Journal of Asthma and Allergy Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Early and Sustained Response to Benralizumab in Severe, Eosinophilic Asthma: A Real-World Observational Study

Daiana Stolz[1,2], Claudio Schuoler[3], Florian Charbonnier[4], Pierre-Olivier Bridevaux[4,5], Peter Jandus[6], Jörg D Leuppi[7], Nikolay Pavlov[8], Andreas Piecyk[9], Thomas Rothe[10]

[1]Pulmonology Clinic, University Hospital Basel, Basel, Switzerland; [2]Clinic of Respiratory Medicine and Faculty of Medicine, University of Freiburg, Freiburg, Germany; [3]Medical Department, AstraZeneca AG, Baar, Switzerland; [4]Pulmonology Division, University Hospital Geneva, Geneva, Switzerland; [5]Service de Pneumologie, Centre Hospitalier du Valais Romand, Sion, Switzerland; [6]Immunology and Allergology Division, University Hospital Geneva, Geneva, Switzerland; [7]University Centre of Internal Medicine, Cantonal Hospital Baselland, Liestal, Switzerland; [8]Department for Pulmonary Medicine, Allergology and Clinical Immunology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [9]Pulmonary Center Hirslanden, Zurich, Switzerland; [10]Pulmonology Clinic, Cantonal Hospital Graubünden, Chur, Switzerland

Correspondence: Claudio Schuoler, AstraZeneca AG, Medical Department, Baar, Switzerland, Email claudio.schuoler@astrazeneca.com

Purpose: Although studies have evaluated benralizumab, a monoclonal IL-5 receptor α antibody in severe eosinophilic asthma (SEA), in real-world settings, additional evidence is needed to further characterize its effectiveness in specific patient populations. Our study aimed to evaluate asthma control over 56 weeks in patients treated with benralizumab in Swiss real-world settings.

Patients and Methods: Conducted across 13 centres, this prospective, observational, non-interventional study involved 73 adults with physician confirmed SEA. Benralizumab 30 mg was administered according to the Swiss label at baseline and up to week 56. Primary outcome was the change in Asthma Control Questionnaire (ACQ-5) scores at week 8 compared to baseline. Exacerbations, use of oral corticosteroids (OCS), and lung function were assessed descriptively.

Results: At baseline, the mean ACQ-5 score was 2.76 (SD 1.26), with 82.2% of patients showing not well-controlled asthma (ACQ-5 > 1.5). At week 8, the mean change in ACQ-5 compared to baseline was −0.95 (95% CI: −1.25, −0.66; $p < 0.001$). More than half of patients (59.1%) reached a clinically relevant improvement (MCID ≥ 0.5) at week 8, with 40.9% of patients doing so at week 1 and 87.2% at week 56. The annualized exacerbation rate (AER) of 3.65 (95% CI: 3.18, 4.18) at baseline was reduced to 0.68 (95% CI: 0.39, 1.19) at week 56. The relative reduction in AER from baseline to week 56 was 81.3%. Maintenance usage of OCS at baseline (median 25.0 mg/day) decreased over the study leading to a median change of 17.50 mg/day (95% CI: 10.0; 40.0) from baseline compared to week 56. The mean pre-bronchodilator FEV1 change from baseline to week 56 was 0.23 L (95% CI: 0.08; 0.38, $p = 0.003$).

Conclusion: Benralizumab demonstrated significant, rapid improvements in asthma control within one week of treatment initiation, with sustained benefits over 56 weeks.

Keywords: severe eosinophilic asthma, asthma symptom control, patient reported outcomes, exacerbation reduction

Introduction

Asthma is a common chronic inflammatory airway disease affecting around 300 million people worldwide.[1] Severe asthma is found in 3% to 10% of patients and is associated with impaired quality of life, frequent exacerbations and hospitalizations, and reduced lung function.[2,3] Severe uncontrolled asthma is a potentially fatal form of the disease.[4,5] Eosinophilic inflammation is a characteristic found in 50% to 80% of patients with severe asthma.[6,7] Patients with severe eosinophilic asthma (SEA) frequently experience dyspnoea, wheezing, nighttime awakenings, limited activities of daily living and exacerbations.[8–10] Especially, frequent exacerbations are most burdensome as patients regularly suffer from several of those attacks per year often even leading to hospitalizations, and potentially airway remodelling.

Received: 18 October 2024
Accepted: 13 December 2024
Published: 24 December 2024

Asthma therapy aims to alleviate symptoms, allows normal physical activity, improves quality of life, normalizes lung function and prevents exacerbations, balancing disease control with costs and minimizing side effects of pharmacotherapy. However, it is important to note that asthma may appear to be difficult-to-treat because of modifiable factors such as incorrect inhaler technique, poor adherence, smoking or comorbidities, or incorrect diagnosis.[2]

For patients with uncontrolled SEA in spite of high dose inhaled corticosteroids (ICS) in combination with long-acting β2-agonists (LABA) and/or other controllers, targeted biologic treatment in addition to inhaled medication is recommended.[2] The choice of biologic therapy is mainly based on the identification of asthma phenotypes using biomarkers such as blood eosinophils, fractional exhaled nitric oxide (FeNO) and immunoglobulin E (IgE). In case of blood eosinophilia, inhibition of the interleukin-5 (IL-5) axis with specific monoclonal antibodies, such as benralizumab, is an effective alternative to continuous OCS therapy, which has serious long-term side effects.[11–13]

The monoclonal antibody benralizumab is directed against the interleukin-5 receptor α subunit (IL-5Rα) which is primarily expressed on human eosinophils, their precursor cells and basophils. It depletes eosinophils by antibody-dependent cell-mediated cytotoxicity.[14,15] In patients with SEA, benralizumab was approved as add-on maintenance therapy because it effectively reduced exacerbations, improved lung function and had OCS-sparing effects.[11,12,16,17]

While several randomized controlled trials (RCT) and real-world studies have demonstrated the therapeutic effects of benralizumab in patients with SEA, evidence on its early response after treatment initiation (ie, within 1–2 weeks) remains limited.[18] The present study (BEEPS, NCT03907137) was conducted to evaluate asthma control in patients with SEA receiving benralizumab up to 56 weeks according to the Swiss label in a real-world setting.[19,20] BEEPS is the first prospective study in Switzerland, and it is also part of an international study network, XALOC-2, comprising similar real-world studies conducted in Belgium, Canada and Germany.[21] Here, we report on the findings from BEEPS focusing on patient-reported outcomes (PROs) and other asthma-related parameters.

