Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Pavord ID, Chanez P, Criner GJ, et al. Mepolizumab for eosinophilic chronic obstructive pulmonary disease. N Engl J Med 2017;377:1613-29. DOI: 10.1056/NEJMoa1708208

SUPPLEMENTARY MATERIALS

Mepolizumab for eosinophilic chronic obstructive pulmonary disease

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3. Countries where the study was conducted

METREX

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METREO

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4. Detailed inclusion and exclusion criteria (METREX and METREO)

Inclusion criteria:

Patients eligible for enrollment in the study met all the following criteria:

1. **Chronic obstructive pulmonary disease (COPD) diagnosis:** Patients had a clinically documented history of COPD for ≥1 year in accordance with the definition provided by the American Thoracic Society/European Respiratory Society.[1]
2. **Severity of COPD:** Patients presented with the following:
    - A measured pre- and post-salbutamol forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio of <0.70 at screening to confirm the diagnosis of COPD.
    - A measured post-salbutamol FEV_1 >20% and ≤80% of predicted normal values, calculated using National Health and Nutrition Examination Survey (NHANES) III reference equations at screening.[2,3]
3. **History of exacerbations:** A well-documented history (e.g., medical record verification) in the 12 months prior to screening of:
    - **≥2 moderate COPD exacerbations:** Moderate is defined as the use of systemic glucocorticoids (intramuscular, intravenous, or oral) and/or treatment with antibiotics. OR
    - **≥1 severe COPD exacerbation:** Severe is defined as having required hospitalization.
    - Note: At least one exacerbation must have occurred while the patient was taking inhaled glucocorticoids (ICS) plus long-acting β_2-agonist (LABA) plus long-acting muscarinic antagonist (LAMA).
    - Note: 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.
4. **Concomitant COPD therapy:** A well-documented requirement for optimized standard of care background therapy that included ICS plus two additional COPD medications (i.e., triple therapy) for the 12 months prior to screening and, prior to screening, minimum of 3 months of use of:
    - ICS at a dose ≥500 µg/day fluticasone propionate dose equivalent, plus LABA and LAMA, and

- For patients who were not continually maintained on ICS plus LABA plus LAMA for the entire 12 months prior to screening, use of following was allowed (but not in the 3 months immediately prior to screening):
    - ICS at a dose ≥500 mcg/day fluticasone propionate dose equivalent plus LABA or LAMA, and
    - Use of at least one other class of COPD medication suggested by the 2013 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for patients who are prone to exacerbation (i.e., phosphodiesterase-4-inhibitors, methylxanthines, or a combination of short-acting β_2-agonist and short-acting muscarinic antagonist).
- Note: Patients must be willing to stay on their standard of care COPD medication for the duration of the study.

5. **Informed consent:** Patients were able to give written informed consent prior to participation in the study, which included the ability to comply with the requirements and restrictions listed in the consent form. Patients were able to read, comprehend, and write at a level sufficient to complete study-related materials.
6. **Gender:** Male or eligible female.
    - To be eligible for entry into the study, females of childbearing potential committed to consistent and correct use of an acceptable method of birth control from the time of consent, for the duration of the trial, and for 4 months after last study drug administration.
7. **Age:** ≥40 years of age at screening.
8. **Smoking status:** Patients with confirmed COPD were eligible to participate independent of their smoking status and smoking history (i.e., current smokers, never smokers, or ex-smokers were enrolled into the study). Note: Pipe and/or cigar use cannot be used to calculate pack-year history.
9. **French patients:** In France, patients were eligible for inclusion in this study only when either affiliated to or a beneficiary of a social security category.

Exclusion criteria

Patients meeting any of the following criteria were not enrolled in the study:

1. **Asthma:**
    - **Current and former smokers:** Patients with a current diagnosis of asthma (those with a prior history were eligible if they met the inclusion criteria for a current diagnosis of COPD).
    - **Never smokers:** Patients with any history of asthma.
2. **Other respiratory disorders:** The investigator judged that COPD was the primary diagnosis accounting for the clinical manifestations of the lung disease. Patients with α1-antitrypsin deficiency as the underlying cause of COPD were excluded. Also excluded were patients with active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, primary pulmonary hypertension, interstitial lung diseases, or other active pulmonary diseases. Patients were also excluded if maintenance use of bi-level positive airway pressure was required for the treatment of respiratory disorder.
3. **COPD stability:** Patients with pneumonia, exacerbation, or lower respiratory infection within the 4 weeks prior to screening were not eligible.
4. **Lung resection:** Patients with lung volume reduction surgery within the 12 months prior to screening were not eligible.
5. **Pulmonary rehabilitation program:** Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to screening. Patients who were in the maintenance phase of a pulmonary rehabilitation program were not excluded.
6. **Oxygen:** Patients receiving treatment with oxygen more than 4.0 L/min. While breathing supplemental oxygen, patients demonstrated an oxyhemoglobin saturation ≤89%.
7. **12-lead electrocardiogram (ECG) finding:** An abnormal and significant ECG finding from the 12-lead ECG conducted at screening if considered to be clinically significant by the investigator. 12-lead ECGs were over-read by a centralized independent cardiologist to assist in consistent evaluation of patient eligibility. Results from the 12-lead ECG over-read were received prior to assessing eligibility at Visit 2.
8. **Unstable or life-threatening cardiac disease:** Patients with any of the following were 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.

9. **Other diseases/abnormalities:** Patients with (historical or) current evidence of clinically significant, neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease) or hematological abnormalities that are uncontrolled. Significant is defined as any disease that, in the opinion of the investigator, would put the safety of the patient at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study.
10. **Eosinophilic disease:** Patients with other conditions that could lead to elevated eosinophils such as hypereosinophilic syndromes including eosinophilic granulomatosis with polyangiitis (also known as Churg-Strauss syndrome), or eosinophilic esophagitis.
11. **Parasitic infection:** Patients with a pre-existing helminth infestation (parasitic worms) within 6 months prior to screening were also excluded.
12. **Malignancy:** A current malignancy or previous history of cancer in remission for less than 12 months prior to screening (patients who had localized carcinoma of the skin or cervix that was resected for cure were not excluded).
    - Note for South Korea: Korean patients with a diagnosis of malignancy within 5 years of screening were excluded.
13. **Immunodeficiency:** A known immunodeficiency (e.g., human immunodeficiency virus – HIV) other than that explained by the use of glucocorticoids taken for COPD.
14. **Liver disease:** Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice), cirrhosis, and known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). Chronic stable hepatitis B and C were acceptable if the patient otherwise met entry criteria (e.g., presence of hepatitis B surface antigen or positive hepatitis C test result within 3 months of screening).
15. **Monoclonal antibodies:** Patients who had received any monoclonal antibody within 5 half-lives of screening.
16. **Investigational medications:** Patients who had received an investigational drug within 30 days of screening or 5 drug half-lives of the investigational drug, whichever was longer (this also includes investigational formulations of a marketed product).
17. **Hypersensitivity:** Patients with a known allergy or intolerance to another monoclonal antibody or biologic including history of anaphylaxis to another biologic.

18. **Inability to read:** In the opinion of the investigator, any patient who was unable to read and/or would not be able to complete study-related materials.
19. **Non-compliance:** Patients at risk of non-compliance or unable to comply with the study procedures. Any infirmity, disability, or geographic location that would limit compliance for scheduled visits.
20. **Questionable validity of consent:** Patients with a history of psychiatric disease, intellectual deficiency, poor motivation, or other conditions that would limit the validity of informed consent to participate in the study.
21. **Drug or alcohol abuse:** A known or suspected history of alcohol or drug abuse within 2 years prior to screening.
22. **Previous participation:** Patients who had previously participated in any study of mepolizumab.
23. **Affiliation with investigator site:** Investigators, sub-investigators, study coordinators, employees of a participating investigator or study site, or immediate family members of the aforementioned involved in this study were excluded.

5. Randomization

In order to be randomized to the study drug, patients met the following randomization criteria at Visit 2:

1. **Blood eosinophils:**
    - **METREX:** While there was no threshold for enrollment, information on eosinophil count was obtained prior to randomization.
    - **METREO:**
        - Documented elevated peripheral blood eosinophil count of ≥300 cells/µL within the past 12 months prior to screening, OR
        - A peripheral blood eosinophil count of ≥150 cells/µL from hematology conducted at screening.
2. **Electronic diary (eDiary) compliance:** Compliance with completion of the eDiary, defined as completion of all questions on 5 or more days out of the 7 days immediately preceding Visit 2.
3. **12-lead ECG:** No evidence of an abnormal and significant ECG finding from the 12-lead ECG conducted at screening as indicated on the over-read provided by the centralized independent cardiologist. Patients with a QT correction Fridericia formula (QTcF) ≥450

msec were not eligible. For patients with a QRS interval ≥ 120 msec, those with QTcF ≥480 msec were not eligible.

4. **Abnormal chest X-ray (or computed tomography [CT] scan)**: No chest X-ray (or CT scan) that revealed evidence of clinically significant abnormalities not believed to be due to the presence of COPD. If a chest X-ray or CT scan was not available within 6 months prior to screening, then a chest X-ray was taken at screening and the results reviewed prior to randomization.
    - For sites in Germany: If a chest X-ray (or CT scan) within 6 months prior to screening (Visit 1) was not available, the patient was not eligible for the study.
5. **Laboratory abnormality:** No evidence of clinically significant abnormality in the hematological, biochemical, or urinalysis screen at screening, as judged by the investigator.
6. **Hepatitis B:** Patients who were HBsAg positive or HBcAb positive did not have a HBV DNA level ≥2000 IU/mL.
7. **Liver function test:** Patients met the following based on results from a sample taken at screening:
    - Alanine aminotransferase (ALT) <2x upper limit of normal (ULN).
    - Alkaline phosphatase (alk phos) ≤2x ULN.
    - Bilirubin ≤1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
8. **Pregnancy:** No patients who were pregnant or breastfeeding. Patients were not enrolled if they planned on becoming pregnant during the time of study participation.

METREX

Randomization was performed using a centralized, computer-generated, permuted-block schedule with a fixed block size of 6. Separate schedules were generated for each country, and each was stratified by blood eosinophil count (patients with [≥150 cells/µL at screening or ≥300 cells/µL in the previous year] or without [<150 cells/µL at screening and no evidence of ≥300 cells/µL in the previous year] an eosinophilic phenotype).

METREO

Randomization was performed by using a centralized, computer-generated, permuted-block design with fixed block size of six; separate schedules were generated for each country.

METREX and METREO

Mepolizumab and placebo preparations were identical in appearance, administered in a blinded fashion, and prepared by staff members who were aware of the trial-group assignments but not involved in the trial assessments. Physicians who were treating and evaluating patients were unaware of the preparation of the trial agents and trial-group assignments and did not have access to blood eosinophil counts after randomization.

6. Other endpoints and pre-specified analyses

Other pre-specified endpoints included:

- Change from baseline in pre-bronchodilator FEV_1.
- Change from baseline in pre-bronchodilator FVC.
- Change from baseline in St. George's Respiratory Questionnaire (SGRQ) domain scores.
- Proportion of SGRQ responders (≥4-point improvement).
- Proportion of COPD Assessment Test (CAT) responders (2-unit improvement).

