Supplementary Appendix

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

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STUDY DESIGN

Multinational, randomized, double-blind, placebo-controlled, parallel-group, 52-week, phase 3 clinical trial to assess the efficacy, safety, and tolerability of dupilumab in patients with moderate-to-severe type 2 inflammatory chronic obstructive pulmonary disease (COPD) characterized by elevated blood eosinophil counts on established long-acting beta-agonist (LABA), long-acting muscarinic antagonist (LAMA), and inhaled glucocorticoid background therapy (inhaled triple therapy, unless inhaled glucocorticoid contraindicated). Study treatments were dupilumab 300 mg once every 2 weeks (q2w) or placebo q2w administered subcutaneously (SC) during the 52-week trial period. The study included 3 study periods: a screening period (4 weeks ±1 week), a randomized investigational medicinal product (IMP) trial period (52 weeks ±3 days), and a post-IMP period (12 weeks ±5 days). Patients who satisfied the inclusion and exclusion criteria were randomized (1:1) to one of the following IMP treatments administered for 52 weeks: dupilumab 300 mg, administered as 1 subcutaneous (SC) injection q2w, or placebo, administered as one SC injection of matching placebo 300 mg q2w. Randomization was stratified by country, inhaled glucocorticoid dose (high-dose inhaled glucocorticoid [yes/no]) at baseline, and smoking status at screening (current or former). For example, the adult high inhaled glucocorticoid dose for fluticasone propionate (dry powder inhaler [DPI] or hydrofluoroalkane [HFA]) was >500 µg (please refer to **Table S1** for definition of high dose for the most common inhaled glucocorticoids). Alerts were built into the interactive voice/web response systems to limit enrollment of patients who were current smokers (as defined by smoking status at screening) to ≤30% of the total patients enrolled.

PATIENT ELIGIBILITY CRITERIA

INCLUSION CRITERIA

- Participants must be 40 to 85 years of age at the time of signing the informed consent form
- Participants must have evidence of type 2 inflammation (blood eosinophil count ≥300 cells/µl at visit 1 (screening)
- Participants must have a body mass index (BMI) ≥16 kg/m^2
- Participants must have physician-diagnosed COPD (for at least 12 months) and meet the below criteria at screening:
    - Current or former smokers with a smoking history of ≥10 pack-years
        - Current smokers are defined as those patients who are active smokers with ≥10 pack-years of smoking (active smoking includes cigarettes, e-cigarettes, cigars, pipes, etc.)
        - Former smokers are defined as those patients who were active smokers with ≥10 pack-years of smoking (active smoking includes cigarettes, e-cigarettes, cigars, pipes, etc.) and who have stopped smoking for at least 6 months prior to visit 1
    - Moderate-to-severe COPD (postbronchodilator forced expiratory volume in 1 s [FEV_1]/forced vital capacity [FVC] ratio <0.70 and postbronchodilator FEV_1 percent predicted >30% and ≤70%)
    - Medical Research Council dyspnea scale grade ≥2 (score ranges from 1 to 5, with higher scores indicating more severe dyspnea)

- Patient-reported history of signs and symptoms of chronic bronchitis (chronic productive cough) for 3 months in the year up to screening in the absence of other known causes of chronic cough
- Documented history of high exacerbation risk, defined as exacerbation history of ≥2 moderate* or ≥1 severe** within the year prior to screening
  - At least one exacerbation should have occurred while the patient was taking inhaled glucocorticoid plus LAMA–LABA (or LAMA–LABA if inhaled glucocorticoid was contraindicated)

    *Moderate exacerbations were recorded by the Investigator and defined as exacerbations that required either systemic corticosteroids (intramuscular, intravenous, or oral) and/or antibiotics. One of the two required moderate exacerbations had to require the use of systemic corticosteroids

    **Severe exacerbations were recorded by the Investigator and defined as exacerbations requiring hospitalization or observation for >24 hours in an emergency department/urgent care facility or resulting in death
- Background triple therapy (inhaled glucocorticoid plus LAMA–LABA) for 3 months prior to randomization with a stable dose of medication for ≥1 month prior to visit 1; double therapy (LAMA–LABA) allowed if inhaled glucocorticoid was contraindicated

- Female participants are eligible if not pregnant or breastfeeding, not of childbearing potential, or are willing to use contraception during the trial period and for at least 12 weeks post-treatment intervention

- Participants must be capable of giving written/signed informed consent

EXCLUSION CRITERIA

- COPD diagnosis for less than 12 months prior to randomization
- A current diagnosis of asthma or history of asthma according to the 2018 Global Initiative for Asthma guidelines or other accepted guidelines
- Significant pulmonary disease other than COPD (e.g., lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension, bronchiectasis, or Churg–Strauss syndrome) or another diagnosed pulmonary or systemic disease associated with elevated peripheral eosinophil count
- Cor pulmonale or evidence of right cardiac failure
- Long-term treatment with oxygen >4.0 l/min or if a participant requires more than 2.0 l/min to maintain oxygen saturation >88%
- Hypercapnia requiring bilevel ventilation
- Exacerbations, as defined in inclusion criteria, within 4 weeks prior to screening or during the screening period
- Respiratory tract infection within 4 weeks prior to screening or during the screening period
- Patients with active tuberculosis or nontuberculous mycobacterial infection, latent untreated tuberculosis, or a history of incompletely treated tuberculosis, unless it was well documented by a specialist that the patient had been adequately treated and could start treatment with a biologic agent, in the medical judgment of the Investigator

and/or infectious disease specialist; tuberculosis testing was performed on a country-by-country basis, according to local guidelines if required by regulatory authorities or ethics boards

- History of systemic hypersensitivity or anaphylaxis to any biologic therapy, including any excipients
- History of or planned pneumonectomy or lung volume reduction surgery
- Patients who had participated in the acute phase of a pulmonary rehabilitation program, specifically, who started rehabilitation <4 weeks prior to screening (note: patients in the maintenance phase of a rehabilitation program could be included)
- Previous use of dupilumab
- Patients who were <80% compliant with controller therapy during screening
- Patients who received a live, attenuated vaccination within 4 weeks prior to visit 1 or had planned live, attenuated vaccinations during the study
- Patients receiving macrolide therapy, unless on stable therapy for >12 months
- Diagnosis of α-1 anti-trypsin deficiency
- Inability to follow the procedures of the study or inability to read, understand, or fill out a questionnaire or use an e-diary without assistance
- Anti-immunoglobulin (Ig) E therapy (omalizumab) within 130 days prior to visit 1 or any other biologic therapy (including anti-interleukin-5 monoclonal antibody [Ab]) or immunosuppressant to treat inflammatory disease or autoimmune disease (e.g., rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic

lupus erythematosus, multiple sclerosis) as well as other diseases within 2 months or 5 half-lives prior to visit 1, whichever is longer

- Exposure to another investigative drug (small molecules as well as monoclonal Abs) within <6 months prior to visit 1; the minimum interval since exposure to any other (non-Ab) investigative study medication is 30 days prior to visit 1
- Clinically significant abnormal electrocardiogram at randomization which, in the judgment of the Investigator, may affect the conduct of the study (e.g., prolonged QTc interval [male >450 msec, female >470 msec, Fridericia correction])
- A history of clinically significant renal, hepatic, cardiovascular, metabolic, neurologic, hematologic, ophthalmologic, respiratory (other than COPD), gastrointestinal, cerebrovascular disease/condition, substance and/or alcohol abuse disorder, or history of or current other significant medical illness or disorder which, in the judgment of the Investigator, could interfere with the study or require treatment that might interfere with the study; specific examples include, but are not limited to, poorly controlled insulin-dependent diabetes and uncontrolled hypertension
- Prior history of malignancy or active malignancy, including lymphoproliferative diseases (except successfully treated carcinoma in situ of the cervix, or nonmetastatic squamous cell or basal cell carcinoma of the skin) within 5 years prior to screening
- Acute myocardial infarction <6 months prior to screening
- Transient ischemic attack or stroke <6 months prior to screening

- Hospitalization for any cardiovascular or cerebrovascular event <6 months prior to screening
- Heart failure New York Heart Association Class III or IV
- Patients on cardiac medications not on a stable dose during the last 6 months (e.g., antiarrhythmics, antihypertensives, and antidiuretics)
- Cardiac arrhythmias including paroxysmal (e.g., intermittent) atrial fibrillation; patients with persistent atrial fibrillation as defined by continuous atrial fibrillation for ≥6 months and controlled with a rate control strategy (i.e., selective beta blocker, calcium channel blocker, pacemaker placement, digoxin, or ablation therapy) and a stable, appropriate level of anticoagulation for ≥6 months may be considered for inclusion
- Unstable ischemic heart disease or other relevant cardiovascular disorder, such as pulmonary embolism or deep vein thrombosis, within ≤6 months from enrollment which, in the judgment of the Investigator, may put the patient at risk or negatively affect the study outcome
- Females who are lactating, breastfeeding, or pregnant
- Women of childbearing potential (premenopausal female biologically capable of becoming pregnant) who:
    - Do not have a confirmed negative serum beta-human chorionic gonadotropin test at visit 1 or negative urine pregnancy test at visit 2
    - Are not willing to use effective contraception for the duration of the study

- Diagnosed active parasitic infection (helminths), or suspected or high risk of parasitic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization
- History of human immunodeficiency virus (HIV) infection or positive HIV 1/2 serology at visit 1
- Known or suspected history of immunosuppression, including history of invasive opportunistic infections despite infection resolution, or unusually frequent, recurrent, or prolonged infections, per the judgment of the Investigator
- Evidence of acute or chronic infection requiring treatment with antibacterials, antivirals, antifungals, antiparasitics, or antiprotozoals within 4 weeks before visit 1, or significant viral infections within 4 weeks before visit 1 that may not have received antiviral treatment

  (e.g., influenza receiving only symptomatic treatment)
- Patients with active autoimmune disease or patients using immunosuppressive therapy for autoimmune disease (e.g., inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis)
- Patients with any of the following results at screening:
    - Positive (or indeterminate) hepatitis B (HB) surface antigen
    - Positive IgM HB core Ab
    - Positive total HB core Ab confirmed by positive HB virus DNA

- Positive hepatitis C virus (HCV) Ab confirmed by positive HCV RNA

- Patients with any of the following clinically significant laboratory tests at screening:
  - Alanine transaminase >3 times the upper limit of the normal range
  - Hemoglobin <10 g/100 ml for males and <9 g/100 ml for females
  - Platelets <100 000/mm^3
  - Creatinine ≥150 µmol/l

KEY CONDUCT

Data Monitoring Committee (DMC)

A DMC that was independent from the Sponsor was established for this study. This committee was composed of externally based individuals with expertise in the disease under study, biostatistics, and/or clinical research. The primary responsibilities of the DMC were to review and evaluate the safety data during the trial, review interim analysis (IA) results, and make appropriate recommendations regarding the conduct of the clinical trial to the Sponsor.

The DMC procedures and the safety data to be reviewed by the DMC were described in the DMC charter. In the above capacities, the DMC was advisory to the Sponsor. The Sponsor was responsible for promptly reviewing and considering in a timely manner the recommendations of the DMC in terms of trial continuation with or without alterations and potential trial termination.

Adjudication Committee

Adjudication was performed by experts independent of the Sponsor to evaluate whether deaths, cardiovascular serious adverse events (SAEs), and respiratory SAEs met the criteria for certain safety end points. A confirmatory adjudication occurred for exacerbations. Adjudicators adjudicated these events in a consistent and unbiased manner throughout the study.

