11 December 2025
EMADOC-1700519818-2683842
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nucala

International non-proprietary name: Mepolizumab

Procedure No. EMA/VR/0000257645

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACO	Asthma-COPD Overlap
ADA	Anti-Drug Antibody
ADR	Adverse Drug Reaction(s)
AE(s)	Adverse Event(s)
AECOPD	Acute Exacerbations of COPD
AESI	Adverse Event(s) of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ASE	All Subjects Enrolled
ASMF	Active Substance Master File
ATS	American Thoracic Society
AUC	Area under the Curve
AUCss	Area Under the Concentration Time Curve at steady state
BEC	Blood Eosinophil Count
BID	Twice Daily
BMI	Body Mass Index
BLA	Biologics License Application
BLQ	Below Limit of Quantification
BUD	Budesonide
CAT	COPD Assessment Test
Cavg	Average Concentration
CCP	Confirmatory Cut-point
CDC	Centre for Disease Control
CEC	Clinical Endpoint Committee
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CCI	Commercially Confidential Information
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
Cmax	Maximum Concentration
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus 2019 Disease
CL	Clearance
CP	Cut-Point
CRL	Complete Response Letter
CRCL	Creatinine Clearance
CRSwNP	Chronic Rhinosinusitis with Nasal Polyps
CSR	Clinical Study Report
CV	Cardiovascular
CV	Coefficient of Variation
CVT	Cardiac, Vascular, and Thromboembolic

CSV	Comma Separated Values
eAF	electronic Application Form
EAIR	Exposure-adjusted Incidence Rate
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eCTD	Electronic Common Technical Document
EAIR	Exposure Adjusted Incidence Rate
ED	Emergency Department
ECLA	Electrochemiluminescent Assay
ECG	Electrocardiogram
ECRF	electronic Case Report Form
EGPA	Eosinophilic Granulomatosis with Polyangiitis
EMA	European Medicines Agency
ELISA	Enzyme-linked Immunosorbent Assay
EoP2	End of Phase 2
EPAR	European Public Assessment Report
ER	Exposure-Response
ERS	European Respiratory Society
E-RS: COPD	Evaluating Respiratory Symptoms in COPD
EU	European Union
EQ5D5L	EuroQol 5Dimension 5Level questionnaire
Fc	Fragment Crystallisable
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 Second
FF	Fluticasone Furoate
FMQ	FDA Medical Queries
FORM	Formoterol
FP	Fluticasone Propionate
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GB	Glycopyrronium Bromide
GDPR	General Data Protection Regulation
GOF	Goodness Of Fit
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
HES	Hypereosinophilic Syndrome
HF	Heart Failure
HIV	Human Immunodeficiency Virus
HLT	High Level Term
HPRA	Health Products Regulatory Authority
HQC	High Quality Control
HR	Hazard Ratio
HRQoL	Health-related Quality of Life

ICH	International Conference on Harmonization
ICE	Intercurrent Event
ICS	Inhaled Corticosteroid
ICU	Intensive Care Unit
ID	Identification
IgE	Immunoglobulin E
IgG1	Immunoglobulin G, Subclass 1
IL-3, IL-4, IL-13	Interleukin 3, Interleukin 4, Interleukin 13
IL-5	Interleukin-5
IL-5R	Interleukin 5 receptor alpha
ILC-2	Type 2 Innate Lympoid Cells
IM	Intramuscular(ly)
IND	Investigational New Drug
IND	Indacaterol
Inh	Inhibited
IP	Investigational Product
IPD	Important Protocol Deviations
ISE	Integrated Summary of Efficacy
ISR	Incurred Sample Reanalysis
ISRs	Injection Site Reactions
ISS	Integrated Summary of Safety
ITT	Intent-to-Treat
IV	Intravenous(ly)
IVRS	Interactive Voice Response System
J2R	Jump to Reference
KA	Absorption rate
KM	Kaplan–Meier
LABA	Long-Acting Beta2 Agonist
LAMA	Long-Acting Muscarinic Antagonist
LBA	Ligand binding assay
LLOQ	Lower Limit of Quantification
LQC	Low Quality Control
LS	Least Squares
LTOT	Long-Term Oxygen Therapy
MAA	Marketing Authorization Application
mAb(s)	Monoclonal Antibody(s)
MACE	Major Adverse Cardiovascular Event(s)
MAH	Marketing Authorisation Holder
MAR	Missing at Random
MCID	Minimal Clinically Important Difference
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency

MI	Myocardial Infarction
mITT	Modified Intent-to-Treat
mITT-H	Modified Intent-to-Treat–High Stratum
mITT-L	Modified Intent-to-Treat–Low Stratum
mMRC	Modified Medical Research Council
MOA	Mechanism of Action
MQC	Mid Quality Control
MRC	Medical Research Council
MSD	Meso-Scale Discovery
NAb	Neutralizing Antibody
NHANES	National Health and Nutrition Examination Survey
NMPA	National Medical Product Administration
NP	Nasal Polyps
NYHA	New York Heart Association
OCS	Oral Corticosteroids
OR	Odds Ratio
OTC	OverThe Counter
PADAC	Pulmonary Allergy Drugs Advisory Committee
PBO	Placebo
PBRER	Periodic Benefit-Risk Evaluation Report
PDE4	Phosphodiesterase-4
PI	Product Information
PK	Pharmacokinetic(s)
PD	Pharmacodynamic(s)
PDAP	Project Data Analysis Plan
PhV	Pharmacovigilance
pM	Picomolar
PopPK	Population Pharmacokinetics
PP	Per-protocol Population
PP-H	Per Protocol – High Stratum
PSUR	Periodic Safety Update Report
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	Patient Reported Outcomes
PT	Preferred Term
PY	Participant Years
Q4W	Every 4 Weeks
QC	Quality Control
QD	Once Daily
QRD	Quality Review of Documents
QT	QT interval
QTcF	QT interval using Friderica’s correction
RECL	Relative Electrochemiluminescence
RFI	Request for Information
RR	Relative Risk

RMP	Risk Management Plan
RSI	Request for Supplementary Information
RT	Room Temperature
RTI	Respiratory Tract Infection
SA	Scientific Advice
SABA	Short Acting Beta2-Agonist
SAE	Serious Adverse Event(s)
SAMA	Short Acting Muscarinic Antagonist
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus
sBLA	Supplemental Biologics License Application
SC	Subcutaneous(ly)
SCP	Screening cut-point
SD	Standard deviation
SE	Standard error
SEA	Severe eosinophilic asthma
SGRQ	St. George’s Respiratory Questionnaire
SGRQ-C	St. George's Respiratory Questionnaire for COPD
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Queries
SOE	Strength of Evidence
SoC	Standard of Care
SOC	System Organ Class
SOP	Standard Operating Procedure
t1/2	Half-Life Time
TEAE	Treatment Emergent Adverse Events
TTFE	Time to First Event
ULOQ	Upper Limits Of Quantification
UMEC	Umeclidinium
UNC	Uncertainty
UPP	United-Pharma Power
V	Volume of distribution
VAS	Visual Analogue Scale
VI	Vilanterol
VPC	Visual Predictive Check

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GlaxoSmithKline Trading Services Limited submitted to the European Medicines Agency on 06 March 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		Type
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication for NUCALA to include treatment of Chronic Obstructive Pulmonary Disease (COPD) based on final results from study 208657 (MATINEE). This is a randomized, double-blind, parallel-group, placebo-controlled study of mepolizumab 100 mg SC as add-on treatment in participants with COPD experiencing frequent exacerbations and characterized by eosinophil levels. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 14.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet, to bring the PI in line with the latest QRD template version 10.4, to update the PI in accordance with the latest EMA excipients guideline, and to implement editorial changes to the PI.

The variation requested variation(s) proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions EMEA-000069-PIP04-13 and EMA/674859/2013 on the granting of a (product-specific) waiver and on the granting of a class waiver CW/1/2015).

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 14th of October 2021 (EMA/SA/0000066628). The Scientific Advice Protocol Assistance pertained to the clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Finbarr Leacy Co-Rapporteur: Petr Vrbata

Timetable	Actual dates
Submission date	05 March 2025
Start of procedure:	22 March 2025
CHMP Rapporteur's preliminary assessment report circulated on:	16 May 2025
PRAC Rapporteur's preliminary assessment report circulated on:	23 May 2025
CHMP Rapporteur's preliminary assessment report circulated on:	27 May 2025
PRAC Rapporteur's updated assessment report circulated on:	28 May 2025
PRAC Outcome	05 June 2025
Joint Rapporteur's updated assessment report circulated on:	12 June 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	19 June 2025
MAH's responses submitted to the CHMP on:	12 August 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	22 September 2025
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	09 October 2025
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	16 October 2025
MAH's responses submitted to the CHMP on:	11 November 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	26 November 2025
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	04 December 2025
CHMP opinion:	11 December 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

COPD is a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnoea, cough, sputum production and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction. COPD results from gene-environment interactions associated with an enhanced chronic inflammatory response in the airways and the lung, mainly caused by tobacco smoking and long-term exposure to noxious particles or gases. There is a genetic risk factor associated with disease, mutations in the SERPINA1 gene that lead to α-1 antitrypsin deficiency, although prevalence is rare.

The disease course is marked by progressive deterioration in airflow and increasing frequency of exacerbations which contribute to the overall disease severity. COPD exacerbations are associated with accelerated lung function decline, a prolonged detrimental impact on Health-related Quality of Life (HRQoL), aggravation of co-morbidities, increased mortality, and significant COPD-related healthcare costs.

State the claimed therapeutic indication

Nucala is indicated in adults as an add-on maintenance treatment for uncontrolled chronic obstructive pulmonary disease (COPD) characterised by raised blood eosinophils on a combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA) (see section 5.1).

Epidemiology

Existing COPD prevalence data vary widely due to differences in survey methods, diagnostic criteria, and analytical approaches and the true prevalence is likely underreported. Recent reports indicate that COPD is highly prevalent, it is estimated that 480 million patients were living with COPD globally in 2020 and approximately 22% of COPD patients are on inhaled triple therapy. The global prevalence of COPD is 10.3% (95% confidence interval (CI) 8.2%, 12.8%), with an overall prevalence of 11.8% (standard error (SE) 7.9) for men and 8.5% for women (SE 5.8) and a prevalence of 3%-11% among never smokers (Global Initiative for Chronic Obstructive Lung Disease (GOLD) report 2025). It is estimated that globally there are 3 million deaths annually due to COPD.

COPD results from gene-environment interactions over the lifetime of the individual that can damage the lungs and/or alter their normal development/aging process. Tobacco smoking and inhalation of toxic particles and gases from household and outdoor pollution are the main environmental exposures leading to COPD. Exacerbations are often triggered by respiratory viral infections although bacterial infections and environmental factors such as pollution and ambient temperature may also initiate and/or amplify these events. When associated with viral infections, exacerbations are often more severe, last longer and precipitate more hospitalizations, as seen during the winter season.

Aetiology and pathogenesis

COPD patients on inhaled triple therapy who continue to experience exacerbations (at least 1 severe or at least 2 moderate exacerbations in the last 12 months) represent approximately 6.2% of the overall COPD population. This subset of patients with COPD can have disease driven by Type 2 inflammation characterized by elevated blood (≥300 cells/μL) and sputum eosinophils, circulating Type 2 Helper (Th2 cells), innate lymphoid cells, and elevated type 2 cytokines (interleukins (ILs) IL-4, IL-5, and IL-13)). Up to 40% of COPD patients have this inflammatory pattern. It has been shown that in severe COPD patients, sputum eosinophils and IL-5 levels are elevated to similar levels as those seen in severe asthmatics. These patients have exacerbations driven by increased eosinophilic airway inflammation and increased Type 2 cytokines including sputum IL-5.

Clinical presentation, diagnosis

Patients with COPD typically complain of dyspnoea, wheezing, chest tightness, fatigue, activity limitation, and/or cough with or without sputum production. Patients may experience exacerbations that influence their health status and prognosis and require specific preventative and therapeutic measures. Spirometry showing the presence of a post-bronchodilator forced expiratory volume in 1 second per forced vital capacity (FEV1/FVC) <0.7 is mandatory to establish the diagnosis of COPD.

As per recent GOLD 2025 guidelines, a combined assessment of the presence of COPD symptoms (modified Medical Research Council (mMRC) dyspnoea scale or COPD Assessment Test (CAT)) and exacerbation history is used to determine disease severity and to guide pharmacological therapy. Four grades (GOLD grades 1-4) based on severity of airflow limitation are defined with GOLD grade 1 (mild, FEV1 ≥80% predicted), GOLD grade 2 (moderate, FEV1 ≥50% and <80% predicted), GOLD grade 3 (severe, FEV1 ≥30% and <50% predicted), or GOLD grade 4 (very severe, FEV1 <30% predicted). These disease grades are part of a combined assessment strategy of symptoms and risk for exacerbations. COPD often coexists with other diseases (comorbidities) that may have a significant impact on disease course. These comorbid conditions can mimic and/or aggravate an acute exacerbation. Cardiovascular diseases are common and important comorbidities in COPD. Lung cancer is frequently seen in people with COPD and is a major cause of death.

Management

There is no cure for COPD and so the aim of COPD management is to reduce symptoms as well as future risk of exacerbations [GOLD 2025]. Smoking cessation is strongly encouraged in all patients with COPD and supports should be made available to patients to do so. The 2025 GOLD report advocates the use of one or more long-acting inhaled bronchodilators (LABA or LAMA) in addition to ICS for patients with more advanced disease, high blood eosinophil count (BEC), and high risk of exacerbations. The concurrent use of these medications (ICS + LABA + LAMA) is often termed ‘triple inhaled maintenance therapy’ and is usually optimal for COPD patients at risk of exacerbations.

Triple therapy has been shown to reduce exacerbations by 15% to 25% compared with dual therapies. Patients with uncontrolled COPD (i.e., patients who continue to exacerbate despite the use of triple inhaled therapy) have limited treatment options and are at risk of poor outcomes, which remains an unmet clinical need. Pharmacotherapy should be guided by the severity of symptoms and risk of exacerbations. Vaccinations against common respiratory pathogens can decrease the incidence of infections and exacerbations. Dupilumab is an IL-4R/IL-13R monoclonal antibody that has recently been approved by CHMP as an add-on therapy for uncontrolled eosinophilic COPD.

2.1.2. About the product

Nucala (mepolizumab) is a humanised monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology.

Mepolizumab is an IL-5 antagonist (IgG1 kappa) that binds to IL-5, inhibiting its bioactivity with nanomolar potency by blocking its binding to the IL-5R alpha complex on the cell surface. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation and survival of eosinophils. In patients where their disease is driven by type 2 inflammation, IL-5 is an important component of the processes driving the pathogenesis of asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), COPD, eosinophilic granulomatosis with polyangiitis (EGPA) and hypereosinophilic syndrome (HES). Additional structural and inflammatory cell types also express the IL-5R alpha e.g., epithelial cells, mast cells, plasma cells, basophils, ILC-2 cells, T cells, smooth muscle cells, neutrophils and fibroblasts. In severe asthma and CRSwNP, inhibition of IL-5 has been associated with an improvement in aspects of airway remodelling. However, the mechanism of action in these cells and across the different diseases has not been definitively established.

The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks

The development programme/compliance with CHMP guidance/scientific advice

Scientific Advice from CHMP was given on the 14th of October 2021 on the development of Mepolizumab for add-on treatment to inhaled corticosteroid-based maintenance treatment for patients with chronic obstructive pulmonary disease (COPD) with an eosinophilic phenotype. The scientific advice pertained to design changes of the ongoing mepolizumab COPD Phase III 208657 (MATINEE) study in order to mitigate the observation of a lower-than-expected overall blinded exacerbation rate, which is considered to be related to the response to the global SARS-CoV-2 pandemic. These changes caused a variation to the study duration as patient data was now assessed at either 52-weeks (Fixed Duration) or ≤104-weeks (Variable Duration) and a potential change to study numbers as it allowed for up to 1,400 participants depending on blinded study power assessment prior to enrolling the 800th participant.

The MAH complied with some of the CHMP guidance recommendations. The potential effect from different treatment durations was evaluated and shown, according to the MAH, as negligible. The rate of moderate/severe exacerbations by treatment duration with shrinkage estimation did show lower exacerbations in the variable duration (0.75 (0.60, 0.93)) compared to fixed duration (0.85 (0.62, 1.16)).

2.1.3. General comments on compliance with GCP

For 208657 (MATINEE) pivotal study, two study sites were inspected, one in US and one in Canada.

The GCP inspection was performed for site 239718 in US. This study centre was closed. Sensitivity analysis for the primary endpoint was performed excluding data from 3 participants enrolled at the study center.

It is mentioned that site 241146 in Germany in relation to study 208657 was investigated for potential suspected scientific misconduct. Although there was no confirmation of this, the study center was still closed early (see also Results and Discussion on efficacy).

For study MEA117106, one study site in Poland was inspected (see also Results and Discussion on efficacy).

No GCP inspection was performed for MEA117113 study.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Mepolizumab is a fully human IgG1κ mAb comprised of natural amino acids. It is not excreted unchanged but is completely metabolized to non-pharmacologically active simple molecules and does not give rise to biologically active metabolites. Due to the physico-chemical nature of the active substance this product is unlikely to pose a risk to the environment and the risk assessment stops. In conclusion, a phase II risk assessment is not required.

2.2.2. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of mepolizumab.

Considering the above data, mepolizumab is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

The Phase 3 global program comprised 3 clinical studies, each with a randomized, double-blind, placebo-controlled, parallel-group design. Each study evaluated efficacy and safety of mepolizumab compared with placebo as add-on treatment to SoC ICS-based triple therapy in COPD participants with an eosinophilic phenotype.

The first 2 studies, MEA117113 and MEA117106, were 52-week studies that were conducted concurrently and designed to: 1) characterize the efficacy and safety of mepolizumab, 2) inform on the appropriate dose, and 3) test the utility of using blood eosinophils to identify a patient population likely to benefit from treatment. The third pivotal study, 208657 (MATINEE), was conducted after the completion of studies MEA117113 and MEA117106. Study 208657 was designed to build on the results from the previous studies and to provide confirmatory evidence of clinical benefit supporting the use of mepolizumab at the proposed marketed dose (100 mg every 4 weeks), for the proposed indication.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1: Tabular overview of clinical studies

Study ID	Study Countries	Study Design, Objective(s)	Healthy Participants or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Participants by Group Enrolled / Completed	Study Reporting Status (Type of Report)	Location
Efficacy and Safety Studies: Controlled Clinical Studies Pertinent to the Claimed Indication							
MEA117106 (2017N318238_00)	Australia, Belgium, Canada, Czech Republic, Estonia, France, Greece, Italy, Mexico, Norway, Peru, Poland, Russian Federation, Spain, Sweden, United States.	Phase 3, R, DB, PC, PG Safety and efficacy	COPD	Mepolizumab 100 mg SC -High Stratum[1] -Low Stratum[2] Placebo SC -High Stratum[1] -Low Stratum[2] One dose every 4 weeks for 52 weeks	417/370 233/213 184/157 419/364 229/202 190/162	Completed (Full CSR)	m5.3.5.1 MEA117106 CSR
MEA117113 (2017N318148_00)	Argentina, Australia, Canada, Chile, Denmark, Germany, Japan, Netherlands, Republic of Korea, Romania, Slovakia, Taiwan, Ukraine, United Kingdom, United States.	Phase 3, R, DB, PC, PG Safety and efficacy	COPD	Mepolizumab 100 mg SC Mepolizumab 300 mg SC Placebo SC One dose every 4 weeks for 52 weeks	223/206 225/195 226/185	Completed (Full CSR)	m5.3.5.1 MEA117113 CSR
208657 (TMF-18580711)	Argentina, Australia, Belgium, Brazil, Canada, China, Denmark, France, Germany, Greece, Hungary, India, Ireland, Israel, Italy, Mexico, Netherlands, New Zealand, Poland, Republic of Korea, Spain, Sweden, Taiwan, United Kingdom, United States	Phase 3, R, DB, PC, PG Safety and efficacy	COPD	Mepolizumab 100 mg SC Placebo SC One dose every 4 weeks for either 52 weeks (fixed duration) or between 52 up to 104 weeks (variable duration)	403/339 401/331	Completed (Full CSR)	m5.3.5.1 208657 CSR

Clinical pharmacology

2.3.2. Pharmacokinetics

Bioanalytical Method Validation

Mepolizumab assay

The measurement of mepolizumab plasma concentrations was carried out using a validated bioanalytical immunoassay method with an LLOQ of 50 ng/mL. The initial assay development was conducted at GSK (historical assay information can be found in prior submissions). Mepolizumab plasma concentrations were quantified with a neutralizing idiotypic antibody specific for the binding portion of mepolizumab, passively adsorbed to a polystyrene microtiter plate as the means of capture. Mepolizumab was then detected using an Fc specific mouse anti-human IgG1 labelled with horseradish peroxidase with a chemiluminescent endpoint. The assay was validated. The studies supported with this assay are listed below.

Table 2: Summary of clinical studies supported by the mepolizumab bioanalytical assay

Study	Study Objectives	Population	Type of Study
208657	Safety and efficacy	COPD	Clinical
MEA117113	Safety and efficacy	COPD	Clinical
MEA117106	Safety and efficacy	COPD	Clinical

Abbreviation: COPD = Chronic obstructive pulmonary disease.

Immunogenicity

Anti-Mepolizumab Antibody Assay

The detection of anti-drug-antibodies (ADA) against mepolizumab in serum to support the clinical development of Mepolizumab was carried out using the same validated ADA method

(screening, confirmation and titer analyses). The ADA assay was developed and improved at GSK, producing the 6th generation ADA assay, currently in use, that incorporates electrochemiluminescence detection and a blocking antibody. Details of the 6th generation ADA assay and prior ADA assays have been provided. The 6th generation ADA assay was validated at GSK and then transferred to a contract research laboratory for validation]. This analytical method was utilised to support sample analysis in the following clinical trials: 208657, MEA117113, and MEA117106. The validated 6th generation assay was also transferred to another contract research laboratory), where it was also validated. This analytical method was used to support clinical study 208657. The method validation reports were provided in the dossier.

Table 3: Summary of ADA method Validation

Anti-Drug Antibody Assays			
Validation Report	**Clinical Studies Supported**	**Summary of Method Description and Validation Parameters**	
Partial Validation of an Electrochemiluminescent Assay for the Detection of anti-SB240563 Antibodies in Human Serum Samples Using the Meso Scale Discovery Platform (Resolian) Report number 2018N366495_00 (19Dec2012), MSD Instruments Amendment 1: 2018N366496_00 (27Aug2015) Whole Blood Stability Amendment 2: 2018N366497_00 (05Oct2017)	MEA117106 MEA117113 208657	Serum samples were diluted with assay diluent, and then incubated with an anti-IL5 blocking antibody. Next, the sample was incubated with biotin-drug and ruthenium-drug conjugates, and transferred to a streptavidin coated MSD plate. The drug conjugate antibody complex was detected with electro chemiluminescence.	
		Screening Cut Point	1.10 RECL (3x 50, normal individuals)
		Confirmation Cut Point	43.18% Inhibition (3x 20 normal individuals with 7.5 ng/mL PC)
		Within-run Precision (%CV)	≤18.7%
		Between-run Precision (%CV)	≤12.2%
		Drug Interference	250 ng/mL PC screening positive with 100 µg/mL drug
		Sensitivity	0.40 ng/mL PC
		Sample Dilution (before conjugates)	1:20 in Assay Diluent or Confirmation Buffer
		Positive Control	Purified rabbit poly clonal, anti-idiotype
		Stability in Whole Blood	Whole blood stability at RT or 4ºC for 24 h
Method Validation Report for the Detection of Anti-SB240563 Antibodies in Human Serum by a Bridging Electrochemiluminescent Assay (ECLA) Using the Meso-Scale Discovery (MSD) Platform (6th Generation Assay) (UPP) Report number 2019n399871_00 (28Oct2019) Amendment 1-LTS 2022n513220_00 (16Sep2022) Amendment 2- cut point 2022n513230_00 (16Sep2022)	208657	Serum samples were diluted with assay diluent, and then incubated with an anti-IL5 blocking antibody. Next, the sample was incubated with biotin-drug and ruthenium-drug conjugates, and transferred to a streptavidin coated MSD plate. The drug conjugate antibody complex was detected with electro chemiluminescence.	
		Screening Cut Point	1.05 RECL (6x50, normal individuals)
		Confirmation Cut Point	14.7% Inhibition (3x50 normal individuals) 50.0% Inhibition (3x 20 normal individuals with 7.5 ng/mL PC)
		Within-run Precision (%CV)	≤19.7%
		Between-run Precision (%CV)	≤19.5%
		Drug Interference	100 ng/mL PC screened positive with 200 µg/mL drug
		Sensitivity	0.3 ng/mL PC at screening cut point 1.95 ng/mL PC at confirmation cut point
		Sample Dilution (before conjugates)	1:20 in Assay Diluent or Confirmation Buffer
		Positive Control	Purified rabbit poly clonal, anti-idiotype

Anti-Drug Antibody Assays			
Validation Report	**Clinical Studies Supported**	**Summary of Method Description and Validation Parameters**	
		Stability in Human Serum	PC in serum at room temperature (RT) for at least 27 hours, refrigerator stability (2-8°C) for up to 27 hours, five freeze thaw cycles (from -70°C to RT). Long term stability at -20°C and -80 °C, confirmed for up to 367 days.
		Matrix Interference	8/10 individuals recovered 10 ng/mL PC as positive. 4/5 lipemia human serum recovered 10 ng/mL PC as positive. 5/5 hemolysis human serum 10 ng/mL PC as positive.

Neutralizing Antibody Assay

The detection of NAb against mepolizumab in serum to support the clinical development of mepolizumab used a validated method. The NAb assay was developed and improved at GSK, producing the 3rd generation NAb Assay, currently in use. Details of the 3rd generation NAb assay and prior NAb assays have been provided. The 3rd generation NAb assay was validated at GSK. This analytical method was utilised by GSK to support the following clinical studies: MEA117113 and MEA117106. The 3rd generation NAb assay was then transferred to a contract research laboratory) and validated. This analytical method was utilised by the contract research laboratory to support 208657. The 3rd generation NAb assay was also transferred to another contract research laboratory and validated. This analytical method was utilised to support 208657. The method validation reports are provided in the dossier

A detailed characterisation of mepolizumab pharmacokinetics (PK) and pharmacodynamics (PD) has been presented in previous submissions for EGPA, SEA and CRSwNP indications. Therefore, only new data from the 3 COPD studies [Study MEA117106 (METREX), Study MEA177113 (METREO), and Study 208657 (MATINEE)] are presented in this report. Data collected from these studies were evaluated in 2 population PK analyses, a PKPD analysis and an exposure-response analysis.

Population PK analysis of data from METREX and METREO

This analysis of data from two Phase III studies in COPD patients was performed to evaluate the consistency of mepolizumab PK between this *de novo* population and the populations with other eosinophilic conditions previously investigated.

Since mepolizumab PK has already been extensively investigated and disease not found to be a determinant of exposure, the most recent population PK model (meta-analysis model) was applied directly to the pooled data from METREX and METREO studies without modification and without estimation step.

The ability of the model to predict observations in the two Phase III COPD studies was assessed using diagnostic plots and goodness of fit (GOF) tests. The effect of prospectively selected covariates on mepolizumab exposure was evaluated graphically (PK parameters vs. covariates), and formally in a forward/backward approach.

Results

A total of 3155 mepolizumab plasma concentration values, obtained from 861 subjects were included in the meta-analysis of studies MEA117106 and MEA117113. Four subjects and overall, 62

concentrations were excluded from the analysis, including 46 measurable concentrations, prior to initiating mepolizumab treatment. The median age of subjects was 66 years (range: 40 to 86 years). The median bodyweight at screening was 73 kg (range: 34 to 170 kg). The median baseline creatinine clearance (CRCL) was 86.2 mL/min (range: 29.7 to 231 mL/min).

The most recent population PK model was generally able to describe the data without further refinement. Apart from bodyweight, creatinine clearance and albumin (which were already included as covariates), there were no apparent trends in any other covariates. The observed and predicted mepolizumab concentrations versus time-profiles are presented in Figure 1and a Visual Predictive Check (VPC) is presented in .

Figure 1: Observed and predicted mepolizumab plasma concentration – time profile (geometric mean 95% CI)

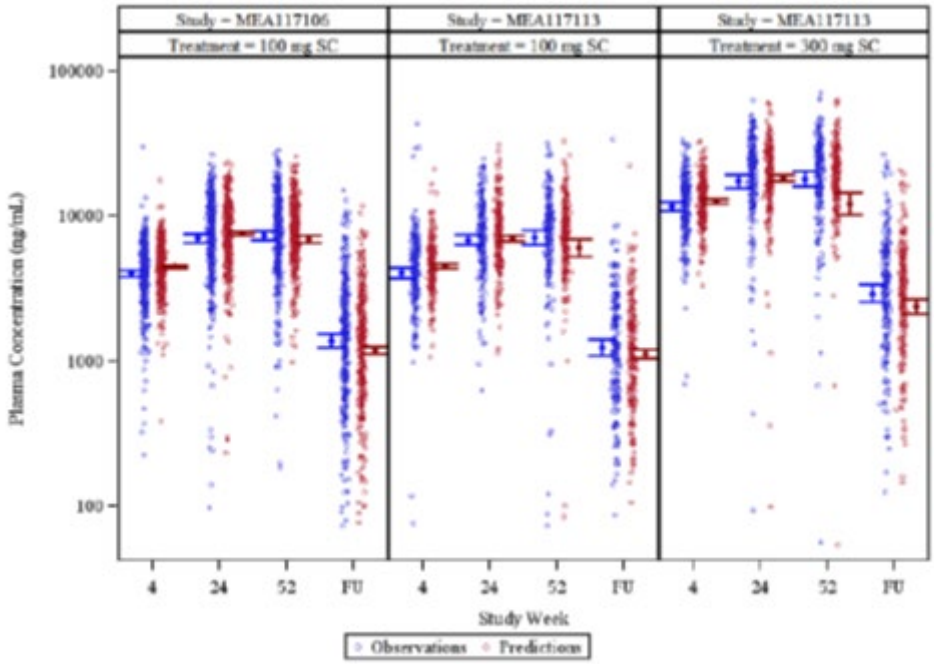
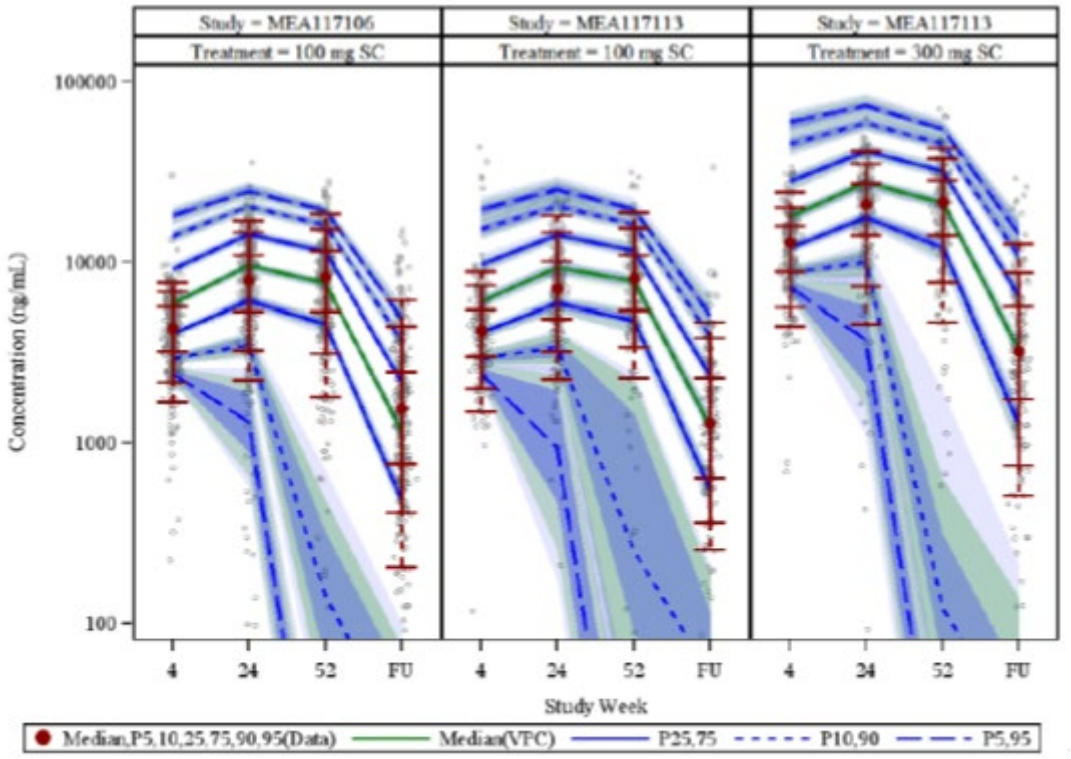


Figure 2: Model Visual Predictive check – as dosed



Concordance between individual model-predicted and observed concentrations in the two Phase III COPD studies was evaluated by GOF tests. Based on the Wilcoxon and Kolmogorov-Smirnov tests, there was no evidence of an absence of model fit at the 5% significance level, and at the 10% significance level for the Ansari-Bradley and Conover tests (tests sensitive to distribution tails). Furthermore, based on the Kolmogorov-Smirnov, Cramér-von Mises and Anderson-Darling tests, there was also no evidence at the 10% significance level to suggest that the observations and predictions were drawn from different distributions.

In COPD subjects in METREX and METREO, the model-predicted geometric mean CL and central volume of distribution were 0.22 L/day [95% CI: 0.215, 0.229] and 3.73 L [95% CI: 3.64, 3.83], respectively. A 1.6-fold accumulation was predicted from Week 4 to Week 24, with no further increase at Week 52. This indicates that steady-state was achieved by at least Week 24. There was no evidence of deviation from dose proportionality between 100 mg and 300 mg SC.

Systemic clearance by bodyweight category defined as ≤60 kg, >60 to ≤75 kg, >75 to ≤90 kg and >90 kg was summarized post-hoc (Table 7). The range of the predicted individual values in the study, obtained by post-hoc Bayesian approach, was 0.03 to 0.80 L/day (note: population CL estimate for a 70 kg subject is 0.21 L/day). An increase in CL was seen with increasing body weight as anticipated. For example, based on the median estimate of each category and using >60 to ≤75 kg as the reference, the change in clearance ranged from a 19% decrease in the ≤60 kg category to a 57% increase in the >90 kg category. The box plots of CL versus age, CRCL, Japanese/non-Japanese and anti-drug antibodies (ADA) (absence or presence) showed no major difference by visual inspection.

Table 4: Summary statistics of individual predicted clearance values by weight category

	Body Weight			
Statistics	<=60 kg	>60 kg <=75 kg	>75 kg <=90 kg	>90 kg
N	188	285	243	145
Mean	0.18	0.22	0.26	0.35
SD	0.053	0.073	0.086	0.113
Median	0.17	0.21	0.25	0.33
Min	0.07	0.09	0.03	0.17
Max	0.36	0.59	0.55	0.80
Geometric Mean (95% CI)	0.17 (0.16, 0.18)	0.21 (0.21, 0.22)	0.25 (0.24, 0.26)	0.33 (0.31, 0.35)

Population PK analysis of data from MATINEE

This analysis assessed PK data from the Phase 3 clinical study MATINEE (Study 208657) in participants with COPD. A meta-analysis external validation approach was taken based on the most recent population PK model (meta-analysis model) for mepolizumab in participants with various eosinophilic conditions.

The most recent population PK model (meta-analysis model) was applied directly to the MATINEE dataset without modification and without estimating the fixed effects. The model was validated prospectively using a set of diagnostic approaches to assess whether simulations from the model can reproduce both the central trend and variability in the observed data from MATINEE. If the prospective model diagnosis showed that the most recent model could reasonably predict the PK data from MATINEE, it was considered that mepolizumab PK in participants with COPD was not different from the PK in participants in other indications.

Results

A total of 153 PK samples from 44 clinical study participants were included in the popPK analysis dataset (Overall population), of which 116 PK samples were measurable, and 37 PK samples were BLQ. Out of the Overall population, 26 (59%) participants were categorized as US non-Asian (1 of the 26 participants included in the US non-Asian population was from Canada) and 18 (41%) were Chinese. Mean age was similar between the US non-Asian and Chinese populations (62.0 and 63.6 years, respectively). Mean body weight in the US non-Asian population (77.2 kg) was slightly higher than in the Chinese population (65.0 kg). Mean creatinine clearance was slightly lower in the Chinese population (76.8 mL/min) compared to the US non-Asian population (82.9 mL/min).

There were no systematic trends in the GoF plots (Figure 3), and the VPC (Figure 4) showed that the most recent popPK model was able to predict the central trend and variability in the observed data adequately. Therefore, no additional model development was performed.

Figure 3: GoF plots

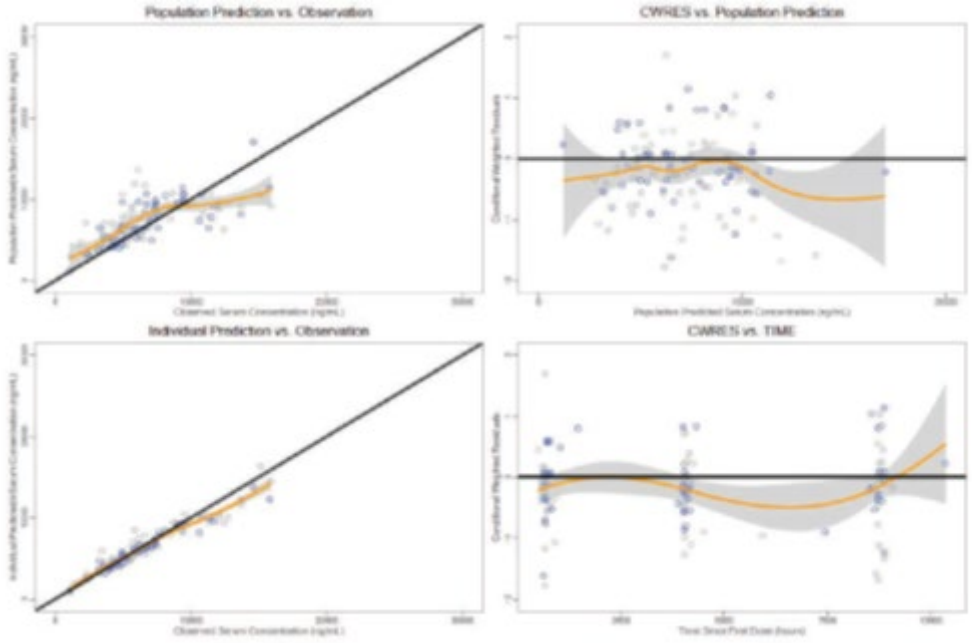
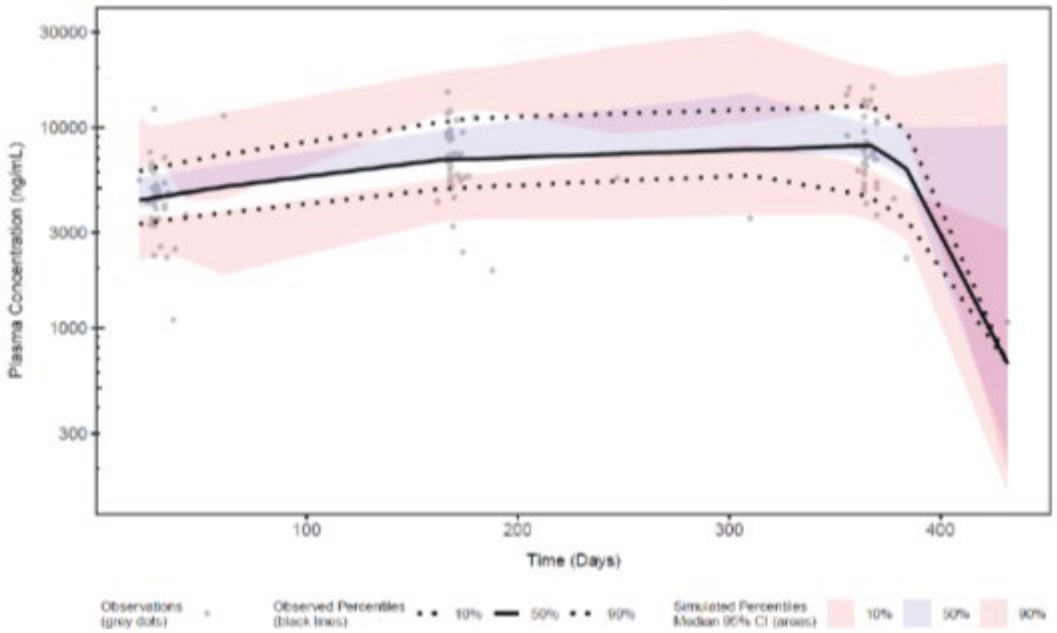


Figure 4: Model VPC (semi logarithmic plot)



The most recent popPK model was used to predict individual mepolizumab plasma concentration-time profiles and individual post hoc PK parameters for participants in the PK sub-study of MATINEE. Figure 5 shows the observed and model-predicted mepolizumab plasma concentration-time profiles.

Figure 5: Observed and predicted (geometric mean [95% CI]) mepolizumab plasma concentration-time profiles

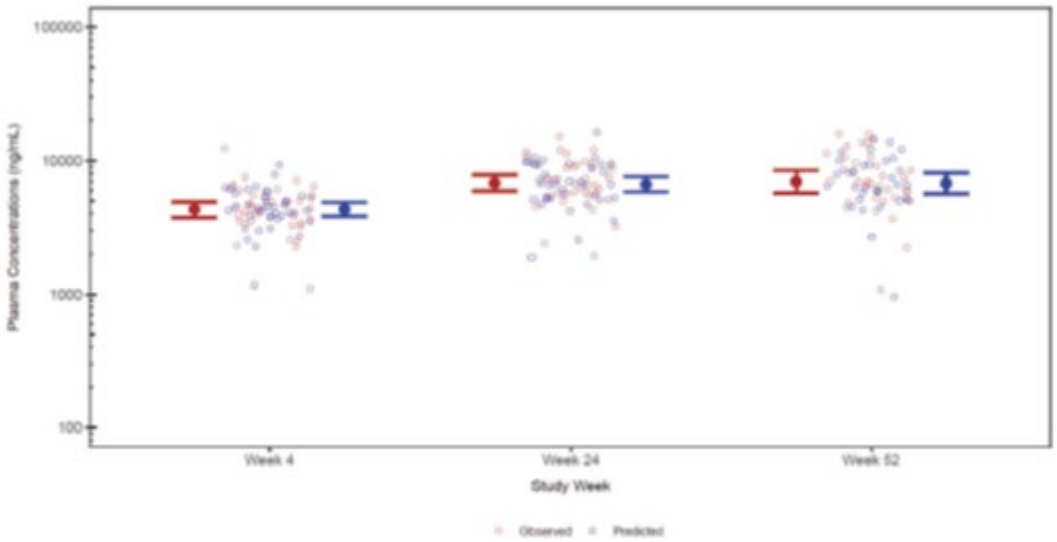


Table 5 provides a summary of post hoc mepolizumab plasma PK parameters for the Overall, US non-Asian, and Chinese populations, and combined METREX and METREO studies. Table 6 provides a summary of mepolizumab derived steady-state exposure parameters for a 100 mg SC Q4W dosing regimen for the Overall, US non-Asian, and Chinese populations, and combined METREX and METREO studies. Figure 6 shows a box and whisker plot of the post hoc AUCss, Cavgss, and Cmaxss in the Overall, US non-Asian, and Chinese populations. Figure 7 shows a box and whisker plot of the post hoc systemic clearance by body weight in the Overall population, split by body weight bands of ≤60 kg (n=12), >60 to ≤75 kg (n=14), and >75 kg (n=18).

Table 5 Summary of post hoc mepolizumab PK parameters for mepolizumab 100 mg SC Q4W in the participants with COPD: Overall, US non-Asian and China (MATINEE, PK population) and combined METREX and METREO studies (PK population)

Population PK analysis Mepolizumab 100 mg SC Q4W	n	CL (L/day)	V2 (L)	V3 (L)	KA (1/day)
208657 (MATINEE)					
Overall	44	0.230 (0.211, 0.251) [28.8]	3.81 (3.52, 4.13) [26.4]	2.22 (2.08, 2.36) [21.3]	0.244 (0.237, 0.251) [9.51]
US non-Asian[a]	26	0.250 (0.221, 0.283) [31.6]	4.19 (3.76, 4.68) [27.5]	2.40 (2.20, 2.61) [21.2]	0.247 (0.237, 0.258) [10.6]
China[a]	18	0.203 (0.185, 0.223) [18.9]	3.33 (3.05, 3.62) [17.5]	1.98 (1.83, 2.14) [15.7]	0.240 (0.231, 0.249) [7.63]
Combined METREX (MEA117106) and METREO (MEA117113)					
Overall	636	0.222 (0.215, 0.229) [41.0]	3.73 (3.64, 3.83) [33.8]	2.44 (2.39 ,2.50) [30.3]	0.244 (0.242, 0.247) [12.6]

a US non-Asian and China are subsets of the Overall PK population

Abbreviations: CI=confidence interval; CL=clearance; COPD=chronic obstructive pulmonary disease; KA=absorption rate constant; n=number of participants; PK=pharmacokinetic; Q4W=every 4 weeks; SC=subcutaneous; V2=volume of distribution of the central compartment; V3=volume of distribution of the peripheral compartment

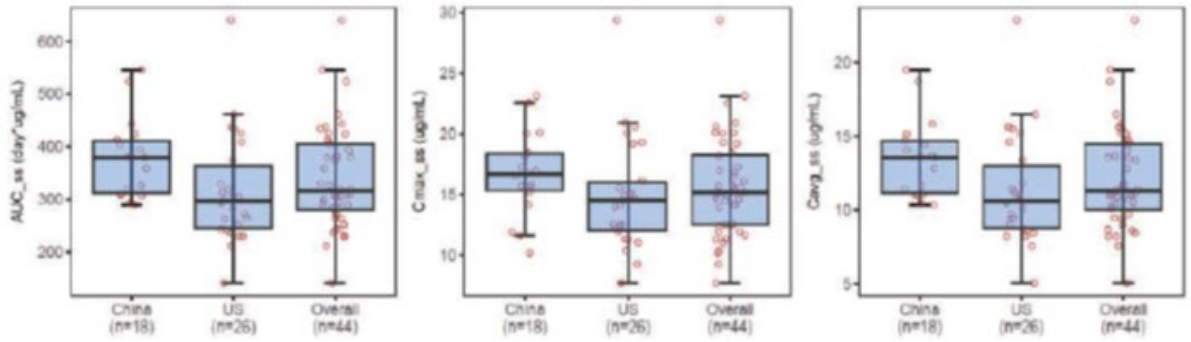
Abbreviations: AUC_ss=area under the concentration-time curve at steady state; Cavg_ss=average concentration at steady state; Cmax_ss=maximum concentration at steady state; CI=confidence interval; n=number of participants in the subgroup; PK=pharmacokinetic; Q4W=every 4 weeks; SC=subcutaneous; t1/2=terminal-phase elimination half-life; US=United States

Table 6 Summary of mepolizumab-derived steady-state exposure parameters following mepolizumab 100 mg SC Q4W in the participants with COPD: Overall, US non-Asian and China (MATINEE, PK population) and combined METREX and METREO studies (PK population)

Mepolizumab 100 mg SC Q4W	n	Cmax_ss (µg/mL)	AUC_ss (day•µg /mL)	Cavg_ss (µg/mL)	t½ (day)
208657 (MATINEE)					
Overall	44	15.1 (13.9, 16.4) [27.1]	329 (302, 358) [28.8]	11.7 (10.8, 12.8) [28.8]	19.8 (19.1, 20.6) [12.8]
US non-Asian[a]	26	14.3 (12.8, 16.1) [29.3]	302 (267, 342) [31.6]	10.8 (9.52, 12.2) [31.6]	20.1 (19, 21.2) [14.1]
China[a]	18	16.3 (14.6, 18.2) [22.1]	372 (338, 408) [18.9]	13.3 (12.1, 14.6) [18.9]	19.5 (18.5, 20.6) [10.9]
Combined METREX (MEA117106) and METREO (MEA117113)					
Overall	636	NC	341 (331, 352) [41.0]	12.2 (11.8, 12.6) [41.0]	21.5 (21.0, 21.9) [28.5]

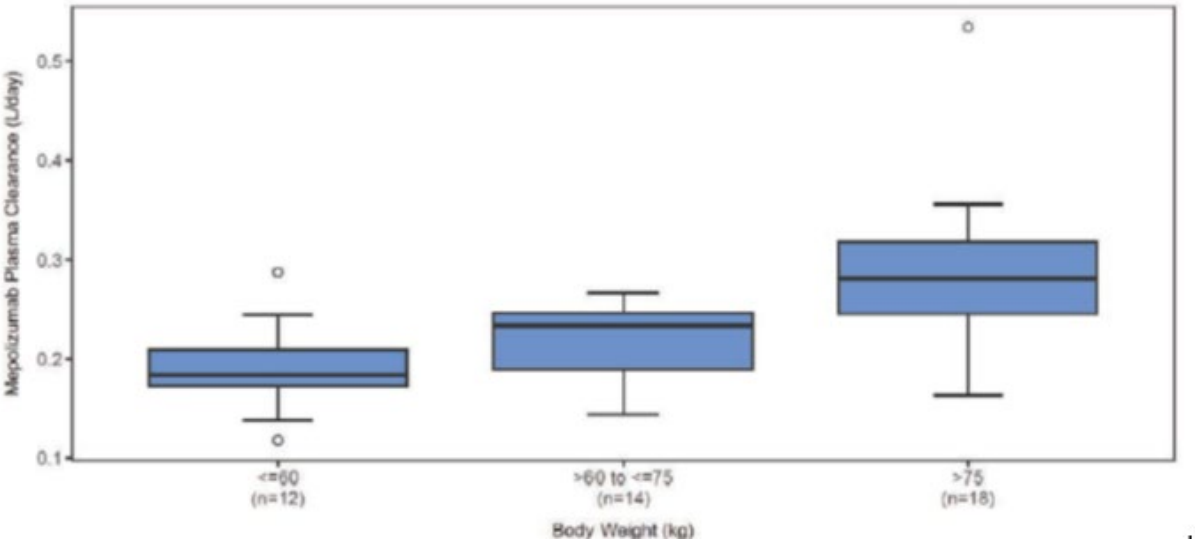
Notes: Data are presented as geometric mean (95% CI) [%CV].
a US non-Asian and China are subsets of the Overall PK population
Abbreviations: AUC_ss=area under the concentration-time curve at steady state; Cavg_ss=average concentration at steady state; CI=confidence interval; Cmax_ss=maximum concentration at steady state; COPD=chronic obstructive pulmonary disease; n=number of participants; NC=not calculated; PK=pharmacokinetic; Q4W=every 4 weeks; SC=subcutaneous; t½=terminal elimination half-life; US=United States

Figure 6 Box and whisker plot of mepolizumab post hoc AUC_ss, Cavg_ss, and Cmax_ss in the Overall, US non-Asian, and Chinese populations



Notes: The box plot shows the median (thick line), interquartile range (boxes), and error bars denoting 10th and 90th percentiles. Individual exposure parameters are superimposed on box plots as red points.
Abbreviations: AUC_ss=area under the concentration-time curve at steady state; Cavg_ss=average concentration at steady state; Cmax_ss=maximum concentration at steady state; n=number of participants; US=United States

Figure 7 Box and whisker plot of post hoc mepolizumab systemic clearance versus body weight in the Overall population



Notes: The box plot shows the median (thick line), interquartile range (boxes), and distance of 1.5 interquartile range (error bar).
Abbreviations: n=number of participants

The analyses indicate the geometric mean mepolizumab clearance was faster in the US non-Asian population compared to the Chinese population (0.250 and 0.203 L/day, respectively, Table 5); however, these values are within clearance values observed in previous studies in COPD and other indications. Given the slight difference in clearance between the US non-Asian population and Chinese population, the geometric mean exposure parameters are slightly lower in the US non-Asian population compared to the Chinese population (e.g., AUCss of 302 and 372 day•µg/mL, respectively, Table 6).

To further illustrate the lack of clinical relevance for exposure differences across body weight, Figure 8 displays the ratio to screening in BEC (GI/L) at Week 52 for individual participants receiving active treatment by weight subgroups. The weight subgroups represent the fifth percentile in females to ninety-fifth percentile in males weight range as established by the US CDC. Across the weight groups, there is no significant difference in the eosinophil reduction relative to weight group with significant overlap in 95% CI of the geometric mean across weight groups. Table 7 provides information on the ratio to screening eosinophil count at Week 52 for individual mepolizumab-treated participants at either extreme in terms of body weight (<40 kg or >130 kg). There is no trend relating body weight to eosinophil ratio.

Figure 8 ratio to screening on-treatment blood eosinophils (GI/L) at Week 52 by weight (208657 + MEA117113 +MEA117106-high stratum, mITT population)

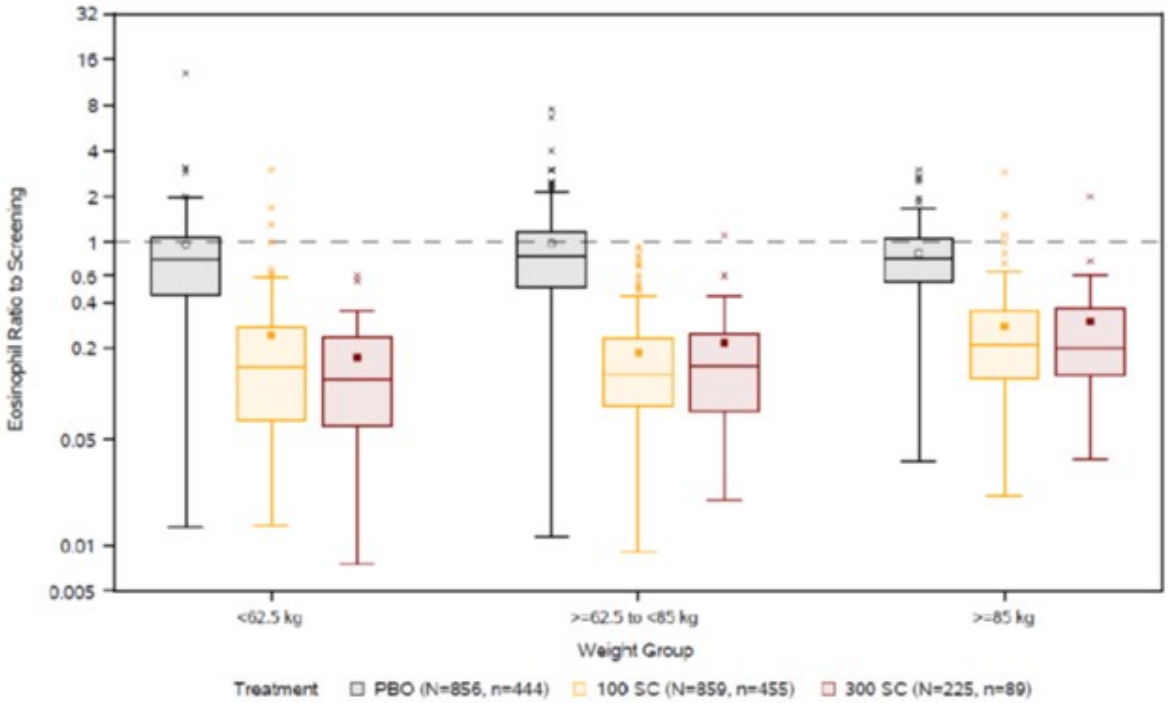


Table 7 Individual participant blood eosinophil ratio to screening at Week 52 for mepolizumab-treated participants with weight <40 kg or>130 kg (208657 + MEA117113 + MEA117106-both strata, mITT population)

Participant	Treatment group	Study	Weight (kg)	Ratio to screening
1	mepolizumab 100 mg	MEA117106	34	0.231*
2	mepolizumab 100 mg	MEA117113	35.7	0.243*
3	mepolizumab 100 mg	MEA117113	37.5	0.071
4	mepolizumab 100 mg	208657	38	0.029
5	mepolizumab 100 mg	MEA117106	39.5	0.500
6	mepolizumab 100 mg	208657	133	0.250
7	mepolizumab 100 mg	MEA117106	134.2	0.154*
8	mepolizumab 100 mg	MEA117106	135.1	0.133*
9	mepolizumab 100 mg	MEA117113	140	0.250
10	mepolizumab 100 mg	208657	146	0.154*
11	mepolizumab 100 mg	MEA117106	148.2	0.133*
12	mepolizumab 100 mg	MEA117106	170	0.214

Note: Asterisk indicates post-treatment

2.3.3 Pharmacodynamics

Mechanism of action

Mepolizumab is an IL-5 antagonist (IgG1 kappa) that binds to IL-5 with a dissociation constant of 100 pM, inhibiting its bioactivity by blocking its binding to the IL-5R alpha complex on the cell surface. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Type 2 inflammation driven by IL-5 is an important component in the pathogenesis of asthma, CRSwNP, COPD, EGPA and HES. Additional structural and inflammatory cell

Primary pharmacology

METREX Study MEA117106

A multi-center, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of SC administration of mepolizumab 100 mg SC Q4W compared with placebo in subjects with COPD at high risk of exacerbations despite the regular use of SoC COPD medication and an eosinophilic phenotype.

Recruitment was not restricted by eosinophil threshold, and randomization was stratified with participants 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 of ≥300 cells/μL
- 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

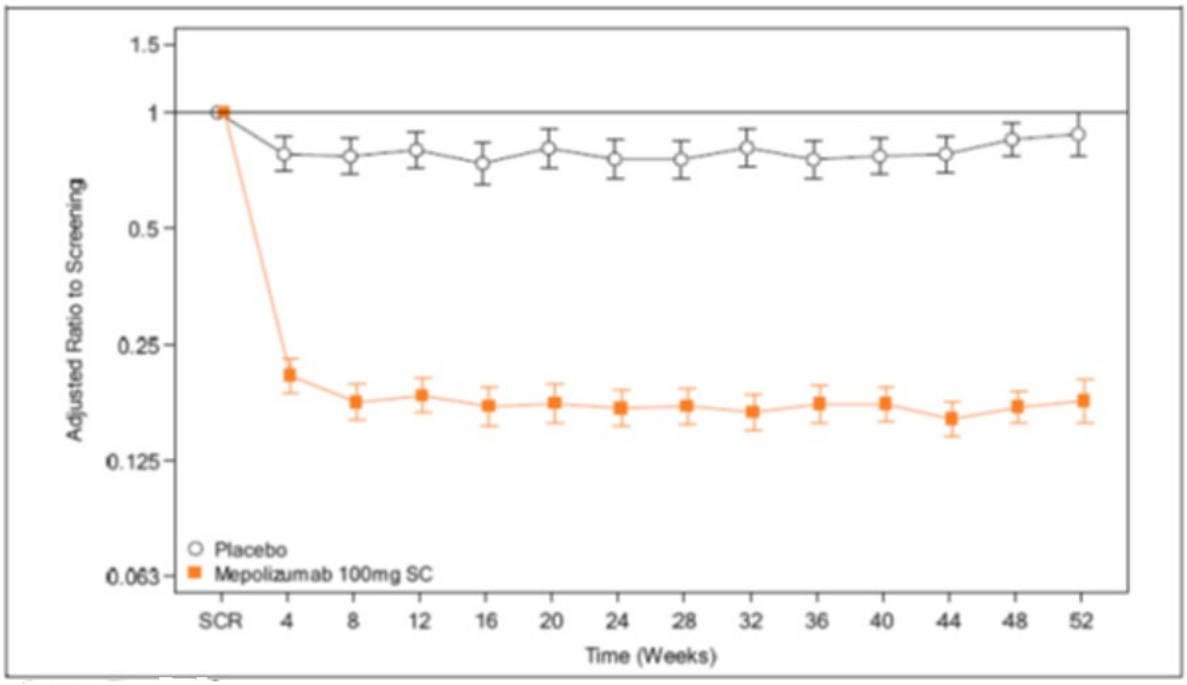
The primary treatment comparison was for participants in the high stratum.

Blood eosinophil counts

Within each stratum, blood eosinophil levels were similar between the placebo and mepolizumab groups at screening (high stratum: 290 cells/μL [range: 100 to 1700 cells/μL] and 250 cells/μL [range: 0 to 1200/μL], respectively, and low stratum: 70 cells/μL [range: 0 to 100 cells/μL] in both groups. At week 52 for the high stratum, geometric mean blood eosinophil count was reduced to 50 cells/μL in the mepolizumab 100 mg group compared with 230 cells/μL in the placebo group. At Week 52 for the low stratum, geometric mean blood eosinophil count was reduced to 30 cells/μL in the mepolizumab 100 mg group compared with 90 cells/μL in the placebo group.

Administration of mepolizumab 100 mg showed a sustained reduction in blood eosinophils over the 52-week treatment period (Figure 9).

Figure 9 Blood eosinophil ratio compared to screening (Study MEA117106, mITT-H Population)



Note: Vertical bars represent 95% confidence intervals.

In the high stratum, treatment with mepolizumab 100 mg produced a 73% reduction in blood eosinophil level by Week 4 compared with placebo, which was maintained throughout the treatment period. At Week 52, treatment with mepolizumab 100 mg had produced an 80% reduction in blood eosinophil level compared with placebo (p<0.001) (Table 8).

Table 8 Analysis of on-treatment blood eosinophil ratio compared to screening at week 52 (Study MEA117106, mITT-H Population)

Blood Eosinophil Ratio to Screening (Week 52)	Placebo N=229	Mepolizumab 100 mg SC N=233
n with analyzable data	222	232
n with analyzable data at time point	96	96
LS mean (SE logs)	0.23 (0.067)	0.05 (0.066)
Ratio to Screening (SE logs)	0.88 (0.067)	0.18 (0.066)
Ratio (mepolizumab/placebo)	---	0.20
95% CI	---	0.17, 0.25
p-value	---	<0.001

Note: Data were log transformed prior to analysis. Where a result of zero was recorded, a small value (0.005) was added prior to log transformation. Analysis performed using mixed model repeated measures with covariates of Screening, geographic region, smoking status (current vs. never/ex-smoker), treatment and visit, plus interaction terms for visit by screening and visit by treatment group. Estimates were based on weighting applied to each level of class variable determined from observed proportions.

Serum Interleukin-5

Geometric mean serum IL-5 levels were similar across the treatment groups at baseline (8.29 to 8.57 ng/L) (Table 9). Since the assay measures both free IL-5 and IL-5 bound to mepolizumab, an increase in IL-5 levels with mepolizumab was an expected response. At Week 24 in the high

stratum groups, geometric mean serum IL-5 levels showed increases to 22.17 ng/L in the mepolizumab 100 mg group, while serum IL-5 levels in the placebo group remained similar to baseline (8.29 ng/L). Twelve weeks after cessation of treatment (Week 60), serum IL-5 levels in the mepolizumab group remained elevated at levels similar to Week 24 values.

Table 9 Serum IL-5 over time in study (Study MEA117106, safety population)

	High Stratum		Low Stratum		Overall Population	
Serum IL-5, ng/L	Placebo N=229	Mepolizumab 100 mg SC N=233	Placebo N=190	Mepolizumab 100 mg SC N=184	Placebo N=419	Mepolizumab 100 mg SC N=417
Baseline						
n	229	230	188	182	417	412
Geometric mean	8.45	8.57	8.49	8.29	8.47	8.45
SD logs	0.418	0.448	0.462	0.304	0.438	0.391
Median	7.80	7.80	7.80	7.80	7.80	7.80
Min, Max	7.8, 312.9	7.8, 200.6	7.8, 467.9	7.8, 59.5	7.8, 467.9	7.8, 200.6
Week 24						
n	205	223	174	160	379	383
Geometric mean	8.29	22.17	8.60	11.48	8.43	16.84
SD logs	0.357	1.130	0.520	0.759	0.440	1.043
Median	7.80	14.79	7.80	7.80	7.80	7.80
Min, Max	7.8, 305.5	7.8, 405.9	7.8, 969.4	7.8, 366.1	7.8, 969.4	7.8, 405.9
Week 60 (Follow Up)						
n	186	208	153	145	339	353
Geometric mean	8.25	17.96	8.76	12.63	8.48	15.54
SD logs	0.297	1.021	0.538	0.918	0.423	0.994
Median	7.80	10.27	7.80	7.80	7.80	7.80
Min, Max	7.8, 128.3	7.8, 418.7	7.8, 402.6	7.8, 695.6	7.8, 402.6	7.8, 695.6

Note: Serum IL-5 values were log-transformed for analysis. Prior to the log transformation, values of zero were imputed with a value of half the lowest value collected across subjects.

Fibrinogen and C-Reactive Protein

Baseline geometric mean fibrinogen and C-reactive protein values were similar across the treatment groups (Table 10). At Week 52 in the high stratum groups, little difference from baseline was observed in geometric mean fibrinogen values in the mepolizumab 100 mg and placebo groups, and ratios to baseline were at or close to 1. At Week 52, the geometric mean C-reactive protein value increased slightly in the mepolizumab 100 mg and placebo groups, and ratios to baseline were slightly above 1 with no difference between groups (1.20 and 1.15, respectively).

Table 10 Fibrinogen and C-reactive protein ratio to baseline at week 52 (Study MEA117106, safety population)

Blood Biomarker	High Stratum		Low Stratum		Overall Population	
	Placebo N=229	Mepolizumab 100 mg SC N=233	Placebo N=190	Mepolizumab 100 mg SC N=184	Placebo N=419	Mepolizumab 100 mg SC N=417
Fibrinogen, mg/L						
Baseline						
n	214	220	181	174	395	394
Geometric mean	3.28	3.40	3.33	3.33	3.30	3.36
SD logs	0.271	0.247	0.276	0.268	0.273	0.256
Week 52						
n	191	206	159	153	350	359
Geometric mean	3.19	3.38	3.10	2.98	3.15	3.20
SD logs	0.307	0.300	0.307	0.345	0.307	0.326
Week 52 Ratio to Baseline						
n	179	195	150	147	329	342
Geometric mean	0.98	1.00	0.93	0.92	0.96	0.96
SD logs	0.325	0.285	0.329	0.311	0.327	0.298
C-Reactive Protein, mg/L						
Baseline						
n	227	228	185	180	412	408
Geometric mean	2.95	3.48	3.29	3.66	3.10	3.56
SD logs	1.147	1.094	1.034	1.279	1.098	1.178
Week 52						
n	190	210	155	155	345	365
Geometric mean	3.27	4.09	3.45	3.02	3.35	3.60
SD logs	1.159	1.204	1.145	1.198	1.151	1.209
Week 52 Ratio to Baseline						
n	189	205	150	152	339	357
Geometric mean	1.15	1.20	1.08	0.86	1.12	1.04
SD logs	1.191	1.226	1.115	1.387	1.157	1.305

Note: Fibrinogen and C-reactive protein values were log-transformed for analysis. Prior to the log transformation, values of zero were imputed with a value of half the lowest value collected across subjects.

METREO Study MEA117113

A multi-center, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of SC administration of mepolizumab 100 mg or 300 mg SC Q4W compared with placebo in subjects with COPD at high risk of exacerbations despite the regular use of SoC COPD medication and an eosinophilic phenotype.

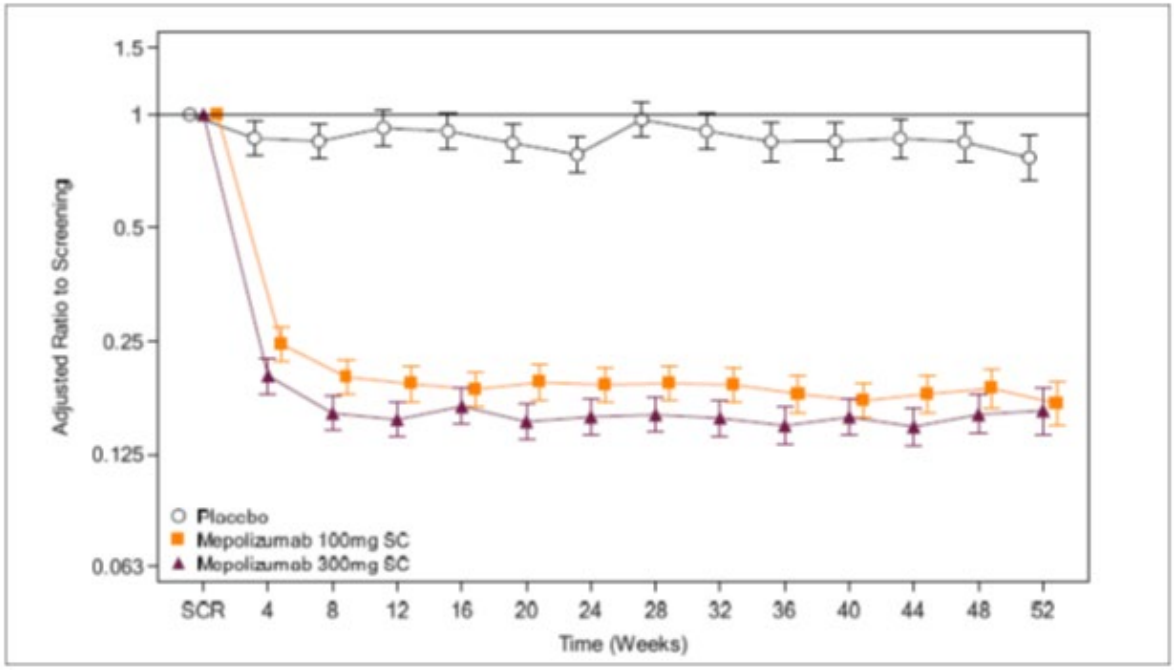
Randomized participants had blood eosinophil count ≥150 cells/µL at screening or a historic blood eosinophil count in the preceding 12 months of ≥300 cells/µL.

Blood eosinophil counts

At screening, geometric mean blood eosinophil count was similar across the treatment groups (230 cells/µL; range 0-2500 cells/µL). At Week 52, geometric mean blood eosinophil count was reduced to 40 cells/µL in the mepolizumab 100 mg and 300 mg groups compared with 180 cells/µL in the placebo group.

Administration of mepolizumab 100 mg and 300 mg showed a sustained reduction in blood eosinophils over the 52-week treatment period (Figure 10), with slightly greater reductions seen in those treated with 300 mg.

Figure 10 Blood eosinophils ratio compared to screening (Study MEA117113, mITT population)



Note: Vertical bars represent 95% confidence intervals

At Week 52, reductions in blood eosinophil counts of 78% and 79%, were observed with mepolizumab 100 mg and 300 mg, respectively, compared with placebo ($p<0.001$) (Table 11).

Table 11 Analysis of blood eosinophils ratio compared to screening at week 52 (Study MEA117113, mITT population)

Blood Eosinophils Ratio to Screening (Week 52)	Placebo N=226	Mepolizumab 100 mg SC N=223	Mepolizumab 300 mg SC N=225
n with analyzable data	220	220	224
n with analyzable data at time point	97	102	90
LS mean	0.18	0.04	0.04
Ratio to Screening	0.77	0.17	0.16
(SE logs) for mean and ratio to Screening	(0.071)	(0.070)	(0.073)
Ratio (mepolizumab/placebo)	---	0.22	0.21
95% CI	---	0.18, 0.27	0.17, 0.26
p-value	---	<0.001	<0.001

Note: Data were log-transformed for analysis. Where a result of 0 was recorded, a small value (0.005) was added prior to log transformation.
Note: Analysis performed using mixed model repeated measures with covariates of screening, geographic region, smoking status (current vs. never/ex-smoker), treatment and visit, plus interaction terms for visit by screening and visit by treatment group. Estimates are based on weighting applied to each level of class variable determined from observed proportions.

Serum Interleukin-5

Geometric mean serum IL-5 levels were similar across the treatment groups at baseline (8.44 to 9.72 ng/L) (Table 12). Since the assay measures both free IL-5 and IL-5 bound to mepolizumab, an increase in IL-5 levels with mepolizumab was an expected response. At Week 24, geometric mean serum IL-5 levels showed increases to 26.48 and 28.43 ng/L in the mepolizumab 100 mg and 300 mg groups, respectively, while serum IL-5 levels in the placebo group remained similar to baseline (8.89 ng/L). Twelve weeks after cessation of treatment (Week 60), serum IL-5 levels in the mepolizumab groups remained elevated at levels similar to Week 24 values.

Table 12 Serum IL-5 over time in study (Study MEA117113, safety population)

Serum IL-5, ng/L	Placebo N=226	Mepolizumab 100 mg SC N=223	Mepolizumab 300 mg SC N=225
Baseline			
n	225	220	222
Geometric mean	8.71	8.44	9.72
SD logs	0.569	0.477	0.772
Median	7.80	7.80	7.80
Min, Max	7.8, 1060.8	7.8, 397.7	7.8, 880.0
Week 24			
n	207	212	212
Geometric mean	8.89	26.48	28.43
SD logs	0.632	1.304	1.321
Median	7.80	19.14	21.33
Min, Max	7.8, 1135.0	7.8, 987.5	7.8, 1059.4
Week 60 (Follow-up)			
n	181	204	196
Geometric mean	8.70	24.49	32.69
SD logs	0.592	1.264	1.335
Median	7.80	18.81	27.81
Min, Max	7.8, 1568.0	7.8, 1265.6	7.8, 1340.5

Note: Serum IL-5 values were log-transformed for analysis. Prior to the log transformation, values of zero were imputed with a value of half the lowest value collected across subjects.

Fibrinogen and C-Reactive Protein

Baseline geometric mean fibrinogen and C-reactive protein values were similar across the treatment groups (Table 13). At week 52, little difference from baseline was observed in geometric mean fibrinogen values and ratios to baseline were at or close to 1 (0.91 to 0.98). At week 52, the geometric mean C-reactive protein value decreased slightly in the placebo group, increased slightly in the mepolizumab 300 mg group, and showed little change in the mepolizumab 100 mg group; overall, ratios to baseline were close to 1 (0.89 placebo, 1.01 mepolizumab 100 mg, and 1.13 mepolizumab 300 mg).

Table 13 Fibrinogen and C-reactive protein ratio to baseline at week 52 (Study MEA117113, safety population)

Blood Biomarker	Placebo N=226	Mepolizumab 100 mg SC N=223	Mepolizumab 300 mg SC N=225
Fibrinogen, mg/L			
Baseline			
n	221	216	218
Geometric mean	3.27	3.29	3.21
SD logs	0.262	0.274	0.278
Week 52			
n	183	198	199
Geometric mean	2.94	3.04	3.18
SD logs	0.326	0.305	0.305
Week 52 Ratio to Baseline			
n	180	191	193
Geometric mean	0.91	0.93	0.98
SD logs	0.342	0.316	0.282
C-Reactive Protein, mg/L			
Baseline			
n	225	219	223
Geometric mean	3.12	3.48	3.10
SD logs	1.219	1.184	1.052
Week 52			
n	178	198	193
Geometric mean	2.69	3.53	3.67
SD logs	1.192	1.151	1.221
Week 52 Ratio to Baseline			
n	177	194	191
Geometric mean	0.89	1.01	1.13
SD logs	1.124	1.205	1.187

Note: Fibrinogen and C-reactive protein values were log-transformed for analysis. Prior to the log transformation, values of zero were imputed with a value of half the lowest value collected across subjects.

MATINEE Study 208657

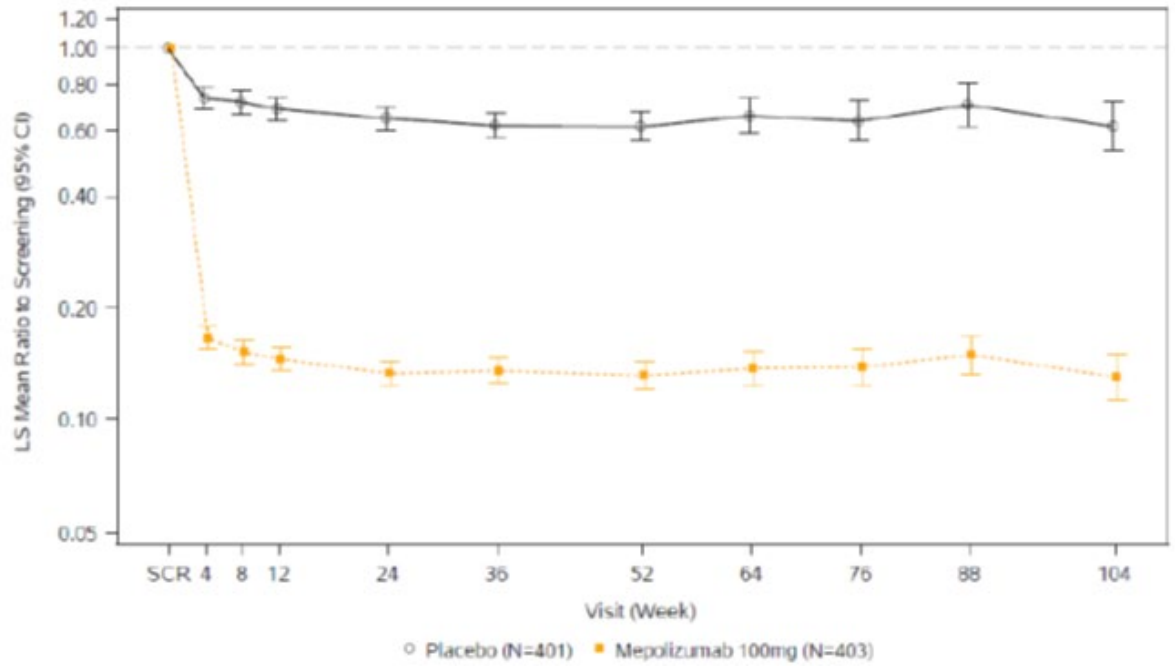
A multi-center, randomized, double-blind, parallel-group, placebo-controlled study of mepolizumab 100 mg SC Q4W as add-on treatment in participants with COPD experiencing frequent exacerbations and characterized by eosinophil levels (blood eosinophil count ≥300 cells/μL at screening and a historic blood eosinophil count in the preceding 12 months of ≥150 cells/μL).

Blood eosinophil counts

At Screening, geometric mean blood eosinophil count was similar in the mepolizumab (0.48 GI/L; range 0.3-2.8 GI/L) and placebo groups (0.48 GI/L; range 0.2-2.3 GI/L). In the mepolizumab group, the geometric mean blood eosinophil count was reduced to 0.08 GI/L by Week 4 and remained at or below this level until the end of treatment period, with 0.06 GI/L reported at both Week 52 and Week 104. In the placebo group, blood eosinophil count remained similar to baseline values from Week 4 (0.35 GI/L) to Week 52 (0.30 GI/L) and Week 104 (0.33 GI/L).

Administration of mepolizumab showed a sustained reduction in blood eosinophil counts over the 104-week treatment period (Figure 11). There was a sustained significant reduction from baseline in blood eosinophil counts with mepolizumab as compared to placebo at every timepoint starting at Week 4. At week 4 there was 77% reduction (ratio: 0.23; 95% CI 0.204 to 0.250), which was maintained throughout the study with a 79% reduction at Week 52 (ratio: 0.21; 95% CI 0.189 to 0.242) and 79% reduction at Week 104 (ratio: 0.21; 95% CI 0.172 to 0.259) (Table 14).

Figure 11 BEC ratio compared to screening (mITT population)



Note: Analysis performed using mixed model repeated measures with covariates of treatment group, geographic region, log(e) screening BEC, smoking status (current versus former smoker), visit plus interaction terms for visit by screening and visit by treatment group. Estimates are based on weighting applied to each level of class variable determined from observed proportions.

Table 14 Analysis of on treatment BEC ratio compared to screening at week 52 and week 104 (mITT population)

	PBO (N=401)	Mepo 100 mg (N=403)
Visit: Week 52		
n [1]	394	397
n [2]	287	301
LS mean (SE logs)	0.29 (0.045)	0.06 (0.044)
LS mean ratio (SE logs)	0.62 (0.045)	0.13 (0.044)
Mepolizumab 100 mg versus placebo		
Ratio (mepolizumab/placebo)		0.21
95% CI		(0.189, 0.242)
p-value		<0.001
Visit: Week 104		
n [1]	394	397
n [2]	82	94
LS mean (SE logs)	0.29 (0.076)	0.06 (0.071)
LS mean ratio (SE logs)	0.62 (0.076)	0.13 (0.071)
Mepolizumab 100 mg versus placebo		
Ratio (mepolizumab/placebo)		0.21
95% CI		(0.172, 0.259)
p-value		<0.001

[1] Number with analysable data for one/more time points.
[2] Number with analysable data at given time point.
Note: Analysis performed using mixed model repeated measures with covariates of treatment group, geographic region, log(e) screening BEC, smoking status (current versus former smoker), visit plus interaction terms for visit by screening and visit by treatment group. Estimates are based on weighting applied to each level of class variable determined from observed proportions.
Note: Blood eosinophil counts were log-transformed for analysis. For counts of 0 the log transformation was based on a value of 0.005.
Note: Includes data reported up to Week 104.
Note: Day 1 on-treatment blood eosinophils values are excluded from the analysis.

A comparison of blood eosinophil count reductions in MATINEE, METREX and METREO is presented in Table 15. The reduction in blood eosinophil counts in Chinese participants compared with US non-Asian participants in MATINEE is also presented in Table 15.

Table 15 Analyss of on-treatment blood eosinophils (GI/L) ratio compared to baseline mixed-model repeated measures at selected time points: Overall (208657, MATINEE, mITT population), US Non-Asian (208657, MATINEE, mITT population), China (208657, MATINEE, mITT population), METREX (Overall, mITT population) and METREO (Overall, mITT population, 100 mg dose data only)

Treatment week	MATINEE: Overall		MATINEE: US non-Asian		MATINEE: China		METREX: Overall		METREO: Overall	
	Placebo N=401	Mepo 100 mg SC N=403	Placebo N=42	Mepo 100 mg SC N=41	Placebo N=29	Mepo 100 mg SC N=28	Placebo N=229	Mepo 100 mg SC N=233	Placebo N=226	Mepo 100 mg SC N=223
Baseline eosinophil counts (GI/L)										
n	401	403	42	41	29	28	229	233	226	223
Geometric mean	0.48	0.48	0.45	0.50	0.46	0.54	0.29	0.25	0.23	0.23
Median	0.44	0.45	0.39	0.48	0.44	0.52	0.25	0.24	0.24	0.24
Min, max	0.2, 2.3	0.3, 2.8	0.3,2.3	0.3,1.0	0.3, 1.2	0.3, 1.9	0.1, 1.7	0.0, 1.2	0.0, 2.5	0.0, 2.4
Change from baseline in eosinophil counts										
Week 4										
n (1)	394	397	40	40	29	28	222	232	220	220
n (2)	358	377	34	38	26	27	214	219	213	210
LS mean (SE logs)	0.35 (0.037)	0.08 (0.036)	0.39 (0.126)	0.09 (0.120)	0.41 (0.159)	0.05 (0.157)	0.21 (0.052)	0.06 (0.051)	0.20 (0.055)	0.06 (0.056)
LS mean ratio (SE logs)	0.73 (0.037)	0.17 (0.036)	0.82 (0.126)	0.18 (0.120)	0.80 (0.159)	0.11 (0.157)	0.78 (0.052)	0.21 (0.051)	0.87 (0.055)	0.25 (0.056)
Mepo 100 mg versus placebo										
Ratio (mepo/ placebo)	-	0.23	-	0.22	-	0.13	-	0.27	-	0.28
95% CI	-	(0.204, 0.250)	-	(0.159, 0.317)	-	(0.085, 0.210)	-	(0.23, 0.31)	-	(0.24, 0.33)
p-value	-	<0.001	-	<0.001	-	<0.001	-	<0.001	-	<0.001
Week 8										
n (1)	394	397	40	40	29	28	222	232	220	220
n (2)	369	368	35	39	25	25	214	221	205	209
LS mean (SE logs)	0.34 (0.038)	0.07 (0.038)	0.38 (0.125)	0.08 (0.119)	0.30 (0.161)	0.05 (0.161)	0.21 (0.055)	0.05 (0.054)	0.20 (0.055)	0.05 (0.055)
LS mean ratio (SE logs)	0.72 (0.038)	0.15 (0.038)	0.81 (0.125)	0.18 (0.119)	0.59 (0.161)	0.10 (0.161)	0.77 (0.055)	0.18 (0.054)	0.85 (0.055)	0.20 (0.055)
Mepo 100 mg versus placebo										
Ratio (mepo/ placebo)	-	0.21	-	0.22	-	0.18	-	0.23	-	0.24
95% CI	-	(0.191, 0.235)	-	(0.159, 0.314)	-	(0.111, 0.277)	-	(0.20, 0.27)	-	(0.20, 0.28)
p-value	-	<0.001	-	<0.001	-	<0.001	-	<0.001	-	<0.001
Week 24										
n (1)	394	397	40	40	29	28	222	232	220	220
n (2)	351	357	30	36	25	24	193	210	188	199
LS mean (SE logs)	0.31 (0.038)	0.06 (0.038)	0.35 (0.133)	0.08 (0.123)	0.34 (0.161)	0.05 (0.165)	0.20 (0.058)	0.05 (0.055)	0.18 (0.056)	0.04 (0.054)
LS mean ratio (SE logs)	0.65 (0.038)	0.13 (0.038)	0.73 (0.133)	0.17 (0.123)	0.67 (0.161)	0.09 (0.165)	0.76 (0.058)	0.17 (0.055)	0.78 (0.056)	0.19 (0.054)
Mepo 100 mg versus placebo										
Ratio (mepo/ placebo)	-	0.21	-	0.23	-	0.14	-	0.23	-	0.24
95% CI	-	(0.185, 0.228)	-	(0.159, 0.326)	-	(0.085, 0.215)	-	(0.19, 0.27)	-	(0.21, 0.28)
p-value	-	<0.001	-	<0.001	-	<0.001	-	<0.001	-	<0.001
Week 52										
n (1)	394	397	40	40	29	28	222	232	220	220
n (2)	252	257	25	22	17	18	96	96	97	102
LS mean (SE logs)	0.30 (0.047)	0.06 (0.046)	0.31 (0.143)	0.09 (0.148)	0.36 (0.182)	0.05 (0.183)	0.23 (0.067)	0.05 (0.066)	0.18 (0.071)	0.04 (0.070)
LS mean ratio (SE logs)	0.62 (0.047)	0.13 (0.046)	0.66 (0.143)	0.19 (0.148)	0.71 (0.182)	0.10 (0.183)	0.88 (0.067)	0.18 (0.066)	0.77 (0.071)	0.17 (0.070)
Mepo 100 mg versus placebo										
Ratio (mepo/ placebo)	-	0.21	-	0.28	-	0.14	-	0.20	-	0.22
95% CI	-	(0.188, 0.243)	-	(0.189, 0.424)	-	(0.081, 0.227)	-	(0.17, 0.25)	-	(0.18, 0.27)
p-value	-	<0.001	-	<0.001	-	<0.001	-	<0.001	-	<0.001

Notes: For blood eosinophil counts of 0, the log transformation was based on a value of 0.005.
METREX results presented are for the High Stratum.
The MATINEE China analysis was performed using a compound symmetry correlation structure; a mixed-model repeated measures analysis was performed for all other analyses.

Surfactant D, fibrinogen and C-reactive protein levels

Baseline geometric mean of surfactant D values were similar between the treatment groups (Table 16). At Week 52 a small change from baseline was observed in the geometric mean of surfactant D values in the mepolizumab and placebo groups, and ratios to baseline were at or close to 1.

Table 16 Blood biomarkers: surfactant protein D (safety population)

Visit			PBO (N=401)	Mepo 100 mg (N=403)
Baseline	Surfactant protein D (µg/L)	n	354	361
		Geo. Mean	188.72	188.24
		Std logs	0.685	0.670
		Median (Min, Max)	178.84 (31.5, 1796.0)	183.57 (31.4, 1757.7)
Week 24	Surfactant protein D (µg/L)	n	341	338
		Geo. Mean	192.98	189.18
		Std logs	0.635	0.649
		Median (Min, Max)	177.80 (37.9, 1759.4)	180.78 (17.2, 951.0)
	Ratio to baseline	n	327	329
		Geo. Mean	1.03	1.04
		Std logs	0.527	0.553
		Median (Min, Max)	1.03 (0.2, 9.1)	1.02 (0.2, 8.6)
Week 52	Surfactant protein D (µg/L)	n	312	319
		Geo. Mean	181.93	175.93
		Std logs	0.620	0.603
		Median (Min, Max)	171.62 (24.4, 1003.9)	167.99 (35.6, 976.8)
	Ratio to baseline	n	299	309
		Geo. Mean	0.99	0.97
		Std logs	0.449	0.489
		Median (Min, Max)	0.98 (0.2, 3.4)	0.99 (0.2, 5.4)

Note: Surfactant Protein D counts were log-transformed for analysis. For counts of 0, the log transformation was based on a value of 0.005.

Baseline geometric mean fibrinogen and C-reactive protein values were similar across the treatment groups (Table 17). At Week 52, little difference from baseline was observed in geometric mean fibrinogen values and ratios to baseline were 1 (1.01 in mepolizumab and 1.00 in placebo).

Table 17 Blood biomarkers: fibrinogen (safety population)

Visit			PBO (N=401)	Mepo 100 mg (N=403)
Baseline	Fibrinogen (10^9/L)	n	341	355
		Geo. Mean	4.57	4.75
		Std Logs	0.212	0.207
		Median (Min, Max)	4.69 (1.8, 6.0)	4.87 (1.2, 6.0)
Week 24	Fibrinogen (10^9/L)	n	330	329
		Geo. Mean	4.63	4.84
		Std Logs	0.216	0.178
		Median (Min, Max)	4.76 (1.9, 6.0)	4.93 (2.5, 6.0)
	Ratio to Baseline	n	308	315
		Geo. Mean	1.01	1.02
		Std Logs	0.230	0.189
		Median (Min, Max)	1.02 (0.3, 2.4)	1.00 (0.5, 2.1)
Week 52	Fibrinogen (10^9/L)	n	303	307
		Geo. Mean	4.60	4.73
		Std Logs	0.227	0.207
		Median (Min, Max)	4.73 (1.7, 6.0)	4.85 (1.9, 6.0)
	Ratio to Baseline	n	280	293
		Geo. Mean	1.00	1.01
		Std Logs	0.230	0.228
		Median (Min, Max)	1.01 (0.4, 3.2)	1.00 (0.4, 4.5)

Note: Fibrinogen counts were log-transformed for analysis. For counts of 0 the log transformation was based on a value of 0.005.

At Week 52, the geometric mean C-reactive protein value increased slightly in both treatment groups; overall, ratios to baseline were more than 1 (1.21 in mepolizumab and 1.13 in placebo) (Table 18).

Table 18 Blood biomarkers: C-reactive protein (safety population)

Visit			PBO (N=401)	Mepo 100 mg (N=403)
Baseline	C-Reactive Protein (mg/L)	n	353	364
		Geo. Mean	2.78	2.81
		Std Logs	1.105	1.171
		Median (Min, Max)	2.88 (0.1, 79.0)	2.60 (0.2, 100.7)
Week 24	C-Reactive Protein (mg/L)	n	350	341
		Geo. Mean	2.92	3.11
		Std Logs	1.199	1.143
		Median (Min, Max)	2.88 (0.1, 117.3)	3.00 (0.2, 109.0)
	Ratio to Baseline	n	335	333
		Geo. Mean	1.06	1.15
		Std Logs	1.025	1.064
		Median (Min, Max)	1.08 (0.0, 99.7)	1.00 (0.0, 112.2)
Week 52	C-Reactive Protein (mg/L)	n	315	322
		Geo. Mean	3.07	3.33
		Std Logs	1.237	1.166
		Median (Min, Max)	2.98 (0.2, 204.1)	3.06 (0.2, 233.5)
	Ratio to Baseline	n	301	314
		Geo. Mean	1.13	1.21
		Std Logs	1.180	1.105
		Median (Min, Max)	1.13 (0.0, 62.4)	1.09 (0.0, 133.2)

Note: C-Reactive protein counts were log-transformed for analysis. For counts of 0 the log transformation was based on a value of 0.005.

Immunogenicity

METREX Study MEA117106

At baseline, 6 subjects tested positive for ADA: 3 subjects in the placebo group (2 in the high stratum and 1 in the low stratum) and 3 subjects in the mepolizumab 100 mg group (high stratum). Two of the 3 placebo subjects (1 in the high stratum and 1 in the low stratum) and none in the mepolizumab 100 mg group tested positive for neutralizing antibodies at baseline.

At any time post baseline, 16 subjects tested positive for ADA: 14 subjects (4%) in the mepolizumab 100 mg group and 2 subjects (<1%) in the placebo group (Table 19). The majority of mepolizumab-treated subjects (10 of 14 subjects) had persistent positive results; both placebo-treated subjects had transient positive results. Median titer of 32 was the same for both treatment groups. One of the 16 subjects (placebo group) tested positive for neutralizing antibodies post baseline and none in the mepolizumab 100 mg group.

Table 19 Immunogenicity – highest confirmatory result any time past baseline (Study MEA117106, safety population)

Immunogenicity Results Post-baseline	High Stratum		Low Stratum		Overall Population	
	Placebo N=229	Mepolizumab 100 mg SC N=233	Placebo N=190	Mepolizumab 100 mg SC N=184	Placebo N=419	Mepolizumab 100 mg SC N=417
Binding Antibody Assay [1]						
n	214	227	181	168	395	395
Assay Result						
Negative	212 (>99)	220 (97)	181 (100)	161 (96)	393 (>99)	381 (96)
Positive [2]	2 (<1)	7 (3)	0	7 (4)	2 (<1)	14 (4)
Persistent positive	0	5 (2)	0	5 (3)	0	10 (3)
Transient positive	2 (<1)	2 (<1)	0	2 (1)	2 (<1)	4 (1)
Titer result						
Median	32.0	32.0	0	32.0	32.0	32.0
Min, Max	32, 32	8, 64	0, 0	16, 64	32, 32	8, 64
Neutralizing Assay						
n	2	7	0	7	2	14
Assay Result						
Negative	1 (50)	7 (100)	0	7 (100)	1 (50)	14 (100)
Positive	1 (50)	0	0	0	1 (50)	

1. Includes only results from subjects who did not have a positive ADA assay prior to the first dose of study treatment.
2. Positive binding confirmatory assay results were further categorized as transient positive (a single positive response that did not occur at the final assessment) or persistent positive (occurred at 2 or more consecutive assessments or at the final assessment).

METREO Study MEA117113

Of the 668 subjects tested for the presence of anti-mepolizumab antibodies at baseline, 5 subjects tested positive for ADA: 1 subject in the placebo group, 3 subjects in the mepolizumab 100 mg group, and 1 subject in the mepolizumab 300 mg group. One subject in the mepolizumab 300 mg group tested positive for neutralizing antibodies at baseline.

At any time post baseline, 20 subjects tested positive for ADA: 3 subjects (1%) in the placebo group, 13 subjects (6%) in the mepolizumab 100 mg group, and 4 subjects (2%) in the mepolizumab 300 mg group (Table 20). The majority of subjects had persistent positive results. Median titers were higher in the mepolizumab groups (32.0 and 20.0) than in the placebo group (8.0). No subject tested positive for neutralizing antibodies post baseline.

Table 20 Immunogenicity – highest confirmatory result any time past baseline (Study MEA117113, safety population)

Immunogenicity Results Post baseline	Placebo N=226	Mepolizumab 100 mg SC N=223	Mepolizumab 300 mg SC N=225
Binding Antibody Assay			
n	217	220	220
Assay Result, n (%)			
Negative	214 (99)	207 (94)	216 (98)
Positive[1]	3 (1)	13 (6)	4 (2)
Transient positive	2 (<1)	4 (2)	1 (<1)
Persistent positive	1 (<1)	9 (4)	3 (1)
Titer result			
Median	8.0	32.0	20.0
Min, Max	2, 16	2, 128	2, 64
Neutralizing Assay			
n	3	13	4
Assay Result, n (%)			
Negative	3 (100)	13 (100)	4 (100)
Positive	0	0	0

1. Positive binding confirmatory assay results were further categorized as transient positive (a single positive response that did not occur at the final assessment) or persistent positive (occurred at 2 or more consecutive assessments or at the final assessment).

MATINEE Study 208657

In the placebo group, the ADA incidence at Baseline was 1% (4/396). In the mepolizumab group, the ADA incidence at Baseline was <1% (4/402), with the study participants being ADA negative after treatment.

Post-baseline in the mepolizumab group, 2% (9/381) of study participants were ADA positive, with a majority being transient ADA positive (2%, 6/381) and some being persistent ADA positive (<1%, 3/381). Titer values were generally low (median value: 16 [range: 4 to 64]). No participants were neutralizing antibody (NAb) positive in the mepolizumab group. One participant in the placebo group was positive for NAb at Baseline and at Visit 15, and NAb negative at Visit 8 and Exit Visit (3 months after Visit 15), with titer values remaining the same between the Baseline visit and the Exit Visit (titer value of 32).

2.3.4. PK/PD modelling

Population PK/PD analysis of data from METREX and METREO

This analysis of data from two phase III studies conducted in COPD patients was performed to evaluate the consistency of mepolizumab PKPD between COPD patients and the populations with other eosinophilic conditions.

Similar to the approach used for the assessment of PK data, the most recent population PKPD model was applied directly to the dataset without estimation step. A fixed effect parameter for baseline blood eosinophil count, obtained by back calculation, was used to capture the low blood eosinophil strata included in study MEA117106 (METREO). Of note, baseline blood eosinophil is

logically higher in study MEA117113 compared to study MEA117106 due to the inclusion of a low blood eosinophil stratum in study MEA117106. Predictions were then generated, and the ability of the model to predict blood eosinophil observations in the two phase III COPD studies assessed using diagnostic plots and goodness of fit tests. The effect of prospectively selected covariates on PD parameters was evaluated graphically (PD parameters vs. covariates), and formally by forward and backward selection.

Results

A total of 20056 blood eosinophil measurements, obtained from 1506 subjects were included in the meta-analysis of studies MEA117106 and MEA117113. The four subjects excluded from the PK analysis were also excluded from the PKPD analysis, and overall 25 blood eosinophil measurements were excluded. The median age was 66 years (range: 39 to 88 years). The median bodyweight at screening was 72 kg (range: 34 to 170 kg).

Apart from the additional parameter to represent the low blood eosinophil strata in study MEA117106, the most recent population PKPD model was able to describe the data from studies MEA117106 and MEA117113 without further refinement. There were no apparent obvious trends in any other covariates. The observed and predicted blood eosinophil count versus time-profiles are presented in Figure 12 and a Visual Predictive Check (VPC) is presented in Figure 13.

Figure 12 Observed and predicted blood eosinophil count versus time-profiles (geometric mean (95% CI))

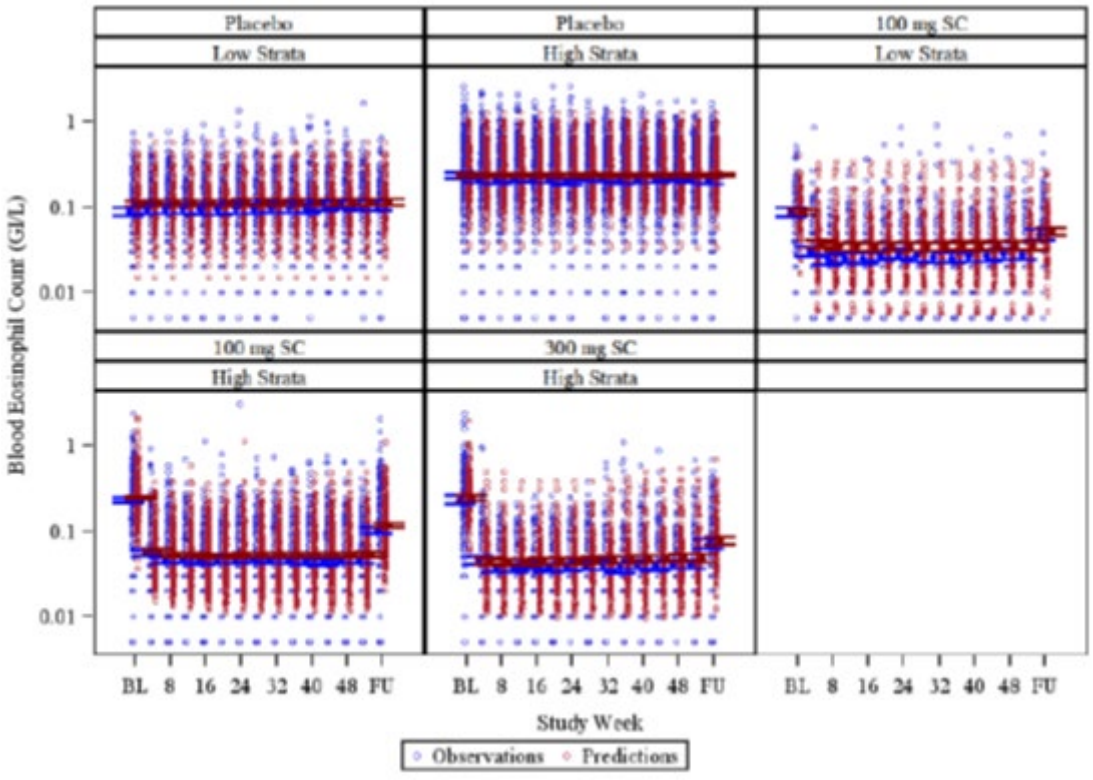
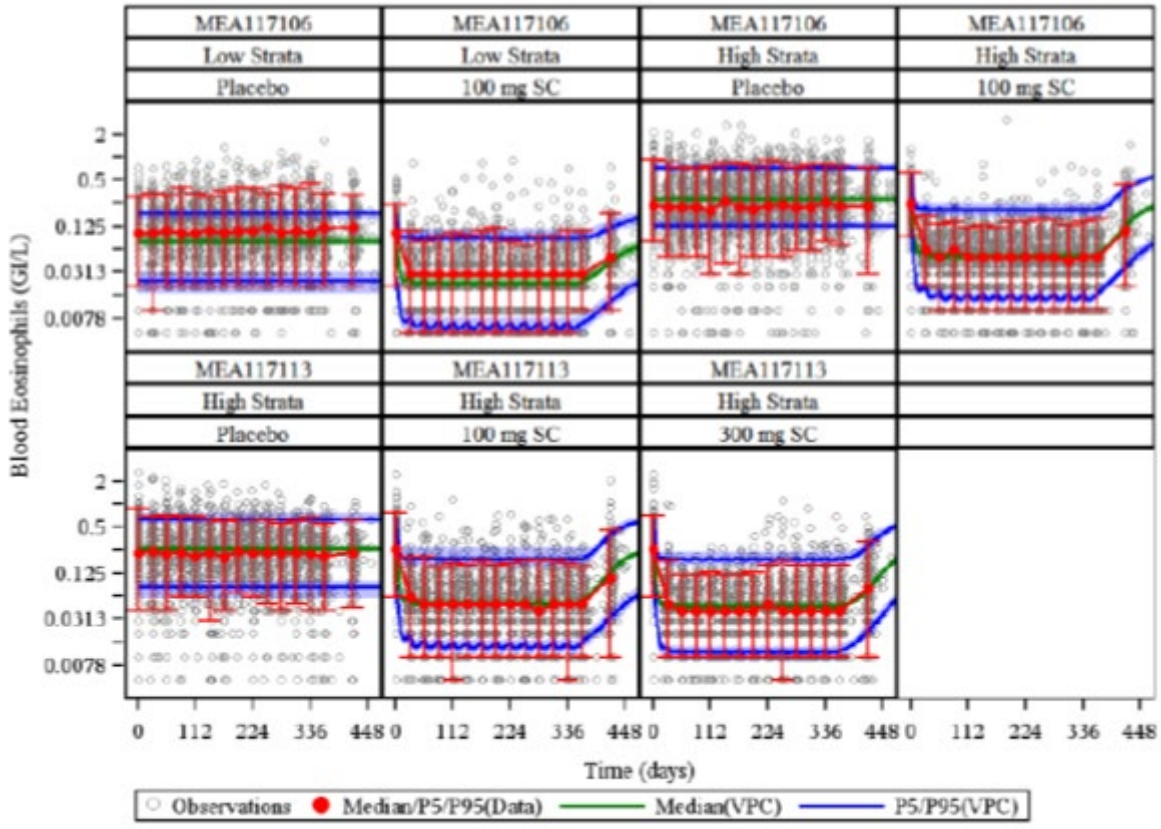


Figure 13 PKPD NONMEM Visual Predictive Check (Semi-log plot)



Concordance between individual model-predicted and observed blood eosinophil counts in the two Phase III COPD studies was evaluated by GOF tests. For all treatment groups, it was not possible to show formal statistical model fit (both location and shape) at the 5% significance level. Likewise, for the Kolmogorov-Smirnov, Cramér-von Mises and Anderson-Darling tests, for both placebo and mepolizumab data, except for the Anderson-Darling test (tails of the distribution) for mepolizumab data, it was not possible to reject at the 5% significance level the null hypothesis that the observations and predictions are drawn from different distributions.

Exposure-response analyses of data from METREX and METREO

Exposure-response (ER) analyses were conducted for the efficacy endpoints of rate of exacerbation and time to first exacerbation. No ER analyses were performed for safety because no specific safety signals were observed in METREX or METREO.