Pre-specified meta-analyses of the primary endpoint in the combined population (METREX mITT-EOS and METREO mITT) were performed according to:

- Blood eosinophil count categories (<150 [history of ≥300 in the previous year] cells/µL, ≥150–<300 cells/µL, ≥300–<500 cells/µL, and ≥500 cells/µL.
- Blood eosinophil count thresholds (150 [history of ≥300 in the previous year] cells/µL, ≥150 cells/µL, ≥300 cells/µL, and ≥500 cells/µL.

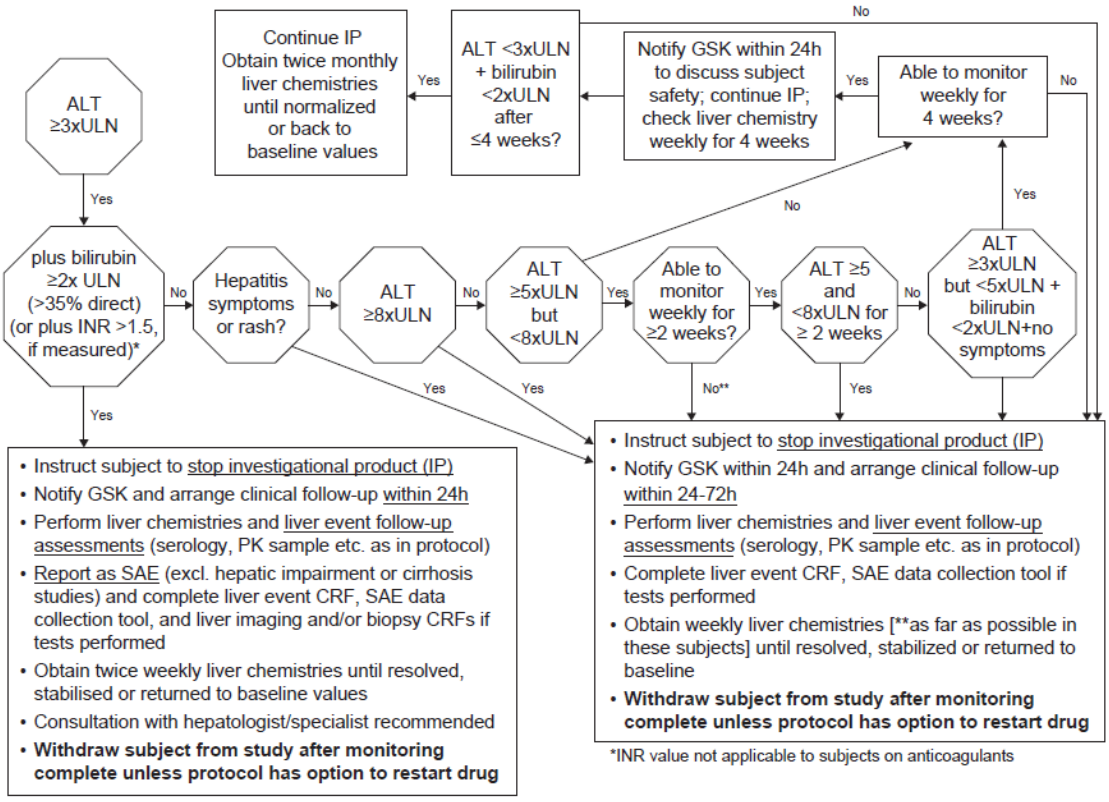
Post-hoc meta-analyses of the primary endpoint were also performed in patients with:

- Blood eosinophil counts <150 cells/µL (regardless of historical blood eosinophil counts): includes all patients from METREX mITT-nonEos, 13 patients from METREX mITT-Eos and 124 patients from METREO mITT.
- Blood eosinophil counts ≥300 cells/µL at screening or in the previous year (METREX mITT-Eos and METREO mITT populations).

The effect of mepolizumab compared to placebo was assessed on moderate/severe exacerbations treated with glucocorticoids (alone or in addition to antibiotics), as well as

those treated with antibiotics alone (METREX mITT-All and METREO mITT populations combined).

7. Liver chemistry stopping criteria



ALT, alanine aminotransferase; CRF, chronic renal failure; INR, International Normalized Ratio; IP, investigational product; PK, pharmacokinetics; SAE, serious adverse event; ULN, upper limit of normal.

8. Sample size calculation

METREX

For the comparison of treatment effect in patients with an eosinophilic phenotype, an estimated 400 patients (200 patients in each group) would provide 90% power to detect a 35% decrease in the rate of moderate/severe exacerbations from 2.0 per year in the placebo group to 1.3 per year in the mepolizumab group at a two-sided 4% alpha level. An additional 400 patients (200 patients in each group) with non-eosinophilic COPD were also included in the trial, providing 90% power to detect a 30% reduction with mepolizumab at a two-sided 1% alpha level in the mITT-All population. The sample-size calculation assumed the number of exacerbations followed a negative binomial distribution with a dispersion parameter of k=0.8, estimated from data observed in the DREAM study.

METREO

An estimated 660 patients (220 patients in each group) were expected to provide the trial with 90% power to detect a 35% decrease in the rate of moderate/severe exacerbations from 2.0 per year in the placebo group to 1.3 per year in each mepolizumab group at a two-sided significance level of 0.05. The sample size calculation assumed the number of exacerbations followed a negative binomial distribution[4] with a dispersion parameter of k=0.8, estimated from data observed in the DREAM study.[5]

9. Adjustment for multiplicity

METREX

For each endpoint, the primary treatment comparison of interest was mepolizumab 100 mg SC versus placebo for patients with an eosinophilic phenotype (mITT-Eos). This comparison was also of interest in the overall population (mITT-All). Due to the two treatment comparisons of interest, the overall α of 0.05 was split such that 0.04 was allocated to treatment comparisons for the group of patients with an eosinophilic phenotype and the remaining 0.01 was allocated to the treatment comparisons for all patients in the study.

Equivalent adjusted P-values were calculated for the primary endpoint by multiplying the unadjusted P-value for the comparison in the stratum of patients with an eosinophilic phenotype by 1.25 and the unadjusted P-value for the comparison of all patients by 5.

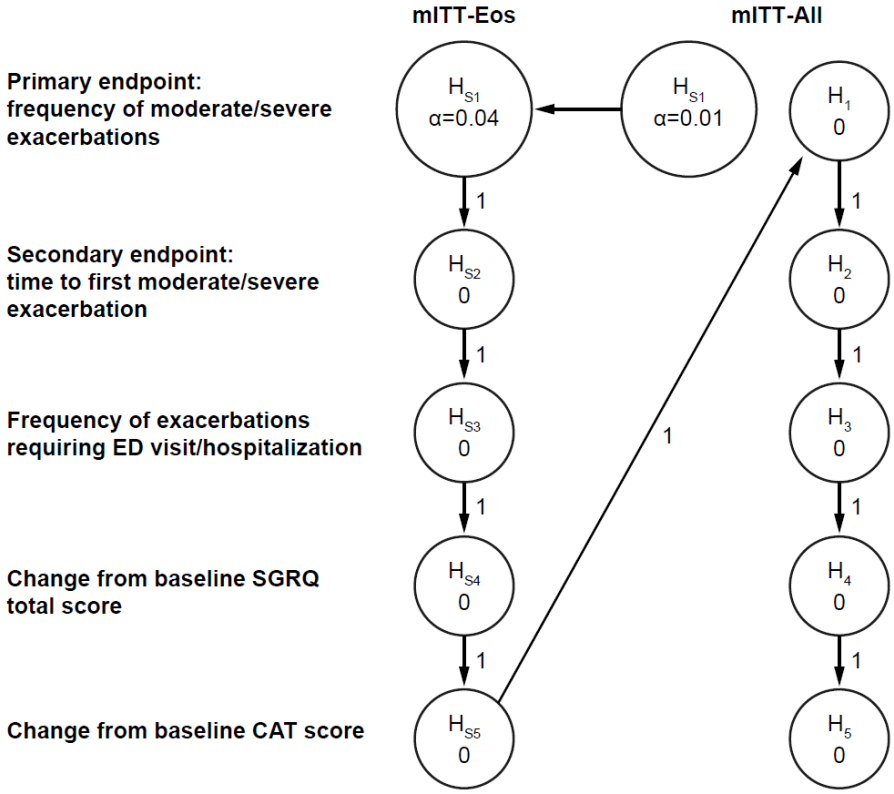
When strong control of the overall type I error for secondary endpoints was required, a hierarchical approach was used. The hierarchy of endpoints was as follows:

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

Significance is only possible at the unadjusted P=0.04 level in patients with an eosinophilic phenotype for each secondary endpoint in the hierarchy if comparisons unadjusted have P<0.04 for the primary and for all preceding secondary endpoints.

Equivalent adjusted P-values were calculated for each secondary endpoint in the patients with an eosinophilic phenotype by multiplying the unadjusted P-value by 1.25 and then

taking the maximum of this value and the adjusted P-value for the previous endpoint in the hierarchy. The figure below details the multiple-testing strategy with hierarchical testing followed for the primary and secondary endpoints in the eosinophilic phenotype and overall populations.



Note: Hsi corresponds to the i=1 to 5 null hypotheses for the primary and secondary endpoints in the patients with an eosinophilic phenotype; Hi corresponds to the i=1 to 5 null hypotheses for the primary and secondary endpoints in the overall population. CAT, COPD Assessment Test; ED, emergency department; SGRQ, St George's Respiratory Questionnaire.

METREO

There are two primary treatment comparisons of interest for the primary and secondary endpoints: mepolizumab 100 mg SC versus placebo and mepolizumab 300 mg SC versus placebo. Multiplicity arising from the two treatment comparisons within each endpoint was controlled using a Hochberg testing procedure.[6] Each dose of mepolizumab was compared with placebo and significance was declared at the 5% level when both of these tests demonstrated statistical significance at the 5% level or when at least one of these tests demonstrated statistical significance at the 2.5% level. This procedure implies the following equivalent adjusted P-values: for the treatment comparison with the smaller of the two P-values, the adjusted P-value is double the unadjusted value (or the unadjusted P-value for

the other comparison if this is smaller). The comparison with the larger unadjusted P-value has the same unadjusted and adjusted P-value.

When strong control of the overall type I error for secondary endpoints was required, a hierarchical approach was used. The hierarchy of endpoints to be tested was as follows:

1. Annual rate of moderate/severe exacerbations (primary endpoint).
2. Time to first moderate/severe exacerbation.
3. Annual rate of COPD exacerbations requiring emergency department (ED) visit and/or hospitalization.
4. Change from baseline mean total SGRQ score.
5. Change from baseline COPD assessment test (CAT) score.

Significance is only possible at the p=0.05 level for each secondary endpoint in the hierarchy if both comparisons unadjusted have p<0.05 for the primary and for all preceding secondary endpoints.

