Predicting response to benralizumab in chronic obstructive pulmonary disease: analyses of GALATHEA and TERRANOVA studies

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INTRODUCTION

Exacerbation reduction is a primary treatment goal for patients with chronic obstructive pulmonary disease (COPD).[1] However, 30–50% of patients receiving triple combination maintenance therapy with inhaled corticosteroids (ICS)/long-acting β_2-agonists (LABA)/long-acting muscarinic antagonists (LAMA) continue to experience moderate or severe COPD exacerbations.[2] Additional treatment options are limited for these patients.[2,3]

COPD is a heterogeneous disease. Different inflammatory mechanisms and pathways may contribute to the pathology and clinical outcomes.[4] Eosinophilic inflammation may be an important component in the pathogenesis of a subpopulation of patients with COPD.[5–8] An estimated 30–40% of patients with COPD have elevated concentrations of eosinophils in the airway as measured by sputum induction.[6,9–12] Elevated sputum eosinophil counts for patients with COPD are associated with decreased forced expiratory volume in 1 second (FEV_1) percentage predicted and greater incidence of exacerbations requiring corticosteroid treatment.[13] In addition, patients with airway eosinophilia have greater airway wall thickening and air trapping than patients with low sputum eosinophil counts.[13–15]

A relationship exists between sputum and blood eosinophil counts for patients with COPD, indicating that greater blood eosinophil counts may be a surrogate of eosinophilic inflammation of the airway epithelia.[13,14,16–18] Blood eosinophil concentration 2% or greater for patients with COPD has been identified to have a positive predictive value of 90% for an increased eosinophil concentration in induced sputum.[19] Elevated blood eosinophil counts for patients with COPD are

associated with increased exacerbation risk and greater ICS treatment efficacy.[2,19–24] Therefore, decreasing blood eosinophil counts for patients with elevated blood eosinophil counts may reflect reductions in airway eosinophilia and provide clinical benefit.

Benralizumab is indicated for add-on maintenance treatment of patients with severe, eosinophilic asthma.[25,26] It significantly reduces exacerbation rates and improves lung function and health-related quality of life (HRQOL) for these patients.[27–29] For patients with asthma, benralizumab induces direct, rapid, and nearly complete eosinophil depletion by antibody-dependent cell-mediated cytotoxicity.[27,28,30] The same effect is observed for patients with COPD and elevated blood eosinophil counts.[31] However, for patients with COPD, benralizumab failed to significantly reduce exacerbation rates (primary endpoints) or improve pre-bronchodilator (BD) FEV_1 relative to placebo, regardless of baseline blood eosinophil counts, in two phase 3 clinical trials.[31] In the GALATHEA phase 3 trial for patients with baseline blood eosinophil counts 220 cells per µL or greater (primary analysis population), rate ratios (RRs; 95% confidence interval [CI]) for annual exacerbations were 0·96 (0·80 to 1·15) and 0·83 (0·69 to 1·00) for benralizumab 30 mg and 100 mg every 8 weeks (Q8W; first three doses every 4 weeks [Q4W]), respectively, versus placebo.[31] In the TERRANOVA phase 3 trial for the same primary analysis population, RRs (95% CI) were 0·85 (0·71 to 1·01), 1·04 (0·88 to 1·23), and 0·93 (0·78 to 1·10) for benralizumab 10 mg, 30 mg, and 100 mg Q8W versus placebo, respectively.[31] Given the non-significant results for the primary endpoints in GALATHEA and TERRANOVA, results for further analyses of these data could not be considered statistically significant. However, benralizumab 100 mg Q8W did reduce severe exacerbations relative to placebo with RRs (95%

CI) of 0·57 (0·36 to 0·91) and 0·68 (0·46 to 1·00) in GALATHEA and TERRANOVA, respectively.[31]

As part of a prespecified exploratory analysis, we hypothesised that identifiable clinical features, together with elevated peripheral blood eosinophil counts, could help identify patients with COPD likely to have greater benralizumab treatment effect. Accordingly, we evaluated individual study and pooled results from GALATHEA and TERRANOVA to identify potential baseline clinical and physiological characteristics of patients demonstrating benralizumab treatment effect on reduction of moderate and severe COPD exacerbations, to generate a hypothesis for identifying patients with COPD who are likely to benefit from benralizumab treatment in future clinical trials.

METHODS

Ethics

The protocols for the GALATHEA and TERRANOVA trials were approved by independent ethics committees of the trial centres or central institutional review boards.[31] These studies were conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent.

Exacerbations

Definitions of COPD exacerbations for these pooled analyses were the same as those used in the original clinical trials.[31] Exacerbations were defined as symptomatic worsening of COPD for at least 2 days that resulted in the use of systemic corticosteroids (3 days or longer) and/or antibiotics and/or hospitalisation or COPD-related death. Exacerbations resulting in hospitalisation or death were considered severe.

Endpoints

Annual exacerbation rate (AER) for benralizumab versus placebo was the primary endpoint evaluated in these analyses. The key secondary endpoints were change from baseline in FEV_1 and St. George's Respiratory Questionnaire (SGRQ) total score.

Study population

Patients included in these analyses were enrolled in GALATHEA and TERRANOVA, were aged 40–85 years, and had moderate to very severe airflow limitation, with a history of at least two

exacerbations or one severe exacerbation in the year before enrolment despite receiving treatment with dual therapy (ICS/LABA or LABA/LAMA) or triple therapy (ICS/LABA/LAMA). Patients were enrolled 2:1 on the basis of blood eosinophil count (220 cells per μL or greater *vs* less than 220 cells per μL) and allocated 1:1:1 or 1:1:1:1, respectively, to receive placebo or benralizumab subcutaneously (30 mg or 100 mg Q8W [first three doses Q4W] in GALATHEA; 10 mg, 30 mg, or 100 mg Q8W [first three doses Q4W] in TERRANOVA) for 56 weeks. Because benralizumab 10 mg Q8W was used in the TERRANOVA trial only, these patients were not included in the pooled analyses. Full details of these studies have been published.[31]

Statistical analyses

We performed analyses with pooled data, as well as individual trial data, for patients who participated in the GALATHEA and TERRANOVA phase 3 clinical trials and received placebo or benralizumab (30 mg or 100 mg Q8W). Given the hypothesis-generating nature of these analyses, evidence of consistent findings replicated across trials was used to support that results were less likely to have occurred by chance alone. We used different statistical analysis methods to identify efficacy-associated factors that were consistent across methods, studies, and benralizumab dosages. Analyses were conducted in SAS version 9.2 (SAS Institute Inc, Cary, NC, USA) and R version 3.2.4 (The R Foundation, Vienna, Austria). The primary results of the main trials have been reported.[31]

A structured exploration was performed to identify baseline factors (continuous or categorical) that ranked as most indicative of potential treatment effect in the individual trials and for the

pooled population. Gradient-boosting models were used to rank factors for their relative influences or impacts on exacerbation rate within the treatment arms, and virtual twins analyses were used to identify the most influential predictors that differentiated treatment effect between benralizumab and placebo groups. Importantly, these methods do not require predefining thresholds for continuous parameters such as post-BD FEV_1 or baseline blood eosinophil count. Factors used in the structured exploration included prespecified clinical variables and accounted for correlation of factors across runs, such that potential factors that may correlate with another factor were not both included in the same analysis run (e.g., post-BD FEV_1/forced vital capacity [FVC] was not run at the same time as post-BD FVC percentage predicted normal [% PN]). The factors used were post-BD FEV_1 % PN, post-BD forced expiratory vital capacity % PN, post-BD FEV_1/FVC, percentage reversibility, sex, age, race, country, baseline blood eosinophil count, COPD medication (dual *vs* triple therapy), number of prior exacerbations, number of prior severe exacerbations, concurrent asthma, history of asthma, COPD-specific comorbidity test (COTE) index, nicotine use status, nicotine consumption, COPD Assessment Test total score, rhinitis diagnosis, emphysema diagnosis, chronic bronchitis diagnosis, oxygen cost of breathing diagnosis, and time since COPD diagnosis. These factors were arranged into three structured analysis runs, with no more than 19 variables in any one run (table 1). The structured exploration was conducted with the pooled data from both trials and also separately by trial to allow for identification of predictors that were consistently most influential in both trials.

Predictors that ranked as highly indicative of a potential treatment effect in the structured exploration were further analysed to identify whether they were negatively or positively predictive of treatment effect. AER reduction was estimated from a negative binomial model,

with adjustments for treatment, trial (in analyses pooled across studies), region, and number of prior exacerbations for subgroups of interest. Locally weighted smoothing regression (LOESS) plots and subgroup analyses by quartile were used to further evaluate the relationship between continuous variables and exacerbation rate and to identify an appropriate threshold associated with treatment effect. Results of these analyses were presented as forest plots to illustrate differences in treatment effect over placebo relative to those observed for the overall primary population. Results were pooled across studies to obtain more accurate estimates of the relationship between efficacy endpoints and baseline clinical characteristics of patients by calculating the estimated pooled treatment effect (RRs) and corresponding 95% CIs for benralizumab 30 mg and 100 mg Q8W versus placebo.

Our analyses were based on baseline characteristics of the primary analysis populations in GALATHEA and TERRANOVA, composed of patients with baseline blood eosinophil counts 220 cells per µL or greater. However, analyses were also performed for patients with blood eosinophil counts less than 220 cells per µL and for the overall population, regardless of baseline blood eosinophil count. Analyses of the effect of benralizumab on AER reduction versus placebo for patients with blood eosinophil counts 300 cells per µL or greater and less than 300 cells per µL were also performed.

Role of the funding source

The funders of this study participated in the study design and data analysis. All authors had access to the data and reviewed and approved the manuscript for submission. The corresponding

author had full access to all data in the study and had final responsibility for the decision to submit the paper for publication.