Rate of exacerbation

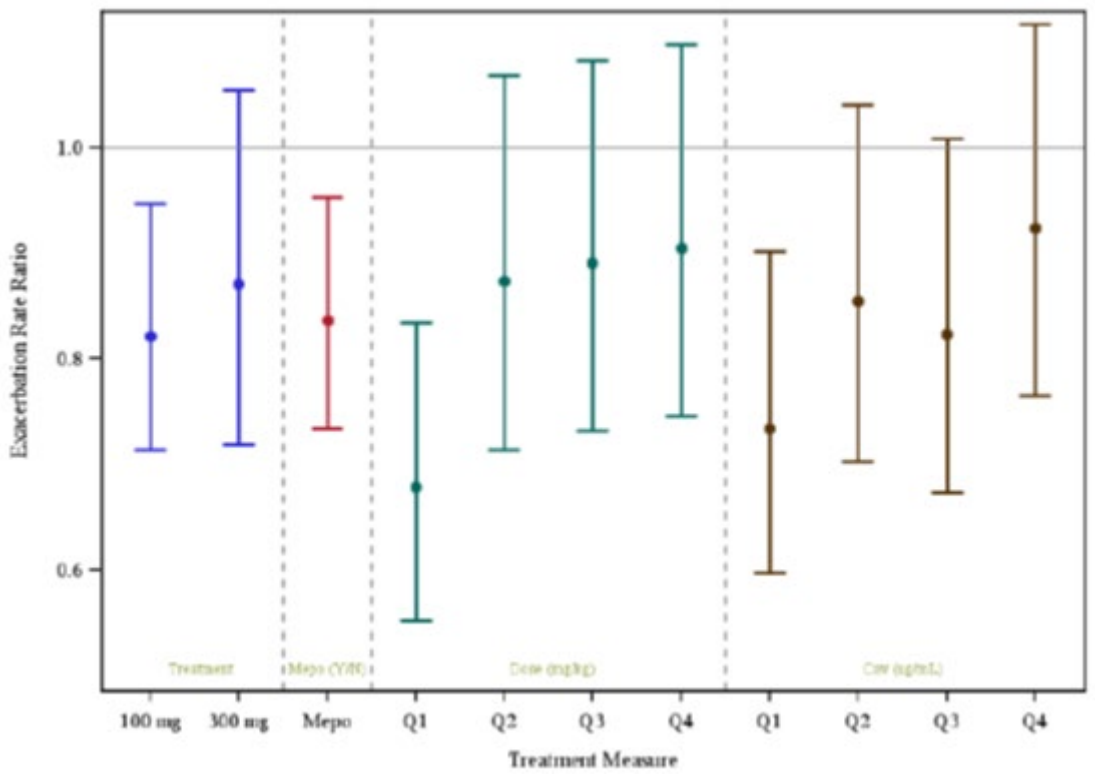
To investigate the relationship between mepolizumab exposure and rate of exacerbation, the integrated summary of efficacy analysis generalised linear model with negative binomial link function and associated covariates was applied to the dataset. The model included mepolizumab treatment as a class effect. Then mepolizumab treatment was considered as a binary treatment (i.e. receiving mepolizumab or not receiving mepolizumab). Mepolizumab exposure defined as the individual weight-based dose or average concentration divided in quartiles were subsequently tested in the model.

Irrespective of the measure of exposure there was no evidence of an increase in efficacy response with increased measure of exposure. On the contrary, lower exposure tended to show a greater response (Table 21and Figure 14).

Table 21 Exacerbation rate ratio exposure response

Exposure	Exposure Measure	Ratio to Placebo	Lower 95% CI	Upper 95% CI
Treatment	100 mg	0.82	0.71	0.95
Treatment	300 mg	0.87	0.72	1.05
Mepo/Placebo	Mepo	0.84	0.73	0.95
Quartile Dose (mg/kg)	Q1	0.68	0.55	0.83
Quartile Dose (mg/kg)	Q2	0.87	0.71	1.07
Quartile Dose (mg/kg)	Q3	0.89	0.73	1.08
Quartile Dose (mg/kg)	Q4	0.90	0.75	1.10
Quartile Cav (ug/mL)	Q1	0.73	0.60	0.90
Quartile Cav (ug/mL)	Q2	0.85	0.70	1.04
Quartile Cav (ug/mL)	Q3	0.82	0.67	1.01
Quartile Cav (ug/mL)	Q4	0.92	0.76	1.12

Figure 14 Exacerbation rate ratio compared with placebo by treatment measure



Time to first exacerbation

To investigate the relationship between mepolizumab exposure and time to first exacerbation, a Cox proportional hazards analysis was conducted using the integrated summary of efficacy model

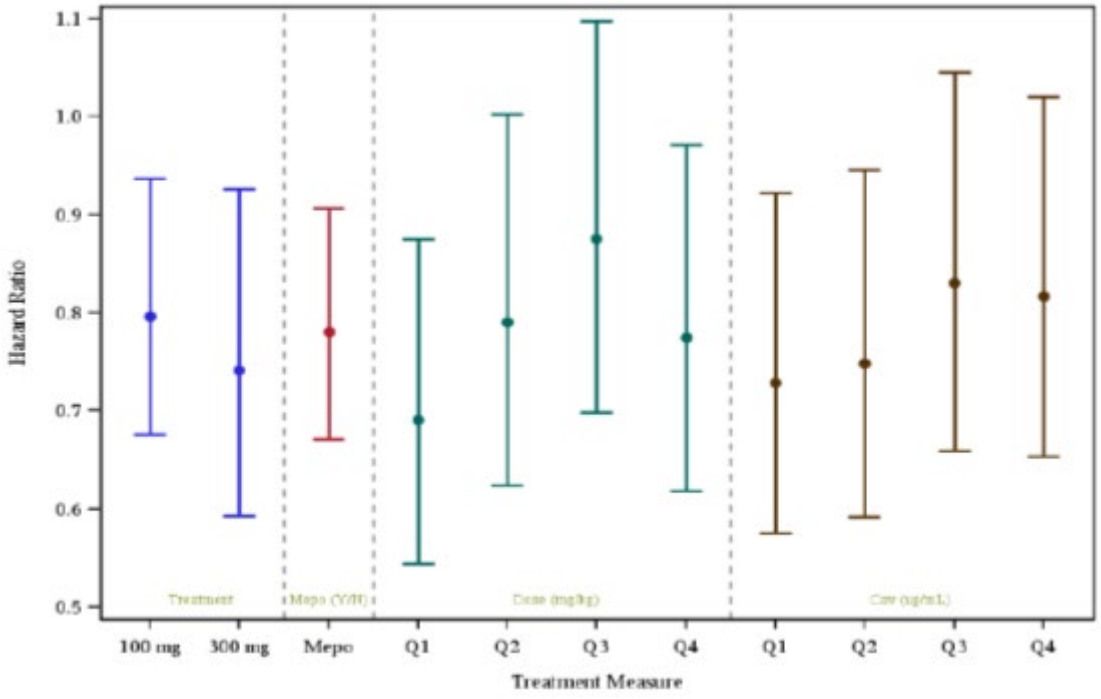
with associated covariates. The same measures of treatment and mepolizumab exposure as in the ER analysis of exacerbation rate were used.

As shown in Table 22 and Figure 15, there was no evidence of increasing efficacy response with higher quartiles of mg/kg dose or average concentration. Indeed, lower exposure tended to provide a better response.

Table 22 Cox proportional hazards model hazard ratio by treatment measure

Exposure	Exposure Measure	Hazard Ratio	95% Lower Confidence Limit for Hazard Ratio	95% Upper Confidence Limit for Hazard Ratio
Treatment	100 mg	0.796	0.676	0.937
Treatment	300 mg	0.741	0.593	0.926
Mepo/Placebo	Mepo	0.780	0.671	0.907
Quartile Dose (mg/kg)	Q1	0.690	0.544	0.875
Quartile Dose (mg/kg)	Q2	0.791	0.624	1.002
Quartile Dose (mg/kg)	Q3	0.875	0.698	1.097
Quartile Dose (mg/kg)	Q4	0.775	0.619	0.971
Quartile Cav (ug/mL)	Q1	0.728	0.575	0.922
Quartile Cav (ug/mL)	Q2	0.748	0.592	0.945
Quartile Cav (ug/mL)	Q3	0.830	0.659	1.045
Quartile Cav (ug/mL)	Q4	0.816	0.654	1.020

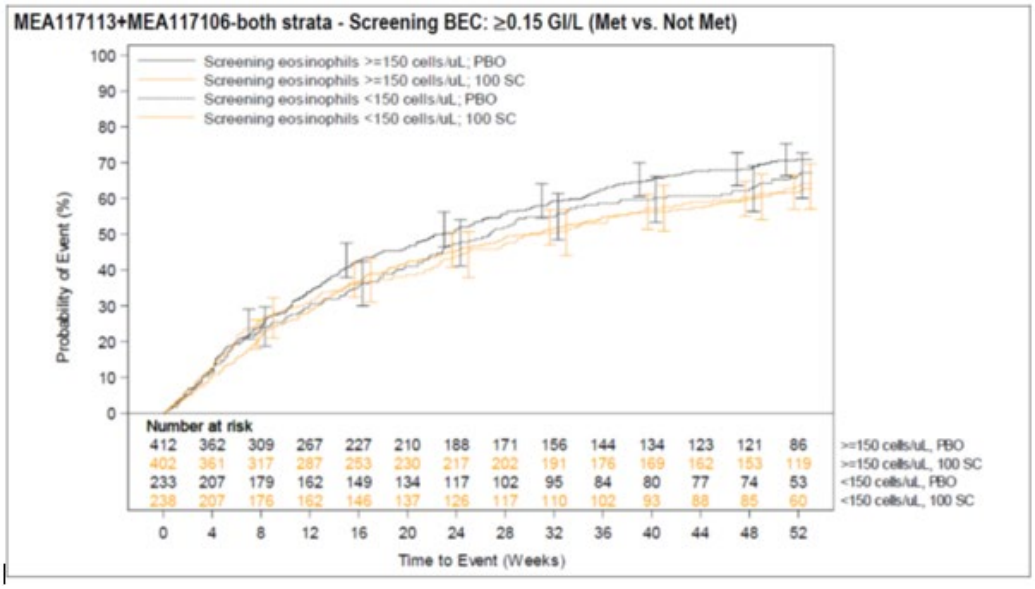
Figure 15 Hazard ratio compared with placebo by treatment measure

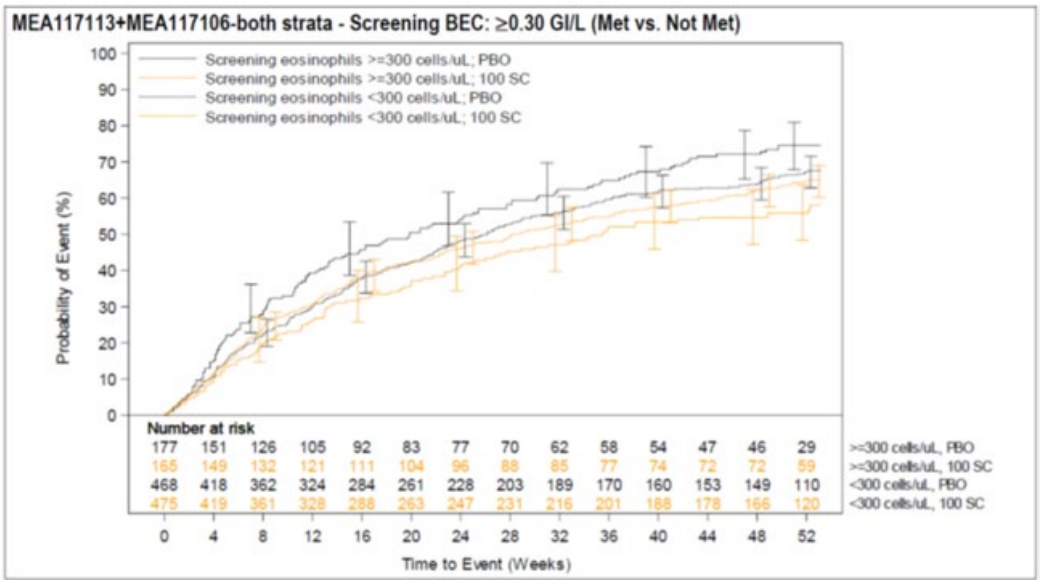


Analyses of eosinophil counts versus efficacy endpoints

To investigate the time to first exacerbation exposure-response relationship, a Kaplan-Meier plot of time to first exacerbation stratified by screening eosinophil count for the pooled MEA117106-both strata and MEA117113 studies is shown in Figure 16. Separation between the mepolizumab and placebo arms are observed in participants for both screening BEC ≥0.15 and BEC ≥0.30 GI/L. A similar evaluation is presented for 208657 in Figure 17, however, with a cut-off of 0.5 GI/L given that all participants required 0.3 GI/L at screening for study entry. In both analyses, a clear separation between mepolizumab arms and placebo are seen when screening eosinophil count is greater than 0.15 GI/L, 0.30 GI/L or 0.5 GI/L respectively. Overall, increased separation between mepolizumab and placebo is observed with increased screening eosinophil count. The same level of separation is not observed for the comparison in participants with screening eosinophil count of <0.15 GI/L.

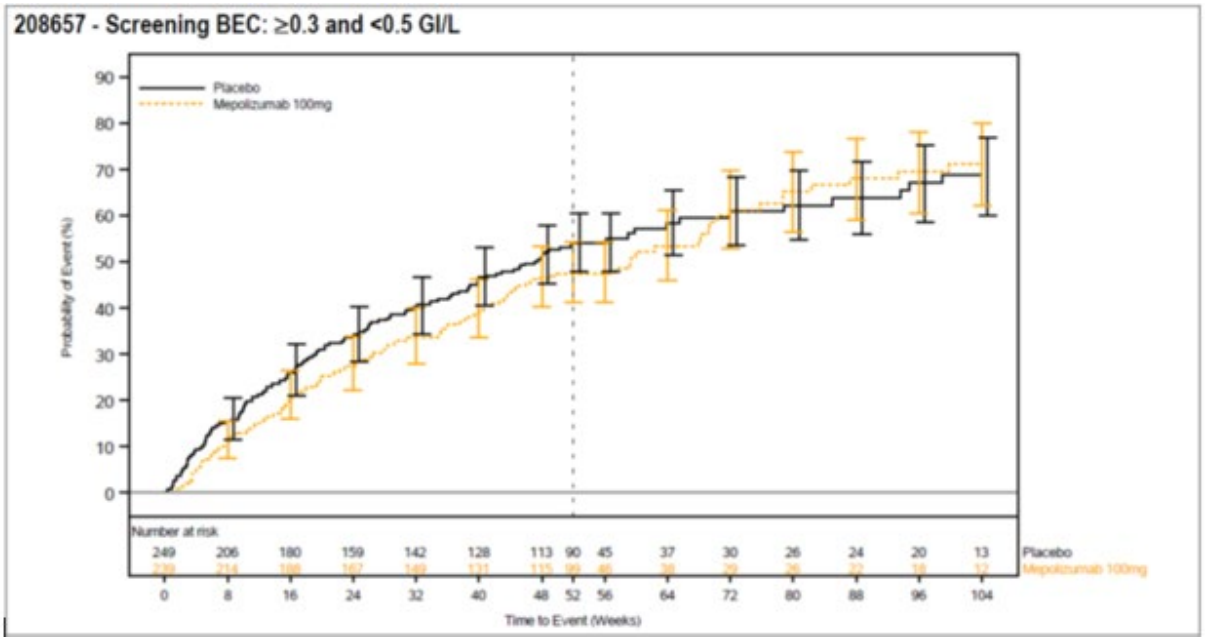
Figure 16 Time to first exacerbation by treatment by screening BEC (A0 ≥0.15 GI/L (B) ≥0.3 GI/L (MEA117113 + MEA117106-both strata, mITT population)

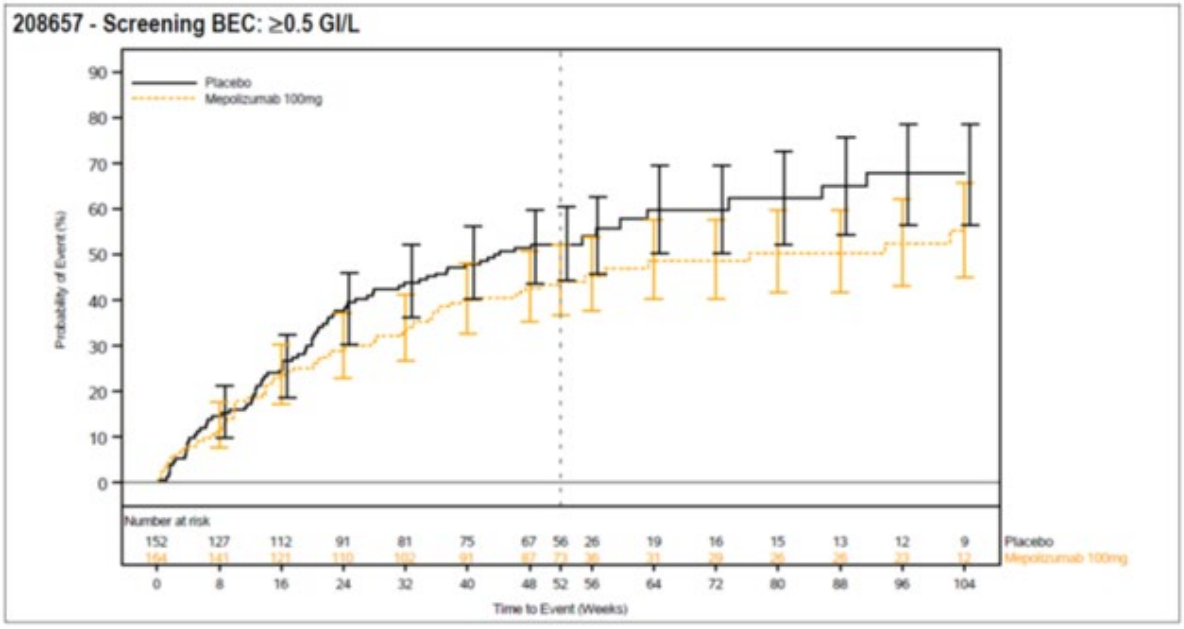




Note: Vertical bars represent 95% confidence interval.

Figure 17 Time to first moderate/severe exacerbation by screening BEC: <0.5 GI/L vs ≥0.5 GI/L (208657, mITT population)

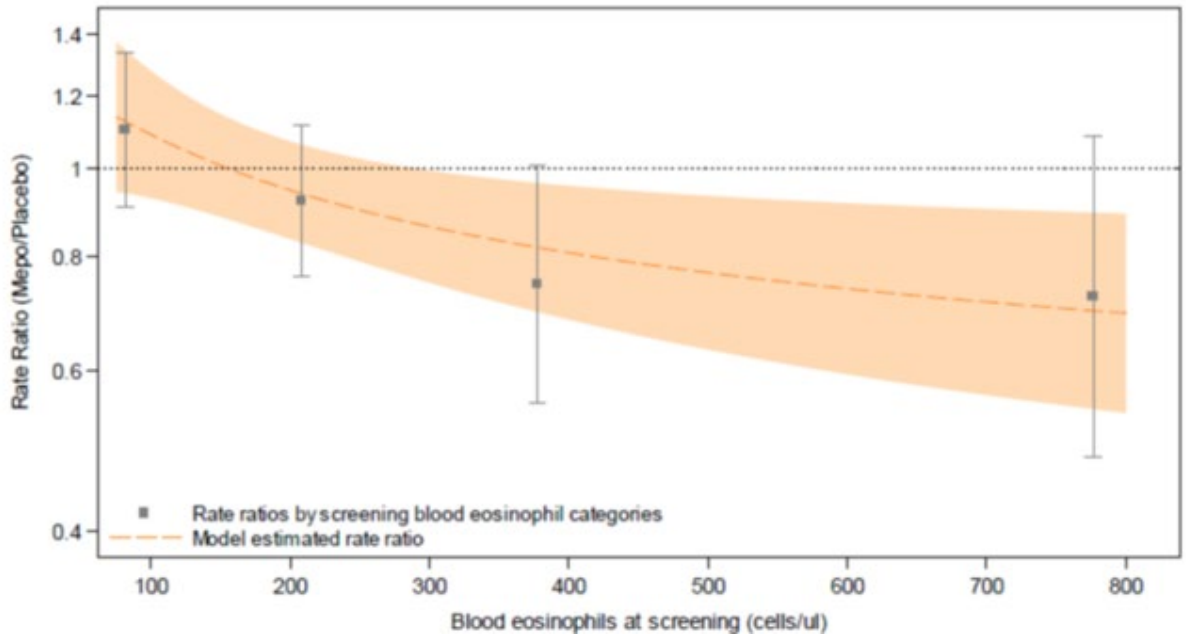




Note: Includes data reported up to Week 104. Vertical bars represent 95% confidence interval.

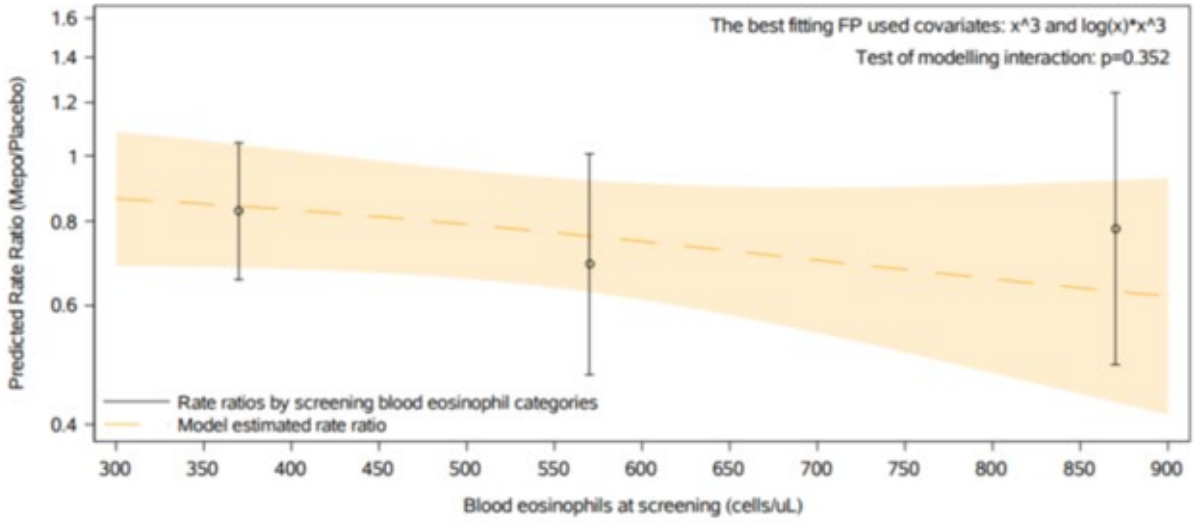
To investigate the relationship between eosinophil count and rate of exacerbation, the efficacy analysis model with negative binomial link with covariates of treatment group, geographic region, number moderate/severe exacerbations in previous year, baseline % predicted FEV1, smoking status, and with logarithm (time on-and off-treatment) as offset variable was applied. In analyses for the pooled studies MEA117113 + MEA117106 and in study 208657, there was a greater benefit of mepolizumab 100 mg SC compared with placebo in participants with higher eosinophil counts at Screening.

Figure 18 Predicted rate ratio of moderate/severe exacerbations by BEC at screening: mepolizumab 100 mg vs placebo (MEA17113 + MEA117106, mITT population)



Estimated rate ratios (and 95% CI) by screening blood eosinophil categories (<0.15 GI/L, 0.15-0.30 GI/L, 0.30-0.50 GI/L, >=0.50 GI/L) 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: p = 0.005 (likelihood ratio test vs. model without interaction terms).

Figure 19 Predicted rate ratio of moderate/severe exacerbations by BEC at screening: mepolizumab 100 mg vs placebo (208657, mITT population)



Note: Shaded areas represent 95% CIs for predicted rates and rate ratios from the model of exacerbation rates against screening blood eosinophil count.
Note: [1] Analysis performed using a negative binomial model with covariates of treatment group, geographic region, number of moderate/severe exacerbations in previous year (<=2, 3, >=4 as ordinal), baseline % predicted FEV1, smoking status (current vs. former smoker) and with logarithm (time on- and off-treatment) as an offset variable.
Note: Best fitting polynomial model from FP(2) class presented utilizing model [1] with best fitting fractional polynomial transformations of screening blood eosinophil count and interactions with treatment.

2.3.5. Discussion on clinical pharmacology

The clinical pharmacology of mepolizumab in adult patients with chronic obstructive pulmonary disease (COPD) was investigated in three Phase III studies (METREX, METREO and MATINEE) and further analysed in population PK, PK/PD and exposure-response analyses.

Bioanalytical methods

Mepolizumab assay validation

The same method (111202.M01) that was used for the determination of mepolizumab in heparinized human plasma in previous applications was used to support the current submission. The validation of this method has been already assessed (EMEA/H/C/003860). The method selectivity in COPD diseased matrix was validated. In this report, validation results have been provided for accuracy, precision, dilution linearity, hook effect, selectivity, stability and cross validation. Accuracy and precision runs were performed with 5 replicates at 5 concentration levels. Within-run accuracy was -16% to 9.3% with the -16% being recorded at the LLOQ. All other within-run and between-run accuracy and precision results were within ±15%, which meets acceptance criteria set out in the International Conference Harmonisation (ICH) M10 guideline. Dilution non-linearity was tested with 5 replicates of 2,400,000 ng/mL, 4,000 ng/mL, 2,000 ng/mL and 150 ng/mL. No dilution linearity issues, or hook effect was observed in these results. For selectivity, all blank samples, 9/10 samples at LLOQ and all samples at ULOQ met the accuracy and precision requirement. Haemolysed and lipemic plasma met selectivity requirements. An additional selectivity study was performed on COPD samples. This study used 10 lots of human plasma samples from COPD patients spiked with mepolizumab. All precision and accuracy results met the requirement set out in ICH M10 demonstrating that there is no matrix effect due to COPD.

For cross validation at the second site in 2019, samples were prepared separately. These cross-validation samples were then assayed alongside a standard curve prepared by UPP only. Six analytical runs (runs 16, 19, 20, 22, 24 and 25) were conducted for cross validation purposes. 4 out of 6 of these runs failed to meet the acceptance criteria. Two of these (runs 19, 22) failed due because the calibration curve standard at LLOQ level was outside the acceptable range. The other two (runs 16, 25) failed because the cross-validation samples did not meet the acceptance criteria. This was considered a partial pass and any results between the LLOQ and Low-QC would be considered non-reportable; however, as no results were obtained between these values, there was no impact to the results or conclusion. In 2024, separate cross-validation was performed: cross-validation QC samples at 3 levels and 21 pooled cross validation study samples were prepared by the CRL. For cross validation, LQC, MQC and HQC levels were assayed in triplicate in 5 independent runs on 5 individual days. For QC samples, the acceptance criteria were set at >20% precision and ±20% accuracy. Acceptance criteria for cross validation samples were that two-thirds of the samples be within ±30% of percentage difference with a percentage bias within >20%. These criteria were met by 81% of the samples tested, therefore the cross validation is considered acceptable. Stability of 101 months is supported. LQC and HQC samples tested in according with ICH M10 following storage at -80°C for 101 months were within >20% precision and ±20% accuracy (1.2% to 2.9% and -6.6% to 6.7%, respectively). The data provided supports the proposed stability period.

For the COPD study sample analysis (studies: 208657, MEA117113 and MEA117106), the results met the requirements that no more than one third deviated from the nominal concentration by more than 20% and that at least 50% of results were within 20% nominal concentration for each QC sample level. The sample analysis reports confirm acceptable assay performance. Incurred sample reanalysis (ISR) was performed on the COPD studies and the percentage of ISR samples

that were within ±30% difference ranged from 92.9% to 100% across the studies, which is an acceptable percentage. The sample analysis reports confirm acceptable assay performance.

Immunogenicity

Anti-Mepolizumab Antibody Assay

The electrochemiluminescence (ECLA) assay (method ID: 120711M01.01) for the detection of anti-mepolizumab antibodies is the 6th generation ADA assay developed and validated at GSK. Samples were pre-treated with an anti-IL5 blocking antibody to prevent false positives caused by IL5, which were occasionally observed previously. The screening cut-point (SCP) was determined to be 1.10 RECL, and the confirmatory cut-point (CCP) was determined to be 43.18% using normal human serum samples. The in-study CP was determined in the study 208657 (SCP 1.06; CCP 16.1%) and in studies MEA117106 and MEA117113 using 25 pre-dose subject samples (COPD matrix) from each study (SCP 1.07). The same confirmatory cut-point as in the validation (%Inh ≥ 43.18%) was used.

The assay has been transferred to another CRL. As part of method transfer, the assay was validated for all important validation parameters at the site. Validation covered the screening cut point, confirmatory cut point, titre, drug tolerance, sensitivity, selectivity, stability and precision. The negative control used throughout validation is pooled normal human serum and the positive control is rabbit anti-mepolizumab polyclonal antibody. Low, middle and high positive controls were prepared using the positive control antibody.

The assessment of immunogenicity follows a three-tier approach as outlined in the EMA guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1). The SCP was calculated to be 1.05, resulting in a real false positivity rate between 2 and 11%, and the CCP was found to be 14.7%. The other CCP was calculated differently to yield a CCP of 50%. The in-study cut point (in study 208657) using pre-dose samples from COPD patients was not evaluated on the basis that the actual false positive rate was within the desirable range of 2 - 11% (7.4%), indicating that the validated cut-points derived from healthy individuals can be applied to studies involving COPD participants. The precision of the assay was acceptable with the highest within-run precision being 19.7% and the highest between-run precision being 19.5%. Less than 20% is a generally accepted level of precision and as results do not exceed 20%, the assay is considered to have an acceptable level of precision. The drug tolerance was established during validation. The assay can tolerate 12.5 µg/mL at 10 ng/mL of positive control and 200 µg/mL of the drug from 100 to 2000 ng/mL of positive control. This is aligned with the original method validation at the previous site and is therefore considered acceptable. Selectivity was investigated in normal healthy human serum, lipemic serum samples and haemolysed serum samples. At least 80% of the samples tested met the acceptance criteria in all three matrices. For stability, acceptance criteria were that two thirds of stability samples should be above the SCP and the assay must have a precision of >20%. These criteria were met to support up to 5 freeze thaws, short term stability at 2-8°C for 27 hr 5 mins and long-term stability at -10 to -30°C or -60 to -90°C for 32 days. The long-term stability was further extended to 367 days at both temperatures through an addendum. The data provided support the proposed stability of the samples.

Sample analysis data has been provided, and acceptable assay performance was observed

Neutralizing Antibody Assay

The current third generation NAb assay has already been used to support previous HES, NP and EGPA indications. It is an indirect competitive LBA that was developed and validated at GSK. The method was subsequently transferred to the CRL site, where it was validated again. The precision

obtained from QC samples during the NAb sample analysis appeared to be highly variable with poor precision particularly HQC samples in the MEA117106 and MEA117113 studies. This poor precision is considered an artifact due to the small values obtained as results. When calculated using percentage inhibition rather than percent response, which is the inverse result, the method was demonstrated to be highly precise, demonstrating the low precision is an artifact of low values.

The method was then subsequently transferred to another CRL. The validation covered assay cut point for healthy population (87.36%) and a population with severe eosinophilic asthma (70.67%). Assay sensitivity, drug tolerance and stability are all validated to an acceptable level. While the within-run precision is considered an acceptable level, the between-run precision is 25.6% for the negative control, 30% for the high positive control sample (HPC) and 34.7% for the background control. All samples were confirmed to be ADA negative and thus no samples were analysed in titre or NAb assays.

Pharmacokinetics

Population PK analysis of data from METREX and METREO

In this analysis, the most recent population PK model of mepolizumab that was developed in 2015 using pooled data from studies in other eosinophilic conditions was used to predict the mepolizumab concentrations observed in COPD patients in two supportive Phase III studies (METREX and METREO).

Concordance between individual model-predicted and observed mepolizumab concentrations was demonstrated by the statistically significant GOF test results. The VPCs indicated that the model tends to overpredict mepolizumab concentrations, particularly up to week 24, which is likely due to limited PK sampling in the included studies. Apart from these deviations, it is generally agreed that observations were broadly consistent with model predictions. It is also recognised that the model serves a supportive role and therefore the misspecification is of limited clinical relevance.

As expected, an increase in clearance was seen with increasing body weight. Compared to >60 to ≤75 kg patients, median clearance is predicted to be 19% lower in ≤60 kg patients and 57% higher in >90 kg patients. PD data across the bodyweight range were presented to support the position that the observed changes in exposure, resulting from variability in clearance associated with bodyweight, are not expected to be clinically relevant.

Population PK analysis of data from MATINEE

In this analysis, the most recent population PK model of mepolizumab was able to predict mepolizumab concentrations observed in COPD patients in the pivotal Phase III study MATINEE adequately without further refinement. This supports the view that the PK of mepolizumab in COPD participants is consistent with that observed previously in other indications. The most recent popPK model was used to predict individual mepolizumab plasma concentration-time profiles and individual post hoc PK parameters for the Overall, US non-Asian, and Chinese populations in MATINEE. The post hoc PK parameters and derived exposure metrics in US non-Asian and Chinese populations were reasonably comparable. Clearance was faster in US non-Asians (0.25 L/day) than Chinese (0.20 L/day).

This resulted in geometric mean exposure parameters slightly lower in the US non-Asian population compared to the Chinese population (e.g., AUCss of 302 and 372 day•µg/mL, respectively, Table 6). However, this was expected given the mean body weight in the US non-Asian population (77.2 kg) is slightly higher than in the Chinese population (65.0 kg), and the clearance of mepolizumab is known to increase with increasing body weight, as demonstrated in Figure 7. In addition, mean creatinine clearance (a covariate on CL in the most recent popPK model) was slightly lower in the

Chinese population (76.8 mL/min) compared to the US non-Asian populations (82.9 mL/min), which may further contribute to the observation of slightly faster geometric mean clearance in US non-Asians compared to Chinese participants in this clinical study. As demonstrated in Table 6 and Figure 6, there was overlap in the 90% to 95% CIs between the US non-Asian and Chinese populations for all exposure parameters (Cmaxss, AUCss and Cavgss). The t1/2 was similar in both populations (20.1 and 19.5 days for the US non-Asian and Chinese populations, respectively).

These differences in exposure are not of clinical relevance. Even though Chinese participants in MATINEE had a greater reduction in blood eosinophil counts at week 52 than US non-Asian participants (86% vs 72%, respectively), this is primarily due to differences in disease characteristics, which are the dominant factor influencing eosinophil reduction, and not to higher drug exposures.

Overall, these analyses demonstrate that the PK profiles in Chinese participants receiving mepolizumab 100 mg SC Q4W in MATINEE were comparable to the PK profile observed in the US non-Asian participants.

Pharmacodynamics

In METREX and METREO participants, mepolizumab 100 mg SC was effective at reducing (within 4 weeks of treatment) blood eosinophil counts and maintaining the reduction throughout the remainder of the treatment period. By contrast, blood eosinophil counts did not decrease from baseline in the placebo groups. At week 52, blood eosinophil reduction relative to placebo was 80% in high stratum METREX participants and 78% in METREO participants. Low Stratum METREX participants had a small treatment response to mepolizumab, suggesting that the treatment response may be related to blood eosinophils. With the exception of low stratum participants, the blood eosinophil response to mepolizumab in COPD participants in these studies was similar to that observed in participants with other eosinophilic conditions.

In MATINEE, mepolizumab 100 mg SC was effective at reducing (within 4 weeks of treatment) blood eosinophil counts and maintaining overall the Week 4 reduction throughout the remainder of the treatment period. By contrast, blood eosinophil count did not decrease from baseline in the placebo group. The magnitude of reduction in blood eosinophil counts at Week 52 in the Overall, US non-Asian and Chinese populations was 79%, 77% and 86%, respectively. The reductions in blood eosinophil counts in COPD participants in MATINEE were consistent with the reductions observed in METREX (high stratum) and METREO, and with the reductions observed in other eosinophilic conditions.

Treatment with mepolizumab had little impact on fibrinogen and C-reactive protein levels. Since the IL5 assay measures free IL5 and IL5 bound to mepolizumab, IL5 levels increased during treatment.

Immunogenicity

In METREX, there was a low incidence of ADA (3% in the high stratum mepolizumab 100 mg group and 4% in the overall mepolizumab 100 mg group). In METREO, there was a low incidence of ADA (6% in the mepolizumab 100 mg group and 2% in the mepolizumab 300 mg group).

In MATINEE, there was a low incidence (2%) of treatment-emergent ADA, which is consistent with the other COPD studies and other mepolizumab indications (≤6% in severe asthma; <1% in EGPA; and 2% in HES). No participant receiving mepolizumab tested positive for neutralizing antibodies post-baseline in METREX, METREO or MATINEE.

PK/PD modelling

Population PK/PD analysis of data from METREX and METREO

In this analysis, a population PKPD model of mepolizumab that was developed using pooled data from studies in other eosinophilic conditions was used to predict the blood eosinophil counts observed in COPD patients in two Phase III studies (METREX and METREO). The GOF tests failed to show concordance between individual model-predicted and observed blood eosinophil counts statistically. Further, the VPC indicates that the previous model is not able to fully capture the observed data from these two COPD studies.

Therefore, based on this analysis, it cannot be concluded that the most recent PKPD model was able to predict blood eosinophil counts in the COPD participants of these studies well. However, it is agreed that observations largely aligned with predictions. It is also acknowledged that the PKPD model serves a supportive role.

Exposure-response analyses of data from METREX and METREO

The exposure-efficacy analyses for rate of exacerbation and time to first exacerbation, using individual weight-based dose or average concentration by quartiles as measures of exposure, did not show any evidence of increased efficacy response with increased exposure measure, indicating a lack of exposure-response relationship.

Additional analyses of eosinophil count vs efficacy endpoints

On request, additional analyses of blood eosinophil count vs efficacy endpoints (rate of exacerbation and time to first exacerbation), based on data from MATINEE and pooled METREX/METREO studies, were presented. These showed a separation between the mepolizumab and placebo arms but only in participants with high screening eosinophil counts (e.g. >=0.3 GI/L). The findings support the contention that baseline eosinophil count is the primary determinant of treatment response to mepolizumab. This is reflected in the SmPC section 4.4 "Data do not support the use of Nucala in patients with COPD with blood eosinophil count <150 cells/mcL and no evidence of blood eosinophil count ≥300 cells/mcL in the previous 12 months."

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology of mepolizumab has been sufficiently characterised for this extension of indication to include COPD in adults.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

The selected dose and schedule of mepolizumab for patients with COPD in study 208657, 100 mg every 4 weeks, was based on data from 2 initial Phase 3 global COPD studies (MEA117106 and MEA117113). The MAH considered that these two studies demonstrated efficacy with an acceptable safety profile for participants with BEC >150 cells/µL at screening or >300 cells/µL in the prior year.

- In studies MEA117106 (high stratum) and MEA117113, treatment with mepolizumab 100 mg every 4 weeks provided a clinically relevant rate reduction in moderate/severe exacerbations at week 52 of 18% and 20%, respectively, compared with placebo.
- In MEA117113, participants in the higher mepolizumab dose group (300 mg) showed no additional efficacy compared with the 100 mg dose group. The reduction in

moderate/severe exacerbations at Week 52 compared with placebo was similar between the mepolizumab 100 mg and 300 dose groups (20% and 14%, respectively).

- The reduction in BEC was also similar between the 2 dose groups (BEC ratio to screening at Week 52: 0.17 and 0.16, i.e., 83% and 84% reduction from screening for the 100 mg and 300 mg groups, respectively.

The selected dose is also supported by the finding from the Phase IIb/III severe asthma study (MEA112997) and asthma PK/PD study that characterized the dose response relationship for blood eosinophils and supporting scientific evidence on the comparability of eosinophils and IL-5 in asthma and COPD patient populations. The lowest investigated efficacious dose of 100 mg observed within the COPD clinical development program represents therefore approximately the dose providing 90% of the maximum effect for blood eosinophils reduction, the magnitude of reduction previously found effective in severe asthma.

2.4.2. Main studies

Confirmatory evidence of clinical efficacy is mainly based on the pivotal phase 3 efficacy Study-208657-MATINEE. This was a multi-centre, randomized, placebo-controlled, double-blind, parallel-group (2-group), trial evaluating mepolizumab 100 mg compared with placebo given every 4 weeks through SC injection of a liquid formulation delivered in a pre-filled safety syringe.

Two studies MEA117113 and MEA117106 with similar trial design conducted prior to Study-208657-MATINEE were also submitted and these studies are discussed together below.

Main study – MATINEE (Study 208657)

Study Title: A multi-centre, randomized, double-blind, parallel-group, placebo-controlled study of mepolizumab 100 mg SC as addon treatment in participants with COPD experiencing frequent exacerbations and characterized by eosinophil levels (Study 208657).

Methods

The study consisted of a screening period of up to 3 weeks (3-21 days before visit 1) followed by a run-in period of 2 weeks.

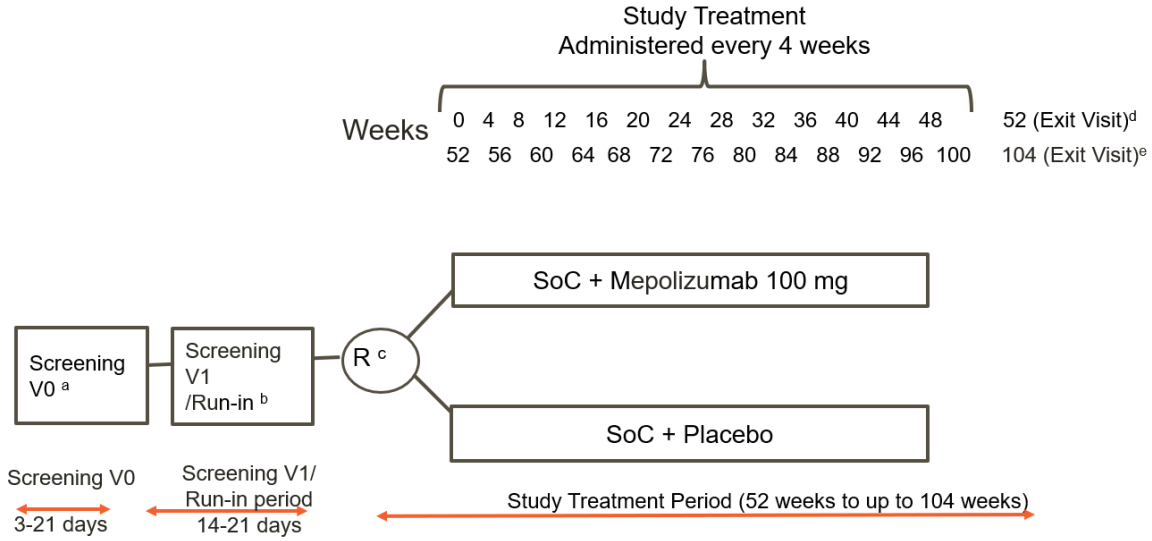
During Screening Visit 0, a mandatory haematology blood sample was collected. The investigator or designee reviewed the results of the Visit 0 BEC prior to initiating Screening Visit 1. Participants with BEC less than 300 cells/μL could not proceed to Screening Visit 1 and were considered a screen failure. Additionally, participants were required to have a documented historical BEC of ≥150 cells/μL in the 12 months prior to Screening Visit 0, which must not have been measured during a COPD exacerbation. Participants with no documented historical BEC of ≥150 cells/μL had to meet this threshold based on the Screening Visit 1 assessment in order to be randomized.

The 2-week run-in period allowed for the assessment of participant understanding and compliance with the daily eDiary to establish Baseline E-RS: COPD symptoms, and to allow adequate time for receipt of results from assessments collected at Screening Visit 1.

Following the screening and run-in period, eligible participants were randomized 1:1 to receive mepolizumab 100 mg SC or placebo for a minimum of 52 weeks and up to 104 weeks following amendment 6 to mitigate the impact of COVID-19 on primary and secondary endpoints of the study.

The timing of the last randomized participant into the study affected the timing of the Exit Visit for participants enrolled beyond 52 weeks. All participants were expected to complete at least 52 weeks of the study. The last randomized participant was scheduled to complete only 52 weeks of the study.

Figure 20 Study scheme



[a] Participants must have an eosinophil count of ≥300 cells/µL at Screening Visit 0 to proceed to Visit 1. They are also required to have a documented historical eosinophil count of ≥150 cells/µL in the 12 months prior to Screening Visit 0.
[b] Participants with no historical eosinophil counts of ≥150 cells/µL must have an eosinophil count ≥150 cells/µL at Screening Visit 1.
[c] R = Randomization: Randomization criteria should be assessed at Week 0 (Visit 2) prior to randomization.
[d] For participants enrolled in the study for 52 weeks, the Exit Visit will be at Week 52, 4 weeks after the last dose.
[e] For participants receiving study treatment beyond 52 weeks, the Exit Visit will be at Week 104 or aligned to the date the last randomized participant is scheduled to complete their Week 52 Exit Visit, whichever is sooner. The Exit Visit will be 4 weeks after the last dose.

Study participants

Key inclusion criteria:

- Participant must be at least 40 years of age at Screening Visit 1
- A peripheral blood eosinophil count of ≥300 cells/µL from the haematology sample collected at Screening Visit 0 **AND** A documented historical blood eosinophil count of ≥150/µL in the 12 months prior to Screening Visit 0 that meets the following: It must have been measured between 12 months and 1 month prior to Visit 0, and it must not have been measured within 14 days of a COPD exacerbation. Participants with no documented historical blood eosinophil count of ≥150 cells/µL must meet this threshold based on the Screening Visit 1 assessment in order to return for Randomization Visit 2.
- **COPD Diagnosis:** Participants with a clinically documented history of COPD for at least 1 year in accordance with the definition by the American Thoracic Society/European Respiratory Society.
- **Severity of COPD:** Participants must present with the following: A measured pre- and post-salbutamol FEV1/FVC ratio of <0.70 at Screening Visit 1 to confirm the diagnosis of COPD and a measured post-salbutamol FEV1>20% and ≤80% of predicted normal values calculated using NHANES III reference equations at Screening Visit 1.
- **History of Exacerbations:** Participants must have a well-documented history (e.g., medical record verification) in the 12 months prior to Screening Visit 1 of: Two or more

moderate COPD exacerbations that were treated with systemic corticosteroids (intramuscular (IM), intravenous, or oral) with or without antibiotics **OR** at least one severe COPD exacerbation requiring hospitalization. At least one exacerbation must have occurred while the participant was taking inhaled triple therapy, ICS plus LABA plus LAMA unless documented intolerance or safety risk with either of the two long-acting bronchodilators. If intolerance is documented, ICS plus LABA or ICS plus LAMA would be allowable after discussion with the Medical Monitor.

- **Concomitant COPD therapy**: Participants must have a well-documented requirement for optimized standard of care background therapy that includes ICS plus 2 additional COPD medications (i.e., ICS-based triple therapy) for the 12 months prior to Screening Visit 1 and meets the following criteria: Immediately prior to Screening Visit 1, minimum of 3 months of use of an **a)** inhaled corticosteroid at a dose ≥500 mcg/day fluticasone propionate dose equivalent plus **b)** LABA and **c)** LAMA unless documentation of safety or intolerance issues related to LABA or LAMA.
    - For participants who **are not** continually maintained on ICS plus LABA plus LAMA for the entire 12 months prior to Visit 1 use of the following is allowed (but not in the 3 months immediately prior to Visit 1):a. inhaled corticosteroid at a dose ≥500 mcg/day fluticasone propionate dose equivalent **plus** b. inhaled LABA or inhaled LAMA **and** c. Phosphodiesterase-4-inhibitors, methylxanthines, or scheduled daily use of short acting beta2-agonist (SABA) and/or short acting muscarinic antagonist (SAMA). Where intolerance or safety risk is documented for either LAMA or LABA, ICS-based inhaled dual maintenance therapy, either ICS plus LABA or ICS plus LAMA, is allowed in the 12 months prior to Visit 1 and during the clinical trial but must be discussed with the Medical Monitor.
- **Smoking Status:** Current or former cigarette smokers with a history of cigarette smoking of ≥10 pack-years at Screening (Visit 1) [number of pack years = (number of cigarettes per day / 20) x number of years smoked]. Former smokers are defined as those who have stopped smoking for at least 6 months prior to Screening Visit 1.

Key exclusion criteria:

- **Asthma:** Participants with a past history or concurrent diagnosis of asthma are excluded regardless of whether they have active or inactive disease.
- **Other respiratory disorders**: The Investigator must judge that COPD is the primary diagnosis accounting for the clinical manifestations of the lung disease. Participants with α1-antitrypsin deficiency as the underlying cause of COPD are excluded. Also, excluded are participants with active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, primary pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases.
- **COPD stability**: Participants with pneumonia, COPD exacerbation, or lower respiratory tract infection within the 4 weeks prior to Screening Visit 1.
- **Lung resection**: Participants with lung volume reduction surgery within the 12 months prior to Screening Visit 1.
- **Pulmonary rehabilitation program**: Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Screening Visit 1. Participants who are in the maintenance phase of a pulmonary rehabilitation program are not excluded.

- **Oxygen:** Participants receiving treatment with oxygen more than 2 L/min at rest over 24 hrs. For Participants receiving oxygen treatment, participants should demonstrate an oxyhaemoglobin saturation greater than or equal to 89% while breathing supplemental oxygen.
- **12-lead ECG at Screening Visit 1**: Participants with a QT interval, from the ECG conducted at Screening Visit 1, corrected with Fridericia's formula (QTcF) >450 msec (or QTcF >480 msec in participants with bundle branch block). Participants are excluded if an abnormal ECG finding from the 12-lead ECG conducted at Screening Visit 1 is considered to be clinically significant and would impact the participant's participation during the study, based on the evaluation of the Investigator.
- **Unstable or life-threatening cardiac disease:** Participants with any of the following would be excluded: Myocardial infarction or unstable angina in the 6 months prior to Screening Visit, unstable or life threatening cardiac arrhythmia requiring intervention in the 3 months prior to Screening Visit 1, (New York Heart Association (NYHA) Class IV) Heart failure.
- **Other diseases/abnormalities**: Participants with (historical or) current evidence of clinically significant, neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease) or haematological abnormalities that are uncontrolled. Significant is defined as any disease that, in the opinion of the Investigator, would put the safety of the participant at risk through participation, or which could affect the efficacy or safety analysis if the disease/condition exacerbated during the study.
- **Eosinophilic disease:** Participants with other conditions that could lead to elevated eosinophils such as Hypereosinophilic syndromes including Eosinophilic Granulomatosis with Polyangiitis (EGPA, also known as Churg-Strauss Syndrome), or Eosinophilic Esophagitis.
- **Parasitic infection:** Participants with a known, pre-existing parasitic infestation within 6 months prior to Screening Visit 1.
- **Malignancy:** A current malignancy or previous history of cancer in remission for less than 12 months prior to Screening Visit 1 (Participants that had localized carcinoma of the skin or cervix which was resected for cure will not be excluded).
- **Immunodeficiency:** A known immunodeficiency (e.g. human immunodeficiency virus - HIV), other than that explained by the use of corticosteroids taken for COPD.
- **Liver disease:** Cirrhosis or current unstable liver disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, oesophageal or gastric varices, or persistent jaundice. Stable non cirrhotic chronic liver disease (including Gilbert' s syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C) is acceptable if the participant otherwise meets entry criteria.
- **Previous mepolizumab studies:** Participants who have received interventional product in previous mepolizumab studies are excluded.
- **Monoclonal antibodies:** Participants who have received any monoclonal antibody within 5 half-lives of Screening Visit 1.

- **Investigational medications:** Participants who have received an investigational drug within 30 days of Visit 1, or within 5 drug half-lives of the investigational drug, whichever is longer (this also includes investigational formulations of a marketed product).
- **Oral corticosteroids:** Participants who have received short term use of oral corticosteroids within 30 days of Visit 1.
-

Treatments

Mepolizumab

Mepolizumab 100 mg administered once every 4 weeks via sub-cutaneous injection (1 mL).

Placebo

Placebo administered once every 4 weeks via sub-cutaneous injection matching mepolizumab 100 mg formulation minus active agent (1 mL).

Table 23 Study treatments

Treatment Group Name	Placebo	Mepolizumab 100 mg
Type	N/A	Biologic
Dose Formulation	120 mg/mL sucrose, 4.16 mg/mL Sodium phosphate dibasic heptahydrate, 0.95 mg/mL Citric Acid Monohydrate, 0.2 mg/mL polysorbate 80, 0.019 mg/mL ethyl enediamine tetra acetic acid (EDTA) Disodium Dihydrate	120 mg/mL sucrose, 4.16 mg/mL Sodium phosphate dibasic heptahydrate, 0.95 mg/mL Citric Acid Monohydrate, 0.2 mg/mL polysorbate 80, 0.019 mg/mL EDTA Disodium Dihydrate
Unit Dose Strength(s)	1.0 mL deliverable	100 mg/mL; 1.0 mL (deliverable)
Dosage Level(s)	Placebo once every 4 weeks	100 mg once every 4 weeks
Route of Administration	Subcutaneous injection	Subcutaneous injection
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labelling	Study treatment was provided in pre-filled safety syringe. Each pre-filled safety syringe was labelled as required per country requirement.	Study treatment was provided in pre-filled safety syringe. Each pre-filled safety syringe was labelled as required per country requirement.
Batch/Lot Numbers	192414436, 202417787, 212423055, 212423056, 222426937, 222426938, 232431080, 202420842	182410302, 182411211, 182411333, 202417040, 212424256, 222426363, 222426364, 222429592, 202420841

Background Medication

Participants had to be on triple background therapy with ICS + LAMA + LABA unless there is evidence of safety and tolerability documentation for the participant that excluded the use of LABA or LAMA for at least 3 months prior to Visit 1.

Participants had to be on optimised SoC ICS-Based triple therapy for 12 months prior to screening visit. 3 months prior to screening visit participants had to be taking ICS at a dose ≥500 mcg/day fluticasone propionate dose equivalent plus LABA and LAMA. If triple therapy was not maintained 12 months prior to (but not within 3 months of) visit 1, Dual therapy of ICS plus either LABA or LAMA and any of Phosphodiesterase-4-inhibitors, methylxanthines, or scheduled daily use of SABA and/or SAMA was allowed. Similarly, where intolerance or safety risk was documented for either LAMA or LABA, ICS-based inhaled dual maintenance therapy, either ICS plus LABA or ICS plus LAMA, was allowed in the 12 months prior to Visit 1 and during the clinical trial

Patients were expected to follow the standard of care which may involve adjusting their medication and they may be required to escalate or de-escalate COPD maintenance medications if clinically crucial for a participant. Investigators were required to discuss all cases with the Medical Monitor before initiating changes to the participants COPD maintenance medication regimen.

Reliever medication
Participants were not allowed to use reliever medications such as Phosphodiesterase-4-inhibitors, methylxanthines, or scheduled daily use of SABA and/or SAMA within 3 months of Visit 1.

Administration Method

Mepolizumab could be self-administered by the patient or administered by a caregiver if their healthcare professional determines that it is appropriate, and the patient or caregiver were trained in injection techniques.

Objectives

Primary Objective

To assess the efficacy of mepolizumab in reducing moderate to severe exacerbations in eosinophilic COPD patients (≥300 BEC) currently being treated with ICS, LAMA, and LABA who still have exacerbations.

Secondary Objectives

- To assess the effects of mepolizumab on COPD exacerbations.
- To assess the effects of mepolizumab on health-related quality of life for participants.
- To assess the effects of mepolizumab on respiratory symptoms.

Endpoints

The primary efficacy endpoint included exacerbations reported after the first dose up to and including the Exit Visit which was logged in their daily eDiary logs. These eDiary logs contained questions to be completed each evening before bedtime.

The hierarchy of the primary and secondary endpoints tested was as follows:

1. Annualized rate of moderate/severe exacerbations **(primary endpoint)**
2. Time to first moderate/severe exacerbation
3. Proportion CAT score responders at Week 52 (≥2-unit reduction in CAT score from baseline)
4. Proportion of SGRQ total score responders at Week 52 (≥4-point reduction in SGRQ total score from Baseline)
5. Proportion of E-RS: COPD responders at Week 52 (≥2-unit reduction in total score from Baseline)
6. Annualized rate of exacerbations requiring ED visit and/or hospitalization

Table 24 Objectives and corresponding endpoints

Objectives		**Endpoints**
Primary	To assess the effects on COPD exacerbations.	Annualized rate of moderate/severe exacerbations
Secondary	To assess the effects on COPD exacerbations.	Time to first moderate/severe exacerbation
Secondary	To assess the effects on participant quality of life.	Proportion CAT score responders at Week 52 (≥2-unit reduction in CAT score from baseline)
Secondary	To assess the effects on participants quality of life.	Proportion of SGRQ total score responders at Week 52 (≥4-point reduction in SGRQ total score from Baseline)
Secondary	To assess the efficacy on COPD respiratory symptoms.	Proportion of E-RS: COPD responders at Week 52 (≥2-unit reduction in total score from Baseline)
Secondary	To assess the effects on COPD exacerbations.	Annualized rate of exacerbations requiring ED and/or hospitalization

Other Endpoints

- Time to first exacerbation requiring ED and/or hospitalization
- **Annualized rate of severe exacerbations**
- Time to first severe exacerbation
- **Percentage of rescue medication free days.**
- Percentage of nights with no awakenings due to COPD symptoms
- Mean number of occasions of rescue medication use/day
- **Change from Baseline in pre-bronchodilator forced expiratory volume in one second (FEV1) and forced vital capacity (FVC)**
- CAT responders at Week 24
- CAT change from baseline at Week 24 and 52
- SGRQ responders at Week 24
- SGRQ change from Baseline at Week 24 and 52
- Proportion of Evaluating Respiratory Symptoms in COPD (E-RS: COPD) responders at Week 24
- Proportion of E-RS: COPD responders: subscales of breathlessness, cough and sputum and chest symptoms at Week 24 and 52
- Change from Baseline in E-RS: COPD Total Score at Week 24 and 52
- **Annualized rate of moderate/ severe exacerbation requiring systemic steroids**

The most important **outcome measures** for the trial:

Exacerbations

For analysis, moderate exacerbations are defined as clinically significant exacerbations that require treatment with oral/systemic corticosteroids and/or antibiotics. Severe exacerbations are defined per protocol as clinically significant exacerbations that require in-patient hospitalization (i.e., ≥24 hrs.) or result in death. The study inclusion criteria required at least 2 moderate COPD exacerbations treated with systemic corticosteroids (intramuscular (IM), intravenous, or oral) with or without antibiotics or at least one severe exacerbation in the 12 months prior to Screening Visit 1. For all summaries and analyses, exacerbations occurring within 7 days of each other within a given participant will be handled as a continuation of the same exacerbation, assigned to the greatest severity. Moderate and severe exacerbations occurring from the start of study treatment were included in the primary analysis regardless of whether the exacerbation occurred after a participant prematurely discontinues from study treatment. For participants who completed the study, all moderate/severe exacerbations occurring up to study completion were included in the primary analysis.

Exacerbations are identified by the following symptoms:

- Worsening of two or more of the following major symptoms for at least two consecutive days: Dyspnea, Sputum volume, Sputum purulence (color), or
- Worsening of any one major symptom together with any one of the following minor symptoms for at least two consecutive days: Sore throat, Colds (nasal discharge and/or nasal congestion), Fever (oral temperature >37.5°C) without other cause, Increased cough, Increased wheeze.

COPD Assessment Test score

CAT was an 8-item questionnaire used to measure the health status of patients with COPD, participants rate their experience on a 6-point scale, ranging from 0 (no impairment) to 5 (maximum impairment) with a scoring range of 0-40. Higher scores indicate greater disease impact.

The variable of interest was the proportion of CAT score responders at Week 52. A participant was considered a responder if they had a 2-point or more improvement (reduction) in CAT score from baseline. Participants who were withdrawn from study prior to Week 52 were included in the analysis as a non-responder. The summary measure of treatment effect was the odds ratio which represents the relative odds of a participant being a responder at Week 52 in the mepolizumab group compared with placebo.

St. George's Respiratory Questionnaire for COPD (SGRQ-C score)

The SGRQ-C was a 40-item questionnaire. A total score and 3 component scores, a Symptoms score, Activity score and Impacts score were calculated based on the scoring algorithm detailed in the SGRQ-C Manual Version 1.3. The total score was expressed as a percentage of overall impairment with 100 representing the worst possible health status and 0 the best possible health status. Higher scores indicate greater impairment of health. The variable of interest was the proportion of SGRQ total score responders at Week 52. A participant was considered a responder if they have a 4-point or more improvement (reduction) in SGRQ total score from baseline. Participants who were withdrawn from study prior to Week 52 were included in the analysis as a non-responder. The summary measure of treatment effect was the odds ratio which represents the

relative odds of a participant being a responder at Week 52 in the mepolizumab group compared with placebo.

Evaluating Respiratory Symptoms in COPD

E-RS: COPD Scores consisted of 11 items from the 14 item EXACT instrument (completed each evening using an eDiary). E-RS: COPD was intended to capture information related to the respiratory symptoms of COPD, i.e., breathlessness, cough, sputum production, chest congestion, and chest tightness. The E-RS: COPD had a scoring range of 0-40, higher scores indicate more severe symptoms. Three sub-scales of the E-RS: COPD were used to describe different symptoms (breathlessness, cough and sputum, and chest symptoms). Daily data was slotted to baseline and 4-week periods relative to the first dose of study treatment as defined in SAP Section 6.2.5.4. The variable of interest was the proportion of E-RS: COPD responders at Week 52, using data from the 4-week period prior to Week 52 (Weeks 49-52). A participant was considered a responder if they have had a 2-point or more improvement (reduction) in their average E-RS: COPD total score during a 4-week period compared to baseline.

eDiary Assessments

Filling out information about - Items from 'Exacerbation of Chronic Pulmonary Disease Tool-Patient Reported Outcomes'. Additional symptoms questions (related to symptoms of an exacerbation), Nighttime awakenings, Use of rescue medication.

Sample size

A total of 800 participants, were to be randomized in a 1:1 ratio to the following treatment groups:

- Mepolizumab 100 mg (+ SoC)
- Placebo (+ SoC)

For the purposes of sample size calculation, the assumed annualised rate of moderate/severe exacerbations for the placebo group was 1.7, following a negative binomial distribution with a dispersion parameter of 0.55. This estimate was based on data observed from studies MEA117113 and MEA117106 (High Stratum).

Sample size calculations were based on the testing of superiority of mepolizumab 100 mg to placebo for annualised rate of moderate/severe exacerbations with a desired power of 90% at a 2-sided 5% significance level. The calculated sample size needed was 756 total participants, based on a true population reduction of 23%. The smallest observed reduction relative to placebo which would result in a statistically significant result was 15%. The sample size calculation also accounted for loss to early withdrawal at a rate of 5.5% of participants-year data equating to 44 total participants. This estimate was based on the level of missing data from study MEA117113. This brought the total sample size to 800 participants.

The study allowed for a blinded sample size re-estimation prior to the randomization of the 800th participant. The purpose of this was to re-calculate the sample size based on available exacerbation data from the study to see if the planned sample size will still provide 90% power. If the re-estimated sample size was less than or equal to the planned sample size of 800, then the study was to continue as planned. Otherwise, if the re-estimated sample size was greater than that planned sample size of 800 the sample may be increased to a maximum of 1400 to preserve power. The study also made allowance for further blinded sample size re-estimations given the emerging exacerbation data from the study.

Randomisation

All participants were to be centrally randomized using an IWRS (Interactive web response system) before the study is initiated. Log in details and directions for accessing the IWRS were to be provided to participating sites. Visit 2 (Day 1) those participants who meet the randomization eligibility criteria were to be randomized in a 1:1 ratio to receive one of the following interventions every 4 weeks: Mepolizumab 100 mg SC or Placebo SC.

A unique Participant Number was to be assigned to participants who have consented. This unique participant number was to be used to identify the individual participant throughout the study and was not to be re-assigned to any other participant. Participants were to be assigned to study intervention in accordance with the randomization schedule. Once a Randomization number had been assigned to a participant, it could not be reassigned to any other participant in the study. The Randomization schedule was to be generated using a validated Randomization software. Separate Randomization schedules were to be created for each country. Equal numbers of participants were to be allocated to each intervention arm.

Blinding (masking)

Study 208657 was double blinded using the following methods:

- Blood samples were sent to a central laboratory to maintain blinding for the duration of the study. Results were provided only if unblinding of a participant's treatment assignment was required. After Randomization, neither the site staff nor GSK personnel were sent results from the central laboratory for: absolute and differential values for eosinophils, lymphocytes, basophils, neutrophils and monocytes. However, sites were sent total white blood counts throughout the study.
- Treatment of mepolizumab and placebo was administered using identical pre-filled safety syringe with both treatment groups containing the same formulation minus the active agent (120 mg/mL sucrose, 4.16 mg/mL Sodium phosphate dibasic heptahydrate, 0.95 mg/mL Citric Acid Monohydrate, 0.2 mg/mL polysorbate 80, 0.019 mg/mL ethyl enediamine tetra acetic acid (EDTA) Disodium Dihydrate).
- The study interventional product and study participant identification was confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.
- The IWRS was programmed with blind-breaking instructions. In case of an emergency, the investigator had the sole responsibility for determining if unblinding of a participants' intervention assignment was warranted. The event or condition which led to the unblinding was recorded in the eCRF.
- If the number of participants was too small within a subgroup category, then the subgroup categories were redefined prior to unblinding the study.
- GSK's Global Clinical Safety and Pharmacovigilance unblinded the intervention assignment for any participant who experienced a SAE.

Blinded re-evaluations of the sample size were carried out prior to randomizing the 800th participant to assess whether, based on the overall annualized rate of moderate/severe exacerbations and the level of dispersion seen within the available data, that the initial planned sample size of 800 randomized participants would continue to provide 90% power for this study.

Statistical methods

Statistical Analysis Plan

The original SAP dated 28-Jul-2022, was amended 3 times. Amendment 1 dated 16-Nov-2023, Amendment 2 dated 18-Jul-2024, and Amendment 3 dated 20-Aug-2024. All amendments to the original SAP are comprehensively described in the Version History section of SAP Amendment 3. Particular amendments that affect the efficacy/safety analyses are summarized below:

SAP Amendment 1 (16-Nov-2023)

- Definition of Extended Treatment Population updated to include all participants who receive at least one dose of trial medication. Population for selected study population and safety summaries, not efficacy summaries.
- Change in handling of intercurrent events of prohibited medication.
- Addition of sensitivity analysis for primary endpoint regarding one of the sites.
- Addition of clarification that time to event analyses are carried out for data up to week 104.
- Change in safety display presentations to include all data up to Week 104, with specific displays summarizing data separately for participants enrolled for 52 weeks only and those in the Extended Treatment population.
- Addition of time to first adjudicated MACE analysis section.
- Addition of subgroup (symptoms of chronic bronchitis) and removal of subgroups (screening eosinophil categories and other comorbidity).
- Update of countries defining geographic regions.
- Addition of analyses for Chinese, East Asia, South Korea and India subpopulations.

SAP Amendment 2 (18-Jul-2024)

- Amendment of wording in the sensitivity analysis for primary endpoint section.
- Change of subgroup definitions – removed screening eosinophil thresholds, added screening eosinophil categories. Added <40 to age subgroup.
- Subgroup analyses updated to include additional analyses for secondary and other endpoints and shrinkage methods in primary endpoint.

Changes to the planned analyses

There are several changes to the protocol planned analyses. These are comprehensively described in SAP Amendment 3. Particular changes that affect the efficacy/safety analyses analysis are summarized below:

- Additional analysis population of mITT Population excluding past/concurrent asthma (mITT2).
- Additional endpoint of Other endpoint of annualized rate of moderate/severe exacerbation by type of treatment required (corticosteroids alone, antibiotics alone, corticosteroids and antibiotics).
- The primary estimand was updated for a treatment policy strategy will be used for the intercurrent events of discontinuation of study medication and investigational product

interruption of 2 or more doses, when these intercurrent events are not associated with disruptions or restrictions imposed due to the COVID-19 pandemic. A hypothetical strategy will be considered when these intercurrent events have occurred as a result of disruptions or restrictions (e.g. lockdown measures, social distancing) imposed due to the COVID-19 pandemic.

Analysis Populations

Population	Definition/Criteria	Analyses Evaluated
All Participants Enrolled Population	All participants for whom a record exists on the study database.	Reasons for Screen Failures and Run-in Failures
Modified Intent-to-Treat Population (mITT)	All randomized participants who receive at least one dose of trial medication. Participants will be analysed by randomized treatment.	Efficacy endpoints
mITT Population excluding past/concurrent asthma (mITT2)	All participants in the mITT population with no evidence of a past history or concurrent diagnosis of asthma. Participants will be analysed by randomized treatment.	Primary and secondary endpoints
Safety Population (Safety)	All randomized participants who receive at least one dose of trial medication. Participants will be analysed based on actual treatment received for more than 50% of treatment administrations.	Safety endpoints
Per-Protocol Population (PP)	All participants in the mITT population not identified as protocol deviators with respect to criteria that are considered to impact the primary efficacy endpoint. The decision to exclude a participant from the PP Population will be made prior to the unblinding of treatment codes.	Supplementary analysis of primary endpoint
Pharmacokinetic (PK)	All participants enrolled in the PK sub-study who received at least one dose of trial medication and for whom at least one pharmacokinetic sample was obtained, analysed and was measurable. Population for the PK	Pharmacokinetics endpoints

	sub-study analysis. Data will be reported according to actual treatment received for more than 50% of treatment administrations.	
Extended Treatment Population	All participants who receive at least one dose of trial medication and who consented to participate in the extended treatment period beyond 52 weeks. Participants within this population are enrolled for up to 104 weeks with variable duration.	Selected Study Population, Efficacy, Safety summaries

Analysis of Primary Endpoint

The primary estimand for the study was the difference between mepolizumab 100mg SC and placebo (both added to optimized standard of care) in the annualized rate of moderate/severe exacerbations in participants with COPD experiencing frequent exacerbations and characterized by eosinophil levels, regardless of IP discontinuation/interruption or changes in background medication/starting a prohibited medication, in the absence of COVID-19 pandemic related intercurrent events.

Population	Participants with COPD experiencing frequent exacerbations and characterised by eosinophil levels
Treatment	Mepolizumab 100mg SC vs Placebo (both as add-on treatment to optimized standard of care)
Variable	Number of moderate/severe exacerbations
Intercurrent Events (ICEs)	- Discontinuation of IP - Interruption of 2 or more consecutive doses of IP - Use of prohibited medications - Change in background medication
Strategy	Treatment Policy: - Discontinuation of IP - Interruption of 2 or more consecutive doses of IP (when not associated with disruptions or restrictions imposed due to the COVID-19 pandemic) - Use of prohibited medications - Change in background medication Hypothetical:

	- All ICEs when they are known to be associated with disruptions or restrictions imposed due to the COVID-19 pandemic
Population-Level Summary	Ratio of the frequency of exacerbations in the mepolizumab arm to the frequency in the placebo arm; Exacerbation rates will be expressed as an annualized exacerbation rate

The primary analysis model was a negative binomial model with treatment group, geographic region, smoking status, baseline disease severity (as % predicted post-bronchodilator FEV1), and number of moderate/severe exacerbations in previous year (≤2, 3, ≥4 as ordinal) as covariates. The analysis model also included an offset variable of $\log_e$ (length of time in study) which reflects the period of time in the study for which exacerbation data has been recorded for inclusion in the analysis.

For the assessment of the primary endpoint, the model estimated mean annualized rate of exacerbations was calculated using the observed marginal distributions of the study population covariates. The treatment comparison was assessed by the rate ratio of the model estimated mean annualized rates of exacerbations for mepolizumab vs placebo with associated 95% confidence interval and p-value.

Sensitivity Analyses

A number of sensitivity analyses for the primary estimand were to be conducted to test the robustness of the assumption of data missing at random.

Sensitivity Analysis 1:

Missing data to be imputed multiple times for each subject based on a combination of their respective covariates and the observed data. The imputed data is combined with the observed data and analysed using the same method as the primary endpoint. This analysis would be repeated multiple times and the results combined across imputations using Rubin's rules. Participants who withdrew from the study early would have missing data imputed for the period of time between withdrawal from the study and their scheduled end of study. Missing data for these participants would be imputed using observed off-treatment data collected from randomized participants (prior to occurrence of intercurrent events of IP discontinuation or interruption of 2 or more consecutive doses of IP associated with the COVID-19 pandemic) who continued in the study following discontinuation of randomized treatment. Participants who have missing data due to occurrence of intercurrent events of IP discontinuation or interruption of 2 or more consecutive doses of IP associated with the COVID-19 pandemic would have missing data imputed for the period of time between occurrence of the intercurrent event and their scheduled end of study. Missing data after the occurrence of the intercurrent event would be imputed using both on-treatment and off-treatment data collected from randomized participants (on-treatment data prior to occurrence of intercurrent events associated with the COVID-19 pandemic, off treatment data from those not experiencing an occurrence of intercurrent events associated with the COVID-19 pandemic).

Sensitivity Analysis 2:

A tipping point analysis was to be performed using the same multiple imputation method as Sensitivity Analysis 1. Participants who withdrew from the study or experienced intercurrent events of IP discontinuation or interruption of 2 of more consecutive doses of IP associated with the COVID-19 pandemic will have missing data imputed for the period of time from study withdrawal/occurrence of event to their scheduled end of study. The missing data would be imputed based on a range of increases in exacerbation rates relative to the estimated rates

obtained within each arm under the MAR assumption. The imputed exacerbation rates would vary independently for the mepolizumab and placebo arms and will include scenarios where participants with missing data in the mepolizumab arm have worse outcomes than participants in the placebo arm. The analysis results are to be used to explore conditions under which there is no evidence of a treatment effect.

Sensitivity Analysis 3:

The primary analysis was to be repeated excluding subjects randomized at Site 239718.

Sensitivity Analysis 4:

The primary analysis was to be repeated following the Treatment Policy strategy for all ICEs, whether or not they are associated with the COVID-19 pandemic. Missing data due to study withdrawal to be handled as MAR.

Sensitivity Analysis 5:

The primary analysis was to be repeated following the Treatment Policy strategy for all ICEs, whether or not they are associated with the COVID-19 pandemic. Missing data imputation to use the same multiple imputation method as Sensitivity Analysis 1. Missing data to be imputed using observed off-treatment data collected from randomized participants who continued in the study following discontinuation of randomized treatment.

Analysis of Ranked Secondary Endpoint(s)

For all secondary endpoints included in the ranked hierarchical testing procedure the analysis population, treatment comparison, and ICEs strategy was to be the same as the primary estimand.

Time to first moderate/severe exacerbation:

A Cox proportional hazards model was to be fitted to the time to first moderate/severe exacerbation for each treatment group with covariates of treatment group, geographic region, smoking status, baseline disease severity (as % predicted post-bronchodilator FEV1), and number of moderate/severe exacerbations in previous year (≤2, 3, ≥4 as ordinal).

Proportion CAT score responders at Week 52/Proportion of SGRQ total score responders at Week 52/Proportion of E-RS: COPD responders at Week 52:

A logistic regression model was to be used to compare the proportion of responders for each treatment group. This model included treatment group, smoking status, geographic region, and baseline score as terms.

Annualized rate of exacerbations requiring ED and/or hospitalization:

This analysis will follow the same methodology as the primary endpoint.

Subgroup Analyses

Subgroup analyses were to be performed on the primary endpoint following the same primary analysis method. No formal hypothesis testing was to be performed. The following subgroups were pre-specified:

- Age (<40, 40-<65, ≥65 years)
- Sex (Male, Female)
- Race (African American/African Heritage, White, Asian, Other)

- Baseline BMI (Low, Medium, High)
- Geographic Region (Europe, Eastern Europe, Asia, South America, North America, Rest of World)
- Exacerbations in the previous year (≤2, 3, ≥4 exacerbations)
- Severe exacerbations in the previous year (0, ≥1 exacerbation)
- Screening blood eosinophil categories (<0.5 GI/L, ≥0.5 GI/L)
- Smoking status at Screening (Current, Former)
- Symptoms of Chronic Bronchitis (Yes, No)
- Cardiovascular Disease Comorbidity (Any past or current medical condition under Cardiac Disorders)
- Modified Medical Research Council score at Screening (<2, ≥2)
- Severity of Airflow Limitation (Mild, Moderate, Severe, Very Severe)
- Treatment Duration (Fixed Duration, Variable Duration)

Subgroup analyses were to be performed for the secondary endpoints by the following:

Subgroups	Endpoints
Screening blood eosinophil categories (<0.5 GI/L, ≥0.5 GI/L)	Time to first moderate/severe exacerbation Proportion of CAT responders Proportion of SGRQ responders
Screening blood eosinophil categories (<0.5 GI/L, ≥0.5 GI/L) Smoking status at Screening (Current, Former) Symptoms of Chronic Bronchitis (Yes, No)	Time to first moderate/severe exacerbation Proportion of CAT responders Proportion of SGRQ responders SGRQ change from baseline
Geographic Region (Europe, Eastern Europe, Asia, South America, North America, Rest of World)	Proportion of SGRQ responders Proportion of E-RS: COPD responders

Subgroup (except Screening blood eosinophil categories) analyses were to be performed for the primary endpoint following Bayesian hierarchical modelling. The rate ratios and standard errors from the standard subgroup analyses were to be included in a Bayesian hierarchical model to obtain shrinkage estimates of the subgroup-specific treatment effects. The subgroup-specific rate ratios were assumed to be Normally distributed with the hyperparameters overall rate ratio and between-subgroup variance. These hyperparameters were to use non-informative and weakly-informative priors. The model was to be fitted using Markov chain Monte Carlo simulations with at least 50,000 iterations, a thinning rate of 5, and a burn-in of at least 1000.

Type I Error Control / Multiplicity Adjustment

The statistical analysis of the primary endpoint and secondary endpoints accounted for multiplicity and controlled the familywise Type I error rate at a 2-sided alpha level of 0.05 by using a

hierarchical testing procedure. Starting with the primary endpoint comparison, mepolizumab was compared to placebo at a 2-sided alpha level of 0.05 (1-sided alpha level of 0.025), the next endpoint in the hierarchy was to be tested only if the test for the previous endpoint in the hierarchy was significant at the 1-sided 2.5% level.

The hierarchy was as follows:

1. Annualized rate of moderate/severe exacerbations (primary endpoint)
2. Time to first moderate/severe exacerbation
3. Proportion CAT score responders at Week 52
4. Proportion of SGRQ total score responders at Week 52
5. Proportion of E-RS: COPD responders at Week 52
6. Annualized rate of exacerbations requiring ED and/or hospitalization

Interim Analysis

There was no interim analysis planned for this study.

A blinded sample size re-estimation was foreseen in the protocol and SAP but was not performed.

Results

Participant flow

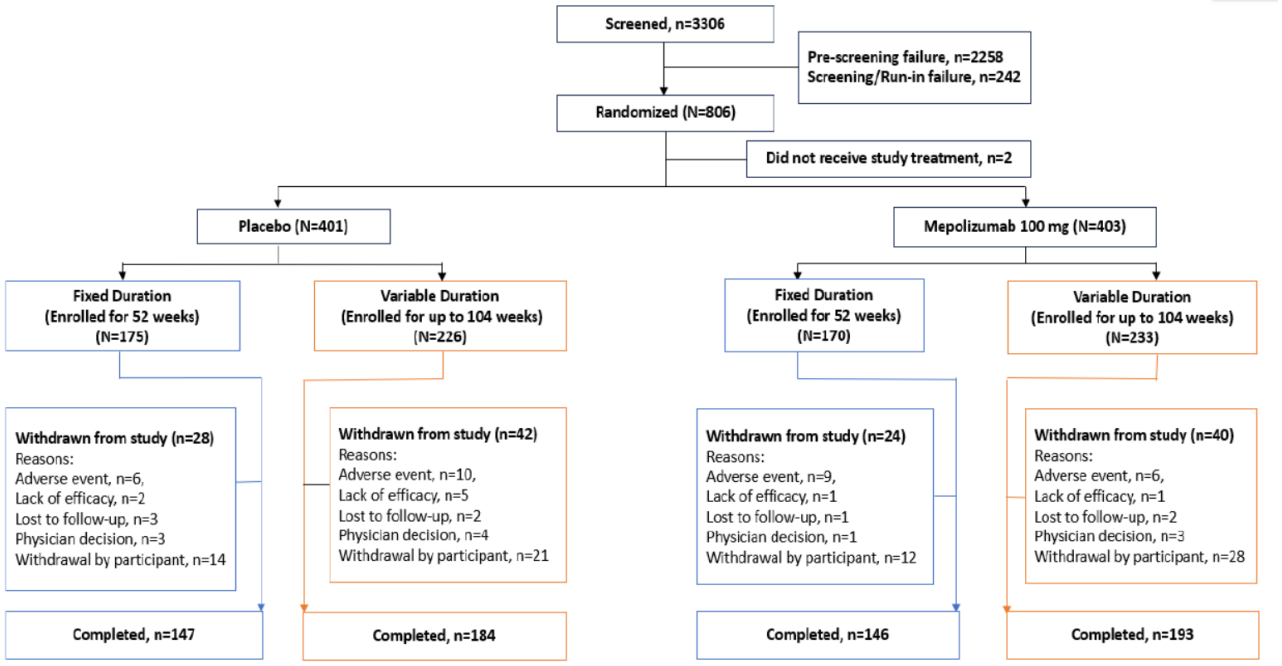
It was estimated that 4000 participants would be enough to achieve a target global randomization of approximately 800 randomized participants.

A total of 3306 participants were screened at 344 study centres in 25 countries.

The countries with the highest number screened were the US (746; 23%), the UK (549; 17%), Germany (377; 11%), and Argentina (371; 11%). Of the 3306 participants screened, 2258 (68%) failed during pre-screening Visit 0 and 242 (7%) failed during screening/run-in. Screening/run-in failures were primarily due to not meeting the inclusion/exclusion criteria at Screening (Visit 1) or Randomization (Visit 2).

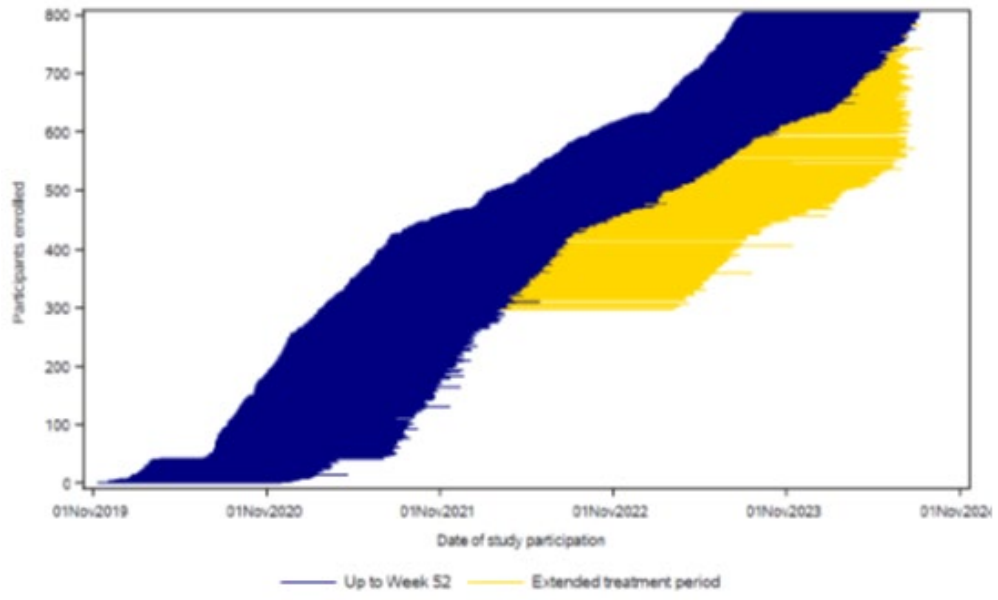
Of the 3306 participants screened, 806 (24%) participants were randomized and 804 (>99%), who received at least 1 dose of study treatment, were included in the mITT analysis population.

Figure 21 Participant disposition (Screened Population)



Amendment 6-STD dated 06 December 2021 was implemented in response to the COVID-19 pandemic which adjusted the study from a fixed to variable model for participants who had not completed the study. It also allowed for up to 1,400 participants to enrol into the study. At the time of the amendment, 330 participants (41%) had completed the study and were not eligible to extend their study duration. Of the remaining 197 (25%) participants who were ongoing, 182 provided reconsent to extend their study participation, while 15 participants did not. After the amendment went into effect, 277 (34%) participants were enrolled in the study under the variable treatment duration design up to a maximum of 104 weeks. The total number of participants that entered the fixed duration group was 345, while 459 participants entered the variable duration group.

Figure 22 Participant enrolment over time (mITT Population)



Note: Recruitment was halted between 23 March 2020 and 09 June 2020 due to the COVID-19 pandemic.

In the overall mITT population, the majority of participants completed the study as scheduled (84% in mepolizumab; 83% in placebo). **The most common reasons for study withdrawal were withdrawal by participant (9%) and AE (4%)**, with similar percentages in each treatment group.

Fixed Duration subgroup (Enrolled for 52 weeks): Of the 804 participants in the mITT population, 345 (42.9%) were enrolled for a fixed 52-week duration, with a similar number in each treatment group. The majority of participants in this subgroup (86% in mepolizumab; 84% in placebo) completed the study at Week 52 (Visit 15). The most common reasons for study withdrawal were withdrawal by participant (8%) and AE (4%), with similar percentages in each treatment group.

Variable Duration subgroup (Enrolled for up to 104 weeks): Of the 804 participants in the mITT population, 459 (57.1%) were enrolled for a variable duration of at least 52 weeks and up to 104 weeks, with a similar number in each treatment group. The majority of participants in this subgroup (83% in mepolizumab; 81% in placebo) completed the study as scheduled, i.e., at Week 104 (Visit 28) or at a scheduled visit on or immediately before the date of the Exit Visit at Week 52 of the last participant randomized into the study. **The most common reasons for study withdrawal were withdrawal by participant (11%) and AE (3%),** with similar percentages in each treatment group.

Both treatment arms had similar reasons for study withdrawal with 70 participants (17%) for placebo and 64 participants (16%) for mepolizumab. There was 35 participants (9%) & 40 participants (10%) withdrawal by participant, 16 participants (4%) & 15 participants (4%) due to an adverse event, and 7 participants (2%) & 2 participants (<1%) due to lack of efficacy for the placebo and mepolizumab groups respectively.First participant enrolled: 30th October 2019

Last participant (end of treatment visit): 8th of August 2024

The analyses presented in this report are based on a database lock date of 29 August 2024.

Note: The timing of the last randomized participant into the study affected the timing of the Exit Visit for participants enrolled beyond 52 weeks. The last randomized participant was scheduled to complete only 52 weeks of the study.

Conduct of the study

Protocol amendments

The study protocol was implemented on the 15th of February 2019. Throughout the course of the study there was an amendment to include a new participating country **and 6 protocol amendments:**

1. Amendment 6-JPN-1 dated 21 September 2022 was implemented to include Japan as a participating country in the study to comply with regulatory requirements, however, no participants were enrolled.
2. Amendment 6-STD dated 06 December 2021 was implemented to account for potential reduced exacerbation rates due to pandemic safety measures. This amendment added a variable treatment group up to 104 weeks and permitted the study population to increase to 1,400 depending on study power.

3. Amendment 5-STD dated 16 October 2020 introduced home healthcare to perform study assessments, updated the primary estimand, updated strategies for handling ICEs, provided clarify to the protocol, and corrected errors.
4. Amendment 4-STD dated 13 September 2019 changed the study design and corrected typographical errors.
5. Amendment 3-STD dated 18 July 2019 changed the study design and integrated the protocol amendments 1-USA-1 and 2-CHI-1 to include a PK sub-study in China and the US. It also corrected typographical errors.
6. Amendment 2-CHI-1 dated 23 May 2019 altered the protocol to allow for an optional PK sub-study to assess potential ethnic differences in the PK of mepolizumab 100 mg in liquid formulation, administered SC by a safety syringe, between non-Asian participants in the US and Chinese participants in China.
7. Amendment 1-USA-1 dated 23 May 2019 altered the protocol to allow for an optional PK sub-study to assess potential ethnic differences in the PK of mepolizumab 100 mg in liquid formulation, administered SC by a safety syringe, between non-Asian participants in the US and Chinese participants in China.

Amendment 4-STD, 3-STD, 2-CHI-1, and 1-USA-1 occurred before any participants were enrolled into the study and amendment 6-JPN-1 did not enrol any participants and so these amendments would not affect the performance or outcomes of the study.

COVID-19 pandemic

Amendment 6-STD dated 06 December 2021 was implemented to account for potential reduced exacerbation rates due to pandemic safety measures. This amendment added a variable treatment group up to 104 weeks and permitted the study population to increase to 1,400 depending on study power.

This amendment is substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union. Non-pharmaceutical interventions led to a reduced exacerbation rate affecting the collection of exacerbation data among enrolled participants and the recruitment of participants into the study.

COVID-19 could have improved knowledge of preventative methods for COPD amongst participants and the environment in general. This could explain the reduced observed exacerbation rates compared to the previous year.

Protocol deviations

Important deviations were defined as deviations that were likely to affect the interpretation of the results and/or led to exclusion of any participant data from an analysis. Important deviations include, but are not limited to, those related to study inclusion or exclusion criteria, adherence to the protocol, conduct of the study, participant management or participant assessment.

Important protocol deviations (IPDs) were identified for 333 (41%) participants: 159 (39%) in the mepolizumab group and 174 (43%) in the placebo group. The most frequently reported IPDs were related to visit completion (15%) with 117 total participants and eligibility criteria not met (12%) with 99 total participants, with similar proportions in each treatment group.

IPDs related to COVID-19 were reported less frequently in the mepolizumab group with 13 participants (3%) compared with placebo with 23 participants (6%); these COVID-19 related IPDs

were predominantly related to visit completion, accounting for 29 of these IPDs total (16 placebo and 13 mepolizumab).

GCP findings

During the study the MAH had 11 study centres audited and found 10 major findings pertaining to management of study centre records and reporting. Corrective and preventive actions were implemented to address the relevant findings.

A study centre closure (239718) led to an announced directed regulatory inspection for non-compliance issues. All participants had completed or withdrawn from the study. Sensitivity analysis for the primary endpoint was performed excluding data from 3 participants enrolled at the study centre.

One study centre (241146) was put on hold and investigated for potential suspected scientific misconduct. Although there was no definitive detection of this, the study centre was closed early. See discussion on clinical efficacy section

Baseline data

Demographics were generally similar between the treatment groups. Most participants were White (84%) and predominantly male (69%); the mean age was 66.2 years. More than half of the participants (61%) were ≥65 years of age. Mean BMI was 27.25 kg/m2. The mean and median ages were similar between treatment groups; however, the proportion of participants ≥65 years of age was higher in the mepolizumab group (65%) compared with the placebo group (57%).

Table 25 Demographic characteristics (mITT Population)

	PBO (n=401)	Mepo 100 mg (n=403)	Total (n=804)
Sex, n (%)			
Female	126 (31)	127 (32)	253 (31)
Male	275 (69)	276 (68)	551 (69)
Age (years) [1]			
Mean (SD)	66.0 (7.91)	66.4 (8.10)	66.2 (8.00)
Median (Min, Max)	66.0 (42, 91)	67.0 (39, 88)	67.0 (39, 91)
Age group 2 (years) [1], n (%)			
<40 years	0	1 (<1)	1 (<1)
40-<65 years	173 (43)	142 (35)	315 (39)
≥65 years	228 (57)	260 (65)	488 (61)
Ethnicity, n (%)			
Hispanic or Latino	95 (24)	94 (23)	189 (24)
Not Hispanic or Latino	306 (76)	309 (77)	615 (76)
High level race, n (%)			
American Indian or Alaska native	2 (<1)	3 (<1)	5 (<1)
Asian	56 (14)	56 (14)	112 (14)
Black or African American	5 (1)	5 (1)	10 (1)
White	335 (84)	338 (84)	673 (84)
Mixed race	3 (<1)	1 (<1)	4 (<1)
Race detail, n (%)			
American Indian or Alaska native	2 (<1)	3 (<1)	5 (<1)
Asian - Central/South Asian heritage	19 (5)	18 (4)	37 (5)
Asian - East Asian heritage	34 (8)	33 (8)	67 (8)
Asian - South East Asian heritage	3 (<1)	5 (1)	8 (<1)
Black or African American	5 (1)	5 (1)	10 (1)
White - Arabic/North African heritage	4 (<1)	5 (1)	9 (1)
White - White/Caucasian/European heritage	331 (83)	333 (83)	664 (83)
Mixed race	3 (<1)	1 (<1)	4 (<1)
Height (cm)			
Mean (SD)	167.4 (9.34)	167.2 (8.98)	167.3 (9.16)
Median (Min, Max)	167.0 (143, 196)	167.0 (140, 193)	167.0 (140, 196)
Weight (kg)			
Mean (SD)	76.36 (17.964)	76.91 (17.970)	76.64 (17.958)
Median (Min, Max)	74.40 (43.3, 145.0)	74.00 (38.0, 146.0)	74.00 (38.0, 146.0)
Body mass index (kg/m^2)			
Mean (SD)	27.13 (5.540)	27.38 (5.342)	27.25 (5.440)
Median (Min, Max)	26.23 (16.1, 50.6)	26.85 (15.2, 43.0)	26.53 (15.2, 50.6)

Baseline disease characteristics

The majority of participants had COPD for >5 to 10 years (143 participants in each treatment arm) or 1 to 5 years (107 and 104 participants for placebo and mepolizumab respectively); the mean (SD) duration was 10.0 (6.28) years.

COPD-related phenotypes were well balanced between the treatment groups with investigator-assessed COPD type showing that 168 & 170 (42% & 42%) participants had chronic bronchitis only, 132 & 120 (33% & 30%) participants had emphysema only, and 62 and 81 (15% & 20%) had both, for placebo and mepolizumab respectively.

While on treatment with optimized standard-of-care for COPD the participants had a mean 2.4 moderate/severe exacerbations in the prior year (665 participants had at least 2 previous moderate exacerbations) and 165 participants reported at least 1 severe exacerbation.

The pooled study population had compromised lung function with 160 & 180 participants (45% & 42%) having severe airflow obstruction (FEV1 ≥30% to <50% predicted) and 57 & 53 participants (14% & 13%) having very severe airflow obstruction (FEV1 <30%) for placebo and mepolizumab respectively.

Baseline CAT score (scale range: 0 to 40, with higher scores indicate your COPD has a greater impact on overall health and well-being) COPD score was 19.2 versus 19.1 for mepolizumab and placebo respectively. Baseline SGRQ total score (scale range: 0-100 with 100 indicating the largest impact on health status/HRQoL) COPD score was 55.3 versus 53.9 for mepolizumab and placebo respectively. Baseline E-RS (scale range of 0 to 40, with higher values indicating more severe respiratory symptoms) COPD score was 13.16 versus 12.94 for mepolizumab and placebo respectively.

Table 26 COPD history and baseline disease characteristics

	Overall		Fixed Duration (Enrolled for 52 weeks)		Variable Duration (Enrolled for up to 104 weeks)	
	PBO (N=401)	Mepo100 mg (N=403)	PBO (N=175)	Mepo100 mg (N=170)	PBO (N=226)	Mepo100 mg (N=233)
COPD type [1], n (%)						
Emphysema	132 (33)	120 (30)	51 (29)	44 (26)	81 (36)	76 (33)
Chronic bronchitis	168 (42)	170 (42)	77 (44)	79 (46)	91 (40)	91 (39)
Emphysema and chronic bronchitis	62 (15)	81 (20)	31 (18)	33 (19)	31 (14)	48 (21)
Neither	37 (9)	32 (8)	16 (9)	14 (8)	21 (9)	18 (8)
Missing	2 (<1)	0	-	-	2 (<1)	0
Duration of COPD, n (%)						
1 to 5 years	107 (27)	104 (26)	45 (26)	48 (28)	62 (27)	56 (24)
>5 to 10 years	143 (36)	143 (35)	65 (37)	58 (34)	78 (35)	85 (36)
>10 to 15 years	90 (22)	89 (22)	37 (21)	39 (23)	53 (23)	50 (21)
>15 to 20 years	40 (10)	39 (10)	16 (9)	17 (10)	24 (11)	22 (9)
>20 to 25 years	13 (3)	16 (4)	7 (4)	4 (2)	6 (3)	12 (5)
>25 years	8 (2)	12 (3)	5 (3)	4 (2)	3 (1)	8 (3)
Duration of COPD (years)						
Mean (SD)	9.7 (5.88)	10.2 (6.65)	9.9 (6.24)	9.8 (6.51)	9.5 (5.59)	10.5 (6.75)
Median (Min, Max)	9.0 (1, 33)	9.0 (1, 40)	9.0 (1, 32)	9.0 (1, 40)	8.0 (1, 33)	9.0 (1, 36)
Severity of airflow limitation [2], n (%)						
Mild: ≥80% predicted	3 (<1)	2 (<1)	1 (<1)	1 (<1)	2 (<1)	1 (<1)
Moderate: ≥50%-<80% predicted	181 (45)	168 (42)	72 (41)	70 (41)	109 (48)	98 (42)
Severe: ≥30%-<50% predicted	160 (40)	180 (45)	78 (45)	77 (45)	82 (36)	103 (44)
Very severe: <30% predicted	57 (14)	53 (13)	24 (14)	22 (13)	33 (15)	31 (13)
Cardiovascular comorbidity [3], n (%)						
Yes	97 (24)	103 (26)	48 (27)	48 (28)	49 (22)	55 (24)
No	304 (76)	300 (74)	127 (73)	122 (72)	177 (78)	178 (76)
Other comorbidity [4], n (%)						
Yes	323 (81)	316 (78)	152 (87)	138 (81)	171 (76)	178 (76)
No	78 (19)	87 (22)	23 (13)	32 (19)	55 (24)	55 (24)
mMRC score at screening, n (%)						
<2	98 (24)	89 (22)	32 (18)	29 (17)	66 (29)	60 (26)
≥2	301 (75)	310 (77)	143 (82)	140 (82)	158 (70)	170 (73)
Missing	2 (<1)	4 (<1)	0	1 (<1)	2 (<1)	3 (1)
Ever diagnosed with GERD, n (%)						
Yes	92 (23)	85 (21)	53 (30)	46 (27)	39 (17)	39 (17)
No	303 (76)	311 (77)	121 (69)	122 (72)	182 (81)	189 (81)
Missing	6 (1)	7 (2)	1 (<1)	2 (1)	5 (2)	5 (2)
BECs (GI/L)			-	-	-	-
n	401	403	-	-	-	-
Geometric Mean	0.48	0.48	-	-	-	-
Std Logs	0.398	0.378	-	-	-	-
Median (Min, Max)	0.44 (0.2, 2.3)	0.45 (0.3, 2.8)	-	-	-	-
CAT score			-	-	-	-
n	393	389	-	-	-	-
Mean (SD)	19.1 (6.75)	19.2 (6.95)	-	-	-	-
Median (Min, Max)	19.0 (0, 38)	19.0 (1, 39)	-	-	-	-
SGRQ-C Total score			-	-	-	-
n	392	388	-	-	-	-
Mean (SD)	53.9 (17.86)	55.3 (17.73)	-	-	-	-
Median (Min, Max)	54.9 (7, 91)	55.9 (9, 93)	-	-	-	-
E-RS: COPD score			-	-	-	-
n	399	403	-	-	-	-
Mean (SD)	12.94 (6.790)	13.16 (6.796)	-	-	-	-
Median (Min, Max)	13.00 (0.0, 32.0)	13.14 (0.0, 34.0)	-	-	-	-

[1] As assessed by the investigator

[2] Classification based on post-bronchodilator FEV_1 at Screening, GOLD Guidelines for COPD.

[3] CV disease comorbidity was defined as past/current medical conditions in the Cardiac Disorder category recorded on the medical conditions CRF (angina pectoris, coronary artery disease, myocardial infarction, arrhythmia, and congestive heart failure) or participants with a history/previous episode of heart failure on the CV Congestive Heart Failure CRF.

[4] Participants with Other comorbidity are defined as participants with any past or current medical condition other than under Cardiac Disorders.

	Overall		Fixed Duration (Enrolled for 52 weeks)		Variable Duration (Enrolled for up to 104 weeks)	
	PBO (N=401)	Mepo 100 mg (N=403)	PBO (N=175)	Mepo 100 mg (N=170)	PBO (N=226)	Mepo 100 mg (N=233)
Number of moderate/severe exacerbations, n (%)						
0	3 (<1)	0	2 (1)	0	1 (<1)	0
≥1	398 (>99)	403 (100)	173 (99)	170 (100)	225 (>99)	233 (100)
1	43 (11)	40 (10)	19 (11)	14 (8)	24 (11)	26 (11)
2	266 (66)	254 (63)	117 (67)	110 (65)	149 (66)	144 (62)
3	64 (16)	70 (17)	25 (14)	29 (17)	39 (17)	41 (18)
4	13 (3)	20 (5)	7 (4)	5 (3)	6 (3)	15 (6)
>4	12 (3)	19 (5)	5 (3)	12 (7)	7 (3)	7 (3)
Mean (SD)	2.2 (0.90)	2.3 (0.98)	2.2 (0.90)	2.4 (1.11)	2.2 (0.91)	2.3 (0.88)
Median (Min, Max)	2.0 (0, 8)	2.0 (1, 7)	2.0 (0, 7)	2.0 (1, 7)	2.0 (0, 8)	2.0 (1, 6)
Number of moderate exacerbations, n (%)						
0	53 (13)	53 (13)	23 (13)	17 (10)	30 (13)	36 (15)
≥1	348 (87)	350 (87)	152 (87)	153 (90)	196 (87)	197 (85)
1	20 (5)	13 (3)	12 (7)	7 (4)	8 (4)	6 (3)
2	252 (63)	251 (62)	112 (64)	108 (64)	140 (62)	143 (61)
3	53 (13)	60 (15)	17 (10)	25 (15)	36 (16)	35 (15)
>3	23 (6)	26 (6)	11 (6)	13 (8)	12 (5)	13 (6)
Number of severe exacerbations, n (%)						
0	324 (81)	315 (78)	138 (79)	138 (81)	186 (82)	177 (76)
≥1	77 (19)	88 (22)	37 (21)	32 (19)	40 (18)	56 (24)
1	63 (16)	67 (17)	30 (17)	24 (14)	33 (15)	43 (18)
2	11 (3)	9 (2)	6 (3)	3 (2)	5 (2)	6 (3)
3	1 (<1)	8 (2)	0	4 (2)	1 (<1)	4 (2)
>3	2 (<1)	4 (<1)	1 (<1)	1 (<1)	1 (<1)	3 (1)
Number of exacerbations treated with systemic corticosteroids and/or antibiotics but did not require hospitalization/ER visit, n (%)						
0	64 (16)	71 (18)	24 (14)	30 (18)	40 (18)	41 (18)
≥1	337 (84)	332 (82)	151 (86)	140 (82)	186 (82)	192 (82)
1	35 (9)	22 (5)	21 (12)	11 (6)	14 (6)	11 (5)
2	226 (56)	223 (55)	101 (58)	92 (54)	125 (55)	131 (56)
3	55 (14)	58 (14)	17 (10)	24 (14)	38 (17)	34 (15)
>3	21 (5)	29 (7)	12 (7)	13 (8)	9 (4)	16 (7)
Number exacerbations required ER visit but not hospitalization, n (%)						
0	349 (87)	359 (89)	153 (87)	145 (85)	196 (87)	214 (92)
≥1	52 (13)	44 (11)	22 (13)	25 (15)	30 (13)	19 (8)
1	31 (8)	20 (5)	12 (7)	11 (6)	19 (8)	9 (4)
2	16 (4)	18 (4)	6 (3)	12 (7)	10 (4)	6 (3)
3	4 (<1)	5 (1)	3 (2)	2 (1)	1 (<1)	3 (1)
>3	1 (<1)	1 (<1)	1 (<1)	0	0	1 (<1)
Number exacerbations required hospitalization in ICU, n (%)						
0	395 (99)	398 (99)	173 (99)	167 (98)	222 (98)	231 (>99)
≥1	6 (1)	5 (1)	2 (1)	3 (2)	4 (2)	2 (<1)
1	6 (1)	5 (1)	2 (1)	3 (2)	4 (2)	2 (<1)
2	0	0	0	0	0	0
3	0	0	0	0	0	0
>3	0	0	0	0	0	0
Number exacerbations required hospitalization in general ward without ICU, n (%)						
0	328 (82)	319 (79)	139 (79)	140 (82)	189 (84)	179 (77)
≥1	73 (18)	84 (21)	36 (21)	30 (18)	37 (16)	54 (23)
1	61 (15)	63 (16)	30 (17)	22 (13)	31 (14)	41 (18)
2	9 (2)	10 (2)	5 (3)	4 (2)	4 (2)	6 (3)
3	1 (<1)	7 (2)	0	3 (2)	1 (<1)	4 (2)
>3	2 (<1)	4 (<1)	1 (<1)	1 (<1)	1 (<1)	3 (1)
Historical causes of exacerbations, n (%)						
Respiratory infection	183 (46)	200 (50)	81 (46)	85 (50)	102 (45)	115 (49)
Upper respiratory infection other than common cold	100 (25)	109 (27)	44 (25)	45 (26)	56 (25)	64 (27)
Cold air / cold weather	93 (23)	106 (26)	33 (19)	37 (22)	60 (27)	69 (30)
Lower respiratory infection	83 (21)	105 (26)	43 (25)	45 (26)	40 (18)	60 (26)
Unknown etiology	89 (22)	98 (24)	41 (23)	41 (24)	48 (21)	57 (24)
Common cold	84 (21)	99 (25)	33 (19)	41 (24)	51 (23)	58 (25)
Air pollution	49 (12)	51 (13)	15 (9)	24 (14)	34 (15)	27 (12)
Tobacco smoke	47 (12)	50 (12)	13 (7)	19 (11)	34 (15)	31 (13)
Exercise	43 (11)	39 (10)	16 (9)	16 (9)	27 (12)	23 (10)
Stress / emotions	28 (7)	36 (9)	12 (7)	20 (12)	16 (7)	16 (7)
Withholding or reducing COPD medication	18 (4)	29 (7)	6 (3)	11 (6)	12 (5)	18 (8)
Allergy	13 (3)	11 (3)	5 (3)	5 (3)	8 (4)	6 (3)
Other NSAIDs	1 (<1)	0	1 (<1)	0	0	0
Beta-blockers	0	1 (<1)	0	1 (<1)	0	0
Aspirin	0	0	0	0	0	0
Other	0	0	0	0	0	0

Screening and Baseline Lung Function Tests

Screening and Baseline lung function was similar between treatment groups. Overall, screening lung function tests showed lung function impairment with mean (SD) pre- and post-bronchodilator FEV1 values of 1243.5 (491.98) mL and 1323.2 (512.22) mL, respectively, and mean (SD) post-bronchodilator percent-predicted FEV1 values of 48.2% (15.77%). Mean (SD) percent FEV1 reversibility at screening was low at 7.4% (12.65%).

Smoking Status and History

Smoking status and history were similar between the treatment groups. A total of 28% participants were current smokers and 72% were former smokers; the study population had a mean (SD) of 43.0 (24.88) smoking pack-years.

Biomarkers at baseline

Participants were required to have historic evidence of ≥150 BECs and ≥300 BEC at visit 0. Mean baseline eosinophil counts were 0.48 GI/L (480 cells/µL) for placebo and mepolizumab.

Baseline geometric mean of surfactant D values were similar between the treatment groups, 188.72 µg/L for placebo and 188.24 µg/L for mepolizumab. Baseline geometric mean fibrinogen (mean 4.69 and 4.87 x $10^{9/L}$ for placebo and mepolizumab respectively) and C-reactive protein (mean 2.78 and 2.81 mg/L for placebo and mepolizumab respectively) values were similar across the treatment groups.

Prior and concomitant medications

Prior and concomitant medications were generally comparable between the treatment groups.

COPD Medications

The use of COPD medications started prior to the study treatment and continued after treatment start was similar between the treatment groups. Most (≥99%) of the participants were on medications in the corticosteroid and long-acting anticholinergic respiratory medication class. Approximately 60% of participants were on long-acting beta-2 agonist - group 3 (BID) and 40% were on long-acting beta-2 agonist - group 2 (QD). The proportions of participants taking medications from the other respiratory medication classes were generally balanced between the treatment groups.

