

FDA Pulmonary-Allergy Advisory Committee Meeting

FDA Opening Remarks

sBLA 125526: Mepolizumab for the add-on treatment to inhaled corticosteroid-based maintenance treatment for the reduction of exacerbations in patients with chronic obstructive pulmonary disease (COPD) guided by blood eosinophil counts

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U.S. Food and Drug Administration

July 25, 2018

Mepoluzimab (Nucala®)



- Monoclonal antibody (mAb) directed against IL5
 - Leads to decreased eosinophil maturation and survival
- Approved Indications
 - Severe asthma with eosinophilic phenotype (Nov 2015)
 - 100 mg subcutaneously once every 4 weeks
 - Eosinophilic granulomatosis with polyangiitis (Dec 2017)
 - 300 mg subcutaneously once every 4 weeks

Mepoluzimab (Nucala®)

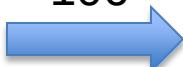


- Proposed indication
 - For the add-on treatment to inhaled corticosteroid-based maintenance treatment for the reduction of exacerbations in patients with chronic obstructive pulmonary disease (COPD) guided by blood eosinophil counts
- Proposed Dose
 - 100 mg subcutaneously once every 4 weeks

Clinical Development Program

FDA

Study
106



METREX

Study
113



METREO

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	Overall² Mepo100 Placebo High Stratum³ Mepo100 Placebo Low Stratum⁴ 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	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	-Change from baseline SGRQ-C score -Change from baseline CAT score -Rate of severe AECOPD ⁷ -Change from baseline FEV1 ⁷	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/ μ L at screening or ≥ 300 cells/ μ L within the last 12 months
4. Low Stratum (LS): subjects with PB-Eos counts < 150 cells/ μ L at screening with no count ≥ 300 cells/ μ L 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

Efficacy Summary – Primary Endpoint



- **Study 106**

- Statistically significant reduction in rate of moderate-to-severe exacerbations in patients in the high eosinophil stratum
- Rate ratio: 0.82 [95% CI: 0.68, 0.98], adjusted p-value: 0.04

- **Study 113**

- Insufficient statistical evidence to support the effect of mepolizumab on the reduction in rate of moderate to severe exacerbations for either the 100 mg or 300 mg dose
- Mepo 100 mg: Rate ratio: 0.80 [95% CI: 0.65, 0.98], adjusted p-value: 0.07
- Mepo 300 mg: Rate ratio: 0.86 [95% CI: 0.70, 1.05], adjusted p-value: 0.14

Efficacy Summary – Secondary Endpoints



- **Study 106**

- Statistically significant reduction in time to first moderate/severe exacerbation in the high eosinophil stratum
- Hazard ratio: 0.75 [95% CI: 0.60, 0.94], adjusted p-value: 0.036
- Other secondary endpoints did not support the primary endpoint

- **Study 113**

- Lack of supportive evidence of the effect of mepoluzimab over placebo with respect to important clinical endpoints

Efficacy Considerations – Patient Selection



- Lack of consensus around the definition/relevance of an eosinophilic COPD phenotype
 - Definitions of High and Low Stratum carried over from asthma program
 - Study 106 Low Stratum, mepolizumab 100 mg showed a numerical increase in the rate of moderate to severe exacerbations [rate ratio: 1.23, 95% CI (0.99, 1.51)]
- Potential inclusion of asthma patients in the COPD program
 - Baseline data on asthma history not collected



Efficacy Considerations – Exacerbations

- Moderate-to-Severe COPD Exacerbations are a clinically meaningful endpoint
- Study 106 demonstrated a significant reduction in exacerbations, while Study 113 did not.
- Clinically important secondary endpoints did not consistently support the primary endpoint in either study.
- Other key endpoints e.g. SGRQ-C, FEV1, and rate of severe exacerbation showed no evidence of benefit.
- Positive results in Study 106 driven by moderate exacerbations

Safety Considerations

- Numerically small imbalances in serious adverse events and adverse events related to:
 - Supraventricular tachyarrhythmias
 - Cardiovascular thrombotic events
 - GI Bleeding
 - Acute pancreatitis
- Other Adverse Events:
 - Oral Candidiasis
 - Herpes Zoster

Discussion Points and Voting Questions

- 1. DISCUSSION:** Discuss the eosinophilic COPD phenotype (i.e., the relevance of peripheral blood eosinophils in COPD patients) and the criteria used in the mepolizumab program to define the patient population.

Discussion Points and Voting Questions

2. **DISCUSSION:** Discuss the efficacy of mepolizumab as add-on treatment to inhaled corticosteroid-based maintenance treatment for the reduction of exacerbations in patients with COPD guided by blood eosinophil counts. Include the following topics in your discussion:
- a. the adequacy of dose exploration in COPD patients
 - b. the potential effect of unmeasured variables (e.g., lack of information regarding asthma history and oral corticosteroid use)
 - c. the lack of statistically significant results for the primary endpoint in one of the two trials *[continued on next slide]*

Discussion Points and Voting Questions

2. **DISCUSSION (cont'd):** Discuss the efficacy of mepolizumab as add-on treatment to inhaled corticosteroid-based maintenance treatment for the reduction of exacerbations in patients with COPD guided by blood eosinophil counts. Include the following topics in your discussion:
- d. the clinical significance of the efficacy results (i.e., efficacy driven by moderate exacerbations)
 - e. lack of robust results for key secondary endpoint
 - f. efficacy results in the low eosinophil stratum that showed a numerical increase in COPD exacerbations
 - g. interpretation of the efficacy results given the uncertainty in the definition of the eosinophilic COPD phenotype

Discussion Points and Voting Questions

3. **VOTE:** Do the data provide substantial evidence of efficacy for mepolizumab as add-on treatment to inhaled corticosteroid-based maintenance treatment for the reduction of exacerbations in patients with chronic obstructive pulmonary disease (COPD) guided by blood eosinophil counts?
 - If no, what data are needed?
4. **VOTE:** Are the safety data adequate to support approval of mepolizumab as add-on treatment to inhaled corticosteroid-based maintenance treatment for the reduction of exacerbations in patients with chronic obstructive pulmonary disease (COPD) guided by blood eosinophil counts?
 - If no, what data are needed?

Discussion Points and Voting Questions

5. **VOTE:** Is the benefit-risk profile adequate to support approval of mepolizumab as add-on treatment to inhaled corticosteroid-based maintenance treatment for the reduction of exacerbations in patients with chronic obstructive pulmonary disease (COPD) guided by blood eosinophil counts?
- If no, what data are needed?



FDA Pulmonary-Allergy Advisory Committee Meeting

Overview of the Clinical Program

sBLA 125526: Mepolizumab for the add-on treatment to inhaled corticosteroid-based maintenance treatment for the reduction of exacerbations in patients with chronic obstructive pulmonary disease (COPD) guided by blood eosinophil counts

Robert Busch, MD, MMSc
Clinical Reviewer

Division of Pulmonary, Allergy, and Rheumatology Products
U.S. Food and Drug Administration
July 25, 2018



Outline

- Overview of the Clinical Program

Robert Busch, MD, MMSC

Medical Officer: DPARP, ODE2, OND, CDER, FDA

- Statistical Review of Efficacy

Yu (Jade) Wang, PhD

Biometrics Reviewer: DB2, OTS, CDER, FDA

- Review of Safety

Robert Busch, MD, MMSC

Medical Officer: DPARP, ODE2, OND, CDER, FDA

- Clinical Considerations and Benefit Risk Assessment

Robert Busch, MD, MMSC

Medical Officer: DPARP, ODE2, OND, CDER, FDA

Overview of the Clinical Program

Overview of the Clinical Program Objectives



Eosinophilic COPD Phenotype

Mepolizumab COPD Development Program

Trial Design and Endpoints

Patient Population Considerations

Eosinophilic COPD Phenotype

Mepolizumab COPD Development Program

Trial Design and Endpoints

Patient Population Considerations

Eosinophilic COPD Phenotype

- Uncertain prevalence due to uncertain definition
 - Sputum eosinophils $\geq 3\%$ of total leukocytes¹⁻⁴
 - Blood eosinophils $\geq 2\%$ of total leukocytes⁵
 - Blood eosinophils ≥ 300 cells/ μL ^{6,7}

References:

1. Bafadhel M, et al. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med* 2011; 184: 662-671.
2. Brightling CE, et al. Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2000; 356: 1480-1485.
3. Pizzichini E, Pizzichini MM, Gibson P, et al. Sputum eosinophilia predicts benefit from prednisone in smokers with chronic obstructive bronchitis. *Am J Respir Crit Care Med* 1998;158:1511-7
4. Siva R, et al. Eosinophilic airway inflammation and exacerbations of COPD: a randomised controlled trial. *Eur*

Respir J 2007; 29: 906-913.

5. Singh D, Kolsum U, Brightling CE, et al. Eosinophilic inflammation in COPD: prevalence and clinical characteristics. *Eur Respir J* 2014;44:1697-700
6. Zeiger RS, Tran TN, Butler RK, et al. Relationship of Blood Eosinophil Count to Exacerbations in Chronic Obstructive Pulmonary Disease. *J Allergy Clin Immunol Pract* 2018;6:944-54 e5
7. Yun JH, et al. Blood eosinophil count thresholds and exacerbations in patients with chronic obstructive pulmonary disease. *J Allergy Clin Immunol* 2018;141:2037-47 e10.

Eosinophilic COPD Phenotype



- Uncertain clinical impact
 - Exacerbation rates¹⁻¹¹
 - Response to therapies²⁻¹¹

References:

1. Singh D, et al. Eosinophilic inflammation in COPD: prevalence and clinical characteristics. *Eur Respir J* 2014; 44: 1697-1700.
2. Pascoe S, et al. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. *Lancet Respir Med* 2015; 3: 435-442.
3. Pavord ID, et al. Blood eosinophils and inhaled corticosteroid/long-acting beta-2 agonist efficacy in COPD. *Thorax* 2016; 71: 118-125.
4. Hastie AT, et al. Association of sputum and blood eosinophil concentrations with clinical measures of COPD severity: an analysis of the SPIROMICS cohort. *Lancet Respir Med* 2017.
5. Burge PS, et al. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000; 320: pp. 1297-130.
6. Calverley P, et al: Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003; 361: pp. 449-456.
7. Dransfield MT, et al: Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. *Lancet Respir Med* 2013; 1: pp. 210-223.
8. Wedzicha JA, et al: Extrafine beclomethasone/formoterol in severe COPD patients with history of exacerbations. *Respir Med* 2014; 108: pp. 1153-1162.
9. Wedzicha JA, et al: The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med* 2008; 177: pp. 19-26.
10. Wedzicha JA, et al: Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. *N Engl J Med* 2016; 374: pp. 2222-2234.
11. Roche N, Chapman KR, Vogelmeier CF, et al. Blood Eosinophils and Response to Maintenance Chronic Obstructive Pulmonary Disease Treatment. Data from the FLAME Trial. *Am J Respir Crit Care Med* 2017;195:1189-97.