The goal of the adjudication was to ensure that all events reported by the site were judged uniformly, using prespecified criteria, by a group independent of the Sponsor. Adjudication Committee members were blinded to treatment allocation. Adjudication Committee members' responsibilities and the process for data review are described in the Adjudication Committee Charter/Manual of Operation.

Monitoring of Patients Across Clinical Factors – Stratification

Randomization was stratified by country and inhaled glucocorticoid dose (high-dose inhaled glucocorticoid [yes/no]) at baseline and by smoking status at screening. Enrollment of current smokers was capped at 30% (as defined by smoking status at screening visit). Adherence to stratification was monitored by Interactive Trial Response technology.

Trial Oversight

The trial protocol, including the statistical analysis plan, is available at NEJM.org. Oversight was provided by the DMC described above. Exacerbations of COPD, and cardiovascular and death events, were adjudicated by the independent Adjudication Committee described above.

Trial Registration

The first patient was screened on June 12, 2020, and enrolled/randomized on July 6, 2020. The clinical trial registration submission, on June 22, 2020, was 10 days after the first patient was screened due to an update to the protocol. No patients were enrolled/randomized prior to clinical trial registration.

STATISTICAL ANALYSIS

Efficacy end points per statistical analysis plan.

PRIMARY EFFICACY END POINT

The primary end point for this study was the annualized rate of moderate or severe COPD exacerbations (as defined below) over the 52-week trial period for dupilumab compared with placebo.

- Moderate exacerbations were recorded by the Investigator and defined as exacerbations that required systemic corticosteroids (intramuscular, intravenous, or oral) and/or antibiotics
- Severe exacerbations were recorded by the Investigator and defined as exacerbations requiring hospitalization or treatment for >24 hours in an emergency department/urgent care facility, or that result in death

For both moderate and severe events to be counted as separate events, they must have been separated by at least 14 days.

The number of moderate or severe exacerbation events during the 52-week trial period was defined as the number of moderate or severe exacerbation events with onset during the 52-week trial period per patient-year. Patients who permanently discontinued the study medication were asked and encouraged to return to the clinic for all remaining study visits and their additional off-treatment moderate or severe exacerbation events up to the visit at week 52 were included. If a patient withdrew from the study prior to the end of the 52-week trial period, all observed moderate or severe exacerbation events up to the last contact date were included in the analysis.

Exacerbations recorded in an electronic case report form underwent confirmatory adjudication by experts independent of the Sponsor. Only the adjudicated-confirmed exacerbations were included in the analysis. The model for the primary end point of the annualized rate of moderate or severe exacerbations consisted of the total number of events occurring during the 52-week trial period as the response variable, with the trial group, region (pooled country), inhaled glucocorticoid dose at baseline (high-dose inhaled glucocorticoid [yes/no]), smoking status at screening, baseline disease severity (as percent predicted postbronchodilator FEV_1), and number of moderate or severe COPD exacerbation events within 1 year prior to study enrollment (≤2, 3, or ≥4) as covariates. In addition, the natural log of the 52-week follow-up duration was included as an offset variable.

SECONDARY EFFICACY END POINTS

The key secondary end points of this study included:

- Change in prebronchodilator FEV_1 from baseline to week 12
- Change in prebronchodilator FEV_1 from baseline to week 52
- Change in the St. George's Respiratory Questionnaire (SGRQ) total score from baseline to week 52
- Proportion of patients with SGRQ total score improvement of ≥4 points from baseline to week 52

A mixed-effect model with repeated measures (MMRM) was used to assess the key secondary end point of mean change from baseline to week 12 in prebronchodilator FEV_1. The model included change from baseline in FEV_1 values up to week 12 as the response variable, and

factors for trial group, age, sex, height, region, inhaled glucocorticoid dose at baseline (high-dose inhaled glucocorticoid [yes/no]), smoking status at screening, visit, trial-by-visit interaction, baseline prebronchodilator FEV_1, and FEV_1 baseline-by-visit interaction as covariates. A similar model was used to analyze the mean change from baseline to week 52 in prebronchodilator FEV_1, including values up to week 52 as response variables. The change from baseline in SGRQ total score at week 52 was analyzed in a similar way as change in prebronchodilator FEV_1 at week 52, except that the MMRM model included the following covariates: trial group, region (pooled country), inhaled glucocorticoid dose at baseline (high-dose inhaled glucocorticoid [yes/no]), smoking status at screening, visit, trial-by-visit interaction, baseline SGRQ total score, and SGRQ baseline-by-visit interaction. The proportion of patients with SGRQ improvement ≥4 points at week 52 was analyzed using a logistic regression model including trial group, region (pooled country), inhaled glucocorticoid dose at baseline (high-dose inhaled glucocorticoid [yes/no]), smoking status at screening, and baseline SGRQ total score as covariates.

End points in the prespecified subgroup of patients with fractional exhaled nitric oxide (FeNO) ≥20 parts per billion (ppb) at baseline included:

- Change in prebronchodilator FEV_1 from baseline to week 12
- Change in prebronchodilator FEV_1 from baseline to week 52
- Annualized rate of moderate or severe COPD exacerbations compared with placebo over the 52-week trial period

Other secondary efficacy end points included:

- Change in prebronchodilator FEV_1 from baseline through weeks other than 12 and 52 (i.e., weeks 2, 4, 8, 24, 36, and 44)
- Change in postbronchodilator FEV_1 from baseline to weeks 2, 4, 8, 12, 24, 36, and 52
- Change in forced expiratory flow at 25 to 75% of FVC ($FEF_{25–75\%}$) from baseline to weeks 2, 4, 8, 12, 24, 36, 44, and 52
- Annualized rate of severe COPD exacerbations compared with placebo over the 52-week trial period
- Time-to-first moderate or severe COPD exacerbation compared with placebo during the 52-week trial period

The time-to-first moderate or severe COPD exacerbation was analyzed using a Cox regression model. The model included the time to the first event as the dependent variable, and trial group, region (pooled country), inhaled glucocorticoid dose at baseline (high-dose inhaled glucocorticoid [yes/no]), smoking status at screening, baseline disease severity (as percent predicted postbronchodilator FEV_1), and number of moderate or severe COPD exacerbation events within 1 year prior to the study (≤2, 3, or ≥4) as covariates. To assess the proportional hazards assumption of the Cox model, a visual inspection of the Kaplan–Meier plots was performed to confirm the curves were parallel.

SELECTED TERTIARY/EXPLORATORY END POINTS

- Change in the Evaluating Respiratory Symptoms in COPD (E-RS: COPD) total score from baseline to week 52

- Annualized rate of COPD exacerbations as assessed by the exacerbations of chronic obstructive pulmonary disease tool (EXACT)
- Change in FVC (percent predicted and absolute values) from baseline to weeks, 12, 24, and 52
- Annualized loss of lung function as assessed by a FEV_1 slope analysis
- Pharmacodynamic response of selected biomarkers (FeNO, total serum IgE, fibrinogen)
- Genetic analyses are not presented in the current manuscript; genetic data will be analyzed and submitted for publication in the future, within a reasonable timeframe, and may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions, and other genetic analyses, including whole-exome sequencing, whole-genome sequencing, DNA copy number variation, and transcriptome sequencing (or other methods for quantitating RNA expression), will also be published when available

ADDITIONAL END POINT INFORMATION

SGRQ

The SGRQ is a 50-item questionnaire designed to measure and quantify health status in adult patients with chronic airflow limitation.[1] It has been recognized as a clinically important patient-reported outcome assessment tool that provides supportive evidence of efficacy in clinical trials and can be used in a range of respiratory diseases, including COPD. The SGRQ is a global score, ranging from 0 to 100, with lower scores indicating a better quality of life. A

decrease in score of at least 4 points has been established as the minimum clinically important difference.[2]

The SGRQ, EXACT (E-RS: COPD), and EuroQol 5-dimension (EQ-5D) instruments are subject to copyright and therefore certain sections are redacted in the accompanying online appendices. Original materials for these instruments may be requested from the copyright holders: St George's University of London (SGRQ), Evidera (EXACT), and EuroQol Research Foundation (EQ-5D).

E-RS: COPD scale

The E-RS: COPD scale is a patient-reported outcome tool that measures the severity of respiratory symptoms in stable COPD.[3] This patient-reported outcome has been recognized by the United States Food and Drug Administration and the European Medicines Agency as a valid and reliable measure of respiratory symptom severity for use in clinical trials of COPD.[4] The E-RS: COPD scale has 3 domains of symptoms: breathlessness, cough and sputum, and chest symptoms.[5] The global score ranges from 0 to 40, with lower scores indicating less severe respiratory symptoms.[3]

Sensitivity analysis

Sensitivity analyses for the primary end point and the key secondary end point of change in prebronchodilator FEV_1 from baseline to week 12 were performed to assess the robustness of the conclusion of the main model.

Control-based Pattern-mixture model-Multiple imputation (PMM-MI)

For each patient with missing data on moderate or severe exacerbation events, individual biweekly event probability was estimated using observation in the placebo arm only, with adjustment of region (pooled country), inhaled glucocorticoid dose at baseline (high-dose inhaled glucocorticoid [yes/no]), smoking status at screening, baseline disease severity (as percent predicted postbronchodilator FEV_1), and number of moderate or severe COPD exacerbation events within 1 year prior to the study ($\leqslant$2, 3, or $\geqslant$4). The total number of moderate or severe exacerbation events (on a biweekly basis) was calculated based on data imputed using multiple imputation. A total of 40 imputation sets were used during multiple imputation.

For change in prebronchodilator FEV_1 from baseline to week 12, missing values were imputed multiple times assuming the placebo rate with adjustment for covariates including trial group, age, sex, height, region (pooled country), inhaled glucocorticoid dose at baseline (high-dose inhaled glucocorticoid [yes/no]), smoking status at screening, and baseline prebronchodilator FEV_1. Each of the complete datasets were analyzed using the analysis of covariance model with change in prebronchodilator FEV_1 from baseline to week 12 as the response variable, and trial group, age, sex, height, region (pooled country), inhaled glucocorticoid dose at baseline (high-dose inhaled glucocorticoid [yes/no]), smoking status at screening, and baseline

prebronchodilator FEV_1 value as covariates. The SAS MIANALYZE procedure was then used to generate statistical inference by combining results using Rubin's formula.

Tipping-point analysis

For each patient with missing data on moderate or severe exacerbation events, the biweekly event probability was imputed in a similar fashion to PMM-MI based on various odds values. If the patient was on dupilumab, the predicted odds value was increased; if the patient was on placebo, the predicted odds value was decreased. The adjusted rate was then used to impute the number of events that would occur during the missing observation period. A sequence of increasing/decreasing ratios was used to generate different imputed datasets. The same negative binomial model described above was used for each of the complete datasets composed of observed and imputed data.

For change in prebronchodilator FEV_1 from baseline to week 12, missing values were imputed by PMM-MI as described above. The imputed values in the placebo group were then shifted by adding a sequence of positive values and the imputed values in the dupilumab group were shifted by subtracting a sequence of positive values. For each combination of the shift parameters, each of the imputed and shifted datasets was analyzed with the ANCOVA model described above.

DETERMINATION OF SAMPLE SIZE

The sample size of the study was determined based on power calculations for the primary end point of annualized rate of moderate or severe COPD exacerbations over the 52-week trial period. Assuming the number of exacerbations follows a negative binomial distribution with a

dispersion parameter of 1, a placebo annualized rate of exacerbations of 1.5, an average treatment duration of 0.95 years (to account for an average of 5% of the planned trial period with missing data), and a randomization ratio of 1:1 to the two treatment arms, with 924 randomized patients (462 for each treatment arm), the study has 90% power to detect a 25% relative risk reduction (i.e., annualized rate of 1.125 for the dupilumab group) in the annualized rate of moderate or severe COPD exacerbations at the 2-tailed significance level of α=0.05.

