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HAL Authorization

Efficacy and safety of tezepelumab versus placebo in adults with moderate to very severe chronic obstructive pulmonary disease (COURSE): a randomised, placebo-controlled, phase 2a trial

Dave Singh, Christopher E Brightling, Klaus F Rabe, MeiLan K Han, Stephanie A Christenson, M Bradley Drummond, Alberto Papi, Ian D Pavord, Nestor A Molfino, Gun Almqvist, Ales Kotalik, Asa Hellqvist, Monika Gołabek, Navreet S Sindhvani, Sandhia S Ponnambal, on behalf of the COURSE study investigators*

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Summary

Background

Tezepelumab is a human monoclonal antibody that blocks thymic stromal lymphopoietin, which has shown increased expression in patients with chronic obstructive pulmonary disease (COPD) compared with healthy individuals. We aimed to assess the efficacy and safety of tezepelumab in patients with moderate to very severe COPD despite receiving triple inhaled therapy.

Methods

COURSE was a double-blind, randomised, placebo-controlled, phase 2a trial across 90 sites in ten countries in Asia, Europe, and North America. Eligible participants were aged 40–80 years, had moderate to very severe airflow limitation, were receiving triple inhaled maintenance therapy, and had at least two moderate to severe COPD exacerbations in the 12 months before enrolment. Patients were randomly assigned (1:1) to receive tezepelumab 420 mg or placebo subcutaneously every 4 weeks for up to 52 weeks. Randomisation was stratified by geographical region and by number of exacerbations in the 12 months before enrolment. Participants, investigators, site staff, and the study sponsor were masked to treatment assignment. The primary endpoint was the annualised rate of moderate or severe COPD exacerbations over 52 weeks. A prespecified subgroup analysis assessed the primary endpoint in patients grouped by baseline blood eosinophil counts (BECs). Efficacy and safety were assessed in all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, NCT04039113 (completed).

Findings

Between July 30, 2019, and Oct 4, 2022, 333 patients (mean age 67.2 years [SD 7.0]; 145 [44%] female and 188 [56%] male; 293 [88%] White, 34 [10%] Asian, and four [1%] Black or African American) were randomly assigned and treated with tezepelumab (n=165) or placebo (n=168). The annualised rate of moderate or severe COPD exacerbations over 52 weeks was 1.75 for tezepelumab versus 2.11 for placebo (rate ratio 0.83 [90% CI 0.64–1.06]; p=0.10 [one-sided]; the primary endpoint was not met). In prespecified subgroup analyses, the annualised rate of moderate or severe COPD exacerbations over 52 weeks was 2.04 with tezepelumab versus 1.71 with placebo (rate ratio 1.19 [95% CI 0.75–1.90]) in patients with a baseline BEC of less than 150 cells per μL , 1.64 versus 2.47 (0.66 [0.42–1.04]) in patients with a baseline BEC of 150 cells per μL to less than 300 cells per μL , and 1.20 versus 2.24 (0.54 [0.25–1.15]) in patients with a baseline BEC of 300 cells per μL or higher. Adverse events occurred in 133 (81%) of 165 patients in the tezepelumab group and 126 (75%) of 168 patients in the placebo group. Serious adverse events occurred in 49 (30%) patients in the tezepelumab group and 50 (30%) patients in the placebo group. Five patients died while receiving study treatment: two in the tezepelumab group and three in the placebo group. No deaths were determined to be causally related to study treatment by investigator assessment.

Interpretation

A significant reduction was not observed in the annualised rate of moderate or severe COPD exacerbations with tezepelumab versus placebo. Further studies are required to evaluate the efficacy of tezepelumab in patients with moderate to very severe COPD, particularly in patients with a baseline BEC of 150 cells per μL or higher. Tezepelumab was well tolerated, with no safety concerns identified.

Funding

AstraZeneca and Amgen.

Research in context

Evidence before this study

Despite the availability of existing therapies, some patients with chronic obstructive pulmonary disease (COPD) still have recurring exacerbations and require hospitalisation. Thymic stromal lymphopoietin (TSLP) is an epithelial cytokine that is produced in response to environmental and pro-inflammatory stimuli, which has a central upstream function across type-2-mediated and non-type-2-mediated inflammatory cascades. TSLP expression is increased in the bronchial epithelium, bronchial submucosa, and airway smooth muscle in patients with COPD compared with healthy individuals. Tezepelumab is a human monoclonal antibody that specifically blocks TSLP from interacting with its heterodimeric receptor. A PubMed search on Aug 12, 2024, using the search string “(thymic stromal lymphopoietin) OR (TSLP) OR (tezepelumab) AND (COPD)”, with no language or date restrictions, returned 82 results, which contained no relevant data from randomised controlled trials.

Added value of this study

COURSE was a multicentre, double-blind, randomised, placebo-controlled, phase 2a study, and is the first study to assess the benefits of the anti-TSLP therapy tezepelumab in patients with COPD. Patients with moderate to very severe COPD who had previous exacerbations despite receiving triple inhaled maintenance therapy received either tezepelumab 420 mg or placebo administered subcutaneously every 4 weeks for up to 52 weeks. Reductions in the annualised rate of moderate or severe COPD exacerbations observed with tezepelumab were not statistically different compared with placebo. Across endpoints, although not significant, there were greater reductions and differences observed with tezepelumab versus placebo in patients with increasing baseline blood eosinophil counts. The safety and tolerability of tezepelumab observed in patients with COPD from COURSE were consistent with what has been previously reported for tezepelumab in patients with asthma.

Implications of all the available evidence

The COURSE study showed that tezepelumab treatment was well tolerated in patients with moderate to very severe COPD. Tezepelumab did not significantly reduce the annualised rate of moderate or severe COPD exacerbations compared with placebo. However, prespecified and post-hoc analyses identified a potential population of patients with a blood eosinophil count of 150 cells per μL or higher who might benefit from tezepelumab treatment. Further clinical investigation is required.

Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease characterised by persistent and often progressive airflow obstruction and chronic respiratory symptoms.¹ In the latest Global Burden of Diseases, Injuries, and Risk Factors Study, conducted in 2019, COPD was listed as one of the top ten leading causes of death worldwide.² Patients with COPD are at risk of acute exacerbations, which can be triggered by bacterial or viral infections, environmental pollutants, or unknown factors.^{1,3} Patients who have at least two COPD exacerbations per year have worse health related quality of life, more rapid decline in lung function, and an increased risk of cardiovascular events and mortality;³ furthermore, 5-year mortality is high in patients who have a COPD exacerbation requiring hospitalisation.¹

The standard of care for patients with COPD who have exacerbations is an inhaled long-acting β_2 agonist (LABA) and an inhaled long-acting muscarinic antagonist (LAMA).¹ Use of an inhaled corticosteroid is additionally recommended for patients with a blood eosinophil count (BEC) of at least 100 cells per μL .¹ Despite the availability of triple inhaled therapy (inhaled corticosteroid–LABA–LAMA), some patients with COPD still have recurring exacerbations and require hospitalisation.^{4–10}

Studies of biologics targeting IL-5, IL-4, IL-13, and IL-33 and its receptor ST2 in patients with moderate to very severe COPD have reported varying efficacies, with higher baseline BECs being the most common factor associated with greater efficacy.^{4–10} Consequently, there remains an unmet need for therapies that reduce exacerbations for the broader population of patients at increased risk of moderate or severe COPD exacerbations despite receiving triple inhaled therapy.

