# Treating eosinophilic exacerbations of asthma and COPD with benralizumab (ABRA): a double-blind, double-dummy, active placebo-controlled randomised trial

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## Summary

**Background** Exacerbations of asthma and chronic obstructive pulmonary disease (COPD) are important events and are associated with critical illness. Eosinophilic inflammation is a treatable trait commonly found during acute exacerbations of asthma and COPD. We hypothesised that for patients with eosinophilic exacerbations, a single injection of benralizumab, a humanised monoclonal antibody against interleukin-5 receptor-α, alone or in combination with prednisolone, will improve clinical outcomes compared with prednisolone, the standard of care.

**Methods** The Acute exacerbations treated with BenRAlizumab trial (ABRA) was a multicentre, phase 2, double-blind, double-dummy, active placebo-controlled randomised trial completed in the UK at Oxford University Hospitals NHS Foundation Trust and Guy's and St Thomas' NHS Foundation Trust. Patients were recruited from urgent care clinics and emergency departments of these two hospitals. At the time of an acute exacerbation of asthma or COPD, adults with blood eosinophil counts of equal to or more than 300 cells per µL were randomly assigned in a 1:1:1 ratio to receive acute treatment with: prednisolone 30 mg once daily for 5 days and 100 mg benralizumab subcutaneous injection once (BENRA plus PRED group); placebo tablets once daily for 5 days and 100 mg benralizumab subcutaneous injection once (BENRA group); or prednisolone 30 mg once daily for 5 days and placebo subcutaneous injection once (PRED group). Randomisation was performed with a centralised interactive computer randomisation service. All patients and study research staff involved in data collection were masked to study blood results and treatment allocation. The co-primary outcomes were proportion of treatment failures over 90 days and total visual analogue scale (VAS) symptoms at day 28 in the pooled benralizumab groups compared with the prednisolone alone group and analysed in the intention-to-treat population. The trial was registered on Clinicaltrials.gov NCT04098718.

**Findings** Between May 13, 2021, and Feb 5, 2024, 287 patients were screened for study inclusion. 129 were excluded due to not having an exacerbation captured or not meeting the eosinophil exclusion criteria. 158 patients were randomly assigned at acute eosinophilic exacerbation of asthma or COPD where 86 (54%) patients were female and 72 (46%) were male with a mean age of 57 years (range, 18–84). 53 patients were randomly assigned to the PRED group, 53 were randomly assigned to the BENRA group, and 52 were assigned to the BENRA plus PRED treatment group. At 90 days, treatment failures occurred in 39 (74%) of 53 in the PRED group, and 47 (45%) of 105 in the pooled-BENRA group (OR 0·26 [95% CI 0·13–0·56]; p=0·0005). The 28-day total VAS mean difference was 49 mm (95% CI 14–84; p=0·0065), favouring the pooled-BENRA group. There were no fatal adverse events and benralizumab was well tolerated. Notably, hyperglycaemia and sinusitis or sinus infection adverse events were related to the prednisolone study drug only.

**Interpretation** Benralizumab can be used as a treatment of acute eosinophilic exacerbations and achieves better outcomes than the current standard of care with prednisolone alone. These results offer a new way of treating eosinophilic endotypes of asthma and COPD exacerbations.

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## Introduction

Exacerbations of chronic obstructive pulmonary disease (COPD) and asthma are a substantial global burden[1,2] and a major cause of morbidity and mortality. Improvements over the past 30 years have occurred in the prevention of exacerbations using monoclonal antibody therapy in severe asthma[3] and more recently in COPD.[4,5] However, the same progress has not been observed for acute treatment of exacerbations. Systemic glucocorticoids are a mainstay of asthma and COPD exacerbation treatment, despite adverse events arising in half of patients treated,[6] and treatment failure

## Research in context

### Evidence before this study

Exacerbations of chronic obstructive pulmonary disorder (COPD) have demonstrated that there are distinct biological clusters or endotypes. Eosinophilic inflammation is common to both asthma and COPD exacerbations. At present, exacerbations are treated with systemic glucocorticoids recommended by international guidelines for the management of acute exacerbations of asthma or COPD. Respiratory diagnoses are the most common indication for the prescription of systemic glucocorticoids globally, and their harmful effects are well reported. Randomised controlled trials of acute exacerbations in primary and secondary hospital care have shown the utility of the blood eosinophil count to identify patients who do not need systemic glucocorticoids. However, in patients with raised blood eosinophil count, in whom there is the highest risk of exacerbations, there is no alternative to systemic glucocorticoids. We searched PubMed using the search terms "randomised clinical trial", "exacerbations", "COPD", "asthma", and "intervention with monoclonal antibodies" on March 19, 2015, for articles published in English, from study inception. Aaron and colleagues investigated intravenous etanercept, a tumour necrosis factor-α (TNF-α) inhibitor against prednisolone for treatment of COPD exacerbations. Separately, Nowak and colleagues tested intravenous benralizumab as an add-on therapy to systemic glucocorticoids in the treatment of asthma exacerbations. Neither study endotyped their participants before treatment and both studies did not reach statistical significance regarding the primary outcomes.

### Added value of this study

Benralizumab, a monoclonal antibody targeting interleukin 5 receptor-α, with a rapid onset in depleting eosinophils, reduced the risk of treatment failure as an acute treatment for eosinophilic exacerbations, irrespective of an asthma or COPD exacerbation. When compared with current standard of care with 30 mg of prednisolone once daily for 5 days, one dose of 100 mg subcutaneous benralizumab, with or without prednisolone, reduced the odds of treatment failure at 90 days four-fold, with a number needed to treat of 4; and significantly improved symptoms of an exacerbation at 28 days. Almost three quarters (74%) of patients who received standard of care needed further treatment within 90 days, indicating the poor outcomes we currently achieve with short-course prednisolone therapy to treat eosinophilic exacerbations. The use of benralizumab was safe as a single injection in acute events and is a potential biologically driven precision treatment for asthma and COPD exacerbations.

### Implications of all the available evidence

In a precision-medicine approach, we have targeted the eosinophilic endotype of acute exacerbations with a biologically plausible pathway and demonstrated efficacy in this phase 2 trial. Exacerbations have been treated with systemic glucocorticosteroids in a one size fits all approach, despite our knowledge that there are exacerbation endotypes aligned to inflammation and the harmful effects of systemic glucocorticoids. The study provides evidence that benralizumab could be the first new treatment for eosinophilic exacerbations of asthma or COPD. This should drive future strategies of treating exacerbations according to endotype.

occurring in at least 30% of exacerbations.[7,8] Frequent courses of systemic glucocorticoids are also associated with an increased risk of mortality.[9]

Eosinophilic inflammation is a recognised treatable trait of airways disease.[10] The eosinophilic endotype is found in up to 30% of COPD exacerbations[11] and in almost 50% of asthma exacerbations.[12] Eosinophil-directed systemic glucocorticoid therapy at exacerbations of COPD has been shown to be effective.[7] However, in patients with eosinophilic inflammation, there is an increased risk of exacerbations[13] and thus a likelihood of repeated glucocorticoid exposure. Less harmful alternatives to reduce the cumulative harm of glucocorticoid therapy are urgently warranted.

