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NUCALA® (mepolizumab) for Treatment of Patients with Chronic Obstructive Pulmonary Disease

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ADVISORY COMMITTEE BRIEFING MATERIALS

AVAILABLE FOR PUBLIC RELEASE

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ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
BLA	Biologics License Application
BMI	body mass index
CAT	COPD Assessment Test
CCI	Charlson Comorbidity Index
CDC	Centers for Disease Control and Prevention
CEC	Clinical Endpoint Committee
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COPD	chronic obstructive pulmonary disease
CVT	cardiac, vascular, and thromboembolic
ECG	electrocardiogram
eCRF	electronic case report form
ED	emergency department
EGPA	eosinophilic granulomatosis with polyangiitis
EU	European Union
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
HES	hypereosinophilic syndrome
HRQoL	health-related quality of life
ICS	inhaled corticosteroid(s)
ID_{90}	dose associated with 90% of the maximal inhibition effect
IgG	immunoglobulin G
IL-5	interleukin-5
IM	intramuscular
IV	intravenous
J2R	Jump to Reference
kg	kilogram
L	liter
LABA	long-acting beta agonist
LAMA	long-acting muscarinic antagonist
mAb	monoclonal antibody
MAR	missing at random
MCID	minimum clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
m	meter
mg	milligram
mITT	modified Intent-to-Treat
mL	millilitre
mMRC	modified Medical Research Council
MMRM	mixed model repeated measures

NHANES	National Health and Nutrition Examination Survey
OR	odds ratio
PCI	potential clinical importance
PD	pharmacodynamic
PK	pharmacokinetic
PT	Preferred Term
QTc	corrected QT interval
QTc(F)	corrected QT interval using Fridericia's formula
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SGRQ	St. George's Respiratory Questionnaire
SMQ	standard MedDRA query
SoC	standard of care
SOC	System Organ Class
µL	microliters
US	United States
yr	year

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EXECUTIVE SUMMARY

Background: Mepolizumab (SB-240563) is a humanized monoclonal antibody (immunoglobulin G [IgG1], kappa, monoclonal antibody [mAb]) that has been developed as an add-on maintenance treatment for COPD. The proposed indication under discussion with the agency is:

> *NUCALA® (mepolizumab) is indicated as add-on treatment to inhaled corticosteroid (ICS)-based maintenance treatment for the reduction of exacerbations in patients with chronic obstructive pulmonary disease (COPD) guided by blood eosinophil counts.*

Mepolizumab has been approved in the United States (US), European Union (EU), and in over 20 other markets, as an add-on maintenance treatment for patients with severe eosinophilic asthma and in the US and Japan as add-on maintenance treatment for patients with eosinophilic granulomatosis with polyangiitis (EGPA).

Mepolizumab binds with high specificity and affinity to human interleukin-5 (IL-5), the key cytokine responsible for regulation of blood and tissue eosinophils. By neutralizing IL-5, mepolizumab results in a reduction of eosinophil levels.

While COPD is generally viewed as a disease driven by neutrophilic inflammation, up to 40% of patients with COPD have an inflammatory pattern that includes elevated sputum eosinophils [Brightling, 2000; Brightling, 2005; Saha, 2006] and blood eosinophils [Bafadhel, 2012b]. Increased eosinophilic inflammation in COPD has been associated with increased risk of exacerbations [Vedel-Krogh, 2016] and control of eosinophilic airway inflammation has been shown to reduce COPD exacerbations [Siva, 2007; Bafadhel, 2012a].

Intended Population: The majority of patients with COPD can be managed by following the recommended treatment guidelines [GOLD, 2017]. Maximal therapy for patients with COPD, and specifically those symptomatic and at high risk for exacerbations (i.e., GOLD Group D), is a fixed combination inhaled corticosteroid (ICS)/long-acting beta agonist (LABA) and long-acting muscarinic antagonist (LAMA) [GOLD, 2017]; often termed 'triple therapy'. While inhaled triple therapy is effective and has been shown to reduce exacerbations by 15-25% compared with dual therapies [Vestbo, 2017; Singh, 2016; Lipson, 2017; Lipson, 2018], approximately 30-40% of patients still continue to experience exacerbations [Vestbo, 2017; Müllerova, 2017].

The intended population for mepolizumab treatment includes patients with severe COPD who continue to exacerbate despite optimized standard of care (SoC) consisting of high-dose inhaled corticosteroid (ICS)-based triple therapy, and an eosinophilic phenotype. Compared with the general (non-mepolizumab eligible) COPD population, this subgroup of patients is at risk for poor outcomes with a 2.3-fold greater risk of either a moderate or severe exacerbation and 26% greater risk of death [GSK Data on File: RF/NLA/0106/17(1)]. Due to limited or no further treatment options for this disease severity, there remains a high unmet need to develop and provide new medications for these patients.

Clinical Development Program: The mepolizumab COPD clinical development program consisted of two randomized, double-blind, parallel-group, placebo-controlled Phase III studies (MEA117106 and MEA117113; hereafter referred to as Study 106 and Study 113) that evaluated the efficacy (exacerbation reduction) and safety of subcutaneous (SC) administration of mepolizumab 100 mg (both studies; currently approved dose for severe eosinophilic asthma) and 300 mg (Study 113 only) every 4 weeks compared with placebo in patients with COPD. Patients enrolled in these studies were required to have a history of ≥2 moderate exacerbations (requiring treatment with systemic corticosteroids and/or antibiotics) or 1 severe exacerbation (requiring hospitalization) in the year prior despite the regular use of optimized SoC COPD medication. In both studies, all patients continued their SoC ICS-based inhaled triple therapy regardless of randomization group. The entry criteria utilized in the mepolizumab COPD program were consistent with international guidelines for the diagnosis of COPD [Celli, 2004], were implemented by investigators with expertise in COPD management, and were similar to those utilized in other COPD clinical development programs.

Blood eosinophil levels have been identified as a predictor of response directly related to the mechanism of action of mepolizumab in patients with severe asthma. Given the similar inflammatory patterns between severe asthma and severe COPD [Bafadhel, 2012a], the blood eosinophil thresholds established in the severe asthma program (≥150 cells/μL at screening or ≥300 cells/μL in prior 12 months) were applied to the mepolizumab COPD program. For the COPD studies, all patients in Study 113 were required to have a blood eosinophil count ≥150 cells/μL at screening or ≥300 cells/μL in the prior year (same threshold as severe asthma). In Study 106, recruitment was not restricted by blood eosinophil threshold and randomization was stratified with patients being assigned to a stratum according to the following:

- High Stratum: Blood eosinophil count ≥150 cells/μL at screening OR a historic blood eosinophil count in the preceding 12 months ≥300 cells/μL (i.e., same population as included in Study 113)
- Low Stratum: Blood eosinophil count <150 cells/μL at screening AND no evidence of a blood eosinophil count ≥300 cells/μL in the preceding 12 months

The primary treatment comparison for efficacy endpoints was for patients in the Study 106 High Stratum and all patients in Study 113 (intended population). Key efficacy endpoints included rate of moderate/severe exacerbation (primary endpoint), time to first moderate/severe exacerbation, frequency of exacerbations requiring emergency department (ED) visit and/or hospitalization, change from baseline in mean St. George's Respiratory Questionnaire (SGRQ) Total Score, and change from baseline in mean COPD Assessment Test (CAT) score (secondary endpoints). Within each individual study, a hierarchical approach was used for strong control of the type I error in adjusting for multiplicity across primary and secondary endpoints (adjusted p-values).

Key safety endpoints included the incidence of adverse events (AEs), immunogenicity, and clinical laboratory and electrocardiogram (ECG) measures.

Pre-specified meta-analyses of data from Studies 106 and 113 were conducted for efficacy and safety endpoints.

Study Population Results: The population enrolled in the two COPD studies was representative of the intended population. The majority of patients were White (81%) and male (64%), the mean age was approximately 65 years. Patients from the US comprised 11% of the total population.

Patients had a diagnosis of COPD for a mean of 9 years and a substantial smoking history (mean 45 pack-years). Despite treatment with optimized SoC, patients were poorly controlled with a mean of 2.6 moderate/severe exacerbations in the prior year with 33% of patients requiring hospitalization for an exacerbation. The study population had significantly compromised lung function: 64% of patients were classified as severe or very severe based on airflow limitation per Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines; mean post-bronchodilator forced expiratory volume in one second (FEV_1) was approximately 1.2 liters or 45% predicted; mean reversibility was approximately 9.5%; and 12% of patients required long-term oxygen therapy. While not a specific inclusion criterion, nearly all patients (95%) met the current criteria for GOLD Group D based on their exacerbation history and increased symptoms. The population also had high burden of disease based on Modified Medical Research Council (mMRC), SGRQ, and CAT scores, and significant co-morbidities.

Efficacy Results: The addition of mepolizumab 100 mg SC to SoC demonstrated a consistent and clinically relevant reduction in the rate of moderate/severe exacerbations compared with placebo in the intended population: 18% in the Study 106 High Stratum (unadjusted p 0.029; adjusted p 0.036) and 20% in Study 113 (unadjusted p 0.034; adjusted p 0.068). In the pre-specified meta-analysis of Study 106 High Stratum and Study 113, mepolizumab resulted in an 18% reduction in the rate of moderate/severe exacerbations compared with placebo (p 0.006). An 18-20% reduction in the rate of moderate/severe exacerbations in a population with severe disease already receiving inhaled triple therapy, which also acts to lower exacerbation rate, is clinically important for this subgroup of COPD patients [Chapman, 2013].

In Study 113, a 14% reduction in the rate of moderate/severe exacerbations was observed between mepolizumab 300 mg and placebo (unadjusted p 0.140; adjusted p 0.140) indicating no additional benefit in rate reduction with the higher dose of 300 mg compared with 100 mg.

The decrease in rate of exacerbations with mepolizumab 100 mg was supported by an increase in the time to first moderate/severe exacerbation in both studies. Compared with placebo, the risk of having a first moderate/severe exacerbation at any time during the study with mepolizumab 100 mg was 25% lower in the Study 106 High Stratum (adjusted p 0.036), 18% lower in Study 113 (adjusted p 0.140), and 20% lower in the meta-analysis (p 0.006).

Mepolizumab 100 mg showed a reduction in rate of exacerbations leading to ED visit/ hospitalization compared with placebo in Study 113, but not in Study 106 High Stratum. Since these events are less frequent, the pre-planned meta-analysis across both studies

provides a more reliable estimate of the effect of mepolizumab; this showed a numerical reduction of 15% (rate ratio 0.85; 95% CI: 0.61, 1.18).

Patients in the Study 106 Low Stratum (eosinophils <150 cells/μL at screening and no history of ≥300 cells/μL) had no treatment response (exacerbation reduction) with mepolizumab, showing that the treatment response in the COPD population is related to having an eosinophilic phenotype. Further, a pre-specified subgroup analysis of the primary endpoint showed that mepolizumab treatment response increased with increasing blood eosinophil count.

Health-related quality of life (HRQoL) measures in the intended population were generally supportive and showed treatment with mepolizumab 100 mg resulted in a numerically higher proportion of SGRQ and CAT responders (patients who had a score reduction from baseline of at least the minimum clinically important difference [MCID] of 4 or 2 points, respectively) than placebo at all time points. Across both studies and in the meta-analysis, numerically greater improvements from baseline were observed for mepolizumab 100 mg compared with placebo at all time points for mean CAT Score and at all time points, except for Week 52 in the Study 106 High Stratum, for mean SGRQ Total Score.

Safety Results: The safety profile of mepolizumab has previously been well-characterized in patients with severe asthma. No new safety concerns with mepolizumab were identified in the COPD population. In the two Phase III COPD studies in patients with severe COPD, the safety profile of mepolizumab 100 mg and 300 mg administered SC every 4 weeks for up to 52 weeks was similar to placebo. The safety profile of the 300 mg dose was similar to the 100 mg dose.

The overall incidences of adverse events (AEs), serious adverse events (SAEs), deaths, and AEs leading to discontinuation of study treatment were similar for mepolizumab and placebo.

The profile of adverse events of special interest (i.e., systemic [hypersensitivity/ non-allergic] reactions, local injection site reactions, infections, malignancies, and cardiovascular events) was comparable with placebo. The incidence of anti-drug antibodies (ADA) with SC administration was 4% for mepolizumab 100 mg compared with <1% for placebo. No patients treated with mepolizumab had detectable neutralizing antibodies post-baseline. There were no treatment-related trends on review of vital signs, clinical laboratory tests, or corrected QT (QTc) interval.

Benefit/Risk: The efficacy and safety data provide evidence of efficacy, a safety profile similar to placebo, and an overall positive benefit to risk profile for mepolizumab 100 mg for patients with COPD and an eosinophilic phenotype who remain symptomatic and continue to have exacerbations despite triple therapy with an ICS + LABA + LAMA. Based on the limitations associated with current therapeutic treatment options, and the significant morbidity experienced by patients with severe COPD, there is an urgent medical need for additional therapeutic options. GlaxoSmithKline (GSK) believes mepolizumab would provide a therapeutic advance for this population with refractory symptoms and exacerbations on optimized therapy.

1. INTRODUCTION

Mepolizumab (SB-240563) is a humanized anti-interleukin 5 (IL-5) monoclonal antibody (IgG1, kappa, mAb) that has been developed as an add-on maintenance treatment for patients with severe chronic obstructive pulmonary disease (COPD) who are at risk of exacerbation despite inhaled triple therapy with an ICS + LABA + LAMA and who have an eosinophilic phenotype. Mepolizumab has been approved in the United States (US), European Union (EU), and over 20 other markets, as an add-on maintenance treatment for patients with severe eosinophilic asthma and in the US and Japan as add-on maintenance treatment for patients with eosinophilic granulomatosis with polyangiitis (EGPA).

Mepolizumab binds with high specificity and affinity to human IL-5, the key cytokine responsible for regulation of blood and tissue eosinophils. By neutralizing IL-5, mepolizumab results in a reduction of eosinophil levels that has been observed consistently across various eosinophil-mediated diseases (severe eosinophilic asthma, EGPA, hypereosinophilic syndrome [HES], nasal polyposis, eosinophilic esophagitis).

While COPD is generally viewed as a disease driven by neutrophilic inflammation, up to 40% of patients with COPD have an inflammatory pattern that includes elevated sputum eosinophils [Brightling, 2000; Brightling, 2005; Saha, 2006] and blood eosinophils [Bafadhel, 2012b]. Increased eosinophilic inflammation in COPD has been associated with increased risk of exacerbations [Vedel-Krogh, 2016] and control of eosinophilic airway inflammation has been shown to reduce COPD exacerbations [Siva, 2007; Bafadhel, 2012a]. These findings support a pathogenic role of eosinophils in COPD and provided a basis for exploring mepolizumab to reduce eosinophilic inflammation in this disease.

Exacerbations of COPD are generally thought to be heterogeneous in nature with respect to their inflammatory component. A study by Siva et al [Siva, 2007] showed that a treatment strategy aimed at minimizing eosinophilic inflammation (reducing sputum eosinophil counts <3%) in COPD was superior to guideline-based therapy in reducing severe exacerbations. Subsequent studies found that increased eosinophilic airway inflammation occurred during COPD exacerbations [Bafadhel, 2011] and that peripheral blood eosinophil levels can be used successfully as a surrogate to predict response to corticosteroid therapy [Bafadhel, 2012b, Pascoe, 2015, Pavord, 2016a]. A more recent study showed that blood eosinophil counts in COPD have been associated with increased risk of exacerbations [Yun, 2017]. These studies suggest that eosinophils are a useful predictor of response to tailor treatment and prevent exacerbations for patients with COPD and an eosinophilic phenotype defined by the level of eosinophils.

1.1. COPD and Unmet Medical Need

COPD is a chronic progressive disease with rising morbidity and mortality and is currently the fourth leading cause of death and the fifth leading cause of disability in the world [GOLD, 2017]. In the US, chronic lower respiratory tract diseases (primarily COPD) were the third leading cause of deaths according to Centers for Disease Control and Prevention (CDC) estimates for 2010 [Murphy, 2012]. COPD exacerbations place a

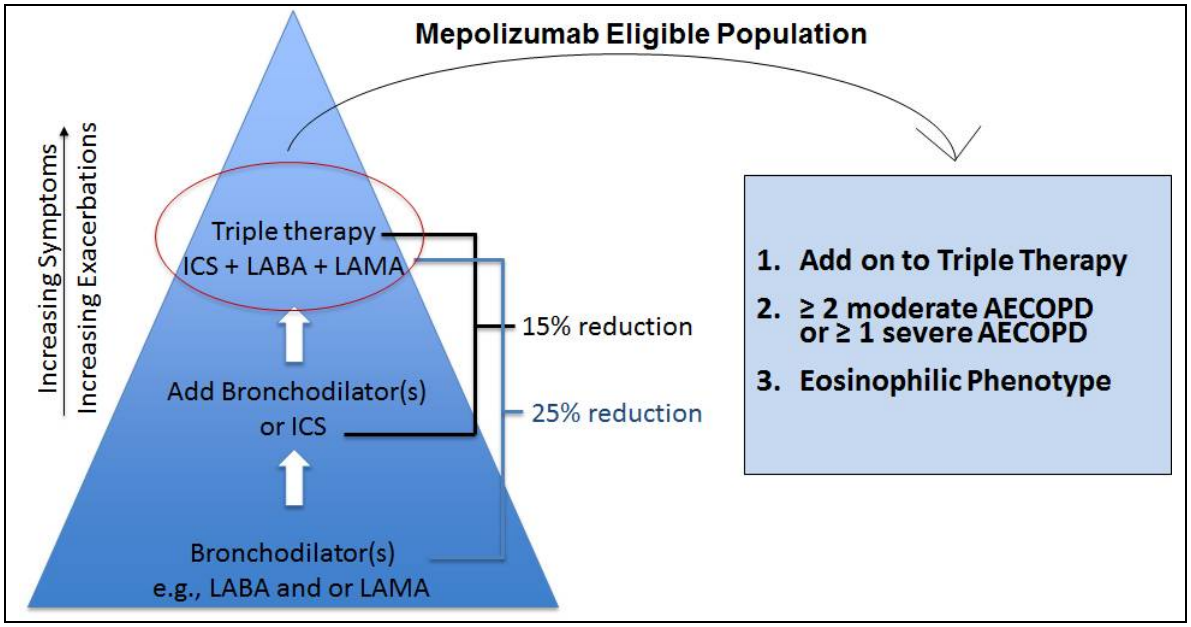
significant burden on the health care system requiring 14.3 million physician office visits and 739,000 hospitalizations annually in the US [NIH-NHLBI, 2012] and 50% to 75% of COPD costs are associated with exacerbations [Celli, 2004].

The disease course of COPD is marked by progressive deterioration in airflow and is punctuated by exacerbations that contribute to the overall disease severity and increase in frequency and severity as disease worsens [Miravitlles, 1999; Hurst, 2010]. COPD exacerbations are characterized by periods of acute worsening of symptoms (breathlessness, chronic cough, sputum production), deterioration in lung function, and decreased health-related quality of life (HRQoL) [Seemungal, 1998; Connors, 1996; Donaldson, 2002]. COPD exacerbations are associated with prolonged detrimental impact on perception of HRQoL, aggravation of co-morbidities, increased mortality, and potentially contribute to further permanent decrements in lung function [Connors, 1996; GOLD, 2017; Vogelmeier, 2017; Dransfield, 2017]. One of the best predictors of future exacerbations is having a history of a previous exacerbation [Hurst, 2010]. A subsequent exacerbation experienced before a previous exacerbation resolves may lead to permanent impairment in health status and increased mortality with increasing number of exacerbations [Soler-Cataluña, 2005; Celli, 2012]. Once a patient with COPD becomes a frequent exacerbating phenotype, each exacerbation event contributes to an accelerated negative health trajectory that can ultimately lead to an increased risk of death. Thus, prevention and treatment of exacerbations is a predominant focus of COPD management [Connors, 1996; GOLD, 2017].

COPD treatment strategy recommends an incremental approach to pharmacological treatment as the disease state progresses, involving the use of combinations of drug classes with different or complementary mechanisms of action to improve airflow obstruction and reduce exacerbation risk [Celli, 2004; GOLD, 2017; van Noord, 2005; van Noord, 2006; Tashkin, 2008]. The majority of patients with COPD can be managed by following the recommended treatment guidelines which are based on an assessment of airflow limitation, symptoms, and exacerbation history [GOLD, 2017]. Maximal therapy for patients with COPD, and specifically those symptomatic and at high risk for exacerbations (i.e., GOLD Group D), is a fixed combination inhaled corticosteroid (ICS)/long-acting beta agonist (LABA) and long-acting muscarinic antagonist (LAMA) [GOLD, 2017]. The use of these medications is often termed 'triple therapy'.

While inhaled triple therapy is effective and has been shown to reduce exacerbations by 15-25% compared with dual therapies [Vestbo, 2017; Singh, 2016; Lipson, 2017; Lipson, 2018]), approximately 30-40% of patients still continue to experience exacerbations [Vestbo, 2017; Müllerova, 2017]. At this disease stage, these patients have limited or no additional treatment options beyond inhaled triple therapy and these patients form the intended population for mepolizumab (Figure 1). Three key factors identify a patient eligible for mepolizumab treatment: 1) patients receiving inhaled high-dose ICS-based triple therapy, 2) history of exacerbations despite this best SoC, and 3) eosinophilic phenotype that contributes to the patient's chronic exacerbation profile.

Figure 1 Effectiveness of Current COPD Treatments in Reducing Exacerbations and Remaining Unmet Need



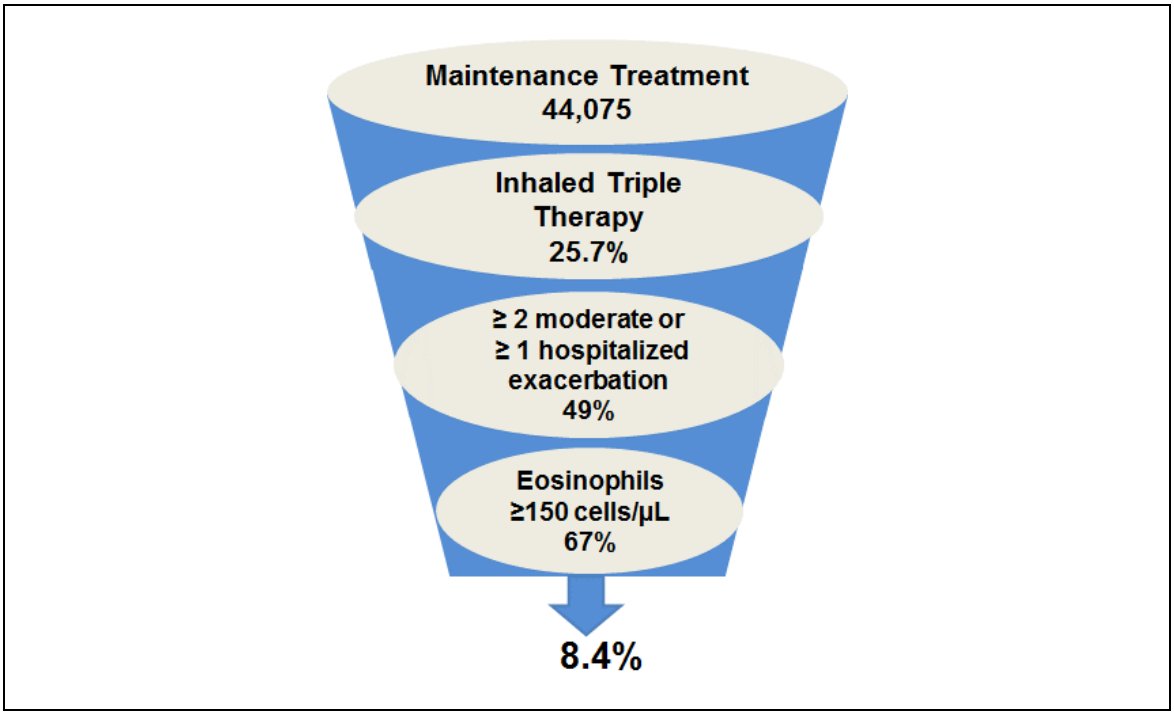
AECOPD = acute exacerbation of COPD; ICS= inhaled corticosteroid; LABA = long-acting beta$_2$ agonist; LAMA = long-acting muscarinic antagonist

Triangle figure adapted from GOLD, 2017

Source for annual rate reduction of exacerbations: Lipson, IMPACT Study, *N Engl J Med*, 2018

Based on a large claims database of patients in the US receiving maintenance treatment for COPD, the potential eligible population for mepolizumab (i.e., those patients that meet the three key eligibility factors) is a small subset and represents only 8.4% of the total treated COPD population (Figure 2).

Figure 2 **Mepolizumab: Stratifying Treatment to a Small, Identifiable US COPD Sub-Population**



Source: GSK Data on File: 2018N364677_00
Note: COPD population was limited to patients with at least one eosinophil value and the following study inclusion criteria: ≥1 claim for COPD, ≥40 years of age, continuous enrollment for 12 months, and ≥1 dispensing/encounter of any inhaled maintenance therapy

A study examining the medical records from over 45,000 patients being treated for COPD showed that the intended mepolizumab population is at risk for poor outcomes with a 2.3-fold higher risk of either a moderate or severe exacerbation and a 26% increased risk of death from all cause compared with the general (non-mepolizumab eligible) COPD population [GSK Data on File: RF/NLA/0106/17(1)]. The intended mepolizumab population has significant burden of disease from severe COPD (e.g., breathlessness, activity limitation, fatigue, cough, sputum production, sleep disturbances) and other co-morbidities (e.g., hypertension, hypercholesterolemia, diabetes mellitus, cardiac disease, osteoporosis, depression/anxiety). Due to lack of treatment options at this advanced state, there remains a high unmet need to develop and provide new medications for these patients.

Mepolizumab addresses the need for a specific, effective, and well-tolerated treatment in the chronic management of patients with severe COPD and an eosinophilic phenotype who continue to be at risk of exacerbation despite receiving treatment with inhaled triple therapy. The effect of mepolizumab on exacerbation reduction and time to first exacerbation, as shown in the Phase III studies (Section 4.2), are clinically meaningful and considered beneficial outcomes for these patients.

1.2. Proposed Indication and Dosage

The following is the proposed indication for mepolizumab in COPD that was submitted to the Food and Drug Administration (FDA) as a framework for discussion:

> *NUCALA® (mepolizumab) is indicated as add-on treatment to inhaled corticosteroid (ICS)-based maintenance treatment for the reduction of exacerbations in patients with chronic obstructive pulmonary disease (COPD) guided by blood eosinophil counts.*

The recommended dosage is 100 mg administered once every 4 weeks by subcutaneous (SC) injection into the upper arm, thigh, or abdomen.

The indication statement for mepolizumab as add-on to ICS-based maintenance therapy is to include those GOLD D patients that may be eligible for mepolizumab but not taking inhaled triple therapy because they are unable to tolerate a LABA or a LAMA.

1.3. Regulatory History

Mepolizumab has been approved as add-on maintenance treatment of patients with severe eosinophilic asthma in the US, in the EU, and in over 20 other markets. In the US, NUCALA (mepolizumab) was approved on 4 November 2015 (Biologics License Application [BLA] 125526). Global submissions and reviews of marketing authorizations continue in other countries for severe eosinophilic asthma. NUCALA was also approved in the US on 12 December 2017 and in Japan on 25 May 2018 for the treatment of adult patients with EGPA.

During the End of Phase 2 meeting for COPD held on 28 August 2013, GSK and the FDA discussed and agreed the following approaches: 1) how to evaluate the effect of mepolizumab in patients with COPD with and without an eosinophilic phenotype, 2) specifying patient selection criteria, and 3) dose selection. Additionally, GSK and FDA discussed individual COPD study designs and the overall design of the registrational program.

At the 1 August 2017 pre-BLA submission meeting, FDA agreed that the clinical data were sufficient to support submission of a supplemental BLA. Review issues discussed included evaluation of peripheral blood eosinophil levels as a predictor of response, confirmation of dose, and characterization of the patient population in the indication statement.

