# Benralizumab in severe eosinophilic asthma in real life: confirmed effectiveness and contrasted effect on sputum eosinophilia *versus* exhaled nitric oxide fraction – PROMISE

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**In this real-life study, benralizumab induced a sharp reduction in exacerbations and OCS and an improvement in asthma control and quality of life. Moreover, there was a marked and maintained reduction in sputum eosinophils without any impact on $F_{ENO}$.** https://bit.ly/3ZC1eVF

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## Abstract

*Background* Randomised controlled trials have shown that benralizumab, an anti-interleukin-5 receptor monoclonal antibody, reduces exacerbations and oral corticosteroid dose and improves asthma control and lung function in severe eosinophilic asthma. The aim of this study was to confirm results of randomised controlled trials in real life in a population of 73 patients with severe eosinophilic asthma treated with benralizumab for at least 12 months.

*Methods* Patients underwent careful monitoring of asthma exacerbations, exhaled nitric oxide fraction, lung function, asthma control and quality of life questionnaire responses and sputum induction, and gave a blood sample at baseline, after 6 months and then every year.

*Results* We found significant reductions in exacerbations (by 92%, p<0.0001) and oral corticosteroid dose (by 83%, p<0.001) after 6 months that were maintained over time, with 78% of patients able to stop oral corticosteroid therapy. Patients improved their Asthma Control Test (ACT) score (from 11.7±5.1 to 16.9±5.35, p<0.0001), Asthma Control Questionnaire (ACQ) score (from 2.88±1.26 to 1.77±1.32, p<0.0001) and Asthma Quality of Life Questionnaire score (+1.04, p<0.0001) at 6 months and this was maintained during follow-up. Only 35% and 43% of patients reached asthma control according to an ACT score ⩾20 and ACQ score <1.5, respectively. We observed stable post-bronchodilation lung function over time and a significant reduction in sputum eosinophil count, with 85% of patients exhibiting sputum eosinophil counts <3% after 6 months (p<0.01) with no effect on exhaled nitric oxide fraction.

*Conclusion* In our real-life study, we confirm the results published in randomised controlled trials showing a sharp reduction in exacerbations and oral corticosteroid therapy, an improvement in asthma control and quality of life, and a dramatic reduction in sputum eosinophil count.

## Introduction

Asthma is a heterogeneous disease of the airways characterised by different clinical phenotypes. Eosinophilic phenotype represents >60% of severe asthma [1, 2]. According to European Respiratory Society/American Thoracic Society guidelines [3], after excluding and managing comorbidities and poor adherence, phenotyping asthma according to airway inflammation makes it possible to identify patients with asthma who are more likely to respond to targeted therapy [4]. Interleukin-5 (IL-5) is a key cytokine

responsible for eosinophil activation, proliferation and survival [5]. Benralizumab is a humanised monoclonal antibody that binds directly to the IL-5 receptor on the surface of eosinophils. Eosinophils are the most conspicuous effector cells that drive the inflammation leading to frequent exacerbations, impaired lung function [6] and asthma symptoms [1]. Benralizumab induces a rapid and nearly complete depletion of eosinophils in the bone marrow, blood and airway tissue. In SIROCCO [7] and CALIMA [8], two phase 3 randomised controlled trials (RCTs) conducted in patients with severe uncontrolled eosinophilic asthma, benralizumab significantly reduced asthma exacerbations by up to 51%, and improved lung function and disease control. The ZONDA [9] and PONENTE [10] trials showed that benralizumab has the potential to reduce maintenance oral corticosteroid (mOCS) use in patients with severe eosinophilic asthma.

In this real-life study, called PROMISE, we investigated the efficacy and safety of benralizumab in a population of patients with severe eosinophilic asthma seen in the asthma clinic of CHU Liege and who had a follow-up of at least 1 year. We compared the real-world effects of benralizumab to results found in RCTs. Furthermore, we also compared our results with other real-world studies. The originality of our study is that we included sputum analysis because sputum induction is part of the routine monitoring of our patients with severe asthma receiving biologicals.

## Methods

### *Objectives*

The primary objective was to assess the reduction in asthma exacerbation rate (AER%) after initiation of benralizumab (follow-up at 6 months, 18 months and 30 months) as compared to baseline. An exacerbation was defined as an increase in asthma symptoms requiring treatment with systemic corticosteroids or an increase in the dose of mOCS for at least 3 days or admission to the emergency room. Exacerbation rate was assessed every 3 months.

The secondary objectives were to assess the change in mOCS, inhaled corticosteroid (ICS) dose, patient-reported asthma control and health-related quality of life, lung function, exhaled nitric oxide fraction ($F_{ENO}$), sputum eosinophils and blood eosinophils before and 6 months, 18 months and 30 months after initiation of benralizumab.