Benralizumab is a humanised monoclonal antibody against interleukin 5 receptor-α alpha (IL-5Rα) that rapidly depletes eosinophils and is approved for long-term exacerbation prevention in the management of chronic eosinophilic asthma. In chronic management of eosinophilic COPD, post-hoc analyses have shown efficacy of benralizumab in a frequent exacerbator group with blood eosinophil counts greater than 300 cells per µL.[14] A previous attempt to treat asthma exacerbations, regardless of the underlying inflammatory endotype, with intravenous benralizumab was unsuccessful.[15] In patients in whom systemic glucocorticoids are contraindicated, case reports have shown that a single benralizumab injection works in acute asthma if eosinophilic inflammation is present.[16]

We hypothesised that targeting the eosinophilic exacerbation endotype and biological pathway with a single dose of subcutaneous benralizumab alone or in combination with systemic glucocorticoids (prednisolone) would be superior to current standard of care with systemic glucocorticoids alone in the acute treatment of exacerbations of asthma and COPD.

## Methods

### Study design and participants

The Acute exacerbations treated with BenRAlizumab (ABRA) trial was a phase 2, multicentre, randomised, double-blind, double-dummy, active placebo-controlled trial done in the UK in two large hospital sites (Oxford University Hospitals NHS Foundation Trust and Guy's and St Thomas' NHS Foundation Trust) recruiting patients from the Thames Valley and South-East England region.

The trial was sponsored by the University of Oxford and approved by the London West and Gene Therapy Advisory Research Ethics Committee (20/LO/0187) and the National Health Research Authority. Oversight of the trial was undertaken by the Oxford Respiratory Trials unit and supported by a trial steering committee. The study was supported by the Thames Valley and South Midlands National Institute for Health Research (NIHR) Clinical Research Network, the Oxford NIHR Biomedical Research Centre, and the King's Health Partners Centre for Translational Medicine. The trial was registered at clinicaltrials.gov (NCT04098718). The trial protocol and supporting statistical analysis plan are available in the appendix (pp 14–86).

Eligible patients for study inclusion were adult men and women aged 18 years or older. Patients with COPD were current or former smokers with a pack-year history of at least 10, and current or historic spirometric evidence of a postbronchodilator forced expiratory volume in 1 s ($FEV_1$) to forced vital capacity (FVC) ratio of less than 0·7. Patients with asthma were never or former smokers with a pack-year history of less than 10 and current or historic evidence of variable airflow limitation (defined as any one of the following: $FEV_1$ bronchodilator reversibility of more than 200 mL; or $FEV_1$ percentage change of at least 12%; or methacholine challenge of less than 8 mg/mL; or peak flow rate (PEF) diurnal variation; or variable $FEV_1$/FVC ratio. Never smokers were defined as those with less than 100 cigarette inhalations in a lifetime, while former smokers had ceased smoking at least 6 months before randomisation. Key exclusion criteria included any allergy to the intervention (prednisolone or benralizumab); any other significant lung disease other than asthma and COPD; regular immunosuppression, including but not limited to daily prednisolone (>10 mg/day equivalent); any unstable cardiovascular, renal, or liver disease; evidence of chronic hypercapnic respiratory failure or hypoxic respiratory requiring treatment with long-term oxygen therapy; or a life expectancy of less than 6 months. At the time of randomisation, the following additional exclusion criteria applied: fever equal to or greater than 38 degrees centigrade; blood eosinophil count less than 300 cells per µL; evidence of pneumonia on chest radiograph; acute respiratory failure requiring non-invasive or invasive ventilation; an alternative cause for the increase in symptoms unrelated to the exacerbation such diagnosis of or high clinical suspicion of pulmonary embolism, pneumonia, pneumothorax, or a major cardiovascular adverse event; pregnancy; and the use of systemic corticosteroids within the past 4 weeks, including the past 12 h. Full details of all inclusion and exclusion criteria are presented in the appendix (pp 34–36).

Patients could also be recruited de-novo for randomisation from the emergency department, or from the study pool. In brief, patients in the study pool were patients with a previous physician-confirmed diagnosis of asthma or COPD, a history of at least one exacerbation in the previous 12 months, and a previous history of blood eosinophil counts greater than 250 cells per µL, as this would be predictive of a subsequent eosinophilic exacerbation.[11] Patients in the study pool could contact the study team at the time of an exacerbation for review and assessment of randomisation eligibility. Sex at birth data were self-reported and ethnicity data were collected as per the NHS data dictionary, which are based on the Office for National Statistics 10-yearly Census. Everyone entered in the study provided informed written consent.

For more on the **NHS data model and dictionary** see https://www.datadictionary.nhs.uk/data_elements/ethnic_category.html

## Randomisation and masking

All exacerbations were assessed and confirmed by a study respiratory physician as needing systemic glucocorticoids before randomisation as per standard guidelines.[17,18] Venous blood samples were processed urgently with an automated counter, with results available within 30 min. The peripheral blood eosinophil count at the time of an exacerbation had to be equal to or more than 300 cells per µL to fulfil eligibility for randomisation.

See **Online** for appendix

Randomisation was performed with a centralised interactive computer randomisation service (SealedEnvelope). Patients with an exacerbation who met the eligibility criteria were randomly assigned by the study team in a 1:1:1 ratio using variable block sizes to receive 30 mg of prednisolone, in tablet form, to be taken orally for 5 days and one dose of a placebo subcutaneous injection (PRED group); or one dose of 100 mg benralizumab subcutaneous injection and 5 days of placebo tablets to be taken orally for 5 days (BENRA group); or 30 mg of prednisolone, in tablet form, to be taken orally for 5 days and one dose of 100 mg of benralizumab subcutaneous injection (BENRA plus PRED group). Subcutaneous benralizumab or placebo syringes were matched for colour and consistency and were manufactured by AstraZeneca (Cambridge, UK). Prednisolone and placebo tablets were matched for taste, shape, and colour and manufactured at TioFarma BV (Oud-Beijerland, Netherlands). Randomisation was stratified by previous physician diagnosis (asthma or COPD), $FEV_1$ at steady state (<50% or ≥50% predicted), smoking status (current, former, or never), and the number of exacerbations in the preceding 12 months (<2 or ≥2).

