Benralizumab for the Prevention of COPD Exacerbations

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ABSTRACT

BACKGROUND

The efficacy and safety of benralizumab, an interleukin-5 receptor alpha–directed cytolytic monoclonal antibody, for the prevention of exacerbations in patients with moderate to very severe chronic obstructive pulmonary disease (COPD) are not known.

METHODS

In the GALATHEA and TERRANOVA trials, we enrolled patients with COPD (at a ratio of approximately 2:1 on the basis of eosinophil count [≥220 per cubic millimeter vs. <220 per cubic millimeter]) who had frequent exacerbations despite receiving guideline-based inhaled treatment. Patients were randomly assigned to receive benralizumab (30 or 100 mg in GALATHEA; 10, 30, or 100 mg in TERRANOVA) every 8 weeks (every 4 weeks for the first three doses) or placebo. The primary end point was the treatment effect of benralizumab, measured as the annualized COPD exacerbation rate ratio (benralizumab vs. placebo) at week 56 in patients with baseline blood eosinophil counts of 220 per cubic millimeter or greater. Safety was also assessed.

RESULTS

In GALATHEA, the estimates of the annualized exacerbation rate were 1.19 per year (95% confidence interval [CI], 1.04 to 1.36) in the 30-mg benralizumab group, 1.03 per year (95% CI, 0.90 to 1.19) in the 100-mg benralizumab group, and 1.24 per year (95% CI, 1.08 to 1.42) in the placebo group; the rate ratio as compared with placebo was 0.96 for 30 mg of benralizumab (P=0.65) and 0.83 for 100 mg of benralizumab (P=0.05). In TERRANOVA, the estimates of the annualized exacerbation rate for 10 mg, 30 mg, and 100 mg of benralizumab and for placebo were 0.99 per year (95% CI, 0.87 to 1.13), 1.21 per year (95% CI, 1.08 to 1.37), 1.09 per year (95% CI, 0.96 to 1.23), and 1.17 per year (95% CI, 1.04 to 1.32), respectively; the corresponding rate ratios were 0.85 (P=0.06), 1.04 (P=0.66), and 0.93 (P=0.40). At 56 weeks, none of the annualized COPD exacerbation rate ratios for any dose of benralizumab as compared with placebo reached significance in either trial. Types and frequencies of adverse events were similar with benralizumab and placebo.

CONCLUSIONS

Add-on benralizumab was not associated with a lower annualized rate of COPD exacerbations than placebo among patients with moderate to very severe COPD, a history of frequent moderate or severe exacerbations, and blood eosinophil counts of 220 per cubic millimeter or greater (Funded by AstraZeneca [GALATHEA and TERRANOVA] and Kyowa Hakko Kirin [GALATHEA]; GALATHEA and TERRANOVA ClinicalTrials.gov numbers, NCT02138916 and NCT02155660.)

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CHRONIC OBSTRUCTIVE PULMONARY DIS-ease (COPD) is characterized by persistent respiratory symptoms and airflow limitation.[1,2] Patients may have episodes of increased respiratory symptoms (exacerbations) that are moderate (leading to enhanced treatment) or severe (leading to hospitalization). Exacerbations negatively affect patients' health status and prognosis and have high societal and economic costs,[1,3] and the prevention of exacerbations is a major therapeutic goal for patients with COPD.

Despite receiving dual or triple inhaled combination therapy (two or three of the following types of agents: inhaled glucocorticoids, long-acting β_2-agonists [LABAs], and long-acting muscarinic antagonists [LAMAs]), patients with COPD may continue to have exacerbations.[4,5] As many as 40% of patients with stable COPD may have eosinophilic inflammation, which is associated with an increased risk of exacerbations as well as glucocorticoid responsiveness.[6,7] Some studies have shown that elevated blood eosinophil counts are associated with an increased risk of exacerbations and that inhaled glucocorticoids are efficacious in preventing exacerbations in this population.[7-11] Targeted treatments to deplete blood eosinophils may also reduce the risk of COPD exacerbations.[12,13]

Benralizumab is an interleukin-5 receptor alpha–directed cytolytic monoclonal antibody that induces direct, rapid, and substantial eosinophil depletion by means of antibody-dependent cellular cytotoxic activity.[14] In a phase 2 trial, benralizumab was not associated with a lower annual rate of COPD exacerbations than placebo in the per-protocol population of patients with COPD.[15] However, a nonsignificant difference in the exacerbation rate, favoring benralizumab, was found for patients with baseline blood eosinophil counts that were 200 per cubic millimeter or greater.[15]

