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#	203313
Drug Name:	Insulin degludec/Insulin aspart 70/30 (Ryzodeg)
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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Keywords: subgroup analyses

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1 EXECUTIVE SUMMARY

This review examined existing data to assess the treatment effect of Ryzodeg on HbA1c reduction within each sex, age, race, and ethnicity subgroup and whether the treatment effect of Ryzodeg on HbA1c reduction 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.

In the single study of patients with T1DM, the small sample size of some subgroups does not provide enough precision in the estimates to satisfy the formal non-inferiority test but because of the consistency in the point estimates across subgroups or the unexpected clinical nature of the finding, these results are not believed to be an indication that the true underlying difference between Ryzodeg and the active comparator exceeds 0.4 in that subgroup. There was statistical evidence of noninferiority of Ryzodeg to insulin glargine and NovoLog Mix 70/30 on change in HbA1c from baseline within all subgroups examined (by sex, age, race, and ethnicity) in patients with T2DM. In specific, this review concludes that

- Ryzodeg is non-inferior to insulin glargine and NovoLog Mix 70/30 with respect to the change in HbA1c from baseline within each sex for patients with T1DM and T2DM. Available data did not give a strong indication that the treatment effect for Ryzodeg is larger in one sex group than the other.

- In T1DM, Ryzodeg is supposed to be (in the context of multiple subgroup analyses with an increased chance of falsely detecting an interaction and a lack of a clinical expectation for differences in efficacy across age groups) non-inferior to insulin detemir with respect to the change in HbA1c from baseline within each age group (below 65 years and 65 years and above). In T2DM, Ryzodeg is non-inferior to insulin glargine and NovoLog Mix 70/30 with respect to the change in HbA1c from baseline within each age group (below 65 years, and 65 years and above). Available data did not give a strong indication that the treatment effect for Ryzodeg is larger in one age group than the other.

- In T1DM, Ryzodeg is non-inferior to insulin detemir in White patients and is supposed to be (based on similarity in response across subgroups) non-inferior to insulin detemir in Black/African American and Other patients. In T2DM, Ryzodeg is non-inferior to insulin glargine with respect to the change in HbA1c from baseline within all race groups examined (White, Black or African American, and Asian). Also in T2DM, Ryzodeg is non-inferior to NovoLog Mix 70/30 with respect to the change in HbA1c from baseline within all race groups examined (White and Asian). Available data did not give a strong indication that the treatment effect for Ryzodeg is different for any race.

In T1DM, Ryzodeg is non-inferior to insulin detemir in Non-Hispanic/Latino patients and is supposed to be (in the context of multiple subgroup analyses with an increased chance of falsely detecting an interaction and a lack of clinical expectation for differences in efficacy across ethnic groups) non-inferior to insulin detemir in Hispanic/Latino patients. In T2DM, Ryzodeg is non-inferior to insulin glargine with respect to the change in HbA1c from baseline within both ethnic groups. Also in T2DM, Ryzodeg is non inferior to NovoLog Mix 70/30 with respect to the change in HbA1c from baseline for non-Hispanic/Latino patients. The number of Hispanic/Latino T2DM patients enrolled in studies with NovoLog Mix 70/30 as the active comparator was insufficient to allow analysis. Available data did not give a strong indication that the treatment effect for Ryzodeg 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 Ryzodeg 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] Ryzodeg to improve glycemic control in adults with diabetes mellitus.

The applicant provided results of one phase 3 trial (referred to in this document as study A) conducted to evaluate the efficacy of Ryzodeg in patients with type 1 diabetes, and four phase 3 trials (referred to in this document as B through E) conducted to evaluate the efficacy of Ryzodeg in patients with type 2 diabetes.

The five studies were all multinational, multicenter, randomized, open-label, parallel-group, active-controlled, treat-to-target trials. Key features of these studies are summarized in Table 1. In all studies, the efficacy of Ryzodeg was evaluated in terms of HbA1c reduction from baseline to the end of the 26-week blinded treatment period. The active comparators in these non-inferiority studies were LANTUS (insulin glargine 100 U/mL), LEVEMIR (insulin detemir 100 U/mL) and NovoLog Mix 70/30 (biphasic insulin aspart). In Study A, Ryzodeg was administered once-daily with the main meal of the day and used with a mealtime insulin at remaining meals in patients with type 1 diabetes. In Studies B-E, Ryzodeg was administered once or twice daily with the main meal(s) in patients with type 2 diabetes when used with common oral anti-diabetic drugs.