The exploratory outcomes included identifying predictors of a super-response, defined as a reduction in exacerbations by 50%, a reduction in the OCS dose of at least 50% in OCS-dependent patients and an improvement in the Asthma Control Questionnaire (ACQ) score of at least 0.5 or an ACQ <1.5 after 6 months.

### *Subject characteristics and study design*

We conducted a prospective follow-up study of 73 patients with severe asthma, recruited from the University Asthma Clinic of Liege between September 2018 and July 2022 and eligible for benralizumab treatment. The reimbursement criteria for benralizumab in Belgium require blood eosinophil counts of $\geqslant$300 cells·μL$^{-1}$ at least once during the last 12 months and at the time of prescription in patients with at least two exacerbations within the last 12 months, with a baseline forced expiratory volume in 1 s ($FEV_1$) <80% predicted. The patients were recruited by two asthma specialists and came from routine practice to the University Hospital. Asthma was diagnosed based on Global Initiative for Asthma guidelines [11].

Nasal polyps and sinusitis were diagnosed by an ear, nose and throat specialist either by endoscopy or sinus computed tomography.

Patients underwent $F_{ENO}$ measurement, spirometry with bronchodilation (BD) and sputum induction, and gave a blood sample. Quality of life was assessed using the self-administered Asthma Quality of Life Questionnaire (AQLQ) [12] and asthma control by the Juniper *et al*. [13] ACQ and the Asthma Control Test (ACT) [14]. Sputum was induced and processed as previously reported [15]. Cell counts were estimated on samples centrifuged (Cytospin) and stained with Diff-Quik after counting 500 cells (Dade Behring, Brussels, Belgium). The follow-up visits, at 6 months and then every year, included the same tests as performed at baseline.

The database used for this study was approved by the Ethics Committee of CHU Liege B70720096732 (2009/161) and all patients signed an informed consent.

### *Statistical analysis*

#### *Sample size estimation*

All patients meeting the inclusion and exclusion criteria of the study in the database were included in the analysis. In order to estimate confidence intervals around the point estimates of the primary outcome, the

exact method for a Poisson variable was applied. A total of 60 patients was considered to be sufficient to show a decrease in asthma exacerbations to 0.5 per year after 6 months.

### *Methods of analysis*

Results are expressed as mean±SD for quantitative variables with a normal distribution or as median (interquartile range (IQR)) for skewed distributions. For qualitative variables, the number of observations and percentages were provided for each modality.

The evolution of the rate of exacerbations (count variable) was assessed using a Poisson model for repeated measures with time considered as the fixed effect and a random intercept for each patient. Overdispersion was tested by the likelihood ratio test. In case of overdispersion, the negative binomial regression was used. For the evolution of quantitative parameters such as doses, scores were analysed by a general linear mixed model (GLMM) with time as the fixed effect including the random intercept for each patient. If the underlying assumptions regarding normality were not fulfilled, a logarithm or square root transformation was applied. For binary outcomes, the evolution was assessed by a logistic regression model accounting for repeated measurements with time considered as the fixed effect and including a random intercept for each patient.

Results were considered significant at the 5% critical level ($p<0.05$). Data analysis was carried out using SAS (version 9.4 for Windows; SAS Institute, Cary, NC, USA) and R (version 4.1.0; www.r-project.org) statistical packages. All analyses were done on the maximum available data.

## Results

Benralizumab was initiated in 73 patients with severe eosinophilic asthma with airway obstruction ($FEV_1$ <80%) who had received at least two courses of systemic steroids within the last 12 months. Their demographic, functional and inflammatory characteristics are summarised in tables 1 and 2.

### *Baseline patient characteristics*

Among the 73 patients included in the study at baseline, 36 (49%) were men and 37 (51%) were women (table 1). More than half of patients were non-smokers or former smokers (55% and 37%, respectively) and five (7%) were current smokers but had attempted to reduce exposure to cigarettes. During the last year, the median number of exacerbations was three (IQR 2–4) and the median number of hospitalisations was 0.57. All patients were treated with high-dose ICS and the median dose was 2000 µg beclomethasone equivalent (IQR 2000–2750 µg) and 19.4% of patients were treated with chronic OCS. Chronic