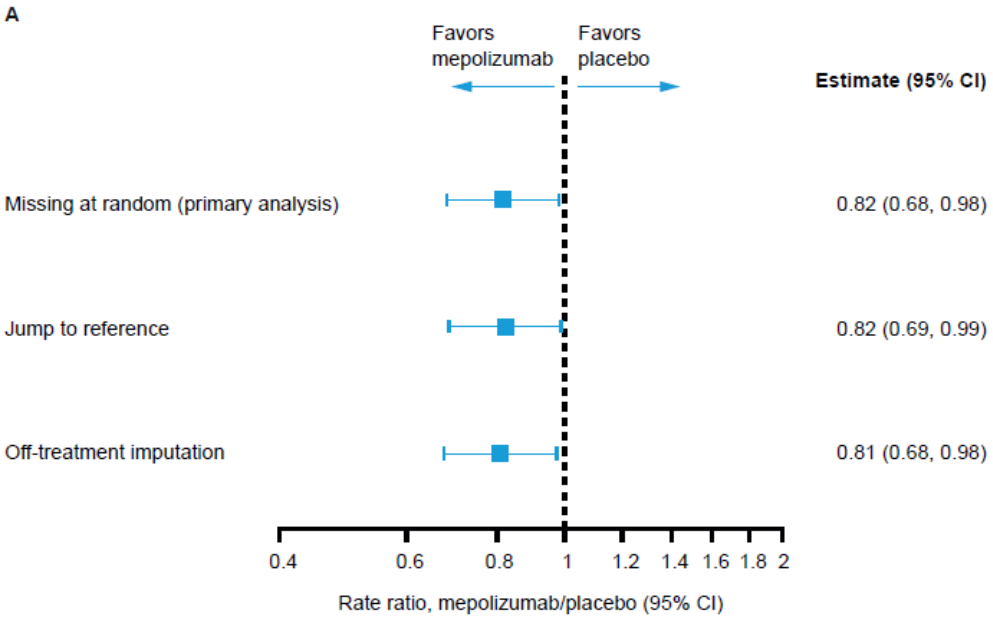
Adjusted P-values for secondary endpoints were calculated as follows. First a Hochberg adjustment is applied as for the primary endpoint above. If there was a larger P-value for the primary or any preceding secondary endpoint in the hierarchy, then the adjusted P-value is set equal to that value.

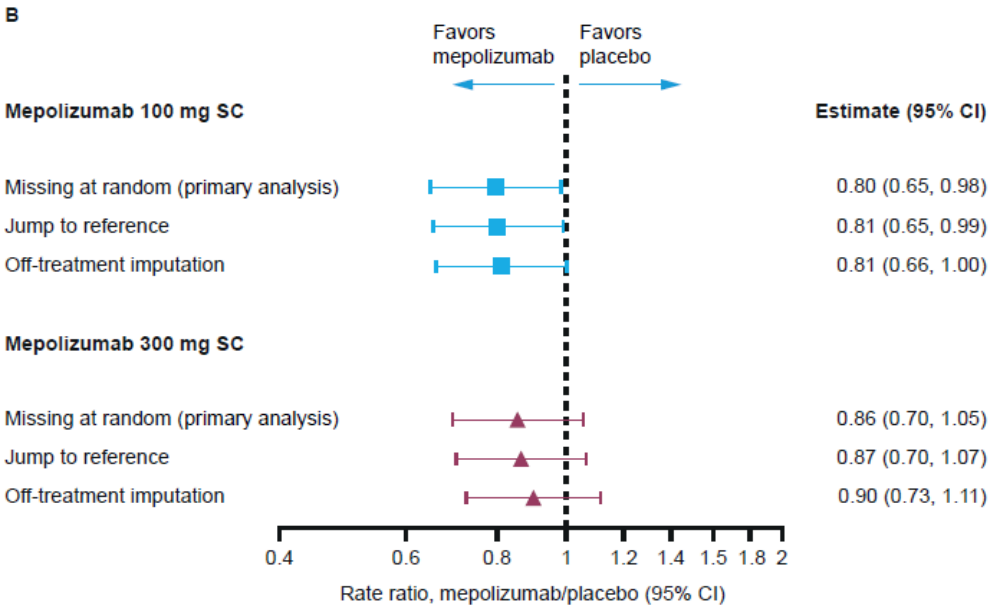
10. Sensitivity analysis for primary endpoint

METREX and METREO

The negative binomial model used for the primary analysis assumes missing data is missing at random; sensitivity analyses performed indicated a robustness of the primary efficacy results in the METREX mITT-Eos population and the METREO mITT population to departures from the assumption regarding missing data. Missing data for patients who withdrew early from the study were imputed for the period between study withdrawal and the Week 52 visit using a jump to reference (J2R, the rate for mepolizumab-treated patients is shifted to that seen in the placebo arm[7]) and an approach whereby imputations were based on the off-treatment data collected within each treatment (see the Sensitivity figure for METREX and METREO below).

Sensitivity analysis for A) METREX and B) METREO





METREX: mITT-Eos population; METREO: mITT population
CI, confidence interval; SC, subcutaneous.

11. Results of other endpoints, subgroup analyses in METREX and METREO, and the results from the METREX mITT-nonEos population

The study designs of METREX and METREO are summarized in **Fig. S1.**

METREX mITT-Eos and mITT-ALL populations, and METREO mITT population: additional patient demographics and characteristics at baseline, and secondary endpoint data
Additional patient demographics and characteristics at baseline are shown in **Table S1.** Additional secondary endpoint data is in **Table S2,** and data for other endpoints is in **Table S3**.

METREX mITT-Eos and METREO mITT populations: secondary endpoints
In METREX, improvements from baseline in SGRQ total score and CAT score with mepolizumab versus placebo were observed until Week 24, after which treatment effects with mepolizumab versus placebo were similar (**Fig. S2A and C**). In METREO, health-related quality of life outcomes (change from baseline at Week 52 in SGRQ total score and CAT scores) were similar for mepolizumab and placebo (**Fig. S2B and D**).

METREX mITT-Eos and METREO mITT: pre-specified meta-analyses
Pre-specified meta-analyses of the primary endpoint by screening blood eosinophil count threshold are shown in **Fig. S3**. This graph also includes a post hoc analysis of patients with blood eosinophil counts <150 cells/µL, regardless of historical blood eosinophil count. The annual rates of moderate/severe exacerbations for mepolizumab and placebo by screening blood eosinophil count categories are shown in **Fig. S4**. Pre-specified meta-analysis of the primary endpoint by region shown in **Fig S6**.

METREX mITT-Eos and METREO mITT: post-hoc meta-analyses
A post-hoc meta-analysis of the rate of moderate/severe exacerbations in patients with blood eosinophil counts ≥300 cells/µL at screening or in the prior year in the METREX mITT-Eos and METREO mITT populations is shown in **Fig. S5**.

METREX mITT-All and METREO mITT: post-hoc meta-analyses

A post hoc meta-analysis of the rate of moderate/severe exacerbations by treated with glucocorticoids (alone or in addition to antibiotics) or antibiotics alone demonstrated greater treatment effects with mepolizumab versus placebo with increasing screening blood eosinophil count for exacerbations treated with glucocorticoids. The annual rate of exacerbations treated with antibiotics alone was broadly similar at all screening blood eosinophil counts in all patients receiving mepolizumab and placebo (**Fig S7**).

METREX mITT-Eos and METREO mITT populations: other endpoints

Mepolizumab compared with placebo reduced blood eosinophil counts from screening by almost 73% in METREX and 72% and 77% with mepolizumab 100 mg and mepolizumab 300 mg, respectively, in METREO within the first 4 weeks, and these low levels were maintained for the duration of the study (**Fig. S8**). Change from baseline FEV_1 and FVC did not differ among the treatment groups throughout the duration of the trials (**Fig. S9**). The proportion of SGRQ and CAT responders at Week 52 (as defined by achievement of their respective minimal clinically important difference [MCID][8-12]) was similar with mepolizumab versus placebo in METREX and METREO (**Table S3**). The effect of mepolizumab on the individual SGRQ domains (symptoms, activity, impacts) was similar to placebo in both trials (**Fig. S10**). In METREX, physician- and patient-rated response to treatment showed a trend towards of improvement with mepolizumab versus placebo (**Table S3**). In METREO, the physician-rated response showed a trend towards improvement in the 100-mg group versus placebo (**Table S3**). This was not as apparent in the patient-rated response (**Table S3**).

METREX safety-Eos and safety-ALL populations, and METREO safety population:

Additional safety data is shown in **Table S4**.

METREX mITT-nonEos population: demographics, primary, and secondary endpoints

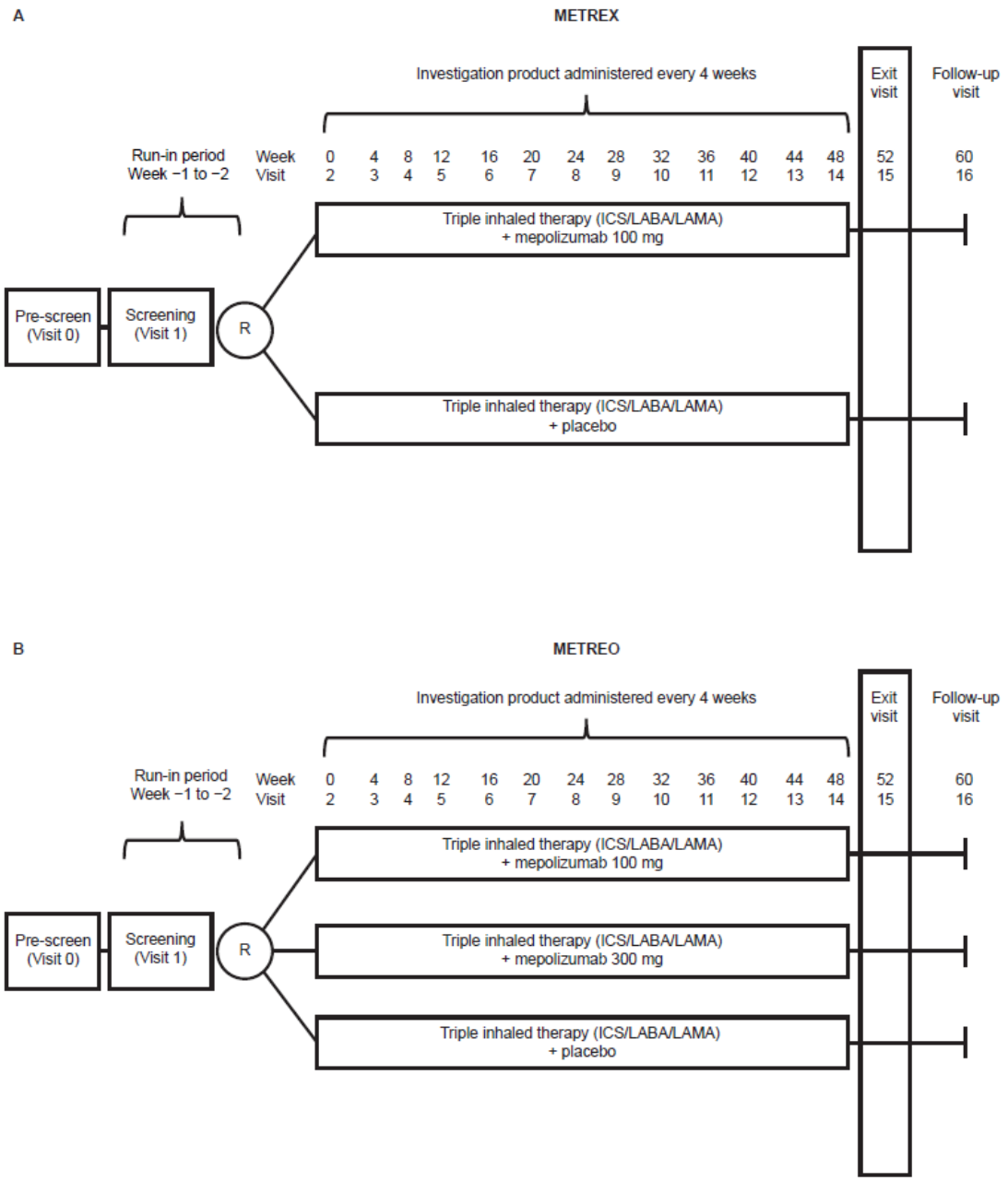
Patient demographics and clinical characteristics are summarized in **Table S5**. There was no significant difference in the annual rate of moderate/severe exacerbations with mepolizumab versus placebo, although a numerical trend for an increase with mepolizumab was observed (**Table S6**). No significant differences in any secondary endpoints were observed with mepolizumab versus placebo (**Table S6**).

