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

BLA#	125526
Drug Name:	Nucala (mepolizumab)
Indication(s):	Treatment of patients with severe eosinophilic asthma
Applicant:	GlaxoSmithKline
Date(s):	Stamp date: November 4, 2014 PDUFA date: November 4, 2015
Review Priority:	Standard
Biometrics Division:	II
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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 mepolizumab on asthma exacerbation rate (defined as worsening of asthma requiring hospitalization, emergency department visits, the use of oral corticosteroids at least double the existing maintenance dose for at least three days and/or for study 88, a single intramuscular injection of corticosteroids) in asthma patients with elevated blood eosinophil counts at baseline within each sex, age, race, and ethnicity subgroup and whether the treatment effect of mepolizumab on asthma exacerbation rate 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 there was statistical evidence of beneficial effects of mepolizuamb on asthma exacerbation rate ratio within all subgroups examined (by sex, age, race, and ethnicity), and the estimated effects were relatively consistent across these subgroups (range of subgroup-specific effects based on analyses combining studies 88 and 97: 0.29 to 0.78). In specific, this review concludes that

- Mepolizumab is statistically significantly better than placebo with respect to the asthma exacerbation rate within each sex and there is no indication that the treatment effect of mepolizumab relative to placebo differs by sex.
- Mepolizumab is statistically significantly better than placebo with respect to the asthma exacerbation rate within patients ages 18 to 64 and patients greater than 65 years old. There is no indication that the treatment effect of mepolizumab relative to placebo differs by age so while the treatment effect in patients ages 12-17 is less precise, the effect of mepolizumab in 12 to 17 year olds is presumed to be similar to that of other age groups.
- Mepolizumab is statistically significantly better than placebo with respect to the asthma exacerbation rate within White and Asian patients. There is little indication that the treatment effect of mepolizumab relative to placebo differs by race so while the treatment effect in African American/Black patients is less precise, the effect of mepolizumab in African American/Black patients is presumed to be similar to that of other racial groups.
- Mepolizumab is statistically significantly better than placebo with respect to the asthma exacerbation rate within Non-Hispanic/Latino patients. There is no indication that the treatment effect of mepolizumab relative to placebo differs by ethnicity so while the treatment effect in Hispanic/Latino patients is less precise, the effect of mepolizumab in Hispanic/Latino patients is presumed to be similar to that of Non-Hispanic/Latino patients.

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 mepolizumab within age, sex, racial, and ethnic subgroups and whether these effects differ across subgroups. This objective is different from the objective of the original Statistical Review and Evaluation of this submission (http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af8039ee8f&showAsPdf=true) and is in supplement to that document. The reader is referred to that document for the full statistical evaluation of the efficacy of the mepolizumab submission.

3 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

3.1 Available Data

The Agency has approved[1] mepolizumab for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.

The applicant provided results of two clinical trials conducted to evaluate mepolizumab for reduction of asthma exacerbation rate (defined as worsening of asthma requiring hospitalization, emergency department visits, the use of oral corticosteroids at least double the existing maintenance dose for at least three days and/or for study 88, a single intramuscular injection of corticosteroids) in asthma patients with elevated blood eosinophil counts at baseline. Studies 97 and 88 were each randomized, parallel-arm, double-blind, placebo-controlled standard of care add-on studies in asthma patients 12 years of age and older. Study 97 enrolled 616 patients and randomized in a 1:1:1:1 ratio to mepolizumab 75 mg IV, 250 mg IV, 750 mg IV, and placebo. Study 88 randomized 576 patients in a 1:1:1 ratio to mepolizumab 75 mg IV, 100 mg SC, and placebo. Study 97 restricted enrollment to patients with symptoms of eosinophilic inflammation (blood eosinophils ≥ 300 / mcL or sputum ≥ 3%, exhaled NO ≥ 50 ppb, or loss of asthma control following ≤ 25% steroid reduction). Study 88 restricted enrollment to patients with screening blood eosinophil counts ≥ 150 / mcL or blood eosinophil counts ≥ 300 / mcL in the year prior to screening.

Consistent with product labeling, these two placebo controlled trials are the basis of the efficacy portion of the "drug snapshot" describing asthma exacerbation reduction and the evaluation of whether treatment effects vary across subgroups.