The supplemental BLA (S-007) was submitted on 7 November 2017 with a proposed indication for patients with COPD receiving ICS-based maintenance therapy whose blood eosinophil levels meet pre-specified criteria associated with benefit. The 120 Day Safety Update (BLA S-101) was submitted on 2 March 2018 and provided additional safety information from mepolizumab clinical studies in progress (no COPD studies were ongoing) that was consistent with data included in BLA S-007; no new safety concerns were identified and the safety profile remains favorable for the treatment of patients with COPD.

2. COPD CLINICAL DEVELOPMENT PROGRAM

2.1. Study Designs

The mepolizumab COPD clinical development program consisted of two Phase III trials designed to: 1) characterize the efficacy (exacerbation reduction) and safety of mepolizumab, 2) test the utility of using blood eosinophils as a predictive biomarker in COPD, 3) inform on the appropriate dose, and 4) evaluate changes in other endpoints including HRQoL.

Studies MEA117106 and MEA117113 (hereafter referred to as Study 106 and Study 113) were 52-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter studies that evaluated the effect of SC administration of mepolizumab every 4 weeks (Figure 3) on the frequency of moderate/severe exacerbations in patients with a history of COPD exacerbations despite the regular use of optimized SoC COPD medication (ICS-based triple therapy). In both studies, all patients continued their SoC medication for the duration of the study regardless of randomization group.

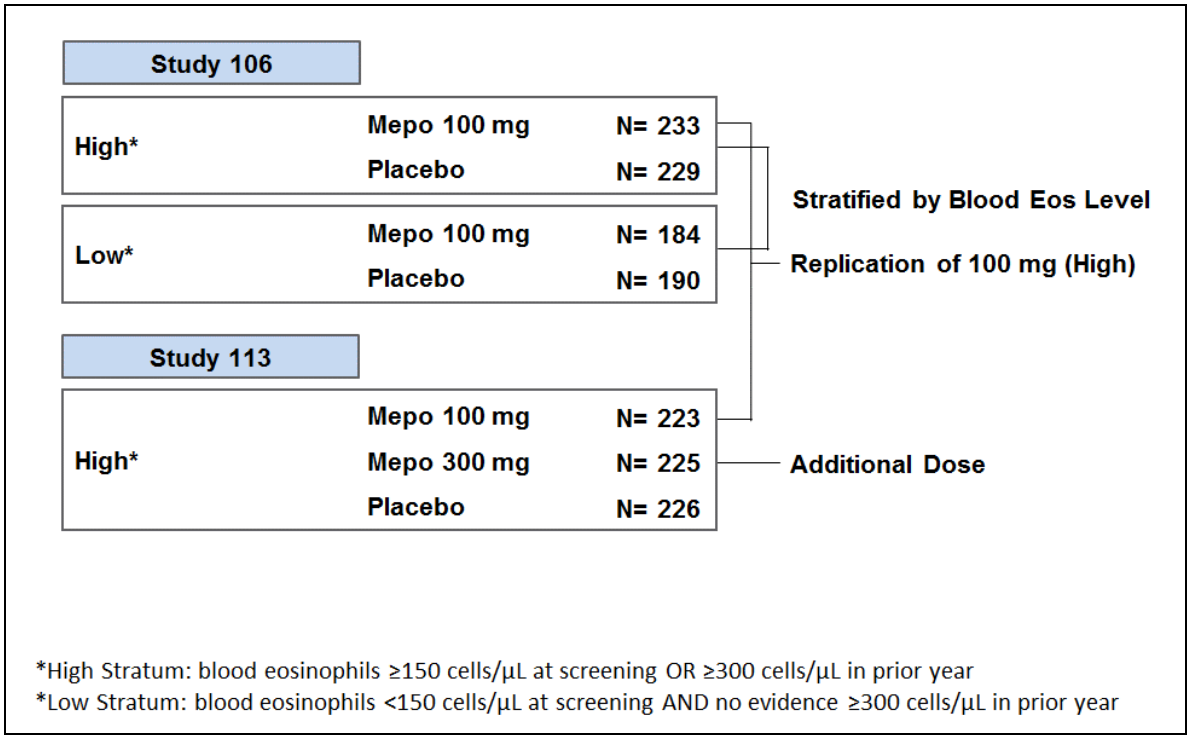
Study 106 was specifically designed to test the utility of blood eosinophils to predict response to mepolizumab. In the severe asthma program, blood eosinophil levels were identified as the best predictor of response (reduction in the frequency of exacerbations) to mepolizumab therapy directly related to the mechanism of action [Pavord, 2012; Ortega, 2014]. Given the similar inflammatory patterns between severe asthma and severe COPD [Bafadhel, 2012a], the blood eosinophil thresholds established in the severe asthma program (≥150 cells/μL at screening or ≥300 cells/μL in prior year) were applied to the mepolizumab COPD program. Recruitment was not restricted by blood eosinophil threshold and randomization was stratified with patients being assigned to a stratum according to the following:

- **High Stratum**: Blood eosinophil count ≥150 cells/μL at screening OR a historic blood eosinophil count in the preceding 12 months ≥300 cells/μL (i.e., same threshold as severe asthma and same population as included in Study 113; this is the mepolizumab-intended population)
- **Low Stratum**: Blood eosinophil count <150 cells/μL at screening AND no evidence of a blood eosinophil count ≥300 cells/μL in the preceding 12 months

Patients in both strata received 100 mg SC since this was the optimal dose established in the severe asthma program and the inflammatory mediators are similar in severe asthma and severe COPD. This design enabled assessment of response to therapy above and below this threshold. Since the Low Stratum included patients with low eosinophilic inflammation, a treatment response was not anticipated in this group.

For Study 113, all patients were required to have a blood eosinophil count ≥150 cells/μL at screening or ≥300 cells/μL in the prior year (same threshold as severe asthma and same population as included in the Study 106 High Stratum). This study included two doses of mepolizumab, 100 mg SC and 300 mg SC, to explore the potential utility of a higher dose in COPD.

Figure 3 Mepolizumab COPD 52-Week Phase III Study Designs



The total duration of patient participation in each study was approximately 62 weeks, consisting of a 1- to 2-week run-in period, 52-week treatment period, and an 8-week follow-up period. Patients who discontinued prematurely from study treatment (for any reason) were not required to withdraw from the study and every effort was made by the investigator/site staff to encourage the patient to remain in the study for continued collection of efficacy and safety data.

Key inclusion criteria for Studies 106 and 113 were:

- Male or female patients ≥40 years of age with a clinically documented history of COPD for at least 1 year
- Forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) <0.70 and FEV_1 >20% to ≤80% of predicted
- Current smoker or former smoker (≥10 pack years and no current diagnosis of asthma), or never/non-smoker (no history of asthma)
- Requirement for high-dose inhaled corticosteroid (ICS; fluticasone propionate 500 mcg or equivalent) plus LABA and LAMA (i.e., inhaled triple therapy)
- History of exacerbations (≥2 moderate or ≥1 severe exacerbation in the past 12 months). Moderate exacerbations required the use of systemic corticosteroids and/or antibiotics and severe exacerbations required hospitalization.

These study entry criteria were similar to the enrollment criteria used in other COPD development programs with the exception of allowing inclusion of patients who were

never/non-smokers. Based on a review of published literature, it is estimated that worldwide 25% to 45% of patients with COPD have never smoked and their disease is primarily due to biomass smoke exposure [Salvi, 2009]. The inclusion of never/non-smokers has not been conventionally used in other COPD programs; however, this subgroup of patients is an important and increasing contributor to the overall epidemiology of COPD. The requirements for all patients to be receiving inhaled triple therapy and to be refractory to this treatment is more restrictive than most COPD studies, ensuring enrollment of patients with the greatest need for additional reduction in exacerbation risk.

While there is substantial clinical overlap between patients with severe asthma and COPD, particularly in older patients with an equivocal smoking history, the mepolizumab COPD and severe asthma programs were specifically designed to target each representative population. The entry criteria utilized in the mepolizumab COPD program were consistent with international guidelines for the diagnosis of COPD [Celli, 2004], were implemented by investigators with expertise in COPD management, and were similar to those utilized in other COPD clinical development programs. The resultant enrollment was a COPD population similar to other COPD registration programs, and different from a severe asthma population.

2.2. Efficacy Endpoints and Statistical Analyses

2.2.1. Efficacy Endpoints

The pre-defined primary (intended) population for evaluation of mepolizumab efficacy was patients who had a blood eosinophil count ≥150 cells/μL at screening or ≥300 cells/μL in the prior year, i.e., the High Stratum in Study 106 and the total population in Study 113. Efficacy analyses were performed for the modified Intent-to-Treat (mITT) Population which consisted of all patients who were randomized and who received at least one dose of study treatment.

The key efficacy endpoints analyzed in the COPD clinical program are outlined in Table 1 and were identical between Studies 106 and 113.

Meta-analysis of Study 113 and the High Stratum from Study 106 was pre-specified. Results from meta-analysis of the two studies provide more precise estimates of the treatment effect of mepolizumab as they are based on a larger number of patients than the individual studies.

In addition to the endpoints presented in Table 1, pre-specified and selected post-hoc analyses were conducted on the primary and secondary endpoints by screening blood eosinophil levels, including modeling of the primary endpoint.

Table 1 Key Efficacy Endpoints in COPD Studies

Endpoint	Study 106	Study 113	Meta-analysis[1]
Exacerbations			
Rate of moderate/severe exacerbations	Primary	Primary	Primary
Time to first moderate/severe exacerbation	Secondary	Secondary	Secondary
Rate of exacerbations requiring ED visit and/or hospitalization	Secondary and meta-analysis	Secondary and meta-analysis	Secondary
Time to first exacerbation requiring ED visit and/or hospitalization	---	---	Meta-analysis only
Rate of severe exacerbations	Other and meta-analysis	Other and meta-analysis	Secondary
Time to first severe exacerbation	---	---	Meta-analysis only
Health-Related Quality of Life			
Change from baseline in mean SGRQ Total Score at Week 52[2]	Secondary	Secondary	Secondary
Proportion of SGRQ responders[2]	Other	Other	Secondary
Change from baseline in mean CAT score at Week 52	Secondary	Secondary	Secondary
CAT score responders	Post-hoc	Post-hoc	Post-hoc
Clinician- and patient-rated response to therapy	Other	Other	Other
Lung Function			
Change from baseline in pre-bronchodilator FEV_1	Other	Other	Other
Symptoms			
Occasions of rescue medication use	Other	Other	Other
Percentage of nights with no awakenings	Other	Other	Other
Blood Eosinophils			
Change from baseline in blood eosinophils	Other	Other	Other

1. Study 106 High Stratum + Study 113 (replicate treatment arms: mepolizumab 100 mg and placebo)
2. Measured using the COPD-specific SGRQ-C

Note: Other = tertiary endpoint

CAT = COPD Assessment Test; ED = emergency department; FEV_1 = forced expiratory volume in 1 second; SGRQ = St. George's Respiratory Questionnaire

2.2.2. Multiplicity

For Study 106, the primary analysis was a comparison of the rate of moderate/severe exacerbations between mepolizumab 100 mg and placebo in the High Stratum; this same analysis was also of interest using data from All Patients (High and Low Strata). For Study 113, the primary analysis was a comparison of the rate of moderate/ severe exacerbations between mepolizumab 100 mg and placebo and between mepolizumab 300 mg and placebo.

In Study 106, the overall α of 0.05 was split such that 0.04 was allocated to the primary treatment comparison for the group of patients with higher eosinophil levels (intended population) and the remaining 0.01 was allocated to the treatment comparison for all patients in the study. In Study 113, multiplicity across the two primary treatment comparisons (100 mg vs. placebo; 300 mg vs. placebo) was controlled using a one-sided (α 0.025) Hochberg testing procedure. Within each individual study, a hierarchical approach was used for strong control of the type I error in adjusting for multiplicity across the primary and secondary endpoints shown in Table 2 [Dmitrienko, 2008]. Adjusted p-values are p-values adjusted for both sources of multiplicity.

Table 2 Primary and Secondary Endpoints (COPD Studies 106 and 113)

Primary Endpoint
1. Frequency of moderate/severe exacerbations Study 106: Mepolizumab 100 mg SC (High Stratum) vs. Placebo Mepolizumab 100 mg SC (All Patients [High & Low Strata]) vs. Placebo Study 113: Mepolizumab 100 mg SC vs. Placebo Mepolizumab 300 mg SC vs. Placebo
Secondary Endpoints
2. Time to first moderate/severe COPD exacerbation
3. Frequency of exacerbations requiring ED visit and/or hospitalization
4. Change from baseline in mean SGRQ Total Score
5. Change from baseline in mean CAT score

2.2.3. Power Calculation

Since there were no previous clinical trials with mepolizumab in COPD, when Studies 106 and 113 were designed, it was anticipated that there would be a 35% reduction in the rate of moderate/severe exacerbations with mepolizumab compared with placebo. Sample size calculations based on this reduction estimated that the studies would have 90% power to observe statistical significance at the two-sided 4% level in the Study 106 High Stratum (100 mg vs. placebo) and at the 5% level for both comparisons (100 mg vs. placebo and 300 mg vs. placebo) in Study 113. The placebo exacerbation rate was predicted to be 2.0 per year since patients enrolled in the studies were required to have ≥2 moderate or ≥1 severe exacerbations in the previous 12 months.

2.2.4. COPD Exacerbations

The primary efficacy endpoint in both studies 106 and 113 was the rate of moderate/severe exacerbations. Moderate exacerbations were defined as COPD exacerbations that required treatment with systemic corticosteroids (intramuscular [IM], intravenous [IV], or oral) and/or antibiotics. Severe exacerbations were defined as COPD exacerbations that required in-patient hospitalization (i.e., ≥24 hours) or resulted in death.

Exacerbation rate was compared across treatment groups using a negative binomial model, including covariates for smoking status, number of exacerbations in the prior year, baseline percent predicted FEV_1, and geographic region with $\log_e$ (time) as an offset variable. Study was included a covariate in the meta-analysis of the 106 and 113 studies.

The COPD studies were designed to continue collecting exacerbation data for up to 52 weeks after randomization for patients who prematurely discontinued from study treatment and remained in the study. All exacerbation data collected for these patients was also included in the primary analysis for a treatment policy (*de facto*) estimand of

treatment effect. Any remaining missing data were considered missing at random (MAR). Sensitivity analyses to assumptions regarding missing data were performed using multiple imputation methods based on pattern mixture models.

The time to first moderate/severe exacerbation was analyzed using a Cox proportional hazards model with covariates as for the primary endpoint and Kaplan-Meier estimates of the cumulative proportion of patients with a moderate/severe exacerbation over time were produced. Exacerbations that resulted in an ED visit or hospitalization and severe exacerbations were analyzed using the same methods and covariates as for the primary endpoint.

2.2.5. Health-related Quality of Life Measures

Change from baseline in St. George's Respiratory Questionnaire (SGRQ) Total Score at Week 52 (measured using the COPD specific SGRQ-C) and change from baseline in COPD Assessment Test (CAT) Score at Week 52 were analyzed using mixed model repeated measures (MMRM) with visit fitted as a categorical variable and adjusting for covariates of baseline, geographic region (as defined for the study/integrated summary of efficacy), smoking status, treatment and visit, plus interaction terms for visit by baseline and visit by treatment group.

SGRQ Total Scores can range from 0 to 100; higher scores indicate a poorer health-related quality of life. For reference, the mean score for a healthy individual is 6 (range 5 to 7) [Jones, 2016]. CAT scores can range from 0 to 40; higher scores indicate greater COPD disease impact. Further details regarding CAT scoring are provided in Appendix Section 8.1. Score reductions for either instrument indicate improvement. The minimum clinically important difference (MCID) for SGRQ is a 4-point reduction from baseline and for CAT is a 2-point reduction from baseline.

Current regulatory guidance [FDA, 2009; FDA, 2016] recommends evaluation of responder analyses when investigating patient-reported outcomes. Use of responder analyses may be more appropriate in active comparator studies where an incremental gain would not be expected to be as great as the difference between an active therapy and placebo [Jones, 2014]. Use of responder analysis may be informative for these two studies where all patients were receiving ICS-based inhaled triple therapy. Thus, responder analyses were conducted using the validated MCIDs for SGRQ (pre-specified) and CAT (post-hoc) as the definition of response. The proportion of SGRQ responders (patients with ≥4-point reduction [improvement] from baseline) and proportion of CAT responders (patients with ≥2-point reduction [improvement] from baseline) were analyzed using a logistic regression model with covariates of baseline value, smoking status, and geographic region. SGRQ and CAT data continued to be collected for patients who prematurely discontinued from study treatment and continued in the study. Remaining missing data was classified as non-response. Nominal p-values provided for these endpoints were not adjusted for multiplicity.

Overall response to therapy was assessed separately by the investigator and the patient at 8 to 12-week intervals during the study using a 7-point rating scale ranging from 1 (significant improvement) to 7 (significant worsening). Patient- and clinician-rated

responses to therapy were analyzed using a proportional odds model. Nominal p-values provided for these endpoints were not adjusted for multiplicity.

2.2.6. Lung Function and Symptoms

Change from baseline in trough FEV_1, mean number of occasions of rescue medication use per day over 4-week intervals, and percentage of nights with no awakenings due to COPD symptoms were analyzed using MMRM.

2.3. Safety Endpoints and Assessment

For the assessment of mepolizumab safety in the COPD development program, safety data from all patients in Study 106 and Study 113 were pooled to compare the placebo arms with the mepolizumab 100 mg arms and mepolizumab All Doses (100 mg and 300 mg arms). Adverse events were coded and grouped by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). Safety analyses were performed on the Safety Population, defined as all patients who received at least one dose of study medication (equivalent to the mITT Population). The relative risks from the integrated COPD studies were evaluated using the Cochran-Mantel-Haenszel (CMH) method [Chuang-Stein, 2011].

2.3.1. Safety Endpoints

Key safety endpoints in the COPD program were:

- Incidence of adverse events (AEs) including systemic reactions (allergic/hypersensitivity reactions and non-allergic reactions) and local injection site reactions
- Mortality (all cause, respiratory, cardiovascular)
- Immunogenicity
- Hematological and clinical chemistry parameters
- Electrocardiogram (ECG) and vital signs measurements

2.3.2. Independent Data Monitoring Committee

An unblinded Independent Data Monitoring Committee (IDMC) was utilized to review unblinded data from Studies 106 and 113 instream. The IDMC reviewed AEs and serious adverse events (SAEs) from both studies for identification of any potential safety signals as well as the primary endpoint of exacerbations to determine whether the risk under consideration was outweighed by assessment of the overall benefits of therapy. No concerns were raised by the IDMC regarding the safety of mepolizumab in the COPD program.

2.3.3. Adjudication of Serious Adverse Event Reports

All SAE reports were adjudicated instream by a blinded independent Clinical Endpoint Committee (CEC). Adjudication was performed on the case/report as a whole; thus, the

case was adjudicated on the primary event (i.e., the event of the greatest medical significance, such as death, or hospitalization, or other reason for seriousness), not on every event comprising a case. The CEC categorized the primary cause of death or the primary cause of the non-fatal SAE into one of five categories: cardiovascular, respiratory, cancer, other, or unknown (inadequate information or indeterminate). Additionally, the CEC determined if deaths were associated with the patients' known COPD.

2.3.4. Adverse Events of Special Interest

Adverse events of special interest (AESI) across the mepolizumab clinical program are systemic reactions (allergic/hypersensitivity and non-allergic), local injection site reactions, infections, malignancies, and serious cardiac, vascular, and thromboembolic [CVT] events. Mepolizumab AESIs were prospectively identified in the severe asthma clinical program and remained AESIs throughout the COPD clinical program. These events were identified based on the theoretical impact of the pharmacologic properties and mechanism of action of mepolizumab. Serious CVT events were included as AESI since a numerical imbalance was observed in the dose-ranging Phase IIB/III severe asthma study that was not observed in the subsequent trials; however, it has remained an AESI across the mepolizumab clinical program.

Administration of a monoclonal antibody could be associated with systemic (allergic/hypersensitivity and non-allergic) reactions or local injection site reactions. Monoclonal antibodies may induce development of anti-drug antibodies; thus, immunogenicity has been assessed in the mepolizumab clinical development program.

Treatment with mepolizumab results in a decrease in eosinophils which is a component of innate immunity, thus, both infections and malignancies have been identified as events of special interest. Since patients in these development programs were taking high dose ICS and/or oral corticosteroids, potential opportunistic infections were also examined.

Systemic reactions and local injection site reactions were collected via targeted electronic case report form (eCRF). Events captured on the eCRF as systemic reactions were further categorized by the investigators as allergic/hypersensitivity reactions or non-allergic reactions. Investigators were asked to assess events they considered to represent systemic reactions against diagnostic criteria for anaphylaxis [Sampson, 2006].

AESIs of opportunistic infections, malignancies, and serious CVT events were identified from a list of relevant preferred terms maintained within a project-level reference dataset created based on the Medical Dictionary for Regulatory Activities (MedDRA) available at the time of creating the integrated data displays.

2.3.5. Pneumonia

While not an AESI for mepolizumab, pneumonia is of interest in the COPD population. Additionally, blood eosinophils less than 2% in patients receiving ICS have been reported to increase the risk of pneumonia [Pavord, 2016b]. AEs of pneumonia were identified from a list of relevant preferred terms that are maintained across GSK respiratory projects.

3. STUDY POPULATION

3.1. Demographics and Baseline Characteristics

Patients enrolled in the COPD studies were representative of the intended mepolizumab population described in Section 1.1.

3.1.1. Demographics

The COPD study population (all patients randomized and treated in Studies 106 and 113) was 64% male and the mean age was 65 years (Table 3). The majority of patients were White (81%) with smaller contingents of Asian (9%), American Indian (5%), multiple race (5%), and African Heritage (1%). Most patients of African Heritage (18/19 patients) were enrolled at US sites and these patients comprised 11% of the total US enrollment (18/167 patients) in the COPD studies. For reference, based on data from the National Health and Nutrition Examination Survey (NHANES), approximately 11% of patients with COPD are African American [Ford, 2013]. Patients of Hispanic/Latino ethnicity comprised 18% of the study population.

Table 3 Demographics (COPD Studies, mITT Population)

Demographic	Study 106 N=836	Study 113 N=674	Total N=1510
Gender, n (%)			
Female	316 (38)	228 (34)	544 (36)
Male	520 (62)	446 (66)	966 (64)
Age, yr			
Mean (SD)	65.4 (8.64)	65.1 (8.89)	65.3 (8.75)
Min, Max	39, 85	42, 88	39, 88
Age Group, n (%)			
40-64 yr	375[1] (45)	315 (47)	690 (46)
≥65 yr	461 (55)	359 (53)	820 (54)
Race, n (%)			
White	680 (81)	542 (80)	1222 (81)
Asian	7 (<1)	124 (18)	131 (9)
American Indian or Alaskan Native	69 (8)	0	69 (5)
Multiple Race	69 (8)	0	69 (5)
African Heritage/African American	11 (1)	8 (1)	19 (1)
US Sites			
Total US Patients	88 (11)	79 (12)	167 (11)
African American[2]	10 (11)	8 (10)	18 (11)
Ethnicity, n (%)			
Not Hispanic/Latino	665 (80)	567 (84)	1232 (82)
Hispanic/Latino	171 (20)	107 (16)	278 (18)
Body Mass Index, kg/m^2			
Mean (SD)	26.9 (5.7)	26.3 (5.5)	26.7 (5.6)
Min, Max	14.3, 60.1	15.7, 54.7	14.3, 60.1
Screening Blood Eosinophils, cells/μL			
Geometric mean (std logs)	265[3] (0.57)	229 (0.85)	---

1. One patient in Study 106 was 39 years old
2. Percentages based on denominator of total US patients
3. Value shown is for the High Stratum, n=462; value for All Patients (High + Low Stratum) = 140 cells/μL (0.95)

3.1.2. Baseline Characteristics

Patients enrolled in the Phase III COPD studies had a diagnosis of COPD for a mean of approximately 9 years and a strong smoking history (mean 45 pack-years) (Table 4). The subgroup of never/non-smokers represented only 4% of the overall mepolizumab COPD population.

Despite treatment with ICS-based triple therapy, patients enrolled in the two Phase III trials were poorly controlled with a mean of 2.6 moderate/severe exacerbations in the prior year with a third of the patients (33%) requiring hospitalization for an exacerbation. The study population had significantly compromised lung function: 64% of patients were classified as severe or very severe based on airflow limitation per GOLD guidelines, mean post-bronchodilator FEV_1 was approximately 1.2 liters and 45% predicted, mean reversibility was approximately 9.5%, and 12% of patients required long-term oxygen therapy. While not a specific inclusion criterion, nearly all patients (95%) met the criteria for GOLD Group D based on their exacerbation history and increased symptoms.

Besides the burden of COPD, 26% of patients had cardiac co-morbidities and 76% had other co-morbidities (e.g., hypertension, hypercholesterolemia, diabetes mellitus, osteoporosis, etc.). The Charlson Comorbidity Index (CCI) [Charlson, 1987; Charlson, 1994] for 45% of patients was ≥5 indicating <21% chance of 10-year survival. The majority of patients (83%) had a modified Medical Research Council (mMRC) score of ≥2 (mean 2.2) indicating functional impairment due to their dyspnea (stops for breath when walking at own pace). In addition, the mean baseline SGRQ Total Score and CAT Score were 54 and 19, respectively, indicating patients had poor HRQoL and significant disease impact on health status. Clinically, these patients suffer significantly despite taking ICS-based triple therapy.