GALATHEA (Benralizumab Efficacy in Moderate to Very Severe Chronic Obstructive Pulmonary Disease with Exacerbation History) and TERRANOVA (Efficacy and Safety of Benralizumab in Moderate to Very Severe Chronic Obstructive Pulmonary Disease with Exacerbation History) were complementary phase 3 trials designed to evaluate the efficacy (measured as the effect on the annualized exacerbation rate) and safety of benralizumab for patients with moderate to very severe COPD, eosinophilic inflamma-tion (blood eosinophil counts ≥220 per cubic millimeter), and an increased risk of exacerbations.
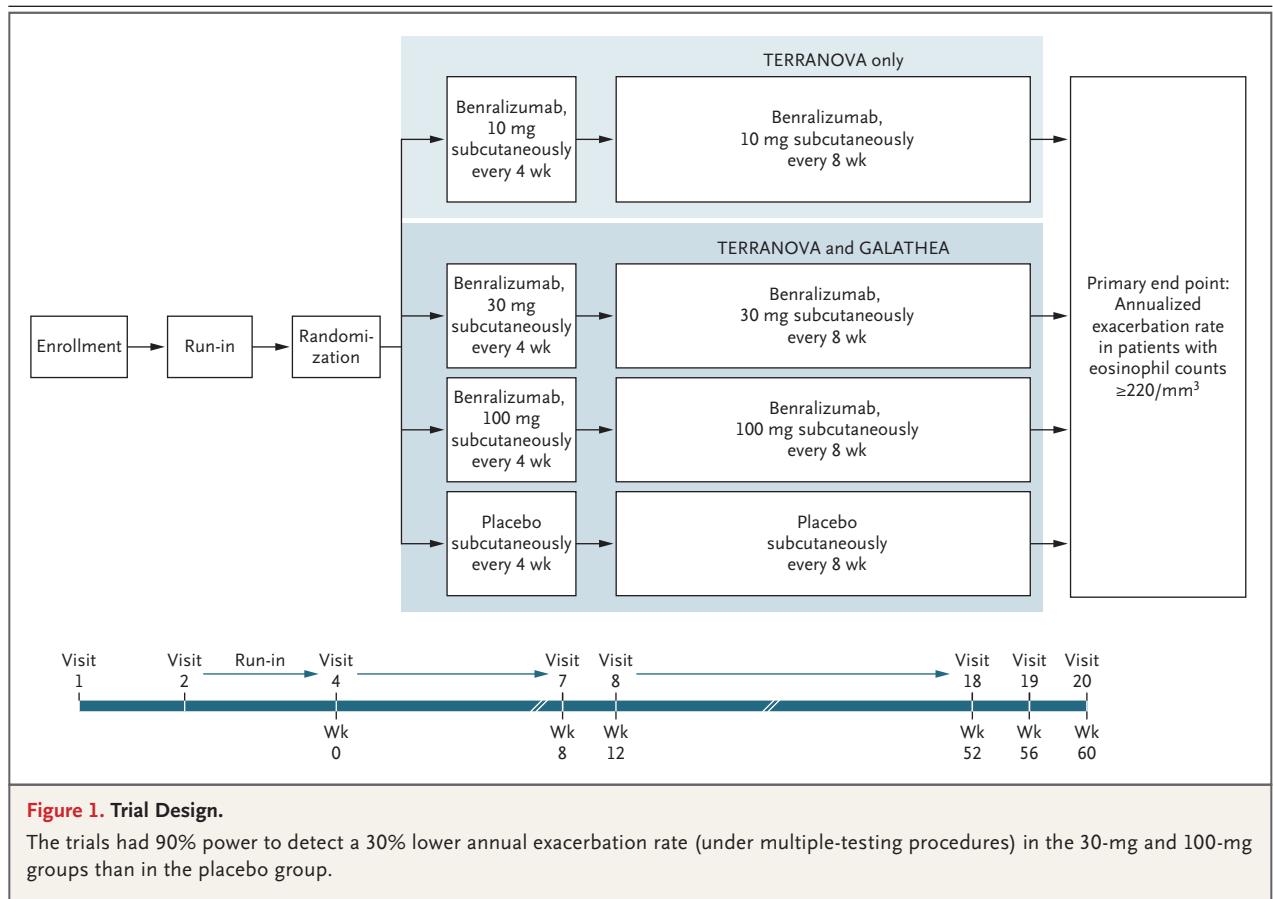
METHODS

TRIAL DESIGN AND OVERSIGHT

GALATHEA and TERRANOVA were phase 3, randomized, double-blind, placebo-controlled, parallel-group trials. Each trial included an enrollment visit, a 3-week screening period, and a 56-week randomized treatment period (Fig. 1).

Independent ethics committees of the trial centers or central institutional review boards approved the trial protocols, available with the full text of this article at NEJM.org. The trials were conducted in accordance with the principles of the Declaration of Helsinki; all patients provided written informed consent. The trials were designed by AstraZeneca and the academic investigators. Trial data were collected by clinical investigators and were analyzed by AstraZeneca employees. All the authors had access to the data and reviewed and approved the manuscript for submission. The first and second authors and the sponsor-employed authors vouch for the accuracy and completeness of the data and for the fidelity of the trials to the protocols. Writing and editing assistance, including preparation of a draft manuscript under direction and guidance of the authors, was funded by AstraZeneca.

Eligible patients were stratified according to country and blood eosinophil count at enrollment (≥300 per cubic millimeter or <300 per cubic millimeter). Recruitment was capped centrally according to baseline blood eosinophil count (<220 per cubic millimeter, 220 to 299 per cubic millimeter, or ≥300 per cubic millimeter) to maintain predefined cohort sizes and an approximate 2:1 ratio of patients with eosinophil counts of 220 per cubic millimeter or greater (primary analysis population) to patients with counts of less than 220 per cubic millimeter. An eosinophil threshold of 220 per cubic millimeter was selected on the basis of the phase 2 trial of benralizumab in patients with COPD, in which modeling of annual exacerbations according to baseline blood eosinophil count indicated that patients with eosinophil counts above a similar threshold were more likely to have a response to benralizumab.[15] The doses selected were 30 mg, the approved dose for asthma treatment; 100 mg, to inform the safety margin; and

Figure 1. Trial Design.

The trials had 90% power to detect a 30% lower annual exacerbation rate (under multiple-testing procedures) in the 30-mg and 100-mg groups than in the placebo group.

10 mg (in TERRANOVA), to evaluate the dose–efficacy relationship.

At randomization, eligible patients were assigned in a 1:1:1 ratio (GALATHEA) or 1:1:1:1 ratio (TERRANOVA) to receive placebo or benralizumab (30 mg or 100 mg in GALATHEA; 10 mg, 30 mg, or 100 mg in TERRANOVA). The trial agent was administered by subcutaneous injection every 4 weeks for the first three doses, then every 8 weeks thereafter. Patients' use of maintenance and rescue medication was recorded daily in an electronic diary; changes in maintenance therapy were permitted only if considered medically necessary by the investigator. The eligibility criteria for randomization included at least 70% adherence to the prescribed inhaled maintenance therapy during the run-in period (based on data from the electronic diary).