METREX safety-nonEos population: safety

There was no difference between the mepolizumab and placebo groups in the proportion of patients who experienced AEs, SAEs, fatal AEs, or systemic/local-site reaction AEs (**Table S7**).

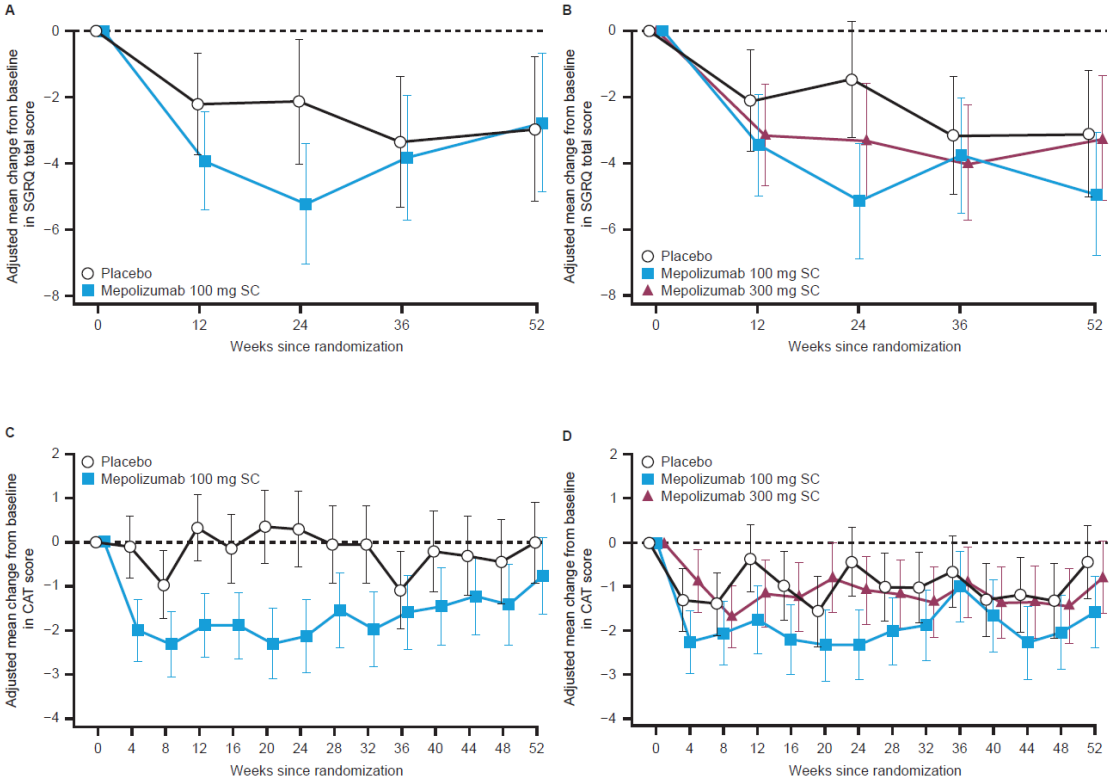
12. Supplementary figures and tables

Fig. S1. Study design of A) METREX and B) METREO.



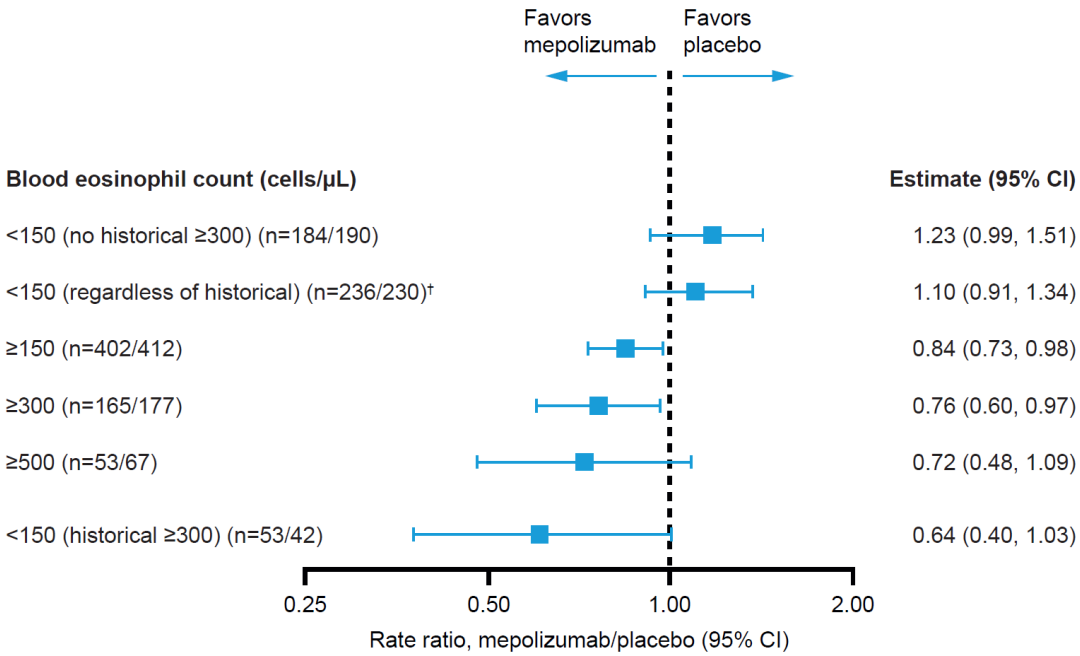
METREX randomization stratified: eosinophilic phenotype (≥150 cells/µL at screening or ≥300 cells/µL at any point in the previous year) or non-eosinophilic phenotype (<150 cells/µL at screening and no evidence of ≥300 cells/µL in the previous year).
ICS, inhaled glucocorticoids; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonists; R, randomization

Fig. S2. Secondary endpoints: change from baseline in SGRQ total score and CAT score during the 52-week study in the METREX mITT-Eos population (A and C) and METREO mITT population (B and D).



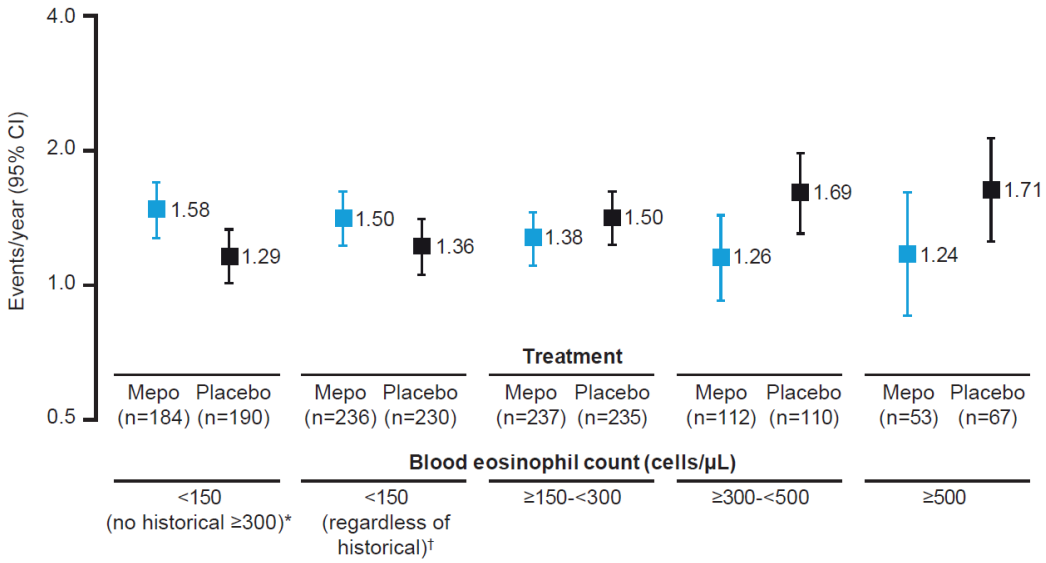
METREX mITT-Eos population: patients with ≥150 cells/µL at screening or ≥300 cells/µL within the previous year.
METREO mITT population: patients receiving ≥1 dose of mepolizumab or placebo.
CAT, COPD Assessment Test score (range, 0–40 points, with higher scores greater disease impact; MCID −2 units).
CAT, COPD Assessment Test; Eos, eosinophils; MCID, minimal clinically important difference; mITT, modified intention-to-treat; SC, subcutaneous; SGRQ, St George's Respiratory Questionnaire total score (range, 0–100 points, with higher scores indicating worse health status; MCID, −4 points).

Fig. S3. Moderate/severe exacerbations by screening blood eosinophil count thresholds for mepolizumab 100 mg versus placebo (meta-analysis of METREX and METREO mITT populations).



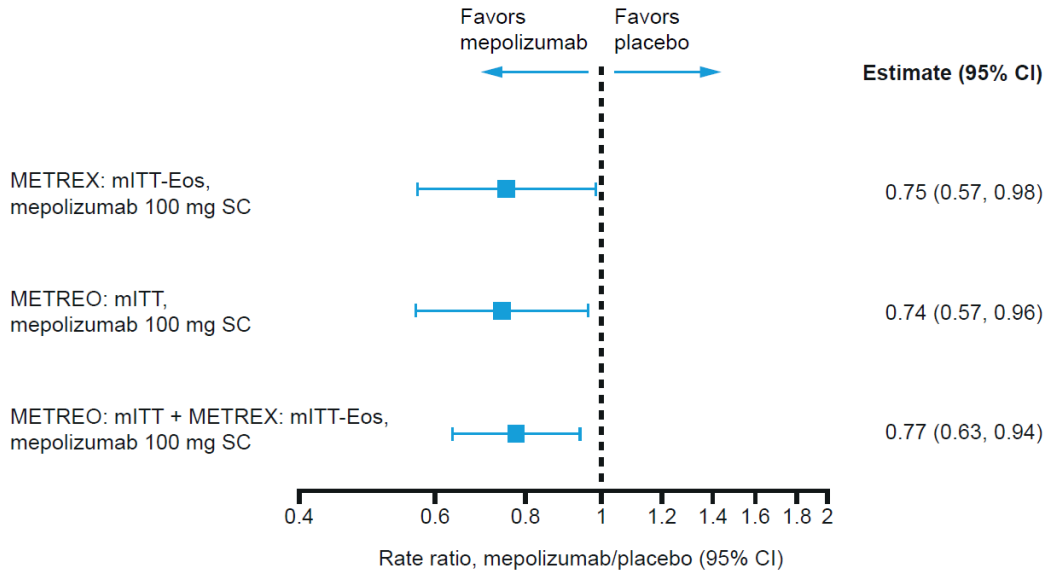
*<150 (no historical ≥300) from the METREX mITT-nonEos population.
†Post hoc analysis of METREX mITT-All and METREO mITT includes patients with an eosinophil count ≥300 cells/µL in previous year.
Remaining analyses are from a pre-specified meta-analysis of data from METREX mITT-Eos and METREO mITT.
The number of patients in each subgroup are shown for mepolizumab 100mg SC/placebo.
METREX mITT-All population: patients receiving ≥1 dose of mepolizumab or placebo;
METREX mITT-Eos population: patients with ≥150 cells/µL at screening or ≥300 cells/µL within the previous year.
METREO mITT population: patients receiving ≥1 dose of mepolizumab or placebo.
CI, confidence interval; Eos, eosinophils; mITT, modified intention-to-treat; SC, subcutaneous.

