Errata to the FDA Briefing Document
PADAC Advisory Committee Meeting
July 25, 2018

Page numbers refer to PDF page number

Division Memorandum

1. On page 6, 5th paragraph, 3rd sentence should read: "Across both trials, a total of ~~836~~ **865** subjects received any dose of mepolizumab while ~~674~~ **645** subjects received placebo."

2. On page 6, 5th paragraph, 6th sentence should read: "Imbalances in cardiovascular SAEs **and AEs** are noteworthy, particularly supraventricular tachyarrhythmias and cardiovascular thrombotic events."

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3. On page 17, 2nd paragraph, 4th sentence should read: "AECOPD classified as moderate necessitated intervention with systemic corticosteroids or antibiotics, while AECOPD classified as severe necessitated inpatient hospitalization of ≥24 hours **or resulted in death**."

4. On page 18, 1st paragraph, 5th sentence should read: "Greater than 85% of randomized subjects completed both MEA117106 and MEA117113 ~~when~~ **if** subjects who died are classified as completers, …"

5. On page 18, 2nd paragraph, 1st sentence should read: "…meeting high PB-Eos criteria receiving mepo100 compared to placebo (1.40 vs 1.71 AECOPD/yr), with a statistically significant rate ratio of 0.82 (95% CI 0.68 to 0.98; adjusted p-value ~~0.038~~ **0.036**)…"

6. On page 18, 3rd paragraph, 2nd sentence should read: "Point estimates describe baseline to week 52 rates of ModSev AECOPD in subjects receiving mepo100 compared to placebo (1.19 vs ~~1.48~~ **1.49** AECOPD/yr) with a rate ratio estimate of 0.80…"

7. On page 18, 3rd paragraph, 3rd sentence should read: "Rates of ModSev AECOPD in subjects receiving mepo300 compared to placebo (1.27 vs ~~1.48~~ **1.49** AECOPD/yr) yield a rate ratio estimate of 0.86 (95% CI 0.70 to ~~1.06~~ **1.05**; adjusted p-value: 0.140) and an absolute difference of 0.21 AECOPD/yr."

8. Page 20, 4th paragraph, 4th sentence should read: "Across both trials, a total of ~~836~~ **865** subjects received any dose of mepolizumab while ~~674~~ **645** subjects received placebo."

9. On page 30, Table 2 "Clinical Trial of Mepolizumab for COPD (Guided by Blood Eosinophils) should be replaced with the following table:

Study ID **Design/Duration** ***Study Dates***	**Treatment arms[1]**	**Subjects randomized**	**Study endpoints[5,6]**	**Study population**
MEA117106 NCT 02105948 R, DB, PC, MC, PG 52 weeks *15 Apr 2014 to 17 Jan 2017*	**Overall[2]** Mepo100 Placebo **High Stratum[3]** Mepo100 Placebo **Low Stratum[4]** Mepo100 Placebo	 417 419 233 229 184 190	1°: Rate of moderate to severe AECOPD 2°: -Time to first moderate to severe AECOPD -Rate of AECOPD requiring ED visit or hospitalization -Change from baseline SGRQ-C score -Change from baseline CAT score -Rate of severe AECOPD[7] -Change from baseline FEV1[7]	COPD patients with frequent AECOPD despite ICS+LABA+LAMA maintenance therapy
MEA117113 NCT 02105961 R, DB, PC, MC, PG 52 weeks *24 Apr 2014 to 16 Jan 2017*	 Mepo100 Mepo300 Placebo	 223 225 226		COPD patients[8] with frequent AECOPD despite ICS+LABA+LAMA maintenance therapy.

1. Treatment groups are the modified intent-to-treat (mITT population); mepo100 - mepolizumab 100 mg by subcutaneous injection every 4 weeks; Mepo300 - mepolizumab 300 mg by subcutaneous injection every 4 weeks;
2. Overall: all subjects regardless of PB-Eos counts
3. High Stratum (HS): subjects with PB-Eos counts ≥150 cells/µL at screening or ≥300 cells/µL within the last 12 months
4. Low Stratum (LS): subjects with PB-Eos counts <150 cells/µL at screening with no count ≥300 cells/µL within the last 12 months.
5. In MEA117106: pre-specified endpoints were evaluated in the mITT Overall: mepo100 vs placebo and mITT-HS: mepo100 vs placebo.
6. In MEA117113: pre-specified endpoints were evaluated in the mITT population for mepo100 vs PBO and mepo300 vs PBO.
7. Analyses of rate of severe AECOPD and change from baseline FEV1 were not pre-specified in the statistical analysis plan.
8. All patients in MEA117113 had peripheral blood eosinophil counts consistent with the High Stratum of Study MEA117106.

