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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA#	203314
Drug Name:	Tresiba (insulin degludec U100 and U200)
Indication(s):	To improve glycemic control in adults with diabetes mellitus
Applicant:	Novo Nordisk
Date(s):	Stamp date: 26 Mar 2015 Review due date: 31 Aug 2015 PDUFA date: 26 Sep 2015
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Biometrics Division:	II
Statistical Reviewer:	Jiwei He, PhD
Concurring Statistical Reviewers:	Ruthanna Davi, PhD Thomas Permutt, PhD Mark Rothmann, PhD
Medical Division:	Metabolism and Endocrinology Products
Clinical Team:	Tania Condarco, MD, Medical Officer Lisa Yanoff, MD, Team Leader Jean-Marc Guettier, MD, Division Director
Project Manager:	Callie CappelLynch
Professional Affairs and Stakeholder Engagement Team:	Naomi Lowy, MD, Medical Officer

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1 EXECUTIVE SUMMARY

This review examined existing data to assess the treatment effect of TRESIBA on change in HbA1c from baseline within each sex, age, race, and ethnicity subgroup and whether the treatment effect of TRESIBA 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

- TRESIBA is non-inferior to insulin glargine with respect to the change in HbA1c from baseline within each sex for patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). TRESIBA is also non-inferior to insulin detemir within each sex with respect to the change in HbA1c in patients with T1DM. TRESIBA is statistically significantly better than Sitagliptin with respect to the change in HbA1c for both sexes in patients with T2DM. Available data did not give a strong indication that the treatment effect for TRESIBA is larger in one sex than the other.

- TRESIBA is or is supposed to be (based on similarity in response across subgroups) non-inferior to insulin glargine with respect to the change in HbA1c from baseline within each age group (below 65 years, and 65 years and above) for patients with T1DM and T2DM. TRESIBA is non-inferior to insulin detemir for those less than 65 years old and or is supposed to be (based on similarity in response across subgroups) for those 65 years old or older with T1DM. TRESIBA is statistically significantly better than Sitagliptin with respect to the change in HbA1c for those less than 65 years old and is supposed to be (based on similarity in response across subgroups) for those 65 years old and older with T2DM. Available data did not give a strong indication that the treatment effect for TRESIBA is larger in one age group than the other.

- TRESIBA is non-inferior to insulin glargine with respect to the change in HbA1c from baseline within T1DM White patients. Patients in the T1DM insulin glargine studies were almost exclusively White so that no assessment of the treatment effect of TRESIBA relative to insulin glargine in T1DM in other races can be made without borrowing information from White patients. TRESIBA is non-inferior to insulin glargine in all racial groups (White, Black or African American, Asian, and other) for patients with T2DM. TRESIBA is non-inferior to insulin detemir for both racial groups studied, White and

Asian patients, with respect to the change in HbA1c in patients with T1DM. TRESIBA is statistically significantly better than Sitagliptin with respect to the change in HbA1c for most racial groups (White, Asian, and other) and is supposed to be (based on similarity in response across subgroups) for Black or African American patients with T2DM. Available data did not give a strong indication that the treatment effect for TRESIBA is different for any race.

- TRESIBA is or is supposed to be (based on similarity in response across subgroups) non-inferior to insulin glargine with respect to the change in HbA1c from baseline within each ethnicity group (Hispanic or Latino and Not Hispanic or Latino) for patients with T1DM and T2DM. TRESIBA is non-inferior to insulin detemir for patients who are not Hispanic or Latino and is supposed to be (based on similarity in response across subgroups) for Hispanic or Latino patients with T1DM. TRESIBA is statistically significantly better than Sitagliptin with respect to the change in HbA1c for patients who are not Hispanic or Latino and is supposed to be (based on similarity in response across subgroups) for Hispanic or Latino patients with T2DM. Available data did not give a strong indication that the treatment effect for TRESIBA is different for any race.

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 TRESIBA 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[1] TRESIBA for use to improve glycemic control in adults with diabetes mellitus.

The applicant provided results of three phase 3 trials (referred to in this document as studies A, B, and C) conducted to evaluate the efficacy of TRESIBA in patients with type 1 diabetes, and six phase 3 trials (referred to in the document as studies D through I) conducted to evaluate the efficacy of TRESIBA in patients with type 2 diabetes.

The nine studies were all multinational, multicenter, randomized, open-label, parallel-group,

[1] http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/203314Orig1s000ltr.pdf

active-controlled, treat-to-target trials. Key features of these studies are summarized in Table 1. In all studies, the efficacy of TRESIBA was evaluated in terms of HbA1c reduction from baseline to the end of blinded treatment. With the exception of study I, a superiority study, all studies were designed as noninferiority studies. The active comparators were LANTUS (insulin glargine 100 U/mL), LEVEMIR (insulin detemir, 100 U/mL) and Sitagliptin (100 mg). In Studies A-C, TRESIBA was administered once-daily either at the same time each day or at any time each day in patients with type 1 diabetes and used in combination with a mealtime insulin. In Studies D-I, TRESIBA was administered once-daily either at the same time each day or at any time each day in patients with type 2 diabetes and used in combination with a mealtime insulin or in combination with common oral anti-diabetic agents. Consistent with product labeling, these nine 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 overall group and assessment of the noninferiority of TRESIBA to the active comparator in each of the studies is summarized in Table 2.