RESULTS

Patient population

The overall trial populations in GALATHEA and TERRANOVA comprised 1,656 and 2,254 patients, respectively. The average age of patients in the pooled data set was 65·3 years, and 1,333/3,910 (34%) of patients were female (table 2). Most patients (2,529/3,910; 65%) were receiving triple maintenance therapy, and 1,253/3,910 (32%) were current nicotine users (table 2).

Factors associated with benralizumab treatment effect on annual exacerbation rate reduction, individual trial data sets

In both the GALATHEA and TERRANOVA trials, influential and consistent covariates for predicting effects on AER for patients with baseline blood eosinophil counts 220 cells per µL or greater included the number of exacerbations in the prior year and baseline lung function measures such as post-BD response % PN (figure 1). Some covariates were strongly influential predictors in only one study but not in the other, and this was later confirmed in the pooled data structured analysis. For example, COTE index was a strongly influential predictor in the TERRANOVA study for benralizumab 100 mg Q8W versus placebo, but this was not replicated in the GALATHEA study. Therefore, COTE index was not selected as a covariate for further analyses. In corresponding analyses of the full data sets containing patients across categories of baseline blood eosinophil counts, number of prior exacerbations and baseline lung function measures were also consistently identified as covariates for predicting effects on AER. In addition, baseline blood eosinophil counts, in general, appeared more influential for patients in

the full analysis set (relative influence of approximately 5–10%; figure S1) than it did for the population with baseline blood eosinophil counts 220 cells per μL or greater (relative influence <5%; figure 1). This indicates greater treatment effect for patients with baseline blood eosinophil counts 220 cells per μL but no clear improvements with increasing blood eosinophil counts above that cut off.

Further analyses of the identified influential predictors were conducted by quartiles to identify their directional influences. There was a greater AER reduction identified for patients with baseline blood eosinophil counts 220 cells per μL or greater receiving benralizumab 100 mg Q8W versus placebo for patients in the lower quartile for baseline post-BD FEV_1 (GALATHEA: post-BD FEV_1 less than 33·2% PN, RR [95% CI]: 0·69 [0·50 to 0·96]; TERRANOVA: post-BD FEV_1 less than 33·1% PN, RR [95% CI]: 0·71 [0·53 to 0·95]; figure 2a). Analysis of the predictive factor baseline post-BD response indicated greater AER reduction for patients in the upper quartile (GALATHEA: post-BD response of 17·5% PN or greater, RR [95% CI]: 0·57 [0·40 to 0·80]; TERRANOVA: post-BD response of 16·2% PN or greater, RR [95% CI]: 0·73 [0·53 to 1·01]; figure 2b).

We also explored effects on AER reduction by baseline post-BD response according to whether patients met the clinical definition of reversibility (defined as post-BD response greater than 12% and a 200-mL increase in FEV_1). There was greater AER reduction with benralizumab 100 mg Q8W versus placebo for patients with baseline post-BD FEV_1 response 15% or greater independent of clinical reversibility status. An equivalent reduction of AER was observed for patients who had post-BD FEV_1 response 15% or greater and also achieved clinical reversibility

status versus those who met post-BD FEV_1 response 15% or greater but did not achieve clinical reversibility status, with RRs (95% CI) of 0·61 (0·38 to 0·97) and 0·60 (0·40 to 0·91), respectively, in GALATHEA and 0·78 (0·51 to 1·18) and 0·70 (0·43 to 1·15), respectively, in TERRANOVA (figure 2c).

Factors associated with benralizumab treatment effect on annual exacerbation rate, pooled data set

In agreement with analyses for the individual GALATHEA and TERRANOVA trials, analysis of pooled data identified number of exacerbations in the prior year and baseline lung function measures, including post-BD response % PN, as covariates associated with AER reduction for patients with baseline blood eosinophil counts 220 cells per µL or greater (figure 1). As in the individual trials, analysis of the full pooled data set consistently identified number of prior exacerbations, baseline blood eosinophil counts, and baseline lung function measures as covariates for predicting effects on AER for patients across the range of baseline blood eosinophil categories (figure S1, Supplementary Appendix page 3).

In the pooled data set, for patients with elevated baseline blood eosinophil counts (220 cells per µL or greater), the RR for annual exacerbations versus placebo was 0·88 (95% CI 0·77 to 0·99) for those receiving benralizumab 100 mg Q8W. The factors identified in the individual studies and pooled data set were examined for benralizumab treatment effect (AER reduction) for the pooled population of patients with elevated blood eosinophil counts (figure 3). Greater treatment effect with benralizumab 100 mg Q8W was observed for patients with a history of three or more exacerbations in the prior year (RR [95% CI] 0·69 [0·56 to 0·83]), but not with benralizumab 30 mg Q8W (RR [95% CI] 0·86 [0·71 to 1·04]). The two identified factors related to lung function

were also associated with greater treatment effects. The RRs (95% CI) for benralizumab 100 mg Q8W were 0·76 (0·64 to 0·91) for post-BD FEV_1 less than 40% PN and 0·67 (0·54 to 0·83) for post-BD response to short-acting β_2-agonists 15% or greater (figure 3).

We also examined the association of background therapy type (dual or triple) on exacerbation reductions during benralizumab treatment. For patients receiving triple therapy, benralizumab 100 mg Q8W had a greater effect on AER reduction versus placebo with RR (95% CI) of 0·81 (0·70 to 0·94), compared with 1·03 (0·82 to 1·28) for patients receiving dual therapy (figure 3). Patients receiving triple therapy tended to have more consistent results across the studies and pooled data set. These factors identified greater treatment effect with benralizumab 100 mg Q8W compared with benralizumab 30 mg Q8W or placebo in reducing AER for patients with baseline blood eosinophil counts 220 cells per µL or greater. Of patients with baseline blood eosinophil counts less than 220 cells per µL, no factors were associated with benralizumab treatment effect (figure 4).

Effects of baseline blood eosinophil counts on annual exacerbation rate

Analysis of pooled data by baseline blood eosinophil count indicated numerically reduced RRs for annual exacerbations in each blood eosinophil count category above 220 cells per µL for patients receiving benralizumab 100 mg Q8W but indicated no evidence for treatment effect for categories less than 220 cells per µL (figure 5). For patients with baseline blood eosinophil counts 300 cells per µL or greater receiving benralizumab 100 mg Q8W, RR versus placebo (95% CI) was 0·85 (0·74 to 0·99). Patients with baseline blood eosinophil counts less than 300

cells per µL receiving benralizumab 100 mg Q8W had an RR versus placebo (95% CI) of 1·00 (0·87 to 1·14), indicating no difference from placebo.

The relationship between baseline blood eosinophil count and exacerbation rate was analysed as a continuous variable for the full analysis sets of GALATHEA and TERRANOVA (figure S2, Supplementary Appendix page 5) and subgroups of patients identified as having greater treatment effect with benralizumab in the pooled data set. These analyses (LOESS plots) indicate that benralizumab treatment effect for patients with three or more exacerbations in the prior year (figure S3, Supplementary Appendix page 6), post-BD FEV_1 <40% predicted (figure S4, Supplementary Appendix page 7), and post-BD response ≥15% (figure S5, Supplementary Appendix page 8) increased marginally with increasing baseline blood eosinophil counts.

Impact of potential predictors on benralizumab treatment effect for annual severe exacerbation rate, pooled data set

Of patients with elevated baseline blood eosinophil counts (220 cells per µL or greater), the RR (95% CI) for annual severe exacerbations versus placebo was 0·63 (0·47 to 0·84) for those receiving benralizumab 100 mg Q8W. The factors found to have the greatest influence on reduction in exacerbations with benralizumab relative to placebo were also analysed for their associations with reduction in severe exacerbations (leading to hospitalisation or death) for patients with elevated blood eosinophil counts. Clinical characteristics that indicated the greatest numerical reductions in severe exacerbations between benralizumab 100 mg and placebo (RR [95% CI]) were post-BD response 15% PN or greater (0·43 [0·24 to 0·75]), three or more exacerbations in the previous year (0·54 [0·32 to 0·91]), triple therapy (0·55 [0·38 to 0·78]), and

baseline blood eosinophil counts 300 cells per μL or greater (0·59 [0·41 to 0·85]). Wide CIs were observed because of the smaller number of severe exacerbation events observed in the studies, but all intervals excluded 1.

Combined factors associated with benralizumab treatment effect on annual exacerbation rate, pooled data set

Prior exacerbations with airflow obstruction or post-bronchodilator response

Given that the frequency of prior exacerbations was the strongest independent predictor of treatment effect with benralizumab 100 mg Q8W for patients with elevated blood eosinophil counts, we evaluated the predictive effect of additional characteristics in combination with history of exacerbations. A greater AER reduction for patients with post-BD FEV_1 <40% was observed if patients also had more frequent prior exacerbations (table 3). Patients with more frequent prior exacerbations and post-BD FEV_1 less than 40% had an annual exacerbation RR (95% CI) of 0·65 (0·48 to 0·88) for benralizumab 100 mg Q8W versus placebo, compared with 0·89 (0·68 to 1·17) for patients with two or less prior exacerbations. In contrast, greater post-BD response was associated with more pronounced AER reduction regardless of the number of prior exacerbations (table 3). Patients with post-BD response 15% or greater receiving benralizumab 100 mg Q8W had RRs (95% CI) versus placebo of 0·60 (0·42 to 0·85) and 0·59 (0·41 to 0·84) for those with two or less and three or greater prior exacerbations, respectively.