For more on **SealedEnvelope** see www.sealedenvelope.com

Investigational medicinal products were provided within 10 min of randomisation. All patients were monitored for a minimum of 2 h after investigational medicinal products were administered. As per the study protocol, no antibiotics were administered at randomisation. All randomisations were thus classified as moderate or severe exacerbations of COPD, or moderate, acute severe, or life-threatening asthma exacerbations. Patients in the pool who had an exacerbation but were not eligible for randomisation because the blood eosinophil count was less than 300 cells per µL, remained in the study pool for rescreening at a future exacerbation timepoint for potential eligibility of randomisation. A patient could be

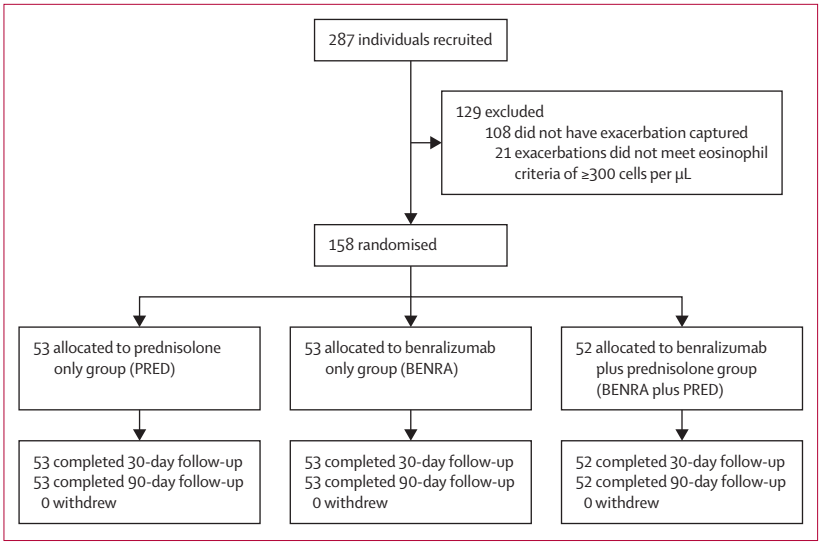


*Figure 1:* **Trial profile**

| | PRED group (n=53) | BENRA group (n=53) | BENRA plus PRED group (n=52) | Total (n=158) |
|---|---|---|---|---|
| Demographics | | | | |
| Females | 22 (42%) | 32 (60%) | 32 (62%) | 86 (54%) |
| Males | 31 (58%) | 21 (40%) | 20 (38%) | 72 (46%) |
| Age, years | 59 (14) | 55 (17) | 58 (14) | 57 (15) |
| Ethnicity | | | | |
| White | 52 (98%) | 51 (96%) | 47 (90%) | 150 (95%) |
| Asian | 1 (2%) | 2 (4%) | 3 (6%) | 6 (4%) |
| Black | 0 | 0 | 1 (2%) | 1 (<1%) |
| Other | 0 | 0 | 1 (2%) | 1 (<1%) |
| Smoking status | | | | |
| Never | 22 (42%) | 21 (40%) | 20 (38%) | 63 (40%) |
| Former | 27 (51%) | 27 (51%) | 26 (50%) | 80 (51%) |
| Current | 4 (8%) | 5 (9%) | 6 (12%) | 15 (9%) |
| Pack-year history | 12·5 (4·8–35·0) | 15·0 (8·4–45·8) | 21·8 (12·6–38·5) | 17·6 (6·8–37·0) |
| Body-mass index, kg/m² | 28·1 (5·1) | 29·0 (7·0) | 30·0 (7·7) | 29·0 (6·7) |
| Diagnosis | | | | |
| Asthma | 35 (66%) | 28 (53%) | 25 (48%) | 88 (56%) |
| COPD | 13 (25%) | 18 (34%) | 20 (38%) | 51 (32%) |
| Asthma and COPD | 5 (9%) | 7 (13%) | 7 (13%) | 19 (12%) |
| Exacerbation frequency requiring systemic glucocorticoids in previous year | 5 (3–7) | 4 (2–5) | 3 (2–7) | 4 (2–6) |
| Inhaled treatment | | | | |
| Glucocorticoids | 53 (100%) | 51 (96%) | 52 (100%) | 156 (99%) |
| Long-acting bronchodilator | 50 (94%) | 51 (96%) | 52 (100%) | 153 (97%) |
| Long-acting antimuscarinic | 22 (42%) | 24 (45%) | 27 (52%) | 73 (46%) |
| Spirometry (post-bronchdilator) | | | | |
| $FEV_1$ at steady state, L | 2·3 (0·9) | 2·2 (1·0) | 1·9 (0·8) | 2·1 (0·9) |
| $FEV_1$ % predicted of normal at steady state | 74·7 (23·4) | 71·0 (23·4) | 69·7 (25·2) | 71·8 (23·9) |
| $FEV_1$/FVC at steady state | 0·62 (0·13) | 0·62 (0·17) | 0·61 (0·16) | 0·62 (0·15) |

(Table 1 continues on next page)

rescreened for randomisation a maximum of four times. Patients could only undergo randomisation once in the study. All patients and study research staff involved in data collection were masked to study blood results and treatment allocation.

## Procedures

Patients were seen at urgent care clinics or in the emergency department across two study sites at the time of an exacerbation and 7, 14, 28, and 90 days after they were randomly assigned, for study measurements. All endpoints were measured at every study visit. At each visit, patients underwent post bronchodilator spirometry (normal values for spirometry were calculated using the race-neutral Global Lung Initiative equations), fractional exhaled nitric oxide, and completed patient reported outcome questionnaires. Medical history, prescription records, and adverse events were also collected at each visit. Patients with asthma completed the asthma control questionnaire-7 ($ACQ_7$), asthma control test (ACT), and asthma quality of life questionnaire (AQLQ). A higher score on the ACT (range 5–25) and AQLQ (range 1–7) indicated better disease control and a higher score on the $ACQ_7$ (range 0–7) indicated worse disease control. The minimally clinical important difference (MCID) for ACT, AQLQ, and $ACQ_7$ was 0·5. Patients with COPD completed the COPD assessment test (CAT) for which a higher score (range 0–40) indicates worse disease control. The CAT MCID is 2. All patients completed the Medical Research Council Dyspnoea scale (MRC), the EuroQoL 5D-3L, and a visual analogue scale (VAS) for the symptoms of cough, wheeze, dyspnoea, sputum production, and sputum purulence. VAS is measured on a 100 mm line for each symptom domain, for which a higher score indicates worse symptoms. The MCID for a single VAS symptom domain is 9 mm. The total VAS score is a sum of each of the individual domains. All patients had safety laboratory tests for measurement of full blood count, blood electrolytes, blood glucose, liver function tests, plasma B natriuretic peptide, and plasma C-reactive protein. Women of childbearing potential had urinary pregnancy testing. An unmasked safety investigator was allocated to review laboratory blood tests only.

## Outcomes

The co-primary outcome was rate of treatment failure within 90 days and total VAS symptom scores at day 28. Treatment failure was defined as a composite of death, admission to hospital, and any need for re-treatment requiring systemic glucocorticoids or antibiotics. Treatment failure was self-reported by patients or by an independent health-care practitioner who was not involved in the study (for example the patients primary care physician). The selection of the primary outcomes was supported by our patient and public involvement committee as a representation of both patient symptoms and health-care utilisation. For the primary outcome

analysis, the individual benralizumab treatment groups (BENRA and BENRA plus PRED) were pooled (pooled-BENRA) due to the prolonged mechanism of action of benralizumab and the phase 2 design of the study. Secondary outcomes included: treatment failure risk within 30 days of randomisation, time to treatment failure, $FEV_1$, PEF, ACQ-7, ACT, MRC, AQLQ, CAT, and EuroQoL. The primary and secondary outcomes were assessed in the intention-to-treat population. Adverse events and serious adverse events were recorded at each study visit. Post hoc analysis investigated the time to treatment failure in the PRED and pooled-BENRA groups according to risk of diagnosis, $FEV_1$ at steady state, smoking history, sex, age, and exacerbation biomarkers (eosinophils and fractional exhaled nitric oxide).