Table 4 Baseline Characteristics (COPD Studies, mITT Population)

Baseline Characteristics	Study 106 N=836	Study 113 N=674	Total N=1510
Duration of COPD, years, mean (SD)	9.3 (6.35)	8.4 (5.86)	8.9 (6.15)
Smoking Status, n (%)			
Current smoker	222 (27)	189 (28)	411 (27)
Former smoker	574 (69)	472 (70)	1046 (69)
Never/non-smoker	40 (5)	13 (2)	53 (4)
Smoking Pack Years[1], mean (SD)	45.6 (26.5)	44.3 (28.0)	45.0 (27.2)
Screening Lung Function, mean (SD)			
Post-bronchodilator FEV_1 (L)	1.2 (0.5)	1.3 (0.5)	---
Post-bronchodilator % predicted FEV1	44.3 (14.9)	46.1 (15.2)	---
Reversibility, %	9.1 (12.0)	9.8 (11.5)	---
Post-bronchodilator FEV_1/FVC	0.5 (0.1)	0.5 (0.1)	---
GOLD Group D[2], n (%)	796 (95)	646 (96)	1442 (95)
Severity of Airflow Limitation[3], n (%)			
Mild: ≥80% predicted	7 (<1)	7 (1)	14 (<1)
Moderate: ≥50% to <80% predicted	268 (32)	264 (39)	532 (35)
Severe: ≥30% to <50% predicted	412 (49)	291 (43)	703 (47)
Very severe: <30% predicted	149 (18)	112 (17)	261 (17)
Long-term Oxygen Use[4], n (%)	101 (12)	77 (11)	178 (12)
Mod/Severe Exacerbations Prior Year, mean (SD)	2.5 (1.2)	2.7 (1.4)	2.6 (1.3)
≥1 Exacerbation in Prior Year Requiring, n (%)			
Systemic corticosteroids and/or antibiotics	650 (78)	569 (84)	1219 (81)
Emergency department visit only	131 (16)	59 (9)	190 (13)
Hospitalization-general ward only	236 (28)	208 (31)	444 (29)
Hospitalization-intensive care unit	33 (4)	18 (3)	51 (3)
mMRC Score[5] ≥2 at Screening, n (%)	682 (82)	565 (84)	1247 (83)
SGRQ Total Score[6], mean (SD)	54.9 (17.0)	52.7 (16.6)	---
COPD Assessment Test (CAT) Score[7], mean (SD)	18.9 (7.7)	19.1 (7.6)	---
Disease Co-morbidity, n (%)			
Cardiovascular co-morbidity (past/current cardiac disorders)	219 (26)	181 (27)	400 (26)
Other co-morbidity	616 (74)	536 (80)	1152 (76)
Charlson Comorbidity Index (CCI)[8]			
1-2	30 (4)	31 (5)	61 (4)
3-4	427 (51)	336 (50)	763 (51)
≥5	378 (45)	302 (45)	680 (45)

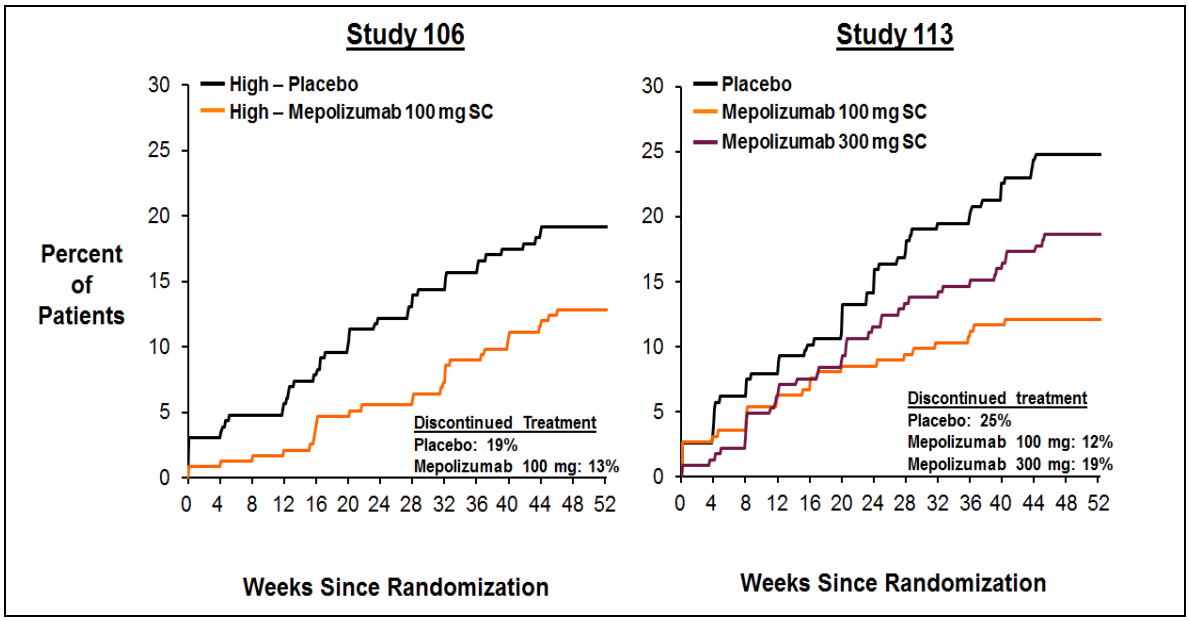
1. Smoking pack years = (number of cigarettes smoked per day/20) x number of years smoked
2. Based on refined ABCD assessment tool, GOLD Guidelines 2017; Group D: ≥2 moderate or ≥1 exacerbation leading to hospital admission with mMRC Score ≥2 or CAT Score ≥10 at screening/baseline
3. Classification based on post-bronchodilator FEV_1 at Screening, GOLD Guidelines for COPD
4. Long-term oxygen use was classified as taking oxygen therapy for 40 days or more.
5. Modified Medical Research Council Score
6. St. George's Respiratory Questionnaire (SGRQ) Total score range 0-100 with higher scores indicating poor quality of life
7. CAT score range 0-40 with higher scores indicating greater COPD disease impact
8. CCI score (predicted 10-year survival probability): 1-2 (>90%), 3-4 (>53%), ≥5 (<21%)

3.2. Premature Discontinuations From Study Treatment

The majority of patients in the primary population completed the 52-week treatment period (Table 5). In both studies, more patients treated with placebo prematurely discontinued study treatment compared with patients treated with mepolizumab (19% placebo vs. 13% 100 mg in Study 106 High Stratum and 25% placebo vs. 12% 100 mg and 19% 300 mg in Study 113) (Figure 4 and Table 5). The most common reasons for treatment discontinuation were adverse event and voluntary withdrawal by the patient (Table 5).

Patients who discontinued study treatment were encouraged to remain in the study and complete scheduled assessments. Thus, the amount of missing data for the primary endpoint was small compared with most COPD studies; as a percentage of scheduled years of follow-up, 6-8% patient-years for placebo and 3-5% for mepolizumab (see Appendix Section 8.3).

Figure 4 Study Treatment Discontinuation (COPD Studies, mITT Primary Population)



Note: Figure depicts time to withdrawal from study treatment. Patients represented from day of first dose to day of last dose.

Table 5 Study Treatment Discontinuation (COPD Studies, mITT Primary Population)

Study Treatment Completion Status	Number (%) of Patients				
	Study 106 High Stratum		Study 113		
	Placebo N=229	Mepo 100 mg SC N=233	Placebo N=226	Mepo 100 mg SC N=223	Mepo 300 mg SC N=225
Completed treatment	185 (81)	203 (87)	170 (75)	196 (88)	183 (81)
Discontinued treatment	44 (19)	30 (13)	56 (25)	27 (12)	42 (19)
Discontinued treatment & continued in study	19 (8)	13 (6)	21 (9)	18 (8)	19 (8)
Completed study with off-treatment assessments	17 (7)	10 (4)	16 (7)	12 (5)	14 (6)
Did not complete study	2 (<1)	3 (1)	5 (2)	6 (3)	5 (2)
Discontinued treatment & study at same time	25 (11)	17 (7)	35 (15)	9 (4)	23 (10)
Primary reason for treatment discontinuation					
Adverse event	20 (9)	16 (7)	27 (12)	9 (4)	25 (11)
Withdrawal by patient	16 (7)	8 (3)	16 (7)	11 (5)	11 (5)
Lack of efficacy	5 (2)	2 (<1)	6 (3)	2 (<1)	2 (<1)
Physician decision	2 (<1)	1 (<1)	2 (<1)	3 (1)	1 (<1)
Protocol deviation	1 (<1)	3 (1)	2 (<1)	0	1 (<1)
Lost to follow-up	0	0	1 (<1)	1 (<1)	1 (<1)
Protocol-defined stopping criteria[2]	0	0	1 (<1)	1 (<1)	0
Investigator site closed	0	0	1 (<1)	0	1 (<1)

1. Patients could have only one primary reason for treatment discontinuation
2. Study 113: Liver function test abnormality (placebo); ECG abnormality (100 mg)

4. EFFICACY RESULTS

The efficacy discussion is focused on the results for mepolizumab 100 mg SC, the dose proposed for registration, in the pre-defined primary (intended) population (Study 106 High Stratum and all patients in Study 113). Efficacy results for the mepolizumab 300 mg dose are shown for the primary endpoint in Section 4.2.1; point estimates for the secondary endpoints are presented in Appendix Section 8.2. Efficacy data for Study 106 All Subjects, including the Low Stratum, are presented in Section 4.6.1.

4.1. Efficacy Summary

In the Phase III COPD Studies 106 and 113:

COPD Exacerbations

- The addition of mepolizumab 100 mg SC to SoC demonstrated a consistent and clinically relevant reduction in the rate of moderate/severe exacerbations (18% in the Study 106 High Stratum and 20% in Study 113) compared with placebo in patients receiving inhaled triple therapy. This reduction was statistically significant in the

Study 106 High Stratum (unadjusted p 0.029; adjusted p 0.036) but not significant after adjusting for multiplicity in Study 113 (unadjusted p 0.034; adjusted p 0.068). Overall, there was a statistically significant 18% rate reduction in the meta-analysis (p 0.006).

- A 14% reduction in the rate of moderate/severe exacerbations was observed between mepolizumab 300 mg and placebo (unadjusted and adjusted p 0.140) in Study 113, indicating no additional benefit with the higher dose.
- Mepolizumab 100 mg increased the time to first moderate/severe exacerbation in both studies. The risk of having a first moderate/severe exacerbation with mepolizumab 100 mg at any time during the study was statistically significantly lower in the Study 106 High Stratum (p 0.036), and numerically lower in Study 113 (p 0.140), compared with placebo. The meta-analysis showed a statistically significantly lower risk with mepolizumab 100 mg compared with placebo (p 0.006).
- Mepolizumab 100 mg showed a numerical reduction in the rate of exacerbations leading to ED visit/hospitalization and in the rate of severe exacerbations compared with placebo in Study 113, but not in Study 106. The pre-planned meta-analysis showed numerical reductions of 15% in the rate of exacerbations leading to ED visit/hospitalization and 12% in the rate of severe exacerbations.
- The risk of having an exacerbation requiring ED visit/hospitalization at any time during the study was 12% lower with mepolizumab 100 mg compared with placebo in the Study 106 High Stratum, 28% lower in Study 113, and 19% lower in the meta-analysis.
- Subgroup analyses of rate of moderate/severe exacerbations indicated consistent reductions with mepolizumab 100 mg compared with placebo across categories of age, gender, geographical region, and smoking status at Screening compared with the overall primary population. However, there was a limited reduction observed in Asian patients and sample sizes were too small to estimate rates in patients of African Heritage and non-smokers.

Health-related Quality of Life

- Treatment with mepolizumab 100 mg resulted in a numerically higher proportion of SGRQ responders (patients who had a Total Score reduction from baseline of at least the MCID of 4 points) than placebo at all time points. Improvements from baseline in mean SGRQ Total Score were numerically greater for mepolizumab 100 mg compared with placebo at all time points in both studies, except for Week 52 in the Study 106 High Stratum. In the meta-analysis, reductions from baseline were observed for mepolizumab 100 mg compared with placebo that were numerically greater at Week 52 (mean treatment difference of -0.7 points; p 0.486).
- Treatment with mepolizumab 100 mg resulted in a numerically higher proportion of CAT responders (patients who had a score reduction from baseline of at least the MCID of 2 points) than placebo at all time points and this was nominally statistically significant at Week 52 in the meta-analysis (odds ratio: 1.39, p 0.024). In both studies, improvements from baseline in mean CAT score were numerically greater

for mepolizumab 100 mg compared with placebo at all time points. In the meta-analysis, reductions from baseline were observed for mepolizumab 100 mg SC compared with placebo that were nominally statistically significantly greater at Week 52 (mean treatment difference of -0.9 points; p 0.039).

- A larger percentage of patients were evaluated (by themselves or by the clinician) as moderately or significantly improved after 52 weeks of treatment with mepolizumab 100 mg compared with placebo in both studies and in the meta-analysis. The odds of being in a better response category were numerically higher in the meta-analysis for the patient ratings (odds ratio 1.26) and nominally statistically significant for clinician ratings (odds ratio 1.41; nominal p 0.008) indicating that the changes experienced with mepolizumab therapy were meaningful to patients and to clinicians.

Other Efficacy Measures

- No clinically relevant improvement in lung function (FEV_1) was observed with mepolizumab 100 mg compared with placebo.
- Numerical reductions in occasions of rescue medication use and increases in the percentage of nights with no awakenings due to COPD symptoms were observed with mepolizumab 100 mg compared with placebo in both studies and the meta-analysis.

Blood Eosinophils and Treatment Response

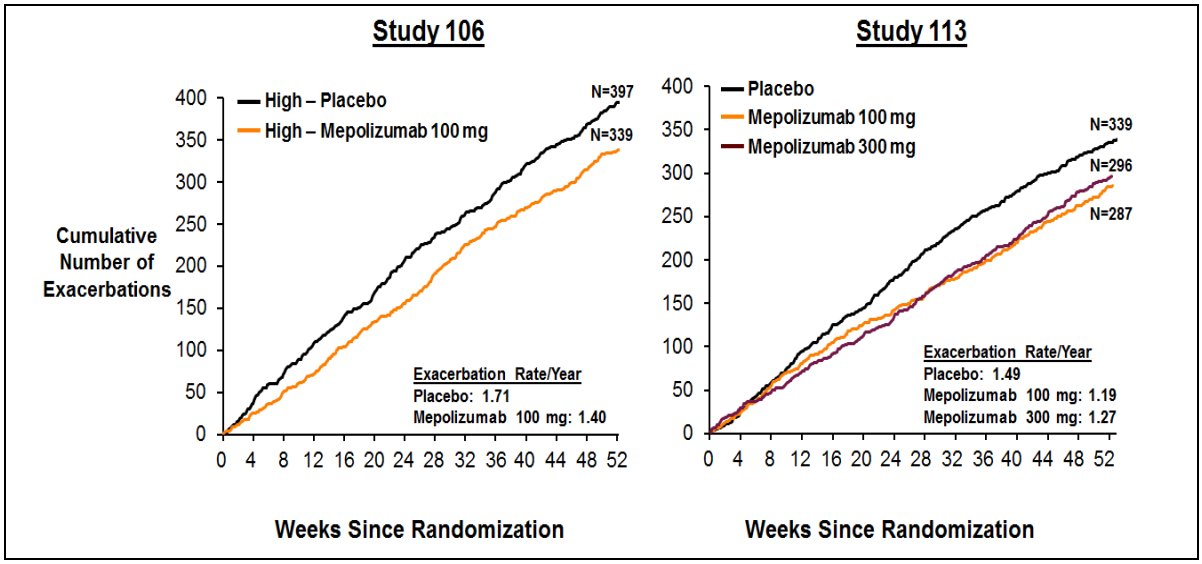
- Treatment with mepolizumab 100 mg resulted in a sustained reduction in blood eosinophils starting at the first post-baseline assessment (Week 4) through Week 52.
- Patients in the Study 106 Low Stratum (eosinophils <150 cells/μL at screening and no history of ≥300 cells/μL) had no treatment response to mepolizumab, showing that the treatment response is related to blood eosinophils.
- The efficacy of mepolizumab was generally greater in patients whose eosinophil count was higher at screening, as assessed via pre-specified subgroup analyses and modeling of efficacy by screening eosinophil count as a continuous variable.

4.2. COPD Exacerbations

4.2.1. Moderate/Severe Exacerbations

Over the 52-week treatment period, in addition to SoC inhaled triple therapy, patients in the primary population receiving placebo experienced more exacerbations than those treated with mepolizumab (Figure 5). Treatment with mepolizumab in addition to SoC inhaled triple therapy consistently decreased the rate of exacerbations in both studies. A separation of treatment response was observed early (by Week 4) in Study 106 and by Week 12 in Study 113. In Study 113, the cumulative number of exacerbations was similar between the mepolizumab 100 mg and 300 mg arms.

Figure 5 **Cumulative Number of Moderate/Severe Exacerbations Over Time: On- and Off-Treatment (COPD Studies, mITT Primary Population)**



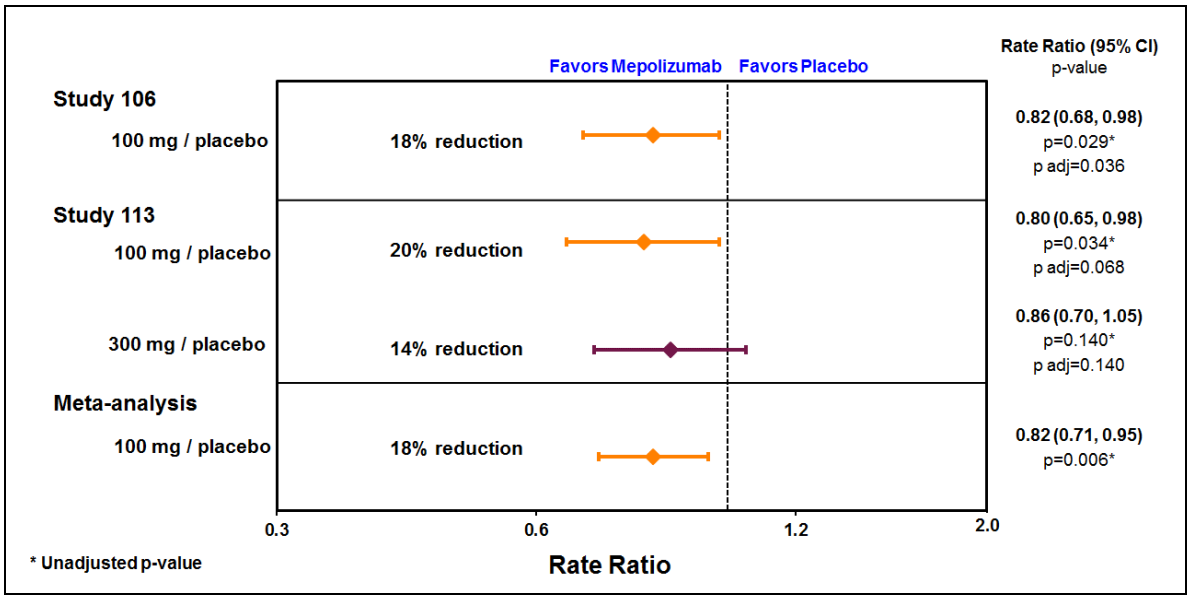
Note: # Events = cumulative number of exacerbations over 52 weeks
Note: All patients were on a background of inhaled triple therapy

Mepolizumab 100 mg demonstrated consistent and clinically relevant reductions of 18% and 20% in the rate of moderate/severe exacerbations compared with placebo in studies 106 and 113, respectively (Figure 6). This reduction was statistically significant in the Study 106 High Stratum (unadjusted p 0.029; adjusted p 0.036) but not significant after adjusting for multiplicity in Study 113 (unadjusted p 0.034; adjusted p 0.068). In the pre-specified meta-analysis, mepolizumab resulted in an 18% reduction compared with placebo that was statistically significant (p 0.006).

In Study 113, a 14% reduction in the rate of moderate/severe exacerbations was observed between mepolizumab 300 mg and placebo (unadjusted p 0.140; adjusted p 0.140), indicating no additional benefit in rate reduction with the higher dose.

Sensitivity analyses of the primary endpoint confirmed the robustness of the primary efficacy results to different assumptions regarding missing data (see Appendix Section 8.2).

Figure 6 **Primary Endpoint: Rate of On- and Off-Treatment Moderate/Severe Exacerbations: Mepolizumab vs. Placebo (COPD Studies, mITT Primary Population)**



Note: Horizontal bars represent 95% confidence intervals for mepolizumab/placebo rate ratio

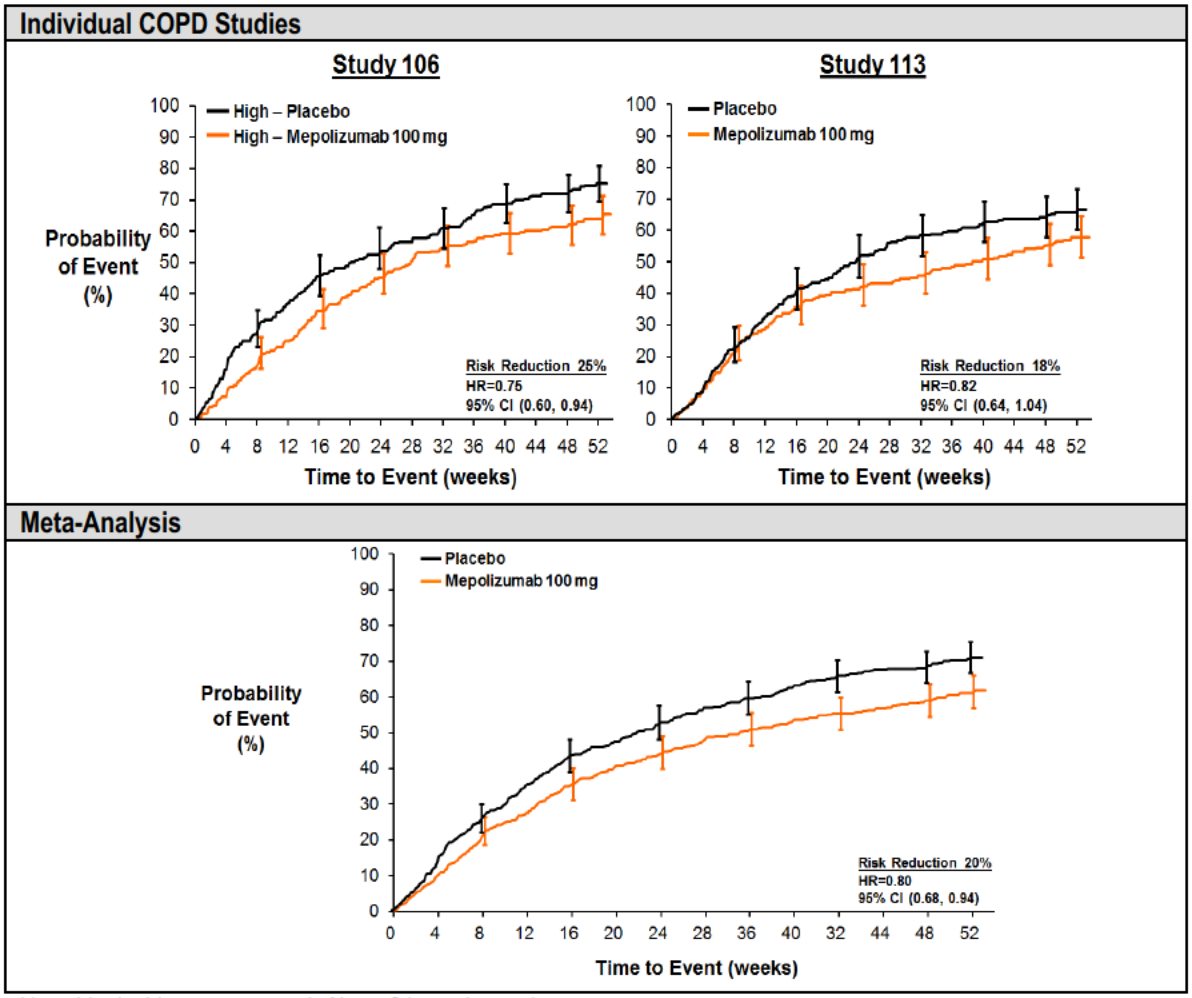
An 18-20% reduction in the rate of moderate/severe exacerbations is a clinically relevant reduction in exacerbation rate for patients with COPD, especially in a population with severe disease already receiving inhaled triple therapy. These classes and combinations of medicines (ICS, LABA, LAMA) lower rates of acute exacerbations of COPD significantly and meaningfully on their own (up to 40% vs. placebo) [Ferguson, 2008; Chapman, 2013; Dransfield, 2013], and therefore the 18-20% exacerbation reduction demonstrated over and above this is clinically important. Additionally, based on a review of relevant literature, a reduction in the rate of COPD exacerbations by 11% is regarded as clinically meaningful and a clinically meaningful reduction could be as low as 4% [Chapman, 2013].

4.2.1.1. Time to First Moderate/Severe Exacerbation

In both studies and in the meta-analysis, the time to first moderate/severe exacerbation was consistent with the primary endpoint and was longer for patients treated with mepolizumab 100 mg compared with placebo (Figure 7). The median time to first moderate/severe exacerbation was 51 days (Study 106 High Stratum), 101 days (Study 113), and 63 days (meta-analysis) longer with mepolizumab 100 mg SC compared with placebo (Table 6).

The risk of having a first moderate/severe exacerbation at any time during the study was lower with mepolizumab 100 mg compared with placebo with similar hazard ratios in each study, this difference was statistically significant in the Study 106 High Stratum (25%; unadjusted p 0.012; adjusted p 0.036) but not in Study 113 (18%; unadjusted p 0.103; adjusted p 0.140) (Figure 7). In the meta-analysis, the risk was 20% lower with mepolizumab 100 mg compared with placebo (p 0.006).

Figure 7 **Kaplan-Meier Cumulative Incidence Curve for Time to First Moderate/Severe Exacerbation: Mepolizumab 100 mg vs. Placebo (COPD Studies, mITT Primary Population)**



Note: Vertical bars represent 95% confidence intervals

Table 6 **Median Time to First Moderate/Severe Exacerbation (COPD Studies, mITT Primary Population)**

	Number of Days					
	Study 106 High Stratum		Study 113		Meta-Analysis	
	Placebo	Mepo 100 mg SC	Placebo	Mepo 100 mg SC	Placebo	Mepo 100 mg SC
Median Time to First Exacerbation	141	192	166	267	155	218
Difference vs. Placebo	---	51	---	101	---	63

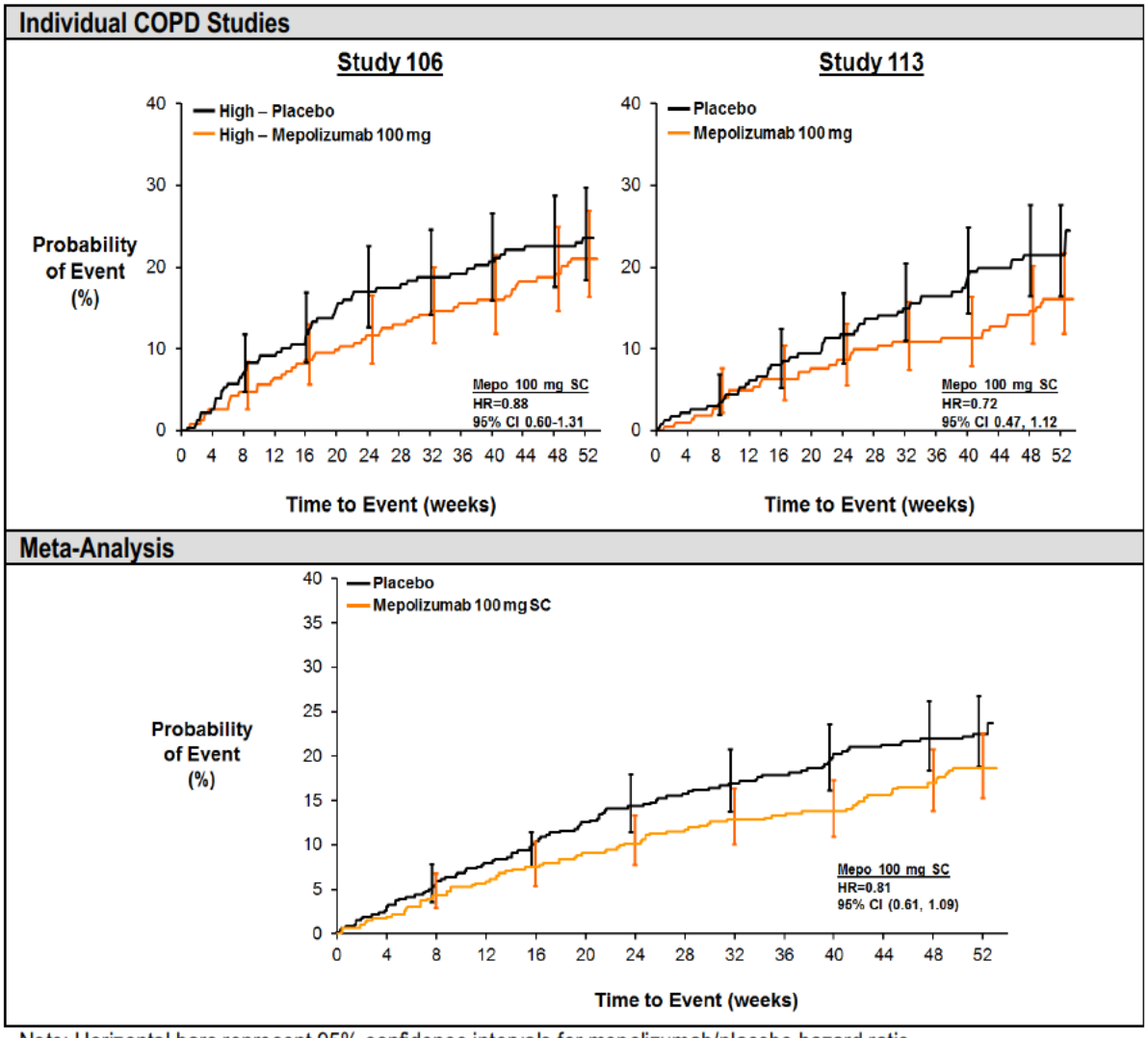
4.2.2. Exacerbations Requiring ED Visit/Hospitalization

Overall, the effect of mepolizumab on more severe exacerbation events was in line with the effect seen for moderate/severe exacerbations.