MULTIPLICITY CONTROL

Multiplicity was considered for performing an IA and for testing multiple end points. The overall type I error rate was controlled at the 2-sided 0.05 level. A fixed-sequence testing procedure is proposed to control the overall type I error rate for testing the primary and selected secondary end points. At the IA, the primary end point was tested with α=0.018 based on a prespecified alpha spending function.[6] After confirming a positive result for the primary end point, all secondary end points were tested at α=0.05, and this early analysis was considered the primary analysis of the study. The 95% confidence intervals reported for other end points/analyses have not been adjusted for multiplicity and should not be used for hypothesis testing.

INTERIM ANALYSIS

An IA was planned when the information fraction was ≥0.92 based on follow-up time for the primary end point of annualized rate of moderate or severe COPD exacerbations over the 52-week trial period. The information fraction at the time of IA was estimated using a conservative approach assuming all ongoing patients complete the 52-week trial period. All participants had complete follow-up for the key secondary end point of change in prebronchodilator FEV_1 from

baseline to week 12. The purpose of this IA was to potentially demonstrate efficacy when ≥92% of the information fraction for the primary end point was available, but prior to all patients completing the 52-week trial period, to provide timely data given the unmet medical need in COPD.

In the IA, the efficacy end points were analyzed using the same methods described in the efficacy end point sections above. The analysis of the end points used all the data collected up to the IA cutoff time. The IA was performed by independent statisticians that support the DMC and were separated from personnel involved in the study conduct. The DMC reviewed the unblinded IA results for the primary end point and recommended whether the criterion for efficacy was met as specified in the statistical analysis plan. The DMC informed the unblinded Sponsor team who performed the additional inferential analyses. Personnel involved in the conduct of the study (patients, investigators, and the blinded study and project team) did not have access to the IA results.

ANALYSIS POPULATIONS

The intention-to-treat (ITT) population included all patients randomized and was analyzed according to the trial group allocated at randomization. The ITT population with an opportunity to reach week 52 included the first 721 randomized patients and was used to analyze the week 52 end points for the IA. The safety population consisted of all patients who received at least one dose or part of a dose of the IMP and was analyzed according to the treatment received. The representativeness of the study participants is presented in **Supplementary Table S11**.

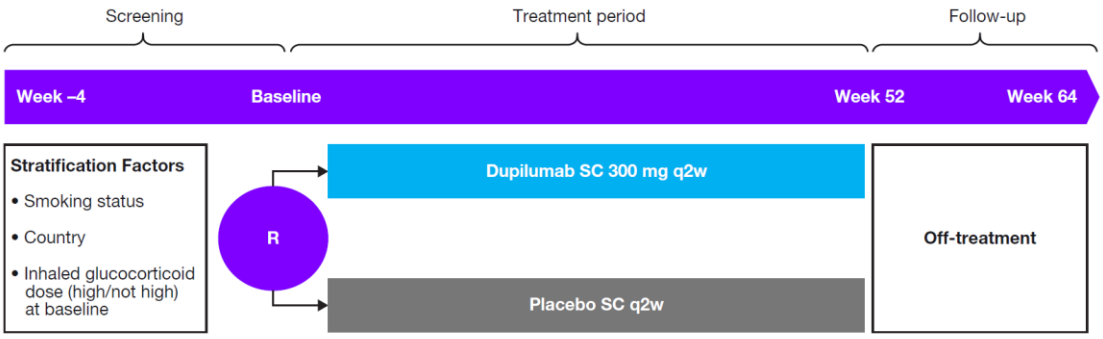
HANDLING OF MISSING DATA

Intercurrent event(s) handling strategy and missing data handling were as follows:

- Primary end point: for discontinuation of the study intervention before week 52, off-study trial data up to week 52 were included in the analysis; for missing data imputation (discontinuing the study follow-up before week 52), analyses were censored at the time of study discontinuation
- Continuous secondary end points (change from baseline to week 12 or week 52 for prebronchodilator FEV_1, SGRQ, and E-RS: COPD): for discontinuation of the study intervention prior to week 12 or week 52, all data collected after discontinuation were used in the analysis; for missing data imputation, missing data were imputed latently by MMRM based on missing at random assumption
- Proportion of SGRQ improvement (≥4 points) at week 52: for discontinuation of the study intervention prior to week 52, off-study intervention data were included in the analysis (treatment policy strategy); for missing data imputation, participants with missing data at week 52 were considered non-responders
- Time to exacerbation event during the 52-week trial period: for discontinuation of study intervention before week 52, off-study intervention data up to week 52 were included in the analysis; for missing data imputation (discontinuation of the study follow-up before week 52), analyses were censored at the time of study discontinuation

FIGURES AND TABLES

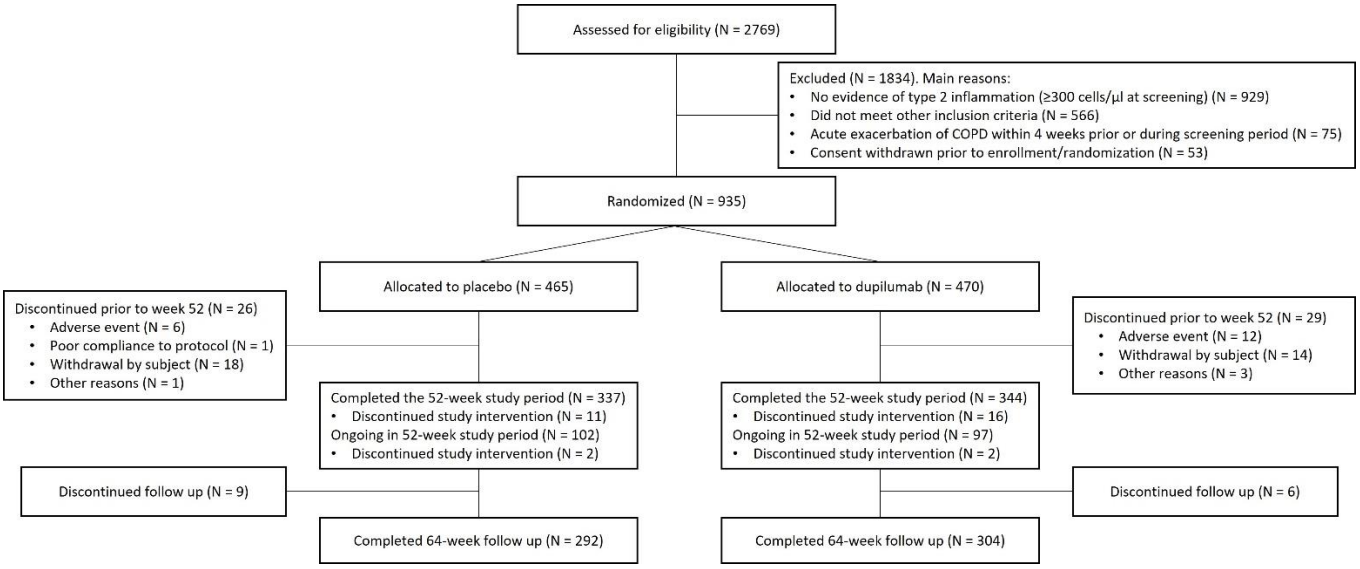
FIGURE S1. TRIAL DESIGN



Background therapy: triple therapy (inhaled glucocorticoid plus LABA–LAMA) for 3 months and a stable dose of ≥1 medication for ≥1 month prior to screening; LABA–LAMA allowed if inhaled glucocorticoid contraindicated.

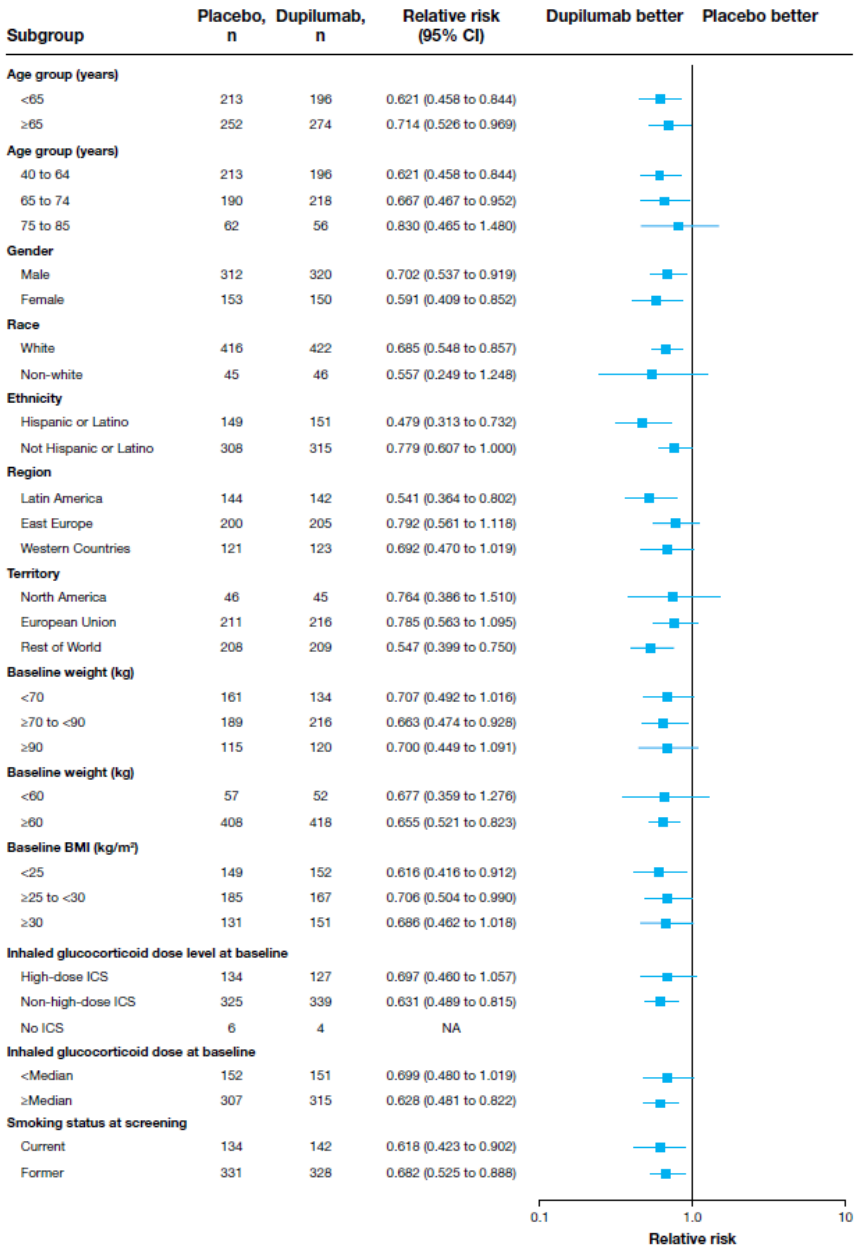
LABA denotes long-acting beta-agonist, LAMA long-acting muscarinic antagonist, q2w every 2 weeks, R randomization, SC subcutaneous.

