Onset of effect and impact on health-related quality of life, exacerbation rate, lung function, and nasal polyposis symptoms for patients with severe eosinophilic asthma treated with benralizumab (ANDHI): a randomised, controlled, phase 3b trial

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Summary

Background ANDHI was done to assess the efficacy of benralizumab, including onset of effect and impact on health-related quality of life (HRQOL), exacerbation rate, lung function, and nasal polyposis symptoms.

Methods This phase 3b, randomised, double-blind, parallel-group, placebo-controlled ANDHI study was completed in adults (aged 18–75 years) with severe eosinophilic asthma with at least 2 exacerbations in the previous year, despite high-dose inhaled corticosteroid plus additional controllers, screening blood eosinophil counts of at least 150 cells per µL, and an Asthma Control Questionnaire 6 (ACQ-6) score of 1·5 or more. Patients who met eligibility criteria were randomly assigned (2:1; stratified by previous exacerbation count [two, or three or more], maintenance oral corticosteroid use, and region), using an integrated web-based response system, to receive benralizumab at 30 mg every 8 weeks (first three doses given 4 weeks apart) or matched placebo for 24 weeks. Primary efficacy measure was annualised asthma exacerbation rate, with rate ratio (RR) calculated over the approximate 24-week follow-up. Secondary efficacy measures included change from baseline to end of treatment (week 24) in St George's Respiratory Questionnaire (SGRQ) total score (key secondary endpoint), FEV_1, peak expiratory flow (PEF), ACQ-6, Predominant Symptom and Impairment Assessment (PSIA), Clinician Global Impression of Change (CGI-C), Patient Global Impression of Change (PGI-C), and Sino-Nasal Outcome Test-22 (SNOT-22). All efficacy analyses, except for SNOT-22, were summarised and analysed using the full analysis set on an intention-to-treat population (all randomly assigned patients receiving investigational product, regardless of protocol adherence or continued participation in the study). SNOT-22 was summarised for the subgroup of patients with physician-diagnosed nasal polyposis with informed consent. This study is registered with ClinicalTrials.gov, NCT03170271.

Findings Between July 7, 2017, and Sept 25, 2019, 656 patients received benralizumab (n=427) or placebo (n=229). Baseline characteristics were consistent with severe eosinophilic asthma. Benralizumab significantly reduced exacerbation risk by 49% compared with placebo (RR estimate 0·51, 95% CI 0·39–0·65; p<0·0001) over the 24-week treatment period and provided clinically meaningful and statistically significant improvement from baseline to week 24 in SGRQ total score versus placebo (least squares mean change from baseline −8·11 (95% CI −11·41 to −4·82; p<0·0001), with similar differences at earlier timepoints. Benralizumab improved FEV_1, PEF, ACQ-6, CGI-C, PGI-C, PSIA, and SNOT-22 at week 24 versus placebo, with differences observed early (within weeks 1 to 4). Adverse events were reported for 271 (63%) of 427 patients on benralizumab versus 143 (62%) of 229 patients on placebo. The most commonly reported adverse events for the 427 patients receiving benralizumab (frequency >5%) were nasopharyngitis (30 [7%]), headache (37 [9%]), sinusitis (28 [7%]), bronchitis (22 [5%]), and pyrexia (26 [6%]). Fewer serious adverse events were reported for benralizumab (23 [5%]) versus placebo (25 [11%]), and the only common serious adverse event (experienced by >1% of patients) was worsening of asthma, which was reported for nine (2%) patients in the benralizumab group and nine (4%) patients in the placebo group.

Interpretation Our results extend the efficacy profile of benralizumab for patients with severe eosinophilic asthma, showing early clinical benefits in patient-reported outcomes, HRQOL, lung function, and nasal polyposis symptoms.

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Research in context

Evidence before this study

We searched PubMed for English-language clinical trial reports on the use of biological medications targeting interleukin-5 (IL-5) or the IL-5 receptor to treat patients with asthma published over the past 10 years (Jan 1, 2010, to Jan 1, 2020). We used the search terms "asthma" AND "interleukin 5" AND "antibody" AND "clinical trial." The search yielded 24 results, including five trials of benralizumab for patients with asthma (one phase 2b, dose-ranging study and four multicentre, randomised, double-blind, placebo-controlled phase 3 trials [three of which were for patients with severe, uncontrolled asthma with eosinophilic inflammation and one in patients with mild to moderate, persistent asthma]), one open-label extension safety trial, and eight publications detailing additional analyses done from the clinical trial data.

In the phase 3 SIROCCO, CALIMA, and ZONDA studies, benralizumab demonstrated improvements in multiple asthma clinical outcomes, including exacerbation rate and asthma symptoms for patients with severe eosinophilic asthma who were poorly controlled, despite high-dosage inhaled corticosteroid or long-acting β_2-agonist therapy. Benralizumab also permitted significant reduction of maintenance oral corticosteroid dosage for oral corticosteroid-dependent asthma patients without loss of asthma control. Pooled analyses of the SIROCCO and CALIMA studies showed that benralizumab provides enhanced clinical benefits for patients with increased blood eosinophil count (BEC), greater exacerbation history, poor lung function, oral corticosteroid use, nasal polyposis, and adult-onset asthma.

Added value of this study

The ANDHI phase 3b study increases confidence in the benralizumab mechanism of action for treating patients with severe eosinophilic asthma through further assessment of the onset and maintenance of clinical effects, benefits in health-related quality of life (HRQOL) measures, and the potential to treat symptoms of nasal polyposis for patients with chronic rhinosinusitis with nasal polyposis. Treatment with benralizumab for patients with severe eosinophilic asthma (BEC ≥150 cells per µL) significantly reduced the risk of asthma exacerbation, which was primarily driven by patients with efficacy associated with known markers of the eosinophilic phenotype.

Implications of all the available evidence

These results support and extend the known benefits of eosinophil depletion by benralizumab for the treatment of severe eosinophilic asthma to include early and sustained improvement in disease-specific HRQOL and patient-reported outcomes, in addition to lung function and asthma control. Improvements reached near maximal benefit by week 12, supporting that 3–4 months is an adequate trial to assess treatment response for biological medications for patients with severe eosinophilic asthma, as recommended by the Global Initiative for Asthma recommendations for severe asthma. In addition to known effects of baseline BEC and exacerbation history, prespecified analyses continue to reinforce the relevance of oral corticosteroid dependency, adult-onset asthma, and nasal polyposis as clinical features of eosinophilic phenotype in which benralizumab treatment response is consistently enhanced. Finally, these findings support further investigation of benralizumab for the treatment of patients with chronic rhinosinusitis with nasal polyposis with and without severe eosinophilic asthma.

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Introduction

Asthma is a chronic inflammatory disease estimated to affect 339 million people globally, with up to 10% of patients having severe asthma.[1–3] Asthma is classified as severe when maximal, high-intensity treatment is needed for symptom control or when it remains uncontrolled despite adherence to such treatments.[4,5] For patients with severe eosinophilic asthma, biological therapies that reduce or deplete eosinophils provide a phenotype-specific treatment approach that has led to significant reductions in asthma symptoms, decreased exacerbation frequency, and improved lung function.[4–6]

Benralizumab is an interleukin-5 (IL-5) receptor α-directed cytolytic monoclonal antibody that induces direct, rapid, and nearly complete depletion of eosinophils via enhanced antibody-dependent, cell-mediated cytotoxicity.[7,8] Repeated doses of benralizumab for patients with mild to severe asthma significantly reduce airway wall and sputum eosinophil counts.[8–10] Benralizumab significantly reduces asthma exacerbations, improves lung function, and reduces oral corticosteroid dose for patients with severe eosinophilic asthma, with treatment effects sustained for up to 2 years.[11–15] Pooled post-hoc analyses of benralizumab studies showed that benralizumab provides enhanced clinical benefits for patients with increased blood eosinophil count (BEC), greater exacerbation history, poor lung function, oral corticosteroid use, adult asthma diagnosis, and nasal polyposis.[12–19]

Approximately 60% of patients with chronic rhinosinusitis with nasal polyposis have asthma, with the frequency of nasal polyposis increasing in patients aged 40 years or older.[20–22] Patients with chronic rhinosinusitis with nasal polyposis and severe, steroid-resistant asthma have reduced asthma control and a high level of disease burden, which negatively affects health-related quality of life (HRQOL).[23–29] For patients with severe eosinophilic asthma with nasal polyposis, the symptoms of chronic rhinosinusitis with nasal

polyposis should be addressed to optimise asthma control and HRQOL.[30–32] A considerable paradigm shift in the management of chronic rhinosinusitis with nasal polyposis has occurred, with several studies showing efficacy for biological medications.[33–42]

Although the efficacy and safety of benralizumab for patients with severe eosinophilic asthma are well studied, additional data supporting the onset of clinical effect and improvement in measures of HRQOL, patient-reported outcomes (PROs), and clinician-reported outcomes are needed. Additionally, little data support the potential of benralizumab to treat symptoms of nasal polyposis beyond case reports.[43–45]

We report the results from the ANDHI trial, a phase 3b trial designed to further investigate the efficacy of repeat dosing of benralizumab at 30 mg subcutaneously compared with placebo, in addition to standard-of-care asthma therapy, for patients with uncontrolled, severe eosinophilic asthma. Prespecified subanalyses were done to help establish the effect of previously identified clinical features of the eosinophilic phenotype that are associated with enhanced clinical benefits of benralizumab. Patients with physician-diagnosed chronic rhinosinusitis with nasal polyposis of any severity ongoing at baseline, who consented to participate in the nasal polyposis substudy, were included in a subanalysis to assess the efficacy of benralizumab on symptoms of nasal polyposis for patients with severe eosinophilic asthma.