In both studies and in the meta-analysis, the time to first exacerbation requiring ED visit/hospitalization was longer with mepolizumab compared with placebo with the risk of having an event remaining lower in the mepolizumab 100 mg group than in the placebo group.

The risk of having an exacerbation requiring ED visit/hospitalization at any time during the study was 12% lower with mepolizumab 100 mg compared with placebo in the Study 106 High Stratum, 28% lower in Study 113, and 19% lower in the meta-analysis (Figure 8). Although these results were not statistically significant, they are clinically relevant in this severe COPD patient population.

Figure 8 **Kaplan-Meier Cumulative Incidence Curve for Time to First Exacerbation Requiring ED Visit/Hospitalization: Mepolizumab 100 mg vs. Placebo (COPD Studies, mITT Primary Population)**



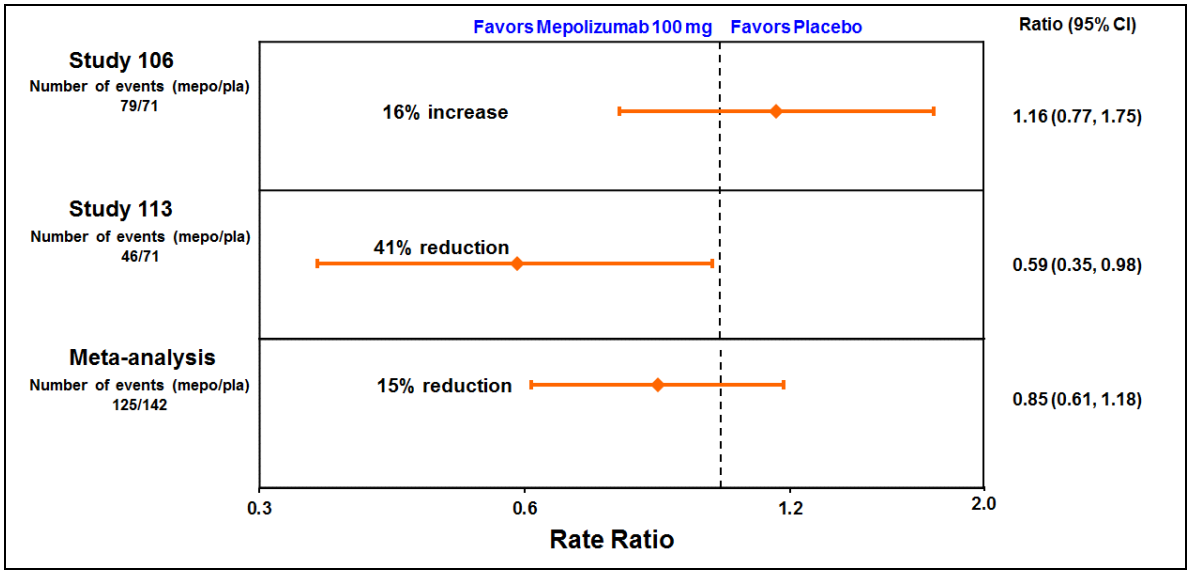
Note: Horizontal bars represent 95% confidence intervals for mepolizumab/placebo hazard ratio

Mepolizumab 100 mg reduced the rate of exacerbations leading to ED visit/ hospitalization by 41% compared with placebo in Study 113, while conversely, a rate increase of 16% was observed in the Study 106 High Stratum (Figure 9). In contrast to the increase in rate, the proportion of patients having at least one exacerbation requiring ED visit/hospitalization was lower for mepolizumab 100 mg compared with placebo (21% vs. 23%) in the Study 106 High Stratum.

More severe exacerbations leading to ED visit/hospitalization are less frequent, thus interpreting results is aided by assessing the pre-specified meta-analysis data from both studies. In the meta-analysis, the proportion of patients having at least one exacerbation requiring ED visit/hospitalization was 18% in the mepolizumab 100 mg group and 22% in the placebo group. The meta-analysis showed a numerical reduction of 15% in the rate

of exacerbations requiring ED visit/hospitalization with mepolizumab 100 mg compared with placebo (Figure 9).

Figure 9 Rate of On- and Off-Treatment Exacerbations Requiring ED Visit/Hospitalization: Mepolizumab 100 mg vs. Placebo (COPD Studies, mITT Primary Population)



Note: Horizontal bars represent 95% confidence intervals for mepolizumab/placebo rate ratio

4.2.3. Severe Exacerbations

The time to first severe exacerbation also showed a similar trend to exacerbations requiring ED visit/hospitalization. In both studies and in the meta-analysis, the time to first severe exacerbation was longer with mepolizumab compared with placebo with the risk of a first event remaining lower in the mepolizumab 100 mg group than in the placebo group throughout both studies. These results were not statistically significant; however, they are clinically relevant in this patient population.

The profile of response for severe exacerbations (hospitalization or death) was similar to exacerbations leading to ED visit/hospitalization. Mepolizumab 100 mg reduced the rate of severe exacerbations by 37% compared with placebo in Study 113, while conversely, a rate increase of 12% was observed in the Study 106 High Stratum. In the meta-analysis, the proportion of patients having at least one severe exacerbation was 16% in the mepolizumab group and 19% in the placebo group. The meta-analysis showed a numerical reduction of 12% in the rate of severe exacerbations with mepolizumab 100 mg compared with placebo.

4.2.4. Analyses of Exacerbations by Demographic Subgroup

Subgroup analysis of the primary endpoint generally showed a consistent response compared with the 18% reduction in moderate/severe exacerbations in the overall primary population across demographic subgroups with point estimates favoring mepolizumab (Table 7). It should be noted that these analyses are not necessarily

expected to show statistical significance. The majority of these subgroups were well represented with over 100 patients. However, due to the small sample sizes of the African American and never/non-smoker subgroups, the statistical models with full covariate adjustment failed to converge and the exacerbation rate reduction was not able to be calculated. For these subgroups, the rates and rate ratios are therefore presented from a model where only study is included for covariate adjustment, estimates for the Asian subgroup are taken from Study MEA117113.

Table 7 Rate of Exacerbations by Subgroup: Mepolizumab 100 mg vs. Placebo (COPD Studies, mITT Primary Population)

Meta-Analysis					
			Exacerbation Rate/Year		Rate Ratio (M/P)
Group	Subgroup	N	Placebo	Mepo 100mg	(95% CI)
All Patients	---	911	1.61	1.32	0.82 (0.71, 0.95)
Age	40-64 years	419	1.68	1.25	0.75 (0.61, 0.92)
	≥65 years	492	1.53	1.37	0.90 (0.74, 1.09)
Gender	Female	324	1.66	1.53	0.92 (0.75, 1.13)
	Male	587	1.58	1.19	0.75 (0.62, 0.91)
Race[1]	African Heritage	12	3.31	2.22	0.67 (0.20, 2.20)
	White	751	1.79	1.35	0.80 (0.69, 0.94)
	Asian	83	1.60	1.36	0.85 (0.48, 1.51)
Region	European Union	459	1.63	1.32	0.81 (0.67, 0.97)
	United States	97	2.04	1.76	0.86 (0.60, 1.24)
	Rest of World	355	1.43	1.21	0.85 (0.66, 1.08)
Smoking status[1]	Current	252	1.92	1.58	0.82 (0.63, 1.07)
	Former	634	1.66	1.37	0.82 (0.69, 0.99)
	Never/non-smoker	25	0.85	0.46	0.54 (0.17, 1.68)

1. Model with only study included for covariate adjustment; Asian subgroup from MEA117113

4.3. Health-related Quality of Life

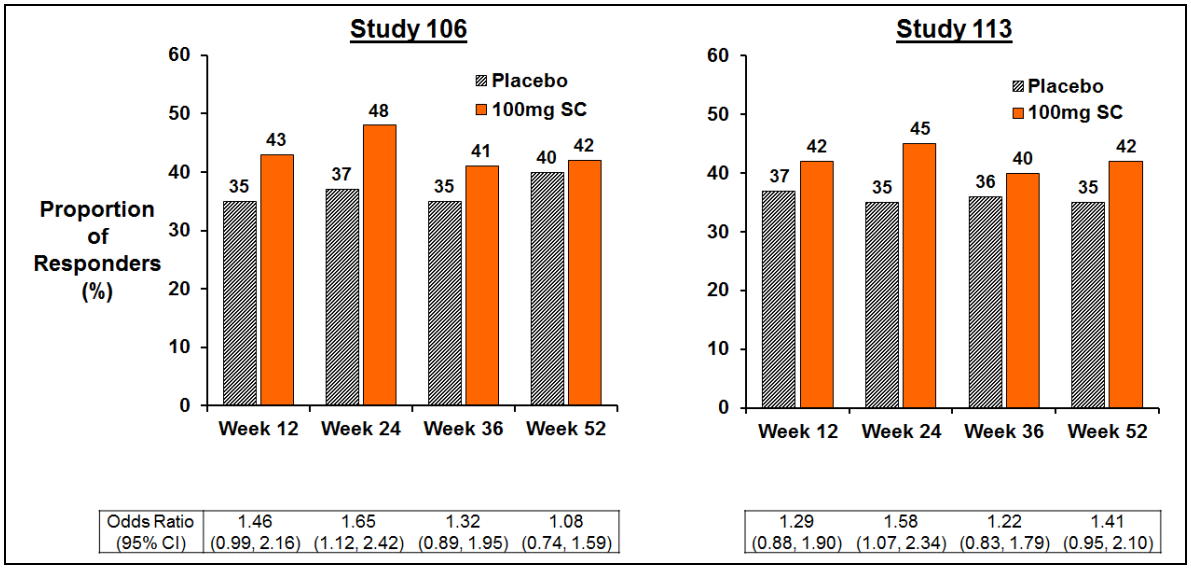
4.3.1. St. George's Respiratory Questionnaire (SGRQ)

4.3.1.1. SGRQ Responder Analysis

In both studies, the proportion of SGRQ responders was numerically higher in the mepolizumab 100 mg group compared with the placebo group at each assessment over the 52-week treatment period and the odds of a patient achieving a clinically significant improvement from baseline in SGRQ total score favored mepolizumab (Figure 10).

In the meta-analysis, a numerically larger proportion of patients in the mepolizumab 100 mg group were SGRQ responders compared with placebo at all time points (odds ratios: 1.23 to 1.60). At Week 52, 42% of patients treated with mepolizumab were SGRQ responders compared with 38% in the placebo group (odds ratio 1.23).

Figure 10 SGRQ Responders: Mepolizumab 100 mg vs. Placebo (COPD Studies, mITT Primary Population)



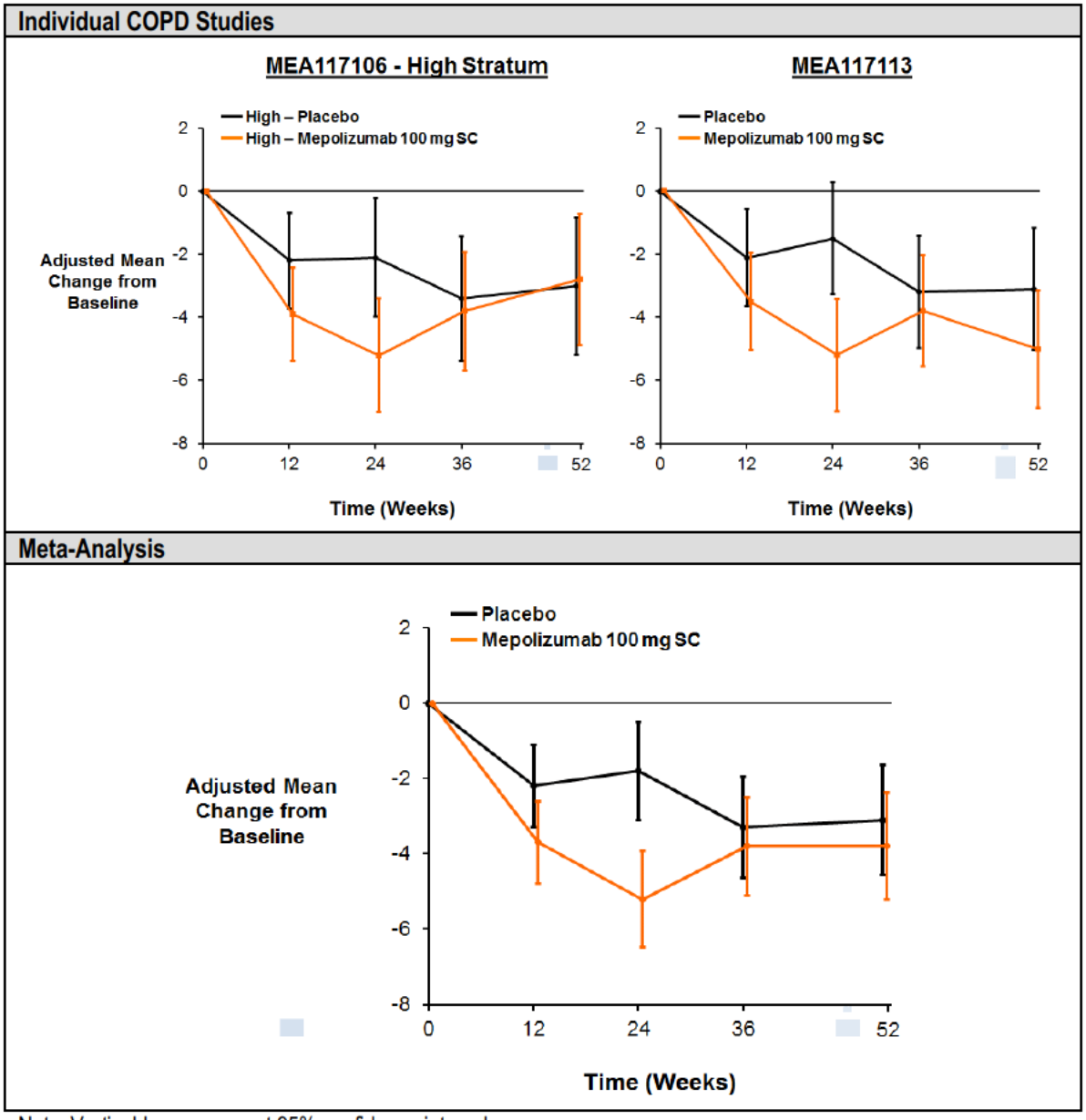
Note: SGRQ Responders = Patients with ≥4-point improvement from baseline in SGRQ Total Score; 4 points is the MCID for SGRQ Total Score; missing data included as non-response

4.3.1.2. SGRQ Change from Baseline

In both studies, numerically greater reductions from baseline in SGRQ Total Score were observed for mepolizumab 100 mg compared with placebo that were greatest at Week 24 (-3.1 in the Study 106 High Stratum and -3.7 in Study 113) (Figure 11). In the Study 106 High Stratum, the improvement in SGRQ Total Score did not exceed that of the placebo at Week 52. In Study 113, improvement against placebo was maintained to Week 52 although the change from baseline was somewhat decreased. The placebo group, which consists of placebo plus inhaled triple therapy, also showed SGRQ Total Score improvements, which is consistent with the trends observed in other COPD studies [Lipson, 2017; Wedzicha, 2013; Jones, 2011; Tashkin, 2008].

The trend for improvement in HRQoL with mepolizumab was demonstrated in the meta-analysis that showed greater reductions in SGRQ Total Score compared with placebo at each time point (treatment differences of -1.5, -3.4, and -0.7 points at Weeks 12, 24 and 52, respectively).

Figure 11 **Change from Baseline in Mean SGRQ Total Score: Mepolizumab 100 mg vs. Placebo (COPD Studies, mITT Primary Population)**



Note: Vertical bars represent 95% confidence intervals.

The reduction in SGRQ Total Score was primarily driven by improvements in the SGRQ Symptom Domain Score in both studies. In the meta-analysis, numerical improvements from baseline in Symptom Domain Score were observed in both groups at all time points with greater mean reductions in the mepolizumab 100 mg group (-5.9 to -8.6 points) compared with placebo (-2.9 to -5.9 points) over the treatment period.

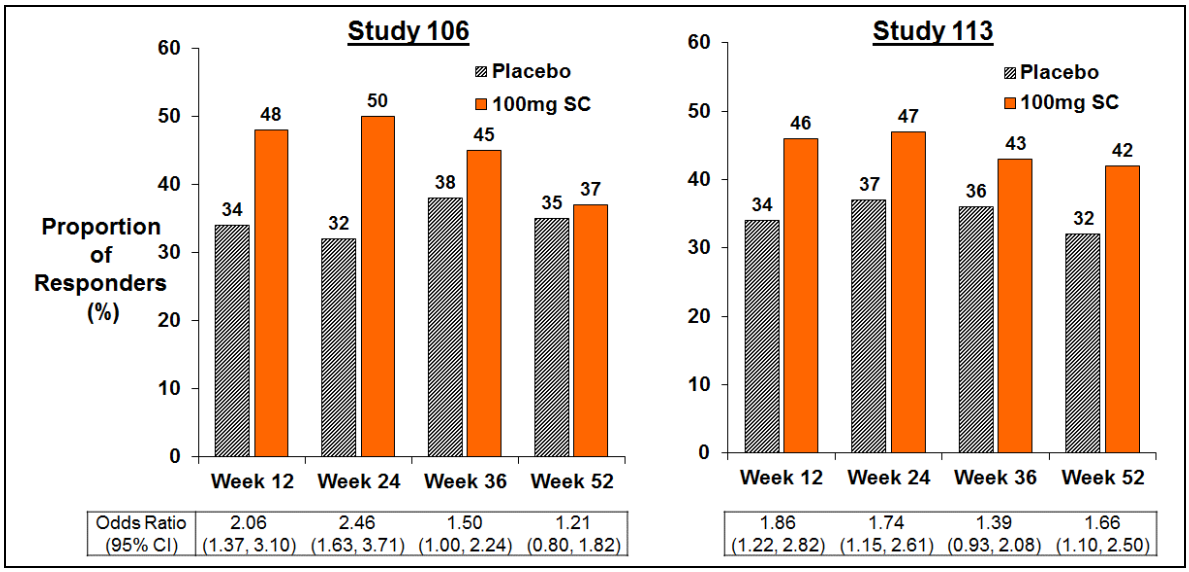
4.3.2. COPD Assessment Test (CAT)

4.3.2.1. CAT Responder Analysis

A post-hoc analysis assessing CAT responders was performed. In both studies, the proportion of CAT responders was higher in the mepolizumab 100 mg group compared with the placebo group at all time points over the 52-week treatment period and the odds of a patient achieving a clinically significant improvement from baseline in CAT score favored mepolizumab. Figure 12 depicts responder results for CAT at the same timepoints as shown for SGRQ for simplification of presentation as CAT data were collected every 4 weeks.

In the meta-analysis, a larger proportion of patients in the mepolizumab 100 mg group were CAT responders compared with placebo at all time points (odd ratios: 1.39 to 2.04). At Week 52, 39% of patients treated with mepolizumab were CAT responders compared with 33% in the placebo group; the odds ratio was nominally statistically significant in favor of mepolizumab (odds ratio 1.39, nominal p 0.024).

Figure 12 CAT Responders: Mepolizumab 100 mg vs. Placebo (COPD Studies, mITT Primary Population)



Note: This is a post-hoc analysis

Note: The CAT was conducted every 4 weeks during the study; however, data for the same timepoints that SGRQ was assessed are shown in these figures for simplicity.

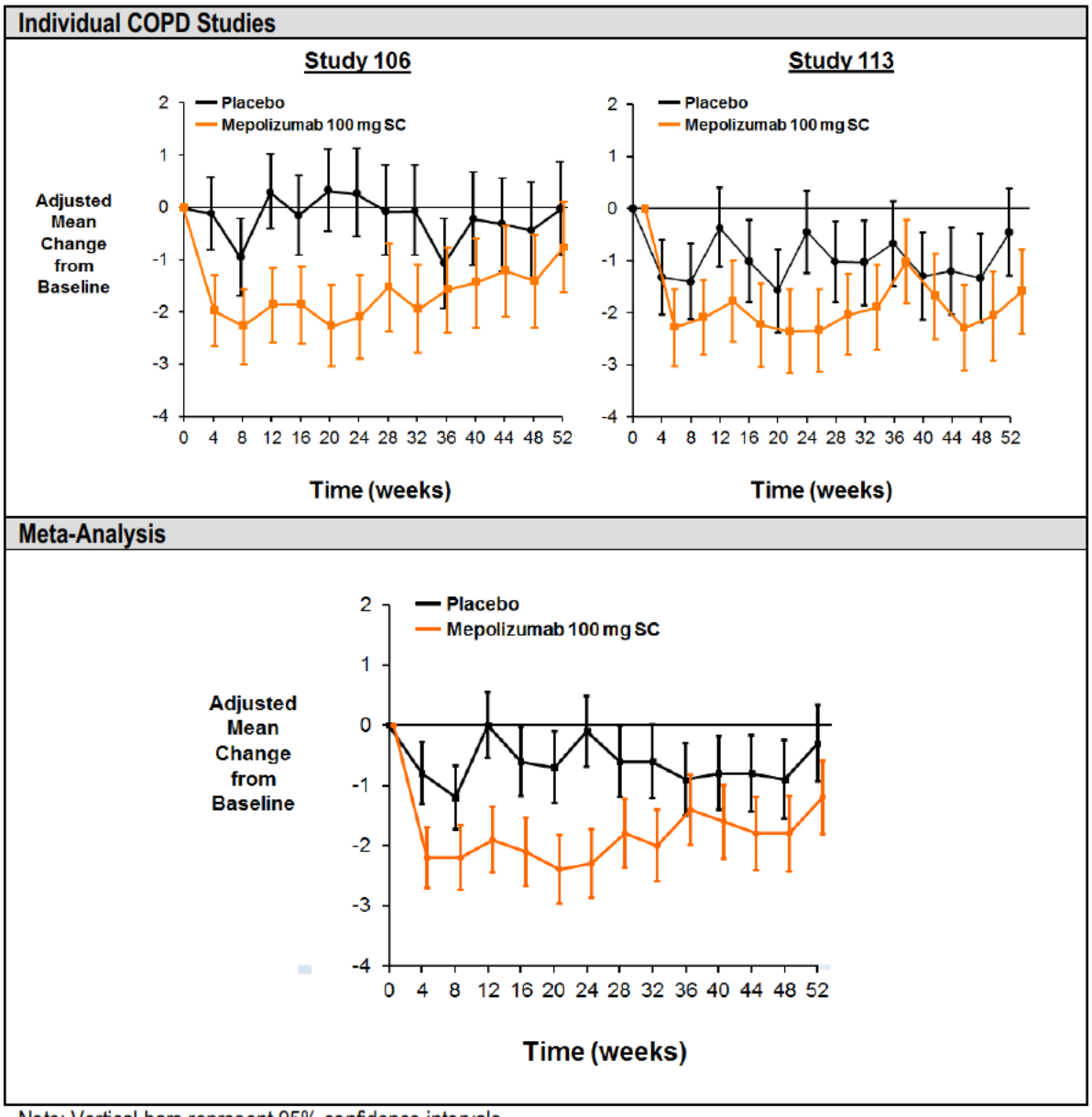
CAT Responders = Patients with ≥2-point improvement from baseline in CAT Score; 2 points is the MCID for CAT score; missing data included as non-response

4.3.2.2. CAT Change from Baseline

In both studies, CAT Score was numerically improved by mepolizumab compared with placebo over the 52-week treatment period, with the greatest treatment differences through Week 32 (Figure 13). The largest treatment difference was at Week 20 in Study 106 (-2.7 points) and at Week 24 in Study 113 (-1.9 points). At Week 52, treatment differences were -0.8 point and -1.1 point in Studies 106 and 113, respectively.

The trend for improvement in health status was supported by reductions in CAT Score at all time points with mepolizumab 100 mg compared with placebo in the meta-analysis; a nominally statistically significant treatment difference was observed at Week 52 (-0.9 points; nominal p 0.039).

Figure 13 Change from Baseline in Mean CAT Score: Mepolizumab 100 mg vs. Placebo (COPD Studies, mITT Primary Population)



Note: Vertical bars represent 95% confidence intervals.

4.3.3. Overall Evaluation of Response to Therapy

A larger percentage of patients were evaluated (by themselves or by the clinician) as moderately or significantly improved after 52 weeks of treatment with mepolizumab 100 mg compared with placebo in both studies (Table 8).

When evaluated by the patient, the odds of being in a better response category at Week 52 was numerically greater for mepolizumab compared with placebo in the Study 106 High Stratum, Study 113, and in the meta-analysis.

When evaluated by the clinician, the odds of being in a better response category after 52 weeks of mepolizumab 100 mg treatment compared with placebo was numerically greater in the Study 106 High Stratum and nominally statistically significantly greater in Study 113 (p 0.040) and in the meta-analysis (p 0.008).

Table 8 Patient Rated and Clinician Rated Response to Therapy at Week 52: Mepolizumab 100 mg vs. Placebo (COPD Studies, mITT Primary Population)

	Study 106 High Stratum		Study 113		Meta-Analysis	
Response to Therapy Rating (Week 52)	Placebo N=229	Mepo 100 mg SC N=233	Placebo N=226	Mepo 100 mg SC N=223	Placebo N=455	Mepo 100 mg SC N=456
Patient-Rated Response						
n	186	205	176	196	362	401
1=Significantly improved	21 (11)	19 (9)	16 (9)	19 (10)	37 (10)	38 (9)
2=Moderately improved	32 (17)	43 (21)	20 (11)	37 (19)	52 (14)	80 (20)
3=Mildly improved	45 (24)	54 (26)	47 (27)	54 (28)	92 (25)	108 (27)
4=No change	60 (32)	68 (33)	76 (43)	65 (33)	136 (38)	133 (33)
5=Mildly worse	18 (10)	16 (8)	13 (7)	18 (9)	31 (9)	34 (8)
6=Moderately worse	9 (5)	3 (1)	4 (2)	3 (2)	13 (4)	6 (1)
7=Significantly worse	1 (<1)	2 (<1)	0	0	1 (<1)	2 (<1)
Odds Ratio	---	1.18	---	1.37	---	1.26
95% CI	---	0.83, 1.69	---	0.95, 1.99	---	0.97, 1.63
Nominal p-value	---	0.360	---	0.095	---	0.077
Clinician-Rated Response						
n	194	211	177	200	371	411
1=Significantly improved	9 (5)	13 (6)	12 (7)	15 (8)	21 (6)	28 (7)
2=Moderately improved	28 (14)	43 (20)	17 (10)	35 (18)	45 (12)	78 (19)
3=Mildly improved	49 (25)	48 (23)	50 (28)	62 (31)	99 (27)	110 (27)
4=No change	87 (45)	92 (44)	83 (47)	69 (35)	170 (46)	161 (39)
5=Mildly worse	18 (9)	13 (6)	12 (7)	13 (7)	30 (8)	26 (6)
6=Moderately worse	2 (1)	1 (<1)	2 (1)	3 (2)	4 (1)	4 (<1)
7=Significantly worse	1 (<1)	1 (<1)	1 (<1)	3 (2)	2 (<1)	4 (<1)
Odds Ratio	---	1.39	---	1.48	---	1.41
95% CI	---	0.97, 2.00	---	1.02, 2.14	---	1.09, 1.83
Nominal p-value	---	0.071	---	0.040	---	0.008

Note: Assessments in Japan were based on the last 3 months instead of since the last visit (Study 113 only).

4.4. Other Efficacy Measures

4.4.1. Lung Function

Numerically greater mean changes from baseline in trough FEV_1 were observed after mepolizumab 100 mg treatment compared with placebo at the majority of time points in both studies and in the meta-analysis; however, these changes were small (≤41 mL for mepolizumab 100 mg and ≤20 mL for placebo) and not clinically meaningful. At

Week 52, no significant differences in lung function between mepolizumab and placebo were observed (Table 9).

