FDA Briefing Document

Pulmonary-Allergy Drugs Advisory Committee Meeting

July 25, 2018

sBLA 125526: 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

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the supplemental Biologic Licensing Application (sBLA) 125526, 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, to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Briefing Document Table of Contents

DIVISION DIRECTOR MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
M E M O R A N D U M

Date: June 27, 2018

From: Sally Seymour, MD, Acting Division Director
Banu A. Karimi-Shah, MD, Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA

To: Members, Pulmonary-Allergy Drugs Advisory Committee

Subject: Overview of the FDA background materials for supplemental biologics licensing application (sBLA) 125526, Nucala (mepolizumab for subcutaneous injection), at a dose of 100 mg every four weeks, 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.

Thank you for your participation in the Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting to be held on July 25, 2018. As members of the PADAC, you provide important expert scientific advice and recommendations to the US Food and Drug Administration (the Agency) on the regulatory decision-making process related to the approval of a drug or biologic product for marketing in the United States. The upcoming meeting is to discuss the supplemental biologics licensing application (sBLA) 125526 from GlaxoSmithKline (GSK) for mepolizumab 100 mg subcutaneous (SC) for 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.

Mepolizumab is a monoclonal antibody directed against interleukin-5 (IL5) that binds IL5 and prevents its interaction with the IL5 receptor, which leads to decreased eosinophil maturation and survival. Mepolizumab is approved under the trade name Nucala® for the treatment of severe asthma with eosinophilic phenotype and eosinophilic granulomatosis with polyangiitis

(EGPA). Asthma and EGPA are diseases that are characterized by eosinophils. COPD is not traditionally characterized by high eosinophil levels, but there is ongoing discussion about a subtype of COPD characterized by eosinophils.

The treatment of patients with COPD based upon blood eosinophil count is a novel indication for any therapeutic agent. Often with novel development programs, there are more uncertainties. While there is much experience with trials in COPD patients and the endpoint of COPD exacerbations is established in multiple clinical development programs, we do not have regulatory experience with targeting therapies in COPD patients based upon eosinophil count. The lack of consensus surrounding the definition of the eosinophilic COPD phenotype creates challenges in defining the group of patients that could derive benefit from mepolizumab. We do not have the benefit of prior precedent and successful clinical programs targeting the IL5 pathway in COPD. Information we do have about targeting the IL5 pathway in patients with COPD raises questions regarding the potential of this target, i.e. recently released results from a clinical program with another IL5 targeting agent (benralizumab) in COPD patients with eosinophil phenotype did not show evidence of effect on the primary endpoint of reduction in COPD exacerbations in two phase 3 clinical trials[1,2].

We typically expect results from two adequate and well-controlled clinical trials to provide substantial evidence of efficacy, particularly for a novel indication in which there are sufficient numbers of patients. GSK conducted neither a proof-of-concept study nor a formal dose-ranging study in COPD patients prior to conducting the phase 3 program with mepolizumab; rather, the dose selection (100 mg every 4 weeks [Q4 wks]) relied on information garnered from the severe asthma development program. The development program in COPD consisted of two phase 3 clinical trials. Both trials were multi-national, randomized, double-blind, placebo-controlled, and 52 weeks in duration in patients with COPD on ICS/LABA/LAMA therapy. One trial (MEA117106) enrolled patients with a broader range of peripheral blood eosinophil counts and stratified by high and low eosinophil counts, but the primary analysis focused on the high eosinophil stratum (≥150 cells/µL at screening or ≥300 cells/µL in the prior 12 months). The peripheral blood eosinophil criteria were based upon the criteria used in the severe asthma development program. The second trial (MEA117113) only enrolled patients that met the same criteria for the high eosinophil stratum. The primary efficacy endpoint in both trials was the rate of moderate-to-severe COPD exacerbations at 52 weeks.

As described in the Review of Efficacy section of the briefing document, one trial (MEA117106) showed a statistically significant reduction in the rate of moderate-to-severe COPD exacerbations with mepolizumab 100 mg SC Q4 wks compared to placebo (rate ratio 0.82 [95% CI: 0.68, 0.98], p-value 0.04) in the high eosinophil stratum. The second trial (MEA11713) did not show a statistically significant reduction in moderate-to-severe COPD exacerbations with either dose of mepolizumab (adjusting for multiplicity): mepolizumab 100 mg SC Q4 wks (rate ratio 0.80 [95% CI: 0.65, 0.98], p-value 0.07) or 300 mg SC Q4 wks (rate ratio 0.86 [95% CI: 0.7,1.05], p-value 0.1). There was no dose response between the 100 and 300 mg dose groups; however, the reduction in exacerbation rate with the 100 mg dose was consistent across the trials. We note that results for the low stratum group in MEA117106 showed a numerical

increase in rate of exacerbations with mepolizumab 100mg (rate ratio 1.23, [95% CI: 0.99,1.51]), which raises concerns about accurately defining the COPD population for mepolizumab use. It is also important to note that the majority of the COPD exacerbation events were considered moderate exacerbations (i.e., exacerbations defined as those treated with antibiotics and/or corticosteroids).

Some key secondary endpoints, such as time to first moderate-to-severe COPD exacerbation showed numerical trends favoring mepolizumab. However, there were no consistent and clinically meaningful differences in severe COPD exacerbation rate, FEV1, or SGRQ between mepolizumab 100 mg and placebo.

During review of the application, some questions were raised about the trial design, including the potential for enrollment of some patients with a history of asthma. At enrollment, GSK did not collect baseline data on asthma history. Since mepolizumab is approved for the treatment of severe asthma, inclusion of patients with asthma in the trial could impact trial results. Given the marginal statistical significance of the single trial that won on the primary endpoint (MEA117106), whether patients with asthma could have been enrolled is an important consideration.

A key question is regarding the entry criteria for patients based upon the baseline and historical eosinophil thresholds used in the program and whether these were the appropriate criteria to determine the group of patients that could derive benefit from mepolizumab. Whether there is substantial evidence of efficacy for mepolizumab for the proposed indication is the primary focus of the discussion. We look forward to your discussion of these issues at the upcoming meeting.

The safety of mepolizumab in COPD relies primarily on the safety databases of the two pivotal trials, MEA117106 and MEA117113. Pooled analysis of the trials was deemed acceptable since these trials shared similar designs and comparable randomized populations. Across both trials, a total of 836 subjects received any dose of mepolizumab while 674 subjects received placebo. Overall, there were no significant imbalances in deaths between mepolizumab-treated patients compared with placebo. Some imbalances in serious adverse events (SAEs) and adverse events (AEs) were noted. Imbalances in cardiovascular SAEs are noteworthy, particularly supraventricular tachyarrhythmias and cardiovascular thrombotic events. As described in the Review of Safety, analyses by both the Applicant and the Agency revealed consistent imbalances in cardiovascular thrombotic events towards mepolizumab despite different analysis methods. Additional serious and non-serious adverse event imbalances are noted in the Review of Safety section of the briefing document. We will be presenting these safety data and will ask for you to discuss the safety of mepolizumab in this patient population.

The Division will make a final determination for this supplemental BLA based upon a benefit risk assessment. The opinions and insights provided by you at this PADAC meeting will be an important factor in our decision on this application. Underlying questions about the patient population (eosinophilic COPD phenotype) impact interpretation of the efficacy and safety

data. For example, marginal statistical significance, the importance of secondary endpoints, and potential enrollment of patients with asthma are more relevant when there are uncertainties about the patient population. Similarly, the numerical increase in COPD exacerbations in the low stratum eosinophil group treated with mepolizumab and small imbalances in adverse events become important considerations in the risk assessment.

The purpose of the PADAC meeting is to discuss the adequacy of the efficacy and safety data submitted by GSK to support the approval of mepolizumab for the proposed indication. The major issues for discussion are: 1) the eosinophilic phenotype of COPD; 2) the adequacy of the efficacy data to support the proposed indication; 3) the adequacy of the safety data to support long-term use of mepolizumab in patients with COPD; and 4) the benefit-risk assessment for mepolizumab for the proposed indication.

The clinical and statistical issues related to the mepolizumab COPD program are the primary focuses of this PADAC meeting. Draft Points to Consider for the upcoming PADAC meeting are attached to this memo. A combined Clinical-Statistical Briefing Document provides a detailed discussion of the clinical program. We look forward to the discussion of this application.

Draft Points to Consider

1. 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 population.

2. 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. Please 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
    d) the clinical significance of the efficacy results (i.e., efficacy driven by moderate exacerbations)
    e) lack of robust results for key secondary endpoints
    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

3. Discuss whether the data provide substantial evidence of efficacy 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.

4. Discuss the safety data 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.

5. Discuss if the benefit-risk profile is 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.

Clinical-Statistical Briefing Document for the Pulmonary Allergy Drugs Advisory Committee Meeting

July 25, 2018

Mepolizumab
(Nucala®)
BLA 125526 S-0007

Proposed Dose:
Mepolizumab 100 mg subcutaneous injection (SC) every 4 weeks

Proposed indication:
"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"

Clinical Reviewer: Robert Busch, MD, MMSc
Statistical Reviewer: Yu Wang, PhD

Department of Health & Human Services

Food & Drug Administration
Center for Drug Evaluation & Research
Division of Pulmonary, Allergy and Rheumatology Products
Silver Spring, MD 20993

Table of Contents

Table of Tables

Table of Figures

Glossary

Protocol-defined Peripheral Blood Eosinophil Strata

≥150-Scr or ≥300-Hist	peripheral blood eosinophil counts ≥150 cells/µL at screening or ≥300 cells/µL in the preceding 12 months • **High Stratum analysis threshold for MEA117106** • **All subjects in MEA117113**
<150-Scr and <300-Hist	peripheral blood eosinophil counts <150 cells/µL at screening and no count ≥300 cells/µL in the preceding 12 months • **Low Stratum analysis threshold in MEA117106**

Acronyms

AC	advisory committee
AE	adverse event
AECOPD	acute exacerbation of COPD
AR	adverse reaction
BLA	biologics license application
BRA	benefit-risk assessment
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COPD	chronic obstructive pulmonary disease
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
FEV1	forced expiratory volume in one second
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICH	International Council for Harmonization
ICS	inhaled corticosteroid
IL4	interleukin 4
IL5	interleukin 5
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intention to treat
LABA	long-acting beta-agonist
LAMA	long-acting muscarinic-antagonist
MDI	metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities

mITT	modified intention to treat
mITT-HS	modified intention to treat – High Stratum
mITT-LS	modified intention to treat – Low Stratum
mITT-pool	MEA117106 mITT-HS and MEA117113 mITT pooled populations
MedDRA	Medical Dictionary for Regulatory Activities
ModSev AECOPD	moderate-to-severe acute exacerbation of COPD
OCS	oral corticosteroid
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PB-Eos	peripheral blood eosinophils
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PRO	patient reported outcome
Q4 wks	every four weeks
SAE	serious adverse event
SAP	statistical analysis plan
SGRQ-C	St. George's Respiratory Questionnaire – COPD
SMQ	Standardized MedDRA Query
SOC	standard of care
TEAE	treatment emergent adverse event
TTF	time-to-first
wks	weeks
yr	year

1. Executive Summary

I. Brief Overview of the Clinical Program

GSK submitted a supplemental biologics licensing application (sBLA) for mepolizumab 100 mg administered by subcutaneous (SC) injection every 4 weeks for 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. COPD is a serious, common, preventable, progressive lung disease characterized by chronic inflammation of the airways and lung parenchyma caused by exposure to particulate matter or gases. Well-designed studies link increased frequency of moderate-to-severe (ModSev) acute exacerbations of COPD (AECOPD) to disease sequelae, and reducing the rate of AECOPD in frequently exacerbating COPD patients is a meaningful endpoint for COPD drug development.

Airway inflammation in COPD is commonly neutrophilic and causes increased mucus production and airway wall thickening. In roughly the last two decades, investigations of a subset of COPD patients who experience airway inflammation with a measurable eosinophilic component led to efforts to characterize "eosinophilic COPD" as a distinct, clinically meaningful phenotype. Despite research, uncertainty still exists regarding accurate defining criteria of the phenotype, the importance of sputum eosinophils versus peripheral blood eosinophils (PB-Eos) as biomarkers, and the clinical impact of the eosinophilic COPD phenotype in patient care and drug development. While multiple drug products are approved to reduce COPD exacerbations and form the standard of care in undifferentiated COPD, currently no drug product is approved for the treatment of COPD guided by blood eosinophil counts.

Mepolizumab is a monoclonal antibody directed against interleukin-5 (IL5) that binds IL5 and prevents its interaction with the IL5 receptor, modulating IL5 signaling; this modulation of IL5 signaling leads to decreased eosinophil maturation and survival as well as effects on other Th2 effector cells. Mepolizumab is approved under the trade name Nucala® for the treatment of severe asthma with eosinophilic phenotype and eosinophilic granulomatosis with polyangiitis (EGPA). The exact mechanism of action of mepolizumab in COPD is uncertain, but the Applicant's trials of mepolizumab in COPD rely on the hypotheses that anti-IL5 therapy will decrease eosinophilic airway inflammation in a patient population enriched for the eosinophilic phenotype by high PB-Eos counts, and that this attenuation will, in turn, lead to a clinically meaningful decrease in COPD exacerbations.

No formal proof-of-concept trial of mepolizumab in COPD or eosinophilic COPD was performed as part of the clinical development program. The Applicant derived the chosen PB-Eos criteria of ≥150 cells/µL at screening or ≥300 cells/µL in the prior 12 months from the severe asthma development program. The subjects who met the PB-eos screening criteria were defined, for the purposes of this development program, as being in the "High Stratum". Those subjects who did not fit this criteria were defined as being in the "Low Stratum".

No formal dose-ranging of mepolizumab in COPD was performed as part of the clinical development program. The Applicant carried over the dose of mepolizumab 100 mg SC every 4 weeks (mepo100) from the severe asthma development program, due to its pharmacodynamic effect in decreasing peripheral blood eosinophils and efficacy in severe asthma with eosinophilic phenotype. The Applicant did include a higher dose of mepolizumab, 300 mg every 4 weeks to provide some dose exploration in the phase 3 program.

The Applicant submitted two pivotal trials, MEA117106 and MEA117113, to support the efficacy of mepolizumab in reducing AECOPD in patients with COPD guided by blood eosinophils. The two trials shared many design elements; they were both multicenter, randomized, double-blind, placebo-controlled clinical trials that evaluated the impact of mepolizumab therapy on the rate of ModSev AECOPD among COPD patients who experienced frequent AECOPD despite standard of care maintenance therapy (i.e., triple therapy or comparable therapeutic regimens). AECOPD were defined by worsening symptoms of cough, sputum purulence, dyspnea, and other accepted symptoms. AECOPD classified as moderate necessitated intervention with systemic corticosteroids or antibiotics, while AECOPD classified as severe necessitated inpatient hospitalization of ≥24 hours. Both trials were 52 weeks in duration.

MEA117106 included subjects in both the high and low strata, with a pre-specified stratified analysis based on those in the high stratum (i.e., PB-Eos criteria of ≥150 cells/µL at screening or ≥300 cells/µL in the prior 12 months). Subjects in each of the strata of MEA117106 were randomized 1:1 to either mepolizumab 100 mg SC every 4 weeks (mepo100) or placebo. MEA117113 included only subjects in the high stratum (with PB-Eos of ≥150 cells/µL at screening or ≥300 cells/µLin the prior 12 months). Subjects in MEA117113 were randomized 1:1:1 to either mepo100, mepolizumab 300 mg SC every 4 weeks (mepo300), or placebo.

The pivotal trials enrolled subjects aged ≥40 years of age with spirometric evidence of COPD including FEV1 between 20% and 80% predicted normal, without current asthma (however a historical diagnosis of asthma was allowed), with symptoms and exacerbation history most consistent with the description of GOLD group D despite standard of care medical therapy.

The primary efficacy endpoint for both trials was the rate of ModSev AECOPD at 52 weeks. MEA117106 compared this endpoint between mepo100 versus placebo, focusing on the high stratum of subjects. MEA117113 compared this endpoint between mepo100 versus placebo and mepo300 versus placebo, with all subjects meeting high PB-Eos criteria. Important secondary efficacy endpoints in both trials included measurement of time-to-first ModSev AECOPD, rate of severe AECOPD, change in lung function measured by FEV1, and change in SGRQ-C scores with additional responder analyses. Safety assessments included adverse events (AE), vital signs, clinical laboratory tests, vital signs, physical examinations, and electrocardiograms.

II. Efficacy

The two pivotal trials randomized a total of 1,510 COPD patients; 836 and 674 subjects were

randomized in MEA117106 and MEA117113, respectively; MEA117106 included 117 sites in 16 countries with 19 US sites, while MEA117113 included 168 sites in 15 countries with 35 US sites. Baseline characteristics were generally balanced across treatment groups, although asthma history and baseline maintenance oral corticosteroid (OCS) use were not measured. The study populations had mean ages of ~65, with 53-55% of each treatment arm >65 years of age. Most patients were male (62-66%), white (80-81%), current or former smokers (95-98%), receiving baseline triple inhaled therapy (>99%). Greater than 85% of randomized subjects completed both MEA117106 and MEA117113 when subjects who died are classified as completers, with higher rates of study completion in the mepolizumab treatment arms compared to placebo.

The pre-specified primary efficacy analysis of MEA117106 shows a mean reduction in the rate of ModSev AECOPD over 52 weeks in those subjects 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) and an absolute difference in rates of 0.31 AECOPD/yr. However, the observed reduction in ModSev AECOPD in trial MEA117106 was driven only by a difference in the rate of moderate AECOPD, without a reduction in severe AECOPD.

The pre-specified primary efficacy analyses of MEA117113 (with all subjects meeting high PB-Eos criteria) do not achieve statistical significance for either the mepo100 or mepo300 dose. Point estimates describe baseline to week 52 rates of ModSev AECOPD in subjects receiving mepo100 compared to placebo (1.19 vs 1.48 AECOPD/yr) with a rate ratio estimate of 0.80 (95% CI 0.65 to 0.98; adjusted p-value 0.068) and an absolute difference of 0.29 AECOPD/yr. Rates of ModSev AECOPD in subjects receiving mepo300 compared to placebo (1.27 vs 1.48 AECOPD/yr) yield a rate ratio estimate of 0.86 (95% CI 0.70 to 1.06; adjusted p-value: 0.140) and an absolute difference of 0.21 AECOPD/yr.

The Applicant presents pre-specified analyses on multiple secondary efficacy endpoints. No secondary endpoints show results that are both statistically significant and clinically significant across both trials in subjects meeting high PB-Eos criteria. Individual trial results and pre-specified meta-analysis of the rates of severe AECOPD through week 52 do not achieve statistical significance to show a reduction in these rare events comparing mepo100 to placebo. Mean change in FEV1 at week 52 did not differ substantially between the mepo100 and placebo arms. The difference between the mepo100 and placebo arms in mean SGRQ-C change over 52 weeks was neither statistically nor clinically significant; SCRQ-C responder analyses showed only a small absolute difference in proportions of subjects in MEA117106 and MEA117113 (2% and 7%, respectively) achieving a minimal clinically important difference of ≥4 points with mepo100 compared to placebo.

Discussion

The primary issue for discussion at the upcoming PADAC meeting is whether there is substantial evidence of efficacy for the proposed indication. The primary efficacy analysis of trial MEA117106 shows a statistically significant effect of mepolizumab 100 mg SC every 4 weeks in reducing the rate of moderate to severe COPD exacerbations; however, the primary efficacy

analysis of trial MEA117113 fails to replicate these findings for the mepolizumab 100 mg dose and also does not show efficacy for the mepolizumab 300 mg dose. The lack of replication and the fact that the higher dose also did not achieve statistically significance raises questions about the efficacy of mepolizumab for the proposed indication. In addition, there are several other issues that we would like to committee to consider, and these are outlined below.

The Applicant did not collect data at baseline on two important patient factors: asthma history and use of chronic maintenance oral corticosteroids for COPD. Since mepolizumab is approved for the treatment of severe asthma (based on a reduction in asthma exacerbations), inclusion of a large proportion of subjects with asthma in the trial could impact trial results. In particular, any observed benefit of mepolizumab on exacerbations could be driven primarily or entirely by an effect in patients with concomitant asthma, given that asthma exacerbations and COPD exacerbations are not well differentiated clinically. Asthma-related adverse events appear in the safety database, suggesting subjects with active asthma were present in the trials. Exploratory efficacy subgroup analyses suggest more favorable efficacy estimates for mepo100 in subjects with younger age, less severe COPD, bronchodilator responsiveness, and higher eosinophil counts. The lack of data collection surrounding asthma, however, does not allow further evaluation of effects within subgroups defined by asthma history. This raises challenges in identifying what proportion of the observed results are due to mepolizumab's effects on asthma rather than potential effects on eosinophilic COPD, and in defining the group of patients that might benefit from mepolizumab.

Furthermore, maintenance OCS use presents an additional set of challenges in trial interpretation. Maintenance OCS use in COPD serves both as a marker of disease severity and as off-label preventative treatment to reduce the rate of AECOPD in clinical practice. OCS are also known to profoundly decrease peripheral blood eosinophil levels, which could influence stratum assignment in MEA117106 or inclusion in trial MEA117113. Baseline imbalances in maintenance OCS use between trial arms could affect the observed rates of AECOPD; additionally, modifications or discontinuations of maintenance OCS during the trial could affect the interpretation of trial results if these maintenance OCS changes were not balanced between arms. Because data on asthma history and maintenance OCS use were not collected, it is not possible to explore whether rates or imbalances between trial arms in either asthma history or OCS use might explain observed differences in outcomes between treatment arms.

The Applicant's proposed mechanism of action for mepolizumab relies on the idea that decreasing eosinophilic inflammation (due to anti-IL5 therapy) in a subset of COPD with markers of eosinophilic inflammation leads to decreased disease manifestations (e.g., exacerbations), that PB-Eos alone are an adequate biomarker of eosinophilic inflammation for treatment initiation, and that PB-Eos are an adequate biomarker for identification of patients that may benefit from anti-IL5 therapy. Given pharmacodynamic data from MEA117113 showing that mepo300 and mepo100 lowered PB-Eos to a comparable degree, a result showing comparable efficacy on clinical endpoints in the mepo300 and mepo100 groups would provide support for the Applicant's proposed role for PB-Eos as an adequate biomarker of eosCOPD and mepolizumab's proposed mechanism of action in COPD. However, the efficacy results of the two pivotal trials do not definitively support these conclusions; further, the lack of efficacy in

the mepo300 group also contributes to the uncertainty as to whether the chosen patient population was adequately defined.

Defining and targeting the correct patient population is important in all drug development programs, but perhaps even more so in the setting of mepolizumab for eosCOPD. Exploratory analyses of MEA117106 show that the rate of ModSev AECOPD was higher in the mepo100 arm compared to placebo (1.58 vs 1.29 AECOPD/yr, rate ratio 1.23) among subjects that did not meet high PB-Eos criteria (low stratum subjects), which may suggest a risk with mepolizumab to patients misdiagnosed with the eosinophilic COPD phenotype. Given the uncertainty in the eosinophilic COPD phenotype's definition and relevance, we conducted exploratory analyses of alternative PB-Eos thresholds and across a variety of PB-Eos subgroups. These exploratory analyses may provide some evidence of trends towards efficacy with increasing screening PB-Eos. However, due to their exploratory nature, they do not eliminate the statistical uncertainty of the primary efficacy analysis result, and raise additional concerns about the appropriate choice of threshold, if any, and about how to identify a group of patients that will benefit.

In summary, questions remain as to whether the data submitted by GSK provide substantial evidence of efficacy of mepolizumab for the proposed indication. One of the two pivotal trials supporting the safety and efficacy of mepolizumab in COPD fails to meet the pre-specified statistical threshold for efficacy in its primary efficacy analysis. Analyses of secondary endpoints do not bolster the results of the primary efficacy analysis. The impact of important unmeasured variables of asthma history and maintenance OCS use creates uncertainty as to whether asthma patients or changes to OCS regimens may have impacted the results of the pivotal trials. The lack of consensus surrounding the definition of the eosinophilic COPD phenotype, as well as the practical considerations of the Applicant's chosen eosinophil criteria, create uncertainty in defining the group of patients that could derive benefit from mepolizumab. Therefore, discussion is necessary as to whether the results of the mepolizumab clinical development program provide substantial evidence of efficacy to support the proposed indication.

III. Safety

While the safety profile of mepolizumab in severe asthma and EGPA is established, the safety of mepolizumab in COPD relies primarily on the safety databases of pivotal trials MEA117106 and MEA117113. Pooled analysis of the trials was deemed acceptable since these trials shared similar designs and comparable randomized populations. Safety assessments in these trials included adverse events (AE), vital signs, clinical laboratory tests, physical examinations, and electrocardiograms. Across both trials, a total of 836 subjects received any dose of mepolizumab while 674 subjects received placebo. Mean treatment duration was similar between trial arms, and exposure to study drug was adequate for the purposes of this sBLA.

There is no clinically significant imbalance in deaths when evaluating the totality of the data among COPD subjects in trials MEA117106 and MEA117113. Review of the safety data do not raise a concern for an effect on the rate of treatment-emergent deaths comparing mepolizumab (28 subjects, 3.2%) compared to placebo (26 subjects, 4.0%).

Proportions of AEs leading to discontinuation are similar across treatment arms in both trials, and analyses of these data do not influence the overall safety review.

Overall, subjects administered mepolizumab experienced a comparable incidence and exposure-adjusted rate of on-treatment SAEs compared to subjects administered placebo in trials MEA117106 and MEA117113, and these data do not raise safety concerns for the overall rates of SAEs.

Exploratory safety analyses of any dose of mepolizumab versus placebo in COPD identify imbalances in the proportion of subjects experiencing SAEs and AEs classified as supraventricular tachyarrhythmias (3.5% vs 2%), cardiovascular thrombotic events (2% vs 1.4%), gastrointestinal bleeding (0.9% vs 0.5%), and acute pancreatitis (0.5% vs 0%).

Submission-specific safety concerns previously identified by the Applicant during mepolizumab drug development include “cardiac, vascular, thromboembolic, and ischemic events”, “hypersensitivity reactions, anaphylaxis, and local injection site reactions”, “serious and opportunistic infections”, and “neoplasms and malignancies”. Analyses by both the Applicant and the Agency reveal consistent imbalances in cardiovascular thrombotic events towards mepolizumab despite different analysis methods. Results of analyses of anaphylaxis, hypersensitivity reactions, and local injection site reactions in the mepolizumab COPD development program are consistent with known and labeled adverse reactions to mepolizumab. While no imbalance in pneumonia events was detected across trial arms, analyses of opportunistic infections by both the Applicant and Agency support imbalances in candida-related events and herpes zoster events towards mepolizumab. Finally, analyses of neoplasms and malignancies do not reveal imbalances between mepolizumab and placebo arms.

Common adverse reactions to mepolizumab occurring with a frequency of >2.5% and more commonly than in subjects administered placebo include back pain, cough, oropharyngeal pain, diarrhea, sinusitis, bronchitis, pain in extremity, nausea, hypertension, constipation, oral candidiasis, fatigue, and contusion.

IV. Risk-Benefit Assessment

In summary, questions remain as to whether the data submitted by GSK provide substantial evidence of efficacy of mepolizumab for the proposed indication. One of the two pivotal trials supporting the safety and efficacy of mepolizumab in COPD fails to meet the pre-specified statistical threshold for efficacy in its primary efficacy analysis. Analyses of secondary endpoints do not bolster the results of the primary efficacy analysis. The impact of important unmeasured variables of asthma history and maintenance OCS use creates uncertainty as to whether asthma patients or changes to OCS regimens may have impacted the results of the pivotal trials. The lack of consensus surrounding the definition of the eosinophilic COPD phenotype, as well as the practical considerations of the Applicant’s chosen eosinophil criteria, create uncertainty in defining the group of patients that could derive benefit from

mepolizumab. Therefore, discussion is necessary as to whether the results of the mepolizumab clinical development program provide substantial evidence of efficacy to support the proposed indication.

The safety analysis of mepolizumab in COPD reveals numerically small imbalances in important adverse events in the COPD patient population. Therefore, we ask the committee to discuss whether the efficacy results, taken with the safety findings, support the benefit-risk assessment of mepolizumab in patients with COPD (guided by blood eosinophils).

2. Introduction and Regulatory Background

2.1. Brief Clinical Background

Chronic obstructive pulmonary disease (COPD) is a serious, common, preventable, progressive lung disease involving chronic inflammation of the airways and lung parenchyma caused by exposure to particulate matter or gases. Tobacco smoke exposure is the most frequent cause of COPD in the United States of America by an overwhelming margin. COPD is characterized by irreversible airflow obstruction and persistent respiratory symptoms. COPD is the fourth leading cause of mortality worldwide[3,4]. Almost 15.7 million Americans report a diagnosis of COPD[5], and COPD is the third leading cause of death in the United States[6]. Currently, there is no cure for COPD, nor any therapeutic intervention that definitively halts or reverses disease progression.