Methods

Study design and participants

ANDHI was a phase 3b, randomised, double-blind, parallel-group, placebo-controlled study done at 221 clinical research centres in Austria, Belgium, Canada, Denmark, Finland, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden, the UK, and the USA (appendix pp 2–5).

Patients were eligible if they were aged 18–75 years, weighing at least 40 kg, with a history of physician-diagnosed asthma requiring treatment and had a history of at least two asthma exacerbations in the 12 months before visit 1, despite treatment with medium-dose to high-dose inhaled corticosteroids plus another asthma controller (eg, long-acting β_2 agonists, long-acting muscarinic antagonists, leukotriene receptor antagonists, methylxanthines, or oral corticosteroid). Patients must have also been on high-dose inhaled corticosteroids plus another asthma controller for 3 months before enrolment. Additional inclusion criteria included prebronchodilator FEV_1 of less than 80% predicted at screening, and BEC of at least 300 cells per µL (or ≥150 with at least one of the following: maintenance oral corticosteroid use at study entry, history of nasal polyposis, ≥3 exacerbations in the previous year, forced vital capacity [FVC] of <65% predicted, or ≥18 years at asthma diagnosis), an Asthma Control Questionnaire 6 (ACQ-6) of at least 1·5 at screening and randomisation visits, and a documented postbronchodilator reversibility of at least 12% (FEV_1 ≥12%) using a short-acting bronchodilator shown at screening or airway hyper-responsiveness or peak expiratory flow (PEF) variability of 10% or more. Full inclusion and exclusion criteria are given in the appendix (p 6). The aim of ANDHI was to establish the effect of benralizumab as an add-on treatment for patients with uncontrolled asthma; thus, patients enrolled in the study continued to receive regularly scheduled standard-of-care treatment (appendix p 9).

Before the study was initiated, the clinical study protocol, the informed consent form, and any other relevant documents were reviewed and approved by an independent ethics committee or an institutional review board at each participating site. All patients signed an informed consent form before participating in any procedure specific to the study. The study was done in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation and Good Clinical Practice, applicable regulatory requirements, and the AstraZeneca company policy on bioethics.

Randomisation and masking

After enrolment at visit 1, eligible patients entered a screening or run-in period of up to 42 days. Patients who met eligibility criteria were randomly assigned on visit 4 (2:1; stratified by earlier exacerbation count [two, or three or more], maintenance oral corticosteroid use at visit 1, and region) to receive benralizumab or placebo, respectively.

The total estimated number of patients to be randomly assigned was updated by protocol amendment from approximately 800 (1:1; benralizumab:placebo) to approximately 630 (2:1; benralizumab:placebo) to mitigate early challenges in recruitment. The change preserved the number of patients receiving active benralizumab treatment, and reduced the number of patients exposed to placebo, while retaining statistical power to detect a treatment difference for both asthma exacerbation rate (AER) and St George's Respiratory Questionnaire (SGRQ) improvement.

Procedures

Patients received benralizumab at 30 mg every 8 weeks subcutaneously (first three doses given 4 weeks apart), or matched placebo, for 24 weeks. This dosing regimen was consistent with the tested phase 3 dosing regimen.[11,12]

Data were collected from all patients throughout the 24-week treatment period, which consisted of eight study visits (week 0, visit 4; week 2, visit 5; week 4, visit 6; week 8, visit 7; week 12, visit 8; week 16, visit 9; week 20, visit 10; week 24, visit 11). The planned baseline visit was visit 4 for SGRQ, ACQ-6, prebronchodilator FEV_1, Clinician Global Impression of Change (CGI-C), Patient Global Impression of Change (PGI-C), and Predominant Symptom and

Impairment Assessment (PSIA); visit 3 was the planned baseline for Sino-Nasal Outcome Test-22 (SNOT-22). Baseline for daily diary measures was the average value over the 7 days before visit 4. Study investigators at each site did prebronchodilator spirometry at screening, then at weeks 0, 2, 4, 8, 16, and 24.

Several assessments were done by the patient at home during the treatment period. PEF was recorded morning and evening. Adherence to regularly scheduled asthma medication was to be recorded once daily. The ACQ-6 was assessed at visit 4 onsite, then by patients at home once every week until visit 6, week 4. After visit 6, ACQ-6 was assessed by patients at home once every 4 weeks until end of treatment (EOT; ie, week 24, visit 11). CGI-C was assessed on-site at each treatment visit through to EOT, and PGI-C was completed at home by the patient every week up to week 4, and every 4 weeks thereafter until EOT. Patients recorded the severity of the symptoms and impairments selected on the individualised PSIA at baseline and every week until week 16, and then weeks 20 and 24.

Outcomes

The primary efficacy endpoint was the annualised AER (defined as total number of exacerbations × 365·25 per total duration of follow-up within the treatment group in days), which was compared across treatment groups to determine the effect of benralizumab versus placebo on the rate of asthma exacerbations over the 24-week treatment period. Time to first asthma exacerbation was analysed as a secondary efficacy variable. An asthma exacerbation was defined as a worsening of asthma that led to any one of the following: use of systemic corticosteroids (or a temporary increase in a stable oral corticosteroid background dosage) for at least 3 days; a single injectable dose of corticosteroids; an emergency room or urgent care visit (<24 h) owing to asthma that required systemic corticosteroids; and an inpatient hospitalisation (≥24 h) because of asthma.

The key secondary efficacy endpoint (to account for multiplicity with a hierarchical testing strategy) was change from baseline (visit 4) to EOT in SGRQ total score to determine the effect of benralizumab on patient-reported disease-specific HRQOL. The SGRQ is a 50-item PRO instrument developed to measure the health status of patients with airway obstruction diseases.[46] The SGRQ total score indicates the impact of disease on overall health status, and is expressed as a percentage of overall impairment (100 indicates worst possible health status and 0 indicates best possible health status). A mean change score of 4 units on the SGRQ is associated with a minimum clinically important difference (MCID) and was used to assess SGRQ total score responder analysis at weeks 4, 12, and 24.

To determine the effect of benralizumab on lung function, FEV_1 was measured using spirometry at the study centre as a secondary endpoint.[47] Asthma medication restrictions were to be followed before spirometry assessments were done. All post-randomisation spirometry assessments were done within 2 h (plus or minus) of the baseline prebronchodilator FEV_1 spirometry. Patients measured their PEF using a peak flow meter each morning after waking, before taking their morning asthma medications, and each evening. Change from baseline in weekly mean morning and mean evening PEF were each summarised and analysed using a mixed-effect model repeated measure (MMRM).

As a secondary endpoint to determine the effect of benralizumab on patient-reported asthma control, ACQ-6[48] was done to assess asthma symptoms. Questions (one bronchodilator use question and five symptom questions) were weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled), with individual change scores of at least 0·5 considered clinically meaningful and used for the responder analysis at week 24. ACQ-6 scores of 0·75 or less indicated well controlled asthma, scores between 0·75 and less than 1·5 indicated partly controlled asthma, and a score of 1·5 or more indicated uncontrolled asthma.

CGI-C and PGI-C assessments captured clinician and patient perceptions of change in disease-specific health status from baseline. The investigator (CGI-C) and the patient (PGI-C) rated the degree of change in overall asthma status compared with the start of treatment at randomisation (visit 4) using a seven-point rating scale (1, very much improved; 2, much improved; 3, minimally improved; 4, no changes; 5, minimally worse; 6, much worse; and 7, very much worse).