### Statistical analysis

Descriptive statistics from each treatment group are presented. For continuous variables, means and SD, geometric means and coefficient of variation, or median and IQR are presented depending on distribution. For categorical variables, number and percentage are presented. All participants randomly assigned to an intervention were included in the intention-to-treat analysis. The treatment failure risk was analysed using logistic regression adjusting for treatment and stratification factors. Treatment difference is given as an odds ratio (OR) with 95% CI. Time to treatment failure was analysed using a stratified log-rank test, and further described with a Cox regression model adjusting for treatment and stratification factors (hazard ratio [HR] with 95% CI). Other continuous endpoints were analysed using a mixed model for repeated measures with treatment, visit, and interaction as factors, baseline as covariate and subject as random below visit (unstructured covariance matrix[19]). Missing continuous data were imputed by multiple imputation using the joint multivariate normal distribution model.[20] The difference between treatment groups is presented as least-square means and 95% CI. P values were not corrected for multiplicity as this was a phase 2 trial.[21]

The study sample size was calculated on improvement of VAS symptom score and treatment failure reduction favouring benralizumab over prednisolone. Comparison of two means using a two-sided test at day 28 of VAS score (mean change 37 [SD 25]), and superiority with benralizumab treatment with α set at 0·05 and with power of 90% the number needed in each group was 44. To detect a reduction in treatment failure risk from an expected risk of 40% in the prednisolone group to 15% in the pooled benralizumab groups at 90 days, with α set at 0·05 and with power of 90%, the number needed in each group was 53. Recalculating the power for the VAS endpoint for 53 participants in each group, and assuming independence, a sample size of 53 in each group will have an α of 0·05 and power of 85% to meet the co-primary endpoint. A detailed statistical analysis plan was written, finalised, and approved before the data lock (appendix pp 68–86). SAS (version 9.4) was used for statistical analysis.

| | PRED group (n=53) | BENRA group (n=53) | BENRA plus PRED group (n=52) | Total (n=158) |
|---|---|---|---|---|
| (Continued from previous page) | | | | |
| $FEV_1$ at exacerbation, L | 1·9 (0·9) | 1·8 (0·9) | 1·7 (0·8) | 1·8 (0·9) |
| $FEV_1$ % predicted of normal at exacerbation | 60·9 (23·7) | 60·6 (22·8) | 60·2 (23·0) | 60·6 (23·0) |
| Biomarkers | | | | |
| Peripheral blood eosinophil count at exacerbation*, cells per µL | 690 (53%) | 520 (41%) | 610 (58%) | 600 (52%) |
| Fractional exhaled nitric oxide at exacerbation*, parts per billion | 48 (118%) | 41 (82%) | 35 (108%) | 41 (103%) |
| Visual analogue scale at exacerbation, mm | | | | |
| Cough | 60 (26) | 54 (27) | 50 (27) | 54 (28) |
| Dyspnoea | 65 (21) | 59 (25) | 61 (24) | 62 (23) |
| Wheeze | 52 (29) | 54 (29) | 54 (30) | 53 (29) |
| Sputum purulence | 37 (28) | 38 (27) | 39 (28) | 38 (28) |
| Sputum production | 48 (28) | 42 (26) | 43 (28) | 44 (27) |
| Exacerbation total | 261 (92) | 247 (97) | 246 (99) | 251 (95) |

Data presented as n (%), mean (SD), or median (IQR). Data on fractional exhaled nitric oxide at exacerbation were available in 153 patients (51 in the PRED group, 50 in the BENRA group, and 52 in the BENRA plus PRED group). The visual analogue scale was measured on a 100 mm scale for which 0 indicated the best symptoms and 100 indicated the worst symptoms. The total indicates the sum of all the individual domains. The PRED group indicates the prednisolone only group. The BENRA group indicates the benralizumab only group. The BENRA plus PRED group indicates the benralizumab plus prednisolone group. COPD=chronic obstructive pulmonary disease. $FEV_1$=forced expiratory volumen in 1 s. FVC=forced vital capacity. *Geometric mean (coefficient of variation, %). For ethnicity, the group other denotes ethnic description not listed, including preferred not to say.

***Table 1:*** **Baseline characteristics**

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

Between May 13, 2021, and Feb 5, 2024, 287 patients were recruited for inclusion in the study. 108 did not have an exacerbation captured and 21 did not meet the eosinophil inclusion criteria; therefore, 158 patients (86 [54%] female and 72 [46%] male with an exacerbation of asthma or COPD and blood eosinophil count equal to or more than 300 cells per µL, were randomly assigned to one of the three treatment groups from urgent care clinics and emergency departments across two large hospital sites in the UK. Patients had a mean age of 57 years (range, 18–84). Most patients reported their ethnicity as White (150 [95%]). 53 patients with exacerbations were randomly assigned to the PRED group, 53 were randomly assigned to the BENRA group, and 52 were assigned to the BENRA plus PRED treatment group (figure 1). All patients randomly

assigned to each group completed both the 30-day and the 90-day follow-ups, and no patients withdrew or were lost to follow-up. There were 88 (56%) patients with asthma, 51 (32%) with COPD, and 19 (12%) with both asthma and COPD. 63 patients (40%) were classified as never smokers, 80 (51%) were classified as former smokers, and 15 (9%) as current smokers. The mean post-bronchodilator $FEV_1$ (L) was 2·1 L (SD 0·9) and $FEV_1$ percent predicted at steady state was 71·8% (23·9). Almost all patients (156 [99%]) were taking inhaled glucocorticoid therapy before randomisation; with 23 (15%), 20 (13%) and 113 (72%) taking low-dose, medium-dose, and high-dose inhaled glucocorticoids, respectively. There were 21 (13%) patients recruited directly from the emergency department. The median symptom duration was 5 days (IQR 3–7). Patient characteristics were similar between treatment groups and are presented in table 1.