Eosinophilic COPD Phenotype

- Uncertainty in peripheral blood eosinophils as a marker
 - Original description of phenotype used sputum eosinophilia
 - Low correlation between sputum and blood eosinophils^{1,2}
 - Can peripheral blood eosinophil thresholds predict sputum eosinophilia thresholds?
 - High sensitivity and moderate specificity^{2,3}; high false discovery rate²

References:

1. Singh D, et al. Eosinophilic inflammation in COPD: prevalence and clinical characteristics. *Eur Respir J* 2014; 44: 1697-1700.
2. Hastie AT, et al. Association of sputum and blood eosinophil concentrations with clinical measures of COPD severity: an analysis of the SPIROMICS cohort. *Lancet Respir Med* 2017.
3. Bafadhel M, et al. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med* 2011; 184: 662-671.

Eosinophilic COPD Phenotype



- High variability in blood eosinophils
 - Diurnal, seasonal and hormonal variation in peripheral blood eosinophil counts^{1,2}
 - Dependent on drugs, allergies, concomitant disease
 - Variability versus phenotype definition
 - Require consistently high eosinophils?
 - Allow variable eosinophil levels?
 - Other defining factors?

References:

1. Hamad GA, et al. Eosinophils in COPD: how many swallows make a summer? Eur Respir J 2018;51
2. Lacher DA, Barletta J, Hughes JP. Biological variation of hematology tests based on the 1999-2002 National Health and Nutrition Examination Survey. Natl Health Stat Report 2012:1-10.

Eosinophilic COPD Phenotype

- Defining criteria are uncertain¹⁻¹⁷
 - Sputum or peripheral blood?
 - ≥ 150 , ≥ 200 , ≥ 300 cells/ μL ?
 - 2%, 3%, higher?
 - Single measurement, persistence over time?

References:

1. Singh D, et al. Eosinophilic inflammation in COPD: prevalence and clinical characteristics. *Eur Respir J* 2014; 44: 1697-1700.
2. Bafadhel M, et al. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med* 2011; 184: 662-671.
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14. Wedzicha JA, et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. *N Engl J Med* 2016; 374: pp. 2222-2234.
15. Hamad GA, et al. Eosinophils in COPD: how many swallows make a summer? *Eur Respir J* 2018; 51.
16. Bafadhel M. Eosinophils in COPD: are we nearly there yet? *Lancet Respir Med* 2017; 5: 913-4.
17. Bafadhel M, Pavord ID, Russell REK. Eosinophils in COPD: just another biomarker? *Lancet Respir Med* 2017; 5: 747-59.

Mechanism of Action



- Mechanism of action of mepolizumab in COPD is unclear
- Proposed rationale relies on the following:
 - The threshold of peripheral blood eosinophilia used in the severe asthma program applies to COPD
 - Interleukin-5 inhibition will decrease eosinophilic airway inflammation
 - Decrease in eosinophilic airway inflammation will cause clinically meaningful changes in validated COPD endpoints

Eosinophilic COPD Phenotype

Mepolizumab COPD Development Program

Trial Design and Endpoints

Patient Population Considerations

Regulatory History

- End-of-Phase 2 Meeting (August 28, 2013)
 - Exacerbations accepted as reasonable primary endpoint for pivotal trials
 - Concerns regarding uncertainty in eosinophilic COPD phenotype/definition
 - Concern about proposed subset of eosinophilic COPD
 - Using only peripheral blood eosinophil counts and frequent exacerbations
 - Potential for results to reflect treatment effect in similar or comorbid diseases such as asthma.
 - Requirements for subsequent trials
 - Characterize the eosinophilic COPD phenotype
 - Evaluate eosinophils as a biomarker
 - Include patients with and without peripheral blood eosinophilia in the trials.
 - FDA recommended proof-of-concept and preliminary dose-ranging trials

Regulatory History

- Pre-sBLA Meeting (August 1, 2017)
 - Concerns about strength of efficacy data
 - FDA reiterated concerns regarding
 - Utility of peripheral blood eosinophils as a biomarker in COPD
 - Definition of eosinophilic COPD phenotype
 - Uncertainty in the scientific literature
 - GSK responded to reiterated concerns regarding phenotype definitions and asthma
 - GSK presented selected demographic and baseline disease characteristic data in COPD program and previous asthma programs
 - This potential uncertainty in trial population with regards to asthma remained a review issue for the application

Eosinophilic COPD Phenotype

Mepolizumab COPD Development Program

Trial Design and Endpoints

Patient Population Considerations

Pivotal Efficacy Trials

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	Overall²	417	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
	Mepo100	419		
	Placebo	419		
	High Stratum³	233		
	Mepo100	229		
	Placebo	229		
	Low Stratum⁴	184		
	Mepo100	190		
	Placebo	190		
MEA117113 NCT 02105961 R, DB, PC, MC, PG 52 weeks 24 Apr 2014 to 16 Jan 2017	Mepo100	223		COPD patients ⁸ with frequent AECOPD despite ICS+LABA+LAMA maintenance therapy.
	Mepo300	225		
	Placebo	226		

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/ μ L at screening or ≥ 300 cells/ μ L within the last 12 months
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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

Source: Reviewer

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Pivotal Efficacy Trials

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Source: Reviewer

Primary Endpoint

- Annualized rate of moderate-to-severe COPD exacerbations over 52 weeks
- Acute Exacerbations of COPD (AECOPD)
 - Worsening of disease symptoms requiring additional medical intervention
 - Severe AECOPD defined by the need for hospitalization, or death
 - Severe AECOPD associated with disease progression, morbidity, and death¹⁻⁵
 - Moderate AECOPD defined by prescription of systemic steroids and/or antibiotics
 - Moderate AECOPD associated with decreased quality of life^{2,3}

References:

1. Celli BR, Barnes PJ. Exacerbations of chronic obstructive pulmonary disease. Eur Respir J 2007;29:1224-38.
2. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157:1418-22.
3. Dransfield MT, Kunisaki KM, Strand MJ, et al. Acute Exacerbations and Lung Function Loss in Smokers with and without Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 2017;195:324-30.
4. Soler-Cataluna JJ, Martinez-Garcia MA, Roman Sanchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax 2005;60:925-31.
5. Celli BR, Locantore N, Yates J, et al. Inflammatory biomarkers improve clinical prediction of mortality in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2012;185:1065-72.

Secondary Endpoints

- Time-to-first moderate-to-severe AECOPD
 - Complements moderate-to-severe AECOPD rate
- Change from baseline in symptom scores
 - St. George's Respiratory Questionnaire for COPD (SGRQ-C)
 - COPD Assessment Test (CAT)
- Rate of AECOPD requiring emergency department visit or hospitalization
- Rate of severe AECOPD
 - Associated with morbidity and mortality
- Change from baseline in forced expiratory volume in one second (FEV1)
 - Accepted measure of COPD severity



Eosinophilic COPD Phenotype

Mepolizumab COPD Development Program

Trial Design and Endpoints

Patient Population Considerations

Entry Criteria Considerations



- Asthma exclusion criterion
 - **Asthma:**
 - **Current and Former Smokers:** Subjects with a current diagnosis of asthma (those with a prior history are eligible if they meet inclusion criteria for a current diagnosis of COPD)
 - **Never-Smokers:** Subjects with any history of asthma
- Asthma's influence on primary endpoint
- Contrast with previous trials¹⁻³

References:

1. Bafadhel M, et al. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. Am J Respir Crit Care Med 2011; 184: 662-671.
2. Siva R, et al. Eosinophilic airway inflammation and exacerbations of COPD: a randomised controlled trial. Eur Respir J 2007; 29: 906-913.

3.

3. Pizzichini E, Pizzichini MM, Gibson P, et al. Sputum eosinophilia predicts benefit from prednisone in smokers with chronic obstructive bronchitis. Am J Respir Crit Care Med 1998;158:1511-7

Disease Characteristics



Disease Parameters	MEA117106				MEA117113		
	High Stratum		Low Stratum		Placebo n = 226	mepo100 n = 223	mepo300 n = 225
	Placebo n = 229	mepo100 n = 233	Placebo n = 190	mepo100 n = 184			
Peripheral Blood Eosinophils							
≥2% of total leukocyte count, n(%)	207 (90)	202 (87)	13 (7)	22 (12)	172 (76)	176 (79)	166 (74)
Geometric mean cells/μL (SD Logs)	290 (560)	250 (580)	70 (780)	70 (700)	230 (870)	230 (860)	230 (810)
COPD Therapies							
ICS	228 (>99)	233 (100)	190 (100)	184 (100)	224 (>99)	222 (>99)	224 (>99)
LABA	228 (>99)	233 (100)	190 (100)	183 (>99)	224 (>99)	222 (>99)	225 (100)
LAMA	226 (99)	231 (>99)	189 (>99)	182 (99)	222 (98)	223 (100)	225 (100)
Chronic oral corticosteroids*	9 (4)*	13 (6)*	7 (4)*	9 (5)*	8 (4)*	12 (5)*	10 (4)*
FEV₁ Bronchodilator Responsiveness							
≥200mL and ≥12% reversibility, n(%)	39 (17)	32 (14)	28 (15)	23 (13)	35 (15)	34 (15)	39 (17)
Mean % reversibility (SD)	10.3 (13.5)	8.9 (11.5)	8.1 (11.3)	9.1 (11.1)	10.2 (11.9)	8.8 (11.0)	10.3 (11.5)

*Baseline chronic OCS was not assessed during routine trial data collection; assessment occurred through post hoc clinical review.