**TABLE 1** Baseline demographics of patients treated with benralizumab

| | |
|---|---|
| **Participants, n** | 73 |
| **Female, %** | 51 |
| **Age, years** | 55.6±14.8 |
| **BMI, kg·m$^{-2}$** | 26.7±4.9 |
| **Smoking status, %** | |
| Never | 55 |
| Current | 7 |
| Ex-smoker | 37 |
| **Age of onset, years** | 37 (15–49) |
| **Disease duration, years** | 18.4 (7.6–33.3) |
| **Atopy, %** | 44.4 |
| **Exacerbations in the last 12 months, n** | 3 (2–4) |
| **Hospitalisations in the last 12 months, n** | 0.57 (0–5) |
| **ICS, µg beclomethasone equivalent** | 2000 (2000–2750) |
| **Maintenance OCS, %** | 19.4 |
| **OCS dose, mg prednisolone equivalent** | 11.7 (4–32) |
| **LABA, %** | 100 |
| **LAMA, %** | 13 |
| **LTRA, %** | 39 |
| **CRSwNP, %** | 40 |

Data are presented as mean±SD or median (interquartile range), unless otherwise indicated. BMI: body mass index; ICS: inhaled corticosteroids; OCS: oral corticosteroids; LABA: long-acting β-agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; CRSwNP: chronic rhinosinusitis with nasal polyps.

**TABLE 2** Baseline functional and inflammatory characteristics of patients treated with benralizumab

| | |
|---|---|
| **ACT score** | 11 (5–19) |
| **ACQ-6 score** | 2.83 (1.9–3.8) |
| **AQLQ score** | 3.6 (2.8–4.7) |
| **$FEV_1$ pre-BD, %** | 65.9±18.8 |
| **$FEV_1$ post-BD, %** | 71.4±19.6 |
| **Dilatation, %** | 9 (3–28) |
| **$FEV_1$/FVC, %** | 67 (60–76) |
| **$FEV_1$/FVC pre-BD, %** | 66.6±11.7 |
| **$FEV_1$/FVC post-BD, %** | 70.8±12.3 |
| **FRC, %** | 130±36 |
| **RV, %** | 134±41 |
| **TLC, %** | 99±16 |
| **$K_{CO}$, %** | 93±11 |
| **$F_{ENO}$, ppb** | 34 (20–60) |
| **Sputum eosinophil count, %** | 6.3 (1.1–36.2) |
| **Sputum neutrophil count, %** | 54.5 (37–80) |
| **Total serum IgE, $kU \cdot L^{-1}$** | 142 (68–421) |
| **Blood eosinophils, $cells \cdot mm^{-3}$** | 440 (300–850) |
| **Blood neutrophils, $cells \cdot mm^{-3}$** | 4530 (3300–6100) |

Data are presented as mean±SD or median (interquartile range). ACT: Asthma Control Test; ACQ-6: Asthma Control Questionnaire-6 item; AQLQ: Asthma Quality of Life Questionnaire; $FEV_1$: forced expiratory volume in 1 s; BD: bronchodilation; FVC: forced vital capacity; FRC: functional residual capacity; RV: residual volume; TLC: total lung capacity; $K_{CO}$: transfer coefficient of the lung for carbon monoxide; $F_{ENO}$: exhaled nitric oxide fraction.

rhinosinusitis with nasal polyps (CRSwNP) was present in 40% of patients, either diagnosed by sinus computed tomography or nasal endoscopy.

Baseline pre-BD and post-BD $FEV_1$ were 65.9±18.8% and 71.4±19.6%, respectively. Pre-BD and post-BD $FEV_1$/forced vital capacity (FVC) were 66.6±11.7% and 70.8±12.3%, respectively. Baseline median $F_{ENO}$ was 34 ppb (IQR 20–60 ppb) (table 2). Median baseline sputum and blood eosinophil counts were 6.3% (1.1–36.2%) and 440 $cells \cdot mm^{-3}$ (300–850 $cells \cdot mm^{-3}$), respectively.

### *Primary outcome*

The AER significantly decreased from baseline (negative binomial estimate±SE= −0.11±0.028, p<0.0001; figure 1). Indeed, after 6 months, the average reduction was 91.6±16.6% and this was maintained over time. Patients were classified according to baseline blood eosinophil counts below or above the median (440 $cells \cdot \mu L^{-3}$). The AER significantly decreased from baseline (p<0.0001) and this decrease was maintained over follow-up and did not differ between the groups (p=0.57). Patients were then classified according to baseline sputum eosinophil counts below and above the median (6.3%). The AER significantly decreased from baseline (p=0.0003) and did not differ between the groups (p=0.62). The same analysis was performed for total serum IgE and $F_{ENO}$ levels; not surprisingly, the reduction in AER did not differ between the groups formed according to median value of total serum IgE and $F_{ENO}$. Last but not least, we analysed the impact of the COVID-19 pandemic on exacerbation rate and AER reduction with benralizumab. AER was found to be significantly lower at baseline in patients in whom benralizumab was initiated during the pandemic (median 2 events (range 2–3 events) *versus* 3 events (3–6 events), p=0.0019). AER significantly decreased from baseline (p<0.0001) whatever the starting period of benralizumab (92% reduction if treatment initiated during the pandemic *versus* 93% reduction before the pandemic).