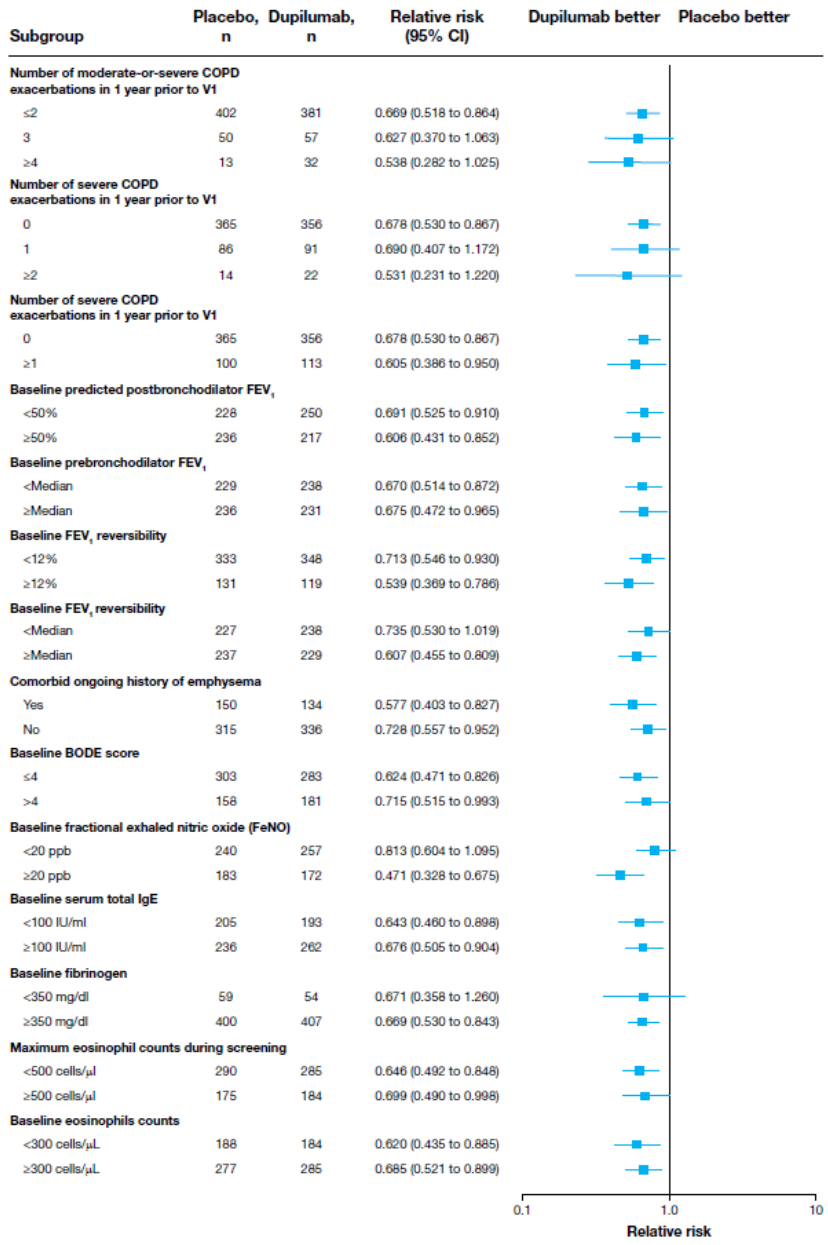
FIGURE S2. PATIENT DISPOSITION*



*At the time of interim analysis.

FIGURE S3. FOREST PLOT OF RATE RATIO IN THE ANNUALIZED RATE OF MODERATE OR SEVERE COPD EXACERBATIONS DURING THE 52-WEEK TRIAL PERIOD BY SUBGROUP

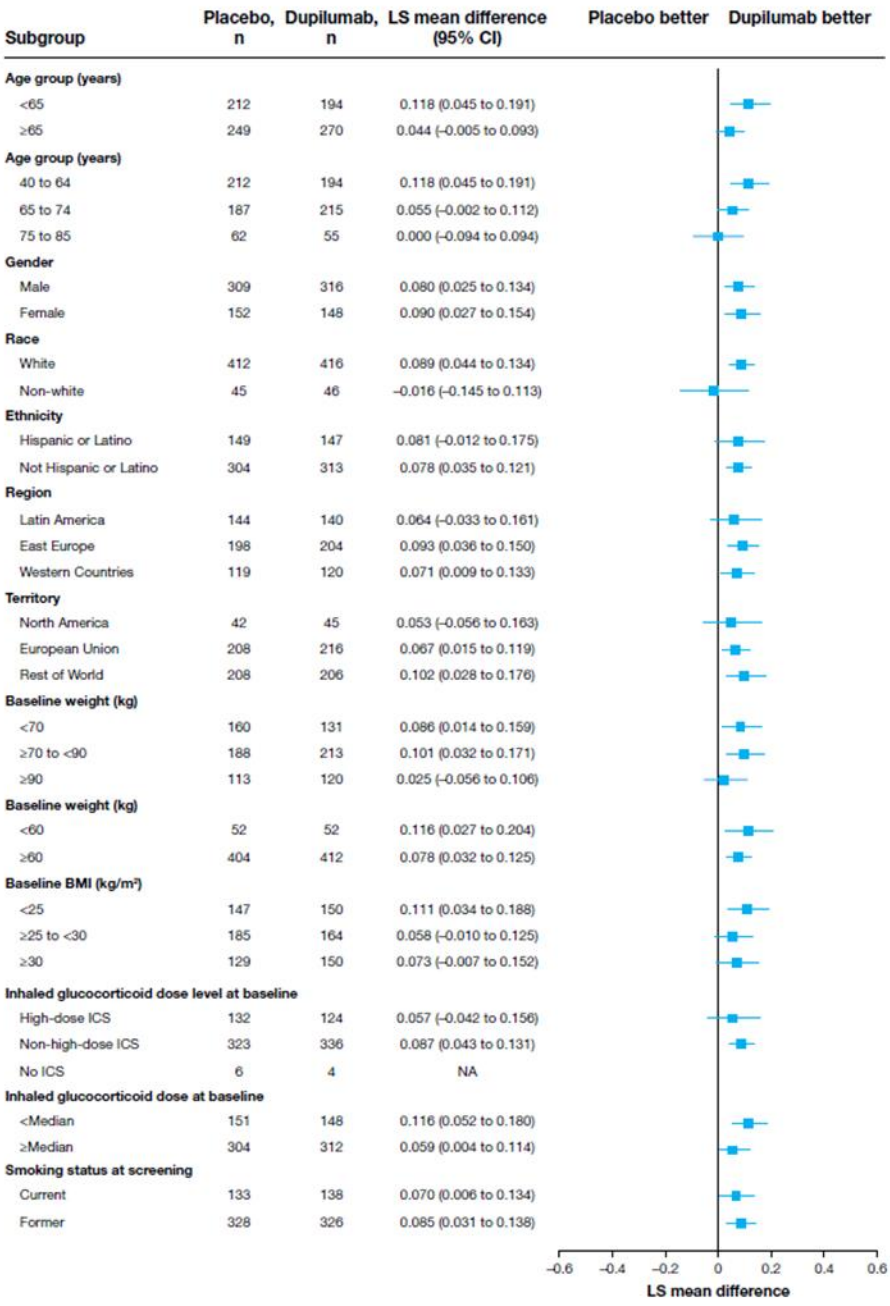


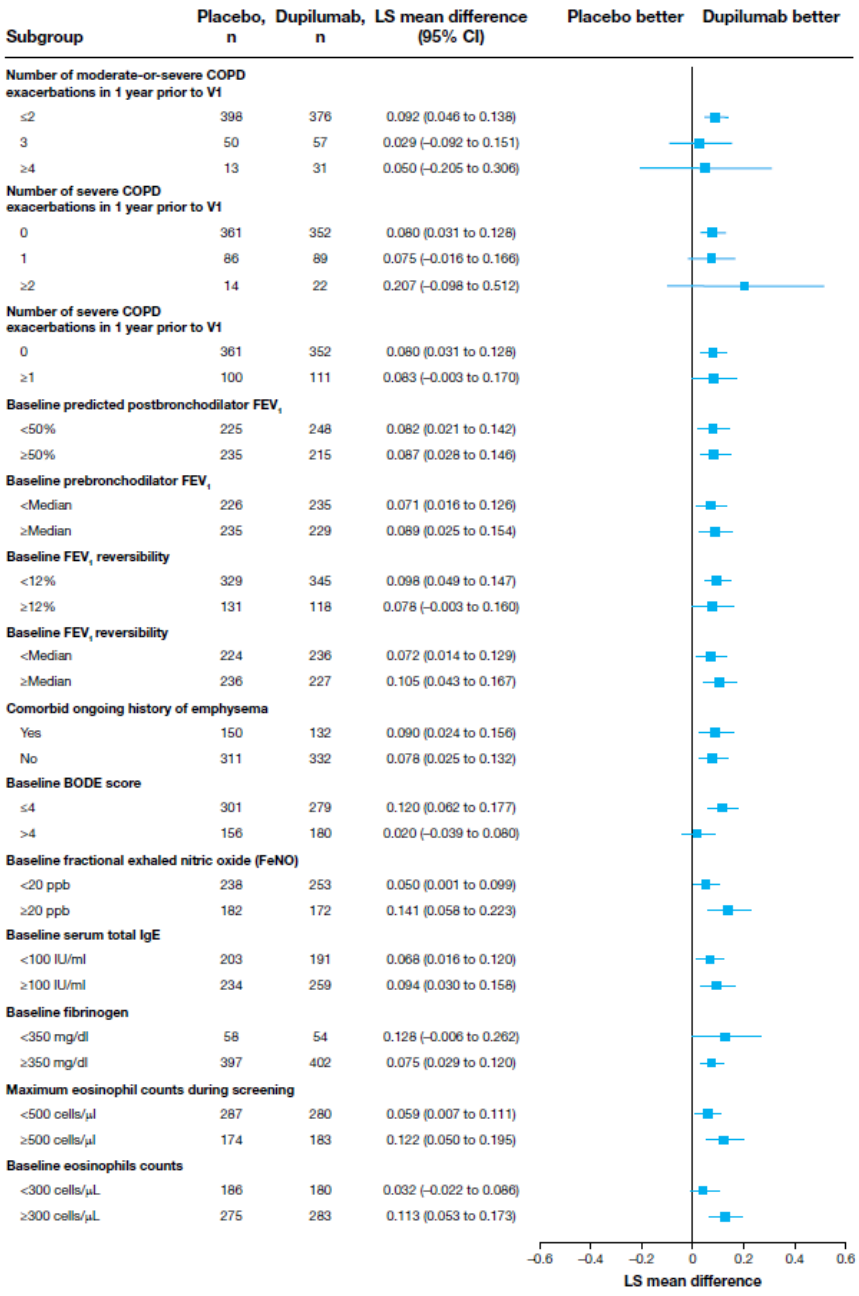


The 95% CIs have not been adjusted for multiplicity and should not be used for hypothesis testing.

BMI denotes body mass index, BODE Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity, CI confidence interval, COPD chronic obstructive pulmonary disease, FEV_1 forced expiratory volume in 1 second, IgE immunoglobulin E, NA not available, ppb parts per billion, V1 visit 1.