Thymic stromal lymphopoietin (TSLP) is an epithelial cell-derived cytokine, produced in response to environmental and pro-inflammatory stimuli.¹¹ TSLP plays a part upstream of type-2-mediated and non-type-2-mediated inflammatory cascades involving mast cells, basophils, eosinophils, dendritic cells, and other immune cells.¹² Increased expression of TSLP in the bronchial epithelium, bronchial submucosa, and airway smooth muscle of patients with COPD compared with healthy individuals has been reported.^{13,14}

Additionally, overproduction of TSLP in response to viral stimuli was observed in primary bronchial epithelial cells of patients with COPD compared with primary cells from healthy individuals.¹⁵

Tezepelumab is a human monoclonal antibody (immunoglobulin G2 λ) that specifically blocks TSLP from interacting with its heterodimeric receptor.¹⁶ Tezepelumab 210 mg administered subcutaneously every 4 weeks has shown efficacy and safety in asthma treatment.^{17–19} Tezepelumab is indicated for the add-on maintenance treatment of adult and paediatric patients aged 12 years and older with severe asthma, with no biomarker or phenotypic restrictions.²⁰ We aimed to assess the efficacy and safety of tezepelumab in patients with COPD who had moderate to very severe airflow limitation and at least two moderate or severe COPD exacerbations in the 12 months before enrolment despite receiving stable triple inhaled therapy.

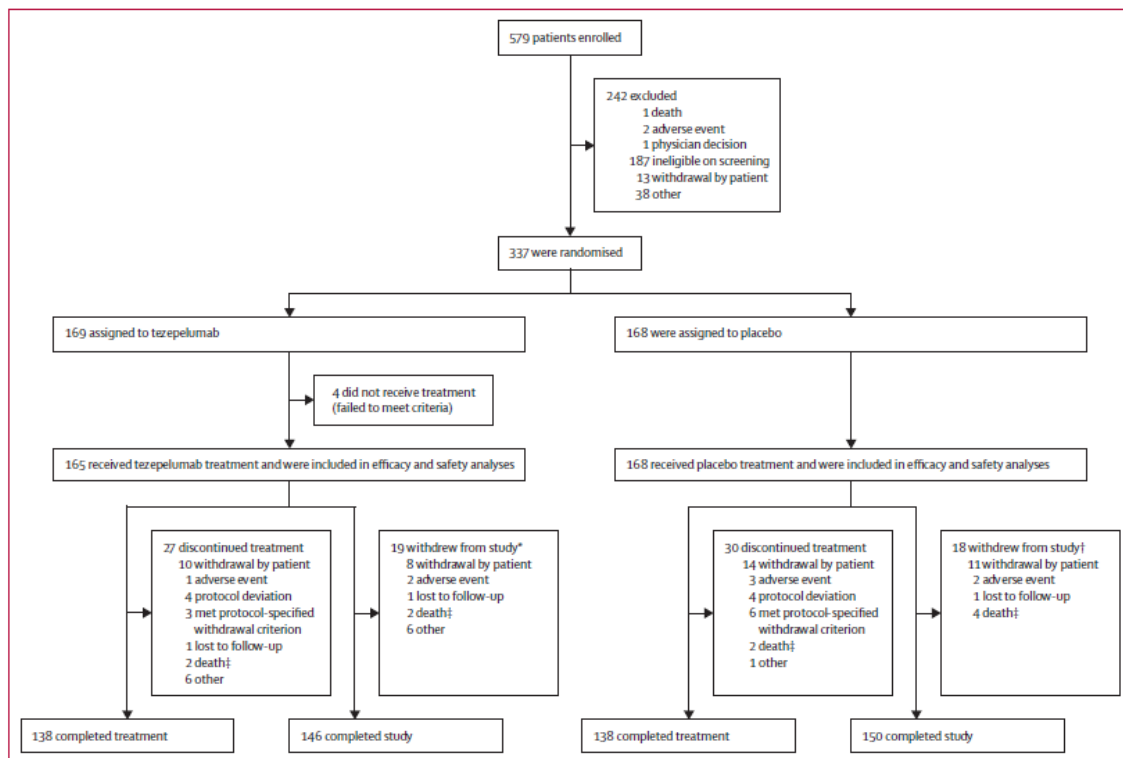


Figure 1: Trial profile

*Of the 19 patients randomly assigned to tezepelumab who received treatment and subsequently withdrew from the study, 17 had discontinued treatment and two had completed treatment. †Of the 18 patients randomly assigned to placebo who received treatment and subsequently withdrew from the study, 17 had discontinued treatment and one had completed treatment. ‡Only deaths that contributed to discontinuation of treatment or study withdrawal are shown.

Methods

Study design and participants

COURSE (NCT04039113) was a multicentre, double-blind, randomised, placebo-controlled, phase 2a study that recruited patients at 90 hospitals, clinics, medical centres, clinical trial centres, and private practices in ten countries (Canada, Denmark, France, Germany, Israel, the Netherlands, South Korea, Spain, the UK, and the USA). Included patients were aged 40–80 years with moderate to very severe COPD diagnosed at least 12 months before enrolment, with a post-bronchodilator FEV1/forced vital capacity ratio of less than 0.7 and a post-bronchodilator FEV1 of 20–80% of predicted normal values at enrolment. Patients must have been receiving triple inhaled maintenance therapy for at least 12 months before enrolment, consisting of an inhaled corticosteroid (total daily dose of fluticasone propionate >250 µg or equivalent), a LABA, and a LAMA. The total cumulative duration that a patient was not receiving triple inhaled maintenance therapy in the 12 months before enrolment could not be more than 2 months, and the dosage of inhaled corticosteroid must have been stable for at least 3 months before enrolment.

Patients must have had two or more documented moderate to severe COPD exacerbations in the 12 months before enrolment. At enrolment, a severe COPD exacerbation was defined as an exacerbation that required hospitalisation (as an inpatient admitted for ≥24 h to a hospital, an observation area, an emergency department, or another equivalent health-care facility depending on the country and health-care system). After enrolment, a severe COPD exacerbation was defined as an exacerbation that led to hospitalisation or death. A COPD

exacerbation was defined as moderate if it did not meet the requirements of a severe exacerbation and required treatment with systemic corticosteroids for at least 3 days (or one injection of depot formulation) or use of antibiotics. Only current or former smokers with a smoking history of at least 10 pack-years were included. Patients with clinically important pulmonary diseases other than COPD (as judged by the investigator), a current or historical diagnosis of asthma, or asthma–COPD overlap syndrome were excluded. Key inclusion and exclusion criteria are provided in the appendix (pp 12, 64). Gender, race, and ethnicity were obtained from electronic case report forms, which were completed by the investigator. All participants provided written, informed consent before enrolment.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. Approvals from independent ethics committees were obtained for each site. The protocol is included in the appendix (pp 19–110).