The patients enrolled in the COPD studies had severely compromised lung function, were non-reversible, and were receiving maximum bronchodilator therapy and an anti-inflammatory; a further effect on lung function with mepolizumab was not expected.

Table 9 Change from Baseline in Trough FEV_1 at Week 52: Mepolizumab 100 mg vs. Placebo (COPD Studies, mITT Primary Population)

	Study 106 High Stratum		Study 113		Meta-Analysis	
FEV_1 (mL)	Placebo N=229	Mepo 100 mg SC N=233	Placebo N=226	Mepo 100 mg SC N=223	Placebo N=455	Mepo 100 mg SC N=456
Baseline						
n	229	233	226	223	---	---
Mean	1145	1140	1225	1223	---	---
(SD)	(468.0)	(461.0)	(507.2)	(491.2)	---	---
Week 52						
n with analyzable data	223	233	224	222	447	455
n with analyzable data at time point	188	205	176	202	364	407
LS mean	1144	1134	1212	1232	1185	1190
LS mean change	-7	-17	-13	6	-10	-5
(SE) for mean/mean chg	(15.9)	(15.3)	(17.6)	(17.0)	(12.0)	(11.6)
Difference (mepo vs. placebo)	---	-10	---	19	---	5
95% CI	---	-54, 33	---	-29, 67	---	-28, 38
Nominal p-value	---	0.644	---	0.435	---	0.764

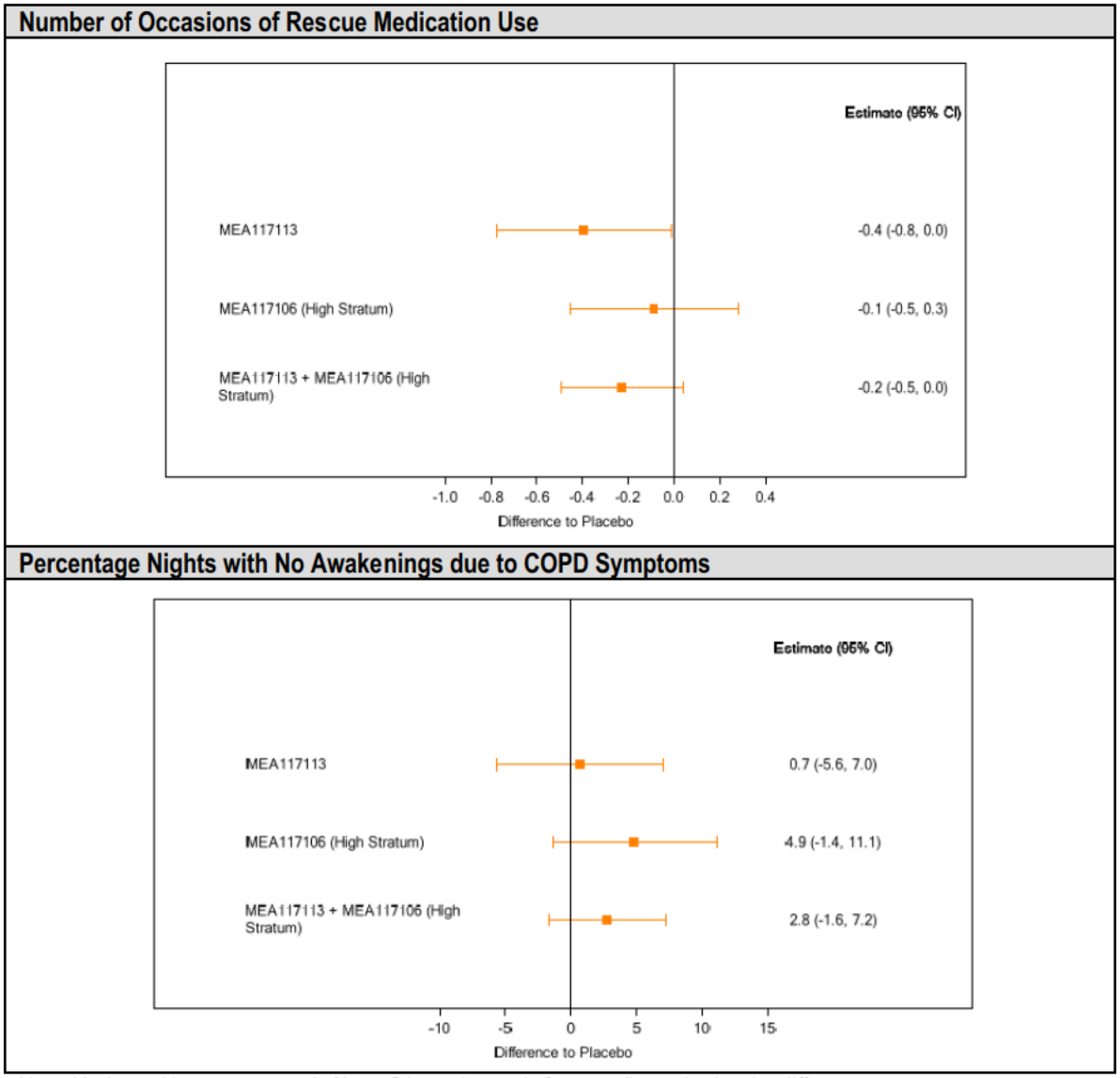
4.4.2. COPD Symptoms

Overall, patients treated with mepolizumab showed numerical reductions in rescue inhaler use and improvement in the percentage of nights with no awakenings due to COPD symptoms compared with patients receiving placebo.

The profile of rescue medication use over time differed between the two studies with greater reductions from baseline in occasions of rescue medication use observed in the mepolizumab 100 mg group compared with placebo over the entire treatment period in Study 113, but this trend was only observed through Week 24 in the Study 106 High Stratum. Thus, a smaller reduction in rescue medication use was observed at Weeks 49-52 in Study 106 High Stratum (-0.1 occasions) than in Study 113 (-0.4 occasions, nominal p 0.044) (Figure 14). The meta-analysis showed numerically greater reductions in the number of occasions of rescue medication use for mepolizumab 100 mg compared with placebo at all time points, with a treatment difference of -0.2 during Weeks 49-52 (nominal p 0.095).

The profile of percentage of nights with no awakenings due to COPD symptoms over time also differed between the two studies with greater increases from baseline observed in the mepolizumab 100 mg group compared with placebo over the entire treatment period in the Study 106 High Stratum, but only slight numerical differences in Study 113. Patients in the mepolizumab group had approximately 5% more nights with no awakenings due to COPD from baseline to Weeks 49 to 52 than patients in the placebo group in the Study 106 High Stratum and little change was noted in Study 113 (0.7%) (Figure 14). The meta-analysis showed patients in the mepolizumab group had 2.8% more nights with no awakenings due to COPD from baseline to Weeks 49-52 than patients in the placebo group.

Figure 14 COPD Symptom Measures at Weeks 49-52: Mepolizumab 100 mg vs. Placebo (COPD Studies, mITT Primary Population)



Note: Horizontal bars represent 95% confidence intervals for mepolizumab-placebo difference

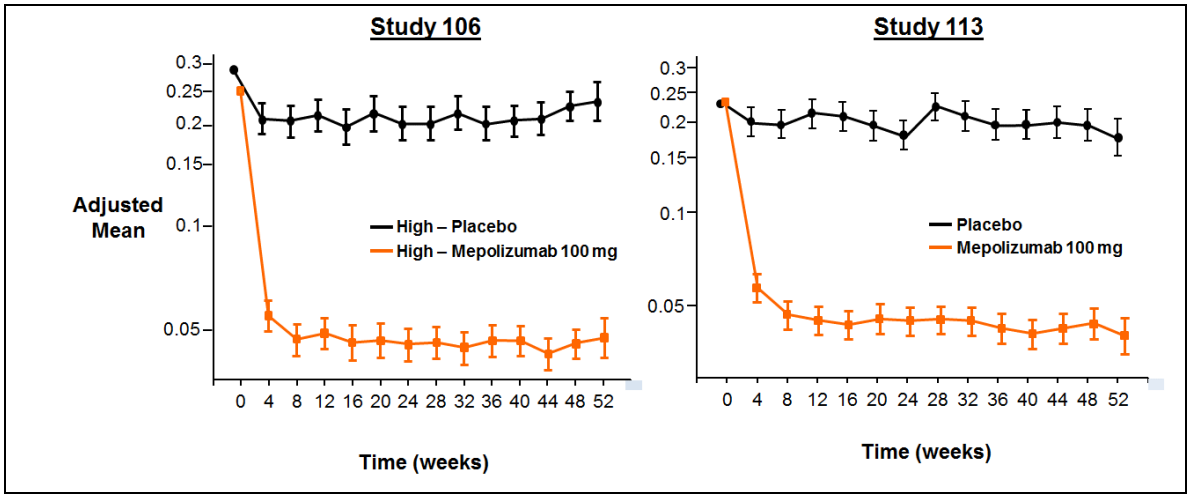
4.5. Pharmacodynamic Effect

Geometric mean screening blood eosinophil levels were 265 cells/µL in the Study 106 High Stratum and 229 cells/µL in Study 113.

In both studies, treatment with mepolizumab resulted in a sustained reduction in blood eosinophils over the 52-week treatment period starting at the first post-baseline assessment (Week 4, reductions >70% compared with placebo) (Figure 15). At Week 52, a reduction of 80% was observed with mepolizumab 100 mg compared with placebo in Study 106, and in Study 113, reductions of 78% and 79% were observed with mepolizumab 100 mg and 300 mg, respectively, compared with placebo. These results

support the known pharmacology of mepolizumab and are consistent with reductions seen across the clinical development program in other eosinophilic conditions including severe eosinophilic asthma.

Figure 15 Blood Eosinophils Absolute Values: Mepolizumab 100 mg vs. Placebo (COPD Studies, mITT Primary Population)



Note: Vertical bars represent 95% confidence intervals

4.6. Blood Eosinophils as a Predictor of Benefit

4.6.1. Utility of Blood Eosinophils as a Predictor of Response: Study 106

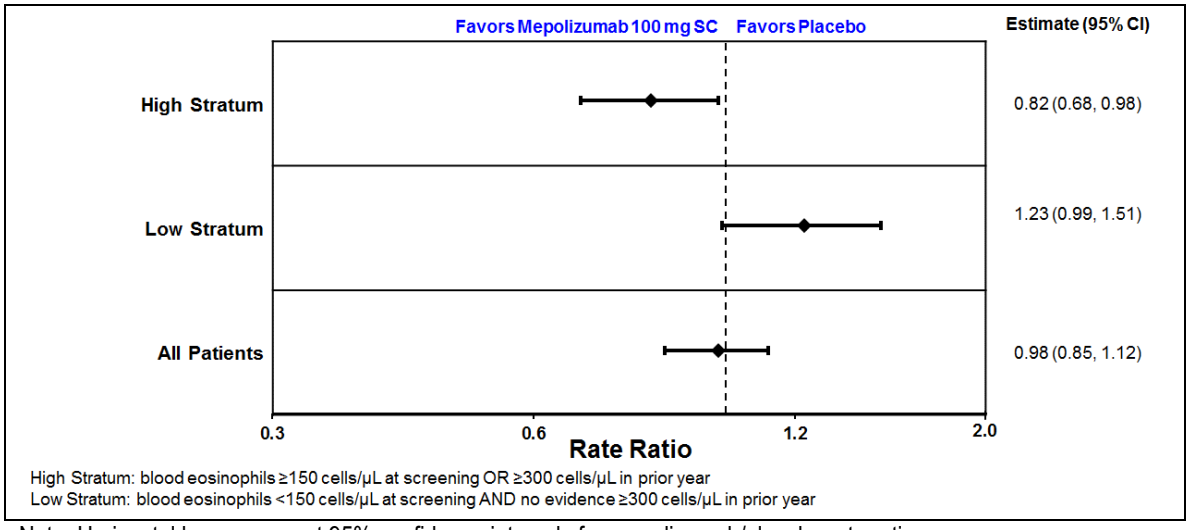
Study 106 was designed specifically to examine the utility of blood eosinophils as a predictor of mepolizumab response above and below the pre-defined threshold and this utility was demonstrated by the differing results from the High Stratum and Low Stratum.

Patients in the High Stratum (intended population: blood eosinophils ≥150 cells/µL at screening OR a historic blood eosinophil level in the preceding 12 months ≥300 cells/µL) treated with mepolizumab had an 18% reduction in the rate of moderate/severe exacerbations compared with placebo (Figure 16). This treatment response was replicated in the same population treated with mepolizumab 100 mg in Study 113 (20% reduction) (see Section 4.2.1).

As expected, mepolizumab provided no treatment benefit for patients in the Low Stratum (blood eosinophils <150 cells/µL at screening AND no evidence of a blood eosinophil level in the year prior ≥300 cells/µL).

These results support that mepolizumab efficacy in the COPD population is related to having an eosinophilic phenotype and this threshold can be used to identify the intended population.

Figure 16 Rate of Moderate/Severe Exacerbations: Mepolizumab 100 mg vs. Placebo (Study 106, mITT Population)



Note: Horizontal bars represent 95% confidence intervals for mepolizumab/placebo rate ratio

In the Low Stratum, the rate ratio for exacerbation reduction in patients treated with mepolizumab was 1.23 compared with placebo. A summary of the exacerbation endpoints for this group are shown in Table 10.

Table 10 Exacerbation Endpoints in Study 106 Low Stratum: Mepolizumab 100 mg vs. Placebo (mITT Population)

		Study 106 Low Stratum	
Exacerbation Endpoint	**Analysis**	**Placebo N=190**	**Mepolizumab 100 mg SC N=184**
Moderate/severe exacerbations	Rate ratio (95% CI)	---	1.23 (0.99, 1.51)
No moderate/severe exacerbations	n (%)	69 (36)	67 (36)
Time to first moderate/severe exacerbation	Hazard ratio (95% CI)	---	1.07 (0.83, 1.39)
Exacerbations requiring ED/hospitalization	Rate ratio (95% CI)	---	1.04 (0.66, 1.67)
Severe exacerbations	Rate ratio (95% CI)	---	0.89 (0.52, 1.53)

These results for the exacerbation endpoints in the Low Stratum show:

- An equal proportion of patients in the mepolizumab and placebo treatment arms had no exacerbations
- The time to first moderate/severe exacerbation was similar for the mepolizumab and placebo arms
- There was no difference between mepolizumab and placebo for the rate of exacerbations requiring ED visit/hospitalization or severe exacerbations

Further examination of the results at the individual patient level revealed that the rate ratio in the Low Stratum was mainly driven by 2 patients in the mepolizumab group having 9 or more moderate/severe exacerbations.

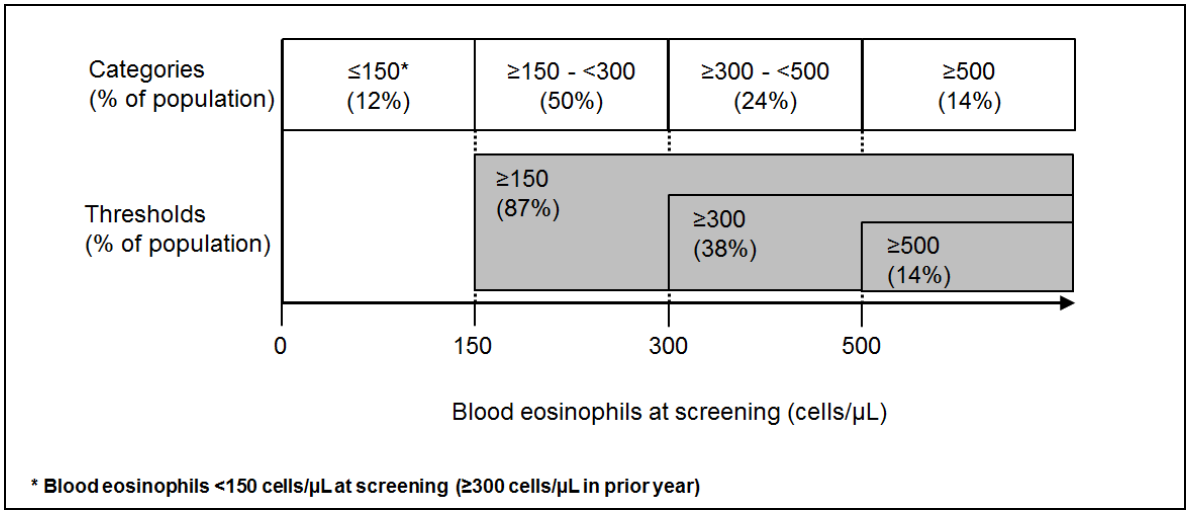
These observations highlight that overall there was no treatment difference compared with placebo and provide reassurance that the result for the moderate/severe exacerbation rate analysis in the Low Stratum, which is not the intended population, does not indicate an untoward effect of mepolizumab.

4.6.2. Blood Eosinophils and Mepolizumab Efficacy

In the severe asthma program, blood eosinophils were established as the most robust predictor of response for mepolizumab. The COPD program was designed to investigate whether these findings would be replicated.

The effect of blood eosinophils on mepolizumab treatment response was analyzed using two pre-specified subgroup analyses: by blood eosinophil categories and blood eosinophil thresholds (Figure 17). In the category analysis, patients were grouped into specific categories based on a defined range of blood eosinophils at screening and could only be in one category. In the threshold analysis, patients were classified based on having blood eosinophils at screening above a specific count and could be included in more than one subgroup based on the threshold.

Figure 17 Blood Eosinophil Thresholds and Categories (COPD Studies 106 and 113, mITT Primary Population)



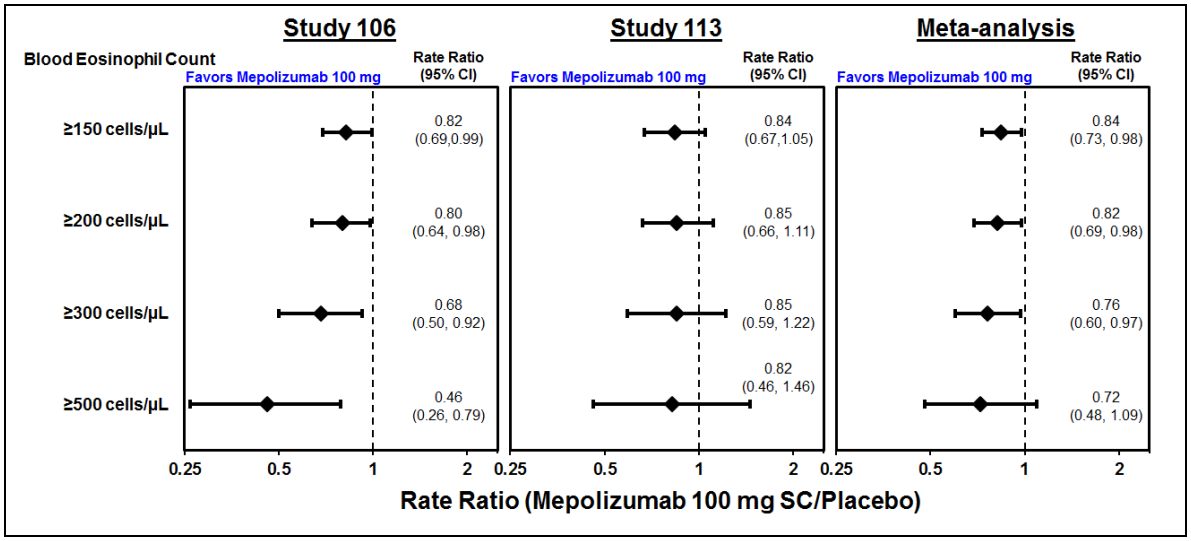
Results of the subgroup analysis of the rate of moderate/severe exacerbations by screening blood eosinophil thresholds (≥150 cells/µL, [≥200 cells/µL-added per FDA request], ≥300 cells/µL, ≥500 cells/µL) within the intended population for the individual studies and the meta-analysis are shown in Figure 18.

In Study 106, there was an increasing treatment response with increasing blood eosinophil thresholds, ranging from an 18% to 54% reduction in the rate of moderate/severe exacerbations for mepolizumab compared with placebo.

In Study 113, while there was less association of increasing treatment response across the eosinophil thresholds, the reduction in the rate of moderate/severe exacerbations in patients with ≥150 cells/µL at screening was consistent with the 18% to 20% reduction seen in the intended population across both studies.

The meta-analysis shows a consistent increase in treatment response with increasing blood eosinophil counts, ranging from 18% to 28% across the various eosinophil thresholds.

Figure 18 Rate of Moderate/Severe Exacerbations by Screening Blood Eosinophil Thresholds: Mepolizumab 100 mg vs. Placebo (COPD Studies, mITT Primary Population)



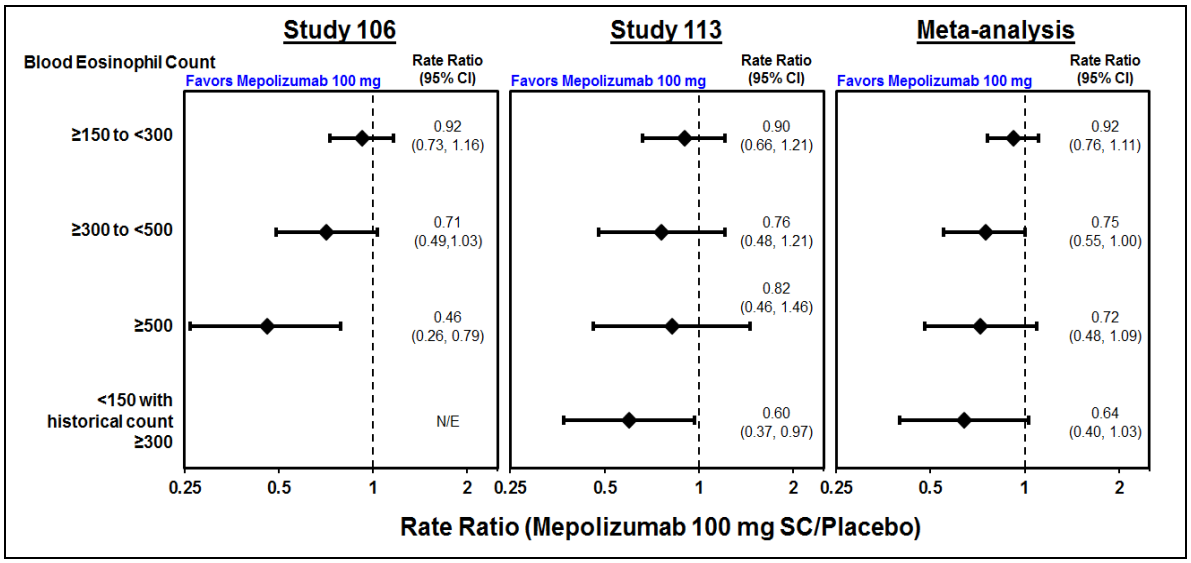
Note: Horizontal bars represent 95% confidence intervals for mepolizumab/placebo rate ratio
Note: ≥200 cells/µL threshold is a post-hoc analysis

Results of the subgroup analysis of the primary endpoint by screening blood eosinophil count categories (≥150 cells/µL to <300 cells/µL, ≥300 cells/µL to <500 cells/µL, ≥500 cells/µL) showed similar results to the blood eosinophil threshold analysis (Figure 19).

In each individual study, there was generally an increasing treatment response with increasing blood eosinophil count category: 8% to 54% in Study 106 and 10% to 24% in Study 113.

In the meta-analysis, the efficacy of mepolizumab was greater for patients whose blood eosinophil count was higher at screening. Greater reductions in the rate of moderate/severe exacerbations were observed in the 300 - <500 cells/µL (25%) and ≥500 cells/µL (28%) categories compared with 150 - <300 cells/µL (8%).

Figure 19 Rate of Moderate/Severe Exacerbations by Screening Blood Eosinophil Categories: Mepolizumab 100 mg vs. Placebo (COPD Studies, mITT Primary Population)



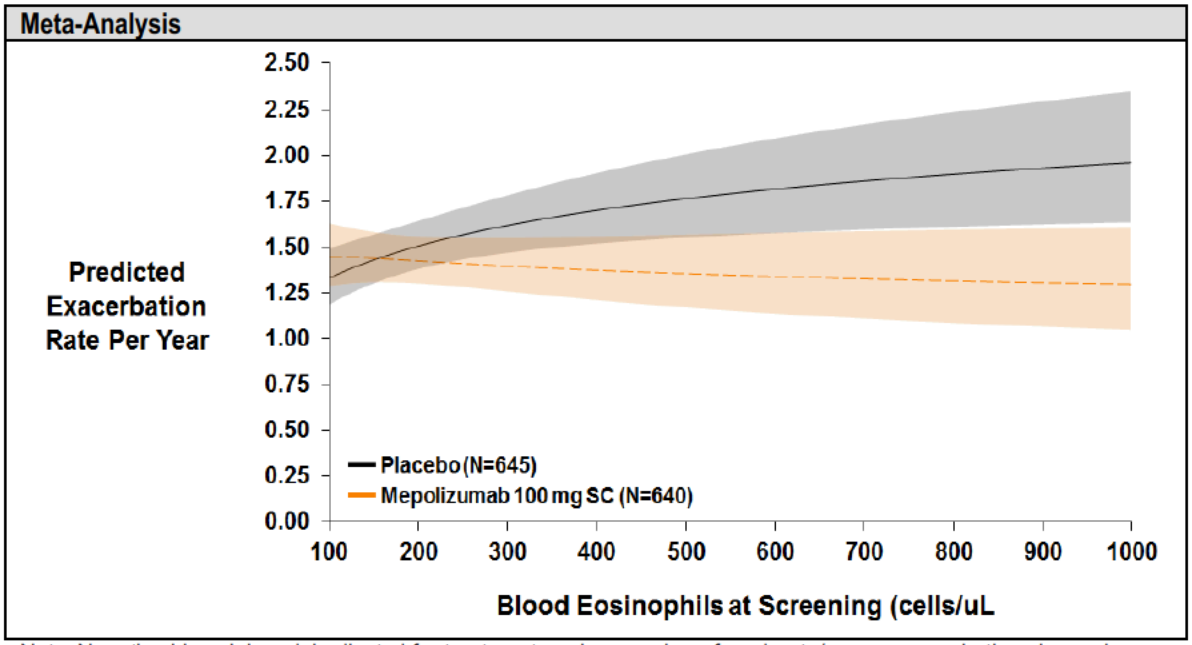
Note: Horizontal bars represent 95% confidence intervals
N/E=non-estimable due to small number of subjects (1 in placebo group and 12 in mepolizumab 100 mg group).

The relationship of increasing mepolizumab response with increasing blood eosinophil count was also evident in the meta-analysis for more severe exacerbations. In patients with a blood eosinophil count ≥500 cells/μL at screening, mepolizumab resulted in a 49% reduction in exacerbations requiring ED visit/hospitalization.

The role of screening blood eosinophil counts on the effectiveness of mepolizumab vs. placebo with respect to reduction in moderate/severe exacerbations was also investigated with statistical modelling. This meta-analysis used a fractional polynomial model [Sauerbrei, 2007] that utilized the data from both studies, including the data from the Study 106 Low Stratum. Screening blood eosinophil count was included in this model as a continuous variable.