| | PRED group (n=53) | Pooled-BENRA group (n=105) | p value |
|---|---|---|---|
| Number of patients with treatment failure at 90 days | 39 (74%) | 47 (45%) | .. |
| Odds ratio (95%CI) *vs* PRED group | .. | 0·26 (0·13 to 0·56) | 0·0005 |
| Change in total VAS symptoms from exacerbation to day 28 | | | |
| Mean change (95% CI) in mm | 103 (75 to 132) | 152 (131 to 173) | .. |
| Least-square mean difference *vs* PRED group | .. | 49 (14 to 84) | 0·0065 |
| Change in total VAS cough from exacerbation to day 28 | | | |
| Mean change (95% CI) in mm | 23 (16 to 30) | 34 (28 to 39) | .. |
| Least-square mean difference *vs* PRED group | .. | 10 (2 to 19) | 0·020 |
| Change in total VAS dyspnoea from exacerbation to day 28 | | | |
| Mean change (95% CI) in mm | 27 (19 to 34) | 34 (28 to 39) | .. |
| Least-square mean difference *vs* PRED group | .. | 7 (–2 to 16) | 0·133 |
| Change in total VAS wheeze from exacerbation to day 28 | | | |
| Mean change (95% CI) in mm | 23 (16 to 29) | 36 (32 to 41) | .. |
| Least-square mean difference *vs* PRED group | .. | 14 (6 to 22) | <0·001 |
| Change in total VAS sputum purulence from exacerbation to day 28 | | | |
| Mean change (95% CI) in mm | 13 (7 to 18) | 24 (20 to 28) | .. |
| Least-square mean difference *vs* PRED group | .. | 11 (4 to 18) | 0·002 |
| Change in total VAS sputum volume from exacerbation to day 28 | | | |
| Mean change (95% CI) in mm | 17 (11 to 23) | 26 (21 to 30) | .. |
| Least-square mean difference *vs* PRED group | .. | 9 (2 to 17) | 0·016 |

The VAS was measured on a 100 mm scale for which 0 indicated the best symptoms and 100 indicated the worst symptoms. For VAS the minimal clinical important difference is 9. All analyses were adjusted for randomisation stratification factors namely diagnostic label, steady state $FEV_1$ predicted, number of exacerbations in the previous year, and smoking status. The PRED group indicates the prednisolone only group. The pooled-BENRA group indicates the benralizumab alone and the benralizumab plus prednisolone groups pooled together.

***Table 2*: Primary endpoint for the PRED and the pooled-BENRA treatment groups**

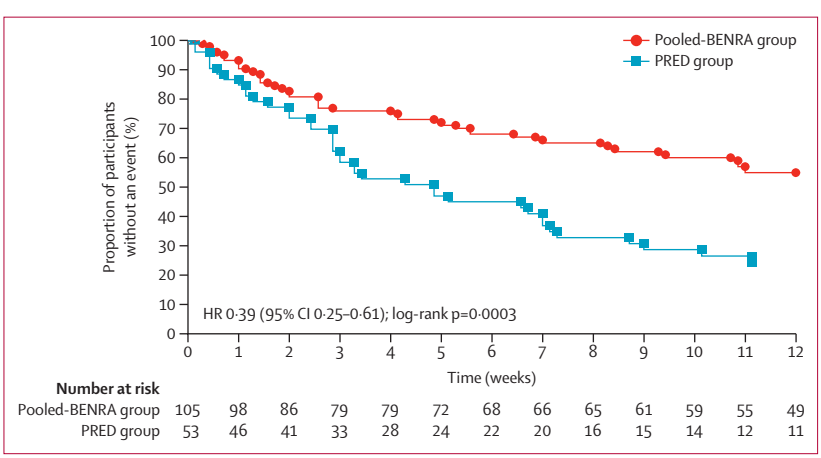


***Figure 2*: Kaplan–Meier plot of time to first treatment failure event in the PRED and pooled-BENRA treatment groups**
The PRED group indicates the prednisolone only group (blue line). The pooled-BENRA group indicates the benralizumab alone and the benralizumab plus prednisolone groups pooled together (red line).

There were 39 (74%) treatment failures in the PRED group, 25 (47%) in the BENRA group, and 22 (42%) in the BENRA plus PRED treatment group. There was a significant difference in proportions of treatment failures between PRED and pooled-BENRA (favouring pooled BENRA, OR 0·26 [95% CI 0·13–0·56]; p=0·0005). The 28-day total VAS symptoms were significantly better in the pooled-BENRA group compared with the PRED group (least-square mean difference, 49 mm [95% CI 14–84]; p=0·0065; table 2). In the individual treatment groups, there was a significant difference in the co-primary outcome favouring BENRA over PRED and in favouring BENRA plus PRED over PRED. For the primary outcome there was no difference between BENRA or BENRA plus PRED (appendix p 4). The number needed to treat with pooled-BENRA to prevent a treatment failure was 4.

The time to first treatment failure event within 90 days was significantly longer in the pooled-BENRA group than in the PRED group (HR 0·39 [95% CI 0·25–0·61], log-rank p=0·0003; figure 2). The time to first treatment failure within 90 days was not different between BENRA and BENRA plus PRED (HR 0·76 [95% CI 0·43–1·36], log-rank p=0·68; appendix p 6). The number of treatment failures within 30 days was 24 (45%) of 53 for the PRED group, 13 (25%) of 53 for the BENRA group, and ten (19%) of 52 for the BENRA plus PRED group. There was a significant reduction in treatment failure risk in pooled-BENRA compared with PRED at 30 days (OR 0·30 [95% CI 0·14–0·63]; p=0·0015); and no difference between BENRA and BENRA plus PRED (OR 0·70 [0·27–1·83]; p=0·47).

At day 28, there was a significant improvement in MRC dyspnoea scale between the pooled-BENRA group compared with the PRED group (difference 0·39 [95% CI 0·08 to 0·69]; p=0·013). The asthma-specific symptom questionnaires showed a significant and clinically meaningful improvement in pooled-BENRA compared with PRED for $ACQ_7$ (mean difference 0·5 [95% CI 0·1 to 0·9]; p=0·029) and $AQLQ_{total}$ (mean difference 0·53 [0·04 to 1·02]; p=0·035) at day 28. These improvements were not seen for the ACT (mean difference 1·6 [95% CI –0·4 to 3·6], p=0·12). The CAT showed a clinically meaningful but non-significant improvement favouring the pooled-BENRA group compared with the PRED group at day 90 (mean difference 3·6 [95% CI –2·9 to 10·1]; p=0·27). There was

no difference in the EuroQoL between pooled-BENRA compared with PRED at day 90. The treatment effect for the individual PRED, BENRA, and BENRA plus PRED treatment groups at each of the study visits are presented in the appendix (pp 7–12). There was no difference between any of these measurements for the BENRA versus BENRA plus PRED groups.

Lung function parameters improved across all treatment groups. There was no difference in the mean improvement change in $FEV_1$, FVC, or PEF between PRED and pooled-BENRA at day 28 (appendix p 13).

The point estimates for time to treatment failure all favoured pooled-BENRA, with HRs ranging between 0·18 and 0·69 (figure 3). This was irrespective of age, sex, disease, baseline $FEV_1$, or the biomarkers at exacerbation; blood eosinophil count and fractional exhaled nitric oxide.

The total number of reported adverse events was 324, occurring in 128 patients. 129 adverse events occurred in 48 (91%) of the 53 patients in the PRED group, 95 adverse events occurred in 41 (77%) of the 53 patients in the BENRA group, and 100 events occurred in 39 (75%) of the 52 patients in the BENRA plus PRED group. Hyperglycaemia and sinusitis or sinus infection only occurred in the treatment groups that were administered prednisolone (table 3). There were no fatal adverse events.