The major pathophysiologic drivers of airflow obstruction in COPD are chronic inflammation of the airways and lung parenchymal destruction in response to chronic noxious stimuli such as tobacco or biomass fuel combustion. Airway inflammation is commonly neutrophilic and causes increased mucus production and airway wall thickening. Emphysematous lung parenchymal destruction contributes to airflow obstruction by decreasing airway tethering, which can cause airways to narrow or collapse.

The clinical course of COPD is heterogeneous and includes both chronic daily symptoms and acute disease exacerbations. Comorbidities, genetic factors, occupational exposures, environmental exposures, and gender all influence the likelihood of acquiring COPD and disease manifestations. Regardless of overarching clinical presentation, the symptomatic burden of COPD is significant. Almost all COPD patients experience chronic and persistent symptoms such as dyspnea, cough, increased mucus production, and exercise limitation. As the disease progresses over time and increases in severity, patients may develop more debilitating symptoms that can negatively impact a patient's health-related quality of life[7] and lead to loss of independence[8] and productivity[5,9].

Clinicians use spirometry to diagnose COPD and judge its severity[3,10]. Demonstration of significant irreversible airflow obstruction confirms the diagnosis, while the degree of airflow obstruction compared to predicted normal values determines severity. Recent international guidelines for COPD diagnosis and management include an assessment of both chronic symptoms and frequency of disease exacerbations as an adjunct classification to better characterize COPD severity[3].

Acute exacerbations of COPD (AECOPD) involve significant worsening of COPD symptoms requiring additional medical intervention[11,12]. Well-designed studies link increased frequency of moderate to severe AECOPD to disease sequelae such as decreased quality of life[13], while severe AECOPD are more directly linked to increased disease progression[14], morbidity, and mortality[15,16]. Some COPD patients still experience frequent AECOPD despite the concomitant use of multiple FDA-approved maintenance therapies designed to reduce the rate of AECOPD.

The frequency of AECOPD and the population of COPD patients experiencing frequent AECOPD have become meaningful drug development targets. Reducing the rate of AECOPD in these frequently exacerbating COPD patients represents an opportunity for meaningful intervention to prevent the sequelae listed above.

In roughly the last two decades, investigations of a subset of COPD patients who experience airway inflammation with a measurable eosinophilic component led to efforts to characterize "eosinophilic COPD" as a distinct, clinically meaningful phenotype[17-21]. Uncertainty still exists regarding the phenotype's exact defining criteria as well as the clinical impact of this phenotype in patient care and drug development. Some studies link sputum or peripheral blood eosinophilia to increased frequency of AECOPD or to increased effectiveness of COPD treatments[22-26] on AECOPD endpoints; other studies do not support these links[27-29]. Recent trials have examined potential associations of sputum or peripheral blood eosinophil levels with rates of AECOPD, and whether these association could guide the use of inhaled corticosteroid therapy. Differences in trial design, study populations, proposed eosinophil levels, and study interventions thwart efforts to draw definitive conclusions from these studies about the relevance of eosinophilic COPD in current clinical practice. Additionally, recently published press releases[1,2] state that two randomized, double-blind, placebo-controlled COPD trials enriched for subjects with higher peripheral blood eosinophil counts evaluating benralizumab (an anti-interleukin 5 receptor monoclonal antibody) versus placebo did not show evidence of effects on their primary efficacy endpoints for reduction of moderate-to-severe AECOPD.

However, acceptance of the phenotype as a target of research has grown in the scientific community, focusing on the potential to identify and treat this proposed subset of COPD patients. The development of anti-interleukin 5 (IL5) therapies that decrease peripheral blood eosinophil counts has paralleled the time course of scientific literature regarding eosinophilic COPD. If eosinophilic COPD can be adequately defined and shown to respond to therapies directed against eosinophils, there exists the potential to provide phenotype-driven personalized therapy to patients with COPD. Uncertainties notwithstanding, the development of anti-IL5 therapies targeting pathways of eosinophilic inflammation has led to scientific interest in evaluating the benefit-risk profile of these medications for COPD patients. This supplemental biologics application (sBLA) for mepolizumab would be a first in class for the use of an anti-IL5 therapy for the novel indication of the treatment of COPD (guided by blood eosinophils). The pivotal trials associated with this application focused primarily on subjects with peripheral blood eosinophil counts ≥150 cells/µL at screening or ≥300 cells/µL in the past 12 months (≥150-Scr or ≥300-Hist).

2.2. Product Information

This sBLA is submitted by GSK in support of mepolizumab at a dose of 100 mg by subcutaneous injection every 4 weeks with a 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.

Mepolizumab is an IgG1 kappa humanized monoclonal antibody targeting interleukin-5 (IL5). Mepolizumab is produced by recombinant DNA technology in Chinese hamster ovary cells. It is a sterile, lyophilized powder for injection. Following reconstitution with Sterile Water for Injection, USP, each single-use vial will deliver 100 mg/mL mepolizumab in 1 mL, as well as 160mg/mL sucrose, 7.14 mg/mL sodium phosphate dibasic heptahydrate, and 0.67 mg/mL polysorbate 80, with a pH of 7.0

2.3. Tables of Currently Available Treatments for Proposed Indications

There are no approved therapies for the treatment of COPD guided by blood eosinophils.

In addition to smoking cessation, international guidelines recommend inhaled medications as first-line medical therapy for COPD[3,10] due to their low systemic exposure and favorable toxicity profile. Inhaled medication classes for maintenance treatment of COPD include long-acting beta-agonists, long-acting muscarinic antagonists, and inhaled corticosteroids, often prescribed in combination (see Table 1). Short acting inhaled medications are approved for the treatment/prevention of bronchospasm, and are routinely used in COPD patients. Oral medications are generally prescribed for specific subpopulations of COPD, or for those patients that do not respond adequately to inhaled medications.

There are no FDA-approved therapies for the acute management of AECOPD, although guidelines agree on standard therapy. Guideline-driven management of AECOPD involves short courses of systemic corticosteroids, antibiotics, and additional supportive care as needed.

Table 1 Summary of Treatment Armamentarium for COPD

Class	Drug substance	Representative trade names	Relevant indication in COPD	Relevant COPD patient population
Single Ingredient Treatments				
SABA Short-acting beta-agonist	albuterol (salbutamol)	ProAir, Proventil, Ventolin,	For reversible airway obstruction	Emphysema and/or chronic bronchitis
LABA Inhaled long-acting beta agonist	arformoterol tartrate, formoterol fumarate, indacaterol maleate, olodaterol hydrochloride, salmeterol xinafoate	Brovana, Perforomist, Arcapta Neohaler, Striverdi Respimat, Serevent	Maintenance treatment of bronchoconstriction, bronchospasm, or airflow obstruction	Emphysema and/or chronic bronchitis
LAMA Inhaled long-acting muscarinic antagonist	aclidinium bromide, glycopyrrolate, tiotropium bromide, umeclidinium bromide	Tudorza Pressair, Seebri Neohaler, Spiriva HandiHaler, Spiriva Respimat, Incruse Ellipta	Maintenance treatment of bronchospasm or airflow obstruction	Emphysema and/or chronic bronchitis
PDE-4 inhibitor	roflumilast	Daliresp	Reduce the risk of AECOPD	Severe COPD, chronic bronchitis, and history of AECOPD

Class	Drug substance	Representative trade names	Relevant indication in COPD	Relevant COPD patient population
Methylxanthine	theophylline	Theophylline, Theo-24, Theochron, Elixophyllin	Treatment of symptoms and reversible airflow obstruction	Emphysema and/or chronic bronchitis
Combination treatments				
ICS/LABA Inhaled corticosteroid + LABA	budesonide/ formoterol, fluticasone propionate/ salmeterol, fluticasone furoate/ vilanterol	Symbicort, Advair Diskus, Advair HFA, Breo Ellipta	Maintenance treatment of airflow obstruction and reducing AECOPD	Emphysema and/or chronic bronchitis, or not specified
LABA/LAMA	formoterol / glycopyrrolate, glycopyrrolate/ indacaterol, olodaterol / tiotropium, umeclidinium / vilanterol	Bevespi Aerosphere, Utibron Neohaler, Stiolto Respimat, Anoro Ellipta	Maintenance treatment of airflow obstruction	Emphysema and/or chronic bronchitis
ICS/LAMA/ LABA	fluticasone furoate/ umeclidinium / vilanterol	Trelegy Ellipta	Maintenance treatment of airflow obstruction and reducing AECOPD	Emphysema and/or chronic bronchitis
Inhaled short-acting beta agonist/short-acting anticholinergic	Albuterol sulfate/ ipratropium bromide	Duoneb, Duoneb HFA, Combivent Respimat	Treatment of acute bronchospasm	Patients taking regular inhaled bronchodilator therapy

Source: Reviewer-created table based on product labeling for currently approved medications indicated for COPD
AECOPD: acute exacerbations of chronic obstructive pulmonary disease. SABA: short-acting beta-agonist. LABA: long-acting beta-agonist. LAMA: long-acting muscarinic antagonist. ICS: inhaled corticosteroid.

2.4. Availability of Proposed Active Ingredient in the United States

Mepolizumab (tradename Nucala) is currently approved for the treatment of severe asthma with eosinophilic phenotype and for the treatment of eosinophilic granulomatosis with polyangiitis (EGPA). Mepolizumab is not approved for the treatment of COPD (including COPD guided by blood eosinophils) anywhere in the world.

2.5. Important Safety Issues With Consideration to Related Drugs

The safety of mepolizumab was evaluated in a severe asthma with eosinophilic phenotype population as well as an eosinophilic granulomatosis with polyangiitis population. During early drug development, GSK identified the following AEs of special interest for mepolizumab:

- systemic reactions of anaphylaxis, allergic/hypersensitivity reactions, and non-allergic reactions;
- local injection site reactions;
- infections, serious infections, and opportunistic infections,
- neoplasms and malignancies,
- cardiac disorders and major adverse cardiovascular events including cardiovascular thrombotic events.

Current mepolizumab USPI includes warnings and precautions describing the risk of hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, and rash), the increased rate of herpes zoster infections observed in subjects receiving mepolizumab in placebo-controlled clinical trials, as well as the potential risk of anti-IL5 therapy in the setting of parasitic (helminth) infections. Labeling also describes common adverse reactions of headache, injection site reaction, back pain, and fatigue, among others.

No biologic is currently approved for the treatment of COPD. However, related drugs (detailed below) provide previously identified safety signals in drug development programs of anti-IL5, anti-IL5R, and anti-interleukin 4 (IL4) biologics for the following indications: severe asthma with eosinophilic phenotype and moderate to severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable

Reslizumab (Cinqair®) is an anti-IL5 monoclonal antibody approved for treatment of patients with severe asthma aged 18 years or older with an eosinophilic phenotype. The product label for reslizumab contains a boxed warning describing anaphylaxis, and warnings and precautions describing the increased rate of malignancy in subjects receiving reslizumab observed in placebo-controlled clinical trials, as well as the potential risk of anti-IL5 therapy in the setting of parasitic (helminth) infections. Reslizumab labeling also describes higher observed rates of creatine phosphokinase elevations compared to placebo, higher observed rates of myalgia compared to placebo, and common adverse reactions such as oropharyngeal pain.

Benralizumab (Fasenra®) is an anti-IL5R α-subunit-directed cytolytic monoclonal antibody approved for treatment of patients with severe asthma aged 12 years and older with an eosinophilic phenotype. The product label for benralizumab contains warnings and precautions describing the risk of hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, and rash) as well as the potential risk of anti-IL5 therapy in the setting of parasitic (helminth) infections. Labeling also describes common adverse reactions of headache, pharyngitis, and pyrexia.

Dupilumab (Dupixent®) is an anti-IL4 monoclonal antibody approved for moderate to severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. The IL4 and IL5 pathways both play a role in humoral and adaptive immunity, help regulate the Th2 immune response, and stimulate B-cell proliferation and induce B-cell class switching, so potential overlap of adverse events involving mepolizumab and dupilumab is plausible. The product label for dupilumab includes labeling in the Warnings and Precautions section describing an increased risk of conjunctivitis and keratitis in patients who received dupilumab. Labeling also describes common adverse reactions such as injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infections, and dry eye.

2.6. Summary of Regulatory Activity Related to Submission

Mepolizumab lyophilized powder for injection (BLA 125526) drug product received FDA approval on 04 Nov 2015 at a dose of 100 mg administered subcutaneously once every 4 weeks for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. On 12 Dec 2017, FDA approved a supplemental BLA for mepolizumab 300 mg administered subcutaneously once every 4 weeks for the add-on treatment to corticosteroids for adult patients with eosinophilic granulomatosis with polyangiitis.

GSK relied on data from mepolizumab's asthma drug development program to inform decision-making about pivotal clinical trials for the COPD indication. GSK did not perform Phase II clinical trials to evaluate dose-ranging, efficacy, and proof-of-concept in COPD patients.

The mepolizumab product was developed for COPD under IND006971. Major regulatory interactions relevant to this submission are summarized below:

<u>August 28, 2013 - End-of-Phase 2 (EOP2) meeting:</u>

- FDA expressed concerns regarding the eosinophilic COPD phenotype, noting uncertainties surrounding the phenotype and its definition.
- FDA expressed concern about defining the proposed subset of eosinophilic COPD using only peripheral blood eosinophil counts and frequent exacerbations due to potential confounding from similar or comorbid diseases such as asthma.
- FDA stated that subsequent trials must characterize the eosinophilic COPD phenotype and evaluate eosinophils as a biomarker by including patients with and without blood eosinophilia in the trials.
- FDA recommended proof-of-concept and preliminary dose-ranging trials, but stated that the Applicant could proceed with their plan to incorporate these concepts into the phase 3 trials using doses and eosinophil count thresholds extrapolated from the asthma program.
- FDA acknowledged that the frequency of moderate-to-severe AECOPD was a reasonable primary endpoint for COPD trials. FDA acknowledged the Applicant's plan to perform a pre-specified meta-analysis of severe AECOPD, noting that interpretation of the meta-analysis would be a review issue.

<u>August 01, 2017 - Pre-sBLA meeting:</u>

- FDA agreed that the COPD clinical program data, nonclinical data, and product quality data proposed by the Applicant appeared sufficient to file the sBLA for review.
- FDA expressed concerns about whether the data in the phase 3 program were sufficient to support the efficacy of mepolizumab in the subgroup of COPD patients that were studied.
- FDA reiterated concerns regarding the utility of eosinophils as a biomarker in COPD and the definition of eosinophilic COPD phenotype, based on uncertainty in the scientific literature.

- FDA suggested that the proposed indication statement for mepolizumab focus on a description of the patient population included in phase 3 clinical trials of COPD, rather than focusing on eosinophil count as a biomarker or phenotypic marker.
- In response to FDA's reiterated concerns regarding potential confounding from similar or comorbid diseases such as asthma, the Applicant presented selected demographic and baseline disease characteristic data to support their contention that the patient populations in their COPD drug development program represented a different population than was studied in their severe asthma program. FDA commented that preliminary review suggested that the enrolled COPD patient population was similar to those enrolled in traditional COPD programs; however, this potential uncertainty in trial population with regards to asthma remained a review issue for the application.

3. Clinical Pharmacology

3.1. Mechanism of Action

While most patients with COPD exhibit neutrophil-predominant lung inflammation, the applicant proposes that eosinophils contribute to airway inflammation in a subset of patients with COPD. Eosinophils recruited to the lung are thought to be the effector cells of this inflammation; the applicant proposes peripheral blood eosinophils (PB-Eos) as a surrogate marker of this eosinophil-predominant inflammation in an eosinophilic COPD phenotype.

Interleukin 5 (IL5) plays a major role in the growth, differentiation, recruitment, activation, and survival of eosinophils. IL5 also plays additional roles in innate and adaptive immunity including basophil differentiation[30] and priming of histamine release[31] as well as B-cell proliferation[32] and class-switching[33].

Mepolizumab is a humanized monoclonal antibody (IgG1 kappa) that competitively binds to human IL5; this binding prevents the interaction between IL5 and the alpha chain of the IL5 receptor and inhibits downstream IL5 signaling. The applicant's mechanism of action relies on the idea that mepolizumab will affect COPD disease manifestations in patients with eosinophil-predominant airway and lung inflammation by producing a sustained and consistent reduction in eosinophil counts.

It is notable that the Applicant did not conduct separate proof-of-concept clinical trials providing robust evidence that baseline PB-Eos levels accurately predict eosinophilic lung inflammation, that decreases in PB-Eos levels are valid surrogates for decreases in eosinophilic lung inflammation, or that decreases in eosinophilic lung inflammation cause clinically meaningful decreases in validated endpoints for COPD. Taking into account the absence of this proof-of-concept data, we ask the committee to consider whether the submitted data adequately support the efficacy of mepolizumab in patients with COPD defined using the guidelines in the proposed indication.

4. Sources of Clinical Data and Review Strategy

4.1. Tables of Clinical Trials

The sources of clinical data utilized in this review are summarized in Table 2.

Table 2 Clinical Trials of Mepolizumab for COPD (Guided by Blood Eosinophils)

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 -Rate of severe AECOPD -Change from baseline SGRQ-C score -Change from baseline CAT score	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[7] 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. All patients 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: Saint George's Respiratory Questionnaire; ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LAMA: long-acting anti-muscarinic NCT: National Clinical Trial

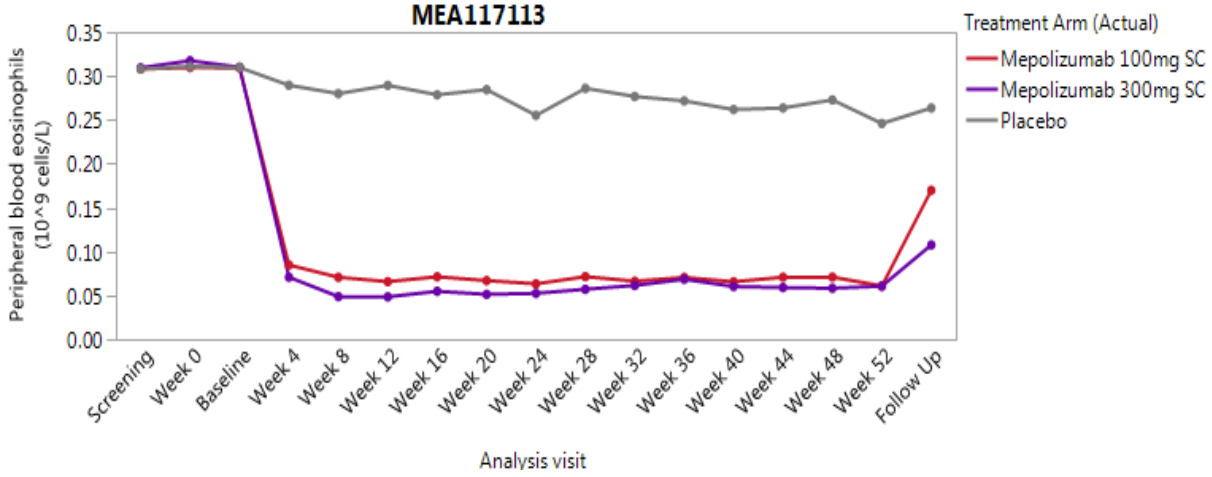
4.2. Dose Selection/Rationale

The Applicant based their mepolizumab dose selection for trials MEA117106 and MEA117113 primarily on information extrapolated from their asthma drug development program showing that the mepolizumab 100 mg SC every 4 weeks (mepo100) dose reduced mean peripheral blood eosinophils (PB-Eos) in subjects with severe asthma with an eosinophilic phenotype.

The Applicant designed MEA117113 to incorporate aspects of dose-ranging, but the trial enrolled and proceeded in parallel to the timeframe of MEA117106, thus dose-ranging data was not informative to the other pivotal trial.

Laboratory data from MEA117106 and MEA117113 support the predicted effect on PB-Eos counts of the mepo100 dose, as well as the marginal added effect of the mepolizumab 300 mg SC every 4 weeks (mepo300) dose on PB-Eos counts compared to placebo (see Figure 1). These PB-Eos decreases mimic the decreases seen in previous mepolizumab trials.

Figure 1 Dose Effect of Mepolizumab on Peripheral Blood Eosinophil Counts



Source: Analysis of MEA117113 ADaM Datasets; Figure created using JMP Clinical software

While the pharmacodynamic decrease in PB-Eos is demonstrated for both doses (with a marginally greater reduction with mepolizumab 300 mg), as will be discussed later in the briefing document; mepolizumab 100 mg demonstrated a statistically significant reduction in ModSev AECOPD in one of two trials, while mepolizumab 300 mg did not.

Please see Section 6.6 Analysis of Primary Endpoint(s) for full details and discussion of these analyses.

In summary, the limited dose-ranging data in COPD patients, which does not show a dose response in efficacy and the differing results for the primary endpoint of reduction in ModSev AECOPD between the two pivotal studies raises uncertainty regarding the proposed dose and proposed mechanism of action of mepolizumab in COPD patients, and will be an important issue for discussion.

4.3. Review Strategy

This sBLA review relies primarily on data and analyses from pivotal trials MEA117106 and MEA117113, pre-specified meta-analysis data from a subset of MEA117106 and MEA117113, and exploratory post-hoc meta-analysis data of the same two trials.

The protocols for the pivotal trials are summarized and reviewed in Section 5.1 Study MEA117106 and Section 5.2 Study MEA117113.

The efficacy review relies on efficacy analyses of pre-specified endpoints in MEA117106 and MEA117113, as well as a pre-specified meta-analysis of subpopulations of the two pivotal trials. For the purposes of this review, statistical and clinical review teams reproduced primary and secondary efficacy analyses of MEA117106, MEA117113, and meta-analysis populations, as well as performed additional exploratory efficacy analyses. Efficacy results and discussion for MEA117106 and MEA117113 are provided in Section 6 Review of Efficacy.

The safety review focuses on individual pivotal trial safety results and pooled safety results from MEA117106 and MEA117113. The clinical review team performed exploratory analyses of deaths, serious adverse events (SAE), adverse events (AE), adverse events of special interest (AESI), standardized MedDRA queries (SMQ), laboratory data, vital signs, and immunogenicity data on the safety population of each pivotal trial and the pooled analyses dataset. Safety analyses and discussion are provided in Section 7 Review of Safety.

5. Design and Conduct of Pivotal Trials

5.1. Study MEA117106

The design of this multi-national study intended to provide primary evidence of proof-of-concept, efficacy, and safety for mepolizumab 100 mg by subcutaneous injection every 4 weeks (mepo100) versus placebo 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.

Study Designation: MEA117106 (METREX)
Study title: Mepolizumab vs. Placebo as add-on treatment for frequently exacerbating COPD patients
Study dates: 15 Apr 2014 to 17 Jan 2017
Study sites: 117 sites in 16 countries; 19 US sites
Study report date: 22 Sep 2017

5.1.1. Trial Objectives

Primary

- To evaluate the efficacy and safety of mepo100 versus placebo on the frequency of moderate to severe COPD exacerbations (ModSev AECOPD) in COPD subjects with peripheral blood eosinophil (PB-Eos) counts ≥150 cells/µL at screening or ≥300 cells/µL in the preceding 12 months, at high risk of AECOPD despite the use of optimized standard of care background therapy

Secondary

- To evaluate the efficacy and safety of mepo100 versus placebo on the frequency of ModSev AECOPD in COPD subjects at high risk of AECOPD despite the use of optimized standard of care background therapy, with or without elevated PB-Eos
- To evaluate other efficacy assessments of mepo100 versus placebo on changes in health care utilization, COPD symptoms, quality of life, and lung function

5.1.2. Trial Design

MEA117106 was a randomized, double-blind, placebo-controlled, multicenter, multinational trial comparing the safety and efficacy of mepo100 versus placebo on the frequency of ModSev AECOPD among a sample COPD subjects that experience frequent AECOPD despite inhaled corticosteroid, long-acting beta-agonist, and long-acting muscarinic antagonist (ICS+LABA+LAMA) maintenance therapy.

Eosinophilic COPD Phenotype Proof of Concept Trial Elements

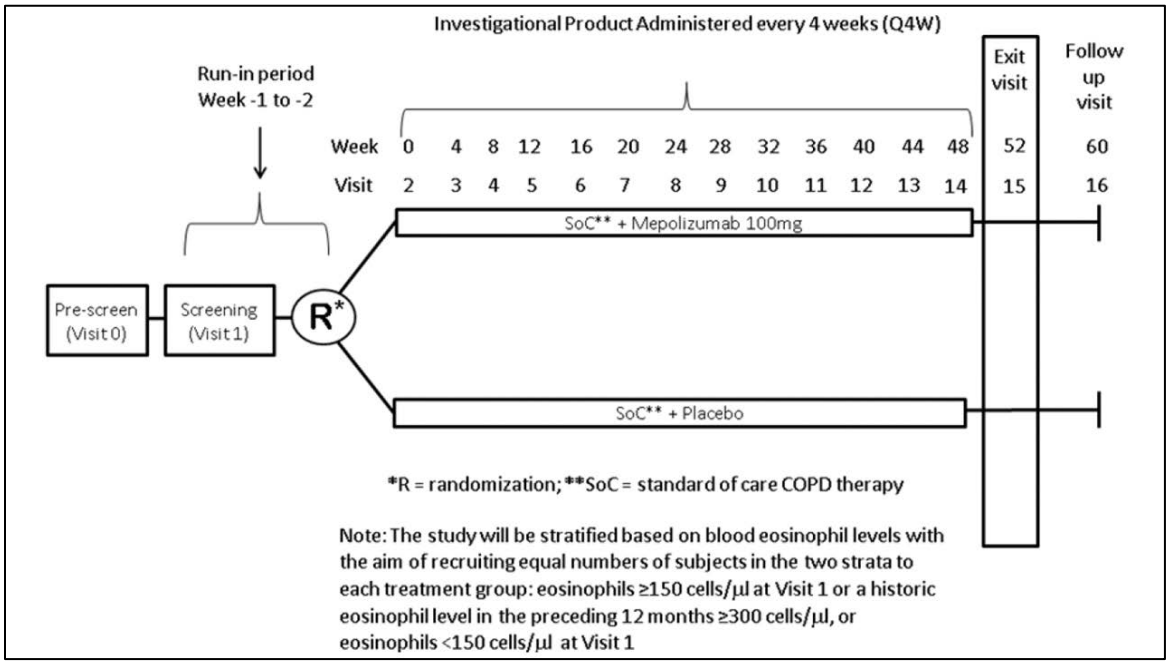
MEA117106 incorporated elements of a proof-of-concept trial for the Applicant's threshold PB-Eos criteria and for eosinophilic COPD (eosCOPD) as a clinically relevant phenotype responsive to anti-IL5 therapy. Threshold PB-Eos counts served as a surrogate marker for the eosCOPD phenotype in this trial. To evaluate the hypothesis that threshold PB-Eos counts predicted differential response to mepolizumab, the Applicant stratified enrolled subjects into a High Eosinophil Stratum (HS) and Low Eosinophil Stratum (LS) for separate pre-specified analyses. The applicant defined the HS using a PB-Eos count ≥150 cells/µL at screening or ≥300 cells/µL in the preceding 12 months; the LS was defined by a PB-Eos count <150 cells/µL at the screening visit and historical values that were not ≥300 cells/µL in the preceding 12 months. This study design allowed for proposed efficacy comparisons of mepolizumab versus placebo among those defined as HS, those patients defined as eosCOPD in the LS, and the overall trial population.

Reviewer's comment: The assumption that higher blood eosinophils alone can accurately identify patients with eosCOPD is vital to the applicant's conclusions and proposed indication statements. The threshold levels chosen by the applicant are based largely on the applicant's experience in the severe eosinophilic asthma drug development program (see Section 2.6). Whether the applicant's threshold eosinophil counts of ≥150 cells/µL screening or ≥300 cells/µL historical have a pathophysiologic basis or significance in discriminating eosCOPD merits discussion with the Advisory Committee; this topic is discussed further in Section 6.9.1 Eosinophil Threshold Subgroups.

Design

The trial design of MEA117106 incorporated a pre-screening period, a screening visit, a 52-week randomized treatment period, and an 8-week follow-up period. PB-Eos evaluation during the screening period classified enrolled subjects into HS or LS. After the screening period, eligible subjects were randomized (1:1) to either mepo100 or placebo treatment arms. During the treatment period of weeks 0 to 52, clinic assessments occurred every 4 weeks for a total of 14 visits, followed by an additional follow-up visit at week 60. The study design is summarized schematically in Figure 2. Study assessments are summarized in Figure 3.