Randomisation and masking

Eligible patients were randomly assigned (1:1) to receive either tezepelumab or placebo according to a computer generated, fixed-block randomisation sequence (appendix p 4). Patients were stratified according to geographical region (Asia, Europe, and North America) and the number of moderate or severe exacerbations in the 12 months before enrolment (two or at least three). The population was also monitored using blinded data while the trial was ongoing to ensure that patients were distributed across the following characteristics: about 30% of patients were to have had at least one severe COPD exacerbation and about 40% of patients were to have had at least three moderate or severe exacerbations in the 12 months before enrolment; at screening, about 20% of patients were to have a BEC of at least 300 cells per μL , about 40% were to have a BEC of 150 cells per μL to less than 300 cells per μL , and a maximum of 40% of patients were to have a BEC of less than 150 cells per μL . When the target proportion of patients within an exacerbation or BEC subgroup was reached, consideration was given to prevent any further patients being randomly assigned to that subgroup. The proportions were selected to ensure that the distribution of baseline BECs was reflective of what is observed in patients with COPD.²¹ Participants, investigators, site staff, and the study sponsor were masked to treatment assignment.

Procedures

Patients received either tezepelumab 420 mg or placebo, administered subcutaneously (using two 210 mg accessorised pre-filled syringes) every 4 weeks between weeks 0 and 48. Changes to background medication for the treatment of COPD were discouraged unless medically necessary. Compliance with triple inhaled maintenance therapy was monitored and recorded during the study. Important protocol deviations were defined as follows: patients included in the study despite not meeting the inclusion and exclusion criteria; investigational treatment deviations (eg, patients who received the wrong treatment or an incorrect dose); use of excluded concomitant medications; study procedure deviations; non-withdrawal from study treatment or participation, respectively, for patients meeting the discontinuation criteria for study treatment or participation; and any other potentially important considerations. Important protocol deviations were not used to exclude any patients or data from any of the analyses and are reported in the appendix (p 5).

Owing to disruptions caused by the COVID-19 pandemic, protocol amendments were introduced to mitigate missed visits and study treatment administration; the amendments permitted telephone, virtual, and drive-up visits, in addition to administration of study treatment at patients' homes or locations other than the study sites. The study comprised a 6-week screening period, a 52-week treatment period, and a 12-week safety follow-up (with follow-up visits at weeks 58 and 64; appendix p 6).

Outcomes

The primary endpoint was the annualised rate of moderate or severe COPD exacerbations over 52 weeks. Secondary endpoints were the annualised rate of severe COPD exacerbations; the time to first moderate or severe COPD exacerbation; the time to first severe COPD exacerbation; the proportion of patients with at least one moderate or severe COPD exacerbation at week 52; the changes from baseline to week 52 in prebronchodilator FEV1 and St George's Respiratory Questionnaire (SGRQ) total score (ranging from 0 [no impairment] to 100 [maximum impairment]; minimal clinically important difference [MCID] is 4 points);²² the proportion of patients at week 52 with an MCID decrease in SGRQ total score; and the change from baseline to week 52 in COPD assessment test (CAT) total score (range 0–40; higher scores denote a more severe effect of COPD on a patient's life).²³

Prespecified exploratory endpoints included the changes from baseline to week 52 in Evaluating Respiratory Symptoms (E-RS) in COPD total score (range 0–40; higher scores indicate more severe symptoms) and biomarker levels (BEC, fractional exhaled nitric oxide [FeNO] level, and blood neutrophil count).²⁴ Safety assessments, including adverse events and serious adverse events, vital signs, laboratory assessments, and electrocardiograms, were recorded. Adverse events were coded using the Medical Dictionary for Regulatory Activities.

As part of prespecified and post-hoc analyses, the primary and secondary endpoints were also assessed in patients grouped by baseline demographics, clinical characteristics, and biomarker levels (appendix p 4).

Statistical analysis

For the primary endpoint in this proof-of-concept study, it was initially estimated that a sample size of 282 patients would be required to achieve an 80% power at a one-sided α level of 5% to detect a 30% reduction in the annualised rate of moderate or severe COPD exacerbations for tezepelumab versus placebo. This assumed a 10% patient dropout, a negative binomial dispersion parameter of 0.6, and an annualised COPD exacerbation rate of 1.6 events in the placebo group. However, it was predicted that the reduction in person-to-person contact and exposure to respiratory infections owing to the COVID-19 pandemic could lower the annualised COPD exacerbation rate to as low as 1.2 events in the placebo group. Assuming the same treatment effects with the lower exacerbation rate, the sample size approximation was updated (on March 15, 2021) to 338 patients as a requirement to maintain the study power. The primary analysis was presented using a 90% CI to support the 5% one-sided test; a 95% CI was also presented for completeness. Analyses of all other endpoints were presented using 95% CIs, with no multiplicity adjustment.

| | Tezepelumab group (n=165) | Placebo group (n=168) |
|----------------------------|---------------------------|-----------------------|
| Age, years | 67.4 (6.8) | 67.1 (7.2) |
| Gender* | | |
| Female | 77 (47%) | 68 (40%) |
| Male | 88 (53%) | 100 (60%) |
| Race* | | |
| White | 147 (89%) | 146 (87%) |
| Asian | 16 (10%) | 18 (11%) |
| Black or African American | 2 (1%) | 2 (1%) |
| Other† | 0 | 2 (1%) |
| Hispanic or Latino* | | |
| Yes | 7 (4%) | 3 (2%) |
| No | 158 (96%) | 165 (98%) |
| Region | | |
| Asia | 16 (10%) | 17 (10%) |
| Europe | 92 (56%) | 92 (55%) |
| North America | 57 (35%) | 59 (35%) |
| BMI, kg/m ² | 27.3 (5.7) | 27.4 (6.4) |
| Smoking status | | |
| Current | 55 (33%) | 51 (30%) |
| Former | 110 (67%) | 117 (70%) |
| Never | 0 | 0 |
| BEC category, cells per µL | | |
| <150 | 73 (44%) | 64 (38%) |
| ≥150 | 92 (56%) | 104 (62%) |
| 150 to <300 | 68 (41%) | 72 (43%) |
| ≥300 | 24 (15%) | 32 (19%) |
| Emphysema | 91 (55%) | 101 (60%) |
| Chronic bronchitis | 85 (52%) | 100 (60%) |
| Bronchiectasis | 10 (6%) | 4 (2%) |
| SGRQ total score | 59.4 (15.9) | 56.6 (15.4) |
| CAT total score | 23.6 (5.2) | 23.0 (5.2) |
| E-RS in COPD total score | 14.8 (6.6) | 15.0 (6.0) |