Material and Methods

Study Design and Procedures

This single-arm, non-interventional, observational, prospective study was conducted in 13 centres across Switzerland between June 2019 and January 2023 (Supplementary. Table 1 for the list of centres). The decision to initiate benralizumab treatment by either a pulmonologist or allergologist was made independently of inclusion and patient informed consent.

Patients (≥18 years) with a physician confirmed diagnosis of SEA according to the American Thoracic Society and the European Respiratory Society (ATS/ERS) guidelines[22] who qualified for treatment with benralizumab according to the Swiss label (asthma requiring high-dose ICS/LABA as maintenance treatment, ≥2 exacerbations in the last 12 months and a documented blood eosinophil count of ≥300 cells/μL) were enrolled. Patients were required to comprehend written instructions including questionnaires required by the protocol. Main exclusion criteria were documented lung diseases other than asthma (eg, COPD), or pregnancy and lactation.

Benralizumab 30 mg was administered subcutaneously at weeks 0 (baseline), 4, 8, and 16. A follow-up visit was conducted after 56 weeks to assess study outcomes. No visits were recorded between week 16 and week 56, though patients continued to receive benralizumab every 8 weeks. The use of other biologics was not allowed during the study.

Outcome measures and efficacy assessments

In this real-life non-interventional study, assessments were performed during routine scheduled clinical visits. Data were collected from medical records, examination results, interviews, and PRO measures consisting of several questionnaires. Those included the 5-item Asthma Control Questionnaire (ACQ-5), the Patient Global Impression of Change (PGI-C), and the Patient Global Impression of Severity (PGI-S) all of which were completed at every visit on paper. To evaluate early response shortly after the first treatment dose at baseline, additional study visits were scheduled at week 1 and 2, which could also be done remotely via phone calls. ACQ-5, PGI-C and PGI-S were available in German, French and Italian according to the preferred language of the patients.

ACQ-5 is a shortened, validated PRO questionnaire where patients recall their asthma experiences during the previous week and respond to five questions (1) Night-time waking by symptoms, (2) Symptoms on waking, (3) Limitation of daily activities, (4) Shortness of breath, and (5) Wheezing, on a 7-point scale (0=no impairment; 6=maximum impairment). All questions are weighted equally, with mean scores of ≤0.75 indicating well-controlled asthma, scores between 0.75 and ≤1.5 indicating partially controlled asthma and scores >1.5 indicating not well-controlled asthma. A score improvement of ≥0.5 is considered the minimally clinically important difference (MCID).[23,24]

PGI-C instruments were applied for an overall evaluation of response to treatment since the first dose of benralizumab at the start of the study conducted separately by the patients on a 7-point scale (1=Much better; 2=Moderately better; 3=A little better; 4=About the same; 5=A little worse; 6=Moderately worse; and 7=Much worse). Patients were asked to rate the degree of change in their overall asthma status compared to the first benralizumab dose. PGI-S instruments were used for an overall evaluation of disease severity asking patients in a single question to rate the degree of severity today on a 6-point scale (1=No symptoms; 2=Very mild; 3=Mild; 4=Moderate; 5=Severe; 6=Very severe).

Exacerbations were defined as worsening of asthma leading to (1) use of systemic corticosteroids, or temporary increase in stable OCS dosage for ≥3 days, or a single injection of corticosteroids; (2) emergency department or visit to an urgent care centre (<24h) resulting in administration of systemic corticosteroids; or (3) hospitalization (≥24h).

The primary outcome measure was the change in the overall score in ACQ-5 at week 8 compared to baseline. Secondary outcome measures included the differences in ACQ-5 after 1, 2, 4, 16 and 56 weeks of benralizumab treatment versus baseline, as well as changes from baseline in ACQ-5 score evaluated by MCID and by changes in asthma control status (well controlled, partially controlled, not well controlled). Additional secondary outcomes included patients on OCS who were able to reduce their OCS dose over the course of the study, the median OCS dose reduction, as well as changes in asthma status and disease severity measured by change from baseline in PGI-C (after 1, 2, 4, 8, and 16 weeks) and in PGI-S (after 1, 2, 4, 8, 16 and 56 weeks) as well as asthma disease history including exacerbations, past treatment status and current medication at baseline. Lung function data, ie, changes in forced expiratory volume in one second (FEV1) after treatment with benralizumab (weeks 8, 16, and 56), were analysed in an exploratory manner. Additionally, patients with documented nasal polyposis were asked for improvements in taste and smell by physician assessments at all visits throughout the study.

Statistical analyses

As the study was descriptive in nature with no pre-specified hypotheses, there was no definition of sequential testing procedures necessary. All outcomes used descriptive summaries and estimates with nominal 95% confidence intervals (CI), any p-values had to be interpreted descriptively with $p < 0.05$ being significant (two-sided). The analyses were performed in the full analysis set (FAS) including all enrolled patients who received at least one dose of benralizumab, irrespective of their protocol adherence and continued participation in the study according to the Intention-to-Treat (ITT) principle. Patients who withdrew from the study were included up to the date of their study participation. The sample size calculation was based on the ability to provide sufficient precision in point estimates for the primary outcome. Applying input parameters: significance level $\alpha = 0.05$, maximum allowed precision (half-width of appropriate CI) $E = 0.3$, standard deviation (SD) of the difference $\sigma d = 1.15$, the minimum sample size was $n = 57$. Considering an anticipated drop-out or non-completion rate of up to 25%, the minimum total number of patients was determined as $n_{tot} = 76$, and thus 77 patients were recruited. Calculation of percentages of PGI-C and PGI-S were based on the number of patients in the FAS with a complete assessment without an imputation for missing values.

Ethics

This study was approved by the independent Cantonal Ethics Committee Zurich (reference number 2019–00144) according to the Swiss laws and complies with the Declaration of Helsinki. Signed and dated patient informed consent was obtained before any specific procedure for the observational study was performed according to GCP guidelines.