R: randomized; DB: double-blind; PC: placebo-controlled; MC: multicenter; PG: parallel group; AECOPD: acute exacerbation of COPD; ED: emergency department; SGRQ-C: Saint George's Respiratory Questionnaire for COPD; CAT: COPD Assessment Test; ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LAMA: long-acting anti-muscarinic NCT: National Clinical Trial; FEV1: forced expiratory volume in one second

10. Page 53, Table 4 "MEA117106: Demographic Characteristics (mITT Population)"
    - In the category "Region":
        i. row "United States", 1st column "Placebo" should read: "~~23 (10)~~ **22 (10)**"
        ii. row "United States", 5th column "Total" should read: "~~89 (11)~~ **88 (11)**"
        iii. row "Non-US", 1st column "Placebo" should read: "~~206 (90)~~ **207 (90)**"
        iv. row "Non-US", 5th column "Total" should read: "~~747 (89)~~ **748 (89)**"
        v. row "Eastern Europe", 5th column "Total" should read: "~~112 (13)~~ **122 (13)**"
        vi. row "Other", 1st column "Placebo" should read: "~~41 (18)~~ **42 (18)**"
        vii. row "Other", 5th column "Total" should read: "~~170 (20)~~ **171 (20)**"
    - Footnotes should include the following: "**mepo100: mepolizumab 100 mg SC every 4 weeks; SD: standard deviation**" and "**Source: Agency created using JMP software**"

11. Page 54, Table 5 "MEA117113: Demographic Characteristics (mITT Population)"
    - In the category "Region":
        i. row "Non-US", 1st column "Placebo" should read: "~~199 (88)~~ **198 (88)**"
        ii. row "Non-US", 4th column "Total" should read: "~~595 (88)~~ **594 (88)**"
        iii. row "Europe", 1st column "Placebo" should read: "~~62 (27)~~ **63 (27)**"
        iv. row "Europe", 4th column "Total" should read: "~~190 (28)~~ **189 (28)**"
    - Footnotes should include the following: "**mepo100: mepolizumab 100 mg SC every 4 weeks; mepo300: mepolizumab 300 mg SC every 4 weeks; SD: standard deviation**" and "**Source: Agency created using JMP software**"

12. Page 55, Table 6 "MEA117106: Baseline Disease Characteristics (mITT Population)"
    - In the category "Peripheral Blood Eosinophils":
        i. row "≥2% of total leukocyte count", 1st column "Placebo" should read: "~~212 (83)~~ **207 (90)**"
        ii. row "≥2% of total leukocyte count", 2nd column "mepo100" should read: "~~211 (81)~~ **202 (87)**"
        iii. row "≥2% of total leukocyte count", 3rd column "Placebo" should read: "~~12 (6)~~ **13 (7)**"
        iv. row "≥2% of total leukocyte count", 4th column "mepo100" should read: "~~25 (14)~~ **22 (12)**"
        v. row "≥2% of total leukocyte count", 5th column "Total" should read: "~~460 (55)~~ **444 (53)**"
    - In the category "Smoking Exposure":
        i. row "Mean pack-years (SD) among Current/former smokers", 1st column "Placebo" should read: "~~37.9 (11.2)~~ **46.4 (27.1)**"

ii. row "Mean pack-years (SD) among Current/former smokers", 2nd column "mepo100" should read: "~~36.8 (10.8)~~ **42.6 (24.3)**"
iii. row "Mean pack-years (SD) among Current/former smokers", 3rd column "Placebo" should read: "~~38.4 (11.5)~~ **44.4 (23.6)**"
iv. row "Mean pack-years (SD) among Current/former smokers", 4th column "mepo100" should read: "~~39.2 (10.9)~~ **49.9 (30.6)**"
v. row "Mean pack-years (SD) among Current/former smokers", 5th column "Total" should read: "~~38 (11.1)~~ **45.6 (26.5)**"