Table 27 COPD medications started prior to and continued after treatment start by respiratory medication class (mITT Population)

Respiratory medication class Ingredient	PBO (N=401)	Mepo 100 mg (N=403)	Total (N=804)
Any medication, n (%)	400 (>99)	403 (100)	803 (>99)
Corticosteroid	398 (>99)	400 (>99)	798 (>99)
Long-acting anticholinergic	396 (99)	397 (99)	793 (99)
Short-acting beta-2 agonist	259 (65)	262 (65)	521 (65)
Long-acting beta-2 agonist - group 3 (twice per day)	244 (61)	260 (65)	504 (63)
Long-acting beta-2 agonist - group 2 (once per day)	166 (41)	162 (40)	328 (41)
Short-acting anticholinergic	54 (13)	49 (12)	103 (13)
Other	26 (6)	31 (8)	57 (7)
Mucolytics	27 (7)	27 (7)	54 (7)
Xanthine	22 (5)	32 (8)	54 (7)
Oxygen	21 (5)	20 (5)	41 (5)
PDE4 Inhibitors	15 (4)	22 (5)	37 (5)
Leukotriene Receptor Antagonist	15 (4)	17 (4)	32 (4)
Antiinfectives (antibiotics, antiseptics)	6 (1)	16 (4)	22 (3)

Note: Includes all COPD medications started prior to and continued after the first dose of study treatment.
Note: Multi-component medications are displayed under the respiratory medication class of each component.

Overall, a smaller number of participants in the mepolizumab group (22%) started COPD medications during treatment compared with the placebo group (27%). The most frequently reported COPD medications started during the study treatment period were from the respiratory medication class of corticosteroids (15%), long-acting anticholinergic (6%), short-acting beta-2 agonist (6%), anti-infective (antibiotics, antiseptics) (6%), other (unspecified) (6%), and long-acting beta-2 agonist - group 3 (BID) (6%).

Long-Term Oxygen Therapy

Use of long-term oxygen therapy prior to screening was infrequent (5% of participants for both treatment groups). The majority of these participants were using ≤1 L/min (2%) or >1 to 2 L/min (2%).

Numbers analysed

Of the 806 participants randomized, 804 (>99%) were included in the mITT and Safety populations, 401 were in the placebo group and 403 were in the mepolizumab treatment group. Investigators were instructed to exclude any participant with past or current history of asthma. However, a small number of participants were found to have a possible history of asthma (typically via additional review of participants' medical records) post randomization. As a result, 21 participants in the mITT population were excluded from mITT2 population. 783 (97%) were included in the mITT2 population that received one dose of study treatment with no evidence of past history or current diagnosis of asthma, 394 were in the placebo group and 389 were in the mepolizumab treatment group. 459 (57%) were included in the extended treatment population that extended beyond 52 weeks and up to 104 weeks, with 226 in the placebo group and 233 in the mepolizumab treatment group.

Table 28 Study populations (All Participants Enrolled)

Population	PBO	Mepo 100 mg	Total
All Participants Enrolled			3306
Randomized	402	404	806
Modified Intent-to-Treat (mITT) [1]	401 (>99)	403 (>99)	804 (>99)
Extended Treatment [2]	226 (56)	233 (58)	459 (57)
Per-Protocol (PP)	356 (89)	360 (89)	716 (89)
Pharmacokinetic (PK)	0	46 (11)	46 (6)
Modified Intent-to-Treat excluding past/concurrent Asthma (mITT2) [3]	394 (98)	389 (96)	783 (97)
Safety [1]	401 (>99)	403 (>99)	804 (>99)
Extended Treatment [4]	226 (56)	233 (58)	459 (57)

Outcomes and estimation

Table 29 Summary of primary and secondary efficacy endpoint results (mITT)

	Placebo	Mepolizumab 100
Primary Efficacy Endpoint		
Rate of Moderate/Severe Exacerbations (On- and Off-treatment)		
n	401	403
Exacerbation rate/year	1.01	0.80
Rate ratio (mepolizumab/placebo)		0.79
95% CI		(0.66, 0.94)
p-value		0.011
Secondary Efficacy Endpoints		
Time to First Moderate/Severe Exacerbation		
By Week 104 [1]		
Participants with event	225 (56)	202 (50)
Probability (%) of an exacerbation	68.3	64.5
95% CI	(61.4, 74.9)	(57.5, 71.4)
Event: first moderate/severe exacerbation, n (%) Censored, n (%)	226 (56)	202 (50)
Censored at study withdrawal	175 (44)	201 (50)
Censored at study completion	24 (6)	31 (8)
Censored due to COVID-19 pandemic related ICE Hazard ratio (mepolizumab/placebo)	143 (36)	162 (40)
95% CI	8 (2)	8 (2)
p-value		0.77 (0.64, 0.93)
		0.009

CAT Score Responders at Week 52		
n	394	391
Responder, n (%)	180 (46)	162 (41)
Non-responder, n (%) No change/worsening	206 (52)	220 (56)
Withdrawal from study prior to visit	150 (38)	167 (43)
Missing visit	36 (9)	33 (8)
Imputed, n (%)	20 (5)	20 (5)
	8 (2)	9 (2)

	Placebo	Mepolizumab 100
Odds ratio to placebo		0.81
95% CI		(0.60, 1.09)
SGRQ Total Score Responders at Week 52		
n	393	390
Responder, n (%)	179 (46)	195 (50)
Non-responder, n (%) No change/worsening	206 (52)	186 (48)
Withdrawal from study prior to visit	149 (38)	133 (34)
Missing visit	36 (9)	33 (8)
Imputed, n (%)	21 (5)	20 (5)
Odds ratio to placebo	8 (2)	9 (2)
95% CI		1.17
p-value		(0.87, 1.57)
		0.291
E-RS: COPD total Score Responders (Weeks 49-52)		

n	399	403
Responder, n (%)	137 (34)	123 (31)
Non-responder, n (%) No change/worsening	254 (64)	271 (67)
Withdrawal from study prior to visit	180 (45)	203 (50)
Missing visit	37 (9)	33 (8)
Imputed, n (%)	37 (9)	35 (9)
Odds ratio to placebo	8 (2)	9 (2)
95% CI		0.82 (0.60, 1.12)
p-value		0.209
Annualized Rate of Exacerbations Requiring ED Visit and/or Hospitalization		
n	401	403
Exacerbation rate/year	0.20	0.13
95% CI	(0.15, 0.27)	(0.10, 0.18)
Rate ratio (mepolizumab/placebo)		0.65
95% CI		(0.43, 0.96)
p-value		0.032*

Primary efficacy endpoint analysis

Annualized frequency of moderate/severe exacerbations (mITT Population)

Treatment with mepolizumab resulted in a statistically significant reduction in the annualized rate of moderate/severe exacerbations compared with placebo (rate ratio: 0.79; 95% CI: 0.66, 0.94; p=0.011). Compared with placebo, there were fewer participants treated with mepolizumab who experienced one or more moderate/severe exacerbations (50% [mepolizumab] versus 56% [placebo] and generally fewer participants with **multiple exacerbations**.

The incidence and frequency of on- and off-treatment moderate/severe exacerbations was lower in the mepolizumab group (50%; **482 events**) compared with the placebo group (56%; **554 events**). The majority of exacerbations occurred while on treatment; hence, a similar trend was observed for on-treatment exacerbations. The frequency of off-treatment exacerbations was low and similar between treatment groups

Results of all sensitivity and supplementary analyses were consistent with the primary analysis and supported the positive result in favour of mepolizumab 100 mg

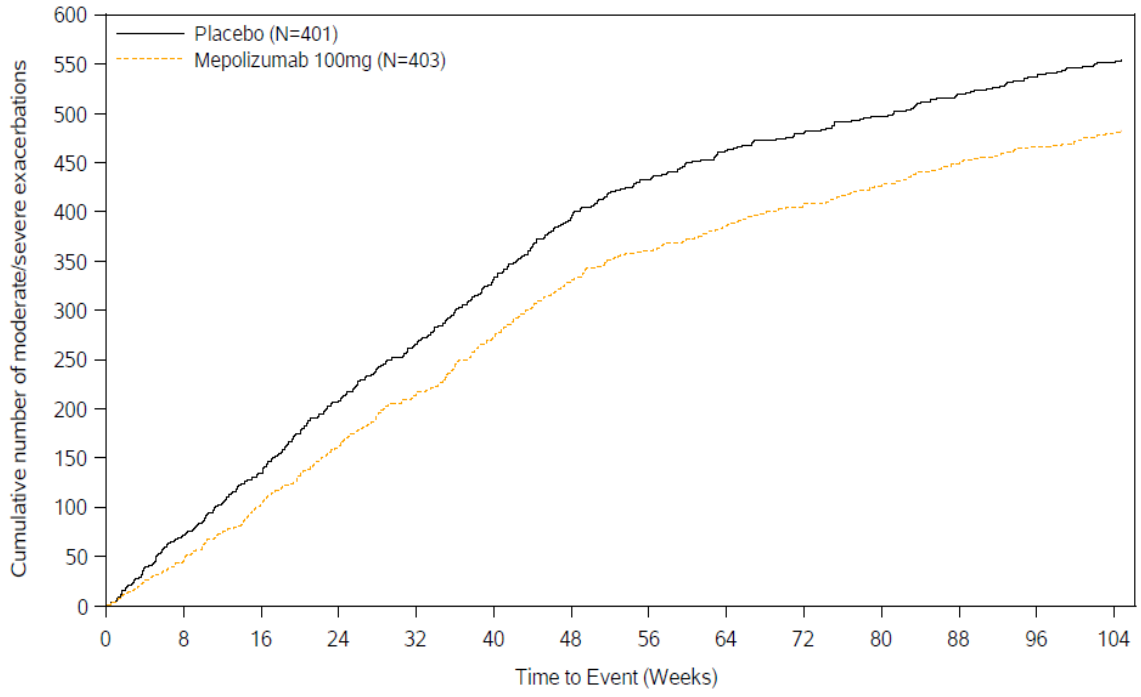
mITT2 population

A sensitivity analysis was conducted in the mITT2 population which **excluded 21 participants** who were found to have a possible history of asthma after randomization. The incidence and frequency of exacerbations in the mITT2 population with annualised rates of 1.01 in PBO and 0.78 in Mepo (rate ratio: 0.77; 95% CI: 0.64, 0.93; p=0.006).

Table 30 Annualized frequency of moderate/severe exacerbations (mITT Population)

	On- and off-treatment	
	PBO (N=40	**Mepo 100 mg**
Number of exacerbations per year [1], n (%)		
0	175 (44)	201 (50)
>0-<1	68 (17)	62 (15)
1-<2	77 (19)	70 (17)
2-<3	36 (9)	30 (7)
3-<4	16 (4)	21 (5)
4-<5	11 (3)	8 (2)
5-<6	6 (1)	5 (1)
6-<7	2 (<1)	3 (<1)
7-<8	2 (<1)	1 (<1)
8-<9	2 (<1)	2 (<1)
9-<10	2 (<1)	0
≥10	4 (<1)	0
Primary analysis		
Annualized rate of moderate/severe exacerbations	1.01	0.80
95% CI	(0.89, 1.15)	(0.70, 0.91)
Comparison mepolizumab versus placebo		
Rate ratio (mepolizumab/placebo)	0.79	
95% CI	(0.66, 0.94)	
p-value	0.011	

Figure 23 Cumulative number of moderate/severe exacerbations (mITT Population)



Summary of Missing Data

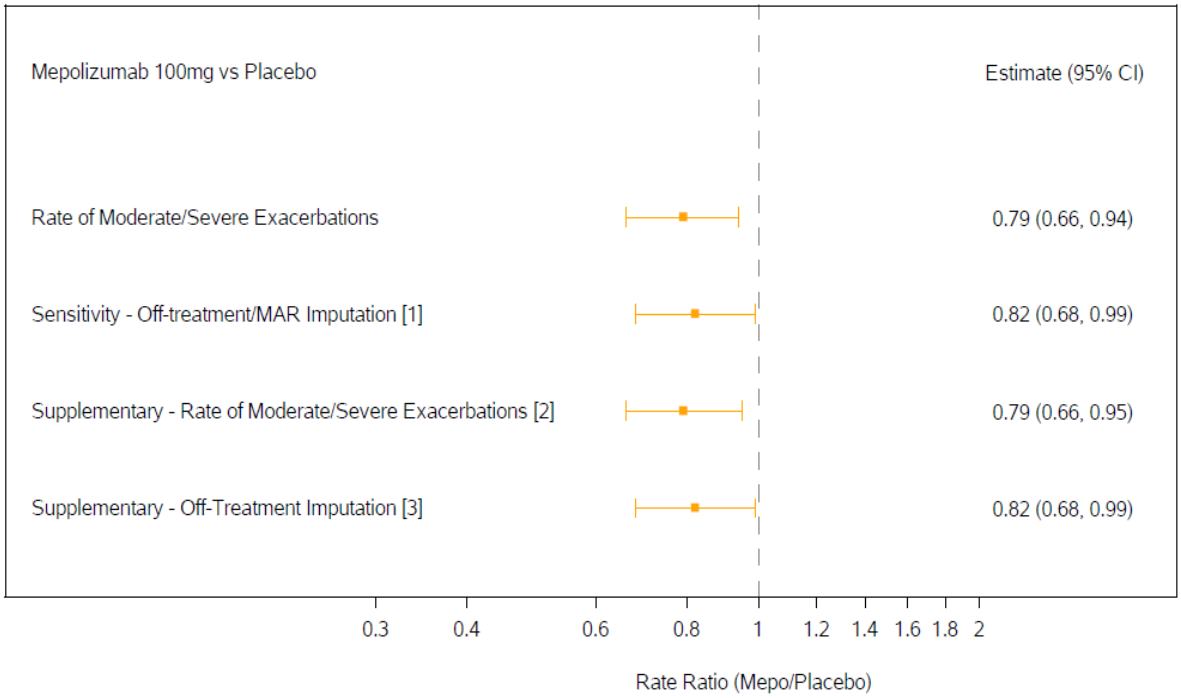
The amount of missing data (PY missing) was generally similar between the treatment groups (36.90 [mepolizumab] versus 47.00 [placebo]), predominantly due to premature treatment discontinuation and withdrawal from study at the same time. When expressed as a percentage of scheduled years follow-up, the amount of missing data was 6.7% for the mepolizumab group and 8.7% for the placebo group. Similar trends were also noticed in the fixed and variable duration subgroups

Sensitivity and Supplementary Analyses

For the primary endpoint analysis, missing data were assumed to be missing at random. A sensitivity analysis was conducted to test the robustness of this assumption. Missing data was imputed for participants who had left the study early using observed off-treatment data from participants who continued in the study after withdrawing early from study treatment, and for those who had intercurrent events of treatment discontinuation or 2 or more consecutive missed doses associated with the COVID-19 pandemic missing data was imputed using observed on-and off-treatment data. The imputed datasets were analyzed multiple times and the results combined using Rubin's formulae.

Supplementary estimands for the primary endpoint were presented for the mITT population, using a treatment policy strategy for all ICEs, irrespective of their association with the COVID-19 pandemic. In the first of these supplementary estimands, all missing data were considered MAR; in the second of these supplementary estimands missing data due to study withdrawal were imputed using off-treatment data from participants who continued in the study after withdrawing early from study treatment. These additional estimands estimated the difference in the annualized rate of moderate/severe exacerbations between mepolizumab 100 mg SC and placebo in participants with COPD, regardless of treatment discontinuation/interruption, medication changes, or the impact of the COVID-19 pandemic.

Figure 24 Overview of sensitivity and supplementary analyses (mITT Population)



Tipping Point Sensitivity Analyses

With the rate for participants with missing data in the placebo group estimated by the MAR assumption (delta=1.0), exacerbation rates for participants with missing data in the mepolizumab group would need to be close to 1.6 times higher than predicted by the MAR assumption for the treatment comparison to show p>0.05. Based on the mean exacerbation rate of 0.8/yr estimated from the analysis model for participants in the mepolizumab group, this would imply an increase in the rate to 1.28/yr.

mITT2 population

A sensitivity analysis was conducted in the mITT2 population which excluded21 participants who were found to have a possible history of asthma after randomization; The incidence and frequency of exacerbations in the mITT2 population was similar to that for the mITT population. Results of the analysis on the mITT2 population were similar to the primary analysis.

Table 31 Analysis of rate of moderate/severe exacerbations – population excluding past/concurrent asthma (mITT2 Population)

	PBO (N=394)	Mepo 100 mg (N=389)
n	394	389
Annualized rate of moderate/severe exacerbations	1.01	0.78
95% CI	(0.89, 1.15)	(0.68, 0.89)
Comparison mepolizumab versus placebo		
Rate ratio (mepolizumab/placebo)	0.77	
95% CI	(0.64, 0.93)	
p-value	0.006	

Note: Analysis performed using a negative binomial model with covariates of treatment group, geographic region, number of moderate/severe exacerbations in previous year (≤2, 3, ≥4 as ordinal), baseline % predicted FEV1 and smoking status (current versus former smoker), and with logarithm (time on- and off-treatment) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

Note: Intercurrent events of treatment interruption or treatment discontinuation related to the COVID-19 pandemic are handled with a hypothetical strategy (data is set to missing following the event). Other COVID-19 related ICEs and any ICEs not related to the COVID-19 pandemic are handled with a treatment policy strategy. Missing data considered MAR.

p-values not adjusted for multiplicity.

Study center with data quality issues

A separate sensitivity analysis was conducted excluding all 3 participants from study center 239718 (with data quality issues) to assess the impact of data from this study center on the primary estimand. This sensitivity analysis showed similar results (rate ratio: 0.79; 95% CI: 0.66, 0.95) to the primary analysis

Supportive Analyses

Results of a supportive analysis using the PP population were similar to the results of the primary analysis

Table 32 Supplementary analysis of rate of moderate/severe exacerbations (PP Population)

	PBO (N=356)	Mepo 100 mg (N=360)
Annualized rate of moderate/severe exacerbations 95% CI	0.94 (0.82, 1.08)	0.75 (0.65, 0.87)
Comparison mepolizumab versus placebo Rate Ratio (mepolizumab/placebo) 95% CI p-value	0.80 (0.66, 0.97) 0.023	

Note: Analysis performed using a negative binomial model with covariates of treatment group, geographic region, number of moderate/severe exacerbations in previous year (≤2, 3, ≥4 as ordinal), baseline % predicted FEV1 and smoking status (current versus former smoker), and with logarithm (time on- and off-treatment) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

Note: Intercurrent events of treatment interruption or treatment discontinuation related to the COVID-19 pandemic are handled with a hypothetical strategy (data is set to missing following the event). Other COVID-19 related ICEs and any ICEs not related to the COVID-19 pandemic are handled with a treatment policy strategy. Missing data considered MAR.

<u>Key secondary efficacy endpoints</u>

1. Time to First Moderate/Severe Exacerbation

The cumulative incidence and KM **estimated probability of a first moderate/severe exacerbation** was lower for mepolizumab compared with placebo over the course of the study (Figure 25 and Table 33). The time to first event analysis showed a statistically significant reduction in the risk of moderate/severe exacerbation for mepolizumab compared with placebo (hazard ratio 0.77; 95% CI: 0.64, 0.93; p=0.009) (Table 33). As seen from the KM plot, the median time to first exacerbation was longer in the mepolizumab group (419 days) compared with 321 days in the placebo group mITT2 population: The time to first moderate/severe exacerbation analysis in the mITT2 population showed similar results to the primary analysis (hazard ratio: 0.76; 95% CI: 0.62, 0.92).

Figure 25 Kaplan-Meier cumulative incidence curve for time to first moderate/severe exacerbation (mITT Population)

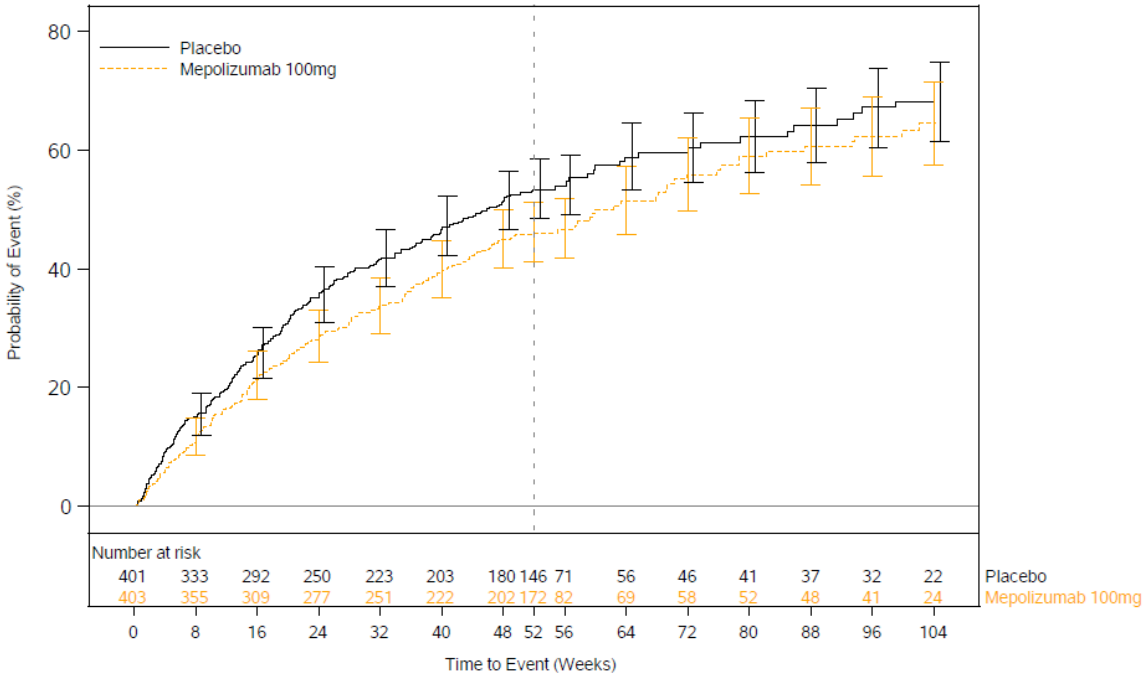


Table 33 Analysis of time to first moderate/severe exacerbation (mITT Population)

	PBO (N=401)	**Mepo 100 mg**
By week 8		
Participants with event, n (%)	60 (15)	45 (11)
% Probability of an exacerbation [1]	15.1	11.3
95% CI	(11.9, 19.0)	(8.5,
By week 24		
Participants with event, n (%)	139 (35)	112 (28)
% Probability of an exacerbation [1]	35.4	28.3
95% CI	(30.9, 40.3)	(24.2, 33.1)
By week 40		
Participants with event, n (%)	184 (46)	155 (38)
% Probability of an exacerbation [1]	47.1	39.8
95% CI	(42.3, 52.2)	(35.1, 44.8)

By week 52 Participants with event, n (%) % Probability of an exacerbation [1] 95% CI	207 (52) 53.4 (48.5, 58.5)	178 (44) 46.1 (41.2, 51.2)
By week 64 Participants with event, n (%) % Probability of an exacerbation [1]	215 (54) 58.9	186 (46) 51. 4

	PBO (N=401)	**Mepo 100 mg**
95% CI	(53.3, 64.6)	(45.8, 57.2)
By week 80 Participants with event, n (%) % Probability of an exacerbation [1] 95% CI	219 (55) 62.3 (56.2, 68.4)	196 (49) 59.0 (52.6, 65.5)
By week 96 Participants with event, n (%) % Probability of an exacerbation [1] 95% CI	224 (56) 67.2 (60.5, 73.8)	200 (50) 62.3 (55.6, 69.0)
By week 104 Participants with event, n (%) [3] % Probability of an exacerbation [1] 95% CI	225 (56) 68.3 (61.4, 74.9)	202 (50) 64.5 (57.5,
Event: first moderate/severe exacerbation, n (%) **Censored, n (%)** Censored at study withdrawal Censored at study completion Censored due to COVID-19 pandemic related ICE	226 (56) 175 (44) 24 (6) 143 (36) 8 (2)	202 (50) 201 (50) 31 (8) 162 (40)
Hazard ratio (mepolizumab/placebo) [2] 95% CI	0.77 (0.64, 0.93)	

Analyses of time to first moderate/severe exacerbation in subgroups of screening BEC categories, symptoms of chronic bronchitis, and smoking status showed similar results to the overall population; treatment estimates consistently favoured mepolizumab across these subgroups.

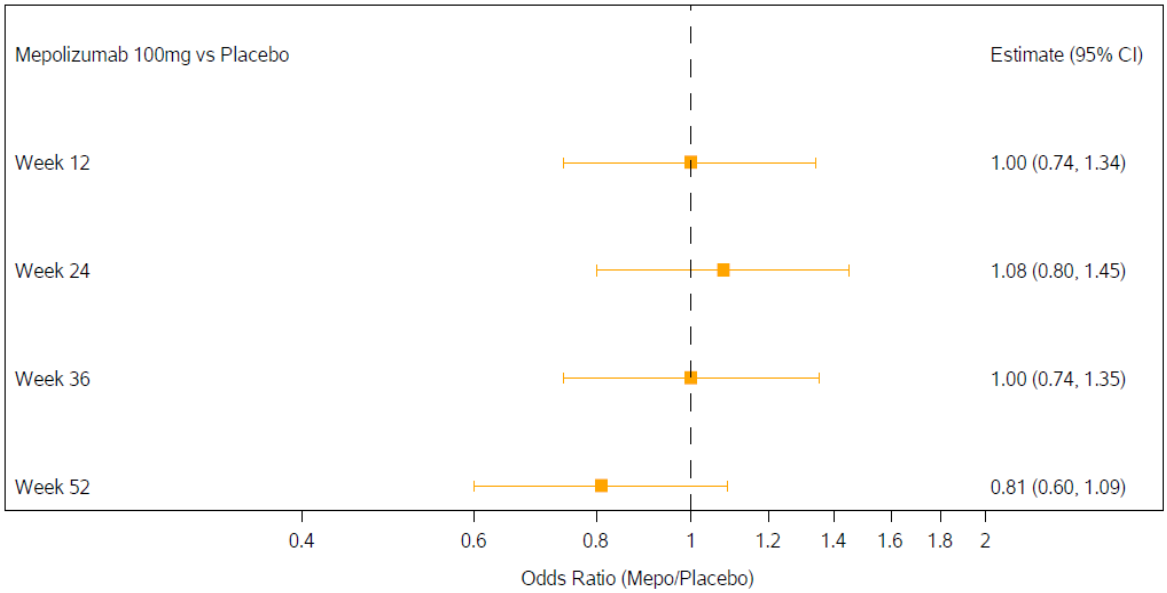
2. COPD Assessment Test

The proportion of CAT responders (achieving ≥2-point improvement in CAT score) at Week 52 was a key secondary endpoint in the study. The proportion of CAT responders at other timepoints were other secondary endpoints not under multiplicity adjustment.

At Baseline, the mean CAT scores were similar between the mepolizumab and placebo groups with a mean (SD) of 19.2 (6.95) and 19.1 (6.75), respectively. **The proportion of CAT responders (achieving ≥2-point improvement in CAT score) at Week 52 was similar between the mepolizumab (41%) and placebo (46%) groups (odds ratio: 0.81; 95% CI: 0.60, 1.09; p=0.161).**

The proportion of CAT responders for mepolizumab compared with placebo at Weeks 12, 24, 36, and 52 did not show any notable differences between the treatment groups over time. Similar results for the analysis of CAT responders were observed in the mITT2 population (Week 52: odds ratio 0.80; 95% CI: 0.59, 1.09).

Table 34 CAT responders (mITT Population)

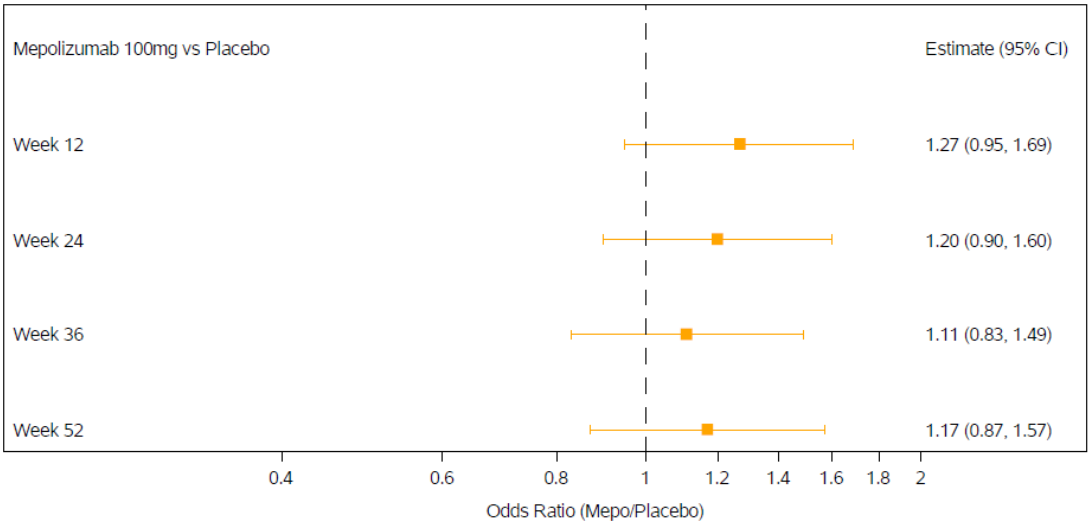


3. St. George's Respiratory Questionnaire

The proportion of SGRQ responders (achieving ≥4-point improvement in SGRQ total score) at Week 52 was a key secondary endpoint in the study. The proportion of SGRQ responders (at other timepoints were other secondary endpoints not under multiplicity adjustment.

At Baseline, the mean SGRQ total scores were similar between the mepolizumab and placebo groups with a mean (SD) of 55.3 (17.73) and 53.9 (17.86), respectively. **The proportion of SGRQ responders (achieving ≥4-point improvement in SGRQ total score) at Week 52 was numerically higher in the mepolizumab group (50%) compared with placebo (46%) (odds ratio: 1.17; 95% CI: 0.87, 1.57)** with the treatment effect directionally consistent across timepoints (Weeks 12, 24, 36, and 52). Similar results for the analysis of SGRQ responders were observed in the mITT2 population (Week 52: odds ratio 1.13; 95% CI: 0.84, 1.52).

Figure 26 SGRQ responders (mITT Population)

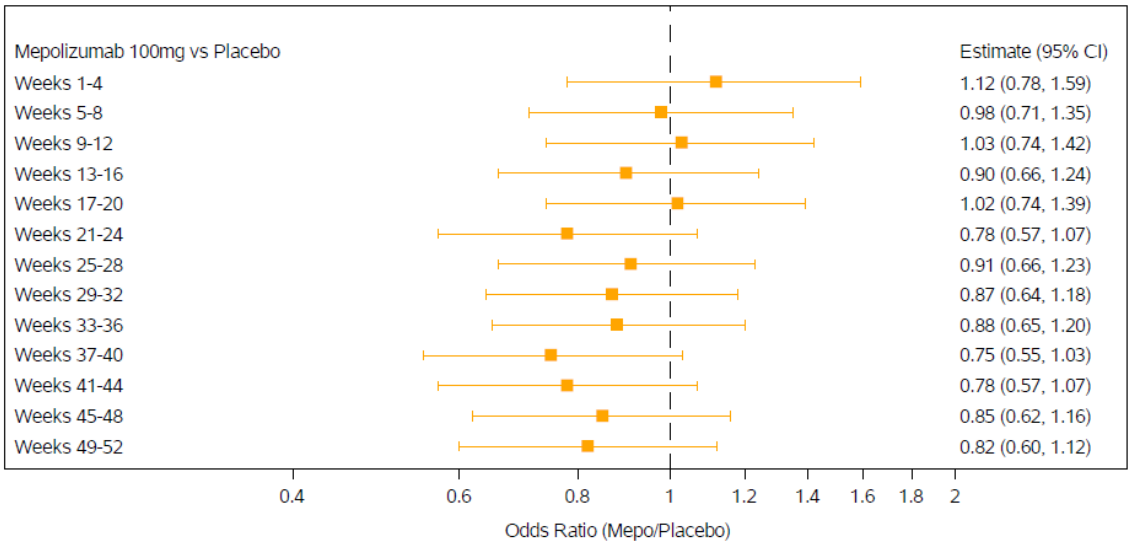


4. Evaluating Respiratory Symptoms in COPD

The proportion of E-RS: COPD responders (achieving ≥2 point improvement in E-RS: COPD score) at Weeks 49-52 was a key secondary endpoint in the study. E-RS: COPD responders at other timepoints were other secondary endpoints not under multiplicity adjustment.

At Baseline, the mean E-RS: COPD scores were similar between the mepolizumab and placebo groups with a mean (SD) of 13.16 (6.796) and 12.94 (6.790), respectively. **The proportion of E-RS: COPD responders (achieving ≥2 point improvement in E-RS: COPD score) at 'Weeks 49-52' was similar between the mepolizumab (31%) and placebo (34%) groups (odds ratio 0.82; 95% CI: 0.60, 1.12; p=0.209)**. The proportion of E-RS: COPD responders for mepolizumab compared with placebo at Weeks 9-12, 21-24, 33-36, and 49-52 were similar, with no benefit seen with mepolizumab over time. Similar results for the analysis of E-RS: COPD responders at Weeks 49- 52 were observed in the mITT2 population (odds ratio 0.81; 95% CI: 0.59, 1.10)

Figure 27 COPD responders (mITT Population)



5. Annualized rate of exacerbations requiring ED and/or hospitalization

Annualized rate of exacerbations requiring ED and/or hospitalization was a key secondary endpoint in the study**.**

Fewer participants treated with mepolizumab (56; 14%) experienced one or more exacerbations requiring an ED visit/hospitalization compared with those who received placebo (71; 18%) (Table 35). Participants treated with mepolizumab showed a 35% reduction in the annualized rate of exacerbations requiring ED visit and/or hospitalization compared with placebo (rate ratio: 0.65; 95% CI: 0.43, 0.96).

Table 35 Annualized frequency of exacerbations requiring ED visit and/or hospitalization (on- and off-treatment) (mITT Population)

	PBO (N=401)	**Mepo 100 mg (N=403)**
Number of exacerbations per year [1], n (%)		
0	330 (82)	347 (86)
>0-<1	31 (8)	20 (5)
1-<2	26 (6)	24 (6)
2-<3	7 (2)	5 (1)
3-<4	2 (<1)	2 (<1)
4-<5	1 (<1)	3 (<1)
5-<6	2 (<1)	0
6-<7	0	0
7-<8	1 (<1)	0
8-<9	0	2 (<1)
9-<10	1 (<1)	0
≥10	0	0
Analysis		
Annualized rate of exacerbations requiring ED visit and/or hospitalization 95% CI	0.20 (0.15, 0.27)	0.13 (0.10, 0.18)
Comparison mepolizumab versus placebo Rate ratio (mepolizumab/placebo) 95% CI p-value	0.65 (0.43, 0.96) 0.032*	

<u>Other secondary endpoints (not controlled for multiplicity)</u>

Other secondary endpoints investigating the effect on exacerbation

Time to first exacerbation requiring ED visit and/or hospitalization

The time to first event analysis showed a reduction in the risk of exacerbation requiring ED visit and/or hospitalization for mepolizumab compared with placebo (hazard ratio 0.73; 95% CI: 0.51, 1.04).

Severe Exacerbations

Severe exacerbations were infrequent; 73 events occurred in 46 (11%) participants in the mepolizumab group, and 85 events occurred in 59 (15%) in the placebo group.

Participants treated with mepolizumab showed a 34% reduction in the annualized rate of severe exacerbations (requiring hospitalization and/or resulting in death) compared with placebo (rate ratio 0.66; 95% CI: 0.43, 1.01)

Table 36 Annualized frequency of severe exacerbations (on- and off treatment) (mITT Population)

	PBO (N=401)	Mepo 100 mg (N=403)
Number of severe exacerbations per year [1], n (%)		
0	342 (85)	357 (89)
>0-<1	26 (6)	21 (5)
1-<2	21 (5)	16 (4)
2-<3	5 (1)	2 (<1)
3-<4	2 (<1)	3 (<1)
4-<5	2 (<1)	3 (<1)
5-<6	2 (<1)	0
6-<7	0	0
7-<8	0	0
8-<9	0	1 (<1)
9-<10	1 (<1)	0
≥10	0	0
Analysis		
Annualized rate of severe exacerbations	0.15	0.10
95% CI	(0.11, 0.21)	(0.07, 0.14)
Comparison mepolizumab versus placebo		
Rate ratio (mepolizumab/placebo)	0.66	
95% CI	(0.43, 1.01)	
p-value	0.055	

[1] Based on the crude annualized rate of exacerbations.
Note: Analysis performed using a negative binomial model with covariates of treatment group, geographic region, number of moderate/severe exacerbations in previous year (≤2, 3, ≥4 as ordinal), baseline % predicted FEV_1 and smoking status (current versus former smoker), and with logarithm (time on- and off-treatment) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.
Note: Intercurrent events of treatment interruption or treatment discontinuation related to the COVID-19 pandemic are handled with a hypothetical strategy (data is set to missing following the event). Other COVID-19 related ICEs and any ICEs not related to the COVID-19 pandemic are handled with a treatment policy strategy. Missing data considered MAR.

Time to first severe exacerbation

The time to first event analysis showed a reduction in the risk of severe exacerbation for mepolizumab compared with placebo (hazard ratio 0.74; 95% CI: 0.50, 1.08).

Annualized rate of exacerbations by type of treatment required treatment with 'corticosteroids and antibiotics'

Mepolizumab reduced the rate of exacerbations requiring treatment with 'corticosteroids and antibiotics' by 24% compared with placebo; mepolizumab also reduced the rate of exacerbations requiring treatment with corticosteroids alone by 20%; lesser impact of treatment with mepolizumab was seen for exacerbations requiring antibiotics alone (8%).

Figure 28 Moderate/severe exacerbations by type of treatment required (mITT Population)

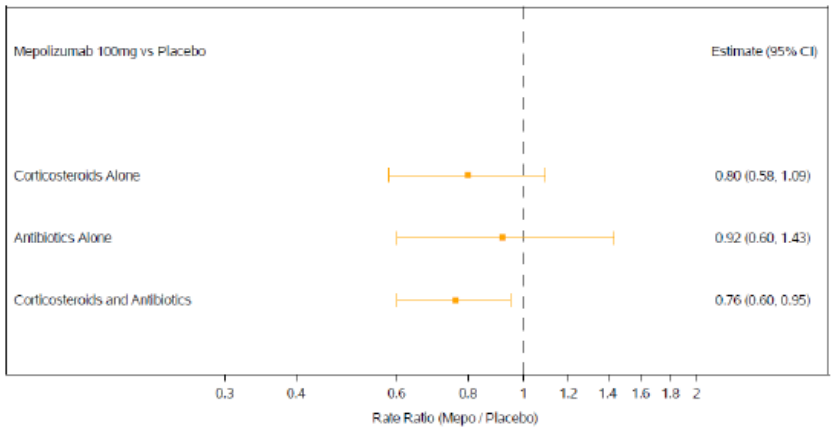


Table 37 Rate of moderate/severe exacerbations by type of treatment required - negative binomial model (mITT Population)

	On- and off-treatment	
	PBO (N=401)	Mepo 100 mg (N=403)
Type of Treatment: Corticosteroids Alone		
Annualized rate of moderate/severe exacerbations	0.29	0.23
95% CI	(0.23, 0.37)	(0.18, 0.30)
Comparison mepolizumab versus placebo Rate ratio (mepolizumab/placebo) 95% CI		0.80 (0.58, 1.09)
Type of Treatment: Antibiotics Alone		
Annualized rate of moderate/severe exacerbations	0.11	0.10
95% CI	(0.08, 0.15)	(0.07, 0.14)
Comparison mepolizumab versus placebo Rate ratio (mepolizumab/placebo) 95% CI		0.92 (0.60, 1.43)
Type of Treatment: Corticosteroids and Antibiotics		
Annualized rate of moderate/severe exacerbations	0.53	0.40
95% CI	(0.45, 0.62)	(0.33, 0.47)
Comparison mepolizumab versus placebo Rate ratio (mepolizumab/placebo) 95% CI		0.76 (0.60, 0.95)

Moderate Exacerbations

The occurrence of at least 1 moderate exacerbation (on- and off-treatment) was lower in the mepolizumab group (409 events in 184 [46%] participants) compared with the placebo group (469 events in 200 [50%] participants).

Other secondary endpoints not investigating the effect on exacerbation

Rescue Medication Use

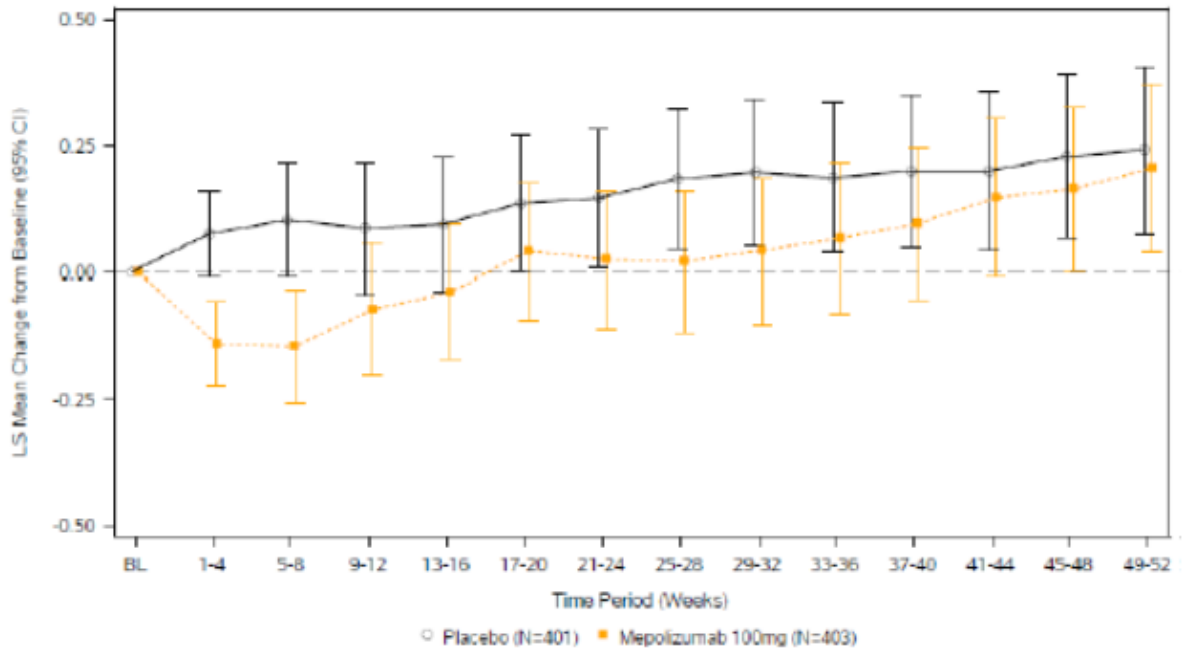
Number of occasions of rescue medications use

At Baseline, the mean number of occasions of rescue medication use was similar between the treatment groups, with a mean (SD) of 1.75 (2.143) and 1.60 (1.929) in the mepolizumab and placebo groups, respectively.

The LS mean change from baseline in the number of occasions of rescue medication use over time showed a numerical trend of less use in the mepolizumab group compared with the placebo group, however, the differences were small.

During Weeks 49 to 52, the LS mean reduction from baseline in occasions of rescue medication use was similar between treatment groups.

Figure 29 Mean number of occasions of rescue medication use (mITT Population)



Note: Includes data reported up to Week 52.
Note: Analysis performed using mixed model repeated measures with covariates of treatment group, geographic region, baseline, smoking status (current versus former smoker), visit plus interaction terms for visit by baseline and visit by treatment group. Estimates are based on weighting applied to each level of class variable determined from observed proportions.

Table 38 Analysis of mean number of occasions of rescue medication use – mixed model repeated measures (mITT Population)

	PBO (N=401)	Mepo 100 mg (N=403)
Weeks 49-52		
n [1]	401	403
n [2]	357	358
LS mean (SE)	1.9 (0.08)	1.9 (0.08)
LS mean change (SE)	0.2 (0.08)	0.2 (0.08)
Mepolizumab 100 mg versus placebo		
Difference (mepolizumab - placebo)		0.0
95% CI		(-0.27, 0.20)
p-value		0.765

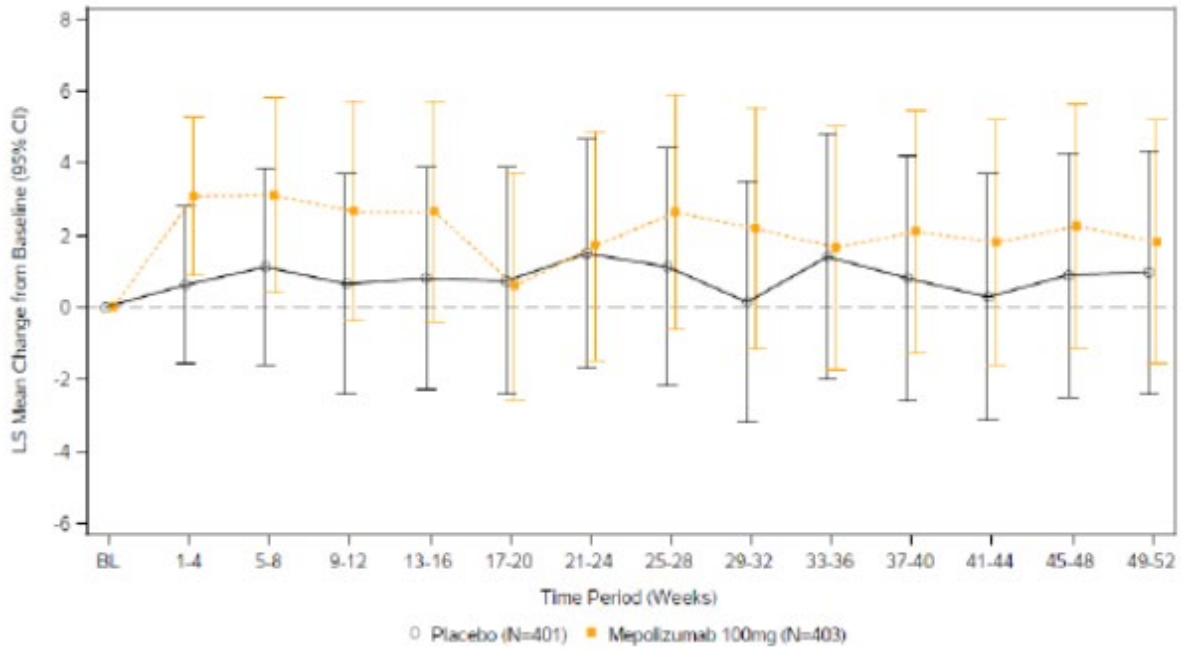
[1] Number with analysable data for one/more time points.
[2] Number with analysable data at given time point.
Note: Analysis performed using mixed model repeated measures with covariates of treatment group, geographic region, baseline, smoking status (current versus former smoker), visit plus interaction terms for visit by baseline and visit by treatment group. Estimates are based on weighting applied to each level of class variable determined from observed proportions.
Note: Includes data reported up to Week 52.

Percentage of rescue medication free days

At Baseline, the percentage of rescue medication free days was similar between the treatment groups, with a mean (SD) of 36.5 (42.26) and 38.2 (43.21) in the mepolizumab and placebo groups, respectively.

The LS mean change from baseline in the percentage of rescue medication free days over time showed marginally more rescue medication free days over time for mepolizumab compared with placebo, however, no notable treatment difference was observed at Weeks 49-52.

Table 39 Percentage rescue medication free days (mITT Population)



Note: Includes data reported up to Week 52.
Note: Analysis performed using mixed model repeated measures with covariates of treatment group, geographic region, baseline, smoking status (current versus former smoker), visit plus interaction terms for visit by baseline and visit by treatment group. Estimates are based on weighting applied to each level of class variable determined from observed proportions.

Table 40 Analysis of percentage rescue medication free days mixed model repeated measures (mITT Population)

	PBO (N=401)	Mepo 100 mg (N=403)
Weeks 49-52		
n [1]	401	403
n [2]	357	358
LS mean (SE)	38.4 (1.73)	39.3 (1.72)
LS mean change (SE)	1.0 (1.73)	1.8 (1.72)
Mepolizumab 100 mg versus placebo		
Difference (mepolizumab - placebo)		0.8
95% CI		(-3.95, 5.63)
p-value		0.731

[1] Number with analysable data for one/more time points.
[2] Number with analysable data at given time point.
Note: Analysis performed using mixed model repeated measures with covariates of treatment group, geographic region, baseline, smoking status (current versus former smoker), visit plus interaction terms for visit by baseline and visit by treatment group. Estimates are based on weighting applied to each level of class variable determined from observed proportions.
Note: Includes data reported up to Week 52.

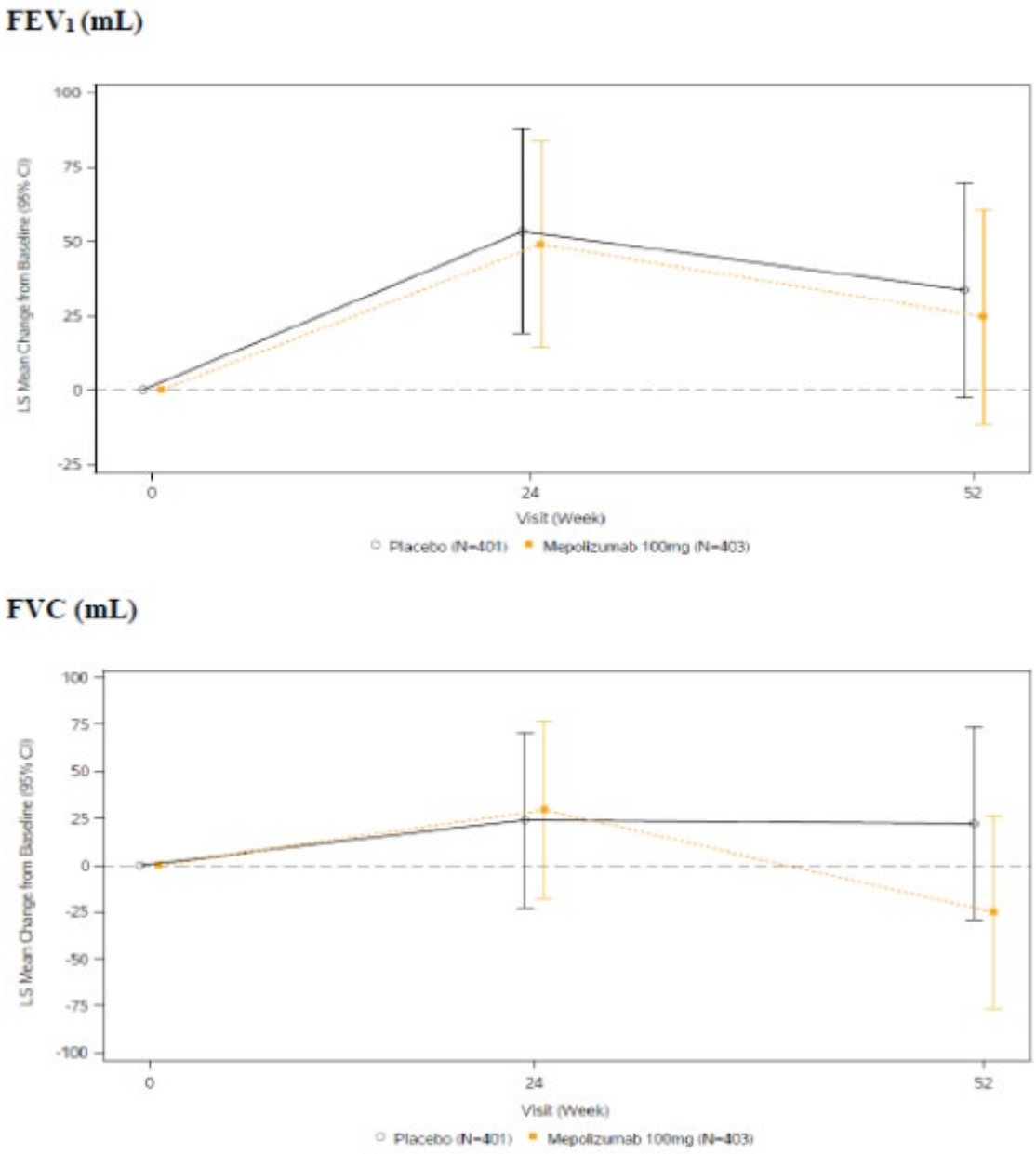
Lung Function

At Baseline, pre-bronchodilator FEV1 was similar between the treatment groups, with a mean (SD) of 1240.4 (482.04) and 1281.8 (537.00) in the mepolizumab and placebo groups, respectively.

At Baseline, pre-bronchodilator FVC was similar between the treatment groups, with a mean (SD) of 2595.6 (827.49) and 2605.0 (782.47), respectively.

The LS mean change from baseline in pre-bronchodilator FEV1 and FVC was similar between treatment groups at Week 24 and Week 52.

Figure 30 Change from Baseline in pre-bronchodilator FEV1 (mL) and FVC (mL) (mITT Population)



Note: Includes data reported up to Week 52.
Note: Analysis performed using mixed model repeated measures with covariates of treatment group, geographic region, baseline, smoking status (current versus former smoker), visit plus interaction terms for visit by baseline and visit by treatment group. Estimates are based on weighting applied to each level of class variable determined from observed proportions.
Note: Vertical bars represent 95% confidence intervals.

At Week 52, little difference was observed between mepolizumab and placebo in change from Baseline in pre-bronchodilator FEV1 or FVC.

Table 41 Analysis of change from baseline pre-bronchodilator FEV1 (mL) and FVC (mL) - mixed model repeated measures (mITT Population)

Lung Function Measure	Week 24		Week 52	
	PBO (N=401)	Mepo 100 mg (N=403)	PBO (N=401)	Mepo 100 mg (N=403)
FEV1 (mL)				
n [1]	384	381	384	381
n [2]	374	367	341	342
LS mean (SE)	1324.9 (17.55)	1320.6 (17.69)	1305.2 (18.38)	1296.2 (18.38)
LS mean change (SE)	53.3 (17.55)	48.9 (17.69)	33.6 (18.38)	24.6 (18.38)
Mepolizumab 100 mg versus placebo				
Difference (mepolizumab - placebo)	-4.3		-9.0	
95% CI	(-53.27, 44.60)		(-60.06, 42.06)	
p-value	0.862		0.730	
FVC (mL)				
n [1]	384	381	384	381
n [2]	374	367	341	342
LS mean (SE)	2620.8 (23.86)	2626.2 (24.03)	2618.9 (26.20)	2571.6 (26.21)
LS mean change (SE)	23.9 (23.86)	29.3 (24.03)	22.0 (26.20)	-25.3 (26.21)
Mepolizumab 100 mg versus placebo				
Difference (mepolizumab - placebo)	5.4		-47.3	
95% CI	(-61.05, 71.90)		(-120.06, 25.48)	
p-value	0.873		0.203	

[1] Number with analysable data for one/more time points.
[2] Number with analysable data at given time point.
Note: Analysis performed using mixed model repeated measures with covariates of treatment group, geographic region, baseline, smoking status (current versus former smoker), visit plus interaction terms for visit by baseline and visit by treatment group. Estimates are based on weighting applied to each level of class variable determined from observed proportions.
Note: Includes data reported up to Week 52.

Ancillary analyses

Subgroup Analyses

Subgroup analyses of the primary endpoint were conducted for the pre-specified subgroups defined in the SAP Section 4.10. Additionally, there was a post-hoc subgroup analysis performed by COPD type as assessed by the investigator.

Table 42 Summary of subgroup analyses for rate of moderate/severe exacerbations (mITT Population)

Category/Subgroup	Placebo		Mepolizumab 100 mg		Comparison of Mepo versus PBO
	n [1]	Rate (95% CI)	n [1]	Rate (95% CI)	Rate ratio (95% CI)
Screening BEC category					
<0.5 GI/L	249	0.98 (0.84, 1.15)	239	0.81 (0.69, 0.95)	0.82 (0.66, 1.03)
≥0.5 GI/L	152	1.03 (0.82, 1.29)	164	0.77 (0.61, 0.97)	0.75 (0.54, 1.04)
Age					
40-<65 years	173	0.76 (0.61, 0.94)	142	0.71 (0.56, 0.90)	0.93 (0.68, 1.28)
≥65 years	228	1.17 (1.00, 1.38)	260	0.85 (0.72, 1.00)	0.72 (0.58, 0.90)
Sex					
Female	126	1.08 (0.87, 1.34)	127	0.81 (0.65, 1.02)	0.75 (0.55, 1.03)
Male	275	0.99 (0.84, 1.16)	276	0.78 (0.66, 0.92)	0.79 (0.63, 0.98)
Race					
African American/African heritage	5	0.85 (0.19, 3.73)	5	0.10 (0.01, 0.89)	0.11 (0.01, 1.04)
White	335	1.07 (0.93, 1.23)	338	0.81 (0.70, 0.93)	0.75 (0.62, 0.92)
Asian	56	0.66 (0.45, 0.97)	56	0.72 (0.49, 1.05)	1.09 (0.65, 1.84)
Other	5	Non-estimable	4	Non-estimable	-
Baseline Body Mass Index					
BMI ≤20 kg/m²	27	0.84 (0.52, 1.36)	19	1.33 (0.83, 2.14)	1.58 (0.77, 3.22)
BMI >20 to ≤30 kg/m²	264	1.07 (0.91, 1.25)	272	0.73 (0.61, 0.86)	0.68 (0.54, 0.85)
BMI >30 kg/m²	110	0.85 (0.66, 1.10)	112	0.88 (0.69, 1.13)	1.04 (0.73, 1.47)
History of Exacerbations					
Exacerbations in Previous Year					
≤2	312	0.91 (0.78, 1.05)	294	0.67 (0.57, 0.79)	0.74 (0.59, 0.92)
3	64	1.11 (0.80, 1.53)	70	1.21 (0.90, 1.64)	1.10 (0.71, 1.70)
≥4	25	2.33 (1.58, 3.43)	39	1.37 (0.96, 1.95)	0.59 (0.35, 1.00)
Severe Exacerbations in Previous Year					
0	324	0.89 (0.77, 1.03)	315	0.70 (0.60, 0.82)	0.79 (0.64, 0.97)
≥1	77	1.59 (1.24, 2.03)	88	1.19 (0.93, 1.52)	0.75 (0.53, 1.06)
Extrinsic Factors					
Geographic Region					
Europe	127	1.61 (1.32, 1.96)	132	1.23 (1.01, 1.51)	0.77 (0.58, 1.01)
Eastern Europe	61	0.60 (0.41, 0.89)	61	0.40 (0.25, 0.62)	0.66 (0.37, 1.18)
Asia	34	1.14 (0.76, 1.69)	33	0.96 (0.63, 1.46)	0.84 (0.47, 1.53)
South America	84	0.81 (0.61, 1.07)	82	0.64 (0.47, 0.87)	0.79 (0.52, 1.20)
North America	51	1.19 (0.77, 1.82)	49	0.81 (0.52, 1.27)	0.68 (0.37, 1.27)
Rest of World	44	0.59 (0.39, 0.89)	46	0.65 (0.45, 0.95)	1.10 (0.64, 1.88)
Smoking Status at Screening					
Current	111	0.99 (0.75, 1.30)	111	0.67 (0.50, 0.91)	0.68 (0.45, 1.03)
Former	290	1.02 (0.88, 1.18)	292	0.84 (0.72, 0.97)	0.82 (0.67, 1.00)
Symptoms of Chronic Bronchitis [2]					
No	126	0.88 (0.71, 1.09)	113	0.64 (0.50, 0.82)	0.73 (0.54, 0.99)
Yes	267	1.06 (0.90, 1.24)	277	0.83 (0.71, 0.98)	0.79 (0.63, 0.99)
Cardiovascular Disease Comorbidities					
Yes	97	1.46 (1.18, 1.81)	103	1.05 (0.84, 1.31)	0.72 (0.53, 0.97)
COPD Disease Severity					
mMRC Score at Screening					
<2	98	0.93 (0.72, 1.22)	89	0.81 (0.61, 1.08)	0.87 (0.59, 1.27)
≥2	301	1.00 (0.86, 1.15)	310	0.78 (0.67, 0.91)	0.78 (0.64, 0.97)
Severity of Airflow Limitation (GOLD Guidelines)					
Mild: ≥80% predicted	3	Non-estimable	2	Non-estimable	-
Moderate: ≥50%-<80% predicted	181	0.59 (0.47, 0.74)	168	0.51 (0.40, 0.65)	0.85 (0.62, 1.18)
Severe: ≥30%-<50% predicted	160	1.48 (1.24, 1.77)	180	1.09 (0.92, 1.30)	0.73 (0.57, 0.94)
Very severe: <30% predicted	57	1.38 (1.00, 1.91)	53	1.11 (0.79, 1.57)	0.81 (0.50, 1.30)
Treatment duration					
Fixed duration subgroup	175	0.89 (0.71, 1.10)	170	0.75 (0.60, 0.94)	0.85 (0.62, 1.16)
Variable duration subgroup	226	1.07 (0.92, 1.26)	233	0.80 (0.68, 0.95)	0.75 (0.60, 0.93)
COPD type (post-hoc) [3]					
Emphysema	132	1.12 (0.91, 1.39)	120	0.92 (0.74, 1.16)	0.82 (0.61, 1.12)
Chronic bronchitis	168	0.87 (0.71, 1.08)	170	0.60 (0.48, 0.76)	0.69 (0.51, 0.93)
Emphysema and chronic bronchitis	62	1.07 (0.77, 1.49)	81	0.88 (0.65, 1.19)	0.82 (0.53, 1.26)
Neither emphysema nor chronic bronchitis	37	0.92 (0.64, 1.31)	32	0.84 (0.56, 1.24)	0.91 (0.54, 1.54)

[1] n = number in subgroup
[2] As assessed by SGRQ-C questionnaire.
[3] As assessed by investigator.

Shrinkage Estimation Methods

Shrinkage estimation methods were carried out in addition to the conventional subgroup analyses using Bayesian Hierarchical Modeling [Jones, 2011].

In general, the shrinkage estimates of treatment effect were similar to those from the conventional subgroup analyses, and also similar across the 3 shrinkage estimates. The treatment effect estimates for race: African American/African Heritage were most impacted with the shrinkage estimation methods as expected given the relatively small sample size of this subgroup. There were 3 subgroups

where the conventional subgroup analysis concluded a treatment effect in favour of placebo while shrinkage estimates showed the effect to be in favour of mepolizumab (geographic region: Rest of World, number of exacerbations in the previous year: 3, and race: Asian.

Studies MEA117106 and MEA117113

Study title:

Study MEA117106: Mepolizumab vs. Placebo as add-on treatment for frequently exacerbating COPD patients

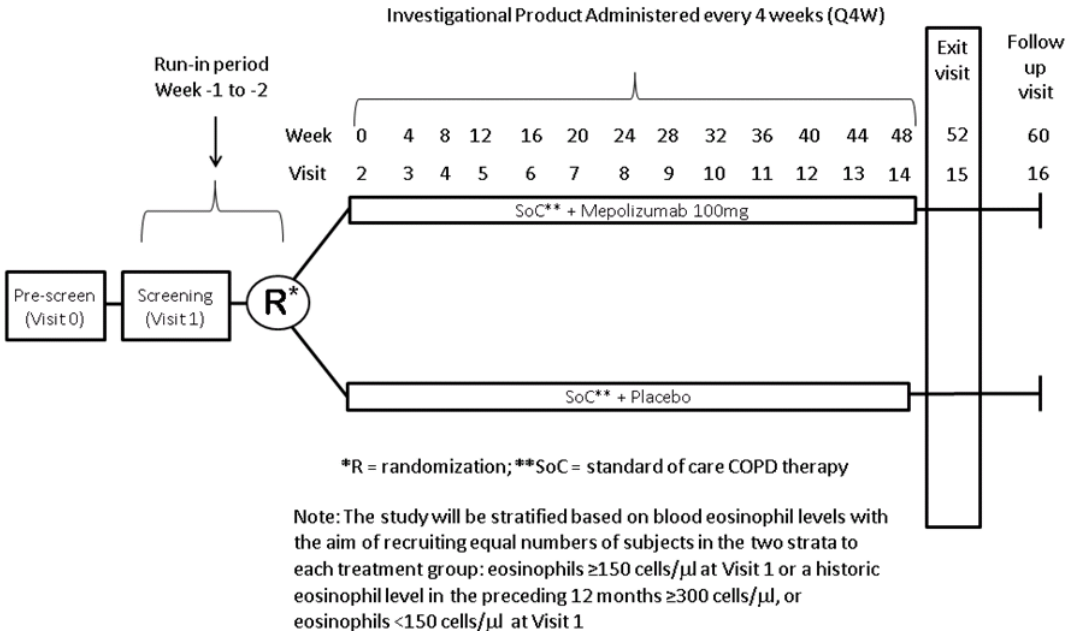
Study MEA117113: Mepolizumab vs. Placebo as add-on treatment for frequently exacerbating COPD patients characterized by eosinophil level

Methods

METREX-MEA117106

METREX was a phase III multicentre, randomized, placebo-controlled, double-blind, parallel-group study that evaluated the efficacy and safety of mepolizumab 100 mg compared with placebo in subjects with COPD at risk of exacerbation. Study treatments were administered by SC injection every 4 weeks. Subjects remained on their SoC COPD medications throughout the entire study (i.e., all study periods). The total duration of subject participation 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.

Figure 31 METREX-MEA117106 Study Schematic

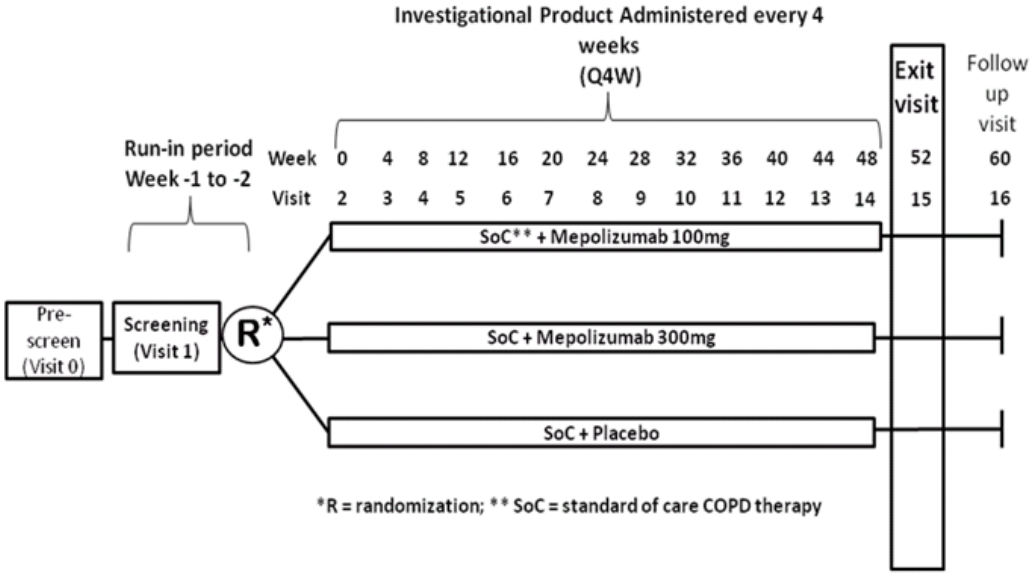


METREO-MEA117113

This was a multicentre, randomized, placebo-controlled, double-blind, parallel-group, study that evaluated the efficacy and safety of two doses of mepolizumab (100 mg and 300 mg) compared with placebo in subjects with COPD at risk of exacerbation. Study treatments were administered by SC injection every 4 weeks. Subjects remained on their SoC COPD medications throughout the

entire study (i.e., all study periods). The total duration of subject participation 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.

Figure 32 METREO-MEA117113 Study Schematic



The design of both studies was similar and therefore they are discussed together. Any differences are clearly highlighted.

The target global enrolment was approximately 800 randomized subjects for **METREX** but 660 for **METREO**. The total duration of subject participation 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. **METREX** was a 2-armed trial with participants randomized at a ratio of 1:1 into 100mg mepolizumab or placebo. **METREO** was a 3-armed trial with participants randomized into either placebo, 100mg of mepolizumab or 300mg of mepolizumab at a ratio of 1:1:1. A subject was considered to have completed study treatment if he/she continued to take study treatment until Visit 14 (Week 48) and completed Visit 15 (Week 52). A subject will be considered to have completed the study if they continue to participate in the study until Visit 15 (Week 52) regardless of whether they continue to take IP.

Studies were conducted in three parts.

Part 1 (Week -1 to -2): Subjects who met all eligibility criteria at Screening (Visit 1) entered a run-in period during which time baseline subject-reported electronic diary (eDiary) data were captured. Laboratory assessments, including a haematology assessment for determination of Screening eosinophil levels, were collected at Visit 1 prior to determining eligibility at Visit 2.

Part 2 (Week 0 to 52): Compared mepolizumab 100mg SC to placebo at 1:1 ratio (MEA117106) or mepolizumab 100mg SC or mepolizumab 300mg SC to placebo (MEA117113) at 1:1:1 ratio every 4 weeks for 8 weeks with final exit visit at week 52.

Part 3 (Week 52 to 60): A final follow up visit at week 60 was conducted for all participants. 8 weeks following the completion of the treatment period.

METREX

The study was stratified based on blood eosinophil levels with the aim of recruiting equal numbers of subjects in the 2 strata to each treatment group. Subjects were assigned to strata according to the following: ≥high Stratum: Blood eosinophils ≥150 cells/μL at Visit 1 (Screening) **OR** historic blood eosinophil level in the preceding 12 months ≥300 cells/μL <Low Stratum: Blood eosinophils <150 cells/μL at Visit 1 (Screening) AND no evidence of a blood eosinophil level in the preceding 12 months ≥300 cells/μL

METREO

Subjects were required to have a baseline blood eosinophil count ☐150 cells/ mL or a documented history of a blood eosinophil count of ≥300 cells/ mL in the past 12 months. Subjects in the treatment arms were assigned either 100mg or 300mg mepolizumab.

Study participants

Male or female (not of child-bearing potential or using acceptable method of birth control per protocol) subjects ≥40 years of age with confirmed **COPD (independent of smoking status and history)** who provided informed consent to participate were eligible provided all of the following criteria were met:

- **COPD diagnosis and severity:** Clinically documented history of COPD for at least 1 year as defined by the American Thoracic Society (ATS)/European Respiratory Society [Celli, 2004]
    - A measured pre- and post-salbutamol FEV1/FVC ratio of <0.70 to confirm the diagnosis of COPD
    - A measured post-salbutamol FEV1>20% and ≤80% of predicted normal values calculated using National Health and Nutrition Examination Survey (NHANES) III reference equations [Hankinson, 1999; Hankinson, 2010]
- **History of exacerbations:** A well-documented history in the 12 months prior to Screening of:
    - At least 2 moderate COPD exacerbations. Moderate was defined as the use of systemic corticosteroids (intramuscular [IM], IV, or oral) **and/or** treatment with antibiotics. Prior use of antibiotics alone did not qualify as a moderate exacerbation unless the use was specifically for the treatment of worsening symptoms of COPD.

OR

    - At least 1 severe COPD exacerbation. Severe was defined as requiring hospitalization.

  Note At least 1 exacerbation must have occurred while the subject was taking ICS plus LABA plus LAMA.

- **Concomitant COPD therapy:** A well-documented requirement for optimized SoC background therapy that included ICS plus two additional COPD medications (i.e., triple therapy) for the 12 months prior to Screening and met the following criteria:
    - Immediately prior to Screening, minimum of 3 months of use of an ICS at a dose ≥500 mcg/day FP dose equivalent plus LABA plus LAMA.

  For subjects who were not continually maintained on ICS plus LABA plus LAMA for the entire 12 months prior to Visit 1, use of following was allowed (but not in the 3 months immediately prior to Screening):

a. Inhaled corticosteroid at a dose ≥500 mcg/day FP dose equivalent plus

b. A LABA or a LAMA and

c. Use of at least 1 other class of COPD medication suggested by the 2013 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for subjects who were prone to exacerbation (e.g., PDE-4 inhibitors, methylxanthines, or a combination of short acting beta2-agonist [SABA] and short acting muscarinic antagonist [SAMA]). **Note:** Subjects must be willing to stay on their SoC COPD medication for the duration of the study.

- **Smoking status:** Subjects with confirmed COPD are eligible to participate independent of their smoking status and smoking history, i.e. current smokers, never smokers or ex-smokers can be enrolled into the study. Note: Pipe and/or cigar use cannot be used to calculate pack-year history.
    - **Current smokers** are defined as those with a history of cigarette smoking of ≥10 pack-years [number of pack years = (number of cigarettes per day / 20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years)].
    - **Former smokers** are defined as those who meet the definition of a current smoker but have stopped smoking for at least 6 months prior to Visit 1.
    - **Never smokers** are those that do not meet the definition of a current or former smoker.

Exclusion criteria

- **Asthma:**
    - Current and Former Smokers: Subjects with a current diagnosis of asthma (those with a prior history are eligible if they meet inclusion criteria for a current diagnosis of COPD)
    - Never-Smokers: Subjects with any history of asthma
- **Other respiratory disorders:** The investigator must judge that COPD is the primary diagnosis accounting for the clinical manifestations of the lung disease. Subjects with α1-antitrypsin deficiency as the underlying cause of COPD are excluded. Also, excluded are subjects with active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, primary pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases. Subjects are also excluded if maintenance use of bi-level positive airway pressure is required for the treatment of respiratory disorder.
- **COPD stability:** Subjects with pneumonia, exacerbation, lower respiratory infection within the 4 weeks prior to Visit 1.
- **Lung resection:** Subjects with lung volume reduction surgery within the 12 months prior to Visit 1.
- **Pulmonary rehabilitation program:** Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1. Subjects who are in the maintenance phase of a pulmonary rehabilitation program are not excluded.
- **Oxygen:** Subjects receiving treatment with oxygen more than 4.0L/min. While breathing supplemental oxygen, subjects should demonstrate an oxyhemoglobin saturation greater than or equal to 89%.

- **12-lead ECG finding:** An abnormal and significant ECG finding from the 12-lead ECG conducted at Visit 1 if considered to be clinically significant by the Investigator. Specific ECG findings that preclude subject enrolment are found in Appendix 2. 12-lead ECGs will be over-read by a centralized independent cardiologist to assist in consistent evaluation of subject eligibility. Results from the 12-lead ECG over-read must be received prior to assessing eligibility at Visit 2.
- **Unstable or life threatening cardiac disease:** Subjects with any of the following would be excluded: Myocardial infarction or unstable angina in the last 6 months, Unstable or life threatening cardiac arrhythmia requiring intervention in the last 3 months, New York Heart Association (NYHA) Class IV Heart failure
- **Other diseases/abnormalities:** Subjects with (historical or) current evidence of clinically significant, neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease) or haematological abnormalities that are uncontrolled. Significant is defined as any disease that, in the opinion of the investigator, would put the safety of the subject at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study.
- **Eosinophilic disease:** Subjects with other conditions that could lead to elevated eosinophils such as Hypereosinophilic syndromes including Eosinophilic Granulomatosis with Polyangiitis (EGPA, also known as Churg-Strauss Syndrome), or Eosinophilic Esophagitis.
- **Parasitic infection:** Subjects with a known, pre-existing parasitic infestation within 6 months prior to Visit 1 are also excluded.
- **Malignancy:** A current malignancy or previous history of cancer in remission for less than 12 months prior to Visit 1 (Subjects that had localized carcinoma of the skin or cervix which was resected for cure will not be excluded).
- **Immunodeficiency:** A known immunodeficiency (e.g human immunodeficiency virus - HIV), other than that explained by the use of corticosteroids taken for COPD.
- **Liver disease:** Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, esophageal or gastric varices, or persistent jaundice), cirrhosis, and known bilary abnormalities (with the exception of Gilbert' s syndrome or asymptomatic gallstones). Chronic stable hepatitis B and C are acceptable if subject otherwise meets entry criteria (e.g., presence of hepatitis B surface antigen or positive hepatitis C test result within 3 months of screening)
- **Monoclonal antibodies**: Subjects who have received any monoclonal antibody within 5 half-lives of Visit 1
- **Investigational medications:** Subjects who have received an investigational drug within 30 days of Visit 1, or within 5 drug half-lives of the investigational drug, whichever is longer (this also includes investigational formulations of a marketed product).
- **Hypersensitivity:** Subjects with a known allergy or intolerance to another monoclonal antibody or biologic including history of anaphylaxis to another biologic

Treatments

MEA117113/MEA117106

The treatment of both studies was similar and therefore they are discussed together. Any differences are clearly highlighted.

Table 43 Studies MEA117113/MEA117106 Treatments

	• MEA117113	• MEA117106
Mepolizumab	• Two dose levels were tested in the study i.e. 300 mg and 100 mg given as subcutaneous injection every 4 weeks for a total of 13 administrations. • Lyophilized mepolizumab was reconstituted with Sterile Water prior to injection.	• One dose level was tested in the study i.e. • 100 mg given as subcutaneous injection every 4 weeks for a total of 13 administrations. • Lyophilized mepolizumab was reconstituted with Sterile Water prior to injection.
Placebo	Placebo of 0.9% sodium chloride solution was administered once every 4 weeks via sub-cutaneous injection (1 mL).	
Prior medication	ICS plus two additional COPD medications for 12 months prior to Screening and minimum of 3 months of use of an ICS plus LABA plus LAMA	
Background Medication **Permitted Medications**	The following medications were permitted for use throughout the study if taken as SoC: ICS, LABA, LAMA, Methylxanthines, PDE-4 inhibitor, oral corticosteroids (OCS; chronic use), antibiotics for the short-term (≤14 days) mucolytic such as acetylcysteine and long term oxygen therapy. Some additional Non-COPD Medications were allowed which were considered that they do not have influence study results.	
Prohibited Medications	The following COPD medications and non-drug therapies were prohibited during the randomized study treatment period: Acute phase of pulmonary rehabilitation (at any time during the study including run-in) Long-term (≥14 days) systemic antibiotic therapy Omalizumab [Xolair] Other monoclonal antibodies Experimental anti-inflammatory drugs (non-biologicals) Immunosuppressive medications, including but not limited to: Corticosteroids intramuscular, long-acting depot if used to treat a condition other than COPD Methotrexate, troleandomycin, cyclosporine, azathioprine	

	Oral gold Chemotherapy used for conditions other than COPD Regular systemic (oral or parenteral) corticosteroids for the treatment of conditions other than COPD Other investigational products (subjects must have not received investigational products for 1 month or 5 half-lives prior to Screening, whichever was longer) Bilevel positive airway pressure other than in an acute care setting Radiation therapy for 12 months prior to Screening and throughout the study
Reliever Medication	Salbutamol metered dose inhaler (MDI) was provided for use as rescue medication by the study centres throughout the study. For the treatment of COPD and COPD exacerbations, Ipratropium bromide, Mucolytics, oral corticosteroids (≤14-days), and antibiotics (≤14-days) were permissible as rescue medication throughout the study. Any course of OCS or antibiotics started within 7-days of finishing a previous course was considered as treatment for the same exacerbation.
Administration Method	All doses of study treatment were administered at the study site by designated blinded site staff via sub-cutaneous injection.

Objectives and Outcomes/endpoints

Table 44 Supporting Studies MEA117113/MEA117106 Objectives and Endpoints

	MEA117113	MEA117106
Primary Objective	To evaluate the efficacy and safety of mepolizumab 100 mg and 300 mg subcutaneous (SC) given every 4 weeks compared with placebo on the frequency of moderate and severe exacerbations in subjects with COPD at high risk of exacerbations despite the use of optimized standard of care background therapy.	To evaluate the efficacy and safety of mepolizumab 100 mg subcutaneous (SC) given every 4 weeks compared with placebo on the frequency of moderate and severe exacerbations in COPD subjects with blood eosinophil counts ≥150 cells/μL at Screening or ≥300 cells/μL in the 12 months prior, at high risk of exacerbations despite the use of optimized SoC background therapy.
Secondary Objectives	To evaluate other efficacy assessments of mepolizumab 100 mg and 300 mg SC compared with placebo on changes in quality of life, health care utilization, and symptoms.	To evaluate the efficacy and safety of mepolizumab 100 mg SC given every 4 weeks compared with placebo on the frequency of moderate and severe exacerbations in COPD

		subjects at high risk of exacerbations despite the use of optimized SoC background therapy, who may or may not have had elevated blood eosinophils. To evaluate other efficacy assessments of mepolizumab 100 mg SC compared with placebo on changes in health care utilization, COPD symptoms, quality of life, and lung function.
Primary Endpoint	Efficacy endpoints were measured from Baseline (Visit 2) through Week 52 (Visit 15). • Frequency of moderate/severe exacerbations.	
Secondary Endpoints	• Time to first moderate/severe exacerbation. • Frequency of COPD exacerbations requiring emergency department (ED) visits and/or hospitalizations. • Change from baseline mean St. George's Respiratory Questionnaire COPD (SGRQ-C) Total Score. • Change from baseline COPD Assessment Test (CAT) score.	
Other Efficacy Endpoints	• Frequency of moderate COPD exacerbations. • Frequency of severe COPD exacerbations. • Occasions of rescue medication use. • Change from baseline mean SGRQ-C domain scores. • Proportion of SGRQ-C responders (reported as SGRQ scores; subjects with ≥4-point improvement from baseline). • Change from baseline in trough FEV1 and FVC. • Change from baseline EuroQol Questionnaire (EQ-5D-5L) score. • Frequency of COPD exacerbations requiring re-hospitalization within 30 days.	
Additional Efficacy Endpoints	• Proportion of CAT responders (subjects with ≥2 point improvement from baseline). • Proportion of subjects with FEV1 increase ≥100 mL. • Number of nighttime awakenings. • Percentage of nights with no awakenings.	

Note: A symptom-defined potential exacerbation was identified and categorised the same across the three studies.

Sample size

MEA117106 study

A total of 400 participants, were to be randomized in a 1:1 ratio to the following treatment groups:

- Mepolizumab 100 mg (+ SoC)
- Placebo (+ SoC)

For the purposes of sample size calculation, the assumed rate of moderate/severe exacerbations per annum for the placebo group was 2, following a negative binomial distribution with a dispersion parameter of 0.8.

Sample size calculations were based on the testing of superiority of mepolizumab 100 mg to placebo for the rate of moderate/severe exacerbations per year with a desired power of 90% at a 2-sided 4% significance level. The calculated sample size needed was 344 total participants, based on a true population reduction of 35%. The smallest observed reduction relative to placebo which would result in a statistically significant result was 23%. The sample size calculation also accounted for loss to early withdrawal at a rate of 12.5% of participants-year data equating to 56 total participants. This brought the total sample size to 400 total participants.

To allow for a treatment comparison in all subjects, an additional 400 subjects (who do not meet mITT-H criteria) would be randomized in a 1:1 ratio to both treatment arms. The treatment comparison for all subjects, at a 1% two-sided significance level with 400 subjects per treatment arm will provide 90% power to detect a statistically significant difference assuming a true population reduction of 30%.

MEA117113 study

A total of 660 participants, were to be randomized in a 1:1:1 ratio to the following treatment groups:

- Mepolizumab 100 mg (+ SoC)
- Mepolizumab 300 mg (+ SoC)
- Placebo (+ SoC)

For the purposes of sample size calculation, the assumed rate of moderate/severe exacerbations per annum for the placebo group was 2, following a negative binomial distribution with a dispersion parameter of 0.8.

Sample size calculations were based on the testing of superiority of mepolizumab 100 mg and mepolizumab 300 mg to placebo for the rate of moderate/severe exacerbations per year with a desired power of 90% at a 2-sided 5% significance level. The calculated sample size need was 573 total participants, based on a true population reduction of 35%. The smallest observed reduction relative to placebo which would result in a statistically significant result for one comparison was 24% and for both comparisons was 21%. The sample size calculation also accounted for loss to early withdrawal at a rate of 12.5% of participants-year data equating to 87 total participants. This brought the total sample size to 660 total participants.

Randomisation

Studies MEA117113/MEA117106

Table 45 Studies MEA117113/MEA117106 Randomisation

	MEA117113	MEA117106
Randomisation and Stratification	The target global enrolment was approximately 660 randomized subjects. At Visit 2 those subjects who met the randomization eligibility criteria were randomized in a 1:1:1 ratio, 100 mg mepolizumab, 300 mg mepolizumab, and placebo.	A total of 800 subjects were planned to be randomized with a randomization ratio of 1:1 placebo:mepolizumab 100 mg SC according to two strata, with 400 subjects in the high stratum and 400 in the low stratum. Randomized subjects were stratified into two groups: subjects with blood eosinophils of ≥150 cells/μL at Screening or ≥300 cells/μL in prior 12 months (**high stratum)** and subjects with blood eosinophils of <150 cells/μL at Screening with no evidence of ≥300 cells/μL in prior 12 months **(low stratum).**
Randomisation System	Subjects were assigned to study treatment in accordance with the randomization schedule generated using the GSK-validated randomization software RandAll NG. Subjects were randomized using an interactive voice response system (IVRS). A separate randomization schedule was created for each country. Equal numbers of subjects were allocated to each treatment.	

Blinding (masking)

Table 46 MEA117113/MEA117106 Blinding

	MEA117113	MEA117106
Blinding Methods	• Double-blinding. • Mepolizumab was prepared at each site by a designated unblinded staff member who remained independent of the study assessments. • Study treatments were identical in appearance, and each was administered as three separate SC injections to maintain the blind of investigators, subjects, and those involved in the administration of treatment and study assessments • After randomization, blood eosinophil counts were blinded to the sponsor and site staff. • Treatment codes could be unblinded by the investigator or treating physician only in the case of a medical emergency or in the event of a serious medical condition.	

Statistical methods

MEA117106 study

Statistical Analysis Plan

The original SAP dated 20-Feb-2017 was amended once, with Amendment 1 dated 15-Mar-2017. The amendment to the original SAP is comprehensively described in section 1.1 of SAP Amendment 1.

Changes to the planned analyses

There were four changes to the protocol planned analyses detailed in SAP Amendment 1. These were detailed in section 2.1 of SAP Amendment 1. Particular changes that affect the efficacy/safety analyses are summarized below:

- Safety Population defined as all randomised subjects who receive at least one dose of trial medication.
- Per-Protocol in high stratum (PPH) defined as all subjects in the mITT-H population not identified as protocol deviators with respect to criteria that are considered to impact the primary efficacy endpoint.
- Implementation of a multiple testing procedure with a prespecified order of testing of endpoints, allowing for transfer of alpha from the primary endpoint comparison in the overall population, if the null hypothesis is rejected, to the high stratum. Overall experiment wise Type 1 error rate controlled at 5%.

Analysis Populations

Population	Definition/Criteria	Analyses Evaluated
All Subjects Enrolled Population (ASE)	All subjects enrolled and for whom a record exists on the study database.	Reasons for Screen Failures and Run-in Failures
Modified Intent-to-Treat Population (mITT)	All randomised subjects who receive at least one dose of trial medication. Subjects are analysed by randomised treatment.	Efficacy endpoints in the overall population
Modified Intent-to-Treat Population – High Stratum (mITT-H)	A subset of the mITT population, consisting of subjects with blood eosinophil counts ≥150 cells/µl at Screening or ≥300 cells/µl in the 12 months prior. Analysis by randomised treatment.	Efficacy endpoints for subjects in the high stratum
Modified Intent-to-Treat Population – Low Stratum (mITT-L)	A subset of the mITT population, consisting of subjects with blood eosinophil counts <150 cells/µl at Screening and no evidence of blood eosinophil ≥300 cells/µl in the 12 months prior. Descriptive analysis by randomised treatment.	Efficacy endpoints for subjects in the low stratum
Safety Population (Safety)	All randomised subjects who receive at least one dose of trial medication. Subjects are analysed based on actual treatment received for more than 50% of treatment administrations.	Safety endpoints

Per Protocol Population (PP)	All subjects in the mITT population who have not been identified as protocol deviators with respect to criteria that are considered to impact the primary efficacy endpoint. The decision to exclude a subject from the PP Population will be made prior to the unblinding of treatment codes.	Supplementary analysis of the primary endpoint
Per Protocol – High Stratum (PP-H)	All subjects in the mITT-H population not identified as protocol deviators with respect to criteria that are considered to impact the primary efficacy endpoint.	Supplementary analysis of the primary endpoint in the high stratum
PK Population	All subjects in the Safety population for whom at least one PK sample was obtained, analysed and measurable.	Pharmacokinetics
PD Population	All subjects in the Safety population who also have a baseline PD measurement and at least one post-treatment PD measurement.	Pharmacodynamics

Analysis of Primary Endpoint

The primary endpoint for this study was the frequency of moderate/severe exacerbations in subjects in the high stratum over the 52-week treatment period.

The primary analysis was to include both on- and off-treatment data for a de facto estimand of treatment effect, with any missing data considered missing at random (MAR). The analysis was carried out for subjects in the high stratum and the overall population.

The primary analysis model was a generalised linear model with a log-link function. The model included geographic region, smoking status, baseline disease severity (as % predicted post-bronchodilator FEV1), and number of moderate/severe exacerbations in previous year (≤2, 3, 4+ as ordinal) as covariates. For the analysis of the overall population actual stratum was also included as a covariate. The analysis model also included an offset variable of $\log_e$ (length of time in study) which reflects the period of time in the study for which exacerbation data has been recorded for inclusion in the analysis.

For the assessment of the primary endpoint, the model estimated mean rate of exacerbations per year was calculated using the observed marginal distributions of the study population covariates. The treatment comparison was assessed by the rate ratio of the model estimated mean rates of exacerbations per year for mepolizumab vs placebo with associated 95% confidence interval and p-value.

Sensitivity Analyses

A number of sensitivity analyses for the primary endpoint were to be conducted to test the robustness of the assumption of data missing at random.

Sensitivity Analysis 1:

Missing data, for subjects who had early withdrawal, was to be imputed for the period of time between withdrawal to Week 52 based on a J2R assumption. The multiple imputation was to be based on pattern mixture models. This was done by fitting the primary analysis negative binomial generalised linear model to the observed data and sampling the model parameters of the independent variables from the posterior distribution. For subjects who had early withdrawal, the number of future exacerbations was estimated from the model parameters assuming they followed

the event rate of the reference group. This imputed number of exacerbations was then combined with the observed data for a complete dataset that was analysed per the primary analysis. This was repeated multiple times and the results combined using Rubin's rules.

An additional analysis was to be performed using the same multiple imputation method but with imputed data based on the off-treatment data collected from subjects who continued in the study following treatment discontinuation.

A tipping point analysis was also planned to be carried out. Subjects who had early withdrawal had missing data imputed for the period of time between withdrawal and Week 52 based on a range of values for the rate of exacerbations per year. The missing data was to be imputed based on a range of increases in exacerbation rates relative to the estimated rates obtained within each arm under the missing at random assumption. The imputed exacerbation rates would vary independently for the mepolizumab and placebo arms and was to include scenarios where participants with missing data in the mepolizumab arm have worse outcomes than participants in the placebo arm.

Sensitivity Analysis 2:

The primary analysis was to be repeated including only on-treatment exacerbation data for a de jure estimand.

Sensitivity Analysis 3:

The primary analysis was to be repeated excluding data from subjects where there was potential accidental unblinding of treatment assignment.

Sensitivity Analysis 4:

The primary analysis was to be repeated using the subjects' randomised strata as assigned at randomisation.

Sensitivity Analysis 5:

The primary analysis was to be repeated excluding subjects who reported a change in smoking status during the study.

Sensitivity Analysis 6:

The primary analysis was to be repeated excluding subjects participating from Site ID: 209775.

Analysis of ranked Secondary Endpoints

Time to first moderate/severe exacerbation:

A Cox proportional hazards model was to be fitted to the time to first moderate/severe exacerbation for each treatment group with covariates of geographic region, smoking status, baseline disease severity (as % predicted post-bronchodilator FEV1), and number of moderate/severe exacerbations in previous year (≤2, 3, ≥4 as ordinal).

Frequency of exacerbations requiring ED visit and/or hospitalisation:

This analysis was to follow the same analysis method as the primary endpoint.

Change from baseline SGRQ-C Total Score/Change from baseline CAT score:

A mixed model repeated measures, with visit fitted as a categorical variable and adjusting for baseline value of endpoint, smoking status, geographic region, visit-by-baseline interaction, and

visit-by-treatment interaction was to be used to analyse change from baseline for each endpoint. Actual stratum was to be included as a covariate for the analysis of the overall population.

Subgroup Analyses

Subgroup analyses were to be performed on the primary endpoint following the same analysis method. The following subgroups have been pre-specified:

- Age (40-<65, ≥65 years)
- Sex (Male, Female)
- Race (African American/African Heritage, White, Asian, Other)
- Baseline BMI (Low, Medium, High)
- Geographic Region (Europe, Eastern Europe, United States, Rest of World)
- Exacerbations in the previous year (≤2, 3, ≥4 exacerbations)
- Severe exacerbations in the previous year (0, ≥1 exacerbation)
- Screening blood eosinophil categories (<150, ≥150-<300, ≥300-<500, ≥500
- cells/µl)
- Screening blood eosinophils (<150, ≥150, ≥300, ≥500 cells/µl)
- Blood Eosinophil Inclusion Criteria (Historical and Screening, Screening only, Historical only)
- Smoking status at Screening (Current, Never, Ex-Smoker)
- Cardiovascular Disease Comorbidity (Any past or current medical condition under Cardiac Disorders)
- Other Comorbidity (Any past or current medical condition other than under
- Cardiac Disorders)
- Modified Medical Research Council score at Screening (<2, ≥2)
- Severity of Airflow Limitation (Mild, Moderate, Severe, Very Severe)

Type I Error Control

The statistical analysis of the primary and selected secondary endpoints accounted for multiplicity and controlled the familywise Type I error rate at a 2-sided alpha level of 0.05 in a pre-specified hierarchy of testing endpoints.

For the primary endpoint analysis, the treatment comparison for subjects in the high stratum was to be tested at an alpha level of 0.04, and the treatment comparison for the overall population was to be tested at an alpha level of 0.01.

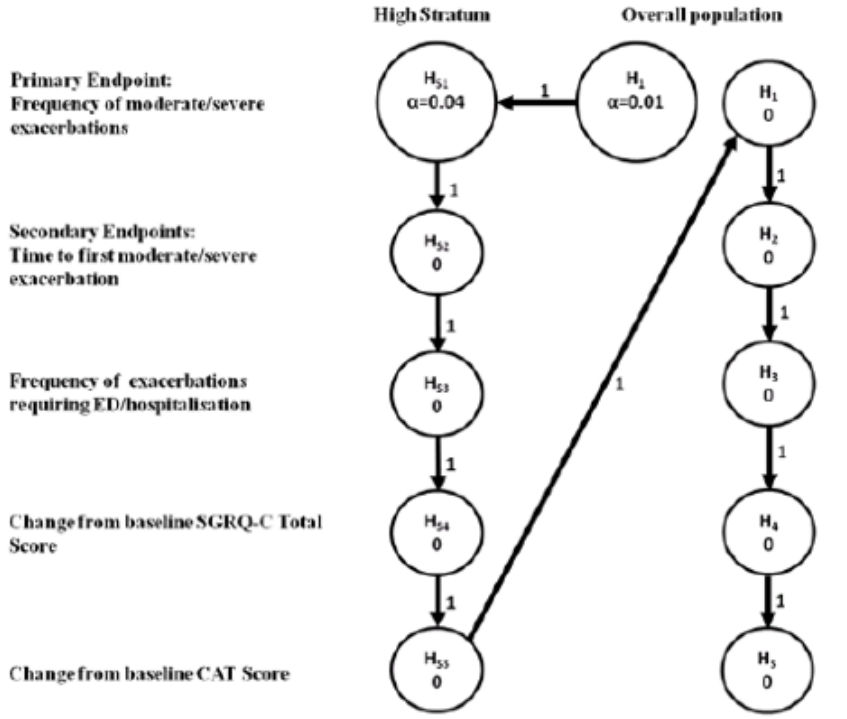
If the null hypothesis for the primary endpoint is rejected in the overall population, then the primary endpoint and subsequent secondary endpoints were to be tested at an alpha level of 0.05 in the high stratum. If the null hypothesis for the primary endpoint is not rejected in the overall population, then the primary endpoint and subsequent secondary endpoints were to be tested at an alpha level of 0.04 in the high stratum.

If the primary endpoint comparison in the high stratum is significant, then testing of the secondary endpoints in the high stratum will continue in the following order:

1. Time to first moderate/severe exacerbation
2. Frequency of exacerbations requiring ED visit and/or hospitalisation
3. Change from baseline SGRQ-C Total Score
4. Change from baseline CAT score

Testing would only progress to the next endpoint of the hierarchy if there was a significant result in the comparison at the immediately preceding endpoint.

Figure 33 Graphical illustration of multiple testing procedure: primary and secondary endpoints in the overall population and high stratum



Note: Hs_i corresponds to the i=1 to 5 null hypotheses for the primary and secondary endpoints in the high stratum; H_i corresponds to the i=1 to 5 null hypotheses for the primary and secondary endpoints in the overall population.

Interim Analysis

There was no interim analysis planned for this study.

MEA117113 study

Statistical Analysis Plan

The original SAP dated 20-Feb-2017 was amended once, with Amendment 1 dated 15-Mar-2017. The amendment to the original SAP is comprehensively described in section 2.1 of SAP Amendment 1.

Changes to planned analyses

There were four changes to the protocol planned analyses detailed in SAP Amendment 1. These were detailed in section 2.1 of SAP Amendment 1. Particular changes that affect the efficacy/safety analyses are summarized below:

- Safety Population defined as all randomised subjects who receive at least one dose of trial medication.

Analysis Populations

Population	Definition/Criteria	Analyses Evaluated
All Subjects Enrolled Population (ASE)	All participants enrolled and for whom a record exists on the study database.	Reasons for Screen Failures and Run-in Failures
Modified Intent-to-Treat Population (mITT)	All randomised participants who receive at least one dose of trial medication. Participants are analysed by randomised treatment.	Efficacy endpoints
Safety Population (Safety)	All randomised participants who receive at least one dose of trial medication. Participants are analysed based on actual treatment received for more than 50% of treatment administrations.	Safety endpoints
Per Protocol Population (PP)	All participants in the mITT population who have not been identified as protocol deviators with respect to criteria that are considered to impact the primary efficacy endpoint. The decision to exclude a subject from the PP Population will be made prior to the unblinding of treatment codes.	Supplementary analysis of the primary endpoint
PK Population	All participants in the Safety population for whom at least one PK sample was obtained, analysed and measurable.	Pharmacokinetics
PD Population	All participants in the Safety population who also have a baseline PD measurement and at least one post-treatment PD measurement.	Pharmacodynamics

Analysis of Primary Endpoint

The primary endpoint for this study was the frequency of moderate/severe exacerbations over the 52-week treatment period.

The primary analysis was to include both on- and off-treatment data for a de facto estimand of treatment effect, with any missing data considered missing at random (MAR).

The primary analysis model was a generalised linear model with a log-link function. The model included geographic region, smoking status, baseline disease severity (as % predicted post-bronchodilator FEV1), and number of moderate/severe exacerbations in previous year (≤2, 3, 4+ as ordinal) as covariates. The analysis model also included an offset variable of $\log_e$ (length of time in study) which reflects the period of time in the study for which exacerbation data has been recorded for inclusion in the analysis.

For the assessment of the primary endpoint, the model estimated mean rate of exacerbations per year was calculated using the observed marginal distributions of the study population covariates. The treatment comparison was assessed by the rate ratio of the model estimated mean rates of exacerbations per year for mepolizumab vs placebo with associated 95% confidence interval and p-value.

Sensitivity Analyses

A number of sensitivity analyses for the primary endpoint were to be conducted to test the robustness of the assumption of data missing at random.

Sensitivity Analysis 1:

Missing data, for participants who had early withdrawal, was to be imputed for the period of time between withdrawal to week 52 based on a jump to reference (J2R) assumption. The multiple imputation was to be based on pattern mixture models. This was done by fitting the primary analysis negative binomial generalised linear model to the observed data and sampling the model parameters of the independent variables from the posterior distribution. For participants who had early withdrawal, the number of future exacerbations was estimated from the model parameters assuming they followed the event rate of the reference group. This imputed number of exacerbations was then combined with the observed data for a complete dataset that was analysed per the primary analysis. This was repeated multiple times and the results combined using Rubin's rules.cAn additional analysis was to be performed using the same multiple imputation method but with imputed data based on the off-treatment data collected from participants who continued in the study following treatment discontinuation. A tipping point analysis was also planned to be carried out. Participants who had early withdrawal had missing data imputed for the period of time between withdrawal and week 52 based on a range of values for the rate of exacerbations per year. The missing data was to be imputed based on a range of increases in exacerbation rates relative to the estimated rates obtained within each arm under the missing at random assumption. The imputed exacerbation rates would vary independently for the mepolizumab and placebo arms and was to include scenarios where participants with missing data in the mepolizumab arm have worse outcomes than participants in the placebo arm.

Sensitivity analysis 2:

The primary analysis was to be repeated including only on-treatment exacerbation data for a de jure estimand.

Sensitivity Analysis 3:

The primary analysis was to be repeated excluding data from participants where there was potential accidental unblinding of treatment assignment.

Sensitivity Analysis 4:

The primary analysis was to be repeated using the participant's randomised strata as assigned at randomisation.

Sensitivity Analysis 5:

The primary analysis was to be repeated excluding participants who reported a change in smoking status during the study.

Analysis of ranked Secondary Endpoints

Time to first moderate/severe exacerbation:

A Cox proportional hazards model was to be fitted to the time to first moderate/severe exacerbation for each treatment group with covariates of geographic region, smoking status, baseline disease severity (as % predicted post-bronchodilator FEV1), and number of moderate/severe exacerbations in previous year (≤2, 3, ≥4 as ordinal).

Frequency of exacerbations requiring ED visit and/or hospitalisation:

This analysis was to follow the same analysis method as the primary endpoint.

Change from baseline SGRQ-C Total Score/Change from baseline CAT score:

A Mixed Model Repeated Measures, with visit fitted as a categorical variable and adjusting for baseline value of endpoint, smoking status, geographic region, visit-by-baseline interaction, and visit-by-treatment interaction was to be used to analyse change from baseline for each endpoint.

Subgroup Analyses

Subgroup analyses were to be performed on the primary endpoint following the same analysis method. The following subgroups have been pre-specified:

- Age (40-<65, ≥65 years)
- Sex (Male, Female)
- Race (African American/African Heritage, White, Asian, Other)
- Baseline BMI (Low, Medium, High)
- Geographic Region (Europe, Eastern Europe, Asia, South America, United States, Rest of World)
- Exacerbations in the previous year (≤2, 3, ≥4 exacerbations)
- Severe exacerbations in the previous year (0, ≥1 exacerbation)
- Screening blood eosinophil categories (<150, ≥150-<300, ≥300-<500, ≥500
- cells/µl)
- Screening blood eosinophils (<150, ≥150, ≥300, ≥500 cells/µl)
- Blood Eosinophil Inclusion Criteria (Historical and Screening, Screening only, Historical only)
- Smoking status at Screening (Current, Never, Ex-Smoker)
- Cardiovascular Disease Comorbidity (Any past or current medical condition under Cardiac Disorders)
- Other Comorbidity (Any past or current medical condition other than under
- Cardiac Disorders)
- Modified Medical Research Council score at Screening (<2, ≥2)
- Severity of Airflow Limitation (Mild, Moderate, Severe, Very Severe)

Type I Error Control

There were two treatment comparisons for each of the primary and key secondary endpoints:

- Mepolizumab 100mg SC vs. placebo
- Mepolizumab 300mg SC vs. placebo

Multiplicity arising from these comparisons was controlled using an approach corresponding to a Hochberg testing procedure to control the familywise type I error rate within each endpoint. A hierarchical approach for secondary endpoints was used to ensure the overall experiment-wise error rate was no greater than a 1-sided alpha level of 0.025.

The hierarchy of the primary and key secondary endpoints that were tested was as follows:

1. Frequency of moderate/severe exacerbations (primary endpoint)
2. Time to first moderate/severe exacerbation
3. Frequency of exacerbations requiring ED visit and/or hospitalisation.
4. Change from baseline mean total SGRQ-C score
5. Change from baseline CAT score

Starting with the primary endpoint, significance was to be declared if both comparisons were significant at the unadjusted 1-sided alpha level of 0.025 or if at least one of the comparisons was significant at the unadjusted 1-sided alpha level of 0.0125. The next endpoint in the hierarchy was only to be tested if both of the primary endpoint comparisons were significant at the unadjusted 1-sided alpha level of 0.025. Testing was to continue to the next endpoint in the hierarchy where a 1-

sided alpha level of 0.025 was to be used. If both treatment comparisons do not demonstrate significance, then testing will not continue. If only one of the tests achieves significance, then this must be demonstrated at the 1-sided alpha level of 0.0125.

Interim Analysis

There was no interim analysis planned for this study.

Results

Participant flow

Study MEA117106:

A total of 1161 subjects were enrolled. In total, 324 (28%) were not randomized, primarily for not meeting the inclusion/exclusion criteria (11%) required for participation in the study. Among the 837 subjects randomized, 1 subject was withdrawn without receiving study treatment. Therefore, 836 randomized subjects were included and 734 (88%) completed the study. Fewer subjects withdrew from the high stratum (12% and 9% from the placebo and mepolizumab 100 mg groups, respectively) compared with the low stratum (15% for both groups). One subject (<1%) withdrew from the study after completing study treatment. The most common reasons for study withdrawal were voluntary withdrawal by the subject (6%) and AE (5%). Incidences were generally similar between treatment groups. Twenty-eight subjects (3%) died during the study.

Table 47 Subject Disposition (Study MEA117106, mITT-H, mITT-L, and mITT Populations)

	Number (%) of Subjects				
	High Stratum		Low Stratum		
	Placebo N=229	Mepolizumab 100 mg SC N=233	Placebo N=190	Mepolizumab 100 mg SC N=184	Total N=836
Completed study	202 (88)	213 (91)	162 (85)	157 (85)	734 (88)
Withdrawn from study	27 (12)	20 (9)	28 (15)	27 (15)	102 (12)
Completed treatment	0	0	1 (<1)	0	1 (<1)
Primary reason for study withdrawal[1]					
Withdrawal by subject	15 (7)	10 (4)	10 (5)	11 (6)	46 (6)
Decision by subject or proxy	0	0	0	1 (<1)	1 (<1)
Adverse event	10 (4)	7 (3)	11 (6)	11 (6)	39 (5)
Death[2]	6 (3)	6 (3)	7 (4)	9 (5)	28 (3)
Physician decision	2 (<1)	2 (<1)	2 (1)	2 (1)	8 (<1)
Lack of efficacy	0	1 (<1)	3 (2)	2 (1)	6 (<1)
Exacerbation	0	1 (<1)	0	0	1 (<1)
Lost to follow-up	0	0	2 (1)	1 (<1)	3 (<1)

1. Subjects could have only one primary reason for withdrawal.
2. Four additional subjects died after completing the study (Subject 002897 and 00303 in the placebo-high stratum group, Subjects 001300 and 005598 in the placebo-low stratum group). One subject (Subject 009315) died after being withdrawn from the study for a reason other than death.