[1] http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/203313Orig1s000ltr.pdf

Consistent with product labeling, these five 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 Ryzodeg 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)				
Study A **NN5401-3594**	IAsp for the remaining insulin requiring meals	26	**Ryzodeg (IDegAsp)**: once daily s.c. at any meal **IDet**: once or twice daily s.c. at main meals	366 182
Type 2 Diabetes Mellitus (T2DM)				
Study B **NN5401-3590**	Oral metformin and/or subcutaneous neutral protamine hagedorn in follow-up	26	**Ryzodeg (IDegAsp)**: once daily s.c. at breakfast **IGlar**: once daily s.c.	266 263
Study C **NN5401-3593**	Oral metformin and/or pioglitazone and/or DPP-4	26	**Ryzodeg (IDegAsp)**: once daily s.c. at main meal **IGlar**: once daily s.c	230 233
Study D **NN5401-3592**	Oral metformin and/or pioglitazone and/or DPP-4	26	**Ryzodeg (IDegAsp)**: twice daily s.c. **BIAsp 30**: twice daily s.c	224 222
Study E **NN5401-3597**	Oral metformin and biphasic human insulin in follow-up	26	**Ryzodeg (IDegAsp)**: twice daily s.c. **BIAsp**: twice daily s.c	280 142
IAsp –NovoLog (insulin aspart); IDegAsp – Insulin degludec/Insulin aspart 70/30 100 U/mL; IDet - LEVEMIR (insulin detemir 100 U/mL); IGlar – LANTUS (insulin glargine 100 U/mL); BIAsp: NovoLog Mix 70/30 (biphasic insulin aspart)				

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

Study	Primary Hypothesis	Treatment Groups	Treatment Difference (Ryzodeg – Control)	
			LS Mean	95% CI
Type 1 Diabetes Mellitus (T1DM)				
Study A NN5401-3594	Non-inferiorty	Ryzodeg (IDegAsp) IDet	-0.05	(-0.18, 0.08)
Type 2 Diabetes Mellitus (T2DM)				
Study B NN5401-3590	Non-inferiorty	Ryzodeg (IDegAsp) IGlar	0.03	(-0.14 ,0.20)
Study C NN5401-3593	Non-inferiorty	Ryzodeg (IDegAsp) IGlar	-0.03	(-0.20, 0.14)
Study D NN5401-3592	Non-inferiorty	Ryzodeg (IDegAsp) BIAsp 30	-0.03	(-0.18, 0.13)
Study E NN5401-3597	Non-inferiorty	Ryzodeg (IDegAsp) BIAsp	0.05	(-0.10, 0.20)
IDegAsp – Insulin degludec/Insulin aspart 70/30 100 U/mL; IDet - LEVEMIR (insulin detemir 100 U/mL); IGlar – LANTUS (insulin glargine 100 U/mL); BIAsp: NovoLog Mix 70/30 (biphasic insulin aspart)				

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, dose regimes or background therapy. While we acknowledge that differences in the treatment effect across differing populations or background medications 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 or background therapy. For example if the treatment effect for Ryzodeg in males is larger than that of females in a population such as used in study A, combining study A with a population such as is used in study B is more agreeable if the treatment effect for Ryzodeg is also larger for males than females in the population used in study B. 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 and background therapies.

As a result of the afore-mentioned considerations, subgroup analyses of each study (A-E) and dose were considered individually. In addition the following combinations of studies were considered:

- The 2 studies in patients with type 2 diabetes with insulin glargine as the active comparator (Studies B, C)
- The 2 studies in patients with type 2 diabetes with NovoLog Mix 70/30 as the active comparator (Studies D, E)

In the original application, treatment effect of Ryzodeg (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%.

For each individual study, the treatment effect of Ryzodeg 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.

In all cases where studies are combined, the treatment effect of Ryzodeg 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 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' 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' in these analyses.