PATIENTS

The trials included patients who were 40 to 85 years of age and had moderate to very severe COPD

(i.e., had a postbronchodilator ratio of the forced expiratory volume in 1 second [FEV_1] to the forced vital capacity of <0.70 at screening and a postbronchodilator FEV_1 of >20% and ≤65% of the predicted normal value)[1], were current smokers or ex-smokers (lifetime smoking exposure, ≥10 pack-years), had COPD symptoms (modified Medical Research Council dyspnea scale score of ≥1 at screening; scores range from 0 [dyspnea only with strenuous exercise] to 4 [too dyspneic to leave the house]; minimal clinically important difference, 1 point), and had a documented history of at least two moderate COPD exacerbations leading to oral glucocorticoid treatment, antibiotic treatment, or both or at least one COPD exacerbation leading to hospitalization within the year before enrollment despite treatment with dual therapy (an inhaled glucocorticoid and a LABA or a LABA and a LAMA) or triple therapy (an inhaled glucocorticoid, a LABA, and a LAMA) throughout that year. Patients were excluded from the trial if they had a primary diagnosis of asthma that was con-

sidered by the local investigator to contribute to their current respiratory symptoms (an earlier history of asthma [e.g., in childhood or adolescence] was permitted). The full list of eligibility criteria is provided in the trial protocols.

END POINTS

The primary population for all analyses was made up of patients with baseline blood eosinophil counts of at least 220 per cubic millimeter. The primary end point in both trials was the treatment effect of benralizumab, measured as the annualized COPD exacerbation rate ratio (benralizumab vs. placebo) at week 56, with sensitivity analysis of the annualized severe COPD exacerbation rate. Key secondary end points were the change from baseline in prebronchodilator FEV_1 and in St. George's Respiratory Questionnaire (SGRQ) total score (scores are based on a 50-item questionnaire and range from 0 to 100, with higher scores indicating worse symptoms; a minimal clinically important difference is a decrease of 4 points). Safety end points included types and frequencies of adverse events.

A COPD exacerbation was defined as a symptomatic worsening of COPD for at least 3 days resulting in any of the following outcomes: the use of systemic glucocorticoids, the use of antibiotics, or hospitalization or COPD-related death (see Section 3.2 in the Supplementary Appendix, available at NEJM.org). Severe exacerbations were those resulting in hospitalization or death. Respiratory symptoms were recorded daily in an electronic diary. Patients completed the SGRQ during center visits. Additional assessments that were used but are not reported are described in Section 4 in the Supplementary Appendix. Safety data were collected at center visits along with spirometry data; the reading of spirometry results was centralized. In GALATHEA, 9% of patients were included in an induced-sputum substudy (see Section 3.7 in the Supplementary Appendix).

STATISTICAL ANALYSIS

We calculated that 348 patients with baseline blood eosinophil counts of at least 220 per cubic millimeter in each treatment group (overall total patients in GALATHEA, 1044; in TERRANOVA, 1392) would be required to provide 90% power for the detection of a 30% lower annualized exacerbation rate in the 30-mg or 100-mg benralizumab group than in the placebo group. For this calculation, we assumed a two-sided 4% alpha level (to reserve an alpha level of 1% for the testing of key secondary end points), an annual rate in the placebo group of 0.93 events per patient (1.0 event per patient over 56 weeks), and a negative binomial shape parameter of 0.4.

Exacerbation rates were compared between the benralizumab groups and the placebo group with the use of a negative binomial model for patients in the primary analysis population (baseline blood eosinophil count, ≥220 per cubic millimeter). The model response variable was the number of exacerbations over the 56-week treatment period. The model included covariates of treatment group, eosinophil-count stratum (220 to 299 per cubic millimeter or ≥300 per cubic millimeter), region, background therapy (an inhaled glucocorticoid plus a LABA, a LABA plus a LAMA, or all three types of agents), and number of exacerbations in the previous year. Adjustment for multiple testing, to maintain the overall type I error rate, was performed with the use of the Hochberg procedure.[16] In TERRANOVA, the 10-mg benralizumab group was not adjusted for multiple testing.

Changes from baseline in the prebronchodilator FEV_1 and SGRQ score were key secondary end points (evaluated in patients with blood eosinophil counts of ≥220 per cubic millimeter). Analysis of secondary end points was not adjusted for multiple testing in TERRANOVA. The change from baseline in prebronchodilator FEV_1 at week 56 was compared between each benralizumab dose group and the placebo group with a repeated-measures analysis. The change from baseline in SGRQ total score at week 56 was analyzed separately with a similar model. Safety measures were analyzed by means of count summaries according to trial period.

We performed prespecified subgroup analyses according to the number of previous exacerbations, evaluated in patients with blood eosinophil counts of 220 per cubic millimeter or greater. The results among patients with baseline blood eosinophil counts of less than 220 per cubic millimeter were used to evaluate the effect of benralizumab on the annualized exacerbation rate according to the baseline blood eosinophil count. The trials were not designed or powered to assess efficacy within these subgroups; these analyses are therefore considered exploratory. Further details of the statistical analysis are provided in Section 5 in the Supplementary Appendix.