Overall, 82% of subjects completed study treatment. In the high stratum, the percentage of subjects who prematurely discontinued study treatment was lower in the mepolizumab 100 mg group (13%) compared with the placebo group (19%), with a higher incidence of withdrawal by subject in the placebo group (7%) compared with the mepolizumab group (3%). This finding was not observed in the low stratum; the percentage of subjects who prematurely discontinued study treatment was similar in the mepolizumab 100 mg group (19%) compared with the placebo group (22%). Of the 18% of subjects who discontinued study treatment in the overall population, 6% completed the study with off-treatment assessments. Like study withdrawals, the most common

reasons for prematurely discontinuing study treatment were AE (8%) and voluntary withdrawal by the subject (6%).

Table 48 Study Treatment Completion Status (Study MEA117106, mITT-H, mITT-L, and mITT Populations)

	Number (%) of Subjects				
	High Stratum		Low Stratum		
Study Treatment Completion Status	Placebo N=229	Mepolizumab 100 mg SC N=233	Placebo N=190	Mepolizumab 100 mg SC N=184	Total N=836
Completed treatment	185 (81)	203 (87)	148 (78)	149 (81)	685 (82)
Discontinued treatment	44 (19)	30 (13)	42 (22)	35 (19)	151 (18)
Discontinued treatment & study at same time	25 (11)	17 (7)	22 (12)	25 (14)	89 (11)
Discontinued treatment & continued in study	19 (8)	13 (6)	20 (11)	10 (5)	62 (7)
Completed study with off-treatment assessments	17 (7)	10 (4)	15 (8)	8 (4)	50 (6)
Did not complete study	2 (<1)	3 (1)	5 (3)	2 (1)	12 (1)
Primary reason for treatment discontinuation[1]					
Adverse event	20 (9)	16 (7)	15 (8)	13 (7)	64 (8)
Withdrawal by subject	16 (7)	8 (3)	11 (6)	15 (8)	50 (6)
Lack of efficacy	5 (2)	2 (<1)	8 (4)	2 (1)	17 (2)
Physician decision	2 (<1)	1 (<1)	4 (2)	2 (1)	9 (1)
Protocol deviation	1 (<1)	3 (1)	3 (2)	0	7 (<1)
Lost to follow-up	0	0	1 (<1)	2 (1)	3 (<1)
Protocol-defined stopping criteria[2]	0	0	0	1 (<1)	1 (<1)

1. Subjects could have only one primary reason for treatment discontinuation.
2. ECG abnormality (100 ms)

Study MEA117113:

Total of 1071 subjects were enrolled at 168 sites in 15 countries.

Of the 1071 subjects enrolled in the study, 396 (37%) were not randomized, primarily for not meeting the continuation/randomization criteria (21%) at the end of the run-in period or not meeting the inclusion/exclusion criteria (9%) required for participation in the study. A total of 675 subjects were randomized. However, one subject randomized to the mepolizumab 300 mg group was withdrawn without receiving study treatment, thus there were 674 subjects included in the study. Most subjects (87%) completed the study. Fewer subjects withdrew from the mepolizumab 100 mg (8%) and 300 mg (13%) groups compared with the placebo group (18%). Five subjects (<1%) were withdrawn from the study after completing study treatment. The most common reasons for study withdrawal were adverse event (6%) and voluntary withdrawal by the subject (5%).

Table 49 Subject Disposition (Study MEA117113, mITT Population)

Disposition	Number (%) of Subjects			
		Mepolizumab		
	Placebo N=226	100 mg SC N=223	300 mg SC N=225	Total N=674
Completed study	185 (82)	206 (92)	195 (87)	586 (87)
Withdrawn from study	41 (18)	17 (8)	30 (13)	88 (13)
Completed treatment	1 (<1)	2 (<1)	2 (<1)	5 (<1)
Primary reason for study withdrawal[1]				
Adverse event	18 (8)	7 (3)	13 (6)	38 (6)
Death[2]	7 (3)	4 (2)	8 (4)	19 (3)
Withdrawal by subject	15 (7)	7 (3)	11 (5)	33 (5)
Physician decision	3 (1)	3 (1)	2 (<1)	8 (1)
Lack of efficacy	3 (1)	0	3 (1)	6 (<1)
Exacerbation	1 (<1)	0	0	1 (<1)
Lost to follow-up	2 (<1)	0	1 (<1)	3 (<1)

1. Subjects could have only one primary reason for withdrawal
2. Two additional subjects in the placebo group (Subject 001703 and Subject 002716) died after completing the study

Overall, 81% of subjects completed study treatment. Fewer subjects in the mepolizumab 100 mg (12%) and 300 mg (19%) groups prematurely discontinued study treatment compared with the placebo group (25%). Time to study treatment discontinuation was longer in the mepolizumab 100 mg and 300 mg groups compared with the placebo group. Of the 19% of subjects who discontinued study treatment, 6% completed the study with off-treatment assessments (Table 50). Like study withdrawals, the most common reasons for prematurely discontinuing study treatment were adverse event (9%) and voluntary withdrawal by the subject (6%).

Table 50 Study Treatment Completion Status (Study MEA117113, mITT Population)

Study Treatment Completion Status	Number (%) of Subjects			
		Mepolizumab		
	Placebo N=226	100 mg SC N=223	300 mg SC N=225	Total N=674
Completed treatment	170 (75)	196 (88)	183 (81)	549 (81)
Discontinued treatment	56 (25)	27 (12)	42 (19)	125 (19)
Discontinued treatment & study at same time	35 (15)	9 (4)	23 (10)	67 (10)
Discontinued treatment & continued in study	21 (9)	18 (8)	19 (8)	58 (9)
Completed study with off-treatment assessments	16 (7)	12 (5)	14 (6)	42 (6)
Did not complete study	5 (2)	6 (3)	5 (2)	16 (2)
Primary reason for treatment discontinuation[1]				
Adverse event	27 (12)	9 (4)	25 (11)	61 (9)
Withdrawal by subject	16 (7)	11 (5)	11 (5)	38 (6)
Lack of efficacy	6 (3)	2 (<1)	2 (<1)	10 (1)
Physician decision	2 (<1)	3 (1)	1 (<1)	6 (<1)
Protocol deviation	2 (<1)	0	1 (<1)	3 (<1)
Lost to follow-up	1 (<1)	1 (<1)	1 (<1)	3 (<1)
Protocol-defined stopping criteria[2]	1 (<1)	1 (<1)	0	2 (<1)
Investigator site closed	1 (<1)	0	1 (<1)	2 (<1)

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

Recruitment

Study MEA117106:

A total of 1161 subjects were enrolled at 117 sites in 16 countries. The US had the largest subject enrolment (154 subjects, 13%) followed by Canada (153 subjects, 13%) and Mexico (137 subjects, 12%). The remaining 13 countries had <10% enrolment at each site. The number of subjects enrolled per center ranged from 1 to 45.

Initiation Date: 15 April 2014

Completion Date: 17 January 2017

Study MEA117113:

Total of 1071 subjects were enrolled at 168 sites in 15 countries. The US had the largest subject enrollment (198 subjects, 18%) followed by Germany (122 subjects, 11%), Argentina (107 subjects, 10%), and Republic of Korea (104 subjects, 10%). The remaining 11 countries had <10% enrolment at each site. The number of subjects enrolled per center ranged from 1 to 19.

Initiation Date: 24 April 2014

Completion Date: 16 January 2017

Conduct of the study

Study amendments

Study MEA117106

The original protocol, dated 03 December 2013, was amended twice and these amendments applied to all study centres.

Protocol Amendment 1, dated 20 December 2013: Section 5.1 of the protocol was updated to reflect that study treatment would be administered by a single SC injection.

Protocol Amendment 2, dated 05 March 2014, made the following key changes:

- Removed the SF-36 health survey as a Health Outcomes endpoint and assessment.
- Updated the chest X-ray randomization criterion for Germany indicating that if a chest X-ray within 6 months prior to Screening was not available, the subject was not eligible for the study.
- Added radiation therapy within the 12 months prior to Screening and anytime during the study as a prohibited therapy.
- Removed the electrocardiogram (ECG) at Visit 2 (Randomization Visit/Baseline) since one was performed at Screening.
- Clarified the definition of severe exacerbations from just those that required in-patient hospitalization to include those that also resulted in death.
- Updated the ECG exclusion criteria to clarify that sustained **and non-sustained** supraventricular tachycardia (>100 bpm) would preclude a subject from entering the trial.
- Added that an ECG finding of sustained supraventricular tachycardia (>100 bpm) would result in a subject being prematurely discontinued from study treatment post-randomization.
- Added adverse event (AE) causality assessment guidance language regarding the investigator's obligation to assess the relationship between study treatment and the occurrence of each AE/SAE.

Study MEA117113

The original protocol, dated 02 December 2013, was amended once and this amendment applied to all study centers.

Protocol Amendment 1, dated 05 March 2014, made the following key changes:

- Removed the SF-36 health survey as a Health Outcomes endpoint and assessment.
- Updated the chest X-ray randomization criterion for Germany indicating that if a chest X-ray within 6 months prior to Screening was not available, the subject was not eligible for the study.
- Added radiation therapy within the 12 months prior to Screening and anytime during the study as a prohibited therapy.
- Removed the electrocardiogram (ECG) at Visit 2 (Randomization Visit/Baseline) since one was performed at Screening.
- Clarified the definition of severe exacerbations from just those that required inpatient hospitalization to include those that also resulted in death.

Protocol deviations

Study MEA117106

Critical or major protocol deviations occurred in 47% of subjects. In the high stratum, the incidence of protocol deviations was lower in the treatment group (45%) compared to the placebo group (53%) but was similar in the low stratum. The majority of these subjects (43%) had deviations that did not lead to exclusion. The most frequent deviations were in the assessments and/or procedures category (33%). 2% of subjects had protocol deviations related to study blinding or unblinding due to accidental reports access. These subjects were not excluded but sensitivity analysis excluding them was performed. 9% of subjects had protocol deviations that led to exclusion from the per-protocol population, primarily for not meeting eligibility criteria (4%) or the use of a prohibited medication or device (3%).

Table 51 Protocol Deviations that Led to Exclusion from the Per-Protocol Population (Study MEA117106, mITT-H, mITT-L, and mITT Populations)

	Number (%) of Subjects				
	High Stratum		Low Stratum		
Protocol Deviation Category	Placebo N=229	Mepolizumab 100 mg SC N=233	Placebo N=190	Mepolizumab 100 mg SC N=184	Total N=836
Any protocol deviation(s)	121 (53)	105 (45)	90 (47)	79 (43)	395 (47)
Led to exclusion from PP Population	20 (9)	25 (11)	15 (8)	14 (8)	74 (9)
Eligibility criteria not met	8 (3)	14 (6)	7 (4)	6 (3)	35 (4)
Prohibited medication or device	9 (4)	10 (4)	4 (2)	4 (2)	27 (3)
Assessments and/or procedures	4 (2)	2 (<1)	3 (2)	3 (2)	12 (1)
Visit, assessment, or time point window	0	0	1 (<1)	1 (<1)	2 (<1)
Other protocol deviation category	0	0	0	0	0

Study MEA117113

Critical or major protocol deviations were recorded for 42% of subjects. The incidence of protocol deviations was similar across the treatment groups. The majority of these subjects (37%) had deviations that did not lead to exclusion. The most frequent deviations were error in assessments and/or procedures (15%) and incorrect visit, assessment, or timepoint window (12%). 3% of subjects had protocol deviations related to study blinding or unblinding procedures due mostly to accidental report access, incorrect drug supply and storage. These subjects were not excluded but sensitivity analysis was performed. 7 % of subjects had protocol deviations that led to exclusion exclusion from the per-protocol population, primarily for not meeting study eligibility criteria (5%).

Table 52 Protocol Deviations that Led to Exclusion from the Per-Protocol Population (Study MEA117113, mITT Population)

Protocol Deviation Category	Number (%) of Subjects			
		Mepolizumab		
	Placebo N=226	100 mg SC N=223	300 mg SC N=225	Total N=674
Any protocol deviation(s)	100 (44)	86 (39)	95 (42)	281 (42)
Led to exclusion from PP Population	19 (8)	13 (6)	16 (7)	48 (7)
Eligibility criteria not met	15 (7)	11 (5)	10 (4)	36 (5)
Prohibited medication or device	2 (<1)	1 (<1)	6 (3)	9 (1)
Visit, assessment, or timepoint window	1 (<1)	0	0	1 (<1)
Other protocol deviation category	1 (<1)	3 (1)	1 (<1)	5 (<1)

Note: Subjects could have more than one protocol deviation

GCP findings

Study MEA117106

One site in Poland had deviations due to non-GCP compliance because of deficiencies in source documentation practices and enrolment of potentially ineligible subjects into the studies. Sensitivity analysis excluding this site revealed similar results to the primary analysis.

Study MEA117113

No GCP issues were reported.

Baseline data

Study MEA117106

Demographic and Other Baseline Characteristics

The study population was primarily White (81%) and more than half were male (62%); the mean age was 65.4 years. Slightly more than half of subjects (55%) were ≥65 years of age. American Indian or Alaskan Native subjects, subjects with multiple race, and subjects of Hispanic/Latino ethnicity comprised 8%, 8%, and 20%, respectively, of the mITT Population. Mean BMI was 26.9 kg/m2.

Table 53 Demographics (Study MEA117106, mITT-H, mITT-L, and mITT Populations)

Demographic	High Stratum		Low Stratum		Total
	Placebo N=229	Mepolizumab 100 mg SC N=233	Placebo N=190	Mepolizumab 100 mg SC N=184	N=836
Gender, n (%)					
Female	79 (34)	84 (36)	77 (41)	76 (41)	316 (38)
Male	150 (66)	149 (64)	113 (59)	108 (59)	520 (62)
Age, years					
Mean (SD)	65.3 (8.53)	65.2 (8.36)	65.2 (8.62)	66.1 (9.14)	65.4 (8.64)
Min, Max	40, 83	43, 83	39, 85	40, 85	39, 85
Age Group, n (%)					
<40 yr [1]	0	0	1 (<1)	0	1 (<1)
40-64 yr	107 (47)	107 (46)	85 (45)	75 (41)	374 (45)
≥65 yr	122 (53)	126 (54)	104 (55)	109 (59)	461 (55)
Race, n (%)					
White	192 (84)	199 (85)	145 (76)	144 (78)	680 (81)
American Indian or Alaskan Native	14 (6)	19 (8)	22 (12)	14 (8)	69 (8)
Multiple	16 (7)	11 (5)	19 (10)	23 (13)	69 (8)
Black or African American	4 (2)	2 (<1)	3 (2)	2 (1)	11 (1)
Asian	3 (1)	2 (<1)	1 (<1)	1 (<1)	7 (<1)
Ethnicity, n (%)					
Not Hispanic/Latino	193 (84)	194 (83)	138 (73)	140 (76)	665 (80)
Hispanic/Latino	36 (16)	39 (17)	52 (27)	44 (24)	171 (20)
Body Mass Index, kg/m²					
Mean (SD)	26.718 (5.5786)	27.128 (5.7218)	27.362 (5.5704)	26.502 (6.0935)	26.931 (5.7325)
Min, Max	15.57, 42.13	14.81, 60.12	16.14, 45.53	14.34, 54.88	14.34, 60.12

1. Subject 008374 was 39 years old.

COPD

Overall, the majority of subjects (69%) had COPD for <10 years and the mean duration was 9.3 years Nearly all subjects (95%) met the criteria for GOLD Group D. The study population was affected by their breathlessness and had poor lung function; 82% had an mMRC score of ≥2, 67% of subjects had severe or very severe airflow limitation, and 12% were using Long Term Oxygen Therapy (LTOT) despite receiving ICS-based triple maintenance therapy. Seventy-four percent of subjects had co-morbidities other than cardiovascular and 26% had cardiovascular co-morbidities. Within the high stratum, COPD history and characteristics were similar between the mepolizumab 100 mg group and the placebo group; treatment groups were well balanced between both strata. In addition, the overall mean baseline SGRQ Total Score and CAT Score were 54.9 and 18.9, respectively, and were indicative of a poor health-related quality of life and significant disease impact on health status. Within each stratum, blood eosinophil levels were similar between treatment groups at Screening.

Table 54 COPD History and Baseline Disease Characteristics (Study MEA117106, mITT-H, mITT-L, and mITT Populations)

	High Stratum		Low Stratum		
	Placebo N=229	Mepolizumab 100 mg SC N=233	Placebo N=190	Mepolizumab 100 mg SC N=184	Total N=836
COPD History and Characteristics					
Duration of COPD, years					
Mean (SD)	9.5 (6.31)	9.5 (6.72)	9.2 (6.78)	8.8 (5.40)	9.3 (6.35)
Median	8.0	8.0	8.0	8.0	8.0
Min, Max	1, 32	1, 35	1, 46	1, 25	1, 46
GOLD Group D [1], n (%)	218 (95)	219 (94)	181 (95)	178 (97)	796 (95)
Severity of airflow limitation [2], n (%)					
Mild: ≥80% predicted	2 (<1)	3 (1)	1 (<1)	1 (<1)	7 (<1)
Moderate: ≥50% to <80% predicted	66 (29)	78 (33)	60 (32)	64 (35)	268 (32)
Severe: ≥30% to <50% predicted	120 (52)	114 (49)	93 (49)	85 (46)	412 (49)
Very severe: <30% predicted	41 (18)	38 (16)	36 (19)	34 (18)	149 (18)
mMRC Score [3] at Screening					
Mean (SD)	2.3 (0.89)	2.2 (0.83)	2.2 (0.86)	2.3 (0.86)	2.2 (0.86)
<2, n (%)	46 (20)	45 (19)	34 (18)	29 (16)	154 (18)
≥2, n (%)	183 (80)	188 (81)	156 (82)	155 (84)	682 (82)
Long-term Oxygen Therapy Use [4], n (%)	24 (10)	27 (12)	20 (11)	30 (16)	101 (12)
Screening blood eosinophils, cells/μL					
Geometric mean (std logs)	290 (0.562)	250 (0.575)	70 (0.778)	70 (0.699)	140 (0.946)
SGRQ Total Score [5]					
n	223	228	184	182	817
Mean (SD)	56.5 (15.81)	54.1 (17.54)	53.8 (17.52)	55.1 (16.93)	54.9 (16.95)

	High Stratum		Low Stratum		
	Placebo N=229	Mepolizumab 100 mg SC N=233	Placebo N=190	Mepolizumab 100 mg SC N=184	Total N=836
CAT Score [6]					
n	218	224	180	179	801
Mean (SD)	19.6 (7.74)	18.5 (7.78)	18.4 (7.69)	18.8 (7.39)	18.9 (7.66)
Co-morbid Disease Characteristics, n (%)					
Cardiovascular co-morbidity [7]	61 (27)	58 (25)	51 (27)	49 (27)	219 (26)
Other co-morbidity [8]	176 (77)	174 (75)	140 (74)	126 (68)	616 (74)
Ever diagnosed with GERD [9]	52 (23)	46 (20)	33 (17)	39 (21)	170 (20)
CCI [10]					
1 to 2	7 (3)	8 (3)	8 (4)	7 (4)	30 (4)
3 to 4	112 (49)	124 (53)	101 (53)	90 (49)	427 (51)
≥5	109 (48)	101 (43)	81 (43)	87 (47)	378 (45)
Missing	1 (<1)	0	0	0	1 (<1)

1. 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
2. Classification based on post-bronchodilator FEV_1 at Screening, GOLD Guidelines for COPD.
3. Modified Medical Research Council Score
4. LTOT use was classified as taking oxygen therapy for 40 days or more.
5. SGRQ Total Score range 0-100 with higher scores indicating poor health-related quality of life
6. CAT score range 0-40 with higher scores indicating greater COPD disease impact
7. Subjects with any past or current medical conditions under Cardiac Disorders.
8. Subjects with any past or current medical conditions other than under Cardiac Disorders.
9. GERD=gastroesophageal reflux disease.
10. Total score (predicted 10 year survival probability): 1 to 2 (>90%), 3 to 4 (>53%), ≥5 (<21%).

Exacerbation

The majority of subjects (77%) had at least 2 moderate exacerbations; 31% had at least 1 severe exacerbation with 78% of patients treated with systemic corticosteroids and/or antibiotics. In the high stratum, exacerbation history in the previous 12 months was similar between the mepolizumab 100 mg group and the placebo group; treatment groups were similar between both strata. Overall, COPD exacerbations in the previous 12 months were primarily caused by respiratory illnesses (59% respiratory infection, 28% common cold, 22% upper respiratory infection other than common cold, and 22% lower respiratory infection) or cold air/cold weather (22%). The historical causes of exacerbations were well balanced between treatment groups and both strata.

Table 55 Exacerbation History (Study MEA117106, mITT-H, mITT-L, and mITT Populations)

Number of Exacerbations in Previous 12 Months	High Stratum		Low Stratum		
	Placebo N=229	Mepolizumab 100 mg SC N=233	Placebo N=190	Mepolizumab 100 mg SC N=184	Total N=836
Moderate/Severe Exacerbations, n (%)					
0	0	0	0	0	0
≥1	229 (100)	233 (100)	190 (100)	184 (100)	836 (100)
1	27 (12)	23 (10)	11 (6)	12 (7)	73 (9)
2	122 (53)	128 (55)	117 (62)	107 (58)	474 (57)
≥3	80 (35)	82 (35)	62 (33)	65 (35)	289 (35)
Mean (SD)	2.5 (1.23)	2.6 (1.34)	2.6 (1.17)	2.5 (1.07)	2.5 (1.22)
Median	2.0	2.0	2.0	2.0	2.0
Min, Max	1, 10	1, 10	1, 9	1, 8	1, 10
Moderate Exacerbations, n (%)					
0	37 (16)	41 (18)	16 (8)	22 (12)	116 (14)
≥1	192 (84)	192 (82)	174 (92)	162 (88)	720 (86)
1	24 (10)	24 (10)	17 (9)	15 (8)	80 (10)
2	101 (44)	106 (45)	109 (57)	93 (51)	409 (49)
≥3	67 (29)	62 (27)	48 (25)	54 (29)	231 (28)
Severe Exacerbations, n (%)					
0	153 (67)	157 (67)	139 (73)	131 (71)	580 (69)
≥1	76 (33)	76 (33)	51 (27)	53 (29)	256 (31)
1	62 (27)	46 (20)	39 (21)	37 (20)	184 (22)
2	9 (4)	17 (7)	8 (4)	12 (7)	46 (6)
≥3	5 (2)	13 (6)	4 (2)	4 (2)	26 (3)

Number of Exacerbations in Previous 12 Months	High Stratum		Low Stratum		
	Placebo N=229	Mepolizumab 100 mg SC N=233	Placebo N=190	Mepolizumab 100 mg SC N=184	Total N=836
Treated w/ systemic corticosteroids and/or antibiotics, no ED visit/hospitalization, n (%)					
0	53 (23)	56 (24)	32 (17)	45 (24)	186 (22)
≥1	176 (77)	177 (76)	158 (83)	139 (76)	650 (78)
1	27 (12)	21 (9)	19 (10)	16 (9)	83 (10)
2	92 (40)	103 (44)	101 (53)	81 (44)	377 (45)
≥3	57 (25)	53 (23)	38 (20)	42 (23)	190 (23)
ED Visit but no hospitalization, n (%)					
0	196 (86)	201 (86)	162 (85)	146 (79)	705 (84)
≥1	33 (14)	32 (14)	28 (15)	38 (21)	131 (16)
1	13 (6)	19 (8)	8 (4)	14 (8)	54 (6)
2	17 (7)	10 (4)	15 (8)	16 (9)	58 (7)
≥3	3 (1)	3 (1)	5 (3)	8 (4)	19 (2)
Hospitalization-general ward, n (%)					
0	157 (69)	166 (71)	143 (75)	134 (73)	600 (72)
≥1	72 (31)	67 (29)	47 (25)	50 (27)	236 (28)
1	61 (27)	41 (18)	37 (19)	36 (20)	175 (21)
2	6 (3)	14 (6)	6 (3)	11 (6)	37 (4)
≥3	5 (2)	12 (5)	4 (2)	3 (2)	24 (3)
Hospitalization-intensive care unit, n (%)					
0	222 (97)	219 (94)	184 (97)	178 (97)	803 (96)
≥1	7 (3)	14 (6)	6 (3)	6 (3)	33 (4)
1	7 (3)	12 (5)	6 (3)	4 (2)	29 (3)
2	0	2 (<1)	0	2 (1)	4 (<1)
≥3	0	0	0	0	0

Smoking history

95% were classified as current or former smokers; subjects had a mean of 45.6 smoking pack years. In the high stratum, smoking history was similar between the mepolizumab 100 mg group and the placebo group; treatment groups were similar between both strata.

Screening and Baseline Lung Function Tests

Overall, Screening lung function tests showed lung function impairment with mean pre- and post-bronchodilator FEV1 values of 1117.0 mL and 1207.4 mL and percent-predicted FEV1 values of

41.0% and 44.3%, respectively. Mean percent FEV1 reversibility was low at 9.1%. In the high stratum, screening lung function test results were similar between the mepolizumab 100 mg group and the placebo group; treatment groups were similar between both strata. Baseline lung function test results were generally similar to screening values.

Medical conditions

In addition to COPD, most subjects (67%) had current medical conditions at Screening based on a pre-specified checklist (see Section 4.6.1). The most frequently reported conditions were hypertension (47%), hypercholesterolemia (29%), diabetes mellitus (14%), and osteoporosis (12%).

Study MEA117113:

Demographic and Other Baseline Characteristics

The study population was primarily White (80%) and predominantly male (66%); the mean age was 65.1 years. Slightly more than half of the subjects (53%) were ≥65 years of age. Asian subjects and subjects of Hispanic/Latino ethnicity comprised 18% and 16%, respectively, of the mITT Population. All 8 African American subjects were enrolled at US sites representing 10% of the 79 randomized US subjects (Table 1.4 and Listing 10). Mean BMI was 26.3 kg/m2. Demographics were balanced across the treatment groups with the exception of a larger proportion of female subjects in the mepolizumab 100 mg group (41%) compared with the placebo (31%) or mepolizumab 300 mg (30%) groups.

Table 56 Demographics (Study MEA117113, mITT Population)

Demographic	Placebo N=226	Mepolizumab 100 mg SC N=223	Mepolizumab 300 mg SC N=225	Total N=674
Gender, n (%)				
Female	70 (31)	91 (41)	67 (30)	228 (34)
Male	156 (69)	132 (59)	158 (70)	446 (66)
Age, years				
Mean (SD)	65.8 (8.64)	64.8 (9.06)	64.8 (8.96)	65.1 (8.89)
Min, Max	43, 88	42, 86	45, 85	42, 88
Age Group, n (%)				
40-64 yr	101 (45)	104 (47)	110 (49)	315 (47)
≥65 yr	125 (55)	119 (53)	115 (51)	359 (53)
Race, n (%)				
White	182 (81)	178 (80)	182 (81)	542 (80)
Asian	42 (19)	41 (18)	41 (18)	124 (18)
Black or African American	2 (<1)	4 (2)	2 (<1)	8 (1)
Ethnicity, n (%)				
Not Hispanic/Latino	192 (85)	187 (84)	188 (84)	567 (84)
Hispanic/Latino	34 (15)	36 (16)	37 (16)	107 (16)
Body Mass Index, kg/m²				
Mean (SD)	25.4 (5.0)	27.1 (6.2)	26.4 (5.2)	26.3 (5.5)
Min, Max	16.7, 48.8	15.9, 54.7	15.7, 40.9	15.7, 54.7

COPD

The majority of subjects (73%) had COPD for <10 years; the mean duration was 8.4 years (Table 57). Nearly all subjects (96%) met the criteria for GOLD Group D. The study population was affected by their breathlessness and had poor lung function; 84% had an mMRC score of ≥2, 60% of subjects had severe or very severe airflow limitation, and 11% were using long-term oxygen therapy despite receiving ICS-based triple maintenance therapy. Eighty percent of the subjects had co-morbidities other than cardiovascular and 27% had cardiovascular co-morbidities. In addition,

the overall mean baseline SGRQ total score and CAT score were 52.7 and 19.1, respectively, indicating the study population had a poor health-related quality of life and significant disease impact on health status. Screening blood eosinophils were similar across the treatment groups (geometric mean 230 cells u/L).

Table 57 COPD History and Baseline Disease Characteristics (Study MEA117113, mITT Population)

	Placebo N=226	Mepolizumab 100 mg SC N=223	Mepolizumab 300 mg SC N=225	Total N=674
COPD History and Characteristics				
Duration of COPD, years				
Mean (SD)	8.8 (5.93)	8.4 (6.46)	7.8 (5.09)	8.4 (5.86)
Median	8.0	7.0	7.0	7.0
Min, Max	1, 38	1, 48	1, 27	1, 48
Gold Group D[1], n (%)	216 (96)	211 (95)	219 (97)	646 (96)
Severity of airflow limitation[2], n (%)				
Mild: ≥80% predicted	2 (<1)	3 (1)	2 (<1)	7 (1)
Moderate: ≥50% to <80% predicted	90 (40)	91 (41)	83 (37)	264 (39)
Severe: ≥30% to <50% predicted	97 (43)	96 (43)	98 (44)	291 (43)
Very severe: <30% predicted	37 (16)	33 (15)	42 (19)	112 (17)
mMRC Score[3] at Screening				
Mean (SD)	2.2 (0.80)	2.2 (0.84)	2.3 (0.82)	2.2 (0.82)
<2, n (%)	35 (15)	41 (18)	32 (14)	108 (16)
≥2, n (%)	191 (85)	181 (81)	193 (86)	565 (84)
Long-term Oxygen Use[4], n (%)	20 (9)	26 (12)	31 (14)	77 (11)
Screening blood eosinophils, cells/μL				
Geometric mean (std logs)	230 (0.869)	230 (0.861)	230 (0.814)	230 (0.847)
SGRQ Total Score[5]				
Mean (SD)	52.9 (15.91)	51.9 (17.32)	53.4 (16.67)	52.7 (16.62)
CAT Score[6]				
Mean (SD)	19.4 (7.53)	18.7 (7.40)	19.4 (7.76)	19.1 (7.56)
Co-morbid Disease Characteristics, n (%)				
Cardiovascular co-morbidity[7]	62 (27)	52 (23)	67 (30)	181 (27)
Other co-morbidity[8]	178 (79)	179 (80)	179 (80)	536 (80)
Ever diagnosed with GERD[9]	37 (16)	42 (19)	32 (14)	111 (16)
Charlson Comorbidity Index (CCI)[10]				
1-2	7 (3)	10 (4)	14 (6)	31 (5)
3-4	113 (50)	114 (51)	109 (48)	336 (50)
≥5	104 (46)	98 (44)	100 (44)	302 (45)
Missing	2 (<1)	1 (<1)	2 (<1)	5 (<1)

1. 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
2. Classification based on post-bronchodilator FEV_1 at Screening, GOLD Guidelines for COPD
3. Modified Medical Research Council Score
4. Long-term oxygen use was classified as taking oxygen therapy for 40 days or more.
5. SGRQ Total Score range 0-100 with higher scores indicating poor health-related quality of life
6. CAT score range 0-40 with higher scores indicating greater COPD disease impact
7. Subjects with any past or current medical conditions under Cardiac Disorders
8. Subjects with any past or current medical conditions other than under Cardiac Disorders
9. GERD=gastroesophageal reflux disease
10. CCI (predicted 10 year survival probability): 1-2 (>90%), 3-4 (>53%), ≥5 (<21%)

Exacerbation

The majority of subjects (77%) had at least two moderate exacerbations; 33% had at least one severe exacerbation. Eighty-four percent of subjects were treated with corticosteroids and/or antibiotics in an outpatient setting for their moderate/severe exacerbation(s) and 34% required hospitalization. Exacerbation history was similar across the treatment groups. COPD exacerbations in the previous 12 months were primarily caused by respiratory illnesses (54% respiratory infection, 36% common cold, 25% lower respiratory infection, and 25% upper respiratory infection other than common cold) or cold air/weather (31%).

Table 58 Exacerbation History (Study MEA117113, mITT Population)

Number of Exacerbations in Previous 12 Months	Placebo N=226	Mepolizumab 100 mg SC N=223	Mepolizumab 300 mg SC N=225	Total N=674
Moderate/Severe Exacerbations, n (%)				
0	0	0	0	0
≥1	226 (100)	223 (100)	225 (100)	674 (100)
1	29 (13)	16 (7)	16 (7)	61 (9)
2	110 (49)	122 (55)	129 (57)	361 (54)
≥3	87 (38)	85 (38)	80 (36)	252 (37)
Mean (SD)	2.6 (1.38)	2.7 (1.43)	2.7 (1.51)	2.7 (1.44)
Median	2.0	2.0	2.0	2.0
Min, Max	1, 10	1, 10	1, 12	1, 12
Moderate Exacerbations, n (%)				
0	39 (17)	24 (11)	28 (12)	91 (14)
≥1	187 (83)	199 (89)	197 (88)	583 (86)
1	23 (10)	25 (11)	13 (6)	61 (9)
2	94 (42)	104 (47)	120 (53)	318 (47)
≥3	70 (31)	70 (31)	64 (28)	204 (30)
Severe Exacerbations, n (%)				
0	141 (62)	147 (66)	164 (73)	452 (67)
≥1	85 (38)	76 (34)	61 (27)	222 (33)
1	63 (28)	58 (26)	45 (20)	166 (25)
2	15 (7)	14 (6)	11 (5)	40 (6)
≥3	7 (3)	4 (2)	5 (2)	16 (2)
Treated w/ systemic corticosteroids and/or antibiotics, no ED visit/hospitalization, n (%)				
0	44 (19)	28 (13)	33 (15)	105 (16)
≥1	182 (81)	195 (87)	192 (85)	569 (84)
1	22 (10)	26 (12)	16 (7)	64 (9)
2	96 (42)	111 (50)	120 (53)	327 (49)
≥3	64 (28)	58 (26)	56 (25)	178 (26)
ED Visit but no hospitalization, n (%)				
0	209 (92)	200 (90)	206 (92)	615 (91)
≥1	17 (8)	23 (10)	19 (8)	59 (9)
1	13 (6)	13 (6)	9 (4)	35 (5)
2	3 (1)	8 (4)	9 (4)	20 (3)
≥3	1 (<1)	2 (<1)	1 (<1)	4 (<1)
Hospitalization-general ward only, n (%)				
0	147 (65)	153 (69)	166 (74)	466 (69)
≥1	79 (35)	70 (31)	59 (26)	208 (31)
1	59 (26)	52 (23)	45 (20)	156 (23)
2	14 (6)	14 (6)	9 (4)	37 (5)
≥3	6 (3)	4 (2)	5 (2)	15 (2)
Hospitalization-intensive care unit, n (%)				
0	218 (96)	217 (97)	221 (98)	656 (97)
≥1	8 (4)	6 (3)	4 (2)	18 (3)
1	7 (3)	6 (3)	4 (2)	17 (3)
2	0	0	0	0
≥3	1 (<1)	0	0	1 (<1)

Smoking history

Most subjects (98%) were classified as a current or former smoker; subjects had a mean of 44.3 smoking pack years (Table 9). Smoking status and history were similar across the treatment groups.

Screening and Baseline Lung Function Tests

Screening lung function tests showed lung function impairment with mean pre- and postbronchodilator FEV1 values of 1177.3 mL and 1277.9 mL and percent predicted FEV1 values of 42.5% and 46.1%, respectively. Mean percent FEV1 reversibility was low at 9.8%. Baseline lung function test results were similar to screening.

Medical conditions

68 % of subjects reported current medical conditions at Screening. The overall incidence was similar across the treatment groups (hypertension (49%), hypercholesterolemia (30%), and diabetes mellitus (18%))

Prior and Concomitant Medications

For both studies

There was inconsistent recording of pre-treatment concomitant medications for the treatment of COPD exacerbations experienced in the 12 months prior to screening.

Per the protocol, medications taken for COPD within the 12 months prior to Screening were expected to be recorded, including maintenance therapies or for treatment of COPD exacerbations in order to confirm eligibility. During source data verification of eligibility criteria, inconsistent recording of pre-treatment concomitant medications for the treatment of COPD exacerbations experienced in the 12 months prior to screening was noted. The lack of consistent recording of these medications was not expected to have an impact on the appropriateness of the population enrolled or the interpretation of efficacy or safety results.

COPD Medications

Study MEA117106

The use of concomitant COPD medications was similar between treatment groups. Most of the participants were on triple therapy (high-dose ICS/LABA/LAMA) (Table 59). In study MEA117106, the most frequently COPD medications used prior to and throughout the study were tiotropium bromide (78% and 74%), FP/salmeterol xinafoate (52% and 48%), and salbutamol (54% and 31%).

Table 59 COPD Medications Used during the Study by Respiratory Medication Class (Study MEA117106, mITT-H, mITT-L, and mITT Populations)

Respiratory Medication Class	Number (%) of Subjects														
	High Stratum						Low Stratum								
	Placebo N=229			Mepolizumab 100 mg SC N=233			Placebo N=190			Mepolizumab 100 mg SC N=184			Total N=836		
	Pre-Treat [1]	During Treat	Post-Treat	Pre-Treat [1]	During Treat	Post-Treat	Pre-Treat [1]	During Treat	Post-Treat	Pre-Treat [1]	During Treat	Post-Treat	Pre-Treat [1]	During Treat	Post-Treat
Long acting beta$_2$-agonist [2]	228 (>99)	227 (>99)	226 (99)	233 (100)	232 (>99)	231 (>99)	190 (100)	190 (100)	188 (99)	183 (>99)	182 (99)	180 (98)	834 (>99)	831 (>99)	825 (99)
Corticosteroid – inhaled [2]	228 (>99)	226 (99)	225 (98)	233 (100)	232 (>99)	230 (99)	190 (100)	190 (100)	188 (99)	184 (100)	183 (>99)	181 (98)	835 (>99)	831 (>99)	824 (99)
Long-acting anticholinergic [3]	226 (99)	227 (>99)	227 (>99)	231 (>99)	230 (99)	227 (97)	189 (>99)	188 (99)	186 (98)	182 (99)	182 (99)	179 (97)	828 (>99)	827 (99)	819 (98)
Short-acting beta$_2$-agonist	171 (75)	126 (55)	106 (46)	171 (73)	119 (51)	103 (44)	146 (77)	81 (43)	75 (39)	131 (71)	86 (47)	68 (37)	619 (74)	412 (49)	352 (42)
Short-acting anticholinergic	88 (38)	89 (39)	65 (28)	82 (35)	85 (36)	64 (27)	74 (39)	50 (26)	43 (23)	63 (34)	59 (32)	31 (17)	307 (37)	283 (34)	203 (24)
Corticosteroid - systemic	120 (52)	150 (66)	61 (27)	111 (48)	131 (56)	47 (20)	99 (52)	93 (49)	30 (16)	94 (51)	99 (54)	30 (16)	424 (51)	473 (57)	168 (20)
Anti-infectives	114 (50)	147 (64)	44 (19)	115 (49)	139 (60)	45 (19)	104 (55)	106 (56)	33 (17)	99 (54)	107 (58)	28 (15)	432 (52)	499 (60)	150 (18)
Xanthine	49 (21)	46 (20)	37 (16)	52 (22)	41 (18)	37 (16)	26 (14)	26 (14)	26 (14)	30 (16)	26 (14)	23 (13)	157 (19)	139 (17)	123 (15)
Oxygen	22 (10)	40 (17)	27 (12)	33 (14)	43 (18)	35 (15)	21 (11)	28 (15)	27 (14)	32 (17)	37 (20)	34 (18)	108 (13)	148 (18)	123 (15)
Mucolytics	32 (14)	53 (23)	23 (10)	32 (14)	42 (18)	23 (10)	21 (11)	26 (14)	13 (7)	20 (11)	26 (14)	16 (9)	105 (13)	147 (18)	75 (9)
Other COPD medications	31 (14)	59 (26)	18 (8)	29 (12)	46 (20)	18 (8)	21 (11)	37 (19)	17 (9)	15 (8)	48 (26)	13 (7)	96 (11)	190 (23)	66 (8)

Respiratory Medication Class	Number (%) of Subjects														
	High Stratum						Low Stratum								
	Placebo N=229			Mepolizumab 100 mg SC N=233			Placebo N=190			Mepolizumab 100 mg SC N=184			Total N=836		
	Pre-Treat [1]	During Treat	Post-Treat	Pre-Treat [1]	During Treat	Post-Treat	Pre-Treat [1]	During Treat	Post-Treat	Pre-Treat [1]	During Treat	Post-Treat	Pre-Treat [1]	During Treat	Post-Treat
PDE-4 inhibitors	14 (6)	13 (6)	11 (5)	14 (6)	11 (5)	12 (5)	16 (8)	13 (7)	12 (6)	11 (6)	11 (6)	11 (6)	55 (7)	48 (6)	46 (6)
Leukotriene receptor antagonist	9 (4)	10 (4)	8 (3)	12 (5)	12 (5)	10 (4)	13 (7)	14 (7)	13 (7)	5 (3)	4 (2)	4 (2)	39 (5)	40 (5)	35 (4)
Corticosteroid – Other	0	5 (2)	2 (<1)	5 (2)	4 (2)	1 (<1)	5 (3)	6 (3)	2 (1)	3 (2)	5 (3)	1 (<1)	13 (2)	20 (2)	6 (<1)

1. Includes all medications started before the first dose of study treatment
2. Includes FP + salmeterol xinafoate, budesonide + formoterol fumarate, etc.
3. Includes tiotropium bromide, glycopyrronium bromide, etc.

Study MEA117113

The use of concomitant COPD medications was similar between treatment groups. Most of the participants were on triple therapy (high-dose ICS/LABA/LAMA) (Table 60). The most frequently used COPD medications prior to and throughout the study were tiotropium bromide (83% and 79%), FP/salmeterol xinafoate (56% and 53%), and salbutamol (50% and 28%).

Table 60 COPD Medications Used During the Study by Respiratory Medication Class (Study MEA117113, mITT Population)

Respiratory Medication Class	Number (%) of Subjects								
	Placebo N=226			Mepolizumab 100 mg SC N=223			Mepolizumab 300 mg SC N=225		
	Pre-Treat[1]	During Treat	Post-Treat	Pre-Treat[1]	During Treat	Post-Treat	Pre-Treat[1]	During Treat	Post-Treat
LABA	224 (>99)	224 (>99)	221 (98)	222 (>99)	223 (100)	223 (100)	225 (100)	225 (100)	223 (>99)
Corticosteroid – inhaled[2]	224 (>99)	224 (>99)	221 (98)	222 (>99)	223 (100)	223 (100)	224 (>99)	224 (>99)	220 (98)
Long-acting anticholinergic[3]	222 (98)	222 (98)	220 (97)	223 (100)	222 (>99)	220 (99)	225 (100)	223 (>99)	222 (99)
SABA	166 (73)	109 (48)	98 (43)	164 (74)	92 (41)	82 (37)	164 (73)	106 (47)	92 (41)
Corticosteroid – systemic	86 (38)	132 (58)	47 (21)	88 (39)	112 (50)	53 (24)	84 (37)	116 (52)	49 (22)
Anti-infectives	79 (35)	120 (53)	33 (15)	80 (36)	112 (50)	37 (17)	78 (35)	108 (48)	47 (21)
Short-acting anticholinergic	57 (25)	58 (26)	46 (20)	53 (24)	44 (20)	35 (16)	53 (24)	59 (26)	46 (20)
Xanthine	57 (25)	53 (23)	45 (20)	51 (23)	40 (18)	35 (16)	55 (24)	43 (19)	41 (18)
Mucolytics	49 (22)	64 (28)	43 (19)	46 (21)	53 (24)	39 (17)	49 (22)	54 (24)	39 (17)
Oxygen	23 (10)	32 (14)	29 (13)	28 (13)	29 (13)	27 (12)	35 (16)	41 (18)	37 (16)
PDE-4 inhibitors	18 (8)	13 (6)	12 (5)	20 (9)	14 (6)	12 (5)	16 (7)	16 (7)	15 (7)
Leukotriene receptor antagonist	16 (7)	17 (8)	16 (7)	16 (7)	15 (7)	12 (5)	14 (6)	13 (6)	13 (6)
Other COPD medications	32 (14)	59 (26)	36 (16)	30 (13)	50 (22)	29 (13)	42 (19)	53 (24)	36 (16)
Corticosteroid – Other	1 (<1)	2 (<1)	2 (<1)	1 (<1)	1 (<1)	0	3 (1)	1 (<1)	1 (<1)
Nedocromil or cromolyn sodium	---	1 (<1)	1 (<1)	---	1 (<1)	0	---	0	0

1. Includes all medications started before the first dose of study treatment
2. Includes fluticasone propionate + salmeterol xinafoate, budesonide + formoterol fumarate, etc.
3. Includes tiotropium bromide, glycopyrronium bromide, etc.

LABA = long acting beta$_2$-agonist, SABA = short-acting beta$_2$-agonist

Non-COPD Medications

Study MEA117106

Non-COPD medications were taken during the treatment period by 90% of subjects with similar incidences between treatment groups and strata (88% to 92%). Main non-COPD medicaments were paracetamol (23% to 33%), acetylsalicylic acid (24% to 26%), influenza vaccine (11% to 16%), omeprazole (11% to 15%), furosemide (10% to 14%), and ibuprofen (9% to 11%).

Study MEA117113

Non-COPD medications were taken during the treatment period by 94% of subjects in each treatment group: 95%, 95% and 92% for placebo, mepolizumab 100 mg and 300 mg respectively.

Main non-COPD medicaments were Paracetamol (27% placebo, 32% mepolizumab 100 mg, and 28% mepolizumab 300 mg), acetylsalicylic acid (25%, 22% and 26%), omeprazole (15%, 11% and 15%), ibuprofen (14%, 12%, and 10%), and influenza vaccine (10%, 9%, and 14%).

Numbers analysed

Study MEA117106

Table 61 Subject Populations (Study MEA117106, All Subjects Enrolled)

	Number (%) of Subjects				
	High Stratum		Low Stratum		
Population	Placebo N=230	Mepolizumab 100 mg SC N=233	Placebo N=190	Mepolizumab 100 mg SC N=184	Total N=1161
Randomized	230	233	190	184	837
Modified ITT[1]	229 (>99)	233 (100)	190 (100)	184 (100)	836 (>99)
Modified ITT-High Stratum	229 (>99)	233 (100)	0	0	462 (55)
Modified ITT-Low Stratum	0	0	190 (100)	184 (100)	374 (45)
Safety[1]	229 (>99)	233 (100)	190 (100)	184 (100)	836 (>99)
Per Protocol	209 (91)	208 (89)	175 (92)	170 (92)	762 (91)
Per Protocol-High Stratum[1]	209 (91)	208 (89)	0	0	417 (50)

Note: Percentages are based on the number of subjects randomized.
1. Subject 006098 was randomized and withdrawn without receiving study treatment.

Study MEA117113

Table 62 Subject Populations (Study MEA117113, All Subjects Enrolled)

	Number (%) of Subjects			
		Mepolizumab		
Population	Placebo	100 mg SC	300 mg SC	Total
Randomized	226	223	226	675
Modified ITT	226 (100)	223 (100)	225 (>99)	674 (>99)
Safety	226 (100)	223 (100)	225 (>99)	674 (>99)
Per-Protocol	207 (92)	210 (94)	209 (92)	626 (93)

Note: Percentages are based on the number of subjects randomized

Outcomes and estimation

Primary efficacy endpoint analysis

MEA117106

Results of the primary endpoint (annual rate of moderate/severe exacerbations) and secondary endpoint (time to first moderate/severe exacerbation) were statistically significant after adjustment for multiplicity in the high stratum; **no results were statistically significant for the overall population.** Results for the low stratum were provided for comparison and were not included in the multiplicity testing.

Table 63 Summary of Primary efficacy endpoint analyses

	High Stratum		Low Stratum		Overall Population	
	Placebo N=229	Mepolizumab 100 mg SC N=233	Placebo N=190	Mepolizumab 100 mg SC N=184	Placebo N=419	Mepolizumab 100 mg SC N=417
Primary Efficacy Endpoint						
Rate of Moderate/Severe Exacerbations (On- and Off-treatment)						
n	229	233	190	184	419	417
Exacerbation rate/year	1.71	1.40	1.29	1.58	1.52	1.49
Rate ratio vs. placebo	---	0.82	---	1.23	---	0.98
95% CI	---	0.68, 0.98	---	0.99, 1.51	---	0.85, 1.12
Unadjusted p-value	---	0.029	---	0.058	---	0.731
Adjusted p-value [1]	---	0.036	---	---	---	>0.999

Over the 52-week treatment period in the high stratum, fewer subjects treated with mepolizumab 100 mg (64%) experienced one or more moderate/severe exacerbations compared with those who received placebo (72%)

In the high stratum, the incidence and frequency of moderate/severe exacerbations occurring on- or off-treatment was lower in the mepolizumab 100 mg group (149 subjects [64%]; 339 events) compared with the placebo group (166 subjects [72%]; 397 events). In the low stratum, the incidence of moderate/severe exacerbations occurring on- or off-treatment was similar between treatment groups (64% in each group), but **the frequency was higher in the mepolizumab 100 mg group** (282 events) compared with the placebo group (247 events). The incidence and frequency of on- and off-treatment exacerbations requiring ED visit/hospitalization was generally similar regardless of treatment group and strata. A similar trend was observed with the analysis of only on-treatment exacerbations. The incidence and frequency of off-treatment exacerbations was low and similar between treatment groups and strata.

Table 64 Overview of Moderate/Severe COPD Exacerbations

	High Stratum				Low Stratum				Overall Population			
	Placebo N=229		Mepolizumab 100 mg SC N=233		Placebo N=190		Mepolizumab 100 mg SC N=184		Placebo N=419		Mepolizumab 100 mg SC N=417	
	n (%)	# Exac	n (%)	# Exac	n (%)	# Exac	n (%)	# Exac	n (%)	# Exac	n (%)	# Exac
On- and off-treatment												
Moderate/Severe	166 (72)	397	149 (64)	339	121 (64)	247	117 (64)	282	287 (68)	644	266 (64)	621
Severe	46 (20)	61	42 (18)	64	29 (15)	44	29 (16)	35	75 (18)	105	71 (17)	99
Moderate	154 (67)	336	133 (57)	275	109 (57)	203	111 (60)	247	263 (63)	539	244 (59)	522
Requiring ED visit/hospitalization	52 (23)	71	48 (21)	79	40 (21)	57	38 (21)	55	92 (22)	128	86 (21)	134
On-treatment												
Moderate/Severe	163 (71)	378	148 (64)	333	119 (63)	232	115 (63)	271	282 (67)	610	263 (63)	604
Severe	46 (20)	60	41 (18)	62	26 (14)	39	29 (16)	35	72 (17)	99	70 (17)	97
Moderate	151 (66)	318	132 (57)	271	107 (56)	193	109 (59)	236	258 (62)	511	241 (58)	507
Requiring ED visit/hospitalization	52 (23)	70	47 (20)	77	36 (19)	51	38 (21)	55	88 (21)	121	85 (20)	132
Off-treatment												
Moderate/Severe	10 (4)	19	6 (3)	6	10 (5)	15	6 (3)	11	20 (5)	34	12 (3)	17
Severe	1 (<1)	1	2 (<1)	2	5 (3)	5	0	0	6 (1)	6	2 (<1)	2
Moderate	9 (4)	18	4 (2)	4	7 (4)	10	6 (3)	11	16 (4)	28	10 (2)	15
Requiring ED visit/hospitalization	1 (<1)	1	2 (<1)	2	6 (3)	6	0	0	7 (2)	7	2 (<1)	2

Note: On-treatment exacerbations occurred between first dose and within 28 days following the last dose; off-treatment exacerbations were those reported after this and up to the date of the Week 52 visit/study conclusion for subjects who completed/did not complete the study, but no later than Day 372.

The majority of subjects in both treatment groups in all strata had 2 or fewer on- or off-treatment moderate/severe exacerbations. The greatest number of on- or off-treatment moderate/severe exacerbations during the study was 8 in the high stratum and 11 in the low stratum. In the high stratum, the cumulative number of moderate/severe exacerbations was lower in the mepolizumab 100 mg group compared with the placebo group from Week 4 through Week 52; this finding was observed to a lesser extent in the overall population.

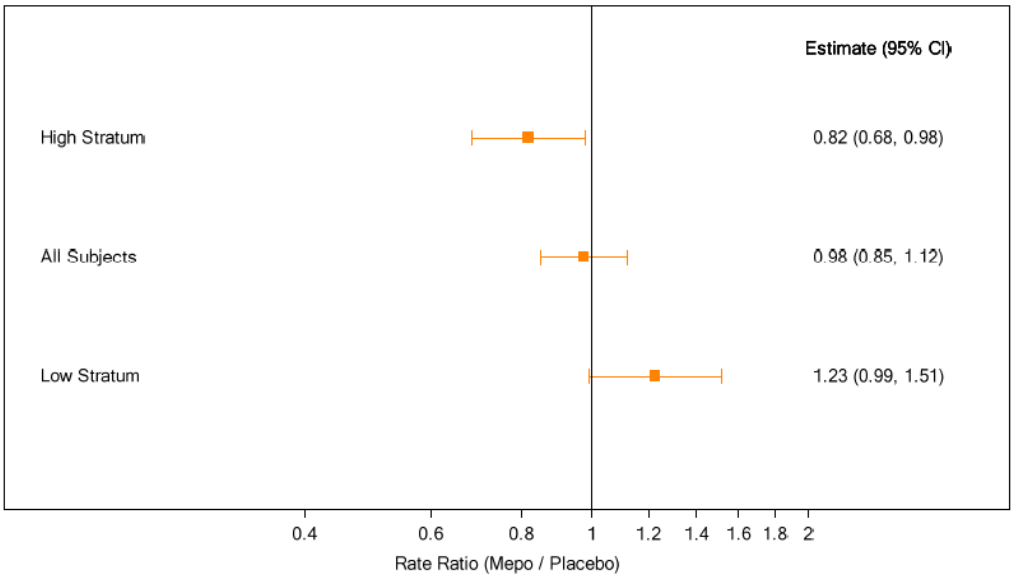
A reversed trend was observed in the low stratum, where the cumulative number **of moderate/severe exacerbations was generally higher in the mepolizumab 100 mg group** compared with the placebo group over time.

Over the 52-week treatment period in the high stratum, fewer subjects treated with mepolizumab 100 mg (64%) experienced one or more moderate/severe exacerbations compared with those who received placebo (72%). In the high stratum, treatment with mepolizumab 100 mg resulted in a statistically significant **18% reduction in the rate** of moderate/severe exacerbations compared with placebo **(rate ratio: 0.82; 95% CI: 0.68, 0.98; unadjusted p=0.029; adjusted for multiplicity p=0.036).** In the overall population, the rate of moderate/severe exacerbations was similar between the treatment groups. In the low stratum, the **rate of moderate/severe exacerbations increased by 23% after treatment** with mepolizumab 100 mg compared with placebo (unadjusted p=0.058).

Table 65 Primary Analysis of Rate of Moderate/Severe COPD Exacerbations (De Facto Estimand) (Study MEA117106, mITT-H, mITT-L, and mITT Populations)

	High Stratum		Low Stratum		Overall Population	
Moderate/Severe Exacerbations (On- and Off-treatment)	Placebo N=229	Mepolizumab 100 mg SC N=233	Placebo N=190	Mepolizumab 100 mg SC N=184	Placebo N=419	Mepolizumab 100 mg SC N=417
Exacerbations, n (%)						
0	63 (28)	84 (36)	69 (36)	67 (36)	132 (32)	151 (36)
1	65 (28)	59 (25)	52 (27)	35 (19)	117 (28)	94 (23)
2	40 (17)	42 (18)	43 (23)	44 (24)	83 (20)	86 (21)
3	28 (12)	21 (9)	7 (4)	15 (8)	35 (8)	36 (9)
4	14 (6)	15 (6)	12 (6)	12 (7)	26 (6)	27 (6)
5	8 (3)	6 (3)	3 (2)	8 (4)	11 (3)	14 (3)
>5	11 (5)	6 (3)	4 (2)	3 (2)	15 (4)	9 (2)
n	229	233	190	184	419	417
Exacerbation rate/year	1.71	1.40	1.29	1.58	1.52	1.49
Rate ratio vs. placebo	---	0.82	---	1.23	---	0.98
95% CI	---	0.68, 0.98	---	0.99, 1.51	---	0.85, 1.12
Unadjusted p-value	---	0.029	---	0.058	---	0.731
Adjusted p-value [1]	---	0.036	---	---	---	>0.999

Figure 34 Figure: Primary Analysis of Rate of Moderate/Severe Exacerbations (De Facto Estimand) (Study MEA117106, mITT-H, mITT-L, and mITT Populations)

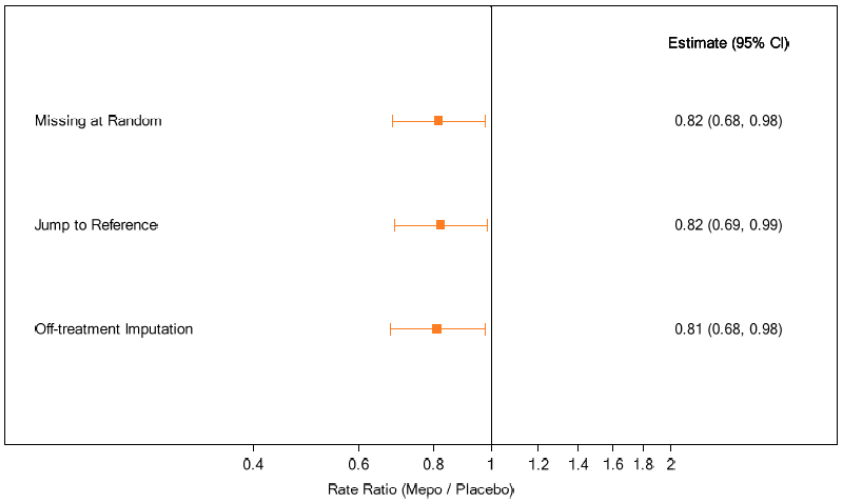


Sensitivity Analysis

Efforts were made to keep subjects in the study; however, some subjects still chose to discontinue participation. When expressed as a % of scheduled years of follow-up, the amount of missing data was 3% for the mepolizumab 100 mg group and 6% for the placebo group.

The tipping point analysis shows the impact on the study results of assuming increases in the rate of exacerbations for subjects with missing data from that estimated by the MAR assumption. Exacerbation rates among subjects in the mepolizumab 100 mg group with missing data post-withdrawal would need to be 1.5 times higher than predicted by the MAR assumption for the treatment comparison to become p>0.05 unadjusted for multiplicity. Based on the mean exacerbation rate of 1.40/yr estimated from the analysis model for subjects treated with mepolizumab 100 mg, this would imply an increase in the rate to 2.1/yr.

Figure 35 Sensitivity Analyses of Rate of Moderate/Severe Exacerbations (De Facto Estimand, Jump to Reference, and Off-Treatment Imputations) (Study MEA117106, mITT-H Population)



MEA117113

Treatment with mepolizumab 100 mg resulted in a 20% reduction in the rate of moderate/severe exacerbations compared with placebo that was not statistically significant after multiplicity correction **(rate ratio 0.80; 95% CI: 0.65, 0.98; adjusted p=0.068).** A 14% reduction in the rate of moderate/severe exacerbations was observed between mepolizumab 300 mg and placebo **(rate ratio 0.86; 95% CI: 0.70, 1.05; adjusted p=0.140)**, indicating a worse rate reduction with the higher dose.

Table 66 Summary of Primary and Secondary Efficacy Endpoint Results (mITT Population)

	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

Overview of Moderate/Severe COPD Exacerbations

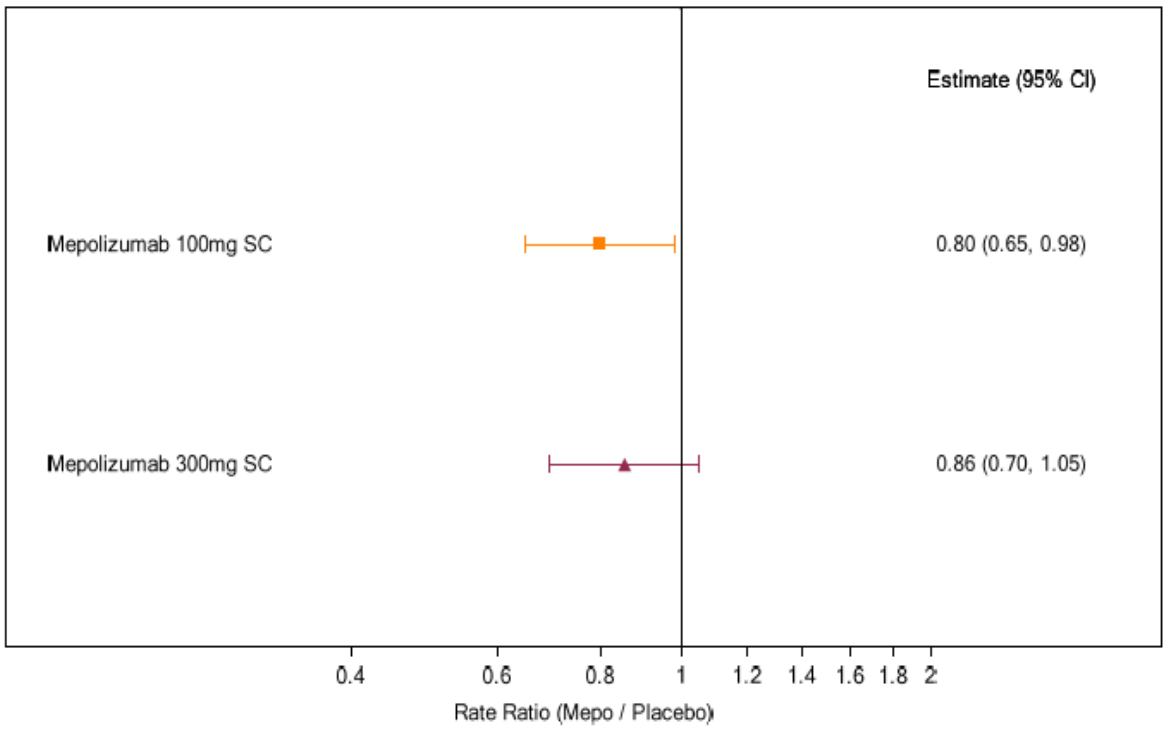
Over the treatment period, the cumulative number of exacerbations was greater in the placebo group compared with the mepolizumab treatment groups. Fewer exacerbations with mepolizumab were evident starting from Week 8 in the 300 mg group and from Week 12 in the 100 mg group.

Over the 52-week treatment period, fewer subjects treated with mepolizumab (57% 100 mg, 58% 300 mg) experienced one or more moderate/severe exacerbations compared with those who received placebo (64%). Treatment with mepolizumab 100 mg resulted in a **20% reduction in the rate** of moderate/severe exacerbations compared with placebo **(rate ratio 0.80; 95% CI: 0.65, 0.98; unadjusted p=0.034 and adjusted for multiplicity p=0.068)**. A **14% reduction in the rate** of moderate/severe exacerbations was observed between mepolizumab 300 mg and placebo **(rate ratio 0.86; 95% CI: 0.70, 1.05; unadjusted and adjusted p=0.140),** indicating worse efficacy with the higher dose. Based on the pre-specified hierarchy employed to account for multiplicity to test the primary and key secondary endpoints, results of the primary endpoint were not statistically significant for either mepolizumab treatment group compared with placebo after adjustment for multiplicity.

Table 67 Primary Analysis of Rate of Moderate/Severe COPD Exacerbations (De facto Estimand) (Study MEA117113, mITT Population

Moderate/Severe Exacerbations (On- and Off-treatment)	Placebo N=226	Mepolizumab 100 mg SC N=223	Mepolizumab 300 mg SC N=225
Exacerbations, n (%)			
0	82 (36)	96 (43)	95 (42)
1	55 (24)	50 (22)	48 (21)
2	40 (18)	35 (16)	40 (18)
3	22 (10)	25 (11)	18 (8)
4	10 (4)	5 (2)	11 (5)
5	11 (5)	7 (3)	9 (4)
>5	6 (3)	5 (2)	4 (2)
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[1]	---	0.068	0.140

Figure 36 Primary Analysis of Rate of Moderate/Severe COPD Exacerbations (De facto Estimand) (Study MEA117113, mITT Population)

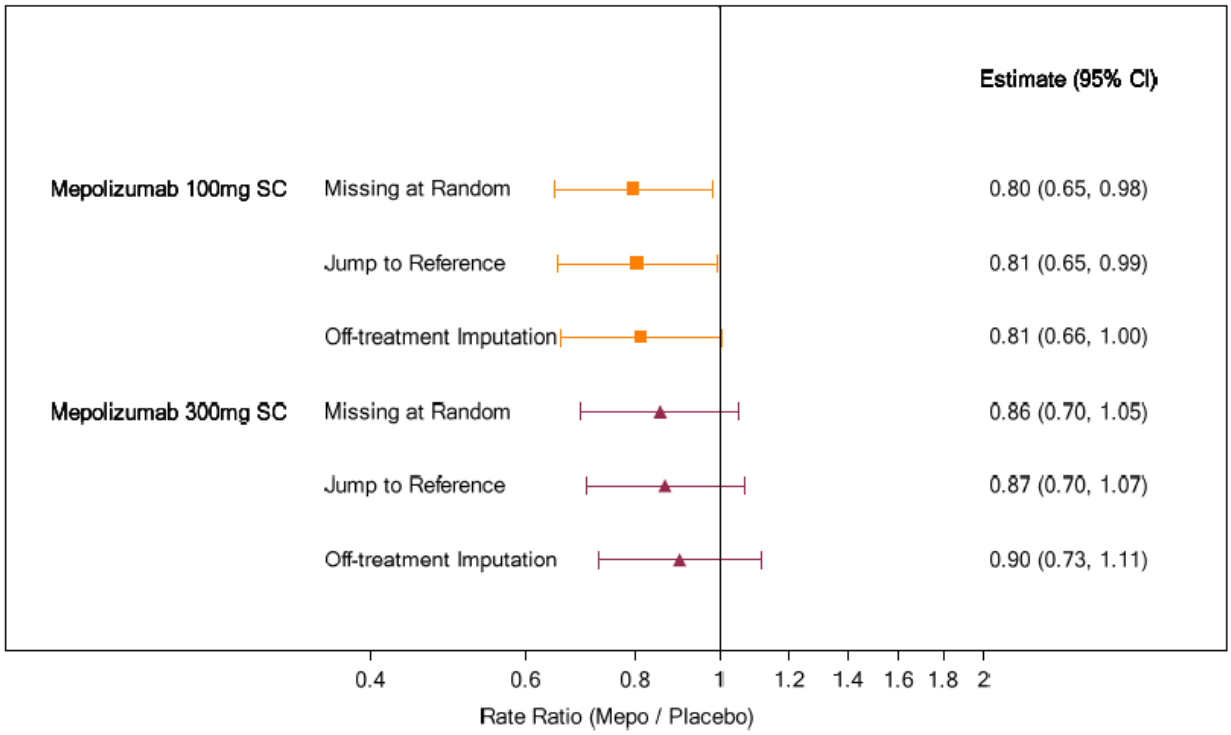


Sensitivity Analysis

Efforts were made to keep subjects in the study, but some subjects chose to discontinue participation. The amount of missing data for the primary endpoint was small and less in the mepolizumab 100 mg and 300 mg groups compared with the placebo group. When expressed as a percentage of scheduled years of follow up, the amount of missing data was 3% and 5% for the mepolizumab 100 mg and 300 mg groups, respectively; missing data for placebo group was 8%.

Exacerbation data for subjects who prematurely discontinued from study treatment and remained in the study were included in the primary analysis for a de facto estimand of treatment effect. Any missing data were considered missing at random (MAR). Sensitivity analyses were conducted to assess departures from the assumption that missing data were MAR. In each of the analyses, missing data for subjects who withdrew early from the study were imputed for the period between withdrawal from the study and the Week 52 Visit. The Jump to Reference and Off-treatment imputations show similar results to the primary analysis indicating robustness to assumptions on missing data.

Figure 37 Sensitivity Analyses of Rate of Moderate/Severe COPD Exacerbations (De facto Estimand, Jump to Reference and Off- Treatment Imputation) (Study MEA117113, mITT Population)



The tipping point analysis shows the impact on the study results of assuming increases in the rate of exacerbations for subjects with missing data from that estimated by the MAR assumption. Exacerbation rates among subjects in the mepolizumab 100 mg group with missing data post-withdrawal would need to be 1.4 times higher than predicted by the MAR assumption for the treatment comparison to become p>0.05 unadjusted for multiplicity. Based on the mean exacerbation rate of 1.19/yr estimated from the analysis model for subjects treated with mepolizumab 100 mg, this would imply an increase in the rate to 1.66/yr. For mepolizumab 300 mg, based on the MAR assumption, the comparison with placebo was already p>0.05 unadjusted for multiplicity.

MEA117106/ MEA117113 Secondary Efficacy Endpoint Results: Time to first moderate/severe exacerbation

MEA117106

The Kaplan-Meier plot shows the median time to first moderate/severe exacerbation was 141 for placebo and 192 days for mepolizumab 100 mg.

The time to moderate/severe exacerbation was similar for mepolizumab 100 mg compared with placebo in the low stratum. In the low stratum, the time to moderate/severe exacerbation was similar for mepolizumab compared with placebo (hazard ratio: 1.07; 95% CI: 0.83, 1.39; unadjusted p=0.592).

In the high stratum, the time to first moderate/severe exacerbation was longer for the mepolizumab 100 mg group compared with the placebo group. The probability of having a moderate/severe exacerbation after treatment with mepolizumab 100 mg was lower when compared to placebo from Week 4 through to week 52 in the high stratum. By Week 52, the probability was 65% for subjects treated with mepolizumab 100 mg compared with 75% for

placebo. The hazard ratio favoured mepolizumab and was statistically significant (0.75; 95% CI: 0.60, 0.94; unadjusted p=0.012; adjusted for multiplicity p=0.036).

Figure 38 Kaplan-Meier Incidence Curve for Time to First Moderate/Severe COPD Exacerbation (Study MEA117106, mITT-H and mITT-L Populations)

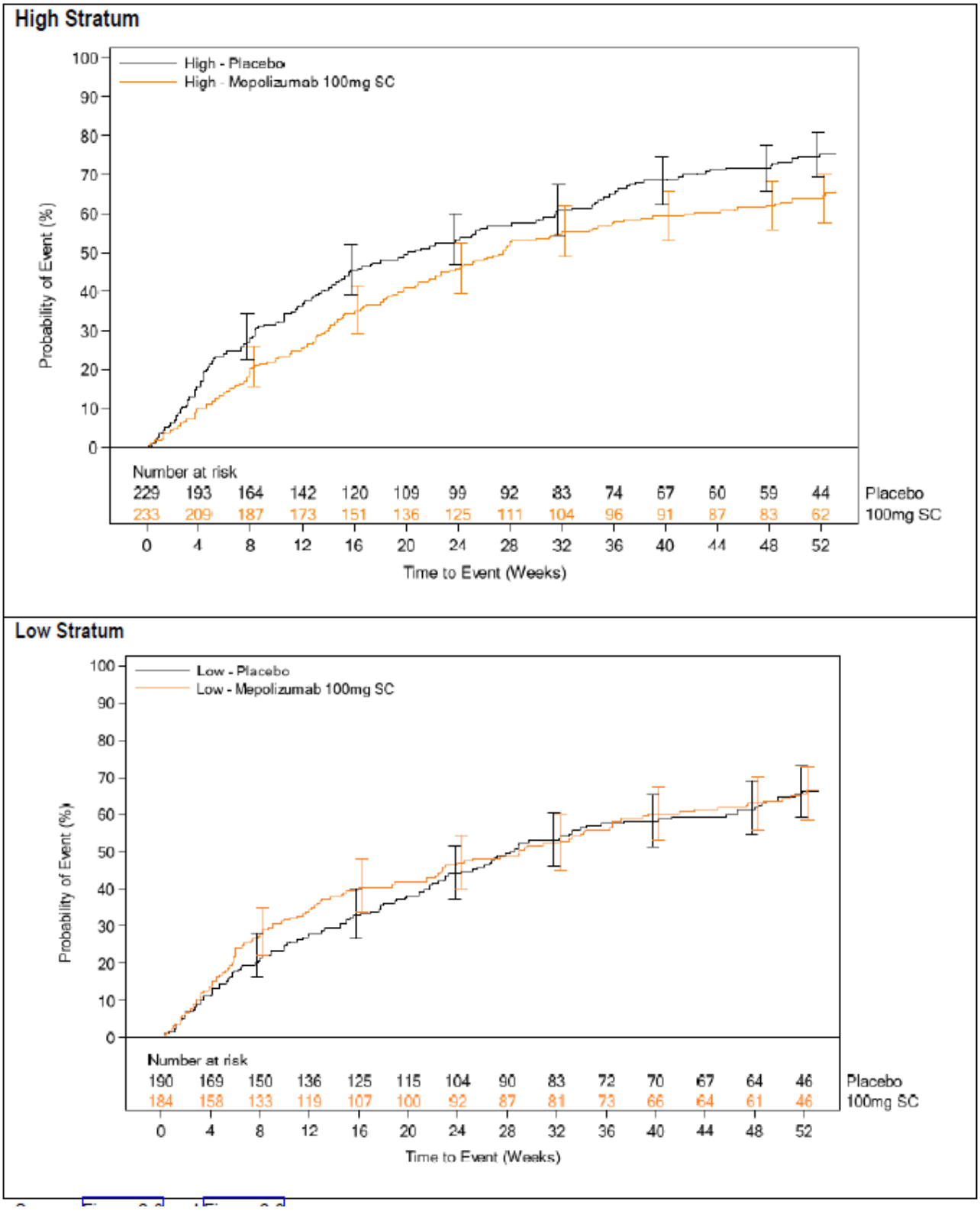


Table 68 Time to First Moderate/Severe COPD Exacerbation (Study MEA117106, mITT Population, mITT-H and mITT-L Populations)

	High Stratum		Low Stratum		Overall Population	
	Placebo N=229	Mepolizumab 100 mg SC N=233	Placebo N=190	Mepolizumab 100 mg SC N=184	Placebo N=419	Mepolizumab 100 mg SC N=417
Time to First Moderate/Severe Exacerbation						
By Week 52						
Probability of an exacerbation (%) [2]	75.2	64.6	66.2	66.6	71.2	65.5
95% CI	69.3, 80.8	58.3, 70.8	59.2, 73.1	59.4, 73.6	66.6, 75.6	60.7, 70.1
Hazard ratio (mepolizumab/placebo) [3]	---	0.75	---	1.07	---	0.89
95% CI	---	0.60, 0.94	---	0.83, 1.39	---	0.75, 1.05
Unadjusted p-value	---	0.012	---	0.592	---	0.160
Adjusted p-value	---	0.036	---	---	---	>0.999

MEA117113

The Kaplan-Meier plot shows the median time to first moderate/severe exacerbation was 166 days for placebo, 267 days for 100mg mepolizumab, and 258 days 300mg mepolizumab. The probability of having a moderate/severe exacerbation was lower with 300mg of treatment by week 8 while it took until week 12 for 100mg to be lower. This difference within the mepolizumab treatment groups was equalised by week 32, with both remaining lower than placebo. By week 52 the probability of having a moderate/severe exacerbation was 58% for 100mg and 59% for 300mg, compared with 67% for placebo. The hazard ratios favoured mepolizumab and were 0.82 for 100 mg (unadjusted p=0.103) and 0.77 for 300 mg (unadjusted p=0.030). However, as there was no statistical significance for the primary endpoint, the hierarchy was broken, and clinical significance cannot be inferred from the improved time to first moderate/severe exacerbation.

Figure 39 Kaplan-Meier Cumulative Incidence Curve for Time to First Moderate/Severe COPD Exacerbation (Study MEA117113, mITT Population)

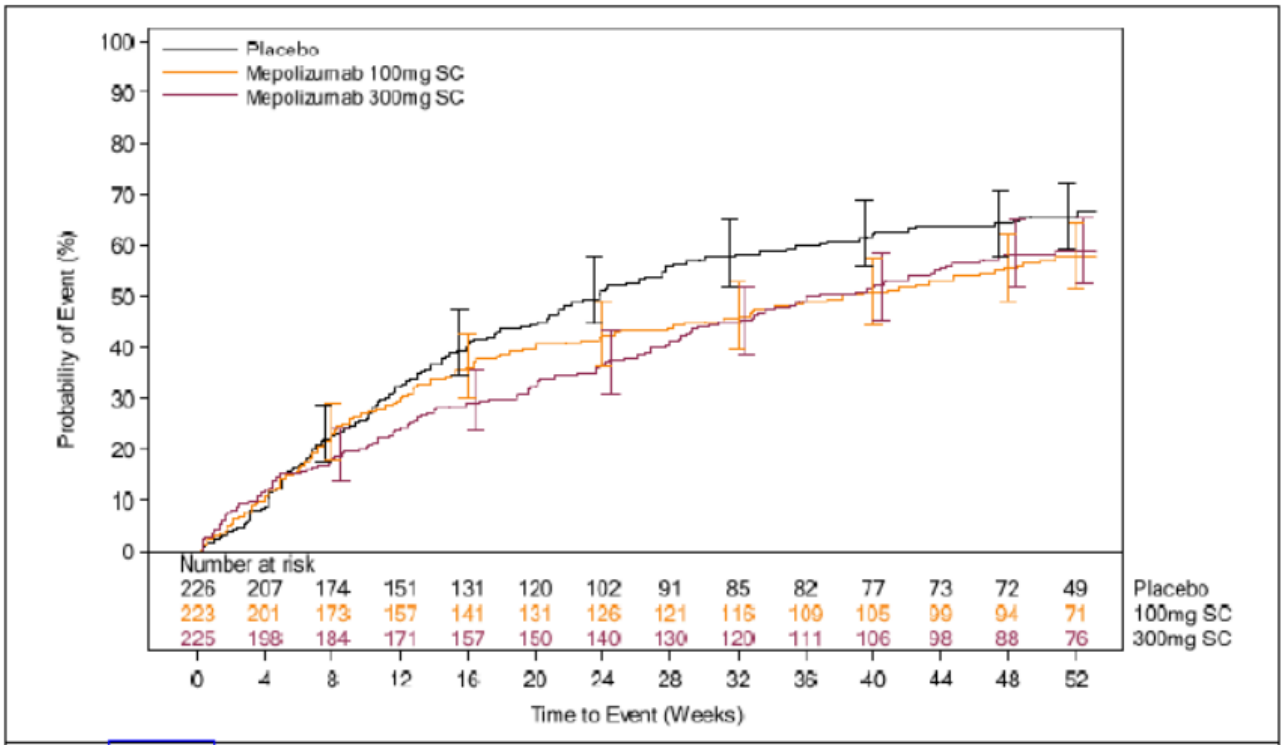


Table 69 Time to First Moderate/Severe COPD Exacerbation (Study MEA117113, mITT Population)

	Placebo N=226	Mepolizumab 100 mg SC N=223	Mepolizumab 300 mg SC N=225
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

MEA117106/ MEA117113 Secondary Efficacy Endpoint Results:

Frequency of COPD exacerbations requiring emergency department (ED) visits and/or hospitalizations.

MEA117106

In the high stratum, the percentage of subjects who experienced one or more exacerbations requiring an ED visit/hospitalization was similar for mepolizumab 100 mg (21%) compared with placebo (23%). However, there was a 16% increase in the rate of exacerbations requiring an ED visit/hospitalization for mepolizumab 100 mg compared with placebo in the high stratum (unadjusted p=0.479) and a 4% increase in the low stratum (unadjusted p=0.854). Considerations should be made when it comes to assessing this data as exacerbations of this severity occur with lower frequency, 0.26 exacerbation rate per year requiring ED visit/hospitalisation with placebo when compared to 0.30 for 100mg mepolizumab in the high stratum group.

Table 70 Analysis of Rate of Exacerbations Requiring Emergency Department Visit/Hospitalization (De facto Estimand) (Study MEA117106, mITT-H, mITT-L, and mITT Populations)

Exacerbations Requiring ED Visit/Hospitalization (On- and Off-treatment)	High Stratum		Low Stratum		Overall Population	
	Placebo N=229	Mepolizumab 100 mg SC N=233	Placebo N=190	Mepolizumab 100 mg SC N=184	Placebo N=419	Mepolizumab 100 mg SC N=417
Exacerbations, n (%)						
0	177 (77)	185 (79)	150 (79)	146 (79)	327 (78)	331 (79)
1	38 (17)	28 (12)	28 (15)	28 (15)	66 (16)	56 (13)
2	10 (4)	13 (6)	7 (4)	5 (3)	17 (4)	18 (4)
3	3 (1)	5 (2)	5 (3)	3 (2)	8 (2)	8 (2)
≥4	1 (<1)	2 (1)	0	2 (1)	1 (<1)	4 (1)
n	229	233	190	184	419	417
Exacerbation rate/year	0.26	0.30	0.25	0.27	0.26	0.29
Rate ratio vs. placebo	---	1.16	---	1.04	---	1.10
95% CI	---	0.77, 1.75	---	0.66, 1.67	---	0.81, 1.49
Unadjusted p-value	---	0.479	---	0.854	---	0.556

Note: Analysis of number of exacerbations performed using a negative binomial model with covariates of treatment group, geographic region, number of moderate/severe exacerbations in previous year (as an ordinal variable), baseline % predicted FEV_1, smoking status (current vs. never/ex-smoker), actual stratum (for overall population only), and with log(time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

MEA117113

Fewer subjects treated with mepolizumab (16% 100 mg and 15% 300 mg) experienced one or more exacerbations requiring an ED visit/hospitalization compared with those who received placebo

(21%). Mepolizumab 100 mg produced a 41% reduction in the rate of exacerbations requiring an ED visit/hospitalization compared with placebo (unadjusted p=0.042). A 17% reduction was observed with mepolizumab 300 mg (unadjusted p=0.447). Considerations should be made when it comes to assessing this data as exacerbations of this severity occur with lower frequency, 0.28 exacerbation rate per year requiring ED visit/hospitalisation with placebo when compared to 0.17 and 0.23 for 100mg and 300mg of mepolizumab respectively.

Table 71 Analysis of Rate of Exacerbations Requiring Emergency Department Visit/Hospitalization (De facto Estimand) (Study MEA117113, mITT Population)

Exacerbations Requiring ED Visit/Hospitalization (on and off treatment)	Placebo N=226	Mepolizumab 100 mg SC N=223	Mepolizumab 300 mg SC N=225
Exacerbations, n (%)			
0	179 (79)	188 (84)	191 (85)
1	36 (16)	27 (12)	19 (8)
2	5 (2)	5 (2)	11 (5)
3	4 (2)	3 (1)	1 (<1)
≥4	2 (<1)	0	3 (1)
n	226	223	225
Exacerbation rate/year	0.28	0.17	0.23
Rate ratio vs. placebo[1]	---	0.59	0.83
95% CI	---	0.35, 0.98	0.51, 1.34
Unadjusted p-value	---	0.042	0.447

Note: Analysis of number of exacerbations performed using a negative binomial model with covariates of treatment group, geographic region, number of moderate/severe exacerbations in previous year (as an ordinal variable), baseline % predicted FEV_1, smoking status (current vs. never/ex-smoker) and with log (time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

MEA117113/MEA117106 Meta-Analysis

The meta-analysis of MEA117113 and MEA117106 (high stratum) showed an overall 15% reduction in the rate of exacerbations requiring ED visit/hospitalization for mepolizumab 100 mg vs. placebo. A 12% reduction was noted with mepolizumab all doses vs. placebo.

Table 72 Meta-Analysis of Rate of Exacerbations Requiring Emergency Department Visit/Hospitalization (MEA117113 + MEA117106 High Stratum)

Exacerbations Requiring ED Visit/ Hospitalization (On- and Off-Treatment)	MEA117113 Placebo N=226	MEA117113 Mepo 100 mg SC N=223	MEA117113 Mepo 300 mg SC N=225	MEA117106 High Stratum Placebo N=229	MEA117106 High Stratum Mepo 100 mg SC N=233	Meta-Analysis MEA117113 + MEA117106 High Stratum Placebo N=455	Meta-Analysis MEA117113 + MEA117106 High Stratum Mepo 100 mg SC N=456	Meta-Analysis MEA117113 + MEA117106 High Stratum Mepo All Doses[1] N=681
Exacerbations, n (%)								
0	179 (79)	188 (84)	191 (85)	177 (77)	185 (79)	356 (78)	373 (82)	564 (83)
1	36 (16)	27 (12)	19 (8)	38 (17)	28 (12)	74 (16)	55 (12)	74 (11)
2	5 (2)	5 (2)	11 (5)	10 (4)	13 (6)	15 (3)	18 (4)	29 (4)
3	4 (2)	3 (1)	1 (<1)	3 (1)	5 (2)	7 (2)	8 (2)	9 (1)
4	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)
≥5	2 (<1)	0	2 (<1)	0	1 (<1)	2 (<1)	1 (<1)	3 (<1)
n	226	223	225	229	233	455	456	681
Exacerbation rate/year	0.28	0.17	0.23	0.26	0.30	0.28	0.24	0.25
Rate ratio vs. placebo	---	0.59	0.83	---	1.16	---	0.85	0.88
95% CI	---	0.35, 0.98	0.51, 1.34	---	0.77, 1.75	---	0.61, 1.18	0.65, 1.19
Unadjusted p-value	---	0.042	0.447	---	0.479	---	0.328	0.411
Adjusted p-value	---	0.140	0.140	---	0.598	---	N/A	N/A

1. All Doses = mepolizumab 100 mg + 300 mg

Note: Analysis performed using a negative binomial regression model with covariates of treatment group, smoking status, number of exacerbations in previous year (as a ordinal variable), baseline % predicted FEV_1, and geographic region with log(time in on-and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions. The meta-analysis includes an additional covariate of study.

MEA117106/ MEA117113 Secondary Efficacy Endpoint Results: St. George's Respiratory Questionnaire COPD (SGRQ-C)

MEA117106

SGRQ-C scores were converted to SGRQ scores [Jones, 2016] prior to analysis.

Mean baseline SGRQ Total Scores were similar between treatment groups in the high stratum, 54.1 points for mepolizumab 100 mg and 56.5 points for placebo.

Mean reductions (improvement) from baseline in the high stratum SGRQ Total Scores were numerically greater in the mepolizumab 100 mg group compared with placebo at the earlier time points, with the greatest reductions compared with placebo observed at Week 24 (-5.2 vs -2.1 with a treatment difference of -3.1 points; unadjusted p=0.020), but this difference was not maintained through week 52 (0.2 points). Changes from baseline with mepolizumab 100 mg approached or exceeded the minimal clinically important difference (MCID) (-4 points) at all time points (ie, weeks 12, 24, 36 [-3.9, -5.2, -3.8], respectively), except week 52 (-2.8 points).

In the high stratum, the proportion of subjects achieving ≥4-point improvement in SGRQ Total Score was similar for the mepolizumab 100 mg group (42%) and the placebo group (40%).

Table 73 Analysis of Change from Baseline in SGRQ Total Score at Week 52 (Study MEA117106, mITT-H, mITT-L, and mITT Populations)

	High Stratum		Low Stratum		Overall Population	
SGRQ (Week 52)	Placebo N=229	Mepolizumab 100 mg SC N=233	Placebo N=190	Mepolizumab 100 mg SC N=184	Placebo N=419	Mepolizumab 100 mg SC N=417
n with analyzable data	214	226	182	171	396	397
n with analyzable data at time point	183	206	148	150	331	356
LS mean (SE)	52.0 (1.11)	52.2 (1.06)	48.8 (1.19)	50.0 (1.21)	50.5 (0.81)	51.3 (0.80)
LS mean change (SE)	-3.0 (1.11)	-2.8 (1.06)	-5.1 (1.19)	-3.9 (1.21)	-4.0 (0.81)	-3.2 (0.80)
Difference (mepolizumab vs. placebo)	---	0.2	---	1.2	---	0.7
95% CI	---	-2.8, 3.2	---	-2.2, 4.5	---	-1.5, 2.9
Unadjusted p-value	---	0.901	---	0.490	---	0.532

Figure 40 Change from Baseline in SGRQ Total Score (Study MEA117106, mITT-H Population)

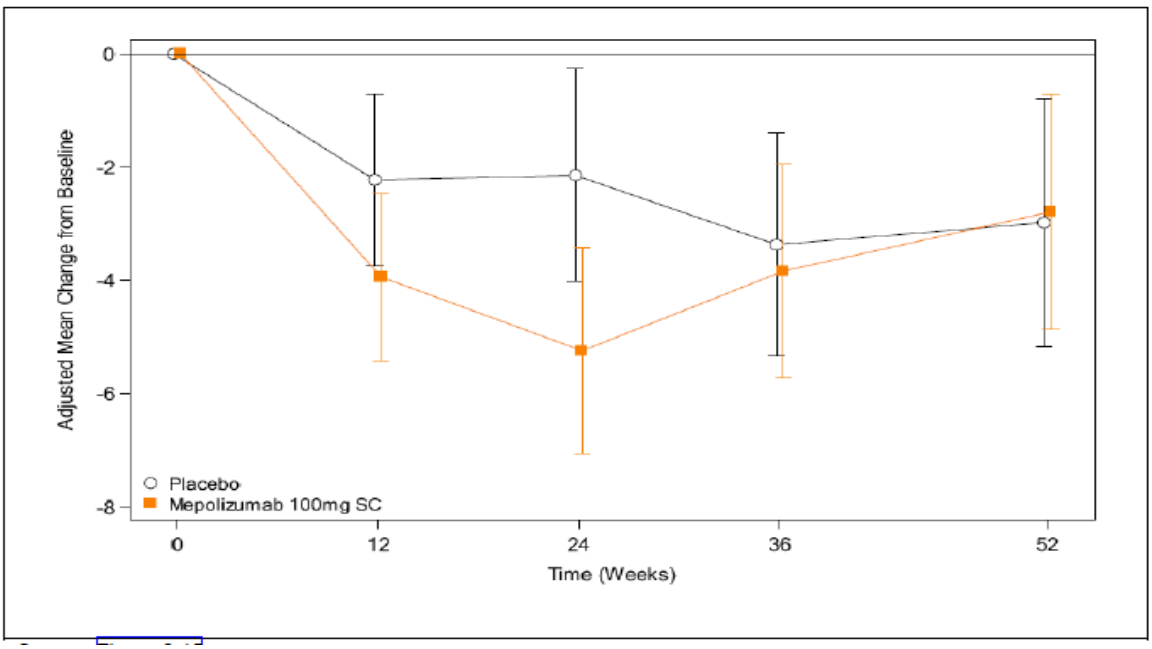


Table 74 Analysis of Proportion of Subjects With at Least a 4-point Improvement in SGRQ Total Score from Baseline at Week 52 (Study MEA117106, mITT-H Population)

SGRQ Total Score (Week 52)	Number (%) of Subjects	
	Placebo N=229	Mepolizumab 100 mg SC N=233
n [1]	223	228
≥4-point reduction	90 (40)	95 (42)
<4-point reduction/increase	93 (42)	111 (49)
Missing	40 (18)	22 (10)
Odds ratio to placebo	---	1.08
95% CI	---	0.74, 1.59
p-value	---	0.677

MEA117113

SGRQ-C scores were converted to SGRQ scores [Jones, 2016] prior to analysis.

Mean baseline SGRQ Total Scores were similar across the treatment groups: 52.9, 51.9, and 53.4 points for placebo, mepolizumab 100 mg, and mepolizumab 300 mg, respectively

Numerically greater mean reductions (improvement) from baseline in SGRQ total score were observed during the treatment period with mepolizumab 100 mg (-3.5 to -5.2 points) compared with placebo (-1.5 to -3.2 points) however this was not consistent throughout the entirety of the study. Changes from baseline with mepolizumab 100 mg exceeded the MCID (-4 points) at weeks 24 and 52 and approached the MCID at week 36 (-3.8). The largest difference of -3.7 points was observed at Week 24, which reduced to -1.8 points at Week 52. A similar trend was observed with mepolizumab 300 mg compared with placebo, but the differences were smaller.

A larger proportion of subjects treated with mepolizumab 100 mg (42%) improved by at least 4 points from baseline in SGRQ total score at eek 52 compared with those treated with placebo (35%). A smaller difference in the proportion of subjects improved by at least 4 points from baseline in SGRQ total score was observed between mepolizumab 300 mg and placebo (38% vs. 35%).

Table 75 Change from Baseline in SGRQ Total Score at Week 52 (Study MEA117113, mITT Population)

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

Figure 41 Change from Baseline in SGRQ Total Score (Study MEA117113, mITT Population)

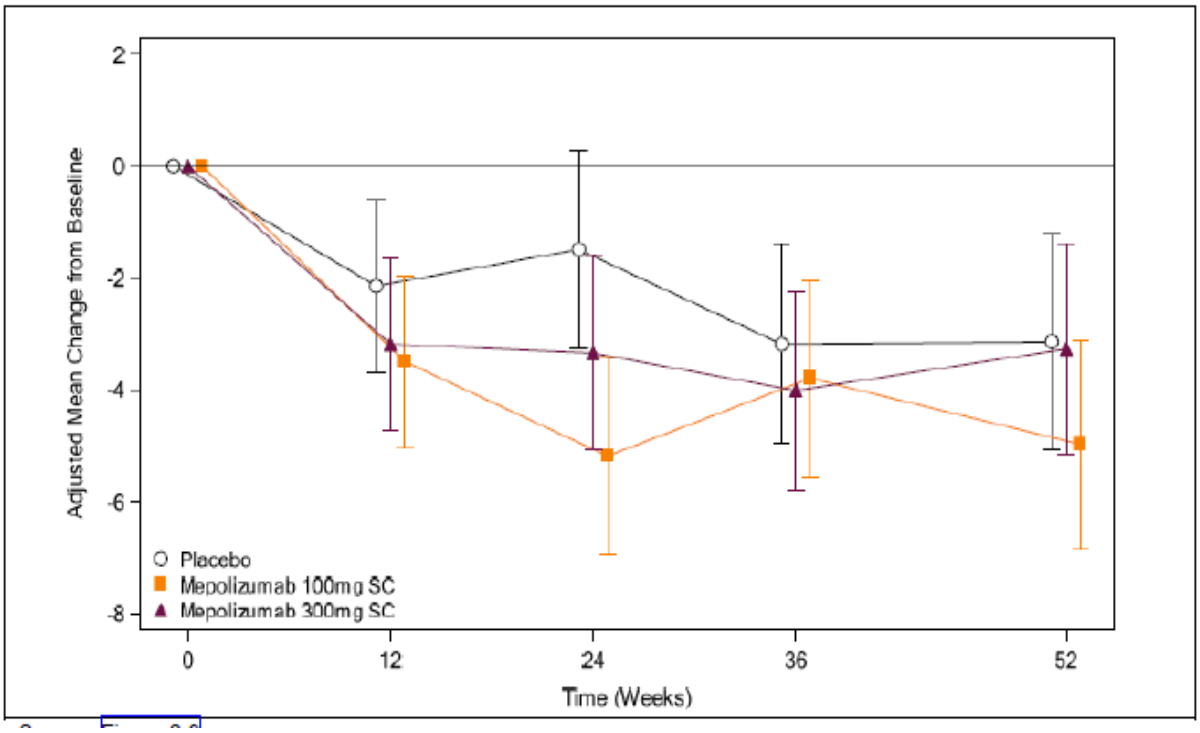


Table 76: Analysis of Proportion of Subjects With at Least a 4-point Improvement in SGRQ Total Score from Baseline at Week 52 (Study MEA117113, mITT Population)

SGRQ Total Score (Week 52)	Number (%) of Subjects		
		Mepolizumab	
	Placebo N=226	100mg SC N=223	300mg SC N=225
n	225	220	222
≥4-point reduction	78 (35)	92 (42)	85 (38)
<4-point reduction/increase	99 (44)	104 (47)	104 (47)
Missing	48 (21)	24 (11)	33 (15)
Odds ratio to placebo	---	1.41	1.17
95% CI	---	0.95, 2.10	0.79, 1.73
p-value	---	0.084	0.436

MEA117106/ MEA117113 Secondary Efficacy Endpoint Results: COPD Assessment Test (CAT) score

MEA117106

Mean baseline CAT scores were similar between treatment groups in the high stratum, 18.5 points for mepolizumab 100 mg and 19.6 points for placebo.

In the high stratum, mean reductions from baseline in CAT scores were numerically greater in the mepolizumab 100 mg group compared with placebo at all assessment times, with greatest improvements observed through Week 32 (-1.5 to -2.3 points vs 0.4 to -1.0 points; mean differences from -1.3 to -2.7 points; unadjusted p≤0.017). However, these reductions were not consistent throughout the study and began returning to near baseline from week 32. mean

reductions in CAT score from baseline to week 52 were numerically greater in the mepolizumab 100 mg group compared with placebo; the treatment difference was -0.8 points.

Changes from baseline with mepolizumab 100 mg approached or exceeded the MCID (-2 points) at Weeks 4, 8, 12, 16, 20, 24, and 32. The proportion of CAT responders in the high stratum was higher for the mepolizumab 100 mg group than the placebo group at all time points. The odds ratio for being a CAT responder was higher for mepolizumab compared with placebo at most time points (odds ratios 1.50 to 2.80, $p<0.05$) except Weeks 8 and 52. In the high stratum, the proportion of subjects achieving ≥2 point improvement in CAT score at Week 52 was similar for the mepolizumab 100 mg group (37%) and the placebo group (35%).

Figure 42 Change from Baseline in CAT Score (Study MEA117106, mITT-H Population)

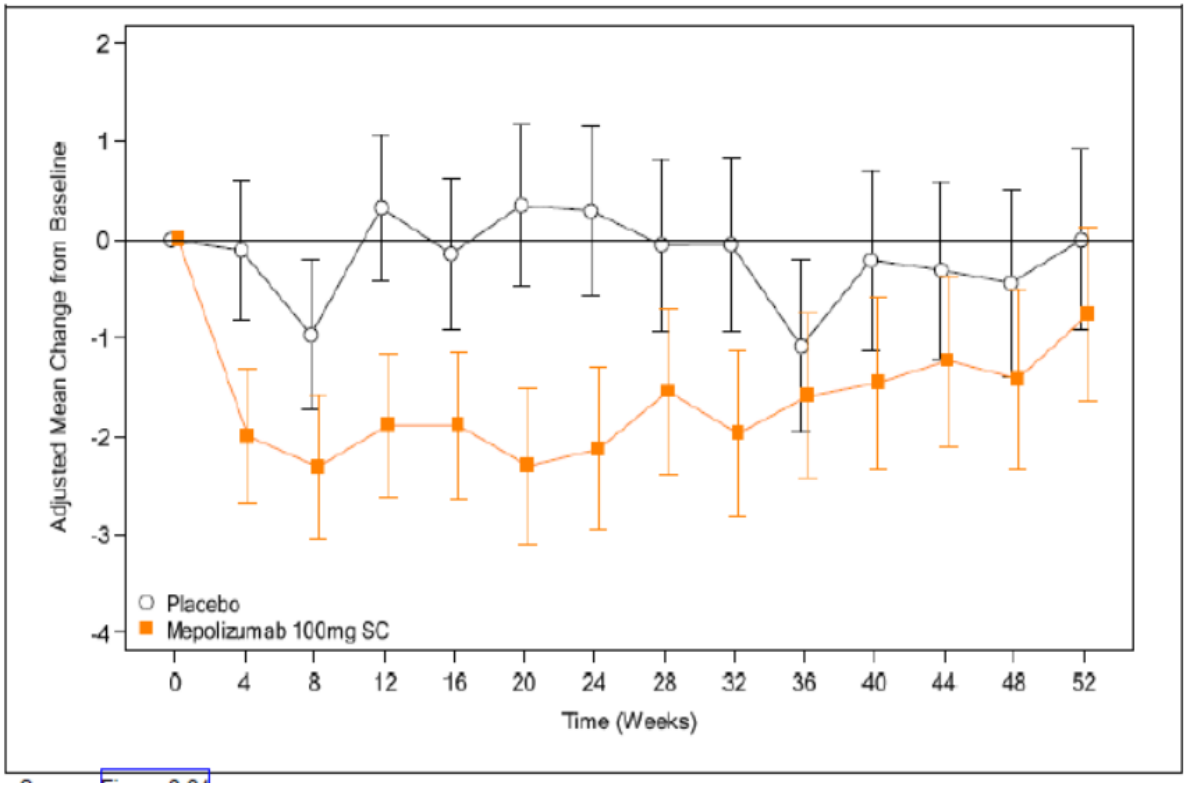


Table 77 Analysis of Change from Baseline in CAT Score at Week 52 (Study MEA117106, mITT-H, mITT-L, and mITT Populations)

	High Stratum		Low Stratum		Overall Population	
CAT Score (Week 52)	Placebo N=229	Mepolizumab 100 mg SC N=233	Placebo N=190	Mepolizumab 100 mg SC N=184	Placebo N=419	Mepolizumab 100 mg SC N=417
n with analyzable data	212	224	180	177	392	401
n with analyzable data at time point	178	195	143	146	321	341
LS mean (SE)	18.9 (0.47)	18.1 (0.45)	17.5 (0.52)	17.1 (0.53)	18.3 (0.35)	17.7 (0.34)
LS mean change (SE)	0.0 (0.47)	-0.8 (0.45)	-0.9 (0.52)	-1.4 (0.53)	-0.4 (0.35)	-1.0 (0.34)
Difference (mepolizumab vs. placebo)	---	-0.8	---	-0.4	---	-0.6
95% CI	---	-2.0, 0.5	---	-1.9, 1.0	---	-1.5, 0.4
Unadjusted p-value	---	0.244	---	0.546	---	0.252

Table 78 Post-hoc Analysis: Proportion of Subjects With at Least a 2-point Improvement in CAT Score from Baseline at Week 52 (Study MEA117106, mITT-H Population)

CAT Score (Week 52)	Number (%) of Subjects	
	Placebo N=229	Mepolizumab 100 mg SC N=233
n [1]	218	224
≥2-point reduction	76 (35)	82 (37)
<2-point reduction/increase	102 (47)	113 (50)
Missing	40 (18)	29 (13)
Odds ratio to placebo	---	1.21
95% CI	---	0.80, 1.82
p-value	---	0.376

MEA117113

Mean baseline CAT Scores were similar across the treatment groups, 19.4 points in the placebo and mepolizumab 300 mg groups and 18.7 points in the mepolizumab 100 mg group.

Mean reductions from baseline in CAT Scores were greater in the mepolizumab 100 mg group compared with placebo at all assessments but treatments did not consistently reduce CAT scores. The greatest reduction was observed at Week 24 (-2.3 vs. -0.4, difference of -1.9 points). At week 36, there was an increase in score which subsequently declined by Week 44 but then increased again though Week 52. At week 52, the mean reduction in CAT Score was greater in the mepolizumab 100 mg (-1.6 points) group compared with placebo (-0.4 point); the treatment difference was -1.1 points. Mean reductions from baseline in CAT Score in the mepolizumab 300 mg group (-0.8 to -1.7 points) were similar to placebo (-0.4 to -1.6 points) over the treatment period.

At all-time points over the treatment period, a larger proportion of subjects treated with mepolizumab 100 mg had ≥2 point improvement in CAT Score compared with placebo (odds ratios 1.39 to 1.86; $p<0.05$ except at weeks 4, 8, 36, and 48). With mepolizumab 300 mg, a larger proportion of subjects had ≥2 point improvement in CAT Score compared with placebo except at Weeks 4 and 20 (odds ratios at weeks 12 and 52 were 1.82 and 1.58, respectively; $p<0.05$). At the end of the treatment period (week 52), larger proportions of subjects in the mepolizumab 100 mg (42%) and 300 mg (41%) groups had ≥2 point improvement in CAT Score compared with placebo (32%) ($p=0.015$ and $p=0.027$, respectively).

Figure 43 Change from Baseline in CAT Score (Study MEA117113, mITT Population)

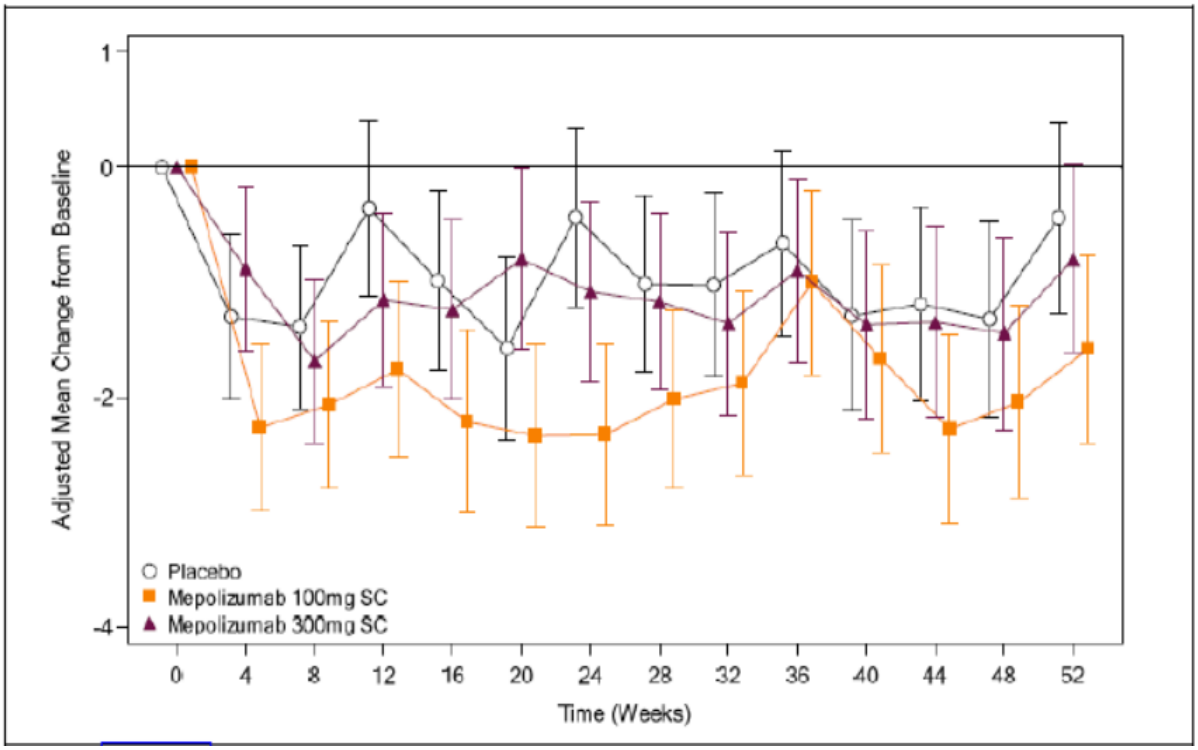


Table 79 Analysis of Change from Baseline in CAT Score at Week 52 (Study MEA117113, mITT Population)

CAT Score (Week 52)	Placebo N=226	Mepolizumab 100 mg SC N=223	Mepolizumab 300 mg SC N=225
n with analyzable data	222	216	219
n with analyzable data at time point	173	190	184
LS mean	18.5	17.4	18.1
LS mean change	-0.4	-1.6	-0.8
(SE) for LS mean and LS mean change	(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

Table 80 Post-hoc Analysis: Proportion of Subjects With at Least a 2-point Improvement in CAT Score from Baseline at Week 52 (Study MEA117113, mITT Population)

CAT Score Responders (Week 52)	Number (%) of Subjects		
		Mepolizumab	
	Placebo N=226	100mg SC N=223	300mg SC N=225
n[1]	224	216	220
≥2-point reduction	71 (32)	90 (42)	91 (41)
<2-point reduction/increase	102 (46)	100 (46)	93 (42)
Missing	51 (23)	26 (12)	36 (16)
Odds ratio to placebo	---	1.66	1.58
95% CI	---	1.10, 2.50	1.05, 2.37
p-value	---	0.015	0.027

MEA117106/ MEA117113 Other Efficacy Endpoint Results

Rescue Medication Use

MEA117106

The mean number of occasions of rescue medication use was slightly higher in the placebo group compared with the mepolizumab 100 mg group in the high stratum (2.10 and 1.85, respectively); a similar finding was observed for the low stratum (1.90 and 1.78, respectively) and the overall population (2.01 and 1.82, respectively).