Table 1 – Study Designs

Study	Background medication	Blinded Trt. Duration (Weeks)	Treatment Groups	Randomized patients
Type 1 Diabetes Mellitus (T1DM)				
3583 (A)	IAsp	52	TRESIBA (IDeg 100) IGlar	472 157
3585 (B)	IAsp	26	TRESIBA (IDeg 100) IDet	303 153
3770 (C)	IAsp	26	TRESIBA (IDeg 100 Flex) TRESIBA (IDeg 100) IGlar	164 165 164
Type 2 Diabetes Mellitus (T2DM)				
3579 (D)	metformin ± DPP-4 inhibitor	52	TRESIBA (IDeg 100) IGlar	773 257
3672 (E)	metformin ± DPP-4 inhibitor	26	TRESIBA (IDeg 200) IGlar	230 230
3586 (F)	± metformin ± SU/glinide ± α-GI	26	TRESIBA (IDeg 100) IGlar	289 146
3668 (G)	± metformin ± SU/glinide ± pioglitazone	26	TRESIBA (IDeg 100 Flex) TRESIBA (IDeg 100) IGlar	229 228 230
3582 (H)	IAsp ± metformin ± pioglitazone	52	TRESIBA (IDeg 100) IGlar	755 251
3580 (I)	± metformin ± SU/glinide ± pioglitazone	26	TRESIBA (IDeg 100 Flex) Sitagliptin	229 229
IDeg 100 – insulin degludec 100 U/mL; IDeg 100 Flex – insulin degludec 100 U/mL at alternating times; IDeg 200 – insulin degludec 200 U/mL; IGlar - insulin glargine 100 U/mL; IDet - insulin detemir 100 U/mL; IAsp- NovoRapid/NovoLog 100 U/mL.				

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

Study	Primary Hypothesis	Treatment Groups	Treatment Difference (TRESIBA – Control)	
			LS Mean	95% CI
Type 1 Diabetes Mellitus (T1DM)				
3583 (A)	Non-inferiority	TRESIBA (IDeg 100) IGlar	-0.01	(-0.14, 0.12)
3585 (B)	Non-inferiority	TRESIBA (IDeg 100) IDet	-0.08	(-0.23, 0.06)
3770 (C)	Non-inferiority	TRESIBA (IDeg 100 Flex) TRESIBA (IDeg 100) IGlar	+0.17 +0.17	(0.04, 0.31) (0.04, 0.30)
Type 2 Diabetes Mellitus (T2DM)				
3579 (D)	Non-inferiority	TRESIBA (IDeg 100) IGlar	+0.08	(-0.05, 0.21)
3672 (E)	Non-inferiority	TRESIBA (IDeg 200) IGlar	+0.05	(-0.11, 0.20)
3586 (F)	Non-inferiority	TRESIBA (IDeg 100) IGlar	+0.08	(-0.05, 0.22)
3668 (G)	Non-inferiority	TRESIBA (IDeg 100 Flex) TRESIBA (IDeg 100) IGlar	+0.04 +0.18	(-0.12, 0.19) (0.02, 0.33)
3582 (H)	Non-inferiority	TRESIBA (IDeg 100) IGlar	+0.07	(-0.06, 0.20)
3580 (I)	Superiority	TRESIBA (IDeg 100 Flex) Sitagliptin	-0.44	(-0.62, -0.25)

IDeg 100 – insulin degludec 100 U/mL; IDeg 100 Flex – insulin degludec 100 U/mL at alternating times; IDeg 200 – insulin degludec 200 U/mL; IGlar - insulin glargine 100 U/mL; IDet - insulin detemir 100 U/mL; IAsp- NovoRapid/NovoLog 100 U/mL.

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 TRESIBA in males is larger than that of females in patients with type 1 diabetes and fixed time dosing, combining this study with a study of patients with type 1 diabetes and alternating time dosing is more agreeable if the treatment effect for TRESIBA is also larger for males than females in patients with type 1 diabetes and alternating time dosing. 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 of each study (A-I) and dosing style were considered individually. In addition the following combinations of studies were considered:

- The two studies in patients with type 1 diabetes with insulin glargine as the active comparator (Studies A, C)
- The five studies in patients with type 2 diabetes with insulin glargine as the active comparator (Studies D, E, F, G, H)

These analyses were requested from and provided by the applicant.

In the original application, the treatment effect of TRESIBA (difference in LSMEAN change from baseline in HbA1c between treatment groups) for the individual trials was estimated from an ANCOVA model with treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age and baseline HbA1c as covariates. Non-inferiority was considered confirmed if the upper bound of the two-sided 95% confidence interval was below or equal to 0.4%. Superiority was considered confirmed if the upper bound of the two-sided 95% confidence interval was below 0%.