Fig S4. Rates of moderate/severe exacerbations by screening blood eosinophil count categories for mepolizumab 100 mg versus placebo (meta-analysis of the METREX and METREO mITT populations).



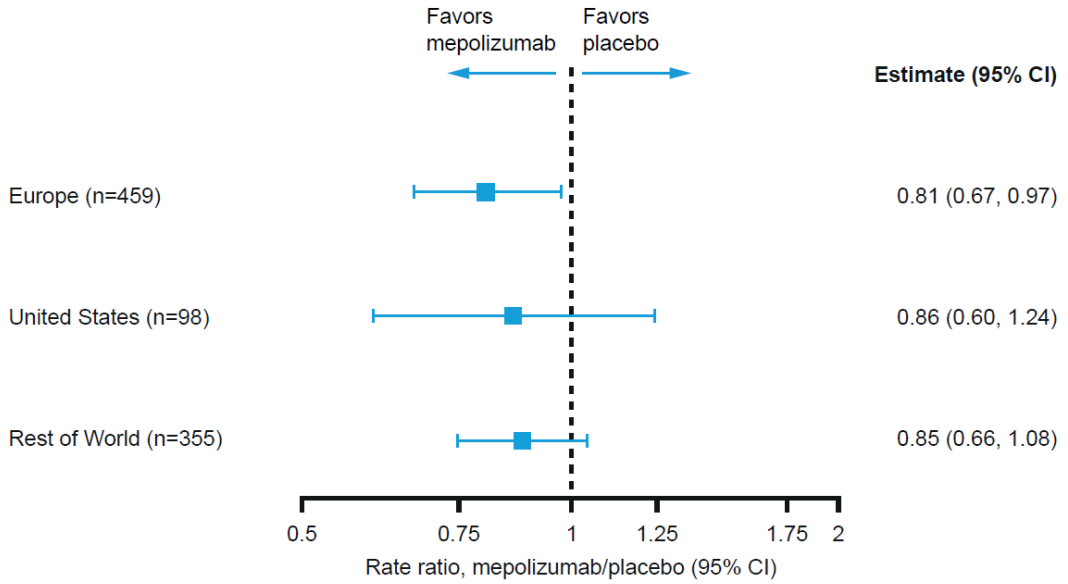
*<150 (no historical ≥300) from the METREX mITT-nonEos population.
†Post hoc analysis of METREX mITT-All and METREO mITT includes patients with an eosinophil count ≥300 cells/µL in previous year.
Remaining analyses are from a pre-specified meta-analysis of data from METREX mITT-Eos and METREO mITT.
The number of patients in each subgroup are shown for mepolizumab 100mg SC/placebo.
METREX mITT-All population: patients receiving ≥1 dose of mepolizumab or placebo;
METREX mITT-Eos population: patients with ≥150 cells/µL at screening or ≥300 cells/µL within the previous year.
METREO mITT population: patients receiving ≥1 dose of mepolizumab or placebo.
CI, confidence interval; Eos, eosinophils; mITT, modified intention-to-treat; SC, subcutaneous.

Fig. S5. Post hoc meta-analysis: moderate/severe exacerbations in patients with blood eosinophil counts ≥300 cells/µL at screening or in the prior year (METREX mITT-Eos and METREO mITT populations).



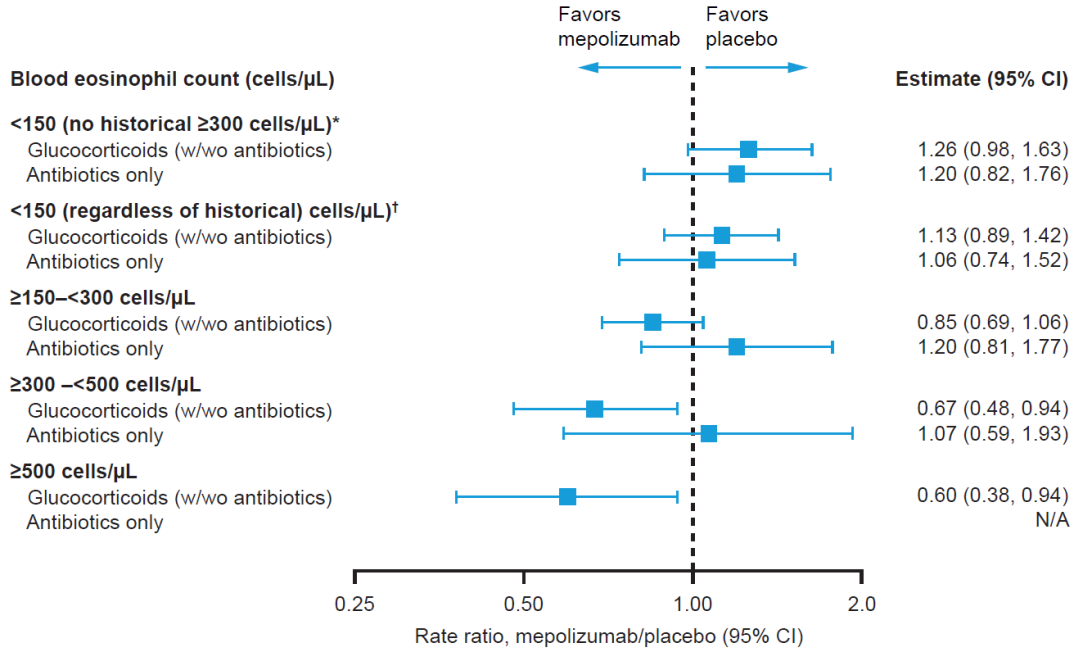
METREX mITT-Eos population: patients with ≥150 cells/µL at screening or ≥300 cells/µL within the previous year.
METREO mITT population: patients receiving ≥1 dose of mepolizumab or placebo.
CI, confidence interval; Eos, eosinophils; mITT, modified intention-to-treat; SC, subcutaneous.

Fig. S6. Pre-specified meta-analysis: moderate/severe exacerbations by region in meta-analysis for mepolizumab 100 mg versus placebo (METREX mITT-Eos and METREO mITT populations).



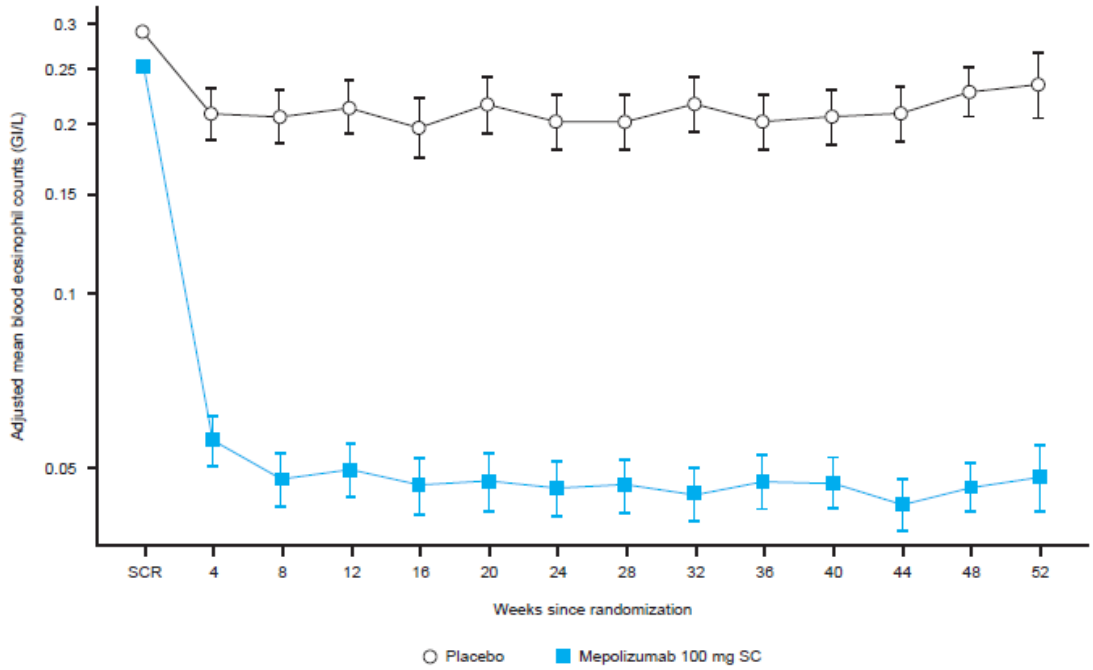
Europe (N=459): METREX: Belgium (n=32), Czech Republic (n=10), Estonia (n=13), France (n=25), Greece (n=28), Italy (n=36), Norway (n=9), Poland (n=56), Spain (n=25), Sweden (n=7); METREO: Denmark (n=15), Germany (n=62), The Netherlands (n=34), Romania (n=51), Slovakia (n=20), United Kingdom (n=15), Ukraine (n=21).
United States (N=98): METREX (n=45); METREO (n=53)
Rest of World (N=355): METREX: Australia (n=23), Canada (n=57), Mexico (n=33), Peru (n=38), Russian Federation (n=26); METREO: Argentina (n=56), Australia (n=7), Canada (n=11), Chile (n=22), Japan (n=27), Republic of Korea (n=47), Taiwan (n=8).
METREX mITT-Eos population: patients with ≥150 cells/µL at screening or ≥300 cells/µL within the previous year.
METREO mITT population: patients receiving ≥1 dose of mepolizumab or placebo.
CI, confidence interval; mITT, modified intention-to-treat.

Sig S7. Post hoc meta-analyses: moderate/severe exacerbations by treatment type (glucocorticoids/antibiotics) stratified by screening blood eosinophil count categories (METREX mITT-All and METREO mITT populations).