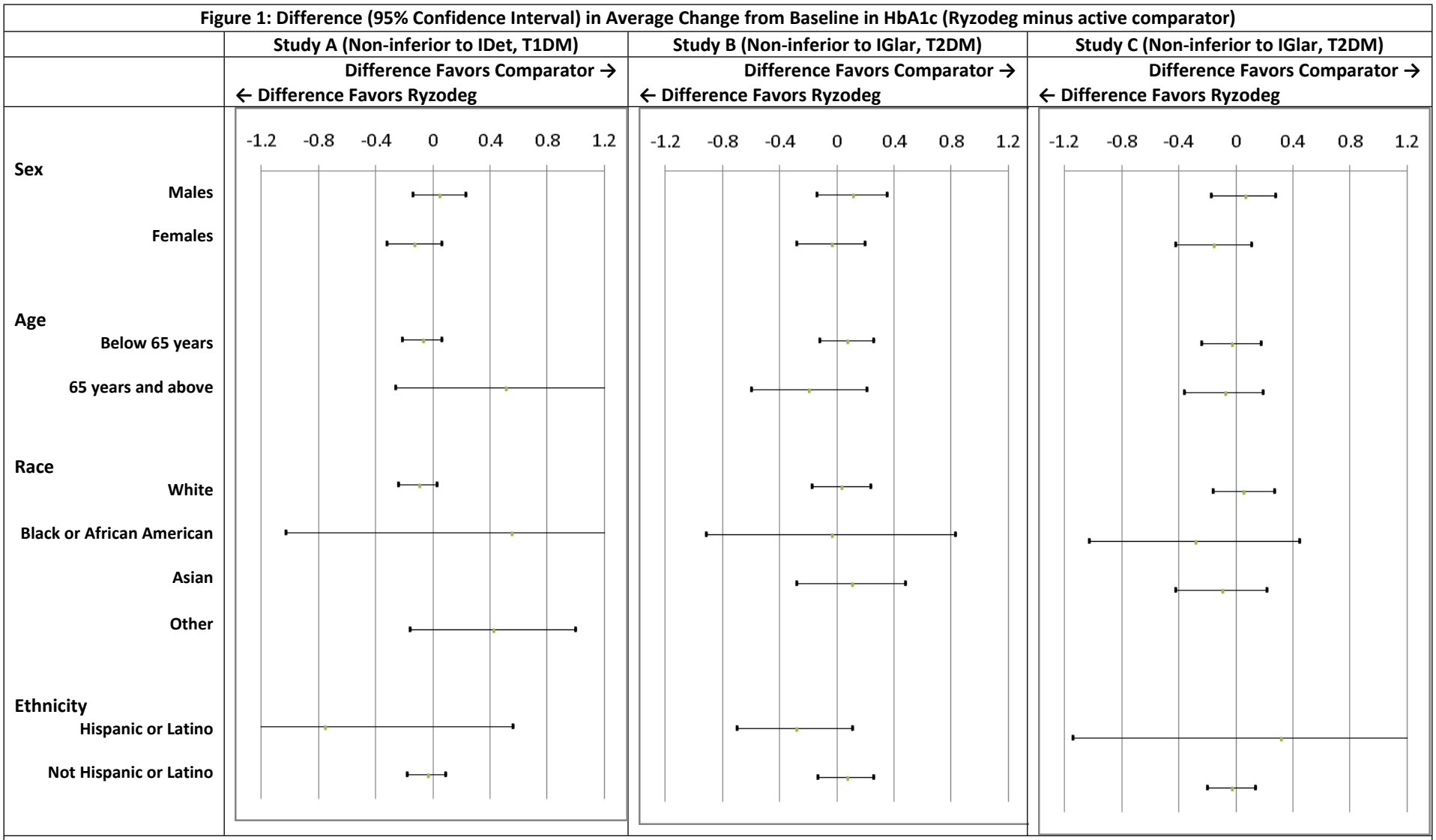
We acknowledge that these analyses are exploratory and the trials were not designed to support such investigations. In general, these comparisons may be limited by multiplicity on one hand and low power considerations on the other. Consistency in the differences in treatment effect across subgroups by 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