For each individual study, the treatment effect of TRESIBA relative to the active comparator within subgroups was estimated by fitting the ANCOVA model for each sub-group separately. To avoid computational issues, treatment effects were only estimated for subgroups where there were at least four subjects in each treatment group. The difference in treatment effect between subgroups was tested by a treatment by sub-group interaction. When performing the test for treatment by sub-group interaction, the ANCOVA model was extended with the factor sub-group and a term for treatment by sub-group interaction. Again only subjects in subgroup levels with at least 4 subjects in each treatment group were included. For the three-arm studies that include an arm where TRESIBA administered at a flexible time (Studies C and G), the two TRESIBA arms were combined into one TRESIBA arm, and the ANCOVA model also included dosing style as a factor.

In all cases where studies are combined, the treatment effect of TRESIBA relative to the active comparator within subgroups was estimated by combining the estimates from the individual studies inversely weighted by their variances. The test for treatment by sub-group 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 sub-group by study interaction and treatment by study interaction). For combinations of studies that include TRESIBA administered at a flexible time, the two TRESIBA arms were combined and dosing style was adjusted in the ANCOVA model as described above for the individual studies. For consistency, when estimating treatment effect and testing for treatment by sub-group interaction in the combination of studies, only subjects from sub-group levels within studies with at least 4 subjects in each treatment arm were included in the analysis, as no estimate was calculated for individual trials where less than 4 subjects contributed.

The factor antidiabetic therapy at screening was defined differently across trials due to the difference in the populations studied in the program. Despite the differences between trials in how this factor was defined it was included also in the pooled analyses when testing for treatment by sub-group interaction in attempt to explain variability in data.

The race sub-groups ‘American Indian or Alaska Native’ and ‘Native Hawaiian or Other Pacific Islander’ that are often considered in a drug snapshot included too few subjects to make valid analyses. Hence, patients within these sub-groups were included in the “other” category. In addition, some ethics committees in France do not allow for collection of race and ethnicity and consequently some subjects from France are categorized as ‘Not Applicable’ for these analyses.

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 on one hand and low power considerations on the other. 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

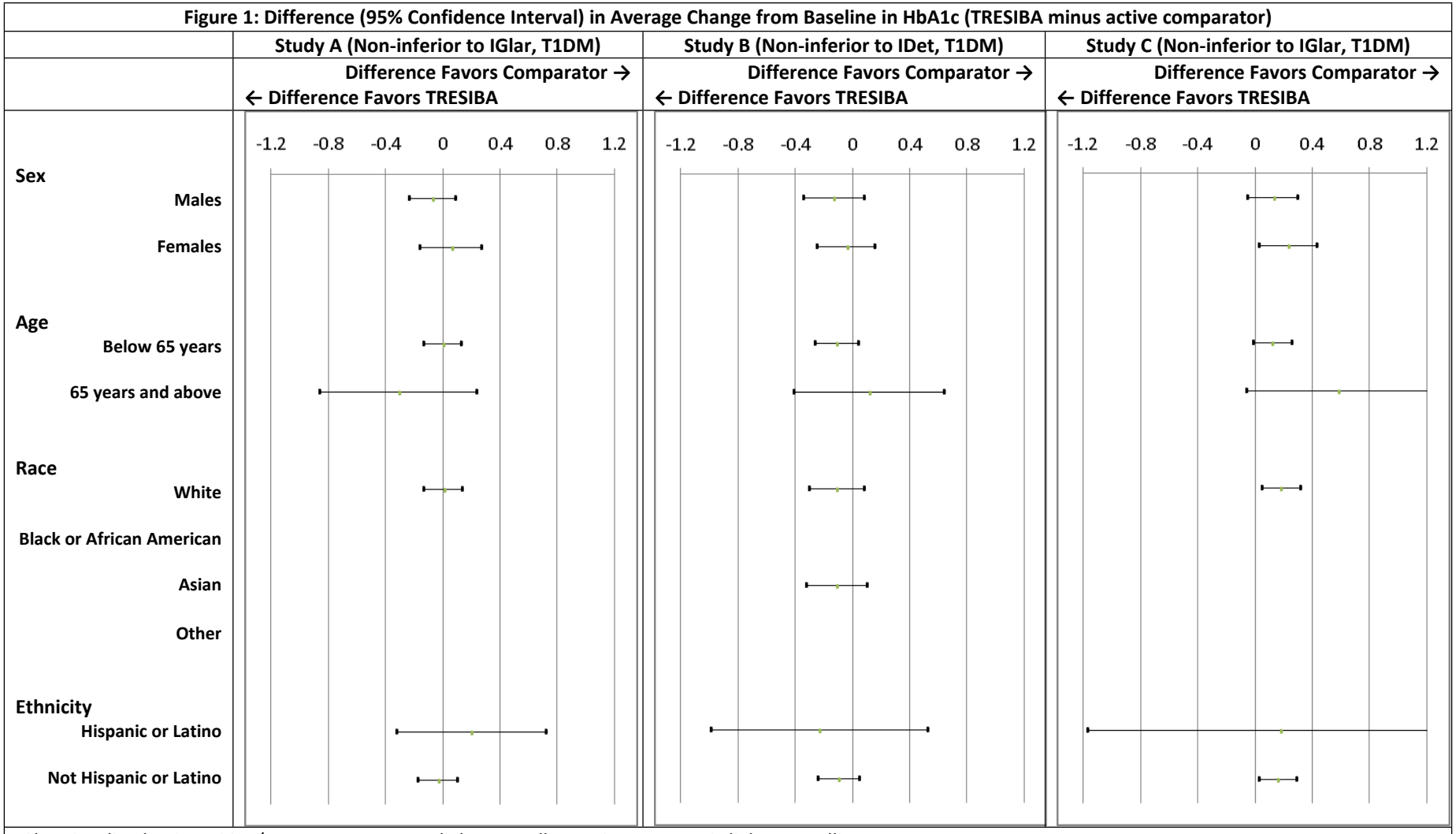
undertaken in the interest of transparency and to provide as much information regarding subgroup differences as is possible using the available data.