Figure 2 Study Schematic for Trial MEA117106



Source: Applicant's mea117106-report.pdf, figure 1, page 34

Figure 3 Schedule of Study Assessments for Trial MEA117106

Protocol Activity	Screen/Run-in		Randomized Treatment (visit window is ± 7 days)													Exit Visit	Follow Up
	V0[a]	V1	V2[b]	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16
	Pre-screening	V1(S)	Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52	Week 60
Study Day			1														
Procedures																	
Written Informed Consent/PGx consent	X[d]																
Demography/child bearing status assessment	X																
Medical history including cardiovascular, COPD, and exacerbation		X															
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion Criteria[e]		X	X														
CCI		X															
mMRC		X															
Smoking Status		X							X							X	
Smoking Cessation Counseling		X														X	
Parasite Screening[f]		X															
Register Visit in RAMOS/IVRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessements																	
Spirometry		X	X	X		X			X			X			X	X	
Reversibility Testing		X															
eDiary data review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Exacerbation and Healthcare Utilization Assessment				X	X	X	X	X	X	X	X	X	X	X	X	X	
SGRQ-C			X			X			X			X				X	
EQ-5D-5L			X						X							X	
CAT			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Subject global rating of activity level			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Subject global rating of activity change				X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinician rated response to therapy					X			X			X			X		X	
Subject rated response to therapy					X			X			X			X		X	
Safety Assessments																	
Adverse Events/Serious Adverse Event Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical Problems Diary Review				X	X	X	X	X	X	X	X	X	X	X	X	X	
COPD symptoms summary report review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination		X[g]	X[h]			X[h]			X[g]			X[h]				X[g]	
Vital Signs (including pulse oximetry)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG		X				X			X			X				X	X
Chest x-ray		X[i]															
Laboratory Assessments																	
Hematology with differential [j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry[s]		X	X	X[k]	X[k]	X			X			X				X	X
Clinical chemistry with lipoproteins (fasting)[l]			X						X							X	
Urine Pregnancy Test[m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGx Sampling (blood)				X[n]													
Hepatitis B and C testing[o]		X															
LFT testing (only in hepatitis B positive subjects)[p]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetic Sample[q]			X	X					X							X	X
Immunogenicity sample			X						X							X	X
Exploratory Lab Assessments																	
Total IgE			X														
Blood Biomarker			X						X							X	
Serum IL-5			X						X								X
Study Supplies and Investigational Product																	
Electronic Diary registration and training		X[r]															
Electronic Diary close out																X	
Administer Investigational Product			X	X	X	X	X	X	X	X	X	X	X	X	X		
Dispense Rescue Salbutamol		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Collect Used Rescue Salbutamol			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Complete electronic Case Report Form (eCRF)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. The pre-screening visit (Visit 0) can occur on the same day as the screening visit (Visit 1) but must be completed prior to initiating any Visit 1 procedures.
b. Visit 2 can occur 1 to 2 weeks after Visit 1. Results from Visit 1 procedures must be available for review of randomization criteria.
c. Omitted
d. Informed consent for optional PGx (pharmacogenetics) research must be obtained before collecting a sample.
e. Inclusion and Exclusion criteria should be assessed at Visit 1 and Randomization Criteria assessed at Visit 2.
f. Parasitic screening is only required in countries with high-risk or for subjects who have visited high-risk countries in the past 6 months. Sites should use local laboratories.
g. A comprehensive physical exam should be conducted.
h. A brief physical exam should be conducted.
i. Only required if results from a chest x-ray or CT-scan, taken within the past 6 months, is not available.
j. Differential results will be blinded from Visit 3 onwards.
k. Liver panel only
l. Subject must be in fasting state. If subject has not fasted they may return to the clinic to provide this sample.
m. Pregnancy testing is only required for females of child bearing potential. An assessment must be made at baseline to determine child bearing potential of each female study participant
n. PGx consent must be obtained prior to collecting the PGx blood sample. The PGx sample can be collected at any visit post-randomization (i.e. at Visit 3 or any visit after Visit 3).
o. If hepatitis C positive confirmation by testing the same sample is required. See Quest manual for details. For subjects who are HBsAg positive or HBcAb positive reflexive testing must be conducted to assess HBV DNA
p. If ALT ≥ 3X ULN, reflexive testing should be conducted for HBV-DNA
q. PK samples must be taken pre-dose
r. Thorough eDiary training should be conducted at Visit 1 and throughout the study on an as-needed basis
s. Clinical chemistry will include analytes and liver chemistry monitoring as detailed in the SPM.

Source: Adapted from applicant's submission for MEA117106, protocol-amend-2.pdf, table 2, pages 44-47

5.1.3. Inclusion and Exclusion Criteria

Key Inclusion Criteria

- Male and female sex
- ≥40 years of age
- ≥1 year history of COPD
- A history of frequent exacerbations (≥2 moderate AECOPD or ≥1 severe AECOPD in prior 12 months)
- With or without PB-Eos (≥150 cells/µL at screening or ≥300 cells/µL in prior 12 months)
- ICS+LABA+LAMA inhaled triple therapy or a comparable regimen
- FEV1/FVC ≤ 0.7
- Post-bronchodilator FEV1 between 20% and 80% of predicted normal

Key Exclusion Criteria for Screening and Randomization

- Current diagnosis of asthma
    - Historical diagnosis of asthma allowed for current and former smokers
- Other major chronic respiratory conditions
- Lung volume reduction surgery or lung resection
- Recent pulmonary rehabilitation participation
- >4 L/min of supplemental oxygen required to maintain oxygen saturation of 89%
- Unstable cardiac disease including myocardial infarction in last 6 months, unstable cardiac arrhythmia in last 3 months, or NHYA Class IV heart failure
- Clinically significant electrocardiogram findings
    - Non-sustained or sustained tachycardia ≥100 bpm
    - Heart rate ≥120 bpm due to sinus tachycardia, multifocal atrial tachycardia, atrial fibrillation, atrial flutter
    - Additional criteria including evidence of myocardial infarction, ventricular arrhythmias, clinically significant heart block, heart rate ≥100 bpm due to junctional tachycardia, corrected and uncorrected QT interval criteria
- Abnormal chest X-ray
- Other eosinophilic disease, parasitic infection, immunodeficiency, malignancy
- Known or suspected history of drug or alcohol abuse
- Any other clinically significant disorder of the following classes: neurological, psychiatric, renal, hepatic, immunological, endocrine, hematological, parasitic.

The protocol does not specify what criteria discriminate active or current diagnosis of asthma compared to a historical diagnosis of asthma. Data on historical diagnosis of asthma was not collected.

Reviewer's comment: The MEA117106 protocol allowed inclusion of subjects with a "historical diagnosis of asthma", but did not collect data on asthma history. If concomitant asthma were present in trial subjects, it could complicate the interpretation of efficacy results due to asthma's effect on the baseline prognosis of respiratory exacerbations, PB-Eos counts, and the clinical response to mepolizumab of subjects in the trial. Whether this unmeasured variable of asthma

limits the interpretation of efficacy results merits discussion by the Advisory Committee, and is discussed further in Section 6.9 Exploratory Subpopulation Efficacy Results.

Subject Removal Criteria

The following events comprised relevant protocol-defined criteria for stopping the investigational drug:

- Positive pregnancy test
- Clinically significant electrocardiogram findings
    - Sustained supraventricular tachycardia (>100 bpm)
    - Elevated QT interval by corrected (QTcF) and uncorrected criteria
    - Ventricular arrhythmia
- Clinically significant increase in transaminases or bilirubin
- Clinically significant increase in HBV DNA from baseline among subjects positive for hepatitis B
- Noncompliance with eDiary data collection

There were no formal criteria for trial withdrawal.

5.1.4. Treatments and Concomitant Medications

Treatment Groups

- *Mepo100*

Subjects in the mepo100 treatment arm received mepolizumab 100 mg (in 1 mL reconstituted solution) by subcutaneous injection every 4 weeks for 52 weeks.

- *Placebo*

Subjects in the placebo treatment arm received placebo (1 mL 0.9% sodium chloride solution) by subcutaneous injection every 4 weeks for 52 weeks.

The blinding in MEA117106 was adequate. Blinded study staff administered the investigational products to randomized subjects and conducted trial assessments. Blinded study staff were not allowed access to hematology assessments of white blood cell differential after randomization to maintain blinding.

Concomitant Medications

The protocol allowed for the use of the following medications and therapies:

- COPD controller medications (see below)
- Study-supplied rescue medication
    - salbutamol and/or ipratropium as MDI or nebules
- Short courses (<14 days) of systemic corticosteroids for the treatment of AECOPD and/or pneumonia
- Short courses (<14 days) of antibiotics for the treatment of AECOPD and/or pneumonia and/or acute infections
- Mucolytics such as acetylcysteine

- Long-term oxygen therapy
- Allergy immunotherapy
- Vaccinations including influenza, pneumonia, and shingles vaccines
- Medications for rhinitis, topical and ophthalmic corticosteroids, localized corticosteroid injections, beta-blockers, cough suppressants, anti-depressants, and anxiolytics
- Continuous positive airway pressure (CPAP) therapy

Because this trial evaluated mepolizumab as an add-on maintenance therapy to standard of care, the protocol required that all patients continue their baseline COPD controller medication regimen throughout the trial period. For almost all the patients in MEA117106, this regimen included inhaled corticosteroid, long-acting beta-agonist, and long-acting muscarinic antagonist (ICS+LABA+LAMA) inhaled triple therapy. Additional allowed COPD controller medications included methylxanthines and phosphodiesterase-4 inhibitors.

The protocol allowed chronic oral corticosteroids (OCS) if prescribed for maintenance control of COPD. Data on baseline chronic maintenance oral corticosteroid (OCS) use for COPD and ongoing maintenance OCS use during the trial were not collected as part of the protocol.

Reviewer's comment: If trial participants were taking OCS maintenance therapy, it could complicate the interpretation of efficacy results due to the known effects of OCS on the baseline prognosis of rates of AECOPD, PB-Eos counts, and the clinical response in the primary endpoint of AECOPD of subjects in the trial. Similarly, changes in participants' OCS regimen during the trial could influence AECOPD trial results. Whether the unmeasured variables of baseline maintenance OCS use and changes to maintenance OCS regimen limit the interpretation of efficacy results merits discussion by the Advisory Committee, and is discussed further in Section 6.9 Exploratory Subpopulation Efficacy Results.

Restricted Medications

The following medications and therapies were prohibited during the trial:

- Long-term antibiotic therapy
- Omalizumab
- Other monoclonal antibodies, other investigational products, or any experimental anti-inflammatory non-biological drugs
- Immunosuppressive medications
    - Systemic corticosteroids, if used for treatment of a condition other than COPD
    - Methotrexate, troleandomycin, cyclosporine, azathioprine, oral gold, chemotherapy for conditions other than COPD
- Bi-level positive airway pressure (NiPPV) therapy

5.1.5. Efficacy Endpoints and Safety Assessments

Primary Endpoint

The primary efficacy endpoint was the frequency of moderate to severe AECOPD (ModSev AECOPD) through week 52. The primary endpoint was analyzed in the modified intention-to-

treat (mITT) population and the modified intention-to-treat High Stratum (mITT-HS) in pre-specified analyses.

A diagnosis of AECOPD required the clinically relevant worsening of at least two of the classic symptoms of dyspnea, sputum volume, or sputum purulence described by Anthonisen et al[11]; alternatively, worsening of only one of the classic symptoms accompanied by either sore throat, a "cold" characterized by nasal discharge or congestion, "fever" defined as an elevated temperature of > 37.5 $^{\circ}$C without other cause, increased cough, or increased wheeze also met criteria for AECOPD diagnosis.

AECOPD requiring an increase in medical therapy including antibiotics or systemic corticosteroids defined a moderate AECOPD. AECOPD requiring inpatient hospitalization for ≥24 hours was defined as severe AECOPD.

Reviewer's comment: The Applicant's definition of AECOPD and AECOPD severity are acceptable and consistent with the definitions used in other COPD drug development programs.

Key Secondary Endpoints

Secondary efficacy endpoints included the following evaluations

- Time to first (TTF) ModSev AECOPD
- Frequency of AECOPD requiring either an emergency department (ED) visit or hospitalization at week 52
- Frequency of severe AECOPD (Sev AECOPD) at week 52
- Change from baseline in post-bronchodilator FEV1 at week 52
- Change from baseline in St. George's Respiratory Questionnaire (SGRQ-C) total score at week 52
- Change from baseline in COPD Assessment Test (CAT) score at week 52

The MEA117106 protocol utilized the St. George's Respiratory Questionnaire for COPD patients (SGRQ-C) as the specific instrument for evaluating the change from baseline in SGRQ score endpoint. The SGRQ-C is a disease-specific health-related quality of life instrument for COPD (grouped into 3 domains) that measures respiratory symptoms from COPD, activity limitations due to breathlessness, and the impact of COPD on psychosocial factors. The SGRQ-C consists of 40-questions evaluating these concepts over an unspecified recall period. The typically used estimate of the minimal clinically important difference in SGRQ is a 4-point change.

Safety Assessments

Monitored safety parameters included the following and were assessed as per Figure 3.

- Spontaneous and elicited adverse events (AEs), serious adverse events (SAEs), discontinuations due to AEs
- Physical examinations
- Clinical laboratory evaluations
- Vital signs
- ECG

- Pregnancy testing

5.1.6. Statistical Methodology

Analysis Populations

The protocol designated 7 analysis populations:

Populations analyzed by randomized (assigned) treatment arm

1. The Modified Intention-to-Treat (mITT) population included all randomized subjects who received at least one dose of study treatment.
   - mITT was the primary efficacy analysis population for the overall analysis evaluating randomized COPD subjects regardless of screening PB-Eos count.
2. The Modified Intention-to-Treat High Stratum (mITT-HS) population included all randomized subjects who met PB-Eos criteria for the High Stratum and received at least one dose of study treatment.
   - mITT-HS was the primary efficacy analysis population for the High Stratum subjects.
3. The Modified Intention-to-Treat Low Stratum (mITT-LS) population included all randomized subjects who met PB-Eos criteria for the Low Stratum and received at least one dose of study treatment.
   - mITT-LS was the primary efficacy analysis population for the Low Stratum subjects.

Population analyzed by actual (treatment received for >50% of administrations) treatment arm

4. The Safety Population included all randomized subjects who received at least one dose of study treatment.
   - This Safety Population was the primary safety analysis population.

Other populations

5. The All Subjects Enrolled (ASE) population included all randomized subjects.
6. The Per-Protocol Population (PPP) comprised all subjects in the mITT population except those identified as protocol deviators.
7. The Per-Protocol Population High Stratum (PPP-HS) comprised all subjects in the mITT-HS population except those identified as protocol deviators.

Primary Estimand and Missing Data Handling

Subjects who permanently stopped investigational product (IP) were not required to withdraw from the study. If for any reason a subject must permanently stop IP every effort was to be made by the principle investigator (PI)/staff to keep the subject in the study to collect important efficacy and safety data. Subjects who had permanently discontinued IP and had not withdrawn consent were supposed to continue with remaining protocol specified visits by in-clinic visits or by phone contact.

The Statistical Analysis Plan (SAP) deemed de facto (also called treatment policy) estimands as the primary estimands for all analyses. For example, the treatment policy estimand targeted by the primary analysis was the ratio of annual rates of moderate or severe exacerbations comparing all patients assigned mepolizumab to all patients assigned placebo, regardless of adherence to treatment or use of ancillary therapies. To target this estimand, both on-treatment data and, where available, off-treatment data were included in the analyses.

However, despite the off-treatment data retrieval plan and effort put forth by the PI/staff, there was still a portion of data missing with unknown missing mechanism behind them. In this regard, the analyses including both on- and off-treatment data still rely on strong and unverifiable missing-at-random (MAR) assumptions to reliably estimate the treatment policy estimand, which is described as often important in the 2010 National Research Council report *The Prevention and Treatment of Missing Data in Clinical Trials* and is an approach typically recommended for COPD trials supporting regulatory submission.

For the primary efficacy endpoints, the applicant pre-planned and conducted a series of sensitivity analyses to explore the potential impact of remaining missing data, including: jump to reference (J2R) analysis, off-treatment imputation, and tipping point analysis. We will use the applicant's tipping point analysis results to examine the robustness of the primary analysis to departures from the MAR assumption.

Statistical Analysis Models

Primary and Secondary Endpoints: Annual Rates of Moderate/Severe COPD Exacerbations and of Exacerbations Requiring Emergency Department Visits and/or Hospitalizations

In primary analyses, the annual moderate/severe exacerbation rate in each mepolizumab group was compared to the annual exacerbation rate in the placebo group using a negative binomial model. The response variable in the model was the number of recorded moderate and severe exacerbations experienced by a patient over the 52-week double-blind treatment period. The model included covariates of treatment group, smoking status (current vs. never/ex-smoker), number of moderate/severe exacerbations in previous year (≤2, 3, 4+ as an ordinal variable), geographical region, and baseline disease severity (as % predicted post-bronchodilator FEV_1). In the analysis of the overall population, the actual eosinophil stratum was also included as a covariate. The logarithm of the patient's period of time in the study for which exacerbation data was recorded was used as an offset variable in the model.

The secondary endpoint annual rate of COPD exacerbations requiring emergency department visits and/or hospitalizations was analyzed with the same model.

Under the applicant's tipping point analysis approach, subjects that withdrew from the study prior to their Week 52 visit had their missing exacerbation data from the date of withdrawal up to their projected Week 52 date imputed. A series of independently varying assumptions expressed as deltas on missing data for each treatment arm (i.e., assumptions about multiplicative shifts in the underlying exacerbation rates among patients with missing follow-up time) were applied to the estimated rates obtained within each arm under the MAR assumption. For each delta combination, multiple complete datasets were generated with a Bayesian multiple imputation method with the shifted deltas. The multiple complete datasets were analyzed with the primary analysis model. Then, the multiple estimates were combined using Rubin's rule. These analysis results could be used to identify the delta combination, i.e., the specific missing data assumptions, under which the p-value associated with the treatment effect is tipped from being statistically significant to being statistically not significant. The

plausibility of these tipping points by clinical judgment will reflect the robustness of the treatment effect.

Time to First COPD Moderate/Severe Exacerbation

Time to first moderate/severe COPD exacerbation was analyzed using a Cox proportional hazards regression model, adjusted by smoking status (current vs. never/ex-smoker), number of moderate/severe exacerbations in previous year (≤2, 3, 4+ as an ordinal variable), geographical region, and baseline disease severity (as % predicted post-bronchodilator FEV_1). Subjects who had not experienced any episode of moderate/severe exacerbation at the end of treatment (treatment end date + 28 days) or death were treated as censored. In the analysis for the overall population, the actual eosinophil stratum was also included as a covariate.

SGRQ-C Total Score and CAT Score

For the analysis of change from baseline SGRQ-C total score and change from baseline CAT score at Week 52, a likelihood-based mixed-effects model for repeated measures (MMRM) was pre-specified. The dependent variable was the change from baseline SGRQ-C total score (or change from baseline CAT score) at each visit. The model included treatment, baseline value of endpoint, smoking status, geographical region, visit, visit by baseline interaction, and treatment group by visit interaction as fixed effect covariates and subject as a random effect. The SGRQ-C total score data from four post-baseline visits (week 12, 24, 36, and 52) were included in the model; the CAT score data from 13 post-baseline visits (week 4 to 52, assessed every 4 weeks) were included in the model. The model utilized an unstructured covariance matrix. In the analysis of the overall population, the actual eosinophil stratum was also included as a covariate.

Exploratory Endpoints: Annual Rates of Severe COPD Exacerbations

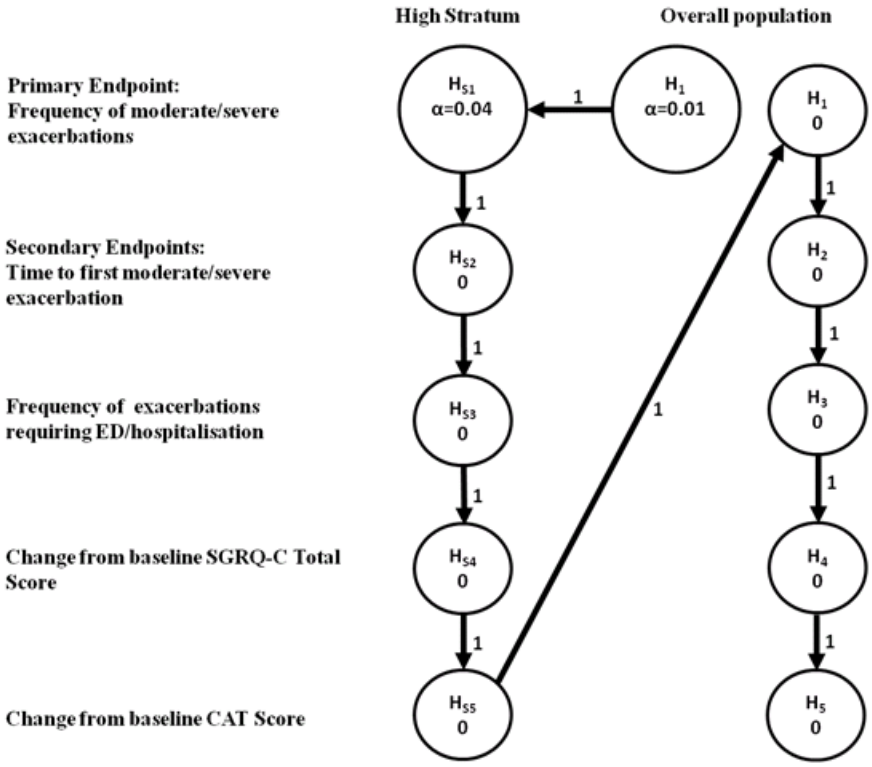
A meta-analysis was pre-specified for the analysis of annual rate of severe COPD exacerbations. The statistical model was same as the primary analysis model except for addition of study (MEA117113, MEA117106) as covariate.

<u>Multiple Testing Procedures (MTPs)</u>

For strong control of the overall type I error, a fallback multiple testing procedure was prespecified to align the multiple testing strategy with the primary objective of assessing efficacy in subjects with high eosinophil counts (the mITT-HS subpopulation). The fallback method is a modification of the fixed-sequence method that provides some opportunity to test an endpoint later in the sequence even if an endpoint tested earlier in the sequence has failed to show statistical significance. The pre-specified hierarchy of testing endpoints and allocation of alpha is illustrated in Figure 4. The primary endpoint, annual rate of moderate/severe exacerbations, was to be compared between subjects receiving mepolizumab 100mg SC and placebo; upon initial α allocation this primary endpoint was to be tested at $\alpha = 0.04$ in the high stratum and at $\alpha = 0.01$ in the overall population. If the null hypothesis for the primary endpoint comparison was rejected in the overall population, the primary endpoint, and subsequent secondary endpoints, were to be tested at $\alpha = 0.05$ in the high stratum. If the null hypothesis for the primary endpoint comparison in the overall population was not rejected, tests in the high stratum were to be carried out at $\alpha = 0.04$. Only upon rejection of the null

hypothesis for the primary endpoint in the high eosinophil stratum could testing of the secondary endpoints in the high stratum continue in the pre-specified order.
If all tests in the high eosinophil stratum were statistically significant, sequential testing was to then continue for the primary and secondary endpoints in the overall population following the same order.

Figure 4. Graphic Illustration of Multiple Testing Procedure: Primary and Secondary Endpoints in the Overall Population and High Eosinophil Stratum in MEA117106



Source: Study MEA117106 Reporting and Analysis Plan

5.1.7. Additional Information

Ethics

The Applicant attests that MEA117106 trial investigators provided written commitments to conduct the trial in accordance with ICH E3 Section 9.6, the Declaration of Helsinki, and the principles of good clinical practice and the study protocol. The trial protocol, amendments, informed consent, and other information were reviewed by a national, regional, or investigational center ethics committee or institutional review board. The applicant further attests that trial monitoring proceeded in accordance with ICH E6.

Protocol Amendments

The Applicant amended the trial protocol twice. Among other minor changes, pertinent amendments to the protocol included:

- Protocol amendment 1 (20 Dec 2013)
    - Updated protocol to state that study treatment would be administered via single subcutaneous injection
- Protocol Amendment 2 (05 Mar 2014)
    - Clarified the definition of severe AECOPD to include AECOPD leading to hospitalization or death
    - Dictated that an electrocardiogram finding of sustained supraventricular tachycardia (>100 bpm) or non-sustained supraventricular tachycardia (>100 bpm) would preclude a subject from entering the trial
    - Dictated that an electrocardiogram finding of sustained supraventricular tachycardia (>100 bpm) would result in a subject being prematurely discontinued from study treatment post-randomization
    - Removed SF-36 health survey as an endpoint

5.2. Study MEA117113

The design of this multi-national study intended to provide primary evidence of dose selection, efficacy, and safety for mepolizumab 100 mg by subcutaneous injection every 4 weeks (mepo100) versus placebo and mepolizumab 300 mg by subcutaneous injection every 4 weeks (mepo300) versus placebo as add-on treatment to inhaled corticosteroid-based maintenance treatment for the reduction of exacerbations in patients with chronic obstructive pulmonary disease guided by blood eosinophil counts. All subjects in trial MEA117113 met peripheral blood eosinophil (PB-Eos) criteria of ≥150 cells/µL at screening or ≥300 cells/µL within the prior 12 months (≥150-Scr or ≥300-Hist).

Study Designation: MEA117113 (METREO)
Study title: Mepolizumab vs. Placebo as add-on treatment for frequently exacerbating COPD patients characterized by eosinophil level
Study dates: 24 Apr 2014 to 16 Jan 2017
Study sites: 168 sites in 15 countries; 35 US sites
Study report date: 19 Oct 2017

5.2.1. Trial Objectives

Primary

- To evaluate the efficacy and safety of mepo100 and mepo300 compared to placebo on the frequency of moderate to severe (ModSev) AECOPD in COPD subjects with PB-Eos ≥150-Scr or ≥300-Hist and at high risk of exacerbations despite the use of optimized standard of care background therapy

Secondary

- To evaluate other efficacy assessments of mepo100 and mepo300 compared to placebo on changes in quality of life, health care utilization, and symptoms

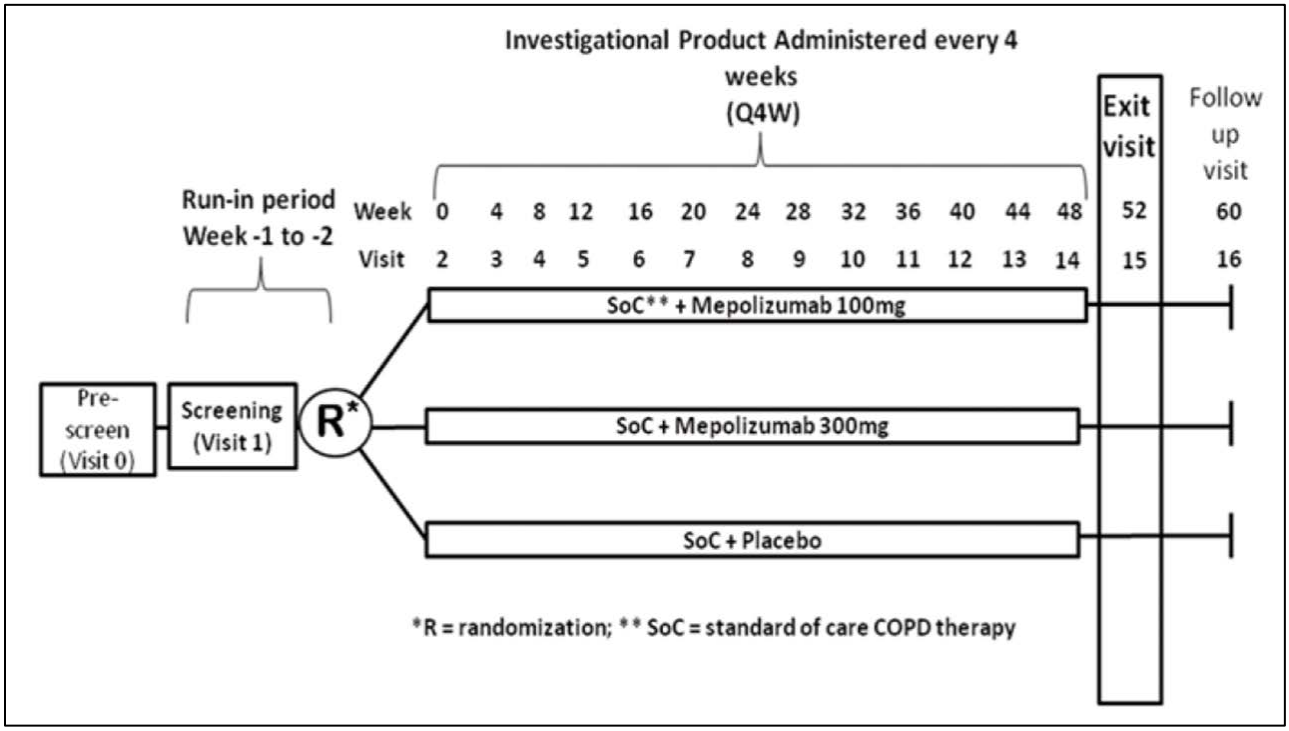
5.2.2. Trial Design

MEA117113 was a randomized, double-blind, placebo-controlled, multicenter, multinational trial comparing the safety and efficacy of mepo100 versus placebo and mepo300 versus placebo on the frequency of ModSev AECOPD among a sample COPD subjects that experience frequent AECOPD despite inhaled corticosteroid, long-acting beta-agonist, and long-acting muscarinic antagonist (ICS+LABA+LAMA) maintenance therapy. All subjects in MEA117113 met PB-Eos criteria ≥150 Scr or ≥300 Hist; these criteria were identical to the High Stratum criteria from MEA117106. This trial ran concurrently with MEA117106, and therefore did not inform dose selection.