RESULTS

TRIAL POPULATIONS

The characteristics of the patients in the two trials were similar in the primary analysis populations (1120 patients in GALATHEA and 1545 patients in TERRANOVA had baseline blood eosinophil counts of ≥220 per cubic millimeter) and in the overall study populations (1656 in GALATHEA and 2254 in TERRANOVA) (Table 1, and Tables S1 and S2 in the Supplementary Appendix). The most common trial-specific reason for exclusion was previous closure of enrollment to the prespecified eosinophil-count stratum of less than 220 per cubic millimeter. In the primary analysis population in both trials, most patients were white men, and the mean age was 65 years. The percentages of patients with current (nonprimary diagnosis) or past asthma were low (current asthma, 5.4% in GALATHEA and 3.3% in TERRANOVA; past asthma, 8.3% in GALATHEA and 6.1% in TERRANOVA; the groups were not mutually exclusive) (Table 1). At baseline, most patients (approximately 93% in both trials) were classified as being in Global Initiative for COPD (GOLD) group D, and 69.6% of the patients in GALATHEA and 58.6% of the patients in TERRANOVA were receiving triple therapy with an inhaled glucocorticoid, a LABA, and a LAMA; 9.0% and 7.2%, respectively, were receiving dual therapy with a LABA and a LAMA. More than 29% of patients (overall and across all treatment groups) had had at least one exacerbation resulting in hospitalization in the year before enrollment, and more than 25% had had more than two moderate or severe exacerbations in the previous year. The percentages of patients overall who changed background maintenance therapy during the treatment and post-treatment periods were less than 5% and less than 1%, respectively.

The reported results are for the primary analysis population. In GALATHEA and TERRANOVA, 84.1% and 84.3% of patients, respectively, completed treatment. The primary reasons for treatment discontinuation were adverse events and patient decision (Figs. S1 and S2 in the Supplementary Appendix).

PRIMARY END POINTS

In GALATHEA, the annualized COPD exacerbation rate ratios (benralizumab vs. placebo) at week 56 did not reach significance. The estimates of the annualized exacerbation rate were 1.19 per year (95% confidence interval [CI], 1.04 to 1.36) in the 30-mg benralizumab group, 1.03 per year (95% CI, 0.90 to 1.19) in the 100-mg benralizumab group, and 1.24 per year (95% CI, 1.08 to 1.42) in the placebo group. The rate ratios were 0.96 for 30 mg of benralizumab (P=0.65) and 0.83 for 100 mg of benralizumab (P=0.05) (Table 2 and Fig. 2).

In TERRANOVA, the annualized COPD exacerbation rate ratios (benralizumab vs. placebo) at week 56 also did not reach significance. The estimates of the annualized exacerbation rate were 0.99 per year (95% CI, 0.87 to 1.13) in the 10-mg benralizumab group, 1.21 per year (95% CI, 1.08 to 1.37) in the 30-mg benralizumab group, 1.09 per year (95% CI, 0.96 to 1.23) in the 100-mg benralizumab group, and 1.17 per year (95% CI, 1.04 to 1.32) in the placebo group. The rate ratios were 0.85 (P=0.06), 1.04 (P=0.66), and 0.93 (P=0.40), respectively (Table 2).

There was no consistent dose effect of benralizumab on the annualized exacerbation rate. The time to first exacerbation for each group is shown in Figure S3 in the Supplementary Appendix. In GALATHEA, the annualized rate of severe exacerbations (sensitivity analysis) was 0.25 per year (95% CI, 0.19 to 0.33) in the 30-mg benralizumab group, 0.12 per year (95% CI, 0.08 to 0.17) in the 100-mg benralizumab group, and 0.21 per year (95% CI, 0.15 to 0.28) in the placebo group; the rate ratio was 1.20 in the 30-mg benralizumab group and 0.57 in the 100-mg benralizumab group (Table 2 and Fig. 2). In TERRANOVA, the annualized rates of severe exacerbations in the 10-mg, 30-mg, and 100-mg benralizumab groups were 0.18 per year (95% CI, 0.14 to 0.25), 0.22 per year (95% CI, 0.17 to 0.28), and 0.17 per year (95% CI, 0.13 to 0.22), respectively, and the annualized rate in the placebo group was 0.25 per year (95% CI, 0.19 to 0.32). The rate ratios were 0.75, 0.88, and 0.68, respectively (Table 2 and Fig. 2).

KEY SECONDARY END POINTS

In GALATHEA, the difference (benralizumab vs. placebo) in the mean change from baseline in prebronchodilator FEV_1 was 7 ml (95% CI, −35 to 48) in the 30-mg benralizumab group and 21 ml (95% CI, −21 to 62) in the 100-mg benralizumab group (Table S3 and Fig. S4 in the Supplemen-

Table 1. Demographic and Baseline Clinical Characteristics of the Patients with Baseline Blood Eosinophil Counts of 220 per Cubic Millimeter or Greater.*