### *Secondary outcomes*

#### *Corticosteroid sparing effect*

The daily mOCS significantly decreased from baseline (GLMM estimate±SE on the square root of mOCS −0.016±0.0059, p=0.0059; figure 1). The reduction expressed in percentage from baseline was limited to patients treated with mOCS at baseline. After 6 months, the average reduction in the dose of OCS was 83±35%, reaching 100% after 30 months.

The proportion of patients with an OCS treatment significantly decreased from baseline (p=0.018) and 78% of patients were able to stop mOCS after 6 months. After 30 months of follow-up, all patients stopped chronic treatment with OCS.

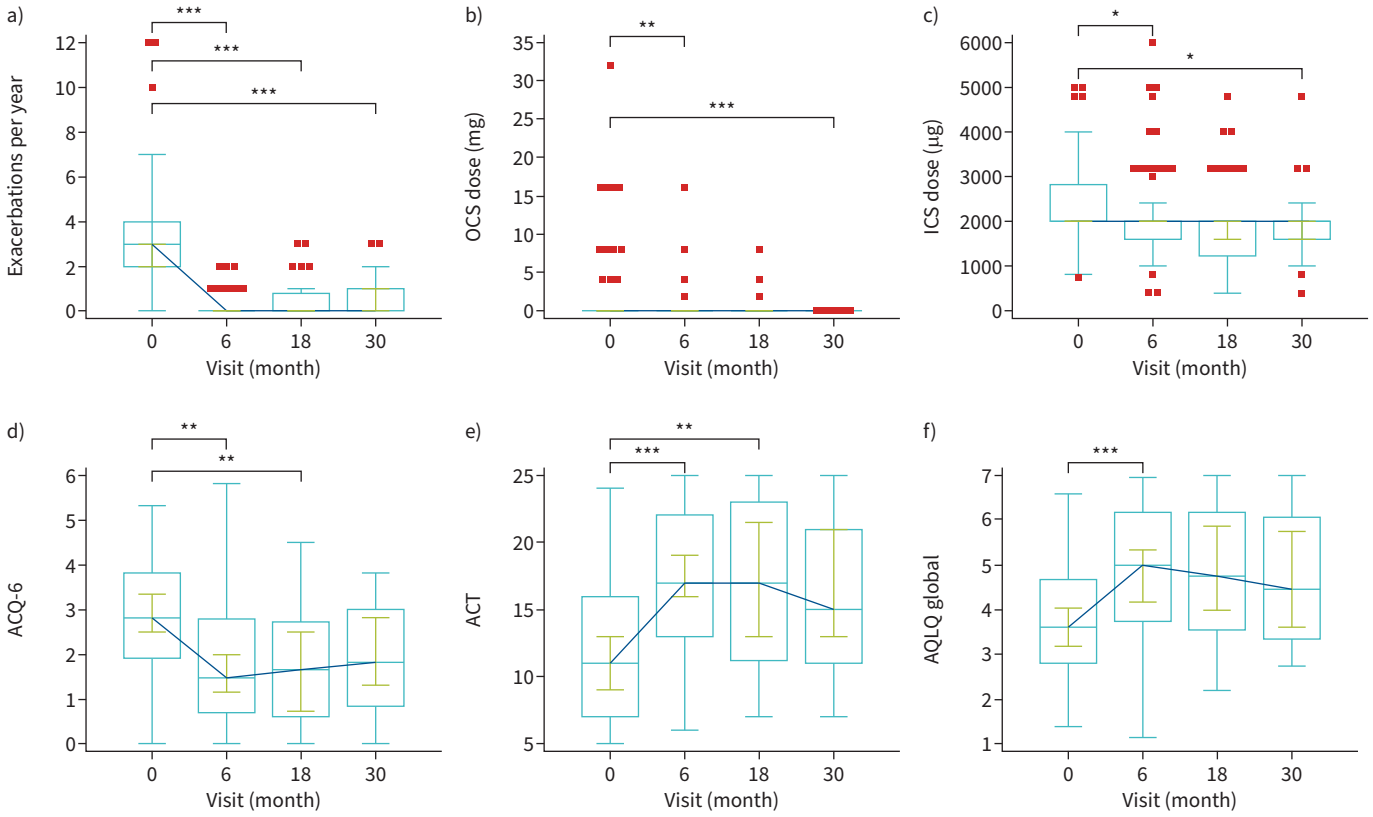


**FIGURE 1** a) Exacerbations, b) oral corticosteroid (OCS) dose (prednisolone equivalent), c) inhaled corticosteroid (ICS) dose (beclomethasone equivalent), d) Asthma Control Questionnaire-6 item (ACQ-6), e) Asthma Control Test (ACT) and f) Asthma Quality of Life Questionnaire (AQLQ) global score at baseline (n=73) and after 6 months (n=73), 18 months (n=44) and 30 months (n=24) of benralizumab treatment. The dark blue line represents the median and the green whiskers represent the 95% CI of the median. The light blue box and whiskers represent the 95% CI of all data. *: p<0.05; **: p<0.001; ***: p<0.0001.

The daily dose of ICS (beclomethasone equivalent) slightly but significantly decreased from baseline (median 2000 µg, range 2000–2750 µg) to the follow-up visit at 6 months (median 2000 µg, range 1600–2000 µg) and 30 months (median 2000 µg, range 1600–2000 µg) (p=0.0078; figure 1).

### *Effect on asthma control and quality of life*

The ACT score significantly increased from baseline by 5.2 points after 6 months (p<0.0001; figure 1), which was maintained over time. The ACQ-6 score significantly decreased by 1.11 points (p=0.0006; figure 1) with a similar sustained effect over time. Based on the ACT, 35% of patients reached good asthma control at 6 months. Based on the ACQ-6, 25% had their asthma controlled and 43% had partial asthma control at 6 months. 65% of patients improved their ACT score by at least 3 points while 68% improved their ACQ-6 score by at least 0.5 points.

The AQLQ score significantly increased from baseline by 1.04 points at 6 months and this improvement was maintained over time (p=0.0001; figure 1). At 6 months, 61% of patients showed an improvement >0.5 points in the AQLQ score.

### *Effect on lung function*

Lung function assessed by post-BD $FEV_1$, post-BD $FEV_1$ % predicted and $FEV_1$/FVC was stable over time (figure 2).

### *Effect on inflammatory markers*

The sputum eosinophil counts decreased significantly from baseline (6.3% to 0%, p<0.0001; figure 2). The sputum neutrophil counts significantly increased from baseline (55% to 70%, p=0.002). 85% of patients