Design

The trial design of MEA117113 incorporated a pre-screening period, a screening visit, a 52-week randomized treatment period, and an 8-week follow-up period. After the screening period, eligible subjects were randomized (1:1:1) to either mepo100, mepo300, or placebo treatment arms. During the treatment period of weeks 0 to 52, clinic assessments occurred every 4 weeks for a total of 14 visits, followed by an additional follow-up visit at week 60. The study design is summarized schematically in Figure 5. Study assessments are summarized in Figure 6.

Figure 5 Study Schematic for Trial MEA117113



Source: Applicant's mea117113-report.pdf, protocol-amend-2.pdf, figure 1, page 30

Figure 6 Schedule of Study Assessment for Trial MEA117113

Protocol Activity	Screen/Run-in		Randomized Treatment (visit window is ± 7 days)													Exit Visit	Follow Up
	V0[a]	V1	V2[b]	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16
	Pre-screening	V1(S)	Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52	Week 60
Study Day			1														
Procedures																	
Written Informed Consent/PGx consent	X[d]																
Demography/child bearing status assessment	X																
Medical history including cardiovascular, COPD, and exacerbation		X															
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion Criteria[e]		X	X														
CCI		X															
mMRC		X															
Smoking Status		X							X							X	
Smoking Cessation Counseling		X														X	
Parasite Screening[f]		X															
Register Visit in RAMOS/IVRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessements																	
Spirometry		X	X	X		X			X			X			X	X	
Reversibility Testing		X															
eDiary data review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Exacerbation and Healthcare Utilization Assessment				X	X	X	X	X	X	X	X	X	X	X	X	X	
SGRQ-C			X			X			X			X				X	
EQ-5D-5L			X						X							X	
CAT			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Subject global rating of activity level			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Subject global rating of activity change				X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinician rated response to therapy					X			X			X			X		X	
Subject rated response to therapy					X			X			X			X		X	
Safety Assessments																	
Adverse Events/Serious Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical Problems Diary Review				X	X	X	X	X	X	X	X	X	X	X	X	X	
COPD symptoms summary report review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination		X[g]	X[h]			X[h]			X[g]			X[h]				X[g]	
Vital Signs (including pulse oximetry)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG		X				X			X			X				X	X
Chest x-ray		X[i]															
Laboratory Assessments																	
Hematology with differential [j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry[e]		X	X	X[k]	X[k]	X			X			X				X	X
Clinical chemistry with lipoproteins (fasting)[l]			X						X							X	
Urine Pregnancy Test[m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGx Sampling (blood)				X[n]													
Hepatitis B and C testing[o]		X															
LFT testing (only in hepatitis B positive subjects)[p]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetic Sample[q]			X	X					X							X	X
Immunogenicity sample			X						X							X	X
Exploratory Lab Assessments																	
Total IgE			X														
Blood Biomarker			X						X							X	
Serum IL-5			X						X								X
Study Supplies and Investigational Product																	
Electronic Diary registration and training		X[r]															
Electronic Diary close out																X	
Administer Investigational Product			X	X	X	X	X	X	X	X	X	X	X	X	X		
Dispense Rescue Salbutamol		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Collect Used Rescue Salbutamol			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Complete electronic Case Report Form (eCRF)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. The pre-screening visit (Visit 0) can occur on the same day as the screening visit (Visit 1) but must be completed prior to initiating any Visit 1 procedures.
b. Visit 2 can occur 1 to 2 weeks after Visit 1. Results from Visit 1 procedures must be available for review of randomization criteria.
c. **Omitted**
d. Informed consent for optional PGx (pharmacogenetics) research must be obtained before collecting a sample.
e. Inclusion and Exclusion criteria should be assessed at Visit 1 and Randomization Criteria assessed at Visit 2.
f. Parasitic screening is only required in countries with high-risk or for subjects who have visited high-risk countries in the past 6 months. Sites should use local laboratories.
g. A comprehensive physical exam should be conducted.
h. A brief physical exam should be conducted.
i. Only required if results from a chest x-ray or CT-scan, taken within the past 6 months, is not available.
j. Differential results will be blinded from Visit 3 onwards.
k. Liver panel only
l. Subject must be in fasting state. If subject has not fasted they may return to the clinic to provide this sample.
m. Pregnancy testing is only required for females of child bearing potential. An assessment must be made at baseline to determine child bearing potential of each female study participant
n. PGx consent must be obtained prior to collecting the PGx blood sample. The PGx sample can be collected at any visit post-randomization (i.e. at Visit 3 or any visit after Visit 3).
o. If hepatitis C positive confirmation by testing the same sample is required. See Quest manual for details. For subjects who are HBsAg positive or HBcAb positive reflexive testing must be conducted to assess HBV DNA
p. If ALT ≥ 3X ULN, reflexive testing should be conducted for HBV-DNA
q. PK samples must be taken pre-dose
r. Thorough eDiary training should be conducted at Visit 1 and throughout the study on an as-needed basis
s. Clinical chemistry will include analytes and liver chemistry monitoring as detailed in the SPM.

Source: Adapted from applicant's submission for MEA117113, protocol-amend-1.pdf, table 2, pages 43-46

5.2.3. Inclusion and Exclusion Criteria

Key Inclusion Criteria

Key inclusion criteria matched those of MEA117106, except that all subjects included in MEA117113 met PB-Eos criteria of ≥150 cells/µL at screening or ≥300 cells/µL in prior 12 months (analogous to High Stratum in MEA117106). See Section 5.1.3 for a list of additional inclusion criteria.

Key Exclusion Criteria for Screening and Randomization

Key exclusion criteria matched those of MEA117106. See Section 5.1.3 for a list of additional inclusion criteria.

Reviewer's comment: As in MEA117106, the MEA117113 protocol allowed inclusion of subjects with a "historical diagnosis of asthma", but did not collect data on asthma history. See reviewer's comment pertaining to collection of data regarding asthma diagnosis in Section 5.1.3; potential effects on interpretation of trial results are discussed further in Section 6.9 Exploratory Subpopulation Efficacy Results.

Subject Removal Criteria

Subject removal criteria matched those in MEA117106. See Section 5.1.3 for a list of subject removal criteria.

There were no formal criteria for trial withdrawal.

5.2.4. Treatments and Concomitant Medications

Treatment Groups

- *Mepo300*

Subjects in the mepo300 treatment arm received mepolizumab 300 mg (3 separate injections, each comprised of 100 mg mepolizumab in 1 mL reconstituted solution) by subcutaneous injection every 4 weeks for 52 weeks.

- *Mepo100*

Subjects in the mepo100 treatment arm received mepolizumab 100 mg (1 injection of 100 mg mepolizumab in 1 mL reconstituted solution) by subcutaneous injection and placebo (2 separate injections, each comprised of 1 mL 0.9% sodium chloride solution, to maintain blind) by subcutaneous injection every 4 weeks for 52 weeks.

- *Placebo*

Subjects in the placebo treatment arm received placebo (3 separate injections, each comprised of 1 mL 0.9% sodium chloride solution) by subcutaneous injection every 4 weeks for 52 weeks.

The blinding in MEA117106 was adequate. Blinded study staff administered the investigational products to randomized subjects and conducted trial assessments. Blinded study staff were not

allowed access to hematology assessments of white blood cell differential after randomization to maintain blinding.

Concomitant Medications

Allowed concomitant medications matched those of MEA117106. See Section 5.1.4 for a list of the allowed concomitant medications.

Because this trial evaluated mepolizumab as an add-on maintenance therapy to standard of care, the protocol required that all patients continue their baseline COPD controller medication regimen throughout the trial period. As in MEA117106, for almost all the patients in MEA117113 this regimen included inhaled corticosteroid, long-acting beta-agonist, long-acting muscarinic antagonist (ICS+LABA+LAMA) inhaled triple therapy.

Reviewer's comment: As in MEA117106, the MEA117113 protocol allowed chronic oral corticosteroids (OCS) if prescribed for maintenance control of COPD, but did not collect data on baseline chronic maintenance OCS use for COPD. Discussion of the potential effect of chronic maintenance OCS on efficacy analyses is detailed in Section 5.1.4; potential effects on interpretation of trial results are discussed further in Section 6.9 Exploratory Subpopulation Efficacy Results.

Restricted Medications

Restricted medications matched those in MEA117106. See Section 5.1.4 for a list of the restricted medications.

5.2.5. Efficacy Endpoints and Safety Assessments

Primary Endpoint

The primary efficacy endpoint was the frequency of moderate to severe AECOPD (ModSev AECOPD) at week 52. The primary endpoint was analyzed in the modified intention to treat (mITT) population evaluating both the mepo100 versus placebo and mepo300 versus placebo comparisons.

The applicant defined AECOPD events and severity were acceptable See Section 5.1.5 Efficacy Endpoints and Safety Assessments for further discussion of the ModSev AECOPD endpoint

Key Secondary Endpoints

Secondary efficacy endpoints matched those in MEA117106. See Section 5.1.5 for a list of the key secondary endpoints.

Safety Assessments

Safety assessments matched those in MEA117106. See Section 5.1.5 for a list of the safety assessments.

5.2.6. Statistical Methodology

Analysis Populations

The protocol designated 4 analysis populations:

Populations analyzed by randomized (assigned) treatment arm

1. The Modified Intention-to-Treat (mITT) population included all randomized subjects who received at least one dose of study treatment.
    - mITT was the primary efficacy analysis population for the overall analyses evaluating mepo100 versus placebo and mepo300 versus placebo among randomized COPD subjects.

Population analyzed by actual (treatment received for >50% of administrations) treatment arm

2. The Safety Population included all randomized subjects who received at least one dose of study treatment.
    - This Safety Population was the primary safety analysis population.

Other populations

3. The All Subjects Enrolled (ASE) population included all randomized subjects.
4. The Per-Protocol Population (PPP) comprised all subjects in the mITT population except those identified as protocol deviators.

Primary Estimand and Missing Data Handling

The definition of primary estimand and methods for handling missing data were consistent with those in MEA117106. See Section 4.1.6 for details.

Statistical Analysis Models

Primary and Secondary Endpoints: Annual Rates of Moderate/Severe COPD Exacerbations and of Exacerbations Requiring Emergency Department Visits and/or Hospitalizations

The statistical analysis models for the primary and the secondary endpoint were consistent with those in MEA117106. See Section 5.1.6 for details.

Time to First COPD Moderate/Severe Exacerbation

The statistical analysis model for this secondary endpoint was consistent with that in MEA117106. See Section 5.1.6 for details.

SGRQ-C Total Score and CAT Score

The statistical analysis models for these secondary endpoints were consistent with those in MEA117106. See Section 5.1.6 for details.

Multiple Testing Procedures (MTPs)

Two treatment comparisons, mepolizumab 100mg SC vs. placebo and mepolizumab 300mg SC vs. placebo, were of interest for each of the primary and key secondary endpoints. A Hochberg testing procedure was used to control multiplicity arising from the two treatment comparisons within each endpoint family (see Table 3). Each endpoint family acted as a serial gatekeeper: only if both the null hypotheses in a family were rejected could the procedure move on to tests for subsequent endpoint families for strong control of the overall type-I error.

Table 3 A Serial Gatekeeping Procedure in MEA117113

Order	Endpoints	Mepolizumab 100mg SC vs. Placebo	Mepolizumab 300mg SC vs. Placebo
1	Annual rate of moderate or severe COPD exacerbations	Hochberg Procedure Both unadjusted p-values < 0.05, or at least one < 0.025	
2	Time to first moderate or severe exacerbation	As Above	
3	Annual rate of COPD exacerbations requiring emergency department (ED) visit and/or hospitalization	As Above	
4	Mean Change from baseline total St. George's Respiratory Questionnaire-COPD (SGRQ-C) score	As Above	
5	Mean Change from baseline COPD Assessment Test (CAT) score	As Above	

Source: Reviewer

In this section, we described the MTPs in terms of decisions rules for individual hypothesis testing using multiplicity-adjusted significance levels. When we report testing results, we can also incorporate the structure of the underlying decision rule by computing multiplicity-adjusted p-values. To capture the degree of multiplicity adjustment, adjusted p-values will be used in summarizing key efficacy results across the studies and endpoints in Section 6.8 (Table 14).

5.2.7. Additional Information

Ethics

The applicant attests that MEA117106 trial investigators provided written commitments to conduct the trial in accordance with ICH E3 Section 9.6, the Declaration of Helsinki, and the principles of good clinical practice and the study protocol. The trial protocol, amendments, informed consent, and other information were reviewed by a national, regional, or investigational center ethics committee or institutional review board. The applicant further attests that trial monitoring proceeded in accordance with ICH E6

Protocol Amendments

The applicant amended the trial protocol once. Among other minor changes, pertinent amendments to the protocol included:

- Protocol Amendment 1 (05 Mar 2014)
    - Dictated that an electrocardiogram finding of sustained supraventricular tachycardia (>100 bpm) or non-sustained supraventricular tachycardia (>100

bpm) would preclude a subject from entering the trial
- Dictated that an electrocardiogram finding of sustained supraventricular tachycardia (>100 bpm) would result in a subject being prematurely discontinued from study treatment post-randomization
- Removed SF-36 health survey as an endpoint

6. Review of Efficacy

6.1. Indication

The proposed indication is mepolizumab 100 mg SC every 4 weeks for 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.

6.2. Methods

The data for the efficacy of mepolizumab in COPD patients are provided by two multicenter, randomized, double-blind, placebo-controlled, parallel group, 52-week trials (MEA117106 and MEA117113) in patients with GOLD II-IV COPD and ≥2 exacerbations per year despite standard of care maintenance therapy (consisting of ICS+LABA+LAMA for ~97% of trial participants) with and without increased peripheral blood eosinophil (PB-Eos) counts.

The primary efficacy endpoint in both trials was the frequency of moderate to severe acute exacerbations of COPD (ModSev AECOPD) through 52 weeks. Key secondary endpoints in both trials included time to first (TTF) ModSev AECOPD, the frequency of AECOPD requiring hospitalization or emergency department (ED) visit through 52 weeks, mean change in forced expiratory volume in one second (FEV1) from baseline at 52 weeks, mean change from baseline in St. George's Respiratory Questionnaire (SGRQ-C) total score at 52 weeks, and mean change from baseline in COPD assessment test (CAT) score at 52 weeks. An additional pre-specified subject-level meta-analysis of MEA117106 and MEA117113 evaluated the rate of severe exacerbations of chronic obstructive pulmonary disease (Sev AECOPD).

MEA117106 included two treatment arms: mepolizumab 100 mg by subcutaneous injection every 4 weeks (mepo100) and placebo by subcutaneous injection every 4 weeks (placebo). Additionally, MEA117106 stratified subjects into two analysis strata based on screening PB-Eos counts:

- High Stratum (HS): Screening PB-Eos counts ≥150 cells/µL or a historical PB-Eos count ≥300 cells/µL in the preceding 12 months
- Low Stratum (LS): Screening PB-Eos counts <150 cells/µL and no historical PB-Eos count ≥300 cells/µL in the preceding 12 months

The Applicant's evaluations in MEA117106 comprised pre-specified analyses of efficacy endpoints comparing mepo100 versus placebo in the overall modified-intention-to-treat (mITT) trial population and in the modified-intention-to-treat High Stratum (mITT-HS) trial population. The Applicant provided results for the modified-intention-to-treat Low Stratum (mITT-LS) as exploratory analyses.

MEA117113 included three treatment arms: mepolizumab 300 mg by subcutaneous injection every 4 weeks (mepo300), mepo100, and placebo. All subjects in MEA117113 met HS criteria based on PB-Eos counts (PB-Eos counts ≥150 Scr or ≥300 Hist). The Applicant's evaluations in MEA117113 comprised pre-specified analyses of efficacy endpoints comparing mepo100 versus

placebo and mepo300 versus placebo in the mITT population.

6.3. Demographics

Table 4 MEA117106: Demographic Characteristics (mITT Population)

Demographic Parameters	High Stratum[6]		Low Stratum[7]		Total n = 836 n (%)
	Placebo n = 229 n (%)	mepo100 n = 233 n (%)	Placebo n = 190 n (%)	mepo100 n = 184 n (%)	
Sex					
Male	150 (66)	149 (64)	113 (59)	108 (59)	520 (62)
Female	79 (34)	84 (36)	77 (41)	76 (41)	316 (38)
Age					
Mean years (SD)	65.3 (8.5)	65.2 (8.4)	65.2 (8.6)	66.1 (9.1)	65.4 (8.6)
Min, max (years)	40, 83	43, 83	39, 85	40, 85	39, 85
Age Group[1]					
≥ 40 - < 65 years	107 (47)	107 (46)	85 (45)	75 (41)	374 (45)
≥ 65 years	122 (53)	126 (54)	104 (55)	109 (59)	461 (55)
Body Mass Index					
Mean kg/m^2 (SD)	26.7 (5.6)	27.1 (5.7)	27.4 (5.6)	26.5 (6.1)	26.9 (5.7)
Race					
White	192 (84)	199 (85)	145 (76)	144 (78)	680 (81)
Black or African American	4 (2)	2 (<1)	3(2)	2 (1)	11 (1)
Asian	3 (1)	2 (<1)	1 (<1)	1 (<1)	7 (<1)
American Indian or Alaska Native	14 (6)	19 (8)	22 (12)	14 (8)	69 (8)
Other[2]	16 (7)	11 (5)	19 (10)	23 (13)	69 (8)
Ethnicity					
Hispanic or Latino	36 (16)	39 (17)	52 (27)	44 (24)	171 (20)
Not Hispanic or Latino	193 (84)	194 (83)	138 (73)	140 (76)	665 (80)
Region					
United States	23 (10)	22 (9)	22 (12)	22 (12)	89 (11)
Non-US	206 (90)	211 (91)	168 (88)	162 (88)	747 (89)
Canada	29 (13)	28 (12)	24 (13)	25 (14)	106 (13)
Mexico	17 (7)	16 (7)	28 (15)	27 (15)	88 (11)
Europe[3]	80 (35)	82 (35)	56 (29)	53 (29)	271 (32)
Eastern Europe[4]	39 (17)	40 (17)	22 (12)	21 (11)	112 (13)
Other[5]	41 (18)	45 (19)	38 (20)	36 (20)	170 (20)

[1]One subject in Low Stratum, Placebo Control Group was 39 years of age
[2]Subjects in this category listed multiple races
[3]Countries categorized as European sites: Belgium, France, Greece, Italy, Norway, Spain, Sweden
[4]Countries categorized as Eastern European sites: Czech Republic, Estonia, Poland
[5]Countries categorized as other sites: Australia, Peru, Russian Federation
[6] High Stratum: Screening PB-Eos counts ≥150 cells/µL or a historical PB-Eos count ≥300 cells/µL in the preceding 12 months
[7] Low Stratum: Screening PB-Eos counts <150 cells/µL and no historical PB-Eos count ≥300 cells/µL in the preceding 12 months

Table 4 shows that mepolizumab and placebo arms of mITT and mITT-HS populations were

similar in terms of demographics. The subjects sampled are representative of a primarily white, not Hispanic or Latino, middle-aged male population with COPD.

Table 5 MEA117113: Demographic Characteristics (mITT Population)

Demographic Parameters	Placebo n = 226 n (%)	mepo100 n = 223 n (%)	mepo300 n = 225 n (%)	Total n = 674 n (%)
Sex				
Male	156 (69)	132 (59)	158 (70)	446 (66)
Female	70 (31)	91 (41)	67 (30)	228 (34)
Age				
Mean years (SD)	65.8 (8.6)	64.8 (9.1)	64.8 (9)	65.1 (8.9)
Min, max (years)	43, 88	42, 86	45, 85	42, 88
Age Group				
≥ 40 - < 65 years	101 (45)	104 (47)	110 (49)	315 (47)
≥ 65 years	125 (55)	119 (53)	115 (51)	359 (53)
Body Mass Index				
Mean kg/m^2 (SD)	25.4 (5)	27.1 (6.2)	26.4 (5.2)	26.3 (5.5)
Race				
White	182 (81)	178 (80)	182 (81)	542 (80)
Black or African American	2 (<1)	4 (2)	2 (<1)	8 (1)
Asian	42 (19)	41 (18)	41 (18)	124 (18)
Ethnicity				
Hispanic or Latino	34 (15)	36 (16)	37 (16)	107 (16)
Not Hispanic or Latino	192 (85)	187 (84)	188 (84)	567 (84)
Region				
United States	27 (12)	26 (12)	26 (12)	79 (12)
Non-US	199 (88)	197 (88)	199 (88)	595 (88)
South America[1]	39 (17)	39 (17)	40 (18)	118 (18)
Asia[2]	42 (19)	40 (18)	40 (18)	122 (18)
Europe[3]	62 (27)	64 (29)	64 (28)	190 (28)
Eastern Europe[4]	47 (21)	45 (20)	46 (20)	138 (20)
Other[5]	9 (4)	9 (4)	10 (4)	28 (4)

[1]Countries categorized as South American sites: Argentina, Chile
[2]Countries categorized as Asian sites: Japan, Taiwan, Republic of Korea
[3]Countries categorized as European sites: Denmark, Germany, Netherlands, United Kingdom
[4]Countries categorized as Eastern European sites: Romania, Slovakia, Ukraine
[5]Countries categorized as other sites: Australia, Canada
Note: All subjects had screening PB-Eos counts ≥150 cells/μL or a historical PB-Eos count ≥300 cells/μL in the preceding 12 months

Table 5 shows that mepolizumab and placebo arms of the MEA117113 mITT population were broadly similar in terms of demographics, with the exception of a higher proportion of females in the mepo100 arm. The subjects sampled are representative of a primarily white, not Hispanic or Latino, middle-aged male population with COPD.

MEA117106 and MEA117113 randomized subjects with similar demographic characteristics both between trials and within trial arms.

6.4. Baseline Disease Characteristics

Table 6 MEA117106: Baseline Disease Characteristics (mITT Population)

Disease Parameters	High Stratum[1]		Low Stratum[2]		Total
	Placebo n = 229 n (%)	mepo100 n = 233 n (%)	Placebo n = 190 n (%)	mepo100 n = 184 n (%)	n = 836 n (%)
Peripheral Blood Eosinophils					
≥2% of total leukocyte count	212 (93)	211 (91)	12 (6)	25 (14)	460 (55)
Geometric Mean cells/µL (SD Logs)	290 (562)	250 (575)	70 (778)	70 (699)	140 (946)
Post-bronchodilator FEV1					
≥80% predicted	2 (<1)	3 (1)	1 (<1)	1 (<1)	7 (<1)
≥50% to <80% predicted	66 (29)	78 (33)	60 (32)	64 (35)	268 (32)
≥30% to <50% predicted	120 (52)	114 (49)	93 (49)	85 (46)	412 (49)
<30% to ≥20% predicted	41 (18)	38 (16)	36 (19)	34 (18)	149 (18)
Mean % predicted (SD)	43.4 (14.5)	45 (15)	44.1 (14.6)	44.6 (15.6)	44.3 (14.9)
GOLD ABCD category					
Group D	218 (95)	219 (94)	181 (95)	178 (97)	796 (95)
COPD Therapies					
ICS	228 (>99)	233 (100)	190 (100)	184 (100)	835 (>99)
LABA	228 (>99)	233 (100)	190 (100)	183 (>99)	835 (>99)
LAMA	226 (99)	231 (>99)	189 (>99)	182 (99)	828 (>99)
Chronic oral corticosteroids*	9 (4)*	13 (6)*	7 (4)*	9 (5)*	38 (5)*
Long-term oxygen therapy	24 (10)	27 (12)	20 (11)	30 (16)	101 (12)
Smoking Exposure					
Never/non-smokers	11 (5)	7 (3)	13 (7)	9 (5)	40 (5)
Current/former smokers	218 (95)	226 (97)	177 (93)	175 (95)	796 (95)
Mean pack-years (SD) among Current/former smokers	37.9 (11.2)	36.8 (10.8)	38.4 (11.5)	39.2 (10.9)	38 (11.1)
Moderate to severe AECOPD in prior 12 months					
Mean (SD)	2.5 (1.2)	2.6 (1.3)	2.6 (1.2)	2.5 (1.1)	2.5 (1.2)
Min, max	1, 10	1, 10	1, 9	1, 8	1, 10
FEV_1 Bronchodilator Responsiveness					
≥200mL and ≥12% reversibility	39 (17)	32 (14)	28 (15)	23 (13)	122 (15)
Mean % reversibility (SD)	10.3 (13.5)	8.9 (11.5)	8.1 (11.3)	9.1 (11.1)	9.1 (12)
Duration of COPD					
Mean years (SD)	9.5 (6.3)	9.5 (6.7)	9.2 (6.8)	8.8 (5.4)	9.3 (6.4)
Min, max (years)	1, 32	1, 35	1, 46	1, 25	1, 46
SGRQ Score†					
Mean (SD)	56.5 (15.8)	54.1 (17.5)	53.8 (17.5)	55.1 (16.9)	54.9 (17)
mMRC Score					
Mean (SD)	2.3 (0.9)	2.2 (0.8)	2.2 (0.9)	2.3 (0.9)	2.2 (0.9)
Charlson Comorbidity Index‡					
1 to 2	7 (3)	8 (3)	8 (4)	7 (4)	30 (4)
3 to 4	112 (49)	124 (53)	101 (53)	90 (49)	427 (51)
≥5	109 (48)	101 (43)	81 (43)	87 (47)	378 (45)

*Baseline chronic OCS was not assessed during routine trial data collection; assessment occurred through post hoc clinical review
†SGRQ score was calculated using data from 223, 228, 184, 182, and 817 subjects, respectively.
‡Charlson Comorbidity Index score data was available for 228, 233, 190, 184, and 835 subjects, respectively.
[1] High Stratum: Screening PB-Eos counts ≥150 cells/µL or a historical PB-Eos count ≥300 cells/µL in the preceding 12 months
[2] Low Stratum: Screening PB-Eos counts <150 cells/µL and no historical PB-Eos count ≥300 cells/µL in the preceding 12 months

Table 6 shows that mepolizumab and placebo arms of both the High Stratum and Low Stratum were similar in terms of baseline disease characteristics with the exception of PB-Eos count at screening. The baseline disease characteristics of MEA117106 describe a group of former smokers with moderate-to-very severe COPD requiring inhaled ICS+LABA+LAMA maintenance therapy who experienced frequent or severe exacerbations in the last 12 months. No data on baseline chronic maintenance OCS are available from the applicant's primary data collection, as described in Section 5.1.4.