In the high stratum, the number of occasions of rescue medication use increased over time in both treatment groups. Small differences from baseline were observed which favoured mepolizumab 100 mg over placebo from weeks 1 to 4 through weeks 21 to 24 (treatment differences ranged from -0.1 to -0.2) after which rescue medication use was generally similar between the groups.

Table 81 Analysis of Number of Occasions of Rescue Medication Use during Weeks 49 to 52 (Study MEA117106, mITT-H Population)

Occasions of Rescue Medication Use (Weeks 49-52)	Placebo N=229	Mepolizumab 100 mg SC N=233
n with analyzable data	229	232
n with analyzable data at time point	192	207
LS mean (SE)	2.4 (0.13)	2.3 (0.13)
LS mean change (SE)	0.4 (0.13)	0.4 (0.13)
Difference (mepolizumab vs. placebo)	—	-0.1
95% CI	—	-0.5, 0.3
p-value	—	0.644

Note: Analysis performed using mixed model repeated measures with covariates of baseline, geographic region, smoking status (current vs. never/ex-smoker), treatment, 4-week period plus interaction terms for 4-week period by baseline, and 4-week period by treatment group.
Estimates were based on weighting applied to each level of class variable determined from observed proportions.

MEA117113

The mean number of occasions of rescue medication use was similar across the treatment groups at baseline: 1.85, 1.66, and 1.82 in the placebo, mepolizumab 100 mg and mepolizumab 300 mg groups, respectively

Table 82 Analysis of Number of Occasions of Rescue Medication Use during Weeks 49-52 (Study MEA117113, mITT Population)

Occasions of Rescue Medication Use (Weeks 49-52)	Placebo N=226	Mepolizumab 100 mg SC N=223	Mepolizumab 300 mg SC N=225
n with analyzable data	225	223	225
n with analyzable data at time point	177	202	196
LS mean	2.3	1.9	2.2
LS mean change	0.6	0.2	0.4
(SE) for LS mean and LS mean change	0.14	0.14	0.14
Difference (mepolizumab vs. placebo)	---	-0.4	-0.1
95% CI	---	-0.8, 0.0	-0.5, 0.2
p-value	---	0.044	0.465

Note: Analysis performed using mixed model repeated measures with covariates of baseline, geographic region, smoking status (current vs. never/ex-smoker), treatment, 4-week period plus interaction terms for 4-week period by baseline and 4-week period by treatment group. Estimates are based on weighting applied to each level of class variable determined from observed proportions.

MEA117106/ MEA117113 Other Efficacy Endpoint Results: FEV1/FVC

MEA117106

Baseline FEV1 and FVC were similar between the mepolizumab 100 mg and placebo groups in the high stratum (FEV1: 1139.6 and 1144.6 mL, respectively, and FVC: 2576.9 and 2618.5 mL, respectively).

In the high stratum, numerically greater adjusted mean changes from baseline in pre-bronchodilator FEV1 favoured mepolizumab 100 mg (7 to 34 mL) compared with placebo (-8 to 20 mL) through Week 48. However, this change was not consistent as by week 52 FEV1 was lower for mepolizumab than placebo. There were no consistent differences observed between treatment groups for FVC through Week 52.

In the high stratum, both treatment groups showed deterioration in pre-bronchodilator FEV1 and FVC at Week 52 compared with baseline, with numerically greater deterioration observed in the mepolizumab 100 mg group compared with placebo. In the high stratum, the proportion of subjects achieving ≥100 mL increase in FEV1 at Week 52 was similar in the mepolizumab 100 mg group (20%) and the placebo group (22%).

Table 83 Analysis of Change from Baseline in Pre-bronchodilator FEV1 and FVC at Week 52 (Study MEA117106, mITT-H Population)

Lung Function Measure (Week 52)	Placebo N=229	Mepolizumab 100 mg SC N=233
FEV_1 (mL)		
n with analyzable data	223	233
n with analyzable data at time point	188	205
LS mean (SE)	1144 (15.9)	1134 (15.3)
LS mean change (SE)	-7 (15.9)	-17 (15.3)
Difference (mepolizumab vs. placebo)	---	-10
95% CI	---	-54, 33
p-value	---	0.644
FVC (mL)		
n with analyzable data	223	233
n with analyzable data at time point	188	205
LS mean (SE)	2577 (34.4)	2522 (33.3)
LS mean change (SE)	-17 (34.4)	-73 (33.3)
Difference (mepolizumab vs. placebo)	---	-55
95% CI	---	-150, 39
p-value	---	0.248

Table 84 Analysis of Proportion of Subjects with Change from Baseline Pre-bronchodilator FEV1 ≥100 mL at Week 52 (Study MEA117106, mITT-H Population)

Pre-bronchodilator FEV_1 (Week 52)	Number (%) of Subjects	
	Placebo N=229	Mepolizumab 100 mg SC N=233
n	229	233
≥100 mL increase	51 (22)	47 (20)
<100 mL increase/decrease	137 (60)	158 (68)
Missing	41 (18)	28 (12)
Odds ratio to placebo	---	0.88
95% CI	---	0.56, 1.38
p-value	---	0.582

MEA117113

Baseline FEV1 and FVC were similar across the treatment groups, 1178 to 1225 mL and 2669 to 2769 mL, respectively.

Greater mean changes from baseline in pre-bronchodilator FEV1 were observed with mepolizumab 100 mg (6 to 41 mL) compared with placebo (-14 to 19 mL) however these changes were small and not maintained for the duration of the study. Compared with placebo, mean changes from baseline in pre-bronchodilator FEV1 in the mepolizumab 300 mg group and mean changes from baseline in FVC in both treatment groups were small and inconsistent with overlapping confidence intervals.

At week 52, little difference was observed between either dose of mepolizumab and placebo in change from baseline in pre-bronchodilator FEV1 or FVC. A larger proportion of subjects in the

mepolizumab 100 mg group (26%) and the mepolizumab 300 mg group (28%) achieved ≥100 mL increase in FEV1 from baseline at Week 52 compared with placebo (17%) (p=0.020 and p=0.003, respectively).

Table 85 Analysis of Change from Baseline in Pre-bronchodilator FEV1 and FVC at Week 52 (Study MEA117113, mITT Population)

Lung Function Measure (Week 52)	Placebo N=226	Mepolizumab 100 mg SC N=223	Mepolizumab 300 mg SC N=225
FEV_1 (mL)			
n with analyzable data	224	222	224
n with analyzable data at time point	176	202	192
LS mean	1212	1232	1247
LS mean change	-13	6	21
(SE) for LS mean and LS mean change	17.6	17.0	17.1
Difference (mepolizumab vs. placebo)	---	19	35
95% CI	---	-29, 67	-14, 83
p-value	---	0.435	0.161
FVC (mL)			
n with analyzable data	224	222	224
n with analyzable data at time point	176	202	192
LS mean	2728	2725	2738
LS mean change	-17	-20	-7
(SE) for LS mean and LS mean change	29.5	28.2	28.5
Difference (mepolizumab vs. placebo)	---	-3	10
95% CI	---	-83, 78	-70, 91
p-value	---	0.950	0.800

Table 86 Analysis of Proportion of Subjects with Change From Baseline Prebronchodilator FEV1 >100 mL at Week 52 (Study MEA117113, mITT Population)

Pre-bronchodilator FEV_1 (Week 52)	Number (%) of Subjects: Placebo N=226	Mepolizumab 100mg SC N=223	Mepolizumab 300mg SC N=225
n	226	223	225
≥100 mL increase	38 (17)	57 (26)	64 (28)
<100 mL increase/decrease	138 (61)	145 (65)	128 (57)
Missing	50 (22)	21 (9)	33 (15)
Odds ratio to placebo	---	1.74	2.01
95% CI	---	1.09, 2.77	1.27, 3.19
p-value	---	0.020	0.003

MEA117113/ MEA117106 Secondary Efficacy Endpoint Results: Other

MEA117106

At week 52, no clinically relevant changes from baseline in EQ-5D-5L VAS scores were observed between treatment groups and across strata (change from baseline EQ-5D-5L: -0.019 (SD: 0.2315) placebo and -0.021 (SD: 0.2158) mepolizumab) (change from baseline VAS: 7.3 (SD: 19.040) placebo and 5.6 (SD: 18.194) mepolizumab).

Between weeks 49 to 52, no clinically relevant changes from baseline in nighttime awakenings due to COPD symptoms were observed between treatment groups and across strata (difference mepolizumab vs. placebo: 4.9 (CI: -1.4, 11.1), p-value 0.125).

In the high stratum, the number of occasions of rescue medication use increased over time in both treatment groups. Between weeks 49 to 52, no clinically relevant changes were observed between treatment groups (difference mepolizumab vs. placebo: -.01 (CI: -0.5, 0.3), p-value 0.644).

MEA117113

At week 52, no clinically relevant changes from baseline in EQ-5D-5L VAS scores were observed across treatment groups (change from baseline EQ-5D-5L: -0.03 (SD: 0.165) placebo, 0.01 (SD: 0.186) 100mg mepolizumab, and 0.00 (SD: 0.195) 300mg mepolizumab) (change from baseline VAS: 4.3 (SD: 17.42) placebo, 6.6 (SD: 18.14) 100mg mepolizumab, and 5.8 (SD: 17.70) 100mg mepolizumab).

Between weeks 49 to 52, no clinically relevant changes from baseline in nighttime awakenings due to COPD symptoms were observed between treatment groups (difference 100mg mepolizumab vs. placebo: 0.7 (CI: -5.6, 7.0), p-value 0.825) (Difference 300mg mepolizumab vs. placebo: -1.4 (CI: -7.8, 4.9), p-value 0.660).

During weeks 49-52, the treatment difference for change from baseline in occasions of rescue medication use between mepolizumab 100 mg and placebo was -0.4 (CI: -0.8, 0.0), p-value 0.044, and between mepolizumab 300 mg and placebo was -0.1 (CI: -0.5, 0.2), p-value 0.465.

Ancillary analyses

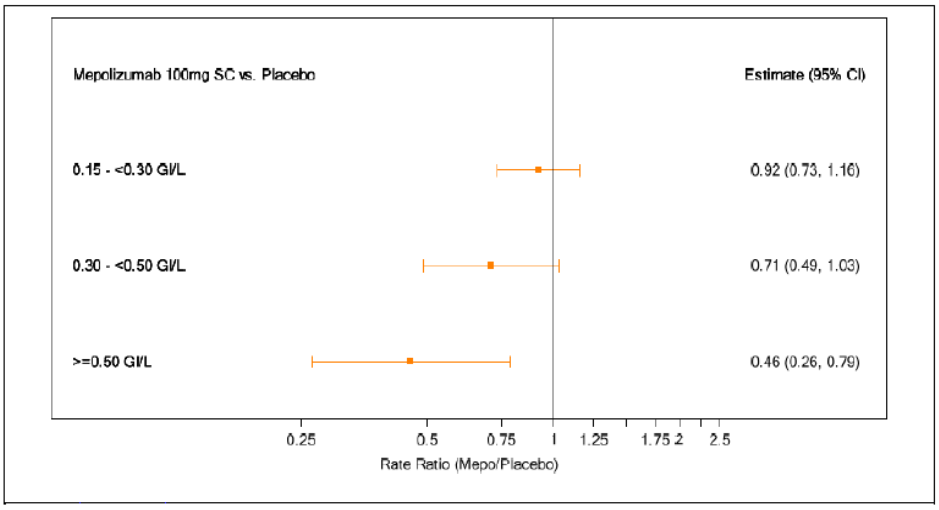
Subgroup Analyses

The rate of moderate/severe exacerbations was also analysed separately by pre-specified baseline characteristic subgroups. All subgroup analyses were conducted for the high stratum only.

Study MEA117106

Blood Eosinophil Subgroups

Figure 44 Rate of Moderate/Severe Exacerbations by Screening Blood Eosinophil Categories (Study MEA117106, mITT-H Population)

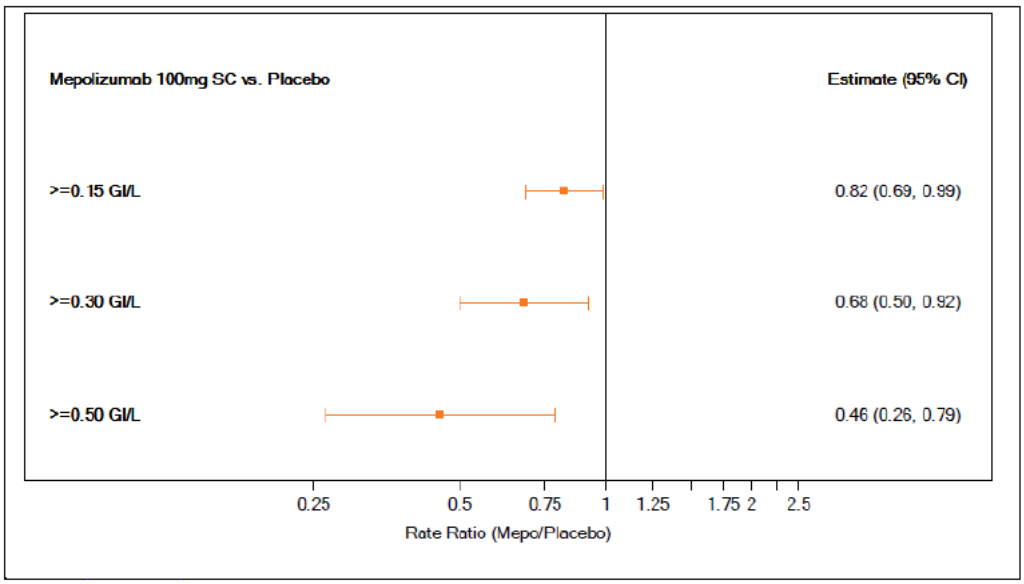


Note: Horizontal bars represent 95% confidence intervals for mepolizumab/placebo rate ratio. Rate ratio for the 150 cells/µL (≥300 cells/µL in prior year) eosinophils group was not estimable.

Screening Blood Eosinophil Thresholds

This threshold analysis is the same as the previous analysis, except that thresholds of ≥150 cells/µL, ≥300 cells/µL, and ≥500 cells/µL are used instead of categories of 150 to<300 cells/µL, 300 to <500 cells/µL, and ≥500 cells/µL.

Figure 45 Rate of Moderate/Severe Exacerbations by Screening Blood Eosinophil Thresholds (Study MEA117106, mITT-H Population)



Note: Horizontal bars represent 95% confidence intervals for mepolizumab/placebo rate ratio. Rate ratio for the 150 cells/µL (≥300 cells/µL in prior year) eosinophils group was not estimable.

Blood Eosinophil Inclusion Criteria

Table 87 Analysis of Rate of Moderate/Severe Exacerbations by Blood Eosinophil Inclusion Criteria (Study MEA117106, mITT-H Population) Blood Eosinophil Inclusion Criteria

Blood Eosinophil Inclusion Criteria	Placebo N=229	Mepolizumab 100 mg SC N=233
Historical only (≥300 cells/µL within the 12 months prior to Screening and <150 cells/µL at Screening)		
n	1	12
Exacerbation rate/year	Non-estimable	Non-estimable
Rate ratio vs. placebo	—	—
95% CI	—	—
Historical and Screening (≥300 cells/µL within the 12 months prior to Screening and ≥150 cells/µL at Screening)		
n	37	31
Exacerbation rate/year	2.06	2.09
Rate ratio vs. placebo	—	1.02
95% CI	—	0.63, 1.64
Screening only (Screening ≥150 cells/µL and no evidence of historical)		
n	191	189
Exacerbation rate/year	1.63	1.31
Rate ratio vs. placebo	—	0.80
95% CI	—	0.66, 0.98

Note: Analysis of number of exacerbations performed using separate negative binomial models for each subgroup presented with covariates of treatment group, geographic region, number of moderate/severe exacerbations in previous year (as an ordinal variable), baseline % predicted FEV1, smoking status (current vs. never/ex-smoker), and with log(time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

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Post-hoc Analysis: Historical or Screening Blood Eosinophils ≥300 cells/uL

Table 88 Post-hoc Analysis: Rate of Moderate/Severe Exacerbations, Historical or Screening Blood Eosinophils >=300 cells/uL

Moderate/Severe Exacerbations (On- and Off-treatment)	Placebo N=229	Mepolizumab 100 mg SC N=233
n	104	108
Exacerbation rate/year	1.92	1.44
Rate ratio vs. placebo	—	0.75
95% CI	—	0.57, 0.98
p-value	—	0.037

Note: Analysis of number of exacerbations performed using a negative binomial model with covariates of treatment group, geographic region, number of moderate/severe exacerbations in previous year (as an ordinal variable), baseline % predicted FEV1, smoking status (current vs. never/ex-smoker), and with log(time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

Demographic Subgroups

Age

Table 89 Analysis of Rate of Moderate/Severe Exacerbations by Age (Study MEA117106, mITT-H Population)

Moderate/Severe Exacerbations (On- and Off-treatment)	Placebo N=229	Mepolizumab 100 mg SC N=233
Age 40-64 years		
n	107	107
Exacerbation rate/year	1.79	1.17
Rate ratio vs. placebo	—	0.66
95% CI	—	0.51, 0.84
Age ≥65 years		
n	122	126
Exacerbation rate/year	1.64	1.60
Rate ratio vs. placebo	—	0.98
95% CI	—	0.75, 1.26

Note: Analysis of number of exacerbations performed using separate negative binomial models for each subgroup presented with covariates of treatment group, geographic region, number of moderate/severe exacerbations in previous year (as an ordinal variable), baseline % predicted FEV1, smoking status (current vs. never/ex-smoker) and with log(time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

Sex

Table 90 Analysis of Rate of Moderate/Severe Exacerbations by Sex (Study MEA117106, mITT-H Population)

Moderate/Severe Exacerbations (On- and Off-treatment)	Placebo N=229	Mepolizumab 100 mg SC N=233
Female		
n	79	84
Exacerbation rate/year	1.68	1.65
Rate ratio vs. placebo	—	0.98
95% CI	—	0.75, 1.30
Male		
n	150	149
Exacerbation rate/year	1.71	1.25
Rate ratio vs. placebo	—	0.73
95% CI	—	0.58, 0.93

Note: Analysis of number of exacerbations performed using separate negative binomial models for each subgroup presented with covariates of treatment group, geographic region, number of moderate/severe exacerbations in previous year (as an ordinal variable), baseline % predicted FEV1, smoking status (current vs. never/ex-smoker) and with log(time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

Race

Table 91 Analysis of Rate of Moderate/Severe Exacerbations by Race (Study MEA117106, mITT-H Population)

Moderate/Severe Exacerbations (On- and Off-treatment) [1]	Placebo N=229	Mepolizumab 100 mg SC N=233
White		
n	192	199
Exacerbation rate/year	1.93	1.51
Rate ratio vs. placebo	—	0.78
95% CI	—	0.65, 0.94
Other		
n	30	30
Exacerbation rate/year	0.54	0.71
Rate ratio vs. placebo	—	1.32
95% CI	—	0.65, 2.68

1. Rates were not estimable due to low numbers for the races of African American/African Heritage (4 in the placebo group and 2 in the mepolizumab group) and Asian (3 in the placebo group and 2 in the mepolizumab group).

Note: Analysis of number of exacerbations performed using separate negative binomial models for each subgroup presented with covariates of treatment group, geographic region, number of moderate/severe exacerbations in previous year (as an ordinal variable), baseline % predicted FEV1, smoking status (current vs. never/ex-smoker) and with log(time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

Baseline Body Mass Index

Table 92 Analysis of Rate of Moderate/Severe Exacerbations by BMI (Study MEA117106, mITT-H Population)

Moderate/Severe Exacerbations (On- and Off-treatment)	Placebo N=229	Mepolizumab 100 mg SC N=233
BMI ≤20 kg/m²		
n	28	21
Exacerbation rate/year	2.00	1.64
Rate ratio vs. placebo	—	0.82
95% CI	—	0.55, 1.22
BMI 21 to ≤30 kg/m²		
n	145	159
Exacerbation rate/year	1.69	1.39
Rate ratio vs. placebo	—	0.82
95% CI	—	0.65, 1.03
BMI >30 kg/m²		
n	56	53
Exacerbation rate/year	1.67	1.09
Rate ratio vs. placebo	—	0.66
95% CI	—	0.45, 0.95

Note: Analysis of number of exacerbations performed using separate negative binomial models for each subgroup presented with covariates of treatment group, geographic region, number of moderate/severe exacerbations in previous year (as an ordinal variable), baseline % predicted FEV1, smoking status (current vs. never/ex-smoker) and with log(time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

History of Exacerbations Subgroups

Exacerbations in Previous Year

Table 93 Analysis of Rate of Moderate/Severe Exacerbations by Exacerbations in Previous Year (Study MEA117106, mITT-H Population)

Moderate/Severe Exacerbations (On- and Off-treatment)	Placebo N=229	Mepolizumab 100 mg SC N=233
≤2 Exacerbations in Previous Year		
n	149	151
Exacerbation rate/year	1.45	1.13
Rate ratio vs. placebo	—	0.77
95% CI	—	0.61, 0.99
3 Exacerbations in Previous Year		
n	49	47
Exacerbation rate/year	2.16	1.90
Rate ratio vs. placebo	—	0.88
95% CI	—	0.60, 1.29
4+ Exacerbations in Previous Year		
n	31	35
Exacerbation rate/year	2.38	2.31
Rate ratio vs. placebo	—	0.97
95% CI	—	0.68, 1.38

Note: Analysis of number of exacerbations performed using separate negative binomial models for each subgroup presented with covariates of treatment group, geographic region, baseline % predicted FEV1, smoking status (current vs. never/ex-smoker) and with log(time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

Extrinsic Factor Subgroups

Geographic Region

Table 94 Analysis of Rate of Moderate/Severe Exacerbations by Geographic Region (Study MEA117106, mITT-H Population)

Moderate/Severe Exacerbations (On- and Off-treatment)	Placebo N=229	Mepolizumab 100 mg SC N=233
Europe		
n	80	82
Exacerbation rate/year	2.25	1.84
Rate ratio vs. placebo	—	0.82
95% CI	—	0.63, 1.06
Eastern Europe		
n	39	40
Exacerbation rate/year	1.32	0.86
Rate ratio vs. placebo	—	0.65
95% CI	—	0.41, 1.03
United States		
n	22	22
Exacerbation rate/year	2.38	1.98
Rate ratio vs. placebo	—	0.83
95% CI	—	0.49, 1.40
Rest of World		
n	88	89
Exacerbation rate/year	1.32	1.20
Rate ratio vs. placebo	—	0.91
95% CI	—	0.65, 1.27

Note: Analysis of number of exacerbations performed using separate negative binomial models for each subgroup presented with covariates of treatment group, number of moderate/severe exacerbations in previous year (as an ordinal variable), baseline % predicted FEV1, smoking status (current vs. never/ex-smoker), and with log(time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

Smoking Status at Screening

Table 95 Analysis of Rate of Moderate/Severe Exacerbations by Smoking Status at Screening (Study MEA117106, mITT-H Population)

Moderate/Severe Exacerbations (On- and Off-treatment)	Placebo N=229	Mepolizumab 100 mg SC N=233
Never/Non-smoker		
n	11	7
Exacerbation rate/year	Non-estimable	Non-estimable
Rate ratio vs. placebo	—	—
95% CI	—	—
Former/Ex-Smoker		
n	146	164
Exacerbation rate/year	1.68	1.35
Rate ratio vs. placebo	—	0.80
95% CI	—	0.64, 1.00
Current Smoker		
n	72	62
Exacerbation rate/year	1.95	1.66
Rate ratio vs. placebo	—	0.85
95% CI	—	0.62, 1.16

Note: Analysis of number of exacerbations performed using separate negative binomial models for each subgroup presented with covariates of treatment group, geographic region, number of moderate/severe exacerbations in previous year (as an ordinal variable), baseline % predicted FEV_1, and with log(time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

COPD Disease Severity Subgroups

Table 96 Analysis of Rate of Moderate/Severe Exacerbations by mMRC Score (Study MEA117106, mITT-H Population)

Moderate/Severe Exacerbations (On- and Off-treatment)	Placebo N=229	Mepolizumab 100 mg SC N=233
mMRC score at Screening: <2		
n	46	45
Exacerbation rate/year	1.93	1.30
Rate ratio vs. placebo	—	0.67
95% CI	—	0.44, 1.02
mMRC score at Screening: ≥2		
n	183	188
Exacerbation rate/year	1.70	1.46
Rate ratio vs. placebo	—	0.86
95% CI	—	0.70, 1.06

Note: Analysis of number of exacerbations performed using separate negative binomial models for each subgroup presented with covariates of treatment group, number of moderate/severe exacerbations in previous year (as an ordinal variable), baseline % predicted FEV1, smoking status (current vs. never/ex-smoker), and with log(time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

Severity of Airflow Limitation (GOLD Guidelines)

Table 97 Analysis of Rate of Moderate/Severe Exacerbations by Severity of Airflow Limitation (GOLD Guidelines) (Study MEA117106, mITT-H Population)

Moderate/Severe Exacerbations (On- and Off-treatment)	Placebo N=229	Mepolizumab 100 mg SC N=233
Mild: ≥80% predicted		
n	2	3
Exacerbation rate/year	Non-estimable	Non-estimable
Rate ratio vs. placebo	—	—
95% CI	—	—
Moderate: ≥50% to <80% predicted		
n	66	78
Exacerbation rate/year	1.59	1.02
Rate ratio vs. placebo	—	0.64
95% CI	—	0.44, 0.94
Severe: ≥30% to <50% predicted		
n	120	114
Exacerbation rate/year	1.69	1.60
Rate ratio vs. placebo	—	0.95
95% CI	—	0.75, 1.20
Very Severe: <30% predicted		
n	41	38
Exacerbation rate/year	1.87	1.42
Rate ratio vs. placebo	—	0.76
95% CI	—	0.54, 1.07

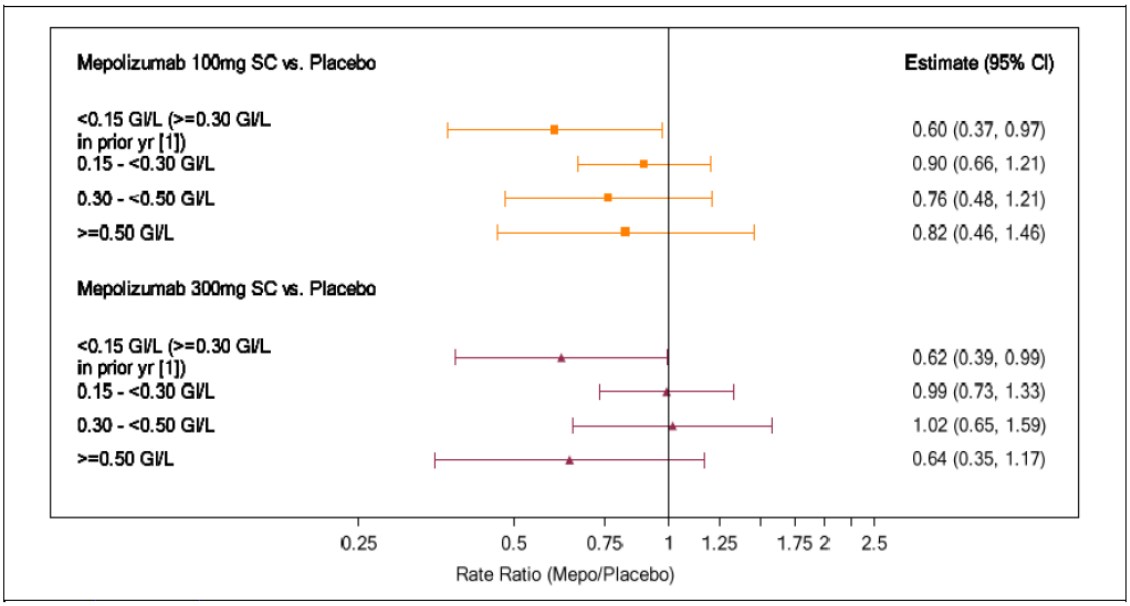
Note: Analysis of number of exacerbations performed using separate negative binomial models for each subgroup presented with covariates of treatment group, geographic region, number of moderate/severe exacerbations in previous year (as an ordinal variable), baseline % predicted FEV1, smoking status (current vs. never/ex-smoker), and with log(time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

Study MEA117113

Blood Eosinophil Subgroups

Screening Blood Eosinophil Categories

Figure 46 Rate of Moderate/Severe COPD Exacerbations by Screening Blood Eosinophil Categories (Study MEA117113, mITT Population)



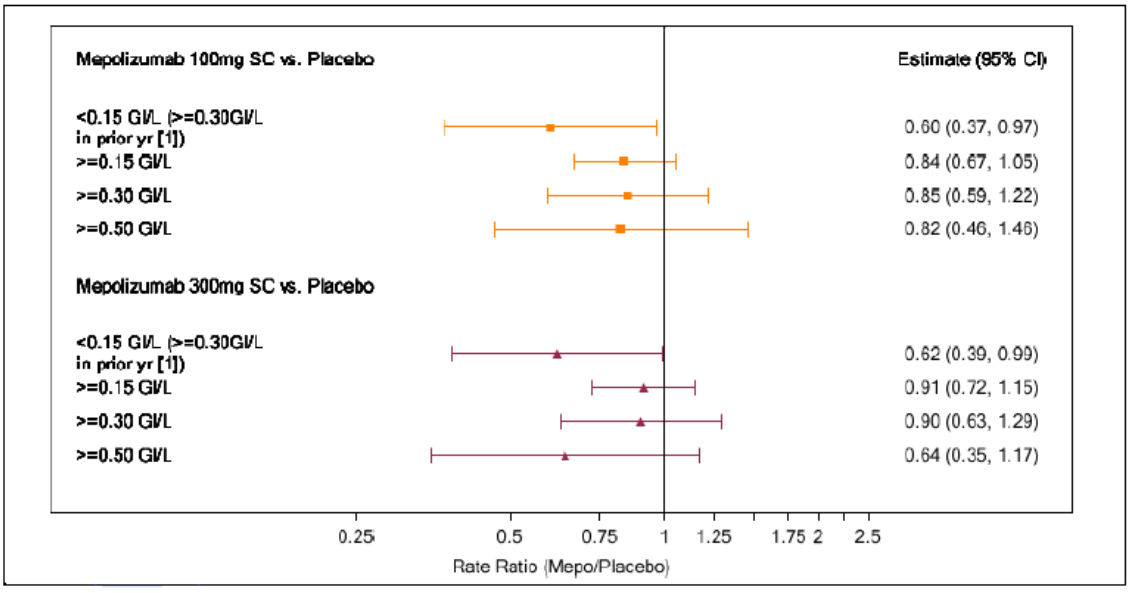
1. Includes one subject randomized to mepolizumab 100 mg with a screening value of 130 cells/μL and no evidence of ≥300 cells/μL in the previous year (protocol deviation).

Note: Two subjects (1 in placebo group and 1 in mepolizumab 300 mg group) were excluded from the analyses due to having a missing blood eosinophil count at Screening.

Note: Horizontal bars represent 95% confidence intervals

Screening Blood Eosinophil Thresholds

Figure 47 Rate of Moderate/Severe COPD Exacerbations by Screening Blood Eosinophil Thresholds (Study MEA117113, mITT Population)



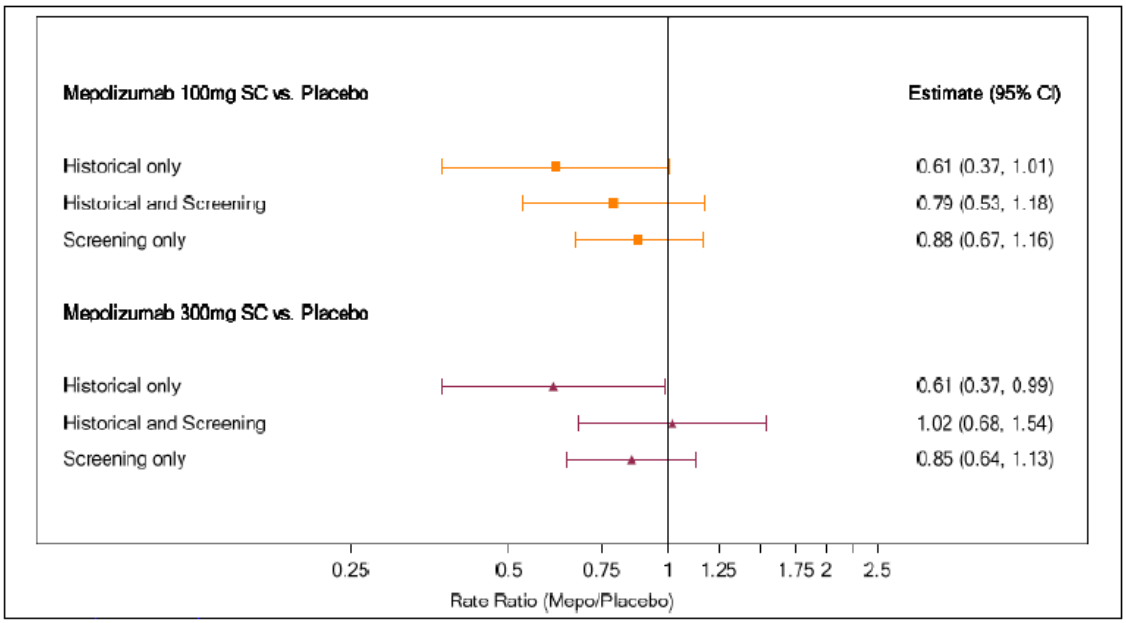
1. Includes one subject randomized to mepolizumab 100 mg with a screening value of 130 cells/μL and no evidence of ≥300 cells/μL in the previous year (protocol deviation).

Note: Two subjects (1 in placebo group and 1 in mepolizumab 300 mg group) were excluded from the analyses due to having a missing blood eosinophil count at Screening.

Note: Horizontal bars represent 95% confidence intervals

Blood Eosinophil Inclusion Criteria

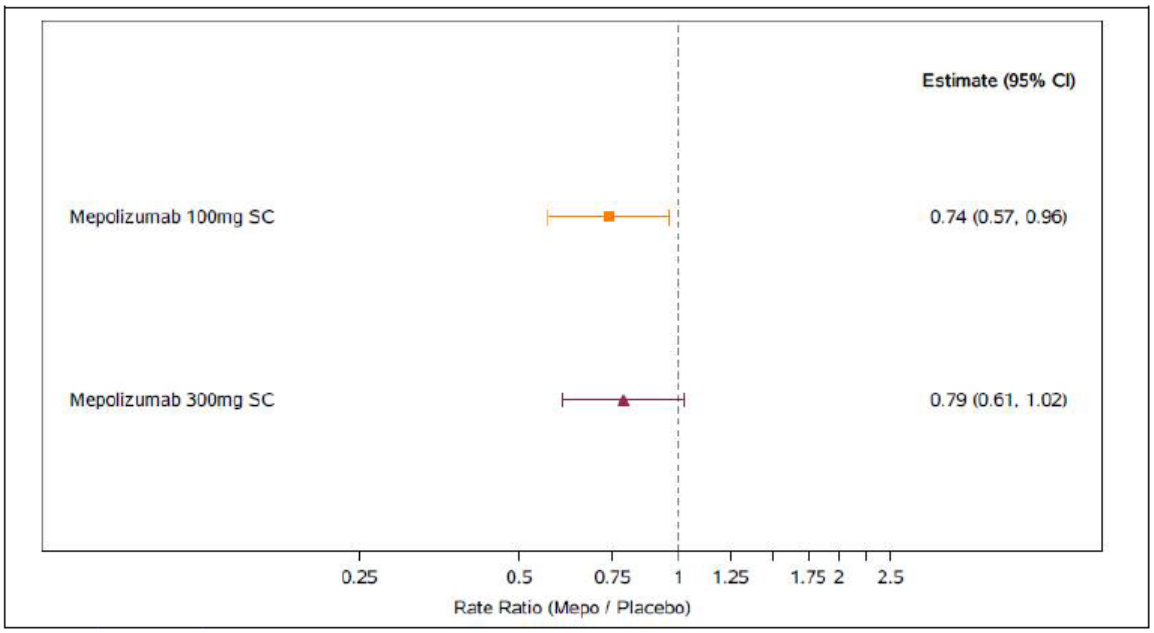
Figure 48 Rate of Moderate/Severe COPD Exacerbations by Blood Eosinophil Inclusion Criteria (Study MEA117113, mITT Population)



Note: Five subjects were excluded from the analysis (1 in placebo group, 2 in mepolizumab 100 mg group and 2 in mepolizumab 300 mg group) as there was insufficient information to determine the category
Note: Horizontal bars represent 95% confidence intervals

Post-hoc Analysis: Historical or Screening Blood Eosinophils ≥300 cells/uL

Figure 49 Post-hoc Analysis: Rate of Moderate/Severe COPD Exacerbations, Historical or Screening Blood Eosinophils >300 cells/uL (Study MEA117113, mITT Population)



Note: Horizontal bars represent 95% confidence intervals

Demographic Subgroups

Age

Table 98 Analysis of Rate of Moderate/Severe COPD Exacerbations by Age (Study MEA117113, mITT Population)

Moderate/Severe Exacerbations (On- and Off-treatment)	Placebo N=226	Mepolizumab 100 mg SC N=223	Mepolizumab 300 mg SC N=225
Age 40-64 years			
n	101	104	110
Exacerbation rate/year	1.44	1.24	1.14
Rate ratio vs. placebo	---	0.86	0.79
95% CI	---	0.63, 1.18	0.58, 1.09
Age ≥65 years			
n	125	119	115
Exacerbation rate/year	1.48	1.14	1.37
Rate ratio vs. placebo	---	0.77	0.93
95% CI	---	0.59, 1.01	0.71, 1.21

Note: Analysis of number of exacerbations performed using separate negative binomial models for each subgroup presented with covariates of treatment group, geographic region, number of moderate/severe exacerbations in previous year (as an ordinal variable), baseline % predicted FEV_1, smoking status (current vs. never/ex-smoker) and with log (time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

Sex

Table 99 Analysis of Rate of Moderate/Severe COPD Exacerbations by Sex (Study MEA117113, mITT Population)

Moderate/Severe Exacerbations (On- and Off-treatment)	Placebo N=226	Mepolizumab 100 mg SC N=223	Mepolizumab 300 mg SC N=225
Female			
n	70	91	67
Exacerbation rate/year	1.51	1.30	1.55
Rate ratio vs. placebo	---	0.86	1.03
95% CI	---	0.64, 1.16	0.75, 1.41
Male			
n	156	132	158
Exacerbation rate/year	1.43	1.12	1.17
Rate ratio vs. placebo	---	0.79	0.82
95% CI	---	0.59, 1.05	0.62, 1.07

Note: Analysis of number of exacerbations performed using separate negative binomial models for each subgroup presented with covariates of treatment group, geographic region, number of moderate/severe exacerbations in previous year (as an ordinal variable), baseline % predicted FEV_1, smoking status (current vs. never/ex-smoker) and with log (time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

Race

Table 100 Analysis of Rate of Moderate/Severe COPD Exacerbations by Race (Study MEA117113, mITT Population)

Moderate/Severe Exacerbations (On- and Off-treatment)	Placebo N=226	Mepolizumab 100 mg SC N=223	Mepolizumab 300 mg SC N=225
African American/African Heritage			
n	2	4	2
Exacerbation rate/year	Non-est	Non-est	Non-est
White			
n	182	178	182
Exacerbation rate/year	1.48	1.14	1.21
Rate ratio vs. placebo	---	0.77	0.82
95% CI	---	0.62, 0.97	0.66, 1.02
Asian			
n	42	41	41
Exacerbation rate/year	1.30	1.28	1.47
Rate ratio vs. placebo	---	0.98	1.13
95% CI	---	0.57, 1.69	0.66, 1.94

Note: Analysis of number of exacerbations performed using separate negative binomial models for each subgroup presented with covariates of treatment group, geographic region, number of moderate/severe exacerbations in previous year (as an ordinal variable), baseline % predicted FEV_1, smoking status (current vs. never/ex-smoker) and with log (time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

Baseline Body Mass Index

Table 101 Analysis of Rate of Moderate/Severe COPD Exacerbations by Baseline Body Mass Index (Study MEA117113, mITT Population)

Moderate/Severe Exacerbations (On- and Off-treatment)	Placebo N=226	Mepolizumab 100 mg SC N=223	Mepolizumab 300 mg SC N=225
BMI ≤20 kg/m²			
n	35	26	29
Exacerbation rate/year	1.43	0.88	1.51
Rate ratio vs. placebo	---	0.62	1.06
95% CI	---	0.34, 1.12	0.62, 1.80
BMI 21 to ≤30 kg/m²			
n	157	146	145
Exacerbation rate/year	1.48	1.30	1.30
Rate ratio vs. placebo	---	0.88	0.88
95% CI	---	0.69, 1.13	0.69, 1.13
BMI >30 kg/m²			
n	34	51	51
Exacerbation rate/year	1.50	0.95	0.85
Rate ratio vs. placebo	---	0.63	0.57
95% CI	---	0.39, 1.02	0.34, 0.95

Note: Analysis of number of exacerbations performed using separate negative binomial models for each subgroup presented with covariates of treatment group, geographic region, number of moderate/severe exacerbations in previous year (as an ordinal variable), baseline % predicted FEV_1, smoking status (current vs. never/ex-smoker) and with log (time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

History of Exacerbations Subgroups

Exacerbations in Previous Year

Table 102 Analysis of Rate of Moderate/Severe COPD Exacerbations by Exacerbations in Previous Year (Study MEA117113, mITT Population)

Moderate/Severe Exacerbations (On- and Off-treatment)	Placebo N=226	Mepolizumab 100 mg SC N=223	Mepolizumab 300 mg SC N=225
≤2 Exacerbations in Previous Year			
n	139	138	145
Exacerbation rate/year	1.23	0.91	1.03
Rate ratio vs. placebo	---	0.74	0.83
95% CI	---	0.56, 0.98	0.63, 1.10
3 Exacerbations in Previous Year			
n	44	42	40
Exacerbation rate/year	1.84	1.17	1.58
Rate ratio vs. placebo	---	0.64	0.86
95% CI	---	0.41, 0.99	0.56, 1.33
4+ Exacerbations in Previous Year			
n	43	43	40
Exacerbation rate/year	2.04	2.11	1.93
Rate ratio vs. placebo	---	1.04	0.95
95% CI	---	0.69, 1.56	0.62, 1.45

Note: Analysis of number of exacerbations performed using separate negative binomial models for each subgroup presented with covariates of treatment group, geographic region, baseline % predicted FEV_1, smoking status (current vs. never/ex-smoker) and with log (time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

Extrinsic Factors Subgroups

Geographic Region

Table 103 Analysis of Rate of Moderate/Severe COPD Exacerbations by Geographic Region (Study MEA117113, mITT Population)

Moderate/Severe Exacerbations (On- and Off-treatment)	Placebo N=226	Mepolizumab 100 mg SC N=223	Mepolizumab 300 mg SC N=225
Europe			
n	62	64	63
Exacerbation rate/year	1.77	1.86	1.59
Rate ratio vs. placebo	---	1.05	0.90
95% CI	---	0.76, 1.44	0.64, 1.25
Eastern Europe			
n	47	45	46
Exacerbation rate/year	1.00	0.38	0.54
Rate ratio vs. placebo	---	0.38	0.54
95% CI	---	0.20, 0.75	0.29, 1.00
Asia			
n	42	40	40
Exacerbation rate/year	1.30	1.28	1.47
Rate ratio vs. placebo	---	0.98	1.13
95% CI	---	0.57, 1.70	0.66, 1.96
United States			
n	27	26	26
Exacerbation rate/year	1.86	1.58	1.60
Rate ratio vs. placebo	---	0.85	0.86
95% CI	---	0.51, 1.41	0.51, 1.45
South America			
n	39	39	40
Exacerbation rate/year	1.55	0.83	1.12
Rate ratio vs. placebo	---	0.54	0.73
95% CI	---	0.30, 0.95	0.42, 1.26
Rest of World			
n	9	9	10
Exacerbation rate/year	2.07	1.90	2.69
Rate ratio vs. placebo	---	0.92	1.30
95% CI	---	0.43, 1.94	0.73, 2.31

Note: Analysis of number of exacerbations performed using separate negative binomial models for each subgroup presented with covariates of treatment group, number of moderate/severe exacerbations in previous year (as an ordinal variable), baseline % predicted FEV_1, smoking status (current vs. never/ex-smoker) and with log (time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

Smoking Status at Screening

Table 104 Analysis of Rate of Moderate/Severe COPD Exacerbations by Smoking Status at Screening (Study MEA117113, mITT Population)

Moderate/Severe Exacerbations (On- and Off-treatment)	Placebo N=226	Mepolizumab 100 mg SC N=223	Mepolizumab 300 mg SC N=225
Never/Non-smoker			
n	2	5	6
Exacerbation rate/year	Non-est	Non-est	Non-est
Former/Ex-Smoker			
n	161	163	148
Exacerbation rate/year	1.42	1.10	1.17
Rate ratio vs. placebo	---	0.77	0.82
95% CI	---	0.61, 0.99	0.64, 1.05
Current Smoker			
n	63	55	71
Exacerbation rate/year	1.61	1.42	1.59
Rate ratio vs. placebo	---	0.88	0.99
95% CI	---	0.59, 1.31	0.68, 1.42

Note: Analysis of number of exacerbations performed using separate negative binomial models for each subgroup presented with covariates of treatment group, geographic region, number of moderate/severe exacerbations in previous year (as an ordinal variable), baseline % predicted FEV_1, and with log (time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

COPD Disease Severity Subgroups

Table 105 Analysis of Rate of Moderate/Severe COPD Exacerbations by mMRC Score at Screening (Study MEA117113, mITT Population)

Moderate/Severe Exacerbations (On- and Off-treatment)	Placebo N=226	Mepolizumab 100 mg SC N=223	Mepolizumab 300 mg SC N=225
mMRC Score <2			
n	35	41	32
Exacerbation rate/year	1.23	1.40	0.94
Rate ratio vs. placebo	---	1.14	0.76
95% CI	---	0.69, 1.88	0.44, 1.31
mMRC Score ≥2			
n	191	181	193
Exacerbation rate/year	1.49	1.13	1.32
Rate ratio vs. placebo	---	0.76	0.89
95% CI	---	0.60, 0.96	0.71, 1.11

Note: Analysis of number of exacerbations performed using separate negative binomial models for each subgroup presented with covariates of treatment group, geographic region, number of moderate/severe exacerbations in previous year (as an ordinal variable), baseline % predicted FEV_1, smoking status (current vs. never/ex-smoker) and with log (time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

Severity of Airflow Limitation (GOLD Guidelines)

Table 106 Analysis of Rate of Moderate/Severe COPD Exacerbations by Severity of Airflow Limitation (GOLD Guidelines) (Study MEA117113, mITT Population)

Moderate/Severe Exacerbations (On- and Off-treatment)	Placebo N=226	Mepolizumab 100 mg SC N=223	Mepolizumab 300 mg SC N=225
Mild ≥80% predicted			
n	2	3	2
Exacerbation rate/year	Non-est	Non-est	Non-est
Moderate ≥50% to <80% predicted			
n	90	91	83
Exacerbation rate/year	0.97	0.73	1.01
Rate ratio vs. placebo	—	0.76	1.05
95% CI	—	0.48, 1.18	0.67, 1.63
Severe ≥30% to <50% predicted			
n	97	96	98
Exacerbation rate/year	1.85	1.34	1.49
Rate ratio vs. placebo	—	0.73	0.81
95% CI	—	0.56, 0.95	0.62, 1.05
Very Severe <30% predicted			
n	37	33	42
Exacerbation rate/year	2.11	2.06	1.31
Rate ratio vs. placebo	—	0.97	0.62
95% CI	—	0.63, 1.50	0.40, 0.95

Note: Analysis of number of exacerbations performed using separate negative binomial models for each subgroup presented with covariates of treatment group, geographic region, number of moderate/severe exacerbations in previous year (as an ordinal variable), baseline % predicted FEV_1, smoking status (current vs. never/ex-smoker) and with log (time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

Summary of main study

The following tables summarise the efficacy results from the pivotal supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 107 Summary of Efficacy for Study 208657o

Title: A multi-center, randomized, double-blind, parallel-group, placebo-controlled study of mepolizumab 100 mg SC as add-on treatment in participants with COPD experiencing frequent exacerbations and characterized by eosinophil levels (Study 208657)		
Study identifier	Study number: 208657; EudraCT Number: 2018-001540-56	
Design	Multi-center, randomized, placebo-controlled, double-blind, parallel-group.	
	Screening period (Visit 0): Screening (Visit 1)/Run-in period: Treatment period:	3 to 21 days 14 to 21 days 52 weeks (fixed duration) or for up to 104 weeks (variable duration)
Hypothesis	Superiority	
Treatment groups	Mepolizumab 100 mg	Mepolizumab 100 mg provided in a pre-filled syringe administered as a subcutaneous injection once every 4 weeks for 52 weeks (fixed duration) or for up to 104 weeks (variable duration). 403 participants treated.
	Placebo	Placebo to match mepolizumab in a pre-filled syringe administered as a subcutaneous injection once every 4 weeks for 52 weeks (fixed duration) or for up to 104 weeks (variable duration). 401 participants treated.
Endpoints and definitions	Primary Endpoint	• Annualized rate of moderate/severe exacerbations
	Secondary Endpoints	• Time to first moderate/severe exacerbation • Proportion of COPD assessment test (CAT) responders (≥2 unit reduction in CAT score from baseline) at Week 52 • Proportion of St. George's Respiratory Questionnaire (SGRQ) total score responders (measured using the St. George's Respiratory Questionnaire for COPD [SGRQ-C], and defined as ≥4 point reduction in SGRQ total score from Baseline) at Week 52 • Proportion of Evaluating Respiratory Symptoms in COPD (E-RS: COPD) responders (≥2 unit reduction in total score from Baseline) at Week 52

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		• Annualized rate of exacerbations requiring Emergency Department (ED) visit and/or hospitalization	
Database lock	29 August 2024		
Results and Analysis			
Analysis description	**Primary Endpoint – annualized rate of moderate/severe exacerbations**		
Analysis population and time point description	Modified Intent-to-Treat (mITT) Population: All randomized participants who received at least one dose of trial medication. Participants were analyzed by randomized treatment. Time point: 52 to 104 weeks		
Descriptive statistics and estimate variability	Treatment group	PBO (N=401)	Mepo 100 mg (N=403)
	Annualized rate of moderate/severe exacerbations	1.01	0.80
	Comparison mepolizumab versus placebo		
	Rate ratio (mepolizumab/placebo)	0.79	
	95% CI	(0.66, 0.94)	
	p-value	0.011	
	PBO = placebo; Mepo = mepolizumab		
Analysis description	**Secondary Endpoint – time to first moderate/severe exacerbation**		
Analysis population and time point description	mITT Population (see primary analysis population for definition) Time point: 52 to 104 weeks		
Descriptive statistics and estimate variability	Treatment group	PBO (N=401)	Mepo 100 mg (N=403)
	By Week 104 [1]		
	Participants with event	225 (56)	202 (50)
	Probability (%) of an exacerbation	68.3	64.5
	95% CI	(61.4, 74.9)	(57.5, 71.4)
	Event: first moderate/severe exacerbation, n (%)	226 (56)	202 (50)
	Censored, n (%)	175 (44)	201 (50)
	Censored at study withdrawal	24 (6)	31 (8)
	Censored at study completion	143 (36)	162 (40)
	Censored due to COVID-19 pandemic related ICE	8 (2)	8 (2)
	Hazard ratio (mepolizumab/placebo)	0.77	
	95% CI	(0.64, 0.93)	

	p-value	0.009	
Analysis description	**Secondary Endpoint – proportion of CAT responders (≥2 unit reduction in CAT score from baseline) at Week 52**		
Analysis population and time point description	mITT Population (see primary analysis population for definition) Time point: Week 52		
Descriptive statistics and estimate variability	Treatment group	PBO (N=401)	Mepo 100 mg (N=403)
	n	394	391
	Responder, n (%)	180 (46)	162 (41)
	Non-responder, n (%)	206 (52)	220 (56)
	No change/worsening	150 (38)	167 (43)
	Withdrawal from study prior to visit	36 (9)	33 (8)
	Missing visit	20 (5)	20 (5)
	Imputed, n (%)	8 (2)	9 (2)
	Odds ratio to placebo	0.81	
	95% CI	(0.60, 1.09)	
	p-value	0.161	
Analysis description	**Secondary Endpoint – proportion of SGRQ total score responders (measured using the SGRQ-C, and defined as ≥4 point reduction in SGRQ total score from Baseline) at Week 52**		
Analysis population and time point description	mITT Population (see primary analysis population for definition) Time point: Week 52		
Descriptive statistics and estimate variability	Treatment group	PBO (N=401)	Mepo 100 mg (N=403)
	n	393	390
	Responder, n (%)	179 (46)	195 (50)
	Non-responder, n (%)	206 (52)	186 (48)
	No change/worsening	149 (38)	133 (34)
	Withdrawal from study prior to visit	36 (9)	33 (8)
	Missing visit	21 (5)	20 (5)
	Imputed, n (%)	8 (2)	9 (2)
	Odds ratio to placebo	1.17	
	95% CI	(0.87, 1.57)	
	p-value	0.291	

Analysis description	**Secondary Endpoint – proportion of E-RS: COPD responders (≥2 unit reduction in total score from Baseline) at Week 52**		
Analysis population and time point description	mITT Population (see primary analysis population for definition) Time point: Weeks 49-52		
Descriptive statistics and estimate variability	Treatment group	PBO (N=401)	Mepo 100 mg (N=403)
	n	399	403
	Responder, n (%)	137 (34)	123 (31)
	Non-responder, n (%)	254 (64)	271 (67)
	No change/worsening	180 (45)	203 (50)
	Withdrawal from study prior to visit	37 (9)	33 (8)
	Missing visit	37 (9)	35 (9)
	Imputed, n (%)	8 (2)	9 (2)
	Odds ratio to placebo	0.82	
	95% CI	(0.60, 1.12)	
	p-value	0.209	
Analysis description	**Secondary Endpoint – annualized rate of exacerbations requiring ED visit and/or hospitalization**		
Analysis population and time point description	mITT Population (see primary analysis population for definition) Time point: 52 to 104 weeks		
Descriptive statistics and estimate variability	Treatment group	PBO (N=401)	Mepo 100 mg (N=403)
	Annualized rate of exacerbations requiring ED visit and/or hospitalization	0.20	0.13
	Comparison mepolizumab versus placebo		
	Rate ratio (mepolizumab/placebo)	0.65	
	95% CI	(0.43, 0.96)	
	p-value	0.032	

Analysis performed across trials (pooled analyses and meta-analysis)

The meta-analysis of data in the 3 COPD studies is based on a pooling strategy that acknowledges the importance and predictive value of BEC on treatment response to mepolizumab.

For the meta-analysis, all participant-level data from study 208657 were pooled with participant-level data for the subpopulation in MEA117113 and MEA117106 characterized by similar screening BEC (≥300 cells/μL at screening). This analysis population is referred to as the mITT-300 population.

Table 108 Table. Analysis sets

Analysis Set	Definition / Criteria*	Analyses Evaluated
Modified Intent-To-Treat Population with Eosinophils 300 cells/μL or more (mITT-300)	All randomized participants who received at least 1 dose of study treatment in study 208657 and all randomized participants who received at least 1 dose of study treatment in studies MEA117113 and MEA117106 who had a Screening BEC of ≥300 cells/μL.	Efficacy endpoints
Modified Intent-To-Treat Population (mITT)	All randomized participants who received at least 1 dose of study treatment.	Exploratory modelling to investigate the relationship between Screening BEC and rate of exacerbations

*For all analysis sets all participants were analyzed by randomized treatment

Analysis population

The mITT-300 population is a subpopulation of the mITT population, for the integrated efficacy analysis in this submission.

Table 109 . Summary of participants in the mITT-300 population.

	mITT population		mITT-300 population	
Study	PBO n (%)	100 SC n (%)	PBO n (%)	100 SC n (%)
208657	401 (38)	403 (39)	401 (69)	403 (71)
MEA117113	226 (22)	223 (21)	87 (15)	83 (15)
MEA117106	419 (40)	417 (40)	90 (16)	82 (14)
208657+MEA117113+MEA117106	1046 (100)	1043 (100)	578 (100)	568 (100)

Participant disposition

In study 208657, the majority of participants completed the study. The percentage of participants who withdrew from the study was similar in both groups and the most common reasons were – withdrawal by the participant and AE. Overall, the proportion of participants who completed the study and who withdrew from the study was similar between the fixed and variable duration subgroups.

In studies MEA117113 and MEA117106, the majority of the participants also completed the study. A higher percentage of participants who withdrew from the study was observed in the placebo group than in mepolizumab 100 mg group in both the studies. The most common reasons for withdrawal were similar to study 208657.

Table 110 Participant disposition (individual studies and meta-analysis, mITT-300 population) Study participant completion status

Study participant completion status	Number (%) of participants								
	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106		
	PBO (N=401) n (%)	100 SC (N=403) n (%)	PBO (N=87) n (%)	100 SC (N=83) n (%)	PBO (N=90) n (%)	100 SC (N=82) n (%)	PBO (N=578) n (%)	100 SC (N=568) n (%)	PBO + 100 SC (N=1146) n (%)
Completed study	331 (83)	339 (84)	69 (79)	76 (92)	81 (90)	77 (94)	481 (83)	492 (87)	973 (85)
Withdrawn early from study	70 (17)	64 (16)	18 (21)	7 (8)	9 (10)	5 (6)	97 (17)	76 (13)	173 (15)
Primary reason for study withdrawal /Subreason for study withdrawal [1], [2]									
Adverse event	16 (4)	15 (4)	9 (10)	2 (2)	2 (2)	1 (1)	27 (5)	18 (3)	45 (4)
Death	11 (3)	11 (3)	4 (5)	2 (2)	1 (1)	1 (1)	16 (3)	14 (2)	30 (3)
Lack of efficacy	7 (2)	2 (<1)	1 (1)	0	0	0	8 (1)	2 (<1)	10 (<1)
Exacerbation	2 (<1)	0	0	0	0	0	2 (<1)	0	2 (<1)
Study terminated by sponsor	0	0	0	0	0	0	0	0	0
Lost to follow-up	5 (1)	3 (<1)	1 (1)	0	0	0	6 (1)	3 (<1)	9 (<1)
Physician decision	7 (2)	4 (<1)	3 (3)	1 (1)	1 (1)	1 (1)	11 (2)	6 (1)	17 (1)
Withdrawal by participant	35 (9)	40 (10)	4 (5)	4 (5)	6 (7)	3 (4)	45 (8)	47 (8)	92 (8)

[1] Participants could have only one primary reason for withdrawal.
[2] Participants were not required to indicate subreasons, if provided, participants may have had more than one subreason underneath a single primary reason.
Note: Study 208657 2/2 (PBO/Mepo 100 SC) participants completed treatment as scheduled but later withdrew from the study. Study MEA117113 1/2 (PBO/Mepo 100 SC) participants completed treatment as scheduled but later withdrew from the study.

Study treatment completion status

In study 208657, the majority of participants completed the study treatment as scheduled. A higher percentage of participants in the placebo group (22%) discontinued treatment compared with mepolizumab 100 mg group (19%). The most common reasons for treatment discontinuation were withdrawal by the participant and AE.

In studies MEA117113 and MEA117106, the majority of the participants also completed the study treatment. Similar trends as seen in study 208657 were observed in these studies for the percentage of participants who discontinued the study treatment and the reasons of treatment discontinuation.

Table 111 Study treatment completion (individual studies and meta-analysis, mITT-300 population)

Study treatment completion status	Number (%) of participants								
	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106		
	PBO (N=401) n (%)	100 SC (N=403) n (%)	PBO (N=87) n (%)	100 SC (N=83) n (%)	PBO (N=90) n (%)	100 SC (N=82) n (%)	PBO (N=578) n (%)	100 SC (N=568) n (%)	PBO + 100 SC (N=1146) n (%)
Completed treatment	314 (78)	326 (81)	66 (76)	75 (90)	72 (80)	74 (90)	452 (78)	475 (84)	927 (81)
Discontinued treatment	87 (22)	77 (19)	21 (24)	8 (10)	18 (20)	8 (10)	126 (22)	93 (16)	219 (19)
Discontinued treatment and study at the same time	38 (9)	42 (10)	7 (8)	2 (2)	4 (4)	2 (2)	49 (8)	46 (8)	95 (8)
Discontinued treatment and continued in study	49 (12)	35 (9)	14 (16)	6 (7)	14 (16)	6 (7)	77 (13)	47 (8)	124 (11)
Completed study with off-treatment assessments	19 (5)	15 (4)	4 (5)	3 (4)	9 (10)	3 (4)	32 (6)	21 (4)	53 (5)
Did not complete study	30 (7)	20 (5)	10 (11)	3 (4)	5 (6)	3 (4)	45 (8)	26 (5)	71 (6)
Primary reason for treatment discontinuation /Subreason for treatment discontinuation [1], [2]									
Adverse event	21 (5)	21 (5)	12 (14)	1 (1)	8 (9)	2 (2)	41 (7)	24 (4)	65 (6)
Death	9 (2)	9 (2)	2 (2)	1 (1)	1 (1)	1 (1)	12 (2)	11 (2)	23 (2)
Lack of efficacy	13 (3)	2 (<1)	1 (1)	0	1 (1)	1 (1)	15 (3)	3 (<1)	18 (2)
Exacerbation	5 (1)	1 (<1)	0	0	0	0	5 (<1)	1 (<1)	6 (<1)
Protocol deviation	1 (<1)	0	1 (1)	0	0	1 (1)	2 (<1)	1 (<1)	3 (<1)
Subject reached protocol-defined stopping criteria	3 (<1)	2 (<1)	0	0	0	0	3 (<1)	2 (<1)	5 (<1)
ECG abnormality	0	1 (<1)	0	0	0	0	0	1 (<1)	1 (<1)
Liver function test abnormality	2 (<1)	0	0	0	0	0	2 (<1)	0	2 (<1)
Study terminated by sponsor	0	0	0	0	0	0	0	0	0
Lost to follow-up	1 (<1)	2 (<1)	0	1 (1)	0	0	1 (<1)	3 (<1)	4 (<1)
Physician decision	5 (1)	5 (1)	1 (1)	1 (1)	2 (2)	1 (1)	8 (1)	7 (1)	15 (1)
Withdrawal by participant	41 (10)	44 (11)	5 (6)	5 (6)	7 (8)	3 (4)	53 (9)	52 (9)	105 (9)
Investigator site closed	1 (<1)	0	1 (1)	0	0	0	2 (<1)	0	2 (<1)

[1] Participants could have only one primary reason for treatment discontinuation.
[2] Participants were not required to indicate subreasons, if given, there may have been more than one subreason underneath a primary reason.

Demographic and baseline characteristics

In study 208657, demographics and baseline characteristics were balanced between the treatment groups. The majority of the participants were White and predominantly male. More than half of the total participants were ≥65 years of age with mean age of 66.2 years (Section 2.1.3.).

The demographic and baseline characteristics were generally similar among the 3 individual COPD Studies (mITT-300 population). Similar racial groups were observed in studies 208657 and MEA117113, with 14 to 21% Asian participants (non- White race). In contrast in study MEA117106, there was only a single Asian participant in the placebo group.

For the pooled studies (mITT-300 population), demographic and baseline characteristics were balanced between the treatment groups.

Table 112 Demographics (individual studies and meta-analysis, mITT-300 population)

	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106		
	PBO (N=401)	100 SC (N=403)	PBO (N=87)	100 SC (N=83)	PBO (N=90)	100 SC (N=82)	PBO (N=578)	100 SC (N=568)	PBO + 100 SC (N=1146)
Age (years)									
Mean (SD)	66.0 (7.91)	66.4 (8.10)	65.8 (8.58)	65.2 (9.28)	64.4 (9.24)	65.5 (8.38)	65.7 (8.24)	66.1 (8.32)	65.9 (8.28)
Median (min, max)	66.0 (42, 91)	67.0 (39, 88)	65.0 (44, 84)	67.0 (43, 82)	65.0 (40, 82)	66.0 (43, 83)	66.0 (40, 91)	67.0 (39, 88)	67.0 (39, 91)
Age group (years), n (%)									
<40	0	1 (<1)	0	0	0	0	0	1 (<1)	1 (<1)
40 - <65	173 (43)	142 (35)	41 (47)	34 (41)	42 (47)	38 (46)	256 (44)	214 (38)	470 (41)
≥65	228 (57)	260 (65)	46 (53)	49 (59)	48 (53)	44 (54)	322 (56)	353 (62)	675 (59)
Sex, n (%)									
Female	126 (31)	127 (32)	28 (32)	33 (40)	33 (37)	29 (35)	187 (32)	189 (33)	376 (33)
Male	275 (69)	276 (68)	59 (68)	50 (60)	57 (63)	53 (65)	391 (68)	379 (67)	770 (67)
Ethnicity, n (%)									
Hispanic or latino	95 (24)	94 (23)	14 (16)	12 (14)	14 (16)	14 (17)	123 (21)	120 (21)	243 (21)
Not hispanic or latino	306 (76)	309 (77)	73 (84)	71 (86)	76 (84)	68 (83)	455 (79)	448 (79)	903 (79)
Race, n (%)									
American Indian or Alaskan Native	2 (<1)	3 (<1)	0	0	5 (6)	9 (11)	7 (1)	12 (2)	19 (2)
Asian	56 (14)	56 (14)	18 (21)	17 (20)	1 (1)	0	75 (13)	73 (13)	148 (13)
Black or African American	5 (1)	5 (1)	1 (1)	1 (1)	2 (2)	2 (2)	8 (1)	8 (1)	16 (1)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0
White	335 (84)	338 (84)	68 (78)	65 (78)	74 (82)	68 (83)	477 (83)	471 (83)	948 (83)
Mixed Race	3 (<1)	1 (<1)	0	0	8 (9)	3 (4)	11 (2)	4 (<1)	15 (1)

	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106		
	PBO (N=401)	100 SC (N=403)	PBO (N=87)	100 SC (N=83)	PBO (N=90)	100 SC (N=82)	PBO (N=578)	100 SC (N=568)	PBO + 100 SC (N=1146)
Height (cm)									
Mean (SD)	167.4 (9.34)	167.2 (8.98)	167.6 (9.43)	167.1 (7.75)	166.6 (10.31)	165.1 (9.18)	167.3 (9.50)	166.9 (8.85)	167.1 (9.18)
Median	167.0	167.0	167.0	168.0	167.0	165.5	167.0	167.0	167.0
(min, max)	(143, 196)	(140, 193)	(143, 193)	(150, 183)	(141, 189)	(138, 192)	(141, 196)	(138, 193)	(138, 196)
Weight (kg)									
Mean (SD)	76.36 (17.964)	76.91 (17.970)	71.03 (14.317)	73.83 (16.162)	77.29 (20.496)	73.46 (16.939)	75.70 (17.973)	75.96 (17.605)	75.83 (17.784)
Median (min, max)	74.40	74.00	69.00	73.00	75.00	70.50	73.00	74.00	74.00
	(43.3, 145.0)	(38.0, 146.0)	(42.7, 114.1)	(35.7, 114.0)	(36.7, 134.0)	(45.0, 118.7)	(36.7, 145.0)	(35.7, 146.0)	(35.7, 146.0)
Body mass index (kg/m)²									
Mean (SD)	27.13 (5.540)	27.38 (5.342)	25.19 (3.975)	26.40 (5.456)	27.58 (5.490)	26.83 (5.191)	26.91 (5.370)	27.16 (5.340)	27.03 (5.354)
Median (min, max)	26.23	26.85	25.72	25.56	27.00	26.80	26.18	26.66	26.39
	(16.1, 50.6)	(15.2, 43.0)	(16.9, 35.2)	(15.9, 41.0)	(17.1, 42.1)	(17.6, 42.8)	(16.1, 50.6)	(15.2, 43.0)	(15.2, 50.6)

Baseline disease characteristics

COPD history

In study 208657, the mean (SD) duration of COPD was 10.2 (6.65) years and 9.7 (5.88) years, in the mepolizumab 100 mg and placebo groups, respectively. Most participants (40% to 45%) had moderate or severe airflow limitation; 13% to 14% had very severe airflow limitation. The majority of participants had significant dyspnea, with an mMRC score of ≥2 at screening. Approximately one quarter of participants had CV co-morbidities and the majority of the participants had co-morbidities other than CV. Nearly all participants met the criteria for GOLD Group E.

Health-related quality of life ((HRQoL)(CAT and SGRQ-C scores)) were similar between treatment groups across the studies. The overall mean scores indicate that the study population had a poor HRQoL and a significant disease impact on health status. Screening BECs were similar between

treatment groups across the studies except in study MEA117106 (wherein screening BEC was marginally lower in the mepolizumab 100 mg group compared to the placebo group)

Similar characteristics as seen in study 208657 COPD history were observed in studies MEA117113 and MEA117106 COPD history for the pooled studies was consistent with study 208657.

Table 113 COPD history and baseline disease characteristics (individual studies and meta-analysis, mITT-300 population)

	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106		
	PBO (N=401)	100 SC (N=403)	PBO (N=87)	100 SC (N=83)	PBO (N=90)	100 SC (N=82)	PBO (N=578)	100 SC (N=568)	PBO + 100 SC (N=1146)
Duration of COPD, n (%)									
≥1 to <5 years	107 (27)	104 (26)	30 (34)	29 (35)	28 (31)	30 (37)	165 (29)	163 (29)	328 (29)
≥5 to <10 years	143 (36)	143 (35)	37 (43)	33 (40)	35 (39)	28 (34)	215 (37)	204 (36)	419 (37)
≥10 to <15 years	90 (22)	89 (22)	12 (14)	8 (10)	16 (18)	11 (13)	118 (20)	108 (19)	226 (20)
≥15 to <20 years	40 (10)	39 (10)	5 (6)	7 (8)	4 (4)	6 (7)	49 (8)	52 (9)	101 (9)
≥20 to <25 years	13 (3)	16 (4)	3 (3)	5 (6)	5 (6)	3 (4)	21 (4)	24 (4)	45 (4)
≥25 years	8 (2)	12 (3)	0	1 (1)	2 (2)	4 (5)	10 (2)	17 (3)	27 (2)
Duration of COPD (years)									
Mean (SD)	9.7 (5.88)	10.2 (6.65)	8.2 (5.10)	8.8 (7.10)	9.3 (6.58)	9.4 (7.06)	9.4 (5.90)	9.9 (6.79)	9.6 (6.36)
Median (min, max)	9.0 (1, 33)	9.0 (1, 40)	7.0 (1, 24)	7.0 (1, 45)	8.0 (1, 32)	8.0 (1, 33)	8.0 (1, 33)	9.0 (1, 45)	8.0 (1, 45)
Severity of airflow limitation [1], n (%)									
Mild: ≥80% predicted	3 (<1)	2 (<1)	1 (1)	2 (2)	2 (2)	1 (1)	6 (1)	5 (<1)	11 (<1)
Moderate: ≥50%-<80% predicted	181 (45)	168 (42)	31 (36)	40 (48)	33 (37)	30 (37)	245 (42)	238 (42)	483 (42)
Severe: ≥30%-<50% predicted	160 (40)	180 (45)	40 (46)	31 (37)	48 (53)	45 (55)	248 (43)	256 (45)	504 (44)
Very severe: <30% predicted	57 (14)	53 (13)	15 (17)	10 (12)	7 (8)	6 (7)	79 (14)	69 (12)	148 (13)
Cardiovascular comorbidity [2], n (%)									
Yes	97 (24)	103 (26)	24 (28)	22 (27)	20 (22)	17 (21)	141 (24)	142 (25)	283 (25)
No	304 (76)	300 (74)	63 (72)	61 (73)	70 (78)	65 (79)	437 (76)	426 (75)	863 (75)
Other comorbidity [3], n (%)									
Yes	323 (81)	316 (78)	72 (83)	66 (80)	68 (76)	61 (74)	463 (80)	443 (78)	906 (79)
No	78 (19)	87 (22)	15 (17)	17 (20)	22 (24)	21 (26)	115 (20)	125 (22)	240 (21)
mMRC score at screening [4], n (%)									
<2	98 (24)	89 (22)	9 (10)	11 (13)	22 (24)	12 (15)	129 (22)	112 (20)	241 (21)
≥2	301 (75)	310 (77)	78 (90)	72 (87)	68 (76)	70 (85)	447 (77)	452 (80)	899 (78)
Missing	2 (<1)	4 (<1)	0	0	0	0	2 (<1)	4 (<1)	6 (<1)
Ever diagnosed with GERD [5], n (%)									
Yes	92 (23)	85 (21)	13 (15)	14 (17)	18 (20)	12 (15)	123 (21)	111 (20)	234 (20)
No	303 (76)	311 (77)	74 (85)	69 (83)	72 (80)	70 (85)	449 (78)	450 (79)	899 (78)
Missing	6 (1)	7 (2)	0	0	0	0	6 (1)	7 (1)	13 (1)
Gold Group E [6]	393 (98)	401 (>99)	87 (100)	83 (100)	90 (100)	82 (100)	570 (99)	566 (>99)	1136 (>99)

	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106		
	PBO (N=401)	100 SC (N=403)	PBO (N=87)	100 SC (N=83)	PBO (N=90)	100 SC (N=82)	PBO (N=578)	100 SC (N=568)	PBO + 100 SC (N=1146)
Screening blood eosinophils, Gi/L									
Geometric mean	0.48	0.48	0.48	0.48	0.50	0.42	0.48	0.47	0.48
(SD Logs)	(0.398)	(0.378)	(0.397)	(0.392)	(0.481)	(0.287)	(0.411)	(0.370)	(0.392)
CAT Total Score [7]									
n	393	389	86	80	85	78	564	547	1111
Mean (SD)	19.1 (6.75)	19.2 (6.95)	19.3 (7.39)	19.4 (7.42)	19.4 (8.10)	18.8 (7.90)	19.2 (7.06)	19.2 (7.15)	19.2 (7.10)
SGRQ-C Total Score [8]									
n	392	388	87	82	88	79	567	549	1116
Mean (SD)	53.9 (17.86)	55.3 (17.73)	53.6 (17.10)	53.4 (16.69)	55.1 (16.27)	54.3 (17.54)	54.0 (17.49)	54.9 (17.53)	54.4 (17.51)

[1] Classification based on post-bronchodilator FEV1 at Screening, Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines for COPD.
[2] Participants with Cardiovascular comorbidity are defined as participants with any past or current medical condition under Cardiac Disorders.
[3] Participants with Other comorbidity are defined as participants with any past or current medical condition other than under Cardiac Disorders.
[4] mMRC=Modified Medical Research Council Score.
[5] GERD=Gastroesophageal Reflux Disease.
[6] Based on refined ABE assessment tool (GOLD Guidelines for COPD 2023). Group E participants have ≥2 moderate exacerbations or ≥1 exacerbation leading to hospitalization.
[7] SGRQ Total Score range 0-100 with higher scores indicating poor health-related quality of life.
[8] CAT score range 0-40 with higher scores indicating greater COPD disease impact.

Exacerbation history

In study 208657, majority of the participants had at least 2 previous moderate/severe exacerbations in the 12 months prior to screening. Moderate exacerbations for inclusion into the trial must have been treated with corticosteroids, with or without antibiotics – in contrast, in studies MEA117113 and MEA117106 exacerbations treated with antibiotics alone could also qualify. Approximately one-fifth of participants had previously reported a severe exacerbation (i.e., requiring hospitalization) in the 12 months prior to screening; very few participants (1%) reported an exacerbation requiring hospitalization in ICU.

The number of participants reporting severe exacerbations were lower in study 208657 compared with studies MEA117113 and MEA117106. Exacerbation history was generally similar between

treatment groups in all 3 COPD studies (mITT-300 population) with respiratory infection being the primary historical cause of the exacerbations across the studies.

For the pooled studies (mITT-300 population), overall, similar profile of the exacerbation history was observed. Overall, participants were not well controlled on their ICS-based triple maintenance therapy and had a mean (SD) of 2.4 (1.13) moderate/severe COPD exacerbations in the 12 months prior to screening. The majority of participants had at least 2 moderate/severe exacerbations (61%) and at least 1 severe exacerbation was reported by 25% of participants in the previous 12 months.

Table 114 Exacerbation history (individual studies and meta-analysis, mITT-300 population)

	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106		
	PBO (N=401)	100 SC (N=403)	PBO (N=87)	100 SC (N=83)	PBO (N=90)	100 SC (N=82)	PBO (N=578)	100 SC (N=568)	PBO + 100 SC (N=1146)
Number of moderate/severe exacerbations, n (%)									
0	3 (<1)	0	0	0	0	0	3 (<1)	0	3 (<1)
≥1	398 (>99)	403 (100)	87 (100)	83 (100)	90 (100)	82 (100)	575 (>99)	568 (100)	1143 (>99)
1	43 (11)	40 (10)	11 (13)	8 (10)	8 (9)	8 (10)	62 (11)	56 (10)	118 (10)
2	266 (66)	254 (63)	45 (52)	43 (52)	48 (53)	46 (56)	359 (62)	343 (60)	702 (61)
3	64 (16)	70 (17)	17 (20)	12 (14)	22 (24)	15 (18)	103 (18)	97 (17)	200 (17)
4	13 (3)	20 (5)	7 (8)	11 (13)	6 (7)	6 (7)	26 (4)	37 (7)	63 (5)
>4	12 (3)	19 (5)	7 (8)	9 (11)	6 (7)	7 (9)	25 (4)	35 (6)	60 (5)
Mean (SD)	2.2 (0.90)	2.3 (0.98)	2.6 (1.34)	2.8 (1.67)	2.6 (1.39)	2.6 (1.38)	2.3 (1.08)	2.4 (1.18)	2.4 (1.13)
Median (min, max)	2.0 (0, 8)	2.0 (1, 7)	2.0 (1, 8)	2.0 (1, 10)	2.0 (1, 10)	2.0 (1, 8)	2.0 (0, 10)	2.0 (1, 10)	2.0 (0, 10)
Number of moderate exacerbations, n (%)									
0	53 (13)	53 (13)	14 (16)	9 (11)	12 (13)	16 (20)	79 (14)	78 (14)	157 (14)
≥1	348 (87)	350 (87)	73 (84)	74 (89)	78 (87)	66 (80)	499 (86)	490 (86)	989 (86)
1	20 (5)	13 (3)	9 (10)	7 (8)	9 (10)	11 (13)	38 (7)	31 (5)	69 (6)
2	252 (63)	251 (62)	38 (44)	40 (48)	43 (48)	37 (45)	333 (58)	328 (58)	661 (58)
3	53 (13)	60 (15)	17 (20)	14 (17)	17 (19)	9 (11)	87 (15)	83 (15)	170 (15)
>3	23 (6)	26 (6)	9 (10)	13 (16)	9 (10)	9 (11)	41 (7)	48 (8)	89 (8)
Number of severe exacerbations, n (%)									
0	324 (81)	315 (78)	54 (62)	54 (65)	61 (68)	50 (61)	439 (76)	419 (74)	858 (75)
≥1	77 (19)	88 (22)	33 (38)	29 (35)	29 (32)	32 (39)	139 (24)	149 (26)	288 (25)
1	63 (16)	67 (17)	25 (29)	26 (31)	24 (27)	17 (21)	112 (19)	110 (19)	222 (19)
2	11 (3)	9 (2)	6 (7)	2 (2)	2 (2)	10 (12)	19 (3)	21 (4)	40 (3)
3	1 (<1)	8 (2)	1 (1)	0	2 (2)	2 (2)	4 (<1)	10 (2)	14 (1)
>3	2 (<1)	4 (<1)	1 (1)	1 (1)	1 (1)	3 (4)	4 (<1)	8 (1)	12 (1)

	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106		
	PBO (N=401)	100 SC (N=403)	PBO (N=87)	100 SC (N=83)	PBO (N=90)	100 SC (N=82)	PBO (N=578)	100 SC (N=568)	PBO + 100 SC (N=1146)
Number of exacerbations treated with systemic corticosteroids and/or antibiotics but did not require hospitalization/ER visit, n (%)									
0	64 (16)	71 (18)	16 (18)	10 (12)	17 (19)	21 (26)	97 (17)	102 (18)	199 (17)
≥1	337 (84)	332 (82)	71 (82)	73 (88)	73 (81)	61 (74)	481 (83)	466 (82)	947 (83)
1	35 (9)	22 (5)	9 (10)	7 (8)	10 (11)	11 (13)	54 (9)	40 (7)	94 (8)
2	226 (56)	223 (55)	39 (45)	44 (53)	39 (43)	34 (41)	304 (53)	301 (53)	605 (53)
3	55 (14)	58 (14)	17 (20)	11 (13)	15 (17)	8 (10)	87 (15)	77 (14)	164 (14)
>3	21 (5)	29 (7)	6 (7)	11 (13)	9 (10)	8 (10)	36 (6)	48 (8)	84 (7)
Number of exacerbations required ER visit but not hospitalization, n (%)									
0	349 (87)	359 (89)	80 (92)	74 (89)	80 (89)	71 (87)	509 (88)	504 (89)	1013 (88)
≥1	52 (13)	44 (11)	7 (8)	9 (11)	10 (11)	11 (13)	69 (12)	64 (11)	133 (12)
1	31 (8)	20 (5)	5 (6)	5 (6)	3 (3)	8 (10)	39 (7)	33 (6)	72 (6)
2	16 (4)	18 (4)	1 (1)	3 (4)	6 (7)	3 (4)	23 (4)	24 (4)	47 (4)
3	4 (<1)	5 (1)	0	1 (1)	0	0	4 (<1)	6 (1)	10 (<1)
>3	1 (<1)	1 (<1)	1 (1)	0	1 (1)	0	3 (<1)	1 (<1)	4 (<1)
Number of exacerbations required hospitalization in general ward without ICU, n (%)									
0	328 (82)	319 (79)	56 (64)	56 (67)	62 (69)	51 (62)	446 (77)	426 (75)	872 (76)
≥1	73 (18)	84 (21)	31 (36)	27 (33)	28 (31)	31 (38)	132 (23)	142 (25)	274 (24)
1	61 (15)	63 (16)	23 (26)	24 (29)	23 (26)	18 (22)	107 (19)	105 (18)	212 (18)
2	9 (2)	10 (2)	6 (7)	2 (2)	2 (2)	8 (10)	17 (3)	20 (4)	37 (3)
3	1 (<1)	7 (2)	1 (1)	0	2 (2)	2 (2)	4 (<1)	9 (2)	13 (1)
>3	2 (<1)	4 (<1)	1 (1)	1 (1)	1 (1)	3 (4)	4 (<1)	8 (1)	12 (1)
Number of exacerbations required hospitalization in ICU, n (%)									
0	395 (99)	398 (99)	84 (97)	81 (98)	89 (99)	78 (95)	568 (98)	557 (98)	1125 (98)
≥1	6 (1)	5 (1)	3 (3)	2 (2)	1 (1)	4 (5)	10 (2)	11 (2)	21 (2)
1	6 (1)	5 (1)	3 (3)	2 (2)	1 (1)	4 (5)	10 (2)	11 (2)	21 (2)
2	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0
>3	0	0	0	0	0	0	0	0	0

Smoking history

In study 208657, approximately two-thirds of the participants were former smokers and one-third participants were reported as current smokers; smokers had a mean (SD) of 43.2 (25.99) and 42.7 (23.74) smoking-pack years in mepolizumab 100 mg group and placebo group, respectively.

Participants without a history of tobacco exposure ('Never smoked') were permitted in studies MEA117113 and MEA117106 but not in study 208657. However, these participants comprised a very small proportion of the respective study populations.

For the pooled studies (mITT-300 population), the smoking history observed were consistent with the study 208657 results.

Comparison of efficacy results of all studies

Moderate/severe COPD exacerbations

Overview of moderate/severe COPD exacerbations

In study 208657, the incidence and frequency of on- and off-treatment moderate/severe exacerbations was lower in the mepolizumab 100 mg group (50%; 482 events) compared with the placebo group (56%; 554 events) The majority of exacerbations occurred while on-treatment; hence, a similar trend was observed for on-treatment exacerbations.

Rate of moderate/severe COPD exacerbations

In study 208657, treatment with mepolizumab 100 mg resulted in a statistically and clinically significant 21% reduction in the annualized rate of moderate/severe exacerbations compared with placebo group, p=0.011. Over the treatment period, the cumulative number of exacerbations was fewer in the mepolizumab 100 mg group than the placebo group.

The treatment estimates in studies MEA117113 and MEA117106 (mITT-300 population) were generally similar with study 208657. Over the treatment period, the cumulative number of exacerbations was fewer in the mepolizumab group compared with the placebo group.

In the meta-analysis, there was a 21% reduction in the annualized rate of moderate/severe exacerbations for mepolizumab compared with placebo.

Figure 50 Forest plot of rate of moderate/severe exacerbations: 100 SC versus placebo: individual studies and meta-analysis (mITT-300 population)

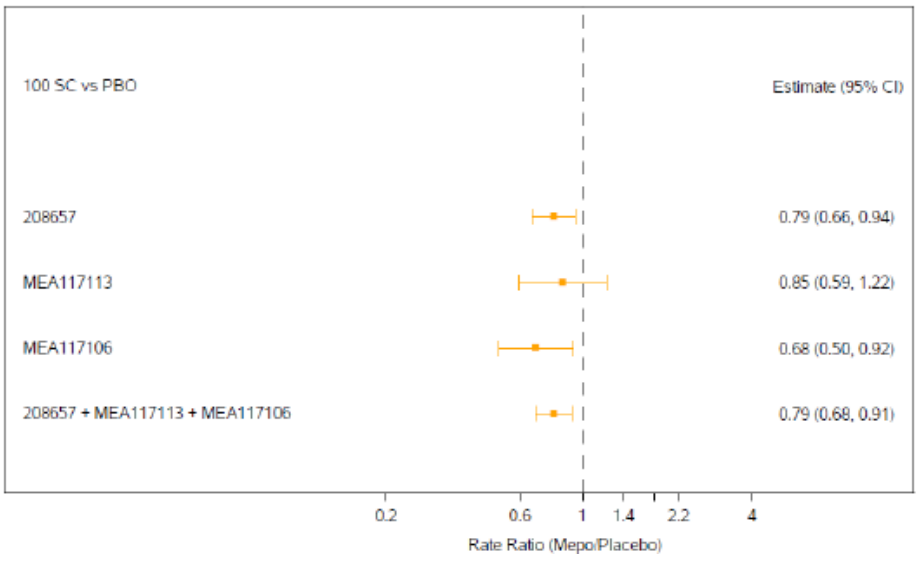


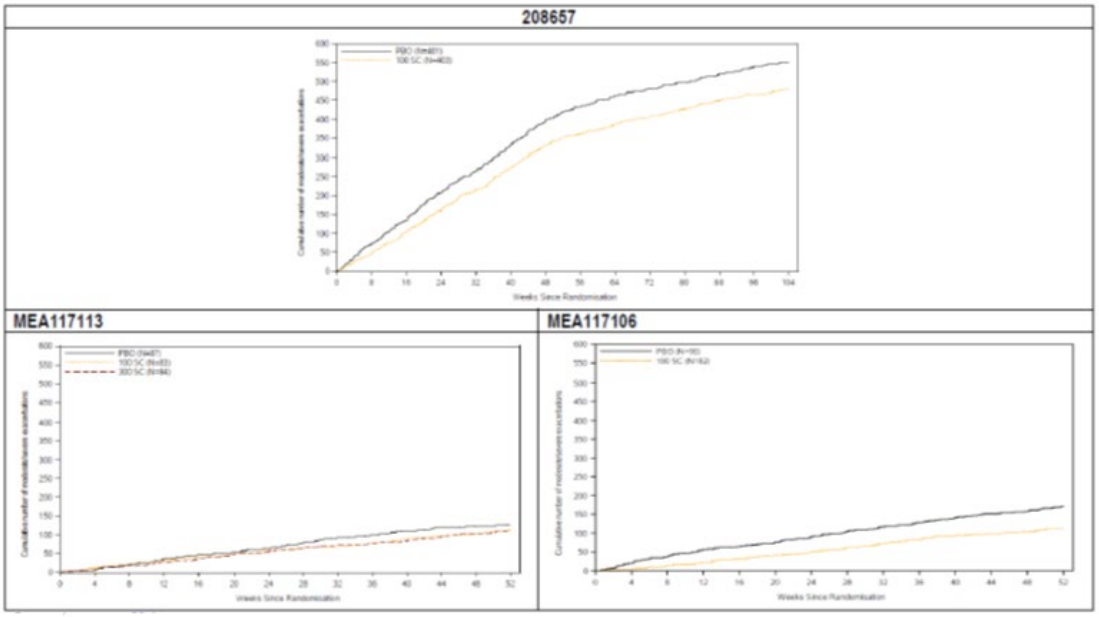
Table 115 Rate of moderate/severe exacerbations: individual studies and meta-analysis (Negative Binomial Model, mITT-300 population)

Moderate/severe exacerbation	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106	
	PBO (N=401)	100 SC (N=403)	PBO (N=87)	100 SC (N=83)	PBO (N=90)	100 SC (N=82)	PBO (N=578)	100 SC (N=568)
n	401	403	87	83	90	82	578	568
Exacerbation rate/year	1.01	0.80	1.43	1.22	1.94	1.32	1.25	0.98
Rate ratio vs placebo [1]		0.79		0.85		0.68		0.79 [2]
95% CI		(0.66, 0.94)		(0.59, 1.22)		(0.50, 0.92)		(0.68, 0.91)
p-value		0.011		0.387		0.013		0.002

[1] Analysis performed using a negative binomial regression model with covariates of treatment group, smoking status, baseline % predicted FEV1, number of exacerbations in previous year (as an ordinal variable), and geographic region (as defined for the study/ISE) with log(time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

[2] Analysis model as in footnote "[1]" with an additional covariate of study.

Figure 51 Cumulative number of moderate/severe exacerbations: individual studies (mITT-300 population)



Note: Contains both on-treatment and off-treatment exacerbation data. X-axes are not drawn to the same scale.

Time to first moderate/severe COPD exacerbation

In study 208657, cumulative incidence as seen in the Kaplan-Meier plot showed that the probability of a first moderate/severe exacerbation was lower for the mepolizumab 100 mg group compared with the placebo group over the course of the study. The time to first event analysis showed a statistically significant reduction in the risk of moderate/severe exacerbation for the mepolizumab 100 mg group compared with the placebo group (hazard ratio: 0.77; 95% CI: 0.64, 0.93; p=0.009).

Consistent results showing estimates of HR that favoured mepolizumab 100 mg treatment were observed in studies MEA117113 and MEA117106 (mITT-300 population).

The results from the pooled studies (mITT-300 population) were consistent with study 208657 as seen in the Kaplan-Meier plot (Figure 6); and the probability of having a moderate/severe exacerbation was lower in the mepolizumab 100 mg group compared with the placebo group with a HR of 0.72 (95% CI: 0.62, 0.85)

Table 116 Time to first moderate/severe exacerbation: individual studies and meta-analysis (mITT-300 population)

Probability of a moderate/severe exacerbation	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106	
	PBO (N=401)	100 SC (N=403)	PBO (N=87)	100 SC (N=83)	PBO (N=90)	100 SC (N=82)	PBO (N=578)	100 SC (N=568)
By Week 8								
Probability of an exacerbation [1]	15.1%	11.3%	21.9%	24.1%	35.7%	16.0%	19.4%	13.8%
95% CI	(11.9%, 19.0%)	(8.5%, 14.8%)	(14.5%, 32.1%)	(16.3%, 34.8%)	(26.7%, 46.5%)	(9.6%, 26.0%)	(16.4%, 22.8%)	(11.2%, 17.0%)
By Week 24								
Probability of an exacerbation [1]	35.4%	28.3%	50.8%	41.1%	57.3%	41.9%	41.1%	32.2%
95% CI	(30.9%, 40.3%)	(24.2%, 33.1%)	(40.7%, 61.9%)	(31.4%, 52.4%)	(47.3%, 67.7%)	(32.1%, 53.4%)	(37.2%, 45.3%)	(28.5%, 36.2%)
By Week 52								
Probability of an exacerbation [1]	53.4%	46.1%	65.8%	54.9%	82.7%	58.6%	59.9%	49.2%
95% CI	(48.5%, 58.5%)	(41.2%, 51.2%)	(55.6%, 75.9%)	(44.5%, 65.9%)	(74.1%, 89.7%)	(48.0%, 69.5%)	(55.8%, 64.0%)	(45.0%, 53.5%)
By Week 64								
Probability of an exacerbation [1]	58.9%	51.4%					64.6%	54.5%
95% CI	(53.3%, 64.6%)	(45.8%, 57.2%)					(59.9%, 69.3%)	(49.5%, 59.5%)
By Week 96								
Probability of an exacerbation [1]	67.2%	62.3%					71.8%	64.7%
95% CI	(60.5%, 73.8%)	(55.6%, 69.0%)					(66.0%, 77.3%)	(58.5%, 70.8%)
By Week 104								
Probability of an exacerbation [1]	68.3	64.5%					72.7%	66.8%
95% CI	(61.4, 74.9)	(57.5%, 71.4%)					(66.8%, 78.3%)	(60.3%, 73.1%)
Hazard ratio (mepo/placebo) [2]		**0.77**		**0.83**		**0.50**		**0.72** [3]
95% CI		(0.64, 0.93)		(0.55, 1.24)		(0.34, 0.72)		(0.62, 0.85)
p-value		0.009		0.363		<0.001		<0.001

[1] Kaplan-Meier estimate.
[2] Estimated from a Cox proportional Hazards Model with covariates of treatment group, smoking status, baseline % predicted FEV1, number of exacerbations in previous year (as an ordinal variable), and geographic region (as defined for the study/ISE).
[3] Analysis model as in footnote "[2]" with an additional covariate of study.

Exacerbations requiring ED visit/hospitalization

Rate of exacerbations requiring ED visit/hospitalization

In study 208657, participants treated with mepolizumab 100 mg showed a 35% reduction in the annualized rate of exacerbations requiring ED visit/hospitalization compared with placebo (rate ratio: 0.65; 95% CI: 0.43, 0.96)Over the treatment period, the cumulative number of exacerbations and percentage of participants with exacerbations requiring ED visit/hospitalization was fewer in the mepolizumab 100 mg group compared with the placebo group.

Similar rate reduction as seen in study 208657 was observed in the mITT-300 population for study MEA117113. A numerically lower reduction in rate of exacerbations was observed in study MEA117106 Similar trends in the cumulative number of exacerbations and percentage of patients with exacerbations requiring ED visit/hospitalization were also observed in studies MEA117113 and MEA117106 (mITT-300 population).

In totality, for the pooled studies (mITT-300 population), participants treated with mepolizumab 100 mg group showed a 29% reduction in annualized rate of exacerbations requiring ED visit and/or hospitalization compared with placebo group.

Figure 52 Forest plot of rate of exacerbations requiring EDvisit/hospitalization: 100 SC versus placebo (mITT-300 population)

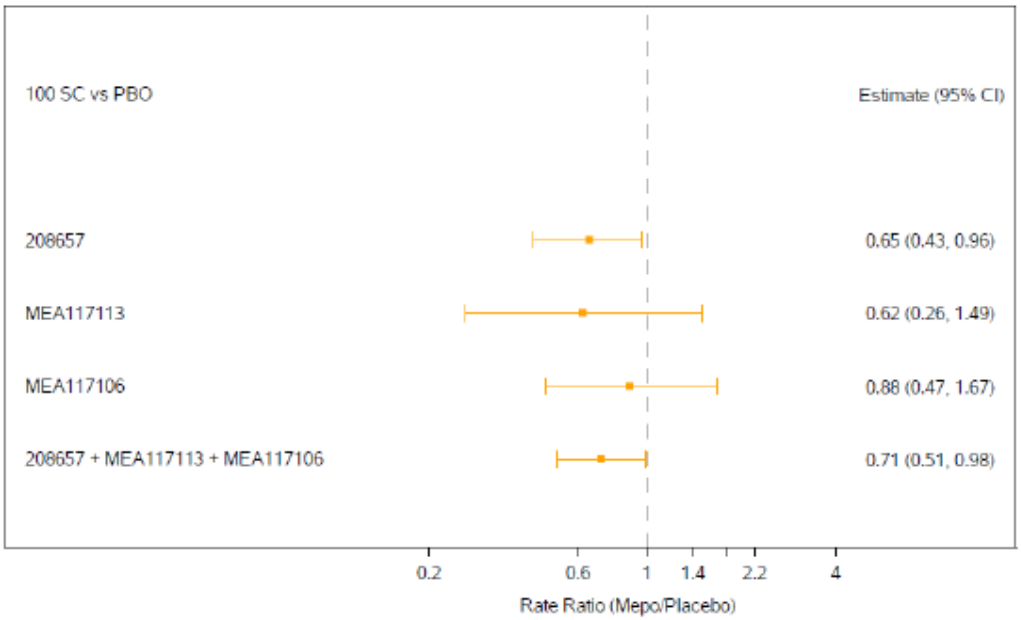


Table 117 Rate of exacerbations requiring ED visit/ hospitalization: individual studies and meta-analysis (Negative Binomial Model) (mITT-300 population)

Exacerbation requiring ED Visit/ Hospitalization	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106	
	PBO (N=401)	100 SC (N=403)	PBO (N=87)	100 SC (N=83)	PBO (N=90)	100 SC (N=82)	PBO (N=578)	100 SC (N=568)
n	401	403	87	83	90	82	578	568
Exacerbation rate/year	0.20	0.13	0.25	0.16	0.24	0.21	0.23	0.16
Rate ratio vs placebo [1]		0.65		0.62		0.88		0.71 [2]
95% CI		(0.43, 0.96)		(0.26, 1.49)		(0.47, 1.67)		(0.51, 0.98)
p-value		0.032		0.285		0.701		0.038

[1] Analysis performed using a negative binomial regression model with covariates of treatment group, smoking status, baseline % predicted FEV1, number of exacerbations in previous year (as an ordinal variable), and geographic region (as defined for the study/ISE) with log (time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.
[2] Analysis model as in footnote "[1]" with an additional covariate of study.

Time to first exacerbation requiring ED visit/hospitalization

In study 208657, cumulative incidence as seen in the Kaplan-Meier plot showed that the probability of a first moderate/severe exacerbation was lower for mepolizumab 100 mg group compared with the placebo group over the course of the study. The time to first event analysis showed a reduction in the risk of exacerbation requiring ED visit and/or hospitalization for mepolizumab compared with placebo (hazard ratio: 0.73; 95% CI: 0.51, 1.04).

Consistent results showing the hazard ratio favored mepolizumab 100 mg treatment were observed across the individual COPD studies (mITT-300 population)

Table 118 Time to first exacerbation requiring ED visit/hospitalization: individual studies and meta-analysis (mITT-300 population)

Probability of an exacerbation requiring ED visit/hospitalization	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106	
	PBO (N=401)	100 SC (N=403)	PBO (N=87)	100 SC (N=83)	PBO (N=90)	100 SC (N=82)	PBO (N=578)	100 SC (N=568)
By Week 8								
Probability of an exacerbation [1]	3.3	3.0%	3.4%	3.6%	7.8%	3.7%	4.0%	3.2%
95% CI	(1.9%, 5.6%)	(1.7%, 5.2%)	(1.1%, 10.3%)	(1.2%, 10.8%)	(3.8%, 15.7%)	(1.2%, 11.0%)	(2.7%, 6.0%)	(2.0%, 5.0%)
By Week 24								
Probability of an exacerbation [1]	9.5%	6.6%	10.6%	9.7%	13.5%	9.9%	10.3%	7.5%
95% CI	(7.0%, 12.9%)	(4.5%, 9.5%)	(5.7%, 19.4%)	(4.9%, 18.4%)	(7.9%, 22.6%)	(5.1%, 18.8%)	(8.0%, 13.1%)	(5.6%, 10.0%)
By Week 52								
Probability of an exacerbation [1]	16.2%	12.7%	21.8%	16.0%	24.2%	18.6%	18.2%	14.1%
95% CI	(12.8%, 20.3%)	(9.8%, 16.5%)	(14.3%, 32.4%)	(9.6%, 25.9%)	(16.5%, 34.6%)	(11.6%, 28.9%)	(15.3%, 21.7%)	(11.4%, 17.3%)
By Week 64								
Probability of an exacerbation [1]	18.8%	14.5%					20.8%	15.8%
95% CI	(14.8%, 23.6%)	(11.1%, 18.8%)					(17.1%, 25.1%)	(12.7%, 19.7%)
By Week 96								
Probability of an exacerbation [1]	22.2%	17.6%					24.1%	18.9%
95% CI	(17.4%, 28.1%)	(13.4%, 23.0%)					(19.6%, 29.6%)	(14.9%, 23.9%)
By Week 104								
Probability of an exacerbation [1]	23.4%	17.6%					25.3%	18.9%
95% CI	(18.2%, 29.7%)	(13.4%, 23.0%)					(20.3%, 31.1%)	(14.9%, 23.9%)
Hazard ratio (mepo/placebo) [2]		**0.73**		**0.81**		**0.68**		**0.74** [3]
95% CI		(0.51, 1.04)		(0.39, 1.67)		(0.35, 1.34)		(0.56, 0.98)
p-value		0.079		0.562		0.267		0.037

[1] Kaplan-Meier estimate.
[2] Estimated from a Cox proportional Hazards Model with covariates of treatment group, smoking status, baseline % predicted FEV1, number of exacerbations in previous year (as an ordinal variable), and geographic region (as defined for the study/ISE).
[3] Analysis model as in footnote "[2]" with an additional covariate of study.

Proportion of participants with at least one exacerbation requiring ED visit/hospitalization

In study 208657, a lower proportion of participants had at least one exacerbation requiring ED visit/hospitalization following mepolizumab 100 mg (14%) treatment compared with placebo (18%). The risk of having at least one exacerbation requiring ED visit/hospitalization was numerically lower for participants treated with mepolizumab 100 mg compared with placebo (relative risk: 0.78; 95% CI: 0.57, 1.08). Consistent results were observed in studies MEA117113 and MEA117106 (mITT-300 population).

Study 208657 results were supported by the meta-analysis (mITT-300 population). The risk of having at least one exacerbation requiring ED visit/hospitalization was numerically lower for participants treated with mepolizumab 100 mg compared with placebo (relative risk: 0.78; 95% CI: 0.60, 1.01).

Table 119 Proportion with at least one exacerbation requiring ED visit/hospitalization: individual studies and meta-analysis (mITT-300 population)

Proportion of participants with at least one exacerbation requiring ED visit/hospitalization	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106	
	PBO (N=401)	100 SC (N=403)	PBO (N=87)	100 SC (N=83)	PBO (N=90)	100 SC (N=82)	PBO (N=578)	100 SC (N=568)
n	401	403	87	83	90	82	578	568
≥1 exacerbation requiring ED/hospitalization, n (%)	71 (18)	56 (14)	18 (21)	13 (16)	21 (23)	15 (18)	110 (19)	84 (15)
Relative risk to placebo		0.78		0.76		0.78		0.78 [1]
95% CI		(0.57, 1.08)		(0.40, 1.45)		(0.43, 1.42)		(0.60, 1.01)
p-value		0.139		0.398		0.419		0.060

Note: Contains both on-treatment and off-treatment exacerbation data.
Note: 208657 study with an extended follow-up period up to 2 years.
[1] CMH adjusted relative risk to placebo.

Severe COPD exacerbations

Rate of severe COPD exacerbations

In study 208657, participants treated with mepolizumab 100 mg resulted in a 34% reduction in the annualized rate of severe exacerbations (requiring hospitalization and/or resulting in death) compared with placebo. Over the treatment period, the cumulative number of severe exacerbations and the percentage of participants with severe exacerbations was lower in the mepolizumab 100 mg group compared with the placebo group. In the individual studies (mITT-300 population), severe exacerbations were generally infrequent. Results from studies MEA117113 and MEA117106 (mITT-300 population) were similar to study 208657. Results from the pooled studies (mITT-300 population) were consistent with study 208657 (rate ratio: 0.75; 95% CI: 0.52, 1.07).

Table 120 Rate of severe exacerbations (negative binomial model): individual studies and meta-analysis (mITT-300 population)

Severe exacerbation	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106	
	PBO (N=401)	100 SC (N=403)	PBO (N=87)	100 SC (N=83)	PBO (N=90)	100 SC (N=82)	PBO (N=578)	100 SC (N=568)
n	401	403	87	83	90	82	578	568
Exacerbation rate/year	0.15	0.10	0.13	0.10	0.19	0.16	0.17	0.13
Rate ratio vs placebo [1]		0.66		0.75		0.85		0.75 [2]
95% CI		(0.43, 1.01)		(0.28, 1.99)		(0.41, 1.77)		(0.52, 1.07)
p-value		0.055		0.568		0.668		0.113

[1] Analysis performed using a negative binomial regression model with covariates of treatment group, smoking status, baseline % predicted FEV1, number of exacerbations in previous year (as an ordinal variable), and geographic region (as defined for the study/ISE) with log(time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.

[2] Analysis model as in footnote "[1]" with an additional covariate of study.