Data are mean (SD), n (%), median (IQR), or n/N (%). BEC=blood eosinophil count. CAT=COPD assessment test. COPD=chronic obstructive pulmonary disease. E-RS=Evaluating Respiratory Symptoms. FeNO=fractional exhaled nitric oxide. FVC=forced vital capacity. ppb=parts per billion. SGRQ=St George's Respiratory Questionnaire. *Gender, race, and ethnicity are presented as captured in electronic case report forms, which were completed by the investigator. †Includes Native Hawaiian or other Pacific Islander and Native American or Alaska Native. ‡FEV₁ reversibility (%) was calculated as ((post-bronchodilator FEV₁ - pre-bronchodilator FEV₁)/pre-bronchodilator FEV₁) × 100. §Global Lung Function Initiative equations were used to determine the predicted normal values and were pre-programmed into the spirometer.²⁵

Table 1: Baseline patient demographics and clinical characteristics (full analysis set)

An interim analysis by an independent data monitoring committee was originally planned to examine the futility of efficacy when 182 patients had been randomly assigned. Owing to the COVID-19 pandemic, the futility analysis was amended to occur when about 30% of the information had been obtained. Futility was to be declared if the lower bound of an 80% CI for the moderate or severe exacerbation rate ratio of tezepelumab versus placebo was greater than 0.80. The futility boundary and method of assessing futility was chosen based on the operating characteristics of approximately a 33% chance of stopping the study under the null hypothesis and about a 4% chance of stopping the study assuming a moderate or severe exacerbation rate ratio of 0.70.

Efficacy was assessed in the full analysis set, which was defined as all patients who received at least one dose of tezepelumab or placebo and analysed according to the treatment group they were assigned to at randomisation. Safety was assessed in the safety analysis set, which was defined as all patients who received at least one dose of tezepelumab or placebo and analysed according to the treatment received (if different from the treatment assigned at randomisation). The annualised rate of moderate or severe COPD exacerbations (primary endpoint) and the annualised rate of severe COPD exacerbations (secondary endpoint) over 52 weeks were analysed using a negative binomial model, with the total number of exacerbations experienced by a patient over the 52-week treatment period as the response variable. The logarithm of the time at risk for an exacerbation was used as an offset variable. The time to first moderate or severe COPD exacerbation was estimated using a Cox proportional hazards model. The proportion of patients with at least one moderate or severe COPD exacerbation at week 52 or patients with a decrease in SGRQ total score of at least 4 points at week 52 were compared between treatment groups using a logistic regression model. All analyses included treatment group, geographical region, and number of exacerbations in the year before study entry (two or at least three) as covariates in the models; SGRQ total score at baseline was included as an additional covariate in the assessment of the proportion of patients with a decrease in SGRQ total score of at least 4 points.

Change from baseline to week 52 in pre-bronchodilator FEV1; total scores for SGRQ, CAT, and E-RS in COPD; and biomarker levels were estimated using a mixed model for repeated measures. Treatment group, respective value at baseline, region, number of previous exacerbations, visit, and treatment-by-visit interaction were included as covariates in the model. Descriptive analyses of changes from baseline to week 52 in BEC and blood neutrophil count were prespecified exploratory endpoints, but analyses using a mixed model for repeated measures were post hoc.

Adverse events and serious adverse events are reported descriptively. An independent data and safety monitoring board reviewed unblinded data at regular intervals to monitor safety aspects of the trial.

All observations during the treatment period were included in the analyses, including post-treatment discontinuation data. Missing data were assumed to be missing at random and were modelled based on what was observed during the study using direct likelihood approaches. Analyses were done with SAS (version 9.4).

Role of the funding source

The funders of the study contributed to the study design and data interpretation and funded medical writing support for this manuscript. The study sponsor, AstraZeneca, conducted the study, coordinated the data management, and conducted the statistical analysis in collaboration with investigators at the academic study sites.

Results

Between July 30, 2019, and Oct 4, 2022, 579 patients were enrolled, and 169 patients were randomly assigned to receive tezepelumab and 168 to receive placebo (figure 1). Of these patients, 333 received study treatment (165 in the tezepelumab group and 168 in the placebo group) and were assessed for efficacy and safety endpoints. As no patients received incorrect treatment, the full analysis set and the safety analysis set are equivalent.

Demographics and clinical characteristics are shown in table 1. At baseline, the mean age of patients was 67.2 years (SD 7.0) and 227 (68%) of 333 patients were former smokers. Median biomarker levels were low at baseline (BEC 170 cells per μL [IQR 110–260] and FeNO 15 parts per billion [ppb; 9–22]). At baseline, the mean percentage predicted pre-bronchodilator FEV1 was 37.5% (SD 12.9), post-bronchodilator FEV1/forced vital capacity ratio was 0.4 (0.1), and FEV1 reversibility was 10.2% (11.6). Mean baseline SGRQ total score was $58 \cdot 0$ (SD 15.7), and mean baseline CAT total score was 23.3 (5.2). The baseline BEC was less than 150 cells per μL for 137 (41%) patients, 150 cells per μL to less than 300 cells per μL for 140 (42%) patients, and 300 cells per μL or higher for 56 (17%) patients.

For the primary endpoint, tezepelumab treatment did not statistically reduce the annualised rate of moderate or severe COPD exacerbations compared with placebo over 52 weeks. The annualised rate of moderate or severe COPD exacerbations over 52 weeks was 1.75 for tezepelumab versus 2.11 for placebo (rate ratio 0.83 [90% CI 0.64–1.06; 95% CI 0.61–1.11]; $p=0.10$ [one-sided]; figure 2).

For the secondary endpoints, the annualised rate of severe COPD exacerbations over 52 weeks was 0.13 for tezepelumab versus 0.25 for placebo (rate ratio 0.52 [95% CI 0.24 to 1.11]; figure 2). The median time to first moderate or severe exacerbation was 253 days with tezepelumab versus 214 days with placebo (hazard ratio [HR] $0 \cdot 80$ [95% CI 0.60 to 1.06]; appendix p 7), and the HR for the median time to first severe exacerbation was 0.70 (95% CI 0.36 to 1.32). At least one moderate or severe exacerbation up to week 52 occurred in 94 (57%) of 165 patients in the tezepelumab group versus 105 (63%) of 168 patients in the placebo group (16 [10%] vs 22 [13%] had a severe exacerbation). The least-squares [LS] mean difference in the change in pre-bronchodilator FEV1 from baseline to week 52 with tezepelumab versus placebo was 0.055 L (95% CI 0.014 to 0.096; table 2). The LS mean difference in the change in SGRQ total score from baseline to week 52 with tezepelumab versus placebo was -2.93 (95% CI -6.23 to 0.36; table 2). An MCID decrease of at least 4 points in SGRQ total score occurred in 65 (40%) of 163 patients in the tezepelumab group versus 59 (36%) of 163 patients in the placebo group (odds ratio 1.10 [95% CI 0.70 to 1.74]). The LS mean difference in the change from baseline to week 52 in CAT total score with tezepelumab versus placebo was -1.86 (95% CI -3.31 to -0.40 ; appendix p 13).