## Discussion

In patients with an eosinophilic exacerbation of asthma or COPD, a single subcutaneous injection of benralizumab, with or without a short course of systemic glucocorticoids (oral prednisolone) reduced treatment failures, prolonged time to first event, and improved respiratory symptoms and disease-specific health quality compared with standard care with oral corticosteroids following an exacerbation.

Current treatment strategies for acute exacerbations are limited to systemic glucocorticoids, antibiotic therapy, or both, with evidence restricted to only a few clinical trials.[8,22] Systemic glucocorticoids are used to reduce treatment failures in COPD exacerbations[22] or relapses in asthma attacks;[8] but repeatedly, treatment failure rates persist and mortality remains a concern.[9] The harm associated with even short courses of systemic corticosteroids has been recognised,[23] with cumulative doses of more than 0·5 g/year associated with an increased risk of unwanted side-effects and co-morbidity in patients with asthma.[24] In

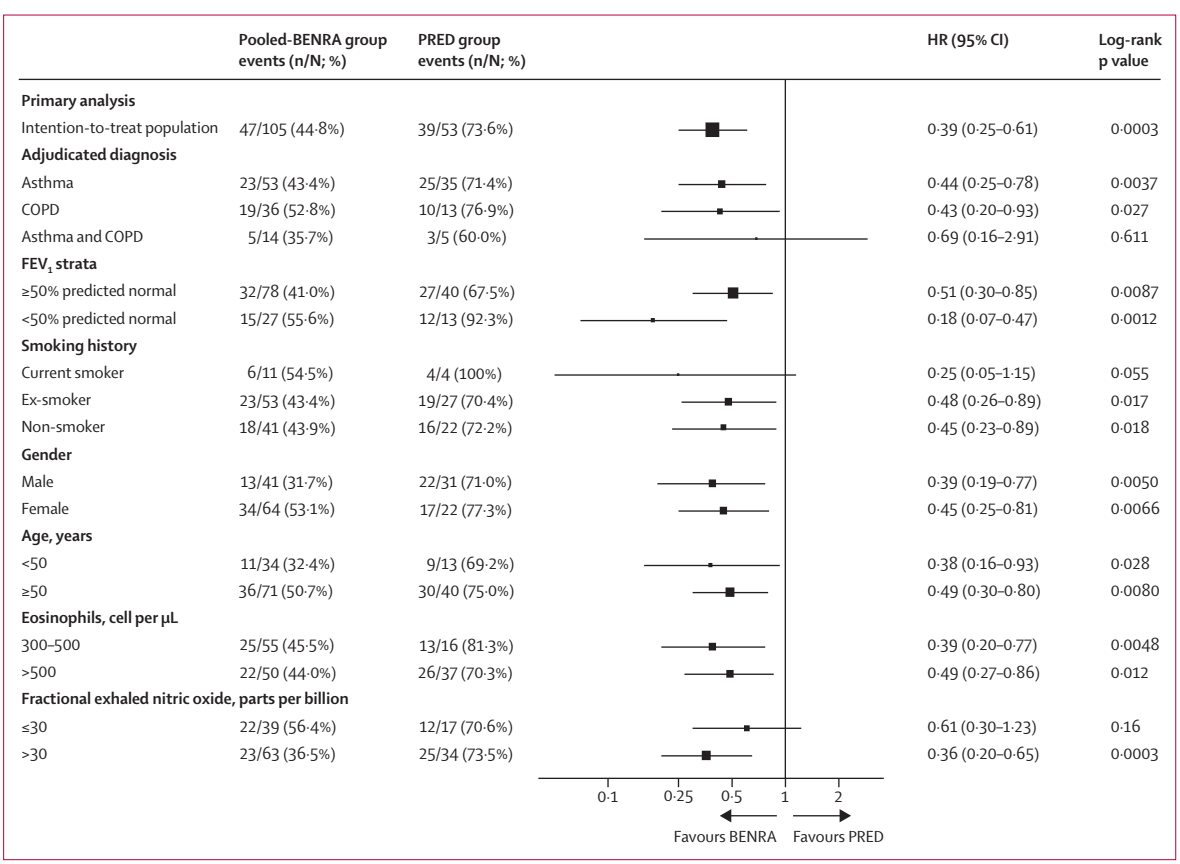


*Figure 3:* **Post-hoc sub-group analysis for time to treatment failure in the PRED and pooled-BENRA study treatment groups**
Data are presented according to diagnosis, steady state lung function, smoking history, sex, age, and exacerbation biomarkers (eosinophils and fractional exhaled nitric oxide). The PRED group indicates the prednisolone only group. The pooled-BENRA group indicates the benralizumab alone and the benralizumab plus prednisolone groups pooled together.

patients with COPD, repeated courses of systemic glucocorticoids has a dose-dependent risk on mortality[25] with expensive side-effects to the patient.[26] Our study findings suggest that benralizumab treatment acutely reduces subsequent systemic glucocorticoid cumulative dosing. Using benralizumab in acute eosinophilic exacerbations can support the vision of eradication of systemic glucocorticoid use in asthma and COPD treatment.[1,2]

Previous studies in COPD have shown that 90-day treatment failure risk following an exacerbation is approximately 40% and systemic glucocorticoids reduce this by 10% to a value of 30%.[8,27] In our study, we found that in patients with eosinophilic exacerbations, the treatment failure rate was 74% in those treated with systemic glucocorticoids alone (standard of care). This was unexpectedly high and indicates a high-risk population with eosinophilic inflammation and the lack of complete efficacy through systemic glucocorticoids. The blood eosinophil count has been shown to indicate increased risk of exacerbations[13] and shorter time to next exacerbation.[28] We have now demonstrated that this understanding of biological endotypes of exacerbations can improve outcomes. Our study, for the first time, shows that exploiting treatment that rapidly depletes eosinophils reduces treatment failure in eosinophilic exacerbations with an unadjusted risk reduction of 74% and a number needed to treat of 4.

Few studies of acute exacerbations have examined the effect of systemic glucocorticoids on symptoms or health quality,[22] and in the studies of patient-reported outcomes and systemic glucocorticoids, the benefit has not been conclusive.[29] Our study showed significant improvements with benralizumab in asthma-related and COPD-related respiratory symptoms and clinical improvement in disease-specific health quality. Not all the disease-specific questionnaires showed both clinical and significant change, potentially reflecting our use of disease-specific scales not designed for acute exacerbations. Notably, improvement in patient-reported outcomes was independent of improvement in lung function. An important innovation of the ABRA study is the prioritisation of participant symptom recovery as an equally important co-primary outcome to treatment failure. This was done as our patient advocacy group felt there has been an over-prioritisation of treatment failure in previous trials investigating exacerbation treatments;[30] and insufficient consideration of patient symptoms.