FIGURE S4. FOREST PLOT OF LS MEAN DIFFERENCE IN THE CHANGE IN PREBRONCHODILATOR FEV_1 (L) FROM BASELINE TO WEEK 12 BY SUBGROUP

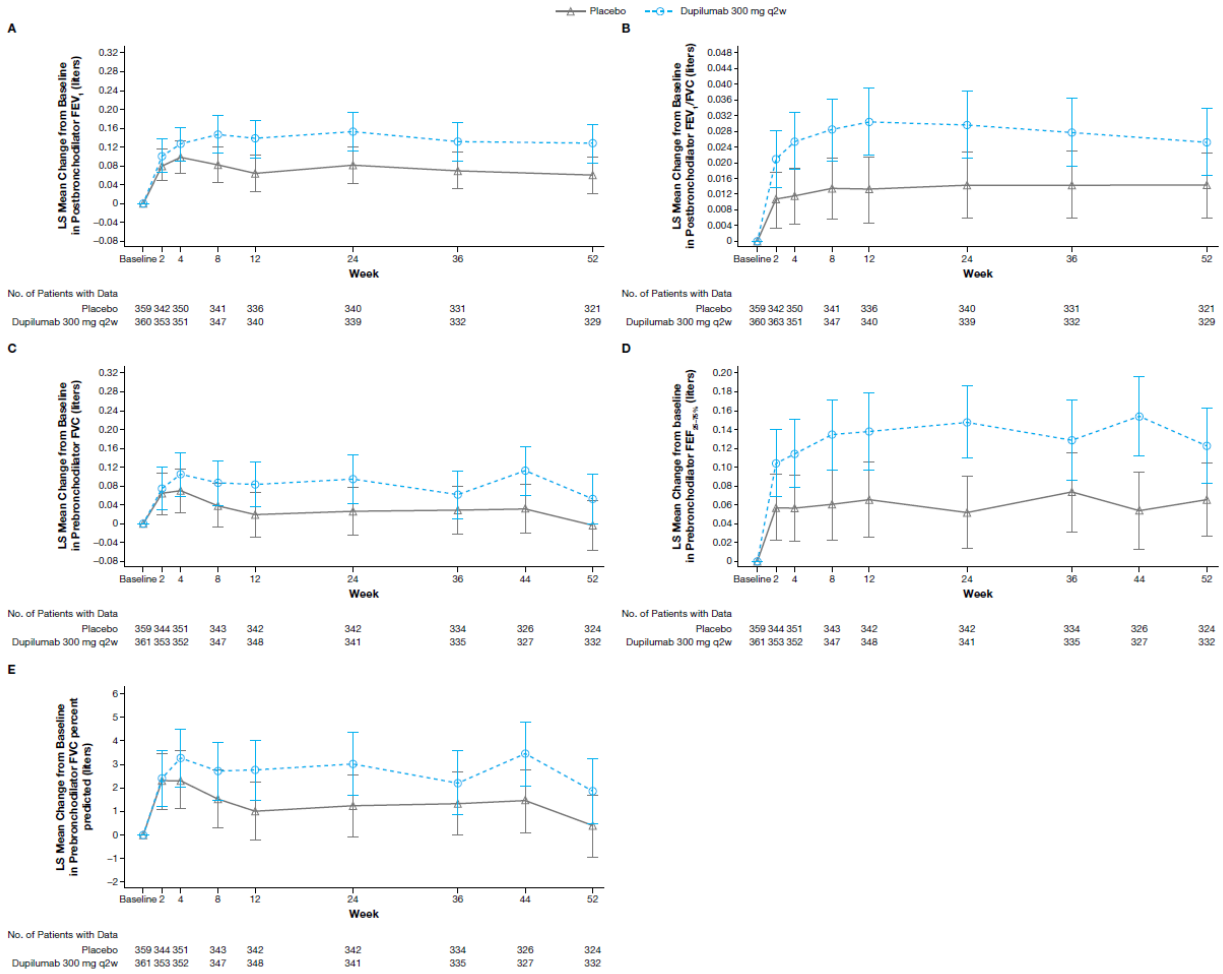




The 95% CIs have not been adjusted for multiplicity and should not be used for hypothesis testing.

BMI denotes body mass index, BODE Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity, CI confidence interval, COPD chronic obstructive pulmonary disease, FEV_1 forced expiratory volume in 1 second, LS least squares, V1 visit 1.

FIGURE S5.[*] (A) CHANGE FROM BASELINE IN POSTBRONCHODILATOR FEV_1, (B) CHANGE FROM BASELINE IN POSTBRONCHODILATOR FEV_1/FVC (C) CHANGE FROM BASELINE IN PREBRONCHODILATOR FVC, (D) CHANGE FROM BASELINE IN PREBRONCHODILATOR $FEF_{25–75\%}$, AND (E) CHANGE FROM BASELINE IN PREBRONCHODILATOR FVC PERCENT PREDICTED OVER THE 52-WEEK TRIAL PERIOD

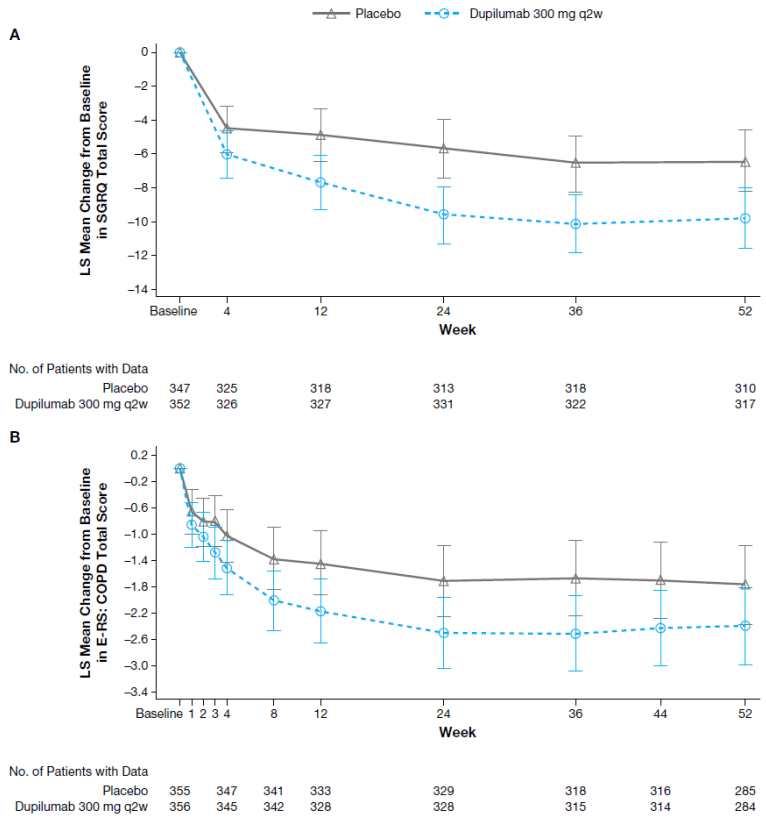


[*]Participants with the opportunity to reach week 52.

Error bars represent 95% CIs. The 95% CIs have not been adjusted for multiplicity and should not be used for hypothesis testing.

CI denotes confidence interval, $FEF_{25–75\%}$ forced expiratory flow at 25% to 75% of forced vital capacity, FEV_1 forced expiratory volume in 1 s, FVC forced vital capacity, LS least squares, q2w every 2 weeks.

FIGURE S6.* (A) SGRQ TOTAL SCORE AND (B) E-RS: COPD TOTAL SCORE DURING THE 52-WEEK TRIAL PERIOD



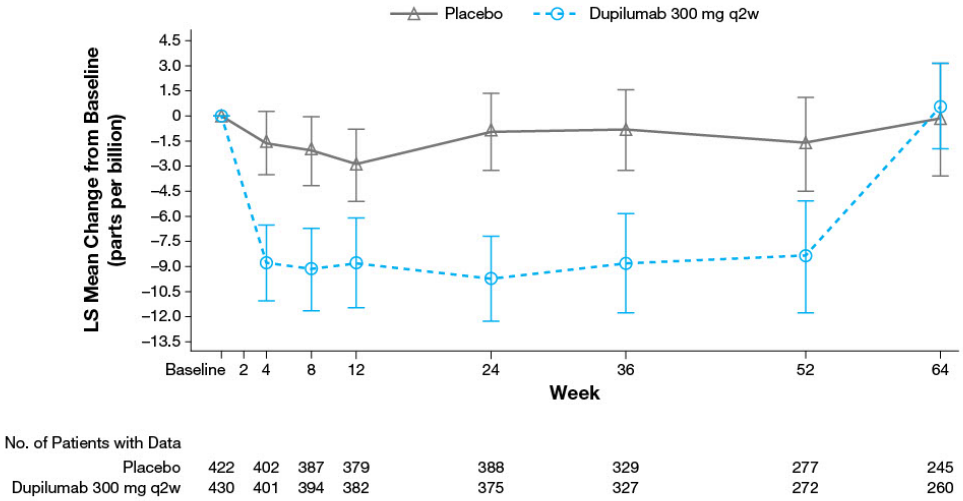
*Participants with the opportunity to reach week 52.

Error bars represent 95% CIs. The 95% CIs have not been adjusted for multiplicity and should not be used for hypothesis testing.

SGRQ is a 50-item questionnaire designed to measure and quantify health status in adult patients with chronic airflow limitation. The global score ranges from 0 to 100, with lower scores indicating a better quality of life; the minimal clinically important difference is ≥4.[2] The E-RS: COPD scale is an 11-item derivative instrument used to measure the effect of treatment on the severity of respiratory symptoms in stable COPD. The global score ranges from 0 to 40, with lower scores indicating less severe respiratory symptoms.[3]

CI denotes confidence interval, COPD chronic obstructive pulmonary disease, E-RS: COPD Evaluating Respiratory Symptoms in COPD, LS least squares, q2w every 2 weeks, SGRQ St. George's Respiratory Questionnaire.

FIGURE S7. FENO FROM BASELINE TO THE END OF THE 52-WEEK TRIAL PERIOD AND FOLLOW-UP 12-WEEK OFF-TRIAL PERIOD IN THE SAFETY POPULATION



Error bars represent 95% CIs. The 95% CIs have not been adjusted for multiplicity and should not be used for hypothesis testing.

CI denotes confidence interval, FeNO fractional exhaled nitric oxide, LS least squares, q2w every 2 weeks.

TABLE S1. INHALED GLUCOCORTICOID DOSING REGIMEN

Inhaled glucocorticoid	Daily dose (μg)	
	High dose	**Lower doses**
Beclomethasone dipropionate (CFC)	>1000	≤1000
Beclomethasone dipropionate (HFA)	>400	≤400
Budesonide (DPI)	>800	≤800
Ciclesonide (HFA)	>320	≤320
Fluticasone propionate (DPI or HFA)	>500	≤500
Mometasone furoate	>440	≤440
Triamcinolone acetonide	>2000	≤2000

CFC denotes chlorofluorocarbon, DPI dry powder inhaler, HFA hydrofluoroalkane.