3.3 Results by Sex, Race, Age, and Ethnicity

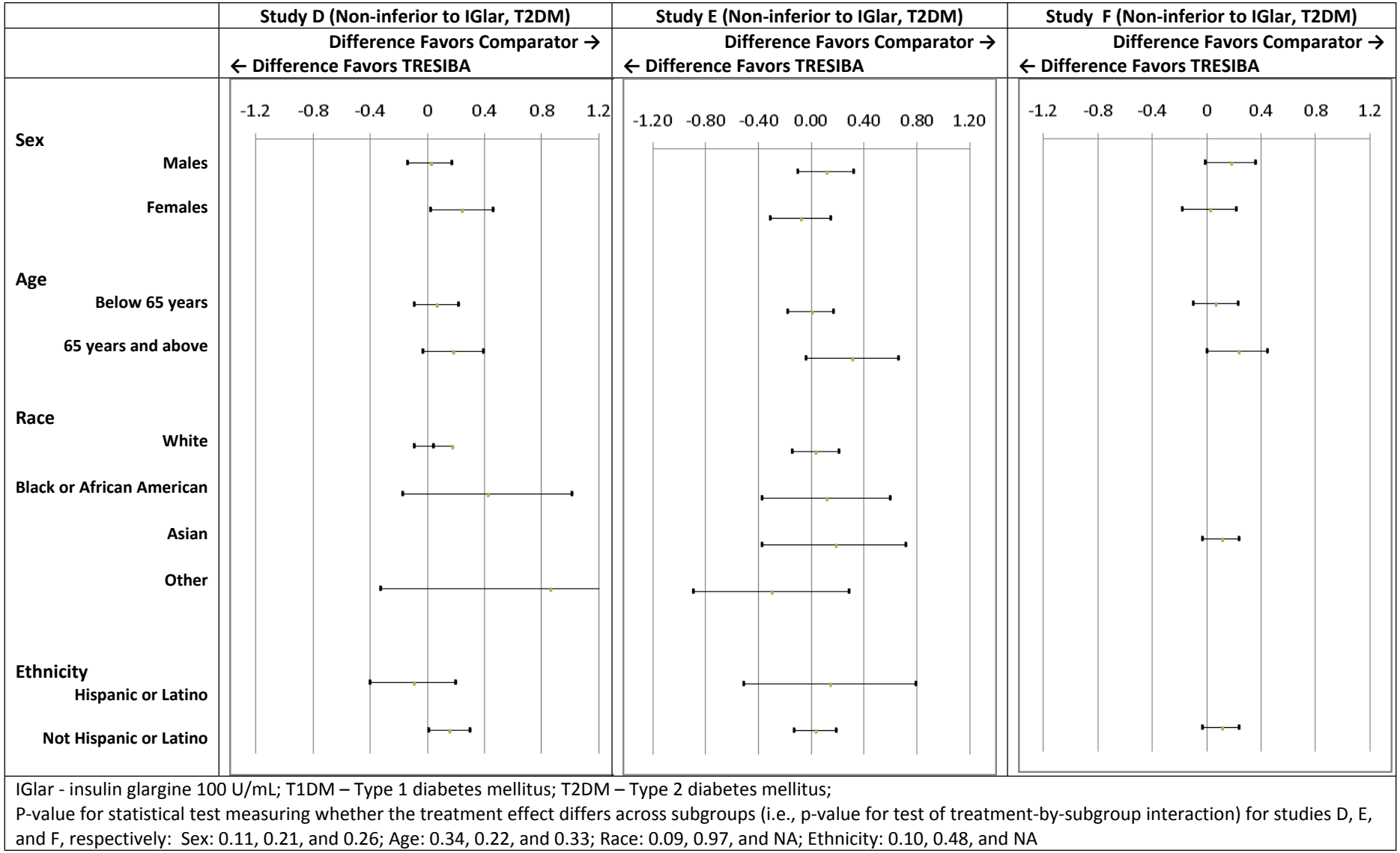
This section provides estimates of the difference between TRESIBA and the active comparators in LSMEAN change from baseline in HbA1c by sex, race, age, and ethnicity subgroups. Approximate 95% confidence intervals for treatment differences within each sub-group were constructed using normal quantiles.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

Figure 1 displays results for each study and dosing style considered individually as well as the combinations of studies and dosing styles.