To our knowledge, there have only been two other studies examining monoclonal antibody therapy at the time of an acute exacerbation of asthma or COPD. The first by Aaron and colleagues[31] compared the effect of etanercept, a TNF-α monoclonal antibody, to systemic glucocorticoids upon lung function at the time of an acute exacerbation of COPD. The second by Nowak and colleagues[15] examined the effect of a single intravenous injection of benralizumab within 7 days of an exacerbation as an add-on therapy to systemic glucocorticoids in reducing asthma relapses within 12 weeks. Both studies did not achieve their primary outcome, probably because neither study endotyped the acute exacerbation event to guide treatment.

A limitation of the ABRA study is that only a minority (one in eight) of exacerbations were recruited from the emergency department. Although exacerbations that result in hospital admission are a significant health burden, the risk of dying at home with an asthma attack[32] or following an exacerbation of COPD[33] must not be underestimated. We have previously shown that it is possible to endotype the exacerbation using near patient point of care testing.[7] Thus, while we believe that treatment with benralizumab should be considered as a first-line treatment for all eosinophilic exacerbations, we acknowledge that more information is needed on efficacy for patients with severe events who have been admitted to hospital, particularly regarding the early efficacy of benralizumab. We hypothesise that benralizumab treatment in severe exacerbations is likely

| | PRED group (n=53) | BENRA group (n=53) | BENRA plus PRED group (n=52) | Total (n=158) |
|---|---|---|---|---|
| Total number of adverse events | 129 | 95 | 100 | 324 |
| Total number of unique adverse events | 93 | 85 | 71 | 249 |
| Patients with at least one adverse event* | 48 (91%) | 41 (77%) | 39 (75%) | 128 (81%) |
| Patients with at least one serious adverse event | 3 (6%) | 3 (6%) | 1 (2%) | 7 (4%) |
| Patients (n, %) with at least one benralizumab (or placebo injection) related adverse event: | | | | |
| At least one definite related adverse event | 38 (72%) | 26 (49%) | 24 (46%) | 88 (56%) |
| At least one probable related adverse event | 6 (11%) | 9 (17%) | 3 (6%) | 18 (11%) |
| At least one possible related adverse event | 3 (6%) | 3 (6%) | 3 (6%) | 9 (6%) |
| Patients (n, %) with at least one prednisolone (or placebo tablets) related adverse event: | | | | |
| At least one definite related adverse event | 38 (72%) | 26 (49%) | 27 (52%) | 91 (58%) |
| At least one probable related adverse event | 5 (9%) | 7 (13%) | 5 (10%) | 17 (11%) |
| At least one possible related adverse event | 2 (4%) | 3 (6%) | 2 (4%) | 7 (4%) |
| Patients with at least one adverse event of | | | | |
| Mild intensity | 20 (38%) | 25 (47%) | 20 (38%) | 65 (41%) |
| Moderate intensity | 43 (81%) | 32 (60%) | 28 (54%) | 103 (65%) |
| Severe intensity | 3 (6%) | 3 (6%) | 1 (2%) | 7 (4%) |
| Patients with a fatal adverse event | 0 | 0 | 0 | 0 |
| Adverse events occurring in ≥5% of patients in any treatment group | | | | |
| Asthma exacerbation | 31 (58%) | 19 (36%) | 18 (35%) | 68 (43%) |
| COPD exacerbation | 8 (15%) | 7 (13%) | 5 (10%) | 20 (13%) |
| COVID-19 infection | 4 (8%) | 4 (8%) | 2 (4%) | 10 (6%) |
| Cough | 4 (8%) | 5 (9%) | 0 | 9 (6%) |
| Chest pain | 1 (2%) | 2 (4%) | 3 (6%) | 6 (4%) |
| Hyperglycaemia | 3 (6%) | 0 | 3 (6%) | 6 (4%) |
| Sinusitis or sinus infection | 7 (13%) | 0 | 3 (6%) | 10 (6%) |

Data are n (%), unless otherwise specified. The PRED group indicates the prednisolone only group. The BENRA group indicates the benralizumab only group. The BENRA plus PRED group indicates the benralizumab plus prednisolone group. *Counted uniquely by reported term within patient.

***Table 3:*** **Summary of treatment-emergent adverse events in safety population**

to reduce the health-care burden associated with re-admissions and this should also be a focus of further studies. Another limitation is that the ABRA trial was not powered to investigate asthma and COPD exacerbations separately, although a clinically important difference in outcomes by diagnostic labels seems unlikely. ABRA tested the paradigm of treating patients according to endotype, aligned to a precision medicine biological pathway approach. In clinical practice, many patients receive both systemic glucocorticoids and antibiotics, regardless of diagnostic label, treated by non-specialists.[34] Our study population were heavily treated and had a high event rate, demonstrating that the intervention was targeted to a high-risk group, and increasing the confidence in the power of the study. We see future studies using a similar recruitment criterion to reflect the current need for treatments in this patient population. A further limitation of the ABRA study is that we have only examined the effect of benralizumab and do not know whether other biologic therapies would have similar efficacy. We purposefully selected the eosinophilic exacerbation endotype, and selected benralizumab because it is known to rapidly reduce peripheral blood eosinophils,[35] has a duration of action of 3 months, and a satisfactory safety profile. Further studies examining the acute treatment effect of other biologics are warranted but we suspect they will need to offer treatments with a rapid mechanism of action.

The ABRA study is the first trial to target the eosinophilic treatable trait, during exacerbations. This study shows that benralizumab is effective as an acute treatment of eosinophilic exacerbations.

#### Contributors

SR, JM, IH, KK, HRM, CM, LB-S, IDP, and MB were responsible for recruitment. SR, KK, CM, and HRM undertook the study assessments. MM was responsible for processing study samples. JM reviewed all unmasked blood tests for safety. SR, REKR, MB, TB, and SP were responsible for data analysis. The study was conceived, designed, set-up, analysed, and interpreted by MB. All authors had direct access to the raw data and MB, SP, and TB have verified the underlying data. All authors accept responsibility for the decision to submit for publication.

#### Declaration of interests

SR declares salary support from the Charlies Foundation for Research and the National Institute for Health and Care Research Clinical Research Network during the study period. Unrelated to the study, SR declares speaker honoraria from AstraZeneca and GlaxoSmithKline and declares conference travel support from AstraZeneca. Unrelated to the study, IDP has received grant funding to his institution from Chiesi and also received consulting fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Regeneron, Sanofi, Teva, Circassia, Dey Pharma, Genentech, Knopp Biosciences, Merck, MSD, Napp Pharmaceuticals, RespiVert, and Schering-Plough. IDP has also received speaker fees from Aerocrine, Almirall, AstraZeneca, Boehringer, Chiesi, GSK, Novartis, Regeneron, Sanofi, Teva. IDP has also received support to attend conference meetings from AstraZeneca, Boehringer, Cheisi, GSK, Novartis, Regeneron, Sanofi, Teva, and Napp Pharmaceuticals. Unrelated to the study, REKR has received speakers honorarium to his institution from AstraZeneca, GSK, and Chiesi. REKR has also received conference travel support from Chiesi. IH declares conference travel support from GSK unrelated to this study. TB and SP have received funding from the University of Oxford for the statistical analysis of the study data. Unrelated to the study, TB and SP declare funding from AstraZeneca for statistical tasks. MB has received grant funding from AstraZeneca to her institution, related to this study. MB has also received grant funding from Asthma+Lung UK, Roche, the NIHR, and Horizon Europe to her institution, unrelated to this study. MB has received consulting fees to her institution from AstraZeneca, Sanofi, GSK, and Areteia, and honoraria from AstraZeneca and GSK paid to her institution. MB has been supported to attend conference meetings from Chiesi. MB is a scientific advisor to AlbusHealth and Proaxsis and is a member of the British Thoracic Society research and scientific committee. All other authors declare no competing interests.