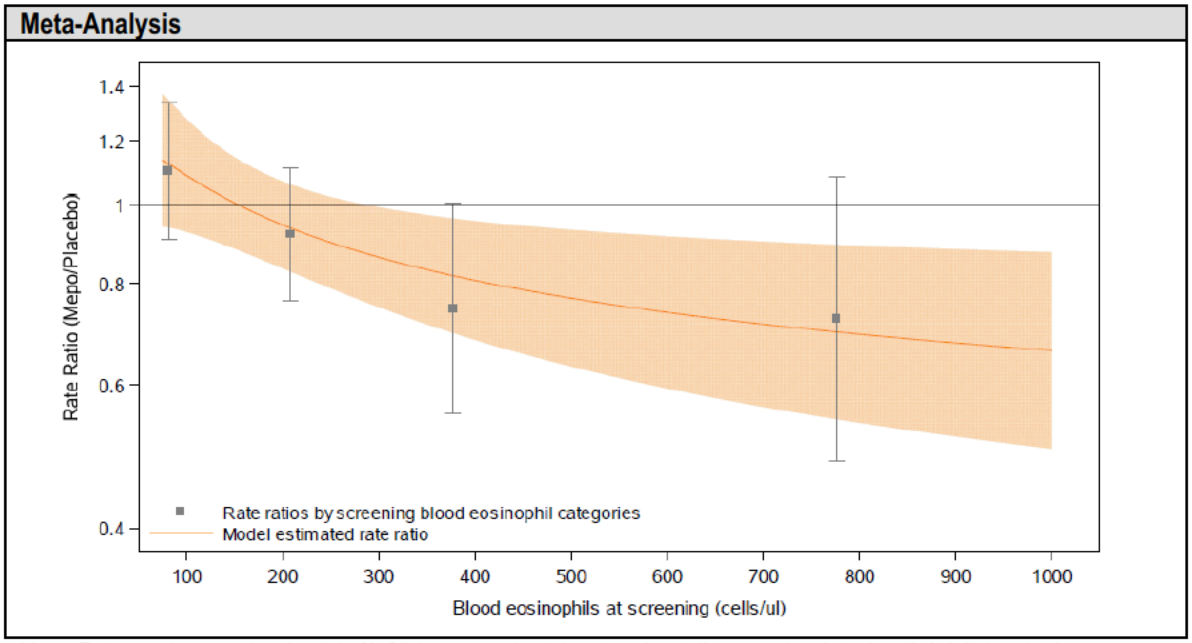
Figure 20 shows the predicted exacerbation rate against screening blood eosinophils and Figure 21 shows the predicted rate ratios. Greater reductions were seen in the predicted rates of exacerbations with mepolizumab relative to placebo with increasing screening blood eosinophil counts (nominal p 0.005 for interaction).

Figure 20 **Predicted Moderate/Severe Exacerbations Rates per Year by Blood Eosinophil Count at Screening: Mepolizumab 100 mg vs. Placebo (COPD Studies, mITT Population)**



Note: Negative binomial model adjusted for treatment, region, number of moderate/severe exacerbations in previous year (as ordinal variable), % predicted FEV_1, smoking status (current/former vs. never/non- smoker), study, 1/sqrt(eos), log(eos)/sqrt(eos) and treatment by 1/sqrt/(eos) and treatment by log(eos)/sqrt(eos) interaction.
Note: Shaded areas represent 95% CIs for predicted rates from the model of exacerbation rates against screening blood eosinophil count.

Figure 21 **Predicted Rate Ratio of Moderate/Severe Exacerbations by Blood Eosinophil Count at Screening: Mepolizumab 100 mg vs. Placebo (COPD Studies, mITT Population)**



Note: Estimated rate ratios (and 95% CI) by screening blood eosinophil categories (<150 cells/µL/ historical count ≥300 cells/µL, 150 - <300 cells/µL, 300 - <500 cells/µL, and ≥500 cells/µL) plotted against mean screening blood eosinophil count within each category. Shaded area represents 95% CI for predicted rate ratio from the model of exacerbation rates against screening blood eosinophil count. P-value for modelled interaction between treatment and screening eosinophil count: nominal p=0.005 (likelihood ratio test vs. model without interaction terms)

Exploratory multivariable modeling was also conducted to examine the potential effects of other baseline variables on predicting differential efficacy of mepolizumab against placebo based on the best fitting fractional polynomial model of screening blood eosinophils. Each candidate variable together with its interaction with treatment was entered separately into the model to distinguish which variables if any would predict a reduction in the rate of exacerbations. Variables investigated were: study, gender, age, race, body mass index (BMI), smoking status, geographical region, comorbidities, number of exacerbations in previous year, historical eosinophil count ≥300 cells/µL, baseline % predicted FEV_1, and mMRC score.

No statistically significant interactions between treatment and other baseline characteristics were found after accounting for the effect of screening blood eosinophil count.

Similar to the mepolizumab severe asthma program, these results from the COPD studies also demonstrate that the efficacy of mepolizumab generally increases as eosinophil count increases.

Overall, these results show that blood eosinophils can identify the eosinophilic COPD patient who is likely to benefit from mepolizumab and can therefore be used to guide therapy with mepolizumab.

4.7. Dose and Regimen Selection

The proposed recommended dose of mepolizumab for patients with COPD is 100 mg every 4 weeks.

The selection of 100 mg, as the expected therapeutic dose, for investigation in a COPD population with blood eosinophils ≥150 cells/µL at screening or ≥300 cells/µL in the prior year was supported by the similarities in sputum IL-5 and eosinophil levels between patients with severe asthma and COPD [Bafadhel, 2012a] and the well-characterized blood eosinophil dose-response established across multiple eosinophilic conditions. This dose is the therapeutic dose in severe eosinophilic asthma. In addition to 100 mg, a higher dose of 300 mg was also included in the COPD clinical development program (Study 113) to inform on the efficacy and safety of mepolizumab at a dose providing greater blood eosinophil reduction.

In patients with blood eosinophils ≥150 cells/µL at screening or ≥300 cells/µL in the prior year, the 100 mg dose provided a clinically relevant reduction in the primary endpoint of moderate/severe exacerbations of approximately 20% compared with placebo. This magnitude of reduction was consistent across the two Phase III studies (18% in the Study 106 High Stratum and 20% in Study 113) and consistent across the two doses of 100 mg and 300 mg investigated (14% and 20% reduction; see Section 4.2.1). The absence of evidence of a greater reduction in the rate of moderate/severe exacerbation and prolonged time to first moderate/severe exacerbation with 300 mg, as well as the absence of evidence of an exposure-response for those endpoints, support the rationale for a 100 mg therapeutic dose administered every 4 weeks in patients with COPD. Furthermore, the safety profile following mepolizumab treatment was comparable to placebo, irrespective of dose, and consistent to that observed in the Phase III severe asthma clinical program. From the well-characterized blood eosinophil dose-response established across multiple eosinophilic conditions, this dose represents approximately the dose providing 90% of the maximal inhibition effect (ID_{90}) for blood eosinophil reduction. This magnitude of reduction was previously also found to be effective in severe asthma.

5. SAFETY RESULTS

5.1. Safety Summary

No new safety concerns were identified in the COPD program. In the integrated COPD Studies 106 (all patients) and 113:

- The safety profile of mepolizumab (All Doses [100 mg and 300 mg]) plus SoC was similar to placebo plus SoC.
- The safety profile of mepolizumab 300 mg was similar to mepolizumab 100 mg.
- The overall incidence of AEs, SAEs, deaths, and AEs leading to study treatment discontinuation were similar for mepolizumab and placebo.
- Externally adjudicated causes of death for fatal SAEs and primary causes of non-fatal SAEs were similar between the mepolizumab and placebo groups.

- Compared with placebo, patients who received mepolizumab did not have an increased risk of systemic reactions, local injection site reactions, infections, malignancies, or serious CVT events.
- ADA positive results anytime post-baseline were seen in 4% of patients in the mepolizumab 100 mg group (median titer 32) and in <1% of patients in the placebo group (median titer 8). No neutralizing antibodies were reported post-baseline for patients receiving mepolizumab.
- No treatment-related trends were observed in clinical laboratory tests, vital signs, or ECGs.

5.2. Extent of Exposure

NUCALA (mepolizumab) has been approved for severe eosinophilic asthma (100 mg every 4 weeks) in numerous markets and for EGPA (300 mg every 4 weeks) in the US and Japan. The cumulative exposure to mepolizumab in the post-marketing setting as of 31 December 2017 was over 23,000 patient-years.

As of 15 December 2017 (cut-off date for 120 Day Safety Update), over 4000 patients have been exposed to mepolizumab in all completed and ongoing GSK-sponsored clinical studies (all indications).

A total of 1510 patients participated in the COPD clinical development program, of these, 865 patients received mepolizumab (Table 11). Of these 865 patients, 640 (74%) received mepolizumab 100 mg. The majority of patients treated with mepolizumab (>80%) were exposed for at least 12 months.

Table 11 Duration of Exposure (COPD Studies 106 and 113, Safety Population)

	Placebo N=645	Mepolizumab	
		100 mg SC N=640	300 mg SC N=225
Exposure (months)			
Mean (SD)	10.6 (3.08)	11.1 (2.65)	10.9 (2.78)
Median	12.0	12.0	12.0
Min, Max	1, 14	1, 13	1, 13
Range of Exposure, n (%)			
<12 months	142 (22)	91 (14)	42 (19)
12 to <24 months	503 (78)	549 (86)	183 (81)
Total Patient-Years[1]	569.72	590.29	203.76

1. Sum across patients of (treatment stop date-treatment start date +29)/365.25

5.3. Adverse Event Overview

In the COPD studies, the incidences of AEs and SAEs for mepolizumab (100 mg, 300 mg, and All Doses) plus SoC were similar to placebo plus SoC (Table 12).

Table 12 Adverse Event Summary (COPD Studies 106 and 113, Safety Population)

Type of Adverse Event	Number (%) of Patients			
		Mepolizumab		
	Placebo N=645	100 mg SC N=640	300 mg SC N=225	All Doses[1] N=865
Adverse Events				
Any event[2]	527 (82)	523 (82)	196 (87)	719 (83)
On-treatment[3]	521 (81)	516 (81)	191 (85)	707 (82)
Drug-related[4]	89 (14)	79 (12)	28 (12)	107 (12)
Led to study treatment discontinuation	62 (10)	40 (6)	25 (11)	65 (8)
Led to study withdrawal	39 (6)	25 (4)	13 (6)	38 (4)
Serious Adverse Events				
Any event[2]	199 (31)	172 (27)	60 (27)	232 (27)
On-treatment[3]	175 (27)	156 (24)	54 (24)	210 (24)
Non-fatal SAEs	168 (26)	152 (24)	48 (21)	200 (23)
Fatal SAEs[2]	26 (4)	20 (3)	8 (4)	28 (3)

1. All Doses includes mepolizumab 100 mg SC and 300 mg SC
2. On-treatment and post-treatment
3. AE/SAE onset on day of starting treatment and up to 4 weeks (28 days) after the last dose of treatment
4. Investigator's judgment of causality

Examination of on-treatment AEs by System Organ Classes (SOCs) shows the highest incidences (>30% of patients in any treatment group) in the Infections and infestations SOC and in the Respiratory, thoracic, and mediastinal disorders SOC (Table 13). The incidence of AEs in these two SOCs was similar between the mepolizumab All Doses and placebo groups. The incidences of on-treatment AEs in other SOCs were also similar between the mepolizumab All Doses and placebo groups.

Table 13 On-treatment Adverse Events by System Organ Class (>=5% in Any Treatment Group) (COPD Studies 106 and 113, Safety Population)

System Organ Class	Number (%) of Patients			
		Mepolizumab		
	Placebo N=645	100 mg SC N=640	300 mg SC N=225	All Doses[1] N=865
Infections and infestations	341 (53)	326 (51)	113 (50)	439 (51)
Respiratory, thoracic and mediastinal disorders	215 (33)	230 (36)	71 (32)	301 (35)
Musculoskeletal and connective tissue disorders	149 (23)	161 (25)	50 (22)	211 (24)
Gastrointestinal disorders	132 (20)	137 (21)	54 (24)	191 (22)
Nervous system disorders	116 (18)	116 (18)	36 (16)	152 (18)
General disorders and administration site conditions	111 (17)	98 (15)	42 (19)	140 (16)
Injury, poisoning and procedural complications	77 (12)	73 (11)	20 (9)	93 (11)
Cardiac disorders	45 (7)	56 (9)	21 (9)	77 (9)
Skin and subcutaneous tissue disorders	55 (9)	55 (9)	22 (10)	77 (9)
Investigations	40 (6)	45 (7)	25 (11)	70 (8)
Vascular disorders	38 (6)	46 (7)	14 (6)	60 (7)
Metabolism and nutrition disorders	46 (7)	35 (5)	12 (5)	47 (5)
Psychiatric disorders	36 (6)	34 (5)	13 (6)	47 (5)
Renal and urinary disorders	28 (4)	30 (5)	9 (4)	39 (5)
Eye disorders	28 (4)	29 (5)	6 (3)	35 (4)

1. All Doses includes mepolizumab 100 mg SC and 300 mg SC

5.4. Adverse Events of Special Interest

AESI are described in Section 2.3.4. Each category and subcategory of AESI occurred with similar incidence between the mepolizumab All Doses and placebo treatment groups (Table 14). The AESI profile was similar for the mepolizumab 100 mg and 300 mg dose groups.

Table 14 Incidence of On-treatment Adverse Events of Special Interest (COPD Studies 106 and 113, Safety Population)

Adverse Event of Special Interest	Placebo N=645	Number (%) of Patients: Mepolizumab 100 mg SC N=640	Mepolizumab 300 mg SC N=225	Mepolizumab All Doses[1] N=865
Systemic Reactions[2]	13 (2)	10 (2)	5 (2)	15 (2)
Non-allergic Reactions	10 (2)	7 (1)	4 (2)	11 (1)
Hypersensitivity Reactions	3 (<1)	4 (<1)	1 (<1)	5 (<1)
Any Anaphylaxis	0	0	1[3]	1[3]
Anaphylaxis considered by the investigator to represent systemic reaction meeting Sampson's criteria	0	0	0	0
Local Injection Site Reactions[2]	21 (3)	18 (3)	11 (5)	29 (3)
All Infections[4]	341 (53)	326 (51)	113 (50)	439 (51)
Serious Infections	60 (9)	57 (9)	22 (10)	79 (9)
Opportunistic Infections[5]	13 (2)	18 (3)	9 (4)	27 (3)
Neoplasms[4]	20 (3)	20 (3)	6 (3)	26 (3)
Malignancies[6]	13 (2)	13 (2)	3 (1)	16 (2)
Cardiac Disorders[4]	45 (7)	56 (9)	21 (9)	77 (9)
Serious Cardiac Disorders	21 (3)	26 (4)	8 (4)	34 (4)
Serious CVT Events[6]	24 (4)	32 (5)	10 (4)	42 (5)

1. All Doses includes mepolizumab 100 mg SC and 300 mg SC
2. As identified by the investigator in eCRF designed for collecting data on systemic reactions or local injection site reactions
3. Considered by the investigator unrelated to study treatment and related to diclofenac; the patient continued mepolizumab and completed the study
4. Infections from Infections and infestations SOC. Neoplasms from Neoplasms benign malignant and unspecified (including cysts and polyps) SOC. Cardiac disorders from Cardiac disorders SOC.
5. Identified based on published list of pathogens and/or presentations of specific pathogens to be considered as opportunistic infections in the setting of biologic therapy [Winthrop, 2015].
6. Defined based on the standardized MedDRA queries (SMQs) and/or list of MedDRA preferred terms pre-specified by the GSK Safety Review Team

5.4.1. Systemic (Allergic/Hypersensitivity and Non-allergic) Reactions

The incidence of systemic reactions was the similar between the mepolizumab and placebo groups (2% each) (Table 15).

All systemic reactions in the mepolizumab groups were non-serious; 2 patients in the placebo group had serious systemic reactions. All systemic reaction events were either mild or moderate in intensity except one allergic/hypersensitivity event (Type III immune complex-mediated reaction) in the placebo group that was considered severe and led to study treatment discontinuation.

All systemic reaction events in the mepolizumab groups resolved/resolved with sequelae with continued study treatment; 5 patients in the placebo group discontinued study treatment due to a systemic reaction.

The most frequently reported (>1 patient) symptoms of systemic reactions were headache, fatigue, and rash in the mepolizumab All Doses group, and fatigue, hypotension, pruritus, and rash in the placebo group.

The majority of systemic reactions occurred on the day of dosing.

Table 15 On-treatment Systemic (Allergic/Hypersensitivity and Non-Allergic) Reactions (COPD Studies 106 and 113, Safety Population)

Systemic Reactions	Number (%) of Patients			
		Mepolizumab		
	Placebo N=645	100 mg SC N=640	300 mg SC N=225	All Doses[1] N=865
Any Event	13 (2)	10 (2)[2]	5 (2)	15 (2)[2]
Allergic/hypersensitivity reaction	3 (<1)	4 (<1)	1 (<1)	5 (<1)
Non-allergic reaction	10 (2)	7 (1)	4 (2)	11 (1)

1. All Doses includes mepolizumab 100 mg SC and 300 mg SC
2. An allergic/hypersensitivity reaction and a non-allergic systemic reaction were reported for one patient in the mepolizumab 100 mg group.

5.4.2. Local Injection Site Reactions

Local injection site reactions were reported with a similar incidence in the mepolizumab and placebo groups (3% each) (Table 14).

None of the local injection site reactions (mepolizumab or placebo) were serious and the majority were mild or moderate in intensity. All events resolved/resolved with sequelae with continued study treatment except for 2 patients (1 each in the placebo and mepolizumab 100 mg groups) who discontinued study treatment due to local injection site reactions, both events with a symptom of pain.

Symptoms reported by >1 patient in the mepolizumab All Doses group were pain, erythema, swelling, itching, and warm to touch, and in the placebo group were pain, swelling, and burning at injection site.

All local injection site reactions were considered related to study treatment by the investigator. The majority of patients had an injection site reaction within 1 hour of receiving study treatment.

5.4.3. Infections

The incidence of AEs in the Infections and infestations SOC was similar between the mepolizumab All Doses (51%) and placebo (53%) groups (Table 16). Nasopharyngitis was the most frequently reported infection with similar incidence in the mepolizumab All Doses group and in the placebo group (17% each) (Table 21).

The incidence of SAEs in the Infections and infestations SOC was also similar between the mepolizumab All Doses and the placebo groups (9% each). Pneumonia was the most common on-treatment SAE (6% mepolizumab All Doses and 7% placebo). Fatal SAEs

in the Infections and infestations SOC were reported for 3 patients (<1%) in the mepolizumab All Doses group (preferred terms [PTs] of sepsis for 2 patients in the 100 mg group and pneumonia for 1 patient in the 300 mg group), and 5 patients (<1%) in the placebo group (PTs of pneumonia for 4 patients and urinary tract infection for 1 patient) (see Table 24).

The incidence of AEs potentially representing opportunistic infections was similar between the mepolizumab All Doses (3%) and placebo (2%) groups (Table 16). No parasitic infections were reported in the COPD studies. Nearly all events potentially representing opportunistic infections were non-serious and did not lead to treatment discontinuation, except for the one serious event of pulmonary tuberculosis reactivation in the mepolizumab 300 mg group, which led to treatment discontinuation.

Table 16 On-treatment Adverse Event of Special Interest: Infections (COPD Studies 106 and 113, Safety Population)

	Number (%) of Patients			
		Mepolizumab		
Infections and Infestations	Placebo N=645	100 mg SC N=640	300 mg SC N=225	All Doses[1] N=865
Any infection	341 (53)	326 (51)	113 (50)	439 (51)
Serious infection	60 (9)	57 (9)	22 (10)	79 (9)
Opportunistic Infections[2]				
Any opportunistic infection event	13 (2)	18 (3)	9 (4)	27 (3)
Herpes zoster	5 (<1)	11 (2)	5 (2)	16 (2)
Candida infection	5 (<1)	5 (<1)	4 (2)	9 (1)
Herpes simplex	1 (<1)	1 (<1)	0	1 (<1)
Oesophageal candidiasis	1 (<1)	1 (<1)	0	1 (<1)
Herpes ophthalmic	0	0	1 (<1)	1 (<1)
Pulmonary tuberculosis	0	0	1 (<1)	1 (<1)
Gastrointestinal candidiasis	1 (<1)	0	0	0

1. All Doses includes mepolizumab 100 mg SC and 300 mg SC
2. AEs potentially representing opportunistic infections

Note: Events matching terms based on a published list considered as opportunistic infections in the setting of biologic therapy [Winthrop, 2015]

5.4.3.1. Pneumonia

Pneumonia AEs (summarized as a composite term from a list of pre-specified PTs) were reported with a similar incidence between the mepolizumab All Doses and placebo groups (11% each) (Table 17). Fatal pneumonia SAEs were reported for 4 patients in the placebo group and 1 patient in the mepolizumab 300 mg group, each with a PT of pneumonia (see Table 24).

Table 17 Pneumonia Adverse Events (COPD Studies 106 and 113, Safety Population)

Pneumonia AEs	Number (%) of Patients			
		Mepolizumab		
	Placebo N=645	100 mg SC N=640	300 mg SC N=225	All Doses[1] N=865
Any pneumonia AE (composite term)	71 (11)	66 (10)	26 (12)	92 (11)
Infections and infestations	70 (11)	65 (10)	26 (12)	91 (11)
Pneumonia	66 (10)	61 (10)	23 (10)	84 (10)
Lung infection	2 (<1)	2 (<1)	0	2 (<1)
Pneumonia pseudomonal	0	0	2 (<1)	2 (<1)
Pneumonia bacterial	0	1 (<1)	0	1 (<1)
Pneumonia klebsiella	0	1 (<1)	0	1 (<1)
Pneumonia pneumococcal	0	1 (<1)	0	1 (<1)
Pneumonia staphylococcal	0	1 (<1)	0	1 (<1)
Pneumonia streptococcal	0	1 (<1)	0	1 (<1)
Pulmonary tuberculosis	0	0	1 (<1)	1 (<1)
Pneumonia haemophilus	1 (<1)	0	0	0
Pneumonia necrotising	1 (<1)	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (<1)	2 (<1)	0	2 (<1)
Pneumonia aspiration	0	1 (<1)	0	1 (<1)
Pneumonitis	0	1 (<1)	0	1 (<1)
Bronchopneumopathy	1 (<1)	0	0	0

1. All Doses includes mepolizumab 100 mg SC and 300 mg SC

5.4.4. Neoplasms and Malignancies

Neoplasms (both benign and malignant) and malignancies were reported with a similar incidence in the mepolizumab All Doses and placebo groups (3% and 2% each, respectively) (Table 18). Malignancies that occurred in more than one patient included basal cell carcinoma, non-small cell lung cancer, prostate cancer, squamous cell carcinoma, bladder cancer, breast cancer, lung adenocarcinoma, metastases to lung, and metastases to the mediastinum. Fatal malignancies occurred in 4 patients (<1%) in the mepolizumab All Doses group and in 3 patients (<1%) in the placebo group (see Table 24). The types of malignancies reported are common in the general population (NIH-NCI, 2018).

Table 18 On-treatment Malignancies (COPD Studies 106 and 113, Safety Population)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Number (%) of Patients			
		Mepolizumab		
	Placebo N=645	100 mg SC N=640	300 mg SC N=225	All Doses[1] N=865
Any event[2]	20 (3)	20 (3)	6 (3)	26 (3)
Any SAE[2]	8 (1)	8 (1)	4 (2)	12 (1)
Malignancies[3]	13 (2)	13 (2)	3 (1)	16 (2)
Basal cell carcinoma	1 (<1)	2 (<1)	0	2 (<1)
Non-small cell lung cancer	1 (<1)	1 (<1)	1 (<1)	2 (<1)
Breast cancer	0	2 (<1)	0	2 (<1)
Lung adenocarcinoma	0	1 (<1)	1 (<1)	2 (<1)
Metastases to lung	0	2 (<1)	0	2 (<1)
Metastases to the mediastinum	0	2 (<1)	0	2 (<1)
Squamous cell carcinoma	1 (<1)	2 (<1)	0	2 (<1)
Prostate cancer	2 (<1)	0	1 (<1)	1 (<1)
Bowen's disease	0	1 (<1)	0	1 (<1)
Colon cancer	0	1 (<1)	0	1 (<1)
Laryngeal cancer recurrent	0	1 (<1)	0	1 (<1)
Lung neoplasm malignant	0	1 (<1)	0	1 (<1)
Retinal melanoma	0	1 (<1)	0	1 (<1)
Bladder cancer	2 (<1)	0	0	0
Plasma cell myeloma	1 (<1)	0	0	0
Gastric cancer recurrent	1 (<1)	0	0	0
Adenocarcinoma of colon	1 (<1)	0	0	0
Squamous cell carcinoma of lung	1 (<1)	0	0	0
Squamous cell carcinoma of skin	1 (<1)	0	0	0
T-cell lymphoma	1 (<1)	0	0	0
Transitional cell carcinoma	1 (<1)	0	0	0

1. All Doses includes mepolizumab 100 mg SC and 300 mg SC
2. Events in the Neoplasms benign, malignant, and unspecified (incl cysts and polyps) SOC
3. Events identified from sub-SMQs under the Malignancy SMQ.

5.4.5. Serious CVT Events

Serious cardiac, vascular and thromboembolic events is a composite term incorporating serious events from the Cardiac disorders SOC, Vascular disorders SOC, and relevant events from other SOCs.

The incidence of on-treatment serious CVT events was 5% in the mepolizumab All Doses group and 4% in the placebo group (Table 19). Serious AEs in the Cardiac disorders SOC were reported for 34 patients (4%) in the mepolizumab All Doses group and 21 patients (3%) in the placebo group. The most frequently reported AE in this SOC was atrial fibrillation (6 patients in both treatment groups). All individual PTs were reported by <1% of patients in all groups.

Table 19 On-treatment Serious Cardiac, Vascular and Thromboembolic Events in a Total of ≥2 Patients (COPD Studies 106 and 113, Safety Population)

Serious CVT Events	Number (%) of Patients			
		Mepolizumab		
	Placebo N=645	100 mg SC N=640	300 mg SC N=225	All Doses[1] N=865
Any serious CVT event	24 (4)	32 (5)	10 (4)	42 (5)
Cardiac disorders	21 (3)	26 (4)	8 (4)	34 (4)
Atrial fibrillation	6 (<1)	6 (<1)	0	6 (<1)
Acute myocardial infarction	4 (<1)	3 (<1)	2 (<1)	5 (<1)
Cardiac failure congestive	3 (<1)	4 (<1)	0	4 (<1)
Cardiac failure	1 (<1)	2 (<1)	0	2 (<1)
Acute coronary syndrome	0	1 (<1)	1 (<1)	2 (<1)
Supraventricular tachycardia	0	0	2 (<1)	2 (<1)
Cardiac arrest	1 (<1)	1 (<1)	0	1 (<1)
Cardiac failure chronic	1 (<1)	1 (<1)	0	1 (<1)
Cor pulmonale	1 (<1)	1 (<1)	0	1 (<1)
Coronary artery disease	1 (<1)	0	1 (<1)	1 (<1)
Myocardial infarction	1 (<1)	0	1 (<1)	1 (<1)
Stress cardiomyopathy	1 (<1)	0	1 (<1)	1 (<1)
Ventricular tachycardia	1 (<1)	1 (<1)	0	1 (<1)
Vascular system disorders	4 (<1)	5 (<1)	0	5 (<1)
Hypertension	1 (<1)	1 (<1)	0	1 (<1)
Hypotension	1 (<1)	1 (<1)	0	1 (<1)
Orthostatic hypotension	1 (<1)	1 (<1)	0	1 (<1)
Nervous system disorders	1 (<1)	3 (<1)	0	3 (<1)
Transient ischemic attack	1 (<1)	2 (<1)	0	2 (<1)
Respiratory, thoracic & mediastinal disorders	0	1 (<1)	2 (<1)	3 (<1)
Pulmonary embolism	0	1 (<1)	2 (<1)	3 (<1)

1. All Doses includes mepolizumab 100 mg SC and 300 mg SC

Note: Serious events in the Cardiac Disorders and Vascular Disorders MedDRA SOCs, thromboembolic events identified via SMQs and sub-SMQs

Twelve patients had fatal serious CVT events (Cardiac disorders SOC): 6 in the mepolizumab 100 mg group (<1%), 3 in the mepolizumab 300 mg group (1%) and 3 in the placebo group (<1%) (see Table 24).