Prior exacerbations for patients receiving dual or triple inhaled therapy

History of more frequent exacerbations (three or more in the prior year) and triple therapy each individually were associated with reduced RR for patients receiving benralizumab compared

with the overall patient population. However, RRs (95% CI) for benralizumab 100 mg Q8W versus placebo were similar when frequent exacerbation history was combined with dual (0·60 [0·42 to 0·87]) or triple therapy (0·70 [0·56 to 0·88]) (table 3). Of patients receiving either dual or triple therapy with a history of severe exacerbations receiving benralizumab 100 mg Q8W, RR (95% CI) versus placebo was 0·59 (0·42 to 0·82) compared with 0·74 (0·58 to 0·94) for patients with no prior severe exacerbations (table 3).

Combination of individual predictors

Although patients receiving triple therapy did not have a substantially greater treatment effect with benralizumab than those receiving dual therapy, more consistent results across the studies and pooled data set were observed for the patient population receiving triple inhaled maintenance therapy. The subpopulation of patients with baseline blood eosinophil counts 220 cells per µL or greater, receiving triple inhaled therapy, and who had three or more exacerbations (previous 12 months) were most likely to benefit from benralizumab 100 mg Q8W treatment for reduction of AER (RR *vs* placebo [95% CI] 0·70 [0·56 to 0·88]) (table 3). The selection of patients who had experienced severe exacerbations prior to entering the studies resulted in more pronounced AER reduction, but only for patients with frequent prior exacerbations. The addition of the identified baseline lung function factors of post-BD FEV_1 less than 40% or post-BD response 15% or greater indicated further reduction of AER with benralizumab 100 mg Q8W versus placebo, with reductions of 35% (95% CI 12% to 52%) and 41% (95% CI 16% to 59%), respectively. However, the addition of baseline post-BD FEV_1 and post-BD response resulted in a dramatically smaller population for modest further improvement in AER reduction (figure 6).

Baseline clinical characteristics of the subgroup of patients likely to have the greatest treatment effect with benralizumab are provided in table 2.

Identification of factors associated with benralizumab treatment effect on pre-bronchodilator forced expiratory volume in 1 second and health-related quality of life, individual trial data sets

No factors suggested consistent benralizumab treatment benefit for pre-BD FEV_1 or SGRQ (figure S6, Supplementary Appendix page 9). There was also no evidence for improved pre-BD FEV_1 benralizumab treatment effect with increasing blood eosinophil counts or history of exacerbations (figures S7 and S8, Supplementary Appendix pp. 10–11). An increasing treatment effect of benralizumab on SGRQ total score was observed with increasing blood eosinophil counts in both GALATHEA and TERRANOVA, although this did not reach nominal statistical significance (figure S7, Supplementary Appendix page 10).

DISCUSSION

In these prespecified exploratory analyses of data from the phase 3 randomised GALATHEA and TERRANOVA trials of benralizumab treatment for patients with moderate to very severe COPD, history of three or more exacerbations in the last 12 months, baseline post-BD FEV_1 less than 40%, and post-BD response of 15% or more were the strongest and most consistent individual baseline clinical characteristics that appeared to predict treatment effect with benralizumab 100 mg Q8W for patients with baseline blood eosinophil counts 220 cells per µL or greater. However, the degree of lung function impairment and a history of severe exacerbations predicted treatment effect only for patients with a history of three or more exacerbations in the previous 12 months. The combination of blood eosinophil counts 220 cells per µL or greater, three or more exacerbations in the prior year, and triple inhaled therapy identified patients who experienced the greatest treatment effect with benralizumab for reduction of exacerbations. If confirmed prospectively in a future study, these easily identifiable clinical characteristics, together with an elevated blood eosinophil count, could potentially help select patients with greater probability of experiencing treatment effect with benralizumab.

There was a lack of consistent treatment effect for patients with COPD receiving benralizumab 30 mg Q8W. It is unclear why benralizumab 30 mg Q8W, which has demonstrated efficacy in asthma,[27,28] failed to provide any clinically significant effect in these COPD studies. However, there are important differences between these diseases. COPD is associated with greater structural lung damage than asthma, as well as altered pulmonary blood flow, chronic bacterial colonisation, and presence of different inflammatory cells and mediators.[1,2,4] These results

support benralizumab 100 mg Q8W as the appropriate dosage for patients with COPD in all future clinical investigations.

Reductions in the rate of severe exacerbations were observed for patients with more frequent prior exacerbations, blood eosinophil counts 300 cells per µL or greater, and post-BD response 15% or greater. However, the number of severe exacerbations for this subgroup was small, and observed reductions did not reach a nominally statistically significantly difference compared with placebo.

The results obtained for benralizumab treatment for patients with moderate to very severe COPD are similar to those obtained with the anti–interleukin-5 monoclonal antibody mepolizumab.[32] In the METREX study, the impact of mepolizumab treatment for all patients with COPD, regardless of eosinophilic inflammation, was minimal, but there appeared to be a relationship between baseline blood eosinophil counts and greater treatment effect. Patients with baseline blood eosinophil counts 150 cells per µL or greater had a 14–20% reduction in annual exacerbations across mepolizumab treatment groups compared with placebo in both the METREX and METREO trials. However, no effect was observed for reduction of severe exacerbations.

The results reported here are for the primary analysis populations in GALATHEA and TERRANOVA who had baseline blood eosinophil counts 220 cells per µL or greater. Our analyses found no evidence of benralizumab treatment effect for patients with blood eosinophil counts less than 220 cells per µL. For the identified patient subpopulations demonstrating

benralizumab treatment effect for exacerbation reduction (three or more exacerbations in the prior year, post-BD FEV_1 <40% predicted, and post-BD response ≥15%), treatment effect was observed to increase marginally with increasing baseline blood eosinophil counts. Our findings support the role of blood eosinophil counts as a potential biomarker to help choose specific treatments for patients with COPD.

We did not identify any clinical characteristics or blood eosinophil count thresholds that described patients likely to improve in FEV_1 and health status with benralizumab treatment. For the patient group receiving background triple therapy in GALATHEA and TERRANOVA, differences were small between benralizumab and placebo for pre-BD FEV_1 and HRQOL measures. This finding is similar to studies of other anti-inflammatory therapies for COPD, such as macrolide antibiotics, which demonstrated significant exacerbation reductions but were not associated with significant improvements in change in FEV_1 or HRQOL.[33] The anticipated primary benefit for patients with COPD receiving benralizumab therapy (if benefit is confirmed in a future trial) would likely be prevention or reduction of future exacerbations, a major therapeutic goal for treatment of patients with COPD.[1,34]

Interpretation of novel findings

Patients with COPD who continue to have frequent exacerbations despite receiving triple inhaled maintenance therapy (ICS/LABA/LAMA) most likely would be an appropriate target patient population for treatment with biologic therapy. Therefore, we used data for those patients to determine benralizumab treatment effect for this specific group of patients with a combination of baseline clinical and physiological factors. We found that a subgroup of patients with COPD

who had a combination of greater baseline blood eosinophil counts, history of three or more exacerbations, and treatment with triple therapy had greater AER reduction versus placebo with add-on benralizumab 100 mg Q8W treatment compared with the overall population. We did not identify a difference in benralizumab treatment effect for AER reduction for patients with three or more prior exacerbations receiving dual versus triple therapy. However, triple therapy was included in the recommended subgroup because patients should already be receiving maximal (triple) inhaled therapy before biologic treatment is considered. Also, patients should be at continued risk of exacerbations despite maximal treatment with inhaled maintenance therapies before biologic treatment is initiated. Thus, these are the most clinically relevant characteristics. Additional combinations of predictive factors provided further AER reductions, but these additions dramatically reduced population sizes and made interpreting their individual contributions to benralizumab treatment effect problematic.

Limitations

Our analyses have several potential limitations. These exploratory analyses are hypothesis-generating only. We evaluated patients with elevated blood eosinophil counts, but our analyses did not study other inflammatory markers and exacerbation phenotypes. Treatment of COPD is also frequently complicated by comorbidities.[35] The complexity of the patient population may limit our ability to identify a clear treatment effect with any single intervention. The primary studies (GALATHEA and TERRANOVA) were not powered to detect differences within groups for some evaluations. For these analyses, we pooled data from the independent trials to obtain a meaningful number of patients. Combining some identified factors reduced the size of the subgroup considerably, consequently limiting the power of these analyses to confirm an effect

for these factors. Finally, as with all subgroup analyses, there is the possibility of "regression towards the mean," such that findings for one population may not be replicated or may indicate a magnitude of treatment effect more towards that observed for the overall population when evaluated in a separate data set. As such, it is important to confirm these results in a prospective study. Additional efficacy and safety data are required from all benralizumab studies in COPD before meta-analyses may be effectively conducted, including calculations of number needed to treat to obtain a specified efficacy outcome (e.g., exacerbation rate reduction of XX%) and number needed to avoid one adverse event (i.e., number needed to harm). However, while these are hypothesis-generating analyses and regression to the mean is a concern, it should be noted that the results were observed in the pooled analysis, as well as in the individual trials, reducing the probability that these results are because of chance alone. It is plausible that these patients with COPD, despite displaying some features observed in asthma, have eosinophilic inflammation that is less responsive to background therapy, including ICS.

Conclusions

The results of our data analyses of GALATHEA and TERRANOVA suggest that a combination of clinical characteristics and elevated blood eosinophil counts could be used to guide the use of biologic therapies such as benralizumab for a subpopulation of patients with COPD. These findings support a prospective clinical trial of benralizumab 100 mg Q8W for patients with COPD with elevated blood eosinophil counts and a history of frequent exacerbations during treatment with triple inhaled therapy. The RESOLUTE trial (NCT04053634) will evaluate efficacy and safety of benralizumab for this patient population.

CONTRIBUTORS

All authors and the funder of this study participated in study design. All authors had access to and analysed and interpreted the data, participated in the development and critical review of the manuscript, approved submission of the manuscript for publication, and are accountable for the accuracy and integrity of the work.