Time to first severe exacerbation

In study 208657, cumulative incidence as seen in the Kaplan-Meier plot showed that the probability of a first severe exacerbation was lower for mepolizumab 100 mg group compared with placebo group over the course of the study. The time to first event analysis showed a reduction in the risk of severe exacerbation for mepolizumab compared with placebo (hazard ratio: 0.74; 95% CI: 0.50, 1.08)

Consistent results showing the hazard ratio favored mepolizumab 100 mg treatment were observed across the individual COPD studies (mITT-300 population)

The results of the meta-analysis (mITT-300 population) were consistent with study 208657, with a hazard ratio of 0.73 (95% CI: 0.53, 1.01).

Proportion of participants with at least one severe exacerbation

In study 208657, a lower proportion of participants had at least one severe exacerbation following mepolizumab 100 mg (11%) treatment compared with placebo (15%). The risk of having at least one severe exacerbation was numerically lower for participants treated with mepolizumab 100 mg compared with placebo (relative risk: 0.78; 95% CI: 0.54, 1.11).

Consistent results were observed in the individual COPD studies (mITT-300 population). Similar results were observed in the meta-analysis (mITT-300 population) with a relative risk of 0.77 (95% CI: 0.58, 1.03).

Table 121 Proportion with at least one severe exacerbation: individual studies and meta-analysis (mITT-300 population)

Proportion of subjects with at least one severe exacerbation	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106	
	PBO (N=401)	100 SC (N=403)	PBO (N=87)	100 SC (N=83)	PBO (N=90)	100 SC (N=82)	PBO (N=578)	100 SC (N=568)
n	401	403	87	83	90	82	578	568
≥1 severe exacerbation, n (%)	59 (15)	46 (11)	14 (16)	10 (12)	17 (19)	12 (15)	90 (16)	68 (12)
Relative risk to placebo 95% CI p-value		0.78 (0.54, 1.11) 0.166		0.75 (0.35, 1.59) 0.451		0.77 (0.39, 1.52) 0.458		0.77 [1] (0.58, 1.03) 0.082

Note: Contains both on-treatment and off-treatment exacerbation data.
Note: 208657 study with an extended follow-up period up to 2 years.
[1] CMH adjusted relative risk to placebo.

CAT

CAT total score responders

In study 208657, the proportion of CAT responders at Week 52 was similar between the mepolizumab 100 mg group (41%) and placebo group (46%).

The results observed in study 208657 were inconsistent with the results in MEA117113 and MEA117106 (mITT-300 populations), both of which showed a numerical trend for a higher proportion of CAT responders in the mepolizumab 100 mg group compared with the placebo group.

The meta-analysis did not show a treatment effect on the proportion of CAT responders (odds ratio: 0.93; 95% CI: 0.73, 1.19).

Figure 53 Forest plot for CAT responders: participants with at least 2-point improvement in total score from baseline at Week 52 (100 SC versus Placebo) (individual studies and meta-analysis [mITT-300 population])

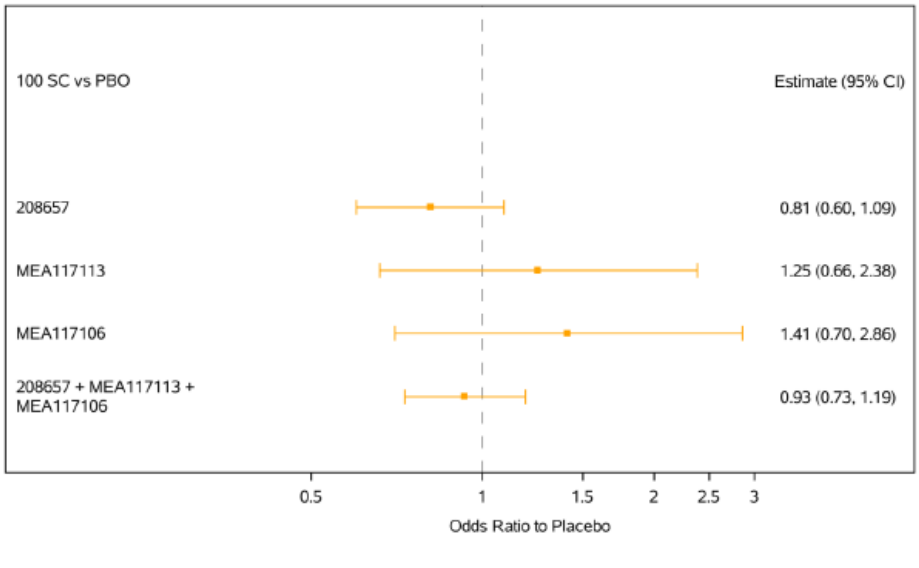


Table 122 CAT responders: participants with at least 2-point improvement in total score from baseline (individual studies and meta-analysis)

n (%)	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106	
	PBO (N=401)	100 SC (N=403)	PBO (N=87)	100 SC (N=83)	PBO (N=90)	100 SC (N=82)	PBO (N=578)	100 SC (N=568)
Visit: Week 52								
n	394	391	86	80	85	78	565	549
Responder [1]	180 (46)	162 (41)	32 (37)	34 (43)	33 (39)	34 (44)	245 (43)	230 (42)
Non-responder	206 (52)	220 (56)	54 (63)	46 (58)	52 (61)	44 (56)	312 (55)	310 (56)
No change/worsening	150 (38)	167 (43)	34 (40)	37 (46)	37 (44)	35 (45)	221 (39)	239 (44)
Withdrawal from study prior to visit	36 (9)	33 (8)	17 (20)	5 (6)	8 (9)	4 (5)	61 (11)	42 (8)
Missing visit	20 (5)	20 (5)	3 (3)	4 (5)	7 (8)	5 (6)	30 (5)	29 (5)
Imputed [2]	8 (2)	9 (2)					8 (1)	9 (2)
Odds ratio to placebo [3]		0.81		1.25		1.41		0.93 [4]
95% CI		(0.60, 1.09)		(0.66, 2.38)		(0.70, 2.86)		(0.73, 1.19)
p-value		0.161		0.491		0.335		0.571

[1] Defined as a participant with a ≥2-point improvement (decrease) from baseline in CAT score.
[2] Participants with an intercurrent event of either treatment interruption or treatment discontinuation related to the COVID-19 pandemic have data set to missing following the event. Missing data was imputed following a MAR assumption based on 2000 imputations.
[3] Analysis performed using a logistic regression model with covariates of baseline score, geographic region (as defined for the study/ISE), smoking status (current versus never/ex-smoker), and treatment group. Estimates combined using Rubin's rules (for study 208657 and meta-analysis).
[4] Analysis model as in footnote "[3]" with an additional covariate of study.
Note: Includes visits up to Week 52 for study 208657.

Analysis of change from baseline in CAT score

In study 208657, at Week 52, the adjusted mean reduction from baseline in CAT score was similar in both the treatment groups.

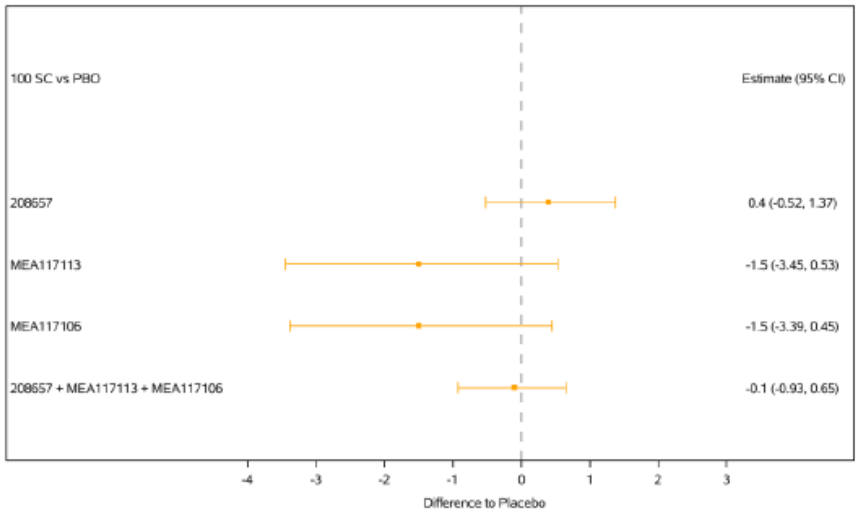
In MEA117113 and MEA117106 studies (mITT-300 population), treatment difference observed at Week 52 favoured mepolizumab 100 mg over placebo. The meta-analysis did not show a treatment effect on the adjusted mean reduction from baseline in CAT score.

Table 123 Change from baseline in CAT score - mixed model repeated measures: individual studies and meta-analysis (mITT-300 population)

	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106	
	PBO (N=401)	100 SC (N=403)	PBO (N=87)	100 SC (N=83)	PBO (N=90	100 SC (N=82)	PBO (N=578)	100 SC (N=568)
Visit: Week 52								
n [1]	384	382	86	80	83	78	547	537
n [2]	338	338	66	71	70	69	474	478
LS mean (SE)	16.6 (0.34)	17.0 (0.34)	18.3 (0.72)	16.9 (0.71)	18.6 (0.68)	17.1 (0.69)	17.4 (0.31)	17.2 (0.31)
LS mean Change (SE)	-2.5 (0.34)	-2.1 (0.34)	-0.5 (0.72)	-2.0 (0.71)	-0.4 (0.68)	-1.8 (0.69)	-1.6 (0.31)	-1.8 (0.31)
Column vs placebo [3]								
Difference		0.4		-1.5		-1.5		-0.1 [4]
95% CI		(-0.52, 1.37)		(-3.45, 0.53)		(-3.39, 0.45)		(-0.93, 0.65)
p-value		0.378		0.150		0.133		0.730

[1] Number of participants with analysable data for one or more time points.
[2] Number of participants with analysable data at the given time point.
[3] Analysis performed using mixed model repeated measures with covariates of baseline score, geographic region (as defined for the study/ISE), smoking status (current versus never/ ex-smoker) and treatment and visit, plus interaction terms for visit by baseline and visit by treatment group.
[4] Analysis model as in footnote "[3]" with an additional covariate of study.
Note: Estimates are based on weighting applied to each level of class variable determined from observed proportions. Intercurrent events of treatment interruption or treatment discontinuation related to the COVID-19 pandemic have data set to missing following the event. Missing data imputed as MAR using 2000 imputations.
Note: Includes visits up to Week 52 for study 208657.

Figure 54 COPD assessment test (CAT) score: change from baseline at Week 52: treatment difference to placebo: 100 SC versus placebo: individual studies and meta-analysis (mITT-300 population)



SGRQ-C

SGRQ-C total scores can range from 0 to 100 with higher scores indicating a poorer HRQoL and reductions in scores indicating improvement in HRQoL. A clinically meaningful improvement in SGRQ-C Total Score is defined as a decrease of ≥4 points from baseline.

SGRQ-C total score responders

In study 208657, the proportion of SGRQ responders (achieving ≥4-point improvement in SGRQ score) at Week 52 was numerically higher in mepolizumab 100 mg group (50%) compared with placebo group (46%) (odds ratio: 1.17; 95% CI: 0.87, 1.57).

Across the individual studies, the mean baseline SGRQ-C total scores were similar between treatment groups (53.4 to 55.3 points) and were indicative of poor health-related quality of life. A consistent trend, i.e., numerically higher SGRQ-C responders in the mepolizumab group compared with placebo group was observed among the individual COPD studies (mITT-300 population). The cumulative distribution for the change from baseline at week 52 in SGRQ-C total score showed a consistent separate curve between the 2 treatment groups in study 208657 and MEA117113 but this was not seen in study MEA117106.

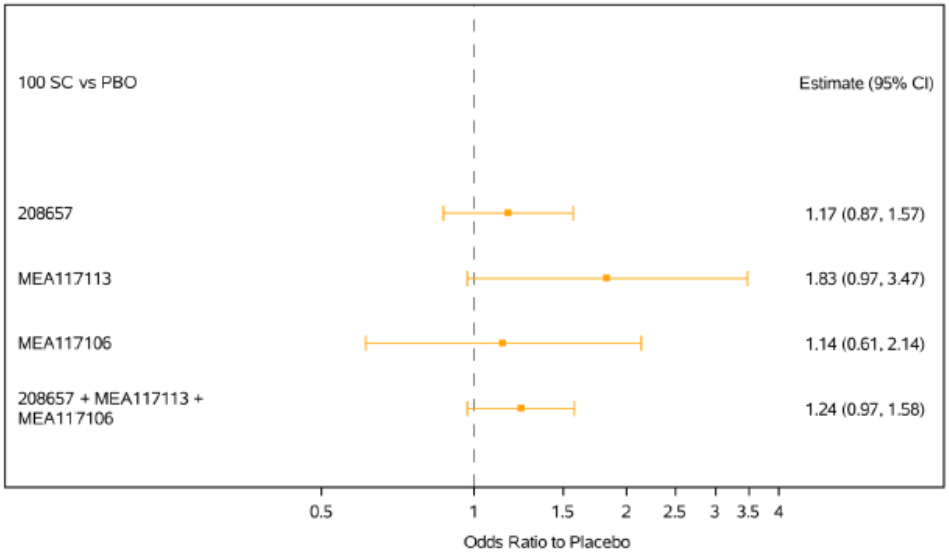
Similar trends were observed in pooled results (mITT-300 population). The proportion of SGRQ responders at Week 52 was numerically higher in mepolizumab 100 mg group (50%) compared with placebo group (44%) (odds ratio: 1.24; 95% CI: 0.97, 1.58).

Table 124 Proportion of participants with at least 4-point improvement in SGRQ-C total score responders from baseline (individual studies and meta-analysis)

n (%)	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106	
	PBO (N=401)	100 SC (N=403)	PBO (N=87)	100 SC (N=83)	PBO (N=90)	100 SC (N=82)	PBO (N=578)	100 SC (N=568)
Visit: Week 52								
n	393	390	87	82	88	79	568	551
Responder [1]	179 (46)	195 (50)	30 (34)	39 (48)	41 (47)	39 (49)	250 (44)	273 (50)
Non-responder	206 (52)	186 (48)	57 (66)	43 (52)	47 (53)	40 (51)	310 (55)	269 (49)
No change/worsening	149 (38)	133 (34)	40 (46)	35 (43)	32 (36)	36 (46)	221 (39)	204 (37)
Withdrawal from study prior to visit	36 (9)	33 (8)	15 (17)	4 (5)	9 (10)	3 (4)	60 (11)	40 (7)
Missing visit	21 (5)	20 (5)	2 (2)	4 (5)	6 (7)	1 (1)	29 (5)	25 (5)
Imputed [2]	8 (2)	9 (2)					8 (1)	9 (2)
Odds ratio to placebo [1]		1.17		1.83		1.14		1.24 [4]
95% CI		(0.87, 1.57)		(0.97, 3.47)		(0.61, 2.14)		(0.97, 1.58)
p-value		0.291		0.064		0.672		0.084

[1] Defined as a participant with a ≥4-point improvement (decrease) from baseline in SGRQ score.
[2] Participants with an intercurrent event of either treatment interruption or treatment discontinuation related to the COVID-19 pandemic have data set to missing following the event. Missing data was imputed following a MAR assumption based on 2000 imputations.
[3] Analysis performed using a logistic regression model with covariates of baseline score, geographic region (as defined for the study/ISE), smoking status (current versus never/ex-smoker), and treatment group. Estimates combined using Rubin's rules (for study 208657 and meta-analysis).
[4] Analysis model as in footnote "[3]" with an additional covariate of study.
Note: Includes visits up to Week 52 for study 208657.
Note: SGRQ scores calculated from conversions applied to SGRQ-C scores (SGRQ-C manual March 2016).

Figure 55 Forest plot of SGRQ-C total score responders from baseline at Week 52 (100 SC versus placebo) (individual studies and meta-analysis [mITT-300 population])



Analysis of change from baseline in SGRQ-C total score at Week 52

In study 208657, at all timepoints, the change from baseline in SGRQ-C score for the mepolizumab 100 mg group was higher when compared with placebo group. At week 52, the LS mean change in SGRQ total score was -8.0 in mepolizumab 100 mg group and -5.7 in placebo group (treatment difference -2.3; 95% CI: -4.64, 0.08).

Across the individual studies (mITT-300 population), at all timepoints, the LS mean reductions in SGRQ-C score from baseline for the mepolizumab 100 mg group was higher when compared with placebo group.

Across the studies, treatment difference observed at Week 52 favoured mepolizumab 100 mg over placebo.

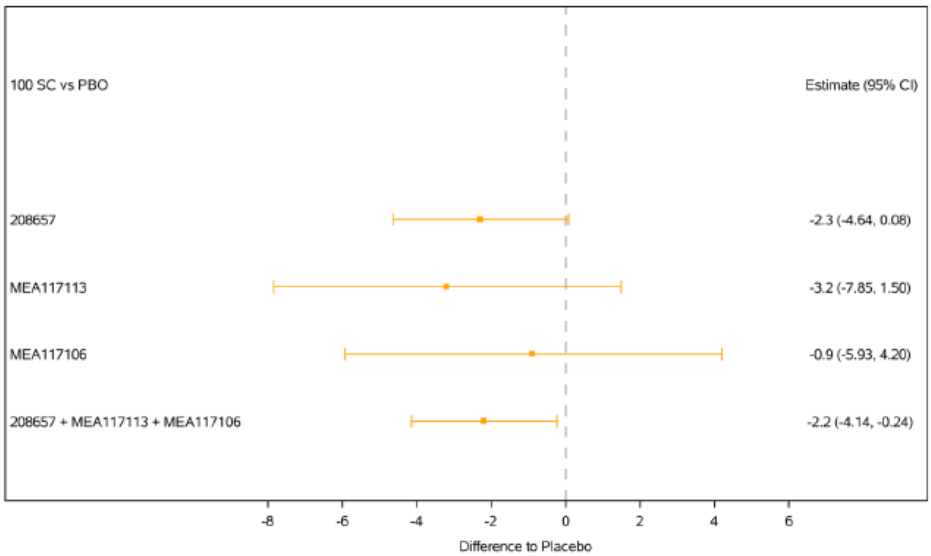
The meta-analysis (mITT-300 population) showed similar trends as seen in study 208657. At Week 52, the LS mean change in SGRQ total score was -7.1 in mepolizumab 100 mg group and -4.9 in placebo group (treatment difference -2.2; 95% CI: -4.14, -0.24).

Table 125 Analysis of change from baseline in SGRQ-C total score - mixed model repeated measures (individual studies and meta-analysis)

	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106	
	PBO (N=401)	100 SC (N=403)	PBO (N=87)	100 SC (N=83)	PBO (N=90)	100 SC (N=82)	PBO (N=578)	100 SC (N=568)
Visit: Week 52								
n [1]	383	380	84	82	85	79	552	541
n [2]	336	337	70	74	73	75	479	486
LS mean (SE)	48.6 (0.85)	46.4 (0.85)	48.8 (1.69)	45.6 (1.67)	50.7 (1.80)	49.8 (1.82)	49.0 (0.70)	46.8 (0.71)
LS mean change (SE)	-5.7 (0.85)	-8.0 (0.85)	-3.3 (1.69)	-6.4 (1.67)	-3.8 (1.80)	-4.6 (1.82)	-4.9 (0.70)	-7.1 (0.71)
Column vs placebo [3]								
Difference		-2.3		-3.2		-0.9		-2.2 [4]
95% CI		(-4.64, 0.08)		(-7.85, 1.50)		(-5.93, 4.20)		(-4.14, -0.24)
p-value		0.059		0.183		0.737		0.028

[1] Number of participants with analysable data for one or more time points.
[2] Number of participants with analysable data at the given time point.
[3] Analysis performed using mixed model repeated measures with covariates of baseline score, geographic region (as defined for the study/ISE), smoking status (current versus never/ ex-smoker) and treatment and visit, plus interaction terms for visit by baseline and visit by treatment group.
[4] Analysis model as in footnote "[3]" with an additional covariate of study.
Note: Estimates are based on weighting applied to each level of class variable determined from observed proportions. Intercurrent events of treatment interruption or treatment discontinuation related to the COVID-19 pandemic have data set to missing following the event. Missing data imputed as MAR using 2000 imputations. SGRQ scores converted from SGRQ-C scores (SGRQ-C manual March 2016).
Note: Includes visits up to Week 52 for study 208657.

Figure 56 Forest plot of change from baseline in SGRQ-C Total Score at Week 52 - treatment difference to Placebo (100 SC versus Placebo): individual studies and meta-analysis (mITT-300 population)



Rescue medication use

In study 208657, at baseline, the mean number of occasions of rescue medication use per day was similar between the treatment groups, with a mean (SD) of 1.75 (2.143) and 1.60 (1.929) in the mepolizumab and placebo groups, respectively (ISE Table 20.39). Over the treatment period, use of rescue medication was lower in mepolizumab 100 mg group versus placebo group, however, the differences were small. By weeks 49 to 52, the LS mean reduction from baseline in occasions of rescue medication use was similar between treatment groups.

The use of rescue medication over time for mepolizumab relative to placebo differed among the 3 studies. In study MEA117113, a treatment difference favouring mepolizumab 100 mg over placebo in the number of occasions of rescue medication use was observed throughout the treatment period. In study MEA117106, a treatment difference favouring mepolizumab 100 mg was only observed during the first half of the study.

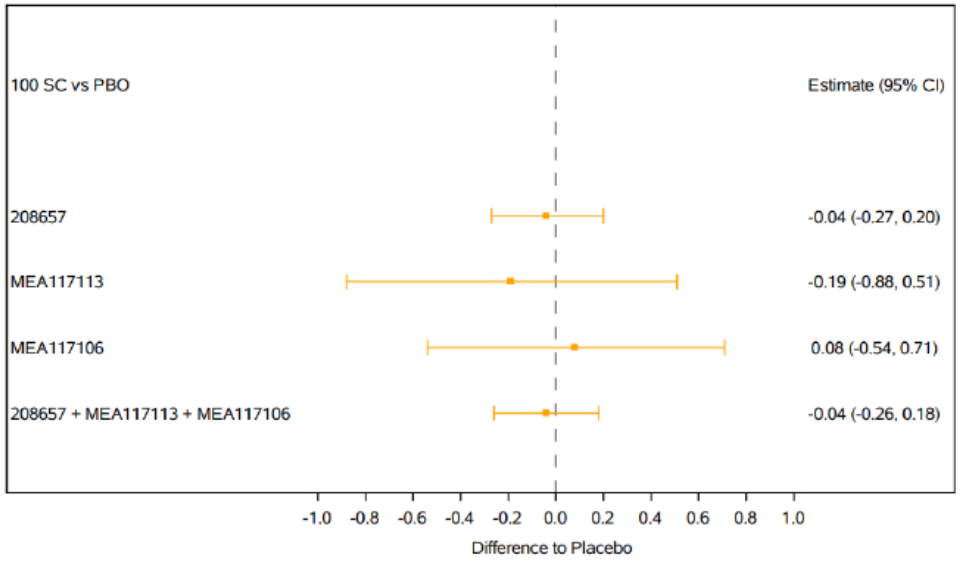
For the pooled studies (mITT-300 population), similar trends were observed as seen in study 208657 in the mean number of occasions of rescue medication use and mean changes from baseline across the treatment groups.

Table 126 Analysis of number of occasions of rescue medication use (occasions per day) - mixed model repeated measures: individual studies and meta-analysis (mITT-300 population)

	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106	
	PBO (N=401)	100 SC (N=403)	PBO (N=87)	100 SC (N=83)	PBO (N=90)	100 SC (N=82)	PBO (N=578)	100 SC (N=568)
Weeks 49-52								
n [1]	401	403	87	83	90	82	578	568
n [2]	357	358	68	75	76	77	501	510
LS mean (SE)	1.9 (0.08)	1.9 (0.08)	2.3 (0.25)	2.1 (0.25)	2.5 (0.22)	2.6 (0.23)	2.1 (0.08)	2.0 (0.08)
LS mean change (SE)	0.2 (0.08)	0.2 (0.08)	0.4 (0.25)	0.3 (0.25)	0.3 (0.22)	0.3 (0.23)	0.3 (0.08)	0.2 (0.08)
Column vs placebo [3]								
Difference		-0.04		-0.19		0.08		-0.04 [4]
95% CI		(-0.27, 0.20)		(-0.88, 0.51)		(-0.54, 0.71)		(-0.26, 0.18)
p-value		0.765		0.599		0.794		0.718

[1] Number of participants with analyzable data for one or more time points.
[2] Number of participants with analyzable data at the given time point.
[3] Analysis performed using mixed model repeated measures with covariates of baseline value, geographic region (as defined for the study/ISE), smoking status (current versus never/ex-smoker), and treatment and visit, plus interaction terms for visit by baseline and visit by treatment group.
[4] Analysis model as in footnote "[3]" with an additional covariate of study.
Note: Estimates are based on weighting applied to each level of class variable determined from observed proportions.
Note: Includes visits up to Week 52 for study 208657.

Figure 57 Forest plot of number of occasions of rescue medication use (occasions per day) during Weeks 49-52: treatment difference to placebo: 100 SC versus placebo (mITT-300 population)



Lung Function

In study 208657, at baseline, pre-bronchodilator FEV1 and FVC were similar between the treatment groups. The LS mean change from baseline in prebronchodilator FEV1 and FVC was similar between treatment groups at Week 24 and Week 52.

In the individual COPD studies, baseline FEV1 and FVC were similar between the mepolizumab 100 mg group and the placebo group and were indicative of poor lung function. At week 52, numerically greater mean changes from baseline in pre-bronchodilator FEV1 and FVC were observed after mepolizumab 100 mg treatment in MEA117113 and MEA117106 studies, though these changes were not clinically meaningful.

Similar trends as seen in study 208657 were observed in the pooled results, the LS mean change from baseline in pre-bronchodilator FEV1 and FVC was similar between treatment groups at Week 24 and Week 52.

Table 127 Change from baseline in pre-bronchodilator FEV1 by mixed model repeated measures (individual studies and meta-analysis, mITT-300 population)

Lung function measure	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106	
	PBO (N=401)	100 SC (N=403)	PBO (N=87)	100 SC (N=83)	PBO (N=90)	100 SC (N=82)	PBO (N=578)	100 SC (N=568)
FEV1 (mL)								
Week 24								
n [1]	384	381	87	82	88	82	559	545
n [2]	374	367	79	80	82	80	535	527
LS mean (SE)	1325 (17.5)	1321 (17.7)	1270 (29.4)	1311 (29.6)	1218 (31.8)	1269 (32.6)	1281 (15.1)	1295 (15.3)
LS mean change (SE)	53 (17.5)	49 (17.7)	32 (29.4)	73 (29.6)	-12 (31.8)	39 (32.6)	33 (15.1)	46 (15.3)
Column vs placebo [3]								
Difference		-4		41		51		13 [4]
95% CI		(-53, 45)		(-41, 123)		(-39, 141)		(-25, 52)
p-value		0.862		0.330		0.265		0.494
Week 52								
n [1]	384	381	87	82	88	82	559	545
n [2]	341	342	66	75	76	74	483	491
LS mean (SE)	1305 (18.4)	1296 (18.4)	1231 (31.3)	1300 (30.6)	1217 (28.8)	1226 (29.4)	1263 (15.5)	1270 (15.5)
LS mean change (SE)	34 (18.4)	25 (18.4)	-6 (31.3)	62 (30.6)	-12 (28.8)	-3 (29.4)	15 (15.5)	21 (15.5)
Column vs placebo [3]								
Difference		-9		68		9		7 [4]
95% CI		(-60, 42)		(-18, 155)		(-72, 91)		(-33, 46)
p-value		0.730		0.120		0.826		0.734

Subgroup analysis

Analysis of the following subgroups were carried out based on data from studies 208657, MEA117113 and MEA117106:

Subgroup	Categories
Screening BEC thresholds	<500; ≥500 cells/µL
Age	<40, 40-<65, ≥65 years
Sex	Male, Female
Race	African American/African Heritage, White, Asian, Other
Geographic Region	EU, US, Rest of World
Exacerbations in the previous year	≤2, 3, ≥4 exacerbations
Smoking status at Screening	Current, Never, Former
Severity of Airflow Limitation (GOLD Guidelines)	Mild, Moderate, Severe, Very Severe
Symptoms of Chronic Bronchitis	Yes/No
Symptoms of Chronic Bronchitis + Screening BEC	Symptoms of Chronic Bronchitis + ≥500 screening blood eosinophils, Symptoms of Chronic Bronchitis + <500 screening blood eosinophils, No Symptoms of Chronic Bronchitis + ≥500 Screening BEC, No Symptoms of Chronic Bronchitis + <500 screening blood eosinophils.

Symptoms of chronic bronchitis=Y, refers to participants with baseline response of "most days of the week" or "several days of the week" to both questions regarding cough and sputum on SGRQ-C questionnaire.

Table 128 Summary of subgroup analyses: meta-analysis

208657+MEA117113+MEA117106					
	Placebo N=578		100 SC N=568		
	n	Exac. rate/year	n	Exac. rate/year	Rate ratio (95% CI)[1]
Screening BEC					
<0.5 GI/L	359	1.21	351	0.99	0.82 (0.68, 0.97)
≥0.5 GI/L	219	1.32	217	0.95	0.72 (0.56, 0.93)
Age (years)					
40 - <65 [2]	256	1.10	214	0.92	0.84 (0.66, 1.06)
≥65	322	1.36	353	1.00	0.73 (0.61, 0.88)
Sex					
Female	187	1.36	189	1.04	0.77 (0.61, 0.96)
Male	391	1.19	379	0.94	0.79 (0.65, 0.95)
Race					
African American/African heritage	8	-	8	-	-
White	477	1.32	471	0.98	0.74 (0.63, 0.87)
Asian	75	0.73	73	0.85	1.18 (0.76, 1.82)
Other	18	-	16	-	-
Geographic region					
Europe	273	1.43	278	1.07	0.75 (0.61, 0.92)
United States	57	1.13	54	0.94	0.83 (0.48, 1.47)
Rest of World	248	1.07	236	0.89	0.83 (0.66, 1.04)
Exacerbations in the previous year					
≤2 exacerbations	424	1.09	399	0.79	0.73 (0.61, 0.87)
3 exacerbations	103	1.37	97	1.42	1.04 (0.74, 1.46)
≥4 exacerbations	51	2.64	72	1.78	0.67 (0.46, 0.98)
Smoking status at screening					
Current	162	1.22	160	1.03	0.84 (0.62, 1.14)
Never/former	408	1.26	407	0.95	0.75 (0.64, 0.89)
Severity of airflow limitation (GOLD guidelines)					
Mild: ≥80% predicted	6	-	5	-	-
Moderate: ≥50%-<80% predicted	245	0.79	238	0.66	0.84 (0.64, 1.10)
Severe: ≥30%-<50% predicted	248	1.73	256	1.24	0.71 (0.59, 0.87)
Very severe: <30% predicted	79	1.49	69	1.46	0.98 (0.66, 1.44)
Symptoms of Chronic Bronchitis					
No	186	1.22	175	0.89	0.73 (0.57, 0.93)
Yes	382	1.28	376	0.99	0.78 (0.65, 0.94)
Symptoms of Chronic Bronchitis + screening BEC					
No Symptoms + ≥500 BEC	68	1.14	67	0.79	0.69 (0.47, 1.02)
Symptoms + ≥500 BEC	145	1.43	147	0.99	0.69 (0.50, 0.97)
No Symptoms + <500 BEC	118	1.24	108	0.92	0.74 (0.54, 1.02)
Symptoms + <500 BEC	237	1.19	229	0.99	0.83 (0.67, 1.03)

[1] Analysis performed using a negative binomial regression model with covariates of treatment group, smoking status, baseline % predicted FEV1, number of exacerbations in previous year (as an ordinal variable), and geographic region (as defined for the study/ISE) with log(time in on- and off-treatment period) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions with an additional covariate of study.

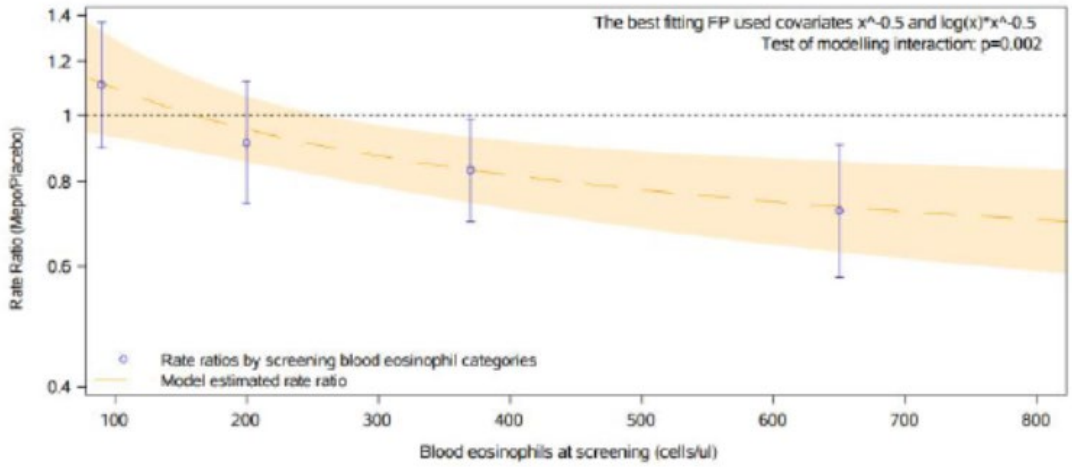
[2] One participant was excluded due to being <40 years old.

Modelling of efficacy by blood eosinophils

Modeling of the primary endpoint was performed to investigate the role of screening BEC on rate of moderate/severe exacerbations with mepolizumab versus placebo using all available data from 208657, MEA117113 and MEA117106 studies. This included participants across all screening BEC levels.

This analysis was predictive of greater reductions in the rate of moderate/severe exacerbations with mepolizumab relative to placebo with increasing screening BEC.

Figure 58 Predicted rate ratio of moderate/severe exacerbations by BEC at screening - mepolizumab 100 SC versus placebo (mITT population)



Note: Shaded area represents 95% CI for predicted rate ratio from the model of exacerbation rates against screening blood eosinophil count.

Note: [1] Analysis performed using a negative binomial model with covariates of treatment group, study, smoking status, geographic region, baseline % predicted FEV1, number of exacerbations in previous year (as an ordinal variable), and with log(time in on- and off-treatment period) as an offset variable.

Note: Best fitting fractional polynomial model from FP(2) class presented utilizing model [1] with best fitting fractional polynomial transformations of screening blood eosinophil count and interactions with treatment.

Note: Estimated rate ratios (and 95% CI) by screening blood eosinophil categories (<150, 150-<300, 300-<500, ≥500 cells/uL) from model [1] with additional interaction term of eosinophil category with treatment plotted against the median of each category.

2.4.3. Discussion on clinical efficacy

Dose response studies

A 100 mg Q4W dose is proposed to be used for the COPD population. This dose is already approved for adult and adolescent patients with severe eosinophilic asthma and adult patients with chronic rhinosinusitis with nasal polyps (CRSwNP).

The 300 mg Q4W dose is approved for other eosinophilic diseases such as eosinophilic granulomatosis with polyangiitis (EGPA) and hypereosinophilic syndrome (HES).

No dose-response studies were performed for this new population of patients. However, the applicant did examine the efficacy of 100 mg dose of Mepolizumab Q4W compared to a 300 mg dose in the MEA117113 study and found that there was no additional benefit observed with an increased dose in the COPD population. In fact, the treatment effect for the reduction in moderate/severe exacerbations with the 300 mg dose was lower as compared to the 100 mg dose.

The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks (See SmPC section 4.1).

Design and conduct of clinical studies

The purpose of this procedure is to extend the indication of Nucala to patients with COPD with "raised blood eosinophils".

The proposed indication is: "Nucala is indicated in adults as an add-on maintenance treatment for uncontrolled chronic obstructive pulmonary disease (COPD) characterised by raised blood eosinophils on a combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA) (see section 5.1)."

Of note, this is in line with other IL receptor antagonists authorized for the same condition.

The proposed indication limits the target population to patients with "raised blood eosinophils' which is acceptable, considering the mechanism of action of mepolizumab and the design of studies presented by the MAH. The level of BEC is stated in the SmPC section 5.1.

Data supporting this application

The Phase 3 COPD development program comprised 3 clinical studies, each with a randomized, double-blind, placebo-controlled, parallel-group design. However, only study 208657 (MATINEE) is considered as pivotal for this application as only this study investigated the proposed target population, i.e. patients who have blood eosinophil levels ≥300 cells/µL**.** In the 2 other studies, MEA117113 (METREO) and MEA117106 (METREX), different blood eosinophil thresholds were used as the basis for enrolment. The MAH also presented a post-hoc analysis of the efficacy data from the subpopulation in MEA117113 and MEA117106 studies characterized by screening BEC ≥300 cells/µL as well as a pooled efficacy analysis of the 208657, MEA117113 and MEA117106 studies.

Study design

Study 208657

The 208657 study had a multi-centre, randomized, placebo-controlled, double-blind, parallel-group (2-group) design. The study design is acceptable and is similar to that used for other products approved for the same condition. At the time this trial began there were no available add-on therapies for patients with eosinophilic-COPD. Thus, choosing placebo-control in addition to maintaining SoC triple therapy is appropriate.

This trial evaluated mepolizumab 100 mg compared with placebo given every 4 weeks through SC injection of a liquid formulation delivered in a pre-filled safety syringe.

Study 208657 consisted of 3 periods, an initial 3-week screening period followed by a 2-week run-in period and a 52-week up to 104-week treatment period.

The study was conducted at the time of the global COVID-19 pandemic (trial start date: 30th October 2019; trial end date: 8th August 2024). Participants were initially intended to be treated for 52-weeks which is in line with EMA guidance recommendations to cover the seasonality of the disease. However, following the CHMP scientific advice (EMA/SA/0000066628), it was decided to increase the treatment duration from a fixed duration of 52 weeks for each patient to a variable duration with the maximum treatment period of 104 weeks. These amendments were aimed at mitigating the effects of non-pharmaceutical interventions introduced by SARS-CoV-2 pandemic measures. At that time the sample size of this study was also permitted to be increased.

The applicant was requested to provide a sensitivity analysis of the treatment effect in different time periods with respect to the application of non-pharmaceutical interventions towards SARS-CoV-2 as requested during scientific advice (EMA/SA/0000066628). As highlighted by the MAH no significant differences in the efficacy and safety outcomes were noted by the duration subgroups (fixed vs. variable duration). Further, the analysis of rate of moderate/severe exacerbations by time periods related to COVID pandemic showed consistent results in favour of mepolizumab for most periods.

In conclusion, it can be agreed that the treatment effect was unlikely to be significantly affected by application of non-pharmaceutical interventions towards SARS-CoV-2.

Studies MEA117106 and MEA117113

The trial design for these studies was largely similar to the 208657 study. All studies were multi-centre, randomized, placebo-controlled, double-blind, parallel-group design. Studies MEA117113 and MEA117106 had 3 consecutive periods: screening/run-in (1 to 2 weeks), study treatment period (52 weeks), and follow-up period (8 weeks) for a total duration of approximately 62 weeks. The study designs are acceptable and similar to those used in approved therapies for the same indication.

Study MEA117106 had 2 treatment arms, placebo and 100mg Q4W. Participants were stratified in both arms into High Stratum (Blood eosinophils ≥150 cells/ mL at Visit 1 (Screening) OR historic blood eosinophil level in the preceding 12 months ≥300 cells/ mL) or Low Stratum (<150 cells/ mL at Visit 1 (Screening) AND no evidence of a blood eosinophil level in the preceding 12 months ≥300 cells/ mL.)

Study MEA117113 had 3 treatment, arms, placebo, 100 mg mepolizumab treatment and 300 mg mepolizumab treatment Q4W and only enrolled patients with blood eosinophil count of ≥300 cells/μL within the past 12 months prior to Screening OR a peripheral baseline blood eosinophil count of ≥150 cells/μL from haematology conducted at Screening.

MEA117113 and MEA117106 studies differed from the pivotal 208657 study by having a follow-up period (week 60) 8 weeks after the last visit (at week 52). These data could be seen as supportive.

Selection of Study Population

Study 208657

The inclusion criteria in the 208657 study were similar to those used in other COPD development programmes. Participants had to be ≥40 years of age as well as be current or former smokers. There did not appear to be a cutoff age as to how old participants could be, although the majority were over 65.

Inclusion criteria based on FEV1/FVC ratio of <0.70 confirm diagnosis of COPD and post-salbutamol FEV1>20% and ≤80% places the participants in moderate to very severe disease categories based on airflow obstruction (GOLD Grades 2-4). Patients with mild disease (GOLD1, FEV1>80%) and those with FEV1 <20% were excluded from the study and this is stated in section 5.1 of the SmPC.

Blood eosinophil count (BEC) at enrolment

Patients were required to have high BEC levels ≥300 cells/μL at Screening Visit 0 as well as a documented historical BEC of ≥150 cells/μL in the 12 months prior to Screening Visit 0, which must not have been measured during a COPD exacerbation. If no historical data was available, BEC should be assessed again during the screening and had to be ≥150 cells/μL.

BEC ≥300 cells/ml is an acceptable threshold to be used in COPD populations as it is associated with an increased exacerbation risk. This threshold was used in studies supporting approved therapies for the same indication.

Exacerbations and symptoms prior to enrolment

Additionally, participants were required to have a history of a) 2 or more moderate COPD exacerbations that were treated with systemic corticosteroids (IM, IV, or oral) with or without

antibiotics, or b) at least 1 severe COPD exacerbation requiring hospitalization, in the year prior to the study eligibility assessment, despite the regular use of optimized SoC COPD medication (ICS + LABA + LAMA).

While a history of exacerbations was part of the inclusion criteria, there was no specific requirement for patients' history of COPD symptoms at the time of enrolment, i.e. characteristic symptoms of COPD such as Dyspnoea (MRC scale). Nevertheless, most patients enrolled reported a high level of symptoms as described in the baseline characteristics of patients (see discussion below).

Prior and background therapy iParticipants were required to be on a triple therapy which is appropriate as the current GOLD guideline strongly recommends the use of ICS as part of 'triple therapy' in patients of GOLD group E with elevated blood eosinophils ≥300 cells/µL. Some patients were allowed to participate in the trial without the triple therapy requirement if they had safety and tolerability documentation that would exclude the use of LABA or LAMA. Even though patients on dual therapy (ICS plus LAMA or ICS plus LABA) were allowed to participate in the study, the proposed indication refers to the 'triple therapy' only, which is in principle acceptable, considering that in fact the majority of patients were on triple therapy in the study.

Exclusion criteria

The exclusion criteria mirror what is normally excluded in similar trials, as well as additional criteria such as excluding asthma patients and oral corticosteroid use. It is understood that the age, smoking status and asthma diagnosis history all contributed to mitigating the inclusion of asthma-induced obstructive airway disease patients. The potential inclusion of patients with a history of asthma and patients receiving oral corticosteroids had been identified as key weaknesses of the previous two studies, which were addressed in this study population. Although patients with atopy were not excluded, later the MAH performed additional post-hoc sensitivity analysis excluding 21 patients with atopy and symptoms suggesting asthma. The result of this analysis was in line with the main analysis. Non-smokers were excluded from the study but as clarified by the MAH the available data do not indicate that the efficacy of the product is lower in non-smokers as compared to smokers.

Studies MEA117106 and MEA117113

MEA117106 and MEA117113 had the same inclusion criteria which were similar to the criteria in the 208657 study. However, a key difference in the MEA117106 and MEA117113 studies compared to 208657 study was that patients with a history of asthma could be enrolled. As history of (resolved) asthma was not collected for studies MEA117106 and MEA117113 a sensitivity analysis excluding these patients as requested could not be conducted. This is main uncertainty regarding the efficacy results generated in MEA117106 and MEA117113 provided in support of COPD indication and therefore these studies are not considered pivotal for the application.

Additionally, if taken as SoC therapy prior to screening, oral corticosteroids (chronic) were allowed to be maintained at a stable dose for the duration of the treatment period in MEA117106 and MEA117113 studies. The use of chronic oral corticosteroids was prohibited in 208657 study. The MAH clarified that few patients were on baseline maintenance OCS in studies MEA117106 (Placebo 9(4%) and mepolizumab 100 mg 13(6%)) and MEA117113 (Placebo 8(4%) and mepolizumab 100 mg 12(5%)). In study 208657 only approximately 1% of participants were on baseline maintenance OCS use. Most of the patients taking OCS remained on a stable dose throughout the study. Further, sensitivity analyses of the primary analysis that excluded patients receiving maintenance OCS revealed comparable results with the overall population. In conclusion it can be

agreed that the use of oral corticosteroids as SoC has not influenced the MEA117106 and MEA117113 study results.

Exacerbations and symptoms prior to enrolment

Similar to 208657 study there was no requirement for symptoms of COPD to be present (dyspnoea, cough etc.) at the time of enrolment.

All participants were required to have at least 2 moderate or 1 severe COPD exacerbations in the 12 months prior to screening. Moderate was defined as the use of systemic corticosteroids (intramuscular [IM], IV, or oral) **and/or** treatment with antibiotics. Prior use of antibiotics alone did not qualify as a moderate exacerbation unless the use was specifically for the treatment of worsening symptoms of COPD. Utilisation of corticosteroids **OR** antibiotics to treat a moderate exacerbation in MEA117106 and MEA117113 studies was a point of difference compared to the 208657 study.

In all three studies a severe exacerbation was defined as an exacerbation that required hospitalisation.

Blood eosinophil count (BEC) at enrolment

A critical difference between the MEA117106 and MEA117113 studies and 208657 study was the requirement for BEC threshold at enrolment.

MEA117106 accepted patients regardless of BEC levels, but screening and historical eosinophil level was obtained prior to randomization and used to assign subjects to the appropriate randomization stratum of <150 BEC/ml or ≥150 BEC/ml. The MEA117113 study only randomized subjects with BEC ≥150 cells/mL at Visit 1 (Screening) or historic blood eosinophil level in the preceding 12 months ≥300 cells/mL".

Background therapy

All participants had to be on treatment regimen of optimized SoC background therapy that included ICS plus two additional COPD medications, i.e. triple therapy for the 12 months prior to Screening. Similarly, as in the 208657 study some patients were allowed to participate in the trial without triple therapy if LABA or LAMA were contraindicated due to safety concerns.

Study treatment

Study 208657

Patients in this trial received either 100 mg of mepolizumab or placebo equivalent through SC injection every 4 weeks for 52 weeks up to a maximum of 104 weeks. This matches the posology for severe eosinophilic asthma patients, from which this dosage was initially derived. This treatment was administered as an add-therapy to patients already receiving maximal SoC therapy of ICS+LAMA+LABA or equivalent treatment where ICS+LABA+LAMA was not possible.

All patients in this trial had their treatment administered in pre-filled safety syringe by a member of staff on site. Injection sites are the abdomen or thigh or upper arm. The SmPC states that mepolizumab can be self-administered by patient. As self-administration was approved for other indications, there is no objection for its use in COPD population.

Reliever medication comprised of short acting bronchodilators (SAMAs or SABAs) was used as needed. The MAH allowed the use of rescue short-acting bronchodilators at any time during the study, but requested that their use be delayed, if possible, for at least 4 hours prior to spirometry testing.

COPD is a chronic disease with no cure and mepolizumab 100 mg is intended for long-term treatment/management of this disease. In line with the recommendations for the asthma indication, section 4.2 of the SmPC was updated to state that "the need for continued therapy is to be considered at least on an annual basis as determined by physician assessment of the patient's disease severity and level of control of exacerbations"**.**

Studies MEA117106 and MEA117113

In the MEA117113 study two doses of mepolizumab were tested (i.e. 100 mg and 300 mg) whereas in the MEA117106 study only the 100 mg dose was investigated. As the proposed posology only recommends the 100 mg dose, the data from the 300 mg arm of the MEA117113 study is not pivotal for the current application.

Similar to study 208657 the study treatment was administered as an add-therapy to patients already receiving maximal SoC therapy of ICS+LAMA+LABA.

Objectives and Outcomes/endpoints

Study 208657

Study 208657 was a superiority trial with a single primary endpoint and 5 key secondary endpoints contained within a clear hierarchical structure for type I error control.

The primary endpoint was the annualized rate of moderate/severe exacerbations over the 52 to 104-week treatment period compared to placebo. The primary endpoint was analysed with a negative binomial regression model to compare the exacerbation rates between the treatment groups, adjusting for selected pre-specified covariates.

According to the recommendations from the CHMP guideline on the investigation of medicinal products for the treatment of COPD (EMA/CHMP/483572/2012), the annual rate of exacerbations is acceptable as a single primary endpoint.

Moderate and severe exacerbations serve as outcome measures for the primary endpoint and two of the key secondary endpoints. Moderate exacerbations are defined as clinically significant exacerbations that require treatment with oral/systemic corticosteroids and/or antibiotics. Severe exacerbations are defined per protocol as clinically significant exacerbations that require in-patient hospitalization (i.e., ≥24 hrs.) or result in death. These are standard definitions of COPD exacerbations and are in line with CHMP guidelines.

Arbitrary numerical criteria (n=7 days) were defined by the MAH to decide whether two or more exacerbations represented different episodes or a single event instead of consistently assessing whether an event met the study criteria for a new exacerbation rather than being a relapse or continuation of a previously recorded exacerbation. Therefore, the sensitivity analysis provided using different minimum time gaps between two exacerbations, i.e. 10 days, 15 days, and 20 days showed consistent results.

The remaining key secondary endpoints were based on the patient's health status and health related quality of life (HRQoL). The health questionnaires chosen were COPD Assessment Test where a participant was considered a responder if they had a 2-point or more improvement (reduction) in CAT score from baseline and the St. George's Respiratory Questionnaire for COPD where a participant was considered a responder if they had a 4-point or more improvement (reduction) in SGRQ total score from baseline. These endpoints are considered appropriate for the proposed target population and the selected responder threshold are appropriate.

Additionally, the MAH used E-RS: COPD to evaluate patient reported COPD symptoms. Of note, the use of E-RS scores in COPD patients in studies supporting MAA was previously discussed during a CHMP qualification procedure in 2015 (EMA/CHMP/SWAP/178465/2015) and it was concluded at that time that the E-RS score is an exploratory endpoint only.

Change from Baseline in pre-bronchodilator forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) were investigated in the study but not as key secondary endpoints and therefore they were not covered by multiplicity adjustment. The MAH has stated that the predicted MOA of mepolizumab was not anticipated to have a direct effect on lung function measurements in the broad COPD patient population.

Studies MEA117106 and MEA117113

MEA117113 and MEA117106 were superiority trials with a single primary endpoint and 4 secondary endpoints, all contained within a clear hierarchical structure for type I error control.

The primary efficacy endpoint in both studies was the frequency rate of moderate or severe COPD exacerbations which was measured over 52-weeks. The primary endpoint was analysed in a similar manner to Study 208657.

Time to first moderate/severe exacerbation was next in the statistical hierarchy as the first secondary endpoint for MEA117113, MEA117106, and study 208657.

The remaining secondary endpoints were frequency of COPD exacerbations requiring emergency department (ED) visits and/or hospitalizations, change from baseline in mean St. George's Respiratory and Questionnaire COPD (SGRQ-C) Total Score and change from baseline COPD Assessment Test (CAT) score.

Sample size

MEA117106 study

The parameters for the sample size calculations were reasonable and well-considered. The MAH has assumed a placebo event rate of 2 exacerbations per annum, following a negative binomial distribution. This is well established for count data such as this. The study enrolled 462 total participants for the primary analysis, exceeding the 344 participants needed to detect a statistically significant result at 90% power.

MEA117113 study

The parameters for the sample size calculations were reasonable and well-considered. The MAH has assumed a placebo event rate of 2 exacerbations per annum, following a negative binomial distribution. This is well established for count data such as these. The study enrolled 674 total participants for the primary analysis, exceeding the 573 participants needed to detect a statistically significant result at 90% power.

Randomisation

Overall, the randomisation plan is endorsed, and the stratification factors are acceptable for the three studies.

Blinding The double blinding was acceptable for the purposes of this study.

Mepolizumab has been shown to reduce blood eosinophil counts therefore in order to maintain the blind sites were not provided with blood eosinophil levels. However, sites were provided with total white blood counts, but this is acceptable.

Statistical methods

Study 208657

The statistical methodology selected for the primary and ranked secondary endpoints is well-specified and acceptable. The primary analysis approach of a negative binomial model has been well-described for modelling count data with overdispersion as in this case. The primary estimand strategies for handling ICEs were well chosen. The treatment policy strategy reflects real-world use of the treatment and is acceptable for the ICEs of discontinuation and interruption of treatment. The hypothetical strategy for handling COVID-19 pandemic related ICEs is acceptable for ICEs that would not have happened in a hypothetical scenario where there is no COVID-19 pandemic. The sensitivity analysis for imputing missing data are extensive and well-described. There were only 6.7% missing participant-years data for the mepolizumab 100 mg group and 8.7% for the placebo group. The sensitivity analyses for imputing missing data were robust enough to test the missing at random assumption and reflected the primary analysis results. The chosen multiple imputation method allows exacerbation counts to be imputed from off-treatment data which is conservative enough to be acceptable. The hierarchy for type I error control is appropriate to preserve the alpha for the primary and ranked secondary endpoint comparisons.

MEA117106 study

The statistical methodology is appropriate for the primary endpoint comparison. There were only 3% missing subject-years data for the mepolizumab 100 mg group and 6% for the placebo group. The sensitivity analyses for imputing missing data were robust enough to test the missing at random assumption and reflected the primary analysis results. The chosen multiple imputation method under a J2R assumption is conservative in its approach and is acceptable. The methods for type I error control are appropriate and preserve the alpha for the primary and ranked secondary endpoint comparisons for both the high stratum and overall population.

MEA117113 study

The statistical methodology is appropriate for the primary endpoint comparison. There were only 3% missing subject-years data for the mepolizumab 100 mg group, 5% for the mepolizumab 300 mg group, and 8% for the placebo group. The sensitivity analyses for imputing missing data were robust enough to test the missing at random assumption and reflected the primary analysis results for the respective comparisons. The chosen multiple imputation method under a J2R assumption is conservative in its approach and i

acceptable. The methods for type I error control are appropriate and preserve the alpha for the primary and ranked secondary endpoint comparisons for both the mepolizumab 100 mg group and the mepolizumab 300 mg group.

Efficacy data and additional analyses

Participant flow

Study 208657

806 participants were randomized and 804 received the study treatment and were included into the mITT population. Of the 804 randomized participants 401 entered the placebo arm including 175 patients enrolled to the fixed 52-week duration and 226 proceeding with the variable 104-week duration. The mepolizumab arm had 403 participants with 170 in the fixed 52-week duration and 233 proceeding with the variable 104-week duration.

In the overall mITT population, most participants completed their study treatment as scheduled (81% in mepolizumab; 78% in placebo). The primary reasons for study withdrawal were withdrawal by participant, adverse event, and lack of efficacy. A low number of participants withdrew due to lack of efficacy, 7 participants & 2 participants for the placebo and mepolizumab groups respectively.

Studies MEA117106 and MEA117113

837 participants were randomized to the MEA117106 study, and 836 randomized subjects received the study treatment. 734 (88%) participants completed the study and the main reason for the study discontinuation was for withdrawal by subject and AE.

The study enrolled subjects to two strata depending on the level of blood eosinophils at screening and in the preceding 12 months. In general, the discontinuation rate was smaller in the high stratum than in the low stratum. Study MEA117113 was slightly smaller. A total of 675 participants were randomized to this study and 674 participants received the study treatment. Only 82% of the placebo group completed the study in comparison to the Mepolizumab groups (100 and 300 mg) with 92% and 87% completion respectively. Withdrawals associated to adverse effects and lack of efficacy were slightly higher for placebo and mepolizumab 300 mg compared to the 100 mg group.

Fewer subjects in the mepolizumab 100 mg (12%) and 300 mg (19%) groups prematurely discontinued study treatment compared with the placebo group (25%).

For both studies, subjects remained on their SoC COPD medications throughout the entire study. However, placebo treated subjects had a higher withdrawal (18 vs 12%) and discontinuation rate (25 vs 19%) for study MEA117113 when compared to study MEA117106.

MEA117113 and MEA117106 study patients with BEC ≥300 cells/ μL at screening

Only 38% (170) of participants enrolled to the placebo and 100 mg arms in the MEA117113 study had baseline screening BEC ≥300 cells/µL. In the MEA117106 study such patients accounted for 20% (172) of the study population.

Conduct of the studies

Study 208657

Amendments

The CHMP acknowledged 6 amendments to the study protocol. Amendment 4-STD, 3-STD, 2-CHI-1, and 1-USA-1 occurred before any participants were enrolled into the study. The first three amendments were similar and related to the addition of PK studies in China and the USA. Amendment 4 changed the inclusion criteria by adding requirement for BEC cells/µl thresholds for enrolment as well as thresholds regarding exacerbation history. Amendment 5-STD dated 16 October 2020 and 6-STD dated 06 December 2021 implemented several measures to account for the COVID-19 pandemic, allowing for assessments to be performed at home instead of onsite, updated the primary estimand, how ICEs were handled, and to account for potential reduced exacerbation rates due to pandemic safety measures by the extension of trial duration from 52 to 104 weeks and the potential increase of sample size to 1400.

Protocol deviations

There was a total of 41% participants with important protocol deviations. Important protocol deviations were evenly distributed across both study arms, and they were predominantly related to visit completion, eligibility criteria and informed consent. 12% (99) of participants appear to have not met the inclusion criteria. The most common protocol deviations were related to Inclusion

criterion #2 and Randomisation Inclusion criterion #1 (required documentation of elevated eosinophils at 2 timepoints).

The MAH mentions within 'Important protocol deviations' (Table 7 – Study Report Body) that there were 18 cases both in placebo and treatment of a deviation in the study blinding/unblinding procedures. However as clarified by the MAH no treatment unblinding events were reported.

Two study sites (239718 and 241146) were closed by the Sponsor. The applicant has provided sufficient detail surrounding the GCP issues at these sites with no impact on the studies integrity.

Studies MEA117106 and MEA117113

There were a total of 47% and 42 % of participants with important protocol deviations in studies MEA117106 and MEA117113, respectively. Deviations appeared evenly distributed across groups in both studies except for the high stratum of study MEA117106 with a lower incidence of deviations in the treatment group compared to placebo. Deviations were mostly associated with assessments and/or procedures category and incorrect visit, assessment, or timepoint window.

In study MEA117106, one site in Poland had deviations due to non-GCP compliance because of deficiencies in source documentation practices and enrolment of potentially ineligible subjects. Sensitivity analysis did not differ and therefore this population was included in the study.

Baseline characteristics

Study 208657

Given that COPD is a disease that is prevalent mainly in patients over 40 years of age, it is unsurprising that the majority of participants (61%) enrolled to the 208657 trial were over 65 years of age with the rest between 40-65 (39%). The average age was 66.2 years with a range of 39-91. This is acceptable as the highest prevalence of COPD is in people over the age of 60 [GOLD 2025].

The population was mainly men (69%) compared to women (31%), which is common in COPD and the vast majority of the participants were Caucasian (84%) or Asian (14%) with all other races making up the remaining 2%.

Mean BMI was 27.25 kg/m^2 with a range of 15.2-50.6 kg/m^2, mepolizumab is given as a flat dose and is not dosed depending on bodyweight, all patients received 100 mg SC. Both weight and BMI in both groups were very similar.

Studies MEA117106 and MEA117113

The age of participants enrolled to the MEA117106 and MEA117113 studies was similar to that reported in the 208657 trial. The average age was 65.4 years for the MEA117106 study and 65.1 the MEA117113 study. In both studies most participants were male (≈62 to 66%) and Caucasian (≈80% in both studies). Asian participants accounted for 1% of the study population in the MEA117106 study and 18% in the MEA117113 study

Baseline disease characteristics

For the 208657 study, in respect of disease type, patients were categorised primarily into either a chronic bronchitis or emphysema.

Most participants had moderate to severe airflow limitation (GOLD Grades 2-3) and these were evenly distributed across treatment and placebo groups. Around 13% of patients had very severe airflow limitation (GOLD 4).

Although there was no specific requirement for patients' history of COPD symptoms at the time of enrolment, 76% of total population had an mMRC dyspnoea score of ≥2. The mean CAT score was 19 indicating significantly impacted quality of life reported for many patients.

Baseline disease characteristics in the MEA117106 and MEA117113 studies indicated a slightly greater disease severity as compared to the 208657 study. Around 95% of patients enrolled in both MEA studies met the GOLD group D criteria, which would be classified as GOLD group E under the most recent GOLD guideline.

In both studies, as in the 208657 trial, the majority of participants had moderate to severe airflow limitation (GOLD Grades 2-3) and these were evenly distributed across treatment and placebo groups. Around 17 % of participants had very severe airflow limitation (GOLD 4). Around 82% to 84% of the total population had an mMRC dyspnoea score of ≥2. The mean CAT score was 19 in both studies.

History of exacerbations

In the 208657 study, despite treatment with optimized SoC for COPD, the participants had a mean 2.4 moderate/severe exacerbations in the prior year, with 83% of the participants having at least 2 moderate/severe exacerbations. Around 1/5 of participants experienced a severe exacerbation prior to study enrolment. The number of exacerbations was balanced between placebo and mepolizumab.

In the MEA117106 and MEA117113 studies the number of moderate/severe exacerbations reported prior to enrolment was slightly higher, i.e. a mean 2.5 exacerbations in the MEA117106 study and 2.7 exacerbations in the MEA117113 study. Severe exacerbations were also more frequently reported (in around 30% of patients).

Differences in the number of exacerbations across the studies could be largely explained by the fact that the 208657 trial was performed during the Covid 19 pandemic.

Primary endpoint results

208657 study

The primary endpoint in the 208657 study was the annualized rate of moderate/severe exacerbations and this primary endpoint was met.

Treatment with mepolizumab resulted in a statistically significant reduction in the annualized rate of moderate/severe exacerbations compared with placebo (rate ratio: 0.79; 95% CI: 0.66, 0.94; p=0.011). A 21% reduction in the annualised rate of exacerbations in the mepolizumab treatment group could be considered as borderline clinically relevant as 20% reduction of rate of moderate/severe exacerbations is suggested to be minimal clinically important difference in COPD patients (Calverley PM et al. 2005).

While statistically significant, there appears to be a small absolute treatment effect of the mepolizumab treatment compared to placebo, with the annualised exacerbation rate reduced from 1.01 exacerbations in placebo to 0.80 exacerbations in the treatment arm.

The results of sensitivity analyses investigating the robustness of results to alternative missing data assumptions were consistent with the primary analysis.

Studies MEA117106 and MEA117113

Both studies MEA117106 and MEA117113 had annualised rate of moderate/severe exacerbations as their primary endpoint, the same as in the pivotal 208657 study. However, these studies did not

clearly demonstrate that mepolizumab treatment was effective in the population ≥150 cells/μL at screening or ≥300 cells/μL within the 12 months prior to enrolment.

In study MEA117106 in the high stratum group, treatment with mepolizumab 100 mg resulted in an 18% reduction in the rate of moderate/severe exacerbations compared with placebo, which falls outside the minimum 20% threshold to be considered clinically relevant (Calverley PM et al. 2005) (rate ratio: 0.82; 95% CI: 0.68, 0.98; unadjusted p=0.029; adjusted for multiplicity p=0.036). More concerning is that in the low stratum, the rate of moderate/severe exacerbations increased by 23% after treatment with mepolizumab 100 mg compared with placebo (unadjusted p=0.058). The MAH stated that 2 mepolizumab-treated patients in the low stratum had 9 exacerbations which could contribute to the poor results.

In study MEA117113 the 100mg dose led to a 20% reduction in the rate of moderate/severe exacerbations, which is the minimum difference that can be considered clinically relevant; however, it was not statistically significant. (rate ratio 0.80; 95% CI: 0.65, 0.98; unadjusted p=0.034 and adjusted for multiplicity p=0.068). A 14% reduction in the rate of moderate/severe exacerbations was observed between mepolizumab 300 mg and placebo (rate ratio 0.86; 95% CI: 0.70, 1.05; unadjusted and adjusted p=0.140), however with the current data set and power of the study, it is not possible to conclude that 300 mg is less effective than 100 mg mepolizumab.

MEA117113 and MEA117106 studies-patients with BEC ≥300 cells/μL at screening and pooled analysis

In the subpopulation characterized by screening BEC ≥300 cells/µL (post hoc analysis) treatment with mepolizumab resulted in 38% reduction in the rate of moderate/severe exacerbations in the MEA117106 study (rate ratio 0.68; 95% CI: 0.50,0.92; nominal p=0.013) and 15% reduction in the rate of moderate/severe exacerbations in MEA117113 study (rate ratio 0.85; 95% CI: 0.59, 1.22; nominal p=0.387). The results of the pooled analysis were consistent with the 208657 study results.

Effect on exacerbations – secondary endpoints

In 208657 study there were several secondary endpoints investigating the effect on exacerbations including two key endpoints under multiplicity adjustment.

The time to first event analysis showed a statistically significant reduction in the risk of moderate/severe exacerbation for mepolizumab compared with placebo (hazard ratio 0.77; 95% CI: 0.64, 0.93; p=0.009).

Although treatment with mepolizumab resulted in a 35% reduction in the annualized rate of exacerbations requiring ED visit and/or hospitalization compared with placebo (rate ratio: 0.65; 95% CI: 0.43, 0.96), no statistical inference can be made on this key endpoint due to the break in statistical testing hierarchy on the proportion of CAT responders' endpoint.

For other endpoints such as time to first exacerbation requiring ED visit and/or hospitalization, severe exacerbations rate, time to first severe exacerbation, moderate exacerbations rate, although improvements with mepolizumab was noted, statistically significance cannot be concluded.

Inconsistent results were reported in relation to exacerbation related endpoints across the MEA117113 and MEA117106 studies. In study MEA117106 the time to moderate/severe exacerbation was longer for the mepolizumab 100 mg group compared with the placebo group (hazard ratio: 0.75; 95% CI: 0.60, 0.94; unadjusted p=0.012; adjusted for multiplicity p=0.036).On the other hand, in the MEA117113 study for 100 mg dose, statistical significance)

was not reached for this endpoint. The hazard ratio for 100 mg dose was 0.82, 95% CI: 0.64, 0.103, (unadjusted p=0.103).

A similar pattern in respect to the time to moderate/severe exacerbation and the rate of exacerbations requiring emergency department visit/hospitalization was seen in the subpopulation characterized by screening BEC ≥300 cells/μL in MEA117106 and MEA117113 studies. For the time to moderate/severe exacerbation, improvement was seen in MEA117106 study but not in MEA117113 for 100 mg dose.

Effects on symptoms, quality of life and daily physical activity

In study 208657**,** the proportion CAT score responders, SGRQ total score responders and E-RS: COPD responders all assessed at Week 52 were key secondary endpoints in the study. These key secondary endpoints were not met as the proportion of CAT score responders, SGRQ total score responders and of E-RS: COPD responders were similar in the mepolizumab group as compared to the placebo group.

The MAH presented the results of a post-hoc analysis of the change in St. George's Respiratory Questionnaire (SGRQ) from baseline in the subpopulation of patients with GOLD grade 2 (subpopulation) and demonstrated a greater response in SGRQ scores in these patients, which is in line with the established MCID (-4 points). This was provided as an example to illustrates how different subpopulations may derive clinical benefit from mepolizumab on PROs.

In MEA117106 and MEA117113 studies there was no difference between the treatment groups in the mean change from baseline SGRQ Total Scores through Week 52 in the mepolizumab group compared with placebo.

Some improvements in the CAT score related endpoints were seen in the MEA117113 study. For change from baseline in CAT Score at Week 52 in this study the LS mean difference for mepolizumab 100 mg dose in comparison to placebo was -1.1 (95% CI -2.3, 0.0; nominal p= 0.055).

For subgroup of patients with BEC ≥300 cells/μL in MEA117113 and MEA117106 studies and in the pooled analysis of three studies only trends towards improvements were noted with the best results seen for the change from baseline in SGRQ-C Total Score endpoint.

Effects on lung function

Change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) were investigated in all three phase 3 studies but as "other" secondary endpoints not under multiplicity adjustment.

In respect to the results, in all three phase 3 study overall populations, and also in MEA117113/MEA117106 patients with BEC ≥300 cells/μL (mITT-300 population), there was no improvement in lung function.

For the 208657 study, the LS mean change from baseline in pre-bronchodilator FEV1 at week 52 for mepolizumab versus placebo was – 9 ml (95% CI -60.06, 42.06, nominal p = 0.730).

As highlighted the predicted MOA of mepolizumab was not anticipated to have a direct effect on lung function measurements. The SmPC section 5.1 states that no improvement in lung function was observed in studies in the COPD population.

Potential negative treatment effect associated with mepolizumab treatment.

It is noted that in patients with low BEC treatment with mepolizumab resulted in an increase in the rate of moderate/severe exacerbations as compared to placebo. In the low stratum in MEA117106 study, the rate of moderate/severe exacerbations increased by 23% (95% CI: 0.99, 1.51) after treatment with mepolizumab 100 mg compared with placebo (unadjusted p=0.058).

Modelling analysis of the primary endpoint which used all available data from 208657, MEA117113 and MEA117106 studies indicated that patients with BEC lower than 150 cells/µL are likely to have an increase in the rate of exacerbations.

The data presented by the MAH is not sufficient exclude a risk of potential harm in patients with low eosinophil levels (< 150 cells/µL). In most analyses presented the HR/Rate ratio is >1 despite post-hoc data exclusion. Therefore, the following warning is included in section 4.4 of the SmPC: *Data do not support the use of Nucala in patients with COPD with blood eosinophil count < 150 cells/µL and no evidence of blood eosinophil count >300 cells/µL in the previous 12 months.*

Ancillary studies

In general, a consistent effect was observed across subgroups investigated.

Although an increase in the rate of moderate/severe exacerbations as compared to placebo was seen in the Asian sub-population in study 208657 (9% increase) and in the pooled analysis of all Phase 3 studies (18% increase), there is no biological explanation as to why lower efficacy could be seen in Asian population. Further the number of participants in these groups is relatively small. Therefore, it can be agreed that the available data is insufficient to claim lower efficacy in the Asian sub-population.

For participants with BMI outside the normal range it is difficult to draw accurate conclusions given the limited number of participants and inconsistent results across studies.

Treatment effects were similar in all geographic regions with high variability, potentially due to low participant numbers in certain regions.

Some variability in responses was seen in subgroups depending on the number of exacerbations reported the previous year.

As requested during the CHMP SA, the MAH compared the treatment effect depending on the treatment duration (fixed versus variable treatment duration). For both subgroups the observed treatment effect was in favour of mepolizumab although slightly better results were reported for patients enrolled to the variable treatment duration period.

Additional expert consultation

Not applicable.

Assessment of paediatric data on clinical efficacy

Not applicable.

2.4.4. Conclusions on the clinical efficacy

Treatment with mepolizumab resulted in a statistically significant and clinically relevant improvement in the annualized rate of moderate/severe exacerbations in the pivotal 208657 study.

As highlighted no improvement in lung function was observed in mepolizumab studies in COPD population and as claimed by the MAH considering MoA of mepolizumab was not anticipated to have a direct effect on lung function measurements. This is reflected in section 5.1. of the SmPC.

Considering that different thresholds were used across studies performed by the MAH, and potential harm for patients with low eosinophil levels cannot be fully excluded, the SmPC section 4.4 provides a warning that data do not support the use of Nucala in patients with COPD with blood eosinophil count <150 cells/mcL and no evidence of blood eosinophil count ≥300 cells/mcL in the previous 12 months.

Supportive results in respect to effect on exacerbations came from MEA117113 and MEA117106 studies although confounding effect of potential enrolment of patients with past history of asthma cannot be excluded. Of note, active asthma patients were excluded from studies MEA117106 and MEA117113.

As MEA117113 and MEA117106 are not considered as pivotal the information on these studies is not included the SmPC.

In conclusion, the efficacy of mepolizumab as a treatment for COPD characterised by raised blood eosinophils on a combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA) has been shown.

2.5. Clinical safety

Introduction

Nucala is indicated as an add-on treatment for severe eosinophilic asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), eosinophilic granulomatosis with polyangiitis (EGPA), and hypereosinophilic syndrome (HES).

While mepolizumab's known safety profile differs between the different populations for which it is indicated, headache is the most commonly reported adverse reaction for all indications. The most commonly reported adverse reactions broken down per indication are listed below:

- headache (20%), injection site reactions (8%) and back pain (6%) for severe eosinophilic asthma
- headache (18%) and back pain (7%) for CRSwNP
- headache (32%) injection site reactions (15%) and back pain (13%) for EGPA
- headache (13%), urinary tract infection (9%), injection site reactions and pyrexia (7% each) for HES

Throughout the mepolizumab clinical development program, and also in the development of the proposed COPD indication the following are considered adverse events of special interest (AESI):

- systemic (including allergic/hypersensitivity) reactions
- local injection site reactions
- infections (including serious and opportunistic),
- malignancies
- cardiac disorders (including serious cardiac, vascular, and thromboembolic [CVT] events and serious ischemic events).

Systemic Reactions including anaphylaxis is currently listed as an important identified risk the Summary of Safety Concerns of the RMP for Nucala, and alterations in immune response (malignancies) and alteration in CVT safety are also listed as important identified risks.

Safety evaluation in COPD

The assessment of mepolizumab safety in the chronic obstructive pulmonary disease (COPD) development program is based on the integrated safety data from 3 placebo-controlled COPD trials, 208657, MEA117113, and MEA117106 (Table 129). Refer to the efficacy section of this report for detail of the design of these studies.

Safety data summaries are presented by treatment groups for the 3 COPD studies individually and for the pooled COPD studies (based on participant level integration of data from the 3 COPD studies). All 3 studies examined the mepolizumab 100 mg SC dose QW4, which is the proposed dose for the sought COPD indication. Study MEA117113 additionally examined a higher dose of mepolizumab 300 mg. Results for the 300 mg dose are included in the integrated safety source tables, and for the pooled COPD studies, results of the 300 mg dose group are included in the mepolizumab 'all doses' group. The focus of this safety evaluation is however the 100 mg dose groups.

Table 129 Phase 3 global COPD clinical studies

Study	N (Safety population)			Study duration
	placebo	mepolizumab 100 mg	mepolizumab 300 mg	
MEA117113 [1]	226	223	225	52 weeks
MEA117106 High stratum [1] Low stratum [2]	419 229 190	417 233 184	---	52 weeks
208657 [3]	401	403	---	52 to 104 weeks [4]

Abbreviations: BEC = blood eosinophil count

[1] BEC ≥150 cells/µL at screening OR a BEC ≥300 cells/µL in the preceding 12 months.

[2] BEC <150 cells/µL at screening AND no evidence of a BEC ≥300 cells/µL in the preceding 12 months.

[3] BEC ≥300 cells/µL at screening AND a BEC of ≥150 cells/µL measured at a second timepoint before randomization (refer to Section 1.4.2.2).

[4] A variable study duration (at least 52 weeks and up to 104 weeks) was implemented in Protocol Amendment 6 (06 December 2021).

For all studies, the Safety population (all randomized participants who received at least 1 dose of study treatment) was the primary population for safety analyses.

The following safety data were collated for the three COPD studies:

- Adverse events, by duration, severity, causality, actions taken and outcome. Adverse events were classified as pre-, on-, or post-treatment with reference to the study treatment start and stop dates and the onset date of the AE. To account for differences in exposure due to differing treatment duration both within study 208657 and among the COPD studies, exposure-adjusted event rates (EAIR) were summarized for on-treatment AEs.

  For study 208657, AEs and SAEs were collected from the start of study intervention until the Exit Visit/Study withdrawal visit as per the schedule of assessments. The exit visit occurred 4 weeks after the last dose of study treatment. In addition, for the screening and Run-in periods that occur prior to the start of study intervention, SAEs (and not AEs) related to study participation were collected from the point that informed consent was signed. After the initial AE/SAE report, the Investigator was required to proactively follow each participant at subsequent visitSContacts. All SAEs and non-serious AEs of special interest were to be followed until the event was resolved, stabilized, otherwise explained, or the participant was lost to follow-up.

AEs and SAEs for studies MEA117113 and MEA117106 were collected in a similar manner, through the Exit visit, 4 weeks after the last dose of study treatment, and also through the 16-week Follow-up period.

For all studies, open ended and non-leading verbal questioning of the participant was stated as the preferred method to inquire about AE occurrence to avoid the introduction of bias.

- Adverse Events of Special Interest (AESIs). Within the mepolizumab clinical development program, the following are considered AESI: systemic (including allergic/hypersensitivity) reactions, local injection site reactions, infections (including serious and opportunistic), malignancies, and cardiac disorders (including serious CVT events and serious ischemic events)
- Adjudicated SAEs. For each of the COPD studies, a blinded SAE report-based prospective adjudication of all SAE reports (case-based) was carried out by an independent Clinical Endpoint Committee (CEC). For all SAE reports with a fatal SAE, the CEC indicated the primary cause of death, as well as determined if the death was associated with the participant's known COPD. For all non-fatal SAE reports, the CEC categorized the primary serious medical event in the non-fatal case
- Adjudicated major adverse cardiovascular event(s) MACE. In accordance with a regulatory request, a formal and blinded adjudication of MACE (CV death, non-fatal MI, and non-fatal stroke) by the independent CEC across the COPD program was conducted prospectively for study 208657 and retrospectively for the earlier studies, MEA117113 and MEA117106.
- Pneumonia Adverse Events
- Additional medical concepts. The safety of mepolizumab in COPD was further evaluated based on the analyses of on-treatment AEs that were pre-specified for the following medical concepts: Defined by FDA medical queries (FMQ), Embolic and thrombotic events, Embolic and thrombotic events-venous, Acute pancreatitis, and Hypertension, and defined by Standarised MedDRA queries SMQ, supraventricular tachyarrhythmias, Gastrointestinal bleeding, and Conjunctival disorders. These medical concepts were identified from regulatory feedback and through consideration of an information request following data review of studies MEA117113 and MEA117106. These additional medical concepts are not identified as potential risks or events of interest for the pharmacovigilance plan for mepolizumab.
- Cardiovascular Adverse Events
- Clinical Laboratory Tests
- Vital Signs
- 12-Lead Electrocardiograms
- Immunogenicity. For study 208657, blood samples were collected for immunogenicity testing at Baseline and at Weeks 24, 52, 76, and 104. Samples were analysed for the presence of ADA. Samples testing positive for ADA were also analysed for the presence of neutralizing antibodies. For studies MEA117113 and MEA117106, blood samples were collected for immunogenicity testing at Baseline and at Weeks 24, 52, and 60 (prior to dosing on applicable visits). Samples were analysed for the presence of anti-mepolizumab antibodies (ADA). Samples testing positive for ADA were also analysed for the presence of

neutralizing antibodies. All 3 COPD studies used the same analytical assays for measurement of mepolizumab plasma concentrations, ADA, and Nab.

Of note, for the pooled COPD studies, Cochran-Mantel-Haenszel (CMH)-adjusted relative risk (RR) estimates were provided for on-treatment common AEs, SAEs, AESI, AEs of additional medical concepts, and MACE. As RR is based on incidence data, it does not take into account different exposures between studies and between treatment groups. Therefore, EAIR event rates also needed to be considered.

The MAH also provided summaries of exposure, demographics, and incidence of SAEs and deaths for the study grouping referred to as 'all studies combined', which comprises completed GSK-sponsored studies (including the 3 COPD studies) and ongoing studies with an interim CSR, across all indications (Table S.2).

Table 130 Study groupings for analysis of safety

Study Grouping	Studies Included	
COPD Studies		
Placebo-controlled	208657, MEA117113, MEA117106	
All Studies Combined[1]		
All Studies (ALL)	COPD	208657, MEA117113, MEA117106
	Severe asthma	MEA112997, MEA115588, MEA115575, MEA115661, MEA115666, 200862, 201810, 201536, 201956, 204471, 201312 200363 (pediatric), 205667, 204959, 209682
	Asthma	SB-240563/006, MEA114092, SB-240563/017, SB-240563/036, SB-240563/001, SB-240563/035
	HES	MHE100185, MHE100901, 200622, 205203
	EoE	MEE103226, MEE103219
	Atopic Dermatitis	SB-240563/045, 205050
	EGPA	MEA115921, MEA116841/201607
	Severe Bilateral Nasal Polyposis	MPP111782, 209692, 205687
	Healthy Participants	SB-240563/018, MEA115705, 204958
Ongoing Studies		
With an interim CSR[2]	HES	MHE104317, 112000, and MHE112562 (Compassionate Use)
Without an iCSR[3]	HES, Asthma, EGPA	215360, 206785, 217102, 220921

Abbreviation: COPD = chronic obstructive pulmonary disease; EGPA = eosinophilic granulomatosis with polyangiitis; EoE = eosinophilic esophagitis; GSK = GlaxoSmithkline; HES = hypereosinophilic syndrome; iCSR = interim clinical study report; PDAP = project data analysis plan

[1] The study grouping referred to as 'All studies combined' comprises completed GSK-sponsored studies (including the 3 COPD studies) and ongoing studies with an iCSR, across all indications.

[2] These studies are ongoing as of 23 March 2024; interim safety results are integrated for this Safety Summary

[3] These studies are ongoing as of 23 March 2024; interim safety results are not available for these studies

Patient exposure

Within each COPD study, duration of exposure (months) and participant-years exposure of the study treatment was calculated based on the therapeutic coverage as follows:

- Duration of Exposure (Months) = (Date of Last Dose – Date of First Dose + 29) × 12/365.25
- Participant-years exposure = (Date of Last Dose – Date of First Dose + 29)/365.25

A total of 1268 participants received at least 1 dose of mepolizumab in the 3 pooled COPD studies (Table 131); of these, 1043 participants were treated with mepolizumab 100 mg. The majority of participants treated with mepolizumab 100 mg or placebo received treatment for 12 months to 15 months (72% and 68%, respectively). The mean number of mepolizumab 100 mg treatments administered in the pooled studies was 13.6 (Table 132).

Treatment exposure was 1097.72 participant-years in the mepolizumab 100 mg group and 1052.92 participant-years in the placebo group (Table 132). Compared with studies MEA117113 and MEA117106, Study 208657 allowed for extended study participation beyond Week 52 (up to 104 weeks) and therefore contributed the highest participant years (PY) exposure (507.43 participant years in the mepolizumab group and 483.19 participant years in the placebo group).

For Study 208657, 403 participants were exposed to at least one dose of mepolizumab 100 mg subcutaneously (SC) (Table 133). The mean exposure was 15.1 months, with 90 (22%) participants being exposed to treatment for a range of 24 to 36 months. The mean number of mepolizumab 100 mg treatments administered in this study was 16.2. For participants in the fixed duration subgroup, exposure to study treatment was similar between the mepolizumab and placebo groups, each with a median exposure of 12 months. The total PY exposure was 155.17 and 155.8 in the mepolizumab and placebo groups, respectively. For participants in the variable duration subgroup, the median duration of exposure to study treatment was slightly higher in the mepolizumab group compared with the placebo group (20.0 months versus 17.0 months). The total PY exposure was 352.26 and 327.35 in the mepolizumab and placebo groups, respectively.

Table 131 Participants in Safety population by dose (COPD studies, Safety population)

Study	PBO (N=1046)	100 SC (N=1043)	300 SC (N=225)	All Doses (N=1268)	Total (N=2314)
208657	401	403	-	403	804
MEA117113	226	223	225	448	674
MEA117106	419	417	-	417	836
208657 + MEA117113 + MEA117106	1046	1043	225	1268	2314

Note: Studies included: 208657, MEA117113 and MEA117106

Table 132 Summary of treatment exposure, number of treatments administered, and duration of exposure (COPD studies, Safety population)

	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106			
	PBO (N=401)	100 SC (N=403)	PBO (N=226)	100 SC (N=223)	PBO (N=419)	100 SC (N=417)	PBO (N=1046)	100 SC (N=1043)	All Doses (N=1268)	Total (N=2314)
Total participant-years exposure[1]	483.19	507.43	196.23	206.78	373.50	383.51	1052.92	1097.72	1301.48	2354.40
Exposure (months)										
n	401	403	226	223	419	417	1046	1043	1268	2314
Mean (SD)	14.5 (6.00)	15.1 (6.23)	10.4 (3.24)	11.1 (2.71)	10.7 (2.99)	11.0 (2.63)	12.1 (4.81)	12.6 (4.81)	12.3 (4.57)	12.2 (4.68)
Median	12.1	12.2	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0
Min, max	1, 25	1, 25	1, 13	1, 13	1, 14	1, 13	1, 25	1, 25	1, 25	1, 25
Range of exposure[2]										
n	401	403	226	223	419	417	1046	1043	1268	2314
1 - <3, n (%)	16 (4)	12 (3)	14 (6)	8 (4)	19 (5)	14 (3)	49 (5)	34 (3)	39 (3)	88 (4)
3 - <6	11 (3)	14 (3)	10 (4)	10 (4)	24 (6)	20 (5)	45 (4)	44 (4)	58 (5)	103 (4)
6 - <9	12 (3)	13 (3)	20 (9)	5 (2)	29 (7)	18 (4)	61 (6)	36 (3)	50 (4)	111 (5)
9 - <12	17 (4)	11 (3)	12 (5)	4 (2)	14 (3)	12 (3)	43 (4)	27 (3)	36 (3)	79 (3)
12 - <15	208 (52)	197 (49)	170 (75)	196 (88)	333 (79)	353 (85)	711 (68)	746 (72)	929 (73)	1640 (71)
15 - <18	25 (6)	29 (7)	0	0	0	0	25 (2)	29 (3)	29 (2)	54 (2)
18 - <21	17 (4)	12 (3)	0	0	0	0	17 (2)	12 (1)	12 (<1)	29 (1)
21 - <24	23 (6)	25 (6)	0	0	0	0	23 (2)	25 (2)	25 (2)	48 (2)
24 - <36	72 (18)	90 (22)	0	0	0	0	72 (7)	90 (9)	90 (7)	162 (7)
Number of Treatments n (%)										
n	401	403	226	223	419	417	1046	1043	1268	2314
1	7 (2)	6 (1)	6 (3)	6 (3)	11 (3)	4 (<1)	24 (2)	16 (2)	18 (1)	42 (2)
2	9 (2)	6 (1)	8 (4)	2 (<1)	8 (2)	10 (2)	25 (2)	18 (2)	21 (2)	46 (2)
3	5 (1)	4 (<1)	4 (2)	4 (2)	2 (<1)	6 (1)	11 (1)	14 (1)	20 (2)	31 (1)
4	2 (<1)	4 (<1)	3 (1)	3 (1)	14 (3)	6 (1)	19 (2)	13 (1)	19 (1)	38 (2)
5	3 (<1)	4 (<1)	3 (1)	3 (1)	7 (2)	8 (2)	13 (1)	15 (1)	17 (1)	30 (1)
6	4 (<1)	6 (1)	8 (4)	1 (<1)	8 (2)	4 (<1)	20 (2)	11 (1)	17 (1)	37 (2)
7	4 (<1)	1 (<1)	5 (2)	1 (<1)	4 (<1)	4 (<1)	13 (1)	6 (<1)	9 (<1)	22 (<1)
8	5 (1)	5 (1)	6 (3)	2 (<1)	12 (3)	4 (<1)	23 (2)	11 (1)	14 (1)	37 (2)
9	3 (<1)	5 (1)	3 (1)	1 (<1)	9 (2)	8 (2)	15 (1)	14 (1)	16 (1)	31 (1)
10	9 (2)	5 (1)	3 (1)	3 (1)	6 (1)	4 (<1)	18 (2)	12 (1)	13 (1)	31 (1)
11	6 (1)	6 (1)	4 (2)	1 (<1)	4 (<1)	3 (<1)	14 (1)	10 (<1)	17 (1)	31 (1)
12	19 (5)	12 (3)	7 (3)	3 (1)	22 (5)	19 (5)	48 (5)	34 (3)	45 (4)	93 (4)
13	167 (42)	164 (41)	163 (72)	187 (84)	310 (74)	335 (80)	640 (61)	686 (66)	854 (67)	1494 (65)
14	14 (3)	12 (3)	3 (1)	6 (3)	2 (<1)	2 (<1)	19 (2)	20 (2)	25 (2)	44 (2)
15	7 (2)	8 (2)	0	0	0	0	7 (<1)	8 (<1)	8 (<1)	15 (<1)
16	9 (2)	9 (2)	0	0	0	0	9 (<1)	9 (<1)	9 (<1)	18 (<1)
17	10 (2)	11 (3)	0	0	0	0	10 (<1)	11 (1)	11 (<1)	21 (<1)
18	7 (2)	7 (2)	0	0	0	0	7 (<1)	7 (<1)	7 (<1)	14 (<1)
19	6 (1)	3 (<1)	0	0	0	0	6 (<1)	3 (<1)	3 (<1)	9 (<1)
20	10 (2)	2 (<1)	0	0	0	0	10 (<1)	2 (<1)	2 (<1)	12 (<1)
21	3 (<1)	2 (<1)	0	0	0	0	3 (<1)	2 (<1)	2 (<1)	5 (<1)
22	5 (1)	10 (2)	0	0	0	0	5 (<1)	10 (<1)	10 (<1)	15 (<1)
23	4 (<1)	7 (2)	0	0	0	0	4 (<1)	7 (<1)	7 (<1)	11 (<1)
24	12 (3)	11 (3)	0	0	0	0	12 (1)	11 (1)	11 (<1)	23 (<1)
25	11 (3)	12 (3)	0	0	0	0	11 (1)	12 (1)	12 (<1)	23 (<1)
26	60 (15)	81 (20)	0	0	0	0	60 (6)	81 (8)	81 (6)	141 (6)
Treatments Administered n (%)										
n	401	403	226	223	419	417	1046	1043	1268	2314
Mean (SD)	15.4 (6.44)	16.2 (6.72)	11.2 (3.52)	12.0 (2.94)	11.5 (3.25)	11.9 (2.89)	12.9 (5.16)	13.6 (5.19)	13.2 (4.93)	13.1 (5.03)
Median	13.0	13.0	13.0	13.0	13.0	13.0	13.0	13.0	13.0	13.0
Min, max	1, 26	1, 26	1, 14	1, 14	1, 14	1, 14	1, 26	1, 26	1, 26	1, 26

Note: Exposure (Therapeutic Coverage) = Treatment stop date - Treatment start date + 29.
[1] Sum across participants of (treatment stop date - treatment start date + 29)/365.25.
[2] Range of exposure based on participant exposure rounded to the nearest whole month.

Table 133 Exposure (therapeutic coverage) to study treatment (Study 208657; Safety Population)

	Overall		Fixed Duration (Enrolled for 52 weeks)		Variable Duration (Enrolled for up to 104 weeks)	
	PBO (N=401)	Mepo 100 mg (N=403)	PBO (N=175)	Mepo 100 mg (N=170)	PBO (N=226)	Mepo 100 mg (N=233)
Exposure (months)						
n	401	403	175	170	226	233
Mean (SD)	14.5 (6.01)	15.1 (6.22)	10.7 (3.19)	11.0 (2.76)	17.4 (6.03)	18.2 (6.28)
Median (Min, Max)	12.0 (1, 25)	12.0 (1, 25)	12.0 (1, 14)	12.0 (1, 13)	17.0 (1, 25)	20.0 (1, 25)
Range of exposure [1]						
1 to <3 months	16 (4)	12 (3)	14 (8)	8 (5)	2 (<1)	4 (2)
3 to <6 months	11 (3)	14 (3)	5 (3)	5 (3)	6 (3)	9 (4)
6 to <9 months	12 (3)	13 (3)	7 (4)	9 (5)	5 (2)	4 (2)
9 to <12 months	17 (4)	11 (3)	6 (3)	7 (4)	11 (5)	4 (2)
12 to <15 months	208 (52)	197 (49)	143 (82)	141 (83)	65 (29)	56 (24)
15 to <18 months	25 (6)	29 (7)	0	0	25 (11)	29 (12)
18 to <21 months	17 (4)	12 (3)	0	0	17 (8)	12 (5)
21 to <24 months	23 (6)	25 (6)	0	0	23 (10)	25 (11)
≥24 months	72 (18)	90 (22)	0	0	72 (32)	90 (39)
Total PY exposure [2]	483.19	507.43	155.84	155.17	327.35	352.26
Exposure up to 52 weeks	372.33	377.10	-	-	-	-
Exposure between 52 to 104 weeks [3]	110.87	130.33	-	-	-	-

[1] Range of exposure based on participant exposure rounded to the nearest whole month.
[2] Sum across participants of (treatment stop date - treatment start date + 29)/365.25.
[3] The number (%) of participants with exposure between 52 and 104 weeks was: 180 (45%) placebo, 204 (51%) mepolizumab.
Note: Exposure (Therapeutic Coverage) = Treatment stop date - Treatment start date + 29.

For the All studies combined pool, a total of 5286 participants received at least 1 dose of mepolizumab and 2724 participants received placebo. The mean treatment exposure across all individual mepolizumab dose groups ranged from 7.0 to 32.3 months. Total treatment exposure for the 3648 participants who received mepolizumab 100 mg was 5704.82 participant-years. A total of 69% (2528 of 3648) participants were treated with mepolizumab 100 mg for >12 months.

Disposition

Study withdrawal

A summary of participant disposition in the pooled COPD studies and in Study 208657 (by fixed and variable duration) is provided in previous Table 110 and Figure 21, respectively.

The study completion rates in the individual studies were high overall and generally similar, with the exception of study MEA117113, where the mepolizumab group had a higher proportion of study completers compared with the placebo group (92% versus 82%, respectively). In study 208657, study completion profiles were generally similar between the participants in the fixed 52-week duration.

Demographics

Demographics were generally balanced between the mepolizumab 100 mg group and placebo group in the 3 pooled COPD studies, except for race, reflecting differences in country selection. In the pooled COPD studies, the majority of the participants were White (82%) and male (66%). Mean BMI was similar between the mepolizumab 100 mg group and the placebo group. See Table 134 for a summary of demographical data for the pooled COPD studies.

Demographics within each study were generally balanced by treatment group. In study 208657, demographics were generally similar between the treatment groups. Most participants were White (84%) and predominantly male (69%); the mean age was 66.2 years. More than half of the participants (61%) were ≥65 years of age. Mean BMI was 27.25 kg/m2. The mean and median ages were similar between treatment groups; however, the proportion of participants ≥65 years of age was higher in the mepolizumab group (65%) compared with the placebo group (57%). Demographic characteristics were also similar between the fixed duration subgroup and the variable duration subgroup.

Table 134 Demographics (COPD studies, Safety population)

	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106			
	PBO	100 SC	PBO	100 SC	PBO	100 SC	PBO	100 SC	All Doses	Total
	(N=401)	(N=403)	(N=226)	(N=223)	(N=419)	(N=417)	(N=1046)	(N=1043)	(N=1268)	(N=2314)
Age (yrs)										
n	401	403	226	223	419	417	1046	1043	1268	2314
Mean (SD)	66.0(7.91)	66.4 (8.1)	65.8 (8.64)	64.8 (9.06)	65.2 (8.56)	65.6 (8.72)	65.7 (8.34)	65.8 (8.57)	65.6 (8.65)	65.6 (8.51)
Median	66.0	67.0	66.5	65.0	65.0	66.0	66.0	67.0	66.0	66.0
Min, max	42, 91	39, 88	43, 88	42, 86	39, 85	40, 85	39, 91	39, 88	39, 88	39, 91
Age group (yrs), n (%)										
18-64	173 (43)	143 (35)	101 (45)	104 (47)	193 (46)	182 (44)	467 (45)	429 (41)	539 (43)	1006 (43)
≥65	228 (57)	260 (65)	125 (55)	119 (53)	226 (54)	235 (56)	579 (55)	614 (59)	729 (57)	1308 (57)
65-74	178 (44)	201 (50)	87 (38)	87 (39)	166 (40)	173 (41)	431 (41)	461 (44)	543 (43)	974 (42)
75-84	46 (11)	56 (14)	37 (16)	31 (14)	59 (14)	61 (15)	142 (14)	148 (14)	180 (14)	322 (14)
≥85	4 (<1)	3 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	6 (<1)	5 (<1)	6 (<1)	12 (<1)
19-64	173 (43)	143 (35)	101 (45)	104 (47)	193 (46)	182 (44)	467 (45)	429 (41)	539 (43)	1006 (43)
≥65	228 (57)	260 (65)	125 (55)	119 (53)	226 (54)	235 (56)	579 (55)	614 (59)	729 (57)	1308 (57)
Sex										
n	401	403	226	223	419	417	1046	1043	1268	2314
Female, n (%)	126 (31)	127 (32)	70 (31)	91 (41)	156 (37)	160 (38)	352 (34)	378 (36)	445 (35)	797 (34)
Male, n (%)	275 (69)	276 (68)	156 (69)	132 (59)	263 (63)	257 (62)	694 (66)	665 (64)	823 (65)	1517 (66)
Ethnicity										
n	401	403	226	223	419	417	1046	1043	1268	2314
Hispanic/ Latino, n (%)	95 (24)	94 (23)	34 (15)	36 (16)	88 (21)	83 (20)	217 (21)	213 (20)	250 (20)	467 (20)
Not Hispanic/ Latino, n (%)	306 (76)	309 (77)	192 (85)	187 (84)	331 (79)	334 (80)	829 (79)	830 (80)	1018 (80)	1847 (80)
Race category										
n	401	403	226	223	419	417	1046	1043	1268	2314
African American/African heritage	5 (1)	5 (1)	2 (<1)	4 (2)	7 (2)	4 (<1)	14 (1)	13 (1)	15 (1)	29 (1)
White	335 (84)	338 (84)	182 (81)	178 (80)	337 (80)	343 (82)	854 (82)	859 (82)	1041 (82)	1895 (82)
Asian	56 (14)	56 (14)	42 (19)	41 (18)	4 (<1)	3 (<1)	102 (10)	100 (10)	141 (11)	243 (11)
Other[1]	5 (1)	4 (<1)	0	0	71 (17)	67 (16)	76 (7)	71 (7)	71 (6)	147 (6)
BMI (kg/m²)										
n	401	403	226	223	419	417	1046	1043	1268	2314
Mean (SD)	27.13 (5.540)	27.38 (5.342)	25.43 (4.977)	27.10 (6.181)	27.01 (5.577)	26.85 (5.890)	26.71 (5.476)	27.11(5.749)	26.98 (5.661)	26.86 (5.579)

	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106			
	PBO	100 SC	PBO	100 SC	PBO	100 SC	PBO	100 SC	All Doses	Total
	(N=401)	(N=403)	(N=226)	(N=223)	(N=419)	(N=417)	(N=1046)	(N=1043)	(N=1268)	(N=2314)
Median	26.23	26.85	24.93	26.30	26.43	26.13	25.98	26.44	26.35	26.19
Min, max	16.1, 50.6	15.2, 43.0	16.7, 48.8	15.9, 54.7	15.6, 45.5	14.3, 60.1	15.6, 50.6	14.3, 60.1	14.3, 60.1	14.3, 60.1

Note: In study 208657, demographic characteristics were similar between the fixed duration and the variable duration subgroups (refer for details to 208657 CSR Section 4.4.1).
[1] All participants enrolled were ≥40 years of age, except 2 participants of 39 years of age, in the mepolizumab 100 mg group in study 208657 [208657 CSR, Table 8], and the placebo group in study MEA117106 [MEA117106 CSR, Table 6], respectively.
[2] Other includes multiple race participant in addition to African American/African heritage and American Indian or Alaska native.

In the 3 pooled COPD studies, COPD history and **baseline disease characteristics** at screening were balanced across the mepolizumab 100 mg group and placebo group. Across the COPD pooled dataset 35% had COPD for greater than 5 to 10 years and 32% for >10 years; the mean duration of COPD was 9.2 years. Participants entering the COPD studies were not well controlled on their current ICS-based triple maintenance therapy regimens and had a mean of 2.5 moderate/severe COPD exacerbations in the 12 months prior to study. Exacerbation history was similar in the mepolizumab 100 mg group and the placebo group. For all participants, COPD exacerbations in the previous 12 months were primarily caused by respiratory illnesses (54% respiratory infection, 29% common cold, 24% lower respiratory tract infection and upper respiratory infection other than common cold) or cold air/weather (26%).

In Study 208657, baseline disease characteristics were also generally similar between the fixed duration subgroup and the variable duration subgroup.

With regards current or former **smoking status**, the majority of the participants in the 3 pooled COPD studies were classified as current or former smokers (27% and 70%, respectively). Participants had significant prior cigarette smoke exposure, with a mean 44.3 pack years of smoking history. Smoking status and history were similar in the mepolizumab 100 mg group and the placebo group. Study 208657 included only current or former cigarette smokers. Study eligibility was independent of smoking status and history for studies MEA117113 and MEA117106, though the majority (>95%) of participants were either former or current smokers in those studies.

With regards to **co-morbidities**, in the 3 pooled COPD studies, a total of 71% of the participants reported 'Any current medical conditions' at screening, with the most common being 'hypertension' (51%) and 'hypercholesterolemia' (31%). The overall prevalence of 'Any current medical condition' was similar in the mepolizumab 100 mg group and the placebo group.

The following medical conditions were identified as relevant for identifying participants with a risk of CV events (based on past and current medical history): Angina pectoris, Coronary artery disease, Myocardial infarction, Arrythmia, Congestive heart failure, Hypertension, Cerebrovascular accident, Carotid or aorto-femoral vascular disease, Hypercholesterolemia, Diabetes mellitus.

In the 3 pooled COPD studies, 69% of all participants had past or current CV-related conditions. The most common past and current CV-related medical conditions were hypertension and hypercholesterolemia (52% and 33%, respectively). Prevalences of past or current CV-related conditions were similar between the mepolizumab 100 mg group and the placebo group.

Adverse events

Overview of adverse events

Table 135 below provides overall incidences of AEs and SAEs, along with incidence and EAIR event rate of on-treatment common AEs, AEs considered to be treatment-related by the investigator and post-treatment AEs reported for the individual and pooled COPD studies.

Table 135 Overview of adverse events (COPD studies, Safety population)

	208657				MEA117113				MEA117106				208657+MEA117113+MEA117106					
	PBO (N=401)		100 SC (N=403)		PBO (N=226)		100 SC (N=223)		PBO (N=419)		100 SC (N=417)		PBO (N=1046)		100 SC (N=1043)		All Doses (N=1268)	
	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]
Any AE																		
On-treatment	307 (77)	2791.8	299 (74)	2770.8	182 (81)	3944.4	186 (83)	4410.4	339 (81)	4607.8	330 (79)	4286.7	828 (79)	3650.8	815 (78)	3609.3	1006 (79)	3716.5
On-treatment Drug-related	17 (4)	68.3	19 (5)	67.0	28 (12)	224.2	28 (13)	178.9	61 (15)	390.9	51 (12)	242.5	106 (10)	211.8	98 (9)	149.4	126 (10)	185.2
On-treatment led to study treatment discontinuation	17 (4)	35.2	12 (3)	23.6	26 (12)	158.0	9 (4)	53.2	29 (7)	96.4	26 (6)	101.7	72 (7)	79.8	47 (5)	56.5	72 (6)	69.9
On- and post treatment led to study treatment discontinuation	18(4)	--	14(3)	--	27(12)	--	9(4)	--	35(8)	--	31(7)	--	80(8)	--	54(5)	--	79(6)	--
On-treatment led to study withdrawal	13 (3)	26.9	13 (3)	25.6	16 (7)	96.8	5 (2)	24.2	15 (4)	48.2	17 (4)	62.6	44 (4)	47.5	35 (3)	38.3	47 (4)	43.0
On- and post treatment led to study withdrawal	16 (4)	--	15 (4)	--	18 (8)	--	7 (3)	--	21 (5)	--	18 (4)	--	55 (5)	--	40 (4)	--	53 (4)	--
Post-treatment	20 (5)	--	23 (6)	--	51 (23)	--	50 (22)	--	83 (20)	--	71 (17)	--	154 (15)	--	144 (14)	--	188 (15)	--
Any SAE																		
On-treatment	112 (28)	393.2	99 (25)	358.7	58 (26)	545.3	52 (23)	561.0	117 (28)	610.4	104 (25)	560.6	287 (27)	498.6	255 (24)	467.3	309 (24)	467.9
Post-treatment	9 (2)	--	12 (3)	--	18 (8)	--	12 (5)	--	33 (8)	--	24 (6)	--	60 (6)	--	48 (5)	--	62 (5)	--
On- and post treatment Fatal	11 (3)	--	11 (3)	--	9 (4)	--	4 (2)	--	17 (4)	--	16 (4)	--	37 (4)	--	31 (3)	--	39 (3)	--

Note: Exposure-adjusted frequency is calculated as: (Total number of adverse events / Total Duration of Exposure in years) *1000.
Note: Studies included 208657, MEA117113 and MEA117106
[1] Represents the frequency of events per 1000 participant-years of exposure.

For the **pooled studies**, the incidence and EAIR rate across all categories were similar between the mepolizumab 100 mg group and the placebo group. In study MEA117113, the incidence and EAIR rate of on-treatment AEs leading to study treatment discontinuation or study withdrawal were lower in the mepolizumab 100 mg group compared with the placebo group, and a similar trend was observed for the corresponding on- and post-treatment AEs.

For **study 208657**, an overview of AEs by treatment duration subgroup (fixed v variable) is provided in Table 136 below.

Table 136 Overview of AEs by treatment duration (Study 208657, Safety Population)

	Overall (N=804)		Fixed Duration (Enrolled for 52 weeks) (N=345)		Variable Duration (Enrolled for up to 104 weeks) (N=459)	
	PBO (N=401) n (%)	Mepo 100 mg (N=403) n (%)	PBO (N=175) n (%)	Mepo 100 mg (N=170) n (%)	PBO (N=226) n (%)	Mepo 100 mg (N=233) n (%)
Any on/post-treatment AE	308 (77)	301 (75)	126 (72)	119 (70)	182 (81)	182 (78)
AEs related to study treatment	17 (4)	19 (5)	10 (6)	9 (5)	7 (3)	10 (4)
AEs leading to permanent discontinuation of study treatment	18 (4)	14 (3)	8 (5)	7 (4)	10 (4)	7 (3)
AEs leading to dose interruption/delay	21 (5)	12 (3)	8 (5)	4 (2)	13 (6)	8 (3)
Any on/post-treatment SAE	115 (29)	101 (25)	47 (27)	36 (21)	68 (30)	65 (28)
SAEs related to study treatment	0	0	0	0	0	0
Fatal SAEs	11 (3)	11 (3)	5 (3)	6 (4)	6 (3)	5 (2)
Fatal SAEs related to study treatment	0	0	0	0	0	0
Any on-treatment AE	307 (77)	299 (74)	125 (71)	117 (69)	182 (81)	182 (78)
Any on-treatment SAE	112 (28)	99 (25)	45 (26)	34 (20)	67 (30)	65 (28)
Any post-treatment AE	20 (5)	23 (6)	10 (6)	16 (9)	10 (4)	7 (3)
Any post-treatment SAE	9 (2)	12 (3)	3 (2)	8 (5)	6 (3)	4 (2)

Incidence and type of AEs

Across both treatment groups in the 3 **pooled COPD studies**, the SOCs with the most frequently reported on-treatment AEs were:

- infections and infestations (49%, 920.1 events per 1000 PY in the mepolizumab 100 mg group and 49%, 925.0 events per 1000 PY in the placebo group)
- respiratory, thoracic, and mediastinal disorders (33%, 612.2 events per 1000 PY and 32%, 576.5 events per 1000 PY in the placebo group).