Table 7 MEA117113: Baseline Disease Characteristics (mITT Population)

Disease Parameters	Placebo n = 226 n (%)	mepo100 n = 223 n (%)	mepo300 n = 225 n (%)	Total n = 674 n (%)
Peripheral Blood Eosinophils				
≥2% of total leukocyte count	173 (77)	177 (79)	165 (73)	515 (76)
Geometric Mean cells/µL (SD Logs)	230 (869)	230 (861)	230 (814)	230 (847)
Post-bronchodilator FEV1				
≥80% predicted	2 (<1)	3 (1)	2 (<1)	7 (1)
≥50% to <80% predicted	90 (40)	91 (41)	83 (37)	264 (39)
≥30% to <50% predicted	97 (43)	96 (43)	98 (44)	291 (43)
<30% to ≥20 % predicted	37 (16)	33 (15)	42 (19)	112 (17)
Mean % predicted (SD)				
GOLD ABCD category				
Group D	216 (96)	211 (95)	219 (97)	646 (96)
COPD Therapies				
ICS	224 (>99)	222 (>99)	224 (>99)	670 (>99)
LABA	224 (>99)	222 (>99)	225 (100)	671 (>99)
LAMA	222 (98)	223 (100)	225 (100)	670 (>99)
Chronic oral corticosteroids*	8 (4)	12 (5)	10 (4)	30 (5)
Long-term Oxygen Therapy	20 (9)	26 (12)	31 (14)	77 (11)
Smoking Exposure				
Never/non-smokers	2 (<1)	5 (2)	6 (3)	13 (2)
Current/former smokers	224 (99)	218 (98)	219 (97)	661 (98)
Mean pack-years (SD) among Current/former smokers	46.1 (27.2)	42.6 (25.9)	44.1 (30.8)	44.3 (28)
Moderate to Severe AECOPD in Prior 12 Months				
Mean (SD)	2.6 (1.4)	2.7 (1.4)	2.7 (1.5)	2.7 (1.4)
Min, max	1, 10	1, 10	1, 12	1, 12
FEV_1 Bronchodilator Responsiveness				
≥200mL and ≥12% reversibility	35 (15)	34 (15)	39 (17)	108 (16)
Mean % reversibility (SD)	10.2	8.8	10.3	9.8
Duration of COPD				

Disease Parameters	Placebo n = 226 n (%)	mepo100 n = 223 n (%)	mepo300 n = 225 n (%)	Total n = 674 n (%)
Mean years (SD)	8.8 (5.9)	8.4 (6.5)	7.8 (5.1)	8.4 (5.9)
Min, max	1, 38	1, 48	1, 27	1, 48
SGRQ Score				
Mean (SD)	52.9 (15.9)	51.9 (17.3)	53.4 (16.7)	52.7 (16.6)
mMRC Score				
Mean (SD)	2.2 (0.8)	2.2 (0.8)	2.3 (0.8)	2.2 (0.8)
Charlson Comorbidity Index[‡]				
1 to 2	7 (3)	10 (4)	14 (6)	31 (5)
3 to 4	113 (50)	114 (51)	109 (48)	336 (50)
≥5	104 (46)	98 (44)	100 (44)	302 (45)

*Baseline chronic OCS was not assessed during routine trial data collection; assessment occurred through post hoc clinical review
[†]SGRQ score was calculated using data from 223, 228, 184, 182, and 817 subjects, respectively.
[‡]Charlson Comorbidity Index score data was available for 228, 233, 190, 184, and 835 subjects, respectively.
Note: All subjects had screening PB-Eos counts ≥150 cells/µL or a historical PB-Eos count ≥300 cells/µL in the preceding 12 months

Table 7 shows that mepolizumab and placebo arms were similar in terms of baseline disease characteristics. The baseline disease characteristics of MEA117113 describe a group of former smokers with moderate to very severe COPD requiring inhaled ICS+LABA+LAMA maintenance therapy who experienced frequent or severe exacerbations in the last 12 months.

The lack of data on baseline chronic maintenance OCS creates uncertainty in understanding the baseline disease characteristics of the treatment arms. Baseline chronic maintenance OCS was not assessed as part of trial data collection in MEA117106 or MEA117113; post-hoc clinical review by the Applicant in response to an information request identified ~5% of subjects in MEA117106 and ~4.5% of subjects in MEA117113 with sufficient clinical review information to classify them as receiving chronic OCS at baseline, with a slightly higher proportion randomized to mepolizumab therapy. Values for the "chronic oral corticosteroids" variable in Table 6 and Table 7 represent best guess from the Applicant's *post hoc* clinical review.

However, it is unclear whether the applicant's clinical review identified all users of chronic maintenance OCS use in the trial. Chronic OCS use would serve as a marker of disease severity at baseline and would likely affect stratum determination by suppressing PB-Eos. Ongoing use has the potential to influence the primary endpoint of the frequency of ModSev AECOPD. Whether this unmeasured variable of baseline OCS use limits the interpretation of efficacy results merits discussion by the committee.

Additionally, as discussed in Sections 5.1.3 and 5.2.3, neither trial gathered data on the proportion of subjects meeting the exclusion criteria exception for "historical diagnosis of asthma". As mepolizumab is already approved for the add-on treatment of severe asthma with an eosinophilic phenotype, differentiating patients with eosCOPD and severe asthma is required. Further, if concomitant asthma were present in trial subjects, it could complicate the interpretation of efficacy results due to asthma's effect on the baseline prognosis, PB-Eos counts, and the clinical response to mepolizumab of subjects in the trial. Whether this

unmeasured variable of asthma limits the interpretation of efficacy results is an important discussion point.

6.5. Subject Disposition

Table 8 MEA117106 and MEA117113: Subject Disposition

	MEA117106				MEA117113		
	High Stratum[1]		Low Stratum[2]				
	Placebo n = 229 n (%)	mepo100 n = 233 n (%)	Placebo n = 190 n (%)	mepo100 n = 184 n (%)	Placebo n = 226 n (%)	mepo100 n = 223 n (%)	mepo300 n = 225 n (%)
Completion Status							
Completed Study	202 (88)	213 (91)	162 (85)	157 (85)	185 (82)	206 (92)	195 (87)
Withdrawn from Study	27 (12)	20 (9)	28 (15)	27 (15)	41 (18)	17 (8)	30 (13)
Completed Treatment	185 (81)	203 (87)	148 (78)	149 (81)	170 (75)	196 (88)	183 (81)
Primary Reason for Withdrawal from Study							
Adverse Event	10 (4)	7 (3)	11 (6)	11 (6)	18 (8)	7 (3)	13 (6)
Death	6 (3)	6 (3)	7 (4)	9 (5)	7 (3)	4 (2)	8 (4)
Lack of Efficacy	0	1 (<1)	3 (2)	2 (1)	3 (1)	0	3 (1)
Lost to Follow-Up	0	0	2 (1)	1 (<1)	2 (<1)	0	1 (<1)
Physician Decision	2 (<1)	2 (<1)	2 (1)	2 (1)	3 (1)	3 (1)	2 (<1)
Withdrawal by Subject	15 (7)	10 (4)	10 (5)	11 (6)	15 (7)	7 (3)	11 (5)

[1] High Stratum: Screening PB-Eos counts ≥150 cells/µL or a historical PB-Eos count ≥300 cells/µL in the preceding 12 months
[2] Low Stratum: Screening PB-Eos counts <150 cells/µL and no historical PB-Eos count ≥300 cells/µL in the preceding 12 months
Source: Adapted from Agency analyses and Sponsor's materials; mea117106-report.pdf and mea117113-report.pdf

Analysis of subject disposition in trials MEA117106 and MEA117113 shows that the total number of subjects withdrawn from the study and the number attributed to each reason were either similar between placebo and mepolizumab treatment groups or higher in the placebo group (see Table 8).

MEA117106 enrolled 1,161 subjects and randomized 837 (72%) of those subjects. After randomization of 837 subjects, 1 additional subject randomized to the placebo group in the HS was withdrawn without receiving study treatment. This left 836 subjects in the modified intention to treat (mITT) population. Of the 836 subjects in the mITT population, 734 (88%) completed the trial, while 102 (12%) did not complete the trial.

MEA117113 enrolled 1,071 subjects and randomized 675 (63%) of those subjects. After randomization of 675 subjects, 1 additional subject randomized to the mepo300 group was withdrawn without receiving study treatment. This withdrawal left 674 subjects in the mITT population. Of the 674 subjects in the mITT population, 586 (87%) completed the trial, while 88 (13%) did not complete the trial.

6.6. Analysis of Primary Endpoint(s)

The primary efficacy analyses of MEA117106 examine the annualized rate of ModSev AECOPD over 52 weeks among subjects administered mepo100 compared to subjects administered placebo using a statistical model that adjusts for categorical variables of smoking status, number of AECOPD in previous year, baseline FEV1, and geographic region. The Applicant declared two pre-specified comparisons of mepo100 to placebo for the primary efficacy analysis (see Section 5.1.6) and provided one additional exploratory analysis: the (pre-specified) comparison in the modified-intention-to-treat High Stratum (mITT-HS) population, the (pre-specified) comparison in the overall modified-intention-to-treat (mITT-Overall) population, and the (exploratory) comparison in the modified-intention-to-treat Low Stratum (mITT-LS) population. The results of the mITT-HS and the mITT-LS analyses are presented in Table 9.

The primary efficacy analyses of MEA117113 examine the annualized rate of ModSev AECOPD over 52 weeks among subjects administered mepo100 or mepo300 compared to subjects administered placebo utilizing the same statistical models used in MEA117106. The Applicant declared two pre-specified comparisons of mepolizumab to placebo among the modified-intention-to-treat population in MEA117113 (see Section 5.2.6): the comparison of mepo100 to placebo among the mITT and the comparison of mepo300 to placebo among the mITT. The results of these comparisons are also presented in Table 9.

Table 9 MEA117106 mITT-HS, mITT-LS, and MEA117113 mITT: Primary Efficacy Analysis Results – Rate of ModSev AECOPD

	MEA117106 (mITT-HS[1])		MEA117106 (mITT-LS[2])		MEA117113 (mITT[3])		
	Placebo n = 229	mepo100 n = 233	Placebo n = 190	mepo100 n = 184	Placebo n = 226	mepo100 n = 223	mepo300 n = 225
Rate of Moderate-to-Severe AECOPD (on and off-treatment)							
ModSev AECOPD/yr	1.71	1.40	1.29	1.58	1.49	1.19	1.27
Rate ratio vs placebo		0.82		1.23		0.80	0.86
95% CI		0.68, 0.98		0.99, 1.51		0.65, 0.98	0.7, 1.05
adjusted p-value[4]		0.036		N/A		0.068	0.14
Absolute risk reduction vs placebo (AECOPD/yr)		0.31		-0.29		0.30	0.22

[1] mITT-HS: Subjects in the modified-intention-to-treat analysis High Stratum (Screening PB-Eos counts ≥150 cells/µL or a historical PB-Eos count ≥300 cells/µL in the preceding 12 months) pre-specified primary analysis group of MEA117106.
[2] mITT-LS: Subjects in the modified-intention-to-treat analysis Low Stratum (Screening PB-Eos counts <150 cells/µL and no historical PB-Eos count ≥300 cells/µL in the preceding 12 months) analysis group of MEA117106.
[3] mITT: Subjects in the modified-intention-to-treat pre-specified primary analysis group of MEA117113.
[4] adjusted p-value: Raw p-values were properly adjusted to compare with the alpha level of 0.05 based on pre-planned multiple testing procedures, a fallback method in MEA117106 and a Hochberg method in MEA117113, respectively.
Note: The pre-specified primary efficacy analysis included the mITT-HS of MEA117106 and the mITT of MEA117113; the mITT-LS analysis was not part of the pre-specified primary efficacy analysis. The rate of moderate-to-severe AECOPD (on- and off-treatment) analysis included AECOPD experienced by subjects on study drug as well as those who discontinued study drug, ascribed to their randomization arm
Source: Agency-created primary efficacy analysis model results using SAS software.

Table 10 MEA117106 mITT-HS, mITT-LS, and MEA117113 mITT: AECOPD Severity Details

AECOPD Severity	MEA117106				MEA117113		
	High Stratum[1]		Low Stratum[2]				
	Placebo n = 229 n (%)	mepo100 n = 233 n (%)	Placebo n = 190 n (%)	mepo100 n = 184 n (%)	Placebo n = 226 n (%)	mepo100 n = 223 n (%)	mepo300 n = 225 n (%)
Number of Patients with On- and Off-Treatment AECOPD							
Moderate/Severe	166 (72)	149 (64)	121 (64)	117 (64)	144 (64)	127 (57)	130 (58)
Moderate	154 (67)	133 (57)	109 (57)	111 (60)	129 (57)	117 (52)	118 (52)
Severe	46 (20)	42 (18)	40 (21)	29 (16)	39 (17)	30 (13)	33 (15)
Number of On- and Off-Treatment AECOPD Events							
Moderate/Severe	397	339	247	282	339	287	296
Moderate	336	275	203	247	280	247	244
Severe	61	64	44	35	59	40	52

[1] High Stratum: Screening PB-Eos counts ≥150 cells/µL or a historical PB-Eos count ≥300 cells/µL in the preceding 12 months
[2] Low Stratum: Screening PB-Eos counts <150 cells/µL and no historical PB-Eos count ≥300 cells/µL in the preceding 12 months
Source: Adapted from Applicant's submitted materials, Table 15 of mea117106-report.pdf and Table 15 of mea117113-report.pdf

MEA117106

In the mITT-HS of MEA117106, the primary efficacy analysis reveals annualized ModSev AECOPD rates of 1.40 AECOPD/yr in the mepo100 arm compared to 1.71 AECOPD/yr in the placebo arm. The pre-specified efficacy analysis comparing mepo100 to placebo yields a statistically significant rate ratio of 0.82 (95% confidence interval [CI] 0.68 to 0.98) with a p-value of 0.036 after adjustment for multiplicity. The rates of AECOPD correspond to an absolute risk reduction of 0.31 AECOPD/yr in the comparison of mepo100 to placebo, implying an estimated number-needed-to-treat (NNT) of 3.2. This NNT can be interpreted as meaning that 3.2 patients would need to be treated for one year to prevent one ModSev AECOPD in one patient. The observed risk reduction in rate of ModSev AECOPD in the mepo100 vs placebo comparison was driven by a reduction in the number of moderate AECOPD alone (see Table 10); indeed, there was a numerically higher number of severe AECOPD observed for mepo100 in this comparison.

In the mITT-Overall of MEA117106 (data not shown), the primary efficacy analysis of MEA117106 reveals annualized ModSev AECOPD rates of 1.49 AECOPD/yr in the mepo100 arm compared to 1.52 AECOPD/yr in the placebo arm. The pre-specified efficacy analysis comparing mepo100 to placebo yields a rate ratio of 0.98 (95% CI 0.85 to 1.12) that does not achieve statistical significance, with a p-value of >0.999 after adjustment for multiplicity.

In the mITT-LS, the exploratory primary efficacy analysis of MEA117106 reveals annualized ModSev AECOPD rates of 1.58 AECOPD/yr in the mepo100 arm compared to 1.29 AECOPD/yr in the placebo arm. Efficacy analysis comparing mepo100 to placebo yields a rate ratio of 1.23 (95% CI 0.99 to 1.51); this result was not a pre-specified analysis so no adjustment for multiplicity was applied, however the Applicant reports a nominal p-value of 0.058 for this comparison (note that this is a 2-sided p-value, with the estimate in the direction of harm). The

rates of AECOPD correspond to an absolute risk increase of 0.29 AECOPD/yr in the comparison of mepo100 to placebo.

To assess robustness of the primary analysis result against missing data assumptions, a tipping point analysis of MEA117106 was conducted. This analysis is presented in Table 11. The column with $\Delta_{Placebo}$ =1 in the table corresponds to the assumption that missing data in placebo patients arise at random. With this assumption, patients with missing data in the placebo arm had their rate imputed as though they responded similarly to other placebo patients without missing data. Moving across rows within the column corresponds to varying assumptions about the missing outcomes of patients in the mepolizumab arm only. Within the column, the statistical significance goes away under the $\Delta_{MEPO\ 100}$ =1.6 assumption, which corresponds to the situation in which patients with missing data in the mepolizumab 100 mg arm had their rate imputed as roughly 60% greater than the mean observed rate of the mepolizumab patients without missing data. This combination of deltas ($\Delta_{Placebo}$ =1, $\Delta_{MEPO\ 100}$ =1.6) became a tipping point, which clinically might be implausible, supporting some robustness of the result regarding missing data. Other observed tipping points given the discrete sets of shifts considered by the applicant were: (0.8, 1.4), (1, 1.6), (1.2, 2.0), (1.4, 2.2), (1.6, 2.6), and (1.8, 2.8).

Table 11 MEA117106 mITT-HS Tipping Point Analysis: Annual Rate of Moderate/Severe COPD Exacerbation (Mepolizumab 100 vs. Placebo)

Multiplicative Delta for MEPO 100 mg SC Rate Imputation ($\Delta_{MEPO100}$)	Multiplicative Delta for Placebo Rate Imputation ($\Delta_{Placebo}$)											
	0.8	1	1.2	1.4	1.6	1.8	2.0	2.2	2.4	2.6	2.8	3.0
0.8	0.033	0.023	0.017	0.012	0.008	0.006	0.004	0.003	0.002	0.002	0.001	<0.001
1	0.040	0.029	0.021	0.015	0.011	0.008	0.006	0.004	0.003	0.002	0.002	0.001
1.2	0.049	0.035	0.026	0.019	0.013	0.010	0.007	0.005	0.004	0.003	0.002	0.002
1.4	**0.059**	0.044	0.032	0.023	0.017	0.012	0.009	0.007	0.005	0.004	0.003	0.002
1.6	0.070	**0.052**	0.040	0.029	0.021	0.016	0.012	0.008	0.006	0.005	0.003	0.003
1.8	0.084	0.063	0.047	0.035	0.026	0.019	0.014	0.011	0.008	0.006	0.004	0.003
2.0	0.098	0.075	**0.057**	0.042	0.032	0.024	0.018	0.013	0.010	0.008	0.006	0.004
2.2	0.117	0.090	0.068	**0.051**	0.039	0.029	0.022	0.016	0.012	0.010	0.007	0.005
2.4	0.136	0.105	0.081	0.061	0.047	0.035	0.027	0.020	0.015	0.011	0.009	0.007
2.6	0.156	0.121	0.094	0.072	**0.056**	0.043	0.033	0.025	0.019	0.015	0.011	0.008
2.8	0.179	0.141	0.110	0.087	0.067	**0.052**	0.039	0.031	0.023	0.017	0.014	0.010
3.0	0.205	0.162	0.128	0.101	0.080	0.062	0.048	0.037	0.029	0.022	0.017	0.013

Source: Adapted from Applicant's mea117106-report.pdf

MEA117113

In the mITT of MEA117113, the primary efficacy analysis reveals annualized ModSev AECOPD rates of 1.19 AECOPD/yr in the mepo100 arm compared to 1.49 AECOPD/yr in the placebo arm. The pre-specified efficacy analysis comparing mepo100 to placebo yields a rate ratio of 0.80 (95% CI 0.65 to 0.98) that does not achieve statistical significance with a p-value of 0.068 after adjustment for multiplicity. The rates of AECOPD correspond to an absolute risk reduction of 0.30 AECOPD/yr and an estimated NNT of 3.3 in the comparison of mepo100 to placebo; however, these estimates should be interpreted with caution given that there was not statistical evidence of a treatment effect in this study. The numeric reduction in rate of

ModSev AECOPD observed in the mepo100 vs placebo comparison included reductions in the number of both moderate and severe AECOPD events (see Table 10).

In the mITT of MEA117113, the primary efficacy analysis reveals annualized ModSev AECOPD rates of 1.27 AECOPD/yr in the mepo300 arm compared to 1.49 AECOPD/yr in the placebo arm. The pre-specified efficacy analysis comparing mepo300 to placebo yields a rate ratio of 0.86 (95% CI 0.70 to 1.05) that does not achieve statistical significance with a p-value of 0.140 after adjustment for multiplicity. The rates of AECOPD correspond to an absolute risk reduction of 0.22 AECOPD/yr in the comparison of mepo300 to placebo.

Summary

In summary, the primary efficacy analysis of trial MEA117106 shows a significant reduction in the rate of moderate to severe COPD exacerbations with mepolizumab 100 mg SC every 4 weeks; however, the primary efficacy analysis of trial MEA117113 fails to replicate these findings for the mepolizumab 100 mg dose and also does not show a significant reduction in the rate of moderate to severe COPD exacerbations with the mepolizumab 300 mg dose. In addition, the numerical increase in moderate to severe COPD exacerbations with mepolizumab in the LS group raises questions about the safety of mepolizumab in patients who could be misdiagnosed with eosCOPD.

6.7. Analysis of Secondary Endpoint(s)

Table 12 MEA117106 mITT-HS and MEA117113 mITT: Pre-Specified Secondary Efficacy Analysis Results

	MEA117106 (mITT-HS)		MEA117113 (mITT)		
	Placebo n = 229	mepo100 n = 233	Placebo n = 226	mepo100 n = 223	mepo300 n = 225
Time to First Moderate to Severe AECOPD					
Probability of AECOPD	0.75	0.65	0.67	0.58	0.59
Hazard ratio vs placebo		0.75		0.82	0.77
95% CI		0.6, 0.94		0.64, 1.04	0.6, 0.97
adjusted p-value		0.036		0.14	0.14
Rate of AECOPD requiring ED Visit or hospitalization					
AECOPD / yr	0.26	0.3	0.28	0.17	0.23
Rate ratio vs placebo		1.16		0.59	0.83
95% CI		0.77, 1.75		0.35, 0.98	0.51, 1.34
adjusted p-value		0.598		0.14	0.447
Rate of Severe AECOPD					
AECOPD / yr	0.22	0.24	0.21	0.13	0.18
Rate ratio vs placebo		1.12		0.63	0.89
95% CI		0.72, 1.74		0.36, 1.09	0.53, 1.5
adjusted p-value		N/A		N/A	N/A

	MEA117106 (mITT-HS)		MEA117113 (mITT)		
	Placebo n = 229	mepo100 n = 233	Placebo n = 226	mepo100 n = 223	mepo300 n = 225
Mean Change in Forced Expiratory Volume in One Second					
n with analyzable data	188	205	176	202	192
LS mean change in mL (SE)	-7 (15.9)	-17 (15.3)	-13	6	21
Change difference vs Placebo in mL		-10		19	35
95% CI		-52, 33		-29, 67	-14, 83
adjusted p-value		N/A		N/A	N/A
Change from baseline mean SGRQ at week 52					
n with analyzable data	183	206	177	196	189
SGRQ LS mean change (SE)	-3 (1.11)	-2.8 (1.06)	-3.1 (0.98)	-5 (0.95)	-3.3 (0.96)
Change difference vs placebo		0.2		-1.8	-0.1
95% CI		-2.8, 3.2		-4.5, 0.8	-2.8, 2.6
adjusted p-value		0.999		0.447	0.926
Change from baseline mean CAT at week 52					
n with analyzable data	178	195	173	190	184
CAT LS mean change (SE)	0 (0.47)	-0.8 (0.45)	-0.4 (0.42)	-1.6 (0.42)	-0.8 (0.42)
Change difference vs placebo		-0.8		-1.1	-0.4
95% CI		-2, 0.5		-2.3, 0	-1.5, 0.8
adjusted p-value		0.999		0.926	0.926

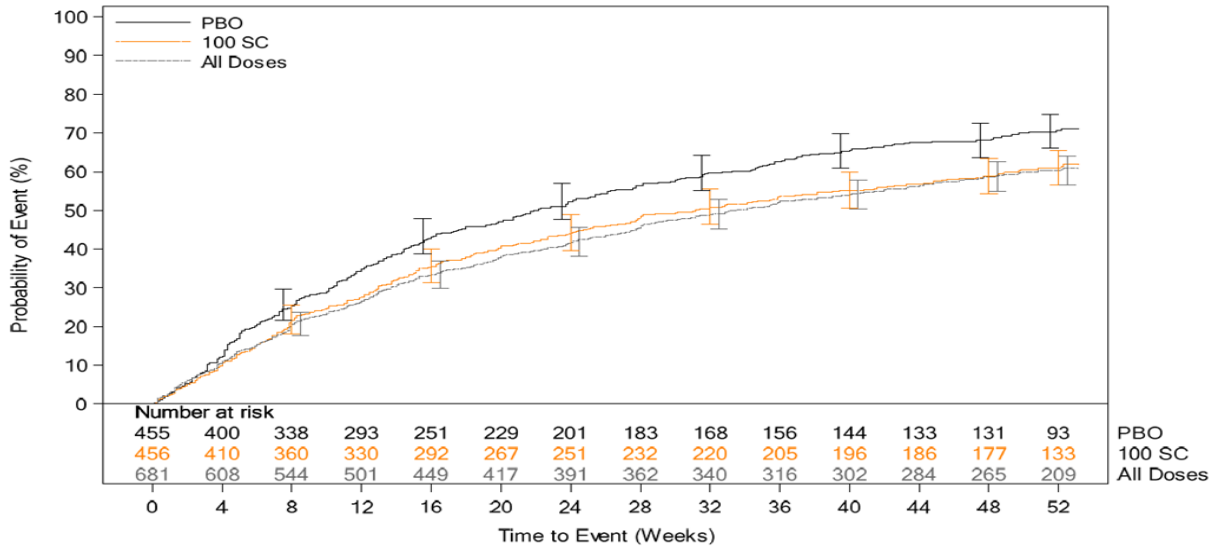
Source: Agency-created efficacy analysis model results using SAS software.

Time to first moderate to severe AECOPD

Time to first (TTF) ModSev AECOPD results from MEA117106 are not replicated in MEA117113 with confidence (see Table 12). The mepo100 versus placebo comparison in MEA117106 reveals a reduction in risk of ModSev AECOPD (Hazard Ratio [HR] 0.75, 95% CI 0.6 to 0.94) with an adjusted p-value of 0.036. The mepo100 versus placebo comparison in MEA117113 reveals a numerical, but not statistically significant, reduction in TTF ModSev AECOPD (HR 0.82, 95% CI 0.64 to 1.04), as does the mepo300 versus placebo comparison (HR 0.77, 95% CI 0.6 to 0.97). The data from MEA117113's comparison of mepo100 versus placebo in the mITT population does not meet the threshold for statistical significance (neither prior to nor after adjustment for multiple comparisons).

Exploratory Kaplan-Meier curves from the pooled analysis of MEA117106 mITT-HS and MEA117113 mITT show an initial separation of curves followed by relatively parallel paths, raising the question of whether mepolizumab's efficacy in COPD may wane over time (see Figure 7).

Figure 7 MEA117106 mITT-HS and MEA117113 mITT: Kaplan-Meier Cumulative Incidence Curve for Time to First ModSev AECOPD



Source: Adapted from Applicant's ISE-data-displays.pdf
PBO: subjects in placebo arm; 100 SC: subjects in mepolizumab 100 mg by subcutaneous injection every 4 weeks arm; All Doses: pooled subjects in either mepolizumab 100 mg or 300 mg by subcutaneous injection every 4 weeks arms

AECOPD requiring hospitalization or emergency department visit

The Applicant chose to evaluate AECOPD requiring hospitalization or requiring emergency department (ED) visit as a separate efficacy endpoint, although this categorization of AECOPD does not specifically fit into accepted categories of moderate or severe AECOPD severity based on documented relationships to relevant clinical outcomes. The mepo100 versus placebo comparison in MEA117106 reveals a numerical, but not statistically significant, increase in the rate of AECOPD requiring hospitalization or ED visit (Rate Ratio [RR] 1.16, 95% CI 0.77 to 1.75) with an adjusted p-value of 0.598. The mepo100 versus placebo comparison in MEA117113 reveals a numerical, but not statistically significant, reduction in AECOPD requiring hospitalization or ED visit (RR 0.59, 95% CI 0.35 to 0.98), and the mepo300 versus placebo comparison (RR 0.83, 95% CI 0.51 to 1.34) is also not statistically significant.

The submitted analysis results for the frequency of AECOPD requiring hospitalization or ED visit in trials MEA117106 and MEA117113 do not achieve statistical significance in either trial (see Table 12). Furthermore, the data from MEA117106's analysis of the mITT-HS population comparing mepo100 to placebo show a nominal point estimate in the direction of increased frequency of this category of AECOPD in the mepo100 group. Finally, the subsequent meta-analysis performed by the Applicant fails to show a statistically significant effect on the endpoint.

Frequency of severe AECOPD

Severe (Sev) AECOPD occurred infrequently during the trial periods; event rates in the two trials were between 0.13 to 0.24 Sev AECOPD per year (see Table 12); this low event rate is consistent with previous exacerbation trials of COPD. Because of the low event rate, formal comparisons are underpowered to support robust efficacy conclusions about Sev AECOPD

rates. Results from the MEA117106 mITT-HS analysis show an efficacy estimate in the direction of increased rate of Sev AECOPD, with a RR of 1.12 (95% CI 0.72 to 1.74) in the comparison of mepo100 versus placebo, while the results of the MEA117113 mITT mepo100 dosing arm show a numerical trend towards reduction in the rate of Sev AECOPD with a RR of 0.63 (95% CI 0.36 to 1.09). Results from the mepo300 dosing arm of MEA117113 reveal a RR of Sev AECOPD of 0.89 (95% CI 0.53 to 1.5).

The applicant performed a pre-specified meta-analysis of the frequencies of Sev AECOPD in MEA117106 and MEA117113; this analysis does not achieve a statistically significant result.