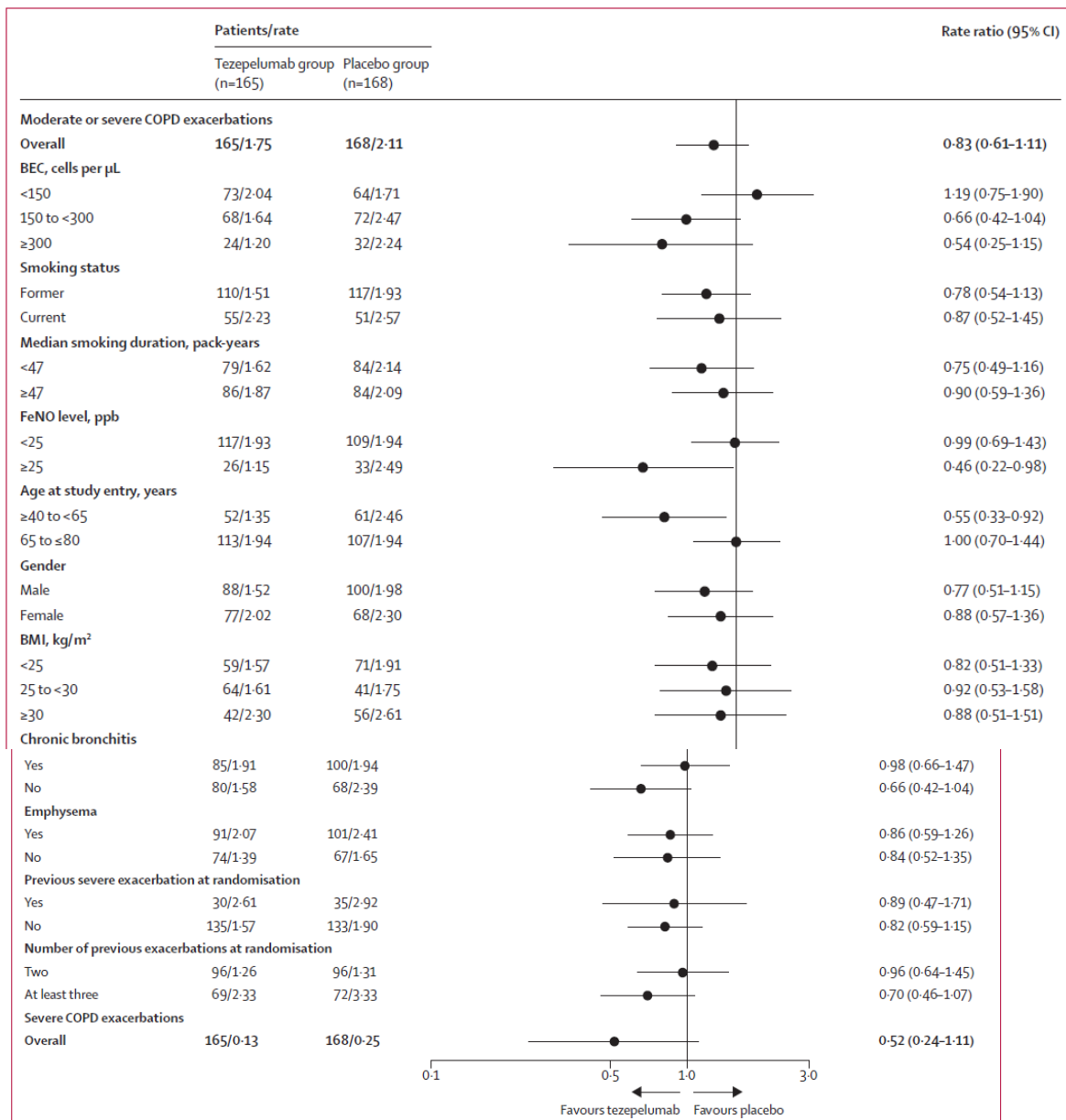


Figure 2: The annualised rate of moderate or severe COPD exacerbations (primary endpoint; full analysis set) for the overall population and in prespecified patient subgroups by baseline demographics and clinical characteristics, and the annualised rate of severe COPD exacerbations (secondary endpoint; full analysis set)
 BEC=blood eosinophil count. COPD=chronic obstructive pulmonary disease. FeNO=fractional exhaled nitric oxide. ppb=parts per billion.

For the prespecified exploratory endpoints, the LS mean difference in the change from baseline to week 52 in E-RS COPD total score with tezepelumab versus placebo was -0.35 (95% CI -1.30 to 0.60 ; appendix p 13). The LS mean difference in the change in BEC from baseline to week 52 for tezepelumab versus placebo was -71.3 cells per μ L (95% CI -90.9 to -51.8). The LS mean difference in the change in FeNO level from baseline to week 52 with tezepelumab versus placebo was -4.8 ppb (95% CI -7.5 to -2.2 ; appendix pp 8, 14). No change in blood neutrophil count was observed over 52 weeks with tezepelumab or placebo (appendix pp 8, 14).

As part of a prespecified subgroup analysis, the primary endpoint was assessed in patients grouped by baseline characteristics (figure 2). The annualised rate of moderate or severe COPD exacerbations over 52 weeks was 2.04 with tezepelumab with versus 1.71 with placebo (rate ratio 1.19 [95% CI 0.75-1.90]) in patients with a baseline BEC of less than 150 cells

per μL , 1.64 versus 2.47 (0.66 [0.42–1.04]) in those with a baseline BEC of 150 cells per μL to less than 300 cells per μL , and 1.20 versus 2.24 (0.54 [0.25–1.15]) in those with a baseline BEC of 300 cells per μL or higher. The annualised rate of moderate or severe COPD exacerbations with tezepelumab was 1.51 versus 1.93 with placebo (rate ratio 0.78 [95% CI 0.54–1.13]) in former smokers and 2.23 versus 2.57 (0.87 [0.52–1.45]) in current smokers. The LS mean changes in prebronchodilator FEV₁ and SGRQ total score from baseline to week 52 in prespecified subgroups are shown in table 2.