DECLARATION OF INTERESTS

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DATA-SHARING STATEMENT

Data underlying the findings described in this manuscript may be requested in accordance with AstraZeneca's data-sharing policy described at https://astrazenecagroup-dt.pharmacm.com/DT/Home.

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***Table 1*: Explanatory variable factors used for each structured analysis run**

Variable	Run 1	Run 2	Run 3
Post-BD FEV_1 % PN	Yes	Yes	No
Post-BD FEVC % PN	Yes	Yes	No
Post-BD FEV_1/FVC	No	No	Yes
Percentage reversibility	No	No	Yes
Sex	Yes	Yes	Yes
Age	Yes	Yes	Yes
Race	Yes	Yes	Yes
Country	No	Yes	No
Baseline blood eosinophil count	Yes	Yes	Yes
COPD medication	Yes	Yes	Yes
Number of prior exacerbations*	Yes	Yes	Yes
Number of prior severe exacerbations*	Yes	Yes	Yes
Concurrent asthma	Yes	Yes	Yes
History of asthma	Yes	Yes	Yes
COTE index	Yes	Yes	Yes
Nicotine use status	Yes	No	No
Nicotine consumption	No	Yes	Yes
CAT total score	Yes	Yes	Yes
Diagnosis of rhinitis	Yes	Yes	Yes
Diagnosis of OCB	Yes	Yes	Yes
Diagnosis of emphysema	Yes	Yes	Yes
Time since COPD diagnosis	Yes	Yes	Yes

BD=bronchodilator. CAT=COPD Assessment Test. COTE=COPD-specific comorbidity test. FEV_1=forced expiratory volume in 1 second. FEVC=forced expiratory vital capacity. FVC=forced vital capacity. OCB=oxygen cost of breathing. PN=predicted normal.

*In the past year.

Nicotine use status refers to categorisation of patients as current smokers, former smokers, or non-smokers. Nicotine consumption refers to the amount of nicotine consumed by the patient (pack-years).

***Table 2*: Key baseline characteristics of overall GALATHEA/TERRANOVA pooled population and those meeting criteria for responders**

Baseline characteristic	Full analysis set (N=3,910)	Patients with blood eosinophil counts ≥220 cells per µL (n=2,665)	Patients with blood eosinophil counts ≥220 cells per µL, ≥3 prior exacerbations, receiving triple therapy (n=515)
Age, mean years (SD)	65·3 (8·3)	65·4 (8·3)	66·1 (8·0)
Female, n (%)	1,333 (34)	849 (32)	164 (32)
Nicotine use history, n (%)			
Current	1,253 (32)	826 (31)	140 (27)
Former	2,657 (68)	1,839 (69)	375 (73)
Median time since COPD diagnosis, years (IQR)	7·0 (4·0 to 11·3)	6·9 (4·0 to 11·1)	7·7 (4·3 to 12·4)
Exacerbations in prior year			
Mean (SD)	2·3 (1·1)	2·3 (1·1)	3·8 (1.3)
≥3, n (%)	1,016 (26)	701 (26)	515 (100)
1 severe, n (%)	1,111 (28)	734 (28)	111 (22)
≥1 severe, n (%)	1,456 (37)	976 (37)	198 (38)
Region, n (%)			
Asia	393 (10)	292 (11)	58 (11)
Eastern Europe	1,141 (29)	788 (30)	87 (17)
Europe	687 (18)	450 (17)	150 (29)
North America	1,028 (26)	692 (26)	145 (28)

ROW	661 (17)	443 (17)	75 (15)
Maintenance COPD medications, n (%)			
ICS/LABA	1,083 (28)	764 (29)	0 (0)
LABA/LAMA	298 (8)	215 (8)	0 (0)
ICS/LABA/LAMA	2,529 (65)	1,686 (63)	515 (100)
Mean FEV_1:			
Pre-BD, % PN (SD)	39·9 (13·2)	40·9 (13·5)	37·7 (13·0)
Post-BD, % PN (SD)	42·2 (12·0)	43·0 (12·0)	40·3 (12·2)
Mean FEV_1/FVC:			
Post-BD, % (SD)	43 (11)	44 (11)	41 (11)
Reversibility, % (SD)	10·1 (13·8)	9·9 (14·2)	11·7 (13·5)
Baseline blood eosinophil count			
Median cells per µL (IQR)	300 (170 to 440)	380 (290 to 540)	380 (290 to 550)
≥300 cells per µL, n (%)	1,990 (51)	1,990 (75)	377 (73)
SGRQ mean total score (SD)	52·6 (17·4)	52·2 (17·4)	55·5 (16·3)
CAT mean total score (SD)	20·1 (7·0)	20·1 (7·0)	21·1 (6·9)
Asthma diagnosis, n (%)			
Current	145 (4)	112 (4)	33 (6)
Previous	266 (7)	188 (7)	53 (10)
Emphysema diagnosis, n (%)	2,155 (55)	1,452 (55)	303 (59)

Chronic bronchitis, n (%)	2,731 (70)	1,862 (70)	371 (72)
Atopic status, n (%)	1,261 (32)	952 (36)	174 (34)

BD=bronchodilator. CAT=COPD Assessment Test. FEV_1=forced expiratory volume in 1 second. FVC=forced vital capacity. ICS=inhaled corticosteroids. IQR=interquartile range. LABA=long-acting β_2-agonists. LAMA=long-acting muscarinic antagonists. PN=predicted normal. ROW=rest of world. SGRQ=St. George's Respiratory Questionnaire.

***Table 3*: Annual exacerbation rate and rate reduction for patient subgroups with frequent versus less frequent exacerbations, receiving dual or triple therapy, and by baseline lung function (pooled GALATHEA/TERRANOVA patients with baseline blood eosinophil counts 220 cells per µL or greater)**

	Benralizumab 30 mg Q8W	Benralizumab 100 mg Q8W	Placebo
≤2 prior exacerbations,* AER (RR *vs* placebo; 95% CI) [n]			
Post-BD FEV_1 <40%	1·24 (0·90; 0·68 to 1·18) [152]	1·23 (0·89; 0·68 to 1·17) [158]	1·39 [127]
Post-BD FEV_1 ≥40%	0·96 (1·13; 0·86 to 1·47) [198]	0·73 (0·86; 0·65 to 1·14) [189]	0·85 [195]
Post-BD response <15%	1·07 (1·08; 0·85 to 1·38) [231]	1·01 (1·02; 0·81 to 1·29) [243]	0·99 [234]
Post-BD response ≥15%	1·08 (0·81; 0·58 to 1·12) [117]	0·80 (0·60; 0·42 to 0·85) [103]	1·34 [87]
≥3 prior exacerbations,* AER (RR *vs* placebo; 95% CI) [n]			
Post-BD FEV_1 <40%	2·33 (0·98; 0·74 to 1·30) [81]	1·54 (0·65; 0·48 to 0·88) [72]	2·38 [80]
Post-BD FEV_1 ≥40%	1·77 (0·94; 0·65 to 1·36) [69]	1·40 (0·74; 0·52 to 1·06) [79]	1·89 [69]
Post-BD response <15%	2·06 (1·11; 0·83 to 1·49) [98]	1·49 (0·80; 0·59 to 1·08) [100]	1·86 [97]
Post-BD response ≥15%	2·07 (0·82; 0·58 to 1·15)	1·49 (0·59; 0·41 to 0·84)	2·54

	[52]	[51]	[51]
Post-BD response <15% and receiving triple therapy, AER (RR *vs* placebo; 95% CI) [n]			
Post-BD FEV_1 <40%	1·59 (1·04; 0·81 to 1·34) [155]	1·45 (0·95; 0·74 to 1·22) [163]	1·53 [143]
Post-BD FEV_1 ≥40%	1·15 (1·18; 0·89 to 1·55) [174]	0·91 (0·92; 0·70 to 1·22) [180]	0·99 [188]
Post-BD response ≥15% and receiving triple therapy, AER (RR *vs* placebo; 95% CI) [n]			
Post-BD FEV_1 <40%	1·68 (0·75; 0·55 to 1·03) [76]	1·02 (0·46; 0·32 to 0·66) [67]	2·24 [63]
Post-BD FEV_1 ≥40%	1·28 (0·99; 0·70 to 1·39) [93]	0·97 (0·75; 0·52 to 1·07) [87]	1·30 [75]
≤2 prior exacerbations,* AER (RR *vs* placebo; 95% CI) [n]			
Dual therapy	0·76 (1·19; 0·90 to 1·58) [221]	0·81 (1·26; 0·94 to 1·67) [209]	0·64 [222]
Triple therapy	1·08 (1·00; 0·82 to 1·21) [350]	0·95 (0·88; 0·73 to 1·08) [348]	1·08 [322]
Prior severe exacerbation*	1·07 (1·06; 0·84 to 1·35) [220]	1·02 (1·02; 0·80 to 1·30) [217]	1·01 [194]
No prior severe exacerbation*	0·90 (1·10; 0·89 to 1·35) [351]	0·82 (0·99; 0·80 to 1·23) [340]	0·82 [350]
≥3 prior exacerbations,* AER (RR *vs* placebo; 95% CI) [n]			
Dual therapy	1·14 (0·53; 0·36 to 0·78) [55]	1·30 (0·60; 0·42 to 0·87) [57]	2·15 [54]
Triple therapy	2·09 (0·99; 0·79 to 1·23) [150]	1·49 (0·70; 0·56 to 0·88) [151]	2·12 [149]
Prior severe exacerbation*	1·98 (0·87; 0·63 to 1·19)	1·35 (0·59; 0·42 to 0·82)	2·29

	[74]	[76]	[83]
No prior severe exacerbation*	1·68 (0·82; 0·64 to 1·05) [131]	1·51 (0·74; 0·58 to 0·94) [132]	2·05 [120]

AER=annual exacerbation rate. BD=bronchodilator. FEV_1=forced expiratory volume in 1 second. Q8W=every 8 weeks (first three doses every 4 weeks). RR=rate ratio.