Change from Baseline in FEV1

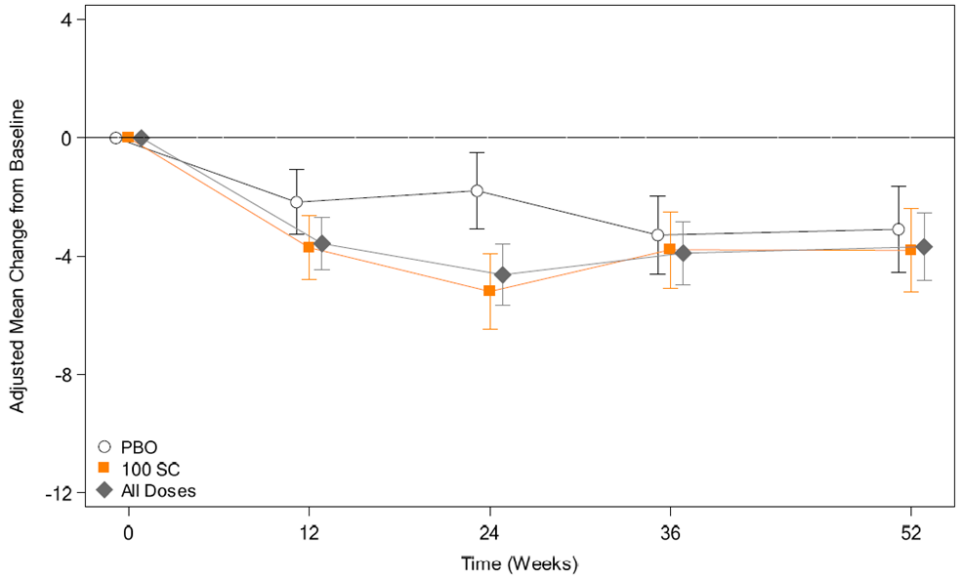
Analyses of both trials fail to show significant mean changes in FEV1 at 52 weeks in the mepo100 versus placebo comparison (see Table 12).

Change from Baseline in SGRQ Score and Responder Analysis

Neither MEA117106 nor MEA117113 show statistically significant differences in mean changes in SGRQ score at 52 weeks between mepo100 and placebo trial arms. Furthermore, mepolizumab trials arms show only small estimated differences compared to placebo arms (see Table 12) considering SGRQ's minimum clinically important difference of 4 points. Analysis of mepo100 versus placebo in MEA117106's mITT-HS population shows a numerically greater symptomatic improvement in the placebo group.

Analyses of pooled results from MEA117106 mITT-HS and MEA117113 mITT show the SGRQ temporal response observed in the trials. Some separation in SGRQ score curves between mepolizumab and placebo groups is seen prior to week 36 in this pooled analysis; this separation does not persist at week 52 (see Figure 8).

Figure 8 MEA117106 mITT-HS and MEA117113 mITT: Mean Change from Baseline SGRQ Total Score



Source: Adapted from Applicant's ISE-data-displays.pdf

PBO: subjects in placebo arm; 100 SC: subjects in mepolizumab 100 mg by subcutaneous injection every 4 weeks arm; All Doses: pooled subjects in either mepolizumab 100 mg or 300 mg by subcutaneous injection every 4 weeks arms

SGRQ-C responder analysis was not a pre-specified endpoint for either pivotal trial, but has been included in previous COPD drug labels. In responder analysis, there was no evidence of an effect of mepolizumab in either study on the proportion of subjects experiencing a ≥4 point decrease in SGRQ at 52 weeks. In MEA117106, there was an estimated 2% greater probability of SGRQ response on mepo100 compared to placebo; the difference in SGRQ responders in MEA117113 was 7% (see Table 13). Neither difference in probability of SGRQ response is statistically significant and it is unclear whether the differences are clinically meaningful.

Table 13 MEA117106 mITT-HS and MEA117113 mITT: SGRQ Responder Analysis Results

	MEA117106 (mITT-HS[1])		MEA117113 (mITT[2])		
	Placebo n = 229	mepo100 n = 233	Placebo n = 226	mepo100 n = 223	mepo300 n = 225
SGRQ Total Score (Week 52)					
n with analyzable data	223	228	225	220	222
Responders (%)	90 (40)	95 (42)	78 (35)	92 (42)	85 (38)
Odds ratio vs placebo		1.08		1.41	1.17
95% CI		0.74, 1.59		0.95, 2.10	0.79, 1.73
adjusted p-value[3]		N/A		N/A	N/A

Note: A response was defined as reduction in SGRQ Total Score ≥ 4.
[1] mITT-HS: Subjects in the modified-intention-to-treat analysis High Stratum (Screening PB-Eos counts ≥150 cells/µL or a historical PB-Eos count ≥300 cells/µL in the preceding 12 months) pre-specified primary analysis group of MEA117106.
[2] mITT: Subjects in the modified-intention-to-treat pre-specified primary analysis group of MEA117113.
[3] adjusted p-value: Raw p-values were properly adjusted to compare with the alpha level of 0.05 based on pre-planned multiple testing procedures, a fallback method in MEA117106 and a Hochberg method in MEA117113, respectively.
Source: Agency-created primary efficacy analysis model results using SAS software.

6.8. Strength of Evidence of Efficacy

Table 14 summarizes the pre-specified test results across the two studies using adjusted p-values, the calculation of which incorporated the structure of the underlying decision rules on multiple testing.

Table 14 Summary of Test Results across the Two Studies

Order	Endpoint (Treatment effect measure)	MEA117106 (mITT-HS[1])	MEA117113 (mITT[2])	
		mepo100 vs Placebo	mepo100 vs Placebo	mepo300 vs Placebo
Primary Endpoint				
1	Frequency of moderate/severe COPD 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 ✓	0.82 (0.64, 1.04) Adjusted p=0.140 ✗	0.77 (0.60, 0.97) Adjusted p=0.140 ✗
3	Frequency of COPD exacerbations requiring emergency department visit and/or hospitalization (rate ratio)	1.16 (0.77, 1.75) Adjusted p=0.598 ✗	0.59 (0.35, 0.98) Adjusted p=0.140 ✗	0.83 (0.51, 1.34) Adjusted p=0.442 ✗
4	Change from baseline SGRQ-C total Score (mean difference)	0.2 (-2.8, 3.2) Adjusted p>0.999 ✗	-1.8 (-4.5, 0.8) Adjusted p=0.442 ✗	-0.1 (-2.8, 2.6) Adjusted p=0.926 ✗
5	Change from baseline CAT score (mean difference)	0.8 (-2.0, 0.5) Adjusted p>0.999 ✗	-1.1 (-2.3, 0.0) Adjusted p=0.926 ✗	-0.4 (-1.5, 0.8) Adjusted p=0.926 ✗

[1] mITT-HS: Subjects in the modified-intention-to-treat analysis High Stratum (Screening PB-Eos counts ≥150 cells/µL or a historical PB-Eos count ≥300 cells/µL in the preceding 12 months) pre-specified primary analysis group of MEA117106.
[2] mITT: Subjects in the modified-intention-to-treat pre-specified primary analysis group of MEA117113.
[3] adjusted p-value: Raw p-values were properly adjusted to compare with the alpha level of 0.05 based on pre-planned multiple testing procedures, a fallback method in MEA117106 and a Hochberg method in MEA117113, respectively.
✓ (✗) indicates the test result was (not) statistically significant at the level of 0.05 after adjustment for multiple testing.
Source: Reviewer

6.9. Exploratory Subpopulation Efficacy Results

6.9.1. Eosinophil Threshold Subgroups

The Applicant's desired indication states that mepolizumab treatment should be guided by peripheral blood eosinophil counts, and the data presented rely on PB-Eos criteria that specify ≥150 cells/µL at screening or ≥300 cells/µL within the prior 12 months. However, the Applicant's indication statement does not define how (and whether) these PB-Eos criteria would be applied in clinical practice to guide treatment decisions, whether alternative thresholds for PB-Eos criteria might better identify the phenotype, how to identify patients responding to mepolizumab, potential stopping criteria for mepolizumab, or how accurately the

criteria define the group of COPD patients who could potentially derive benefit from mepolizumab.

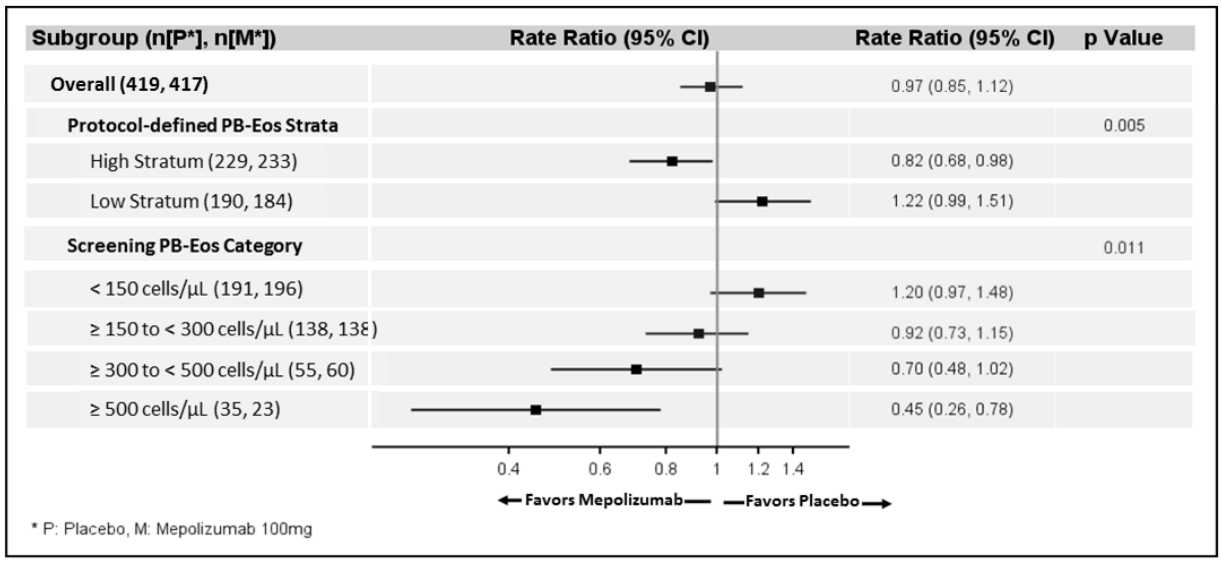
Approval of mepolizumab could give implicit acceptance of the Applicant's PB-Eos criteria for clinical use. Practically, if a provider adhered to the PB-Eos criteria (≥150 Scr or ≥300 Hist) used in the pivotal trials to initiate mepolizumab to frequently exacerbating COPD patients despite inhaled ICS+LABA+LAMA comparable to those examined in the trials, these criteria would define the patient population selected for treatment, such that:

- Patients with a single measurement of PB-Eos ≥150 cells/µL alone would be administered mepolizumab
- Patients with a single measurement of PB-Eos <150 cells/µL alone would not be administered mepolizumab
- Patients with either a current PB-Eos measurement ≥150 cells/µL or a historical measurement ≥300 cells/µL would be administered mepolizumab
- Patients with both a current PB-Eos measurement ≥150 cells/µL and a historical measurement ≥300 cells/µL would be administered mepolizumab

The fact that subjects randomized to mepo100 in the Low Stratum of MEA117106 (defined by PB-Eos criteria of <150 cells/µL screening and no measurement of ≥300 cells/µL in the prior 12 months) showed a trend towards higher rates of ModSev AECOPD with a RR of 1.23 (see Table 9 and Figure 9) compared to placebo raises questions that misdiagnosis with eosinophilic COPD or inappropriate use of mepolizumab could increase the risk of moderate to severe COPD exacerbations.

We note that there was strong evidence that the treatment effect differs by screening eosinophil level in Study MEA117106, with a p-value for the interaction between treatment and eosinophil stratum of 0.005. To further explore the nature of this interaction, we conducted several exploratory analyses of trial MEA117106, because this study did not enrich by eosinophil level and therefore provides the best data to evaluate this relationship. These analyses consistently showed a trend of greater estimated treatment effects with greater eosinophil levels. For example, Figure 9 shows the results within the High and Low Stratums, as well as results within several subgroups defined by the screening eosinophil level in trial MEA117106. These trends – combined with the visit- to-visit variability in PB-Eos counts seen in clinical practice – raise concerns regarding the most appropriate choice of threshold, if any, for use of mepolizumab, and about a potential lack of reduction or even an increase in ModSev AECOPD in patients treated with mepolizumab based upon a single measure of PB-Eos counts (e.g., ≥150 cells/µL).

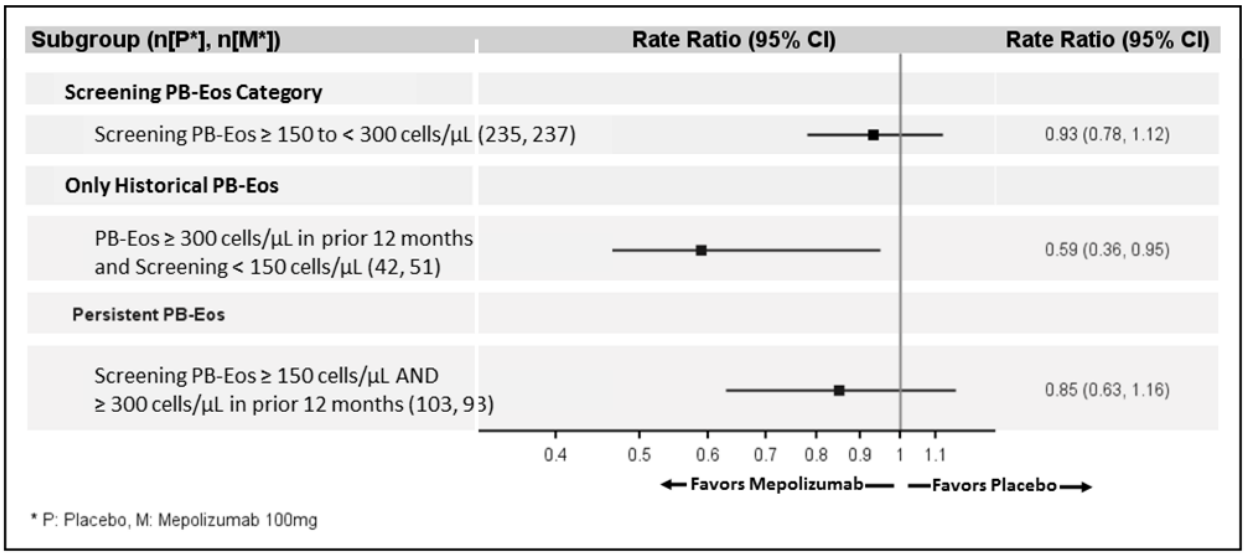
Figure 9 MEA117106 mITT-HS and mITT-LS: Analyses of Rate of Moderate to Severe AECOPD by Eosinophil Stratum and by Screening Peripheral Blood Eosinophil Categories



Source: Reviewer
Note: P-values shown are for interactions between the subgroup factor and treatment
Rate Ratio: rate ratio of moderate to severe COPD exacerbations in the mepolizumab 100 mg by subcutaneous injection every 4 weeks arm versus placebo arm; 95% CI: 95% confidence interval; n[P*]: number in placebo arm; n[M*]: number in mepolizumab arm

To further evaluate the relationship between PB-eos and COPD exacerbations, the Agency also conducted several exploratory analyses using different PB-Eos thresholds and categories among the pooled mITT populations in trials MEA117106 and MEA117113 (mITT-Pooled). The pooled analyses primarily focus on patients with screening levels of at least 150 cells/µL, given that patients with screening levels <150 cells/µL in trial MEA117113 had to have a historical level >300 cells/µL and therefore likely are not representative of patients with a single level <150 cells/µL in clinical practice. These analyses examined practical application of the Applicant's criteria, as well as higher or more stringent PB-Eos thresholds. Discussions of the practical considerations of analyses and treatment decisions based on only single PB-Eos measurements as well as both screening and historical measurements are shown using illustrative groups in Figure 10 and discussed below.

Figure 10 MEA117106 mITT-HS and MEA117113 mITT: Exploratory Analyses of Rate of Moderate to Severe AECOPD by Screening Peripheral Blood Eosinophil Categories



Source: Reviewer
Rate Ratio: rate ratio of moderate to severe COPD exacerbations in the mepolizumab 100 mg by subcutaneous injection every 4 weeks arm versus placebo arm; 95% CI: 95% confidence interval; n[P*]: number in placebo arm; n[M*]: number in mepolizumab arm

Subjects with Screening Eosinophils 150 – 300 cells/µL

First, while the primary efficacy analyses of mepo100 versus placebo in both trials include subjects with ≥150 cells/µL at screening ***or*** a historical value of ≥300 cells/µL and report effect estimates near 0.8, analyses among the subgroup of subjects with screening PB-Eos between 150 and 300 cells/µL in both trials (see Figure 10) show equivocal efficacy estimates that are not clinically significant (RR 0.93) in the mepo100 versus placebo comparison. This result raises concern that a PB-Eos threshold based on a single measurement of PB-Eos between 150 to 300 cells/µL may not correctly identify the relevant patient population.

Subjects with Historical ≥300 cells/µL Only

Second, while the primary efficacy analyses of MEA117106 mITT-HS and MEA117113 mITT report efficacy RR estimates of 0.82 and 0.80, respectively, for the mepo100 versus placebo comparison, the eosCOPD subgroup defined by ***only*** meeting historical PB-Eos criteria (but with screening PB-Eos values <150 cells/µL) showed more favorable efficacy estimates for mepo100 (RR 0.59), despite apparently "normal" levels of PB-Eos at screening (see Figure 10). This subgroup was small, and confidence intervals were wide, however analysis of this subgroup raises concern that a treatment decision based on a PB-Eos single measurement may not correctly identify the relevant patient population.

Subjects Meeting Both Historical and Screening Criteria – Persistently Elevated Eosinophils

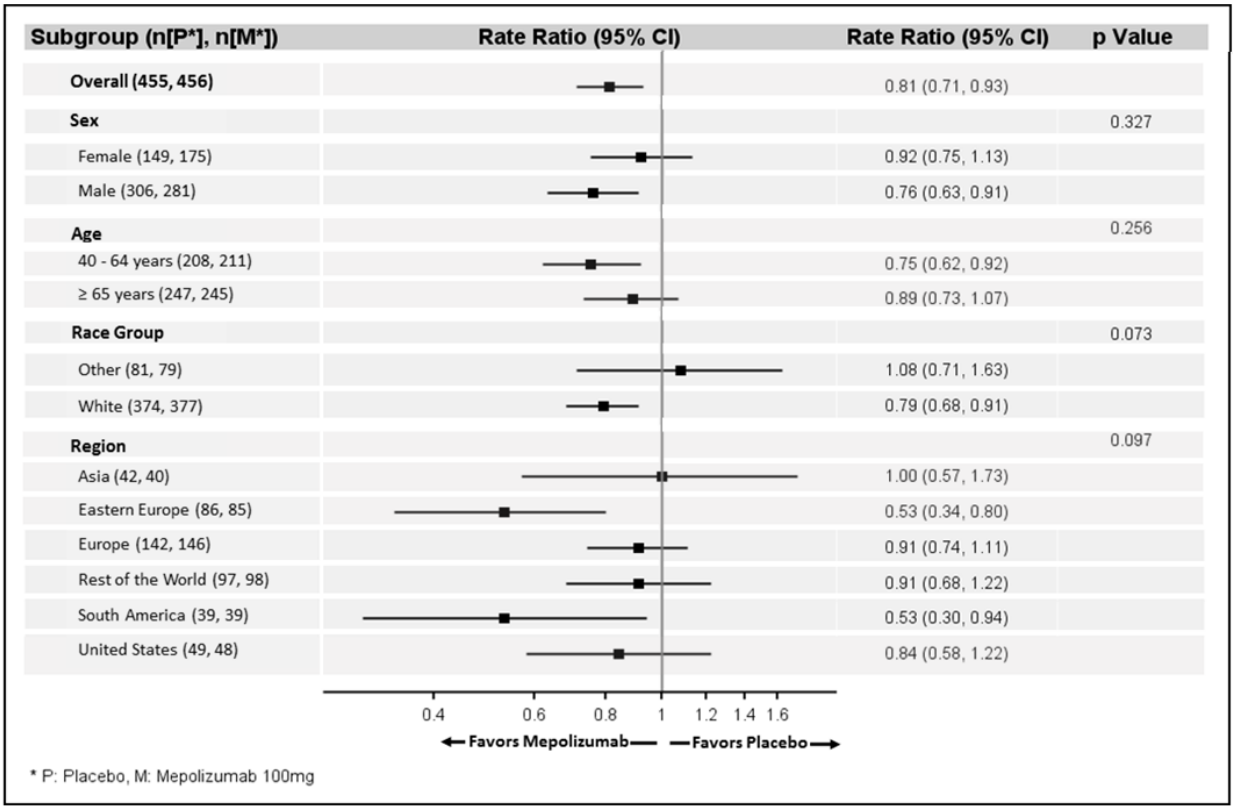
Finally, since the aforementioned subgroup analyses raised concerns about mepolizumab treatment decisions based on a single PB-Eos measurement, data among subjects showing high PB-Eos counts over time are of special interest; therefore, we examined the subgroup with screening PB-Eos ≥150 cells/µL ***and*** historical PB-Eos ≥300 cells/µL, since these subjects exhibit

evidence of persistently elevated PB-Eos over time (see Figure 10). The persistent PB-Eos subgroup demonstrates a comparatively less favorable efficacy estimate (RR 0.88) in pooled analysis of mepo100 versus placebo compared to the primary efficacy analysis results from either MEA117106 mITT-HS (RR 0.82) and MEA117113 mITT (RR 0.80). The paradoxically less favorable efficacy estimate in this "persistently eosinophilic" subgroup creates uncertainty about whether the Applicant's criteria are meaningful and durable over time.

While these PB-Eos subgroup analyses are exploratory, not pre-specified, and less precise due to smaller sample size, they provide valuable insight into better understanding how anti-IL5 therapy might affect different groups of COPD patients with varying criteria for eosCOPD, because the defining criteria and clinical validity of the eosCOPD phenotype are not well-established. The exploratory analyses are provided to help further inform the discussion as to whether the Applicant has adequately defined the eosCOPD phenotype and subsequently provided sufficient evidence of the efficacy of mepolizumab in the treatment of these patients.

6.9.2. Demographic Subgroups

Figure 11 MEA117106 mITT-HS and MEA117113 mITT: Exploratory Analyses of Rate of Moderate to Severe AECOPD by Demographic Subgroups

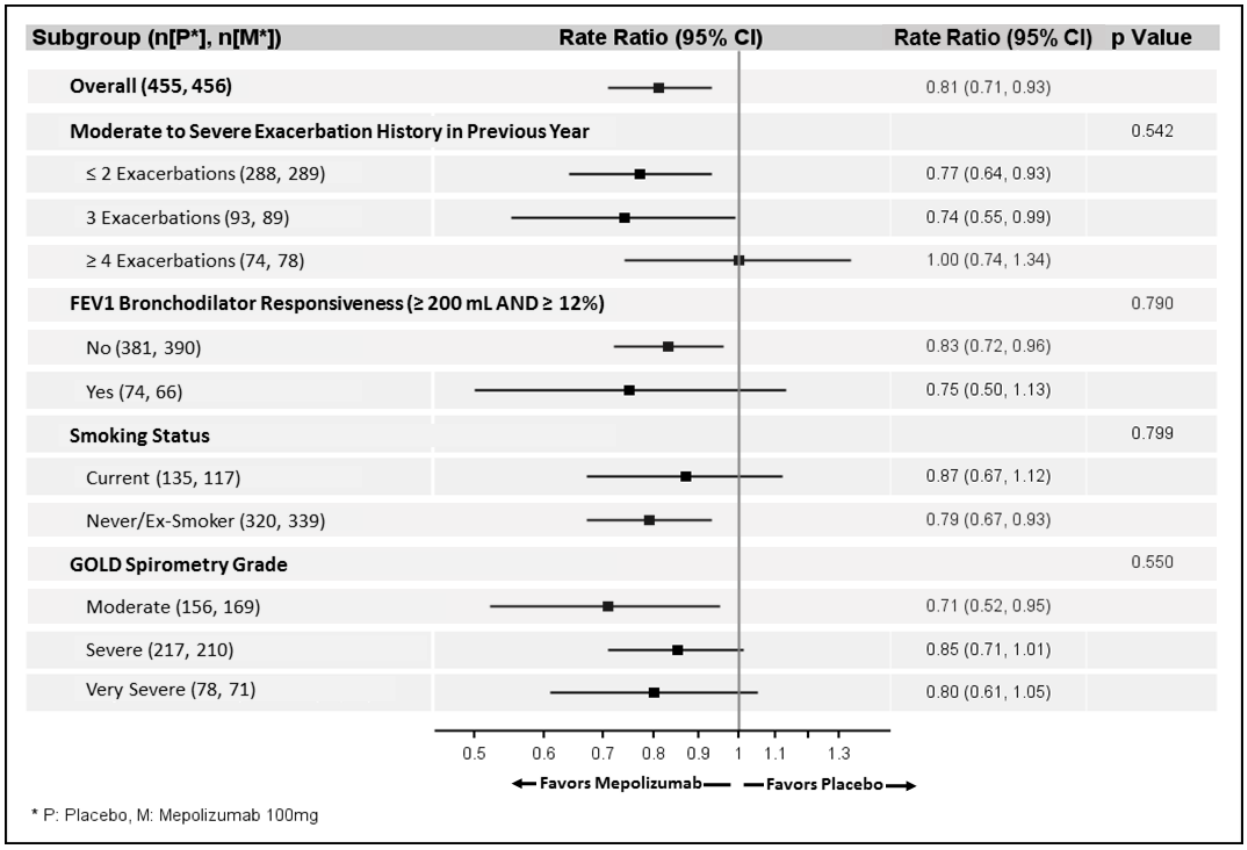


Source: Reviewer
Note: P-values shown are for interactions between the subgroup factor and treatment
Rate Ratio: rate ratio of moderate to severe COPD exacerbations in the mepolizumab 100 mg by subcutaneous injection every 4 weeks arm versus placebo arm; 95% CI: 95% confidence interval; n[P*]: number in placebo arm; n[M*]: number in mepolizumab arm

Although subgroup results are exploratory, and there was not statistical evidence of interactions with treatment effect, pooled subgroup analyses of the primary efficacy endpoint among MEA117113 mITT and MEA117106 mITT-HS (mITT-Pool) suggest less favorable or equivocal efficacy estimates of mepo100 versus placebo in subjects ≥65 years of age, female subjects, and subjects with non-white race when compared to the primary efficacy analysis results of mepo100 in MEA117106 and MEA117113.

6.9.3. Baseline Disease Characteristic Subgroups

Figure 12 MEA117106 mITT-HS and MEA117113 mITT: Exploratory Analyses of Rate of Moderate to Severe AECOPD by Baseline Disease Characteristics



Source: Reviewer
Rate Ratio: rate ratio of moderate to severe COPD exacerbations in the mepolizumab 100 mg by subcutaneous injection every 4 weeks arm versus placebo arm; 95% CI: 95% confidence interval; n[P*]: number in placebo arm; n[M*]: number in mepolizumab arm; GOLD: Global Initiative for Chronic Obstructive Lung Disease; Moderate: FEV1 ≥ 50% to < 80% predicted; Severe: FEV1 ≥ 30% to < 50% predicted; Very Severe: FEV1 < 30% predicted
Note: P-values shown are for interactions between the subgroup factor and treatment

Additional pooled exploratory subgroup analyses of subjects in the mITT-Pool classified by COPD disease characteristics reveal ModSev AECOPD efficacy estimates that are less favorable (compared to the primary efficacy analysis results of mepo100 in MEA117106 and MEA117113) among subjects with a history of more ModSev AECOPD in the previous year, subjects with greater severity in baseline spirometric stage of COPD, and current smokers (see Figure 12).

Subjects with ≥4 ModSev AECOPD in the previous year comprised 17% of the mITT-Pool population. Pooled analysis results show equivocal efficacy (RR of 0.96) on the rate of ModSev AECOPD among subjects with ≥4 ModSev AECOPD in the previous year. Subjects with severe (GOLD III) or very severe (GOLD IV) COPD by spirometric stage comprised 47% and 16% of the mITT-Pool population, respectively. Pooled analysis results in severe COPD and very severe COPD subgroups show rates of ModSev AECOPD efficacy estimates that are less favorable than results seen in the primary analysis (RR 0.85 and RR 0.85, respectively). Subjects reporting current smoking at screening comprised 28% of the mITT-Pool population. Pooled analyses in this subgroup show equivocal efficacy (RR 0.89) on the rate of ModSev AECOPD among current smokers.

Potential Influence of Unmeasured Asthma Subgroup

Exploratory pooled analyses show trends of more favorable efficacy results among subgroups of subjects who are younger (see Figure 11), with less airflow obstruction, and bronchodilator responsive (see Figure 12), although there was not statistical evidence of interactions between these factors and treatment. Furthermore, there was evidence to suggest greater efficacy among subgroups with higher levels of eosinophilia (see Figure 9).

These subgroup characteristics are reminiscent of clinical criteria for asthma compared to COPD. These results create further uncertainty in discerning mepolizumab's effect on eosCOPD because of the uncertainty surrounding the eosCOPD phenotype's relationship to prior or concomitant asthma highlighted in the Agency's meetings with the applicant (see Section 2.6 Summary of Regulatory Activity Related to Submission). Because mepolizumab has proven efficacy for the reduction of asthma exacerbations, any group including higher numbers of subjects with active asthma exacerbations would influence the primary analysis towards mepolizumab.