[1] http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/125526Orig1s000Ltr.pdf

Table 1. Summary of study designs

Study	Population	Design	Primary Endpoint	Treatment arms (sample size)
Study 97	Asthma patients ages 12 to 65 years with ≥2 exacerbations in the past year and symptoms of eosinophilic inflammation (defined as blood eosinophils ≥ 300/mcL or sputum eosinophils ≥ 3% or exhaled NO ≥ 50ppb or loss of asthma control following ≤25% steroid reduction)	R, DB, PC, PG 52 weeks	Asthma exacerbation rate	placebo (n=155) mepolizumab 75 mg IV (n=153) mepoliaumab 250 mg IV (n=152) mepolizumab 750 mg IV (n=156)
Study 88	Asthma patients ages 12 and older with ≥2 exacerbations in the past year and screening blood eosinophil counts ≥ 150 / mcL or blood eosinophil counts ≥ 300 / mcL in the year prior to screening	R, DB, PC, PG 32 weeks	Asthma exacerbation rate	placebo (n=191) mepolizumab 75 mg IV (n=191) mepolizumab 100 mg SC (n=194)

Source: Original FDA Statistical Review and Evaluation of this submission
http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af8039ee8f&showAsPdf=true

Table2. Asthma exacerbation rate

	Exacerbations rate per year	Risk ratio	95% Confidence Interval
Study 97			
placebo (n=155)	2.4		
mepolizumab 75 mg IV (n=153)	1.2	0.5	(0.4, 0.7)
mepoliaumab 250 mg IV (n=152)	1.5	0.6	(0.5, 0.8)
mepolizumab 750 mg IV (n=156)	1.2	0.5	(0.4, 0.6)
Study 88			
placebo (n=191)	1.7		
mepolizumab 75 mg IV (n=191)	0.9	0.5	(0.4, 0.7)
mepolizumab 100 mg SC (n=194)	0.8	0.5	(0.4, 0.6)

Source: Original FDA Statistical Review and Evaluation of this submission
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125559Orig1s000StatR.pdf

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 and doses to provide increased power for small subgroups are weighed against the merits of analyzing all studies and doses separately so as not to miss possible clinical settings where differences in treatment effect across subgroups differ for different populations or doses. While we acknowledge that differences in the treatment effect across differing populations and/or doses 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. What is necessary for this type of analysis is that if there are differences in the way the treatment acts in certain subgroups these differences by subgroup must extend to the other disease populations and doses. For example if the treatment effect for a low dose of mepolizumab in males is larger than that of females combining this dose with another dose is more agreeable if the treatment effect for the other dose of mepolizumab is also larger for males than females. We believe that in general this type of assumption is much more likely to be true than the former. As a result, all mepolizumab dose groups were combined in the analyses provided in this review. Subgroup analyses of studies 97 and 88 were each considered individually as well as combined.

Analysis for the individual studies used the protocol specified primary efficacy analysis method, a negative binomial model, adjusting for covariates of treatment (mepolizumab or placebo), baseline maintenance OCS therapy (OCS vs. no OCS), region (United States, European Union, rest of world), exacerbations in the year prior to the study (as an ordinal variable), baseline percent predicted FEV_1, with logarithm of time on treatment as an offset variable. For each demographic subgroup, the model included a covariate for the subgroup and the interaction of the subgroup with treatment group. The rate ratio relative to placebo and the 95% confidence interval was estimated within each level of the subgroup. An interaction test is provided to quantitatively assess whether there is evidence that the treatment effect differs by subgroup.

For the analysis of the combined studies, the rate ratio for mepolizumab relative to placebo within subgroups and its associated standard error was obtained by combining the estimates from the individual studies inversely weighted by their variances on the log scale. For the interaction test of the treatment effect by subgroup for the combination of studies, the model included all of the covariates in the model for each individual study and in addition the model included terms for study, interaction of treatment and study, interaction of subgroup and study and interaction terms with study for each covariate used in the individual study analysis.