High Stratum: peripheral blood eosinophils ≥150 cells/μL at screening or ≥300 cells/μL in the last 12 months; Low Stratum: peripheral blood eosinophils <150 cells/μL at screening and no measurement ≥300 cells/μL in the last 12 months; mepo100: mepolizumab 100 mg SC every 4 weeks; mepo300: mepolizumab 300 mg SC every 4 weeks; ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist; SD: standard deviation

Safety Characteristics



Disease Parameters	MEA117106					MEA117113		
	High Stratum		Low Stratum			Placebo n = 226	mepo100 n = 223	mepo300 n = 225
	Placebo n = 229	mepo100 n = 233	Placebo n = 190	mepo100 n = 184				
Age								
Mean years (SD)	65.3 (8.5)	65.2 (8.4)	65.2 (8.6)	66.1 (9.1)		65.8 (8.6)	64.8 (9.1)	64.8 (9)
Min, max (years)	40, 83	43, 83	39, 85	40, 85		43, 88	42, 86	45, 85
Age Category								
≥ 40 - < 65 years	107 (47)	107 (46)	85 (45)	75 (41)		101 (45)	104 (47)	110 (49)
≥ 65 years	122 (53)	126 (54)	104 (55)	109 (59)		125 (55)	119 (53)	115 (51)
Smoking Exposure								
Never/non-smokers	11 (5)	7 (3)	13 (7)	9 (5)		2 (<1)	5 (2)	6 (3)
Current/former smokers	218 (95)	226 (97)	177 (93)	175 (95)		224 (99)	218 (98)	219 (97)
Mean pack-years (SD) among Current/former smokers	46.4 (27.1)	42.6 (24.3)	44.4 (23.6)	49.9 (30.6)		46.1 (27.2)	42.6 (25.9)	44.1 (30.8)
Charlson Comorbidity Index [‡]								
1 to 2	7 (3)	8 (3)	8 (4)	7 (4)		7 (3)	10 (4)	14 (6)
3 to 4	112 (49)	124 (53)	101 (53)	90 (49)		113 (50)	114 (51)	109 (48)
≥5	109 (48)	101 (43)	81 (43)	87 (47)		104 (46)	98 (44)	100 (44)

*Charlson Comorbidity Index (CCI) score data was available for 228, 233, 190, 184, and 835 subjects, respectively, in MEA117106. CCI score data was available for 224, 222, 223, and 669 subjects, respectively, in MEA117113
mepo100: mepolizumab 100 mg SC every 4 weeks; mepo300: mepolizumab 300 mg SC every 4 weeks; High Stratum: peripheral blood eosinophils ≥150 cells/μL at screening or ≥300 cells/μL in the last 12 months; Low Stratum: peripheral blood eosinophils <150 cells/μL at screening and no measurement ≥300 cells/μL in the last 12 months;
Source: Reviewer

Summary

- Eosinophilic COPD Phenotype
 - Uncertain definition, prevalence, and impact
- Mepolizumab COPD Development Program
 - Eosinophil thresholds carried over from asthma
 - No dose-ranging or proof-of-concept trials in COPD
- Trial Design and Endpoints
 - Secondary endpoints to support primary endpoints
- Patient Population Considerations
 - Asthma exclusion criteria permissive

Outline



- Overview of the Clinical Program

Robert Busch, MD, MMSC

Medical Officer: DPARP, ODE2, OND, CDER, FDA

- Statistical Review of Efficacy

Yu (Jade) Wang, PhD

Biometrics Reviewer: DB2, OTS, CDER, FDA

- Review of Safety

Robert Busch, MD, MMSC

Medical Officer: DPARP, ODE2, OND, CDER, FDA

- Clinical Considerations and Benefit Risk Assessment

Robert Busch, MD, MMSC

Medical Officer: DPARP, ODE2, OND, CDER, FDA

FDA Pulmonary-Allergy Advisory Committee Meeting

Statistical Review of Efficacy

sBLA 125526: Mepolizumab for the add-on treatment to inhaled corticosteroid-based maintenance treatment for the reduction of exacerbations in patients with chronic obstructive pulmonary disease (COPD) guided by blood eosinophil counts

Yu Wang, PhD
Statistical Reviewer
Division of Biometrics II, Office of Biometrics
Office of Translational Sciences
U.S. Food and Drug Administration
July 25, 2018

Outline

- Statistical Analysis Plans
 - MEA117106 (METREX): Study 106
 - MEA117113 (METREO): Study 113
- Key Efficacy Analysis Methods and Results
- Exploratory Analysis Results
 - Subgroup Analyses
 - Analyses of Treatment Effect by Eosinophil Level
- Efficacy Review Summary

STATISTICAL ANALYSIS PLAN

Program Objective and Primary Estimand

- Key Objective: to demonstrate an exacerbation reduction
- Primary estimand: **de facto or treatment policy**
 - Endpoint: annual rate of moderate or severe COPD exacerbations
 - Measure for treatment comparison: ratio of annual rates
 - Intercurrent event handling: **regardless of treatment discontinuation**
 - Primary analysis based on both **on-treatment and, where available, off-treatment data**

Impact of Missing Data

- Sensitivity analyses conducted to assess robustness of results to alternative missing data assumptions
- Missing-not-at-random assumptions were studied
 - Jump to Reference method: multiple imputation based on control group data
 - Tipping point analysis: systematically and comprehensively varying assumptions

Type I Error Control

- Sequential gatekeeping procedure was employed to address multiple endpoints in both studies
 - **Study 106: Fallback method** was used for eosinophil high stratum subgroup and overall population analyses
 - **Study 113: Hochberg method** was used for Mepolizumab 100 mg vs Placebo and Mepolizumab 300 mg vs Placebo comparisons
- Methods are considered appropriate

Primary and Key Secondary Efficacy Endpoints

	Order	Endpoint
Endpoints Included in Multiple Testing Procedure	Primary Efficacy Endpoint	
	1	Annual rate of moderate or severe COPD exacerbations
	Secondary Efficacy Endpoint	
	2	Time to first moderate or severe exacerbation
	3	Annual rate of COPD exacerbations requiring emergency department (ED) visits and/or hospitalizations
	4	Change from baseline total St. George's Respiratory Questionnaire-COPD (SGRQ-C) score
	5	Change from baseline COPD Assessment Test (CAT) score
Other Efficacy Endpoints		Annual rate of moderate COPD exacerbation
		Annual rate of severe COPD exacerbations
		Proportion with at least 4-point improvement from baseline total SGRQ-C score
		Change from baseline in trough FEV ₁

DISPOSITION AND PRIMARY ENDPOINT RESULTS

Study 106: Patient Disposition

	Overall			High Stratum		
	Placebo	Mepolizumab 100mg SC	Total	Placebo	Mepolizumab 100mg SC	Total
N (mITT)	419	417	836	229	233	462
Study Completion Status						
Completed	364 (87%)	370 (89%)	734 (88%)	202 (88%)	213 (91%)	415 (90%)
Withdrawn	55 (13%)	47 (11%)	102 (12%)	27 (12%)	20 (9%)	47 (10%)
Study Withdrawal Reason						
Adverse event	21 (38%)	18 (38%)	39 (38%)	10 (37%)	7 (35%)	17 (36%)
Lack of efficacy	3 (5%)	3 (6%)	6 (6%)	0	1 (5%)	1 (2%)
Lost to follow-up	2 (4%)	1 (2%)	3 (3%)	0	0	0
Physician decision	4 (7%)	4 (9%)	8 (8%)	2 (7%)	2 (10%)	4 (9%)
Withdrawal by subject	25 (45%)	21 (45%)	46 (45%)	15 (56%)	10 (50%)	25 (53%)

Study 106: Primary Endpoint Analysis Results



	Primary Analyses				Exploratory Analysis	
	Overall Population		High Stratum		Low Stratum	
Treatment (N)	Placebo (419)	Mepolizumab 100mg (417)	Placebo (229)	Mepolizumab 100mg (233)	Placebo (190)	Mepolizumab 100mg (184)
Number of patients with event (%)	287 (68%)	266 (64%)	166 (72%)	149 (64%)	121 (64%)	117 (64%)
Mean annual rate	1.52	1.48	1.71	1.40	1.29	1.58
Mepolizumab vs. placebo						
Rate ratio		0.98		0.82		1.23
95% CI		0.85, 1.12		0.68, 0.98		0.99, 1.51
Nominal p-value		0.724		0.029		0.058
Adjusted p-value		>0.999		0.036		NA
Rate difference		0.04		0.31		-0.29
Number needed to treat		25		3.2		NA

Study 113: Patient Disposition

	Placebo	Mepolizumab 100mg SC	Mepolizumab 300mg SC	Total
N (mITT)	226	223	225	674
Study: Completion Status				
Completed	185 (82%)	206 (92%)	195 (87%)	586 (87%)
Withdrawn	41 (18%)	17 (8%)	30 (13%)	88 (13%)
Study Withdrawal Reason				
Adverse Event	18 (44%)	7 (41%)	13 (43%)	38 (43%)
Lack of Efficacy	3 (7%)	0	3 (10%)	6 (7%)
Lost to follow-up	2 (5%)	0	1 (3%)	3 (3%)
Physician decision	3 (7%)	3 (18%)	2 (7%)	8 (9%)
Withdrawal by subject	15 (37%)	7 (41%)	11 (37%)	33 (38%)

Study 113: Primary Analysis Results

Treatment (N)	Placebo (226)	Mepolizumab 100mg (223)	Mepolizumab 300mg (225)
Number of patients with event (%)	144 (64%)	127 (57%)	130 (58%)
Mean annual rate	1.49	1.19	1.27
Mepolizumab vs. placebo			
Rate ratio		0.80	0.86
95% CI		0.65, 0.98	0.70, 1.05
Nominal p-value		0.034	0.140
Adjusted p-value		0.068	0.140
Rate difference		0.29	0.21
Number needed to treat		3.4	4.8

SECONDARY AND EXPLORATORY ENDPOINT RESULTS

Analyses of Secondary Exacerbation Endpoints

	Study 106 High Stratum		Study 113		
Treatment (N)	Placebo (229)	Mepolizumab 100mg SC (233)	Placebo (226)	Mepolizumab 100mg SC (223)	Mepolizumab 300mg SC (225)
Time to First Moderate/Severe Exacerbation					
Number of Event (%)	166 (72%)	149 (64%)	144 (64%)	127 (57%)	130 (58%)
Hazard Ratio (95% CI)		0.75 (0.60, 0.94)		0.82 (0.64, 1.04)	0.77 (0.61, 0.98)
Adjusted p-value		0.036		0.140	0.140
Annual Rate of Exacerbations Requiring ED* Visit/Hospitalization					
Rate	0.26	0.30	0.28	0.17	0.23
Rate Ratio (95% CI)		1.16 (0.77, 1.75)		0.59 (0.35, 0.98)	0.83 (0.51, 1.34)
Adjusted p-value		0.598		0.140	0.447
Annual Rate of Severe Exacerbation					
Number of Patients (%)	46 (20%)	42 (18%)	39 (17%)	30 (13%)	33 (15%)
Number of Events (Rate*)	61 (0.22)	64 (0.24)	59 (0.22)	40 (0.13)	52 (0.18)
Rate Ratio (95% CI)		1.12 (0.72, 1.74)		0.63 (0.36, 1.09)	0.89 (0.53, 1.50)