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 safety data suggests that the trial design did not eliminate enrollment of subjects with active asthma. Moreover, these asthma safety events highlight the lack of clear criteria that would allow an investigator to differentiate an asthma exacerbation in a subject with COPD and concomitant "active" asthma from an AECOPD in a subject with COPD and "inactive" asthma. This reviewer contends that these two entities of asthma exacerbation and AECOPD cannot be reliably disentangled using clinical data among subjects with both asthma and COPD.

Active asthma was an exclusion criterion, yet evidence of active asthma is present in the pivotal trials' safety data and no data on asthma history were collected in either pivotal trial. It is not clear how many subjects had asthma, yet efficacy results show a trend towards greater efficacy in subjects with characteristics compatible with a concomitant asthma diagnosis.

Potential Influence of Unmeasured Baseline Chronic Maintenance OCS Subgroup

The Applicant did not collect data on baseline chronic maintenance OCS use. A group of subjects with evidence of chronic maintenance OCS use was identified by the applicant through post-hoc clinical review. It is unclear how many additional patients may have used chronic

maintenance OCS during the trial. In addition, some patients identified as maintenance OCS subjects changed their dosing or discontinued OCS during the trial entirely.

OCS administration decreases PB-Eos counts, which may have complicated the assignment to High and Low Strata of MEA117106. Maintenance OCS are prescribed off-label to prevent AECOPD among patients with frequent AECOPD despite additional therapies. If trial arms contained an imbalance in the proportion of subjects with chronic OCS, it may have influenced the efficacy outcomes of the placebo and mepolizumab groups in MEA117106 and MEA117113. Whether the inclusion of subjects using chronic maintenance OCS would be expected to increase or decrease the observed efficacy of mepolizumab on the rate of ModSev AECOPD is a complicated question. Unfortunately, this question cannot be adequately answered using the submitted data submitted.

6.10. Analysis of Clinical Information Relevant to Dosing Recommendations

No formal dose ranging was conducted for mepolizumab in COPD; while MEA117113 investigated two doses (100 mg and 300 mg), this study was conducted in parallel with MEA117106, and therefore was not used to inform dose selection. For an endpoint such as ModSev AECOPD, it is difficult to envision the demonstration of a robust dose-response; however, it is notable that the results of MEA11713 showed that the mepo300 dose did not demonstrate a statistically significant reduction in ModSev AECOPD compared to placebo (see Table 9).

Considering that the mepo300 dose was as effective in reducing PB-Eos counts throughout the trial, its comparative lack of efficacy on clinical endpoints creates uncertainty in the clinical impact of the eosCOPD phenotype defined in this application and the efficacy of mepolizumab anti-IL5 treatment of COPD in general. More notably, the differing clinical results between the mepo100 and mepo300 doses (that equally reduce PB-Eos) raise questions about the proposed mechanism of action that relies on high eosinophils as a driver of AECOPD in the defined patient population, and proposes efficacy via reduction in eosinophils.

6.11. Discussion of Persistence of Efficacy and/or Tolerance Effects

The data from MEA117106 and MEA117113 suggest that the efficacy of mepolizumab on ModSev AECOPD and SGRQ scores may be limited to the first 24-30 weeks of the trial (see Figure 7 and Figure 8). After approximately the 30 weeks timepoint, the Kaplan Meier plots of incident ModSev AECOPD in each study show that both the mepolizumab and placebo curves follow a parallel course, suggesting that the initial trend of efficacy may not be persistent despite mepolizumab's continued suppression of eosinophil levels. Similar trends in the SGRQ score analyses reinforce the suggestion that any effect of mepolizumab on clinical endpoints may not be durable.

Separate from clinical endpoints, trial results demonstrate that the effect of mepolizumab on PB-Eos counts is consistent in onset, duration, and durability (see Figure 1).

6.12. Additional Efficacy Issues/Analyses

The uncertainty surrounding the role of eosinophils in stable COPD and exacerbations of COPD complicates the evaluation of mepolizumab's efficacy on rates of ModSev AECOPD. Should providers expect decreased IL5 signaling and depletion of eosinophils to have an effect in all AECOPD, or just a subset of AECOPD driven by eosinophilic inflammation? Are there some AECOPDs that have a greater eosinophilic inflammatory component that could be clinically impactful? Do eosinophils play a primary role in the inflammatory response in AECOPDs caused by a bacterial or viral infection? Is eosinophilic inflammation always the primary driver of AECOPD in the subset of patients with elevated PB-Eos at baseline? All of these questions are of importance to the evaluation of mepolizumab's effect on COPD.

The scientific literature surrounding these questions is limited. A previous study by Bafadhel, et al (partially supported by the Applicant, GSK) prospectively collected AECOPD serum and sputum biomarker data from subjects at stable and exacerbation clinic visits for COPD[21]. Notably, the investigators collected three simple tests at the time of AECOPD to clinically classify AECOPD: sputum bacterial culture, sputum respiratory virus panel PCR, and sputum eosinophil counts. Subsequent cluster analysis of stable and exacerbation biomarkers led the authors to identify and characterize COPD subjects by "AECOPD phenotype" clusters that were recognizable through biomarker characterization in the stable state. These clusters correlated to bacterial (55%), viral (29%), and eosinophilic (28%) AECOPD, as well as a fourth "pauci-inflammatory" type.

Previous data suggest that 50-70% of AECOPD may be due to respiratory infections[34], 10% may be due to environmental pollutants[35], and up to 30% have unclear inciting factors[36]. Data from bronchoscopic investigations of severe AECOPD suggest an association with a potential pathogenic bacterial species in over 70%[37]. The clustering study by Bafadhel, et al, notes that bacterial and sputum eosinophil-associated exacerbations rarely coexisted[21]. It is unclear how to gauge the impact of these data in the context of the submitted mepolizumab trials.

The studies described above were not designed to examine treatment responses among subjects with bacterial, viral, eosinophilic, or other causes of AECOPD. The timeframe of the above studies also limit interpretation of the results over periods longer than one year. However, these studies provoke questions about the potential value of characterizing the causes of AECOPD through relatively simple tests in drug development programs.

Further assessment of the impact of the causes of AECOPD within MEA117106 and MEA117113 on treatment response to mepolizumab is not possible in the submitted datasets, however, because no data related to cause of AECOPD were collected in the mepolizumab development program.

This lack of data on inciting events of AECOPDs is not uncommon in COPD development programs, and not limited to the current application. While AECOPD are recognized as impactful disease endpoints in COPD, data collected in drug development clinical trials provides

little insight to further characterize individual AECOPD or to show whether a drug is impacting a specific class of AECOPD. Whether additional data collection about AECOPD inciting events would be useful in COPD development programs is an open question.

6.13. Efficacy Summary

The Agency typically expects two adequate and controlled clinical trials to provide substantial evidence of efficacy, particularly for a novel indication. It is not clear that the data from the mepolizumab COPD program provide substantial evidence of efficacy for the proposed indication. One of the two pivotal studies supporting the safety and efficacy of mepolizumab in COPD fails to meet the pre-specified statistical threshold for efficacy in its primary efficacy analysis (see Table 9).

Moreover, there is no well-supported minimal clinically important difference for rate of ModSev AECOPD. Considering this lack of a clear standard, the clinical significance of the nominal reduction of ModSev AECOPD in the mepo100 versus placebo comparison in trials MEA117106 (RR 0.82, Absolute Risk Reduction [ARR] 0.31 ModSev AECOPD/yr) and MEA117113 (RR 0.8, ARR 0.3 ModSev AECOPD/yr) is unclear. The fact that the observed reduction in ModSev AECOPD in trial MEA117106 only involved moderate AECOPD (see Table 10) further limits the clinical significance of these findings.

A consistent reduction of Sev AECOPD could support the clinical relevance of mepolizumab on COPD disease progression and sequelae that would bolster the clinical impact of the statistically uncertain ModSev AECOPD results. However, a consistent signal for Sev AECOPD is not present in the trials (RR 1.12 in MEA117106, RR 0.63 in MEA117113). The data do not support an effect of mepolizumab on Sev AECOPD rates; this may further limit the clinical significance of the results.

The primary efficacy analysis results from MEA117106 (see Table 9) yield an estimated NNT of 3.2; a similar estimated NNT could be calculated from the results of trial MEA117113. However, given the lack of robust statistical support from trial MEA117113, these NNT estimates should be interpreted with caution. Taking these uncertainties into account, a clinical interpretation of these results implies that approximately 38.4 monthly in-office injections with mepolizumab could potentially prevent one ModSev AECOPD in subjects with eosCOPD phenotype defined by the PB-Eos criteria described in these trials' primary analyses. Given that the number and annualized rate of Sev AECOPD were numerically higher in the trial that achieved a statistically significant difference in the rate of ModSev AECOPD (MEA117106), the best available evidence suggests that the reduction in the frequency of ModSev AECOPD observed in the trials may be driven primarily by a reduction in the frequency of moderate AECOPD alone.

Secondary AECOPD endpoints that could support the primary efficacy analysis show inconsistent results. Mepolizumab's effect on time to first (TTF) ModSev AECOPD in MEA117106 is not replicated in MEA117113 with confidence (see Table 12). Analyses of Sev AECOPD rates from MEA117106's analysis of the mITT-HS population comparing mepo100 to placebo show a numerical increase in Sev AECOPD rates with mepo100 compared to placebo; analyses of rates of AECOPD requiring hospitalization or ED visit mirror this result. These results create uncertainty in the determination of mepolizumab's effects on AECOPD as well as uncertainty in the validity of subsequent meta-analyses of these endpoints across trials.

Analyses of FEV1 reveal no clinically significant effect on lung function of mepolizumab treatment compared to placebo in MEA117106 or MEA117113.

Analyses of SGRQ data show similar percentages of SGRQ responders (≥4 point decrease) at week 52 among placebo and mepolizumab arms (see Table 13). Neither MEA117106 nor MEA117113 show mean changes in SGRQ score at 52 weeks that differ in a statistically significant way from placebo (see Table 12) and the observed estimated differences are small, considering SGRQ's minimum clinically important difference of 4 points. Further raising questions, analysis of mepo100 versus placebo in MEA117106's mITT-HS population shows a nominally greater SGRQ improvement in the placebo group.

Analyses of pooled results from MEA117106 mITT-HS and MEA117113 mITT reinforce the uncertainty surrounding the durability of mepolizumab's efficacy, as shown by the SGRQ temporal response seen in each trial; while some separation in SGRQ score curves between treatment groups is seen early in both trials, this effect does not appear to be durable over the 52-week trial period (see Figure 8).

The Applicant's proposed mechanism of action for mepolizumab relies on the idea that decreasing eosinophilic inflammation in a subset of COPD with markers of eosinophilic inflammation leads to decreased disease manifestations, that PB-Eos alone are an adequate biomarker of eosinophilic inflammation for treatment initiation, that PB-Eos are an adequate biomarker for identification of patients that may benefit from anti-IL5 therapy, and that a decrease in eosinophils due to anti-IL5 therapy impacts disease manifestations. Given data from MEA117113 showing that mepo300 lowered PB-Eos to a comparable or marginally greater degree than mepo100, a result showing equal or marginally greater efficacy on clinical endpoints in the mepo300 group would support the applicant's proposed role for PB-Eos as an adequate biomarker of eosCOPD and mepolizumab's proposed mechanism of action in COPD. However, the efficacy results of the mepo300 group instead create additional uncertainty in these parameters.

Finally, given the lack of definitive trends in the results and uncertainty in the phenotype's definition and relevance, the exploratory analyses of PB-Eos thresholds (detailed in Section 6.9.1 Eosinophil Threshold Subgroups) provide information for hypothesis generation but do not provide adequate information to overturn the statistical uncertainty of the primary efficacy analysis result.

Overall, analyses of the primary and secondary endpoints across MEA117106 and MEA117113 leave uncertainty with respect to the efficacy of mepolizumab in COPD. Whether these data support the efficacy of mepolizumab in COPD as "add-on treatment to ICS-based maintenance treatment for the reduction of exacerbations in patients with COPD guided by blood eosinophil counts" merits discussion with the Advisory Committee.

7. Review of Safety

7.1. Methods

7.1.1. Clinical Trials Used to Evaluate Safety

GSK submitted safety data from the 52-week pivotal trials MEA117106 and MEA117113 as primary datasets for safety evaluation. GSK also submitted a pooled safety dataset including all complete trials of mepolizumab throughout GSK's mepolizumab drug development programs.

The safety review of this supplement relies primarily on the data provided by trials assessing the effect of mepolizumab in patients with COPD, MEA117106 and MEA117113. These trials comprised the placebo-controlled safety dataset and included a total of 1,510 subjects: 865 administered mepolizumab and 645 administered placebo.

Adverse events of special interest for the mepolizumab drug development program included the following:

- systemic reactions of anaphylaxis, allergic/hypersensitivity reactions, and non-allergic reactions
- local injection site reactions
- infections, serious infections, and opportunistic infections
- neoplasms and malignancies
- cardiac disorders and major adverse cardiovascular events.

In addition, reviewers identified a safety signal for herpes zoster in asthma clinical trial data and post-marketing data that was subsequently included in labeling.

7.1.2. Categorization of Adverse Events

The Applicant defined an adverse event (AE) as any untoward medical occurrence in a patient during the study; this definition did not require a causal relationship with the study drug. Investigators also reported any abnormal laboratory assessment, electrocardiogram finding, vital sign, or physical exam finding that the investigator judged to be a clinically significant worsening from baseline as adverse events.

The Applicant coded AE terms in both pivotal trials using MedDRA version 19.1. Treatment-emergent AEs were defined as AEs that occurred between the treatment start date and 28 days after the last dose of treatment.

The Applicant defined serious adverse events (SAE) as any untoward medical occurrence that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, or is a congenital anomaly/birth defect. All SAEs were adjudicated by a blinded independent clinical endpoint committee. The Applicant did not

reference a defined scale for grading the severity of AEs in the trial protocols; the clinical investigators determined severity grading.

7.1.3. Pooling of Data Across Clinical Trials to Estimate and Compare Incidence

Except as noted below, the safety analyses presented in this briefing document rely on pooled data from the safety populations of MEA117106 (including both HS and LS subjects) and MEA117113, comparing any dose of mepolizumab to placebo. The mepolizumab pooled analysis group comprises the mepo100 arm of trial MEA117106 and the mepo100 and mepo300 arms of trial MEA117113. The placebo pooled analysis group comprises placebo arms of MEA117106 and MEA117113.

The similar inclusion/exclusion criteria, demographics, baseline disease criteria, and study designs between trials MEA117106 and MEA117113 provide reasonable grounds for pooling these data; in addition, it is reasonable to pool the mepo100 and mepo300 treatment arms given the comparable effect of the mepo300 dose on eosinophil levels compared to the mepo100 dose. However, some of the safety analyses presented are exploratory in nature, intended for potential signal detection, and should be interpreted with caution.

7.2. Adequacy of Safety Assessments

7.2.1. Overall Exposure at Appropriate Doses/Durations and Demographics of Target Population

The extent and duration of exposure to mepolizumab provided by the pivotal trials MEA117106 and MEA11713 allows sufficient evaluation of the drug's safety for the proposed indication. See Table 15 for details.

Table 15 Extent of Exposure to Mepolizumab

Safety Database for Mepolizumab Individuals exposed to any treatment in this development program for the indication under review n = 6177 (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	2963 (3667)	1704 (1117.6)

Source: Reviewer created, adapted from mea117106-report.pdf and mea117113-report.pdf

The Agency reviewed the safety profile of mepolizumab in severe asthma and EGPA as part of its approval for those indications. While the previous asthma and EGPA drug development

programs provide perspective on the safety results in COPD, the patient populations of those previous programs differ from the COPD population in relevant characteristics such as age and comorbidities. Therefore, the focus of this review will be the COPD safety database; comparisons to the safety of mepolizumab in other conditions should be interpreted with caution.

7.2.2. Explorations for Dose Response

The phase 3 trial MEA117113 evaluated two doses of mepolizumab to allow for an analysis of dose related safety. These analyses are embedded throughout this review of safety when relevant. No potential safety signal showed a consistent dose response comparing mepo100 to mepo300.

7.2.3. Routine Clinical Testing

Figure 3 and Figure 6 depict the schedules of routine clinical tests including vital signs, spirometry, serum extended chemistry panels, hematology panels, and electrocardiograms for trials MEA117106 and MEA117113, respectively.

7.2.4. Metabolic, Clearance, and Interaction Workup

The Applicant relied primarily on data from the previous severe asthma and EGPA development programs to address metabolism, clearance, and drug interactions. No additional studies examining drug metabolism, clearance, and potential for interaction were performed by the applicant in the COPD development program.

7.2.5. Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Currently, no other monoclonal antibody biologic product targeting the IL5 pathway is approved for the treatment of COPD. However, comparison of adverse events identified in the drug development programs of non-COPD indications of mepolizumab, reslizumab (anti-IL5 monoclonal antibody), benralizumab (anti-IL5-receptor [IL5R] monoclonal antibody), and dupilumab (anti-IL4 monoclonal antibody) each contribute context to the safety evaluation of mepolizumab in COPD. These adverse events are discussed in Section 2.5. In each case, the comparator study population represents a younger group with fewer comorbidities than the COPD population investigated in trials MEA117106 and MEA117113.

7.3. Deaths

Fifty-four (n=54) treatment-emergent deaths occurred in the mepolizumab COPD drug development program, including both on-treatment and off-treatment deaths. Sixteen (n=16) deaths occurred in the mepolizumab arm of trial MEA117106, while 17 deaths occurred in the placebo arm. Trial MEA117113 had fewer deaths overall; 8 deaths occurred in the mepolizumab 300mg Q4 wks arm, 4 deaths occurred in the mepolizumab 100mg Q4 wks arm,

and 9 deaths occurred in the placebo arm.

The number of deaths in the mepolizumab drug development program are consistent with expectations for COPD subjects with significant burdens of comorbidities, substantial airways obstruction, and frequent exacerbations. There was no significant imbalance between deaths observed in those receiving mepolizumab (N = 28, 3.2% of all subjects receiving mepolizumab) and those receiving placebo (N = 26, 4.0% of all subjects receiving placebo), and these data do not support a treatment-related effect of mepolizumab on death. Further analyses of the death case narratives suggested no clinically significant safety signals for cause of death among subjects receiving mepolizumab compared to those receiving placebo.

7.4. Serious Adverse Events

The numbers and rates of serious adverse events (SAE) between mepolizumab and placebo trial arms do not raise concerns for higher rates of SAEs overall. Full listing of on-treatment SAE events and exposure-adjusted event rates organized by MedDRA system organ class (SOC) is provided in Table 16.

Table 16 On-treatment SAEs by System Organ Class in Trials MEA117106 and MEA117113

Adverse Event	**Mepolizumab** Any dose strength (Subject years = 794.1)		**Placebo** (Subject years = 569.7)	
System Organ Class	Number of Events	Exposure-adjusted event rate	Number of events	Exposure-adjusted event rate
-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 (incl cysts and polyps)	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
-Metabolism and nutrition disorders	2	2.5	7	12.3
-General disorders and administration site conditions	5	6.3	3	5.3
-Psychiatric disorders	3	3.8	3	5.3
-Hepatobiliary disorders	2	2.5	3	5.3
-Eye disorders	2	2.5	1	1.8
-Investigations	1	1.3	1	1.8
-Blood and lymphatic system disorders	0	0	1	1.8
-Endocrine disorders	1	1.3	0	0

-Product issues	0	0	1	1.8
ALL Events	401	505.0	321	563.4

Source: adapted from data presented in Table 3.42 of applicant's integrated summary of safety

The most frequent SAEs in the mepolizumab COPD development program were AECOPD, which are to be expected given the baseline disease characteristics of the subjects in both trials. Imbalances seen in the counts of SAEs in the Respiratory, Thoracic, and Mediastinal disorders SOC, and the Infections and infestations SOC were not supported by exposure-adjusted event rates. The imbalance observed in the Gastrointestinal disorders SOC is discussed in the analysis of gastrointestinal bleeding in Section 7.5. The imbalance seen in the Renal and Urinary disorders SOC comprised multiple single adverse events without a trend.

Additional safety analyses that include SAEs are described in Section 7.5 Standardized MedDRA Query Safety Analyses and Section 7.7 Submission Specific Safety Concerns.

7.5. Standardized MedDRA Query Safety Analyses

SMQ analysis of SAEs and AEs in the mepolizumab COPD drug development program suggest potential safety signals for supraventricular tachyarrhythmia, embolic and thrombotic events, gastrointestinal hemorrhage, and acute pancreatitis (see Table 17). The gastrointestinal hemorrhage and acute pancreatitis signals are discussed below, while the cardiac signals are discussed in Section 7.7.1 Cardiac, Vascular, Thromboembolic, and Ischemic Adverse Events

Standardized MedDRA Queries (SMQ) are collections of adverse event (AE) terms related to a particular clinical topic and curated by MedDRA for use in adverse event signal detection in drug development. The goal of an SMQ is to identify the many different adverse event terms that may describe similar or related events in a reproducible way.

For example, a safety reviewer attempting to find a signal for heart attacks might perform a simple analysis for the term "myocardial infarction" in a clinical trial dataset and show no difference between placebo and drug arms. However, this simple analysis may miss related adverse events that still describe heart attacks but are coded in different ways, such as "myocardial infarction with ST segment elevation", "STEMI", "T2 NSTEMI", "acute myocardial infarction", and "acute coronary syndrome", and others. An SMQ related to myocardial ischemia includes these terms, so it can capture all the adverse event terms in a reproducible way for a more complete assessment of heart attacks in the trial.

SMQ analysis facilitates reproducible signal detection, however some SMQs capture events that may be too broad for the relevant medical concept. The "Narrow" categorization of SMQs include more specific terms for a concept. Only Narrow SMQs were used in the data presented below. In addition, to verify that captured SAEs and AEs represented real events, individual SAEs and AEs in each analysis presented below were confirmed and examined in the datasets for accuracy.

Table 17 Treatment Emergent SAE Safety Signals in MEA117106 and MEA117113

Adverse Event	Mepolizumab Any dose strength N = 865		Placebo N = 645	
SMQ (Level)	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: Reviewer analysis of TEAE using MAED software.

Gastrointestinal bleeding

A higher proportion of subjects administered mepolizumab experienced serious and non-serious gastrointestinal bleeding events (GIB) in MEA117113. Analysis of GIB events captured by Standardized MedDRA Query (SMQ) revealed an imbalance in serious or non-serious GIB in pooled analysis of both trials; 0.92% of subjects administered mepolizumab experienced GIB compared to 0.47% administered placebo, with a risk ratio (RR) of 2.0. Available case narratives were reviewed to confirm the diagnoses. Reviewer analysis and information requests to the applicant showed no baseline difference in concomitant anti-platelet or anti-coagulant use at baseline between trial arms. Given the average age of the COPD trial population, one could expect a higher overall frequency of GIB than in previous clinical trials with mepolizumab; however, the imbalance of GI bleeds between trial arms is unexpected.

No mechanism linking decreased eosinophils to bleeding events is established and recognized in clinical practice, however eosinophil biology and coagulopathy are pathologically connected. Eosinophilia in conditions such as hypereosinophilic syndrome is linked to hypercoagulability through dysregulation of eosinophil - mast cell interactions; the proposed mechanism of hypercoagulability in hypereosinophilic syndrome relies on increased release of pro-coagulant molecules eosinophilic cationic protein (ECP), major basic protein (MBP), and eosinophil peroxidase (EP)[38-41]. A potential mechanistic link between abnormally low eosinophil counts and GIB relies on the converse of this eosinophil - mast cell mechanism. Limited literature supports that abnormally low eosinophil counts contribute to bleeding diathesis through decreased release of the same pro-coagulant molecules: ECP, MBP, and EP. Based on limited *in vitro* studies, depletion of eosinophils and decreased release of these pro-coagulant substances could be hypothesized to affect coagulation through subsequent dysregulated release of endogenous heparin from mast cells normally regulated by eosinophil activity[38,42-45], a phenomenon observed in normal human endometrium during menstruation[46].

The coagulation cascade is complex and includes many inputs and effectors; it is possible that additional coagulopathic factors are required in an additive manner to cross the threshold required for a clinical event of GIB in individual patients in trials MEA117106 and MEA117113. However, the data provided do not allow for accurate determination of these additional factors, and the imbalance would not be otherwise predicted in a randomized clinical trial of this size. Whether this imbalance in GIB events represents a potential safety signal for mepolizumab in patients with COPD merits discussion with the Advisory Committee.

Acute pancreatitis

The Sponsor's datasets reveal an imbalance in SAEs of acute pancreatitis in MEA117106 (2 in mepolizumab arm, 0 in placebo arm); MEA117113 shows a corresponding imbalance in non-serious episodes of acute pancreatitis (2 in mepolizumab dosing arms, 0 in placebo arm). Each captured adverse event term was examined in the COPD dataset, and available case narratives were reviewed to confirm the diagnosis.

7.6. Dropouts and/or Discontinuations

Analysis of trial data in both MEA117106 and MEA117113 shows a greater proportion of study withdrawals and treatment discontinuations in the placebo arms than in the mepolizumab arms (see Table 8), and further investigation reveals no clinically significant imbalances in dropouts due to adverse events between mepolizumab and placebo arms.

7.7. Submission Specific Safety Concerns

7.7.1. Cardiac, Vascular, Thromboembolic, and Ischemic Adverse Events

Analysis of cardiovascular, thromboembolic, and ischemic adverse events in the mepolizumab COPD drug development program suggest potential safety risks related to supraventricular tachyarrhythmias, as well as multiple safety signals related to serious thrombotic events. Trials MEA117106 and MEA117113 include subjects with older age, significant cardiovascular risk factors, and significant cardiovascular comorbidities. The cardiovascular, thromboembolic, and ischemic adverse events data were examined within this contextual framework.

Supraventricular tachyarrhythmia

SMQ analysis reveals an imbalance in treatment-emergent serious and non-serious AE terms for supraventricular tachyarrhythmias (SVTA) towards subjects receiving mepolizumab (see Table 17). The signal is driven by MedDRA preferred terms "Atrial fibrillation", "Atrial flutter", and "Supraventricular tachycardia". In MEA117106, 3.1% of subjects in the mepolizumab arm experienced SVTA events compared to 1.5% of subjects in the placebo arm; similarly, in MEA117113, 3.9% of subjects in the mepolizumab arms experienced SVTA events compared to 2.7% of subjects in the placebo arm. Baseline to maximum shift plots for pulse rate also reflect these imbalances in both trials. Each captured adverse event term was examined in the COPD datasets, and available case narratives were reviewed to confirm the diagnoses.

Review of relevant literature does not present a clear mechanism linking anti-IL5 therapy and decreased PB-Eos with increased susceptibility to supraventricular tachycardia events. Whether the observed imbalance is important in the risk evaluation of mepolizumab in COPD will be an issue for discussion.

Thrombotic events: Agency Analyses

SMQ analysis of embolic and thrombotic events (ETE) reveals an imbalance in treatment-emergent serious and non-serious ETE events towards subjects receiving mepolizumab (see Table 17). In pooled analysis of MEA117106 and MEA117113, 2.0% of subjects in the mepolizumab arms experienced ETE events to 1.4% of subjects in the placebo arms. The most common MedDRA preferred terms captured by the SMQ were "Acute myocardial infarction" and "Myocardial infarction", with additional contributing terms. Each captured adverse event term was examined in the COPD dataset, and available case narratives were reviewed to confirm the diagnosis.

Supporting these results, three additional SMQ analyses involving thrombotic processes show trends similar to that seen in the ETE SMQ analysis (see Table 17), albeit with lower numbers of events. While the event rates for these three SMQ analyses are low, they are presented to help inform the clinical interpretation of the observed ETE imbalance.

First, SMQ analysis of ischemic heart disease events (IHD) reveals an imbalance towards mepolizumab in treatment-emergent serious and non-serious IHD events in analyses of trials MEA117106 and MEA117113 reinforce the results of the ETE and VTE analyses. In MEA117106, 1.5% of subjects in the mepolizumab arm experienced IHD events compared to 1.0% of subjects in the placebo arm; similarly, in MEA117113, 2.5% of subjects in the mepolizumab arms experienced ischemic heart disease AE terms compared to 1.8% of subjects in the placebo arm. The most common MedDRA preferred terms captured by the SMQ were "Myocardial infarction", "Acute coronary syndrome", and "angina unstable", with additional related contributing terms.

Second, SMQ analysis of venous embolic and thrombotic events (VTE) reveals an imbalance towards mepolizumab in treatment-emergent serious and non-serious VTE events in pooled analysis of trials MEA117106 and MEA117113. In pooled analysis of MEA117106 and MEA117113, 0.5% of subjects in the mepolizumab arms experienced VTE events compared to 0.2% of subjects in the placebo arms. The most common MedDRA preferred terms captured by the SMQ were "Pulmonary embolus" and "Deep vein thrombosis".