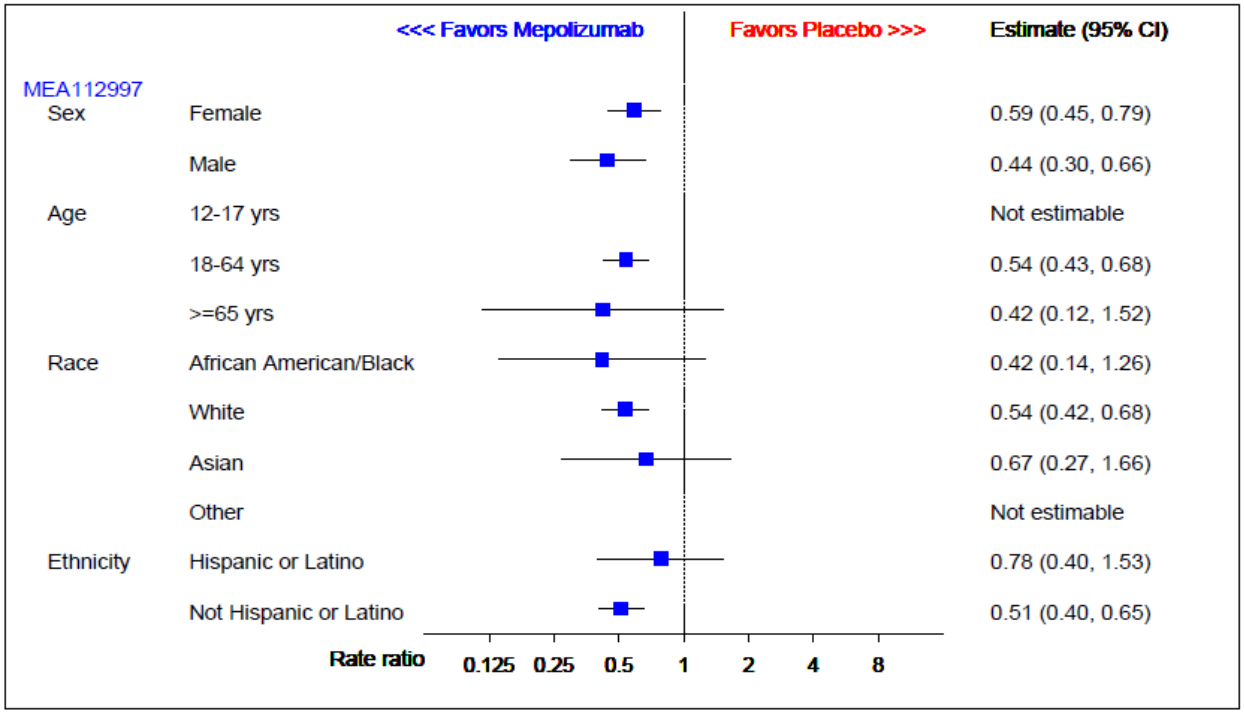
We acknowledge that these analyses are exploratory and the trials were not designed to support such investigations. In general, these comparisons may be limited by multiplicity on one hand and low power considerations on the other. Consistency in the differences in

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. Limitations due to low power are somewhat mitigated for this application by combining doses to increase the sample sizes available within each age, sex, race, and ethnicity subset and allow increased precision in the estimate of the treatment effect. 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

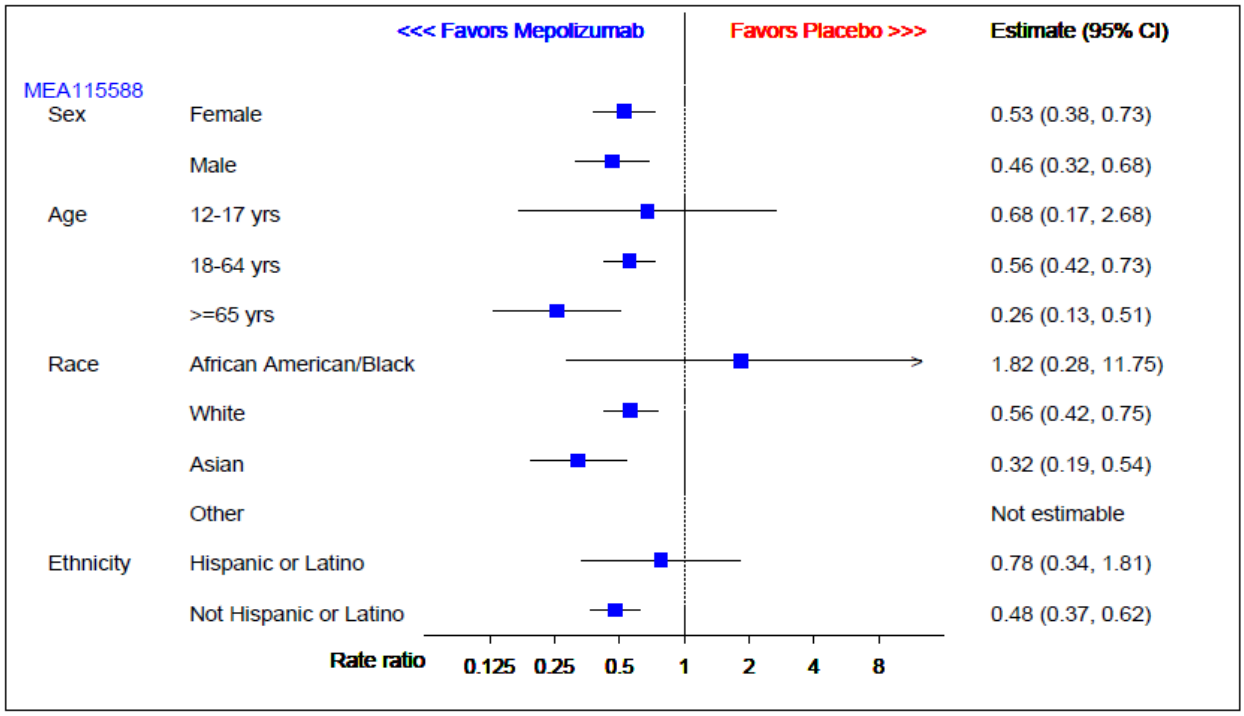
This section provides estimates of the exacerbation rate for the mepolizumab (all doses) and placebo groups and the rate ratio (and 95% confidence interval) of mepolizumab relative to placebo by sex, race, age, and ethnicity subgroups. Tests for the treatment-by-subgroup interaction are also provided. Figure 1 and Figure 2 display the results for studies 97 and 88, respectively. Figure 3 displays results for the combined analysis of studies 97 and 88.