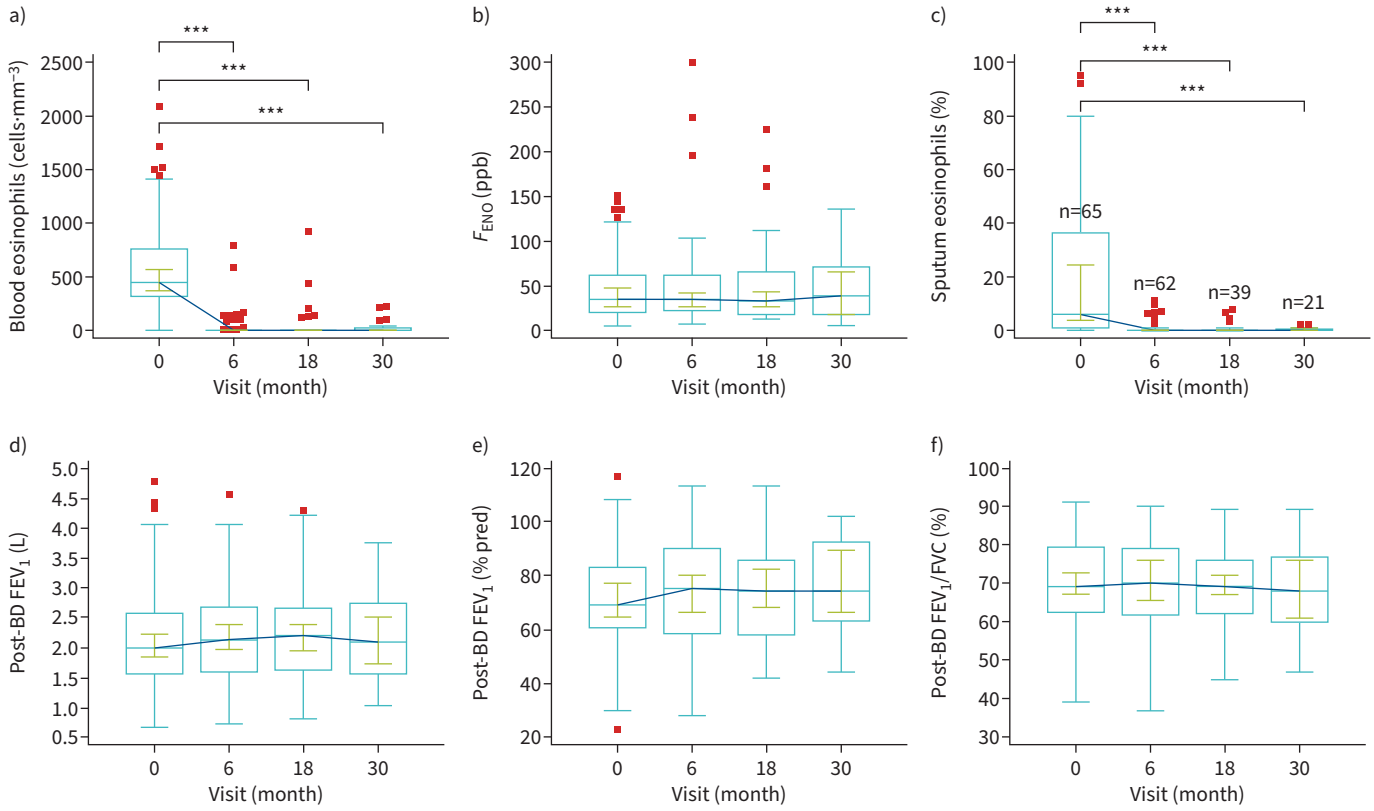


**FIGURE 2** a) Blood eosinophil count, b) fraction of exhaled nitric oxide ($F_{ENO}$), c) sputum eosinophil count, d) absolute post-bronchodilation (BD) forced expiratory volume in 1 s (FEV$_1$), e) post-BD FEV$_1$ % predicted and f) post-BD FEV$_1$/forced vital capacity (FVC) at baseline (n=73) and after 6 months (n=73), 18 months (n=44) and 30 months (n=24) of benralizumab treatment. Number of data available for sputum eosinophils are indicated on c. The dark blue line represents the median and the green whiskers represent the 95% CI of the median. The light blue box and whiskers represent the 95% CI of all data. ***: p<0.0001.

receiving benralizumab for 6 months normalised their sputum eosinophil counts to <3% and this figure reached 100% after 30 months. $F_{ENO}$ levels did not change significantly over time (figure 2).

Not surprisingly, blood eosinophil counts decreased significantly from baseline (440 cells·mm$^{-3}$, range 300–850 cells·mm$^{-3}$ to 0 cells·mm$^{-3}$, p=0.0004; figure 2) and this effect was maintained over time. No change was observed for fibrinogen level, blood neutrophil counts, C-reactive protein or total serum IgE levels.

### *Influence of COVID-19 pandemic*

We evaluated the effect of treatment with benralizumab on the different outcomes assessed according to the time of introduction of anti-IL-5 receptor with respect to the COVID-19 pandemic. The reduction in daily mOCS, the reduction in blood and sputum eosinophil counts and the improvements in lung function, asthma control and quality of life did not differ between patients who received benralizumab before and during the COVID-19 pandemic.

### *Treatment failure*

In our study conducted in 73 patients with severe eosinophilic asthma treated with benralizumab, we found that treatment was successful in 81% of patients with a reduction by half in exacerbations and in mOCS. 14 patients (19.2%) stopped benralizumab after 6 months. The pulmonologist decided to stop benralizumab after 6 months in 12 patients (16.4%) owing to insufficient reduction in exacerbations or in the dose of OCS as compared to baseline. Two patients (2.74%) decided to stop benralizumab owing to side effects such as headache, myalgia and fatigue (figure 3).

### *Exploratory outcomes*

53% of patients responded to the definition of super-responders after 6 months' treatment with benralizumab. Super-responders did not differ (p>0.05) from partial/non-responder patients regarding age,