*In the past year.

FIGURE LEGENDS

***Figure 1*: Structured exploration of data from a) GALATHEA and b) TERRANOVA separately and c) GALATHEA/TERRANOVA pooled data for patients with baseline blood eosinophil counts 220 cells per µL or greater**

BD=bronchodilator. CAT=COPD Assessment Test. COTE=COPD-specific comorbidity test. FEV_1=forced expiratory volume in 1 second. FEVC=forced expiratory vital capacity. OCB=oxygen cost of breathing. PN=predicted normal. Q8W=every 8 weeks (first three doses every 4 weeks).
Post-BD response was included in Run 3 and was found to be greatly associated with treatment response. Prior exacerbations are exacerbations in the year before study entry.

***Figure 2*: Effects of baseline a) post-BD FEV_1 (% PN), b) post-BD response, and c) clinically defined reversibility on reduction of annual exacerbation rate with benralizumab versus placebo for patients with baseline blood eosinophil counts 220 cells per µL or greater**

BD=bronchodilator. FEV_1=forced expiratory volume in 1 second. NC=not calculated. PN=predicted normal. Q8W=every 8 weeks (first three doses every 4 weeks).

***Figure 3*: Effects of benralizumab treatment on annual exacerbation rate for patients with baseline blood eosinophil counts 220 cells per µL or greater by identified individual predictors of response**

BD=bronchodilator. FEV_1=forced expiratory volume in 1 second. PN=predicted normal. Q8W=every 8 weeks (first three doses every 4 weeks).

*Combination of two or three of the following: inhaled corticosteroids, long-acting β_2-agonists, and long-acting muscarinic antagonists.

Prior exacerbations are exacerbations in the year before study entry.

***Figure 4*: Pooled data for benralizumab treatment effect versus placebo on annual exacerbation rate for patients with baseline blood eosinophil counts 220 cells per µL or greater and less than 220 cells per µL by identified individual predictors of response**

BD=bronchodilator. FEV_1=forced expiratory volume in 1 second. Q8W=every 8 weeks (first three doses every 4 weeks).

Prior exacerbations are exacerbations in the year before study entry.

Methodology used for the generation of data in these plots was different from other exploratory analyses, leading to some differences in values for some data points.

***Figure 5*: Effects of baseline blood eosinophil count on annual exacerbation rate in pooled data set**

Q8W=every 8 weeks (first three doses every 4 weeks).

***Figure 6*: Impact of combining predictors on placebo exacerbation rate and benralizumab 100 mg Q8W treatment effect size**

BD=bronchodilator. ERR=exacerbation rate reduction. FEV_1=forced expiratory volume in 1 second. Q8W=every 8 weeks (first three doses every 4 weeks).

Prior exacerbations are exacerbations in the year before study entry.

Figure 1

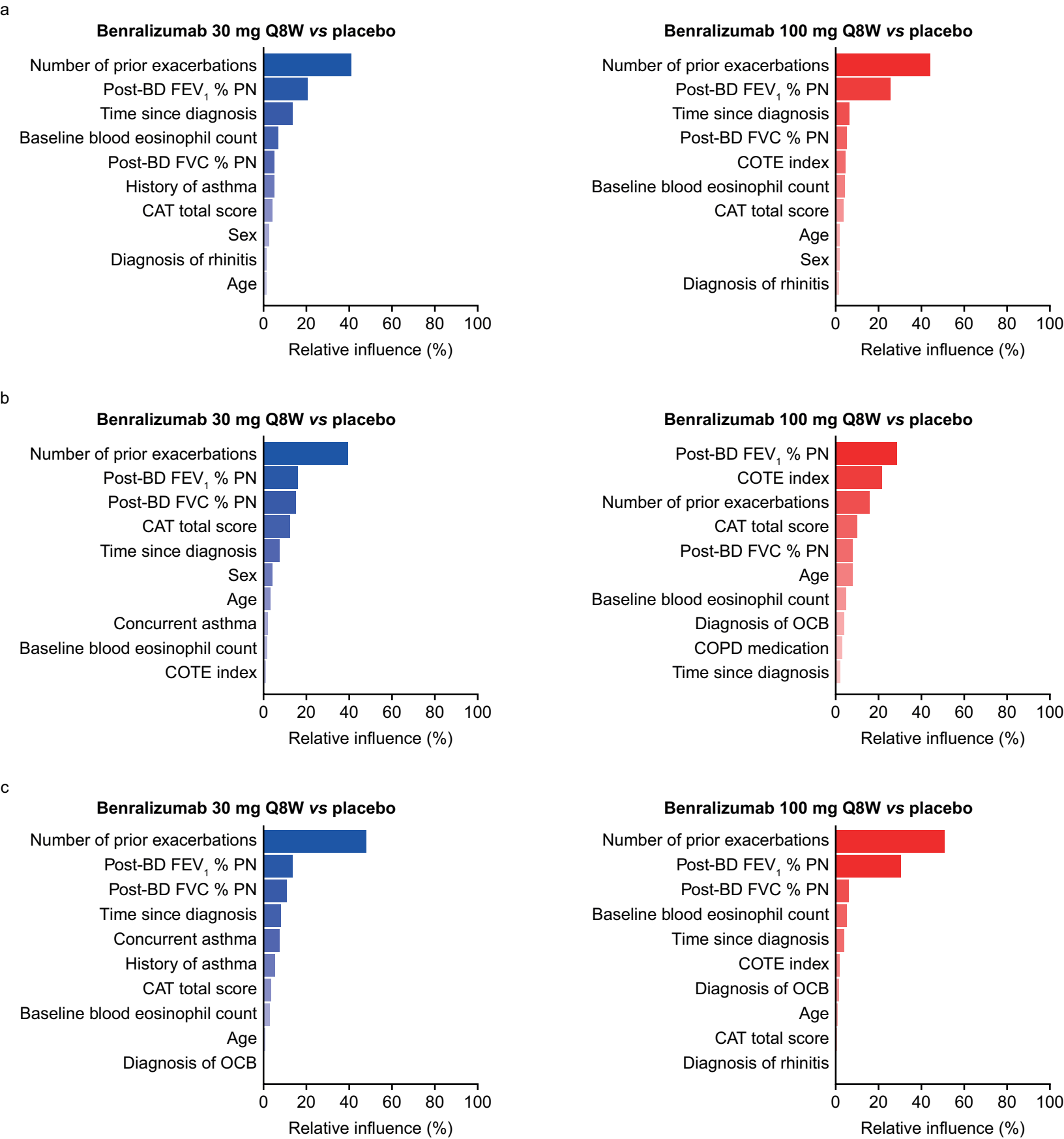

a
Benralizumab 30 mg Q8W *vs* placebo
Number of prior exacerbations
Post-BD FEV1 % PN
Time since diagnosis
Baseline blood eosinophil count
Post-BD FVC % PN
History of asthma
CAT total score
Sex
Diagnosis of rhinitis
Age
0 20 40 60 80 100
Relative influence (%)
Benralizumab 100 mg Q8W *vs* placebo
Number of prior exacerbations
Post-BD FEV1 % PN
Time since diagnosis
Post-BD FVC % PN
COTE index
Baseline blood eosinophil count
CAT total score
Age
Sex
Diagnosis of rhinitis
0 20 40 60 80 100
Relative influence (%)
b
Benralizumab 30 mg Q8W *vs* placebo
Number of prior exacerbations
Post-BD FEV1 % PN
Post-BD FVC % PN
CAT total score
Time since diagnosis
Sex
Age
Concurrent asthma
Baseline blood eosinophil count
COTE index
0 20 40 60 80 100
Relative influence (%)
Benralizumab 100 mg Q8W *vs* placebo
Post-BD FEV1 % PN
COTE index
Number of prior exacerbations
CAT total score
Post-BD FVC % PN
Age
Baseline blood eosinophil count
Diagnosis of OCB
COPD medication
Time since diagnosis
0 20 40 60 80 100
Relative influence (%)
c
Benralizumab 30 mg Q8W *vs* placebo
Number of prior exacerbations
Post-BD FEV1 % PN
Post-BD FVC % PN
Time since diagnosis
Concurrent asthma
History of asthma
CAT total score
Baseline blood eosinophil count
Age
Diagnosis of OCB
0 20 40 60 80 100
Relative influence (%)
Benralizumab 100 mg Q8W *vs* placebo
Number of prior exacerbations
Post-BD FEV1 % PN
Post-BD FVC % PN
Baseline blood eosinophil count
Time since diagnosis
COTE index
Diagnosis of OCB
Age
CAT total score
Diagnosis of rhinitis
0 20 40 60 80 100
Relative influence (%)