Figure 1. Asthma Exacerbation Rate Ratio by Age, Sex, Race, and Ethnicity (Study 97)



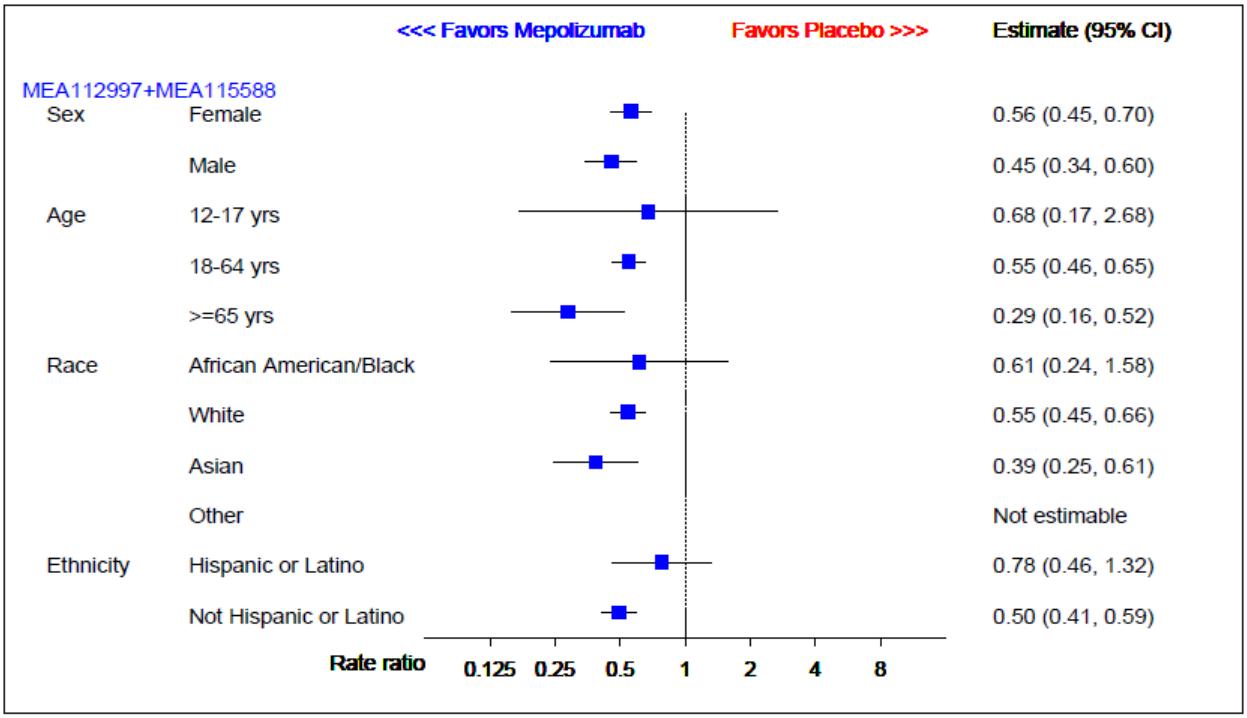
P-value for statistical test measuring whether the treatment effect differs across subgroups (i.e., p-value for test of treatment-by-subgroup interaction) for sex p= 0.246, age p=0.707, race p=0.803, and ethnicity p=0.249

Figure 2. Asthma Exacerbation Rate Ratio by Age, Sex, Race, and Ethnicity (Study 88)



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 sex p= 0.620, age p=0.106, race p=0.030, and ethnicity p=0.275.