Results

Patient demographics and clinical characteristics at baseline

In this observational study, FAS included data from 73 patients who received at least one dose of benralizumab. Four patients out of the planned sample size (n = 77) had to be excluded due to protocol deviation (not completing week 1) (Table 1). At the start of the study, patients had a mean age of 53.8 years ranging from 19 to 83 years, with the majority being female (61.6%), Caucasian (89.0%) and overweight or obese (60.3% with a body mass index (BMI) ≥25 kg/m^2) (Table 2). About half of the patients never smoked (54.8%) compared to current (5.5%) or former (39.7%) smokers accumulating a mean pack-year history of 30.5. The earliest and latest timepoints of asthma diagnosis were at the age 0 and 73, respectively. The mean duration of asthma was 19.3 years. Almost half of the patients (47.9%, n = 35) had positive allergy tests in the past, compared to 31.5% (n = 23) with negative tests. The allergy testing status was unknown in 15 patients (20.5%). The most common comorbidity at baseline was chronic rhinosinusitis (56.2% of all patients). Other frequent comorbidities (reported by ≥10 patients) included nasal polyposis (34.2%), gastroesophageal reflux disease and metabolic diseases (20.5% each), cardiovascular diseases (19.2%), obstructive sleep apnoea (16.4%), and depression/anxiety (13.7%).

Patients´ asthma status and burden of disease at baseline

The mean ACQ-5 score at baseline was 2.76 (SD 1.26). Not well-controlled asthma (ACQ-5 > 1.5) was found in 60 out of 73 patients (82.2%), only three patients (4.1%) reported well-controlled asthma (Table 2).

The annualized asthma exacerbation rate (AER) was 3.65 during 12 months prior to the study (Table 2). 15 patients reported ≥5 exacerbations (20.5%), 32 patients had 3–4 exacerbations (43.8%), 24 patients had 2 exacerbations (32.9%) and 1 patient each (1.4%) had 0 or 1 exacerbation, respectively.

The mean blood eosinophil count was 685 cells/µL. The mean total IgE level was 346.1 IU/mL, and the mean FeNO was 53.1 ppb (Table 2).

Prior to enrolment, all patients (n = 73) received asthma maintenance therapy for the last 12 months. At baseline, ICS/LABA combination was the most frequent maintenance treatment used by 80.8% of patients, with budesonide/formoterol (69.5%) being the most frequent type. Long-acting muscarinic antagonists (LAMA) (52.1%), short-acting β2-agonists (SABA) (46.6%), ICS (32.9%), as well as OCS and leukotriene receptor antagonists (LTRA) (each 27.4%) were also commonly used treatments (Table 3). Biologics had been used by 27.4% of patients (n = 20) in the past 12 months prior to the study, most often mepolizumab (n = 13), followed by omalizumab (n = 6) and dupilumab (n = 2).

Table 1 Recruitment Summary

Category	Number of patients
Patients enrolled	77
Patients excluded (not completing week 1)	4
Patients withdrawn (total number)	23
Due to Adverse event	1
Due to Consent withdrawal	5
Due to Insufficient efficacy	11
Due to Lost to follow-up	6
Patients administered ≥1 dose of benralizumab	73
Patients who completed 16 weeks of observations	66
Patients who completed 56 weeks of observations	50

Table 2 Baseline Demographics and Clinical Characteristics of Patients

Parameter/Clinical characteristics	Value
Number of patients — n	73
Female sex — n (%)	45 (61.6%)
Age [years] — mean (min; max)	53.8 (19; 83)
Weight [kg] — mean (SD)	74.8 (17.1)
Normal (BMI <25 kg/m^2)	29 (39.7%)
Overweight (BMI ≥25 kg/m^2 and <30 kg/m^2)	30 (41.1%)
Obese (BMI ≥30 kg/m^2)	14 (19.2%)
ACQ-5 score — mean (SD)	2.76 (1.26)
Proportion of patients with — n (%) Well-controlled asthma (ACQ-5 ≤ 0.75) Partially controlled asthma (ACQ-5 > 0.75 and ≤ 1.5) Not well-controlled asthma (ACQ-5 > 1.5)	3 (4.1%) 10 (13.7%) 60 (82.2%)
FEV1 [L] – mean (SD)	1.99 (0.78)
Biomarkers (last available)	
Blood eosinophil count [cells/µL] — mean (SD) Blood eosinophil count [cells/µL] —median (min; max)	685 (580.2) 600 (280; 4800)
Eosinophilic cationic protein [µg/L] — mean (SD) Eosinophilic cationic protein [µg/L] — median (min; max)	50.8 (32.7) 37.9 (15.2; 104.0)
Total IgE [IU/mL] — mean (SD) Total IgE [IU/mL] — median (min; max)	346.1 (745.2) 85.0 (2; 4475)
FeNO [ppb] — mean (SD) FeNO [ppb] — median (min; max)	53.1 (45.0) 37.0 (6; 202)
Annualized exacerbation rate (95% CI)	3.65 (3.18; 4.18)
History of positive allergy test Positive Negative Unknown	35 (47.9%) 23 (31.5%) 15 (20.5%)

Abbreviations: ACQ-5, asthma control questionnaire; BMI, body mass index; CI, confidence interval; FeNO, fractional exhaled nitric oxide, IgE, immunoglobulin E; SD, standard deviation.

Table 3 Asthma Therapy Used at Baseline at Enrolment into BEEPS

Medication group	Number of patients (%)	
ICS/LABA	59	80.8%
LAMA	38	52.1%
SABA	34	46.6%
ICS	24	32.9%
LTRA	20	27.4%

(*Continued*)

Table 3 (Continued).

Medication group	Number of patients (%)	
mOCS	20	27.4%
SABA/SAMA	8	11.0%
LABA/LAMA	6	8.2%
LABA	4	5.5%
ICS/LAMA/LABA	1	1.4%
SAMA	1	1.4%

Abbreviations: LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; ICS, inhaled corticosteroid; mOCS, maintenance oral corticosteroid; SABA, short-acting β2-agonist; SAMA, short-acting muscarinic antagonist.