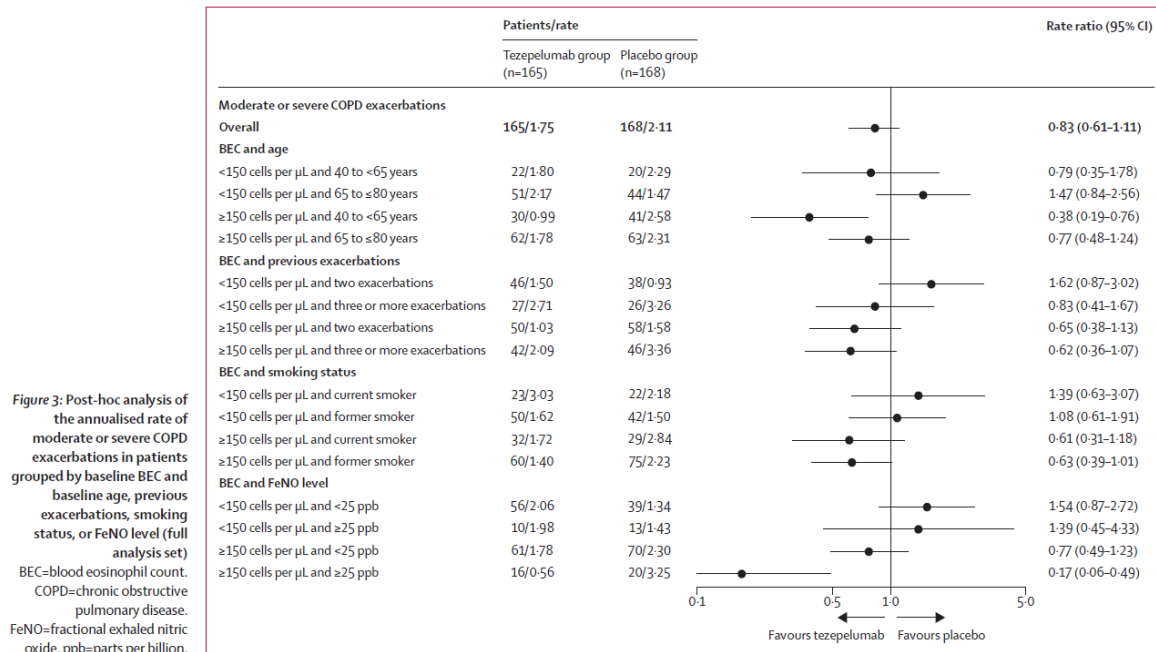
| | Tezepelumab group (n=165) | | Placebo group (n=168) | | LS mean difference (95% CI) |
|--|---------------------------|----------------|-----------------------|----------------|-----------------------------|
| | n | LS mean (SE) | n | LS mean (SE) | |
| Pre-bronchodilator FEV₁, L | | | | | |
| Overall | 163 | 0.026 (0.015) | 166 | -0.029 (0.015) | 0.055 (0.014 to 0.096) |
| Baseline BEC, cells per μL | | | | | |
| <150 | 73 | -0.002 (0.022) | 63 | -0.053 (0.023) | 0.051 (-0.012 to 0.114) |
| 150 to <300 | 66 | 0.010 (0.023) | 72 | -0.025 (0.022) | 0.034 (-0.028 to 0.097) |
| ≥ 300 | 24 | 0.160 (0.038) | 31 | 0.013 (0.035) | 0.146 (0.044 to 0.248) |
| Baseline FeNO level, ppb | | | | | |
| <25 | 117 | 0.009 (0.018) | 107 | -0.022 (0.019) | 0.031 (-0.020 to 0.082) |
| ≥ 25 | 25 | 0.118 (0.038) | 33 | 0.000 (0.035) | 0.118 (0.016 to 0.220) |
| SGRQ total score | | | | | |
| Overall | 157 | -4.80 (1.18) | 156 | -1.86 (1.19) | -2.93 (-6.23 to 0.36) |
| Baseline BEC, cells per μL | | | | | |
| <150 | 69 | -1.91 (1.75) | 60 | -0.30 (1.89) | -1.62 (-6.69 to 3.45) |
| 150 to <300 | 66 | -6.05 (1.81) | 69 | -3.64 (1.75) | -2.41 (-7.36 to 2.55) |
| ≥ 300 | 22 | -10.22 (3.14) | 27 | -0.68 (3.01) | -9.53 (-18.11 to -0.96) |
| Baseline FeNO level, ppb | | | | | |
| <25 | 112 | -4.46 (1.43) | 102 | -2.28 (1.49) | -2.18 (-6.24 to 1.88) |
| ≥ 25 | 24 | -7.23 (3.08) | 29 | -1.90 (2.87) | -5.33 (-13.56 to 2.91) |

BEC=blood eosinophil count. FeNO=fractional exhaled nitric oxide. LS=least-squares. ppb=parts per billion. SGRQ=St George's Respiratory Questionnaire.

Table 2: Change from baseline to week 52 in pre-bronchodilator FEV₁ and SGRQ total score in the overall population (secondary endpoint) and in prespecified patient subgroups by baseline BEC and FeNO level (full analysis set)

In a post-hoc analysis of the primary endpoint in patients with a baseline BEC of 150 cells per μL or higher, the annualised rate of moderate or severe COPD exacerbations over 52 weeks was 1.52 for tezepelumab versus 2.40 for placebo (rate ratio 0.63 [95% CI 0.43–0.93]; appendix p 9). Post-hoc analyses of the annualised rate of moderate or severe COPD exacerbations in patients grouped by FEV₁ reversibility and Global Initiative for Chronic Obstructive Lung Disease grade are shown in the appendix (p 9). When evaluating the annualised rate of moderate or severe COPD exacerbations in patients across the baseline BEC continuum, there was an inflection point at a baseline BEC of about 150 cells per μL , which was sustained with increasing BEC (appendix p 10). A further post-hoc subgroup

analysis evaluated moderate or severe COPD exacerbations in patients treated with tezepelumab versus placebo grouped by baseline BEC (<150 cells per μL or ≥ 150 cells per μL) combined with baseline age, previous exacerbations, smoking status, or FeNO level (figure 3).



As part of a post-hoc analysis of the secondary endpoints, the annualised rate of severe COPD exacerbations with tezepelumab versus placebo was assessed in patients grouped by baseline BEC of less than 150 cells per μL (rate ratio 0.58 [95% CI 0.20–1.66]) and 150 cells per μL or higher (0.42 [0.14–1.23]; appendix p 11). The LS mean difference in changes from baseline to week 52 in pre-bronchodilator FEV1 and SGRQ total score for tezepelumab versus placebo (post-hoc analysis) in patients with a baseline BEC of less than 150 cells per μL and in those with a baseline BEC of 150 cells per μL or higher and across the baseline BEC continuum is shown in the appendix (pp 10, 15).