#### Data sharing

De-identified individual participant data and a data dictionary defining each field in the set can be made available on approval of a written request to the corresponding author. The request will be evaluated by a committee formed by a subset of co-authors to determine the research value. A data sharing agreement will be required and approved before any data transfer.

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#### References

1 Stolz D, Mkorombindo T, Schumann DM, et al. Towards the elimination of chronic obstructive pulmonary disease: a Lancet Commission. *Lancet* 2022; **400:** 921–72.
2 Pavord ID, Beasley R, Agusti A, et al. After asthma: redefining airways diseases. *Lancet* 2018; **391:** 350–400.
3 Busse WW. Biological treatments for severe asthma: a major advance in asthma care. *Allergol Int* 2019; **68:** 158–66.
4 Bhatt SP, Rabe KF, Hanania NA, et al. Dupilumab for COPD with type 2 inflammation indicated by eosinophil counts. *N Engl J Med* 2023; **389:** 205–14.
5 Bhatt SP, Rabe KF, Hanania NA, et al. Dupilumab for COPD with blood eosinophil evidence of type 2 inflammation. *N Engl J Med* 2024; **390:** 2274–83.
6 Leuppi JD, Schuetz P, Bingisser R, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. *JAMA* 2013; **309:** 2223–31.
7 Ramakrishnan S, Jeffers H, Langford-Wiley B, et al. Blood eosinophil-guided oral prednisolone for COPD exacerbations in primary care in the UK (STARR2): a non-inferiority, multicentre, double-blind, placebo-controlled, randomised controlled trial. *Lancet Respir Med* 2024; **12:** 67–77.
8 Rowe BH, Spooner CH, Ducharme FM, Bretzlaff JA, Bota GW. Corticosteroids for preventing relapse following acute exacerbations of asthma. *Cochrane Database Syst Rev* 2007; **3:** CD000195.
9 Connors AF Jr, Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). *Am J Respir Crit Care Med* 1996; **154:** 959–67.
10 Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J* 2016; **47:** 410–19.
11 Bafadhel M, McKenna S, Terry S, et al. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med* 2011; **184:** 662–71.
12 Hasegawa K, Stoll SJ, Ahn J, Bittner JC, Camargo CA Jr. Prevalence of eosinophilia in hospitalized patients with asthma exacerbation. *Respir Med* 2015; **109:** 1230–32.

13 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.

14 Criner GJ, Celli BR, Singh D, et al. Predicting response to benralizumab in chronic obstructive pulmonary disease: analyses of GALATHEA and TERRANOVA studies. *Lancet Respir Med* 2020; **8:** 158–70.

15 Nowak RM, Parker JM, Silverman RA, et al. A randomized trial of benralizumab, an antiinterleukin 5 receptor α monoclonal antibody, after acute asthma. *Am J Emerg Med* 2015; **33:** 14–20.

16 Ramakrishnan S, Camp JR, Vijayakumar B, et al. The use of benralizumab in the treatment of near-fatal asthma: a new approach. *Am J Respir Crit Care Med* 2020; **201:** 1441–43.

17 National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. 2018. https://www.nice.org.uk/guidance/ng115 (accessed April 30, 2024).

18 Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008; **31:** 143–78.

19 Chakraborty H, Gu H. A mixed model approach for intent-to-treat analysis in longitudinal clinical trials with missing values. Research Triangle Park (NC): RTI Press, 2009.

20 Huque MH, Carlin JB, Simpson JA, Lee KJ. A comparison of multiple imputation methods for missing data in longitudinal studies. *BMC Med Res Methodol* 2018; **18:** 168.

21 Bender R, Lange S. Adjusting for multiple testing—when and how? *J Clin Epidemiol* 2001; **54:** 343–49.

22 Walters JA, Tan DJ, White CJ, Gibson PG, Wood-Baker R, Walters EH. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2014; **2014:** CD001288.

23 Waljee AK, Rogers MA, Lin P, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. *BMJ* 2017; **357:** j1415.

24 Price DB, Trudo F, Voorham J, et al. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. *J Asthma Allergy* 2018; **11:** 193–204.

25 Tse G, Emmanuel B, Ariti C, et al. A long-term study of adverse outcomes associated with oral corticosteroid use in COPD. *Int J Chron Obstruct Pulmon Dis* 2023; **18:** 2565–80.

26 Barry LE, Sweeney J, O'Neill C, Price D, Heaney LG. The cost of systemic corticosteroid-induced morbidity in severe asthma: a health economic analysis. *Respir Res* 2017; **18:** 129.

27 Niewoehner DE, Erbland ML, Deupree RH, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1999; **340:** 1941–47.

28 Millett ER, Brightling CE, Pavord I, Russell R, Bafadhel M. The blood eosinophil trajectory of patients with copd through stable state, exacerbation and recovery. San Francisco: American Thoracic Society; 2016.

29 De Jong Y, Uil S, Grotjohan H, Postma D, Kerstjens H, Van den Berg J. A comparison of intravenous versus oral administration of corticosteroids in the treatment of patients admitted to the hospital with an exacerbation of COPD. *Eur Respir J* 2004; **24:** 64s.

30 Howell I, Howell A, Ramakrishnan S, Bafadhel M, Pavord I. How have we measured trial outcomes of asthma attack treatment? A systematic review. *ERJ Open Res* 2024; **10:** 10.

31 Aaron SD, Vandemheen KL, Maltais F, et al. TNFα antagonists for acute exacerbations of COPD: a randomised double-blind controlled trial. *Thorax* 2013; **68:** 142–48.

32 Levy ML. The national review of asthma deaths: what did we learn and what needs to change? *Breathe (Sheff)* 2015; **11:** 14–24.

33 Donaldson GC, Hurst JR, Smith CJ, Hubbard RB, Wedzicha JA. Increased risk of myocardial infarction and stroke following exacerbation of COPD. *Chest* 2010; **137:** 1091–97.

34 Bafadhel M, Clark TW, Reid C, et al. Procalcitonin and C-reactive protein in hospitalized adult patients with community-acquired pneumonia or exacerbation of asthma or COPD. *Chest* 2011; **139:** 1410–18.

35 Moran AM, Ramakrishnan S, Borg CA, et al. Blood eosinophil depletion with mepolizumab, benralizumab, and prednisolone in eosinophilic asthma. *Am J Respir Crit Care Med* 2020; **202:** 1314–16.