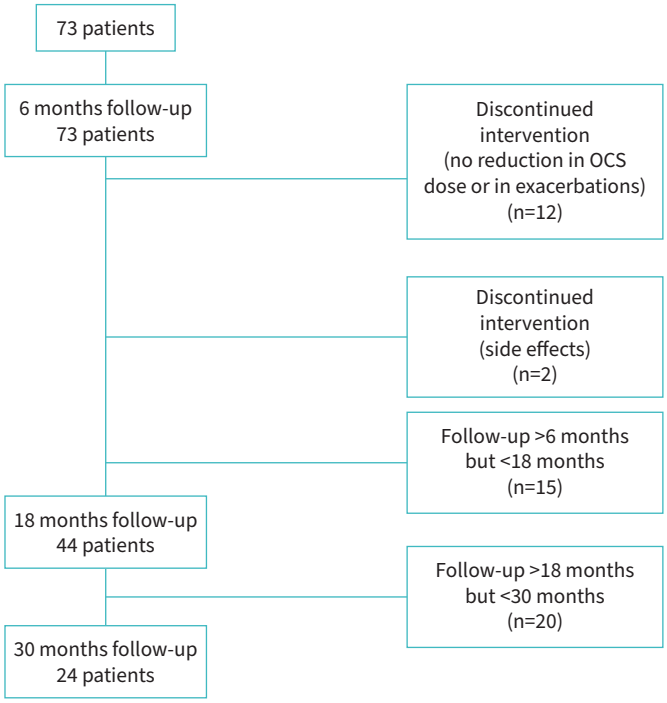


FIGURE 3 Study flow chart. OCS: oral corticosteroid.

gender, body mass index, history of exacerbations, asthma control and quality of life, treatments, lung function or blood leukocytes at baseline. The super-responder group was, however, characterised by a higher sputum eosinophil count at baseline, the absence of current smokers and a higher frequency of comorbid CRSwNP. Notably, blood eosinophil counts were similar between super-responders and partial/non-responders.

Patients presenting with comorbid CRSwNP had a greater reduction in exacerbation rate (−2.7 events·year$^{-1}$ *versus* −1.6 events·year$^{-1}$, p<0.0001), greater improvement in ACT score (+6.2 *versus* +4, p<0.0001) and ACQ-6 score (−1.88 *versus* −0.83, p<0.0001), and a greater improvement in asthma quality of life (AQLQ +1.4 *versus* +0.8, p<0.0001) compared to those without CRSwNP after 6 months of treatment with benralizumab. Patients with severe asthma and CRSwNP showed higher baseline $F_{ENO}$ (48 ppb *versus* 29 ppb), slightly higher baseline blood eosinophil count (499 cells·mm$^{-3}$ *versus* 426 cells·mm$^{-3}$) and higher sputum eosinophil counts (median 24.8% *versus* 5.9%, p=0.003) than other patients.

## Discussion

In the current PROMISE study, benralizumab allowed significant improvements in all clinical outcomes in our real-world severe eosinophilic asthma cohort. It sharply reduced the exacerbation rate while improving patient-reported outcomes. Moreover, the PROMISE study shows an impressive reduction in sputum eosinophils but no reduction in $F_{ENO}$, which remained at high levels. More than half of the patients were considered super-responders after 6 months of treatment with benralizumab and higher sputum eosinophil counts at baseline was a predictor of super-response.

### *Baseline characteristics*

Our PROMISE cohort demographics may show some slight differences compared to the ones in RCTs. The proportion of females was lower in our cohort than the proportions reported in CALIMA (62%) [8], ZONDA (64%) [9], ANDHI (62%) [16] and SIROCCO (63%) [7]. Further information can be found in the supplementary tables. We have previously reported a predominance of male gender in severe eosinophilic asthma in clinical practice [1]. Our population had a longer disease duration as compared to CALIMA (17 years) [8], ZONDA (16 years) [9] and SIROCCO (14.4 years) [7]. Our population had a slightly lower body mass index than those in SIROCCO [7], CALIMA [8], ZONDA [9] and ANDHI [16] and had similar asthma control and quality of life at baseline. The number of exacerbations in the previous year and the number of hospitalisations was higher in our cohort and we had a lower proportion of patients

presenting with sensitisation to aero-allergens as compared to CALIMA [8] and SIROCCO [7]. The main difference was the inclusion of a higher proportion of former smokers in our study, as can be seen in most real-life studies. Smoking is a recognised factor in asthma severity [17]. Furthermore, a recent study has suggested that smoking may drive eosinophilic systemic and airway inflammation [18] so it not surprising that patients with a smoking history may become candidates for treatment targeting eosinophilic inflammation. Regarding ear, nose and throat comorbidities, 40% of the patients had CRSwNP, which is higher than reported in a general population of patients with severe asthma in Belgium [2] and higher than reported in SIROCCO (19%) [7] and CALIMA (15%) [8]. However, our study confirmed that chronic rhinosinusitis is a frequent asthma comorbidity. The prevalence of chronic rhinosinusitis in our cohort was similar to a previous assessment in real clinical settings.

The patients with severe asthma treated with benralizumab in our study had a better baseline pre-BD $FEV_1$ value than the patients in CALIMA (58%) [8], SIROCCO (56%) [7], ZONDA (59%) [9] and ANDHI (54%) [16].