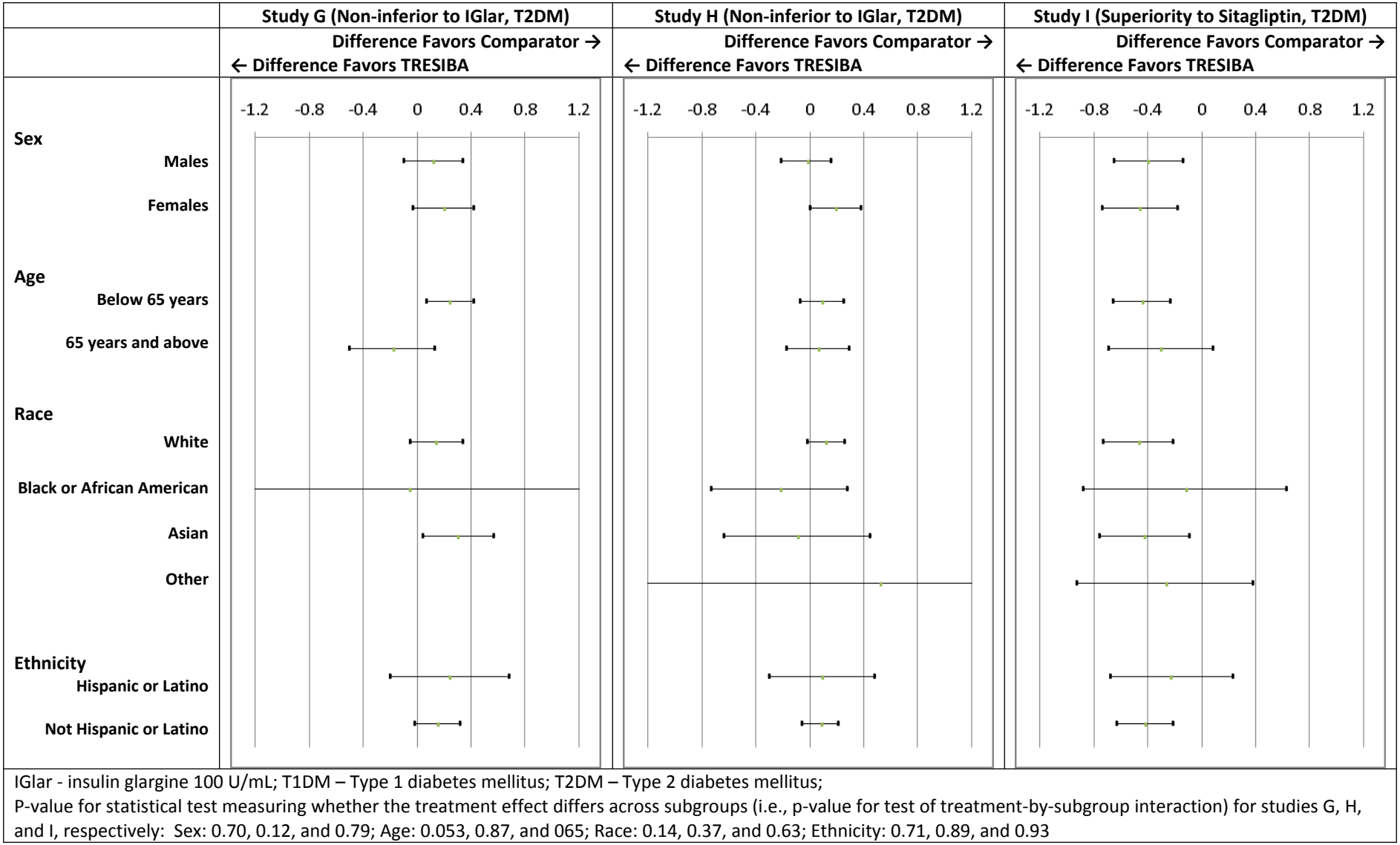
Figure 1: Difference (95% Confidence Interval) in Average Change from Baseline in HbA1c (TRESIBA minus active comparator)