Asthma symptom control and additional effectiveness outcomes during the study

After 8 weeks of treatment with benralizumab, the mean ACQ-5 score decreased from 2.76 at baseline to 1.71 (Figure 1). Using paired observations (n = 66 patients), the mean ACQ-5 score decreased from 2.66 to 1.71. Hence, the mean change in ACQ-5 compared to baseline was −0.95 (95% CI: −1.25, −0.66; p < 0.001) (Table 4). After 56 weeks of treatment, the

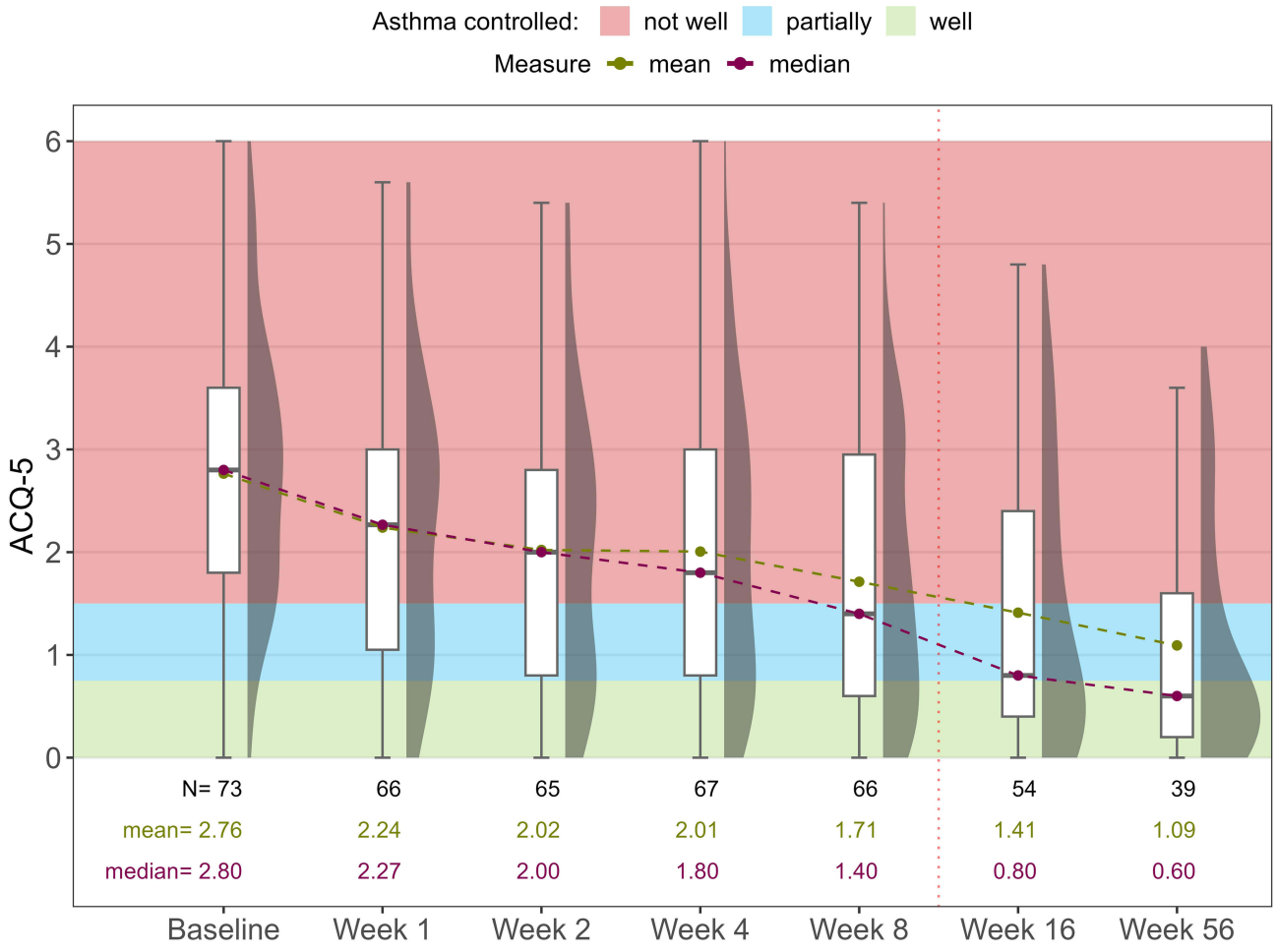

Figure 1 ACQ-5 scores over time. Score distribution over 56 weeks (mean, median) presented for all observations together with achieved asthma control levels.

Table 4 Change in ACQ-5 Scores Compared to Baseline Mean Changes from Baseline in ACQ-5 Scores and Proportion of Patients Achieving MCID (Presented for Paired Observations)

Measure	Week 1	Week 2	Week 4	Week 8	Week 16	Week 56
Number of paired observations	66	65	67	66	54	39
Mean change	−0.39	−0.61	−0.68	−0.95	−1.22	−1.53
95% CI for mean	−0.63; −0.16	−0.89; −0.34	−0.99; −0.38	−1.25; −0.66	−1.58; −0.86	−1.91; −1.15
p-value	p=0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
Minimally clinically important difference (MCID)						
N (%)	27 (40.9%)	34 (52.3%)	37 (55.2%)	39 (59.1%)	37 (68.5%)	34 (87.2%)
*95% CI (%)	29.0; 53.7	39.6; 64.9	42.6; 67.4	46.3; 71.0	54.4; 80.5	72.6; 95.7

***Notes**: Clopper-Pearson (exact) 95% confidence intervals for proportion.
Abbreviations: ACQ-5, asthma control questionnaire; CI, confidence interval; MCID, minimally clinically important difference.

mean change in ACQ-5 was −1.53 (95% CI: −1.91, −1.15; $p < 0.001$). Compared to baseline, more than half of patients (59.1%) reached a clinically relevant improvement (MCID ≥ 0.5) at week 8 (Table 4). 40.9% of patients reached this MCID already at week 1 and 87.2% at week 56, respectively. The mean changes in ACQ-5 scores were statistically significant ($p \leq 0.001$) and clinically relevant from week 2 onwards (Table 4).

During the 56-weeks, both mean and median values of ACQ-5 scores decreased consistently (Figure 1). At week 8, more than half of the patients achieved at least a partially controlled asthma with a median ACQ-5 score of 1.40 (Figure 1). The percentage of patients who achieved a clinically relevant improvement (MCID) in ACQ-5 consistently increased over the whole study period (Table 4).

The high proportion of patients with uncontrolled asthma (82.2%, n = 60) at baseline decreased to 48.5% (n = 32) after 8 weeks and to 28.2% (n = 11) after 56 weeks of treatment with benralizumab. Vice versa, the low proportion of patients with well-controlled asthma (4.1%, n = 3) at baseline increased to 27.3% (n = 18) after 8 weeks and to 56.4% (n = 22) at the end of the study (Figure 2). Most patients who achieved well-controlled asthma maintained this level of control over the course of the study (Supplementary Figure 1).