TABLE S2. BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS FOR ITT AND ITT52 (PARTICIPANTS WHO HAD THE OPPORTUNITY TO REACH WEEK 52) POPULATIONS

	ITT			ITT-52		
Characteristic	**Placebo (n = 465)**	**Dupilumab (n = 470)**	**All (N = 935)**	**Placebo (n = 359)**	**Dupilumab (n = 362)**	**All (N = 721)**
Age – mean (SD), yr	64.9 (8.5)	65.2 (8.1)	65.0 (8.3)	64.6 (8.4)	65.0 (8.0)	64.8 (8.2)
Male sex – no. (%)	312 (67.1)	320 (68.1)	632 (67.6)	236 (65.7)	256 (70.7)	492 (68.2)
Race or ethnic group – no. (%)						
White	416 (89.5)	422 (89.8)	838 (89.6)	332 (92.5)	331 (91.4)	663 (92.0)
Black	8 (1.7)	4 (0.9)	12 (1.3)	4 (1.1)	2 (0.6)	6 (0.8)
Asian	3 (0.6)	7 (1.5)	10 (1.1)	1 (0.3)	3 (0.8)	4 (0.6)
American Indian or Alaska Native	26 (5.6)	22 (4.7)	48 (5.1)	16 (4.5)	14 (3.9)	30 (4.2)
Native Hawaiian or Pacific Islander	0	1 (0.2)	1 (0.1)	0	1 (0.3)	1 (0.1)
Multiple	8 (1.7)	12 (2.6)	20 (2.1)	5 (1.4)	9 (2.5)	14 (1.9)
Not reported	4 (0.9)	2 (0.4)	6 (0.6)	1 (0.3)	2 (0.6)	3 (0.4)
Hispanic or Latino – no. (%)						
Hispanic or Latino	149 (32.0)	151 (32.1)	300 (32.1)	108 (30.1)	108 (29.8)	216 (30.0)
Non-Hispanic or non-Latino	308 (66.2)	315 (67.0)	623 (66.6)	250 (69.6)	251 (69.3)	501 (69.5)
Unknown	2 (0.4)	0	2 (0.2)	0	0	0
Not reported	6 (1.3)	4 (0.9)	10 (1.1)	1 (0.3)	3 (0.8)	4 (0.6)
Smoking status – no. (%)						
Former smoker	331 (71.2)	328 (69.8)	659 (70.5)	236 (65.7)	233 (64.4)	469 (65.0)

Current smoker	134 (28.8)	142 (30.2)	276 (29.5)	123 (34.3)	129 (35.6)	252 (35.0)
Smoking history – mean (SD), pack-yr	42.1 (30.2)	38.6 (23.7)	40.3 (27.2)	42.7 (31.5)	38.2 (22.4)	40.5 (27.9)
Emphysema – no. (%)	150 (32.3)	134 (28.5)	284 (30.4)	123 (34.3)	105 (29.0)	228 (31.6)
BMI – mean (SD), kg/m^2	27.8 (5.6)	28.1 (5.3)	27.9 (5.4)	28.1 (5.5)	28.2 (5.4)	28.1 (5.4)
Background medication – no. (%)						
Triple therapy*	458 (98.5)	466 (99.1)	924 (98.8)	354 (98.6)	358 (98.9)	712 (98.8)
High-dose inhaled glucocorticoid	134 (28.8)	127 (27.0)	261 (27.9)	109 (30.4)	98 (27.1)	207 (28.7)
Biomarkers of type 2 inflammation						
Blood eosinophil count – cells/µL						
Mean (SD)	402 (314)	412 (357)	407 (336)	397 (291)	397 (281)	397 (286)
Median (Q1, Q3)	330 (220, 470)	340 (230, 460)	330 (220, 460)	340 (220, 480)	350 (250, 450)	340 (230, 460)
FeNO – ppb						
Mean (SD)	24.4 (23.4)	24.8 (28.3)	24.6 (26.0)	24.0 (24.4)	24.8 (28.9)	24.4 (26.7)
Median (Q1, Q3)	16.0 (10.0, 30.0)	16.0 (10.0, 27.0)	16.0 (10.0, 29.0)	15.0 (9.0, 30.0)	16.0 (10.0, 27.0)	15.0 (9.0, 29.0)
FeNO category – no. (%), ppb						
<20	240 (56.7)	257 (59.9)	497 (58.3)	196 (59.8)	203 (60.6)	399 (60.2)
≥20	183 (43.3)	172 (40.1)	355 (41.7)	132 (40.2)	132 (39.4)	264 (39.8)
No. of moderate or severe COPD exacerbations in the prior yr – mean (SD)	2.1 (0.7)	2.2 (1.0)	2.1 (0.9)	2.1 (0.8)	2.2 (1.0)	2.1 (0.9)

Moderate	1.8 (1.0)	1.9 (1.1)	1.8 (1.0)	1.8 (1.0)	1.9 (1.1)	1.9 (1.1)
Severe	0.3 (0.6)	0.3 (0.6)	0.3 (0.6)	0.3 (0.6)	0.3 (0.6)	0.3 (0.6)
Time since the first diagnosis of COPD – mean (SD), yr	9.0 (6.7)	9.6 (6.0)	9.26 (6.4)	9.0 (6.6)	9.4 (5.8)	9.2 (6.2)
Age at onset of COPD – mean (SD), yr	56.5 (9.1)	56.1 (9.1)	56.3 (9.1)	56.1 (8.9)	56.1 (8.9	56.1 (8.9)
Lung function						
Prebronchodilator FEV_1 – mean (SD), liters	1.38 (0.50)	1.35 (0.49)	1.36 (0.50)	1.40 (0.49)	1.36 (0.49)	1.38 (0.49)
Postbronchodilator FEV_1 – mean (SD), liters	1.46 (0.50)	1.43 (0.49)	1.45 (0.49)	1.48 (0.50)	1.44 (0.48)	1.46 (0.49)
Prebronchodilator FEV_1 percent predicted – mean (SD), %	47.9 (13.0)	46.6 (13.0)	47.2 (13.0)	48.3 (12.8)	46.6 (12.8)	47.4 (12.8)
Postbronchodilator FEV_1 percent predicted – mean (SD), %	50.7 (12.6)	49.5 (12.6)	50.1 (12.6)	51.2 (12.6)	49.4 (12.2)	50.3 (12.4)
Prebronchodilator FVC – mean (SD), liters	2.86 (0.85)	2.82 (0.87)	2.84 (0.86)	2.87 (0.82)	2.88 (0.88)	2.87 (0.85)
Prebronchodilator FEV_1/FVC ratio – mean (SD)	0.49 (0.12)	0.49 (0.12)	0.49 (0.12)	0.49 (0.12)	0.48 (0.12)	0.49 (0.12)

Postbronchodilator FEV_1/FVC ratio – mean (SD)	0.50 (0.12)	0.50 (0.12)	0.50 (0.12)	0.50 (0.12)	0.49 (0.12)	0.50 (0.12)
Prebronchodilator $FEF_{25–75\%}$ – mean (SD), liters/s	0.55 (0.34)	0.54 (0.33)	0.55 (0.34)	0.57 (0.35)	0.54 (0.34)	0.55 (0.34)
FEV_1 percent reversibility – mean (SD), %[†]	7.5 (11.4)	7.8 (12.4)	7.6 (11.9)	7.4 (11.4)	7.5 (12.1)	7.4 (11.7)
FEV_1 reversibility >12% and >0.2 liters – no. (%)	78 (16.8)	73 (15.6)	151 (16.2)	63 (17.5)	53 (14.7)	116 (16.1)
SGRQ total score (0–100) – mean (SD)[§]	51.1 (16.5)	52.0 (17.5)	51.5 (17.0)	51.0 (16.1)	52.7 (17.0)	51.8 (16.6)
SGRQ symptoms	60.9 (19.2)	61.9 (18.6)	61.4 (18.9)	61.3 (19.7)	63.5 (18.2)	62.4 (19.0)
SGRQ activity	68.1 (18.5)	67.4 (19.6)	67.7 (19.1)	68.1 (18.1)	68.0 (18.8)	68.0 (18.4)
SGRQ impact	38.3 (19.5)	40.0 (20.5)	39.2 (20.0)	38.0 (18.9)	40.5 (20.1)	39.3 (19.6)
E-RS: COPD total score (0–40) – mean (SD)[‡]	13.3 (7.2)	13.4 (6.7)	13.3 (7.0)	13.1 (7.1)	13.7 (6.7)	13.4 (6.9)
E-RS: COPD breathlessness	6.6 (3.8)	6.6 (3.5)	6.6 (3.6)	6.5 (3.8)	6.8 (3.5)	6.7 (3.6)
E-RS: COPD cough and sputum	3.4 (1.9)	3.4 (1.7)	3.4 (1.8)	3.3 (1.8)	3.5 (1.7)	3.4 (1.8)
E-RS: COPD chest symptoms	3.3 (2.2)	3.3 (2.1)	3.3 (2.1)	3.2 (2.2)	3.4 (2.1)	3.3 (2.1)
BODE index score – mean (SD)	3.0 (1.6)	4.1 (1.7)	4.0 (1.6)	3.9 (1.6)	4.1 (1.6)	4.0 (1.6)

0–2, no. (%)	90 (19.5)	81 (17.5)	171 (18.5)	73 (20.4)	61 (17.0)	134 (18.7)
3–4, no. (%)	213 (46.2)	202 (43.5)	415 (44.9)	167 (46.6)	158 (44.1)	325 (45.4)
5–6, no. (%)	128 (27.8)	141 (30.4)	269 (29.1)	98 (27.4)	109 (30.4)	207 (28.9)
7–10, no. (%)	30 (6.5)	40 (8.6)	70 (7.6)	20 (5.6)	30 (8.4)	50 (7.0)
EQ-5D-5L score – mean (SD)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)
EQ VAS score – mean (SD)	64.0 (15.6)	62.6 (16.9)	63.3 (16.3)	63.2 (15.4)	62.0 (16.1)	62.6 (15.7)
GOLD severity at baseline – no. (%)						
Grade 1	7 (1.5)	4 (0.9)	11 (1.2)	5 (1.4)	3 (0.8)	8 (1.1)
Grade 2	229 (49.4)	213 (45.6)	442 (47.5)	184 (51.3)	163 (45.3)	347 (48.3)
Grade 3	216 (46.6)	239 (51.2)	455 (48.9)	161 (44.8)	186 (51.7)	347 (48.3)
Grade 4	12 (2.6)	11 (2.4)	23 (2.5)	9 (2.5)	8 (2.2)	17 (2.4)

[*]Triple therapy unless inhaled glucocorticoid is contraindicated.

[†]Baseline reversibility was defined as (postbronchodilator FEV_1(L)–prebronchodilator FEV_1(L))/prebronchodilator FEV_1(L) multiplied by 100.

[§]The SGRQ is a 50-item questionnaire designed to measure and quantify health status in adult patients with chronic airflow limitation. The global score ranges from 0 to 100, with lower scores indicating a better quality of life; the minimal clinically important difference is ≥4.

[‡]The E-RS: COPD scale is an 11-item derivative instrument used to measure the effect of treatment on the severity of respiratory symptoms in stable COPD. The global score ranges from 0 to 40, with lower scores indicating less severe respiratory symptoms.

BMI body mass index, BODE Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity, COPD chronic obstructive pulmonary disease, EQ VAS EuroQol visual analog scale, EQ-5D-5L EuroQol 5-dimension, 5-line, E-RS: COPD Evaluating Respiratory Symptoms in COPD, $FEF_{25–75\%}$ forced expiratory flow at 25% to 75% of forced vital capacity, FeNO fractional exhaled nitric oxide, FEV_1 forced expiratory volume in 1 s, FVC forced vital capacity, GOLD Global Initiative for Chronic Obstructive Lung Disease, ppb parts per billion, Q quartile, SGRQ St. George's Respiratory Questionnaire.

TABLE S3. REPRESENTATIVENESS OF TRIAL PARTICIPANTS[7–10]

Category	Description
Disease, problem, or condition under investigation	COPD with type 2 inflammation.
Special conditions related to:	
Sex and gender	Prevalence of COPD is similar between males and females but varies by region and exposure to environmental factors (e.g., smoking and biomass). Females may be more likely to have undiagnosed COPD.
Age	Prevalence of COPD increases with age and is more likely among those >40 years of age.
Race or ethnic group	Prevalence of COPD in the United States of America varies by race and ethnicity, with similar prevalence in Black and Non-Hispanic White patients and lower rates in Hispanic patients. There are important racial disparities in COPD. Black patients in the United States of America may be less likely to be diagnosed with COPD and more likely to have more severe airflow obstruction than is typical for their age and smoking burden.
Geography	COPD has important variability by geographic region related to patterns of environmental exposures (e.g., smoking and biomass).

