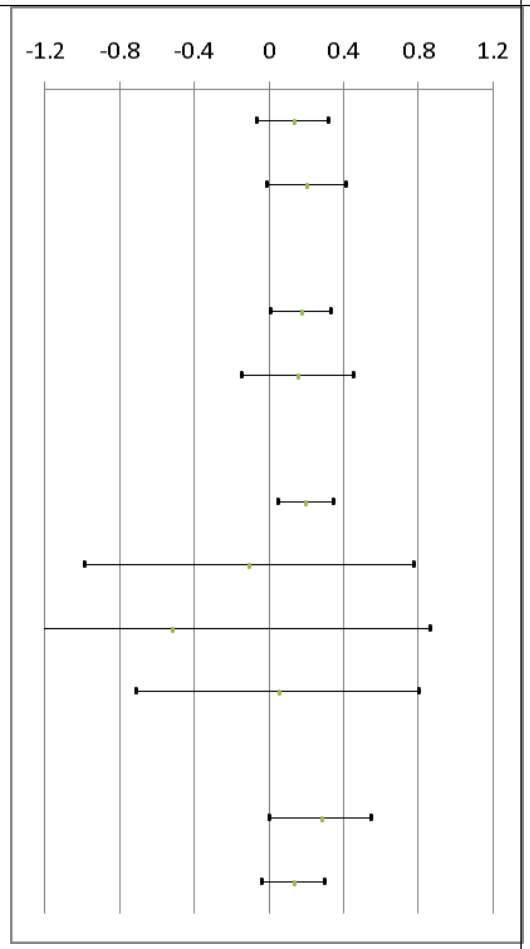
Figure 1 displays results for pooled placebo-controlled studies and two individual active-controlled studies including 3 active comparators in total.

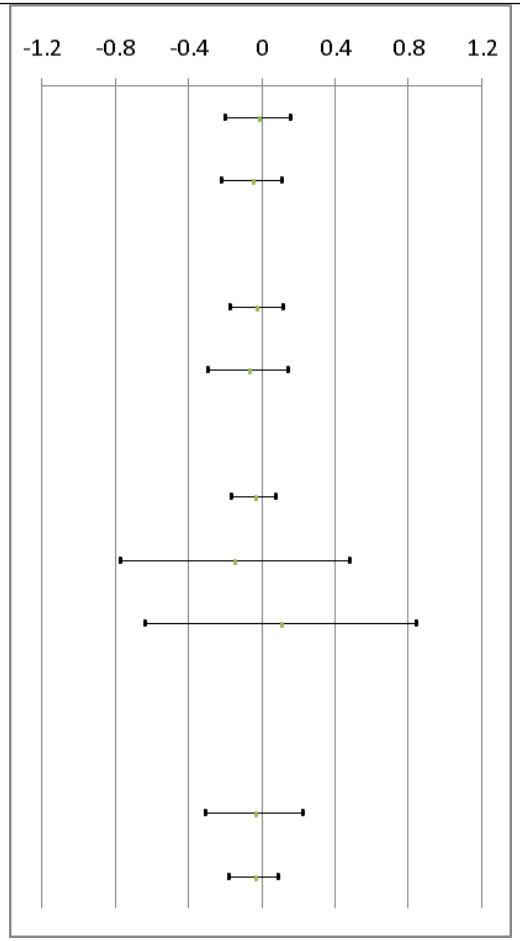
Figure 1: Difference (95% Confidence Interval) in Average Change from Baseline in HbA1c (lixisenatide minus control)