For the safety endpoints, on-treatment adverse events occurred in 133 (81%) of 165 patients in the tezepelumab group and 126 (75%) of 168 patients in the placebo group (table 3). The most frequently reported adverse events (occurring in $\geq 10\%$ of patients) were COVID-19 (24 [15%] patients in the tezepelumab group vs 14 [8%] in the placebo group) and COPD (20 [12%] vs 28 [17%]; table 3; adverse events by System Organ Class are reported in the appendix, p 16). There were no anaphylactic reactions to tezepelumab or placebo. Discontinuation of treatment owing to adverse events occurred in four (2%) patients in the tezepelumab group and six (4%) patients in the placebo group (table 3; adverse events resulting in treatment discontinuation by System Organ Class and Preferred Term are reported in the appendix, p 17). Serious adverse events occurred in 49 (30%) patients in the tezepelumab group and 50 (30%) patients in the placebo group; COPD was the most frequently reported serious adverse event (occurring in $\geq 5\%$ of patients), observed in 16 (10%) patients in the tezepelumab group and 23 (14%) patients in the placebo group (table 3; serious adverse events by System Organ Class are reported in the appendix, p 18). COVID-19 occurred as a serious adverse event in one (1%) patient in the tezepelumab group and three (2%) patients in the placebo group. On-treatment serious malignancies and serious cardiac

disorders were few and generally balanced between treatment groups (appendix p 18). Five patients died while receiving study treatment: two in the tezepelumab group and three in the placebo group (table 3). No deaths were determined to be causally related to study treatment by investigator assessment.

| | Tezepelumab group (n=165) | Placebo group (n=168) |
|--|---------------------------|-----------------------|
| Any adverse event | 133 (81%) | 126 (75%) |
| Mild | 32 (19%) | 30 (18%) |
| Moderate | 56 (34%) | 62 (37%) |
| Severe | 45 (27%) | 34 (20%) |
| Any adverse event resulting in death | 2 (1%) | 3* (2%) |
| Any serious adverse event | 49 (30%) | 50 (30%) |
| Any adverse event leading to treatment discontinuation | 4 (2%) | 6 (4%) |
| Most frequent adverse events† | | |
| COVID-19 | 24 (15%) | 14 (8%) |
| COPD | 20 (12%) | 28 (17%) |
| Most frequent serious adverse events‡ | | |
| COPD | 16 (10%) | 23 (14%) |

Data are n (%). COPD=chronic obstructive pulmonary disease. *One patient had an adverse event that started during treatment but whose death occurred after discontinuation of treatment and study withdrawal. †Adverse events that occurred in at least 10% of patients in any treatment group, irrespective of causality. ‡Serious adverse events that occurred in at least 5% of patients in any treatment group, irrespective of causality.

Table 3: Summary of on-treatment adverse events (safety analysis set)

Discussion

The phase 2a COURSE study is the first study to assess the potential benefits of an anti-TSLP therapy, tezepelumab, in patients with COPD. The primary endpoint was not met, but a non-statistically significant rate ratio of 0.83 (corresponding to a reduction of 17%) was observed in the annualised rate of moderate or severe COPD exacerbations with tezepelumab versus placebo in patients with at least two previous exacerbations in the 12 months before enrolment despite receiving triple inhaled maintenance therapy. Across endpoints, patients with increasing baseline BECs showed numerically greater differences with tezepelumab versus placebo, but these findings were not significant.

COPD is a heterogeneous condition and has multiple driving mechanisms.²⁶ Exacerbations in patients with COPD are often caused by an acute inflammatory response to an infectious or non-infectious trigger.³ Different inflammatory profiles in the airways during exacerbations have been observed, including neutrophilia and eosinophilia, although more research is required to identify treatable inflammatory traits for optimal treatment with biologics.^{3,26} TSLP regulates the expression of multiple type 2 inflammatory mediators; consequently, it is an upstream regulator of eosinophil function, migration, and survival.^{27,28}

Completed studies of mepolizumab, benralizumab, and dupilumab in COPD have shown that efficacy generally improved with increasing or higher baseline BECs.^{4–10} In COURSE, when evaluating moderate or severe exacerbations in the prespecified baseline BEC subgroups, there were greater reductions observed with tezepelumab versus placebo in patients with a BEC of 150 cells per μL or higher, but these findings were not significant. A post-hoc analysis to evaluate moderate or severe exacerbations across the baseline BEC continuum was conducted. An inflection point for tezepelumab versus placebo was observed in patients with a baseline BEC of about 150 cells per μL , which was sustained with increasing BEC. This was also observed across patients grouped by baseline clinical characteristics; there were greater reductions in moderate or severe exacerbations with tezepelumab versus placebo in patients with a BEC of 150 cells per μL or higher irrespective of FeNO level (<25 ppb or ≥ 25 ppb), smoking status, and previous number of exacerbations at randomisation.

COPD is generally associated with non-type 2 inflammation and includes T helper 1 cell, macrophage, and neutrophil involvement.²⁹ TSLP has been shown to have different roles in inflammation within different epithelial barriers such as in the skin, the lungs, and the gut.²⁸ In the lungs, TSLP is released at epithelial barrier surfaces from a range of cells, including macrophages, and can induce dendritic cells to produce chemotactic factors that in turn can attract neutrophils.²⁷ Respiratory system viruses, double-stranded RNA, cigarette smoke, and proinflammatory cytokines that activate nuclear factor- κB can all lead to exacerbations in COPD and have also been shown to result in TSLP production in patients with COPD.²⁹ This finding suggests that TSLP might be involved in the development of COPD or COPD exacerbations. Therefore, the outcome of tezepelumab treatment in patients with COPD who did not have traditional markers of type 2 airway inflammation is of interest.

In patients with a BEC of less than 150 cells per μL , lung function did not change with tezepelumab treatment, whereas a decline in lung function was observed with placebo. Given that patients with COPD generally have an annual decline in FEV₁,³⁰ this warrants further investigation to assess the potential of tezepelumab treatment to stabilise lung function. The efficacy of tezepelumab might also vary with age or disease severity, potentially due to irreversible airway remodelling and damage over time.³¹ Further studies are needed to understand the mechanism of action of tezepelumab in COPD.

The 420 mg tezepelumab dose every 4 weeks used in COURSE was two times higher than the licensed asthma dose of 210 mg.²⁰ The COURSE study was designed before the licensed dose for asthma was established, and the dosing regimen was selected to ensure that any signals of clinical efficacy were not missed due to underdosing. The dose was selected based on the efficacy, safety, and exposure–response relationships found with tezepelumab treatment in patients with severe asthma, as well as safety data from phase 1 studies in healthy volunteers and in patients with atopic dermatitis.^{32–34} The safety and tolerability of

tezepelumab observed in patients with COPD from COURSE were consistent with what has been previously reported for tezepelumab in patients with asthma.²⁰ Additionally, no anaphylactic reactions were observed.