- Footnotes should include the following: "**mepo100: mepolizumab 100 mg SC every 4 weeks: mepo300: mITT: modified intention-to-treat; GOLD: Global Initiative for Chronic Obstructive Lung Disease; AECOPD: acute exacerbation of COPD; FEV1: forced expiratory volume in one second; mMRC: modified Medical Research Council; SGRQ: St. George's Respiratory Questionnaire for COPD**" and "**Source: Agency created using JMP software**"

13. Page 56, Table 7 "MEA117113: Baseline Disease Characteristics (mITT Population)"
    - In the category "Peripheral Blood Eosinophils":
      i. row "≥2% of total leukocyte count", 1st column "Placebo" should read: "~~173 (77)~~ **172 (76)**"
      ii. row "≥2% of total leukocyte count", 2nd column "mepo100" should read: "~~177 (79)~~ **176 (79)**"
      iii. row "≥2% of total leukocyte count", 3rd column "mepo300" should read: "~~165 (73)~~ **166 (74)**"
      iv. row "≥2% of total leukocyte count", 4th column "Total" should read: "~~515 (76)~~ **514 (76)**"
    - In the category "FEV1 Bronchodilator Responsiveness":
      i. row "Mean % reversibility (SD)", 1st column "Placebo" should read: "10.2 **(11.9)**"
      ii. row "Mean % reversibility (SD)", 2nd column "mepo100" should read: "8.8 **(11.0)**"
      iii. row "Mean % reversibility (SD)", 3rd column "mepo300" should read: "10.3 **(11.5)**"
      iv. row "Mean % reversibility (SD)", 4th column "Total" should read: "9.8 **(11.5)**"
    - Footnotes should read: "†SGRQ score was calculated using data from ~~223~~ **226**, ~~228~~ **220**, ~~184~~ **222**, ~~182, and 817~~ **and 667** subjects, respectively. ‡Charlson Comorbidity Index score data was available for ~~228~~ **224**, ~~233~~ **222**, ~~190~~ **223**, ~~184, and 835~~ **and 669** subjects, respectively.
    - Footnotes should include the following: "**mepo100: mepolizumab 100 mg SC every 4 weeks: mepo300: mepolizumab 300 mg SC every 4 weeks; mITT: modified intention-to-treat; GOLD: Global Initiative for Chronic Obstructive Lung Disease; AECOPD: acute exacerbation of COPD; FEV1: forced expiratory volume in one second; mMRC: modified Medical Research Council; SGRQ: St. George's Respiratory**

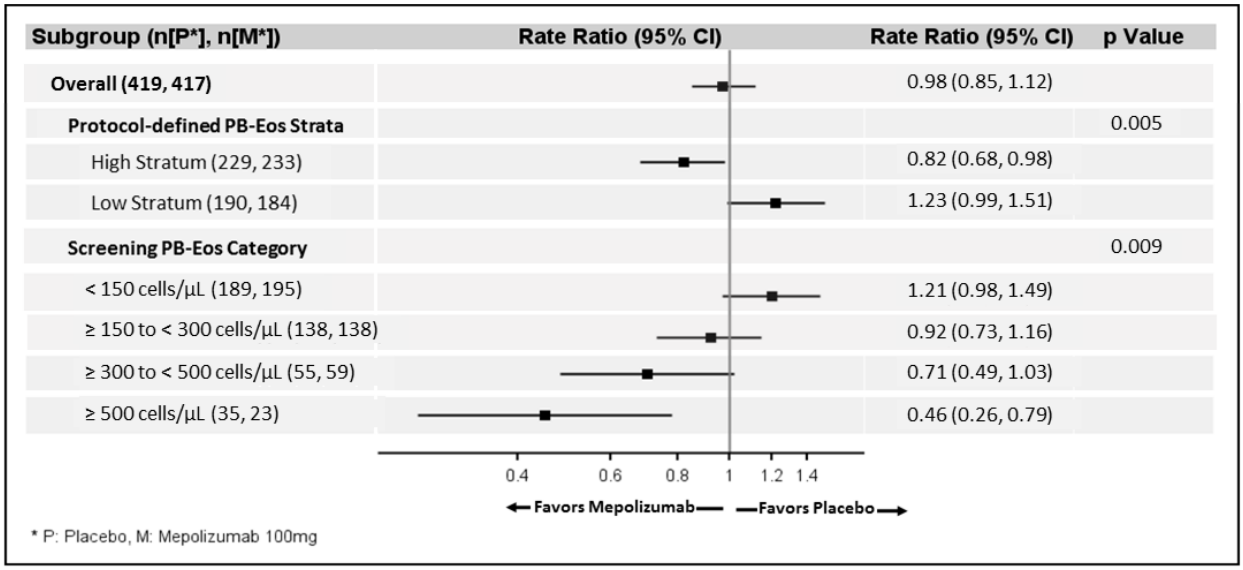
Questionnaire for COPD" and "**Source: Agency created using JMP software**"