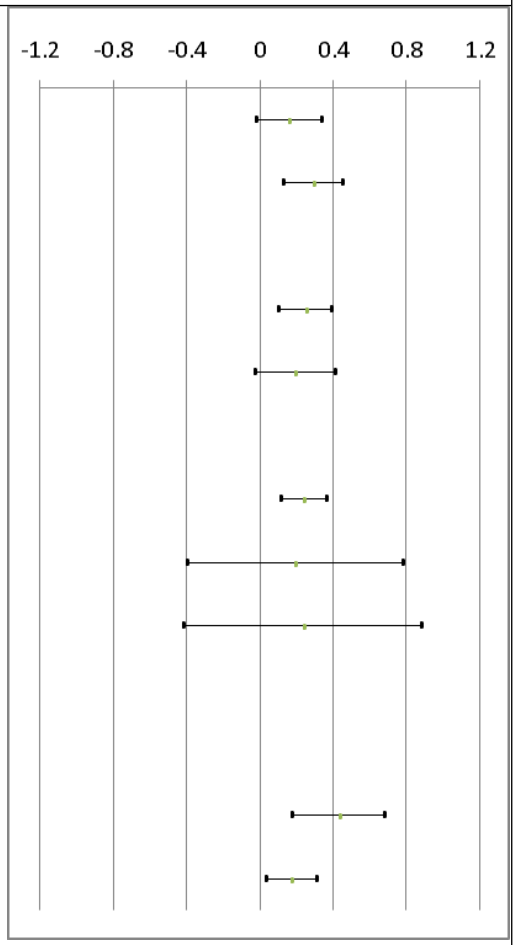


P-value for statistical test measuring whether the treatment effect differs across subgroups (i.e., p-value for test of treatment-by-subgroup interaction) for pooled placebo-controlled studies: Sex: 0.11; Age: 0.06; Race: 0.03; Ethnicity: 0.17. Since studies EFC10887 and EFC11321 were conducted in Asia (i.e., Asian patients only), the estimates for race were based on 6 global placebo-controlled studies only.

	Study EFC6019 (versus Exenatide BID)	Study EFC12626 (versus insulin glargine QD)	Study EFC12626 (versus insulin glargine TID)
	Difference Favors Comparator → ← Difference Favors Lixisenatide	Difference Favors Comparator → ← Difference Favors Lixisenatide	Difference Favors Comparator → ← Difference Favors Lixisenatide
Sex			
Males			
Females			
Age			
Below 65 years			
65 years and above			
Race			
White			
Black or African American			
Asian			
Other			
Ethnicity			
Hispanic or Latino			
Not Hispanic or Latino			







P-value for statistical test measuring whether the treatment effect differs across subgroups for Study EFC6019: Sex: 0.07; Age: 0.09; Race: 0.52; Ethnicity: 0.25, and for Study EFC12626: Sex: 0.38; Age: 0.07; Race: 0.85; Ethnicity: 0.13.

Examination of treatment effect by sex: There is evidence that lixisenatide is superior to placebo with respect to the change in HbA1c from baseline within each sex, based on results from pooled placebo-controlled studies. The upper bound of 95% confidence interval for the treatment effect was below 0 within each sex. There is also evidence that lixisenatide is non-inferior to exenatide BID and insulin glargine QD and TID within each sex. In some individual non-inferiority studies, the upper bound of 95% confidence interval for the treatment effect was slightly greater than the non-inferiority margin 0.4%. This is likely because the small sample size within the subgroup did not provide enough precision in the estimate to satisfy the formal non-inferiority test and is not thought to be an indication that the true underlying difference between lixisenatide and the active comparator exceeds 0.4% in that subgroup.

No study gave a strong indication that the treatment effect for TRESIBA is larger in one sex than the other as is evidenced by the p-values associated with the treatment-by-sex interaction.

Examination of treatment effect by age : There is evidence that lixisenatide is superior to placebo with respect to the change in HbA1c from baseline within each age group, based on results from pooled placebo-controlled studies. The upper bound of 95% confidence interval for the treatment effect was below 0 within each age group. There is also evidence that lixisenatide is non-inferior to exenatide BID and insulin glargine QD and TID within each age group. In some individual non-inferiority studies, the upper bound of 95% confidence interval for the treatment effect was slightly greater than the non-inferiority margin 0.4%. This is likely because the small sample size within the subgroup did not provide enough precision in the estimate to satisfy the formal non-inferiority test and is not thought to be an indication that the true underlying difference between lixisenatide and the active comparator exceeds 0.4% in that subgroup.

No study gave a strong indication that the treatment effect for lixisenatide is larger in one age group than the other as is evidenced by the p-values associated with the treatment-by-age interaction.