The PSIA was developed for use in the ANDHI study as a patient-driven assessment of impactful symptoms and impairments; given that this is the first use of the assessment, the measurement properties have not been established. As a PRO, the PSIA evaluated the degree to which patient-stated bothersome symptoms and impairments improved throughout the study. An individualised profile of symptoms and impairments, ranked by the patient in order of importance, was done at visit 3. Patients were presented with a prespecified list of eight cardinal symptoms and impairments of asthma (ie, shortness of breath, wheeze, cough, chest tightness, difficulty sleeping due to asthma, limited typical daily activities, limited physical intense activities, and sensitivity to environmental conditions), and asked to select those symptoms and impairments that impacted them over the past year. Patients then ranked the selected symptoms or impairments in order of impact from most impactful or top ranked (1) to least impactful (8). The PSIA was then individualised for each patient on the basis of the top ranked symptoms and impairments, and administered throughout the study. Patients were asked to report the severity of the symptom or impairment over the previous 7 days on the individualised PSIA using an 11-point numeric rating scale from 0 (did not experience) to 10 (worst I can imagine).

SNOT-22 was a secondary endpoint used to determine the effect of benralizumab on disease-specific HRQOL for patients with physician-diagnosed chronic sinusitis with nasal polyposis. SNOT-22 assesses the symptoms, sleep, and functional and emotional consequences of chronic rhinosinusitis with nasal polyposis through responses to 22 items by using a six-category scale from 0 (no problem) to 5 (problem as bad as it can be).[49] The smallest change in the SNOT-22 that can be detected by a patient and associated with an MCID is 8·9.[49]

Lung function (FEV_1) was measured at each study centre by spirometry; equipment was provided by a central spirometry vendor. Spirometry was done by the investigator or authorised delegate according to American Thoracic Society and European Respiratory Society guidelines.[47]

Safety and tolerability were assessed through reported adverse events and laboratory values. The investigator at each site was responsible for ensuring that all staff involved in the study were familiar with the definitions, recording, and reporting of adverse events and serious adverse events during the study. Adverse events were collected throughout the treatment period from the time of signature of informed consent through the EOT and throughout the follow-up period (visit 12, week 26).

Statistical analysis

The study was powered for the primary objective (ie, to determine the effect of benralizumab on the AER) through the primary endpoint, and for the key secondary endpoint (ie, change from baseline to EOT in SGRQ). Previous benralizumab phase 3 asthma exacerbation studies[11,12] indicated that an annualised AER in the placebo group of 1·25, a 40% reduction in AER for the benralizumab group, and a common negative binomial shape dispersion parameter of 1·2 might be expected. A difference of 5 points and a common SD of 19 points was assumed for the change from baseline in SGRQ total score based on related measures from previous benralizumab exacerbation studies[11,12] and on results from mepolizumab pivotal trials.[50,51] Under these assumptions, a 630 patient study randomised to benralizumab or placebo in a ratio of 2:1 (ie, 420 benralizumab-treated and 210 placebo-treated patients) has approximately 91% power with respect to the primary endpoint (assessed over a 24-week period) and 87% power with respect to the key secondary endpoint (assuming a two-sided 5% significance level in both cases).

AER for patients treated with benralizumab was compared with placebo using a negative binomial model. The response variable in the model was the number of asthma exacerbations over the 24-week treatment period. The model included covariates of treatment group, number of exacerbations in the year before the study, region, and the use of maintenance oral corticosteroid. The logarithm of the follow-up time was used as an offset variable in the model. The estimated treatment effect (ie, the rate ratio [RR] of benralizumab *vs* placebo), corresponding 95% CI, and two-sided p value for the RR were included. Time to first asthma exacerbation was analysed using a Cox proportional hazard model as a secondary efficacy variable with results presented as a hazard ratio (HR) and 95% CI.

To account for multiplicity to test one primary and one key secondary variable, a hierarchical testing strategy to control for the overall type I error (0·05) was adopted. First, the annualised AER was tested at the two-sided 5% significance level. If the AER was significant (ie, p value <0·05 for benralizumab *vs* placebo), then the SGRQ total score change from baseline to EOT visit was to be tested at the two-sided 5% significance level. With the exception of the primary and key secondary endpoints, all results of formal statistical analyses are presented with two-sided nominal p values (unadjusted for multiplicity). Conclusions around statistical significance were only made for the multiplicity-protected endpoints and analyses.

Differences in least squares mean change from baseline in SGRQ total score, FEV_1, and ACQ-6 at week 24 for patients treated with benralizumab versus placebo were analysed. For SGRQ, FEV_1, and ACQ-6, analysis was via an MMRM with adjustment for treatment, baseline measure, region, number of exacerbations in previous year, maintenance oral corticosteroid use at baseline visit, visit, and treatment×visit (FEV_1 adjusted also for age and sex). For SGRQ, only the week 24 comparison was controlled for multiplicity. ACQ-6 and FEV_1 were not multiplicity-controlled analyses; therefore, all ACQ-6 and FEV_1 p values were nominal. Responder analyses for SGRQ and ACQ-6 were analysed via a logistic regression model (adjusted for treatment, baseline score, region, number of exacerbations in the previous year, and baseline maintenance oral corticosteroid use) with results reported as an odds ratio (OR) with associated 95% CI and nominal p value.

For CGI-C and PGI-C, responses were summarised by treatment group and week as number and percentage of patients. The number and percentage of patients defined as responders based on categorised responses for CGI-C and PGI-C (improved, much improved, and very much improved) were assessed by treatment group and visit responder status (much improved and very much improved) for CGI-C and PGI-C at EOT, and were analysed using logistic regression models. No baseline response was included in the model.

For each of the PSIA symptom or impairment concepts, the number and percentage of patients ranking the concepts first through eighth were summarised by treatment group. The number and percentage of patients who did not endorse a symptom or impairment as relevant is shown as not scored. Estimate of the mean change from baseline (visit 4) at each timepoint in severity score for each patient's top ranked symptom or impairment, based on numeric rating scale responses, was summarised and

analysed using an MMRM with treatment, baseline score, region, exacerbations in previous year, oral corticosteroid use at baseline visit, visit, and treatment×visit as covariates. This analysis was repeated for each of the second and third top ranked symptoms or impairments and for the average of the top three ranked symptoms or impairments.

All efficacy analyses, except for SNOT-22, were summarised and analysed using the full-analysis set on an intention-to-treat population (all randomly assigned patients receiving investigational product, regardless of protocol adherence or continued participation in the study). SNOT-22 was summarised for the subgroup of patients with physician-diagnosed nasal polyposis with signed consent. Change from baseline at each timepoint for SNOT-22 was compared between benralizumab and placebo using a repeated measures analysis method similar to the other secondary endpoints, with all p values being nominal.

To explore the uniformity of the detected overall treatment effect on AER, SGRQ, ACQ-6, and FEV_1, exploratory subgroup analyses were done on the full-analysis set via statistical modelling, which included testing for an interaction between treatment and subgroup effects. FVC% predicted at baseline (<65%, ≥65%), maintenance oral corticosteroid use at baseline (yes, no), number of exacerbations in previous year (two, or three or more exacerbations), nasal polyposis (yes, no), age at asthma onset (<18, ≥18 years), and screening BEC (>150 to <300 cells per µL, ≥300 cells per µL) were included in the analyses.

Safety analyses were based on the actual treatment regimen received and included all patients receiving at least one dose of study drug.

The statistical analyses were done in accordance with the statistical analysis plan using SAS, version 9.4 or higher. Adverse events were coded using Medical Dictionary for Regulatory Activities, version 22.0.

This study is registered with ClinicalTrials.gov, NCT03170271.

Role of the funding source

The funders of the study participated in the study design. All authors, including those employed by the funders of the study, participated in the data collection, data analysis, data interpretation, and writing of the Article. All authors had full access to the totality of the study data and had final responsibility for the decision to submit for publication.

Results

Between July 7, 2017, and Sept 25, 2019, 1530 patients were enrolled, and 1217 entered eligibility screening. 660 patients met study criteria and were randomly assigned (appendix p 11): 431 to receive benralizumab and 229 to receive placebo. 656 (99%) patients received investigational product (n=427 [99%] benralizumab; n=229 [100%] placebo). 616 (93%) of these 656 patients completed the double-blind period of the study, with 398 (92%) patients in the benralizumab group and 218 (95%) patients in the placebo group completing treatment. Six patients (five in the benralizumab group and one in the placebo group) who had received all treatments were withdrawn before the EOT visit. 34 (5%) patients discontinued treatment, with the main reason being patient decision (18 [3%] patients).

Demographics and baseline clinical characteristics of the study population, which was representative of a patient population with severe eosinophilic asthma, are given in the table. Most patients were White (482 [86%] of 656) and female (399 [61%] of 656). The mean age was 52·8 years, and mean body-mass index was 29·94 kg/m². All patients reported exacerbations over the previous 12 months, with approximately half of the patients in each group having three or more exacerbations. Lung function at screening, mean SGRQ total score, and mean ACQ-6 were also similar between groups. Mean PSIA severity scores at baseline for each of the top three ranked impairments or symptoms, and for the average of the top three ranked impairments or symptoms, were similar for both groups.