14. Page 60, Table 10 "MEA117106 mITT-HS, mITT-LS, and MEA117113 mITT: AECOPD Severity Details"
    - In the category "Number of Patients with On- and Off-Treatment AECOPD":
        i. row "Severe", 3rd column "Placebo" should read: "~~40 (21)~~ **29 (15)**"

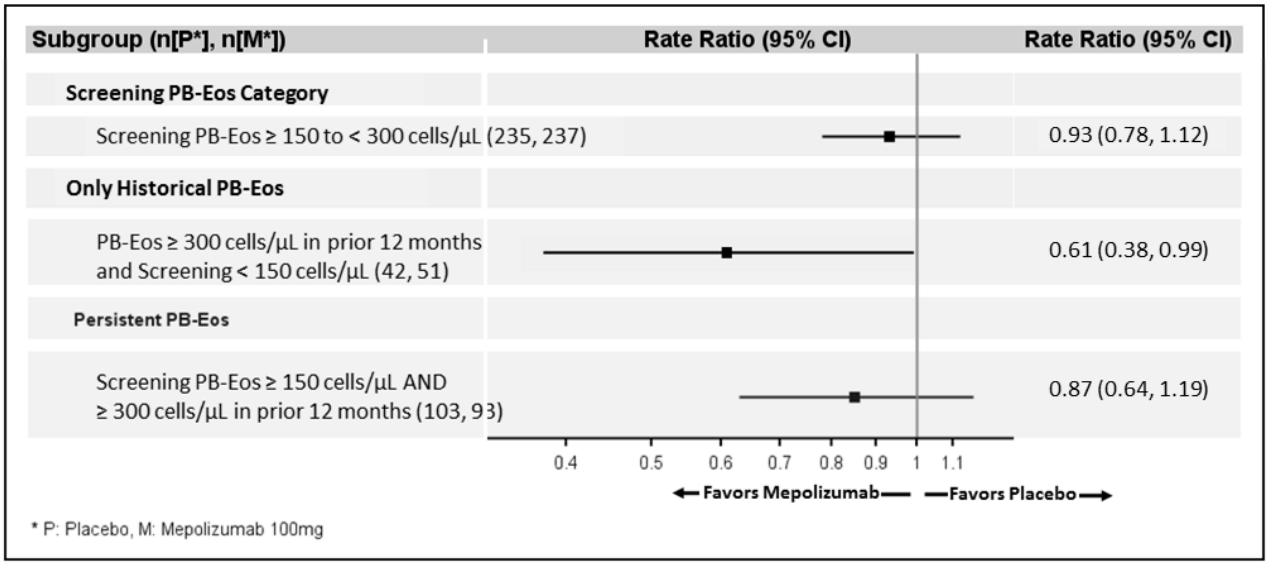
15. Page 62, Table 12 "MEA117106 mITT-HS and MEA117113 mITT: Pre-Specified Secondary Efficacy Analysis Results"
    - Title should read "MEA117106 mITT-HS and MEA117113 mITT: Pre-Specified **and Key** Secondary Efficacy ~~Analysis~~ **Analyses** Results"
    - In the category "Mean Change in Forced Expiratory Volume in One Second":
        i. row "LS mean change in mL (SE)", 3rd column "Placebo" should read: "-13 **(17.6)**"
        ii. row "LS mean change in mL (SE)", 4th column "mepo100" should read: "6 **(17.0)**"
        iii. row "LS mean change in mL (SE)", 5th column "mepo300" should read: "21 **(17.1)**"
    - Footnotes should include the following: "**Analyses of Rate of Severe AECOPD and Mean Change in Forced Expiratory Volume in One Second were not pre-specified in the statistical analysis plan**" and "**mITT: modified intention-to-treat; HS: High Stratum; mepo100: mepolizumab 100 mg SC every 4 weeks: mepo300: mepolizumab 300 mg SC every 4 weeks; AECOPD: acute exacerbation of COPD; ED: emergency department; FEV1: forced expiratory volume in one second; mMRC: modified Medical Research Council; SGRQ: St. George's Respiratory Questionnaire for COPD; AECOPD: acute exacerbation of COPD**"