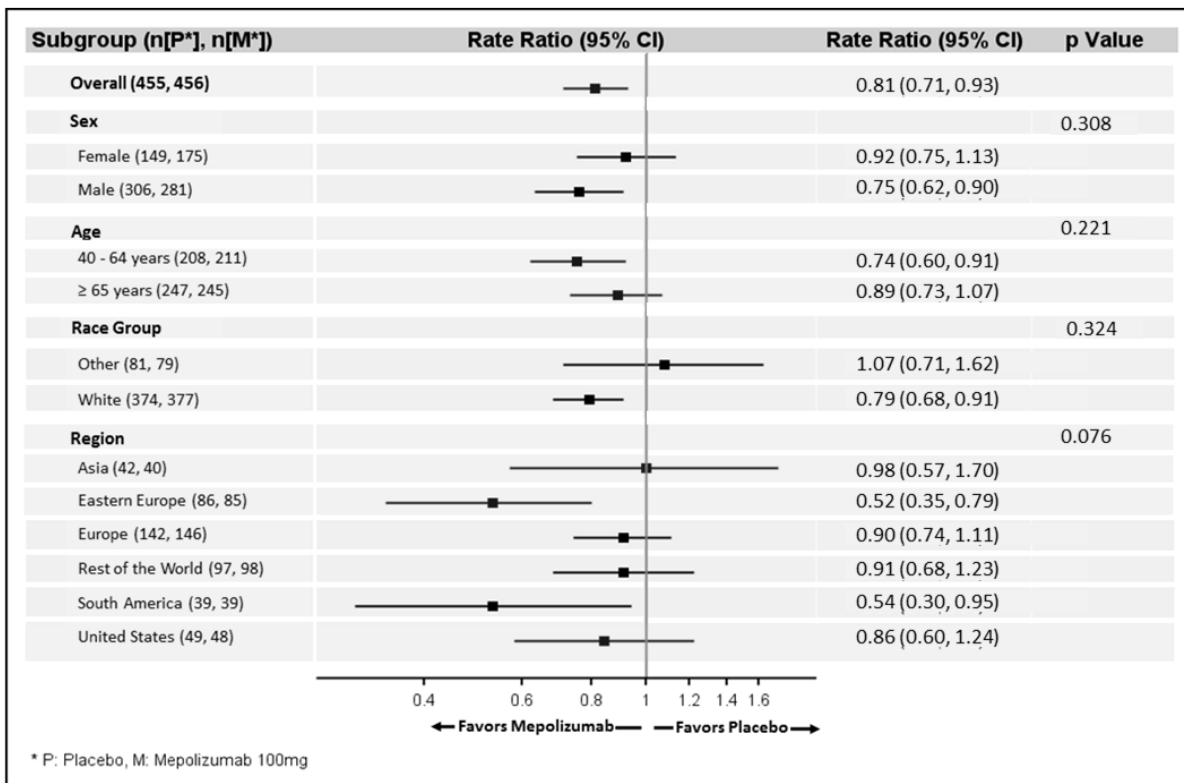
Analyses of Additional Secondary Endpoints: Patient-Reported Outcomes and Lung Function



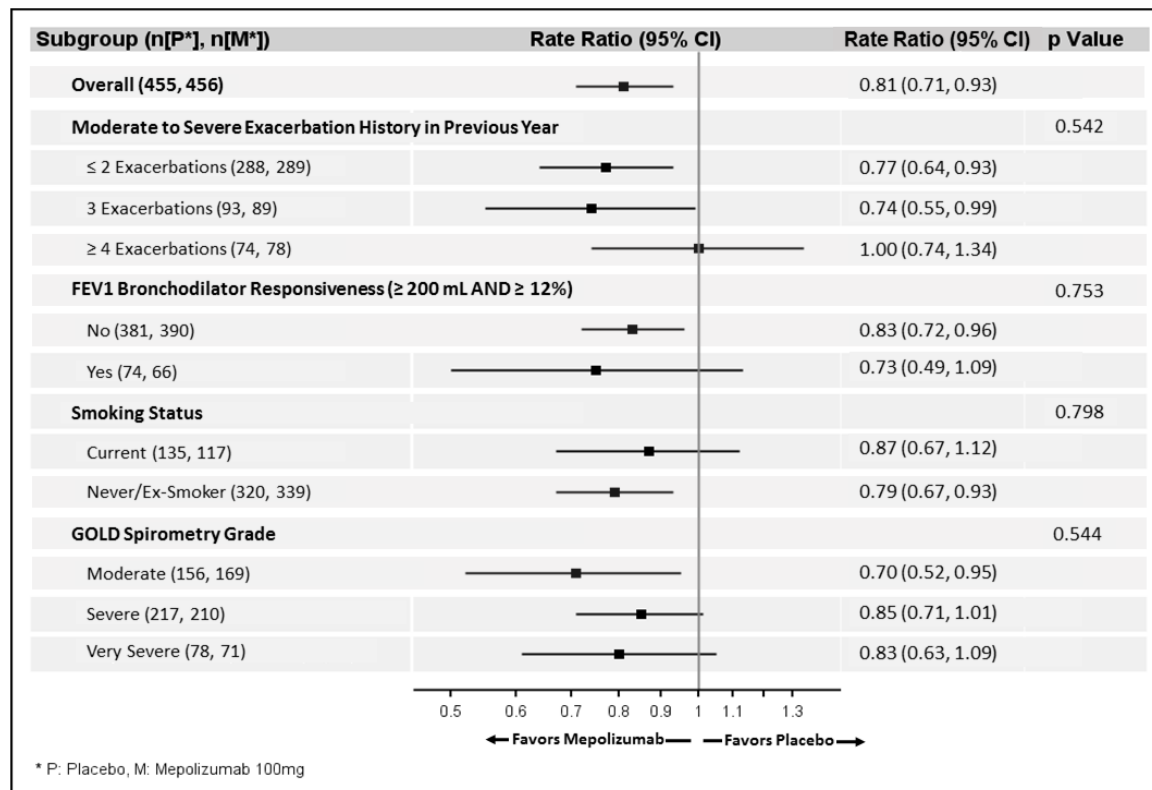
	Study 106 High Stratum		Study 113		
Treatment (N)	Placebo (229)	Mepolizumab 100mg SC (233)	Placebo (226)	Mepolizumab 100mg SC (223)	Mepolizumab 300mg SC (225)
Change from Baseline SGRQ-C Total Score at Week 52					
Adjusted Mean Change	-3.0	-2.8	-3.1	-5.0	-3.3
Mean Difference (95% CI)		0.2 (-2.8, 3.2)		-1.8 (-4.5, 0.8)	-0.1 (-2.8, 2.6)
Responder Analysis of SGRQ-C Total Score at Week 52					
Number of Responder (%)	90 (39%)	95 (41%)	83 (37%)	92 (42%)	85 (38%)
Odds Ratio (95% CI)		1.08 (0.74, 1.59)		1.41 (0.95, 2.10)	1.17 (0.79, 1.73)
Change from Baseline CAT Score at Week 52					
Adjusted Mean Change	-0.0	-0.8	-0.4	-1.6	-0.8
Mean Difference (95% CI)		-0.8 (-2.0, 0.5)		-1.1 (-2.3, 0.0)	-0.4 (-1.5, 0.8)
Change from Baseline FEV₁ at Week 52 (mL)					
Adjusted Mean Change	-7	-17	-13	6	21
Mean Difference (95% CI)		-10 (-54, 33)		19 (-29, 67)	35 (-14, 83)

SUBGROUP ANALYSES

Exacerbation Results by Demographic Subgroups (Pooled Population: Study 106 High Stratum and Study 113)



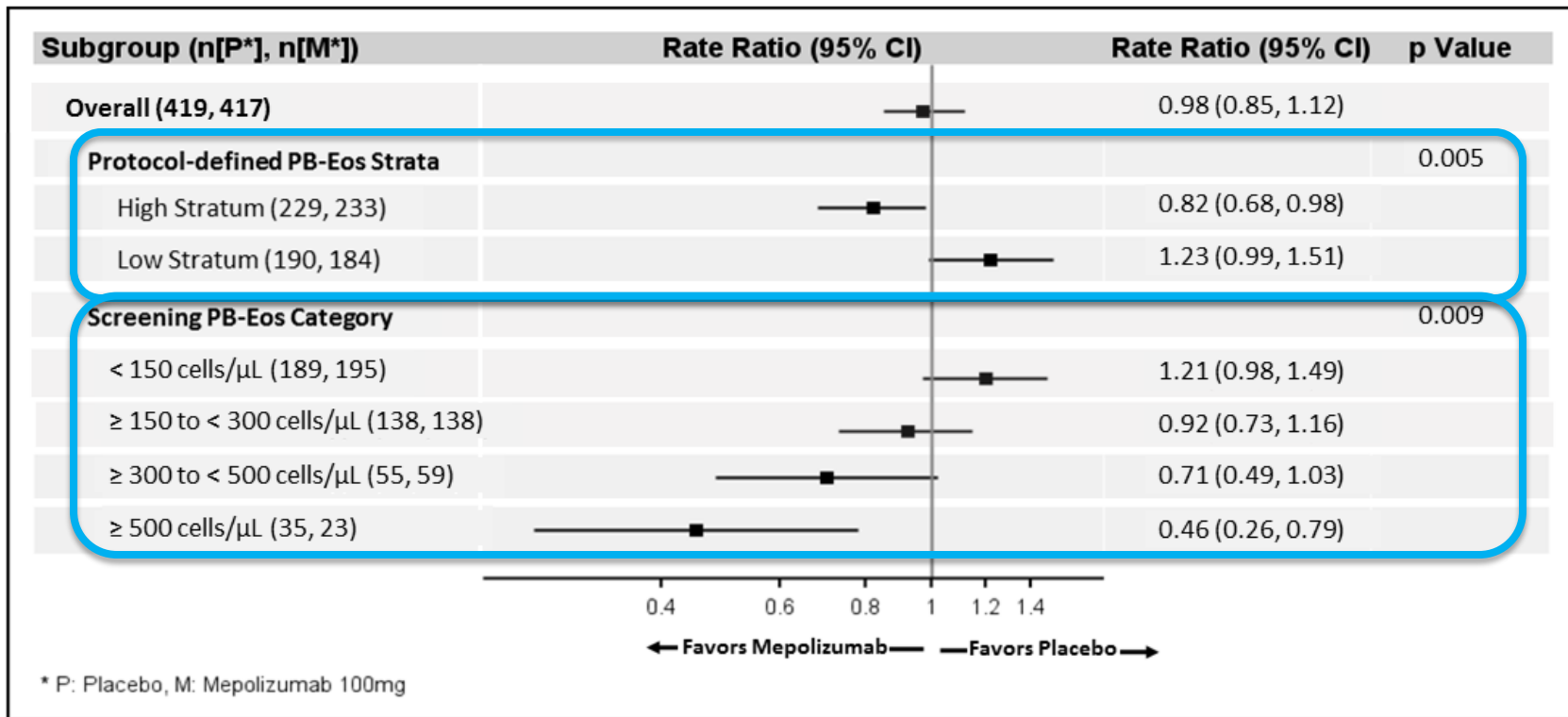
Exacerbation Results by Baseline Disease Characteristics (Pooled Population: Study 106 High Stratum and Study 113)



Analyses of Association between Mepolizumab Effect and Baseline Eosinophil Level (Study 106)