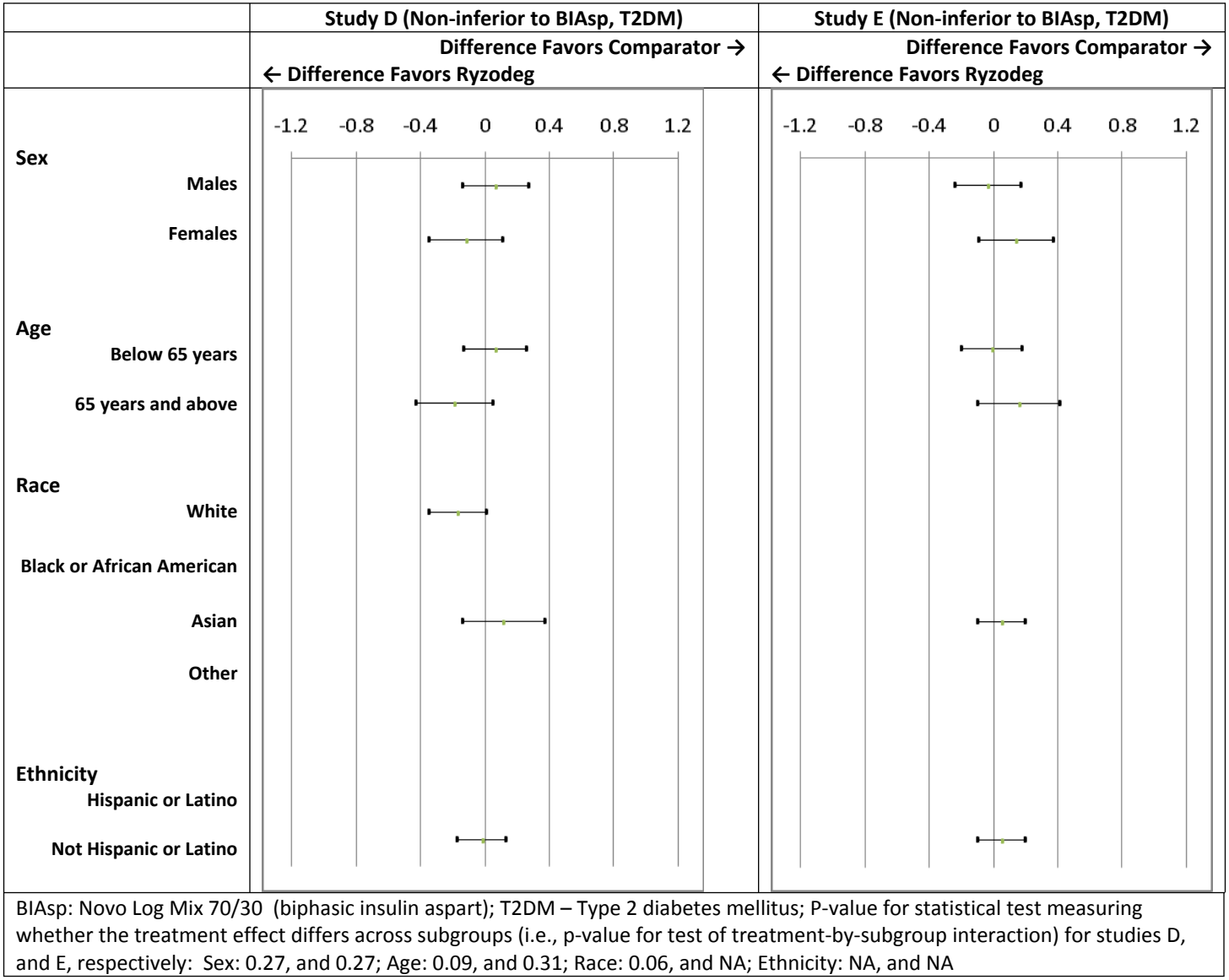
This section provides estimates of the difference between Ryzodeg and the active comparators in LSMEAN change from baseline in HbA1c by sex, race, age, and ethnicity subgroups. Approximate 95% confidence intervals for treatment differences within each sub-group were constructed using normal quantiles.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