Category	Description
Overall representativeness of this trial	The patients in the present trial demonstrated a ratio of males to females as expected with the regional variation in smoking (e.g., higher rates of smoking among males in Asia and Eastern Europe). The age of the patients in the trial was consistent with the disease epidemiology and the trial included patients up to 85 years of age. The study enrolled patients from 29 countries and multiple regions around the world. Patients from high-income, upper middle-income, and lower middle-income countries were included. The proportion of self-identified Black patients who underwent randomization overall was small; they were underrepresented in the population of patients with COPD. Approximately 32% of patients enrolled were of Hispanic ethnicity, consistent with the regions where patients were randomized.

COPD denotes chronic obstructive pulmonary disease.

TABLE S4. SENSITIVITY ANALYSIS OF THE ANNUALIZED RATE OF MODERATE OR SEVERE COPD EXACERBATIONS DURING THE 52-WEEK TRIAL PERIOD

	Placebo (n = 465)	Dupilumab (n = 470)
Control-based PMM-MI*		
Adjusted annualized moderate or severe exacerbation event rate		
Estimate (95% CI)	1.22 (0.99 to 1.51)	0.82 (0.66 to 1.01)
Rate ratio vs. placebo (95% CI)	—	0.67 (0.54 to 0.83)

All moderate or severe adjudicated exacerbation events that occurred during the 52-week trial period are included, regardless of whether the participant was on-treatment or not. The 95% CIs have not been adjusted for multiplicity and should not be used for hypothesis testing.

*Derived using a negative binomial model with the total number of events occurring during the 52-week trial period as the response variable, trial group, region (pooled country), inhaled glucocorticoid dose, smoking status at screening, baseline disease severity, and number of moderate or severe COPD exacerbation events within 1 year prior to the study as covariates, and log-transformed 52-week follow-up duration as an offset variable. Missing data due to study discontinuation imputed based on the observed events in the placebo group using MI.

CI denotes confidence interval, COPD chronic obstructive pulmonary disease, PMM pattern mixture model, MI multiple imputation.

TABLE S5. SENSITIVITY ANALYSIS OF THE RATE RATIO (P VALUE) OF ANNUALIZED EVENT RATE OF MODERATE OR SEVERE COPD EXACERBATIONS DURING THE 52-WEEK TRIAL PERIOD BASED ON TIPPING-POINT ANALYSIS

	Deflation ratio on the biweekly odds† for early-study-withdrawal participants in the placebo arm					
Inflation ratio on the biweekly odds* for early-study-withdrawal participants in the dupilumab arm	**1**	**0.8**	**0.5**	**0.25**	**0.125**	**0.1**
1	0.66 (0.0001)	0.67 (0.0002)	0.68 (0.0003)	0.68 (0.0005)	0.69 (0.0006)	0.69 (0.0007)
1.25	0.67 (0.0002)	0.67 (0.0003)	0.68 (0.0004)	0.69 (0.0007)	0.69 (0.0009)	0.69 (0.0009)
2	0.69 (0.0005)	0.69 (0.0007)	0.70 (0.0010)	0.71 (0.0016)	0.71 (0.0020)	0.71 (0.0020)
4	0.73 (0.0041)	0.73 (0.0052)	0.74 (0.0072)	0.75 (0.0101)	0.76 (0.0121)	0.76 (0.0125)
8	0.79 (0.0321)	0.79 (0.0385)	0.80 (0.0502)	0.81 (0.0648)	0.82 (0.0737)	0.82 (0.0751)
10	0.81 (0.0622)	0.82 (0.0731)	0.83 (0.0928)	0.84 (0.1162)	0.84 (0.1301)	0.84 (0.1324)

*Predicted odds of having a moderate or severe COPD exacerbation in each bi-weekly segment for the placebo group are deflated by the deflation ratio.

COPD denotes chronic obstructive pulmonary disease.

TABLE S6. SENSITIVITY ANALYSIS OF THE CHANGE FROM BASELINE IN PREBRONCHODILATOR FEV_1 (LITERS) AT WEEK 12

	Placebo (n = 465)	Dupilumab (n = 470)
Control-based PMM-MI*		
LS mean (95% CI)	0.060 (0.025 to 0.095)	0.141 (0.106 to 0.176)
LS mean difference vs. placebo (95% CI)	—	0.081 (0.039 to 0.124)

The 95% CIs have not been adjusted for multiplicity and should not be used for hypothesis testing.

*Prebronchodilator FEV_1 values were imputed multiple times using the results in the placebo group with adjustment for covariates including trial group, age, sex, height, geographical region (pooled country), inhaled glucocorticoid dose at baseline, smoking status at screening, and baseline prebronchodilator FEV_1. Post hoc analysis.

Each of the complete datasets was analyzed using an ANCOVA model with change from baseline in prebronchodilator FEV_1 at week 12 as the response variable, and treatment, age, sex, height, region (pooled country), inhaled glucocorticoid dose at baseline, smoking status at screening, and baseline prebronchodilator FEV_1 values as covariates. The statistical inference was generated by combining results using Rubin's formula.

CI confidence interval, FEV_1 forced expiratory volume in 1 s, LS least squares, MI multiple imputation, PMM pattern-mixture model.

TABLE S7. SENSITIVITY ANALYSIS OF LS MEAN DIFFERENCE (P VALUE) BASED ON TIPPING-POINT ANALYSIS OF CHANGE IN PREBRONCHODILATOR FEV_1 FROM BASELINE TO WEEK 12

Shift in dupilumab (liters)*	Shift in placebo (liters)†									
	0.05	**0.10**	**0.15**	**0.20**	**0.25**	**0.30**	**0.35**	**0.40**	**0.45**	**0.50**
–0.05	0.08 (0.0002)	0.08 (0.0004)	0.07 (0.0005)	0.07 (0.0008)	0.07 (0.0013)	0.07 (0.0019)	0.07 (0.0028)	0.06 (0.0040)	0.06 (0.0058)	0.06 (0.0083)
–0.10	0.08 (0.0003)	0.07 (0.0005)	0.07 (0.0008)	0.07 (0.0012)	0.07 (0.0018)	0.07 (0.0026)	0.06 (0.0038)	0.06 (0.0055)	0.06 (0.0078)	0.06 (0.0110)
–0.15	0.07 (0.0005)	0.07 (0.0008)	0.07 (0.0012)	0.07 (0.0017)	0.07 (0.0025)	0.06 (0.0037)	0.06 (0.0053)	0.06 (0.0075)	0.06 (0.0105)	0.05 (0.0146)
–0.20	0.07 (0.0008)	0.07 (0.0011)	0.07 (0.0017)	0.07 (0.0024)	0.06 (0.0035)	0.06 (0.0051)	0.06 (0.0072)	0.06 (0.0101)	0.05 (0.0140)	0.05 (0.0193)
–0.25	0.07 (0.0011)	0.07 (0.0016)	0.07 (0.0024)	0.06 (0.0035)	0.06 (0.0049)	0.06 (0.0070)	0.06 (0.0098)	0.05 (0.0136)	0.05 (0.0186)	0.05 (0.0251)
–0.30	0.07 (0.0016)	0.07 (0.0024)	0.06 (0.0034)	0.06 (0.0048)	0.06 (0.0068)	0.06 (0.0095)	0.05 (0.0132)	0.05 (0.0180)	0.05 (0.0243)	0.05 (0.0325)
–0.35	0.07 (0.0023)	0.06 (0.0034)	0.06 (0.0048)	0.06 (0.0067)	0.06 (0.0093)	0.05 (0.0128)	0.05 (0.0175)	0.05 (0.0237)	0.05 (0.0316)	0.05 (0.0417)
–0.40	0.06 (0.0033)	0.06 (0.0047)	0.06 (0.0066)	0.06 (0.0092)	0.06 (0.0126)	0.05 (0.0171)	0.05 (0.0231)	0.05 (0.0308)	0.05 (0.0406)	0.04 (0.0529)
–0.45	0.06 (0.0047)	0.06 (0.0066)	0.06 (0.0090)	0.06 (0.0124)	0.05 (0.0168)	0.05 (0.0226)	0.05 (0.0301)	0.05 (0.0396)	0.04 (0.0516)	0.04 (0.0665)
–0.50	0.06 (0.0065)	0.06 (0.0090)	0.06 (0.0123)	0.05 (0.0166)	0.05 (0.0222)	0.05 (0.0295)	0.05 (0.0388)	0.04 (0.0504)	0.04 (0.0649)	0.04 (0.0826)

*Imputed FEV_1 values in the dupilumab group are subtracted by the shifting value. Negative imputed values are replaced with 0.

†Imputed FEV_1 values in the placebo group are increased by the shifting value.

FEV_1 forced expiratory volume in 1 s, LS least squares.

TABLE S8. SGRQ DOMAIN CHANGES IN ITT POPULATION WITH AN OPPORTUNITY TO REACH WEEK 52 (ITT52)

	Placebo (n = 359)	Dupilumab 300 mg q2w (n = 362)
Change from baseline in SGRQ impact to week 52		
LS mean change (95% CI)*	–6.2 (1.1)	–9.5 (1.0)
LS mean difference vs. placebo (95% CI)†	–3.3 (–6.0 to –0.52)	
Change from baseline in SGRQ activity to week 52		
LS mean change (95% CI)*	–5.6 (1.1)	–8.8 (1.1)
LS mean difference vs. placebo (95% CI)†	–3.2 (–6.1 to –0.4)	
Change from baseline in SGRQ symptoms to week 52		
LS mean change (95% CI)*	–9.4 (1.1)	–12.7 (1.1)
LS mean difference vs. placebo (95% CI)†	–3.43 (–6.4 to –0.4)	

[*]Only participants who had the opportunity to reach week 52 assessments were analyzed for the continuous and proportion-type endpoints at week 52.

[†]Analysis is post hoc and has not been adjusted for multiplicity.

SGRQ is a 50-item questionnaire designed to measure and quantify health status in adult patients with chronic airflow limitation. The global score ranges from 0 to 100, with lower scores indicating a better quality of life; the minimal clinically important difference is ≥4.[2]

CI denotes confidence interval, ITT intention-to-treat, LS least squares, q2w every 2 weeks, SGRQ St. George's Respiratory Questionnaire.

TABLE S9. OTHER PLANNED END POINTS

	Placebo (n= 465)	Dupilumab (n = 470)
COPD exacerbations assessed by the EXACT over 52 weeks		
Number of participants with ≥1 exacerbation event by EXACT, no. (%)	184 (39.6)	178 (37.9)
Adjusted annualized exacerbation event rate		
Estimate (95% CI)	1.11 (0.87 to 1.41)	0.99 (0.79 to 1.24)
Rate ratio vs. placebo (95% CI)	—	0.89 (0.72 to 1.12)
Severe COPD exacerbations over the 52-week trial period		
Number of participants with ≥1 severe exacerbation event	32 (6.9)	21 (4.5)
Adjusted annualized severe exacerbation event rate		
Estimate (95% CI)	0.12 (0.07 to 0.22)	0.07 (0.04 to 0.12)
Rate ratio vs. placebo (95% CI)	—	0.56 (0.31 to 1.02)
Postbronchodilator FEV_1 slope during the 52-week trial period after week 4[a]		
LS mean (95% CI) – liter/year*	–0.01 (–0.04 to 0.02)	–0.02 (–0.05 to 0.01)
LS mean difference vs. placebo (95% CI)[†]	—	–0.01 (–0.05 to 0.04)
Time to first severe COPD exacerbation event during the 52-week trial period		
Probability of ≥1 event (95% CI)	0.08 (0.05 to 0.10)	0.05 (0.03 to 0.08)

	Placebo (n= 465)	Dupilumab (n = 470)
Hazard ratio vs. placebo (95% CI)	—	0.51 (0.29 to 0.90)

The 95% CIs have not been adjusted for multiplicity and should not be used for hypothesis testing.