Assessing PGI-S, the proportion of patients reporting severe (27.8%) or very severe (9.7%) symptoms at baseline was reduced to 7.7% and 0% at week 56, respectively. Correspondingly, more patients reported no (20.5%) or very mild (33.3%) symptoms at week 56 compared to baseline (6.9% and 5.6%, respectively) (Table 5 and Supplementary Figure 2). Compared to baseline, the proportion of patients perceiving no change in asthma symptoms ("about the same") decreased from 41.5% at week 1 to 23.6% at week 16 as assessed by PGI-C. The proportion of patients rating their symptoms as "much better" increased from 12.3% at week 1 to 47.3% at week 16 (Table 6 and Supplementary Figure 3).

Throughout the study, 74% of patients (n = 54) did not experience any exacerbation, while 13.7% (n = 10) reported one exacerbation, and the remaining 9 patients (12.3%) experienced ≥2 exacerbations. The mean AER decreased from 3.65 (95% CI: 3.18, 4.18) at baseline to 0.68 (95% CI: 0.39, 1.19) at week 56 with benralizumab representing a relative reduction in AER of 81.3%.

The mean maintenance OCS (mOCS) dosage at baseline was 26.6 mg/day (SD 15.0), with a median of 25.0 mg/day (min: 5; max: 50). The mOCS decreased after 56 weeks of treatment with benralizumab with a mean change from baseline of 21.69 mg/day (95% CI: 12.80; 30.58), corresponding to −83.9% average relative dose reduction. The median change from baseline in mOCS at week 56 was 17.50 mg/day (95% CI: 10.0; 40.0). After 56 weeks, 14 patients reduced their mOCS by ≥50%, and 12 of them were able to discontinue OCS completely.

The change in pre-bronchodilator FEV1 from baseline to week 56 was statistically significant with a mean increase of 0.23 L (95% CI: 0.08; 0.38, p = 0.003). Raw mean FEV1 values for unpaired observations of 1.99 L (SD 0.78 L) at baseline increased over the course of the study to 2.24 L (SD 0.89 L) at week 56.

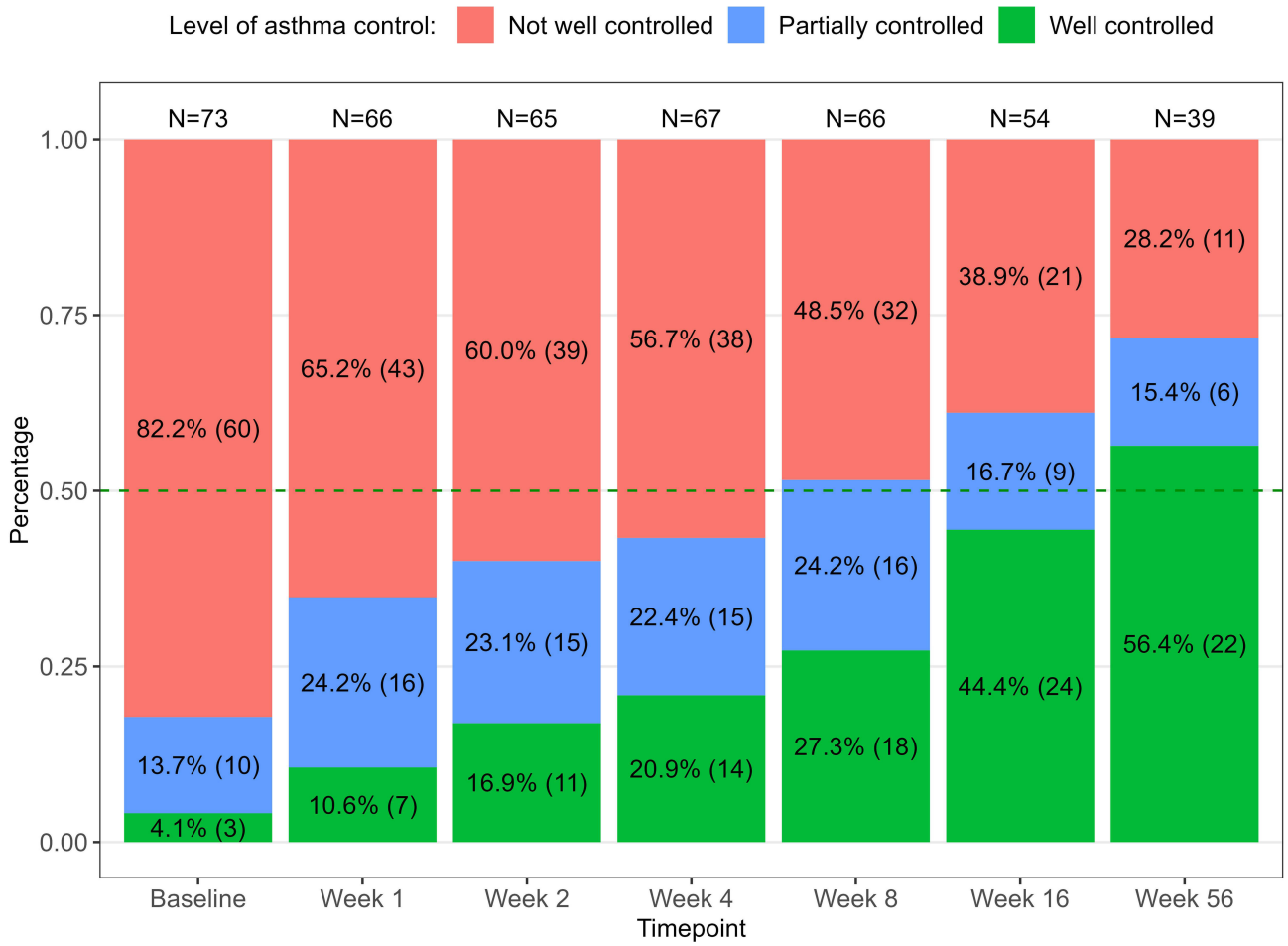

Figure 2 Proportion of patients split per asthma control levels over time. Development of ACQ-5 levels (well controlled, partially controlled, not well controlled) in patients over the course of the study.

In patients with nasal polyposis at baseline (n = 25), the status of their taste and smell improved in 38.9% of patients (7 out of 18 available at week 56) according to physicians´ assessments at week 56 of the study.