Figure 2

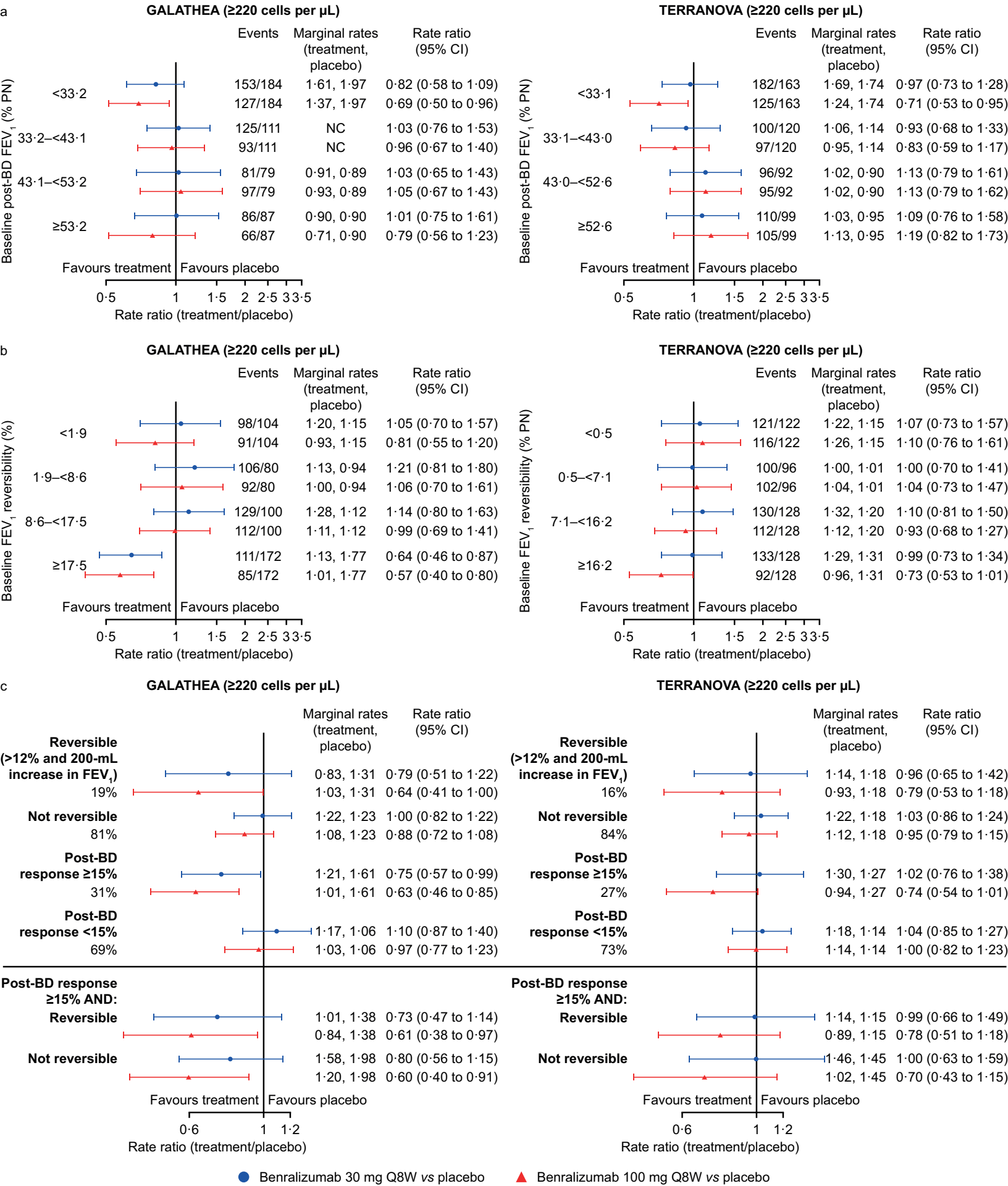

a
GALATHEA (≥220 cells per µL)
TERRANOVA (≥220 cells per µL)
Events
Marginal rates (treatment, placebo)
Rate ratio (95% CI)
Baseline post-BD FEV1 (% PN)
<33·2
153/184
1·61, 1·97
0·82 (0·58 to 1·09)
127/184
1·37, 1·97
0·69 (0·50 to 0·96)
33·2–<43·1
125/111
NC
1·03 (0·76 to 1·53)
93/111
NC
0·96 (0·67 to 1·40)
43·1–<53·2
81/79
0·91, 0·89
1·03 (0·65 to 1·43)
97/79
0·93, 0·89
1·05 (0·67 to 1·43)
≥53·2
86/87
0·90, 0·90
1·01 (0·75 to 1·61)
66/87
0·71, 0·90
0·79 (0·56 to 1·23)
<33·1
182/163
1·69, 1·74
0·97 (0·73 to 1·28)
125/163
1·24, 1·74
0·71 (0·53 to 0·95)
33·1–<43·0
100/120
1·06, 1·14
0·93 (0·68 to 1·33)
97/120
0·95, 1·14
0·83 (0·59 to 1·17)
43·0–<52·6
96/92
1·02, 0·90
1·13 (0·79 to 1·61)
95/92
1·02, 0·90
1·13 (0·79 to 1·62)
≥52·6
110/99
1·03, 0·95
1·09 (0·76 to 1·58)
105/99
1·13, 0·95
1·19 (0·82 to 1·73)
Favours treatment
Favours placebo
0·5
1
1·5
2
2·5
3
3·5
Rate ratio (treatment/placebo)
b
GALATHEA (≥220 cells per µL)
TERRANOVA (≥220 cells per µL)
Events
Marginal rates (treatment, placebo)
Rate ratio (95% CI)
Baseline FEV1 reversibility (%)
<1·9
98/104
1·20, 1·15
1·05 (0·70 to 1·57)
91/104
0·93, 1·15
0·81 (0·55 to 1·20)
1·9–<8·6
106/80
1·13, 0·94
1·21 (0·81 to 1·80)
92/80
1·00, 0·94
1·06 (0·70 to 1·61)
8·6–<17·5
129/100
1·28, 1·12
1·14 (0·80 to 1·63)
112/100
1·11, 1·12
0·99 (0·69 to 1·41)
≥17·5
111/172
1·13, 1·77
0·64 (0·46 to 0·87)
85/172
1·01, 1·77
0·57 (0·40 to 0·80)
Baseline FEV1 reversibility (% PN)
<0·5
121/122
1·22, 1·15
1·07 (0·73 to 1·57)
116/122
1·26, 1·15
1·10 (0·76 to 1·61)
0·5–<7·1
100/96
1·00, 1·01
1·00 (0·70 to 1·41)
102/96
1·04, 1·01
1·04 (0·73 to 1·47)
7·1–<16·2
130/128
1·32, 1·20
1·10 (0·81 to 1·50)
112/128
1·12, 1·20
0·93 (0·68 to 1·27)
≥16·2
133/128
1·29, 1·31
0·99 (0·73 to 1·34)
92/128
0·96, 1·31
0·73 (0·53 to 1·01)
Favours treatment
Favours placebo
0·5
1
1·5
2
2·5
3
3·5
Rate ratio (treatment/placebo)
c
GALATHEA (≥220 cells per µL)
TERRANOVA (≥220 cells per µL)
Marginal rates (treatment, placebo)
Rate ratio (95% CI)
Reversible (>12% and 200-mL increase in FEV1)
19%
0·83, 1·31
0·79 (0·51 to 1·22)
1·03, 1·31
0·64 (0·41 to 1·00)
Not reversible
81%
1·22, 1·23
1·00 (0·82 to 1·22)
1·08, 1·23
0·88 (0·72 to 1·08)
Post-BD response ≥15%
31%
1·21, 1·61
0·75 (0·57 to 0·99)
1·01, 1·61
0·63 (0·46 to 0·85)
Post-BD response <15%
69%
1·17, 1·06
1·10 (0·87 to 1·40)
1·03, 1·06
0·97 (0·77 to 1·23)
Reversible (>12% and 200-mL increase in FEV1)
16%
1·14, 1·18
0·96 (0·65 to 1·42)
0·93, 1·18
0·79 (0·53 to 1·18)
Not reversible
84%
1·22, 1·18
1·03 (0·86 to 1·24)
1·12, 1·18
0·95 (0·79 to 1·15)
Post-BD response ≥15%
27%
1·30, 1·27
1·02 (0·76 to 1·38)
0·94, 1·27
0·74 (0·54 to 1·01)
Post-BD response <15%
73%
1·18, 1·14
1·04 (0·85 to 1·27)
1·14, 1·14
1·00 (0·82 to 1·23)
Post-BD response ≥15% AND:
Reversible
1·01, 1·38
0·73 (0·47 to 1·14)
0·84, 1·38
0·61 (0·38 to 0·97)
Not reversible
1·58, 1·98
0·80 (0·56 to 1·15)
1·20, 1·98
0·60 (0·40 to 0·91)
Post-BD response ≥15% AND:
Reversible
1·14, 1·15
0·99 (0·66 to 1·49)
0·89, 1·15
0·78 (0·51 to 1·18)
Not reversible
1·46, 1·45
1·00 (0·63 to 1·59)
1·02, 1·45
0·70 (0·43 to 1·15)
Favours treatment
Favours placebo
0·6
1
1·2
Rate ratio (treatment/placebo)
Benralizumab 30 mg Q8W vs placebo
Benralizumab 100 mg Q8W vs placebo