129 (30%) of 427 patients in the benralizumab group and 63 (28%) of 229 patients in the placebo group had BEC of 150 to less than 300 cells per µL at screening. Overall, 275 [42%] of 656 patients had a baseline BEC of 450 or more cells per µL, 220 (34%) of 656 patients had less than 300 cells per µL, and 161 (25%) of 656 had 300 to less than 450 cells per µL; both treatment groups were balanced within each of these categories (table). Median baseline BEC was identical for both treatment groups (390 cells per µL).

The major categories of maintenance asthma medication used at baseline were generally balanced between groups. All patients were taking inhaled corticosteroids and another asthma controller per inclusion criteria. 129 (20%) of 656 patients were taking oral corticosteroid (table).

The overall median age at asthma diagnosis was 31 years, with most patients (479 [73%] of 656) in the adult-onset (≥18 years) group. An imbalance was noted between groups, with a lower percentage of benralizumab patients in the adult-onset asthma group (302 [71%] of 427) compared with the placebo group (177 [77%] of 229).

For the primary efficacy variable, benralizumab significantly reduced annualised AER over the 24-week period, compared with placebo, by 49% (from 1·86 in the placebo group to 0·94 in the benralizumab group) in the overall population (RR estimate 0·51 [95% CI 0·39–0·65]; appendix p 12). Model-estimated and crude annualised rates within each treatment group were consistent (appendix p 12), and the treatment effect equated to a –0·92 difference in the annualised rate of exacerbations (p<0·0001). Time to first asthma exacerbation was longer for patients in the benralizumab

	Benralizumab (n=427)	Placebo (n=229)
Sex		
Female	263 (62%)	136 (59%)
Male	164 (38%)	93 (41%)
Age, years	52·5 (12·7)	53·3 (12·5)
Race or ethnicity		
White	314 (74%)	168 (73%)
Black	35 (8%)	18 (8%)
Asian	11 (3%)	7 (3%)
Native Hawaiian or other Pacific Islander	0	1 (<1%)
Hispanic or Latino	49 (12%)	25 (11%)
Other	5 (1%)	2 (1%)
Missing	62 (15%)	33 (14%)
Body-mass index, kg/m²	29·85 (7·37)	30·10 (7·89)
BEC group at screening		
≥300 cells per µL	297 (70%)	165 (72%)
≥150 to <300 cells per µL	129 (30%)	63 (28%)
BEC at baseline, cells per µL*	390 (40–7970)	390 (20–5600)
<300 cells per µL	146 (34%)	74 (32%)
≥300 to <450 cells per µL	105 (25%)	56 (25%)
≥450 cells per µL	176 (41%)	99 (43%)
IgE values, IU/µL	139·65 (1·5–6363·7)	134·25 (1·5–11821·5)
Phadiatop positive	227 (53%)	125 (54%)
Exacerbations in the previous 12 months		
Rate	3·2	3·1
Two	206 (48%)	113 (49%)
Three or more	221 (52%)	116 (51%)
Oral corticosteroid use at baseline	85 (20%)	44 (19%)
SGRQ total score†	58·19 (17·71)	56·69 (18·09)
Prebronchodilator FEV_1, mL	1630 (609)	1720 (629)
Prebronchodilator FEV_1, percent predicted normal	54·0% (14·2)	55·9% (13·6)
Postbronchodilator FEV_1, mL	2060 (734)	2110 (727)
Postbronchodilator FEV_1 percent predicted normal	68·0% (16·44)	68·6% (15·24)
Reversibility	28·2% (20·43)	24·9% (19·15)
ACQ-6†	3·04 (0·874)	3·07 (0·965)
PSIA‡		
Top ranked symptom or impairment	6·40 (2·16)	6·60 (1·93)
Top three ranked symptoms or impairments	6·16 (1·82)	6·32 (1·85)
SNOT-22§	51·5 (20·4)	48·2 (21·2)

Data are n (%), mean (SD), or median (range). BEC=blood eosinophil counts. SGRQ=St George's Respiratory Questionnaire. ACQ-6=Asthma Control Questionnaire 6. PSIA=Predominant Symptom and Impairment Assessment. SNOT-22=Sino-Nasal Outcome Test-22. *Baseline eosinophil count was the last non-missing assessment before the first dose of study treatment. Data missing for one patient in the benralizumab group and one patient in the placebo group. †Baseline measurement was the last non-missing assessment before or on the day of the first dose of study treatment. ‡Baseline measurement was the last non-missing assessment before the first dose of study treatment; if time was collected, the assessment done the same day but before the first dose of study treatment was included in baseline definition; if time was not collected, the assessment done the same day was included in baseline definition. §Subgroup of patients providing consent to be included in the nasal polyposis substudy for the SNOT-22 baseline (benralizumab [n=96], placebo [n=57]).

Table: **Demographics and baseline clinical characteristics**

group, as indicated by a 48% lower risk of having an asthma exacerbation compared with placebo (HR 0·52 [95% CI 0·40–0·67]; p<0·0001). 123 (29%) of 427 patients in the benralizumab group versus 107 (47%) of 229 patients in the placebo group reported asthma exacerbations from baseline up to week 24. For patients with baseline eosinophils of at least 300 cells per µL, benralizumab significantly reduced AER over the 24-week period, compared with placebo, by 59% (RR 0·41 [0·30–0·56]).

A clinically meaningful and statistically significant difference in least squares mean change from baseline in SGRQ total score at week 24 was observed for patients treated with benralizumab compared with placebo (–8·11, 95% CI –11·41 to –4·82; p<0·0001), and those improvements were evident from week 4 (first timepoint assessed) onward, with the greatest decrease seen at week 24 (–23·06 units for benralizumab *vs* –14·94 units for placebo; figure 1). For patients with screening eosinophils ≥300 cells per µL, a greater difference in least squares mean change from baseline in SGRQ total score was shown at week 24 for benralizumab compared with placebo (–11·16; appendix p 13). The percentage of patients with a clinically meaningful improvement in SGRQ total score (≥4-point decrease from baseline in total score) was consistently greater for the benralizumab group, compared with the placebo group, at all timepoints (week 4, 300 [70%] of 427 *vs* 135 [59%] of 229; week 12, 301 [71%] of 427 *vs* 139 [61%] of 229; week 24, 308 [72%] of 427 *vs* 144 [63%] of 229, respectively; appendix p 14). Similarly, a lower percentage of patients in the benralizumab group reported a deterioration in their SGRQ total score of 4 or more units during the treatment period compared with placebo (week 4, 26 [6%] of 427 *vs* 40 [18%] of 229; week 12, 25 [6%] of 427 *vs* 30 [13%] of 229; week 24, 23 [5%] of 427 *vs* 32 [14%] of 229, respectively; appendix p 14). The likelihood of achieving a clinically meaningful improvement in SGRQ total score (MCID of 4 units) at EOT was greater for patients treated with benralizumab compared with placebo (314 [80%] of 392 *vs* 144 [68%] of 212, respectively; OR 1·91 [95% CI 1·30–2·81]; p=0·0010; appendix p 15).

Benralizumab improved lung function at week 24, when compared with placebo (least squares mean difference 160 mL, 95% CI 90–230; p<0·0001), with improvements observed from the first timepoint assessed (week 2 90 mL, 30–150; p=0·0041) onward (figure 1). For patients with screening eosinophils of at least 300 cells per µL, a greater improvement in lung function was shown at week 24, when compared with placebo (191 mL; appendix p 13). The least squares mean change from baseline in morning and evening PEF observed for the benralizumab group throughout the treatment period was greater than for the placebo group from week 1 (p=0·0214, morning) and at all subsequent timepoints through to week 24 (p=0·0031, morning), indicating an early and sustained improvement. Results of the treatment comparisons for change from baseline in home morning and evening PEF are summarised for the full-analysis set in the appendix (p 16).