Non-serious adverse events (AEs) were reported in 49 patients. In 14 patients, AEs were related to benralizumab. The most frequent AE was headache (n = 4). All other benralizumab-related AEs occurred in <5% of patients. Overall, 13 patients reported serious AEs during the study, all of which were not related to benralizumab Supplementary Tables 2–4. One patient was withdrawn from the study due to a serious AE (generalised tonic-clonic seizure) not related to benralizumab (Table 1).

Table 5 PGI-S Over Time Summary of Patient Responses on Asthma Severity by Scale Items

Scale item	Baseline N=72	Week 1 N=66	Week 2 N=65	Week 4 N=66	Week 8 N=66	Week 16 N=55	Week 56 N=39
1=no symptoms	5 (6.9%)	5 (7.6%)	7 (10.8%)	6 (9.1%)	9 (13.6%)	12 (21.8%)	8 (20.5%)
2=very mild	4 (5.6%)	9 (13.6%)	14 (21.5%)	14 (21.2%)	19 (28.8%)	14 (25.5%)	13 (33.3%)
3=mild	14 (19.4%)	17 (25.8%)	15 (23.1%)	17 (25.8%)	10 (15.2%)	11 (20.0%)	8 (20.5%)
4=moderate	22 (30.6%)	26 (39.4%)	20 (30.8%)	21 (31.8%)	21 (31.8%)	10 (18.2%)	7 (17.9%)
5=severe	20 (27.8%)	6 (9.1%)	8 (12.3%)	8 (12.1%)	6 (9.1%)	8 (14.5%)	3 (7.7%)
6=very severe	7 (9.7%)	3 (4.5%)	1 (1.5%)	0 (0%)	1 (1.5%)	0 (0%)	0 (0%)

Abbreviation: PGI-S, patient global impression of severity.

Table 6 PGI-C Over Time Summary of Patient Responses on Change in Asthma Severity Compared to Baseline by Scale Items

Scale item	Week 1 N=65	Week 2 N=65	Week 4 N=67	Week 8 N=66	Week 16 N=55
1=much better	8 (12.3%)	11 (16.9%)	20 (29.9%)	20 (30.3%)	26 (47.3%)
2=moderately better	7 (10.8%)	11 (16.9%)	8 (11.9%)	14 (21.2%)	6 (10.9%)
3=a little better	20 (30.8%)	17 (26.2%)	17 (25.4%)	15 (22.7%)	8 (14.5%)
4=about the same	27 (41.5%)	22 (33.8%)	16 (23.9%)	14 (21.2%)	13 (23.6%)
5=a little worse	1 (1.5%)	3 (4.6%)	4 (6.0%)	3 (4.5%)	1 (1.8%)
6=moderately worse	2 (3.1%)	1 (1.5%)	2 (3.0%)	0 (0%)	1 (1.8%)
7=much worse	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Abbreviation: PGI-C, patient global impression of change.

Discussion

The described real-world data on the effectiveness of benralizumab in patients with SEA in Switzerland demonstrate a significant improvement in asthma symptom control over one year. The ACQ-5 score decreased from 2.66 at baseline to 1.71 after 8 weeks of benralizumab treatment for paired observations (−0.95 mean change versus baseline). A statistically significant reduction in ACQ-5 score was observed already one week after initiation of treatment with a mean change of −0.39 versus baseline (p = 0.001), supporting existing evidence of early onset of effectiveness of benralizumab from Kavanagh et al who found significant improvements in PRO measures after four weeks.[25] At this early timepoint at week 1 of our study, the improvement in ACQ-5 score was clinically relevant, exceeding the MCID of 0.5 in 40.9% of patients. In contrast, a real-world effectiveness study with mepolizumab, an anti-IL5 monoclonal antibody, reported a clinically significant improvement in ACQ-5 score only at month 3.[26] This underscores the rapid effectiveness of benralizumab compared to other treatments and highlights its potential as a valuable option for patients requiring fast asthma control.

In addition, the achieved symptom control with benralizumab had a long-lasting impact on patients over the whole study period. Asthma control was maintained continuously throughout the study with 87.2% of patients experiencing a clinically relevant improvement of their asthma symptoms after one year. The robustness of our data was reflected in different data analyses showing consistent improvement in asthma symptoms. Missing observations such as a non-responder analysis assigning patients with missing data to the "non-MCID"-group or the last-observation-carried-forward (LOCF) analysis increased the credibility of our results. Similar to improving asthma symptoms seen with ACQ-5, patient reported outcomes covered in PGI-C and PGI-S also reflected an increasing level of asthma control over the course of the study.

The reduction in asthma symptoms and improvements in asthma control observed with benralizumab in the current real-world study align with results from RCT. In two pivotal Phase 3 trials, patients with SEA showed improved asthma symptoms in addition to a reduced AER and an increased FEV1 compared to placebo when treated with benralizumab over 48–56 weeks.[11,16] These two clinical trials utilized the ACQ-6, a six-item questionnaire, which assessed rescue medication use in addition to daytime and night-time symptoms as in ACQ-5 used in our study.[23] The least square (LS) mean change in ACQ-6 compared to baseline was −1.16 or −0.19 when compared to placebo (95% CI: −0.30; −0.07; p = 0.0015) at the end of the study, which is in accordance to the data presented here.[27]

In our study, the majority of patients (82.2%) had not well-controlled asthma symptoms and frequent exacerbations. Both are strongly associated with an increased risk of future exacerbations.[2] Thus, it should be highlighted that alongside the decrease in asthma symptoms, treatment with benralizumab was also associated with a significant reduction in exacerbations. Prior to enrolment, almost all patients (n = 71) had reported ≥2 exacerbations compared to only 9 patients during the entire study. Thus, the high mean AER of 3.65 in the year prior to the study was reduced by >80% to 0.68

after 56 weeks, which confirms findings from RCT showing a significant reduction of exacerbations of up to 51% compared to placebo.[11,16]

Many patients with severe asthma still rely on OCS for disease control despite of recommendations to use OCS only as "a last resort" due to their serious long-term side effects.[2] In our study, 91.8% of patients had used OCS prior to enrolment, which included both short-term OCS treatment courses for acute exacerbations as well as for maintenance treatment. After 56 weeks of benralizumab treatment, patients treated with mOCS were able to reduce their mean OCS dosage by about 80%. Simultaneously, patients´ level of asthma control could not only be maintained but it significantly improved. Furthermore, mOCS reduction did not adversely affect the FEV1, which exhibited a slight increase during our study. These findings provide further evidence for the OCS sparing effect of benralizumab in patients with severe asthma, as reported before.[12,28]

Exacerbations and OCS use were identified as negative predictors for asthma control in the ongoing Swiss Severe Asthma Registry (SSAR) whereas the use of biologics was associated with an improved asthma control.[29] In addition, a higher BMI ≥25 kg/m^2 was also found to be a negative predictor for asthma control, present in 62.6% of patients of the SSAR. Similarly, in the current study, the majority of patients (60.3%) showed an elevated BMI ≥25 kg/m^2 at enrolment, however their levels of asthma control significantly improved over the course of the study.