All serious events, including fatal events, were independently adjudicated to assess primary cause of the event. The adjudicated fatal and non-fatal events with cardiovascular as the primary cause of the death or the non-fatal event were reported with similar incidences between the mepolizumab and placebo treatment groups (Table 25 and Table 27, respectively).

5.5. Immunogenicity

Mepolizumab showed low immunogenic potential in patients with COPD. At any time post-baseline, the incidence of treatment-emergent positive ADA results was 4% in the

mepolizumab All Doses group and <1% in the placebo group (Table 20). Median titers were 32.0 in the mepolizumab All Doses group and 8.0 in the placebo group. No patients treated with mepolizumab tested positive for neutralizing antibodies post-baseline. No trends were apparent in review of the AEs in ADA positive vs. ADA negative patients. Anti-mepolizumab antibodies did not discernibly impact the pharmacokinetic (PK) or pharmacodynamic (PD) effects of mepolizumab treatment in the majority of patients.

Table 20 Immunogenicity – Highest Treatment-Emergent Confirmatory Result Any Time Post-Baseline (COPD Studies 106 and 113, Safety Population)

Immunogenicity Results Post-baseline	Placebo N=645	Mepolizumab 100 mg SC N=640	Mepolizumab 300 mg SC N=225	Mepolizumab All Doses[1] N=865
Binding Antibody Assay				
n	608	609	219	828
Assay result, n (%)				
Negative	605 (>99)	584 (96)	215 (98)	799 (96)
Positive	3 (<1)	25 (4)	4 (2)	29 (4)
Persistent positive	0	17 (3)	3 (1)	20 (2)
Transient positive	3 (<1)	8 (1)	1 (<1)	9 (1)
Titer result				
Median	8.0	32.0	20.0	32.0
Min, Max	2, 32	2, 128	2, 64	2, 128
Neutralizing Antibody Assay				
n	5	27	4	31
Negative	4 (80)	27 (100)	4 (100)	31 (100)
Positive	1 (20)	0	0	0

1. All Doses includes mepolizumab 100 mg SC and 300 mg SC

Note: Includes only patients who did not have a positive binding antibody assay result prior to first dose and who had both baseline and post-baseline samples.

Note: A patient was considered 'Positive - Transient positive' if they had a single positive immunogenic response that did not occur at the final study assessment. A patient was considered 'Positive - Persistent positive' if they had a positive immunogenic response for at least 2 consecutive assessments or a single result at the final study assessment. A patient was considered 'Negative' if they had all negative post-baseline binding ADA assay results.

5.6. Common Adverse Events

The overall incidence of on-treatment AEs was similar between the mepolizumab All Doses and placebo groups (Table 21). The most frequently reported AEs (≥10% of patients in any treatment group) also occurred with similar incidence between the mepolizumab All Doses and placebo groups (nasopharyngitis 17% each; COPD 16% and 17%; and headache 11% and 12%).

Table 21 Common (≥3% Incidence in Any Treatment Group) On-Treatment Adverse Events (COPD Studies 106 and 113, Safety Population)

	Number (%) of Patients			
		Mepolizumab		
Adverse Event (Preferred Term)	Placebo N=645	100 mg SC N=640	300 mg SC N=225	All Doses[1] N=865
Any On-treatment AE	521 (81)	516 (81)	191 (85)	707 (82)
Any Common AE	425 (66)	416 (65)	144 (64)	560 (65)
Nasopharyngitis	111 (17)	103 (16)	40 (18)	143 (17)
COPD[2]	109 (17)	104 (16)	35 (16)	139 (16)
Headache	76 (12)	76 (12)	22 (10)	98 (11)
Pneumonia	59 (9)	53 (8)	20 (9)	73 (8)
Back pain	42 (7)	48 (8)	17 (8)	65 (8)
Oropharyngeal pain	22 (3)	39 (6)	11 (5)	50 (6)
Upper respiratory tract infection	42 (7)	37 (6)	13 (6)	50 (6)
Cough	27 (4)	36 (6)	16 (7)	52 (6)
Diarrhoea	29 (4)	34 (5)	8 (4)	42 (5)
Dyspnoea	30 (5)	29 (5)	10 (4)	39 (5)
Sinusitis	20 (3)	27 (4)	7 (3)	34 (4)
Pain in extremity	21 (3)	26 (4)	6 (3)	32 (4)
Arthralgia	25 (4)	23 (4)	6 (3)	29 (3)
Urinary tract infection	22 (3)	24 (4)	2 (<1)	26 (3)
Influenza	35 (5)	22 (3)	4 (2)	26 (3)
Hypertension	12 (2)	21 (3)	7 (3)	28 (3)
Nausea	15 (2)	19 (3)	9 (4)	28 (3)
Injection site reaction	22 (3)	18 (3)	11 (5)	29 (3)
Bronchitis	21 (3)	17 (3)	12 (5)	29 (3)
Oral candidiasis	17 (3)	17 (3)	8 (4)	25 (3)
Fatigue	10 (2)	15 (2)	8 (4)	23 (3)
Pyrexia	23 (4)	14 (2)	13 (6)	27 (3)
Pharyngitis	22 (3)	17 (3)	4 (2)	21 (2)
Dizziness	21 (3)	16 (3)	3 (1)	19 (2)
Non-cardiac chest pain	17 (3)	13 (2)	7 (3)	20 (2)
Musculoskeletal pain	14 (2)	9 (1)	7 (3)	16 (2)

1. All Doses includes mepolizumab 100 mg SC and 300 mg SC
2. COPD exacerbation

5.7. Serious Adverse Events

Investigator-reported Fatal and Non-Fatal SAEs

In the COPD Studies, the incidence of investigator-reported on-treatment SAEs (fatal and non-fatal) was similar between the mepolizumab All Doses group (24%) and the placebo group (27%) (Table 22). Examination of SAEs by SOC shows the highest incidences (≥10% of patients in any treatment group) in the Respiratory, thoracic, and mediastinal disorders and Infections and infestations SOCs and the incidences were similar between the mepolizumab All Doses and placebo groups. The incidence of SAEs across the SOCs in the mepolizumab 300 mg group was similar to the mepolizumab 100 mg group.

Table 22 On-treatment Serious Adverse Events (Fatal and Non-Fatal) by System Organ Class (COPD Studies 106 and 113, Safety Population)

System Organ Class	Number (%) of Patients			
		Mepolizumab		
	Placebo N=645	100 SC N=640	300 SC N=225	All Doses N=865
Any On-treatment SAE[1]	175 (27)	156 (24)	54 (24)	210 (24)
Respiratory, thoracic and mediastinal disorders	108 (17)	94 (15)	29 (13)	123 (14)
Infections and infestations	60 (9)	57 (9)	22 (10)	79 (9)
Cardiac disorders	21 (3)	26 (4)	8 (4)	34 (4)
Gastrointestinal disorders	4 (<1)	14 (2)	4 (2)	18 (2)
Renal and urinary disorders	5 (<1)	11 (2)	0	11 (1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (1)	8 (1)	4 (2)	12 (1)
Nervous system disorders	5 (<1)	6 (<1)	1 (<1)	7 (<1)
Injury, poisoning and procedural complications	13 (2)	5 (<1)	0	5 (<1)
Musculoskeletal and connective tissue disorders	5 (<1)	5 (<1)	0	5 (<1)
Vascular disorders	4 (<1)	5 (<1)	0	5 (<1)
General disorders and administration site conditions	3 (<1)	4 (<1)	2 (<1)	6 (<1)
Psychiatric disorders	2 (<1)	3 (<1)	0	3 (<1)
Hepatobiliary disorders	3 (<1)	2 (<1)	0	2 (<1)
Metabolism and nutrition disorders	6 (<1)	2 (<1)	0	2 (<1)
Endocrine disorders	0	1 (<1)	0	1 (<1)
Investigations	1 (<1)	1 (<1)	0	1 (<1)
Reproductive system and breast disorders	2 (<1)	1 (<1)	0	1 (<1)
Blood and lymphatic system disorders	1 (<1)	0	0	0
Eye disorders	1 (<1)	0	1 (<1)	1 (<1)
Product issues	1 (<1)	0	0	0

1. Includes fatal and non-fatal events

Adjudicated Fatal and Non-Fatal SAEs

The incidences of CEC-adjudicated fatal and non-fatal SAE reports in each category were similar for mepolizumab All Doses and placebo (Table 23). The most frequent cause of the primary SAE was categorized as respiratory (19% mepolizumab All Doses, 21% placebo).

Table 23 Adjudicated Fatal and Non-Fatal Serious Adverse Event Reports by Category (COPD Studies 106 and 113, Safety Population)

Primary Cause of SAE/Death	Placebo N=645	Mepolizumab 100 mg SC N=640	Mepolizumab 300 mg SC N=225	Mepolizumab All Doses[1] N=865
Total	199 (31)	172 (27)	60 (27)	232 (27)
Cardiovascular	27 (4)	28 (4)	10 (4)	38 (4)
Respiratory	138 (21)	115 (18)	48 (21)	163 (19)
Cancer	14 (2)	10 (2)	4 (2)	14 (2)
Unknown (inadequate information)	3 (<1)	3 (<1)	0	3 (<1)
Other	50 (8)	41 (6)	6 (3)	47 (5)

1. All Doses includes mepolizumab 100 mg SC and 300 mg SC
Note: Incidence is rounded to the nearest whole percent

5.7.1. Deaths

Investigator-reported Fatal SAEs

Fatal SAEs were reported for 54 patients with similar incidence between the mepolizumab All Doses (3%) and placebo (4%) groups (Table 24). The most frequently reported fatal SAEs were COPD exacerbation and pneumonia which occurred with similar incidence across the treatment groups.

Table 24 Fatal Serious Adverse Events (COPD Studies 106 and 113, Safety Population)

System Organ Class Fatal SAE (Preferred Term)	Number (%) of Patients			
		Mepolizumab		
	Placebo N=645	100 mg SC N=640	300 mg SC N=225	All Doses[1] N=865
Any Fatal SAE[2]	26 (4)	20 (3)	8 (4)	28 (3)
Respiratory, thoracic & mediastinal disorders	10 (2)	8 (1)	3 (1)	11 (1)
COPD[3]	5 (<1)	6 (<1)	2 (<1)	8 (<1)
Acute respiratory failure	2 (<1)	1 (<1)	0	1 (<1)
Respiratory failure	0	1 (<1)	2 (<1)	3 (<1)
Pneumothorax	1 (<1)	0	0	0
Pneumothorax spontaneous	1 (<1)	0	0	0
Respiratory arrest	1 (<1)	0	0	0
Cardiac disorders	3 (<1)	6 (<1)	3 (1)	9 (1)
Cardiac arrest	2 (<1)	1 (<1)	0	1 (<1)
Acute myocardial infarction	1 (<1)	0	1 (<1)	1 (<1)
Cardiac failure congestive	0	2 (<1)	0	2 (<1)
Cardio-respiratory arrest	0	1 (<1)	1 (<1)	2 (<1)
Cardiomyopathy	0	1 (<1)	0	1 (<1)
Cardiopulmonary failure	0	1 (<1)	0	1 (<1)
Myocardial infarction	0	0	1 (<1)	1 (<1)
Infections and infestations	5 (<1)	2 (<1)	1 (<1)	3 (<1)
Pneumonia	4 (<1)	0	1 (<1)	1 (<1)
Sepsis	0	2 (<1)	0	2 (<1)
Urinary tract infection	1 (<1)	0	0	0
Neoplasms, benign, malignant & unspecified	3 (<1)	4 (<1)	0	4 (<1)
Lung neoplasm malignant	0	2 (<1)	0	2 (<1)
Gastric cancer	0	1 (<1)	0	1 (<1)
Lung adenocarcinoma	1 (<1)	0	0	0
Lung adenocarcinoma stage IV	1 (<1)	0	0	0
Retinal melanoma	0	1 (<1)	0	1 (<1)
Small cell lung cancer	1 (<1)	0	0	0
Other SOCs	5 (<1)	1 (<1)	1 (<1)	2 (<1)
Death[4]	1 (<1)	0	1 (<1)	1 (<1)
Multiple organ dysfunction syndrome	0	1 (<1)	0	1 (<1)
Gastrointestinal haemorrhage	2 (<1)	0	0	0
Respiratory fume inhalation disorder	1 (<1)	0	0	0
Haemorrhagic stroke	1 (<1)	0	0	0

1. All Doses includes mepolizumab 100 mg SC and 300 mg SC
2. On-treatment and post-treatment
3. COPD exacerbation
4. Placebo group: unwitnessed sudden death, history of myocardial infarction, stroke, diabetes mellitus. Mepolizumab 300 mg: Death at a camping site, previous history of anteroseptal myocardial infarction and reduced left ventricular ejection fraction.

Adjudicated Fatal SAEs

CEC-adjudicated causes of death for fatal SAEs were similar between treatment groups (3% mepolizumab All Doses and 4% placebo) (Table 25). The most frequent adjudicated primary causes of death categories were respiratory and cardiovascular. The CEC considered half of the deaths in each treatment group were associated with COPD.

Table 25 Adjudicated Fatal Serious Adverse Event Reports (COPD Studies 106 and 113, Safety Population)

	Number (%) of Patients			
		Mepolizumab		
Primary Cause of Death Category-Subcategory	Placebo N=645	100 mg SC N=640	300 mg SC N=225	All Doses[1] N=865
Total Fatal SAE Reports	26 (4.0)	20 (3.1)	8 (3.6)	28 (3.2)
Respiratory	12 (1.9)	8 (1.3)	4 (1.8)	12 (1.4)
COPD exacerbation w/ evidence of pneumonia	3 (0.5)	3 (0.5)	1 (0.4)	4 (0.5)
COPD exacerbation w/o evidence of pneumonia	5 (0.8)	5 (0.8)	3 (1.3)	8 (0.9)
Pneumonia/RTI w/o COPD exacerbation	1 (0.2)	0	0	0
Other respiratory cause[2]	3 (0.5)	0	0	0
Cardiovascular	7 (1.1)	3 (0.5)	4 (1.8)	7 (0.8)
Sudden death	4 (0.6)	1 (0.2)	4 (1.8)	5 (0.6)
Congestive heart failure	0	2 (0.3)	0	2 (0.2)
Myocardial infarction/ischemic heart disease	2 (0.3)	0	0	0
Stroke (hemorrhagic)	1 (0.2)	0	0	0
Cancer	3 (0.5)	4 (0.6)	0	4 (0.5)
Lung	3 (0.5)	2 (0.3)	0	2 (0.2)
Melanoma	0	1 (0.2)	0	1 (0.1)
Gastric carcinoma	0	1 (0.2)	0	1 (0.1)
Other	3 (0.5)	3 (0.5)	0	3 (0.3)
Clonazepam overdose	0	1 (0.2)	0	1 (0.1)
Urinary sepsis	1 (0.2)	0	0	0
GI hemorrhage/bleed/bleeding	2 (0.3)	1 (0.2)	0	1 (0.1)
Sepsis, ruptured diverticulum, and stroke	0	1 (0.2)	0	1 (0.1)
Unknown (inadequate information)	1 (0.2)	2 (0.3)	0	2 (0.2)
Death associated with COPD				
Yes	13 (2.0)	10 (1.6)	4 (1.8)	14 (1.6)
No	10 (1.6)	8 (1.3)	3 (1.3)	11 (1.3)
Inadequate information or indeterminate	3 (0.5)	2 (0.3)	1 (0.4)	3 (0.3)

1. All Doses includes mepolizumab 100 mg SC and 300 mg SC
2. Other respiratory cause includes: acute smoke inhalation, pneumothorax, and spontaneous pneumothorax

RTI=respiratory tract infection

5.7.2. Non-fatal Serious Adverse Events

Investigator-reported Non-Fatal SAEs

The incidence of non-fatal on-treatment SAEs reported by the investigator was similar between the mepolizumab All Doses (23%) and placebo (26%) groups (Table 26). The most frequently reported non-fatal SAEs were COPD and pneumonia, which occurred

with similar incidence across the treatment groups. All other non-fatal SAEs occurred with an incidence of <1%; those reported in at least 5 patients in the mepolizumab All Doses or placebo groups included atrial fibrillation (6 patients each group), respiratory failure (6 patients mepolizumab and 5 patients placebo), acute respiratory failure (5 patients mepolizumab and 5 patients placebo), and infective exacerbation of chronic obstructive airways disease (6 patients mepolizumab and 4 patients placebo).

Table 26 Non-Fatal Serious On-treatment Adverse Events Occurring in More Than 2 Patients Across Treatment Groups (COPD Studies 106 and 113, Safety Population)

	Number (%) of Patients			
		Mepolizumab		
System Organ Class Non-fatal SAE (Preferred Term)	Placebo N=645	100 mg SC N=640	300 mg SC N=225	All Doses[1] N=865
Any on-treatment non-fatal SAE	168 (26)	152 (24)	48 (21)	200 (23)
Respiratory, thoracic & mediastinal disorders				
COPD[2]	97 (15)	81 (13)	26 (12)	107 (12)
Respiratory failure	5 (<1)	6 (<1)	0	6 (<1)
Acute respiratory failure	5 (<1)	5 (<1)	0	5 (<1)
Pneumothorax	1 (<1)	1 (<1)	1 (<1)	2 (<1)
Pulmonary embolism	0	1 (<1)	2 (<1)	3 (<1)
Infections and infestations				
Pneumonia	39 (6)	35 (5)	12 (5)	47 (5)
Infective exacerbation of chronic obstructive airways disease	4 (<1)	4 (<1)	2 (<1)	6 (<1)
Urinary tract infection	2 (<1)	3 (<1)	1 (<1)	4 (<1)
Lower respiratory tract infection	2 (<1)	2 (<1)	1 (<1)	3 (<1)
Bronchitis	3 (<1)	0	1 (<1)	1 (<1)
Sepsis	2 (<1)	2 (<1)	0	2 (<1)
Influenza	2 (<1)	0	1 (<1)	1 (<1)
Cardiac disorders				
Atrial fibrillation	6 (<1)	6 (<1)	0	6 (<1)
Acute myocardial infarction	4 (<1)	3 (<1)	1 (<1)	4 (<1)
Cardiac failure congestive	3 (<1)	3 (<1)	0	3 (<1)
Cardiac failure	1 (<1)	2 (<1)	0	2 (<1)
Gastrointestinal disorders				
Diarrhoea	0	3 (<1)	1 (<1)	4 (<1)
Neoplasms benign, malignant, and unspecified				
Non-small cell lung cancer	1 (<1)	1 (<1)	1 (<1)	2 (<1)
Injury, poisoning & procedural complications				
Foot fracture	1 (<1)	2 (<1)	0	2 (<1)
Renal & urinary disorders				
Acute kidney injury	1 (<1)	2 (<1)	0	2 (<1)
Renal colic	1 (<1)	2 (<1)	0	2 (<1)
Urinary retention	1 (<1)	2 (<1)	0	2 (<1)
Nervous system disorders				
Syncope	2 (<1)	2 (<1)	1 (<1)	3 (<1)
Transient ischaemic attack	1 (<1)	2 (<1)	0	2 (<1)
General disorders				
Non-cardiac chest pain	2 (<1)	1 (<1)	0	1 (<1)
Reproductive system disorders				
Benign prostatic hyperplasia	2 (<1)	1 (<1)	0	1 (<1)

1. All Doses includes mepolizumab 100 mg SC and 300 mg SC
2. COPD exacerbation

Adjudicated Non-fatal SAEs

The incidences of CEC-adjudicated non-fatal SAEs overall and for each primary category were similar between the mepolizumab All Doses (25%) and placebo (28%) groups (Table 27). The most frequent causes of the primary SAE were categorized as respiratory and cardiovascular and the incidences were also similar between mepolizumab and placebo in both the primary category and virtually all subcategories. The majority of events in the 'Other' category were infections, followed by musculoskeletal events, the majority of which were bone fractures.

Table 27 Adjudicated Non-Fatal Serious Adverse Event Reports (COPD Studies 106 and 113, Safety Population)

	Number (%) of Patients			
		Mepolizumab		
Primary Cause of SAE Category-Subcategory	**Placebo N=645**	**100 mg SC N=640**	**300 mg SC N=225**	**All Doses[1] N=865**
Total Non-fatal SAE Reports	181 (28.1)	160 (25.0)	54 (24.0)	214 (24.7)
Respiratory	131 (20.3)	110 (17.2)	45 (20.0)	155 (17.9)
COPD exacerbation with evidence of pneumonia	34 (5.3)	22 (3.4)	11 (4.9)	33 (3.8)
COPD exacerbation without evidence of pneumonia	97 (15.0)	81 (12.7)	30 (13.3)	111 (12.8)
Pneumonia/RTI w/o COPD exacerbation	10 (1.6)	23 (3.6)	9 (4.0)	32 (3.7)
Pulmonary embolism	1 (0.2)	2 (0.3)	2 (0.9)	4 (0.5)
Exacerbation asthma associated	0	1 (0.2)	0	1 (0.1)
Other respiratory cause	3 (0.5)	2 (0.3)	3 (1.3)	5 (0.6)
Cardiovascular	21 (3.3)	26 (4.1)	6 (2.7)	32 (3.7)
Myocardial infarction/ischemic heart disease	6 (0.9)	7 (1.1)	2 (0.9)	9 (1.0)
Congestive heart failure	4 (0.6)	7 (1.1)	0	7 (0.8)
Stroke (indeterminate)	0	1 (0.2)	0	1 (0.1)
Other cardiovascular cause	13 (2.0)	13 (2.0)	4 (1.8)	17 (2.0)
Cancer	11 (1.7)	6 (0.9)	4 (1.8)	10 (1.2)
Lung	1 (0.2)	1 (0.2)	2 (0.9)	3 (0.3)
Breast	1 (0.2)	2 (0.3)	0	2 (0.2)
Colorectal	1 (0.2)	2 (0.3)	0	2 (0.2)
Other cancer cause	8 (1.2)	1 (0.2)	2 (0.9)	3 (0.3)
Other[2]	47 (7.3)	40 (6.3)	6 (2.7)	46 (5.3)
Nephrolithiasis	0	2 (0.3)	0	2 (0.2)
Diverticulitis	1 (0.2)	1 (0.2)	0	1 (0.1)
Gastroenteritis	1 (0.2)	1 (0.2)	0	1 (0.1)
Benign prostatic hypertrophy	1 (0.2)	1 (0.2)	0	1 (0.1)
Cataract	1 (0.2)	0	1 (0.4)	1 (0.1)
Urinary tract infection	0	1 (0.2)	1 (0.4)	1 (0.1)
Unknown (inadequate information)	2 (0.3)	1 (0.2)	0	1 (0.1)

1. All Doses includes mepolizumab 100 mg SC and 300 mg SC
2. Only events reported in more than one patient are shown.

Note: For a report with multiple SAEs, the primary event was adjudicated.

Note: Two patients in Study 113 with unknown primary cause of SAE had reason of 'inadequate information' that was captured on the eCRF, but was not included in the database.

RTI=respiratory tract infection

5.8. Adverse Events Leading to Discontinuation of Study Treatment/Withdrawal from the Study

AEs leading to permanent discontinuation of study treatment occurred with similar incidences between the mepolizumab All Doses (8%) and placebo (10%) groups as did AEs leading to study withdrawal (4% mepolizumab All Doses and 6% placebo) (Table 28). The most frequent AEs leading to discontinuation of study treatment and/or withdrawal from the study were COPD exacerbation and pneumonia.

Table 28 Adverse Events Leading to Discontinuation of Study Treatment or Withdrawal from the Study Occurring in More than One Patient Across Treatment Groups (COPD Studies 106 and 113, Safety Population)

AE Leading to Discontinuation of Study Treatment or Withdrawal from the Study (Preferred Term)	Number (%) of Patients			
		Mepolizumab		
	Placebo N=645	100 mg SC N=640	300 mg SC N=225	All Doses[1] N=865
Any AE Leading to Study Treatment Discontinuation	62 (10)	40 (6)	25 (11)	65 (8)
COPD[1]	14 (2)	11 (2)	6 (3)	17 (2)
Pneumonia	3 (<1)	6 (<1)	2 (<1)	8 (<1)
Respiratory failure	1 (<1)	4 (<1)	2 (<1)	6 (<1)
Atrial fibrillation	0	2 (<1)	1 (<1)	3 (<1)
Acute respiratory failure	1 (<1)	2 (<1)	0	2 (<1)
Cardiac failure congestive	0	2 (<1)	0	2 (<1)
Sepsis	1 (<1)	2 (<1)	0	2 (<1)
Lung adenocarcinoma	1 (<1)	1 (<1)	1 (<1)	2 (<1)
Alanine aminotransferase increased	0	0	2 (<1)	2 (<1)
Cardiac arrest	2 (<1)	1 (<1)	0	1 (<1)
Prostate cancer	2 (<1)	0	1 (<1)	1 (<1)
Acute myocardial infarction	1 (<1)	1 (<1)	0	1 (<1)
Headache	1 (<1)	1 (<1)	0	1 (<1)
Injection site reaction	1 (<1)	1 (<1)	0	1 (<1)
Muscle spasms	1 (<1)	1 (<1)	0	1 (<1)
Bundle branch block right	1 (<1)	0	1 (<1)	1 (<1)
Death[2]	1 (<1)	0	1 (<1)	1 (<1)
Fatigue	1 (<1)	0	1 (<1)	1 (<1)
Myocardial infarction	1 (<1)	0	1 (<1)	1 (<1)
Nausea	1 (<1)	0	1 (<1)	1 (<1)
Injection-related reaction	4 (<1)	0	0	0
Any AE Leading to Withdrawal from the Study	39 (6)	25 (4)	13 (6)	38 (4)
COPD[1]	6 (<1)	6 (<1)	3 (1)	9 (1)
Pneumonia	6 (<1)	2 (<1)	1 (<1)	3 (<1)
Anaemia	0	2 (<1)	0	2 (<1)
Lung neoplasm malignant	0	2 (<1)	0	2 (<1)
Sepsis	1 (<1)	2 (<1)	0	2 (<1)
Atrial fibrillation	0	1 (<1)	1 (<1)	2 (<1)
Cardio-respiratory arrest	0	1 (<1)	1 (<1)	2 (<1)
Respiratory failure	1 (<1)	1 (<1)	1 (<1)	2 (<1)
Acute respiratory failure	2 (<1)	1 (<1)	0	1 (<1)
Cardiac arrest	2 (<1)	1 (<1)	0	1 (<1)
Death[2]	1 (<1)	0	1 (<1)	1 (<1)
Lung adenocarcinoma	1 (<1)	0	1 (<1)	1 (<1)
Gastrointestinal haemorrhage	2 (<1)	0	0	0

1. COPD exacerbation
2. Placebo group: unwitnessed sudden death, history of myocardial infarction, stroke, diabetes mellitus. Mepolizumab 300 mg: Death at a camping site, previous history of anteroseptal myocardial infarction and reduced left ventricular ejection fraction.

5.9. Safety in Subgroups

Within subgroups of age, gender, race, ethnicity, and BMI, the overall incidences of AEs in the mepolizumab All Doses and placebo groups were similar to the incidence of AEs in the entire safety population (Table 29).

Table 29 Overall Incidence of On-treatment Adverse Events by Subgroup (COPD Studies 106 and 113, Safety Population)

	Number (%) of Patients			
		Mepolizumab		
Group	Placebo N=645	100 mg SC N=640	300 mg SC N=225	All Doses[1] N=865
Entire Safety Population	521 (81)	516 (81)	191 (85)	707 (82)
Age Group, years				
40 - <65	232 (79)	227 (79)	91 (83)	318 (80)
≥65	289 (82)	289 (82)	100 (87)	389 (83)
Gender				
Female	195 (86)	212 (84)	58 (87)	270 (85)
Male	326 (78)	304 (78)	133 (84)	437 (80)
Race				
White	422 (81)	424 (81)	153 (84)	577 (82)
Asian	40 (87)	37 (84)	36 (88)	73 (86)
African American/African Heritage	8 (89)	7 (88)	2 (100)	9 (90)
Other[2]	51 (72)	48 (72)	0	48 (72)
Ethnicity				
Hispanic or Latino	94 (77)	83 (70)	29 (78)	112 (72)
Not Hispanic or Latino	427 (82)	433 (83)	162 (86)	595 (84)
BMI category, kg/m²				
≤20	57 (84)	51 (86)	20 (83)	71 (86)
>20 - ≤30	340 (81)	336 (80)	125 (86)	461 (81)
>30	124 (79)	129 (81)	46 (82)	175 (81)

1. All Doses includes mepolizumab 100 mg SC and 300 mg SC
2. Other includes American Indian or Alaskan Native and Mixed Race (American Indian Alaskan Native and White). There were no patients of 'Other' race in the 300 mg SC group.