Examination of treatment effect by race: There is evidence that lixisenatide is superior to placebo with respect to the change in HbA1c from baseline within each race group, based on results from pooled 6 global placebo-controlled studies. Studies EFC10887 and EFC11321 were conducted in Asia (i.e., Asian patients only). The upper bound of 95% confidence interval for the treatment effect was below 0 within each race group. The majority of patients in the two active-controlled studies are white. There is evidence that lixisenatide is non-inferior to exenatide BID and insulin glargine QD and TID within white patients. The estimates for the other races had very wide confidence intervals due to small sample sizes. Therefore, it is not feasible to make conclusions about race subgroups other than white based on the active-controlled studies.

In the pooled placebo-controlled studies, there is some evidence that the treatment effect for lixisenatide differs between at least two races as suggested by the overall p-value associated

with the treatment-by-race interaction (p-value = 0.03). It appeared that the treatment effect within the Asian subgroup was bigger than that within the white subgroup (-0.66 versus -0.40, p-value = 0.003). The potential difference was quantitative rather than qualitative.

Examination of treatment effect by ethnicity: There is evidence that lixisenatide is superior to placebo with respect to the change in HbA1c from baseline within each ethnic group, based on results from pooled placebo-controlled studies. The upper bound of 95% confidence interval for the treatment effect was below 0 within each age group. There is also evidence that lixisenatide is non-inferior to exenatide BID and insulin glargine QD and TID within each ethnic group. In some individual non-inferiority studies, the upper bound of 95% confidence interval for the treatment effect was greater than the non-inferiority margin 0.4%. This is likely because the small sample size within the subgroup did not provide enough precision in the estimate to satisfy the formal non-inferiority test and is not thought to be an indication that the true underlying difference between lixisenatide and the active comparator exceeds 0.4% in that subgroup.

No study gave a strong indication that the treatment effect for lixisenatide is larger in one ethnic group than the other as is evidenced by the p-values associated with the treatment-by-ethnicity interaction.

4. SUMMARY AND CONCLUSIONS

This review examined existing data to assess the treatment effect of lixisenatide on change in HbA1c from baseline within each sex, age, race, and ethnicity subgroup and whether the treatment effect of lixisenatide on change in HbA1c from baseline differs by sex, age, race, or ethnicity. We acknowledge that the analyses provided in this review are exploratory and the trials were not designed to support such investigations. Despite possible statistical limitations, these investigations were undertaken in the interest of transparency and to provide as much information regarding subgroup differences as is possible using the available data.

This review concludes that

- For subgroup analyses by sex,
    - Lixisenatide is superior to placebo with respect to the change in HbA1c from baseline within each sex.
    - Lixisenatide is or is supposed to be (based on similarity in response across subgroups) non-inferior to exenatide BID and insulin glargine QD and TID within each sex.
    - Available data did not give a strong indication that the treatment effect for lixisenatide is larger in one sex than the other.

- For subgroup analyses by age group (< 65, ≥ 65 years of age),
    - Lixisenatide is superior to placebo with respect to the change in HbA1c from baseline within each age group.
    - Lixisenatide is or is supposed to be (based on similarity in response across subgroups) non-inferior to exenatide BID and insulin glargine QD and TID within each age group.
    - Available data did not give a strong indication that the treatment effect for lixisenatide is larger in one age group than the other.

- For subgroup analyses by race,
    - Lixisenatide is superior to placebo with respect to the change in HbA1c from baseline within each race group.
    - Lixisenatide is non-inferior to exenatide BID and insulin glargine QD and TID within white patients. It is not feasible to make conclusions about race subgroups other than white based on the active-controlled studies, since the majority of patients in the two active-controlled studies are white.
    - In the pooled placebo-controlled studies, it appeared that the treatment effect within the Asian subgroup was slightly bigger than that within the white subgroup (-0.66 versus -0.40, p-value=0.003).

- For subgroup analyses by ethnic group (Hispanic, Non-Hispanic),

- Lixisenatide is superior to placebo with respect to the change in HbA1c from baseline within each ethnic group.
- Lixisenatide is or is supposed to be (based on similarity in response across subgroups) non-inferior to exenatide BID and insulin glargine QD and TID within each ethnicity group.
- Available data did not give a strong indication that the treatment effect for lixisenatide is larger in one ethnic group than the other.

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/s/

JIWEI HE
08/29/2016

MARK D ROTHMANN
08/29/2016
I concur