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

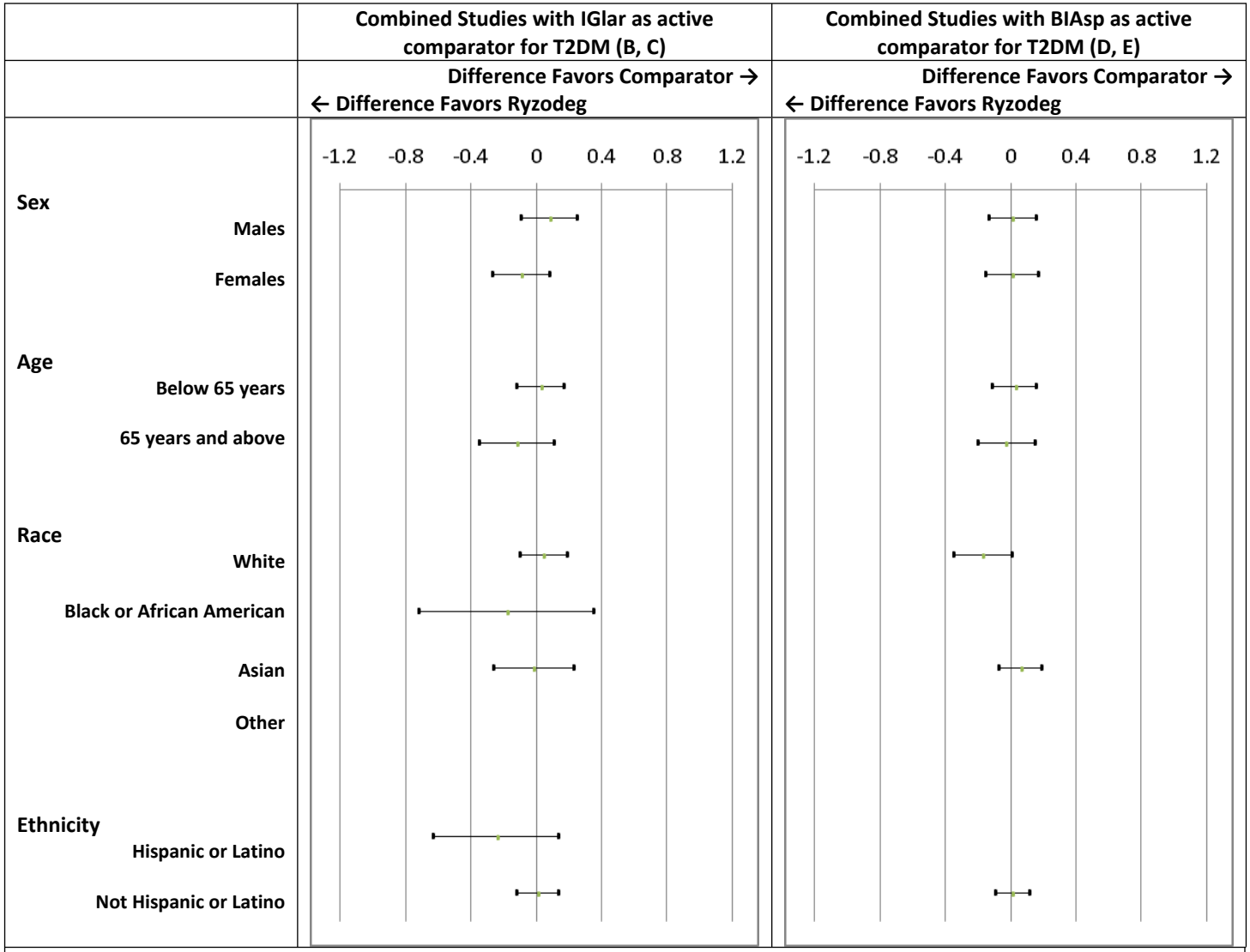
Figure 1: Difference (95% Confidence Interval) in Average Change from Baseline in HbA1c (Ryzodeg minus active comparator)



IDet - LEVEMIR (insulin detemir 100 U/mL); IGlar – LANTUS (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: 0.19, 0.38, and 0.13; Age, 0.07, 0.32, and 0.91; Race: 0.18, 0.93, and 0.51; Ethnicity: 0.06, 0.14, and 0.53



BIAsp: Novo Log Mix 70/30 (biphasic insulin aspart); 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, and E, respectively: Sex: 0.27, and 0.27; Age: 0.09, and 0.31; Race: 0.06, and NA; Ethnicity: NA, and NA



IGlar – LANTUS (insulin glargine 100 U/mL); BIAsp: Novo Log Mix 70/30 (biphasic insulin aspart); 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 B and C and combined analysis of studies D and E, respectively: Sex: 0.10, and 0.90; Age: 0.42, and 0.55; Race: 0.65, and 0.051; Ethnicity: 0.10, and NA

Examination of treatment effect by sex: There is evidence in both T1DM and T2DM that Ryzodeg is non-inferior to the active comparator with respect to the change in HbA1c from baseline within each sex. For T1DM, this conclusion is drawn primarily from study A with insulin detemir as the active comparator. For T2DM this conclusion is drawn primarily from the combined analysis of studies B and C with insulin glargine as the active comparator and the combined analysis of studies D and E with NovoLog Mix 70/30 as the active comparator. Conclusions of subgroup analyses by sex within the individual studies are consistent with those of the combined analyses. None of the studies or analyses gives a strong indication that the treatment effect for Ryzodeg 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 Ryzodeg in males versus females on the change in HbA1c from baseline could reliably be achieved by displaying results from the following.