Characteristic	GALATHEA				TERRANOVA				
	Benralizumab, 30 mg (N=382)	Benralizumab, 100 mg (N=379)	Placebo (N=359)	Total (N=1120)	Benralizumab, 10 mg (N=377)	Benralizumab, 30 mg (N=394)	Benralizumab, 100 mg (N=386)	Placebo (N=388)	Total (N=1545)
Age — yr	65.8±7.95	65.5±8.29	65.6±8.56	65.6±8.25	65.1±8.49	65.9±8.26	64.9±8.17	65.0±8.38	65.2±8.33
Male sex — no. (%)	270 (70.7)	262 (69.1)	260 (72.4)	792 (70.7)	252 (66.8)	269 (68.3)	250 (64.8)	253 (65.2)	1024 (66.3)
White race — no. (%)†	339 (88.7)	334 (88.1)	315 (87.7)	988 (88.2)	300 (79.6)	312 (79.2)	296 (76.7)	303 (78.1)	1211 (78.4)
BMI‡	27.37±5.67	27.81±6.17	27.37±6.07	27.52±5.97	26.81±5.57	27.15±6.67	26.82±5.80	26.51±5.74	26.82±5.96
Smoking status — no. (%)§									
Current	140 (36.6)	129 (34.0)	115 (32.0)	384 (34.3)	108 (28.6)	108 (27.4)	108 (28.0)	118 (30.4)	442 (28.6)
Former	242 (63.4)	250 (66.0)	244 (68.0)	736 (65.7)	269 (71.4)	286 (72.6)	278 (72.0)	270 (69.6)	1103 (71.4)
Cigarette consumption — pack-yr¶	44.2±21.61	43.5±22.74	41.0±20.26	42.9±21.61	41.9±23.82	45.7±29.99	44.4±25.81	44.1±25.54	44.0±26.43
Baseline eosinophil count — cells/mm³‖	451.3±281.5	458.5±276.6	449.8±283.4	453.2±280.25	518.2±420.1	503.2±388.6	504.2±403.6	492.9±359.6	504.5±393.08
Maintenance therapy — no. (%)‖									
ICS and LABA	72 (18.8)	80 (21.1)	86 (24.0)	238 (21.2)	131 (34.7)	127 (32.2)	133 (34.5)	133 (34.3)	524 (33.9)
LABA and LAMA	33 (8.6)	37 (9.8)	31 (8.6)	101 (9.0)	29 (7.7)	42 (10.7)	16 (4.1)	25 (6.4)	112 (7.2)
ICS, LABA, and LAMA	276 (72.3)	262 (69.1)	242 (67.4)	780 (69.6)	216 (57.3)	224 (56.9)	237 (61.4)	229 (59.0)	906 (58.6)
No. of exacerbations in the previous 12 mo	2.31±1.17	2.33±1.15	2.35±1.42	2.33±1.25	2.25±1.02	2.22±0.98	2.30±1.01	2.34±1.04	2.28±1.01
Prebronchodilator FEV₁ — % of predicted normal value	39.7±13.1	40.5±12.5	41.1±14.9	40.4±13.6	42.7±14.3	40.5±13.2	40.9±13.6	41.2±13.0	41.3±13.5
Postbronchodilator lung function									
FEV₁ — % of predicted normal value	42.4±11.8	43.5±12.0	43.4±12.8	43.1±12.2	43.7±11.8	42.6±12.1	42.5±12.3	42.9±11.5	42.9±11.9
FEV₁:FVC ratio — % of predicted normal value	43±11	44±11	44±12	43±12	45±11	44±11	45±11	45±11	45±11
FEV₁ — liters	1.203±0.416	1.234±0.423	1.237±0.448	1.224±0.429	1.204±0.406	1.152±0.383	1.175±0.426	1.171±0.393	1.175±0.402
Current diagnosis of asthma — no. (%)	17 (4.5)	26 (6.9)	18 (5.0)	61 (5.4)	6 (1.6)	17 (4.3)	12 (3.1)	16 (4.1)	51 (3.3)
Previous diagnosis of asthma — no. (%)	26 (6.8)	38 (10.0)	29 (8.1)	93 (8.3)	18 (4.8)	21 (5.3)	28 (7.3)	28 (7.2)	95 (6.1)

* Plus–minus values are means ±SD. Benralizumab or placebo was given every 8 weeks (the first three doses were given every 4 weeks). FEV₁ denotes forced expiratory volume in 1 second, FVC forced vital capacity, ICS inhaled glucocorticoid, LABA long-acting β₂-agonist, and LAMA long-acting muscarinic antagonist.
† Race was reported by the patient.
‡ Body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
§ Data are for smoking status as assessed at the time of entry into the trial.
¶ Data are for cigarette consumption as measured before entry into the trial.
‖ One patient in the 30-mg benralizumab group in GALATHEA was receiving an ICS and a LAMA. One patient in the 10-mg benralizumab group and one patient in the placebo group in TERRANOVA were receiving an ICS and a LAMA. One patient in the 30-mg benralizumab group in TERRANOVA was receiving an ICS and a LAMA. These four patients are not included here.

tary Appendix). The difference (benralizumab vs. placebo) in the change from baseline in SGRQ total score was −1.011 (95% CI, −2.887 to 0.865) in the 30-mg benralizumab group and −2.136 (95% CI, −4.020 to −0.251) in the 100-mg benralizumab group (Table S3 and Fig. S4 in the Supplementary Appendix).

In TERRANOVA, the difference (benralizumab vs. placebo) in the mean change from baseline in prebronchodilator FEV_1 was 15 ml (95% CI, −29 to 59), −7 ml (95% CI, −51 to 37), and 20 ml (95% CI, −24 to 64) in the 10-mg, 30-mg, and 100-mg benralizumab groups, respectively (Table S3 and Fig. S4 in the Supplementary Appendix). The difference (benralizumab vs. placebo) in the change from baseline in SGRQ total score in the 10-mg, 30-mg, and 100-mg benralizumab groups was −1.011 (95% CI, −3.192 to 1.171), −1.388 (95% CI, −3.562 to 0.786), and −0.602 (95% CI, −2.763 to 1.560), respectively (Table S3 and Fig. S4 in the Supplementary Appendix). Over the course of the trial, the SGRQ total scores for patients in the placebo group showed large improvements, with mean changes of −3.913 in GALATHEA and −6.863 in TERRANOVA (Table 2).

In both trials, all benralizumab doses led to substantial depletion of blood eosinophils from week 4 to the end of the trial, whereas no depletion of eosinophils occurred with placebo (Fig. S5 in the Supplementary Appendix). In a GALATHEA substudy (153 patients, 9%), we analyzed sputum eosinophil counts and found a correlation between the baseline blood eosinophil count and the baseline percentage of sputum eosinophils (Spearman rank correlation coefficient, 0.57). Benralizumab produced substantial depletion of sputum eosinophils by week 24 (mean, 0.02% for 30 mg [24 patients] and 0.13% for 100 mg [17 patients], as compared with 5.38% for placebo [29 patients]).