Figure 3

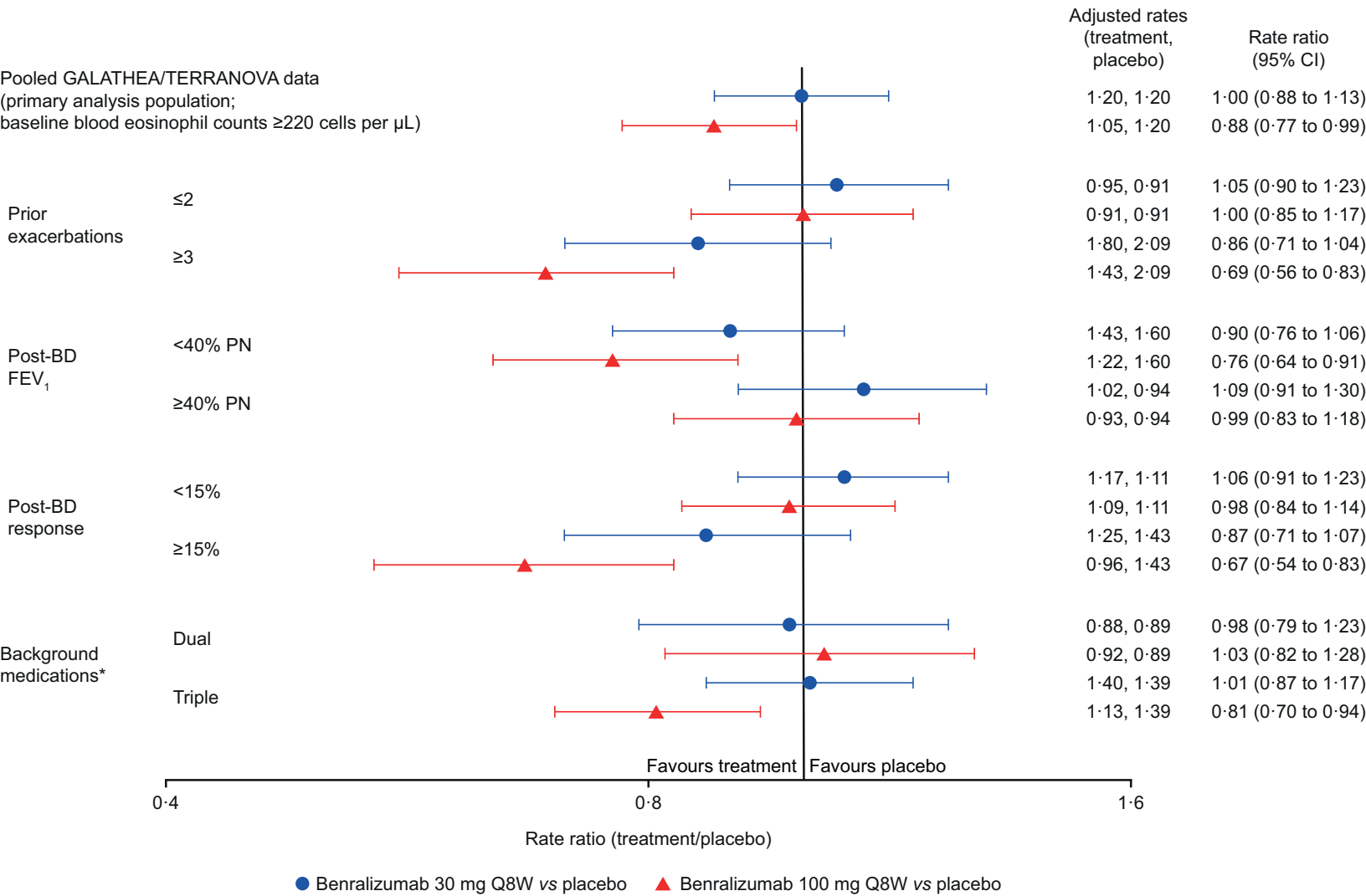

Adjusted rates (treatment, placebo)
Rate ratio (95% CI)
Pooled GALATHEA/TERRANOVA data (primary analysis population; baseline blood eosinophil counts ≥220 cells per µL)
1·20, 1·20
1·00 (0·88 to 1·13)
1·05, 1·20
0·88 (0·77 to 0·99)
Prior exacerbations
≤2
0·95, 0·91
1·05 (0·90 to 1·23)
0·91, 0·91
1·00 (0·85 to 1·17)
≥3
1·80, 2·09
0·86 (0·71 to 1·04)
1·43, 2·09
0·69 (0·56 to 0·83)
Post-BD FEV1
<40% PN
1·43, 1·60
0·90 (0·76 to 1·06)
1·22, 1·60
0·76 (0·64 to 0·91)
≥40% PN
1·02, 0·94
1·09 (0·91 to 1·30)
0·93, 0·94
0·99 (0·83 to 1·18)
Post-BD response
<15%
1·17, 1·11
1·06 (0·91 to 1·23)
1·09, 1·11
0·98 (0·84 to 1·14)
≥15%
1·25, 1·43
0·87 (0·71 to 1·07)
0·96, 1·43
0·67 (0·54 to 0·83)
Background medications*
Dual
0·88, 0·89
0·98 (0·79 to 1·23)
0·92, 0·89
1·03 (0·82 to 1·28)
Triple
1·40, 1·39
1·01 (0·87 to 1·17)
1·13, 1·39
0·81 (0·70 to 0·94)
Favours treatment
Favours placebo
0·4
0·8
1·6
Rate ratio (treatment/placebo)
Benralizumab 30 mg Q8W vs placebo
Benralizumab 100 mg Q8W vs placebo

Figure 4

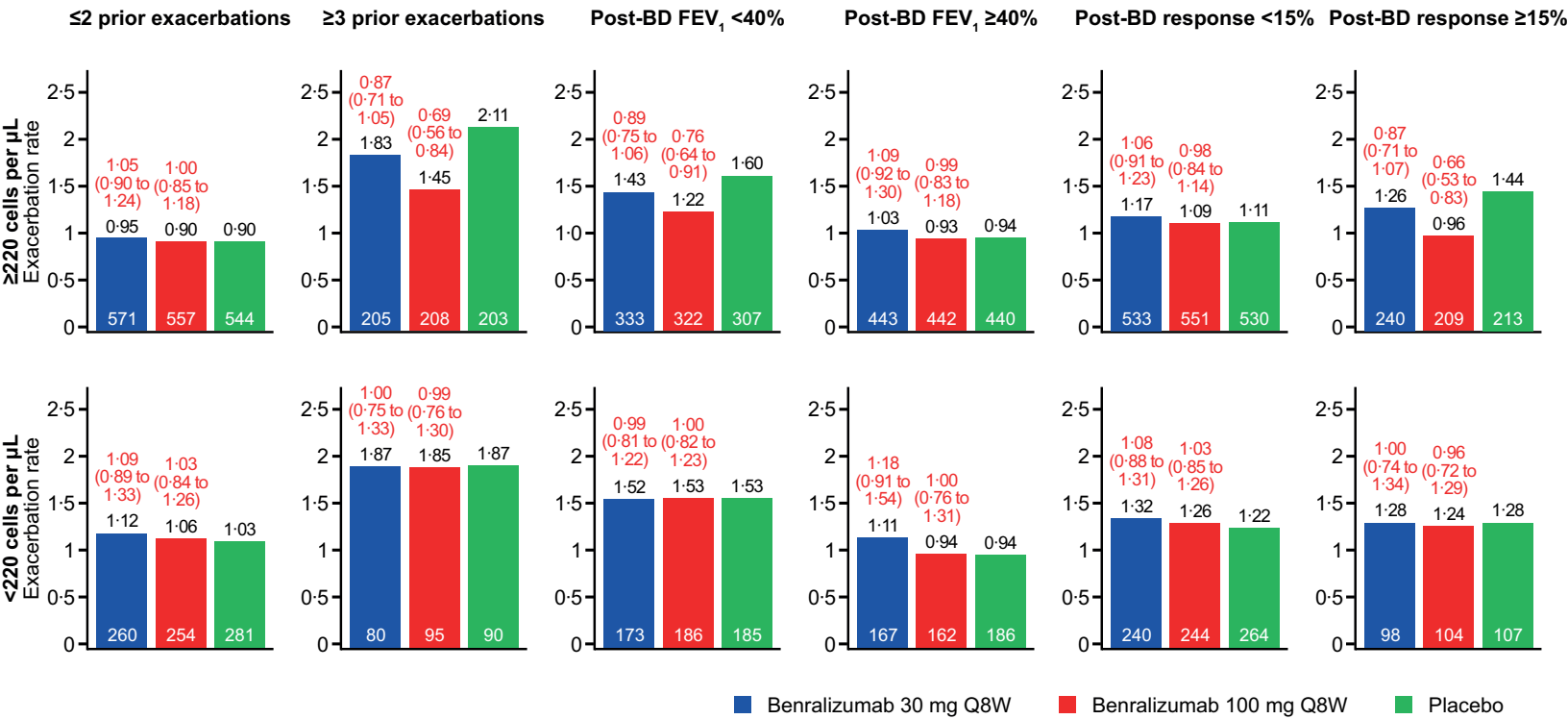

≤2 prior exacerbations
≥3 prior exacerbations
Post-BD FEV1 <40%
Post-BD FEV1 ≥40%
Post-BD response <15%
Post-BD response ≥15%
≥220 cells per µL Exacerbation rate
<220 cells per µL Exacerbation rate
1·05 (0·90 to 1·24)
1·00 (0·85 to 1·18)
0·95
0·90
0·90
571
557
544
0·87 (0·71 to 1·05)
0·69 (0·56 to 0·84)
1·83
1·45
2·11
205
208
203
0·89 (0·75 to 1·06)
0·76 (0·64 to 0·91)
1·43
1·22
1·60
333
322
307
1·09 (0·92 to 1·30)
0·99 (0·83 to 1·18)
1·03
0·93
0·94
443
442
440
1·06 (0·91 to 1·23)
0·98 (0·84 to 1·14)
1·17
1·09
1·11
533
551
530
0·87 (0·71 to 1·07)
0·66 (0·53 to 0·83)
1·26
0·96
1·44
240
209
213
1·09 (0·89 to 1·33)
1·03 (0·84 to 1·26)
1·12
1·06
1·03
260
254
281
1·00 (0·75 to 1·33)
0·99 (0·76 to 1·30)
1·87
1·85
1·87
80
95
90
0·99 (0·81 to 1·22)
1·00 (0·82 to 1·23)
1·52
1·53
1·53
173
186
185
1·18 (0·91 to 1·54)
1·00 (0·76 to 1·31)
1·11
0·94
0·94
167
162
186
1·08 (0·88 to 1·31)
1·03 (0·85 to 1·26)
1·32
1·26
1·22
240
244
264
1·00 (0·74 to 1·34)
0·96 (0·72 to 1·29)
1·28
1·24
1·28
98
104
107
Benralizumab 30 mg Q8W
Benralizumab 100 mg Q8W
Placebo