(1.) Study A alone as this is the only study of T1DM patients
(2.) The combined analysis of studies B and C as patterns in each of the individual studies were similar to that of the combined analysis and the same active comparator (insulin glargine) was used.
(3.) The combined analysis of studies D and E as patterns in each of the individual studies were similar to that of the combined analysis and the same active comparator (Novo Log Mix 70/30) was used.

Examination of treatment effect by age: There is evidence from study A in T1DM patients less than 65 years old that Ryzodeg is non-inferior to insulin detemir with respect to the change in HbA1c from baseline. In T1DM patients 65 years old and older in study A, there is insufficient data to demonstrate non-inferiority of Ryzodeg to insulin detemir with a trend towards Ryzodeg being inferior to insulin detemir with respect to the change in HbA1c from baseline. There is a small amount of statistical evidence suggesting that the effect of Ryzodeg relative to insulin detemir may be different in the two age groups as evidenced by a p-value associated with the treatment-by-age interaction of 0.07. However in the context of the number of subgroup analyses being considered, increasing the chance of falsely detecting an interaction, and the lack of a clinical expectation for this finding, this result is not believed to be an indication that there is a true underlying difference in the comparison of Ryzodeg and insulin detemir in patients less than 65 years old versus 65 years old or older. In summary, based on these considerations, we suppose that Ryzodeg is also non-inferior to insulin detemir in patients 65 years old and older.

There is evidence in T2DM that Ryzodeg is non-inferior to the active comparators with respect to the change in HbA1c from baseline within each age group. This conclusion is drawn primarily from the combined analysis of studies B and C with insulin glargine as the active comparator and the combined analysis of studies D and E with NovoLog Mix 70/30 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 Ryzodeg and the active comparator exceeds 0.4 in that subgroup in T2DM. None of the studies or analyses gives a strong indication that the treatment effect for Ryzodeg is larger in one age group than the other in T2DM as is evidenced by the p-values associated with the treatment-by-sex interaction.

Display of data to describe the effect of Ryzodeg 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: There is evidence from study A in White T1DM patients less than 65 years old that Ryzodeg is non-inferior to insulin detemir with respect to the change in HbA1c from baseline. In Black/African American or Other T1DM patients in study A, there is insufficient data to demonstrate non-inferiority of Ryzodeg to insulin detemir with a trend towards Ryzodeg being inferior to insulin detemir with respect to the change in HbA1c from baseline. However, there is no statistical evidence suggesting that the effect of Ryzodeg relative to insulin detemir may be different in the racial groups as evidenced by a p-value associated with the treatment-by-age interaction of 0.18. In summary, based on these considerations, we conclude that Ryzodeg is likely also non-inferior to insulin detemir in Black/African American or Other patients with T1DM.

There is evidence in T2DM that Ryzodeg is non-inferior to the active comparators with respect to the change in HbA1c from baseline within each racial group examined. This conclusion is drawn primarily from the combined analysis of studies B and C with insulin glargine as the active comparator and including White, Black or African American, and Asian patients and the combined analysis of studies D and E with NovoLog Mix 70/30 as the active comparator and including White and Asian patients. Point estimates for the treatment effect within each racial 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 Ryzodeg and the active comparator exceeds 0.4 in that subgroup in T2DM. None of the studies or analyses gives a strong indication that the treatment effect for Ryzodeg is different across racial groups in T2DM as is evidenced by the p-values associated with the treatment-by-sex interaction.

Display of data to describe the effect of Ryzodeg 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 from study A in Non-Hispanic/Latino T1DM patients that Ryzodeg is non-inferior to insulin detemir with respect to the change in HbA1c from baseline. In Hispanic or Latino T1DM patients in study A, there is insufficient data to demonstrate non-inferiority of Ryzodeg to insulin detemir with a trend in the point estimate towards Ryzodeg being better than insulin detemir with respect to the change in HbA1c from baseline. There is a small amount of statistical evidence suggesting that the effect of Ryzodeg relative to insulin detemir may be different in the ethnicity groups as evidenced by a p-value associated with the treatment-by-race interaction of 0.06. However in the context of the number of subgroup analyses being considered, increasing the chance of falsely detecting an interaction, and the lack of a clinical expectation for this finding, this result is not believed to be an indication that there is a true underlying difference in the comparison of Ryzodeg and insulin detemir in Hispanic/Latino and Non-Hispanic/Latino patients. In summary, based on these considerations, we suppose that Ryzodeg is also non-inferior to insulin detemir in Non-Hispanic/Latino patients.