There were several strengths to this study. COURSE recruited patients with moderate to very severe COPD with a history of moderate or severe previous exacerbations despite triple inhaled therapy, and the study recruited from several countries and treatment centres. The inclusion and exclusion criteria did not restrict entry based on a history of chronic bronchitis, BEC, or current or former smoking status, which permitted assessment of treatment response across these variables. Patients with asthma or asthma–COPD overlap syndrome were excluded. The population of patients recruited in COURSE was representative of patients with moderate to very severe COPD; included patients met the Global Initiative for Chronic Obstructive Lung Disease 2019 COPD criteria,³⁵ had symptomatic COPD (as shown by their baseline CAT and SGRQ total scores), and had low BEC and FeNO levels at baseline.

A limitation of COURSE was that it took place during the COVID-19 pandemic, which led to a recruitment pause of 8 months from April to November, 2020; during this time, participants still in screening were excluded from the study. To mitigate the impact of COVID-19 on the COURSE study, the protocol was amended to allow visits virtually and at locations other than study treatment sites. The study sample size was increased in anticipation of reduced exacerbation rates due to limited person-to-person contact and reduced exposure to respiratory infections associated with COVID-19-related face covering and physical distancing. During the COVID-19 pandemic, notable reductions in COPD exacerbations requiring hospitalisation were reported globally.¹ Therefore, we cannot rule out the possibility that the reduced exposure to respiratory viruses changed the proportion of different exacerbation types and modified the response to tezepelumab. There were also limitations beyond the impact of the COVID-19 pandemic. Caution is required when interpreting findings for severe exacerbations and subgroup analyses because of the low number of patients in some subgroups; additionally, secondary, prespecified subgroup and post-hoc analyses were not controlled for multiplicity. Another limitation was that the presence of chronic bronchitis or emphysema was determined based on patient responses to questions asked by an investigator and captured in the electronic case report form without confirmatory diagnosis. Additionally, because all patients received triple inhaled maintenance therapy, the effect of tezepelumab on patients receiving dual inhaled maintenance therapy could not be assessed.

In conclusion, a significant reduction in the annualised rate of moderate or severe COPD exacerbations was not observed with tezepelumab versus placebo. Further studies are required to evaluate the efficacy of tezepelumab in patients with moderate to very severe COPD. Prespecified and post-hoc analyses identified a potential population of patients with a baseline BEC of 150 cells per μL or higher who might benefit from tezepelumab treatment.

Contributors

All authors contributed to the study design, data interpretation, and drafting of the manuscript, with support from a medical writer funded by AstraZeneca and Amgen. All authors provided critical feedback and final approval for submission, and they vouch for the completeness and accuracy of the data and analyses and the adherence of the trial to the protocol. All authors had full access to and verified the data in the study, and they had final responsibility for the decision to submit for publication.

Declaration of interests

DS has received personal fees from Aerogen, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, CSL Behring, EpiEndo Pharmaceuticals, Genentech, Glenmark Pharmaceuticals, Gossamer Bio, GSK, Kinaset Therapeutics, Menarini Group, Novartis, PULMATRiX, Sanofi, Synairgen, Teva Pharmaceuticals, Theravance Biopharma, and Verona Pharma, and has a leadership or fiduciary role in the Global Initiative for Chronic Obstructive Lung Disease (science committee). CEB has received grants and consultancy fees from 4D Pharma, Areteia Therapeutics, AstraZeneca, Chiesi, Genentech, Global Access Diagnostics, GSK, Novartis, Regeneron Pharmaceuticals, Roche, and Sanofi. KFR has received payment or fees for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, Chiesi, GSK, Novartis, Regeneron Pharmaceuticals, Roche, and Sanofi, and has received fees for advisory board participation from AstraZeneca, Boehringer Ingelheim, Regeneron Pharmaceuticals, and Sanofi. MKH has received grant support from the American Lung Association, AstraZeneca, Biodesix, Boehringer Ingelheim, the COPD Foundation, Gala Therapeutics, Novartis, Nuvaira, Sanofi, Sunovion, and the US National Institutes of Health; has received royalties from Norton Publishing, Penguin Random House, and UpToDate; has received consultancy fees from Aerogen, Altesa BioPharma, Amgen, Apreo Health, AstraZeneca, Boehringer Ingelheim, DevPro Biopharma, Genentech, GSK, Merck, Mylan, Novartis, Polarian, Pulmonx, Regeneron Pharmaceuticals, Roche, RS Biotherapeutics, Sanofi, Teva Pharmaceuticals, and Verona Pharma; has received personal fees from AstraZeneca, Boehringer Ingelheim, GSK, and Novartis; has received speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GSK, Integrity, Medscape, MedWiz Pharmacy, and NACE; has received fees for advisory board participation from Novartis and Medtronic; owns stock in Alesa BioPharma and Meissa Vaccines; and has leadership or fiduciary roles in the COPD Foundation (scientific committee and volunteer spokesperson), the American Thoracic Society (journal editor), the Global Initiative for Chronic Obstructive Lung Disease (science committee), and the Emerson School Board, Ann Arbor, MI, USA. SAC has received fees for advisory board participation from AstraZeneca, Glenmark Pharmaceuticals, and Regeneron Pharmaceuticals; has received consultancy fees from Sanofi; has received fees for authorship from UpToDate for an article about Genomic Tools; and has received fees for non-branded talks by AstraZeneca, GSK, Regeneron Pharmaceuticals, and Sanofi. MBD has received grants from Boehringer Ingelheim, Midmark, and Teva Pharmaceuticals, and has received personal fees from AstraZeneca, Becker Pharma, Boehringer Ingelheim, Chiesi, GSK, Midmark, Optimum Patient Care, Polarean, Teva Pharmaceuticals, and Verona Pharma. AP has received grants from AstraZeneca, Chiesi, GSK, the Italian Medicines Agency, and Sanofi; has received consultancy fees from AstraZeneca, Avillion, Chiesi, ELPEN Pharmaceuticals, GSK, Novartis, and Sanofi; has received presentation fees from AstraZeneca, Avillion, Chiesi, Edmond Pharma, ELPEN Pharmaceuticals, GSK, IQVIA, Menarini Group, Mundipharma, Novartis, Sanofi, and Zambon; has participated in advisory boards for AstraZeneca, Avillion, Chiesi, ELPEN Pharmaceuticals, GSK, IQVIA, MSD, Novartis, and Sanofi; and has a leadership or fiduciary role in the Global Initiative for Chronic Obstructive Lung Disease (science committee). IDP has received speaker fees from Aerocrine AB, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Regeneron Pharmaceuticals, Sanofi, and Teva Pharmaceuticals; has received payments for organisation of educational events from AstraZeneca, GSK, Regeneron Pharmaceuticals, Sanofi, and Teva Pharmaceuticals; has received consultancy fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Dey Pharma, Genentech, GSK, Knopp Biosciences, Merck,

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Data sharing

Data underlying the findings described in this manuscript can be obtained in accordance with AstraZeneca's data sharing policy.

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