Figure 3. Asthma Exacerbation Rate Ratio by Age, Sex, Race, and Ethnicity (Studies 97 and 88)



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 sex p= 0.239, age p=0.129, race p=0.152, and ethnicity p=0.114.

Examination of treatment effect by sex: Mepolizumab is statistically significantly better than placebo with respect to the asthma exacerbation rate within each sex in each individual study as well as in the combined analysis of studies 97 and 88. There is no indication that the treatment effect of mepolizumab relative to placebo differs by sex as evidenced by a large p-value associated with the treatment-by-sex interaction in each analysis.

Examination of treatment effect by age: Mepolizumab is statistically significantly better than placebo with respect to the asthma exacerbation rate within patients ages 18 to 64 and patients greater than 65 years old, as is evidenced by the combined analysis of studies 97 and 88. The treatment effect in patients ages 12-17 is less precise; however, since neither individual study or the combined analysis of studies 97 and 88 give an indication that the treatment effect for mepolizumab is larger in one age group than the others as is evidenced by the large p-value associated with the treatment-by-sex interaction, the effect of mepolizumab in 12 to 17 year olds is presumed to be similar to that of other age groups.

Examination of treatment effect by race: Mepolizumab is statistically significantly better than placebo with respect to the asthma exacerbation rate within White and Asian patients, as is evidenced by the combined analysis of studies 97 and 88. The treatment effect in African American/Black patients is less precise; however, taken together, studies 97 and 88 and the combined analysis of studies 97 and 88 do not give an indication that the treatment effect for mepolizumab is larger in one racial group than the others as is evidenced by the p-values associated with the treatment-by-sex interaction so the effect of mepolizumab in African American/Black patients is presumed to be similar to that of other racial groups.

Examination of treatment effect by ethnicity: Mepolizumab is statistically significantly better than placebo with respect to the asthma exacerbation rate within Non-Hispanic/Latino patients, as is evidenced by each of the individual studies and the combined analysis of studies 97 and 88. The treatment effect in Hispanic/Latino patients is less precise; however, since neither of the individual studies or the combined analysis of studies 97 and 88 give an indication that the treatment effect for mepolizumab is larger in one ethnicity group than the other as is evidenced by the p-values associated with the treatment-by-sex interaction, the effect of mepolizumab in Hispanic/Latino patients is presumed to be similar to that of Non-Hispanic/Latino patients.

Display of data to describe the effect of Mepolizumab across demographic subgroups could reliably be achieved by displaying results from the combined analysis of studies 88 and 97 as the treatment effects within subgroups were fairly consistent between the individual studies.

4 SUMMARY AND CONCLUSIONS

This review examined existing data to assess the treatment effect of mepolizumab on asthma exacerbation rate (defined as worsening of asthma requiring hospitalization, emergency department visits, the use of oral corticosteroids at least double the existing maintenance dose

for at least three days and/or for study 88, a single intramuscular injection of corticosteroids) in asthma patients with elevated blood eosinophil counts at baseline within each sex, age, race, and ethnicity subgroup and whether the treatment effect of mepolizumab on asthma exacerbation rate 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.

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- Mepolizumab is statistically significantly better than placebo with respect to the asthma exacerbation rate within White and Asian patients. There is little indication that the treatment effect of mepolizumab relative to placebo differs by race so while the treatment effect in African American/Black patients is less precise, the effect of mepolizumab in African American/Black patients is presumed to be similar to that of other racial groups.
- Mepolizumab is statistically significantly better than placebo with respect to the asthma exacerbation rate within Non-Hispanic/Latino patients. There is no indication that the treatment effect of mepolizumab relative to placebo differs by ethnicity so while the treatment effect in Hispanic/Latino patients is less precise, the effect of mepolizumab in Hispanic/Latino patients is presumed to be similar to that of Non-Hispanic/Latino patients.