ACQ-6 score improvements were greater for the benralizumab group compared with the placebo group from week 2 (least squares mean difference –0·36 units

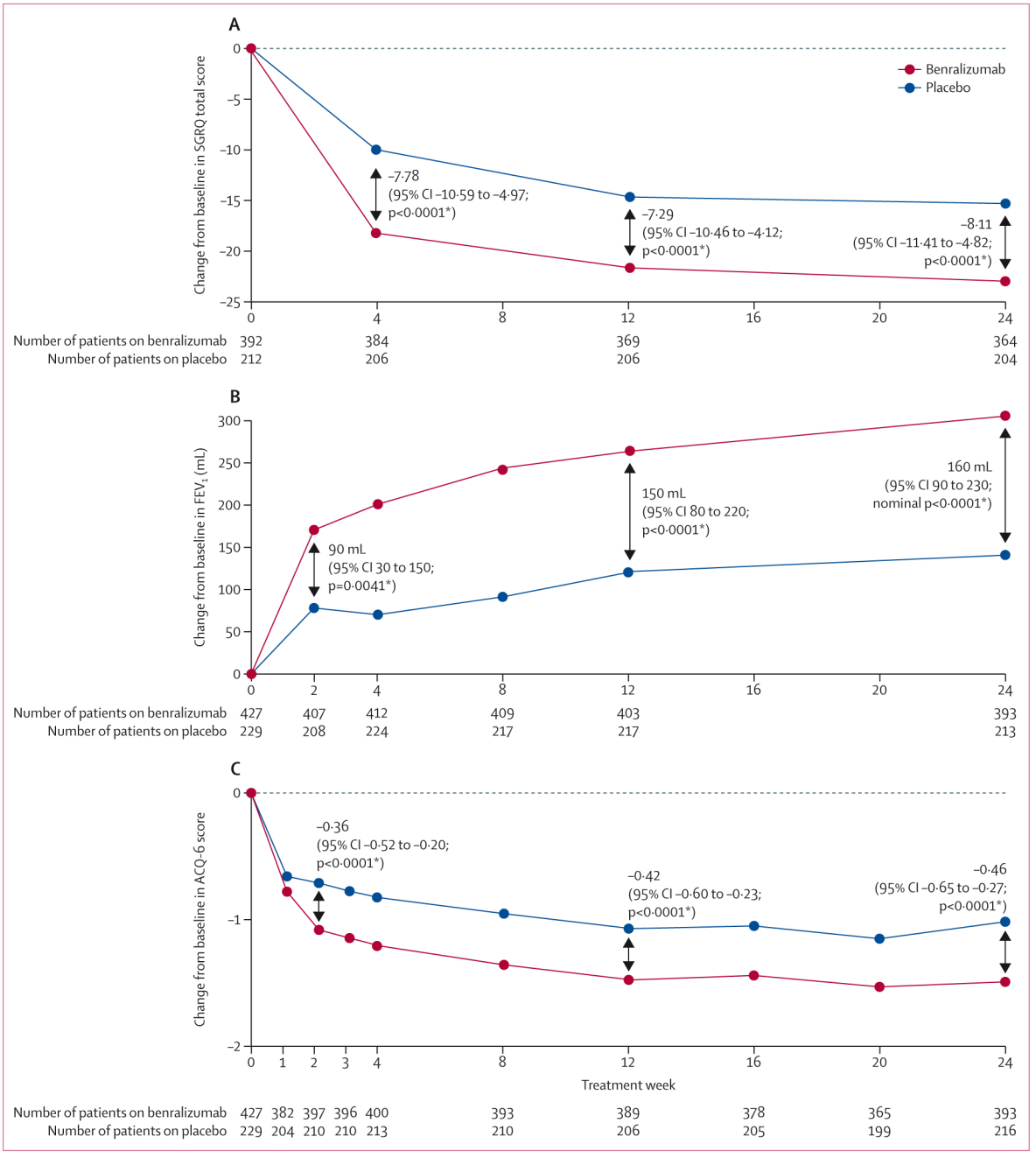

Figure 1: **Improvement from baseline in SGRQ total score, FEV_1, and ACQ-6 for patients treated with benralizumab versus placebo**
Difference in least squares mean change from baseline in SGRQ total score (A), FEV_1 (B), and ACQ-6 (C) at week 24 for patients treated with benralizumab versus placebo. ACQ-6=Asthma Control Questionnaire 6. SGRQ=St George's Respiratory Questionnaire. *For SGRQ, FEV_1, and ACQ-6, analysis via mixed model for repeated measures with adjustment for treatment, baseline measure, region, exacerbations in previous year, oral corticosteroid use at baseline visit, and treatment by visit (for FEV_1 adjusted also age and sex). For SGRQ, only the week 24 comparison was controlled for multiplicity. ACQ-6 and FEV_1 were not multiplicity-controlled analyses; therefore, all p values are nominal.

95% CI –0·52 to –0·20; p<0·0001) through to week 24 (–0·46 units, –0·65 to –0·27; p<0·0001), indicating an early and sustained improvement in ACQ-6 score throughout the treatment period (figure 1). For patients with screening eosinophils of at least 300 cells per µL, a greater difference in least squares mean change from baseline in ACQ-6 was shown at week 24 for benralizumab compared with placebo (–0·61; appendix p 13). The likelihood of achieving a minimum clinically meaningful improvement in ACQ-6 score at EOT (MCID –0·5 or less) was greater for patients treated with benralizumab (313 [73%] of 427) compared with placebo (150 [66%]

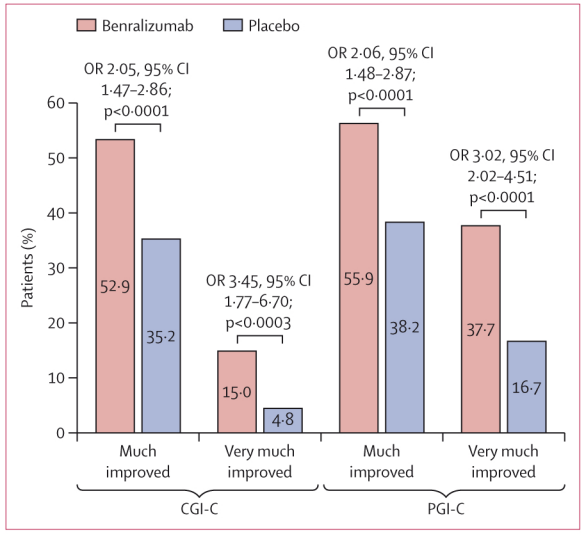

Figure 2: **CGI-C and PGI-C responders at end of treatment by improvement type**

Responder defined as very much improved or much improved on the CGI-C or PGI-C. Estimate of the log odds of being a responder in the benralizumab treatment group compared with the placebo treatment group using a logistical regression model with adjustment for treatment, region, exacerbations in previous year, and oral corticosteroid use at baseline visit. Percentage of responders was calculated from the number of patients included in the analysis (CGI-C benralizumab n=420, placebo n=229; PGI-C benralizumab n=424, placebo n=228). For patients with missing data at the end of treatment (week 24) completing the study, last evaluable post-baseline score was used to define responder status. Patients who did not complete were treated as non-responders. All p values are nominal. OR=odds ratio. CGI-C=Clinician Global Impression of Change. PGI-C=Patient Global Impression of Change.

of 229). There was a greater probability of achieving responder status per MCID at EOT in the benralizumab group compared with the placebo group (OR 1·53 [95% CI 1·07–2·20]; p=0·0193; appendix p 15).

Assessment of perceived change from baseline showed a greater percentage of improved patients (very much improved, much improved, and minimally improved) in the benralizumab group throughout the treatment period compared with patients in the placebo group for CGI-C (week 2, 246 [58%] of 427 *vs* 87 [38%] of 229; week 12, 273 [64%] of 427 *vs* 120 [52%] of 229; and week 24, 289 [68%] of 427 *vs* 126 [55%] of 229, respectively) and PGI-C (week 2, 253 [59%] of 427 *vs* 96 [42%] of 229; week 12, 309 [72%] of 427 *vs* 127 [56%] of 229; and week 24, 303 [71%] of 427 *vs* 133 [58%] of 229, respectively (appendix p 17). Patients tended to report more improvement (PGI-C) than clinicians (CGI-C; appendix pp 17–18). The likelihood of being a responder (defined as very much improved or much improved on the CGI-C or PGI-C for overall asthma status at EOT was greater for the benralizumab group compared with the placebo group for CGI-C and PGI-C (figure 2).

The benralizumab and placebo groups were similar in terms of the top ranked PSIA symptoms or impairments at initial assessment. Shortness of breath was the most commonly reported symptom or impairment for patients in the benralizumab and placebo groups (174 [41%] of 427 *vs* 100 [44%] of 229), followed by limited physically intense activities (60 [14%] *vs* 28 [12%]), cough (50 [12%] *vs* 29 [13%]), and wheeze (42 [10%] *vs* 25 [11%]) regardless of patient rank (appendix p 19). Patients reported greater improvement on the symptom or impairment rated as most important and the average of the top three symptoms or impairments in the benralizumab group compared with the placebo group (figure 3). Greater least squares mean decreases from baseline were observed for the benralizumab group compared with the placebo group from week 2 onward, demonstrating an early and sustained improvement in the symptoms that patients viewed as most impactful, as captured by PSIA.