- Pre-defined Subgroup Analysis
 - High eosinophil stratum defined by baseline level ≥ 150 cells/ μL or historical level ≥ 300 cells/ μL
- Exploratory Subgroup Analysis
 - Categories defined by baseline eosinophil level thresholds:
 - < 150 cells/ μL
 - ≥ 150 to < 300 cells/ μL
 - ≥ 300 to < 500 cells/ μL
 - ≥ 500 cells/ μL
 - Continuous and assume linearity for the effect

Exacerbation Results by Pre-defined Eosinophil Level Stratum (Study 106)



SUMMARY OF STATISTICAL REVIEW

Totality of Evidence: Summary of Key Results with Multiplicity-Adjusted P-values



Order	Endpoint (Treatment effect measure)	Study 106 HS	Study 113	
		Mepo 100mg vs. Placebo	Mepo 100mg vs. Placebo	Mepo 300mg vs. Placebo
Primary Endpoint				
1	Frequency of moderate/severe exacerbations (rate ratio)	0.82 (0.68, 0.98) Adjusted p=0.036	0.80 (0.65, 0.98) Adjusted p=0.068	0.86 (0.70 1.05) Adjusted p=0.140
Secondary Endpoints				
2	Time to first moderate/severe exacerbation (hazard ratio)	0.75 (0.60, 0.94) Adjusted p=0.036		
3	Frequency of COPD exacerbations requiring ED visit and/or hospitalization (rate ratio)	1.16 (0.77, 1.75) Adjusted p=0.598		
4	Change from baseline SGRQ-C total score (mean difference)			
5	Change from baseline CAT score (mean difference)			

Statistical Review Summary

- **Primary Efficacy Endpoint Results**

- Study 106: evidence that mepolizumab 100 mg decreased the annual rate of moderate or severe exacerbations in high eosinophil stratum
- Study 113: insufficient evidence of effect of mepolizumab 100 mg, insufficient evidence of effect of 300 mg, on annual rate of moderate or severe exacerbations

- **Secondary Efficacy Endpoint Results**

- Lack of consistent evidence of effects of mepolizumab over placebo with respect to important secondary endpoints such as rate of severe exacerbations, SGRQ-C total score

- **Treatment Effect by Eosinophil Level**

- Evidence to suggest ***trend for benefit*** among subgroups with higher levels of eosinophil
- Estimates in low stratum not in direction of benefit
- Uncertainty in appropriate use of eosinophil levels to guide treatment decisions



U.S. FOOD & DRUG
ADMINISTRATION

FDA Pulmonary-Allergy Advisory Committee Meeting

Review of Safety

Clinical Considerations and Benefit-Risk Assessment

sBLA 125526: Mepolizumab for the add-on treatment to inhaled corticosteroid-based maintenance treatment for the reduction of exacerbations in patients with chronic obstructive pulmonary disease (COPD) guided by blood eosinophil counts

Robert Busch, MD, MMSc
Clinical Reviewer

Division of Pulmonary, Allergy, and Rheumatology Products
U.S. Food and Drug Administration
July 25, 2018

Outline



- Overview of the Clinical Program

Robert Busch, MD, MMSC

Medical Officer: DPARP, ODE2, OND, CDER, FDA

- Statistical Review of Efficacy

Yu (Jade) Wang, PhD

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Robert Busch, MD, MMSC

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Review of Safety

Review of Safety Objectives

Extent of Exposure

Deaths and Serious Adverse Events

SMQ Safety Analyses

Adverse Events of Special Interest

- Cardiovascular and Thrombotic Events
- Serious and Opportunistic Infections

Asthma Adverse Events

Extent of Exposure

Deaths and Serious Adverse Events

SMQ Safety Analyses

Adverse Events of Special Interest

- Cardiovascular and Thrombotic Events
- Serious and Opportunistic Infections

Asthma Adverse Events

Extent of Exposure



Safety Database for Mepolizumab

Clinical Trial Groups	Mepolizumab, any dose n (subject-years)	Placebo n (subject-years)
Controlled trials conducted for this indication (MEA117106 and MEA117113)	865 (794.1)	645 (569.7)
Controlled trials conducted for other indications (Severe asthma, EGPA)	2522 (3661)	1059 (547.9)

Extent of Exposure

Deaths and Serious Adverse Events

SMQ Safety Analyses

Adverse Events of Special Interest

- Cardiovascular and Thrombotic Events
- Serious and Opportunistic Infections

Asthma Adverse Events

Deaths



Fatal Adverse Events	Mepolizumab, Any dose strength (Subject years = 794.1)		Placebo (Subject years = 569.7)	
	Number of events	Exposure-adjusted rate (Deaths/1000 patient-years)	Number of events	Exposure-adjusted rate (Deaths/1000 patient-years)
All On-treatment Deaths	26	32.7	14	24.6
Respiratory, thoracic, and mediastinal disorders	12	15.1	6	10.5
Infections and infestations	3	3.8	4	7.0
Cardiac disorders	7	8.8	1	1.8
Gastrointestinal disorders	0	0	2	3.5
Injury, poisoning, and procedural complications	0	0	1	1.8
Neoplasm benign, malignant and unspecified	2	3.5	0	0
General disorders and administration site conditions	2*	3.5	0	0
Hepatobiliary disorders	1	1.8	0	0
Note: The exposure-adjusted values above represent only fatal on-treatment serious adverse events, and do not account for 12 subjects in the placebo arms and 2 subjects in the mepolizumab arms who had fatal serious adverse events off-treatment. These events are displayed below for clarity				
* Fatal events classified under General disorders and administration site conditions include the preferred terms "death", and "multiorgan dysfunction syndrome"				
All On- and Off-treatment Deaths	28	N/A	26	N/A

Source: MEA117106 and MEA117113 safety populations. Reviewer created using data from Table 3.42 and 3.45 of applicant's integrated summary of safety.

Serious Adverse Events

Adverse Event	Mepolizumab Any dose strength (Subject years = 794.1)		Placebo (Subject years = 569.7)	
System Organ Class (SOC)	Number of Events	Exposure-adjusted rate (Event/1000 subject-years)	Number of events	Exposure-adjusted rate (Event/1000 subject-years)
All On-treatment Events	401	505.0	321	563.4
Respiratory, thoracic, and mediastinal disorders	181	227.9	143	251.0
Infections and infestations	97	122.2	77	135.2
Cardiac disorders	33	41.6	27	47.4
Gastrointestinal disorders	23	29.0	4	7.0
Injury, poisoning, and procedural complications	6	7.6	18	31.6
Neoplasm benign, malignant and unspecified	10	12.6	8	14.0
Renal and urinary disorders	13	16.4	5	8.8
Nervous system disorders	8	10.1	5	8.8
Musculoskeletal and connective tissue disorders	6	7.6	6	10.5
Vascular disorders	7	8.8	5	8.8

Source: MEA117106 and MEA117113 safety populations. Adapted from data presented in Table 3.42 of applicant's integrated summary of safety

Serious Adverse Event: An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

Extent of Exposure

Deaths and Serious Adverse Events

SMQ Safety Analyses

Adverse Events of Special Interest

- Cardiovascular and Thrombotic Events
- Serious and Opportunistic Infections

Asthma Adverse Events

SMQ Safety Analyses



Serious and Non-serious Adverse Events	Mepolizumab Any dose strength N = 865		Placebo N = 645	
	Captured AE Terms	Subjects (N%)	Captured AE Terms	Subjects (N%)
Supraventricular tachyarrhythmias (4)	33	30 (3.5)	18	13 (2)
Ischemic heart disease (1)	17	17 (2)	8	8 (1.2)
Embolic and thrombotic events (1)	17	17 (2)	9	9 (1.4)
Gastrointestinal hemorrhage (2)	9	8 (0.9)	3	3 (0.5)
Central nervous system hemorrhages and cerebrovascular conditions (2)	5	5 (0.6)	1	1 (0.2)
Acute pancreatitis (1)	4	4 (0.5)	0	0
Embolic and thrombotic events, venous (2)	4	4 (0.5)	1	1 (0.2)

Source: MEA117106 and MEA117113 safety populations. Reviewer analysis of treatment emergent serious and non-serious adverse events using MAED software.

Extent of Exposure

Deaths and Serious Adverse Events

SMQ Safety Analyses

Adverse Events of Special Interest

- **Cardiovascular and Thrombotic Events**
- **Serious and Opportunistic Infections**

Asthma Adverse Events

AESI: Cardiovascular and Thrombotic Events



Adverse Event	Mepolizumab Any dose strength N = 865		Placebo N = 645	
	Captured AE Terms	Subjects (N%)	Captured AE Terms	Subjects (N%)
Supraventricular tachyarrhythmias (4)	33	30 (3.5)	18	13 (2)
Ischemic heart disease (1)	17	17 (2)	8	8 (1.2)
Embolic and thrombotic events (1)	17	17 (2)	9	9 (1.4)
Central nervous system hemorrhages and cerebrovascular conditions (2)	5	5 (0.6)	1	1 (0.2)
Embolic and thrombotic events, venous (2)	4	4 (0.5)	1	1 (0.2)

Source: MEA117106 and MEA117113 safety populations. Reviewer analysis of treatment emergent serious and non-serious adverse events using MAED software.

AESI: Cardiovascular and Thrombotic Events



Adverse Event	Mepolizumab Any dose strength N = 865		Placebo N = 645	
	Captured AE Terms	Subjects (N%)	Captured AE Terms	Subjects (N%)
Supraventricular tachyarrhythmias (4)	33	30 (3.5)	18	13 (2)
Ischemic heart disease (1)	17	17 (2)	8	8 (1.2)
Embolic and thrombotic events (1)	17	17 (2)	9	9 (1.4)
Central nervous system hemorrhages and cerebrovascular conditions (2)	5	5 (0.6)	1	1 (0.2)
Embolic and thrombotic events, venous (2)	4	4 (0.5)	1	1 (0.2)

Source: MEA117106 and MEA117113 safety populations. Reviewer analysis of treatment emergent serious and non-serious adverse events using MAED software.