The incidence of on-treatment AEs by SOC was generally similar between the mepolizumab 100 mg group and the placebo group.

In the 3 pooled COPD studies, incidence and EAIR of any on-treatment common AEs (defined as occurring in ≥3% of participants in any 1 treatment group) by PT were generally similar between the mepolizumab 100 mg group (78%, 3609.3 events per 1000 PY) and the placebo group (79%, 3650.8 events per 1000 PY). These data are presented in Table 137 below.

The most common AEs by PT (reported by ≥10% of the participants in any of the treatment groups) were:

- COPD exacerbation (16%, 243.1 events per 1000 PY for placebo; 15%, 232.3 events per 1000 PY for mepolizumab 100 mg)
- nasopharyngitis (14%, 185.2 events per 1000 PY for placebo; 14%, 179.5 events per 1000 PY for mepolizumab 100 mg)
- headache (10%, 177.6 events per 1000 PY for placebo; 10%, 177.6 events per 1000 PY for mepolizumab 100 mg)

All on-treatment common AEs were reported with a similar incidence and EAIR between the mepolizumab 100 mg group and the placebo group (differences were <2% in incidence and <17 events per 1000 PY in event rate).

Table 137 On-treatment common (at least 3% Incidence in any treatment group) adverse events (COPD studies, Safety population)

	208657				MEA117113				MEA117106				208657 + MEA117113 + MEA117106					
	PBO (N=401) (PY=483.19)		100 SC (N=403) (PY=507.43)		PBO (N=226) (PY=196.23)		100 SC (N=223) (PY=206.78)		PBO (N=419) (PY=373.50)		100 SC (N=417) (PY=383.51)		PBO (N=1046) (PY= 1052.92)		100 SC (N=1043) (PY= 1097.72)		All Doses (N=1268) (PY= 1301.48)	
Preferred Term	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]
Any event, n (%)	307 (77)	2791.8	299 (74)	2770.8	182 (81)	3944.4	186 (83)	4410.4	339 (81)	4607.8	330 (79)	4286.7	828 (79)	3650.8	815 (78)	3609.3	1006 (79)	3716.5
COPD	62 (15)	190.4	49 (12)	163.6	35 (15)	249.7	28 (13)	203.1	74 (18)	307.9	76 (18)	339.0	171 (16)	243.1	153 (15)	232.3	188 (15)	248.2
Nasopharyngitis	32 (8)	86.9	41 (10)	110.4	48 (21)	331.2	39 (17)	275.6	63 (15)	235.6	64 (15)	219.0	143 (14)	185.2	144 (14)	179.5	184 (15)	191.3
Headache	27 (7)	82.8	31 (8)	120.2	20 (9)	147.8	34 (15)	299.8	56 (13)	315.9	42 (10)	187.7	103 (10)	177.6	107 (10)	177.6	129 (10)	179.8
Pneumonia	27 (7)	70.4	30 (7)	76.9	22 (10)	127.4	24 (11)	154.8	39 (9)	120.5	31 (7)	93.9	88 (8)	98.8	85 (8)	97.5	105 (8)	100.7
Back pain	23 (6)	80.7	26 (6)	90.7	11 (5)	61.2	15 (7)	87.0	31 (7)	91.0	32 (8)	99.1	65 (6)	80.7	73 (7)	92.9	90 (7)	94.5
Upper respiratory tract infection	20 (5)	60.0	25 (6)	80.8	21 (9)	147.8	16 (7)	91.9	21 (5)	69.6	21 (5)	65.2	62 (6)	79.8	62 (6)	77.4	75 (6)	77.6
Arthralgia	16 (4)	39.3	22 (5)	55.2	7 (3)	40.8	13 (6)	67.7	28 (7)	107.1	16 (4)	57.4	51 (5)	63.6	51 (5)	58.3	63 (5)	59.9
Dyspnoea	20 (5)	74.5	20 (5)	59.1	18 (8)	96.8	12 (5)	67.7	12 (3)	37.5	17 (4)	62.6	50 (5)	65.5	49 (5)	61.9	59 (5)	65.3
Cough	14 (3)	31.0	13 (3)	29.6	12 (5)	81.5	14 (6)	67.7	15 (4)	45.5	22 (5)	75.6	41 (4)	45.6	49 (5)	52.8	65 (5)	61.5
Diarrhoea	12 (3)	37.3	22 (5)	45.3	14 (6)	71.3	16 (7)	91.9	15 (4)	66.9	18 (4)	57.4	41 (4)	54.1	56 (5)	58.3	64 (5)	59.2
COVID-19	49 (12)	103.5	50 (12)	108.4	0	0	0	0	0	0	0	0	49 (5)	47.5	50 (5)	50.1	50 (4)	42.3
Influenza	19 (5)	43.5	19 (5)	47.3	11 (5)	61.2	6 (3)	33.9	24 (6)	80.3	16 (4)	54.8	54 (5)	59.8	41 (4)	47.4	45 (4)	43.0
Hypertension	27 (7)	62.1	17 (4)	33.5	3 (1)	15.3	9 (4)	48.4	9 (2)	24.1	12 (3)	31.3	39 (4)	39.9	38 (4)	35.5	45 (4)	35.3

	208657				MEA117113				MEA117106				208657 + MEA117113 + MEA117106					
	PBO (N=401) (PY=483.19)		100 SC (N=403) (PY=507.43)		PBO (N=226) (PY=196.23)		100 SC (N=223) (PY=206.78)		PBO (N=419) (PY=373.50)		100 SC (N=417) (PY=383.51)		PBO (N=1046) (PY= 1052.92)		100 SC (N=1043) (PY= 1097.72)		All Doses (N=1268) (PY= 1301.48)	
Preferred Term	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]
Oropharyngeal pain	4 (<1)	22.8	7 (2)	23.6	4 (2)	20.4	15 (7)	72.5	18 (4)	53.5	24 (6)	70.4	26 (2)	33.2	46 (4)	49.2	57 (4)	51.5
Urinary tract infection	7 (2)	14.5	18 (4)	39.4	7 (3)	40.8	9 (4)	53.2	15 (4)	50.9	15 (4)	44.3	29 (3)	32.3	42 (4)	43.7	44 (3)	38.4
Pyrexia	9 (2)	24.8	12 (3)	29.6	10 (4)	51.0	6 (3)	33.9	13 (3)	48.2	8 (2)	28.7	32 (3)	38.0	26 (2)	30.1	39 (3)	39.2
Pain in extremity	6 (1)	14.5	11 (3)	21.7	5 (2)	30.6	7 (3)	33.9	16 (4)	72.3	19 (5)	49.5	27 (3)	38.0	37 (4)	33.7	43 (3)	36.1
Sinusitis	7 (2)	18.6	9 (2)	21.7	7 (3)	56.1	8 (4)	53.2	13 (3)	37.5	19 (5)	54.8	27 (3)	32.3	36 (3)	39.2	43 (3)	40.0
Bronchitis	11 (3)	31.0	8 (2)	15.8	9 (4)	45.9	8 (4)	58.0	12 (3)	48.2	9 (2)	26.1	32 (3)	39.9	25 (2)	27.3	37 (3)	35.3
Dizziness	11 (3)	26.9	9 (2)	21.7	3 (1)	15.3	6 (3)	29.0	18 (4)	50.9	10 (2)	33.9	32 (3)	33.2	25 (2)	27.3	28 (2)	26.1
Nausea	6 (1)	12.4	5 (1)	9.9	3 (1)	15.3	9 (4)	48.4	12 (3)	64.3	10 (2)	31.3	21 (2)	31.3	24 (2)	24.6	33 (3)	30.7
Constipation	4 (<1)	8.3	9 (2)	17.7	10 (4)	51.0	7 (3)	38.7	6 (1)	18.7	12 (3)	36.5	20 (2)	19.9	28 (3)	28.2	33 (3)	28.4
Oedema peripheral	7 (2)	16.6	10 (2)	19.7	3 (1)	15.3	7 (3)	33.9	13 (3)	34.8	9 (2)	26.1	23 (2)	22.8	26 (2)	24.6	30 (2)	25.4
Pharyngitis	4 (<1)	8.3	6 (1)	13.8	4 (2)	20.4	5 (2)	24.2	18 (4)	50.9	12 (3)	36.5	26 (2)	25.6	23 (2)	23.7	27 (2)	23.1
Injection site reaction	0	0	1 (<1)	2.0	10 (4)	86.6	6 (3)	29.0	12 (3)	48.2	12 (3)	57.4	22 (2)	33.2	19 (2)	26.4	30 (2)	43.0
Oral candidiasis	4 (<1)	8.3	3 (<1)	5.9	5 (2)	35.7	3 (1)	14.5	12 (3)	40.2	14 (3)	41.7	21 (2)	24.7	20 (2)	20.0	28 (2)	23.8
Non-cardiac chest pain	5 (1)	10.3	4 (<1)	7.9	8 (4)	40.8	6 (3)	43.5	9 (2)	24.1	7 (2)	20.9	22 (2)	20.9	17 (2)	19.1	24 (2)	22.3
Rhinitis	5 (1)	18.6	7 (2)	15.8	5 (2)	30.6	7 (3)	43.5	9 (2)	24.1	9 (2)	23.5	19 (2)	22.8	23 (2)	23.7	27 (2)	23.1
Abdominal pain upper	8 (2)	18.6	5 (1)	9.9	1 (<1)	5.1	9 (4)	43.5	8 (2)	21.4	7 (2)	26.1	17 (2)	17.1	21 (2)	21.9	26 (2)	22.3
Fatigue	4 (<1)	8.3	4 (<1)	9.9	4 (2)	20.4	6 (3)	29.0	6 (1)	37.5	9 (2)	28.7	14 (1)	20.9	19 (2)	20.0	27 (2)	23.1
Contusion	1 (<1)	2.1	3 (<1)	13.8	2 (<1)	10.2	7 (3)	33.9	9 (2)	34.8	12 (3)	31.3	12 (1)	15.2	22 (2)	23.7	25 (2)	22.3

Note: Exposure-adjusted frequency is calculated as: (Total number of adverse events / Total Duration of Exposure in years)*1000.
Note: Common AEs are defined as AEs with frequency ≥3% prior to rounding in any treatment group.
Note: COPD refers to COPD exacerbation.
[1] Represents the frequency of events per 1000 participant-years of exposure.

While rates between studies varied, the profile of common AEs was generally similar within the individual studies, with the exception that COVID-19 only affected study 208657 and was reported with similar incidences and EAIR in the mepolizumab 100 mg group (12% of participants, 108.4

events per 1000 PY) and in the placebo group (12% of participants, 103.5 events per 1000 PY). In each study, common AEs by PT with the highest rates for each treatment group were COPD, nasopharyngitis and headache (and COVID-19 for study 208657 only).

In the 3 pooled COPD studies, CMH-adjusted cumulative proportions and CMH-adjusted RR of on-treatment common AEs are summarized in Table 138for mepolizumab 100 mg versus placebo. The RR 95% CIs for all common AEs include 1, with the exception of oropharyngeal pain. Oropharyngeal pain showed a numerically higher relative risk (RR 1.77; 95% CI:1.11, 2.85) for mepolizumab 100 mg versus placebo. The difference in incidence between treatment groups for oropharyngeal pain was driven by study MEA117113 (7%; 15 of 223 in the mepolizumab 100 mg group and 2%, 4 of 226 in the placebo group), while the difference in study 208657 was <1% in incidence and <1 event per 1000 PY between treatment groups (Table S.13 above). RR is based on incidence data, which does not account for different exposures between studies and between treatment groups. The exposure adjusted event rate in the pooled studies for oropharyngeal pain was 49.2 events per 1000PY in the mepolizumab 100 mg group and 33.2 events per 1000 PY in the placebo group. There were no cases of serious oropharyngeal pain in any study or cases of oropharyngeal pain leading to treatment discontinuation.

Table 138 Common On-Treatment Adverse Events (≥3% in Any Treatment Group) Mepolizumab 100 mg vs Placebo (COPD studies, Safety Population)

Preferred Term	Treatment N (PBO)=1046 N (100 SC) =1043	Number (%) with Event	Adjusted Cumulative Proportion (%)[1]	CMH-Adjusted Relative Risk (95% CI)[2]
Contusion	PBO 100 SC	12 (1.1) 22 (2.1)	1.1 2.1	1.84 (0.91, 3.70)
Oropharyngeal pain	PBO 100 SC	26 (2.5) 46 (4.4)	2.5 4.4	1.77 (1.11, 2.85)
Urinary tract infection	PBO 100 SC	29 (2.8) 42 (4.0)	2.8 4.0	1.45 (0.91, 2.31)
Constipation	PBO 100 SC	20 (1.9) 28 (2.7)	1.9 2.7	1.40 (0.80, 2.48)
Pain in extremity	PBO 100 SC	27 (2.6) 37 (3.5)	2.6 3.5	1.37 (0.84, 2.24)
Diarrhoea	PBO 100 SC	41 (3.9) 56 (5.4)	3.9 5.4	1.37 (0.92, 2.03)
Fatigue	PBO 100 SC	14 (1.3) 19 (1.8)	1.3 1.8	1.36 (0.69, 2.70)
Sinusitis	PBO 100 SC	27 (2.6) 36 (3.5)	2.6 3.5	1.34 (0.82, 2.19)
Abdominal pain upper	PBO 100 SC	17 (1.6) 21 (2.0)	1.6 2.0	1.24 (0.66, 2.33)
Rhinitis	PBO 100 SC	19 (1.8) 23 (2.2)	1.8 2.2	1.21 (0.67, 2.22)
Cough	PBO 100 SC	41 (3.9) 49 (4.7)	3.9 4.7	1.20 (0.80, 1.80)
Nausea	PBO 100 SC	21 (2.0) 24 (2.3)	2.0 2.3	1.15 (0.64, 2.05)
Oedema peripheral	PBO 100 SC	23 (2.2) 26 (2.5)	2.2 2.5	1.13 (0.65, 1.97)
Back pain	PBO 100 SC	65 (6.2) 73 (7.0)	6.2 7.0	1.13 (0.82, 1.56)
Headache	PBO 100 SC	103 (9.8) 107 (10.3)	9.8 10.3	1.04 (0.81, 1.35)

Preferred Term	Treatment N (PBO)=1046 N (100 SC) =1043	Number (%) with Event	Adjusted Cumulative Proportion (%)[1]	CMH-Adjusted Relative Risk (95% CI)[2]
COVID-19	PBO	49 (4.7)	4.7	
	100 SC	50 (4.8)	4.8	1.02 (0.70, 1.50)
Nasopharyngitis	PBO	143 (13.7)	13.7	
	100 SC	144 (13.8)	13.8	1.01 (0.81, 1.25)
Arthralgia	PBO	51 (4.9)	4.9	
	100 SC	51 (4.9)	4.9	1.00 (0.69, 1.46)
Upper respiratory tract infection	PBO	62 (5.9)	5.9	
	100 SC	62 (5.9)	5.9	1.00 (0.71, 1.41)
Dyspnoea	PBO	50 (4.8)	4.8	
	100 SC	49 (4.7)	4.7	0.98 (0.67, 1.44)
Hypertension	PBO	39 (3.7)	3.7	
	100 SC	38 (3.6)	3.6	0.98 (0.63, 1.51)
Pneumonia	PBO	88 (8.4)	8.4	
	100 SC	85 (8.1)	8.2	0.97 (0.73, 1.29)
Oral candidiasis	PBO	21 (2.0)	2.0	
	100 SC	20 (1.9)	1.9	0.96 (0.52, 1.75)
COPD	PBO	171 (16.3)	16.3	
	100 SC	153 (14.7)	14.7	0.90 (0.73, 1.10)
Pharyngitis	PBO	26 (2.5)	2.5	
	100 SC	23 (2.2)	2.2	0.89 (0.51, 1.54)
Injection site reaction	PBO	22 (2.1)	2.1	
	100 SC	19 (1.8)	1.8	0.87 (0.47, 1.59)
Pyrexia	PBO	32 (3.1)	3.1	
	100 SC	26 (2.5)	2.5	0.81 (0.49, 1.36)
Bronchitis	PBO	32 (3.1)	3.1	
	100 SC	25 (2.4)	2.4	0.78 (0.47, 1.31)
Dizziness	PBO	32 (3.1)	3.1	
	100 SC	25 (2.4)	2.4	0.78 (0.47, 1.31)
Non-cardiac chest pain	PBO	22 (2.1)	2.1	
	100 SC	17 (1.6)	1.6	0.77 (0.41, 1.45)
Influenza	PBO	54 (5.2)	5.2	
	100 SC	41 (3.9)	3.9	0.76 (0.51, 1.13)

Note: Common AEs are defined as AEs with frequency >=3% (prior to rounding) in any treatment group.
Note: Studies included: 208657, MEA117113 and MEA117106.
[1] Adjusted using Cochran-Mantel-Haenszel weights
[2] Calculated using the Cochran-Mantel-Haenszel method

In **study 208657**, the incidence and EAIR of on-treatment AEs by SOC were generally similar between the placebo and active treatment groups. The SOCs with the highest incidence and rate of on-treatment AEs for both treatment groups were:

- infections and infestations (47%, 768.6 events per 1000 PY in the mepolizumab 100 mg group and 43%, 703.7 events per 1000 PY in the placebo group)
- respiratory, thoracic and mediastinal disorders (27%, 425.7 events per 1000 PY in the mepolizumab 100 mg group and 30%, 473.9 events per 1000 PY in the placebo group)
- musculoskeletal and connective tissue disorders (19%, 289.7 events per 1000 PY in the mepolizumab 100 mg group and 18%, 231.8 events per 1000 PY in the placebo group).

The incidence and event rates of common on-treatment AEs by PT were generally similar between the mepolizumab and placebo groups. The most common on-treatment AEs were

- COPD (12%, 163.6 events per 1000 PY in the mepolizumab 100 mg group and 15%, 190.4 events per 1000 PY in the placebo group)
- COVID-19 (12%, 108.4 events per 1000 PY in the mepolizumab 100 mg group and 12%, 103.5 events per 1000 PY in the placebo group)
- nasopharyngitis (10%, 110.4 events per 1000 PY in the mepolizumab 100 mg group and 8%, 86.9 events per 1000 PY in the placebo group).

Common on-treatment AEs with a treatment group difference of ≥2% in incidence were COPD (3% lower in mepolizumab), hypertension (3% lower in mepolizumab), urinary tract infection (3% higher in mepolizumab), nasopharyngitis (2% higher in mepolizumab), and diarrhoea (2% higher

in mepolizumab). The differences between treatment groups in EAIR events rates for each common AE were <40 events/1000 PY.

When comparing fixed duration versus variable duration subgroups, the incidences of common on-treatment AEs by PT were generally higher in the former, regardless of treatment group. The pattern of incidences and EAIR of common on-treatment AEs across treatment groups was generally similar in the fixed duration and variable duration subgroups (Table 139).

Table 139 Common on-treatment AEs in fixed and variable duration subgroups (Study 208657, Safety Population)

	Fixed duration (Enrolled for 52 weeks)				Variable duration (Enrolled for up to 104 weeks)			
	PBO (N=175; PY=155.84)		Mepo 100 mg (N=170; PY=155.17)		PBO (N=226; PY=327.35)		Mepo 100 mg (N=233; PY=352.26)	
Preferred Term	n (%)	Rate [1]	n (%)	Rate [1]	n (%)	Rate [1]	n (%)	Rate [1]
Chronic obstructive pulmonary disease	19 (11)	186.1	13 (8)	116.0	43 (19)	192.5	36 (15)	184.5
COVID-19	16 (9)	102.7	16 (9)	116.0	33 (15)	103.9	34 (15)	105.0
Nasopharyngitis	9 (5)	57.8	12 (7)	83.8	23 (10)	100.8	29 (12)	122.1
Headache	9 (5)	89.8	8 (5)	141.8	18 (8)	79.4	23 (10)	110.7
Pneumonia	10 (6)	83.4	11 (6)	77.3	17 (8)	64.2	19 (8)	76.6
Back pain	10 (6)	77.0	7 (4)	154.7	13 (6)	82.5	19 (8)	62.5
Upper respiratory tract infection	3 (2)	25.7	6 (4)	58.0	17 (8)	76.4	19 (8)	90.8
Hypertension	9 (5)	64.2	4 (2)	25.8	18 (8)	61.1	13 (6)	36.9
Dyspnoea	9 (5)	83.4	7 (4)	45.1	11 (5)	70.3	13 (6)	65.3
Arthralgia	6 (3)	44.9	7 (4)	77.3	10 (4)	36.7	15 (6)	45.4
Influenza	2 (1)	12.8	2 (1)	12.9	17 (8)	58.0	17 (7)	62.5
Diarrhoea	5 (3)	64.2	9 (5)	64.4	7 (3)	24.4	13 (6)	36.9
Cough	6 (3)	38.5	3 (2)	19.3	8 (4)	27.5	10 (4)	34.1
Urinary tract infection	2 (1)	12.8	11 (6)	77.3	5 (2)	15.3	7 (3)	22.7

[1] Represents the frequency of events per 1000 PY of exposure.
Note: Exposure-adjusted frequency is calculated as: (Total number of AEs / Total duration of exposure in years)*1000.
Note: The PTs and order of the data is aligned with Table 52.

Analysis of common on-treatment AEs by time of onset showed that the overall incidence was generally similar between treatment groups for Up to week 52 and after week 52 (Table 140). There was a lower incidence of common AEs in the 'after week 52' period compared to the 'Up to week 52' period. In the after week 52 period, differences in incidences should be interpreted in the context of differential exposure between mepolizumab (130.33 PY) and placebo (110.87 PY) groups.

Table 140 Common on-treatment AEs by time of onset (Study 208657, Safety Population)

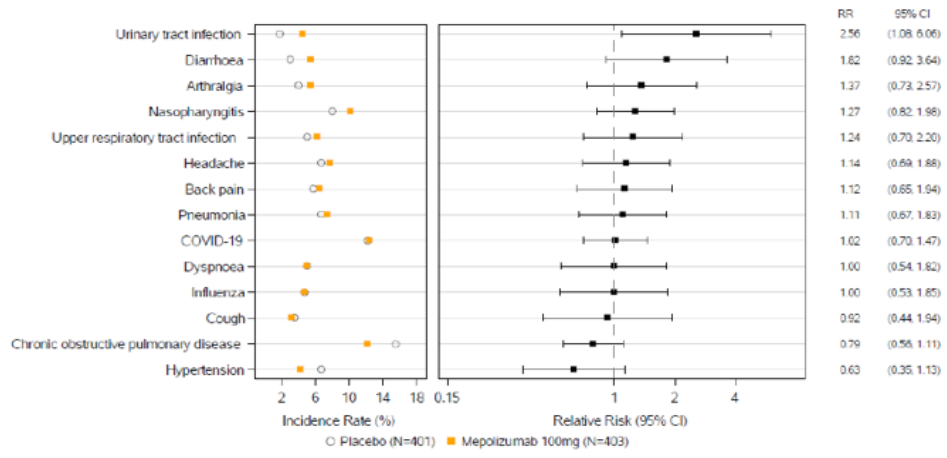
Preferred Term	Time of onset			
	Up to Week 52		After Week 52	
	PBO (N=401) n (%)	Mepo 100 mg (N=403) n (%)	PBO (N=180) n (%)	Mepo 100 mg (N=204) n (%)
Chronic obstructive pulmonary disease	52 (13)	40 (10)	12 (7)	15 (7)
COVID-19	41 (10)	42 (10)	8 (4)	9 (4)
Nasopharyngitis	24 (6)	33 (8)	11 (6)	14 (7)
Headache	23 (6)	26 (6)	4 (2)	6 (3)
Pneumonia	23 (6)	26 (6)	4 (2)	5 (2)
Back pain	15 (4)	21 (5)	9 (5)	6 (3)
Upper respiratory tract infection	17 (4)	22 (5)	5 (3)	5 (2)
Hypertension	25 (6)	14 (3)	2 (1)	3 (1)
Dyspnoea	18 (4)	15 (4)	6 (3)	7 (3)
Arthralgia	14 (3)	17 (4)	3 (2)	5 (2)
Influenza	10 (2)	13 (3)	10 (6)	7 (3)
Diarrhoea	9 (2)	19 (5)	3 (2)	3 (1)
Cough	13 (3)	11 (3)	2 (1)	2 (<1)
Urinary tract infection	6 (1)	16 (4)	1 (<1)	3 (1)

Note: The PTs and order of the data is aligned with Table 52.

The RR for common on-treatment AEs is presented in Table 141. For all common on-treatment AEs, apart from urinary tract infection, the RR confidence intervals crossed 1.

With respect to urinary tract infection, the RR was 2.56 (incidence: 4% in mepolizumab and 2% in placebo) and the EAIR was 39.4 and 14.5 events/1000 PY in the mepolizumab and placebo groups, respectively. Urinary tract infection is listed as an adverse drug reaction (frequency 'common') in the authorised SmPC.

Table 141 Common (≥3% in any treatment group) on-treatment AE incidence rates and relative risk (Study 208657, Safety Population)



Note: Common AEs are defined as AEs with frequency ≥3% (prior to rounding) in any treatment group. When comparing the differences between the mepolizumab and placebo groups in the text, the incidence was considered prior to rounding (percentage).
Note: The CI corresponds to the Wald (Normal approximation) CI.

Adverse Events by Maximum Intensity

In the **pooled COPD studies**, the maximum intensity for the majority of participants who reported on-treatment AEs was mild or moderate in the mepolizumab 100 mg (23% and 32%, respectively) and the placebo group (20% and 35%, respectively).

On-treatment AEs that were severe in intensity were reported for 22% of the participants in the mepolizumab 100 mg group and 23% in the placebo group. Severe AEs by SOC were generally balanced between treatment groups, including Cardiac disorders. AEs with severe intensity reported by ≥5% of participants in either treatment group were under the SOCs Infections and infestations (7% participants in both mepolizumab 100 mg group and placebo group), and Respiratory, thoracic and mediastinal disorders (13% of participants in the mepolizumab 100 mg group and 14% of participants in the placebo group).

Severe COPD exacerbation was reported by 11% and 13% of participants in the mepolizumab 100 mg group and the placebo group, respectively. No other severe AEs were reported in ≥5% of participants in either treatment group.

Incidences and trends for on-treatment AEs by maximum intensity were generally similar within individual studies.

Treatment-related on-treatment AEs

For the **pooled COPD studies**, the incidence and EAIR event rate of any on-treatment AEs considered to be drug-related by the investigator were similar between the mepolizumab 100 mg group (9%, 149.4 events per 1000 PY) and placebo group (10%, 211.8 events per 1000 PY) (Table S.17).

The most commonly reported on-treatment drug-related AEs in either the mepolizumab 100 mg or placebo group were:

- injection site reactions (2% in each group; 19 of 1043 participants in the mepolizumab 100 mg group and 22 of 1046 participants in the placebo group)
- injection related reaction (<1% in each group; 7 of 1043 participants in the mepolizumab 100 mg group and 9 of 1046 participants in the placebo group)
- headache (<1%, [5 of 1043] in the mepolizumab 100 mg group, 1%, [12 of 1046] in the placebo group).

Most drug-related AEs were mild (6% of participants in the mepolizumab 100 mg group and 5% in the placebo group) or moderate (3% of participants in the mepolizumab 100 mg group and 4% in the placebo group) in intensity. Of the 232 participants in COPD studies who had drug-related AEs, <1% (15 of 232) participants had drug-related AEs of severe intensity: 5 participants in the mepolizumab 100 mg group, and 9 in the placebo group.

Table 142 Most frequent (at least 5 participants across treatment groups) on-treatment drug-related adverse events (COPD studies, Safety population)

	208657				MEA117113				MEA117106				208657 + MEA117113 + MEA117106					
	PBO (N=401) (PY= 483.19)		100 SC (N=403) (PY= 507.43)		PBO (N=226) (PY= 196.23)		100 SC (N=223) (PY= 206.78)		PBO (N=419) (PY= 373.50)		100 SC (N=417) (PY= 383.51)		PBO (N=1046) (PY= 1052.92)		100 SC (N=1043) (PY= 1097.72)		All Doses (N=1268) (PY= 1301.48)	
Preferred Term	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]
ANY EVENT	17 (4)	68.3	19 (5)	67.0	28 (12)	224.2	28 (13)	178.9	61 (15)	390.9	51 (12)	242.5	106 (10)	211.8	98 (9)	149.4	126 (10)	185.2
Injection site reaction	0	0	1 (<1)	2.0	10 (4)	86.6	6 (3)	29.0	12 (3)	48.2	12 (3)	57.4	22 (2)	33.2	19 (2)	26.4	30 (2)	43.0
Injection related reaction	0	0	0	0	3 (1)	20.4	2 (<1)	9.7	6 (1)	21.4	5 (1)	13.0	9 (<1)	11.4	7 (<1)	6.4	11 (<1)	9.2
Headache	3 (<1)	8.3	1 (<1)	2.0	0	0	0	0	9 (2)	72.3	4 (<1)	10.4	12 (1)	29.4	5 (<1)	4.6	7 (<1)	5.4
Nausea	2 (<1)	4.1	1 (<1)	2.0	1 (<1)	5.1	0	0	3 (<1)	32.1	2 (<1)	5.2	6 (<1)	14.2	3 (<1)	2.7	6 (<1)	6.9
Fatigue	1 (<1)	2.1	2 (<1)	5.9	0	0	2 (<1)	9.7	2 (<1)	26.8	2 (<1)	10.4	3 (<1)	10.4	6 (<1)	8.2	8 (<1)	8.5
Nasopharyngitis	0	0	0	0	1 (<1)	5.1	1 (<1)	4.8	3 (<1)	8.0	2 (<1)	5.2	4 (<1)	3.8	3 (<1)	2.7	5 (<1)	3.8
Hypersensitivity	0	0	1 (<1)	2.0	0	0	1 (<1)	4.8	2 (<1)	5.4	3 (<1)	23.5	2 (<1)	1.9	5 (<1)	10.0	6 (<1)	9.2
Arthralgia	0	0	0	0	0	0	0	0	3 (<1)	18.7	2 (<1)	7.8	3 (<1)	6.6	2 (<1)	2.7	4 (<1)	3.8
Diarrhoea	0	0	0	0	2 (<1)	10.2	1 (<1)	4.8	2 (<1)	5.4	0	0	4 (<1)	3.8	1 (<1)	0.9	2 (<1)	2.3
Pruritus	1 (<1)	2.1	1 (<1)	2.0	1 (<1)	5.1	0	0	2 (<1)	5.4	0	0	4 (<1)	3.8	1 (<1)	0.9	2 (<1)	1.5
Pyrexia	0	0	1 (<1)	2.0	0	0	0	0	2 (<1)	5.4	1 (<1)	2.6	2 (<1)	1.9	2 (<1)	1.8	3 (<1)	2.3
Abdominal pain upper	1 (<1)	2.1	1 (<1)	2.0	0	0	1 (<1)	4.8	0	0	0	0	1 (<1)	0.9	2 (<1)	1.8	4 (<1)	3.1
Dizziness	1 (<1)	4.1	2 (<1)	3.9	1 (<1)	5.1	0	0	1 (<1)	2.7	0	0	3 (<1)	3.8	2 (<1)	1.8	2 (<1)	1.5
Rash	1 (<1)	6.2	0	0	0	0	1 (<1)	4.8	2 (<1)	5.4	0	0	3 (<1)	4.7	1 (<1)	0.9	2 (<1)	1.5
Myalgia	1 (<1)	2.1	0	0	1 (<1)	10.2	0	0	2 (<1)	5.4	0	0	4 (<1)	4.7	0	0	1 (<1)	0.8
Oropharyngeal pain	0	0	0	0	1 (<1)	5.1	1 (<1)	4.8	1 (<1)	2.7	1 (<1)	2.6	2 (<1)	1.9	2 (<1)	1.8	3 (<1)	2.3

[1] Represents the frequency of events per 1000 participant-years of exposure.
Note: Exposure-adjusted frequency is calculated as: (Total number of adverse events / Total Duration of Exposure in years)*1000

Post-treatment adverse events

A post-treatment AE was defined as an AE with an onset more than 4 weeks (28 days) after the last dose of treatment. There was no follow-up period in study 208657. The study Exit Visit occurred 4 weeks after the last dose of study treatment, up to which time AEs were still reportable. Studies MEA117113 and MEA117106 had an 8-week post-treatment follow-up period starting 4 weeks after the last dose of treatment. In all 3 COPD studies, post-treatment AEs could be reported if participants remained in the study following discontinuation of study treatment.

The incidence of post-treatment AEs, reported by study and for the 3 pooled COPD studies, is presented in Table 143 below. For individual studies and the pooled data, the incidence of any post-treatment AEs was similar between the mepolizumab 100 mg group and the placebo group.

Table 143 Summary of number of participants with post-treatment adverse events by study (COPD studies, Safety population)

Study, n (%)	PBO (N=1046)	100 SC (N=1043)	All Doses (N=1268)	Total (N=2314)
208657	20/401 (5)	23/403 (6)	23/403 (6)	43/804 (5)
MEA117113	51/226 (23)	50/223 (22)	94/448 (21)	145/674 (22)
MEA117106	83/419 (20)	71/417 (17)	71/417 (17)	154/836 (18)
208657 + MEA117113 + MEA117106	154/1046 (15)	144/1043 (14)	188/1268 (15)	342/2314 (15)

Note: Studies included: 208657, MEA117106 and MEA117113.

In 1 SOC (Infections and infestations), incidence of post-treatment AEs was ≥5%. Any post-treatment AE reported by ≥3% of participants in either treatment group was COPD exacerbations (2% in the mepolizumab 100 mg group and 3% in the placebo group).

Serious adverse event/deaths/other significant events

Deaths

The incidence of any on-and post-treatment fatal SAEs was similar between the mepolizumab 100 mg group (3%, 31 of 1043 participants) and the placebo group (4%, 37 of 1046 participants) and

are outlined in Table S.19 below. The incidence of any on-treatment fatal SAEs was similar between the mepolizumab 100 mg group (2%, 25 of 1043) and the placebo group (2%, 22 of 1046).

Fatal SAEs were most frequently reported in the SOC Respiratory, thoracic and mediastinal disorders, followed by Cardiac disorders and Infections and infestations. The incidence of any fatal SAEs in the SOC Cardiac disorders was <1% of participants in the mepolizumab 100 mg group (10 of 1043) and 1% in the mepolizumab All doses group (13 of 1268), versus <1% of participants in the placebo group (4 of 1046)

The most frequently reported fatal SAE (PT) was COPD exacerbation, reported by <1% of participants in both the mepolizumab 100 mg group (8 of 1043) and the placebo group (8 of 1046).

Table 144 On- and post-treatment fatal adverse events by Preferred Term (COPD studies, Safety population)

	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106		
Preferred Term, n (%)	PBO (N=401)	100 SC (N=403)	PBO (N=226)	100 SC (N=223)	PBO (N=419)	100 SC (N=417)	PBO (N=1046)	100 SC (N=1043)	All Doses (N=1268)
Any event	11 (3)	11 (3)	9 (4)	4 (2)	17 (4)	16 (4)	37 (4)	31 (3)	39 (3)
COPD	3 (<1)	2 (<1)	1 (<1)	0	4 (<1)	6 (1)	8 (<1)	8 (<1)	10 (<1)
Respiratory failure	1 (<1)	0	0	0	0	1 (<1)	1 (<1)	1 (<1)	3 (<1)
Acute respiratory failure	0	0	1 (<1)	0	1 (<1)	1 (<1)	2 (<1)	1 (<1)	1 (<1)
Haemoptysis	0	1 (<1)	0	0	0	0	0	1 (<1)	1 (<1)
Pneumothorax	0	0	0	0	1 (<1)	0	1 (<1)	0	0
Pneumothorax spontaneous	0	0	1 (<1)	0	0	0	1 (<1)	0	0
Pulmonary oedema	1 (<1)	0	0	0	0	0	1 (<1)	0	0
Respiratory arrest	0	0	0	0	1 (<1)	0	1 (<1)	0	0
Cardiac arrest	0	2 (<1)	1 (<1)	0	1 (<1)	1 (<1)	2 (<1)	3 (<1)	3 (<1)
Acute myocardial infarction	1 (<1)	0	1 (<1)	0	0	0	2 (<1)	0	1 (<1)
Cardiac failure congestive	0	1 (<1)	0	0	0	2 (<1)	0	3 (<1)	3 (<1)
Cardio-respiratory arrest	0	0	0	1 (<1)	0	0	0	1 (<1)	2 (<1)
Arteriosclerosis coronary artery	0	1 (<1)	0	0	0	0	0	1 (<1)	1 (<1)
Cardiomyopathy	0	0	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
Cardiopulmonary failure	0	0	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
Myocardial infarction	0	0	0	0	0	0	0	0	1 (<1)
Pneumonia	0	0	2 (<1)	0	2 (<1)	0	4 (<1)	0	1 (<1)
COVID-19	1 (<1)	3 (<1)	0	0	0	0	1 (<1)	3 (<1)	3 (<1)
Sepsis	0	0	0	1 (<1)	0	1 (<1)	0	2 (<1)	2 (<1)
Infective exacerbation of chronic obstructive airways disease	1 (<1)	0	0	0	0	0	1 (<1)	0	0
Urinary tract infection	0	0	0	0	1 (<1)	0	1 (<1)	0	0
Lung neoplasm malignant	0	0	0	1 (<1)	0	1 (<1)	0	2 (<1)	2 (<1)
Gastric cancer	0	0	0	1 (<1)	0	0	0	1 (<1)	1 (<1)
Lung adenocarcinoma	0	0	0	0	1 (<1)	0	1 (<1)	0	0
Lung adenocarcinoma stage IV	0	0	0	0	1 (<1)	0	1 (<1)	0	0
Retinal melanoma	0	0	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
Small cell lung cancer	0	0	0	0	1 (<1)	0	1 (<1)	0	0
Small cell lung cancer metastatic	1 (<1)	0	0	0	0	0	1 (<1)	0	0

	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106		
Preferred Term, n (%)	PBO (N=401)	100 SC (N=403)	PBO (N=226)	100 SC (N=223)	PBO (N=419)	100 SC (N=417)	PBO (N=1046)	100 SC (N=1043)	All Doses (N=1268)
Death	0	2 (<1)	0	0	1 (<1)	0	1 (<1)	2 (<1)	3 (<1)
Multiple organ dysfunction syndrome	0	0	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
Gastrointestinal haemorrhage	0	0	1 (<1)	0	1 (<1)	0	2 (<1)	0	0
Aortic aneurysm rupture	1 (<1)	0	0	0	0	0	1 (<1)	0	0
Circulatory collapse	1 (<1)	0	0	0	0	0	1 (<1)	0	0
Respiratory fume inhalation disorder	0	0	0	0	1 (<1)	0	1 (<1)	0	0
Haemorrhagic stroke	0	0	1 (<1)	0	0	0	1 (<1)	0	0

Serious adverse events

In the **pooled COPD studies**, the incidence and EAIR of any on-treatment SAEs (fatal and non-fatal) were similar between the mepolizumab 100 mg group (24%, 467.3 events per 1000 PY) and

the placebo group (27%, 498.6 events per 1000 PY) (Table 145). Differences at SOC level were <1% in incidence and <15 events per 1000 PY in rate, with the exception of the Respiratory, thoracic, and mediastinal disorders SOC (difference of 2%, 20 events per 1000 PY in favour of the mepolizumab 100 mg group).

The most frequently reported on-treatment SAEs by PT were:

- COPD exacerbations (reported by ≥10% of participants in both treatment groups)
- pneumonia (reported by 5% of participants in both groups).

The incidence and rate differences across all PTs were similar between the mepolizumab 100 mg group and the placebo group (difference of <1% in incidence and <4 events per 1000 PY), with the exception of COPD exacerbations, which was less frequent in the mepolizumab 100 mg group (12%, 170.4 events per 1000 PY) compared with the placebo group (15%, 190.9 events per 1000 PY). All other on-treatment SAEs were reported in less than 1% of participants.

Table 145 On-treatment serious adverse events by Preferred Term (at least 5 participants across treatment groups, COPD studies, Safety population

	208657				MEA117113				MEA117106				208657 + MEA117113 + MEA117106					
	PBO (N=401) (PY= 483.19)		100 SC (N=403) (PY= 507.43)		PBO (N=226) (PY= 196.23)		100 SC (N=223) (PY= 206.78)		PBO (N=419) (PY= 373.50)		100 SC (N=417) (PY= 383.51)		PBO (N=1046) (PY= 1052.92)		100 SC (N=1043) (PY= 1097.72)		All Doses (N=1268) (PY= 1301.48)	
Preferred Term	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]
ANY EVENT	112 (28)	393.2	99 (25)	358.7	58 (26)	545.3	52 (23)	561.0	117 (28)	610.4	104 (25)	560.6	287 (27)	498.6	255 (24)	467.3	309 (24)	467.9
Chronic obstructive pulmonary disease	55 (14)	149.0	46 (11)	126.1	32 (14)	203.8	23 (10)	145.1	65 (16)	238.3	61 (15)	242.5	152 (15)	190.9	130 (12)	170.4	157 (12)	177.5
Pneumonia	14 (3)	33.1	14 (3)	31.5	16 (7)	81.5	15 (7)	91.9	26 (6)	80.3	21 (5)	67.8	56 (5)	58.9	50 (5)	55.6	63 (5)	56.9
Respiratory failure	2 (<1)	4.1	2 (<1)	3.9	1 (<1)	5.1	1 (<1)	4.8	4 (<1)	10.7	6 (1)	15.6	7 (<1)	6.6	9 (<1)	8.2	11 (<1)	8.5
Infective exacerbation of chronic obstructive airways disease	4 (<1)	8.3	1 (<1)	2.0	3 (1)	20.4	1 (<1)	4.8	1 (<1)	2.7	3 (<1)	7.8	8 (<1)	8.5	5 (<1)	4.6	7 (<1)	5.4
Atrial fibrillation	1 (<1)	2.1	2 (<1)	3.9	3 (1)	30.6	3 (1)	14.5	3 (<1)	8.0	3 (<1)	10.4	7 (<1)	9.5	8 (<1)	8.2	8 (<1)	6.9
Acute respiratory failure	0	0	3 (<1)	5.9	2 (<1)	10.2	3 (1)	14.5	4 (<1)	13.4	2 (<1)	7.8	6 (<1)	6.6	8 (<1)	8.2	8 (<1)	6.9
Acute myocardial infarction	2 (<1)	4.1	0	0	2 (<1)	10.2	1 (<1)	4.8	2 (<1)	5.4	2 (<1)	5.2	6 (<1)	5.7	3 (<1)	2.7	5 (<1)	3.8
Cardiac failure congestive	2 (<1)	4.1	1 (<1)	2.0	0	0	1 (<1)	4.8	2 (<1)	5.4	3 (<1)	10.4	4 (<1)	3.8	5 (<1)	5.5	5 (<1)	4.6
COVID-19	4 (<1)	8.3	4 (<1)	7.9	0	0	0	0	0	0	0	0	4 (<1)	3.8	4 (<1)	3.6	4 (<1)	3.1
Pneumothorax	1 (<1)	2.1	3 (<1)	5.9	0	0	0	0	1 (<1)	2.7	1 (<1)	2.6	2 (<1)	1.9	4 (<1)	3.6	5 (<1)	3.8
Urinary tract infection	0	0	0	0	0	0	3 (1)	14.5	3 (<1)	8.0	0	0	3 (<1)	2.8	3 (<1)	2.7	4 (<1)	3.1
Cardiac arrest	1 (<1)	2.1	4 (<1)	7.9	1 (<1)	5.1	0	0	0	0	1 (<1)	2.6	2 (<1)	1.9	5 (<1)	4.6	5 (<1)	3.8
Pulmonary embolism	2 (<1)	4.1	1 (<1)	2.0	0	0	0	0	0	0	1 (<1)	2.6	2 (<1)	1.9	2 (<1)	1.8	4 (<1)	3.1
Acute kidney injury	2 (<1)	4.1	1 (<1)	2.0	1 (<1)	5.1	0	0	0	0	3 (<1)	7.8	3 (<1)	2.8	4 (<1)	3.6	4 (<1)	3.1
Syncope	1 (<1)	2.1	0	0	0	0	0	0	2 (<1)	5.4	2 (<1)	5.2	3 (<1)	2.8	2 (<1)	1.8	3 (<1)	2.3

	208657				MEA117113				MEA117106				208657 + MEA117113 + MEA117106					
	PBO (N=401) (PY= 483.19)		100 SC (N=403) (PY= 507.43)		PBO (N=226) (PY= 196.23)		100 SC (N=223) (PY= 206.78)		PBO (N=419) (PY= 373.50)		100 SC (N=417) (PY= 383.51)		PBO (N=1046) (PY= 1052.92)		100 SC (N=1043) (PY= 1097.72)		All Doses (N=1268) (PY= 1301.48)	
Preferred Term	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]
Transient ischaemic attack	3 (<1)	6.2	0	0	1 (<1)	5.1	0	0	0	0	2 (<1)	5.2	4 (<1)	3.8	2 (<1)	1.8	2 (<1)	1.5
Sepsis	0	0	0	0	1 (<1)	5.1	2 (<1)	9.7	1 (<1)	2.7	2 (<1)	5.2	2 (<1)	1.9	4 (<1)	3.6	4 (<1)	3.1
Bronchitis	0	0	1 (<1)	2.0	1 (<1)	5.1	0	0	2 (<1)	5.4	0	0	3 (<1)	2.8	1 (<1)	0.9	2 (<1)	1.5
Influenza	1 (<1)	2.1	1 (<1)	2.0	1 (<1)	5.1	0	0	1 (<1)	2.7	0	0	3 (<1)	2.8	1 (<1)	0.9	2 (<1)	1.5
Lower respiratory tract infection	0	0	0	0	1 (<1)	5.1	1 (<1)	4.8	1 (<1)	2.7	1 (<1)	2.6	2 (<1)	1.9	2 (<1)	1.8	3 (<1)	2.3
Cardiac failure	0	0	2 (<1)	3.9	0	0	0	0	1 (<1)	5.4	2 (<1)	5.2	1 (<1)	1.9	4 (<1)	3.6	4 (<1)	3.1
Coronary artery disease	1 (<1)	2.1	2 (<1)	3.9	1 (<1)	5.1	0	0	0	0	0	0	2 (<1)	1.9	2 (<1)	1.8	3 (<1)	2.3
Lung neoplasm malignant	2 (<1)	4.1	2 (<1)	3.9	0	0	1 (<1)	4.8	0	0	0	0	2 (<1)	1.9	3 (<1)	2.7	3 (<1)	2.3

Note: Exposure-adjusted frequency is calculated as: (Total number of adverse events / Total Duration of Exposure in years)*1000.
[1] Represents the frequency of events per 1000 participant-years of exposure.

The incidence of post-treatment SAEs was similar between the mepolizumab 100 mg group (5%) and placebo group (6%).

Serious adverse events by drug-relatedness

In study 208657, there were no SAEs, fatal or non-fatal, reported that were considered drug-related by the investigator.

In study MEA117113, two subjects had a non-fatal SAE reported that was considered drug-related by the investigator; 1 subject in the placebo group (injection-related reaction) and 1 subject in the mepolizumab 100 mg group (diarrhoea)

Another subject:, 84 days after the first dose and 28 days after the most recent dose of mepolizumab, the subject developed moderate - grade 2 diarrhoea. Serious criteria included hospitalization. The subject was treated with loperamide and mepolizumab was discontinued on 7th May 2015. Dechallenge was positive. The outcome of diarrhoea was recovered/resolved on 3rd July 2015. The investigator considered that there was a reasonable possibility that the diarrhoea may have been caused by the study treatment.

In study MEA117106, there was one fatal SAE considered drug related by the investigator (placebo group).

Six subjects had on-treatment non-fatal SAEs that were considered drug related by the investigator: 2 subjects in the mepolizumab 100 mg group (pneumonia/sepsis and COPD exacerbation and 4 subjects in the placebo group (urinary tract infection, COPD exacerbation, ventricular extrasystoles, and injection-related reaction). No events were reported by more than one subject.

One subject:, 17 days after the first dose and 17 days after the most recent dose of mepolizumab, the subject developed severe - grade 3 pneumonia. Serious criteria included hospitalization. The subject was treated with azithromycin, ceftriaxone sodium, methylprednisolone sodium succinate, ipratropium + salbutamol, and sodium chloride. Mepolizumab was continued with no change. The outcome of pneumonia was resolved with sequelae on 25 April 2015 (13 days after initial reporting of the SAE). The outcome of the additional event (sepsis) was reported as recovered/resolved on the same date. The investigator considered that there was a reasonable possibility that the pneumonia and sepsis may have been caused by the study treatment.

Another subject:. on 7th April 2015, 204 days after the first dose and 8 days after the most recent dose of mepolizumab, the subject developed severe - grade 3 chronic obstructive airways disease exacerbated. Serious criteria included hospitalization. Additional event(s) included severe - grade 3 pneumonia on 7th April 2015 with serious criteria of hospitalization. The subject was treated with cefotaxime sodium, doxycycline hydrochloride and betamethasone sodium phosphate. Mepolizumab was continued with no change. The outcome of chronic obstructive airways disease exacerbated was recovered/resolved on 10th May 2015. The outcome(s) of the additional event(s) included pneumonia (recovered/resolved on 19th April 2015). The investigator considered that there was a reasonable possibility that the chronic obstructive airways disease exacerbated may have been caused by the study treatment, but that there was no reasonable possibility that the pneumonia may have been caused by the study treatment. Other possible cause(s) of the chronic obstructive airways disease exacerbated included activity related to study participation.

Adjudicated SAE reports

All fatal and non-fatal SAE reports were adjudicated by the CEC. In the 3 pooled COPD studies, the majority of fatal SAEs were adjudicated a having a CV or respiratory primary cause. For fatal/non-fatal combined SAE reports and non-fatal SAE reports, more than 65% of cases were adjudicated as having a respiratory primary cause (Table 146). The incidence and profile of primary causes of adjudicated SAE reports were similar between treatment groups.

Table 146 Overview (primary causes) of on- and post-treatment fatal and nonfatal adjudicated SAE reports (COPD studies, Safety Population)

	208657 + MEA117113 + MEA117106		
n (%)	PBO (N=1046)	100 SC (N=1043)	All Doses (N=1268)
Primary cause of fatal SAE report			
Total	37 (4)	31 (3)	39 (3)
Cardiovascular	11 (1)	8 (<1)	12 (<1)
Respiratory	15 (1)	12 (1)	16 (1)
Cancer	5 (<1)	4 (<1)	4 (<1)
Unknown	2 (<1)	4 (<1)	4 (<1)
Other	4 (<1)	3 (<1)	3 (<1)
Primary cause of fatal/non-fatal SAE report			
Total	314 (30)	273 (26)	333 (26)
Cardiovascular	54 (5)	48 (5)	58 (5)
Respiratory	206 (20)	176 (17)	224 (18)
Cancer	22 (2)	17 (2)	21 (2)
Unknown	4 (<1)	6 (<1)	6 (<1)
Other	76 (7)	70 (7)	76 (6)
Primary cause of non-fatal SAE report			
Total	288 (28)	255 (24)	309 (24)
Cardiovascular	44 (4)	42 (4)	48 (4)
Respiratory	198 (19)	168 (16)	213 (17)
Cancer	17 (2)	13 (1)	17 (1)
Unknown	2 (<1)	2 (<1)	2 (<1)
Other	72 (7)	69 (7)	75 (6)

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

Adjudicated fatal SAE reports

In the 3 pooled COPD studies, the incidence of any adjudicated death was similar between the mepolizumab 100 mg group (3% [31 of 1043]) and the placebo group (4% [37 of 1046]) (Table S.22).

Deaths adjudicated within the subcategories of CV primary cause were generally balanced between treatment groups. Of note, a small numerical difference was noted for participants with fatal SAE reports adjudicated as the subcategory of Congestive heart failure: 3 participants in the mepolizumab 100 mg group and 0 participant in the placebo group. Regarding the 3 fatal SAE reports adjudicated as congestive heart failure in the mepolizumab 100 mg group, the fatal events for these 3 participants had adjudicated MACE in the subcategory of heart failure.

Table 147 On- and post-treatment adjudicated fatal SAE reports (COPD studies, Safety Population)

	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106		
n (%)	PBO (N=401)	100 SC (N=403)	PBO (N=226)	100 SC (N=223)	PBO (N=419)	100 SC (N=417)	PBO (N=1046)	100 SC (N=1043)	All Doses (N=1268)
Primary cause of fatal SAE report									
Total	11 (3)	11 (3)	9 (4)	4 (2)	17 (4)	16 (4)	37 (4)	31 (3)	39 (3)
Cardiovascular	4 (<1)	5 (1)	3 (1)	0	4 (<1)	3 (<1)	11 (1)	8 (<1)	12 (<1)
Respiratory	3 (<1)	4 (<1)	4 (2)	1 (<1)	8 (2)	7 (2)	15 (1)	12 (1)	16 (1)
Cancer	2 (<1)	0	0	2 (<1)	3 (<1)	2 (<1)	5 (<1)	4 (<1)	4 (<1)
Unknown	1 (<1)	2 (<1)	1 (<1)	0	0	2 (<1)	2 (<1)	4 (<1)	4 (<1)
Other	1 (<1)	0	1 (<1)	1 (<1)	2 (<1)	2 (<1)	4 (<1)	3 (<1)	3 (<1)
Death associated with COPD									
Yes	3 (<1)	3 (<1)	4 (2)	1 (<1)	9 (2)	9 (2)	16 (2)	13 (1)	17 (1)
No	7 (2)	7 (2)	3 (1)	3 (1)	7 (2)	5 (1)	17 (2)	15 (1)	18 (1)
Inadequate information	1 (<1)	0	1 (<1)	0	0	0	2 (<1)	0	0
Indeterminate	0	1 (<1)	1 (<1)	0	1 (<1)	2 (<1)	2 (<1)	3 (<1)	4 (<1)
Fatal cardiovascular									
Any event	4 (<1)	5 (1)	3 (1)	0	4 (<1)	3 (<1)	11 (1)	8 (<1)	12 (<1)
Sudden death	2 (<1)	3 (<1)	1 (<1)	0	3 (<1)	1 (<1)	6 (<1)	4 (<1)	8 (<1)
Myocardial infarction/ischemic heart disease	1 (<1)	1 (<1)	1 (<1)	0	1 (<1)	0	3 (<1)	1 (<1)	1 (<1)
Congestive heart failure	0	1 (<1)	0	0	0	2 (<1)	0	3 (<1)	3 (<1)
Stroke	0	0	1 (<1)	0	0	0	1 (<1)	0	0
Haemorrhagic	0	0	1 (<1)	0	0	0	1 (<1)	0	0
Thromboembolic	0	0	0	0	0	0	0	0	0
Indeterminate	0	0	0	0	0	0	0	0	0
Other cardiovascular cause	1 (<1)	0	0	0	0	0	1 (<1)	0	0
Fatal respiratory									
Any event	3 (<1)	4 (<1)	4 (2)	1 (<1)	8 (2)	7 (2)	15 (1)	12 (1)	16 (1)
COPD exacerbation	3 (<1)	0	2 (<1)	1 (<1)	6 (1)	7 (2)	11 (1)	8 (<1)	12 (<1)
With pneumonia	1 (<1)	0	0	0	3 (<1)	3 (<1)	4 (<1)	3 (<1)	4 (<1)
Without pneumonia	2 (<1)	0	2 (<1)	1 (<1)	3 (<1)	4 (<1)	7 (<1)	5 (<1)	8 (<1)
Pneumonia/respiratory tract infection w/out COPD exacerbation	0	0	1 (<1)	0	0	0	1 (<1)	0	0
Pulmonary embolism	0	0	0	0	0	0	0	0	0
Asthma associated	0	0	0	0	0	0	0	0	0
Other respiratory cause	0	4 (<1)	1 (<1)	0	2 (<1)	0	3 (<1)	4 (<1)	4 (<1)
Fatal cancer									
Any event	2 (<1)	0	0	2 (<1)	3 (<1)	2 (<1)	5 (<1)	4 (<1)	4 (<1)
Lung	1 (<1)	0	0	1 (<1)	3 (<1)	1 (<1)	4 (<1)	2 (<1)	2 (<1)
Breast	1 (<1)	0	0	0	0	0	1 (<1)	0	0
Colorectal	0	0	0	0	0	0	0	0	0
Unknown primary	0	0	0	0	0	0	0	0	0
Other cancer cause	0	0	0	1 (<1)	0	1 (<1)	0	2 (<1)	2 (<1)
Fatal unknown cause									
Any event	1 (<1)	2 (<1)	1 (<1)	0	0	2 (<1)	2 (<1)	4 (<1)	4 (<1)
Inadequate information	0	2 (<1)	1 (<1)	0	0	2 (<1)	1 (<1)	4 (<1)	4 (<1)
Indeterminate	1 (<1)	0	0	0	0	0	1 (<1)	0	0

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

Adjudicated fatal and non-fatal SAE reports

In the 3 pooled COPD studies, the incidence of any adjudicated fatal/non-fatal SAE reports was numerically higher in the placebo group (30% [314 of 1046]) compared with the mepolizumab 100 mg group (26% [273 of 1043]; Table 148). This treatment difference was primarily driven by SAE reports with an adjudicated respiratory primary cause (20% in the placebo group versus 17% in the mepolizumab 100 mg group). The incidence of adjudicated SAE reports in each of the other

primary cause categories (CV, Cancer, Unknown, and Other) was similar between the treatment groups.

Of note, congestive heart failure was adjudicated as a subcategory of CV primary cause in 1% participants in the mepolizumab 100 mg group (14 of 1043 participants) and <1% participants in the placebo group (6 of 1046). As reported above (*Adjudicated fatal SAE reports*), the SAE was fatal for 3 participants in the mepolizumab 100 mg group. The MAH undertook a review of participant information for all SAE reports adjudicated as Congestive heart failure, including a review of study adjudication packages. The review yielded no obvious trends and did not suggest a plausible causal association between mepolizumab and SAEs adjudicated with CV subcategory of Congestive heart failure.

Table 148 On- and post-treatment adjudicated fatal and non-fatal SAEs (COPD studies, Safety Population)

	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106		
n (%)	PBO (N=401)	100 SC (N=403)	PBO (N=226)	100 SC (N=223)	PBO (N=419)	100 SC (N=417)	PBO (N=1046)	100 SC (N=1043)	All Doses (N=1268)
Primary cause of fatal and non-fatal SAE report									
Total	115 (29)	101 (25)	68 (30)	57 (26)	131 (31)	115 (28)	314 (30)	273 (26)	333 (26)
Cardiovascular	27 (7)	20 (5)	11 (5)	8 (4)	16 (4)	20 (5)	54 (5)	48 (5)	58 (5)
Respiratory	68 (17)	61 (15)	46 (20)	35 (16)	92 (22)	80 (19)	206 (20)	176 (17)	224 (18)
Cancer	8 (2)	7 (2)	6 (3)	4 (2)	8 (2)	6 (1)	22 (2)	17 (2)	21 (2)
Unknown	1 (<1)	3 (<1)	2 (<1)	1 (<1)	1 (<1)	2 (<1)	4 (<1)	6 (<1)	6 (<1)
Other	26 (6)	29 (7)	15 (7)	18 (8)	35 (8)	23 (6)	76 (7)	70 (7)	76 (6)
Fatal and non-fatal cardiovascular									
Any event	27 (7)	20 (5)	11 (5)	8 (4)	16 (4)	20 (5)	54 (5)	48 (5)	58 (5)
Sudden death[1]	2 (<1)	3 (<1)	1 (<1)	0	3 (<1)	1 (<1)	6 (<1)	4 (<1)	8 (<1)
Myocardial infarction/ischemic heart disease	4 (<1)	4 (<1)	4 (2)	2 (<1)	3 (<1)	5 (1)	11 (1)	11 (1)	13 (1)
Congestive heart failure	2 (<1)	6 (1)	0	1 (<1)	4 (<1)	7 (2)	6 (<1)	14 (1)	14 (1)
Stroke	3 (<1)	2 (<1)	1 (<1)	0	0	1 (<1)	4 (<1)	3 (<1)	3 (<1)
Haemorrhagic	0	0	1 (<1)	0	0	0	1 (<1)	0	0
Thromboembolic	3 (<1)	2 (<1)	0	0	0	0	3 (<1)	2 (<1)	2 (<1)
Indeterminate	0	0	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
Other cardiovascular cause	16 (4)	7 (2)	5 (2)	5 (2)	8 (2)	8 (2)	29 (3)	20 (2)	24 (2)
Fatal and non-fatal respiratory									
Any event	68 (17)	61 (15)	46 (20)	35 (16)	92 (22)	80 (19)	206 (20)	176 (17)	224 (18)
COPD exacerbation	60 (15)	47 (12)	42 (19)	29 (13)	84 (20)	68 (16)	186 (18)	144 (14)	180 (14)
With pneumonia	26 (6)	18 (4)	13 (6)	9 (4)	24 (6)	15 (4)	63 (6)	42 (4)	54 (4)
Without pneumonia	40 (10)	35 (9)	31 (14)	24 (11)	69 (16)	60 (14)	140 (13)	119 (11)	151 (12)
Pneumonia/respiratory tract infection w/out COPD exacerbation	7 (2)	7 (2)	3 (1)	11 (5)	8 (2)	12 (3)	18 (2)	30 (3)	39 (3)
Pulmonary embolism	2 (<1)	1 (<1)	1 (<1)	0	0	2 (<1)	3 (<1)	3 (<1)	5 (<1)
Asthma associated	0	0	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
Other respiratory cause	6 (1)	12 (3)	2 (<1)	0	4 (<1)	2 (<1)	12 (1)	14 (1)	17 (1)
Fatal and non-fatal cancer									
Any event	8 (2)	7 (2)	6 (3)	4 (2)	8 (2)	6 (1)	22 (2)	17 (2)	21 (2)
Lung	6 (1)	4 (<1)	1 (<1)	1 (<1)	3 (<1)	2 (<1)	10 (<1)	7 (<1)	9 (<1)
Breast	1 (<1)	1 (<1)	1 (<1)	1 (<1)	0	1 (<1)	2 (<1)	3 (<1)	3 (<1)
Colorectal	0	0	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	2 (<1)	2 (<1)
Unknown primary	0	0	0	0	0	0	0	0	0
Other cancer cause	1 (<1)	2 (<1)	3 (1)	1 (<1)	5 (1)	2 (<1)	9 (<1)	5 (<1)	7 (<1)
Fatal and non-fatal unknown cause									
Any event	1 (<1)	3 (<1)	1 (<1)	0	1 (<1)	2 (<1)	3 (<1)	5 (<1)	5 (<1)
Inadequate information	0	2 (<1)	1 (<1)	0	1 (<1)	2 (<1)	2 (<1)	4 (<1)	4 (<1)
Indeterminate	1 (<1)	1 (<1)	0	0	0	0	1 (<1)	1 (<1)	1 (<1)

Note: For a report/case with multiple SAEs the primary event was adjudicated
[1] Only relates to Fatal Cardiovascular events.

Adjudicated non-fatal SAE reports

In the 3 pooled COPD studies, the incidence of any adjudicated non-fatal SAE reports was numerically higher in the placebo group (28% [288 of 1046] of participants) compared with the mepolizumab 100 mg group (24% [255 of 1043] of participants) (Table 149). This treatment

difference was primarily driven by non-fatal SAE reports with a respiratory cause (19% of participants in the placebo group versus 16% of participants in the mepolizumab 100 mg group). The incidence and profile of primary causes of non fatal adjudicated SAE reports were similar to the primary cause of fatal and non-fatal adjudicated SAE reports.

Table 149 On- and post-treatment adjudicated non-fatal SAE reports (COPD studies, Safety Population)

	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106		
n (%)	PBO (N=401)	100 SC (N=403)	PBO (N=226)	100 SC (N=223)	PBO (N=419)	100 SC (N=417)	PBO (N=1046)	100 SC (N=1043)	All Doses (N=1268)
Primary cause of non-fatal SAE report									
Total	107 (27)	95 (24)	62 (27)	54 (24)	119 (28)	106 (25)	288 (28)	255 (24)	309 (24)
Cardiovascular	23 (6)	16 (4)	8 (4)	8 (4)	13 (3)	18 (4)	44 (4)	42 (4)	48 (4)
Respiratory	67 (17)	58 (14)	45 (20)	34 (15)	86 (21)	76 (18)	198 (19)	168 (16)	213 (17)
Cancer	6 (1)	7 (2)	6 (3)	2 (<1)	5 (1)	4 (<1)	17 (2)	13 (1)	17 (1)
Unknown	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)	0	2 (<1)	2 (<1)	2 (<1)
Other	25 (6)	29 (7)	14 (6)	18 (8)	33 (8)	22 (5)	72 (7)	69 (7)	75 (6)
Non-fatal cardiovascular									
Any event	23 (6)	16 (4)	8 (4)	8 (4)	13 (3)	18 (4)	44 (4)	42 (4)	48 (4)
Myocardial infarction/ischemic heart disease	3 (<1)	3 (<1)	3 (1)	2 (<1)	3 (<1)	5 (1)	9 (<1)	10 (<1)	12 (<1)
Congestive heart failure	2 (<1)	6 (1)	0	1 (<1)	4 (<1)	6 (1)	6 (<1)	13 (1)	13 (1)
Stroke	3 (<1)	2 (<1)	0	0	0	1 (<1)	3 (<1)	3 (<1)	3 (<1)
Haemorrhagic	0	0	0	0	0	0	0	0	0
Thromboembolic	3 (<1)	2 (<1)	0	0	0	0	3 (<1)	2 (<1)	2 (<1)
Indeterminate	0	0	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
Other cardiovascular cause	15 (4)	7 (2)	5 (2)	5 (2)	8 (2)	8 (2)	28 (3)	20 (2)	24 (2)
Non-fatal respiratory									
Any event	67 (17)	58 (14)	45 (20)	34 (15)	86 (21)	76 (18)	198 (19)	168 (16)	213 (17)
COPD exacerbation	59 (15)	47 (12)	42 (19)	28 (13)	79 (19)	64 (15)	180 (17)	139 (13)	172 (14)
With pneumonia	25 (6)	18 (4)	13 (6)	9 (4)	21 (5)	13 (3)	59 (6)	40 (4)	51 (4)
Without pneumonia	39 (10)	35 (9)	31 (14)	23 (10)	66 (16)	58 (14)	136 (13)	116 (11)	146 (12)
Pneumonia/respiratory tract infection w/out COPD exacerbation	7 (2)	7 (2)	2 (<1)	11 (5)	8 (2)	12 (3)	17 (2)	30 (3)	39 (3)
Pulmonary embolism	2 (<1)	1 (<1)	1 (<1)	0	0	2 (<1)	3 (<1)	3 (<1)	5 (<1)
Asthma associated	0	0	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
Other respiratory cause	6 (1)	9 (2)	1 (<1)	0	2 (<1)	2 (<1)	9 (<1)	11 (1)	14 (1)
Non-fatal cancer									
Any event	6 (1)	7 (2)	6 (3)	2 (<1)	5 (1)	4 (<1)	17 (2)	13 (1)	17 (1)
Lung	5 (1)	4 (<1)	1 (<1)	0	0	1 (<1)	6 (<1)	5 (<1)	7 (<1)
Breast	0	1 (<1)	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	3 (<1)	3 (<1)
Colorectal	0	0	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	2 (<1)	2 (<1)
Unknown primary	0	0	0	0	0	0	0	0	0
Other cancer cause	1 (<1)	2 (<1)	3 (1)	0	5 (1)	1 (<1)	9 (<1)	3 (<1)	5 (<1)
Non-fatal unknown cause									
Any event	0	1 (<1)	0	0	1 (<1)	0	1 (<1)	1 (<1)	1 (<1)
Inadequate information	0	0	0	0	1 (<1)	0	1 (<1)	0	0
Indeterminate	0	1 (<1)	0	0	0	0	0	1 (<1)	1 (<1)

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

Other significant events

Pneumonia adverse events

Investigator reported Pneumonia AEs were summarized using pre-specified pneumonia PTs (based on the Infective pneumonia SMQ) and are presented for the 3 COPD studies in Table 150 below.

Table 150 On-treatment Adverse events of Pneumonia (COPD studies, Safety population)

	208657				MEA117113				MEA117106				208657 + MEA117113 + MEA117106					
	PBO (N=401) (PY= 483.19)		100 SC (N=403) (PY= 507.43)		PBO (N=226) (PY= 196.23)		100 SC (N=223) (PY= 206.78)		PBO (N=419) (PY= 373.50)		100 SC (N=417) (PY= 383.51)		PBO (N=1046) (PY= 1052.92)		100 SC (N=1043) (PY= 1097.72)		All Doses (N=1268) (PY= 1301.48)	
Preferred Term	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]
Any event	30 (7)	80.7	35 (9)	86.7	24 (11)	147.8	24 (11)	169.3	39 (9)	120.5	33 (8)	99.1	93 (9)	107.3	92 (9)	106.6	114 (9)	109.9
Pneumonia	27 (7)	70.4	30 (7)	76.9	22 (10)	127.4	24 (11)	154.8	39 (9)	120.5	31 (7)	93.9	88 (8)	98.8	85 (8)	97.5	105 (8)	100.7
Pneumonia bacterial	1 (<1)	2.1	2 (<1)	3.9	0	0	1 (<1)	4.8	0	0	0	0	1 (<1)	0.9	3 (<1)	2.7	3 (<1)	2.3
Atypical pneumonia	2 (<1)	4.1	0	0	0	0	0	0	0	0	0	0	2 (<1)	1.9	0	0	0	0
COVID-19 pneumonia	1 (<1)	2.1	1 (<1)	2.0	0	0	0	0	0	0	0	0	1 (<1)	0.9	1 (<1)	0.9	1 (<1)	0.8
Pneumonia pseudomonal	0	0	1 (<1)	2.0	0	0	0	0	0	0	0	0	0	0	1 (<1)	0.9	2 (<1)	1.5
Pneumonia streptococcal	0	0	1 (<1)	2.0	0	0	0	0	0	0	1 (<1)	2.6	0	0	2 (<1)	1.8	2 (<1)	1.5
Pulmonary tuberculosis	1 (<1)	2.1	0	0	0	0	0	0	0	0	0	0	1 (<1)	0.9	0	0	1 (<1)	0.8
Haemophilus infection	0	0	0	0	1 (<1)	5.1	0	0	0	0	0	0	1 (<1)	0.9	0	0	0	0
Lung abscess	0	0	0	0	1 (<1)	5.1	0	0	0	0	0	0	1 (<1)	0.9	0	0	0	0
Pneumonia haemophilus	0	0	0	0	1 (<1)	5.1	0	0	0	0	0	0	1 (<1)	0.9	0	0	0	0
Pneumonia klebsiella	0	0	0	0	0	0	0	0	0	0	1 (<1)	2.6	0	0	1 (<1)	0.9	1 (<1)	0.8
Pneumonia necrotising	0	0	0	0	1 (<1)	5.1	0	0	0	0	0	0	1 (<1)	0.9	0	0	0	0
Pneumonia pneumococcal	0	0	0	0	0	0	1 (<1)	4.8	0	0	0	0	0	0	1 (<1)	0.9	1 (<1)	0.8
Pneumonia staphylococcal	0	0	0	0	0	0	1 (<1)	4.8	0	0	0	0	0	0	1 (<1)	0.9	1 (<1)	0.8

Note: Exposure-adjusted frequency is calculated as: (Total number of adverse events / Total Duration of Exposure in years)*1000.
Note: Pneumonia AEs identified by SMQ (Section 1.1.7.4).
[1] Represents the frequency of events per 1000 participant-years of exposure.

Additional medical concepts

The incidence, EAIR, and CMH-adjusted relative risk and risk difference of any on-treatment AEs in the 3 pooled COPD studies that were pre-specified as additional medical concepts are provided in Table 151 below.

Table 151 On-treatment AEs for the evaluation of additional medical concepts: incidence, CMH-adjusted relative risk and risk difference (COPD studies, Safety population)

	PBO N=1046 (PY=1052.92)		100 SC N=1043 (PY=1097.72)		All doses N=1268 (PY=1301.48)		100 SC versus PBO		All doses versus PBO	
	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	CMH-adjusted RR (95% CI)	% risk diff. (exact 95% CI)	CMH-adjusted RR (95% CI)	% risk diff. (exact 95% CI)
Embolic and Thrombotic Events[2]	26 (2)	26.6	19 (2)	20.0	26 (2)	22.3	0.73 (0.41,1.32)	-0.7 (-5.0,3.6)	0.82 (0.48,1.41)	-0.4 (-4.5,3.7)
Embolic and Thrombotic Events,Venous[2]	5 (<1)	4.7	6 (<1)	5.5	8 (<1)	6.1	1.20 (0.37,3.93)	0.1 (-4.2,4.4)	1.32 (0.43,4.02)	0.2 (-3.9,4.2)
Acute Pancreatitis[3]	0		3 (<1)	2.7	4 (<1)	3.1	--	--	--	--
Hypertension[4]	43 (4)	48.4	50 (5)	47.4	59 (5)	46.9	1.17 (0.78,1.74)	0.7 (-3.6,5.0)	1.13 (0.77,1.66)	0.5 (-3.6,4.6)
Supraventricular Tachyarrhythmias[5]	24 (2)	26.4	26 (2)	28.8	36 (3)	30.0	1.09 (0.63,1.88)	0.2 (-4.1,4.5)	1.24 (0.74,2.06)	0.5 (-3.5,4.6)
Gastrointestinal Bleeding[6]	6 (<1)	5.7	9 (<1)	9.1	11 (<1)	9.2	1.50 (0.54,4.21)	0.3 (-4.0,4.6)	1.51 (0.56,4.08)	0.3 (-3.8,4.4)
Conjunctival Disorders[7]	21 (2)	23.7	24 (2)	21.9	30 (2)	23.1	1.15 (0.64,2.05)	0.3 (-4.0,4.6)	1.18 (0.68,2.05)	0.4 (-3.7,4.4)
Cardiac failure[8] (post-hoc analysis)	50 (5)	53.2	58 (6)	60.1	67 (5)	59.9	1.16 (0.80, 1.68)	0.8 (-3.5, 5.1)	1.11 (0.77, 1.58)	0.5 (-3.6, 4.6)

Note: Studies included: 208657, MEA117113 and MEA117106.
Note: Exposure-adjusted frequency is calculated as:(Total number of adverse events / Total Duration of Exposure in years)*1000.
[1] Represents the frequency of events per 1000 participant-years of exposure.
[2] Evaluated based on the FMQ Thrombosis (narrow)
[2] Evaluated based on the FMQ Thrombosis Venous (narrow)
[3] Evaluated based on the FMQ Pancreatitis (narrow)
[4] Evaluated based on the FMQ Systemic Hypertension (narrow)
[5] Evaluated based on the SMQ Supraventricular Tachyarrhythmias (narrow)
[6] Evaluated based on the SMQ Gastrointestinal Hemorrhage (narrow)
[7] Evaluated based on the SMQ Conjunctival Disorders (narrow)
[8] Evaluated based on the SMQ Cardiac Failure (broad and narrow

Adverse events of special interest

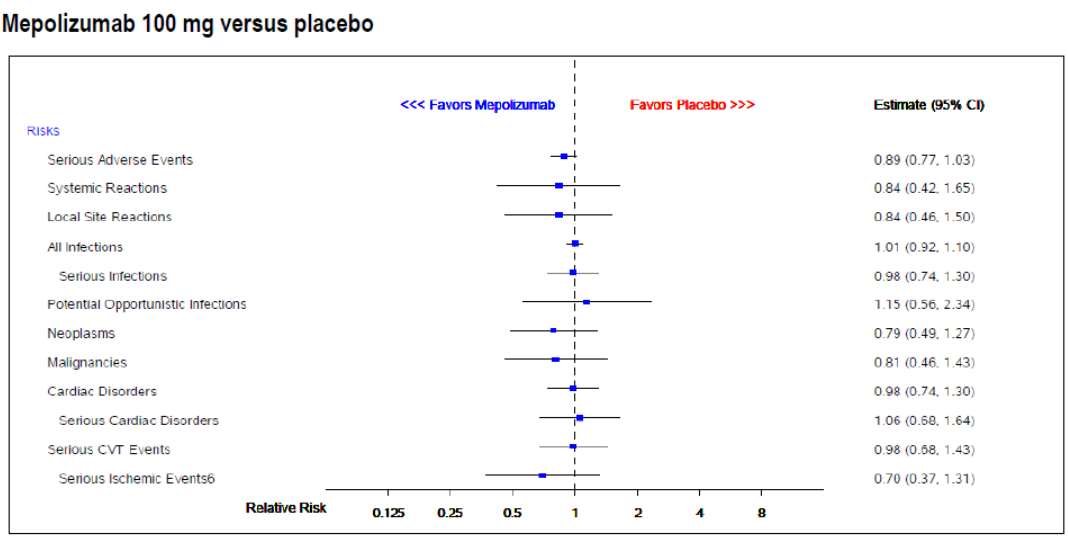
The following were considered on-treatment AESIs for the mepolizumab clinical development program: Systemic reactions, Local injection site reactions, Infections (including Serious and Potential opportunistic), Neoplasms (SOC), Malignancies, Cardiac disorders (including Serious cardiac disorders), and Serious CVT events (including Serious ischemic events). On-treatment SAEs and AESI incidence and CMH-adjusted relative risk and risk difference in the 3 pooled COPD studies, are summarised in Table 152 and Figure 59.

Table 152 On-treatment SAEs and AESI: incidence, CMH-adjusted relative risk and risk difference (COPD studies, Safety population)

	PBO N=1046 (PY=1052.92)		100 SC N=1043 (PY=1097.72)		All doses N=1268 (PY=1301.48)		100 SC versus PBO		All doses versus PBO	
	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	CMH-adjusted RR	% risk diff.	CMH-adjusted RR (95% CI)	% risk diff.
Serious Adverse Events	287 (27)	498.6	255 (24)	467.3	309 (24)	467.9	0.89 (0.77,1.03)	-3.0% (-7.3,1.3)	0.89 (0.77,1.02)	-3.1% (-7.2,1.0)
Systemic Reactions[2]	18 (2)	20.9	15 (1)	23.7	20 (2)	24.6	0.84 (0.42,1.65)	-0.3% (-4.6,4.0)	0.92 (0.49,1.72)	-0.1% (-4.2,3.9)
...Anaphylaxis	0		0		0					
Local Site Reactions2	24 (2)	35.1	20 (2)	27.3	31 (2)	43.8	0.84 (0.46,1.50)	-0.4% (-4.7,3.9)	1.07 (0.63,1.80)	0.2% (-3.9,4.2)
All Infections[3]	513 (49)	925.0	516 (49)	920.1	629 (50)	933.6	1.01 (0.92,1.10)	0.4% (-3.9,4.7)	1.01 (0.93,1.10)	0.6% (-3.5,4.7)
...Serious Infections	91 (9)	115.9	89 (9)	111.1	111 (9)	111.4	0.98 (0.74,1.30)	-0.2% (-4.5,4.1)	1.01 (0.77,1.31)	0.1% (-4.0,4.1)
Potential Opportunistic Infections[4]	14 (1)	13.3	16 (2)	18.2	22 (2)	20.7	1.15 (0.56,2.34)	0.2% (-4.1,4.5)	1.30 (0.67,2.52)	0.4% (-3.7,4.5)
Neoplasms[3]	37 (4)	40.8	29 (3)	32.8	35 (3)	32.3	0.79 (0.49,1.27)	-0.8% (-5.1,3.5)	0.78 (0.50,1.23)	-0.8% (-4.9,3.3)
Malignancies[5]	26 (2)	29.4	21 (2)	25.5	24 (2)	23.8	0.81 (0.46,1.43)	-0.5% (-4.8,3.8)	0.76 (0.44,1.32)	-0.6% (-4.7,3.5)
Cardiac Disorders[3]	89 (9)	114.9	87 (8)	106.6	108 (9)	110.6	0.98 (0.74,1.30)	-0.2% (-4.5,4.1)	1.00 (0.77,1.31)	0.0% (-4.1,4.1)
...Serious Cardiac Disorders	37 (4)	41.8	39 (4)	41.9	47 (4)	42.3	1.06 (0.68,1.64)	0.2% (-4.1,4.5)	1.05 (0.69,1.60)	0.2% (-3.9,4.3)
Serious CVT Events[6]	53 (5)	61.7	52 (5)	61.0	62 (5)	59.9	0.98 (0.68,1.43)	-0.1% (-4.4,4.2)	0.97 (0.68,1.38)	-0.2% (-4.3,3.9)
Serious Ischemic Events[7]	23 (2)	21.8	16 (2)	14.6	22 (2)	16.9	0.70 (0.37,1.31)	-0.7% (-5.0,3.6)	0.79 (0.44,1.41)	-0.5% (-4.6,3.6)

[1] Represents frequency of events per 1000 participant-years of exposure. Exposure-adjusted frequency is calculated as: (Total number of adverse events / Total Duration of exposure in years)*1000
[2] Systemic, Local reactions were collected via a targeted study eCRF.
[3] Infections from Infections and infestations SOC. Neoplasms from Neoplasms benign malignant and unspecified (including cysts and polyps) SOC. Cardiac disorders from Cardiac disorders SOC.
[4] Identified from SMQs or events with the preferred term of herpes zoster.
[5] Identified from SMQs.
[6] Serious CVT events identified from Cardiac disorders SOC, Vascular disorders SOC and SMQs.
[7] Subset of Serious CVT events identified through SMQs.
Note: Studies included: 208657, MEA117113 and MEA117106.

Figure 59 On-treatment serious AEs and AESI: CMH-adjusted relative risk (COPD studies, Safety population)



Anaphylaxis

There were no events of anaphylaxis considered by the investigator to represent systemic reaction and meeting Sampson's criteria for anaphylaxis in any of the 3 COPD studies.

Systemic reactions

In studies MEA117113 and MEA117106, the AESI of Systemic reactions was further categorized as allergic/hypersensitivity reactions or non-allergic reactions. For study 208657, the AESI of Systemic reactions was further categorized as Allergic (type I hypersensitivity) reactions or Other systemic reactions. Reported events are presented, respectively in Table 153 and Table 154.

Table 153 On-treatment Systemic (Allergic/Hypersensitivity and Non-Allergic) Reactions (MEA117113 and MEA1171106 studies, Safety population)

	MEA117113		MEA117106	
Systemic Reactions Preferred Term	**PBO (N=226) n (%)**	**100 SC (N=223) n (%)**	**PBO (N=419) n (%)**	**100 SC (N=417) n (%)**
Any Event	4 (2)	3 (1)	9 (2)	7 (2)

	MEA117113		MEA117106	
Systemic Reactions Preferred Term	**PBO (N=226) n (%)**	**100 SC (N=223) n (%)**	**PBO (N=419) n (%)**	**100 SC (N=417) n (%)**
Allergic/Hypersensitivity Reaction	1 (<1)	1 (<1)	2 (<1)	3 (<1)
Hypersensitivity	0	1 (<1)	2 (<1)	3 (<1)
Type III immune complex mediated reaction	1 (<1)	0	0	0
Non-allergic Reaction	3 (1)	2 (<1)	7 (2)	5 (1)
Injection-related reaction	3 (1)	2 (<1)	7 (2)	5 (1)

Table 154 On-Treatment Systemic reactions - Allergic (Type I Hypersensitivity) and Other systemic reactions (208657 study, Safety population)

	208657	
Systemic Reactions Preferred Term	**PBO (N=401) n (%)**	**100 SC (N=403) n (%)**
Any Event	5 (1)	5 (1)
Allergic (Type I Hypersensitivity)	0	1 (<1)
Urticaria	0	1 (<1)
Other Reaction	4 (<1)	4 (<1)
Dizziness	1 (<1)	1 (<1)
Headache	2 (<1)	0
Tremor	0	1 (<1)
Nausea	1 (<1)	0
Paraesthesia oral	1 (<1)	0
Fatigue	0	2 (<1)
Eye irritation	0	1 (<1)
Hypersensitivity	0	1 (<1)
Hypotension	0	1 (<1)

Note: 'Other reaction' refers to 'Other systemic reaction'.

Note: In the placebo group, there was 1 participant (103011) for whom information was not provided on the type of systemic reaction within their eCRF, therefore they had no value to count in the sublevel (Source: Analysis Adverse Events of Special Interest [ADAESI] data).

Local injection site reactions

In the 3 pooled COPD studies, the incidence of any Local injection site reactions (ISRs) was similar for the mepolizumab 100 mg group and the placebo group (2% each); the EAIR was 27.3 events per 1000 PY in the mepolizumab 100 mg group and 35.1 events per 1000 PY in the placebo group. The most frequently reported event (by PT) was injection site reaction; the event occurred in 2% of

participants in both the mepolizumab 100 mg group and the placebo group (19 of 1043, and 21 of 1046 participants, respectively). All local ISRs were considered related to study treatment and were reported as non-serious events. All local ISR events in the mepolizumab treatment group were mild or moderate in severity.

On-treatment AESIs reported for study 208657 are summarised in Table 155 below.

Table 155 On-treatment AESI: events reported by the investigator as local injection site reactions (Study 208657; Safety Population)

System Organ Class Preferred Term, n (%)	PBO (N=401)	Mepo 100 mg (N=403)
Any event	3 (<1)	2 (<1)
General disorders and administration site conditions		
Any event	3 (<1)	1 (<1)
Injection site erythema	1 (<1)	0
Injection site haematoma	1 (<1)	0
Injection site reaction	0	1 (<1)
Injection site swelling	1 (<1)	0
Skin and subcutaneous tissue disorders		
Pruritus	0	1 (<1)

Infections and potential opportunistic infections

For the 3 pooled COPD studies, a summary of on- and post-treatment AEs reported for Infections and infestations SOC and potential opportunistic infection are presented in Table 156 and Table 157, respectively.

Of note, studies MEA117113 and MEA117106 were re-evaluated for Potential opportunistic infections using the identification process described for Study 208657.

Table 156 On- and post-treatment AEs and SAEs in the Infections and infestations SOC (3 most frequent, COPD studies, Safety Population)

	208657				MEA117113				MEA117106				208657 + MEA117113 + MEA117106					
	PBO (N=401) (PY= 483.19)		100 SC (N=403) (PY= 507.43)		PBO (N=226) (PY= 196.23)		100 SC (N=223) (PY= 206.78)		PBO (N=419) (PY= 373.50)		100 SC (N=417) (PY= 383.51)		PBO (N=1046) (PY= 1052.92)		100 SC (N=1043) (PY= 1097.72)		All Doses (N=1268) (PY= 1301.48)	
Infections and Infestations	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]
Any AE	172 (43)	703.7	190 (47)	768.6	127 (56)	1202.7	120 (54)	1151.0	214 (51)	1065.6	206 (49)	996.1	513 (49)	925.0	516 (49)	920.1	629 (50)	933.6
On-treatment																		
Nasopharyngitis	32 (8)	86.9	41 (10)	110.4	48 (21)	331.2	39 (17)	275.6	63 (15)	235.6	64 (15)	219.0	143 (14)	185.2	144 (14)	179.5	184 (15)	191.3
Pneumonia	27 (7)	70.4	30 (7)	76.9	22 (10)	127.4	24 (11)	154.8	39 (9)	120.5	31 (7)	93.9	88 (8)	98.8	85 (8)	97.5	105 (8)	100.7
Upper respiratory tract infection	20 (5)	60.0	25 (6)	80.8	21 (9)	147.8	16 (7)	91.9	21 (5)	69.6	21 (5)	65.2	62 (6)	79.8	62 (6)	77.4	75 (6)	77.6
Any SAE	31 (8)	84.9	32 (8)	88.7	24 (11)	163.1	23 (10)	164.4	36 (9)	131.2	34 (8)	112.1	91 (9)	115.9	89 (9)	111.1	111 (9)	111.4
On-treatment																		
Pneumonia	14 (3)	33.1	14 (3)	31.5	16 (7)	81.5	15 (7)	91.9	26 (6)	80.3	21 (5)	67.8	56 (5)	58.9	50 (5)	55.6	63 (5)	56.9
Infective exacerbation of chronic obstructive airways disease	4 (<1)	8.3	1 (<1)	2.0	3 (1)	20.4	1 (<1)	4.8	1 (<1)	2.7	3 (<1)	7.8	8 (<1)	8.5	5 (<1)	4.6	7 (<1)	5.4
COVID-19	4 (<1)	8.3	4 (<1)	7.9	0	0	0	0	0	0	0	0	4 (<1)	3.8	4 (<1)	3.6	4 (<1)	3.1
Non-fatal SAEs	31 (8)	82.8	29 (7)	82.8	23 (10)	158.0	23 (10)	159.6	34 (8)	123.2	33 (8)	109.5	88 (8)	111.1	85 (8)	106.6	106 (8)	106.8
On-treatment																		
Pneumonia	14 (3)	33.1	14 (3)	31.5	15 (7)	76.4	15 (7)	91.9	24 (6)	75.0	21 (5)	67.8	53 (5)	56.0	50 (5)	55.6	62 (5)	56.1
Infective exacerbation of chronic obstructive airways disease	3 (<1)	6.2	1 (<1)	2.0	3 (1)	20.4	1 (<1)	4.8	1 (<1)	2.7	3 (<1)	7.8	7 (<1)	7.6	5 (<1)	4.6	7 (<1)	5.4
Urinary tract infection	0	0	0	0	0	0	3 (1)	14.5	2 (<1)	5.4	0	0	2 (<1)	1.9	3 (<1)	2.7	4 (<1)	3.1

	208657				MEA117113				MEA117106				208657 + MEA117113 + MEA117106					
	PBO (N=401) (PY= 483.19)		100 SC (N=403) (PY= 507.43)		PBO (N=226) (PY= 196.23)		100 SC (N=223) (PY= 206.78)		PBO (N=419) (PY= 373.50)		100 SC (N=417) (PY= 383.51)		PBO (N=1046) (PY= 1052.92)		100 SC (N=1043) (PY= 1097.72)		All Doses (N=1268) (PY= 1301.48)	
Infections and Infestations	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]
Fatal SAEs On-and post-treatment	2 (<1)	-	3 (<1)	-	2 (<1)	-	1 (<1)	-	3 (<1)	-	1 (<1)	-	7 (<1)	-	5 (<1)	-	6 (<1)	-
Pneumonia	0	-	0	-	2 (<1)	-	0	-	2 (<1)	-	0	-	4 (<1)	-	0	-	1 (<1)	-
COVID-19	1 (<1)	-	3 (<1)	-	0	-	0	-	0	-	0	-	1 (<1)	-	3 (<1)	-	3 (<1)	-
Sepsis	0	-	0	-	0	-	1 (<1)	-	0	-	1 (<1)	-	0	-	2 (<1)	-	2 (<1)	-

Note: Exposure-adjusted frequency is calculated as: (Total number of adverse events / Total Duration of Exposure in years)*1000.
[1] Represents the frequency of events per 1000 participant-years of exposure.

Table 157 On-treatment adverse events of special interest: potential opportunistic infections (COPD studies, Safety population)

	208657				MEA117113				MEA117106				208657 + MEA117113 + MEA117106					
	PBO (N=401) (PY= 483.19)		100 SC (N=403) (PY= 507.43)		PBO (N=226) (PY= 196.23)		100 SC (N=223) (PY= 206.78)		PBO (N=419) (PY= 373.50)		100 SC (N=417) (PY= 383.51)		PBO (N=1046) (PY= 1052.92)		100 SC (N=1043) (PY= 1097.72)		All Doses (N=1268) (PY= 1301.48)	
Preferred Term	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]
ANY EVENT	7 (2)	14.5	4 (<1)	9.9	4 (2)	20.4	5 (2)	29.0	3 (<1)	8.0	7 (2)	23.5	14 (1)	13.3	16 (2)	18.2	22 (2)	20.7
Herpes zoster	2 (<1)	4.1	3 (<1)	7.9	4 (2)	20.4	4 (2)	19.3	1 (<1)	2.7	7 (2)	23.5	7 (<1)	6.6	14 (1)	15.5	19 (1)	16.9
Oesophageal candidiasis	1 (<1)	2.1	1 (<1)	2.0	0	0	1 (<1)	9.7	1 (<1)	2.7	0	0	2 (<1)	1.9	2 (<1)	2.7	2 (<1)	2.3
Pulmonary tuberculosis	1 (<1)	2.1	0	0	0	0	0	0	0	0	0	0	1 (<1)	0.9	0	0	1 (<1)	0.8
Fungal oesophagitis	0	0	0	0	0	0	0	0	1 (<1)	2.7	0	0	1 (<1)	0.9	0	0	0	0
Herpes ophthalmic	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (<1)	0.8
Nocardiosis	1 (<1)	2.1	0	0	0	0	0	0	0	0	0	0	1 (<1)	0.9	0	0	0	0
Ophthalmic herpes zoster	1 (<1)	2.1	0	0	0	0	0	0	0	0	0	0	1 (<1)	0.9	0	0	0	0
Upper respiratory fungal infection	1 (<1)	2.1	0	0	0	0	0	0	0	0	0	0	1 (<1)	0.9	0	0	0	0

Note: Exposure-adjusted frequency is calculated as: (Total number of adverse events / Total Duration of Exposure in years)*1000.
Note: Potential opportunistic infections were identified as events within Opportunistic infections SMQ (narrow) plus Herpes Zoster PT (see Section 7.1).
[1] Represents the frequency of events per 1000 participant-years of exposure.

Neoplasms and malignancies

On-treatment adverse events of neoplasms and malignancies reported in the 3 pooled COPD studies are presented in Table 158 below.

Table 158 On-treatment adverse events of special interest: neoplasms and malignancies (more than 1 participant across treatment groups, COPD studies, Safety population)

Neoplasms, benign, malignant and unspecified (incl cysts and polyps)	208657				MEA117113				MEA117106				208657 + MEA117113 + MEA117106					
	PBO (N=401) (PY= 483.19)		100 SC (N=403) (PY= 507.43)		PBO (N=226) (PY= 196.23)		100 SC (N=223) (PY= 206.78)		PBO (N=419) (PY= 373.50)		100 SC (N=417) (PY= 383.51)		PBO (N=1046) (PY= 1052.92)		100 SC (N=1043) (PY= 1097.72)		All Doses (N=1268) (PY= 1301.48)	
	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]
Any event[2]	17 (4)	45.5	9 (2)	19.7	4 (2)	20.4	6 (3)	38.7	16 (4)	45.5	14 (3)	46.9	37 (4)	40.8	29 (3)	32.8	35 (3)	32.3
Malignancies[3]	13 (3)	35.2	8 (2)	17.7	3 (1)	15.3	3 (1)	24.2	10 (2)	29.5	10 (2)	36.5	26 (2)	29.4	21 (2)	25.5	24 (2)	23.8
..Lung neoplasm malignant	2 (<1)	4.1	2 (<1)	3.9	0	0	1 (<1)	4.8	0	0	0	0	2 (<1)	1.9	3 (<1)	2.7	3 (<1)	2.3
..Basal cell carcinoma	1 (<1)	4.1	0	0	0	0	0	0	1 (<1)	2.7	2 (<1)	7.8	2 (<1)	2.8	2 (<1)	2.7	2 (<1)	2.3
..Breast cancer	1 (<1)	4.1	1 (<1)	2.0	0	0	1 (<1)	4.8	0	0	1 (<1)	2.6	1 (<1)	1.9	3 (<1)	2.7	3 (<1)	2.3
..Lung adenocarcinoma	2 (<1)	4.1	0	0	0	0	0	0	0	0	1 (<1)	2.6	2 (<1)	1.9	1 (<1)	0.9	2 (<1)	1.5
..Prostate cancer	1 (<1)	2.1	0	0	1 (<1)	5.1	0	0	1 (<1)	2.7	0	0	3 (<1)	2.8	0	0	1 (<1)	0.8
..Bladder cancer	0	0	1 (<1)	3.9	0	0	0	0	2 (<1)	5.4	0	0	2 (<1)	1.9	1 (<1)	1.8	1 (<1)	1.5
..Non-small cell lung cancer	0	0	0	0	1 (<1)	5.1	0	0	0	0	1 (<1)	2.6	1 (<1)	0.9	1 (<1)	0.9	2 (<1)	1.5
..Squamous cell carcinoma	0	0	0	0	0	0	0	0	1 (<1)	2.7	2 (<1)	5.2	1 (<1)	0.9	2 (<1)	1.8	2 (<1)	1.5
..Metastases to lung	0	0	0	0	0	0	1 (<1)	4.8	0	0	1 (<1)	5.2	0	0	2 (<1)	2.7	2 (<1)	2.3
..Metastases to the mediastinum	0	0	0	0	0	0	1 (<1)	4.8	0	0	1 (<1)	2.6	0	0	2 (<1)	1.8	2 (<1)	1.5
..Plasma cell myeloma	1 (<1)	2.1	0	0	0	0	0	0	1 (<1)	2.7	0	0	2 (<1)	1.9	0	0	0	0

Note: Exposure-adjusted frequency is calculated as: (Total number of adverse events / Total Duration of Exposure in years)*1000.
[1] Represents the frequency of events per 1000 participant-years of exposure.
[2] Neoplasms from Neoplasms benign malignant and unspecified (including cysts and polyps) SOC.
[3] Malignancies identified from SMQs (see Section 8.1)

In study 208657, the incidence of on-treatment AESI of malignancies were generally similar between the treatment groups in the fixed duration subgroup (2% each) and in the variable duration subgroup (2% in mepolizumab, 4% in placebo).

Cardiac disorders

On-treatment AEs and on- and post-treatment SAEs in Cardiac disorder SOC reported in the 3 pooled COPD studies are summarised in Table 159 and Table 160, respectively.

Table 159 On treatment AEs in Cardiac disorder SOC (COPD studies, Safety population)

Cardiac disorders	208657				MEA117113				MEA117106				208657 + MEA117113 + MEA117106					
	PBO (N=401) (PY= 483.19)		100 SC (N=403) (PY= 507.43)		PBO (N=226) (PY= 196.23)		100 SC (N=223) (PY= 206.78)		PBO (N=419) (PY= 373.50)		100 SC (N=417) (PY= 383.51)		PBO (N=1046) (PY= 1052.92)		100 SC (N=1043) (PY= 1097.72)		All Doses (N=1268) (PY= 1301.48)	
Preferred Term	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]
Any AE (On-treatment)	44 (11)	130.4	31 (8)	82.8	15 (7)	91.7	16 (7)	111.2	30 (7)	107.1	40 (10)	135.6	89 (9)	114.9	87 (8)	106.6	108 (9)	110.6
Atrial fibrillation	8 (2)	18.6	4 (<1)	7.9	3 (1)	30.6	6 (3)	33.9	5 (1)	16.1	6 (1)	20.9	16 (2)	19.9	16 (2)	17.3	20 (2)	17.7
Cardiac failure congestive	4 (<1)	8.3	1 (<1)	2	0	0	1 (<1)	4.8	3 (<1)	8	4 (<1)	13	7 (<1)	6.6	6 (<1)	6.4	7 (<1)	6.1
Cardiac failure	3 (<1)	6.2	4 (<1)	7.9	0	0	0	0	2 (<1)	8	4 (<1)	10.4	5 (<1)	5.7	8 (<1)	7.3	8 (<1)	6.1
Palpitations	3 (<1)	6.2	5 (1)	11.8	0	0	0	0	1 (<1)	2.7	2 (<1)	7.8	4 (<1)	3.8	7 (<1)	8.2	9 (<1)	8.5
Tachycardia	0	0	4 (<1)	7.9	0	0	2 (<1)	9.7	3 (<1)	10.7	3 (<1)	13	3 (<1)	3.8	9 (<1)	10	9 (<1)	8.5
Acute myocardial infarction	2 (<1)	4.1	0	0	2 (<1)	10.2	1 (<1)	4.8	2 (<1)	5.4	2 (<1)	5.2	6 (<1)	5.7	3 (<1)	2.7	5 (<1)	3.8
Cardiac arrest	1 (<1)	2.1	4 (<1)	7.9	1 (<1)	5.1	0	0	0	0	1 (<1)	2.6	2 (<1)	1.9	5 (<1)	4.6	5 (<1)	3.8
Sinus tachycardia	0	0	1 (<1)	2	4 (2)	20.4	0	0	0	0	1 (<1)	2.6	4 (<1)	3.8	2 (<1)	1.8	3 (<1)	2.3
Supraventricular tachycardia	1 (<1)	2.1	1 (<1)	2	0	0	0	0	0	0	2 (<1)	5.2	1 (<1)	0.9	3 (<1)	2.7	6 (<1)	4.6
Ventricular extrasystoles	1 (<1)	2.1	2 (<1)	3.9	1 (<1)	5.1	0	0	2 (<1)	5.4	0	0	4 (<1)	3.8	2 (<1)	1.8	3 (<1)	2.3
Angina pectoris	1 (<1)	2.1	1 (<1)	2	0	0	3 (1)	14.5	0	0	1 (<1)	2.6	1 (<1)	0.9	5 (<1)	4.6	5 (<1)	3.8

Note: Exposure-adjusted frequency is calculated as: (Total number of adverse events / Total Duration of Exposure in years)*1000.
[1] Represents the frequency of events per 1000 participant-years of exposure.

Table 160 On- and post-treatment SAEs in Cardiac disorder SOC (COPD studies, Safety population)

	208657				MEA117113				MEA117106				208657 + MEA117113 + MEA117106					
	PBO (N=401) (PY= 483.19)		100 SC (N=403) (PY= 507.43)		PBO (N=226) (PY= 196.23)		100 SC (N=223) (PY= 206.78)		PBO (N=419) (PY= 373.50)		100 SC (N=417) (PY= 383.51)		PBO (N=1046) (PY= 1052.92)		100 SC (N=1043) (PY= 1097.72)		All Doses (N=1268) (PY= 1301.48)	
Cardiac disorders																		
Preferred Term	**n (%)**	**Rate[1]**	**n (%)**	**Rate[1]**	**n (%)**	**Rate[1]**	**n (%)**	**Rate[1]**	**n (%)**	**Rate[1]**	**n (%)**	**Rate[1]**	**n (%)**	**Rate[1]**	**n (%)**	**Rate[1]**	**n (%)**	**Rate[1]**
Any SAE On-treatment	16 (4)	33.1	13 (3)	29.6	8 (4)	56.1	7 (3)	38.7	13 (3)	45.5	19 (5)	60	37 (4)	41.8	39 (4)	41.9	47 (4)	42.3
Atrial fibrillation	1 (<1)	2.1	2 (<1)	3.9	3 (1)	30.6	3 (1)	14.5	3 (<1)	8	3 (<1)	10.4	7 (<1)	9.5	8 (<1)	8.2	8 (<1)	6.9
Acute myocardial infarction	2 (<1)	4.1	0	0	2 (<1)	10.2	1 (<1)	4.8	2 (<1)	5.4	2 (<1)	5.2	6 (<1)	5.7	3 (<1)	2.7	5 (<1)	3.8
Cardiac failure congestive	2 (<1)	4.1	1 (<1)	2	0	0	1 (<1)	4.8	2 (<1)	5.4	3 (<1)	10.4	4 (<1)	3.8	5 (<1)	5.5	5 (<1)	4.6
Cardiac arrest	1 (<1)	2.1	4 (<1)	7.9	1 (<1)	5.1	0	0	0	0	1 (<1)	2.6	2 (<1)	1.9	5 (<1)	4.6	5 (<1)	3.8
Cardiac failure	0	0	2 (<1)	3.9	0	0	0	0	1 (<1)	5.4	2 (<1)	5.2	1 (<1)	1.9	4 (<1)	3.6	4 (<1)	3.1
Coronary artery disease	1 (<1)	2.1	2 (<1)	3.9	1 (<1)	5.1	0	0	0	0	0	0	2 (<1)	1.9	2 (<1)	1.8	3 (<1)	2.3
Angina unstable	1 (<1)	2.1	2 (<1)	3.9	0	0	1 (<1)	4.8	0	0	0	0	1 (<1)	0.9	3 (<1)	2.7	3 (<1)	2.3
Myocardial infarction	1 (<1)	2.1	0	0	0	0	0	0	1 (<1)	2.7	0	0	2 (<1)	1.9	0	0	1 (<1)	0.8
Stress cardiomyopathy	1 (<1)	2.1	0	0	1 (<1)	5.1	0	0	0	0	0	0	2 (<1)	1.9	0	0	1 (<1)	0.8
Ventricular tachycardia	1 (<1)	2.1	0	0	0	0	0	0	1 (<1)	2.7	1 (<1)	2.6	2 (<1)	1.9	1 (<1)	0.9	1 (<1)	0.8
Acute coronary syndrome	0	0	0	0	0	0	0	0	0	0	1 (<1)	2.6	0	0	1 (<1)	0.9	2 (<1)	1.5

	208657				MEA117113				MEA117106				208657 + MEA117113 + MEA117106					
	PBO (N=401) (PY= 483.19)		100 SC (N=403) (PY= 507.43)		PBO (N=226) (PY= 196.23)		100 SC (N=223) (PY= 206.78)		PBO (N=419) (PY= 373.50)		100 SC (N=417) (PY= 383.51)		PBO (N=1046) (PY= 1052.92)		100 SC (N=1043) (PY= 1097.72)		All Doses (N=1268) (PY= 1301.48)	
Cardiac disorders																		
Preferred Term	**n (%)**	**Rate[1]**	**n (%)**	**Rate[1]**	**n (%)**	**Rate[1]**	**n (%)**	**Rate[1]**	**n (%)**	**Rate[1]**	**n (%)**	**Rate[1]**	**n (%)**	**Rate[1]**	**n (%)**	**Rate[1]**	**n (%)**	**Rate[1]**
Any non-fatal SAE (on-treatment)	15 (4)	31	11 (3)	25.6	7 (3)	51	7 (3)	38.7	13 (3)	45.5	15 (4)	49.5	35 (3)	39.9	33 (3)	36.4	38 (3)	35.3
Atrial fibrillation	1 (<1)	2.1	2 (<1)	3.9	3 (1)	30.6	3 (1)	14.5	3 (<1)	8	3 (<1)	10.4	7 (<1)	9.5	8 (<1)	8.2	8 (<1)	6.9
Acute myocardial infarction	1 (<1)	2.1	0	0	2 (<1)	10.2	1 (<1)	4.8	2 (<1)	5.4	2 (<1)	5.2	5 (<1)	4.7	3 (<1)	2.7	4 (<1)	3.1
Cardiac failure congestive	2 (<1)	4.1	1 (<1)	2	0	0	1 (<1)	4.8	2 (<1)	5.4	2 (<1)	7.8	4 (<1)	3.8	4 (<1)	4.6	4 (<1)	3.8
Cardiac failure	0	0	2 (<1)	3.9	0	0	0	0	1 (<1)	5.4	2 (<1)	5.2	1 (<1)	1.9	4 (<1)	3.6	4 (<1)	3.1
Coronary artery disease	1 (<1)	2.1	2 (<1)	3.9	1 (<1)	5.1	0	0	0	0	0	0	2 (<1)	1.9	2 (<1)	1.8	3 (<1)	2.3
Angina unstable	1 (<1)	2.1	2 (<1)	3.9	0	0	1 (<1)	4.8	0	0	0	0	1 (<1)	0.9	3 (<1)	2.7	3 (<1)	2.3
Cardiac arrest	1 (<1)	2.1	2 (<1)	3.9	0	0	0	0	0	0	0	0	1 (<1)	0.9	2 (<1)	1.8	2 (<1)	1.5
Stress cardiomyopathy	1 (<1)	2.1	0	0	1 (<1)	5.1	0	0	0	0	0	0	2 (<1)	1.9	0	0	1 (<1)	0.8
Ventricular tachycardia	1 (<1)	2.1	0	0	0	0	0	0	1 (<1)	2.7	1 (<1)	2.6	2 (<1)	1.9	1 (<1)	0.9	1 (<1)	0.8
Acute coronary syndrome	0	0	0	0	0	0	0	0	0	0	1 (<1)	2.6	0	0	1 (<1)	0.9	2 (<1)	1.5
Cardiac failure chronic	0	0	0	0	0	0	0	0	1 (<1)	2.7	1 (<1)	2.6	1 (<1)	0.9	1 (<1)	0.9	1 (<1)	0.8

	208657				MEA117113				MEA117106				208657 + MEA117113 + MEA117106					
	PBO (N=401) (PY= 483.19)		100 SC (N=403) (PY= 507.43)		PBO (N=226) (PY= 196.23)		100 SC (N=223) (PY= 206.78)		PBO (N=419) (PY= 373.50)		100 SC (N=417) (PY= 383.51)		PBO (N=1046) (PY= 1052.92)		100 SC (N=1043) (PY= 1097.72)		All Doses (N=1268) (PY= 1301.48)	
Cardiac disorders																		
Preferred Term	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]
Any fatal SAE (On-and Post-treatment)	1 (<1)	--	4 (<1)	--	2 (<1)	--	1 (<1)	--	1 (<1)	--	5 (1)	--	4 (<1)	--	10 (<1)	--	13 (1)	--
Cardiac arrest	0	--	2 (<1)	--	1 (<1)	--	0	--	1 (<1)	--	1 (<1)	--	2 (<1)	--	3 (<1)	--	3 (<1)	--
Acute myocardial infarction	1 (<1)	--	0	--	1 (<1)	--	0	--	0	--	0	--	2 (<1)	--	0	--	1 (<1)	--
Cardiac failure congestive	0	--	1 (<1)	--	0	--	0	--	0	--	2 (<1)	--	0	--	3 (<1)	--	3 (<1)	--
Cardio-respiratory arrest	0	--	0	--	0	--	1 (<1)	--	0	--	0	--	0	--	1 (<1)	--	2 (<1)	--
Arteriosclerosis coronary artery	0	--	1 (<1)	--	0	--	0	--	0	--	0	--	0	--	1 (<1)	--	1 (<1)	--
Cardiomyopathy	0	--	0	--	0	--	0	--	0	--	1 (<1)	--	0	--	1 (<1)	--	1 (<1)	--
Cardiopulmonary failure	0	--	0	--	0	--	0	--	0	--	1 (<1)	--	0	--	1 (<1)	--	1 (<1)	--
Myocardial infarction	0	--	0	--	0	--	0	--	0	--	0	--	0	--	0	--	1 (<1)	--

Note: Exposure-adjusted frequency is calculated as: (Total number of adverse events / Total Duration of Exposure in years)*1000.
[1] Represents the frequency of events per 1000 participant-years of exposure.