Subanalyses of key endpoints to investigate the treatment effect within predefined subgroups, defined by the presence of specific clinical features previously associated with the asthma eosinophilic phenotype or enhanced benralizumab response, or both, are depicted in figure 4. For AER, subgroup analyses indicated that eosinophils of at least 300 cells per µL ($p_{interaction}$=0·0130), the presence of adult-onset asthma (p=0·0033) and a medical history of nasal polyposis (p=0·0616) were associated with an enhanced treatment response (at a 10% significance level). Eosinophils of at least 300 cells per µL (p=0·0056) and the presence of adult-onset asthma (p=0·0095) were also associated with an enhanced SGRQ response. Eosinophils of at least 300 cells per µL (p=0·0020), adult-onset asthma (p=0·0676), and three or more exacerbations in the previous year (p=0·0376) were associated with an enhanced ACQ-6 response. Adult-onset asthma (p=0·0179), baseline oral corticosteroid use (p=0·0264), and three or more exacerbations (p=0·0365) were associated with an enhanced FEV_1 response. For AER, SGRQ, and ACQ-6, the treatment effect in those with baseline oral corticosteroid use was numerically greater than in the overall population, although not significantly different from those without oral corticosteroid use. Similarly, a medical history of nasal polyposis and three or more exacerbations in the previous 12 months showed a numerically greater treatment effect in terms of SGRQ response, without statistical significance.

The subgroup analysis was repeated for the subpopulations of patients with screening BEC of at least 300 cells per µL. Results were consistent with the main subgroup analyses. Data for the subgroup of patients with screening BEC of at least 300 cells per µL are included in the appendix (p 20).

228 (35%) of 656 patients had a medical history of nasal polyposis. Of these patients, 153 (23%) had nasal polyposis at study entry and provided consent to be included into the nasal polyposis substudy (96 and 57 patients randomly assigned to benralizumab and placebo, respectively). This population had a lower percentage of female patients (53 [55%] of 96 in the benralizumab group and 24 [42%] of 57 in the placebo group *vs* approximately 60% in each group in the full

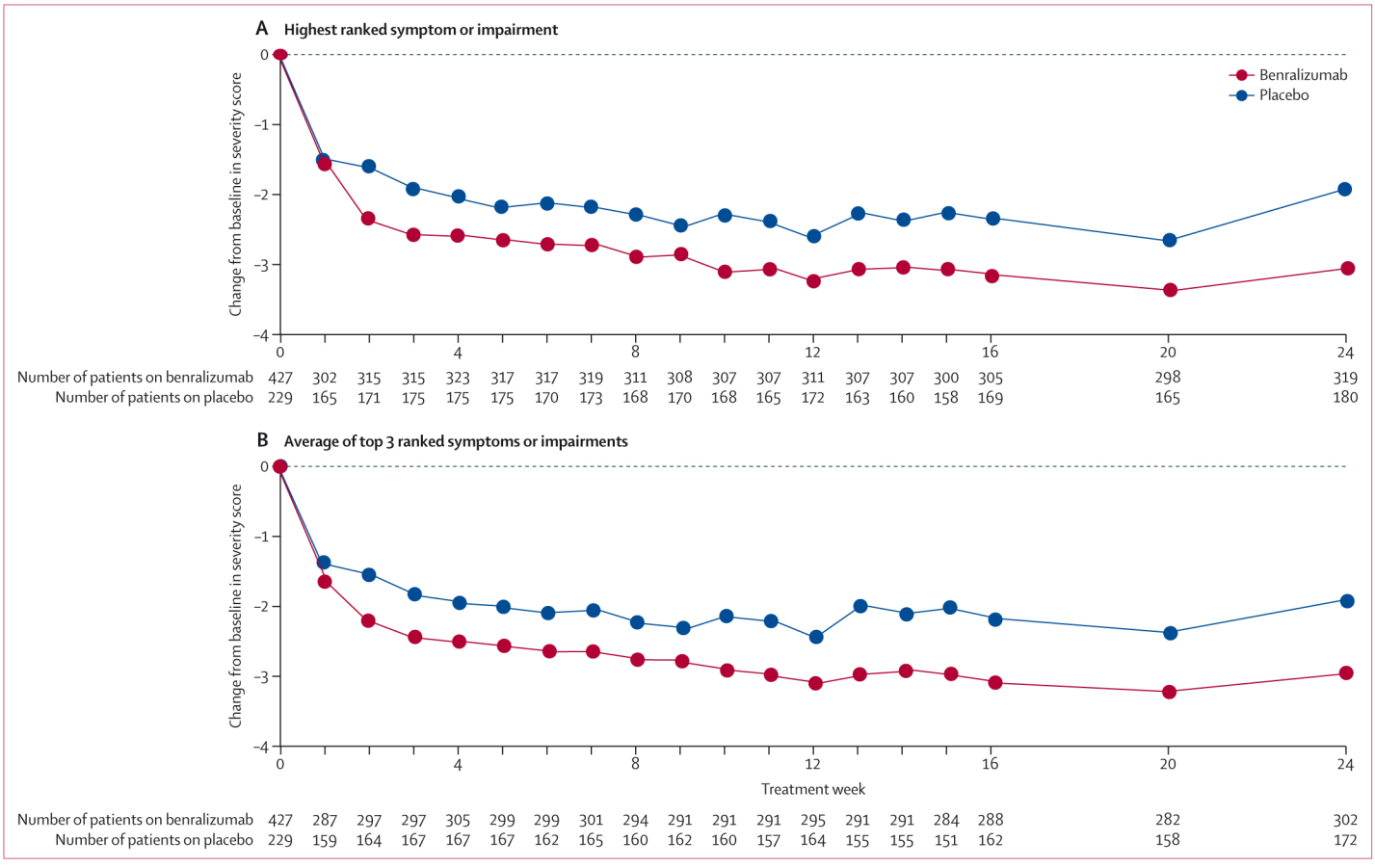

Figure 3: **Improvements in PSIA change from baseline based on top ranked and average of top three ranked symptoms or impairments**
Estimate of the mean change from baseline at each timepoint for PSIA for top ranked symptom or impairment (A) and average of top three ranked symptoms or impairments (B) in the benralizumab group compared with the placebo group using a repeated measures analysis. For change from baseline in top ranked symptom or impairment (A) and average PSIA score of top three ranked symptoms or impairments (B), analysis was done via mixed-effect model repeated measure with adjustment for treatment, baseline, region, exacerbations in previous year, oral corticosteroid use at baseline visit, and treatment by visit as covariates. Baseline measurement is the last non-missing assessment before the first dose of study treatment. If time was collected, the assessment done the same day but at a time before the first dose of study treatment is included in the baseline definition. If time was not collected, the assessment performed the same day is included in the baseline definition.
PSIA=Predominant Symptom and Impairment Assessment.

study population) and greater baseline median BEC (approximately 500 cells per µL for patients in the nasal polyposis substudy compared with 390 cells per µL in the full study population). For the 153 patients in this substudy analysis, mean SNOT-22 at baseline was 50·2, with similar mean SNOT-22 scores for patients in the benralizumab (51·5) and placebo (48·2) groups.

Benralizumab patients demonstrated greater improvement from baseline in SNOT-22 total scores compared with placebo patients at visit 11, week 24 (–8·91, 95% CI –16·42 to –1·40; p=0·0204). Greater least squares mean decreases from baseline in SNOT-22 total scores were seen beginning at the first timepoint assessed (ie, week 4; –7·47, –13·16 to –1·77; p=0·0105) to EOT for the benralizumab group compared with the placebo group (figure 5).