AESI: Cardiovascular and Thrombotic Events



- Applicant's analyses
 - Reported Cochran-Mantel-Haenszel adjusted risk ratios (CMH-RR) for SAE and AE groupings
 - All doses mepolizumab vs placebo
 - Serious cardiovascular thromboembolic disorders CMH-RR: 1.33
 - Cardiac disorders CMH-RR: 1.3
 - Serious cardiac disorders CMH-RR: 1.23
 - Serious ischemic events CMH-RR: 1.35
 - Mepo100 vs placebo
 - Serious cardiovascular thromboembolic disorders CMH-RR: 1.34
 - Cardiac disorders CMH-RR: 1.25
 - Serious cardiac disorders CMH-RR: 1.25
 - Serious ischemic events CMH-RR: 1.26

AESI: Serious and Opportunistic Infections



Adverse Event		Mepolizumab (Any dose strength) n = 865		Placebo n = 645	
Pathogen type	Preferred Term	Number of Events	Subjects n (%)	Number of Events	Subjects n (%)
Yeast/Mold	Oral candidiasis	28	25 (2.9)	22	17 (2.6)
	Candida infection	10	9 (1)	5	5 (0.8)
	Esophageal candidiasis	2	1 (0.1)	1	1 (0.2)
	Gastrointestinal candidiasis	0	0	1	1 (0.2)
	Oropharyngitis, fungal	2	2 (0.2)	0	0
	Fungal esophagitis	0	0	1	1 (0.2)
	Oral fungal infection	0	0	3	2 (0.3)
	Tongue fungal infection	0	0	1	1 (0.2)
Mycobacteria	Pulmonary tuberculosis	1	1 (0.1)	0	0
Herpes viridae	Herpes zoster	18	16 (1.9)	5	5 (0.8)
	Oral herpes	5	4 (0.5)	3	3 (0.5)
	Herpes ophthalmic	1	1 (0.1)	0	0
	Herpes simplex	1	1 (0.1)	1	1 (0.2)

Extent of Exposure

Deaths and Serious Adverse Events

SMQ Safety Analyses

Adverse Events of Special Interest

- Cardiovascular and Thrombotic Events
- Serious and Opportunistic Infections

Asthma Adverse Events

Asthma Adverse Events



- Protocols excluded “current diagnosis of asthma”
 - Allowed “prior history of asthma”
- Asthma events in pivotal trials
 - “overlap syndrome of asthma/COPD”
 - “asthma symptoms increase”
- Asthma as an unmeasured variable

Safety Summary



- Deaths
 - Numerical increase in on-treatment deaths
 - On- and off-treatment deaths comparable between mepolizumab and placebo
- Imbalances in Safety Data
 - Cardiovascular thrombotic events
 - Supraventricular tachyarrhythmias
 - GI Bleeds
 - Acute Pancreatitis
 - Increased COPD exacerbation rate in Low Stratum
- Other Adverse Events
 - Oral Candidiasis
 - Herpes Zoster

Outline



- Overview of the Clinical Program

Robert Busch, MD, MMSC

Medical Officer: DPARP, ODE2, OND, CDER, FDA

- Statistical Review of Efficacy

Yu (Jade) Wang, PhD

Biometrics Reviewer: DB2, OTS, CDER, FDA

- Review of Safety

Robert Busch, MD, MMSC

Medical Officer: DPARP, ODE2, OND, CDER, FDA

- Clinical Considerations and Benefit Risk Assessment

Robert Busch, MD, MMSC

Medical Officer: DPARP, ODE2, OND, CDER, FDA

Clinical Considerations and Benefit Risk Assessment

Clinical Considerations and Benefit-Risk Discussion Points



Mepolizumab Dose Exploration

Durability of Effect

Peripheral Blood Eosinophil Thresholds and Efficacy

Efficacy Subgroups and Asthma

Phenotypic Uncertainty and Identifying Responders

Efficacy Results in Context

Safety Results in Context

Mepolizumab Dose Exploration

Durability of Effect

Peripheral Blood Eosinophil Thresholds and Efficacy

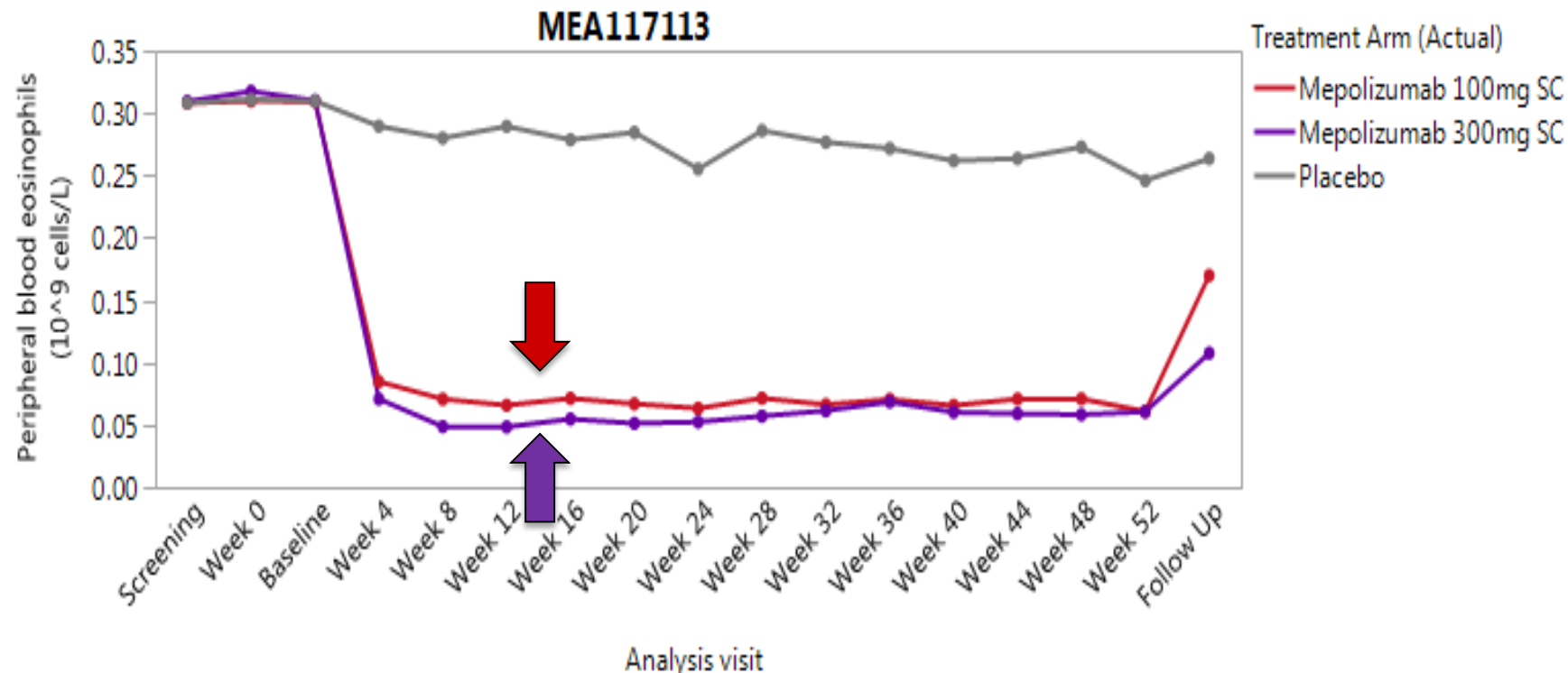
Efficacy Subgroups and Asthma

Phenotypic Uncertainty and Identifying Responders

Efficacy Results in Context

Safety Results in Context

Mepolizumab Dose Exploration



Mepolizumab Dose Exploration

Durability of Effect

Peripheral Blood Eosinophil Thresholds and Efficacy

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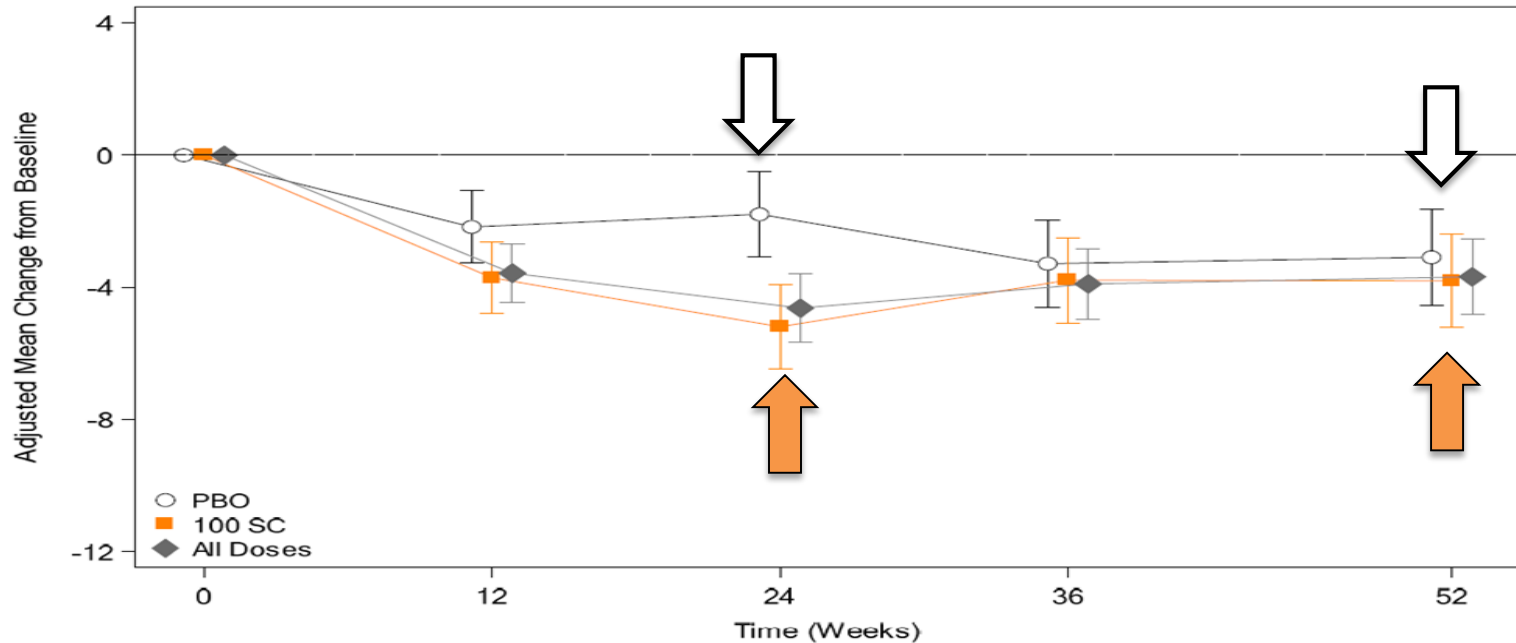
Phenotypic Uncertainty and Identifying Responders

Efficacy Results in Context

Safety Results in Context

Durability of Response

Figure 2.11
Figure of St. George's Respiratory Questionnaire (SGRQ) Total Score:
Change from Baseline: Meta-Analysis