PRESPECIFIED SUBGROUP ANALYSES

Data on treatment response according to previous exacerbations and baseline blood eosinophil counts are provided in Figures S6, S7, and S8 in the Supplementary Appendix. There was no association between baseline eosinophil count (divided into categories ranging from <150 to >400 per cubic millimeter) and treatment effect.

SAFETY

In both trials, the types and frequencies of adverse events were similar in the benralizumab and placebo groups. Mortality (all-cause and adverse event–related) was low (<4% in each group) (Table 3). The most common adverse events were related to COPD or respiratory conditions. Fewer than 14% of patients in each group had a positive antidrug-antibody response (data not shown). These responses had no apparent effect on clinical outcomes.

DISCUSSION

In the GALATHEA and TERRANOVA trials, involving patients with moderate to very severe COPD who were receiving double or triple inhaled therapy, had a history of COPD exacerbations, and had blood eosinophil counts of at least 220 per cubic millimeter, the annual rates of COPD exacerbations associated with benralizumab given as add-on maintenance treatment over 56 weeks were not significantly lower than those associated with placebo. The approved benralizumab dose for the treatment of patients with severe eosinophilic asthma is 30 mg.[17] Further studies will be needed to determine whether a higher dose of benralizumab may be required to achieve a treatment response in patients with COPD than in patients with asthma. However, the fact that the dose of benralizumab we used reduced blood eosinophils to very low counts suggests that such a strategy may not be successful.

The results we observed with benralizumab were, in general, similar to those of the METREO (Mepolizumab vs. Placebo as Add-on Treatment for Frequently Exacerbating COPD Patients Characterized by Eosinophil Level) and METREX (Mepolizumab vs. Placebo as Add-on Treatment for Frequently Exacerbating COPD Patients) phase 3 trials, which evaluated the efficacy and safety of mepolizumab (an anti–interleukin-5 monoclonal antibody) for patients with COPD and a history of exacerbations.[13] In METREX (but not in METREO), mepolizumab at a dose of 100 mg was associated with a significantly lower annual rate of moderate or severe COPD exacerbations than placebo among patients who had baseline blood eosinophil counts of at least 150 per cubic millimeter at screening or at least 300 per cubic millimeter in the previous year. Key differences between our trials and those trials include the sizes of the patient populations included in the primary analysis, which were larger in GALATHEA (1120 patients) and TERRANOVA (1545) than in METREO (674) and

Table 2. Analysis of Efficacy in Patients with Baseline Blood Eosinophil Counts of 220 per Cubic Millimeter or Greater.*
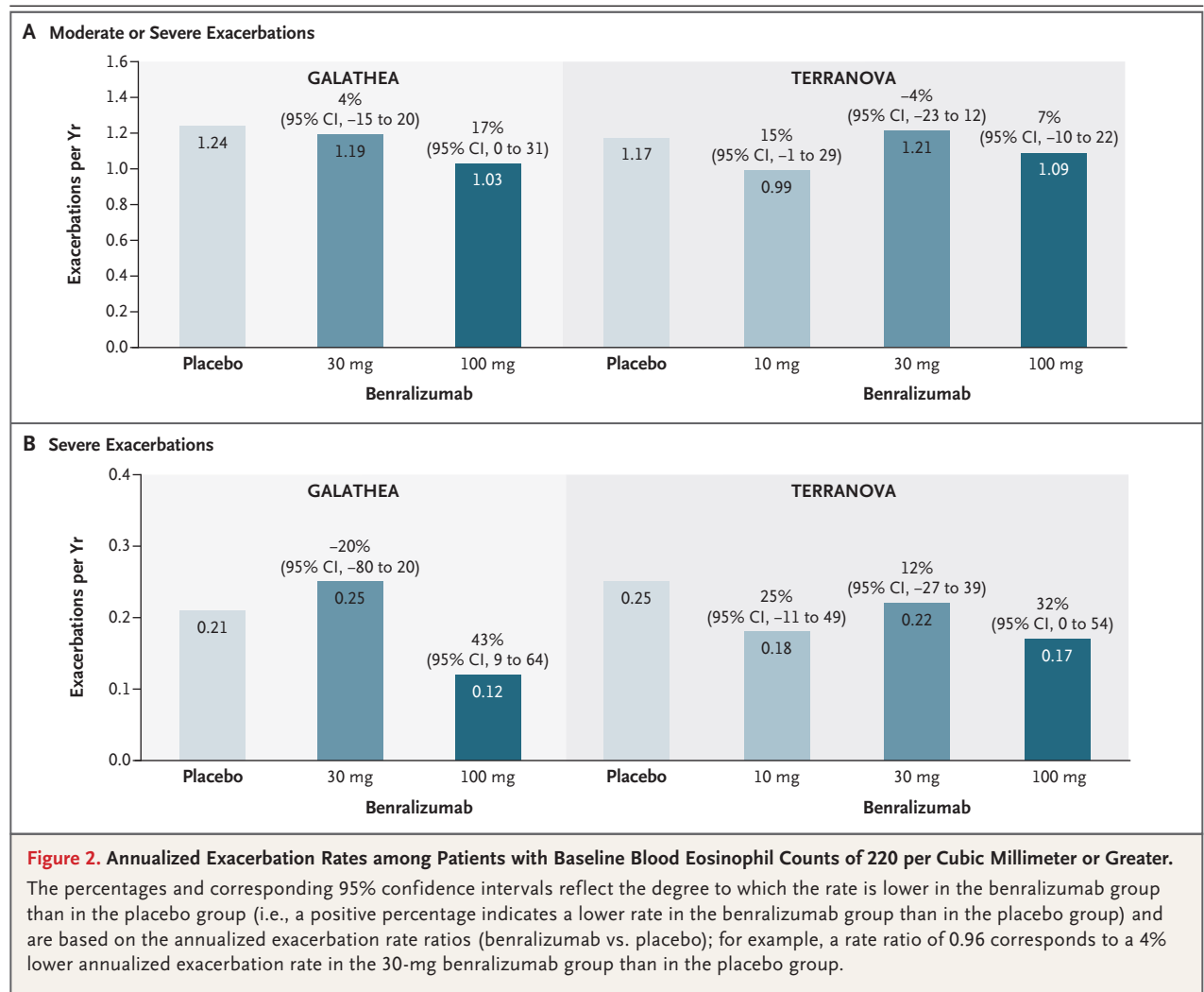
End Point	GALATHEA			TERRANOVA			
	Benralizumab, 30 mg (N=382)	Benralizumab, 100 mg (N=379)	Placebo (N=359)	Benralizumab, 10 mg (N=377)	Benralizumab, 30 mg (N=394)	Benralizumab, 100 mg (N=386)	Placebo (N=388)
Exacerbations							
Estimated annual rate (95% CI) — exacerbations/yr	1.19 (1.04–1.36)	1.03 (0.90–1.19)	1.24 (1.08–1.42)	0.99 (0.87–1.13)	1.21 (1.08–1.37)	1.09 (0.96–1.23)	1.17 (1.04–1.32)
Rate ratio, benralizumab vs. placebo (95% CI)†	0.96 (0.80–1.15)	0.83 (0.69–1.00)	—	0.85 (0.71–1.01)	1.04 (0.88–1.23)	0.93 (0.78–1.10)	—
Unadjusted P value	0.65	0.05	—	0.06	0.66	0.40	—
Severe exacerbations							
Estimated annual rate (95% CI) — exacerbations/yr	0.25 (0.19–0.33)	0.12 (0.08–0.17)	0.21 (0.15–0.28)	0.18 (0.14–0.25)	0.22 (0.17–0.28)	0.17 (0.13–0.22)	0.25 (0.19–0.32)
Rate ratio, benralizumab vs. placebo (95% CI)‡	1.20 (0.80–1.80)	0.57 (0.36–0.91)	—	0.75 (0.51–1.11)	0.88 (0.61–1.27)	0.68 (0.46–1.00)	—
Lung function							
No. of patients with data	329	326	317	325	322	347	344
Change from baseline to wk 56 in prebronchodilator FEV_1 — liters	0.014±0.282	0.031±0.294	0.010±0.275	0.021±0.346	0.011±0.289	0.033±0.291	0.016±0.292
Health-related quality of life							
No. of patients with data	338	331	317	331	329	354	349
Change from baseline to wk 56 in SGRQ total score§	−5.025±14.677	−6.723±15.723	−3.913±15.039	−7.733±14.996	−8.674±17.910	−7.257±15.989	−6.863±16.344