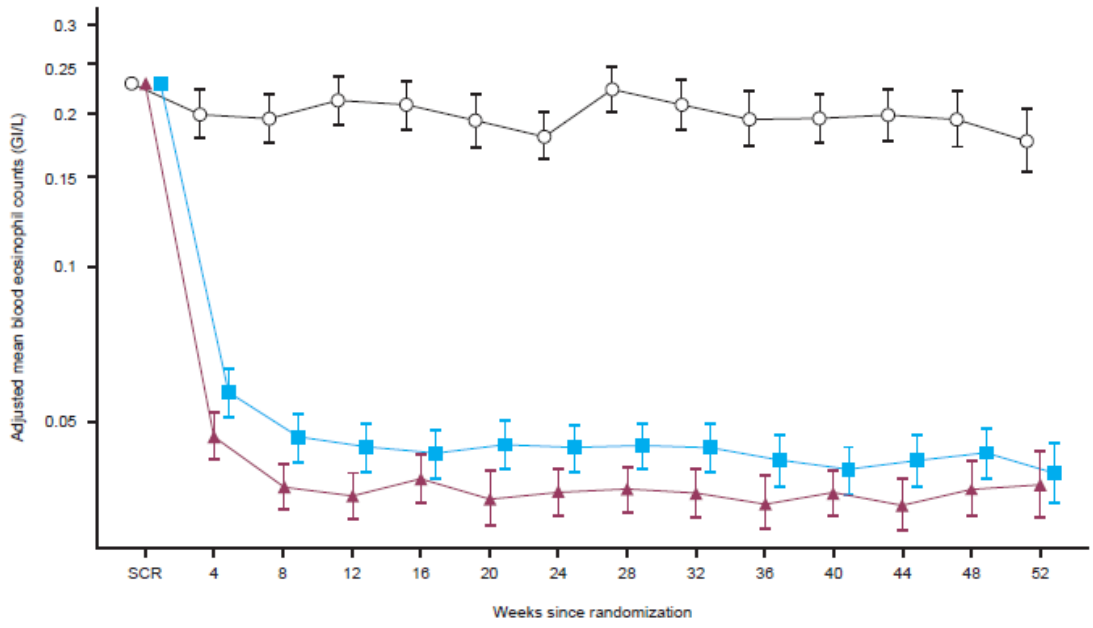


*<150 (no historical ≥300) from the METREX mITT-nonEos population.
†Post hoc analysis of METREX mITT-All and METREO mITT includes patients with an eosinophil count ≥300 cells/µL in previous year.
Analysis uses the mepolizumab 100mg SC group.
METREX mITT-All population: patients receiving ≥1 dose of mepolizumab or placebo;
METREX mITT-Eos population: patients with ≥150 cells/µL at screening or ≥300 cells/µL within the previous year.
METREO mITT population: patients receiving ≥1 dose of mepolizumab or placebo.
CI, confidence interval; Eos, eosinophils; mITT, modified intention-to-treat; SC, subcutaneous; w/wo, with or without.

Fig. S8. Adjusted mean blood eosinophil counts during the 52-week study in the METREX mITT-Eos population (A) and METREO mITT population (B).

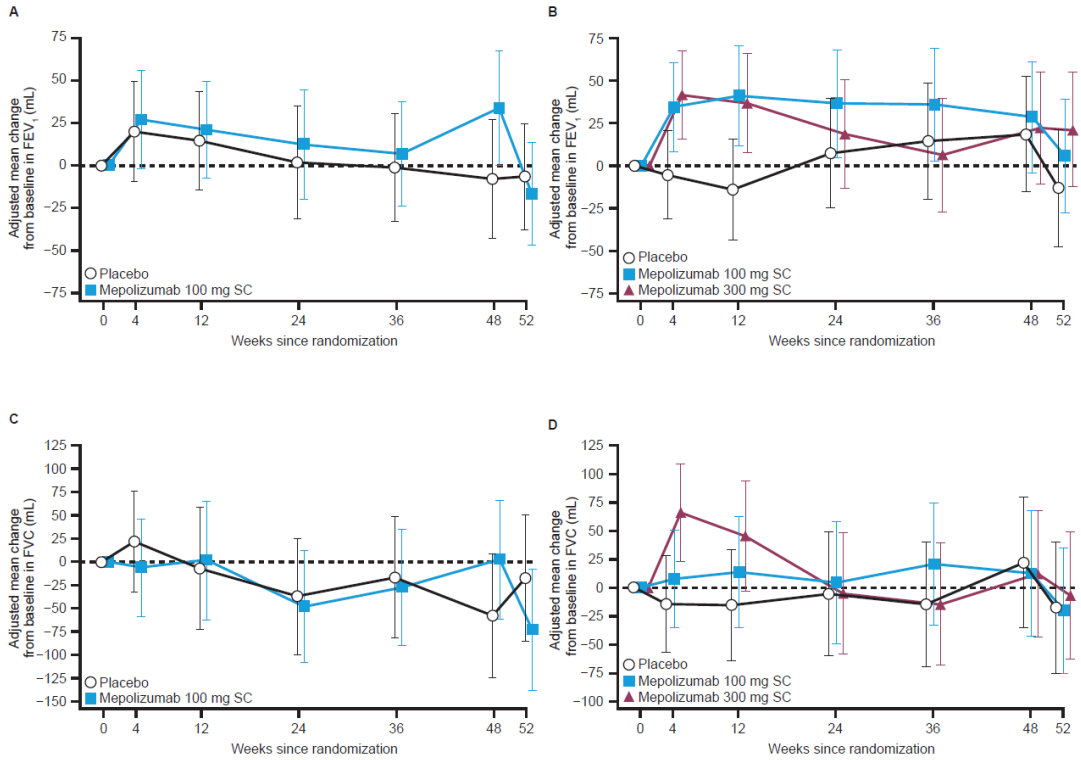


B



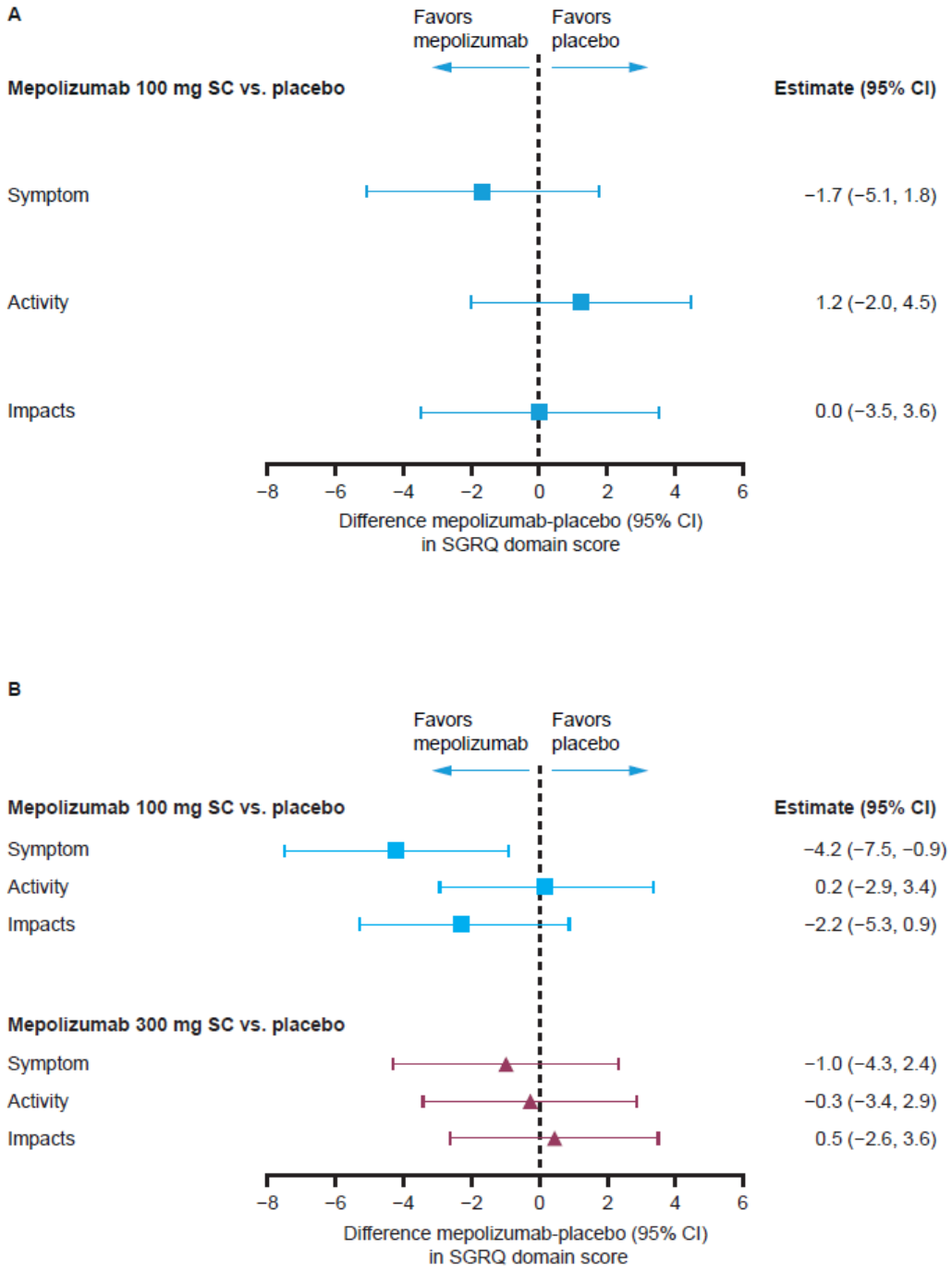
METREX mITT-Eos population: patients with ≥150 cells/µL at screening or ≥300 cells/µL within the previous year.
METREO mITT population: patients receiving ≥1 dose of mepolizumab or placebo.
Eos, eosinophils; mITT, modified intention-to-treat; SC, subcutaneous.

Fig. S9. Other endpoints: change from baseline in pre-bronchodilator FEV_1 and pre-bronchodilator FVC during the 52-week study in the METREX mITT-Eos population (A and C) and METREO mITT population (B and D).



METREX mITT-Eos population: patients with ≥150 cells/µL at screening or ≥300 cells/µL within the previous year.
METREO mITT population: patients receiving ≥1 dose of mepolizumab or placebo.
Eos, eosinophils; FEV_1, forced expiratory volume in 1s; FVC, forced vital capacity; mITT, modified intention-to-treat; SC, subcutaneous.

Fig. S10. Other endpoints: SGRQ domain scores at Week 52 in the METREX mITT-Eos population (A) and METREO mITT population (B).



METREX mITT-Eos population: patients with ≥150 cells/µL at screening or ≥300 cells/µL within the previous year.
METREO mITT population: patients receiving ≥1 dose of mepolizumab or placebo.
CI, confidence interval; Eos, eosinophils; mITT, modified intention-to-treat; SC, subcutaneous;
SGRQ, St George's Respiratory Questionnaire (range 0–100 points, with higher scores indicating worse health status; MCID −4 points).

Table S1. Additional patient demographics and characteristics at baseline for METREX (mITT-Eos and mITT-All Populations) and METREO (mITT population).