Mepolizumab Dose Exploration

Durability of Effect

Peripheral Blood Eosinophil Thresholds and Efficacy

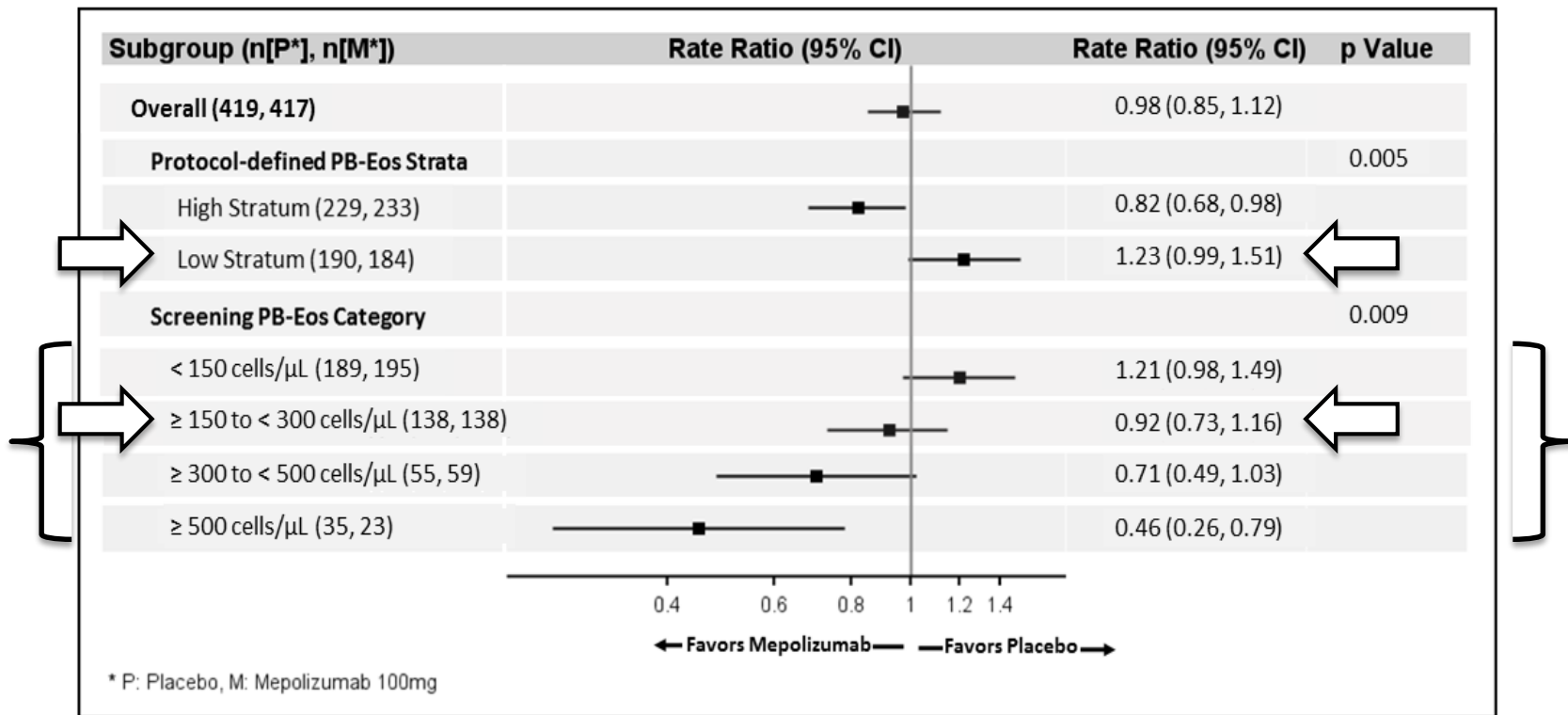
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Eosinophil Thresholds and Efficacy

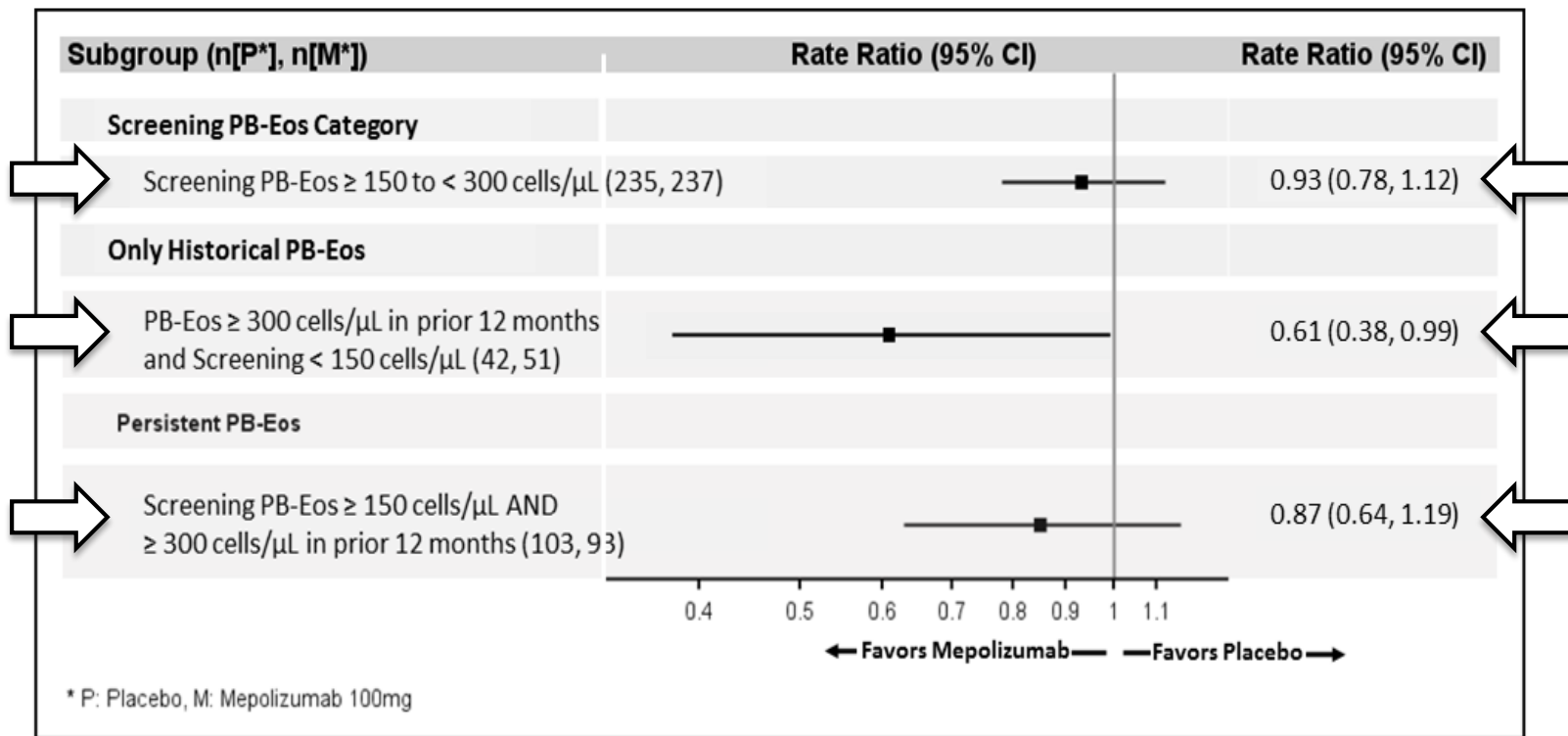


Eosinophil Thresholds and Efficacy



- How does a provider respond to the following:
 - Current peripheral blood eosinophils ≥ 150 cells/ μL
 - Current peripheral blood eosinophils < 150 cells/ μL
 - Historical measurement of peripheral blood eosinophils ≥ 300 cells/ μL
 - Current ≥ 150 cells/ μL AND historical ≥ 300 cells/ μL