5.10. Clinical Laboratory Data

In the COPD Studies, few patients had changes in values to outside the normal range for the majority of clinical chemistry and hematology parameters. The incidence of chemistry/hematology values outside the normal range at any time post-baseline occurred with comparable incidence across the treatment groups. No treatment-related trends were apparent.

A few isolated laboratory values of potential clinical importance (PCI) were observed (clinical chemistry: high/low glucose, high potassium, and high sodium; hematology: high/low hematocrit, high/low hemoglobin, and low platelets), but the incidence of events was similar between the mepolizumab and placebo groups (<1% each).

Two patients, both in the placebo group, had elevated liver function tests that met the protocol-defined liver stopping criteria. Both events resolved during the treatment period.

5.11. Electrocardiograms and Vital Signs

There was no evidence of corrected QT interval (QTc) prolongation or an increase in ECG abnormalities with mepolizumab in the COPD studies. Most patients in the mepolizumab All Doses (90%) and placebo (95%) groups had maximum post-baseline corrected QT interval using Fridericia's formula (QTc[F]) values ≤450 msec. The incidence of abnormal, clinically significant ECG findings post-baseline was similar between the placebo and mepolizumab All Doses groups (2% each group).

No treatment-related trends in vital sign assessments were observed. Over the 52-week treatment period in both studies 106 and 113, mean changes from baseline in all vital sign parameters (systolic and diastolic blood pressure, pulse rate, and oxygen saturation) were similar across the treatment groups.

5.12. Pregnancies

No pregnancies were reported in the COPD studies.

6. BENEFIT-RISK ASSESSMENT AND CONCLUSIONS

6.1. Therapeutic Justification

Patients with severe COPD currently being treated with ICS-based triple therapy who are still at risk of acute exacerbations have limited or no further treatment options. Therefore, a critical treatment goal in this population is the reduction of moderate/severe exacerbations. Additionally, this patient population has significant burden of disease from COPD and other co-morbidities leading to poor clinical outcomes and increased mortality, all of which are aggravated by acute exacerbations. Thus, there remains a high unmet need to develop and provide new medications for these patients.

Mepolizumab, through its neutralization of IL-5, provides a specific, effective and well-tolerated treatment in the chronic management of severe COPD patients with an eosinophilic phenotype who continue to be at risk of exacerbation despite optimized ICS-based triple therapy. The effect of mepolizumab on exacerbation reduction and increasing the time to first exacerbation is a beneficial outcome for these patients.

A dose regimen of mepolizumab 100 mg SC once every 4 weeks in addition to SoC is recommended based on the favorable benefit:risk profile and PD effect of this dose in lowering blood eosinophil counts.

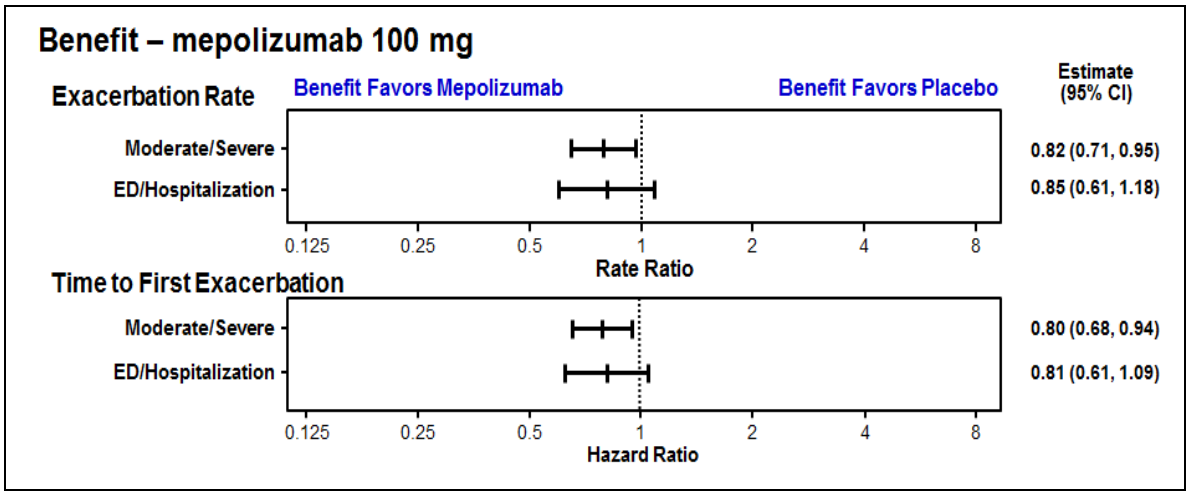
6.2. Assessment of Benefits and Risks

Treatment with mepolizumab 100 mg SC reduced the rate of moderate/severe exacerbations by a clinically meaningful 18-20% on top of ICS-based inhaled triple therapy compared with placebo in patients with severe COPD; additionally, the time to first moderate/severe exacerbation was longer for patients treated with mepolizumab. Although the p-value for the comparison of the mepolizumab 100 mg dose to placebo for reduction in the rate of moderate/severe exacerbations was marginally larger than the $p<0.05$ threshold (p 0.068) after adjustment for multiplicity in Study 113, the totality of

evidence for efficacy benefit should be considered rather than focusing on this specific threshold [Wasserstein, 2016]. In the meta-analysis of both studies (Study 106 High Stratum and Study 113), there was a statistically significant 18% reduction in rate of exacerbations and a 20% lower risk of having a moderate/exacerbation at any time during the study for mepolizumab compared with placebo (Figure 22).

For more severe exacerbations, the pre-specified meta-analysis showed numerical reductions of 15% in the rate of exacerbations requiring ED visit/hospitalization (Figure 22) and 12% in the rate of severe exacerbations with mepolizumab 100 mg compared with placebo. The risk of having a first exacerbation requiring ED visit/hospitalization or a first severe exacerbation at any time during the study was also lower with mepolizumab treatment compared with placebo.

Figure 22 Key Benefits Mepolizumab 100 mg SC vs. Placebo (COPD Studies 106 and 113)



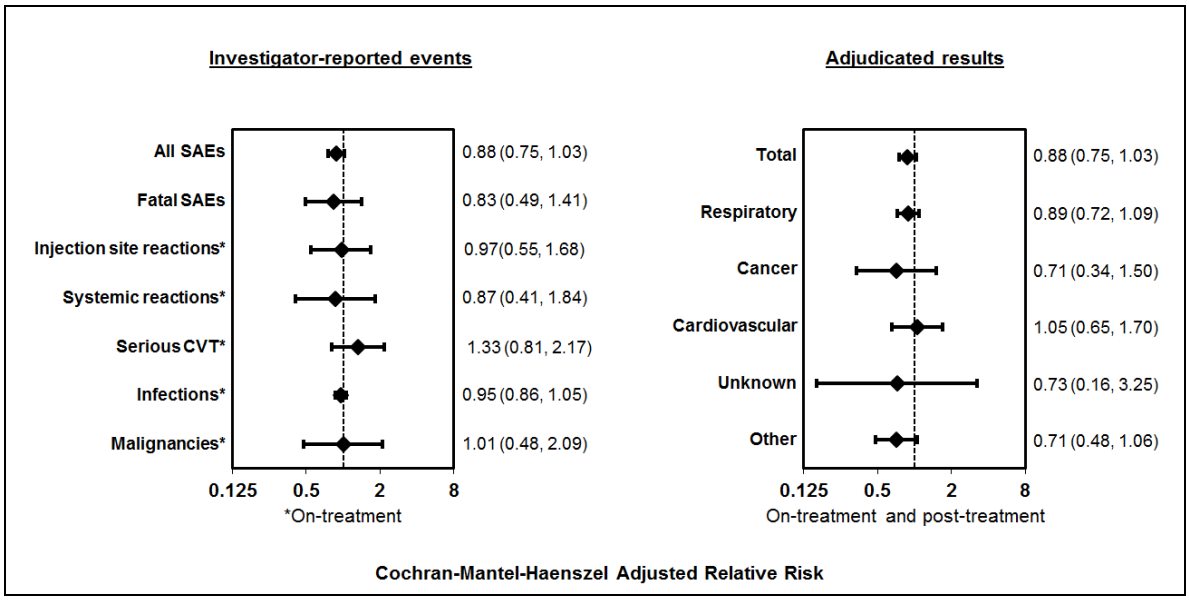
Overall, these reductions in exacerbation of any type (moderate/severe, requiring ED visit/hospitalization, and severe) support mepolizumab having a consistent impact on exacerbation reduction. This benefit could potentially lead to reductions in morbidity and fatal events due to COPD [Groenewegen, 2003; Müllerova, 2015].

For HRQoL, as assessed by SGRQ and CAT, the proportion of patients achieving at least the MCID improvement at Week 52 was generally higher in the meta-analysis for mepolizumab 100 mg compared with placebo. While the pattern of change over time in the mepolizumab 100 mg group was consistent with other COPD studies [Lipson, 2017; Wedzicha, 2013; Jones, 2011; Tashkin, 2008] the changes observed in the placebo group were not typical and may to some extent have been driven by the differential drop out of patients between treatment groups. Given that patients were on a background of maximal therapy, the observed improvement in responder rates with mepolizumab is important for this severely debilitated COPD population.

The safety profile of mepolizumab administered every 4 weeks for up to 52 weeks in combination with ICS-based inhaled triple therapy was similar to placebo plus ICS-based inhaled triple therapy in the two Phase III COPD studies in patients with severe COPD

(Figure 23). All point estimates favor mepolizumab except for investigator-reported serious CVT events, and all confidence intervals include 1. The incidence and relative risks for independently adjudicated fatal and non-fatal SAE reports were similar between the mepolizumab and placebo groups, including for the cardiovascular category. Based on the overall results, no new safety issues with mepolizumab were identified in this population. The incidence of immunogenicity was low with no post-baseline neutralizing antibodies on mepolizumab.

Figure 23 Risk Profile Mepolizumab All Doses[1] vs. Placebo (COPD Studies 106 and 113)



1. All Doses includes mepolizumab 100 mg SC and 300 mg SC
Note: Horizontal bars represent 95% confidence intervals
Note: Adjudicated results relative risk is a post-hoc analysis

6.3. Overall Benefit Risk Conclusions

Studies 106 and 113 enrolled patients with severe COPD whose disease was uncontrolled despite ICS-based triple therapy and demonstrated that a standard clinical readily available laboratory test, the blood eosinophil count, identifies patients most likely to benefit from IL-5 inhibition by mepolizumab. The consistent reduction in the primary endpoint of rate of moderate/severe exacerbations (18-20%) observed with mepolizumab 100 mg compared with placebo on top of high-dose ICS-based inhaled triple therapy, which already significantly lowers the rate of exacerbations of COPD, is clinically meaningful in this severe COPD population.

This benefit was accompanied by a lower risk of having a first moderate/severe exacerbation at any time during the study. Trends for improvement in HRQoL were observed. The mepolizumab-eligible COPD patient receiving ICS-based triple therapy and who presents with an eosinophilic phenotype is likely to be severely debilitated and suffer from a poor HRQoL, therefore the therapeutic efficacy demonstrated is clinically meaningful. The blood eosinophil count guides the physician in selecting appropriate

patients for mepolizumab and in the magnitude of benefit to be expected in this COPD population consisting of mostly GOLD Group D patients.

The safety profile of mepolizumab 100 mg SC and 300 mg SC administered every 4 weeks for up to 52 weeks was similar to placebo in the two Phase III COPD studies in patients with severe COPD. No new safety concerns with mepolizumab were identified in this population.

Overall, based on the favorable benefit:risk profile, the limited therapeutic options, and the significant morbidity in those COPD patients with an eosinophilic phenotype who continue to have exacerbations despite optimized care, GSK believes mepolizumab would provide a therapeutic advance for this population as outlined in this briefing document.

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8. APPENDIX

8.1. Interpretation of COPD Assessment Test (CAT) Scores

CAT Score	Impact Level	Broad Clinical Picture of the Impact of COPD by CAT Score
>30	Very High	Their condition stops them doing everything they want to do and they never have any good days. If they can manage to take a bath or shower, it takes them a long time. They cannot go out of the house for shopping or recreation, or do their housework. Often, they cannot go far from their bed or chair. They feel as if they have become an invalid.
>20	High	COPD stops them doing most things that they want to do. They are breathless walking around the home and when getting washed or dressed. They may be breathless when they talk. Their cough makes them tired and their chest symptoms disturb their sleep on most nights. They feel that exercise is not safe for them and everything they do seems too much effort. They are afraid and panic and do not feel in control of their chest problem.
10-20	Medium	COPD is one of the most important problems that they have. They have a few good days a week, but cough up sputum on most days and have one or two exacerbations a year. They are breathless on most days and usually wake up with chest tightness or wheeze they get breathless on bending over and can only walk up a flight of stairs slowly. They either do their house work slowly or have to stop for rests.
<10	Low	Most days are good, but COPD causes a few problems and stops people doing one or two things that they would like to do. They usually cough several days a week and get breathless when playing sports and games and when carrying heavy loads. They have to slow down or stop when walking up hills or it they hurry when walking on level ground. They get exhausted easily.
5	--	Upper limit of normal in healthy non-smokers

Source: CAT Healthcare Professional User Guide, 2016
Note: CAT scoring range is 0-40

8.2. Study 113 - Results for Mepolizumab 300 mg

In Study 113, there was no evidence of a dose response or additional benefit with mepolizumab 300 mg across the primary and secondary efficacy endpoints (Table 30).

Table 30 Primary and Secondary Efficacy Endpoints Results (Study MEA117113, mITT Population)

Efficacy Endpoint	Placebo N=226	Mepolizumab 100 mg SC N=223	Mepolizumab 300 mg SC N=225
Primary Efficacy Endpoint			
Rate of Moderate/Severe Exacerbations (On- and Off-treatment)			
n	226	223	**225**
Exacerbation rate/year	1.49	1.19	**1.27**
Rate ratio vs. placebo	---	0.80	**0.86**
95% CI	---	0.65, 0.98	**0.70, 1.05**
Unadjusted p-value	---	0.034	**0.140**
Adjusted p-value	---	0.068	**0.140**
Secondary Efficacy Endpoints			
Time to First Moderate/Severe Exacerbation			
By Week 52			
Probability (%) of an exacerbation	66.7	57.9	**58.8**
95% CI	60.2, 73.1	51.5, 64.5	**52.4, 65.3**
Hazard ratio (mepolizumab/placebo)		0.82	**0.77**
95% CI	---	0.64, 1.04	**0.60, 0.97**
Unadjusted p-value	---	0.103	**0.030**
Adjusted p-value	---	0.140	**0.140**
Rate of Exacerbations Requiring ED Visit/Hospitalization			
n	226	223	**225**
Exacerbation rate/year	0.28	0.17	**0.23**
Rate ratio vs. placebo	---	0.59	**0.83**
95% CI	---	0.35, 0.98	**0.51, 1.34**
Unadjusted p-value	---	0.042	**0.447**
Adjusted p-value	---	0.140	**0.447**
Change from Baseline in SGRQ Total Score at Week 52			
n with analyzable data	218	218	**219**
n with analyzable data at time point	177	196	**189**
LS mean change	-3.1	-5.0	**-3.3**
(SE)	(0.98)	(0.95)	**(0.96)**
Difference (mepolizumab vs. placebo)	---	-1.8	**-0.1**
95% CI	---	-4.5, 0.8	**-2.8, 2.6**
Unadjusted p-value	---	0.180	**0.926**
Adjusted p-value	---	0.447	**0.926**
Change from Baseline in CAT Score at Week 52			
n with analyzable data	222	216	**219**
n with analyzable data at time point	173	190	**184**
LS mean change	-0.4	-1.6	**-0.8**
(SE)	(0.42)	(0.42)	**(0.42)**
Difference (mepolizumab vs. placebo)	---	-1.1	**-0.4**
95% CI	---	-2.3, 0.0	**-1.5, 0.8**
Unadjusted p-value	---	0.055	**0.547**
Adjusted p-value	---	0.926	**0.926**

8.3. Sensitivity Analyses of the Primary Endpoint

Extensive efforts were made to keep patients in the studies following discontinuation from randomized treatment, but some patients chose to discontinue participation. The primary endpoint of rate of moderate/severe exacerbations was based on the time in the study for all patients up to Week 52; for patients discontinuing the study, this time corresponds to the period of observation before they discontinued. As a percentage of scheduled years of follow-up, the amount of missing data in study MEA117113 was 8% for placebo and 3% and 5% for the mepolizumab 100 mg and 300 mg groups, respectively (Table 31). In MEA117106 High Stratum, the amount of missing data was 6% for the placebo group and 3% for the mepolizumab 100 mg group.

Table 31 Summary of Missing Data for the Primary Endpoint (COPD Studies, mITT Primary Population)

	Patient-Years (%) of Follow-up[1]				
	Study 106 High Stratum		Study 113		
All Patients	Placebo N=229	Mepo 100 mg SC N=233	Placebo N=226	Mepo 100 mg SC N=223	Mepo 300 mg SC N=225
On-treatment	204.9 (89)	220.4 (94)	195.4 (86)	205.9 (92)	203.0 (90)
Off-treatment	11.3 (5)	5.7 (2)	13.2 (6)	10.0 (4)	10.8 (5)
Missing follow-up	13.5 (6)	7.6 (3)	18.1 (8)	7.3 (3)	12.0 (5)

1. Percentages shown are based on total time on-treatment, off-treatment and estimated number of missing years follow-up.

The primary analysis made a standard assumption known as the Missing At Random (MAR) assumption. This assumes that future exacerbations for those who withdraw can be predicted from their exacerbation history prior to withdrawal and from the exacerbation rate of similar patients on the same treatment.

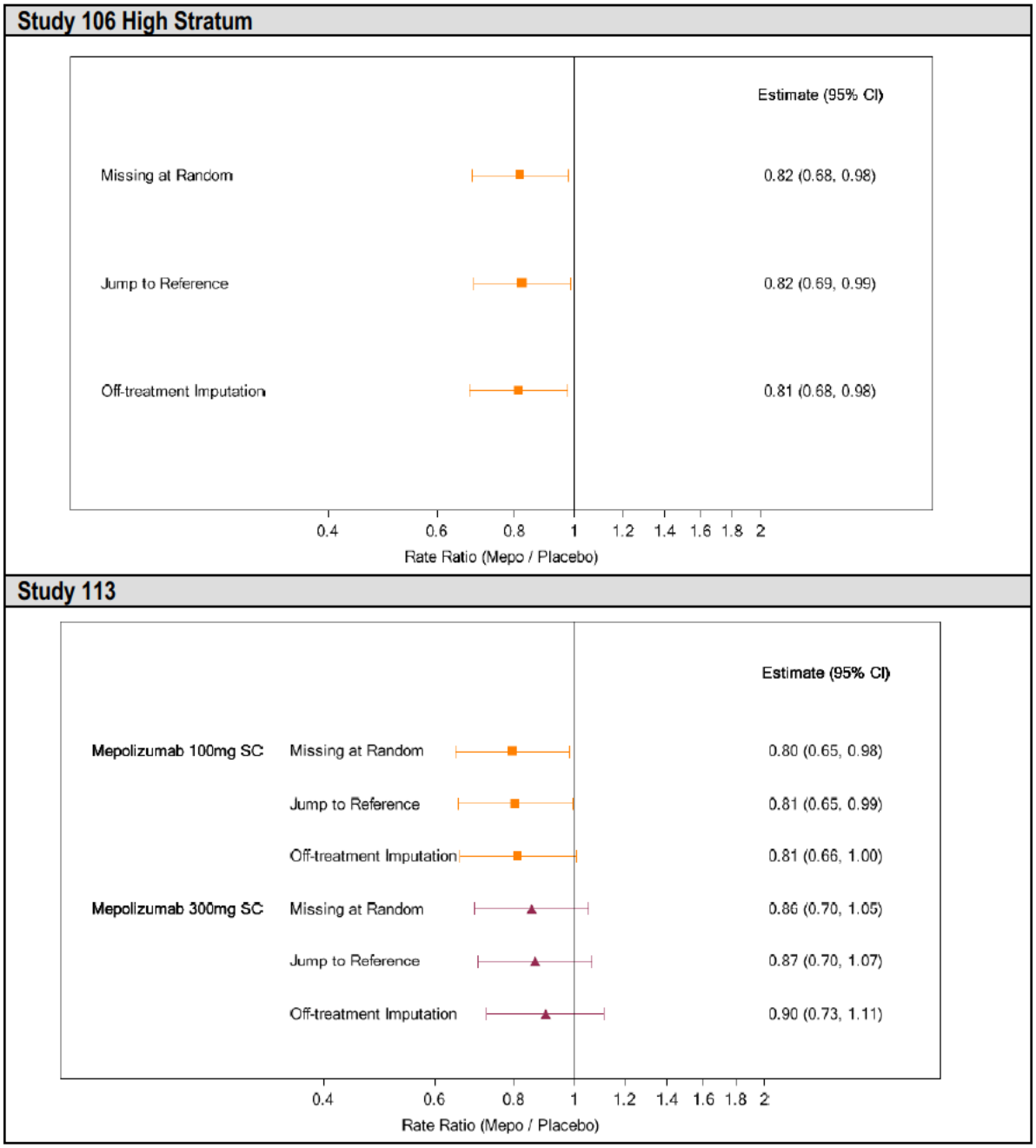
Sensitivity analyses were conducted to assess departures from the assumption that missing data were MAR:

- **Jump to reference (J2R)**: Missing data in the mepolizumab treatment arms was imputed, assuming that the patient's expected event rate was shifted to that of the placebo arm [Keene, 2014].
- **Off treatment imputation**: Missing data were imputed based on the off-treatment data collected from patients who continued in the study following discontinuation of randomized treatment.
- **Tipping point**: Missing data were imputed based on a plausible range of values for the rate of exacerbations per year following study withdrawal. The values to be investigated were based on increases relative to the estimated rates obtained within each arm under the MAR assumption. The imputed exacerbation rates varied independently for the mepolizumab and placebo arms.

In each of the analyses, missing data for patients who withdrew early from the study were imputed for the period between withdrawal from the study and the Week 52 Visit. The

J2R and Off-treatment imputations showed similar results to the primary analysis in both studies indicating robustness to assumptions regarding missing data (Figure 24).

Figure 24 Sensitivity Analyses of Rate of Moderate/Severe Exacerbations (Treatment Policy Estimand, Jump to Reference, and Off-Treatment Imputations) (COPD Studies, mITT Primary Population)

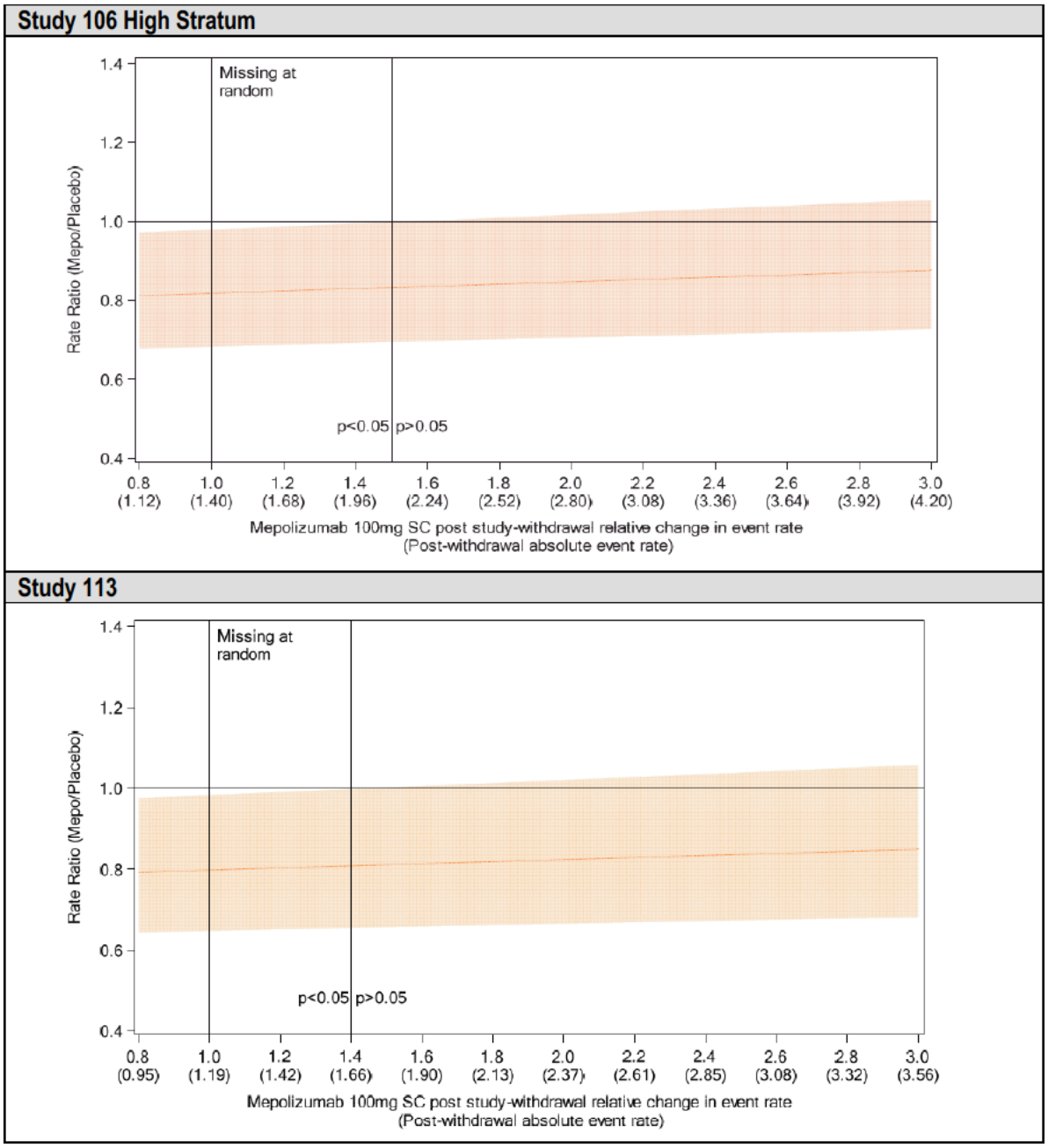


Note: Horizontal bars represent 95% confidence intervals for mepolizumab/placebo rate ratio

Additionally, results of a tipping point analysis showed the impact on the study results of assuming increases in the rate of exacerbations for patients with missing data from that estimated by the MAR assumption. Exacerbation rates among patients in the

mepolizumab 100 mg group with missing data post-withdrawal would need to be 1.4 times higher in Study 113 and 1.5 times higher in Study 106 High Stratum than predicted by the MAR assumption for the treatment comparison to become p>0.05 unadjusted for multiplicity (Figure 25). Based on the mean exacerbation rates of 1.19/year and 1.40/year estimated from the primary analysis model for patients treated with mepolizumab 100 mg in Study 113 and 106 High Stratum, respectively, this would imply an increase in the rate to 1.66/year in Study 113 and 2.1/year in Study 106 High Stratum.

Figure 25 **Sensitivity Analyses of Rate of Moderate/Severe Exacerbations under the Missing at Random Assumption in Placebo (Treatment Policy Estimand, Tipping Point) (COPD Studies, mITT Primary Population)**



Note: Shaded region represents 95% confidence interval

All three sensitivity analyses confirmed the robustness of the primary efficacy results to different assumptions regarding missing data.