The most frequently reported on-treatment AE and SAE in the Cardiac disorders SOC was atrial fibrillation; both were reported with a similar incidence between the mepolizumab 100 mg and placebo groups. In studies MEA117113 and MEA117106, the rate of on-treatment AEs in the Cardiac disorders SOC was numerically higher in the mepolizumab group compared with placebo; however, the trend was reversed in study 208657.

On- and post-treatment fatal SAEs in the Cardiac disorders SOC were reported for 10 of 1043 (<1%) participants in the mepolizumab 100 mg group and 4 of 1046 (<1%) participants in the placebo group in the 3 pooled COPD studies. The most notable imbalance between mepolizumab 100 mg and placebo was SAE congestive cardiac failure, with 3 events reported in the former and none in the latter. Refer to *Adjudicated fatal and non-fatal SAE reports* for further discussion of the MAH's evaluation of reported AEs of congestive heart failure.

Serious CVT events

A summary of exposure-adjusted on-treatment AESIs of serious cardiac, vascular and thromboembolic events are presented in Table 161 below.

Table 161 Summary of exposure-adjusted on-treatment adverse events of special interest: serious cardiac, vascular and thromboembolic events (more than 1 participant across treatment groups) (COPD studies, Safety population)

	208657				MEA117113				MEA117106				208657 + MEA117113 + MEA117106					
	PBO (N=401) (PY= 483.19)		100 SC (N=403) (PY= 507.43)		PBO (N=226) (PY= 196.23)		100 SC (N=223) (PY= 206.78)		PBO (N=419) (PY= 373.50)		100 SC (N=417) (PY= 383.51)		PBO (N=1046) (PY= 1052.92)		100 SC (N=1043) (PY= 1097.72)		All Doses (N=1268) (PY= 1301.48)	
Preferred Term	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]
ANY EVENT	29 (7)	64.2	20 (5)	47.3	9 (4)	66.2	9 (4)	72.5	15 (4)	56.2	23 (6)	73.0	53 (5)	61.7	52 (5)	61.0	62 (5)	59.9
Atrial fibrillation	1 (<1)	2.1	2 (<1)	3.9	3 (1)	30.6	3 (1)	14.5	3 (<1)	8.0	3 (<1)	10.4	7 (<1)	9.5	8 (<1)	8.2	8 (<1)	6.9
Acute myocardial infarction*	2 (<1)	4.1	0	0	2 (<1)	10.2	1 (<1)	4.8	2 (<1)	5.4	2 (<1)	5.2	6 (<1)	5.7	3 (<1)	2.7	5 (<1)	3.8
Cardiac failure congestive	2 (<1)	4.1	1 (<1)	2.0	0	0	1 (<1)	4.8	2 (<1)	5.4	3 (<1)	10.4	4 (<1)	3.8	5 (<1)	5.5	5 (<1)	4.6
Cardiac arrest	1 (<1)	2.1	4 (<1)	7.9	1 (<1)	5.1	0	0	0	0	1 (<1)	2.6	2 (<1)	1.9	5 (<1)	4.6	5 (<1)	3.8
Transient ischaemic attack*	3 (<1)	6.2	0	0	1 (<1)	5.1	0	0	0	0	2 (<1)	5.2	4 (<1)	3.8	2 (<1)	1.8	2 (<1)	1.5
Pulmonary embolism	2 (<1)	4.1	1 (<1)	2.0	0	0	0	0	0	0	1 (<1)	2.6	2 (<1)	1.9	2 (<1)	1.8	4 (<1)	3.1
Cardiac failure	0	0	2 (<1)	3.9	0	0	0	0	1 (<1)	5.4	2 (<1)	5.2	1 (<1)	1.9	4 (<1)	3.6	4 (<1)	3.1
Coronary artery disease*	1 (<1)	2.1	2 (<1)	3.9	1 (<1)	5.1	0	0	0	0	0	0	2 (<1)	1.9	2 (<1)	1.8	3 (<1)	2.3
Angina unstable*	1 (<1)	2.1	2 (<1)	3.9	0	0	1 (<1)	4.8	0	0	0	0	1 (<1)	0.9	3 (<1)	2.7	3 (<1)	2.3
Hypertension	1 (<1)	2.1	1 (<1)	2.0	0	0	1 (<1)	4.8	1 (<1)	2.7	0	0	2 (<1)	1.9	2 (<1)	1.8	2 (<1)	1.5
Myocardial infarction*	1 (<1)	2.1	0	0	0	0	0	0	1 (<1)	2.7	0	0	2 (<1)	1.9	0	0	1 (<1)	0.8
Stress cardiomyopathy*	1 (<1)	2.1	0	0	1 (<1)	5.1	0	0	0	0	0	0	2 (<1)	1.9	0	0	1 (<1)	0.8
Ventricular tachycardia	1 (<1)	2.1	0	0	0	0	0	0	1 (<1)	2.7	1 (<1)	2.6	2 (<1)	1.9	1 (<1)	0.9	1 (<1)	0.8
Hypotension	0	0	1 (<1)	2.0	0	0	1 (<1)	4.8	1 (<1)	2.7	0	0	1 (<1)	0.9	2 (<1)	1.8	2 (<1)	1.5

	208657				MEA117113				MEA117106				208657 + MEA117113 + MEA117106					
	PBO (N=401) (PY= 483.19)		100 SC (N=403) (PY= 507.43)		PBO (N=226) (PY= 196.23)		100 SC (N=223) (PY= 206.78)		PBO (N=419) (PY= 373.50)		100 SC (N=417) (PY= 383.51)		PBO (N=1046) (PY= 1052.92)		100 SC (N=1043) (PY= 1097.72)		All Doses (N=1268) (PY= 1301.48)	
Preferred Term	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]	n (%)	Rate[1]
Acute coronary syndrome*	0	0	0	0	0	0	0	0	0	0	1 (<1)	2.6	0	0	1 (<1)	0.9	2 (<1)	1.5
Cardiac failure chronic	0	0	0	0	0	0	0	0	1 (<1)	2.7	1 (<1)	2.6	1 (<1)	0.9	1 (<1)	0.9	1 (<1)	0.8
Cor pulmonale	0	0	0	0	0	0	1 (<1)	4.8	1 (<1)	2.7	0	0	1 (<1)	0.9	1 (<1)	0.9	1 (<1)	0.8
Myocardial ischaemia*	1 (<1)	2.1	0	0	0	0	0	0	0	0	1 (<1)	2.6	1 (<1)	0.9	1 (<1)	0.9	1 (<1)	0.8
Supraventricular tachycardia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2 (<1)	1.5
Circulatory collapse	1 (<1)	2.1	1 (<1)	2.0	0	0	0	0	0	0	0	0	1 (<1)	0.9	1 (<1)	0.9	1 (<1)	0.8
Orthostatic hypotension	0	0	0	0	0	0	1 (<1)	4.8	1 (<1)	2.7	0	0	1 (<1)	0.9	1 (<1)	0.9	1 (<1)	0.8
Peripheral arterial occlusive disease	0	0	1 (<1)	2.0	0	0	0	0	0	0	1 (<1)	2.6	0	0	2 (<1)	1.8	2 (<1)	1.5
Cerebral infarction*	1 (<1)	2.1	0	0	0	0	0	0	0	0	1 (<1)	2.6	1 (<1)	0.9	1 (<1)	0.9	1 (<1)	0.8

Note: Exposure-adjusted frequency is calculated as: (Total number of adverse events / Total Duration of Exposure in years)*1000.
Note: Serious CVT events identified from Cardiac disorders SOC, Vascular disorders SOC and SMQs.
*Serious Ischemic events:Subset of Serious CVT events identified through SMQs.
[1] Represents the frequency of events per 1000 participant-years of exposure

A summary of serious CVT events by CV disease comorbidity (No/Yes) is presented below in Table 162 below.

Table 162 On-treatment adverse events of special interest by cardiovascular disease comorbidity: serious cardiac, vascular and thromboembolic events (COPD studies, Safety population)

	208657 + MEA117113 + MEA117106		
	PBO (N=1046)	100 SC (N=1043)	All Doses (N=1268)
Comorbidity NO			
Number of Participants (n) ANY EVENT n (%)	775 27 (3)	781 26 (3)	939 34 (4)
Comorbidity YES			
Number of Participants (n) ANY EVENT n (%)	271 26 (10)	262 26 (10)	329 28 (9)

Note: Comorbidity: Cardiovascular Disease Comorbidity was defined as past/current medical conditions in the Cardiac disorder category recorded on the medical conditions CRF or participants with a history/previous episode of heart failure on the CV Congestive heart failure CRF.

The most frequently reported on-treatment serious CVT event was atrial fibrillation followed by acute MI and cardiac failure congestive; all were reported with a low incidence in the mepolizumab 100 mg group and the placebo group (<1%). The event was considered treatment-related for 1 participant in the placebo group. The most frequently reported Serious ischemic events in the mepolizumab 100 mg group and the placebo group were acute MI and transient ischemic attack (<1% of participants in both groups). None were considered treatment related.

The rate of any on-treatment serious CVT events between treatment groups were not directionally consistent across studies.

In the 3 pooled COPD studies, the incidence of any Serious CVT event was similar between treatment groups for participants with a CV disease comorbidity (10% each for mepolizumab 100 mg group and placebo group) and for participants with no CV disease comorbidity (3% each for mepolizumab 100 mg and placebo group).

Adjudicated MACE

In the 3 pooled COPD studies, a total of 416 potential on- and post-treatment MACE (fatal and non-fatal) in 302 participants were identified for referral to the CEC for adjudication. A summary of On- and post-treatment adjudicated fatal and non-fatal MACE for the 3 COPD studies is presented in Table 163 below.

Table 163 On- and post-treatment adjudicated fatal and non-fatal MACE (COPD studies, Safety population)

	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106		
	PBO (N=401)	100 SC (N=403)	PBO (N=226)	100 SC (N=223)	PBO (N=419)	100 SC (N=417)	PBO (N=1046)	100 SC (N=1043)	All Doses (N=1268)
On- and Post-treatment									
Any MACE	11 (2.7)	11 (2.7)	5 (2.2)	1 (0.4)	6 (1.4)	8 (1.9)	22 (2.1)	20 (1.9)	28 (2.2)
Cardiovascular Death									
Any Event	3 (0.7)	6 (1.5)	4 (1.8)	0	4 (1.0)	3 (0.7)	11 (1.1)	9 (0.9)	14 (1.1)
Acute Myocardial Infarction	1 (0.2)	0	1 (0.4)	0	0	0	2 (0.2)	0	0
STEMI	0	0	1 (0.4)	0	0	0	1 (<0.1)	0	0
NSTEMI	1 (0.2)	0	0	0	0	0	1 (<0.1)	0	0
Unknown	0	0	0	0	0	0	0	0	0
Type 1	1 (0.2)	0	1 (0.4)	0	0	0	2 (0.2)	0	0
Sudden Cardiac Death	1 (0.2)	4 (1.0)	2 (0.9)	0	4 (1.0)	1 (0.2)	7 (0.7)	5 (0.5)	10 (0.8)
Heart Failure	0	1 (0.2)	0	0	0	2 (0.5)	0	3 (0.3) [1]	3 (0.2)
Stroke	0	0	1 (0.4)	0	0	0	1 (<0.1)	0	0
Intracerebral hemorrhage	0	0	1 (0.4)	0	0	0	1 (<0.1)	0	0
Cardiovascular Hemorrhage (Including Non-Stroke Intracranial Hemorrhage)	1 (0.2)	1 (0.2)	0	0	0	0	1 (<0.1)	1 (<0.1)	1 (<0.1)
Ruptured aortic aneurysm	1 (0.2)	0	0	0	0	0	1 (<0.1)	0	0
Other cardiovascular hemorrhage	0	1 (0.2)	0	0	0	0	0	1 (<0.1)	1 (<0.1)
Non-fatal Myocardial Infarction									
Any Event	6 (1.5)	2 (0.5)	2 (0.9)	1 (0.4)	3 (0.7)	3 (0.7)	11 (1.1)	6 (0.6)	8 (0.6)
STEMI	1 (0.2)	1 (0.2)	1 (0.4)	0	0	1 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)
NSTEMI	5 (1.2)	1 (0.2)	1 (0.4)	1 (0.4)	3 (0.7)	1 (0.2)	9 (0.9)	3 (0.3)	5 (0.4)
Unknown	0	0	0	0	0	1 (0.2)	0	1 (<0.1)	1 (<0.1)
Type 1	3 (0.7)	1 (0.2)	2 (0.9)	1 (0.4)	3 (0.7)	3 (0.7)	8 (0.8)	5 (0.5)	6 (0.5)
Type 2	3 (0.7)	1 (0.2)	0	0	0	0	3 (0.3)	1 (<0.1)	2 (0.2)
Non-fatal Stroke									
Any Event	3 (0.7)	3 (0.7)	1 (0.4)	0	0	2 (0.5)	4 (0.4)	5 (0.5)	6 (0.5)
Intracerebral hemorrhage	0	0	1 (0.4)	0	0	0	1 (<0.1)	0	0
Subarachnoid hemorrhage	0	0	0	0	0	0	0	0	0
Ischemic (non-hemorrhagic) stroke	3 (0.7)	3 (0.7)	0	0	0	2 (0.5)	3 (0.3)	5 (0.5)	6 (0.5)

	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106		
	PBO (N=401)	100 SC (N=403)	PBO (N=226)	100 SC (N=223)	PBO (N=419)	100 SC (N=417)	PBO (N=1046)	100 SC (N=1043)	All Doses (N=1268)
Fatal and non-fatal Myocardial Infarction									
Any Event	6 (1.5)	2 (0.5)	2 (0.9)	1 (0.4)	3 (0.7)	3 (0.7)	11 (1.1)	6 (0.6)	8 (0.6)
STEMI	1 (0.2)	1 (0.2)	1 (0.4)	0	0	1 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)
NSTEMI	5 (1.2)	1 (0.2)	1 (0.4)	1 (0.4)	3 (0.7)	1 (0.2)	9 (0.9)	3 (0.3)	5 (0.4)
Unknown	0	0	0	0	0	1 (0.2)	0	1 (<0.1)	1 (<0.1)
Type 1	3 (0.7)	1 (0.2)	2 (0.9)	1 (0.4)	3 (0.7)	3 (0.7)	8 (0.8)	5 (0.5)	6 (0.5)
Type 2	3 (0.7)	1 (0.2)	0	0	0	0	3 (0.3)	1 (<0.1)	2 (0.2)
Fatal and non-fatal Stroke									
Any Event	3 (0.7)	3 (0.7)	1 (0.4)	0	0	2 (0.5)	4 (0.4)	5 (0.5)	6 (0.5)
Intracerebral hemorrhage	0	0	1 (0.4)	0	0	0	1 (<0.1)	0	0
Ischemic (non-hemorrhagic) stroke	3 (0.7)	3 (0.7)	0	0	0	2 (0.5)	3 (0.3)	5 (0.5)	6 (0.5)

Note: STEMI=ST segment elevation myocardial infarction, NSTEMI=Non-ST segment elevation myocardial infarction.
Note: Participants may have multiple conditions leading to death and may have multiple non-fatal events
[1] For 3 participants (ID 102410 in study 208657, ID 009315 and ID 009686 in study MEA117106) in the mepolizumab 100 mg group, fatal events adjudicated in the MACE subcategory heart failure correspond to the 3 fatal SAE reports adjudicated in the Congestive heart failure subcategory (see Table 28).

CMH-adjusted relative risk and risk difference for adjudicated MACE in the 3 COPD studies and analysis of time to first fatal or non-fatal adjudicated MACE is presented in Table 164 and Table 165, respectively, below.

Table 164 Fatal and non-fatal adjudicated MACE: incidence, relative risk and risk difference (COPD studies, Safety population)

				Mepolizumab 100 mg vs Placebo		Mepolizumab All doses vs Placebo	
	PBO (N=1046) n (%)	100 SC (N=1043) n (%)	All Doses (N=1268) n (%)	CMH Adjusted Relative Risk (95% CI)	% Risk Difference (Exact 95% CI)	CMH Adjusted Relative Risk (95% CI)	% Risk Difference (Exact 95% CI)
On-and Post-treatment							
Any MACE	22 (2)	20 (2)	28 (2)	0.91 (0.50,1.66)	-0.2% (-4.5,4.1)	1.05 (0.60,1.82)	0.1% (-4.0,4.2)
Cardiovascular Death	11 (1)	9 (<1)	14 (1)	0.82 (0.34,1.97)	-0.2% (-4.5,4.1)	1.05 (0.48,2.30)	0.1% (-4.0,4.1)
Non-fatal Myocardial Infarction	11 (1)	6 (<1)	8 (<1)	0.55 (0.20,1.47)	-0.5% (-4.8,3.8)	0.60 (0.24,1.49)	-0.4% (-4.5,3.7)
Non-fatal Stroke	4 (<1)	5 (<1)	6 (<1)	1.25 (0.34,4.66)	0.1% (-4.2,4.4)	1.24 (0.35,4.37)	0.1% (-4.0,4.2)
On-treatment							
Any MACE	18 (2)	16 (2)	22 (2)	0.89 (0.46,1.74)	-0.2% (-4.5,4.1)	1.01 (0.54,1.87)	0.0% (-4.1,4.1)
Cardiovascular Death	6 (<1)	7 (<1)	11 (<1)	1.17 (0.39,3.47)	0.1% (-4.2,4.4)	1.51 (0.56,4.08)	0.3% (-3.8,4.4)
Non-fatal Myocardial Infarction	10 (<1)	5 (<1)	7 (<1)	0.50 (0.17,1.46)	-0.5% (-4.8,3.8)	0.58 (0.22,1.51)	-0.4% (-4.5,3.7)
Non-fatal Stroke	3 (<1)	4 (<1)	4 (<1)	1.34 (0.30,5.96)	0.1% (-4.2,4.4)	1.10 (0.25,4.90)	0.0% (-4.1,4.1)

Note: Studies included: 208657, MEA117113 and MEA117106.

Table 165 Analysis of time to first fatal or non- fatal adjudicated MACE (COPD studies, Safety population)

208657 + MEA117113 + MEA117106	PBO (N=1046)	100 SC (N=1043)
On-and Post-treatment		
~By week 52		
Participants with event n(%)	19 (2)	16 (2)
Probability of a MACE[1] (%)	1.9	1.6
95% CI	(1.2, 3.0)	(1.0, 2.6)
Hazard ratio (Mepo/Placebo)[2]		0.88
95% CI		(0.48, 1.61)
Unadjusted p-value		0.668
Event: MACE n (%)	22 (2)	20 (2)
Censored	1024 (98)	1023 (98)
Censored at study withdrawal	159 (15)	113 (11)
Censored at study completion	865 (83)	910 (87)
On-treatment		
~By week 52		
Participants with event n (%)	17 (2)	15 (1)
Probability of a MACE[1] (%)	1.8	1.5
95% CI	(1.1, 2.9)	(0.9, 2.5)
Hazard ratio (Mepo/Placebo) [2]		0.86
95% CI		(0.44, 1.68)
Unadjusted p-value		0.653
Event: MACE n (%)	18 (2)	16 (2)
Censored	1028 (98)	1027 (98)
Censored at study withdrawal	24 (2)	20 (2)
Censored at study completion	110 (11)	119 (11)
Censored at IP end date + 28 days	894 (85)	888 (85)

Note: The meta-analysis includes an additional covariate of study.
[1] Kaplan-Meier estimate
[2] Estimated from Cox Proportional Hazards Model with covariates of treatment group.

In the pooled COPD studies, the incidence of any on- and post-treatment adjudicated MACE was low and similar between the mepolizumab 100 mg (1.9%) and the placebo group (2.1%), with similar observations for on-treatment MACE (1.5% and 1.7%, respectively). Estimates of risk (CMH-adjusted RR, risk difference, and HR for time to first MACE) were consistent with a similar risk of MACE for mepolizumab compared with placebo.

The incidence within each component and subcategory of MACE was low and broadly similar (<0.6% difference) between the treatment groups. Small numerical differences were noted in both directions (non-fatal MI; CV death: Sudden cardiac death; and CV death: Heart failure). The MAH conducted an internal review of all available participant information for adjudicated Sudden cardiac death and Heart failure and concluded that data did not support a plausible causal association between mepolizumab and these events.

Overview of CV safety

The CV safety profile of mepolizumab in the treatment of COPD was evaluated on the basis of a review of:

- Investigator reported on-treatment CV AESI (presented in the *Adverse events of special interest* section of the Clinical Safety section of this report) and analysis of CV-related additional medical concepts (presented in the *Serious adverse event/deaths/other significant events* section of the Clinical Safety section of this report) including the post-hoc analysis of Cardiac failure, for the 3 pooled COPD studies
- Adjudicated on- and post-treatment SAE reports with a CV primary cause (presented in the *Serious adverse event/deaths/other significant events* section of the Clinical Safety section of this report)
- Adjudicated MACE (presented in the *Adverse events of special interest* section of the Clinical Safety section of this report)

A summary of the data derived from the above evaluations are provided in Table 166 below.

Table 166 Overview of CV safety (COPD studies, Safety Population)

	208657 + MEA117113 + MEA117106							
	On- and post-treatment			On-treatment				
	PBO (N=1046) n (%)	100 SC (N=1043) n (%)	% risk difference (exact 95% CI)	PBO (N=1046) n (%)	Rate[1]	100 SC (N=1043) n (%)	Rate[1]	% risk difference (exact 95% CI)
Investigator reported AEs								
AESI								
Cardiac Disorders				89 (9)	[114.9]	87 (8)	[106.6]	-0.2% (-4.5,4.1)
Serious Cardiac Disorders				37 (4)	[41.8]	39 (4)	[41.9]	0.2% (-4.1,4.5)
Serious CVT Events				53 (5)	[61.7]	52 (5)	[61.0]	-0.1% (-4.4,4.2)
Serious Ischemic Events				23 (2)	[21.8]	16 (2)	[14.6]	-0.7% (-5.0,3.6)
FMQ/SMQs								
Thrombosis FMQ				26 (2)	[26.6]	19 (2)	[20.0]	-0.4% (-4.5,3.7)
Thrombosis venous FMQ				5 (<1)	[4.7]	6 (<1)	[5.5]	0.2% (-3.9,4.2)
Systemic Hypertension FMQ				43 (4)	[48.4]	50 (5)	[47.4]	0.5% (-3.6,4.6)
Supraventricular Tachyarrhythmias SMQ				24 (2)	[28.5]	26 (2)	[26.4]	0.5% (-3.5,4.6)
Cardiac failure SMQ (post-hoc)	55 (5)	63 (6)	0.8% (-3.5,5.1)	50 (5)	[53.2]	58 (6)	[60.1]	0.8% (-3.5,5.1)
Serious cardiac failure SMQ	10 (<1)	14 (1)	0.4% (-3.9,4.7)	10 (<1)	[10.4]	12 (1)	[12.8]	0.2% (-4.1,4.5)
Adjudicated events								
Any SAE reports with CV primary cause, n (%)								
Fatal and non-fatal	54 (5)	48 (5)						
Sudden death	6 (<1)	4 (<1)						
Myocardial infarction/ischemic heart disease	11 (1)	11 (1)						
Congestive heart failure	6 (<1)	14 (1)						
Stroke	4 (<1)	3 (<1)						
Other cardiovascular cause	29 (3)	20 (2)						
Fatal	11 (1)	8 (<1)						
Non-fatal	44 (4)	42 (4)						
Any MACE	22 (2.1)	20 (1.9)	-0.2% (-4.5,4.1)	18 (1.7)		16 (1.5)		-0.2% (-4.5,4.1)
CV Death	11 (1)	9 (<1)	-0.2% (-4.5,4.1)	6 (<1)		7 (<1)		0.1% (-4.2,4.4)
Non-fatal MI	11 (1)	6 (<1)	-0.5% (-4.8,3.8)	10 (<1)		5 (<1)		-0.5% (-4.8,3.8)
Non-fatal Stroke	4 (<1)	5 (<1)	0.1% (-4.2,4.4)	3 (<1)		4 (<1)		0.1% (-4.2,4.4)
Time to first MACE								

	208657 + MEA117113 + MEA117106							
	On- and post-treatment			On-treatment				
	PBO (N=1046) n (%)	100 SC (N=1043) n (%)	% risk difference (exact 95% CI)	PBO (N=1046) n (%)	Rate[1]	100 SC (N=1043) n (%)	Rate[1]	% risk difference (exact 95% CI)
First MACE by Week 52, n (%)	19 (2)	16 (2)		17 (2)		15 (1)		
% Probability of a MACE[2] (95% CI)	1.9% (1.2, 3.0)	1.6% (1.0, 2.6)		1.8% (1.1, 2.9)		1.5% (0.9, 2.5)		
HR (mepo/placebo)[3] (95% CI)		HR 0.88 (0.48, 1.61)				HR 0.86 (0.44, 1.68)		

Note: The meta-analysis includes an additional covariate of study.
Note: Exposure-adjusted frequency is calculated as: (Total number of adverse events / Total Duration of Exposure in years)*1000.
[1] Represents the frequency of events per 1000 participant-years of exposure.
[2] Kaplan-Meier estimate
[3] Estimated from Cox Proportional Hazards Model with covariates of treatment group.

Adverse drug reactions

Inferential and descriptive analytical criteria were used to triage AEs from across the 3 pooled COPD studies for further qualitative analyses. Medical judgement was used in determining and establishing reasons to support or refute causal association for AEs identified through quantitative analyses.

From review of all safety data across the 3 pooled COPD studies, no new AEs were identified as adverse drug reactions beyond those already identified from the wider clinical development program and post-marketing experience.

Laboratory findings, vital signs, and other

Clinical chemistry

Clinical chemistry changes from baseline relative to normal range any time post-baseline (incidence >10% in any treatment group) in the 3 pooled COPD studies are shown in Table 167.

Most participants in the mepolizumab 100 mg and placebo group had no changes in values outside the normal range for the majority of clinical chemistry parameters at any time post-baseline. Of the participants with clinical chemistry shifts, values of potential clinical concern were observed at any time post-baseline in <1% of participants in both groups. These shifts were similar between the 2 groups.

Table 167 Clinical chemistry changes from baseline relative to normal range any time post-baseline (incidence >10% in any treatment group) (COPD studies, Safety population)

		208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106		
Clinical Chemistry Parameter	Change Category	PBO (N=401)	100 SC (N=403)	PBO (N=226)	100 SC (N=223)	PBO (N=419)	100 SC (N=417)	PBO (N=1046)	100 SC (N=1043)	All Doses (N=1268)
Alanine Aminotransferase	To High	41/391 (10)	36/394 (9)	24/221 (11)	10/218 (5)	19/409 (5)	17/409 (4)	84/1021 (8)	63/1021 (6)	80/1245 (6)
Alkaline Phosphatase	To High	46/391 (12)	48/394 (12)	9/221 (4)	7/218 (3)	28/409 (7)	19/409 (5)	83/1021 (8)	74/1021 (7)	94/1245 (8)
C Reactive Protein	To High	-	-	45/199 (23)	44/210 (21)	84/374 (22)	72/382 (19)	129/573 (23)	116/592 (20)	146/799 (18)
Calcium	To Low	55/391 (14)	46/395 (12)	3/210 (1)	6/216 (3)	6/401 (1)	9/399 (2)	64/1002 (6)	61/1010 (6)	68/1227 (6)
	To High	50/391 (13)	42/395 (11)	2/210 (<1)	5/216 (2)	9/401 (2)	13/399 (3)	61/1002 (6)	60/1010 (6)	66/1227 (5)
Cholesterol	To High	0	0	24/200 (12)	28/211 (13)	52/377 (14)	44/381 (12)	76/577 (13)	72/592 (12)	101/801 (13)
Creatinine	To Low	24/391 (6)	20/395 (5)	17/210 (8)	18/216 (8)	36/401 (9)	47/399 (12)	77/1002 (8)	85/1010 (8)	112/1227 (9)
	To High	72/391 (18)	56/395 (14)	3/210 (1)	7/216 (3)	8/401 (2)	15/399 (4)	83/1002 (8)	78/1010 (8)	80/1227 (7)
Glucose	To Low	71/391 (18)	72/395 (18)	11/210 (5)	9/216 (4)	17/401 (4)	18/399 (5)	99/1002 (10)	99/1010 (10)	106/1227 (9)
	To High	151/391 (39)	133/395 (34)	27/210 (13)	33/216 (15)	48/401 (12)	35/399 (9)	226/1002(23)	201/1010 (20)	238/1227 (19)
Ldl Cholesterol	To High	0	0	21/200 (11)	19/210 (9)	45/376 (12)	40/380 (11)	66/576 (11)	59/590 (10)	88/797 (11)
Potassium	To High	81/391 (20)	89/394 (23)	14/210 (7)	7/216 (3)	12/401 (3)	20/399 (5)	107/1002 (11)	116/1009 (11)	122/1226 (10)
Triglycerides	To High	0	0	22/200 (11)	21/211 (10)	24/377 (6)	26/381 (7)	46/577 (8)	47/592 (8)	70/801 (9)
Urea	To High	90/391 (23)	72/395 (18)	12/210 (6)	5/216 (2)	23/401 (6)	27/399 (7)	125/1002 (12)	104/1010 (10)	112/1227 (9)
Vldl Cholesterol	To High	0	0	21/200 (11)	21/210 (10)	28/376 (7)	28/380 (7)	49/576 (9)	49/590 (8)	72/797 (9)

Note: Studies included: 2208657, MEA117106 and MEA117113
Participants are counted in the category that their value changes to (low, normal or high). Where category remains unchanged (e.g., High to High), or becomes normal, these are recorded in the "To Normal or No Change" category.
Note: Participants may be counted in more than one category. Participants with missing baseline values are assumed to have normal baseline value.

Liver function tests and liver events

In the 3 pooled COPD studies, in total ≤1% of participants in both the mepolizumab 100 mg group (2 of 1043 participants) and the placebo group (11 of 1046 participants) had abnormal liver functions tests that met protocol-specified liver monitoring criteria. No participants in the mepolizumab 100 mg group had liver function tests that met the liver stopping criteria. In the placebo group 3 of 11 participants had liver function tests that met the stopping criteria. All events occurred while participants were on-treatment, and all resolved.

In the 3 pooled COPD studies, <1% of participants had elevations in ALT, ALP or bilirubin. The incidence of abnormal liver function tests was broadly similar in the mepolizumab 100 mg group and the placebo group.

Haematology

In the 3 pooled COPD studies, few participants in the mepolizumab and placebo groups had changes in values to outside the normal range for the majority of hematology parameters (Table 168). In participants with hematology shifts, at any time post-baseline, values of potential clinical concern were observed in <1% participants in both the mepolizumab 100 mg group and the placebo group. These shifts occurred for hematocrit, hemoglobin, leukocytes and platelets, and the incidence was similar (<1% participants) between the 2 groups.

Table 168 Haematology changes from baseline relative to normal range any time post-baseline (incidence >20% in any treatment group) (COPD studies, Safety population)

		208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106		
Hematology Parameter	Change From Baseline	PBO (N=401)	100 SC (N=403)	PBO (N=226)	100 SC (N=223)	PBO (N=419)	100 SC (N=417)	PBO (N=1046)	100 SC (N=1043)	All Doses (N=1268)
Eosinophils	To Low	41/394 (10)	240/397(60)	56/220 (25)	180/220 (82)	125/408 (31)	341/414(82)	222/1022 (22)	761/1031 (74)	954/1255(76)
	To High	111/394 (28)	11/397 (3)	44/220 (20)	6/220 (3)	64/408 (16)	9/414 (2)	219/1022 (21)	26/1031 (3)	30/1255 (2)
Eosinophils/Leukocytes	To High	118/394 (30)	15/397 (4)	44/220 (20)	4/220 (2)	70/408 (17)	7/414 (2)	232/1022 (23)	26/1031 (3)	28/1255 (2)
Erythrocytes. Mean Corpuscular Hgb Concentration	To Low	0	0	115/220 (52)	122/220 (55)	225/409 (55)	226/414 (55)	340/629 (54)	348/634 (55)	453/858 (53)
Erythrocytes Distribution Width	To High	140/394 (36)	131/397 (33)	88/220 (40)	94/220 (43)	164/409 (40)	163/414 (39)	392/1023 (38)	388/1031(38)	457/1255 (36)
Hematocrit	To High	69/394 (18)	58/397 (15)	49/220 (22)	52/220 (24)	90/409 (22)	91/414 (22)	208/1023 (20)	201/1031 (19)	259/1255 (21)
Leukocytes	To High	117/394 (30)	69/397 (17)	70/220 (32)	76/220 (35)	134/408 (33)	129/414 (31)	321/1022 (31)	274/1031 (27)	353/1255 (28)
Lymphocytes Atypical/Leukocytes	To High	1/3 (33)	1/3 (33)	0	0	0	0	1/3 (33)	1/3 (33)	1/3 (33)
Lymphocytes/Leukocytes	To Low	121/394 (31)	104/397(26)	82/220 (37)	75/220 (34)	163/408 (40)	148/414 (36)	366/1022 (36)	327/1031 (32)	398/1255(32)
Monocytes	To Low	58/394 (15)	50/397 (13)	46/220 (21)	72/220 (33)	93/408 (23)	86/414 (21)	197/1022 (19)	208/1031 (20)	257/1255 (20)
Neutrophils	To High	92/394 (23)	76/397 (19)	74/220 (34)	83/220 (38)	148/408 (36)	143/414 (35)	314/1022 (31)	302/1031 (29)	385/1255 (31)
Neutrophils Band Form	To High	0	0	0	0	3/4 (75)	5/12 (42)	3/6 (50)	5/14 (36)	6/15 (40)
Neutrophils Band Form/Leukocytes	To High	0	0	0	0	1/4 (25)	3/12 (25)	1/5 (20)	3/14 (21)	4/15 (27)
Neutrophils, Segmented	To High	0	0	74/220 (34)	82/220 (37)	148/408 (36)	143/414 (35)	222/628 (35)	225/634 (35)	308/858 (36)
Neutrophils, Segmented/Leukocytes	To High	122/394 (31)	134/397 (34)	94/220 (43)	108/220 (49)	178/408 (44)	190/414 (46)	394/1022 (39)	432/1031 (42)	536/1255 (43)

		208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106		
Hematology Parameter	Change From Baseline	PBO (N=401)	100 SC (N=403)	PBO (N=226)	100 SC (N=223)	PBO (N=419)	100 SC (N=417)	PBO (N=1046)	100 SC (N=1043)	All Doses (N=1268)
Neutrophils/Leukocytes	To High	122/394 (31)	134/397 (34)	94/220 (43)	108/220 (49)	178/408 (44)	190/414 (46)	394/1022 (39)	432/1031(42)	535/1255 (43)

Note: Studies included: 205687, MEA117106 and MEA117113
Participants are counted in the category that their value changes to (low, normal or high). Where category remains unchanged (e.g., High to High), or becomes normal, these are recorded in the "To Normal or No Change" category.
Note: Participants may be counted in more than one category. Participants with missing baseline values are assumed to have normal baseline value.

Vital signs

No treatment-related or dose-related trends were observed in vital sign assessments in each individual COPD study.

Electrocardiograms

ECG findings

In the 3 pooled COPD studies, at baseline, abnormal, clinically significant ECG findings were reported in <1% (6 of 1043) of participants in the mepolizumab 100 mg group and 1% (13 of 1046) of participants in the placebo group. At any visit post-baseline, where the worst-case finding was reported for each participant, abnormal, clinically significant findings were reported for 3% participants in both the mepolizumab 100 mg (24 of 1043) group and the placebo group (29 of 1046).

In the 3 pooled COPD studies, mean baseline ECG values were similar between the mepolizumab 100 mg and placebo group. Over the 52-week treatment period (and the 104-week treatment period for study 208657), mean changes from baseline in all ECG measures were small and similar across the treatment groups.

mean baseline ECG values were similar between the mepolizumab 100 mg and placebo group. Over the 52-week treatment period (and the 104-week treatment period for study 208657), mean changes from baseline in all ECG measures were small and similar across the treatment groups.

QTc intervals

In the 3 pooled COPD studies, the percentage of participants who had maximum increases ≥30 msec - 60 msec from baseline was the same (8%) in both treatment groups (79 of 1043 in the mepolizumab 100 mg group and 82 of 1046 in the placebo group). Less than 1% participants in the mepolizumab 100 mg group and 1% in the placebo group had a change in QTcF of 60 msec or greater.

Immunogenicity

Incidence and characterization of anti-mepolizumab antibodies

In the 3 pooled COPD studies, at any time post-baseline, 2% (34 of 990) of participants in the mepolizumab 100 mg group had treatment-emergent positive results for ADA, with 1% (14 of 990) of participants being transiently positive and 2% (20 of 990) of participants being persistently positive. The titer values were generally low (i.e., the minimum titer possible is 2), with a median titer value of 24 (range: 2 to 128) and no study participant showing increasing titer values at the respective study timepoints. None of the ADA positive participants (0 of 36) tested positive for NAb post-baseline.

Similar immunogenicity incidences were observed across the 3 individual COPD studies.

Association of anti-mepolizumab antibodies to adverse events

On-treatments AEs were presented by SOC by ADA status. The number of participants with a transient positive result or a persistent positive result post-baseline was too small to make meaningful comparisons across subgroups or to the overall population. In general, in the 3 pooled COPD studies, the ADA positive participants in the mepolizumab 100 mg group reported a similar profile of AEs as observed in ADA negative participants.

No systemic reactions or local injection site reactions were reported for study participants with positive ADA results.

Overall, similar incidences of AEs in ADA negative and ADA positive were observed between the 3 COPD studies.

Safety in special populations

Intrinsic factors

GENDER

In the 3 pooled COPD studies, incidences of any AEs were generally similar between mepolizumab 100 mg group and the placebo group within each gender subgroup.

The incidence of any AEs was greater in females (81% in the mepolizumab 100 mg group and 83% in the placebo group) than males (76% in the mepolizumab 100 mg group and 77% in the placebo group) (Table S.44). The incidence of AEs reported under almost all SOCs was higher in females. Differences between gender subgroups were greater than 5% in the mepolizumab 100 mg group for SOCs Infections and infestations (53% versus 47%, female versus male), Respiratory, thoracic and mediastinal disorders (37% versus 30%, female versus male), Musculoskeletal and connective

tissue disorders (28% versus 20%, female versus male) and Gastrointestinal disorders (24% versus 18%, female versus male).

Table 169 On-treatment adverse events by selected System Organ Class by gender (COPD studies, Safety population)

System Organ Class	208657 + MEA117106 + MEA117113		
	PBO (N=1046) n (%)	100 SC (N=1043) n (%)	All Doses (N=1268) n (%)
Female, Ns	352	378	445
ANY EVENT	293 (83)	308 (81)	366 (82)
Infections and infestations	179 (51)	201 (53)	231 (52)
Respiratory, thoracic and mediastinal disorders	117 (33)	141 (37)	171 (38)
Musculoskeletal and connective tissue disorders	91 (26)	106 (28)	124 (28)
Gastrointestinal disorders	80 (23)	91 (24)	113 (25)
Nervous system disorders	80 (23)	70 (19)	82 (18)
General disorders and administration site conditions	61 (17)	60 (16)	81 (18)
Injury, poisoning and procedural complications	40 (11)	55 (15)	62 (14)
Cardiac disorders	21 (6)	23 (6)	26 (6)
Skin and subcutaneous tissue disorders	38 (11)	32 (8)	37 (8)
Vascular disorders	26 (7)	27 (7)	35 (8)
Investigations	23 (7)	28 (7)	34 (8)
Metabolism and nutrition disorders	27 (8)	27 (7)	33 (7)
Psychiatric disorders	24 (7)	29 (8)	34 (8)
Renal and urinary disorders	14 (4)	21 (6)	23 (5)
Eye disorders	15 (4)	11 (3)	13 (3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (2)	10 (3)	12 (3)
Blood and lymphatic system disorders	8 (2)	13 (3)	14 (3)
Ear and labyrinth disorders	13 (4)	10 (3)	11 (2)
Immune system disorders	11 (3)	11 (3)	15 (3)
Reproductive system and breast disorders	2 (<1)	4 (1)	4 (<1)
Hepatobiliary disorders	6 (2)	7 (2)	7 (2)
Endocrine disorders	3 (<1)	5 (1)	5 (1)
Congenital, familial and genetic disorders	0	1 (<1)	2 (<1)
Male, Ns	694	665	823
ANY EVENT	535 (77)	507 (76)	640 (78)
Infections and infestations	334 (48)	315 (47)	398 (48)
Respiratory, thoracic and mediastinal disorders	218 (31)	198 (30)	239 (29)
Musculoskeletal and connective tissue disorders	131 (19)	131 (20)	163 (20)
Gastrointestinal disorders	108 (16)	118 (18)	150 (18)
Nervous system disorders	103 (15)	104 (16)	128 (16)
General disorders and administration site conditions	95 (14)	90 (14)	111 (13)
Injury, poisoning and procedural complications	68(10)	50(8)	63(8)
Cardiac disorders	68 (10)	64 (10)	82 (10)
Skin and subcutaneous tissue disorders	39 (6)	50 (8)	67 (8)
Vascular disorders	55 (8)	58 (9)	64 (8)
Investigations	53 (8)	39 (6)	58 (7)
Metabolism and nutrition disorders	53 (8)	48 (7)	54 (7)
Psychiatric disorders	25 (4)	21 (3)	29 (4)
Renal and urinary disorders	37 (5)	25 (4)	32 (4)
Eye disorders	33 (5)	30 (5)	34(4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	30 (4)	19 (3)	23 (3)
Blood and lymphatic system disorders	22 (3)	16 (2)	18 (2)
Ear and labyrinth disorders	14 (2)	18 (3)	21 (3)
Immune system disorders	9 (1)	8 (1)	12 (1)
Reproductive system and breast disorders	20 (3)	16 (2)	18 (2)
Hepatobiliary disorders	17 (2)	13 (2)	13 (2)
Endocrine disorders	3 (<1)	2 (<1)	2 (<1)
Congenital, familial, and genetic disorders	2 (<1)	1 (<1)	1 (<1)

Note: Ns indicates the number of participants falling within sex category.

AGE

In the 3 pooled COPD studies, the incidence of any AEs in all SOCs were broadly similar for the mepolizumab 100 mg group and the placebo group within both the 40 to <65 years old and ≥65 years old categories. The SOC AE profile for participants in the 40 to <65 years and ≥65 years and older categories was similar to the overall population.

The SOC with the largest difference between the age subgroups in the mepolizumab 100 mg group was Cardiac disorders which were more frequently reported in elderly participants (11% in the mepolizumab 100 mg group and 10% in the placebo group) compared with adults 40 to <65 years of age (5% in the mepolizumab 100 mg group and 7% in the placebo group). In other SOCs, differences between age subgroups were not more than 4% in the mepolizumab 100 mg group.

RACE

In the 3 pooled COPD studies, the AE profile of the 5 most frequently reported SOCs for White race and Asian participants was similar to the AE profile of these SOCs in the overall COPD population. Incidences of any event in the other SOCs were low and difficult to interpret.

For White, Asian and Other races, the incidence of any AEs in all SOCs were broadly similar for the mepolizumab 100 mg group and the placebo group.

The number of African American participants (n=29) enrolled in the COPD studies was small (n=14 in PBO; n=13 in mepolizumab 100 SC; n=15 in mepolizumab All Doses), making meaningful interpretation of differences in incidence between mepolizumab 100 mg group and the placebo group difficult. However, there were no notable numerical imbalances observed between placebo and mepolizumab 100 mg groups in the reporting of AEs with the exception of SOC Musculoskeletal and connective tissue disorder (n=0 in PBO; n=4 in mepolizumab 100 SC). Of those 4 AEs, no PT was reported more than once.

REGION

In the 3 pooled COPD studies, the SOC AE profile was similar for participants from different regions (Europe, US) with the overall COPD population. The incidence of any AEs in all SOCs were broadly similar for the mepolizumab 100 mg group and the placebo group for these regions. The most frequently reported PTs were COPD and nasopharyngitis in the Europe participants and COPD and pneumonia in US participants.

Extrinsic factors

Study 208657 was conducted during the COVID-19 pandemic, while studies MEA117113 and MEA117106 were completed prior to the pandemic. COVID-19 was not reported in studies MEA117113 and MEA117106.

In study 208657, AEs of COVID-19 were reported with similar incidences (12% in each) and EAIRs in the mepolizumab 100 mg group (108.4 events per 1000 PY) and in the placebo group (103.5 events per 1000 PY). SAEs of COVID-19 were reported with similar incidences (<1% in each) and EAIRs in the mepolizumab 100 mg group (7.9 events per 1000 PY) and in the placebo group (8.3 events per 1000 PY).

AEs of COVID-19 leading to permanent discontinuation of study treatment were reported by <1% participants in each mepolizumab 100 mg (1 of 1043) and the placebo group (1 of 1046). On-treatment AEs of COVID-19 leading to withdrawal from the study was reported by <1% participants (3 of 1043) in the mepolizumab 100 mg group and none in the placebo group. On-and

post-treatment AEs of COVID-19 leading to withdrawal from study were reported by <1% participants in each mepolizumab 100 mg group (3 of 1043) and the placebo group (1 of 1046).

Pregnancy

No pregnancies were reported during the conduct of any of the COPD studies.

Based on safety data (cut-off date of 22 July 2024) from completed and ongoing clinical studies across all indications and post-marketing reports, there are approximately 461 exposures to mepolizumab during pregnancy, with 159 documented pregnancy outcomes. Based on the information provided, there were no trends of concern in the pregnancy outcomes reported. An internal review of clinical and post-marketing data did not reveal any new significant safety information related to the use of mepolizumab in pregnant or lactating patients.

Safety related to drug-drug interactions and other interactions

Mepolizumab is considered to have a low potential for drug-drug interactions because it selectively binds and neutralizes the cytokine IL-5. There are no reports of IL-5 receptors being expressed on hepatocytes. Neutralization of IL-5 is, therefore, not expected to alter gene expression of cytochrome P450 or transporters. Therefore, no formal drug interaction studies have been conducted.

Study treatment discontinuation

A summary of participant study treatment discontinuation in the pooled COPD studies and in Study 208657 (by fixed and variable duration) is provided in Table 170 and Table 171, respectively.

Table 170 Study treatment completion status (COPD studies, Safety population)

	208657		MEA117113		MEA117106		208657 + MEA117113 + MEA117106			
n (%)	PBO (N=401)	100 SC (N=403)	PBO (N=226)	100 SC (N=223)	PBO (N=419)	100 SC (N=417)	PBO (N=1046)	100 SC (N=1043)	All Doses (N=1268)	Total (N=2314)
Study treatment completion status										
Completed study treatment as scheduled	314 (78)	326 (81)	170 (75)	196 (88)	333 (79)	352 (84)	817 (78)	874 (84)	1057 (83)	1874 (81)
Withdrew early from study treatment	87 (22)	77 (19)	56 (25)	27 (12)	86 (21)	65 (16)	229 (22)	169 (16)	211 (17)	440 (19)
Prematurely discontinued study treatment and study at the same time	38 (9)	42 (10)	35 (15)	9 (4)	47 (11)	42 (10)	120 (11)	93 (9)	116 (9)	236 (10)
Prematurely discontinued study treatment and continued in study	49 (12)	35 (9)	21 (9)	18 (8)	39 (9)	23 (6)	109 (10)	76 (7)	95 (7)	204 (9)
Completed study with off-treatment assessments	19 (5)	15 (4)	16 (7)	12 (5)	32 (8)	18 (4)	67 (6)	45 (4)	59 (5)	126 (5)
Did not complete study	30 (7)	20 (5)	5 (2)	6 (3)	7 (2)	5 (1)	42 (4)	31 (3)	36 (3)	78 (3)
Primary reason for discontinuation of study treatment/ Subreason for discontinuation of study treatment[1,2]										
Adverse event: No subreasons	12 (3)	12 (3)	0	0	0	0	12 (1)	12 (1)	12 (<1)	24 (1)
Lack of efficacy: No subreasons	8 (2)	1 (<1)	0	0	0	0	8 (<1)	1 (<1)	1 (<1)	9 (<1)
Participant reached protocol-defined stopping criteria: No subreasons	1 (<1)	1 (<1)	0	0	0	0	1 (<1)	1 (<1)	1 (<1)	2 (<1)
Adverse event	21 (5)	21 (5)	27 (12)	9 (4)	35 (8)	29 (7)	83 (8)	59 (6)	84 (7)	167 (7)
Death	9 (2)	9 (2)	5 (2)	2 (<1)	8 (2)	14 (3)	22 (2)	25 (2)	32 (3)	54 (2)
Lack of efficacy	13 (3)	2 (<1)	6 (3)	2 (<1)	13 (3)	4 (<1)	32 (3)	8 (<1)	10 (<1)	42 (2)
Exacerbation	5 (1)	1 (<1)	3 (1)	2 (<1)	2 (<1)	1 (<1)	10 (<1)	4 (<1)	4 (<1)	14 (<1)
Protocol deviation	1 (<1)	0	2 (<1)	0	4 (<1)	3 (<1)	7 (<1)	3 (<1)	4 (<1)	11 (<1)
Participant reached protocol-defined stopping criteria	3 (<1)	2 (<1)	1 (<1)	1 (<1)	0	1 (<1)	4 (<1)	4 (<1)	4 (<1)	8 (<1)
ECG abnormality	0	1 (<1)	0	1 (<1)	0	1 (<1)	0	3 (<1)	3 (<1)	3 (<1)
Liver function test abnormality	2 (<1)	0	1 (<1)	0	0	0	3 (<1)	0	0	3 (<1)
Lost to follow-up	1 (<1)	2 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)	3 (<1)	5 (<1)	6 (<1)	9 (<1)
Physician decision	5 (1)	5 (1)	2 (<1)	3 (1)	6 (1)	3 (<1)	13 (1)	11 (1)	12 (<1)	25 (1)
Withdrawal by participant	41 (10)	44 (11)	16 (7)	11 (5)	27 (6)	23 (6)	84 (8)	78 (7)	89 (7)	173 (7)
Investigator site closed	1 (<1)	0	1 (<1)	0	0	0	2 (<1)	0	1 (<1)	3 (<1)

Note: In 208657, participant 100642 in 100 SC group died after completing treatment and has a non-missing reason for withdrawal. This participant appears in both Study treatment completion status as completer and in Primary reason for discontinuation panel. Participants 100508 and 101561 in 100 SC group and 100521 in Placebo group have missing reason for discontinuation of study treatment.

1. Participants may have only one primary reason.
2. Participants are not required to indicate subreasons, if given there may be more than one subreason.

Table 171 Study 208657 treatment status and reasons for discontinuation of study treatment (mITT Population) by fixed and variable duration

	Overall		Fixed Duration (Enrolled for 52 weeks)		Variable Duration (Enrolled for up to 104 weeks)	
	PBO (N=401)	Mepo 100 mg (N=403)	PBO (N=175)	Mepo 100 mg (N=170)	PBO (N=226)	Mepo 100 mg (N=233)
Study treatment completion status, n (%)						
Completed study treatment as scheduled	314 (78)	326 (81)	143 (82)	141 (83)	171 (76)	185 (79)
Withdrew early from study treatment	87 (22)	77 (19)	32 (18)	29 (17)	55 (24)	48 (21)
Prematurely discontinued study treatment and study at the same time	38 (9)	42 (10)	18 (10)	13 (8)	20 (9)	29 (12)
Prematurely discontinued study treatment and continued in study	49 (12)	35 (9)	14 (8)	16 (9)	35 (15)	19 (8)
Completed study with off-treatment assessments	19 (5)	15 (4)	6 (3)	7 (4)	13 (6)	8 (3)
Did not complete study	30 (7)	20 (5)	8 (5)	9 (5)	22 (10)	11 (5)
Primary reason for discontinuation of study treatment [1]/ subreason for discontinuation of study treatment [2], n (%)						
Adverse event	21 (5)	21 (5)	7 (4)	11 (6)	14 (6)	10 (4)
Death	9 (2)	9 (2)	4 (2)	4 (2)	5 (2)	5 (2)
No Subreasons	12 (3)	12 (3)	3 (2)	7 (4)	9 (4)	5 (2)
Lack of efficacy	13 (3)	2 (<1)	4 (2)	2 (1)	9 (4)	0
Exacerbation	5 (1)	1 (<1)	2 (1)	1 (<1)	3 (1)	0
No Subreasons	8 (2)	1 (<1)	2 (1)	1 (<1)	6 (3)	0
Protocol deviation	1 (<1)	0	0	0	1 (<1)	0
Participant reached protocol-defined stopping criteria	3 (<1)	2 (<1)	2 (1)	0	1 (<1)	2 (<1)
ECG abnormality	0	1 (<1)	0	0	0	1 (<1)
Liver function test abnormality	2 (<1)	0	2 (1)	0	0	0
No Subreasons	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Lost to follow-up	1 (<1)	2 (<1)	1 (<1)	1 (<1)	0	1 (<1)
Physician decision	5 (1)	5 (1)	3 (2)	2 (1)	2 (<1)	3 (1)
Withdrawal by participant	41 (10)	44 (11)	13 (7)	12 (7)	28 (12)	32 (14)
Investigator site closed	1 (<1)	0	1 (<1)	0	0	0

[1] Participants might have had only one primary reason. [2] Participants were not required to indicate subreasons, if given there may be more than one subreason.
Note: 2/2 (placebo/mepolizumab) participants completed treatment as scheduled but later withdrew from the study.
Note: Participant 100642 in the mepolizumab 100 mg group died after completing study treatment and has a non-missing reason for withdrawal (death) (Listing 4). This participant appears in both study treatment completion status as completer and in primary reason for discontinuation panel. Participants 100508 and 101561 in mepolizumab 100 mg group and 100521 in placebo group have missing reason for discontinuation of study treatment (Source: Analysis Disposition [ADDS] Data).

Discontinuation due to adverse events

Adverse Events Leading to Permanent Discontinuation of Study Treatment

The incidence and EAIR of any on-treatment AEs leading to treatment discontinuation were similar between the mepolizumab 100 mg group (5%, 56.5 events per 1000 PY) and the placebo group (7%, 79.8 events per 1000 PY). In study MEA117113, the incidence and EAIR of any on-treatment AE leading to treatment discontinuation were lower in the mepolizumab 100 mg group (4%; 53.2 events per 1000 PY) compared with the placebo group (12%, 158 events per 1000 PY) while these were similar between the mepolizumab 100 mg group and the placebo group in studies 208657 and MEA117106.

The most frequently reported on-treatment AE leading to treatment discontinuation was COPD exacerbations, which was reported by <1% (9 of 1043) of participants in the mepolizumab 100 mg group and 1% (14 of 1046) in the placebo group, followed by pneumonia and respiratory failure.

Adverse Events Leading to Withdrawal from the Study

The incidence and EAIR of any on-treatment AEs leading to study withdrawal were similar between the mepolizumab 100 mg group (3%, 38.3 events per 1000 PY) and the placebo group (4%; 47.5 events per 1000 PY). The most frequently reported on-treatment AE leading to study withdrawal was under SOC Respiratory, thoracic and mediastinal disorders: COPD exacerbations: <1% of participants in both the mepolizumab 100 mg group (6 of 1043) and the placebo group (8 of 1046);Pneumonia: <1% of participants in both the mepolizumab 100 mg group (2 of 1043) and the placebo group (4 of 1046).

In study MEA117113, the incidence and EAIR of any AE leading to study withdrawal were lower in the mepolizumab 100 mg group (2%, 24.2 events per 1000 PY) compared with the placebo group (7%, 96.8 events per 1000 PY). Incidence and exposure-adjusted rate were similar between the mepolizumab 100 mg group and the placebo group in studies 208657 and MEA117106.

Incidences of on- and post-treatment AEs leading to study withdrawal were similar between the mepolizumab 100 mg group (4% [40 of 1043]) and the placebo group (5% [55 of 1046]).

Withdrawal and rebound

In all 3 COPD studies, if a participant withdrew from study treatment, investigators made reasonable attempts to keep the participant in the study until completion. There was no follow-up period in study 208657. For studies MEA117113 and MEA117106, there was a post-treatment follow-up period to evaluate AEs following discontinuation of study treatment.

The incidence of post-treatment AEs was similar between the mepolizumab 100 mg group and the placebo group (14% and 15%, respectively) in the COPD studies. The most common post-treatment AE was COPD exacerbation, which was reported at a similar incidence in the mepolizumab 100 mg group and the placebo group (2% and 3%, respectively). The incidence of post-treatment AEs of COPD exacerbation was lower compared with the incidence of on-treatment AEs of COPD exacerbation in the mepolizumab 100 mg group (19%) and the placebo group (21%). There were no verbatim reports of 'rebound' of disease.

Post marketing experience

As of the data cut-off date for the most recent PBRER/EU-PSUR submitted to regulatory authorities at the time of authoring (23 March 2024), mepolizumab is approved for SEA, CRSwNP, EGPA, and HES. The cumulative exposure to mepolizumab in the postmarketing setting is estimated to be 438 477 PY. The safety profile of mepolizumab from post-marketing sources remains generally similar to that known at initial market authorization (04 November 2015). During the post-marketing period, following a review of spontaneous post-marketing reports of anaphylaxis, the mepolizumab label was updated to include "anaphylaxis" in the existing Warning regarding hypersensitivity reactions and in the Adverse Reactions section. Based on the post-marketing experience to date, the benefit-risk profile of mepolizumab for the above approved indications, at the approved doses every 4 weeks, continues to be positive.

2.5.1. Discussion on clinical safety

Overview of COPD safety dossier

Safety data in support of the proposed COPD indication have been derived from 3 placebo controlled clinical studies (studies 208657, MEA117113 and MEA117106). Notwithstanding the differences between the 3 COPD studies with respect to study population (e.g. BEC enrolment criteria, asthma history, smoking status), design (e.g. fixed versus variable duration, follow-up period, intervention dose and formulation) and conduct (e.g. prior to/during COVID-19 pandemic), the pooling of safety data, and the MAH's approach to its evaluation, is generally considered acceptable. The CHMP safety evaluation focuses on the mepolizumab 100 mg and placebo treatment groups in the pooled COPD data, with additional focus on longer-term safety data derived from Study 207657, the confirmatory efficacy study whose population is most representative of the target COPD population.

The extensive exposure in the pooled COPD population and the availability of longer-term safety data (up to week 104 from study 208657) have contributed to a comprehensive characterisation of the safety profile of mepolizumab 100 mg SC Q4W in the treatment of COPD and is in accordance with ICH E1.

Exposure (numbers) and duration of exposure in COPD

In terms of exposure, 2314 participants were exposed to treatment in the 3 pooled COPD studies. 1043 participants were exposed to at least one dose of mepolizumab 100 mg SC. The majority of participants treated with mepolizumab 100 mg or placebo received treatment for 12 months to 15 months (72% and 68%, respectively). The mean number of mepolizumab 100 mg treatments administered in the pooled studies was 13.6. Overall treatment exposure was 1097.72 participant-years in the mepolizumab 100 mg group and 1052.92 participant-years in the placebo group.

Study completion rates in both treatment groups, across all studies, were generally high. No concerns were identified with respect to differing rates and reasons for study withdrawal or study treatment discontinuations in the pooled COPD data or within different duration subgroups of Study 208657. The most common reasons for both were 'withdrawal by participant' and 'AE'.

Safety population demographics, disease characteristics, concomitant therapies

In the pooled COPD studies, the majority of participants were White (82%) and male (66%), with a mean age of 65.6 years. Participants' baseline COPD disease characteristics were consistent with a population with moderate to severe disease (GOLD 2 and GOLD 3, respectively) and characteristic of GOLD Group E with respect to exacerbation history [GOLD 2025]. As would be expected in this population, the incidence of co-morbidities was high overall (71%), with the majority of participants having a past or current history of CV-related disease (69%). Demographics and baseline disease characteristics were generally well-balanced by treatment group in the pooled safety population.

As per CHMP request, the MAH provided a comprehensive tabular analysis of prior and concomitant COPD and non-COPD medications, including long-term oxygen therapy (LTOT), across the three pivotal COPD studies. Minor imbalances were identified, but these were adequately explained by differences in regional prescribing practices, study protocols, and coding conventions. The response highlighted that these variations were not systematic or clinically significant and did not compromise the integrity of pooled safety data or interpretation of safety outcomes.

Separate summaries of AEs from the COPD studies were also provided by the MAH for each of the following subgroups of interest: Age: <40, 40 to <65; ≥65 years; Sex: Male, Female; Race: African American/African Heritage, White, Asian, Other; Region: Europe, United States, Rest of World(See safety in special populations section of this report).

Adverse events

In the pooled COPD studies, the overall incidence and EAIR of any TEAE were similar between the placebo and the mepolizumab 100 mg SC treatment groups (79% and 3650.8 events/1000 PY versus 78% and 3609.3 events/1000 PY).

The SOCs with the most frequently reported on-treatment AEs (>30%) were infections and infestations and respiratory, thoracic, and mediastinal disorders. The most common on-treatment AEs by PT (at least 10% incidence in any treatment group) were COPD exacerbation, COVID-19 (study 208657 only), nasopharyngitis, and headache, with a similar incidence and EAIR between the placebo and mepolizumab 100 mg groups.

The CMH-adjusted cumulative proportions and CMH-adjusted RR of on-treatment common AEs were provided for mepolizumab 100 mg versus placebo. The RR 95% CIs for all common AEs include 1, with only 'oropharyngeal pain' showing a numerically higher relative risk (RR 1.77; 95% CI:1.11, 2.85) for mepolizumab 100 mg versus placebo. The MAH's rationale that this observation is largely driven by MEA117113 data is accepted. Of note, data show a similar incidence and EAIR of

on-treatment drug-related adverse events of 'oropharyngeal pain' between placebo and mepolizumab 100 mg treatment groups in individual and pooled COPD studies.

Further analysis of TEAEs reported in study 208657 by duration subgroup did not identify any new safety concerns. Higher incidences of on-treatment AEs by SOC were observed in the variable duration subgroup compared with the fixed duration subgroup, which is consistent with the increased treatment exposure for the variable duration subgroup. The pattern of incidences and exposure-adjusted rates of common on-treatment AEs across treatment groups was generally similar in the fixed duration and variable duration subgroups. Both duration subgroups generally reflected the pattern in the pooled COPD population.

With regards to the intensity of reported TEAEs, the majority of AEs were reported as mild or moderate in intensity in the mepolizumab 100 mg and the placebo group, and those reported as severe were generally well balanced between treatment groups. Severe COPD exacerbation was reported by 11% and 13% of participants in the mepolizumab 100 mg group and the placebo group, respectively.

In terms of relatedness of an AE to treatment, the incidence and EAIR event rate of any on-treatment AEs considered to be treatment-related by the investigator were similar between the mepolizumab 100 mg group and placebo group. The most commonly reported on-treatment drug-related AEs reported by ≥1% of participants in either the mepolizumab 100 mg or placebo group were injection site reactions, followed by injection related reaction and headache. Most drug-related AEs were mild to moderate in intensity, with <1% of all drug-related AEs being reported as severe.

For individual studies and the pooled data, the incidence of any post-treatment AEs was similar between the mepolizumab 100 mg group and the placebo group, with the most common being reported as COPD exacerbations. Of note, there was no follow-up period in study 208657, whereas studies MEA117113 and MEA117106 had a post-treatment follow-up period, to evaluate AEs following discontinuation of study treatment. In studies MEA117113 and MEA117106, there was greater opportunity to collect posttreatment AEs, since these studies had an 8-week follow-up period starting 4 weeks after the last dose of treatment, whereas study 208657 had not. The MAH provided the rationale for the shortened follow-up period in study 208657. It was based on emerging safety, pharmacokinetic and immunogenicity data as part of the overall mepolizumab development programme. It was not considered to have detracted from the overall characterisation of the safety and immunogenic profile of mepolizumab in the COPD population.

SAEs/deaths

Of the 31 (3%) and 37 (4%) on- and post-treatment deaths reported in the pooled COPD studies for the mepolizumab 100 mg and placebo groups, respectively, none (but one in the placebo group) was considered to be treatment-related by the investigator.

The most frequently reported fatal SAE was COPD exacerbation (<1% in each treatment group). The adjudicated primary causes of death (CV, respiratory, cancer, unknown, and other) were similar between treatment groups, with respiratory and cardiovascular being the most frequent adjudicated primary cause of death, with over 40% of the overall deaths considered by the CEC to be associated with COPD. Overall, no new safety signals emerged from the reported fatal events.

Overall, on-treatment SAEs (fatal and non-fatal) were reported with a similar incidence and EAIR between the mepolizumab 100 mg group (24%, 467.3 events/1000 PY) and placebo group (27%, 498.6 events/1000 PY).

The most frequently reported SAEs were COPD exacerbation (12%, 170.4 events/1000 PY in the mepolizumab 100 mg group; 15%, 242.5 events/1000 PY in the placebo group) and pneumonia (5% of participants in both groups with 58.9 and 67.8 events/1000 PY in the mepolizumab 100 mg and placebo groups, respectively). Of all reported on- and post-treatment SAEs, the investigator considered that there was a reasonable possibility that 3 non-fatal events (diarrhoea, pneumonia/sepsis, COPD exacerbation), reported in 3 patients, were caused by mepolizumab 100 mg treatment. The reported SAE of 'diarrhoea' led to study treatment discontinuation. The SAEs 'pneumonia/sepsis' and 'COPD exacerbation' did not result in study treatment discontinuation. All were reported recovered/resolved, except for 'pneumonia' which was reported as resolved with sequalae. The incidence and profile of primary causes of adjudicated SAE reports were similar between treatment groups with the most frequent primary causes being categorized as respiratory and cardiovascular.

On-treatment pneumonia AEs (based on the Infective pneumonia SMQ) were reported with a similar incidence and EAIR across treatment groups: mepolizumab 100 mg (9%, 106.6 events/1000 PY) and placebo (9%, 107.3 events/1000 PY) groups. Similarly, the frequency of on- and post-treatment pneumonia AEs and adjudicated SAE reports of COPD exacerbation with evidence of pneumonia were balanced across treatment groups.

Regarding additional medical concepts evaluated by the MAH, in the pooled studies, the incidence and risk (based on CMH-adjusted RR and risk difference) of on-treatment AEs of the additional medical concepts for mepolizumab 100 mg were each similar to placebo with no clinically meaningful differences.

With regards to the reporting of AEs of 'COPD exacerbation', the MAH clarified that a consistent approach was taken in the reporting of AEs/SAEs of 'COPD exacerbation' across all three COPD studies. This approach was in line with that previously employed in the mepolizumab development programme and accepted clinical trial regulatory guidance. It is therefore agreed that there was no negative impact on the integrity of the pooled safety data with respect to this event.

AESIs and other safety topics of interest

No new safety concerns emerged from the MAH's evaluation of on-treatment pneumonia AEs (based on the Infective pneumonia SMQ) and additional medical concepts, defined by FMQ, embolic and thrombotic events, embolic and thrombotic events-venous, acute pancreatitis, and hypertension, and defined by SMQ, supraventricular tachyarrhythmias, gastrointestinal bleeding, and conjunctival disorders.

AESIs and other selected AEs of interest included systemic reactions, local injection site reactions, infections (including serious and potential opportunistic), neoplasms (SOC), malignancies, cardiac disorders (including serious cardiac disorders), and serious CVT events (including serious ischemic events). In the pooled studies, each category and subcategory of on-treatment AESI occurred with similar incidence and EAIR across treatment arms (mepolizumab 100 mg and placebo). The treatment estimates for CMH-adjusted RR and risk difference were consistent with a similar risk of AESI between the mepolizumab group (100 mg and the placebo group).

There were no reported events of anaphylaxis in the pooled COPD studies.

Similar incidences and EAIR were reported for any systemic reactions in the pooled COPD studies: 1% (23.7 events/1000 PY) in the mepolizumab 100 mg group and 2% (20.9 events/1000 PY) in the placebo group. Of the participants in the mepolizumab 100 mg group (15 participants) and placebo group (18 participants) who had an on-treatment systemic reaction, all but 1 (in the placebo group) of the systemic reactions were reported by the investigator to be related to study

treatment. No serious or severe systemic reaction events were reported in the mepolizumab 100 mg group.

The incidence of any local injection site reactions was similar for the mepolizumab 100 mg group and the placebo group (2% each); the EAIR was 27.3 events/1000 PY in the mepolizumab 100 mg group and 35.1 events/1000 PY in the placebo group. All reported events were considered by the investigator to be study treatment related. All events were non-serious and all but one (in the placebo group) were reported as mild to moderate in intensity. The MAH has proposed wording pertaining to the occurrence of local injection site reactions in the pooled COPD studies in section 4.8 of the SmPC. This was considered acceptable with minor revision.

The incidence and EAIR of any on-treatment AEs of All infections (SOC Infections and infestations) were numerically lower in study 208657 compared with studies MEA117113 and MEA117106. This observation is likely due to the conduct of study 208657 during the COVID-19 pandemic, and as a consequence of varying non-pharmaceutical interventions (NPIs) being in place at that time. Overall incidence of any AEs and SAEs reported as an AESI under the SOC Infections and Infestations was broadly similar between treatment arms in all 3 COPD studies. The most frequently reported on-treatment infection was nasopharyngitis and the most frequently reported serious infection was pneumonia; both occurred with a similar incidence between the mepolizumab 100 mg and placebo groups in each of the 3 COPD studies.

All participants with on-treatment potential opportunistic infections had non-serious and non-severe events, except for 1 participant in the placebo group with a serious and severe event, 1 participant in the mepolizumab 100 mg group with a serious event, and 1 participant in the mepolizumab 100 mg group with a severe event. A potential opportunistic infection was considered to be treatment-related for 1 participant in the mepolizumab 100 mg group and 1 participant in the placebo group. All events resolved with continued treatment except for 1 participant in the placebo group. Herpes zoster was the most frequently reported on-treatment potential opportunistic infection, both in the mepolizumab 100 mg group (1%) and the placebo group (<1%), with the EAIR in the former (15.5 events/1000 PY) being twice that of the latter (6.6 events/1000 PY). Herpes zoster infection is listed as an 'uncommon' ADR in Nucala's current PI. As part of this variation procedure, the MAH proposed revision of its frequency of occurrence to 'common', and to add the footnote "herpes zoster was reported uncommonly in severe asthma studies". Justification for the proposed update, in response to RFI, was considered acceptable.

No parasitic infections were reported in any COPD study.

The incidence and EAIR for on-treatment AEs of neoplasms in the SOC Neoplasms benign malignant and unspecified (including cysts and polyps) was similar in the mepolizumab 100 mg group (3%, 32.8 events/1000 PY) and the placebo group (4%, 40.8 events/1000 PY). The types of on-treatment AEs of malignancies reported in the COPD studies were those that are common in the general population. The most frequently reported on-treatment malignancy was lung neoplasm malignant (3 participants in the mepolizumab 100 mg group, 2 participants in the placebo group). None of the malignancies were considered by the investigator to be treatment related. The incidence of on- and post-treatment AEs of malignancies was balanced between the mepolizumab (2%) and placebo (3%) groups. Longer-term data from study 208657 did not give rise to any new or additional safety concerns with respect to reported malignancies.

The MAH assessment of CV safety data in the 3 COPD studies, included:

- Investigator-reported CV AESIs: Incidence, RR, risk difference, and EAIR of AESIs reported under Cardiac disorders (including serious Cardiac disorders) and Serious CVT (including Serious

ischaemic events) was consistent with a similar risk between mepolizumab 100 mg and placebo groups.

- CV-related additional medical concepts: The incidence, risk, and EAIR data for investigator-reported on-treatment AEs were similar between the mepolizumab 100 mg and the placebo groups across prespecified CV-related additional medical concepts of Embolic and thrombotic events, Embolic and thrombotic events-venous, Hypertension, and Supraventricular tachyarrhythmias.

- Adjudicated SAE reports with a CV primary cause: The incidence and profile of CV primary causes of adjudicated on- and post-treatment SAE reports (fatal and non-fatal) were similar between the mepolizumab 100 mg and placebo groups. Small numerical differences (<1% in incidence) between the mepolizumab 100 mg and placebo groups in the subcategories of Congestive heart failure and Other CV cause were noted, which were in opposite directions. An internal review of participant information did not suggest a plausible causal association between mepolizumab and Congestive heart failure events.

- Adjudicated MACE: The overall incidence and risk of adjudicated MACE was low and similar between the mepolizumab 100 mg and the placebo groups. The incidence within each component and subcategory of MACE was also broadly similar (<0.6% difference). Small numerical imbalances were noted in both directions. An internal review of participant information for adjudicated events adjudicated as Sudden cardiac death and Heart failure did not support a plausible causal association between mepolizumab and these events.

Overall, the MAH conducted a comprehensive review of CV safety data from the pooled COPD studies. Data for mepolizumab 100 mg were broadly comparable with that for placebo and no new CV safety concerns for mepolizumab 100 mg in the COPD population were identified. Alterations in cardiovascular safety continues to be listed as an important potential risk in the Summary of Safety Concerns in Nucala's RMP.

Adverse drug reactions

The MAH's approach to analysis and identification of new AEs and ADRs is acknowledged.

The method for screening ADRs has been provided. The screening was carried out using the Crowe method and was conducted at both HLT (high level terms) and PT (preferred terms) level. After that, medical judgement was used to assess causal association for AE identified through this quantitative analysis. This approach is considered acceptable. However, the review of all safety data across the 3 pooled studies was initially not found in the documentation, only the MAH's statement that no new AE was identified to complement the already previously established safety profile of mepolizumab is written in the Safety Summary. In response to a request for further information, the MAH provided a more detailed assessment and clarified in which part of the documentation supporting information could be found.

The MAH is proposing the addition of the following text under the summary of safety profile in section 4.8 of the SmPC for the COPD population:

In three placebo-controlled studies in patients with COPD, the most commonly reported adverse reactions during treatment were headache (10%), back pain (7%) and arthralgia (5%).

The method used to determine ADRs for inclusion in the summary of safety profile of the SmPC was provided by the MAH and considered acceptable.

Laboratory measurements, and vitals

In the 3 pooled COPD studies, apart from a higher incidence of changes to below the normal range for eosinophils in the mepolizumab 100 mg group (74%) compared with the placebo group (22%) the incidences of changes of haematology parameters to outside the normal range at any time post-baseline were similar between the mepolizumab 100 mg group and the placebo group. The observed imbalance between treatment groups with respect to eosinophils would be expected based on the mechanism of action of mepolizumab and the inclusion criteria (with respect to BEC) in the target COPD study population.

Overall, in the pooled studies, the incidence of chemistry/haematology values outside the normal range at any time post-baseline occurred with similar incidence across the treatment groups. The percentage of participants who experienced a post-baseline change in a haematology/chemistry parameter that was of potential clinical concern was low (<1%) and similar between treatment groups.

In the pooled studies, ≤1% of participants in both the mepolizumab 100 mg group (2 of 1043 participants) and the placebo group (11 of 1046 participants) had abnormal liver functions tests that met protocol-specified liver monitoring criteria. No participants in the mepolizumab 100 mg group had liver function tests that met liver stopping criteria. There were no cases of Hy's law.

There was no evidence of QTc prolongation or an increase in ECG abnormalities with mepolizumab treatment in the COPD studies.

Overall, no new safety concerns related to haematology/chemistry laboratory values, vital signs, and ECGs were identified in the 3 COPD studies. There were no treatment-related trends observed.

Antidrug antibodies

In the pooled COPD studies, at any time post-baseline, the incidence of treatment-emergent positive ADA results was low (2%) in the mepolizumab 100 mg group. No participants were positive for NAb. Titers were generally low. Similar incidences of AEs in ADA negative and ADA positive participants were observed between the 3 COPD studies. ADA status did not appear to affect the safety profile of mepolizumab in the study population. Findings were consistent with mepolizumab's known low immunogenic potential in other indications. The MAH proposed wording in Section 5.1 of the SmPC to reflect the results of immunogenicity data (up to 104 weeks) derived from the pivotal COPD study, study 208657. This was considered acceptable.

Safety in special populations

The incidence of AEs was assessed in the subgroups of the mepolizumab COPD studies to determine if there were clinically important differences between the subgroups and the overall population of participants in these studies. For intrinsic factors, the subgroups examined included gender, age, race and region. For extrinsic factors, the influence of the COVID-19 pandemic on the safety profile of mepolizumab across the 3 COPD studies was evaluated.

The majority of participants in the 3 pooled COPD studies were male (66%). The MAH provided an assessment of the incidence of AEs (any and by SOC) by gender. While it is acknowledged that there is a trend of a higher incidence being reported in the female mepolizumab group when compared to the male mepolizumab group for any AEs and AEs by SOC, the incidence of any AEs was generally similar between the mepolizumab 100 mg group and the placebo group within each gender subgroup. A similar pattern (higher incidence within the female subgroup) was observed in the authorisation of mepolizumab in the eosinophilic asthma indication. The observation does not

impact the overall safety profile of mepolizumab in the COPD indication and will not be pursued further.

The mean age of participants in the COPD studies was 65.6 years. More than half (57%) of the participants were ≥65 years of age. The largest observed imbalance between the age subgroups in the mepolizumab 100 mg treatment groups was under the SOC Cardiac disorders. Increasing age is a known independent risk factor for cardiac conditions and events, and hence this picture is not unexpected. The assessment of the incidence of AEs by age (40-<65 years versus ≤65 years) did not identify any new or unexpected trends that would give rise to safety concerns.

With respect to race, the majority of the participants in the 3 pooled COPD studies were White (82%) with 11% of participants being of Asian heritage followed by Other (6%) and African American (1%). Within each subgroup, the incidence of on-treatment AEs was broadly similar across mepolizumab and placebo treatment groups. However, the number of participants with African American/African Heritage enrolled in the 3 studies was very limited (n=29), making it difficult to draw any meaningful conclusions about the safety profile of mepolizumab in this subgroup of the COPD population. This is a limitation of the safety dataset.

No pregnancies were reported in the COPD program. Section 4.6 of Nucala's SmPC states that *There is a limited amount of data (less than 300 pregnancy outcomes) from the use of mepolizumab in pregnant women. Mepolizumab crosses the placental barrier in monkeys. Animal studies do not indicate reproductive toxicity (see section 5.3). The potential for harm to a human fetus is unknown. As a precautionary measure, it is preferable to avoid the use of Nucala during pregnancy. Administration of Nucala to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus*. "Limited data in pregnant and lactating patients" continues to be listed in the summary of safety concerns of Nucala's of RMP.

COVID-19 pandemic

In consideration of the impact of the COVID-19 pandemic on the safety evaluation of mepolizumab in the COPD population, the CHMP agreed with the MAH's conclusion that, based on overall similar safety results for study 208657 and the previously conducted studies MEA117113 and MEA117106, the pandemic did not appear to have had an impact. While the conduct of study 208657 was undoubtedly impacted by the COVID-19 pandemic, as was evident from the mid-study protocol amendment (Protocol Amendment 6) that resulted in study extension, no new concerns with respect to the safety profile of mepolizumab in the COPD population were raised on evaluation of the results of pre-specified additional analyses by duration subgroup (fixed versus variable duration). The change in the study duration did not notably affect the on-treatment AE profiles between treatment groups. The pattern of on-treatment AEs, SAEs, and AESI across treatment groups were generally similar by duration subgroup. Within each duration subgroup, the incidence and rate of AEs, SAEs, and AESI were broadly similar between treatment groups. Mepolizumab's safety profile in study 208657 was generally similar to that evaluated in studies MEA117113 and MEA117106. The availability of longer-term safety data (up to week 104) in study 208657 was beneficial to the overall safety evaluation.

*Discontinuation due to adverse events*In the pooled safety population, a similar percentage of participants in the placebo group (16%) withdrew from the study compared with participants in the mepolizumab 100 mg group (17%). Study withdrawal was most frequently due to 'withdrawal by participant' and 'AE'. In the pooled studies, the percentage of participants who prematurely discontinued treatment was higher in the placebo group (22%) compared with the mepolizumab group (16%). This trend was consistent in each study and most pronounced in MEA117113 (25%

and 12% in placebo and mepolizumab 100 mg groups, respectively). The most common reasons for treatment discontinuation were 'withdrawal by participant' and 'AE'.

COPD exacerbations was the most commonly reported AE leading to permanent discontinuation of the study treatment and withdrawal from the study, with an incidence and EAIR favouring the mepolizumab treatment group.

Within Study 208657, study completion profiles were generally similar between participants in the fixed and variable duration subgroups; 83% and 79% in the active treatment arm compared to 82% and 76% the placebo arm for fixed and variable subgroups, respectively. The most common primary reason for treatment discontinuation for both the fixed and variable duration subgroup was 'withdrawal by participant', followed by 'adverse events', being reported at a similar rate between.

No concerns were identified with respect to differing rates and reasons for study withdrawal or study treatment discontinuations in the pooled COPD data or within Study 208657, and high rates of study completion were observed.

Withdrawal and rebound

The CHMP agrees with the MAH's conclusion that data derived from reported post-treatment AEs (largely from Studies MEA117113 and MEA117106) indicate absence of symptoms on discontinuation of mepolizumab 100 mg treatment.

Post marketing experience

The MAH's summary of post marketing experience for Nucala and provision of the Periodic Benefit Risk Evaluation Report, covering the period 24 September 2023 to 23 September 2024, is acknowledged. The PRAC/CHMP further note the conclusion of the most recent PSUR (EMEA/H/C/PSUSA/00010456/202409) for mepolizumab in April 2025, covering the same period.

The PRAC/CHMP concluded that the risk-benefit balance of medicinal products containing mepolizumab remained unchanged and recommended the maintenance of the marketing authorisation(s). No updates to Product Information were recommended.

Overall, based on the safety data derived from studies 208657, MEA117113 and MEA117106, mepolizumab appears to have an acceptable safety profile in the COPD population that is similar to the safety profile presented by the MAH for other indications for which mepolizumab is already approved. No new safety signals were apparent in the COPD population.

2.5.2. Conclusions on clinical safety

Overall, mepolizumab 100 mg, administered subcutaneously every 4 weeks as per the proposed posology, appears to be well-tolerated in the COPD population. The safety profile observed in COPD patients is largely consistent with the well characterised safety profile of mepolizumab to date.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The (main) proposed RMP changes were the following:

The data from the COPD studies and on the new proposed indication have been included in the updated RMP.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 16 is acceptable.

The CHMP endorsed the Risk Management Plan version 16 with the following content:

Safety concerns

The MAH submitted updated RMP version 16 with this application.

No changes were proposed to the summary of safety concerns, which remains, as follows:

Table 172: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Systemic Reactions including anaphylaxis
Important potential risks	Alterations in immune response (malignancies) Alterations in cardiovascular safety
Missing information	Limited data in pregnant and lactating patients Safety of mepolizumab in children with EGPA

Pharmacovigilance plan

Table 173 On-going and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization under exceptional circumstances				
None				
Category 3- Required additional pharmacovigilance activities				
218065 A post-marketing study to evaluate the safety and effectiveness of mepolizumab in children aged 6 – 17 years with EGPA	To evaluate the safety and effectiveness of mepolizumab in children aged 6 – 17 years with EGPA	Use in children aged 6 – 17 years	Final Report	31 Dec 2029

The pharmacovigilance activities remained unchanged, no new activities have been included for the new indication. As the summary of safety concerns remained unchanged, this is accepted.

Risk minimisation measures

Table 174 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risk Systemic reactions including anaphylaxis	**Routine risk minimisation measures:** The SmPC includes appropriate information in Section 4.4 (Special Warnings and Precautions) and Section 4.8 (Undesirable effects). Equivalent wording is included in the patient leaflet Section 2 and Section 4. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: A targeted follow-up questionnaire is used to collect data on severe hypersensitivity/anaphylaxis. **Additional pharmacovigilance activities**: None
Important Potential Risk Alterations in immune response (malignancies)	**Routine risk minimisation measures:** None proposed **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Important Potential Risk Alterations in cardiovascular safety	**Routine risk minimisation measures:** None proposed **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** To further evaluate this potential risk targeted follow-up questionnaires to collect data on MI/Unstable Angina, Cerebral Vascular Accident/Transient Ischemic Attack, Deep Vein Thrombosis/Pulmonary Embolism and Peripheral Arterial Thromboembolism. **Additional pharmacovigilance activities:** None
Missing Information Limited data in pregnant and lactating patients	**Routine risk minimisation measures:** The SmPC Section 4.6, Fertility, Pregnancy and Lactation, of the SmPC advises prescribers on the non-clinical reproductive toxicity data available on NUCALA. **Additional risk minimisation measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Enhanced data collection aimed at capturing key variables for further characterization **Additional pharmacovigilance activities:** None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	None	
Missing Information Safety of mepolizumab in children with EGPA	**Routine risk minimisation measures:** SmPC Section 4.2, Posology and method of administration, advises prescribers on the dose of mepolizumab for children. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** A post-marketing study to evaluate the safety and effectiveness of mepolizumab in children aged 6 – 17 years with EGPA.

The risk minimization activities remained unchanged, no new activities have been included for the new indication. As the summary of safety concerns remained unchanged, this is accepted.

Overall conclusion on the RMP

The changes to the RMP are acceptable.

2.7. Update of the Product information

As a result of the proposed extension of indication for COPD, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

Changes are also made to the PI to bring it in line with the EU Excipients Guideline (17 Apr 2024) information on (the amount of) polysorbate 80 as referenced in m3.2.P.1. This has resulted in updates to sections 2, 4.4 and 6.1 of the SmPC and corresponding sections of the PL.

Changes arising from PSUSA/00010456/202309 have resulted in minor linguistic changes throughout the SmPC and corresponding sections of the PL

Changes have been proposed to section 4.8 of the SmPC to address a post-approval commitment, following conclusion of Article 46 for study 201956 (EMEA/H/C/003860/P46/016), to update paediatric exposure data.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of bridging reports making reference to the currently authorised package leaflets for Nucala 100 mg powder and Nucala 100 mg pre-filled -pen and -syringe. The bridging reports submitted by the MAH were found to be acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

COPD is a complex heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnoea, cough, and sputum production) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction. Patients typically complain of dyspnoea, activity limitation and/or cough with or without sputum production. COPD often coexists with other diseases (comorbidities) that may have a significant impact on disease course.

The disease results from gene-environment interactions and occurs in response to chronic exposure to noxious stimuli including tobacco smoke, pollutants, biomass, and gases. Host factors (including abnormal lung development and accelerated lung aging) can also contribute. Periods of acute worsening of respiratory symptoms, called acute exacerbations of COPD can occur that lead to further disease progression by means of airflow obstruction. Exacerbations contribute to disease severity and often require specific preventative measures.

3.1.2. Available therapies and unmet medical need

COPD is a progressive condition characterized by irreversible airflow limitation with frequent exacerbations potentially accelerating disease progression and mortality. Although treatment recommendations for the management of severe COPD exist, no currently approved therapy is able to prevent the decline in lung function. In addition to smoking cessation, the 2025 GOLD report advocates the use of 'triple therapy' consisting of inhaled bronchodilators (LABA +LAMA) in addition to ICS for patients with more advanced disease, high BEC, and high risk of exacerbations. Despite this, certain adult COPD patients with an eosinophilic phenotype continue to have a history of exacerbations despite optimized SoC consisting of ICS-based triple maintenance therapy.

Dupilumab, an IL-4R/13R inhibitor, has been approved by EMA, Food and Drug Administration (FDA), and National Medical Product Administration (NMPA) as an add-on maintenance treatment for adults with uncontrolled COPD characterized by raised blood eosinophils that targets features of Type-2 inflammation, including eosinophils. The mepolizumab-COPD program is also targeting this COPD population with a high eosinophilic phenotype that continue to experience exacerbations while on triple therapy by inhibiting IL-5 instead of IL-4/IL-13.

The proposed indication for mepolizumab is as follows:

*Nucala is indicated in adults as an add-on maintenance treatment for uncontrolled chronic obstructive pulmonary disease (COPD) characterised by raised blood eosinophils on a combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA) (see section 5.1)***.**

3.1.3. Main clinical studies

The phase 3 COPD development programme comprised 3 clinical studies, each with a randomized, double-blind, placebo-controlled, parallel-group design. Study 208657 (MATINEE) is considered as pivotal for this application as this study investigated the proposed target population, i.e. patients who have blood eosinophil levels ≥300 cells/µL**.** In 2 of the studies, MEA117113 (METREO) and MEA117106 (METREX), different blood eosinophil thresholds were used as the basis of enrolment.

The MAH also presented a supportive post-hoc analysis of the efficacy data from the subpopulation in MEA117113 and MEA117106 studies characterized by screening BEC ≥300 cells/µL 100mg dosing regimen as well as the pooled efficacy analysis of the data from 208657, MEA117113 and MEA117106 studies.

The pivotal 208657 study had a multi-centre, randomized, placebo-controlled, double-blind, parallel-group (2-group) design and investigated the efficacy and safety of mepolizumab 100 mg given every 4 weeks by SC injection compared to placebo. It consisted of 3 periods, an initial 3-week screening period followed by a 2-week run-in period and a 52-week up to 104-week treatment period.

3.2. Favourable effects

The Phase 3 COPD development programme comprised 3 clinical studies, each with a randomized, double-blind, placebo-controlled, parallel-group design. Study 208657 (MATINEE) is considered as pivotal for this application.

The primary endpoint in the 208657 study was the annualized rate of moderate/severe exacerbations, and this primary endpoint was met.

Treatment with mepolizumab resulted in a statistically significant reduction in the annualized rate of moderate/severe exacerbations compared with placebo (rate ratio: 0.79; 95% CI: 0.66, 0.94; p=0.011). A 21% reduction in the annualised rate of exacerbations in the mepolizumab treatment group could be considered as borderline clinically relevant as 20% reduction of rate of moderate/severe exacerbations is suggested to be minimal clinically important difference in COPD patients (Calverley PM et al. 2005).

The results of sensitivity analyses investigating the robustness of results to alternative missing data assumptions were consistent with the primary analysis.

In study 208657 there were several secondary endpoints investigating the effect on exacerbations including two key endpoints under multiplicity adjustment.

The time to first event analysis showed a statistically significant reduction in the risk of moderate/severe exacerbation for mepolizumab compared with placebo (hazard ratio 0.77; 95% CI: 0.64, 0.93; p=0.009).

Both studies MEA117106 and MEA117113 had annualised rate of moderate/severe exacerbations as their primary endpoint, the same as in the pivotal 208657 study.

In study MEA117106 in the high stratum group (blood eosinophils ≥150 cells/µL at Visit 1 (Screening) OR historic blood eosinophil level in the preceding 12 months ≥300 cells/ µL), treatment with mepolizumab 100 mg every 4 weeks resulted in an 18% reduction in the rate of moderate/severe exacerbations compared with placebo (rate ratio: 0.82; 95% CI: 0.68, 0.98; unadjusted p=0.029; adjusted for multiplicity p=0.036).

In study MEA117113 the 100mg dose led to a 20% reduction in the rate of moderate/severe exacerbations, which is the minimum difference that can be considered clinically relevant (rate ratio 0.80; 95% CI: 0.65, 0.98; unadjusted p=0.034 and adjusted for multiplicity p=0.068).

3.3. Uncertainties and limitations about favourable effects

Confounding effect of potential enrolment of patients with history of asthma into MEA117106 and MEA117113 studies.

MEA117106 and MEA117113 had the same inclusion criteria which were similar to the criteria in the 208657 study. However, a key difference in the MEA117106 and MEA117113 studies compared to 208657 study was that patients with a history of asthma could be enrolled. The MAH clarified that active asthma patients were excluded from studies MEA117106 and MEA117113. However, patients with prior asthma could participate if they were current/former smokers with a significant tobacco smoking history. As history of (resolved) asthma was not collected for studies MEA117106 and MEA117113 a sensitivity analysis excluding these patients as requested could not be conducted. It is difficult to estimate on how many patients with COPD with a history of asthma, who are current smokers could be enrolled to the study. Population studies have shown that as many as 30% of patients with fixed airflow obstruction have a past history of asthma [Weiss ST, 2011]. This is main uncertainty regarding the efficacy results generated in MEA117106 and MEA117113 provided in support of COPD indication. For these reasons these studies are not considered as pivotal and therefore they are not included in the section 5.1 of the SmPC.

Strength of evidence provided by secondary endpoints

For Study 208657 the secondary endpoints investigated the time to event analysis showed a statistically significant reduction in the risk of moderate/severe exacerbation for mepolizumab compared with placebo (hazard ratio 0.77; 95% CI: 0.64, 0.93; p=0.009). However, this is the only statistically significant key secondary endpoint, and it is not independent of the primary endpoint.

Although treatment with mepolizumab resulted in a 35% reduction in the annualized rate of exacerbations requiring ED visit and/or hospitalization compared with placebo (rate ratio: 0.65; 95% CI: 0.43, 0.96), no statistical inference can be made on this key endpoint due to the break in statistical testing hierarchy on the proportion of CAT responders' endpoint. Although treatment with mepolizumab resulted in a 34% reduction in the annualized rate of severe exacerbations compared to placebo (rate ratio: 0.66; 95% CI: 0.43, 1.01), this did not achieve statistical significance (p=0.055).

For other endpoints such as time to first exacerbation requiring ED visit and/or hospitalization, severe exacerbations rate, time to first severe exacerbation, moderate exacerbations rate, although improvements with mepolizumab was noted, statistical significance cannot be concluded. While the results on these endpoints cannot be considered to provide confirmatory evidence, they can provide supportive evidence to the efficacy conclusion. Further, as specific information on reduction in the annualised rate of severe exacerbations can be of benefit to health care professionals, it is included in section 5.1.

In the 208657 study, there was no clear benefit for other outcome measures investigated. This is explained in the SmPC section 5.1.

In the supportive studies MEA117106 and MEA117113 below borderline (18%) or borderline (20%) clinically relevant reduction in the rate of moderate/severe exacerbations compared with placebo was observed, and in the study MEA117113 it was not statistically significant (rate ratio 0.80; 95% CI: 0.65, 0.98; unadjusted p=0.034 and adjusted for multiplicity p=0.068).

In both supporting studies MEA117106 and MEA117113, there was no clear benefit for other outcome measures investigated.

Potential negative treatment effects associated with mepolizumab treatment.

It is noted that in patients with low BEC treatment with mepolizumab resulted in an increase in the rate of moderate/severe exacerbations as compared to placebo. In the low stratum in MEA117106 study, the rate of moderate/severe exacerbations increased by 23% (95% CI: 0.99, 1.51) after treatment with mepolizumab 100 mg compared with placebo (unadjusted p=0.058). Sensitivity analysis was performed excluding participants with ≥9 exacerbations in the mepolizumab arm which lowered the rate ratio to 1.16 (0.94, 1.43).

Modelling analysis of the primary endpoint which used all available data from 208657, MEA117113 and MEA117106 studies indicated that patients with BEC lower than 150 cells/µL are likely to have an increase in the rate of exacerbations.

The data presented by the MAH is not sufficient exclude a risk of potential harm in patients with low eosinophil levels (< 150 cells/µL). In most analyses presented the HR/Rate ratio is >1 despite post-hoc data exclusion. Therefore, the following warning is included in section 4.4 of the SmPC: *Data do not support the use of Nucala in patients with COPD with blood eosinophil count <150 cells/mcL and no evidence of blood eosinophil count ≥300 cells/mcL in the previous 12 months.*

3.4. Unfavourable effects

The safety dataset submitted in support of mepolizumab 100 mg SC Q4W in the COPD population was derived from the 3 placebo-controlled studies described above.

The overall incidence and EAIR of any TEAE was similar between the placebo and the mepolizumab 100 mg SC treatment groups (79% and 3650.8 events/1000 PY versus 78% and 3609.3 events/1000 PY). The most common on-treatment AEs by PT were COPD exacerbation, COVID-19 (study 208657 only), headache (10%), back pain (7%) and arthralgia (5%; SmPC section 4.8), with a similar incidence and EAIR between the placebo and mepolizumab 100 mg groups. The risk of common AEs was generally balanced between the groups and the majority were mild to moderate in intensity.

On-treatment SAEs were reported with a similar incidence and EAIR between the mepolizumab 100 mg group (24%, 467.3 events/1000 PY) and placebo group (27%, 498.6 events/1000 PY). Of all reported on- and post-treatment SAEs, 3 non-fatal events (diarrhoea, pneumonia/sepsis, COPD exacerbation) reported in 3 patients were considered by the investigator to be treatment-related in the mepolizumab 100 mg group. The incidence and profile of primary causes of adjudicated SAE reports were similar between treatment groups with the most frequent primary causes being categorized as respiratory and cardiovascular.

Of the 31 (3%) and 37 (4%) on- and post-treatment deaths reported in the pooled COPD studies for the mepolizumab 100 mg and placebo groups, respectively, none (but one in the placebo group) was considered to be treatment-related by the investigator. The most frequently reported fatal SAE was COPD exacerbation (<1% in each treatment group). The adjudicated primary causes of death (CV, respiratory, cancer, unknown, and other) were similar between treatment groups.

On-treatment AESIs (systemic reactions, local injection site reactions, infections, including serious and potential opportunistic, neoplasms and malignancies) were reported with a similar incidence and exposure-adjusted event rate between the mepolizumab 100 mg and the placebo groups. The treatment estimates for CMH-adjusted RR and risk difference for all AESI categories and subcategories were consistent with a similar risk of AESI between the treatment groups.

Regarding CV safety data across the mepolizumab COPD program, no signal of increased risk for CV events was identified for mepolizumab. The overall incidence and risk of adjudicated MACE was low and similar between the mepolizumab 100 mg and the placebo groups.

The incidence of immunogenicity following mepolizumab (100 mg) administration was low, with 2% ADA positive participants, and no safety trends were apparent in review of the AEs in antibody positive versus antibody negative participants.

In the 52- to 104-week placebo-controlled study, systemic allergic (type I hypersensitivity) reactions were reported in 1 patient (<1%) in the group receiving mepolizumab 100 mg and in no patients in the placebo group. Other systemic reactions were reported by 4 patients (<1%) in the group receiving mepolizumab 100 mg and in 4 patients (<1%) in the placebo group (SmPC section 4.8).

In the two 52-week placebo-controlled studies, systemic allergic/hypersensitivity reactions were reported in 4 patients (<1%) in the groups receiving mepolizumab 100 mg and in 3 patients (<1%) in the placebo groups. Systemic non-allergic reactions were reported by 7 patients (1%) in the groups receiving mepolizumab 100 mg and in 10 patients (2%) in the placebo groups (SmPC section 4.8).

No new safety concerns emerged from the COPD safety dataset and no new ADRs have been proposed. Overall, the safety profile seen in the COPD population was consistent with the known safety profile of mepolizumab.

3.5. Uncertainties and limitations about unfavourable effects

There are no remaining uncertainties about unfavourable effects.

3.6. Effects Table

Table 175 Table. Effects Table for Nucala as an add-on maintenance treatment in adults for uncontrolled chronic obstructive pulmonary disease (COPD) characterised by raised blood eosinophils on a combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA)

Effect	Short description	Unit	Treatment Mepolizumab 100 mg Q4W	Control Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
AECOPD	Annualised rate of moderate or severe COPD exacerbations over the 52-104 week treatment period	Annualised rate	0.80	1.01	**Rate ratio** mepolizumab/placebo 0.79 95% CI (0.66, 0.94) p-value 0.011 **SOE**: Borderline clinically relevant 21% improvement (p-value = 0.011)	mITT 208657 (MATINEE) mITT population

Effect	Short description	Unit	Treatment Mepolizumab 100 mg Q4W	Control Placebo	Uncertainties / Strength of evidence	References
TTFE	Time to first (moderate/severe exacerbations) event	Days (median)	median time to first exacerbation 419	median time to first exacerbation 321	**Hazard ratio** mepolizumab/placebo: 0.77 95% CI (0.64, 0.93) p-value 0.009 **Unc**: Sole statistically significant supportive secondary endpoint	208657 (MATINEE) mITT population
AECOPD	Annualised rate of severe COPD exacerbations over the 52-104 week treatment period	Annualised rate	0.10	0.15	**Rate ratio** mepolizumab/ placebo: 0.66 95% CI (0.43, 1.01) p-value: N.S. **SOE**: Not statistically significant	mITT 208657 (MATINEE) mITT population
Unfavourable Effects						
AEs	Any on-treatment AE	Incidence (%); EAIR (events/1000 PY)	78; 3609.3	79; 3650.8	Majority were mild to moderate in intensity. No notable trends of concern between treatment groups in the pooled data or within individual studies.	Pooled COPD studies
Treatment-related AE	Any on -treatment AE considered by the investigator to be related to the treatment	Incidence (%); EAIR (events/1000 PY)	9; 149.4	10; 211.8	No fatal AEs reported as treatment-related in the mepolizumab 100 mg group.	Pooled COPD studies
SAEs	Any on-treatment SAE	Incidence (%); EAIR (events/1000 PY)	24; 467.3	27; 498.6	Majority were not considered related. No trends of concern in those reported as treatment-related SAEs	Pooled COPD studies
Deaths	On- and post-treatment SAEs	No. of participants (n); Incidence (%)	31 (3)	37 (4)	No fatal AEs were reported as treatment-related in the mepolizumab 100 mg group. SAE reports were adjudicated by the CEC.	Pooled COPD studies

Abbreviations: AECOPD, acute exacerbation of COPD; COPD, chronic obstructive pulmonary disease; TTFE, Time To First Event; SOE, Strength of Evidence; UNC, Uncertainty; EAIR = exposure-adjusted incidence rate; CEC = clinical endpoint committee; N.S., not statistically significant

Notes: participants were on background therapy including LABA+LAMA+ICS (unless ICS was contraindicated)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

COPD is a deleterious chronic disease of the airways, characterised by (deteriorating) airflow obstruction.

At the time these studies were initiated, there was no additional treatment option to COPD patients that continued to have exacerbations despite being on maximal SoC triple therapy with high eosinophil levels: however, dupilumab, a monoclonal antibody targeting IL-4R/IL-13R, has since been approved in this patient population.

Treatment with mepolizumab resulted in a statistically significant reduction in the annualized rate of moderate/severe exacerbations compared with placebo (rate ratio: 0.79; 95% CI: 0.66, 0.94; p=0.011). A 21% reduction in the annualised rate of exacerbations in the mepolizumab treatment group is considered clinically relevant in the context of the proposed indication. Additionally, mepolizumab appears to increase the amount of time it takes before a COPD patient will have their first (next) exacerbation event.

The safety profile seen in the COPD population was overall consistent with the known unfavourable effects of mepolizumab. No notable imbalances of clinical significance were observed between the mepolizumab and placebo treatment groups with respect to the incidence and EAIRs of AEs, SAEs and AESIs. No new safety concerns were identified.

3.7.2. Balance of benefits and risks

The efficacy of mepolizumab as a treatment for COPD characterised by raised blood eosinophils on a combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA) has been shown in respect to the effect on exacerbations. In addition, there is a trend towards the effect on symptoms. The safety profile of mepolizumab is well characterised and manageable.

The benefits of mepolizumab are considered to outweigh the risks in the proposed indication.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of Nucala as add-on maintenance treatment in adults for uncontrolled chronic obstructive pulmonary disease (COPD) characterised by raised blood eosinophils on a combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA) is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include treatment of treatment of Chronic Obstructive Pulmonary Disease (COPD); as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 16 of the RMP is approved. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet, to bring the PI in line with the latest QRD template version 10.4, to update the PI in accordance with the latest EMA excipients guideline, and to implement editorial changes to the PI.

The variation requested variation(s) proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, IIIA, IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.