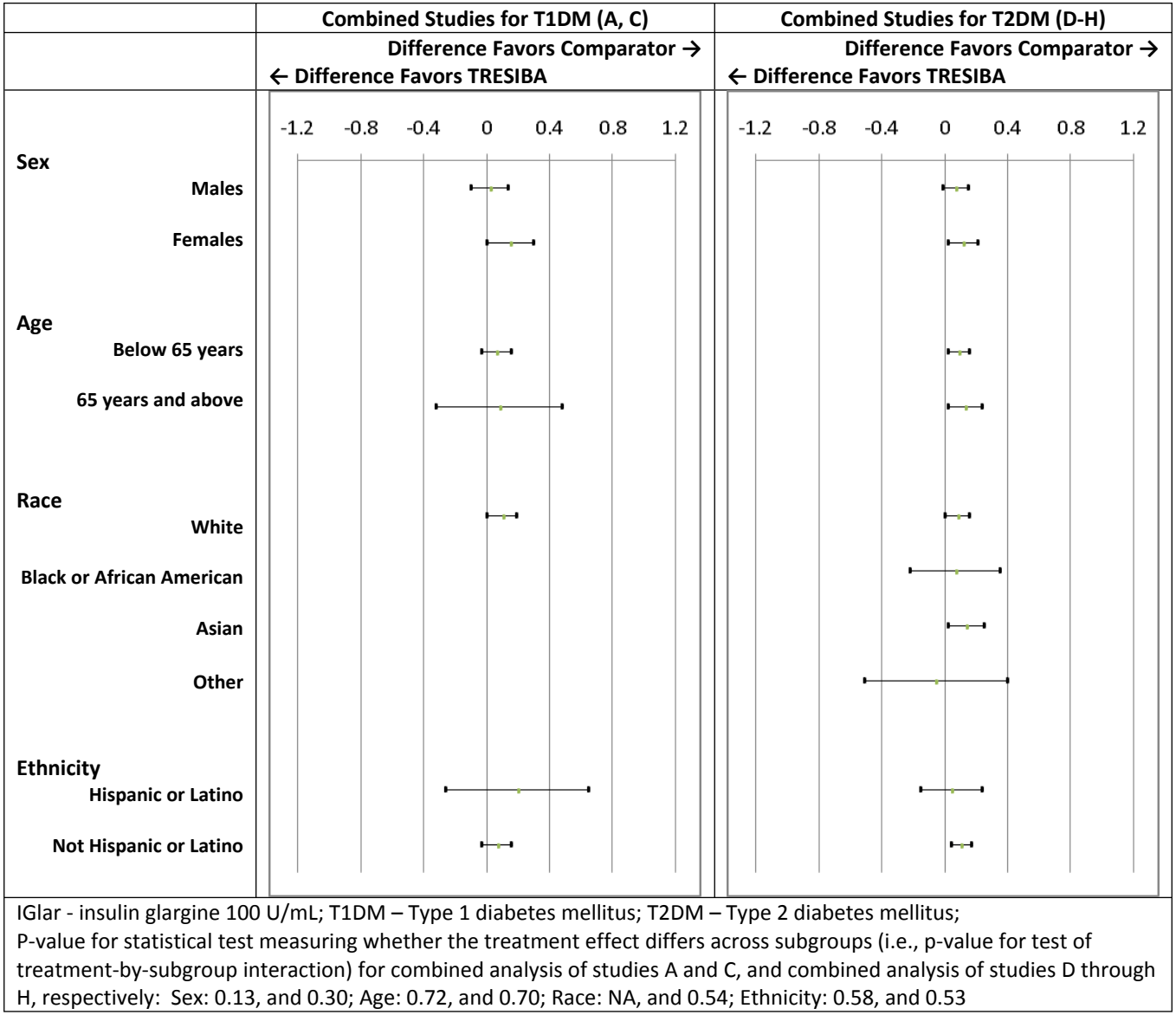
IGlar - insulin glargine 100 U/mL; T1DM – Type 1 diabetes mellitus; T2DM – Type 2 diabetes mellitus;
P-value for statistical test measuring whether the treatment effect differs across subgroups (i.e., p-value for test of treatment-by-subgroup interaction) for studies A, B, and C, respectively: Sex: 0.34, 0.60, and 0.21; Age, 0.36, 0.52, and 0.07; Race: NA, 0.72, and NA; Ethnicity: 0.33, 0.75, and 0.58



IGlar - insulin glargine 100 U/mL; T1DM – Type 1 diabetes mellitus; T2DM – Type 2 diabetes mellitus;
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 studies D, E, and F, respectively: Sex: 0.11, 0.21, and 0.26; Age: 0.34, 0.22, and 0.33; Race: 0.09, 0.97, and NA; Ethnicity: 0.10, 0.48, and NA



IGlar - insulin glargine 100 U/mL; T1DM – Type 1 diabetes mellitus; T2DM – Type 2 diabetes mellitus;
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 studies G, H, and I, respectively: Sex: 0.70, 0.12, and 0.79; Age: 0.053, 0.87, and 065; Race: 0.14, 0.37, and 0.63; Ethnicity: 0.71, 0.89, and 0.93



IGlar - insulin glargine 100 U/mL; T1DM – Type 1 diabetes mellitus; T2DM – Type 2 diabetes mellitus;
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 combined analysis of studies A and C, and combined analysis of studies D through H, respectively: Sex: 0.13, and 0.30; Age: 0.72, and 0.70; Race: NA, and 0.54; Ethnicity: 0.58, and 0.53

Examination of treatment effect by sex: There is evidence in both T1DM and T2DM that TRESIBA is noninferior to the active comparator (either insulin glargine or insulin detemir) with respect to the change in HbA1c from baseline within each sex. For T1DM, this conclusion is drawn primarily from the combined analysis of studies A and C with insulin glargine as the active comparator and the individual analysis of study B with insulin detemir as the active comparator. For T2DM this conclusion is drawn primarily from the combined analysis of studies D through H with insulin glargine as the active comparator. Point estimates for the treatment effect within each sex within individual studies are consistent with those of the combined analyses; however, in some individual non-inferiority studies, the upper bound of 95% confidence interval for the treatment effect is greater than the non-inferiority margin 0.4. This is likely because the small sample size within the subgroup does 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 TRESIBA and the active comparator exceeds 0.4 in that subgroup.