The mean duration of exposure was 109 days in the benralizumab group and 111 days in the placebo group. Adverse events during the treatment period were reported by similar percentages of patients who received benralizumab (271 [63%] of 427) and placebo (143 [62%] of 229; appendix p 21). Most adverse events reported were assessed as mild or moderate in intensity. The most commonly reported adverse events for the 427 patients receiving benralizumab (frequency >5%) were nasopharyngitis (30 [7%]), headache (37 [9%]), sinusitis (28 [7%]), bronchitis (22 [5%]), and pyrexia (26 [6%]; appendix p 21). Fewer serious adverse events were reported for patients in the benralizumab group (23 [5%] of 427) than the placebo group (25 [11%] of 229). The only common serious adverse event (experienced by >1% of patients) was worsening of asthma, which was reported for nine [2%] of 427 patients in the benralizumab group and nine [4%] of 229 patients in the placebo group. Four serious adverse events in the benralizumab group were judged by the investigator to be related to treatment (cytokine release syndrome, mydriasis, pneumonia, and urticaria); all serious adverse events reported in the placebo group were assessed as not related to treatment. The incidence of adverse events leading to discontinuation

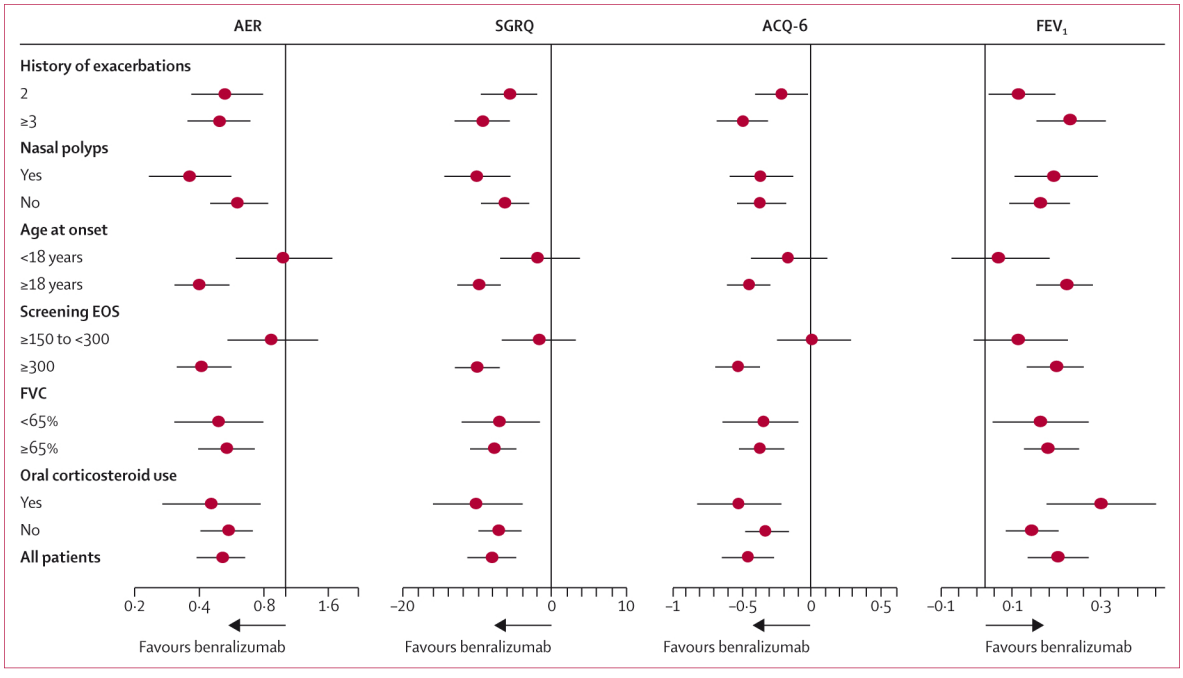

Figure 4: **Baseline factor effect on asthma exacerbation rate, SGRQ total score, ACQ-6, and FEV_1 with benralizumab for the overall treatment population (full analysis set)**

To explore the uniformity of the detected overall treatment effect, subgroup analyses were done for the primary variable, key secondary variable, and secondary variables. A negative binomial model was used for the primary variable (AER), with additional terms for the subgroup main effect and treatment by subgroup interaction, and mixed-effect model repeated measure was used for the key secondary and secondary variables (SGRQ, ACQ-6, and FEV_1). ACQ-6=Asthma Control Questionnaire 6. AER=asthma exacerbation rate. EOS=eosinophil count at screening. FVC=forced vital capacity. SGRQ=St George's Respiratory Questionnaire.

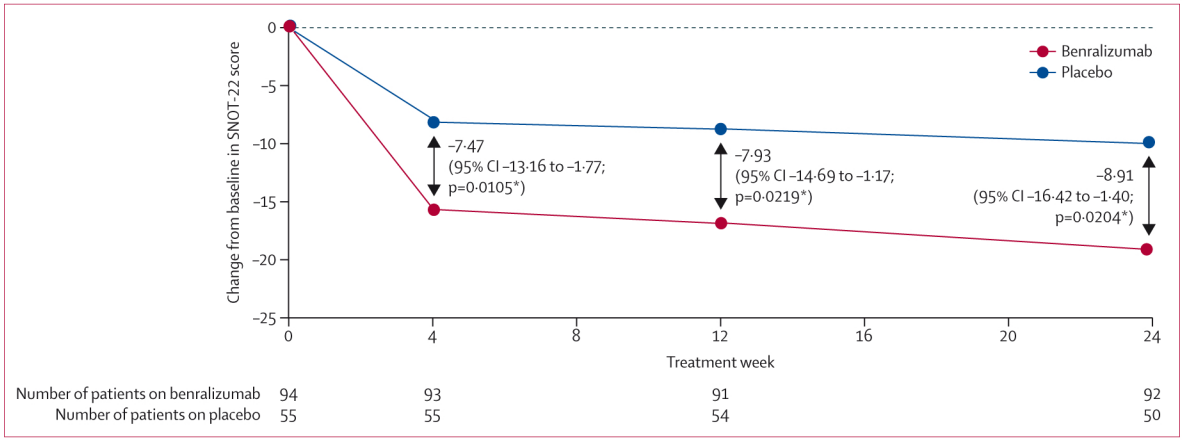

Figure 5: **Improvement from baseline in SNOT-22 for patients treated with benralizumab versus placebo: nasal polyposis substudy**

Change from baseline in SNOT-22 by timepoint for patients treated with benralizumab versus placebo for all patients in the subgroup of patients included in the nasal polyposis substudy. Mean SNOT-22 total scores at baseline were similar for both treatment groups. SNOT-22=Sino-Nasal Outcome Test-22. *Analysis via mixed model for repeated measures with adjustment for treatment, baseline measure, region, exacerbations in previous year, oral corticosteroid use at baseline, visit, and treatment x visit; SNOT-22 was not multiplicity controlled. Therefore, all p values are nominal.

was low in both treatment groups (six [1%] of 427 patients on benralizumab, and two [<1%] of 229 patients on placebo). No patients had an adverse event with an outcome of death. The incidence of injection-site reactions was low in both treatment groups (four [1%] of 427 for the benralizumab group and three [1%] of 229 for the placebo group), with all injection-site reactions being mild or moderate, non-serious, and transient. No adverse events of anaphylaxis were reported. The incidence of malignancy was low overall, with two skin cancers reported for the benralizumab group and one skin cancer reported for the placebo group. Detailed information for specific hypersensitivity adverse events is included in the appendix (p 22).

Although 150 (35%) of 427 patients in the benralizumab group and 95 (41%) of 229 patients in the placebo group

reported adverse events in the system organ class of infections and infestations, the incidence of infections reported as serious adverse events was low for both groups (three [1%] of 427 patients in the benralizumab group and six [3%] of 229 patients in the placebo group). Pneumonia was the most commonly reported serious infection in both groups (two [<1%] of 427 and two [1%] of 229 patients in the benralizumab and placebo groups, respectively). No cases of helminth infections were reported.

Discussion

Although the efficacy and safety of benralizumab for patients with severe eosinophilic asthma are well established, the phase 3b ANDHI trial confirms and extends the efficacy profile of benralizumab for patients with severe eosinophilic asthma in terms of onset of clinical effect, disease-specific HRQOL data, patient and clinician perception of response, and preliminary evidence on the effect of benralizumab for patients with nasal polyposis. The primary and key secondary objectives of AER reduction (49%) and greater change in SGRQ total score (–8·11) relative to placebo were met. Early (within 1 to 4 weeks) and sustained (to week 24) improvements in FEV_1, PEF, ACQ-6, CGI-C, PGI-C, PSIA, and SNOT-22 (for patients with nasal polyposis at baseline) were also demonstrated.

The results reinforce the exacerbation reduction benefit of benralizumab observed in the pivotal studies, particularly for patients with blood eosinophil counts of at least 300 cells per µL, for whom exacerbation reduction versus placebo was 59%, similar to the 51% reduction observed for the primary analysis population of patients with at least 300 cells per µL in SIROCCO,[11] and results seen in other patient populations.[52] Newer results in this study include significant and clinically meaningful improvements in disease-specific HRQOL based on change in total SGRQ score beginning at the first post-baseline timepoint. The SGRQ effect size and response characteristic are similar to that observed in the recently reported benralizumab SOLANA trial at week 12 (–7·25; p=0·0003),[53] and substantially more robust than the Asthma Quality of Life Questionnaire for 12 years and older (AQLQ[S]+12) response previously reported for benralizumab.[11,12] This result supports the observation that SGRQ might be a more sensitive indicator of treatment effect for patients with severe eosinophilic asthma compared with AQLQ(S)+12.