16. Page 67, Table 14 "Summary of Test Results across the Two Studies"
    - In the category "Secondary Endpoints"
        i. row "Frequency of COPD exacerbations requiring emergency department visit and/or hospitalization (rate ratio)", 3rd column "mepo300 vs Placebo" should read: "0.83 (0.51, 1.34) Adjusted p= ~~0.442~~ **0.447**"
        ii. row "Change from baseline SGRQ-C total Score (mean difference)", 2nd column "mepo100 vs Placebo" should read: -1.8 (-4.5, 0.8) Adjusted p= ~~0.442~~ **0.447**"
        iii. row "Change from baseline CAT score (mean difference)", 1st column "mepo100 vs Placebo" should read: "~~0.8~~ **-0.8** (-2.0, 0.5) Adjusted p>0.999"
    - Footnotes should include the following: "**mepo100: mepolizumab 100 mg SC every 4 weeks; mepo300: mepolizumab 300 mg SC every 4 weeks; SGRQ-C: St. George's Respiratory Questionnaire for COPD; CAT: COPD Assessment Test**"

17. On page 71, Figure 9 “MEA117106 mITT-HS and mITT-LS: Analyses of Rate of Moderate to Severe AECOPD by Eosinophil Stratum and by Screening Peripheral Blood Eosinophil Categories” should be replaced with the following figure:

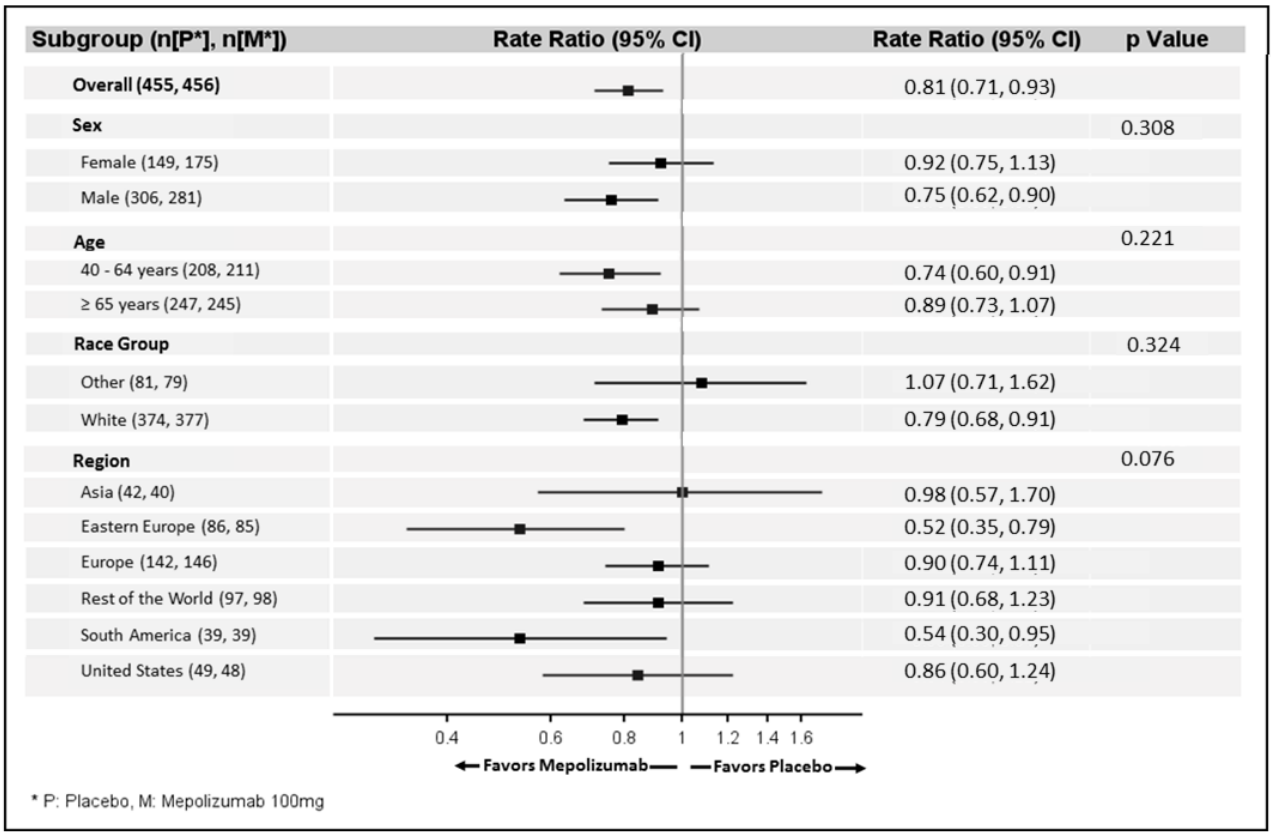


18. On page 72, Figure 10 “MEA117106 mITT-HS and MEA117113 mITT: Exploratory Analyses of Rate of Moderate to Severe AECOPD by Screening Peripheral Blood Eosinophil Categories” should be replaced with the following figure:

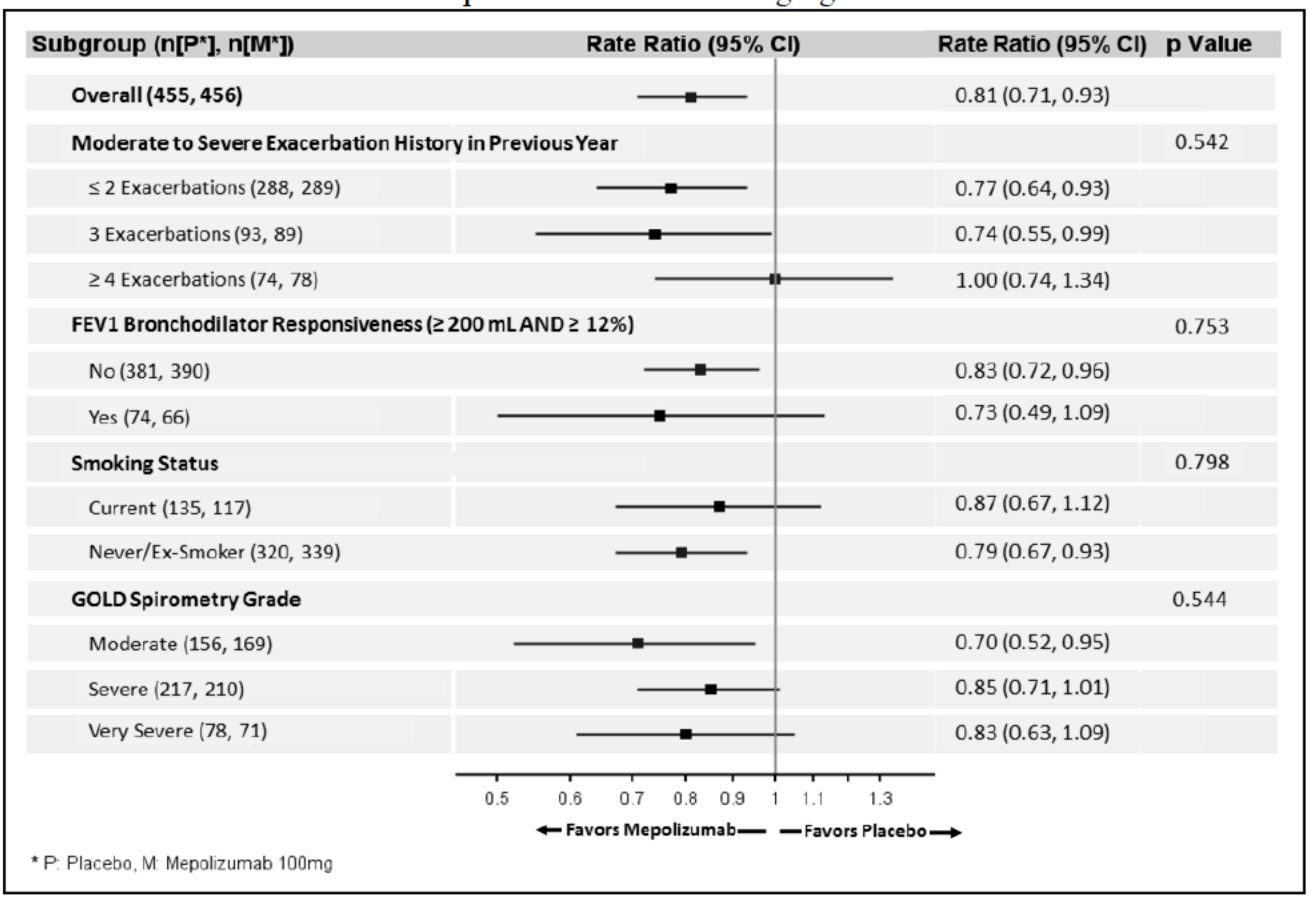


19. Page 73, 4th Paragraph, 1st sentence should read: "The presence of two adverse events classified with verbatim terms "asthma symptoms increase" and one classified as "overlap syndrome of asthma/COPD" in the ~~MEA117113~~ **MEA117106** safety data suggests that the trial design did not eliminate enrollment of subjects with active asthma"

20. On page 73, Figure 11 "MEA117106 mITT-HS and MEA117113 mITT: Exploratory Analyses of Rate of Moderate to Severe AECOPD by Demographic Subgroups" should be replaced with the following figure:



21. On page 74, Figure 12 "MEA117106 mITT-HS and MEA117113 mITT: Exploratory Analyses of Rate of Moderate to Severe AECOPD by Baseline Disease Characteristics" should be replaced with the following figure:



22. On Page 82, Table 15 "Extent of Exposure to Mepolizumab" should be replaced by:

Safety Database for Mepolizumab Individuals exposed to any treatment in the mepolizumab development program n = 4682 (n is the sum of all available numbers from the columns below)		
Clinical Trial Groups	**Mepolizumab, any dose n (subject-years)**	**Placebo n (subject-years)**
Controlled trials conducted for this indication	865 (794.1)	645 (569.7)
Controlled trials conducted for other indications	2522 (3661)	1059 (547.9)

23. On page 84, Table 17: “Treatment Emergent SAE Safety Signals in MEA117106 and MEA117113”
    - Table Title should read: Treatment Emergent ~~SAE~~ **SMQ** Safety Signals in MEA117106 and MEA117113”

24. On page 85, 5th paragraph, 3rd sentence should read: “In MEA117106, 3.1% of subjects in the mepolizumab arm experienced SVTA events compared to ~~1.5%~~ **1.4%** of subjects in the placebo arm; similarly, in MEA117113, ~~3.9%~~ **3.8%** of subjects in the mepolizumab arms experienced SVTA events compared to ~~2.7%~~ **3.1%** of subjects in the placebo arm”

25. On page 87, 6th paragraph, 1st sentence should read: “~~Two~~ ~~subjects~~ **One subject** experienced a treatment-emergent ~~events~~ **event** classified with the AE term “anaphylactic reaction” ~~in~~ **across** trials MEA117113 and MEA117106, ~~both subjects~~ **and that subject** received mepolizumab; no anaphylactic reactions were observed in the placebo arms of MEA117113 or MEA117106.”

26. On page 90, Table 20 “Common Adverse Reactions in Trials MEA117106 and MEA117113”
    - In the category “Preferred Term”
        i. Row “Pain in extremity”, 2nd column “Subjects (N%)” should read: ”32 (3.7)”

27. On page 91, 1st paragraph, 1st sentence, should read: “Analysis of treatment-emergent hypertension AE terms in MEA117106 shows that ~~3.38%~~ **3.4%** of subjects in the mepolizumab arm experienced hypertension AE terms compared to 2.9% of subjects in the placebo arm; similarly, analysis of hypertension AE terms in MEA117113 shows that ~~5.5%~~ **5.4%** of subjects in the mepolizumab arm experienced hypertension AE terms compared to ~~2.3%~~ **2.2%** of subjects in the placebo arm.