* Plus–minus values are means ±SD.
† Rates are from a negative binomial model with adjustment for treatment group, eosinophil-count stratum (220 to 299 per cubic millimeter or ≥300 per cubic millimeter), geographic region, background therapy (ICS plus LABA, LABA plus LAMA, or triple therapy [ICS, LABA, and LAMA]), and number of previous exacerbations. The trial was designed to test against an alpha level of 0.04.
‡ Confidence intervals have not been adjusted for multiplicity, and inferences drawn from the intervals may not be reproducible.
§ Scores on the St. George's Respiratory Questionnaire (SGRQ), a 50-item health-related quality-of-life questionnaire, range from 0 to 100, with higher scores indicating worse quality of life (a minimal clinically important difference is a decrease of 4 points).

Figure 2. Annualized Exacerbation Rates among Patients with Baseline Blood Eosinophil Counts of 220 per Cubic Millimeter or Greater.

The percentages and corresponding 95% confidence intervals reflect the degree to which the rate is lower in the benralizumab group than in the placebo group (i.e., a positive percentage indicates a lower rate in the benralizumab group than in the placebo group) and are based on the annualized exacerbation rate ratios (benralizumab vs. placebo); for example, a rate ratio of 0.96 corresponds to a 4% lower annualized exacerbation rate in the 30-mg benralizumab group than in the placebo group.

METREX (836). In addition, different cutoff values for the eosinophil count were used (220 per cubic millimeter in GALATHEA and TERRANOVA as compared with 150 per cubic millimeter in METREO and METREX), and patients had to receive treatment with triple inhaled therapy in METREO and METREX, whereas treatment with dual or triple inhaled therapy was required in GALATHEA and TERRANOVA. Furthermore, all patients in METREO and METREX had been receiving long-term treatment with inhaled glucocorticoids before enrollment, whereas up to 9% of patients in GALATHEA and TERRANOVA had not been receiving inhaled glucocorticoids. Moreover, in METREO and METREX, the patients' history of asthma was not well characterized. In GALATHEA and TERRANOVA, no more than 10% of patients had a current secondary or pre-vious diagnosis of asthma; these patients were unlikely to have disproportionately affected the results.

In our trials, adverse events and serious adverse events were balanced across the treatment groups, and all-cause mortality was less than 4% across all treatment groups. These safety data are consistent with those reported in the phase 3 trials of benralizumab for severe, uncontrolled eosinophilic asthma.[18,19]

The data from our two large trials showed improvements in SGRQ total score in the placebo groups that were greater than anticipated. Another potential limitation of the trials is that we did not account for an effect of the type of exacerbation treatment (i.e., systemic glucocorticoids only vs. antibiotics only vs. antibiotics plus glucocorticoids) on the response to benralizumab in

Table 3. Safety of Benralizumab during the Trial Period (Safety Analysis Population).