Change from baseline in the patient's global assessment of their overall asthma status (PGI-C), and in the severity of their most bothersome PSIA, also favoured treatment. The Global Initiative for Asthma recommendations for severe asthma emphasise the importance of PROs and clinician-reported outcomes in effective asthma management and the need to be individualised for each patient.[54] As a PRO, PSIA is a novel tool that captures several symptoms or impairments with importance or burden to patients. Assessing a patient's level of asthma control is a key part of asthma management,[54] and additional measurement tools and approaches to documentation, such as the PSIA, are needed to improve patient-focused, high-quality asthma care.[55] Similar to other clinical assessments,[55] PROs assessing the importance of symptoms have proven to be key clinical indicators in asthma management. The results from the current study focus on symptoms or impairments that are more burdensome to the patient, assess if improvement is reported with treatment, and add to the results from PROs from the ACQ-6, which focus on symptoms that might have limited relevance and varying burden to the patient and therefore might not show improvement. These PROs, along with the PGI-C showing improvement with benralizumab versus placebo, provide additional robust evidence of benralizumab treatment efficacy and the importance of such outcomes in achieving symptom control for effective asthma management.

Benralizumab rapidly depletes blood eosinophils,[8–9,53] so onset of clinical effects is of interest in the assessment of biologic medication treatment response for patients with severe asthma. Improvements in ambulatory and clinic visit lung function were observed as early as weeks 1 and 2, respectively, and asthma control based on ACQ-6 began to differentiate from placebo at week 2, which is earlier than established in SIROCCO and CALIMA,[11,12] and similar to the early observed changes in PROs reported in SOLANA despite an observed lesser effect on FEV_1.[53] The early improvements seen were sustained up to week 24, with SGRQ, FEV_1, ACQ-6, CGI-C, PGI-C, and PSIA reaching near maximal benefit by week 12 in the current study, supporting that 3 to 4 months is an adequate trial to assess treatment response for biological medications for patients with severe asthma as recommended by Global Initiative for Asthma for severe asthma.[54,56]

Beyond elevated BEC, patients with severe eosinophilic asthma also present with specific clinical characteristics, including more frequent exacerbations, a positive response to oral corticosteroid, chronic rhinosinusitis with nasal polyposis, and adult-onset asthma.[57] Previous post-hoc analyses of the benralizumab CALIMA and SIROCCO studies[14,17] indicated that maintenance oral corticosteroid use, history of nasal polyposis, prebronchodilator FVC less than 65% of predicted, three or more exacerbations in the previous year, and age at asthma diagnosis of 18 years or older were all associated with enhanced responsiveness to benralizumab, particularly opposite an exacerbation reduction endpoint. Analysis of the overall population of patients with severe eosinophilic asthma (BEC ≥150 cells per µL) in the current study reinforces the observation that, in addition to BEC, the presence of adult-onset asthma, a medical history of nasal polyposis, or oral corticosteroid dependence generally predicts a numerically greater treatment effect than the population average for asthma exacerbation rate reduction and disease-specific HRQOL

improvement for patients with uncontrolled, severe eosinophilic asthma, as demonstrated by key endpoints. Adult-onset asthma was associated with enhanced response to AER, SGRQ, ACQ-6, and FEV_1, followed by eosinophils of at least 300 cells per µL, which was associated with enhanced response to AER, SGRQ, and ACQ-6 and a numerically greater treatment effect in FEV_1. Additionally, in patients with at least three exacerbations in the previous year, a greater treatment response was observed for ACQ-6 and FEV_1. For patients with a medical history of nasal polyposis, an enhanced response to benralizumab was observed for AER. In patients with oral corticosteroid use, FEV_1 response was enhanced and, although not statistically significantly different, point estimates suggest a greater treatment effect for AER, SGRQ, and ACQ-6; however, the low number of patients with oral corticosteroid use prevents a definitive conclusion. Likewise, a medical history of nasal polyposis and three or more exacerbations showed a numerically greater treatment effect in terms of SGRQ response, without statistical significance.

Chronic rhinosinusitis with nasal polyposis is a complex inflammatory disorder, which is often resistant to medical and surgical management, leading to the study of biologics as treatment for these patients, with promising results.[24,37–42,58,59] For patients with nasal polyposis refractory to standard-of-care treatment, inhibition of both IL-4 and IL-13 signalling (dupilumab), and IgE (omalizumab) have produced improvement in nasal polyposis scores and symptoms of nasal blockage in phase 3 studies, with similar treatment effects reported for the eosinophil-lowering anti-IL-5 monoclonal antibody (mepolizumab), as shown by the severity of nasal polyposis symptoms decreasing on the numerical analogue scale.[39–42] Benralizumab has also been reported to induce shrinkage of nasal polyps and improve related symptoms in asthma patients with nasal polyposis, but, at present, these results are limited to case series.[43–45] The findings from the current study indicate that benralizumab improves disease-specific HRQOL for patients with severe eosinophilic asthma and nasal polyposis of any severity, as shown by the early and sustained improvement in SNOT-22. The treatment effect observed was clinically meaningful.[49] A limitation of this result is that the diagnosis of nasal polyposis was based on medical history alone; nasal polyposis was not confirmed before treatment with CT or rhinoscopy and the type of inflammatory infiltrate, such as eosinophilic versus non-eosinophilic, was not determined. A phase 3 confirmatory study of benralizumab treatment for patients with nasal polyposis (with or without asthma) is ongoing (NCT03401229), and will address such limitations and add to the exploratory HRQOL findings in the current study.

Our safety results are consistent with those observed in 1-year, phase 3, placebo-controlled studies of benralizumab,[11–13,53] and the 1-year, open-label, BORA phase 3 extension study.[18] Similar to the findings in these previous studies, in the current study benralizumab was generally well tolerated by patients with severe eosinophilic asthma, with six (1%) of 427 patients discontinuing treatment because of adverse events.

Beyond the aforementioned limitation around the historical nature of the nasal polyposis diagnosis subpopulation, the study population was largely shifted towards patients with high eosinophil counts; therefore, drawing conclusions for patients with eosinophil counts less than 300 cells per µL is difficult. Importantly, one of the PROs used to assess improvement in predominant symptoms, the PSIA, was developed for use in the ANDHI study; therefore, the measurement properties have not been established. In addition, patients randomly assigned to placebo were not expected to obtain benefit in terms of asthma control but, in the current study, placebo patients might have benefited from the close medical monitoring and would have received alternate therapies whenever clinically indicated.

The ANDHI trial confirms and extends the efficacy and safety profile of benralizumab for patients with severe eosinophilic asthma, including early improvements in PROs, lung function, asthma control, and disease-specific HRQOL based on SGRQ after the first dose, as well as preliminary evidence of effect on chronic rhinosinusitis symptoms for patients with asthma with nasal polyposis. The early and sustained change in patient-reported overall asthma status (PGI-C), and in the severity of predominant asthma symptoms, are supportive of the effect on HRQOL. The magnitude of treatment effects was consistently larger for patients with baseline BEC of 300 or more cells per µL, oral corticosteroid-dependent asthma, nasal polyposis, and adult-onset asthma, reinforcing the importance of the clinical features when defining the eosinophilic phenotype.

Contributors

All authors and the funder of this study participated in study design. All authors 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. AB and FM accessed and verified the data.

Declaration of interests

TWH reports grants from the National Institute for Health Research UK and AstraZeneca; and personal fees and non-financial support from AstraZeneca, GlaxoSmithKline (GSK), Vectura, Boehringer Ingelheim, Chiesi, and Synairgen. PC has served as an advisory board member, consultant, or lecturer, and has previously received honoraria or grants from ALK, Boehringer Ingelheim, Almirall, Centocor, GSK, Merck Sharp & Dohme, AstraZeneca, Novartis, Teva, Chiesi, Schering Plough, and Amu. FM has received research grants from AstraZeneca, Novartis, and Sanofi; and lecture fees and advisory board fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Mundipharma, Novartis, and Sanofi. GWC has previously received grant or research support from Boehringer Ingelheim, ALK, and Stallergenes; and honoraria or consultation fees from Menarini, GSK, Sanofi, Teva, Hal, AstraZeneca, and Novartis. RL has received unrestricted research grants from GSK, AstraZeneca, Novartis, and Chiesi; and lecture or advisory board fees from GSK, AstraZeneca, Novartis, and Sanofi. BGC has received honoraria for speaking at sponsored meetings from AstraZeneca, Teva, Mundipharma, Boehringer Ingelheim, Chiesi, Esteve, GSK, Novartis, and Rovi; he has received

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Data sharing

Data underlying the findings described in this Article can be requested in accordance with AstraZeneca's data sharing policy, described online.

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