Eosinophil Thresholds and Efficacy



Mepolizumab Dose Exploration

Durability of Effect

Peripheral Blood Eosinophil Thresholds and Efficacy

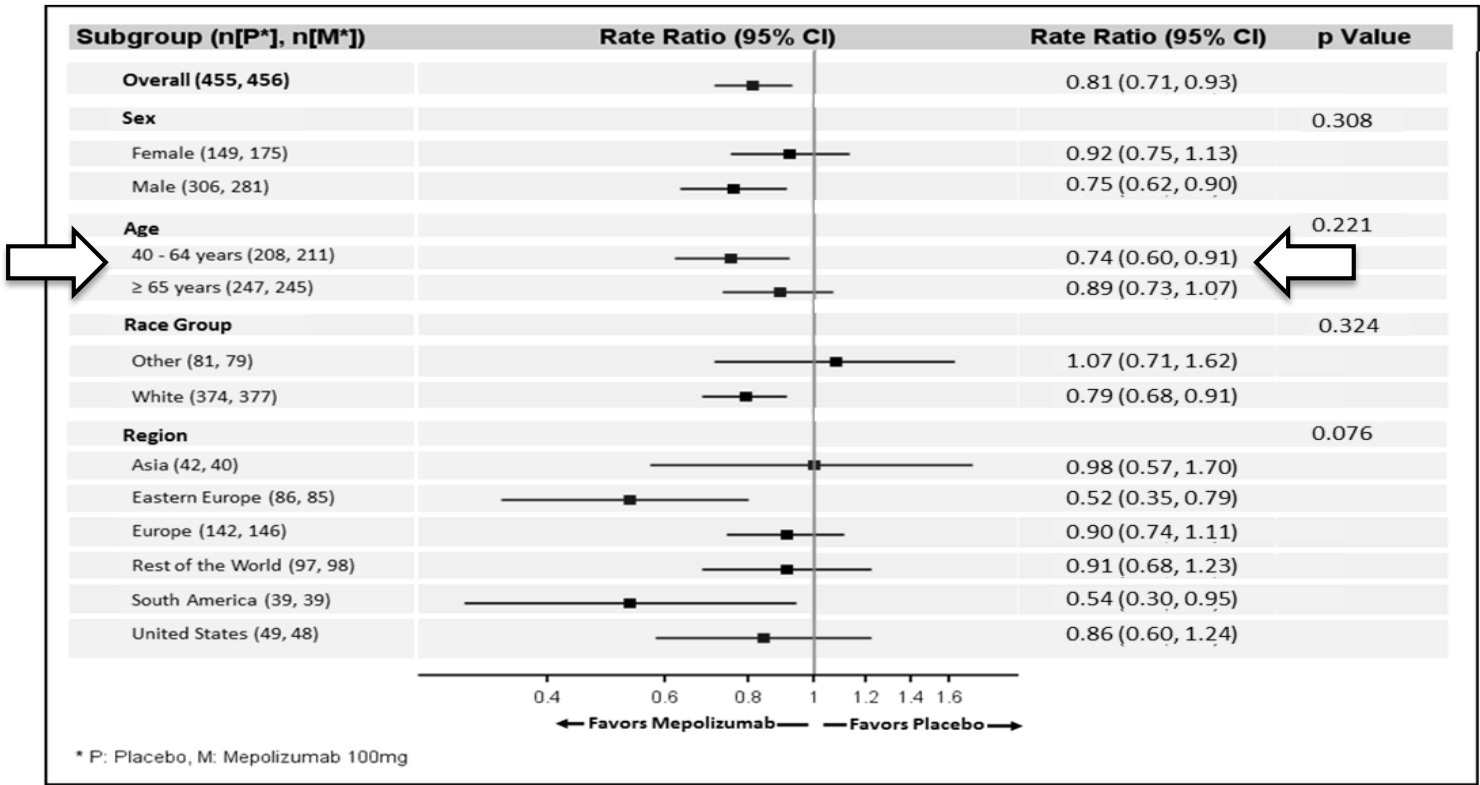
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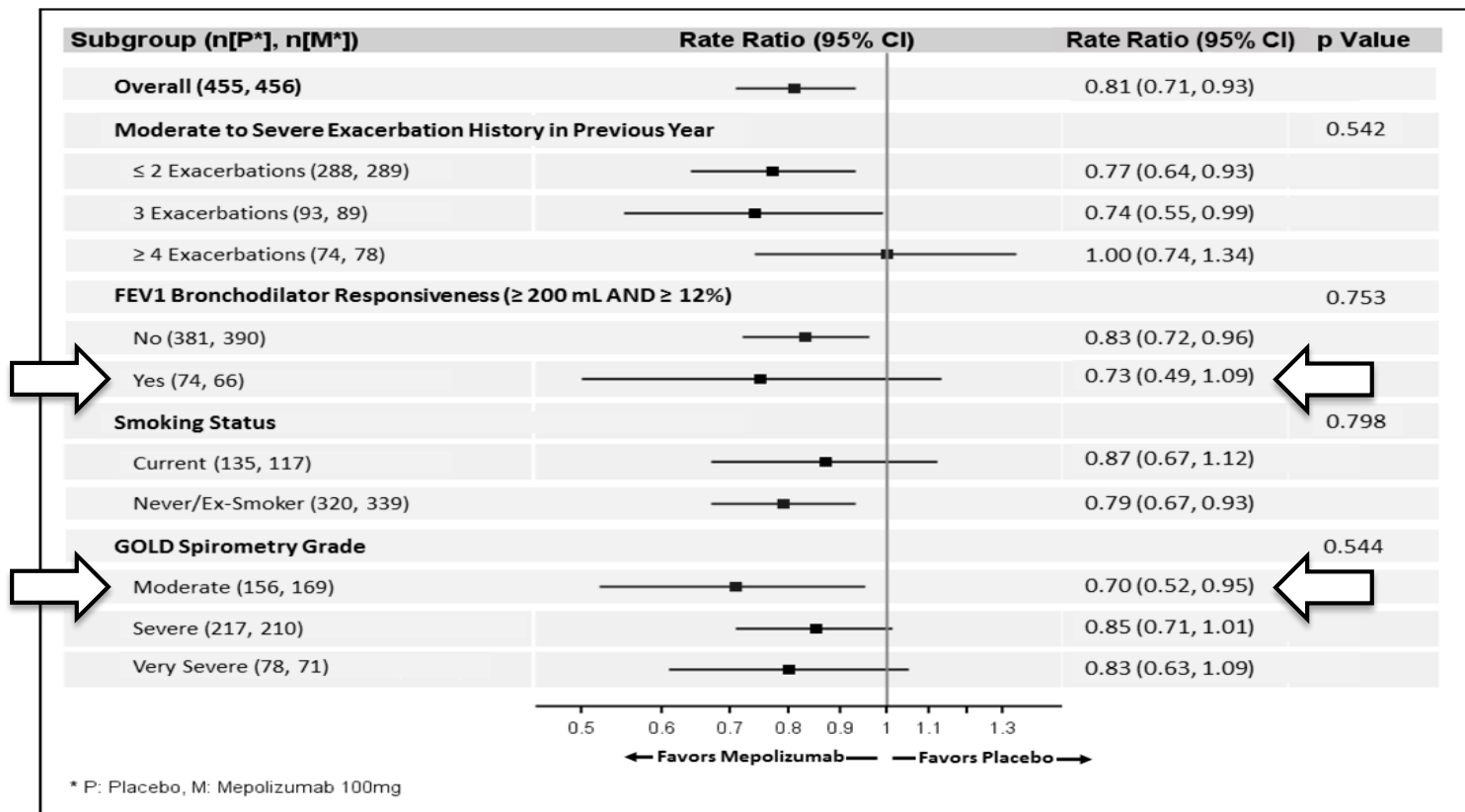
Efficacy Results in Context

Safety Results in Context

Demographic Subgroups



Baseline Disease Subgroups



Asthma as Unmeasured Variable



- Subgroups with more favorable efficacy estimates
 - Young, moderate obstruction, bronchodilator responsive
 - Higher eosinophils
- Known efficacy of mepolizumab in severe asthma
- Adequacy of asthma exclusion criteria and “historical diagnosis of asthma”
 - No data collection on asthma history
 - No specified timeframe or criteria for asthma symptom abatement
- Asthma adverse events captured during COPD program

Mepolizumab Dose Exploration

Durability of Effect

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Efficacy Results in Context

Safety Results in Context

Phenotypic Uncertainty

- Can peripheral blood eosinophil levels consistently and accurately identify the phenotype?
- Are peripheral blood eosinophil levels alone adequate to identify those who could benefit from anti-IL5 therapy?
- If so, do we know what threshold of peripheral blood eosinophils is appropriate?
- If so, what is the timeframe of these measurements?

Identifying responders

- Can we identify who is gaining benefit?
 - Eosinophils inevitably fall
 - SGRQ response uncertain and not durable
 - FEV1 response uncertain
 - Observable AECOPD response not practical in individuals

Mepolizumab Dose Exploration

Durability of Effect

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Efficacy Results in Context

Safety Results in Context

Efficacy Results in Context

- Statistical uncertainty of primary results
- Potential clinical benefit
 - Absolute risk difference for moderate to severe AECOPD
 - ~0.3 AECOPD/year or lower
 - NNT: ~3 patients treated for 1 year
 - ~36 monthly injections to prevent 1 moderate to severe AECOPD
 - Effect limited to moderate AECOPD?
 - No evidence of benefit on Severe AECOPD
 - No evidence of benefit on SGRQ-C
 - No evidence of benefit on FEV1



Mepolizumab Dose Exploration

Durability of Effect

Peripheral Blood Eosinophil Thresholds and Efficacy

Efficacy Subgroups and Asthma

Phenotypic Uncertainty and Identifying Responders

Efficacy Results in Context

Safety Results in Context

Safety Results in Context



- Potential safety signals identified
 - Numerically small imbalances
- Potential for increased exacerbations among Low Stratum patients
- Otherwise comparable to placebo



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ADMINISTRATION

FDA Pulmonary-Allergy Advisory Committee Meeting

Charge to the Committee

sBLA 125526: Mepolizumab for the add-on treatment to inhaled corticosteroid-based maintenance treatment for the reduction of exacerbations in patients with chronic obstructive pulmonary disease (COPD) guided by blood eosinophil counts

Banu A. Karimi-Shah, MD

Clinical Team Leader

Division of Pulmonary, Allergy, and Rheumatology Products

U.S. Food and Drug Administration

July 25, 2018

Efficacy Considerations – Patient Selection



- Lack of consensus around the definition/relevance of an eosinophilic COPD phenotype
 - Definitions of High and Low Stratum carried over from asthma program
 - Study 106 Low Stratum, mepolizumab 100 mg showed a numerical increase in the rate of moderate to severe exacerbations [rate ratio: 1.23, 95% CI (0.99, 1.51)]
- Potential inclusion of asthma patients in the COPD program
 - Baseline data on asthma history not collected



Efficacy Considerations – Exacerbations

- Study 106 demonstrated a significant reduction in exacerbations, while Study 113 did not.
- Clinically important secondary endpoints did not consistently support the primary endpoint in either study.
- Other key endpoints e.g. SGRQ-C, FEV1, and rate of severe exacerbation showed no evidence of benefit.
 - Positive results in Study 106 driven by moderate exacerbations

Safety Considerations

- Numerically small imbalances in serious adverse events and adverse events related to:
 - Supraventricular tachyarrhythmias
 - Cardiovascular thrombotic events
 - GI Bleeding
 - Acute pancreatitis
- Other Adverse Events:
 - Oral Candidiasis
 - Herpes Zoster

Approval of an Application

21 CFR 314.105 (c)

- “FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling.”

Efficacy Standard

21 CFR 314.125



Refusal to Approve an Application

- (b)(5) “...substantial evidence consisting of adequate and well-controlled investigations...that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.”

Safety Standard

21 CFR 314.125



Refusal to Approve an Application

- (b)(2) “...do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.”
- (b)(3) “The results of the test show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions.”
- (b)(4) “There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.”

Discussion Points and Voting Questions

- 1. DISCUSSION:** Discuss the eosinophilic COPD phenotype (i.e., the relevance of peripheral blood eosinophils in COPD patients) and the criteria used in the mepolizumab program to define the patient population.

Discussion Points and Voting Questions

2. **DISCUSSION:** Discuss the efficacy of mepolizumab as add-on treatment to inhaled corticosteroid-based maintenance treatment for the reduction of exacerbations in patients with COPD guided by blood eosinophil counts. Include the following topics in your discussion:
- a. the adequacy of dose exploration in COPD patients
 - b. the potential effect of unmeasured variables (e.g., lack of information regarding asthma history and oral corticosteroid use)
 - c. the lack of statistically significant results for the primary endpoint in one of the two trials *[continued on next slide]*

Discussion Points and Voting Questions

2. **DISCUSSION (cont'd):** Discuss the efficacy of mepolizumab as add-on treatment to inhaled corticosteroid-based maintenance treatment for the reduction of exacerbations in patients with COPD guided by blood eosinophil counts. Include the following topics in your discussion:
- d. the clinical significance of the efficacy results (i.e., efficacy driven by moderate exacerbations)
 - e. lack of robust results for key secondary endpoint
 - f. efficacy results in the low eosinophil stratum that showed a numerical increase in COPD exacerbations
 - g. interpretation of the efficacy results given the uncertainty in the definition of the eosinophilic COPD phenotype

Discussion Points and Voting Questions

3. **VOTE:** Do the data provide substantial evidence of efficacy for mepolizumab as add-on treatment to inhaled corticosteroid-based maintenance treatment for the reduction of exacerbations in patients with chronic obstructive pulmonary disease (COPD) guided by blood eosinophil counts?
 - If no, what data are needed?
4. **VOTE:** Are the safety data adequate to support approval of mepolizumab as add-on treatment to inhaled corticosteroid-based maintenance treatment for the reduction of exacerbations in patients with chronic obstructive pulmonary disease (COPD) guided by blood eosinophil counts?
 - If no, what data are needed?

Discussion Points and Voting Questions

- 5. VOTE:** Is the benefit-risk profile adequate to support approval of mepolizumab as add-on treatment to inhaled corticosteroid-based maintenance treatment for the reduction of exacerbations in patients with chronic obstructive pulmonary disease (COPD) guided by blood eosinophil counts?
- If no, what data are needed?



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