In Study I, TRESIBA is statistically significantly better than Sitagliptin with respect to the change in HbA1c for both sexes in patients with T2DM.
None of the studies give 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.

Display of data to describe the effect of TRESIBA in males versus females on the change in HbA1c from baseline could reliably be achieved by displaying results from the following.

(1.) The combined analysis of Studies A and C as patterns in each of the individual studies were similar to that of the combined analysis
(2.) Study B alone as this is the only noninferiority study with insulin detemir as the active comparator
(3.) The combined analysis of Studies D through H as patterns in each of the individual studies were similar to that of the combined analysis
(4.) Study I alone as it is the only study designed to demonstrate superiority over Sitagliptin

Examination of treatment effect by age: There is evidence in both T1DM and T2DM that TRESIBA is noninferior to the active comparator (either insulin glargine or insulin detemir) with respect to the change in HbA1c from baseline within each age group. For T1DM, this conclusion is drawn primarily from the combined analysis of studies A and C with insulin glargine as the active comparator and the individual analysis of study B with insulin detemir as the active comparator. In T1DM patients 65 years old and older, estimates of the treatment effect from studies A and C and the combined analysis of studies A and C are insufficiently precise to allow a formal noninferiority conclusion. However, the lack of any evidence suggesting that the treatment effect varies with age provide reassurance that a noninferiority supposition in the older age group is likely reasonable. For T2DM this conclusion is drawn primarily from the combined analysis of studies D through H with insulin glargine as the active comparator. Point estimates for the treatment effect within each age group within individual studies are

consistent with those of the combined analyses; however, in some individual non-inferiority studies, the upper bound of 95% confidence interval for the treatment effect is greater than the non-inferiority margin 0.4. This is likely because the small sample size within the subgroup does 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 TRESIBA and the active comparator exceeds 0.4 in that subgroup.

In Study I, TRESIBA is statistically significantly better than Sitagliptin with respect to the change in HbA1c for for T2DM patients below 65 years old. In T2DM patients 65 years old and older, the treatment effect from study I is insufficiently precise to allow a formal superiority conclusion. However, the lack of any evidence suggesting that the treatment effect varies with age provides reassurance that a superiority supposition for T2DM even in the older age group is likely reasonable.

None of the studies give 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-age interaction.

Display of data to describe the effect of TRESIBA in patients in each age group on the change in HbA1c from baseline could reliably be achieved by displaying the same analyses described above for sex.

Examination of treatment effect by race The patients in the combined (studies A and C) noninferiority analysis with insulin glargine as the active comparator in T1DM are almost exclusively White so that no assessment of the treatment effect of TRESIBA relative to insulin glargine in T1DM in other races can be made whithout borrowing information from White patients. In Study B, TRESIBA is non-inferior to insulin detemir within both racial groups represented, White and Asian subgroups, with respect to the change in HbA1c in patients with T1DM. TRESIBA is non-inferior to insulin glargine with respect to the change in HbA1c from baseline within all race groups (White, Black or African American, Asian, and other) in the combined analysis (Studies D through H) for patients with T2DM. Point estimates for the treatment effect in T2DM within some races within individual studies are consistent with those of the combined analyses; however, in some individual non-inferiority studies, the upper bound of 95% confidence interval for the treatment effect is greater than the non-inferiority margin 0.4. This is likely because the small sample size within the subgroup does 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 TRESIBA and the active comparator exceeds 0.4 in that subgroup.

In Study I, TRESIBA is statistically significantly better than Sitagliptin with respect to the change in HbA1c for White and Asian T2DM patients. In Black T2DM patients, the treatment effect from Study I is insufficiently precise to allow a formal superiority conclusion. However, the lack

of any evidence suggesting that the treatment effect varies with race provides reassurance that a superiority supposition for T2DM Black patients is likely reasonable.
None of the studies give a strong indication that the treatment effect for TRESIBA is larger in one race group than the other as is evidenced by the p-values associated with the treatment-by-race interaction.
Display of data to describe the effect of TRESIBA in patients in each racial group on the change in HbA1c from baseline could reliably be achieved by displaying the same analyses described above for sex.