Adverse Event*	GALATHEA			TERRANOVA			
	Benralizumab, 30 mg (N=554)	Benralizumab, 100 mg (N=552)	Placebo (N=550)	Benralizumab, 10 mg (N=561)	Benralizumab, 30 mg (N=563)	Benralizumab, 100 mg (N=562)	Placebo (N=568)
	number of patients (percent)			*number of patients (percent)*			
Any adverse event	427 (77.1)	445 (80.6)	421 (76.5)	395 (70.4)	424 (75.3)	397 (70.6)	406 (71.5)
Adverse event leading to death	15 (2.7)	11 (2.0)	13 (2.4)	17 (3.0)	21 (3.7)	17 (3.0)	19 (3.3)
Any severe adverse event	151 (27.3)	177 (32.1)	176 (32.0)	144 (25.7)	177 (31.4)	127 (22.6)	158 (27.8)
Adverse event leading to discontinuation of trial agent	30 (5.4)	33 (6.0)	26 (4.7)	20 (3.6)	33 (5.9)	26 (4.6)	16 (2.8)
COPD-related event	98 (17.7)	83 (15.0)	105 (19.1)	97 (17.3)	113 (20.1)	85 (15.1)	93 (16.4)
Viral upper respiratory tract infection	83 (15.0)	95 (17.2)	66 (12.0)	62 (11.1)	47 (8.3)	60 (10.7)	70 (12.3)
Bronchitis	60 (10.8)	86 (15.6)	83 (15.1)	66 (11.8)	73 (13.0)	64 (11.4)	66 (11.6)
Upper respiratory tract infection	69 (12.5)	75 (13.6)	66 (12.0)	68 (12.1)	71 (12.6)	68 (12.1)	67 (11.8)
Lower respiratory tract infection	50 (9.0)	32 (5.8)	29 (5.3)	26 (4.6)	23 (4.1)	15 (2.7)	21 (3.7)
Pneumonia	32 (5.8)	29 (5.3)	24 (4.4)	28 (5.0)	33 (5.9)	22 (3.9)	38 (6.7)
Urinary tract infection	24 (4.3)	23 (4.2)	15 (2.7)	25 (4.5)	26 (4.6)	28 (5.0)	19 (3.3)
Death from any cause	15 (2.7)	12 (2.2)	13 (2.4)	17 (3.0)	21 (3.7)	17 (3.0)	19 (3.3)

* Adverse events were classified in accordance with the *Medical Dictionary for Regulatory Activities*, version 20.0, preferred terms.

the analysis plan. Modifying the trial design to account for greater changes than anticipated in clinical outcomes in the placebo group during the trial and for the effects of the different therapies used to treat exacerbations could help in the planning of future trials involving similar patients with COPD.

COPD is a complex condition driven by a diverse range of mechanisms, which leads to a wide spectrum of clinical presentations.[20] Biologic agents such as benralizumab target a discrete potential pathologic mechanism (eosinophilic inflammation). By week 4, and through to week 56, benralizumab resulted in substantial depletion of blood eosinophils, and substantial depletion of sputum eosinophils had occurred by week 24. However, in contrast to the results in benralizumab-treated patients with severe eosinophilic asthma,[18,19] this eosinophil depletion did not correspond to a significant difference in the rate of exacerbations. This finding, together with the effect on eosinophils — with minimal effect on the COPD exacerbation rate — that was observed in the mepolizumab trials, suggests that eosinophil depletion is unlikely to ameliorate exacerbation outcomes for the majority of patients with COPD. Future investigation is required to identify additional clinical factors or biomarkers that may characterize the patients with COPD who are most likely to benefit from anti–interleukin-5 receptor antibody therapy.

APPENDIX

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REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive lung disease (2019 report). 2019 (https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf).
2. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 report: GOLD executive summary. Am J Respir Crit Care Med 2017;195:557-82.
3. MacIntyre N, Huang YC. Acute exacerbations and respiratory failure in chronic obstructive pulmonary disease. Proc Am Thorac Soc 2008;5:530-5.
4. Chen S, Small M, Lindner L, Xu X. Symptomatic burden of COPD for patients receiving dual or triple therapy. Int J Chron Obstruct Pulmon Dis 2018;13:1365-76.
5. Miravitlles M, Worth H, Soler Cataluña JJ, et al. Observational study to characterise 24-hour COPD symptoms and their relationship with patient-reported outcomes: results from the ASSESS study. Respir Res 2014;15:122.
6. Agusti A, Fabbri LM, Singh D, et al. Inhaled corticosteroids in COPD: friend or foe? Eur Respir J 2018;52(6).
7. Yun JH, Lamb A, Chase R, et al. Blood eosinophil count thresholds and exacerbations in patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol 2018;141(6):2037.e10-2047.e10.
8. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. Lancet Respir Med 2015;3:435-42.
9. Kerkhof M, Sonnappa S, Postma DS,

et al. Blood eosinophil count and exacerbation risk in patients with COPD. Eur Respir J 2017;50(1):170076.

10. Bafadhel M, Peterson S, De Blas MA, et al. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. Lancet Respir Med 2018;6:117-26.

11. Bafadhel M, McKenna S, Terry S, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. Am J Respir Crit Care Med 2012;186:48-55.

12. Siva R, Green RH, Brightling CE, et al. Eosinophilic airway inflammation and exacerbations of COPD: a randomised controlled trial. Eur Respir J 2007;29:906-13.

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

14. Kolbeck R, Kozhich A, Koike M, et al. MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. J Allergy Clin Immunol 2010;125(6): 1344.e2-1353.e2.

15. Brightling CE, Bleecker ER, Panettieri RA Jr, et al. Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study. Lancet Respir Med 2014;2:891-901.

16. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988;75:800-2.

17. Fasenra (benralizumab) prescribing information. Cambridge, United Kingdom: AstraZeneca, 2017 (https://www .azpicentral.com/fasenra/fasenra.pdf).

18. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet 2016;388:2115-27.

19. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2016;388: 2128-41.

20. Singh D, Martin U. Biologics for chronic obstructive pulmonary disease: present and future. BRN Rev 2018;4:34-52.

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