In RCT with benralizumab, greater baseline blood eosinophil counts were associated with greater improvements in asthma symptoms.[11] Therefore, it will be of interest to explore a possible relationship between blood eosinophil count and asthma symptom control in the planned subgroup analyses of BEEPS. As our study is also part of the real-world study network XALOC-2 in patients with SEA in Canada, Belgium, and Germany, in addition to Switzerland, the anticipated new data will add on to the understanding of the efficacy of benralizumab.[21] Preliminary data from an interim analysis of 413 patients showed a LS mean reduction in ACQ-6 over the first 8 weeks of benralizumab treatment with a decrease of –0.7 (95% CI: –0.8; –0.6) at week 1 and –1.2 (95% CI: –1.3; –1.1) at week 8. An improvement of ≥0.5 MCID was observed in 58% of patients at week 1, fitting well with the presented data from BEEPS.

Furthermore, real-world studies, such as the one by Nolasco et al, have demonstrated the effectiveness of benralizumab in patients with SEA, including those with chronic rhinosinusitis with nasal polyps, reporting significantly improved 22-item Sino-Nasal Outcome Test (SNOT-22).[30] In the present study, 39% of patients reported an improvement of their taste and smell related to their nasal polyposis.

Our study has some limitations. First, BEEPS recruited a relatively small number of patients and was conducted during the COVID-19 pandemic, which affected inclusion of patients and the usual standard of care. This might have influenced the study results, eg, less exacerbations due to social distancing and hygiene measures. The pandemic also likely contributed to patients lost to follow-up (n = 6) or withdrawing their informed consent (n = 5). Second, 11 out of 13 participating study centres were hospitals, which might imply a bias as more severe asthma cases were included compared to private practices. An additional bias might be that more than one-third of patients were included by one study centre. Third, while already running, the study duration was amended and prolonged to 56 weeks to allow a long-term follow-up. This might have contributed to the lower number of participants (n = 50) who were able to complete the 56 weeks follow-up. Finally, due to the real-world character of our study, there was no comparator for unblinded benralizumab treatment and the general performance criteria were not restricted as in RCT. On the other hand, real-world studies provide a more realistic picture of treatment effects across more heterogeneous patient populations.

The majority of patients suffered from severe asthma and impaired quality of life prior to enrolment in this study. Most patients with a long history of asthma (mean duration of 19.3 years) presented with not well-controlled asthma symptoms (82.2%) in addition to frequent exacerbations and a need of OCS at baseline. Despite this high burden of disease, treatment with benralizumab provided a fast and long-lasting improvement in asthma control, reductions of exacerbations, and decreased OCS use, consistent with reported outcomes for clinical remission, which can be as high as 42% in a real-world setting.[31,32]

Conclusion

Targeting eosinophilic inflammation in SEA with benralizumab was associated with a significant and early onset improvement of asthma control detectable as early as one week after treatment initiation, along with a sustained treatment response over 56 weeks of treatment.

Data Sharing Statement

No data from this study, aside from what is published here, will be made available.

Acknowledgments

We thank Christine Schmid-Wirlitsch from "advice4med" for her professional support by providing writing assistance and language editing, and proofreading.

Funding

AstraZeneca supported this study financially.

Disclosure

Some results of this paper were presented at the ERS International Congress 2023, Milan, Italy, 09–13 September, and at the SSP/SSTS Joint Annual Meeting 2024, Baden, Switzerland, 29–30 May, as a poster presentation with interim findings. The poster's abstracts were published in 'Poster Abstracts' in European Respiratory Journal (2023) 62 (suppl 67) PA1903 (DOI: 10.1183/13993003.congress-2023.PA1903) and in Respiration (2024) 103 (7): 417–460 P24 (DOI: 10.1159/000538686).

DS has received payments or honoraria for lectures, presentations, advisory boards, speakers' bureaus, manuscript writing or educational events from AstraZeneca, Berlin-Chemie/Menarini, Boehringer Ingelheim, Chiesi, CSL Behring, Curetis, GSK, Merck, MSD, Novartis, Roche, Sanofi and Vifor.

CS is an employee of AstraZeneca.

FC has received payments for lectures from AstraZeneca, Novartis, Sanofi and Vifor, and for advisory boards from AstraZeneca and GSK.

POB has received payments for lectures from AstraZeneca, GSK and Sanofi, for advisory boards from AstraZeneca and GSK, and research support from Ligue Pulmonaire Valaisanne and AstraZeneca.

PJ has received payments for lectures from CSL Behring and Shire, for advisory boards from AstraZeneca, CSL Behring, GSK, Sanofi and Shire, for travel grants from Biotest, CSL Behring, Octapharma and Shire, and for research grants to his institution from AstraZeneca, CSL Behring, Novartis and Shire.

JDL has received unrestricted grants from AstraZeneca, GSK, OM Pharma and Sanofi.

NP has received payments for lectures from AstraZeneca, CSL Behring, GSK, HTHC, Novartis, Olympus, OM Pharma, Philips Respironics and Sanofi, for advisory boards from AstraZeneca, GSK, Novartis, OM Pharma and Sanofi, and research support from AstraZeneca.

AP reports no conflicts of interest in this work.

TR has received payments for lectures from AstraZeneca, GSK, Novartis, OM Pharma and Sanofi, for advisory boards from AstraZeneca, GSK, Novartis, OM Pharma and Sanofi, and research support from AstraZeneca.