	METREX				METREO		
	mITT-Eos		mITT-All		mITT		
	Mepolizumab 100 mg SC (N=233)	**Placebo (N=229)**	**Mepolizumab 100 mg SC (N=417)**	**Placebo (N=419)**	**Mepolizumab 100 mg SC (N=223)**	**Mepolizumab 300 mg SC (N=225)**	**Placebo (N=226)**
Body mass index, kg/m^2, mean (SD)*	27.1 (5.7)	26.7 (5.6)	26.9 (5.9)	27.0 (5.6)	27.1 (6.2)	26.4 (5.2)	25.4 (5.0)
Smoking history							
Non-smoker, n (%)	7 (3)	11 (5)	16 (4)	24 (6)	5 (2)	6 (3)	2 (<1)
Current smoker, n (%)	62 (27)	72 (31)	106 (25)	116 (28)	55 (25)	71 (32)	63 (28)
Former smoker, n (%)	164 (70)	146 (64)	295 (71)	279 (67)	163 (73)	148 (66)	161 (71)
Pack-years, mean (SD)	43 (24)	46 (27)	46 (27)	46 (26)	42.6 (25.9)	44.1 (30.8)	46.1 (27.2)
History of moderate/severe exacerbations in the 12 months prior to screening, Mean (SD)	2.6 (1.3)	2.5 (1.2)	2.5 (1.2)	2.5 (1.2)	2.7 (1.4)	2.7 (1.5)	2.6 (1.4)
≥1 treated with SCS and/or antibiotics but did not require ED visit/hospitalization, n (%)	177 (76)	176 (77)	316 (76)	334 (80)	195 (87)	192 (85)	182 (81)
≥1 requiring ED only, n (%)	32 (14)	33 (14)	70 (17)	61 (15)	23 (10)	19 (8)	17 (8)
≥1 requiring hospitalization without ICU, n (%)	67 (29)	72 (31)	117 (28)	119 (28)	70 (31)	59 (26)	79 (35)
≥1 requiring hospitalization in ICU, n (%)	14 (6)	7 (3)	20 (5)	13 (3)	6 (3)	4 (2)	8 (4)
Severity of airflow limitation (FEV_1 % predicted range), n (%)[a]							
Mild (≥80% predicted)	3 (1)	2 (<1)	4 (<1)	3 (<1)	3 (1)	2 (<1)	2 (<1)
Moderate (≥50-<80% predicted)	78 (33)	66 (29)	142 (34)	126 (30)	91 (41)	83 (37)	90 (40)
Severe (≥30-<50% predicted)	114 (49)	120 (52)	199 (48)	213 (51)	96 (43)	98 (44)	97 (43)
Very severe (<30% predicted)	38 (16)	41 (18)	72 (17)	77 (18)	33 (15)	42 (19)	37 (16)
Pre-bronchodilator lung function (at screening)							
FEV_1, L, mean (SD)	1.14 (0.45)	1.12 (0.44)	1.12 (0.46)	1.11 (0.44)	1.19 (0.46)	1.17 (0.49)	1.17 (0.48)
FEV_1 % predicted, mean (SD)	41.8 (14.7)	39.8 (13.8)	41.6 (15.0)	40.4 (13.9)	44 (15)	42 (15)	42 (14)

FVC, L, mean (SD)	2.56 (0.84)	2.56 (0.79)	2.51 (0.82)	2.52 (0.79)	2.61 (0.77)	2.67 (0.86)	2.70 (0.83)
FEV_1:FVC ratio, mean (SD)	0.5 (0.1)	0.4 (0.1)	0.5 (0.1)	0.4 (0.1)	0.5 (0.1)	0.4 (0.1)	0.4 (0.1)

METREX mITT-Eos population: patients with ≥150 cells/µL at screening or ≥300 cells/µL within the previous year.
METREX mITT-All population: patients receiving ≥1 dose of mepolizumab or placebo.
METREO mITT population: patients receiving ≥1 dose of mepolizumab or placebo.
*P<0.05 for between-group differences in METREO. All other group comparisons were not significantly different, including comparison between METREX mITT-Eos and mITT-ALL populations;
[a]Severity of airflow limitation is based on the GOLD Guidelines for COPD.
ED, emergency department; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICU, intensive care unit; mITT, modified intention-to-treat; SC, subcutaneous; SCS, systemic glucocorticoids; SD, standard deviation.

Table S2. Additional details of secondary efficacy endpoints in METREX (mITT-Eos and mITT-All Populations) and METREO (mITT population).

	METREX				METREO		
	mITT-Eos		mITT-All		mITT		
	Mepolizumab 100 mg SC (N=233)	Placebo (N=229)	Mepolizumab 100 mg SC (N=417)	Placebo (N=419)	Mepolizumab 100 mg SC (N=223)	Mepolizumab 300 mg SC (N=225)	Placebo (N=226)
Secondary: time to first moderate/severe exacerbation							
Estimated probability of a moderate/severe exacerbation, % (95% CI)[a]							
By Week 8	20.2 (15.6, 26.0)	28.1 (22.7, 34.4)	23.6 (19.8, 28.0)	25.1 (21.3, 29.6)	22.9 (17.9, 29.0)	18.3 (13.8, 24.0)	22.6 (17.7, 28.6)
By Week 24	45.8 (39.6, 52.4)	53.4 (47.0, 60.1)	46.3 (41.6, 51.3)	49.2 (44.5, 54.1)	42.4 (36.2, 49.2)	36.7 (30.8, 43.4)	51.1 (44.6, 57.8)
By Week 40	59.3 (53.0, 65.7)	68.5 (62.2, 74.5)	59.7 (54.9, 64.5)	63.8 (59.1, 68.5)	50.8 (44.4, 57.6)	51.8 (45.4, 58.6)	62.3 (55.8, 68.7)
By Week 52	64.6 (58.3, 70.8)	75.2 (69.3, 80.8)	65.5 (60.7, 70.1)	71.2 (66.6, 75.6)	57.9 (51.5, 64.5)	58.8 (52.4, 65.3)	66.7 (60.2, 73.1)
HR, mepolizumab/placebo, (95% CI)	0.75 (0.60, 0.94);		0.89 (0.75, 1.05);		0.82 (0.64,1.04)	0.77 (0.60, 0.97)	
P-value (unadjusted/adjusted)	P=0.012/0.036		P=0.160/>0.999		P=0.103/0.140	P=0.030/0.140	

METREX mITT-Eos population: patients with ≥150 cells/µL at screening or ≥300 cells/µL within the previous year.

METREX mITT-All population: patients receiving ≥1 dose of mepolizumab or placebo.

METREO mITT population: patients receiving ≥1 dose of mepolizumab or placebo.

[a]Kaplan-Meier estimate.

CI, confidence interval; HR, hazard ratio; LS, least squares; MCID, minimal clinically important difference; mITT, modified intention-to-treat; RR, rate ratio; SC, subcutaneous; SE, standard error.

Table S3. Other Efficacy Endpoints (METREX mITT-Eos and METREO mITT Populations)

	METREX		METREO		
	mITT-Eos		mITT		
	Mepolizumab (N=233)	Placebo (N=229)	Mepolizumab 100 mg SC (N=223)	Mepolizumab 300 mg SC (N=225)	Placebo (N=226)
SGRQ responders (≥4-point improvement in total score) at Week 52					
n[a]	228	223	220	222	225
Number of responders (%)	95 (42)	90 (40)	92 (42)	85 (38)	78 (35)
Odds ratio, mepolizumab/placebo, (95% CI)	1.08 (0.74, 1.59)		1.41 (0.95, 2.10)	1.17 (0.79, 1.73)	-
CAT score responders (≥2-unit improvement) at Week 52					
n[b,c]	224	218	216	220	224
Number of responders (%)	82 (37)	76 (35)	90 (42)	91 (41)	71 (32)
Odds ratio, mepolizumab/placebo, (95% CI)	1.21 (0.80, 1.82)		1.66 (1.10, 2.50)	1.58 (1.05, 2.37)	-
Physician-rated response to therapy at Week 52, n (%)					
n	211	194	200	193	177
1. Significantly improved	13 (6)	9 (5)	15 (8)	13 (7)	12 (7)
2. Moderately improved	43 (20)	28 (14)	35 (18)	32 (17)	17 (10)
3. Mildly improved	48 (23)	49 (25)	62 (31)	53 (27)	50 (28)
4. No change	92 (44)	87 (45)	69 (35)	79 (41)	83 (47)
5. Mildly worse	13 (6)	18 (9)	13 (7)	10 (5)	12 (7)
6. Moderately worse	1 (<1)	2 (1)	3 (2)	6 (3)	2 (1)
7. Significantly worse	1 (<1)	1 (<1)	3 (2)	0 (0)	1 (<1)
Patient-rated response to therapy at Week 52, n (%)					
n	205	186	196	187	176
1. Significantly improved	19 (9)	21 (11)	19 (10)	12 (6)	16 (9)
2. Moderately improved	43 (21)	32 (17)	37 (19)	40 (21)	20 (11)
3. Mildly improved	54 (26)	45 (24)	54 (28)	35 (19)	47 (27)
4. No change	68 (33)	60 (32)	65 (33)	84 (45)	76 (43)
5. Mildly worse	16 (8)	18 (10)	18 (9)	11 (6)	13 (7)
6. Moderately worse	3 (1)	9 (5)	3 (2)	2 (1)	4 (2)
7. Significantly worse	2 (1)	1 (<1)	0 (0)	3 (2)	0 (0)

[a]Missing 22(10%) and 40 (18%) of the patients in the METREX mITT-Eos mepolizumab 100 mg and placebo groups, respectively, and 24 (11%), 33 (15%) and 48 (21%) in the METREO mepolizumab 100mg, 300mg and placebo groups, respectively; for analysis combined with patients not achieving a 4-point improvement.
[b]Missing 29 (13%) and 40 (18%) of the patients in the METREX mITT-Eos mepolizumab 100 mg and placebo groups, respectively, and 26 (12%), 36 (16%) and 51 (23%) in the METREO mepolizumab 100mg, 300mg and placebo groups, respectively; for analysis combined with patients not achieving a 2-point improvement.
[c]Statistical comparison conducted post hoc.
METREX mITT-Eos population: patients with ≥150 cells/µL at screening or ≥300 cells/µL within the previous year.
METREO mITT population: patients receiving ≥1 dose of mepolizumab or placebo.
CAT, COPD Assessment Test score (range 0–40 points, with higher scores indicating greater disease impact; MCID −2 units); CI, confidence interval; C, chronic obstructive pulmonary disease; Eos, eosinophils; MCID, minimal clinically important difference; mITT, modified intention-to-treat; RR, rate ratio; SGRQ, St George's Respiratory Questionnaire total score (range 0–100 points, with higher scores indicating worse health status; MCID −4 points).

Table S4. AEs in METREX (Safety-Eos and Safety-All Populations) and METREO (safety population).

	METREX				METREO		
	Safety-Eos		Safety-All		Safety		
	Mepolizumab 100 mg SC (N=233)	Placebo (N=229)	Mepolizumab 100 mg SC (N=417)	Placebo (N=419)	Mepolizumab 100 mg SC (N=223)	Mepolizumab 300 mg SC (N=225)	Placebo (N=226)
	No. of patients (%)						
Deaths[a]							
Any event[a]	6 (3)	8 (3)	15 (4)	16 (4)	3 (1)	8 (4)	9 (4)
Cardiovascular	0	2 (<1)	3 (<1)	4 (1)	0	4 (2)	3 (1)
Respiratory	4 (2)	3 (1)	6 (1)	8 (2)	1 (<1)	4 (2)	4 (2)
Cancer	0	2 (<1)	2 (<1)	3 (<1)	2 (<1)	0	0
Unknown	1 (<1)	0	2 (<1)	0	0	0	1 (<1)
Other	1 (<)	1 (<1)	2 (<1)	1 (<1)	0	0	1 (<1)
On-treatment AEs occurring in ≥5% of patients in any arm							
COPD exacerbation or worsening	40 (17)	44 (19)	76 (18)	74 (18)	28 (13)	35 (16)	35 (15)
Nasopharyngitis	38 (16)	32 (14)	64 (15)	63 (15)	39 (17)	40 (18)	48 (21)
Headache	24 (10)	31 (14)	42 (10)	56 (13)	34 (15)	22 (10)	20 (9)
Pneumonia	14 (6)	23 (10)	29 (7)	37 (9)	24 (11)	20 (9)	22 (10)
Back pain	17 (7)	16 (7)	33 (8)	31 (7)	15 (7)	17 (8)	11 (5)
Oropharyngeal pain*	15 (6)	6 (3)	24 (6)	18 (4)	15 (7)	11 (5)	4 (2)
Upper respiratory tract infection	10 (4)	10 (4)	21 (5)	21 (5)	16 (7)	13 (6)	21 (9)
Influenza	8 (3)	11 (5)	16 (4)	24 (6)	6 (3)	4 (2)	11 (5)
Cough	12 (5)	9 (4)	22 (5)	15 (4)	14 (6)	16 (7)	12 (5)
Pain in extremity	7 (3)	6 (3)	19 (5)	16 (4)	7 (3)	6 (3)	5 (2)
Arthralgia	9 (4)	8 (3)	13 (3)	19 (5)	10 (4)	6 (3)	6 (3)
Sinusitis	14 (6)	7 (3)	19 (5)	13 (3)	8 (4)	7 (3)	7 (3)
Dyspnea	11 (5)	8 (3)	17 (4)	12 (3)	12 (5)	10 (4)	18 (8)
Diarrhea	10 (4)	6 (3)	18 (4)	15 (4))	16 (7)	8 (4)	14 (6)
Bronchitis	5 (2)	9 (4)	9 (2)	12 (3)	8 (4)	12 (5)	9 (4)