[*]Individual postbronchodilator FEV_1 slopes were calculated as the slope of a linear regression model with the postbronchodilator FEV_1 at each visit up to week 52 as the response variable and the time since randomization as the independent variable.

[†]Estimated from a mixed-effect model with repeated postbronchodilator FEV_1 as the outcome up to week 52, and treatment, age, sex, height, geographical region (pooled country), inhaled glucocorticoid dose, smoking status at screening, time since randomization, treatment-by-time interaction, and baseline postbronchodilator FEV_1 as covariates. Intercept and time since randomization were random effects.

[a]Only participants who had the opportunity to reach week 52 assessments were analyzed.

CI confidence interval, COPD chronic obstructive pulmonary disease, EXACT exacerbations of chronic obstructive pulmonary disease tool, FEV_1 forced expiratory volume in 1 s, LS least squares.

TABLE S10. SUMMARY OF OCCURRENCE OF MODERATE OR SEVERE COPD EXACERBATIONS DURING THE 52-WEEK TRIAL PERIOD

	Placebo (n = 465)	Dupilumab (n = 470)
Total number of moderate or severe events	352	263
Number of severe events	39	26
Number of moderate events	313	237
Treated with systemic corticosteroid medications only, no.	107	70
Rate ratio vs. placebo (95% CI)*	—	0.59 (0.40 to 0.89)
Treated with systemic antibiotics (with corticosteroids), no.	150	127
Rate ratio vs. placebo (95% CI)*	—	0.74 (0.54 to 1.02)
Treated with systemic antibiotics (without corticosteroids), no.	56	40
Rate ratio vs. placebo (95% CI)*	—	0.69 (0.44 to 1.10)

All moderate or severe adjudicated exacerbation events that occurred during the 52-week trial period are included, regardless of whether the participant was on treatment. The 95% CIs have not been adjusted for multiplicity and should not be used for hypothesis testing.

*Post-hoc analyses.

CI denotes confidence interval, COPD chronic obstructive pulmonary disease.

TABLE S11. SUMMARY OF MISSING DATA IN END POINTS INCLUDED IN THE HIERARCHY

	Placebo	Dupilumab 300 mg q2w
Annualized rate of moderate or severe COPD exacerbations, no. (%)	**n = 465**	**n = 470**
Participants with missing data	128 (27.5)	128 (27.2)
Estimated in the negative binomial model*	127 (27.3)	125 (26.6)
Excluded from the negative binomial model†	1 (0.2)	3 (0.6)

Change in prebronchodilator FEV_1 from baseline to week 12, no. (%)	**n = 465**	**n = 470**
Participants with missing data	21 (4.5)	21 (4.5)
Estimated in the MMRM	17 (3.7)	15 (3.2)
Missing/excluded from MMRM‡	4 (0.9)	6 (1.3)
Change in prebronchodilator FEV_1 from baseline to week 52, no. (%)	**n = 359**	**n = 362**
Participants with missing data	35 (9.7)	30 (8.3)
Estimated in the MMRM	32 (8.9)	27 (7.5)
Missing/excluded from MMRM‡	3 (0.8)	3 (0.8)
Change in prebronchodilator FEV_1 from baseline to week 12 among participants with a baseline FeNO level ≥20 ppb, no. (%)	**n = 183**	**n = 172**
Participants with missing data	6 (3.3)	4 (2.3)
Estimated in the MMRM	5 (2.7)	4 (2.3)
Missing/excluded from MMRM‡	1 (0.5)	0

Change in prebronchodilator FEV_1 from baseline to week 52 among participants with a baseline FeNO level ≥20 ppb, no. (%)	**n = 132**	**n = 132**
Participants with missing data	16 (12.1)	10 (7.6)
Estimated in the MMRM	15 (11.4)	10 (7.6)
Missing/excluded from MMRM‡	1 (0.8)	0
Change in SGRQ total score from baseline to week 52, no. (%)	**n = 359**	**n = 362**
Participants with missing data	49 (13.6)	45 (12.4)
Estimated in the MMRM	32 (8.9)	33 (9.1)
Missing/excluded from MMRM‡	17 (4.7)	12 (3.3)
SGRQ total score improvement ≥4 points at week 52, no. (%)	**n = 359**	**n = 362**
Imputed non-responders	49 (13.6)	45 (12.4)
Discontinued from study prior to week 52	22 (6.1)	19 (5.2)
Completed week 52 but missing SGRQ	27 (7.5)	26 (7.2)

Change in E-RS: COPD total score from baseline to week 52, no. (%)	**n = 359**	**n = 362**
Participants with missing data	74 (20.6)	78 (21.5)
Estimated in the MMRM	70 (19.5)	72 (19.9)
Missing/excluded from MMRM‡	4 (1.1)	6 (1.7)
Annualized rate of moderate or severe COPD exacerbations, no. (%)	**n = 183**	**n = 172**
Participants with missing data	61 (33.3)	46 (26.7)
Estimated in the negative binomial model*	61 (33.3)	46 (26.7)

Analysis is post hoc.

*Includes participants who are ongoing in the 52-week period.

†Participants with missing percent predicted postbronchodilator FEV_1 at baseline. These participants had no reported moderate or severe exacerbations.

‡Participants with no baseline or no postbaseline measurements.

COPD denotes chronic obstructive pulmonary disease, E-RS: COPD Evaluating Respiratory Symptoms in COPD, FeNO fractional exhaled nitric oxide, FEV_1 forced expiratory volume in 1 s, MMRM, mixed-effect model with repeated measures; SGRQ St. George's Respiratory Questionnaire.

TABLE S12. CHANGE IN BIOMARKERS FROM BASELINE TO WEEK 52 – SAFETY POPULATION

	Placebo (n = 464)	Dupilumab (n= 469)
Blood eosinophils, cells/µl		
Baseline		
N	464	468
Median	330	340
Q1, Q3	220.0, 470.0	230.0, 460.0
Percent change from baseline at week 52		
N	279	288
Median	–12.5	–17.0
Q1, Q3	–36.0, 18.2	–45.1, 34.0
FeNO, ppb		
Baseline		
N	422	430
Median	16.0	16.0
Q1, Q3	10.0, 30.0	10.0, 27.0
Percent change from baseline at week 52		
N	277	272

	Placebo (n = 464)	Dupilumab (n= 469)
Median	3.1	–20.9
Q1, Q3	–29.2, 44.4	–46.2, 6.7
Serum total IgE, IU/ml		
Baseline		
N	440	455
Median	123.5	130.0
Q1, Q3	39.9, 316.0	48.6, 437.0
Percent change from baseline at week 52		
N	267	294
Median	–5.0	–64.2
Q1, Q3	–29.9, 23.2	–74.9, –47.5
Fibrinogen, mg/dl		
Baseline		
N	458	461
Median	484.0	481.0
Q1, Q3	400.0, 560.0	408.0, 566.0

	Placebo (n = 464)	Dupilumab (n= 469)
Percent change from baseline at week 52		
N	286	299
Median	3.0	–1.9
Q1, Q3	–9.6, 18.9	–15.2, 16.7

FeNO denotes fractional exhaled nitric oxide, IgE immunoglobulin E, ppb parts per billion, Q quartile.

TABLE S13. SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS BY SYSTEM ORGAN CLASS AND MAJOR ADVERSE CARDIOVASCULAR EVENTS – SAFETY POPULATION

	Placebo (n = 464)	Dupilumab (n = 469)	Risk difference* (95% CI)
Adverse events occurring in ≥5% of patients in either group, no. (%)			
COVID-19	38 (8.2)	44 (9.4)	1.19 (–2.48 to 4.89)
Headache	30 (6.5)	35 (7.5)	1.00 (–2.32 to 4.35)
COPD	36 (7.8)	23 (4.9)	–2.85 (–6.11 to 0.28)
Nasopharyngitis	24 (5.2)	29 (6.2)	1.01 (–2.02 to 4.08)
Primary system organ class, no. (%)†			
Any class	306 (65.9)	313 (66.7)	0.79 (–5.27 to 6.85)
Infections and infestations	179 (38.6)	197 (42.0)	3.43 (–2.87 to 9.70)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	8 (1.7)	8 (1.7)	–0.02 (–1.87 to 1.82)
Blood and lymphatic system disorders	13 (2.8)	12 (2.6)	–0.24 (–2.47 to 1.95)
Immune system disorders	2 (0.4)	1 (0.2)	–0.22 (–1.37 to 0.80)
Endocrine disorders	5 (1.1)	2 (0.4)	–0.65 (–2.12 to 0.59)
Metabolism and nutrition disorders	30 (6.5)	22 (4.7)	–1.77 (–4.85 to 1.20)
Psychiatric disorders	11 (2.4)	7 (1.5)	–0.88 (–2.88 to 0.98)

Nervous system disorders	48 (10.3)	47 (10.0)	–0.32 (–4.26 to 3.60)
Eye disorders	5 (1.1)	10 (2.1)	1.05 (–0.63 to 2.93)
Ear and labyrinth disorders	5 (1.1)	5 (1.1)	–0.01 (–1.56 to 1.53)
Cardiac disorders	22 (4.7)	23 (4.9)	0.16 (–2.68 to 3.01)
Vascular disorders	28 (6.0)	21 (4.5)	–1.56 (–4.55 to 1.35)
Respiratory, thoracic, and mediastinal disorders	53 (11.4)	48 (10.2)	–1.19 (–5.23 to 2.83)
Gastrointestinal disorders	60 (12.9)	54 (11.5)	–1.42 (–5.67 to 2.81)
Hepatobiliary disorders	2 (0.4)	7 (1.5)	1.06 (–0.24 to 2.67)
Skin and subcutaneous tissue disorders	12 (2.6)	18 (3.8)	1.25 (–1.07 to 3.69)
Musculoskeletal and connective tissue disorders	59 (12.7)	57 (12.2)	–0.56 (–4.84 to 3.70)
Renal and urinary disorders	16 (13.4)	9 (1.9)	–1.53 (–3.82 to 0.58)
Reproductive system and breast disorders	3 (0.6)	6 (1.3)	0.63 (–0.76 to 2.19)
General disorders and administration site conditions	13 (2.8)	28 (6.0)	3.17 (0.56 to 5.98)
Investigations	18 (3.9)	15 (3.2)	–0.68 (–3.20 to 1.77)
Injury, poisoning, and procedural complications	61 (13.1)	55 (11.7)	–1.42 (–5.70 to 2.84)
Surgical and medical procedures	1 (0.2)	0	–0.22 (–1.21 to 0.60)
Major adverse cardiovascular events[§], no. (%)[†]			
Overall	7 (1.5)	3 (0.6)	–0.87 (–2.52 to 0.54)
Cardiovascular death	1 (0.2)	1 (0.2)	–0.00 (–1.01 to 1.00)
Nonfatal MI	4 (0.9)	0	–0.86 (–2.20 to –0.05)

Nonfatal stroke	2 (0.4)	2 (0.4)	–0.00 (–1.18 to 1.16)

[*]95% CI calculated using the Miettinen–Nurminen method.

[†]Participants with at least 1 event.

[§]Major adverse cardiovascular events (adjudicated) included cardiovascular death, nonfatal MI, and/or nonfatal stroke.

CI denotes confidence interval, COPD chronic obstructive pulmonary disease, COVID-19 coronavirus disease 2019, MI myocardial infarction.

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