References

1. Global Initiative for Asthma. Asthma management and prevention. Pocket guide for health professionals. 2021. Available from www.ginasthma.org. Accessed May 1, 2024.
2. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2024. Available from www.ginasthma.org. Accessed June 1, 2024.
3. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43:343–373. doi:10.1183/09031936.00202013
4. de Groot JC, Ten Brinke A, Bel EHD, de Groot EH. Management of the patient with eosinophilic asthma: a new era begins. *ERJ Open Res*. 2015;1:00024–2015. doi:10.1183/23120541.00024-2015
5. Gaga M, Zervas E, Chanez P. Update on severe asthma: what we know and what we need. *Eur Respir Rev*. 2009;18:58–65. doi:10.1183/09059180.00001009
6. Zhang JY, Wenzel SE. Tissue and BAL based biomarkers in asthma. *Immunol Allergy Clin North Am*. 2007;27:623–632. doi:10.1016/j.iac.2007.09.003
7. Heaney LG, Perez de Llano L, Al-Ahmad M, et al. Eosinophilic and Noneosinophilic Asthma. An Expert Consensus Framework to Characterize Phenotypes in a Global Real-Life Severe Asthma Cohort. *Chest*. 2021;160(3):814–830. doi:10.1016/j.chest.2021.04.013
8. Pavord ID, Beasley R, Agusti A, et al. After asthma: redefining airways diseases. *Lancet*. 2018;391:350–400. doi:10.1016/S0140-6736(17)30879-6

9. Price D, Wilson AM, Chisholm A, et al. Predicting frequent asthma exacerbations using blood eosinophil count and other patient data routinely available in clinical practice. *J Asthma Allergy*. 2016;9:1–12. doi:10.2147/JAA.S97973
10. Talini D, Novelli F, Bacci E, et al. Sputum eosinophilia is a determinant of FEV1 decline in occupational asthma: results of an observational study. *BMJ Open*. 2015;5:e005748. doi:10.1136/bmjopen2014-005748
11. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an antiinterleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388:2128–2141. doi:10.1016/S0140-6736(16)31322-8
12. Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med*. 2017;376:2448–2458. doi:10.1056/NEJMoa1703501
13. Leuppi JD, Schmid-Grendelmeier P, Rothe T, et al. Benralizumab: der IL-5-Rezeptor als Ziel bei schwerem eosinophilem Asthma. *Praxis*. 2019;108:469–476. doi:10.1024/1661-8157/a003222
14. Busse WW, Katial R, Gossage D, et al. Safety profile, pharmacokinetics, and biologic activity of MEDI-563, an anti-IL-5 receptor alpha antibody, in a Phase I study of subjects with mild asthma. *J Allergy Clin Immunol*. 2010;125:1237–1244.e2. doi:10.1016/j.jaci.2010.04.005
15. Wilson TM, Maric I, Shukla J, et al. IL-5 receptor α levels in patients with marked eosinophilia or mastocytosis. *J Allergy Clin Immunol*. 2011;128:1086. doi:10.1016/j.jaci.2011.05.032
16. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016;388:2115–2127. doi:10.1016/S0140-6736(16)31324-1
17. Harrison TW, Chanez P, Menzella F, et al. 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. *Lancet Respir Med*. 2021;9:260–274. doi:10.1016/S2213-2600(20)30414-8
18. Nolasco S, Campisi R, Intravaia R, et al. Case Report: acute effect of benralizumab on asthma exacerbation without concomitant corticosteroid use. *F1000Res*. 2020;9:637. doi:10.12688/f1000research.24603.2
19. SmPC Fasenra. Available From: www.swissmedicinfo.ch. Accessed December 18, 2024.
20. ClinicalTrials.org: https://classic.clinicaltrials.gov/ct2/show/NCT03907137. Accessed December 18, 2024.
21. Penz E, Rothe T, Dupont L, et al. Early Asthma Control Improvement with Benralizumab: 8-Week Interim Integrated Analysis from the Real-World XALOC-2 Study. *J Allergy Clin Immunol*. 2023;151(Suppl AB13):AB13. doi:10.1016/j.jaci.2022.12.048
22. European Respiratory Society Guidelines. Available From: https://erj.ersjournals.com/content/early/2019/09/19/13993003.00588-2019. Accessed December 18, 2024.
23. Juniper EF, Svensson K, Mörk AC, et al. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med*. 2005;99:553–558. doi:10.1016/j.rmed.2004.10.008
24. Juniper EF, Bousquet J, Abetz L, et al. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respir Med*. 2006;100:616–621. doi:10.1016/j.rmed.2005.08.012
25. Kavanagh JE, Hearn AP, Dhariwal J, et al. Real-World Effectiveness of Benralizumab in Severe Eosinophilic Asthma. *Chest*. 2021;159:496–506. doi:10.1016/j.chest.2020.08.2083
26. Pilette C, Canonica GW, Chaudhuri R, et al. REALITI-A Study: real-world oral corticosteroid sparing effect of mepolizumab in severe asthma. *J Allergy Clin Immunol Pract*. 2022;10:2646–2656. doi:10.1016/j.jaip.2022.05.042
27. FitzGerald JM, Bleecker ER, Menzies-Gow A, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. *Lancet Respir Med*. 2018;6:51–64. doi:10.1016/S2213-2600(17)30344-2
28. Menzies-Gow A, Gurnell M, Heaney LG, et al. Oral corticosteroid elimination via a personalised reduction algorithm in adults with severe, eosinophilic asthma treated with benralizumab (PONENTE): a multicentre, open-label, single-arm study. *Lancet Respir Med*. 2021.
29. Jaun F, Tröster LM, Giezendanner S, et al. Characteristics of severe asthma patients and predictors of asthma control in the Swiss severe asthma registry. *Respiration*. 2023;102:863–878. doi:10.1159/000533474
30. Nolasco S, Crimi C, Pelaia C, et al. Benralizumab Effectiveness in Severe Eosinophilic Asthma with and without Chronic Rhinosinusitis with Nasal Polyps: a Real-World Multicenter Study. *J Allergy Clin Immunol Pract*. 2021;9(12):4371–4380.e4. doi:10.1016/j.jaip.2021.08.004
31. Menzies-Gow A, Bafadhel M, Busse WW, et al. An expert consensus framework for asthma remission as a treatment goal. *J Allergy Clin Immunol*. 145:757–765. doi:10.1016/j.jaci.2019.12.006
32. Pelaia C, Crimi C, Benfante A, et al. Sustained remission induced by 2 years of treatment with benralizumab in patients with severe eosinophilic asthma and nasal polyposis. *Respirology*. 2024;29(10):869–879. doi:10.1111/resp.14767