Pyrexia	7 (3)	9 (4)	18 (2)	13 (3)	6 (3)	13 (6)	10 (4)
Pharyngitis	7 (3)	12 (5)	12 (3)	18 (4)	5 (2)	4 (2)	4 (2)
Injection site reactions	7 (3)	7 (3)	12 (3)	12 (3)	6 (3)	11 (5)	10 (4)
Summary of on- and off-treatment pneumonia events, n (%)							
Any event	22 (9)	28 (12)	40 (10)	44 (11)	26 (12)	26 (12)	27 (12)
Infections and infestations[b]							
Pneumonia	18 (8)	25 (11)	35 (8)	41 (10)	26 (12)	23 (10)	25 (11)
Lung infection	2 (<1)	2 (<1)	2 (<1)	2 (<1)	0	0	0
Pneumonia klebsiella	1 (<1)	0	1 (<1)	0	0	0	0
Pneumonia streptococcal	1 (<1)	0	1 (<1)	0	0	0	0
Pneumonia pseudomonal	0	0	0	0	0	2 (<1)	0
Pneumonia bacterial	0	0	0	0	1 (<1)	0	0
Pneumonia haemophilus					0	0	1 (<1)
Pneumonia necrotising	0	0	0	0	0	0	1 (<1)
Pneumonia pneumococcal	0	0	0	0	1 (<1)	0	0
Pneumonia staphylococcal	0	0	0	0	1 (<1)	0	0
Pulmonary tuberculosis	0	0	0	0	0	1 (<1)	0
Respiratory, thoracic and mediastinal disorders							
Bronchopneumopathy	0	1 (<1)	0	1 (<1)	0	0	0
Pneumonitis	0	0	1 (<1)	0	0	0	0
Pneumonia aspiration	0	0	0	0	1 (<1)	0	0

Oropharyngeal Pain: *P<0.05 for between-group differences in METREO (post hoc analysis).

[a]Adjudicated fatal events by primary cause of death.

[b]Pneumonia events include both on- and post-treatment events based on a group of relevant preferred terms.

Safety-Eos population: patients with ≥150 cells/µL at screening or ≥300 cells/µL within the previous year.

Safety-All population: patients receiving ≥1 dose of mepolizumab or placebo;

AE, adverse event; COPD, chronic obstructive pulmonary disease; RSI, respiratory tract infection; SC, subcutaneous.

Table S5. Summary of patient demographics and clinical characteristics (METREX mITT-nonEos population).

	Mepolizumab (N=184)	Placebo (N=190)
Age, mean (SD)	66.1 (9.1)	65.2 (8.6)
Females, n (%)	76 (41)	77 (41)
Body mass index, kg/m^2, mean (SD)	26.5 (6.1)	27.4 (5.6)
Smoking history		
Never smoked, n (%)	9 (5)	13 (7)
Current smoker, n (%)	44 (24)	44 (23)
Former smoker, n (%)	131 (71)	133 (70)
Pack years, mean (SD)	50 (31)	44 (24)
Duration of COPD, mean (SD)	8.8 (5.4)	9.2 (6.8)
History of moderate and severe exacerbations in the 12 months prior to screening		
Mean (SD)	2.5 (1.1)	2.6 (1.2)
≥1 treated with SCS and/or antibiotics but did not require ED visit/hospitalization, n (%)	139 (76)	158 (83)
≥1 requiring ED visit only, n (%)	38 (21)	28 (15)
≥1 requiring hospitalization without ICU, n (%)	50 (27)	47 (25)
≥1 requiring hospitalization in ICU, n (%)	6 (3)	6 (3)
Severity of airflow limitation (FEV_1 % predicted range), n (%)[a]		
Mild (≥80% predicted)	1 (<1)	1 (<1)
Moderate (≥50–<80% predicted)	64 (35)	60 (32)
Severe (≥30–<50% predicted)	85 (46)	93 (49)
Very severe (<30% predicted)	34 (18)	36 (19)
GOLD category		
GOLD D	178 (97)	181 (95)
Lung function (at screening)		
Pre-bronchodilator		
FEV_1 (L), mean (SD)	1.10 (0.46)	1.11 (0.44)
FEV_1 % predicted, mean (SD)	41.4 (15.36)	41.1 (13.88)
FVC (L), mean (SD)	2.43 (0.79)	2.47 (0.79)
FEV_1:FVC ratio, mean (SD)	0.5 (0.1)	0.5 (0.1)
Post-bronchodilator		
FEV_1 (L), mean (SD)	1.19 (0.48)	1.18 (0.46)
FEV_1 % predicted, mean (SD)	44.6 (15.6)	44.1 (14.6)
FVC (L), mean (SD)	2.59 (0.85)	2.60 (0.80)
FEV_1:FVC ratio, mean (SD)	0.5 (0.1)	0.5 (0.1)
Health-related quality of life (at baseline)		
SGRQ total score,[b] mean (SD)	55.1 (16.9)	53.8 (17.5)
CAT score,[c] mean (SD)	18.8 (7.4)	18.4 (7.7)

[a]Severity of airflow limitation is based on the GOLD Guidelines for COPD.

[b]Determined by the SGRQ-COPD questionnaire; Range, 0–100 points, with higher scores indicating worse health status; MCID, − 4 units.

[c]Range, 0–40 points, with higher scores indicating greater disease impact; MCID, −2 units.

METREX mITT-nonEos: patients with <150 cells/µL at screening and no evidence of ≥300 cells/µL within the previous year.

CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; ED, emergency department; Eos, eosinophils; FEV_1, forced expiratory volume in 1s; FVC, forced vital capacity; ICU, intensive care unit; mITT, modified intention-to-treat; SCS, systemic corticosteroid; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire.

Table S6. Summary of primary and secondary efficacy endpoints

(METREX mITT-nonEos population).

	Mepolizumab (N=184)	Placebo (N=190)
Primary: moderate/severe exacerbations		
Annual rate (events/year)	1.58	1.29
RR, mepolizumab/placebo, (95% CI); P-value	1.23 (0.99, 1.51); P=0.058	
Secondary: time to first moderate/severe exacerbation		
Estimated probability of a moderate/severe exacerbations, % (95% CI)[a]		
By Week 8	27.8 (21.9, 34.9)	21.6 (16.4, 28.2)
By Week 24	46.9 (40.0, 54.5)	44.1 (37.4, 51.5)
By Week 40	60.1 (52.9, 67.3)	58.2 (51.2, 65.4)
By Week 52	66.6 (59.4, 73.6)	66.2 (59.2, 73.1)
HR, mepolizumab/placebo, (95% CI); P-value	1.07 (0.83, 1.39); P=0.592	
Secondary: annual rate of exacerbations requiring ED visit/hospitalization		
Annual rate (events/year)	0.27	0.25
RR (mepolizumab/placebo), (95% CI); P-value	1.04 (0.66, 1.67); P=0.854	
Secondary: SGRQ total score at Week 52[b]		
Change from baseline, LS mean (SE)	-3.9 (1.2)	-5.1 (1.2)
Treatment difference (95% CI); P-value	1.2 (-2.2, 4.5); P=0.490	
Secondary: CAT score at Week 52[c]		
Change from baseline, LS mean (SE)	-1.4 (0.5)	-0.9 (0.5)
Treatment difference (95% CI); P-value	-0.4 (-1.9, 1.0); P=0.546	

[a]Kaplan−Meier estimate.

[b]Range, 0–100 points, with higher scores indicating worse health status; MCID, −4 points.

[c]Range, 0–40 points, with higher scores indicating greater disease impact; MCID −2 units.

METREX mITT-nonEos: patients with <150 cells/μL at screening and no evidence of ≥300 cells/μL within the previous year.

CAT, COPD Assessment Test; CI, confidence interval; C, chronic obstructive pulmonary disease; ED, emergency department; Eos, eosinophils; HR, hazard ratio; LS, least squares; MCID, minimal clinically important difference; mITT, modified intention-to-treat; RR, rate ratio; SD, standard deviation; SE, standard error; SGRQ, St George's Respiratory Questionnaire.

Table S7. Overview of AEs (METREX Safety-nonEos population).

	Mepolizumab (N=184)	Placebo (N=190)
	No. of patients (%)	
AEs[a]		
Any event	142 (77)	153 (81)
Leading to treatment discontinuation	15 (8)	15 (8)
Event leading to trial withdrawal	11 (6)	11 (6)
SAEs[a]		
Any event	50 (27)	51 (27)
Deaths[b]		
Any event	9 (5)	8 (4)
Cardiovascular	3 (2)	2 (1)
Respiratory	2 (1)	5 (3)
Cancer	2 (1)	1 (<1)
Unknown	1 (<1)	0
Other	1 (<1)	0
On-treatment AEs occurring in ≥5% of patients in either arm		
COPD exacerbation or worsening	36 (20)	30 (16)
Nasopharyngitis	26 (14)	31 (16)
Headache	18 (10)	25 (13)
Back pain	16 (9)	15 (8)
Pneumonia	15 (8)	14 (7)
Pain in extremity	12 (7)	10 (5)
Upper respiratory tract infection	11 (6)	11 (6)
Cough	10 (5)	6 (3)
Oropharyngeal pain	9 (5)	12 (6)
Influenza	8 (4)	13 (7)
Dizziness	7 (4)	12 (6)
Abdominal pain	5 (3)	9 (5)
Arthralgia	4 (2)	11 (6)
Summary of on- and off-treatment pneumonia events, n (%)		
Any event	18 (10)	16 (8)
Infections and infestations[c]		
Pneumonia	17 (9)	16 (8)
Respiratory, thoracic and mediastinal disorders		
Pneumonitis	1 (<1)	0
On-treatment systemic/local-site reaction AEs[d]		
Systemic reactions	4 (2)	5 (3)
Injection-site reactions	5 (3)	4 (2)
Anaphylaxis	0	0

[a]Both on- and off-treatment occurrences are shown.
[b]Adjudicated fatal events by primary cause of death.
[b]Pneumonia events include both on- and post-treatment events based on a group of relevant preferred terms.
[d]Systemic or local-site reactions were identified by means of an electronic case report form that was designed for the collection of data on systemic reactions or local injection site reactions.
METREX Safety-nonEos: patients with <150 cells/µL at screening and no evidence of ≥300 cells/µL within the previous year.
AE, adverse event; COPD, chronic obstructive pulmonary disease; Eos, eosinophils; SAE, serious adverse event.

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