There is evidence in T2DM that Ryzodeg is non-inferior to insulin glargine with respect to the change in HbA1c from baseline within each ethnicity group. This conclusion is drawn primarily from the combined analysis of studies B and C with insulin glargine as the active comparator. Point estimates for the treatment effect within each ethnicity group within individual studies B and C 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 Ryzodeg and insulin glargine exceeds 0.4 in that subgroup in T2DM. Neither study B or C nor the combined analysis of these studies give a strong indication that the treatment effect for Ryzodeg is larger in one ethnic group than the other in T2DM as is evidenced by the p-values associated with the treatment-by-sex interaction.

There is evidence in T2DM that Ryzodeg is non-inferior to insulin NovoLog Mix 70/30 with respect to the change in HbA1c from baseline in Non-Hispanic/Latino patients. The number of Hispanic/Latino T2DM patients enrolled in studies D and E with NovoLog Mix 70/30 as the active comparator was insufficient to allow analysis.

Display of data to describe the effect of Ryzodeg in patients in each 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 Ryzodeg on change in HbA1c from baseline within each sex, age, race, and ethnicity subgroup and whether the

treatment effect of Ryzodeg 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.

In the single study of patients with T1DM, the small sample size of some subgroups does not provide enough precision in the estimates to satisfy the formal non-inferiority test but because of the consistency in the point estimates across subgroups or the unexpected clinical nature of the finding, these results are not believed to be an indication that the true underlying difference between Ryzodeg and the active comparator exceeds 0.4 in that subgroup. There was statistical evidence of noninferiority of Ryzodeg to insulin glargine and NovoLog Mix 70/30 on change in HbA1c from baseline within all subgroups examined (by sex, age, race, and ethnicity) in patients with T2DM. In specific, this review concludes that

- Ryzodeg is non-inferior to insulin glargine and NovoLog Mix 70/30 with respect to the change in HbA1c from baseline within each sex for patients with T1DM and T2DM. Available data did not give a strong indication that the treatment effect for Ryzodeg is larger in one sex group than the other.

- In T1DM, Ryzodeg is supposed to be (in the context of multiple subgroup analyses with an increased chance of falsely detecting an interaction and a lack of a clinical expectation for differences in efficacy across age groups) non-inferior to insulin detemir with respect to the change in HbA1c from baseline within each age group (below 65 years and 65 years and above). In T2DM, Ryzodeg is non-inferior to insulin glargine and NovoLog Mix 70/30 with respect to the change in HbA1c from baseline within each age group (below 65 years, and 65 years and above). Available data did not give a strong indication that the treatment effect for Ryzodeg is larger in one age group than the other.

- In T1DM, Ryzodeg is non-inferior to insulin detemir in White patients and is supposed to be (based on similarity in response across subgroups) non-inferior to insulin detemir in Black/African American and Other patients. In T2DM, Ryzodeg is non-inferior to insulin glargine with respect to the change in HbA1c from baseline within all race groups examined (White, Black or African American, and Asian). Also in T2DM, Ryzodeg is non-inferior to NovoLog Mix 70/30 with respect to the change in HbA1c from baseline within all race groups examined (White and Asian). Available data did not give a strong indication that the treatment effect for Ryzodeg is different for any race.

- In T1DM, Ryzodeg is non-inferior to insulin detemir in Non-Hispanic/Latino patients and is supposed to be (in the context of multiple subgroup analyses with an increased chance of falsely detecting an interaction and a lack of clinical expectation for differences in efficacy across ethnic groups) non-inferior to insulin detemir in Hispanic/Latino patients. In T2DM, Ryzodeg is non-inferior to insulin glargine with

respect to the change in HbA1c from baseline within both ethnic groups. Also in T2DM, Ryzodeg is non-inferior to NovoLog Mix 70/30 with respect to the change in HbA1c from baseline for non-Hispanic/Latino patients. The number of Hispanic/Latino T2DM patients enrolled in studies with NovoLog Mix 70/30 as the active comparator was insufficient to allow analysis. Available data did not give a strong indication that the treatment effect for Ryzodeg is different for any race.

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