Examination of treatment effect by ethnicity: There is evidence in both T1DM and T2DM that TRESIBA is noninferior to the active comparator (either insulin glargine or insulin detemir) with respect to the change in HbA1c from baseline within each ethnic group. For T1DM, this conclusion is drawn primarily from the combined analysis of studies A and C with insulin glargine as the active comparator and the individual analysis of study B with insulin detemir as the active comparator. In T1DM Hispanic or Latino patients, estimates of the treatment effect from studies A, B, and C and the combined analysis of studies A and C are insufficiently precise to allow a formal noninferiority conclusion. However, the lack of any evidence suggesting that the treatment effect varies with age provide reassurance that a noninferiority supposition in the Hispanic or Latino group is likely reasonable. For T2DM this conclusion is drawn primarily from the combined analysis of studies D through H with insulin glargine as the active comparator. Point estimates for the treatment effect in T2DM within each ethnic group within individual studies are consistent with those of the combined analyses; however, in some individual non-inferiority studies, the upper bound of 95% confidence interval for the treatment effect is greater than the non-inferiority margin 0.4. This is likely because the small sample size within the subgroup does 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 TRESIBA and the active comparator exceeds 0.4 in that subgroup.

In Study I, TRESIBA is statistically significantly better than Sitagliptin with respect to the change in HbA1c for T2DM patients who are not Hispanic or Latino. In Hispanic or Latino T2DM patients, the treatment effect from study I is insufficiently precise to allow a formal superiority conclusion. However, the lack of any evidence suggesting that the treatment effect varies with ethnicity provides reassurance that a superiority supposition for T2DM even in the Hispanic or Latino group is likely reasonable.

None of the studies give a strong indication that the treatment effect for TRESIBA is larger in one ethnic group than the other as is evidenced by the p-values associated with the treatment-by-sex interaction.

Display of data to describe the effect of TRESIBA in patients in ethnic group on the change in HbA1c from baseline could reliably be achieved by displaying the same analyses described above for sex.

4. SUMMARY AND CONCLUSIONS

This review examined existing data to assess the treatment effect of TRESIBA on change in HbA1c from baseline within each sex, age, race, and ethnicity subgroup and whether the treatment effect of TRESIBA 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

- TRESIBA is non-inferior to insulin glargine with respect to the change in HbA1c from baseline within each sex for patients with T1DM and T2DM. TRESIBA is also non-inferior to insulin detemir within each sex with respect to the change in HbA1c in patients with T1DM. TRESIBA is statistically significantly better than Sitagliptin with respect to the change in HbA1c for both sexes in patients with T2DM. Available data did not give a strong indication that the treatment effect for TRESIBA is larger in one sex than the other.

- TRESIBA is or is supposed to be (based on similarity in response across subgroups) non-inferior to insulin glargine with respect to the change in HbA1c from baseline within each age group (below 65 years, and 65 years and above) for patients with T1DM and T2DM. TRESIBA is non-inferior to insulin detemir for those less than 65 years old and or is supposed to be (based on similarity in response across subgroups) for those 65 years old or older with T1DM. TRESIBA is statistically significantly better than Sitagliptin with respect to the change in HbA1c for those less than 65 years old and is supposed to be (based on similarity in response across subgroups) for those 65 years old and older with T2DM. Available data did not give a strong indication that the treatment effect for TRESIBA is larger in one age group than the other.

- TRESIBA is non-inferior to insulin glargine with respect to the change in HbA1c from baseline within T1DM White patients. Patients in the T1DM insulin glargine studies were almost exclusively White so that no assessment of the treatment effect of TRESIBA relative to insulin glargine 100 u/mL in T1DM in other races can be made without borrowing information from White patients. TRESIBA is non-inferior to insulin glargine 100 u/mL in all racial groups (White, Black or African American, Asian, and other) for patients with T2DM. TRESIBA is non-inferior to insulin detemir for both racial groups studied, White and Asian patients, with respect to the change in HbA1c in patients with T1DM. TRESIBA is statistically significantly better than Sitagliptin with respect to the change in HbA1c for most racial groups (White, Asian, and other) and is supposed to be (based on similarity in response across subgroups) for Black or African American patients with T2DM. Available data did not give a strong indication that the treatment effect for TRESIBA is different for any race.

- TRESIBA is or is supposed to be (based on similarity in response across subgroups) non-inferior to insulin glargine with respect to the change in HbA1c from baseline within each ethnicity group (Hispanic or Latino and Not Hispanic or Latino) for patients with T1DM and T2DM. TRESIBA is non-inferior to insulin detemir for patients who are not Hispanic or Latino and is supposed to be (based on similarity in response across subgroups) for Hispanic or Latino patients with T1DM. TRESIBA is statistically significantly better than Sitagliptin with respect to the change in HbA1c for patients who are not Hispanic or Latino and is supposed to be (based on similarity in response across subgroups) for Hispanic or Latino patients with T2DM. Available data did not give a strong indication that the treatment effect for TRESIBA is different for any race.

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

/s/

JIWEI HE
12/03/2015

RUTHANNA C DAVI
12/04/2015

THOMAS J PERMUTT
12/15/2015
I concur.

MARK D ROTHMANN
12/15/2015
I Concur