Third, SMQ analysis of central nervous system hemorrhages and cerebrovascular conditions (CVA) reveals an imbalance towards mepolizumab in treatment-emergent serious and non-serious CVA events in pooled analysis of trials MEA117106 and MEA117113. In pooled analysis of MEA117106 and MEA117113, 0.6% of subjects in the mepolizumab arms experienced CVA AE terms compared to 0.2% of subjects in the placebo arms. The most common MedDRA preferred terms captured by the SMQ were "TIA", "Transient ischemic attack".

Thrombotic events: Applicant Analyses

The Applicant's submitted safety analyses comparing any dose of mepolizumab versus placebo corroborate the potential thromboembolic cardiovascular safety signals discussed above, albeit using different techniques and tools. In the comparison of any mepolizumab dose versus placebo among the pooled safety analysis populations of MEA117106 and MEA117113, the applicant reports higher on-treatment Cochran-Mantel-Haenszel (CMH) adjusted risk ratios for cardiac disorders (RR 1.3), serious cardiac disorders (RR 1.23), serious cardiovascular thromboembolic disorders (RR 1.33), and serious ischemic events (RR 1.35).

The Applicant's submitted safety analyses comparing only mepo100 versus placebo reveals similar results. In the comparison of mepo100 versus placebo among the pooled safety analysis populations of MEA117106 and MEA117113, the Applicant reports higher on-treatment CMH adjusted risk ratios for cardiac disorders (RR 1.25), serious cardiac disorders (RR 1.25), serious cardiovascular thromboembolic disorders (RR 1.34), and serious ischemic events (RR 1.26). While the Applicant's definitions for each of these categories differ from the Agency's analyses presented above, the replication of these trends may lend additional support to the validity of this potential safety signal for serious thrombotic events.

The potential safety signal for cardiovascular thromboembolic events in subjects administered mepolizumab presents itself in multiple analyses by both the Agency and the applicant. Review of relevant literature does not present a clear mechanism linking anti-IL5 therapy and decreased PB-Eos with increased susceptibility to cardiovascular thrombotic events. Whether the observed imbalance is important in the risk evaluation of mepolizumab in COPD will be an issue for discussion.

We acknowledge that the review of safety data identified potential safety signals involving both increased clotting and increased bleeding events for mepolizumab. These seemingly paradoxical signals are somewhat scientifically unsatisfying and no clear mechanism of action could be identified. These events are not common and with examination of a large number of safety issues, imbalances are likely to be noted. However, it is difficult to discount the imbalances for GIB and thrombotic events.

7.7.2. Hypersensitivity Reactions, Anaphylaxis, and Local Injection Site Reactions

The current mepolizumab product label includes wording describing risks of anaphylaxis and hypersensitivity. Examination of results from the pivotal COPD trials of mepolizumab including Narrow SMQ analysis, serious adverse events analysis, and AE analysis do not reveal new safety concerns.

Two subjects experienced treatment-emergent events classified with the AE term "anaphylactic reaction" in trials MEA117113 and MEA117106, both subjects received mepolizumab; no anaphylactic reactions were observed in the placebo arms of MEA117113 or MEA117106. Analysis of hypersensitivity AE terms showed similar rates of hypersensitivity events across mepolizumab and placebo trial arms in MEA117113 and MEA117106.

7.7.3. Serious and Opportunistic Infectious Events

Analysis of serious and opportunistic adverse events in the mepolizumab COPD drug development program reinforce a known safety signal related to herpes zoster infections. There was no clinically significant imbalance in pneumonia adverse events related to mepolizumab administration in the submitted data.

Opportunistic Infections

Examination of opportunistic infections in the mepolizumab COPD drug development program reveals imbalances in events related to herpes infections (specifically herpes zoster AEs). Current labeling for mepolizumab provides warnings and precautions for the risk of herpes zoster; data from trials MEA117106 and MEA117113 reinforces this safety signal and shows that it may affect the COPD population with greater frequency than previous trial populations. The proportion of subjects reporting herpes zoster adverse events in the mepolizumab trial arms (1.9%) of MEA117106 and MEA117113 was more than twice the proportion observed in the placebo arms (0.8%) of these trials (see Table 18).

Table 18 Opportunistic Infection AEs in Trials MEA117106 and MEA117113

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)

Source: Reviewer analysis of TEAE using MAED software.

The applicant presents tables of pooled data from trials MEA117106 and MEA117113 showing a CMH-adjusted risk ratio of 1.45 for on-treatment opportunistic infections. Subject incidence tables of on-treatment opportunistic infections from the same analysis support these results. Regarding the preferred term "candida infection", clinical review by the applicant revealed that each of these infections were resolved in less than 14 days. Because of this short timeframe

until resolution, the applicant contends that these events likely represent non-invasive candida infections.

The data suggest that non-invasive presentations of candida infections were not uncommon events in trials MEA117106 and MEA117113. While most of these events likely represent non-invasive candida infections of the oropharynx, other less frequent candida adverse event terms such as esophageal candidiasis did occur in subjects treated with mepolizumab. In Section 7.8 of this review, oral candidiasis is designated as a common adverse reaction (see Table 20 Common Adverse Reactions in Trials MEA117106 and MEA117113) which would likely adequately describe the most frequent manifestation seen within the program.

Serious Infections: Pneumonia

Table 19 shows similar rates of pneumonia among subjects administered mepolizumab compared to subjects administered placebo. Applicant analyses of pneumonia show similar results.

Table 19 Treatment Emergent Pneumonia AEs in Trials MEA117106 and MEA117113

Adverse Event	Mepolizumab (Any dose strength) N = 865		Placebo N = 645	
Preferred Term	**Number of Events**	**Subjects (N%)**	**Number of Events**	**Subjects (N%)**
Pneumonia	90	73 (8.4)	68	59 (9.2)
Lung infection	2	2 (0.2)	2	2 (0.3)
Pneumonia bacterial	1	1 (0.1)	0	0
Pneumonia klebsiella	1	1 (0.1)	0	0
Pneumonia pneumococcal	1	1 (0.1)	0	0
Pneumonia pseudomonal	1	1 (0.1)	0	0
Pneumonia staphylococcal	1	1 (0.1)	0	0
Pneumonia streptococcal	1	1 (0.1)	0	0
Pneumonia necrotizing	0	0	1	1 (0.2)
Pneumonia hemophilus	0	0	1	1 (0.2)
Bronchopneumopathy	0	0	1	1 (0.2)

Source: Reviewer analysis of TEAE using MAED software. Note: Applicant's analysis of pneumonia includes the following single event/single subject terms: pulmonary tuberculosis, pneumonitis, and pneumonia aspiration in mepolizumab arms; bronchopneumopathy in placebo arms.

7.7.4. Neoplasms and Malignancies

Examination of results from the pivotal COPD trials of mepolizumab including Narrow SMQ analysis, serious adverse events analysis, and AE analysis do not suggest a malignancy signal in the mepolizumab COPD safety database.

7.8. Common Adverse Events

The adverse reactions in Table 20 may be relevant for the mepolizumab COPD indication. Current severe asthma labeling of adverse reactions to mepolizumab includes headache, injection site reaction, back pain, fatigue, influenza, urinary tract infection, abdominal pain upper, pruritus, eczema, and muscle spasms. Current EGPA labeling of adverse reactions to mepolizumab does not identify additional adverse reactions.

Table 20 presents common adverse reactions in the COPD clinical trials, defined as AE occurring in ≥2.5% of subjects in mepolizumab trial arms and more frequently than in placebo arms.

Table 20 Common Adverse Reactions in Trials MEA117106 and MEA117113

Adverse Event	Mepolizumab (Any dose strength) N = 865		Placebo N = 645	
Preferred Term	Number of Events	Subjects (N%)	Number of Events	Subjects (N%)
Back pain	78	65 (7.5)	46	42 (6.5)
Cough	65	52 (6)	33	27 (4.2)
Oropharyngeal pain	55	50 (5.8)	24	22 (3.4)
Diarrhea	54	42 (4.9)	39	29 (4.5)
Sinusitis	41	34 (3.9)	25	20 (3.1)
Bronchitis	38	29 (3.4)	27	21 (3.3)
Pain in extremity	36	32 (3.8)	33	21 (3.3)
Nausea	35	28 (3.2)	27	15 (2.3)
Hypertension	29	28 (3.2)	12	12 (1.9)
Constipation	28	24 (2.8)	17	16 (2.5)
Oral candidiasis	28	25 (2.9)	22	17 (2.6)
Fatigue	25	23 (2.7)	18	10 (1.6)
Contusion	22	22 (2.5)	15	11 (1.7)

Source: Reviewer analysis of TEAE using MAED and JMP Clinical software.

Additional adverse reactions, defined as treatment emergent AE occurring in ≥1% of subjects in mepolizumab trial arms and ≥2 times more frequently than in placebo arms, included rhinorrhea, nasal congestion, herpes zoster, rash, conjunctivitis, and C-reactive protein increased.

7.9. Subpopulation Safety Results

7.9.1. Demographic Subgroups

Stratification of safety analyses by age and sex did not reveal consistent and well-supported safety signals within strata, nor did they change the safety assessment discussed previously in this review. The data do not include sufficient subjects of non-white race to draw meaningful race-specific safety conclusions.

7.10. Vital Signs, Laboratory Findings, and ECGs

Vital Signs

Analysis of treatment-emergent hypertension AE terms in MEA117106 shows that 3.38% 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% of subjects in the mepolizumab arm experienced hypertension AE terms compared to 2.3% of subjects in the placebo arm. The hypertension signal was driven by MedDRA preferred terms "Hypertension", "Blood pressure increased", and "Essential hypertension". Additionally, hypertension as a single AE term is also identified as a common adverse reaction in Table 20.

Despite this imbalance, blood pressure measurement data does not reveal a clinically significant signal for increases in blood pressure that would require closer observation among subjects receiving mepolizumab when compared with placebo. These results imply that if mepolizumab does play a role in treatment-emergent hypertension, the impact would likely not necessitate additional medical monitoring or intervention beyond routine medical care.

Examinations of vital sign data including analyses of oxygen saturation data, weight, and height show no clinically meaningful signals for safety between mepolizumab and placebo arms. Evaluation of heart rate reveals no additional safety signals other than the imbalance in supraventricular tachycardia described in Section 7.7.1.

Laboratory Findings

Review of laboratory findings do not identify a clinically meaningful imbalance in laboratory findings between mepolizumab and placebo groups in either trial, except for expected decreases in PB-Eos.

MEA117106 and MEA117113 measured PB-Eos levels at each study visit, but not during AECOPD. Predictably, subjects administered mepolizumab exhibited a persistent, significantly lower PB-Eos count in both trials compared to subjects administered placebo. This effect appeared stable over the 52-week trial period in both trials. Representative time trend figures of mean PB-Eos count for MEA117113 are presented in Section 4.2 above as Figure 1.

ECG Findings

Review of ECG data does not reveal clinically significant differences in ECG findings between subjects administered mepolizumab and subjects administered placebo in analyses including SMQ analyses, adverse events data, and sponsor-provided tables. Thorough QT clinical trials were not conducted (nor required) for this application. Available data do not support a clinically significant effect of mepolizumab on QT interval.

Full assessment of cardiovascular events including supraventricular tachycardia events as adverse events of special interest is discussed in Section 7.7.1.

7.11. Immunogenicity

Among both pivotal trials, there was not a clinically significant difference between trial arms in the number of subjects that tested positive for anti-drug antibodies or neutralizing antibodies at baseline. While observed rates of anti-drug antibodies were higher in the mepolizumab trials arms, no subject administered mepolizumab tested positive for neutralizing antibodies post-baseline (see Table 21). No dose effect was observed for immunogenicity results. No systemic reactions or local injection site reactions were reported among subjects with anti-drug antibodies.

Table 21 Immunogenicity Results Summary in Trial MEA117106 and MEA117113

	MEA117106		MEA117113		
Immunogenicity Result	**mepo100 n = 417 n (%)**	**PBO n = 419 n (%)**	**mepo100 n = 223 n (%)**	**mepo300 n = 225 n (%)**	**PBO n = 226 n (%)**
Anti-drug antibody detected	14 (4)	2 (<1)	13 (6)	4 (2)	3 (1)
Neutralizing antibody detected	0	1 (<1)	0	0	0

7.12. Other Safety Explorations

The Applicant presents data including the death of a 49 year-old female subject receiving mepo100 attributed to AECOPD and respiratory syncytial virus (RSV) noted in a mepo100 subject in MEA117106. While RSV is not generally classified as an opportunistic infection, this death is of special interest due to a possible mechanistic connection with anti-IL5 therapy, immune suppression, and eosinophil depletion. Data suggest that eosinophils may play a role in host defense against viral pathogens[47-50], and specifically against RSV[51-54], although few human *in vivo* data exist in the literature to confirm that these mechanistic hypotheses are clinically impactful. These potential mechanistic links raise questions about mepolizumab's influence on host defense and immunity against infections from RSV, influenza A, parainfluenza, and other respiratory viridae.

Since respiratory viral infections are frequent causes of AECOPD, data assessing a drug's impact on the frequency and severe infections by respiratory viridae could be of importance to patients and providers. Further assessment of the impact of viral infections on deaths and severe adverse events is not possible in the submitted datasets, however, because few data related to cause of AECOPD were collected in the mepolizumab development program. The lack of data collection regarding AECOPD cause (discussed in Section 6.12 Additional Efficacy Issues/Analyses) has implications for efficacy, however the same questions about AECOPD-inciting event impact the safety evaluation as well. Whether additional data collection about AECOPD inciting events would improve benefit and risk assessment of clinical trials examining reduction in AECOPD is an important issue for discussion.

7.13. Safety Summary

The safety review of mepolizumab for the COPD indication comprises exploratory analyses performed on the placebo-controlled safety datasets from trial MEA117106 and MEA117113. These safety datasets included a total of 1,510 subjects: 865 administered mepolizumab and 645 administered placebo. Pooling of data across trials MEA117106 and MEA117113 was deemed acceptable since these trials were similar in design, duration, and the randomized patient populations. Safety assessments in these studies included collection of adverse events, physical examination, vital signs, clinical laboratory testing, and ECG assessment.

Review of the safety data do not raise a concern for an effect of mepolizumab on deaths compared to placebo. There is no clinically significant imbalance in deaths when evaluating the totality of the data among COPD subjects in trials MEA117106 and MEA117113.

Overall, subjects administered mepolizumab experienced a comparable number and exposure-adjusted rate of on-treatment SAEs compared to subjects administered placebo in trials MEA117106 and MEA117113, and these data do not raise safety concerns for the overall rates of SAEs.

The safety review of mepolizumab in COPD identifies imbalances in SAEs and AEs related to supraventricular tachyarrhythmias (see Section 7.7.1), cardiovascular thrombotic events (see Section 7.7.1), gastrointestinal bleeding (Section 7.5), and acute pancreatitis (Section 7.5), in addition to the safety signal for increased rate of ModSev AECOPD among Low Stratum subjects discussed with the efficacy analyses (Section 6.9.1 and Table 9).

AEs leading to discontinuation were similar across treatment arms in both trials, and analyses of these data do not influence the overall safety review.

Submission-specific safety concerns previously identified by the Applicant during mepolizumab drug development include “cardiac, vascular, thromboembolic, and ischemic events”, “hypersensitivity reactions, anaphylaxis, and local injection site reactions”, “serious and opportunistic infections”, and “neoplasms and malignancies”. Analyses by both the Applicant and the Agency reveal consistent imbalances in cardiovascular thrombotic events towards mepolizumab despite different analysis methods, while the Agency’s analyses also reveal an imbalance in supraventricular tachyarrhythmia events towards mepolizumab. Results of analyses of anaphylaxis, hypersensitivity reactions, and local injection site reactions in the mepolizumab COPD development program are consistent with known and labeled adverse reactions to mepolizumab. While analyses of serious infections (and specifically pneumonia events) show no imbalance across trial arms, analyses of opportunistic infections by both the Applicant and Agency support imbalances in candida-related events and herpes zoster events. Finally, analyses of neoplasms and malignancies do not reveal imbalances between mepolizumab and placebo arms.

Common adverse reactions to mepolizumab occurring with a frequency of >2.5% and more commonly than in subjects administered placebo include back pain, cough, oropharyngeal pain,

diarrhea, sinusitis, bronchitis, pain in extremity, nausea, hypertension, constipation, oral candidiasis, fatigue, and contusion. Additional adverse reactions, defined as treatment emergent AE occurring in ≥1% of subjects in mepolizumab trial arms and ≥2 times more frequently than in placebo arms, included rhinorrhea, nasal congestion, herpes zoster, rash, conjunctivitis, and C-reactive protein increased.

This safety database is adequate to assess the safety of mepolizumab in COPD. The safety findings should be factored in to the risk-benefit assessment of mepolizumab treatment in patients with COPD guided by blood eosinophils.

8. Postmarket Experience

8.1. Postmarket Surveillance and Epidemiology Data

The postmarketing safety of mepolizumab has been assessed in three separate reviews by the Division of Pharmacovigilance I (DPV-I) in the Office of Surveillance and Epidemiology (OSE).

On October 10, 2017, DPV-I completed a Postmarket Drug Surveillance Summary (Surveillance Summary), which summarized the postmarket safety of mepolizumab from November 4, 2015 (U.S. approval date) to July 31, 2017. The purpose of the Surveillance Summary was to identify new serious adverse events, known adverse events reported in unusual number or associated with an increase in severity, or other new potential safety issues. DPV-I reviewed information retrieved from the following data sources: the FDA Adverse Event Reporting System (FAERS) database, a disproportionality analysis of the FAERS data using Empirica Signal, the medical literature, pre-approval clinical data, and periodic safety reports. DPV-I did not identify any new safety signals with mepolizumab after review of the data sources mentioned above. DPV-I identified 44 unique reports of herpes zoster in the FAERS database from November 4, 2015 to July 31, 2017; however, the signal of herpes zoster was identified in the original clinical trials for mepolizumab and is already included in the mepolizumab product labeling. DPV-I recommended close monitoring of the signal of herpes zoster.[i]

On December 15, 2017, in accordance with the FDA Amendments Act (FDAAA) and Pediatric Research Equity Act (PREA), DPV-I completed a Pediatric Postmarketing Pharmacovigilance Review for mepolizumab. DPV-I evaluated all pediatric adverse event reports with mepolizumab in the FAERS database from November 4, 2015 (U.S. approval date) to July 31, 2017. No new safety signals were identified with mepolizumab in pediatric patients after review of the cases. DPV-I recommended to continue routine postmarketing surveillance of all adverse events with the use of mepolizumab.[ii]

Most recently, on July 12, 2018, DPV-I evaluated available postmarketing data in the FAERS database and medical literature for an association between the potential safety signals of acute pancreatitis, supraventricular tachyarrhythmias, gastrointestinal hemorrhage, and embolic and thrombotic events with mepolizumab use from November 4, 2015 (U.S. approval date) to April 4, 2018. This review was prompted by exploratory safety analyses of any dose of mepolizumab versus placebo in the COPD population (see Section 6.14) that identified imbalances in the proportion of subjects experiencing serious adverse events and adverse events classified as supraventricular tachyarrhythmia, cardiovascular thrombotic events, gastrointestinal bleeding, and acute pancreatitis. The search of the FAERS database identified 36 cases of acute pancreatitis (n=4), supraventricular tachyarrhythmias (n=7), gastrointestinal hemorrhage (n=6), and embolic and thrombotic events (n=19) associated with mepolizumab use. A search of the

[i] Logan, J. Postmarket Drug Surveillance Summary for mepolizumab. October 10, 2017.
[ii] Logan, J. Pediatric Postmarketing Pharmacovigilance Review for mepolizumab. December 15, 2017.

medical literature identified zero cases. No postmarketing safety signals were identified after review of the limited number of cases identified in the FAERS database because the cases lacked sufficient information to determine the contribution of mepolizumab to the event. DPV-I recommended to continue routine pharmacovigilance monitoring for mepolizumab.[iii]

[iii] Kalra, D. Pharmacovigilance Memo for acute pancreatitis, supraventricular tachyarrhythmias, gastrointestinal hemorrhage, and embolic and thrombotic adverse events with mepolizumab. June 12, 2018.

9. Appendices

9.1. Reference List

1. AstraZeneca. Update on TERRANOVA Phase III trial for Fasenra in chronic obstructive pulmonary disease. 2018.
2. AstraZeneca. AstraZeneca provides update on GALATHEA Phase III trial for Fasenra in chronic obstructive pulmonary disease. 2018.
3. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. Am J Respir Crit Care Med 2017;195:557-82.
4. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS, Committee GS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med 2001;163:1256-76.
5. Wheaton AG, Cunningham TJ, Ford ES, Croft JB, Centers for Disease C, Prevention. Employment and activity limitations among adults with chronic obstructive pulmonary disease--United States, 2013. MMWR Morb Mortal Wkly Rep 2015;64:289-95.
6. Statistics NCfH. Health, United States, 2015: With Special Feature on Racial and Ethnic Health Disparities. Hyattsville (MD)2016.
7. Wheaton AG, Ford ES, Thompson WW, Greenlund KJ, Presley-Cantrell LR, Croft JB. Pulmonary function, chronic respiratory symptoms, and health-related quality of life among adults in the United States--National Health and Nutrition Examination Survey 2007-2010. BMC Public Health 2013;13:854.
8. Greenlund KJ, Liu Y, Deokar AJ, Wheaton AG, Croft JB. Association of Chronic Obstructive Pulmonary Disease With Increased Confusion or Memory Loss and Functional Limitations Among Adults in 21 States, 2011 Behavioral Risk Factor Surveillance System. Prev Chronic Dis 2016;13:E02.
9. DiBonaventura M, Paulose-Ram R, Su J, et al. The impact of COPD on quality of life, productivity loss, and resource use among the elderly United States workforce. COPD 2012;9:46-57.
10. Qaseem A, Wilt TJ, Weinberger SE, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med 2011;155:179-91.
11. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987;106:196-204.
12. Celli BR, Barnes PJ. Exacerbations of chronic obstructive pulmonary disease. Eur Respir J 2007;29:1224-38.
13. 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.

14. 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.
15. 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.
16. 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.
17. Ronchi MC, Piragino C, Rosi E, Amendola M, Duranti R, Scano G. Role of sputum differential cell count in detecting airway inflammation in patients with chronic bronchial asthma or COPD. Thorax 1996;51:1000-4.
18. Chanez P, Vignola AM, O'Shaugnessy T, et al. Corticosteroid reversibility in COPD is related to features of asthma. Am J Respir Crit Care Med 1997;155:1529-34.
19. Keatings VM, Jatakanon A, Worsdell YM, Barnes PJ. Effects of inhaled and oral glucocorticoids on inflammatory indices in asthma and COPD. Am J Respir Crit Care Med 1997;155:542-8.
20. Singh D, Kolsum U, Brightling CE, et al. Eosinophilic inflammation in COPD: prevalence and clinical characteristics. Eur Respir J 2014;44:1697-700.
21. Bafadhel M, McKenna S, Terry S, et al. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. Am J Respir Crit Care Med 2011;184:662-71.
22. Vedel-Krogh S, Nielsen SF, Lange P, Vestbo J, Nordestgaard BG. Blood Eosinophils and Exacerbations in Chronic Obstructive Pulmonary Disease. The Copenhagen General Population Study. Am J Respir Crit Care Med 2016;193:965-74.
23. Siddiqui SH, Guasconi A, Vestbo J, et al. Blood Eosinophils: A Biomarker of Response to Extrafine Beclomethasone/Formoterol in Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 2015;192:523-5.
24. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. 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;3:435-42.
25. Pavord ID, Lettis S, Locantore N, et al. Blood eosinophils and inhaled corticosteroid/long-acting beta-2 agonist efficacy in COPD. Thorax 2016;71:118-25.
26. Bafadhel M, McKenna S, Terry S, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. Am J Respir Crit Care Med 2012;186:48-55.
27. Barnes NC, Sharma R, Lettis S, Calverley PM. Blood eosinophils as a marker of response to inhaled corticosteroids in COPD. Eur Respir J 2016;47:1374-82.
28. 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.
29. Brightling CE, Bleecker ER, Panettieri RA, Jr., et al. Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study. Lancet Respir Med 2014;2:891-901.

30. Denburg JA, Silver JE, Abrams JS. Interleukin-5 is a human basophilopoietin: induction of histamine content and basophilic differentiation of HL-60 cells and of peripheral blood basophil-eosinophil progenitors. Blood 1991;77:1462-8.
31. Bischoff SC, Brunner T, De Weck AL, Dahinden CA. Interleukin 5 modifies histamine release and leukotriene generation by human basophils in response to diverse agonists. J Exp Med 1990;172:1577-82.
32. Takatsu K. Interleukin-5 and IL-5 receptor in health and diseases. Proc Jpn Acad Ser B Phys Biol Sci 2011;87:463-85.
33. Purkerson JM, Isakson PC. Interleukin 5 (IL-5) provides a signal that is required in addition to IL-4 for isotype switching to immunoglobulin (Ig) G1 and IgE. J Exp Med 1992;175:973-82.
34. Ball P. Epidemiology and treatment of chronic bronchitis and its exacerbations. Chest 1995;108:43S-52S.
35. Sunyer J, Saez M, Murillo C, Castellsague J, Martinez F, Anto JM. Air pollution and emergency room admissions for chronic obstructive pulmonary disease: a 5-year study. Am J Epidemiol 1993;137:701-5.
36. Connors AF, Jr., Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). Am J Respir Crit Care Med 1996;154:959-67.
37. Soler N, Torres A, Ewig S, et al. Bronchial microbial patterns in severe exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. Am J Respir Crit Care Med 1998;157:1498-505.
38. Samoszuk M, Corwin M, Hazen SL. Effects of human mast cell tryptase and eosinophil granule proteins on the kinetics of blood clotting. Am J Hematol 2003;73:18-25.
39. Fredens K, Dahl R, Venge P. In vitro studies of the interaction between heparin and eosinophil cationic protein. Allergy 1991;46:27-9.
40. Fauci AS, Harley JB, Roberts WC, Ferrans VJ, Gralnick HR, Bjornson BH. NIH conference. The idiopathic hypereosinophilic syndrome. Clinical, pathophysiologic, and therapeutic considerations. Ann Intern Med 1982;97:78-92.
41. Venge P, Dahl R, Hallgren R. Enhancement of factor XII dependent reactions by eosinophil cationic protein. Thromb Res 1979;14:641-9.
42. Valent P, Baghestanian M, Bankl HC, et al. New aspects in thrombosis research: possible role of mast cells as profibrinolytic and antithrombotic cells. Thromb Haemost 2002;87:786-90.
43. Smith TF, Welch TR, Allen JB, Sondheimer JM. Cutaneous mastocytosis with bleeding: probable heparin effect. Cutis 1987;39:241-4.
44. Brunnee T, Reddigari SR, Shibayama Y, Kaplan AP, Silverberg M. Mast cell derived heparin activates the contact system: a link to kinin generation in allergic reactions. Clin Exp Allergy 1997;27:653-63.
45. Colman RW, Schmaier AH. Contact system: a vascular biology modulator with anticoagulant, profibrinolytic, antiadhesive, and proinflammatory attributes. Blood 1997;90:3819-43.
46. Jeziorska M, Salamonsen LA, Woolley DE. Mast cell and eosinophil distribution and activation in human endometrium throughout the menstrual cycle. Biol Reprod 1995;53:312-20.

47. Eng SS, DeFelice ML. The Role and Immunobiology of Eosinophils in the Respiratory System: a Comprehensive Review. Clin Rev Allergy Immunol 2016;50:140-58.
48. Lacy P. 28 days later: eosinophils stop viruses. Blood 2014;123:609-11.
49. Drake MG, Bivins-Smith ER, Proskocil BJ, et al. Human and Mouse Eosinophils Have Antiviral Activity against Parainfluenza Virus. Am J Respir Cell Mol Biol 2016;55:387-94.
50. Samarasinghe AE, Melo RC, Duan S, et al. Eosinophils Promote Antiviral Immunity in Mice Infected with Influenza A Virus. J Immunol 2017;198:3214-26.
51. Soukup JM, Becker S. Role of monocytes and eosinophils in human respiratory syncytial virus infection in vitro. Clin Immunol 2003;107:178-85.
52. Rosenberg HF, Domachowske JB. Eosinophils, eosinophil ribonucleases, and their role in host defense against respiratory virus pathogens. J Leukoc Biol 2001;70:691-8.
53. Phipps S, Lam CE, Mahalingam S, et al. Eosinophils contribute to innate antiviral immunity and promote clearance of respiratory syncytial virus. Blood 2007;110:1578-86.
54. Rosenberg HF, Dyer KD, Domachowske JB. Respiratory viruses and eosinophils: exploring the connections. Antiviral Res 2009;83:1-9.