Figure 5

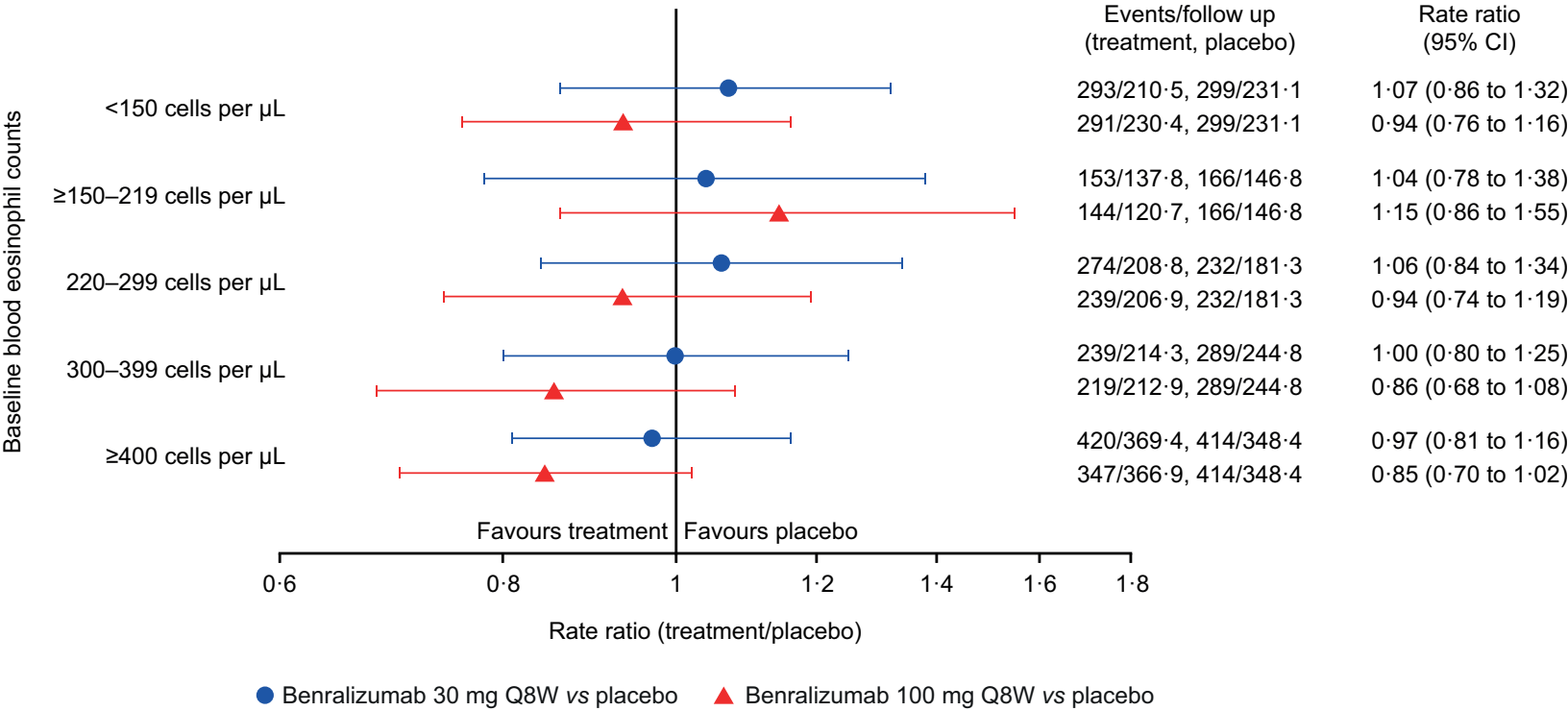
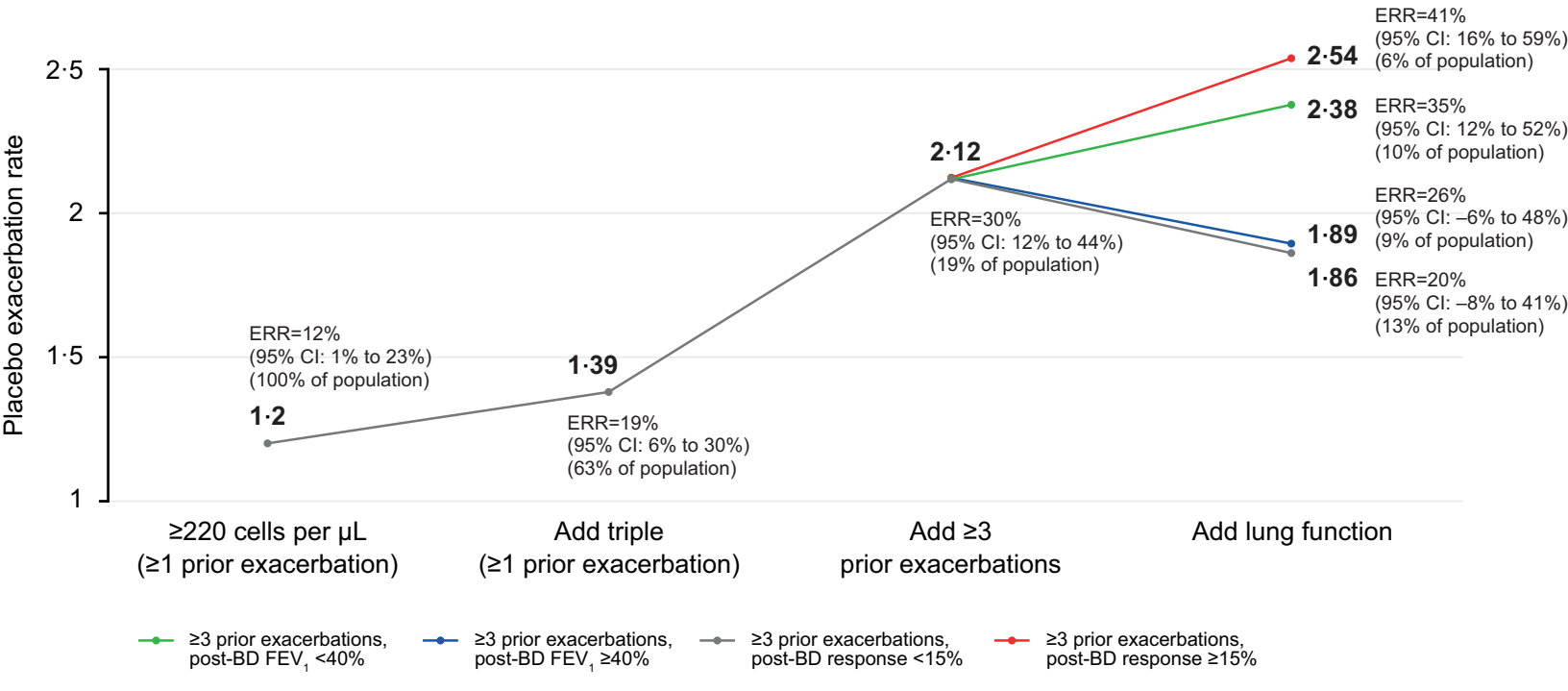

Baseline blood eosinophil counts
<150 cells per µL
≥150–219 cells per µL
220–299 cells per µL
300–399 cells per µL
≥400 cells per µL
Events/follow up (treatment, placebo)
Rate ratio (95% CI)
293/210·5, 299/231·1
1·07 (0·86 to 1·32)
291/230·4, 299/231·1
0·94 (0·76 to 1·16)
153/137·8, 166/146·8
1·04 (0·78 to 1·38)
144/120·7, 166/146·8
1·15 (0·86 to 1·55)
274/208·8, 232/181·3
1·06 (0·84 to 1·34)
239/206·9, 232/181·3
0·94 (0·74 to 1·19)
239/214·3, 289/244·8
1·00 (0·80 to 1·25)
219/212·9, 289/244·8
0·86 (0·68 to 1·08)
420/369·4, 414/348·4
0·97 (0·81 to 1·16)
347/366·9, 414/348·4
0·85 (0·70 to 1·02)
Favours treatment
Favours placebo
0·6
0·8
1
1·2
1·4
1·6
1·8
Rate ratio (treatment/placebo)
Benralizumab 30 mg Q8W vs placebo
Benralizumab 100 mg Q8W vs placebo

Figure 6


Placebo exacerbation rate
2·5
2
1·5
1
ERR=12%
(95% CI: 1% to 23%)
(100% of population)
1·2
1·39
ERR=19%
(95% CI: 6% to 30%)
(63% of population)
2·12
ERR=30%
(95% CI: 12% to 44%)
(19% of population)
2·54
ERR=41%
(95% CI: 16% to 59%)
(6% of population)
2·38
ERR=35%
(95% CI: 12% to 52%)
(10% of population)
1·89
ERR=26%
(95% CI: –6% to 48%)
(9% of population)
1·86
ERR=20%
(95% CI: –8% to 41%)
(13% of population)
≥220 cells per µL
(≥1 prior exacerbation)
Add triple
(≥1 prior exacerbation)
Add ≥3
prior exacerbations
Add lung function
≥3 prior exacerbations, post-BD FEV1 <40%
≥3 prior exacerbations, post-BD FEV1 ≥40%
≥3 prior exacerbations, post-BD response <15%
≥3 prior exacerbations, post-BD response ≥15%

Appendix_TC

Click here to download Necessary Additional Data: GT Subanalysis appendix rev2_FINAL_tc.docx

Appendix_CLEAN

Click here to download Necessary Additional Data: Griner et al Supplementary Appendix.pdf