Patients had a type-2 profile at baseline, with high levels of exhaled nitric oxide treated with high doses of ICS, high sputum eosinophil counts and high blood eosinophil counts. Baseline blood eosinophil counts were similar to what has previously been reported in RCTs. The total serum IgE level was similar to what was reported in ANDHI [16].

Regarding baseline treatments, 20% of our patients were on mOCS, which is similar to the proportion in ANDHI (20%) [16] and SIROCCO (18%) [7] and higher than in CALIMA (10%) [8], with a similar OCS daily dose as in CALIMA (9.7 mg prednisolone equivalent·day$^{-1}$) [8] and ZONDA (10 mg prednisolone equivalent·day$^{-1}$) [9] but lower than SIROCCO (15.2 mg prednisolone equivalent·day$^{-1}$) [7].

Only 13% of our patients received treatment with long-acting antimuscarinic agents, which is close to what was reported in CALIMA (9%) [8] and SIROCCO (8%) [7].

### *Follow-up data*

Our observational PROMISE study confirmed that benralizumab was associated with a sharp reduction in exacerbation rate by 92% and this was even greater than what was reported (*versus* placebo) in the RCTs SIROCCO (51%) [7], CALIMA (28%) [8], ZONDA (70%) [9] and ANDHI (49%) [16]. The greater effect observed in real life can probably be explained by the lack of placebo group in our real-world study. Moreover, the reduction in exacerbations observed in PROMISE was similar to that observed in the ANANKE study [19] and higher than reported in other real-world studies [20, 21]. The reduction in exacerbations seen with benralizumab in our study was maintained for up to 30 months. We also found that treatment with benralizumab allowed a reduction in the dose of mOCS by 84% after 6 months, with 78% of patients able to completely stop maintenance treatment with OCS. This is higher than what was reported in other real-world studies [19, 20, 22, 23]. Our study found a significant reduction in the dose of ICS. This observation may have two explanations. First, depleting both systemic and sputum eosinophils with benralizumab has sometimes tempted the respiratory physician to reduce the dose of ICS. Second, improvement in asthma control and quality of life have been associated with a reduction in the dose of ICS by the patients themselves. This decrease in the ICS dose was, however, not associated with a loss of asthma control or recurrence of exacerbations and was in keeping with the ANDHI in practice study [23], which showed background medication reduction, including ICS dosage. This is in line with previous reports showing that non-adherence to ICS in patients treated with benralizumab was not associated with worse outcomes [24]. Benralizumab induced a very quick and nearly complete depletion of eosinophils.

The improvement in asthma control and quality of life seen in our study is more impressive when compared with what has previously been reported in SIROCCO (ACQ −0.25, AQLQ +0.30) [7], CALIMA (ACQ −0.25, AQLQ +0.24) [8], ZONDA (ACQ −0.55, AQLQ +0.45) [9] and ANDHI (ACQ −0.36) [16], with the improvement reaching double the minimal clinically important difference in our study. The better improvement in patient-related outcomes likely results from the absence of a placebo control group in our study. One third of patients with severe asthma in PROMISE reached asthma control, which is similar to what has previously been reported with mepolizumab [25]. There are different reasons for the absence of complete asthma control in two thirds of the patients treated with benralizumab. First, most of the patients had a long disease duration associated with airway remodelling, allowing improved but not total symptom control. This supports the interest in starting anti-IL-5 treatments earlier in the management of severe eosinophilic asthma. Second, some of the patients had comorbidities that could have contributed to poor symptom control. Similar to SIROCCO [7], CALIMA [8], ZONDA [9] and ANDHI [16] (using St George's Respiratory Questionnaire), we were able to find a significant improvement in asthma quality of

life in our real-life study, which was maintained over time and superior to what was found in RCTs, reflecting the cumulative impact of pharmacological effect and an attentive care path in our real-life setting.

We demonstrated stable lung function over time in our population of patients with severe asthma treated with benralizumab. The ZONDA study [9] in cortico-dependent patients with severe asthma found similar results. SIROCCO [7], CALIMA [8] and ANDHI [16], however, reported an improvement of $FEV_1$ of 159 mL, 116 mL and 160 mL as compared to placebo, respectively. Another real-life study found a similar effect on lung function [21]. However, the patients included in our real-life study had a longer disease duration with possible airway remodelling.

Regarding inflammatory biomarkers, we confirmed a depletion in blood eosinophil counts, maintained over time. We found a sharp reduction in sputum eosinophils with normalisation in 85% of patients with severe eosinophilic asthma. This is a better outcome than what was observed in another study with mepolizumab [25]. Targeting the IL-5 receptor with subsequent depletion in systemic eosinophils seems to result in better control of airway eosinophilic inflammation. Increased sputum eosinophil counts have been associated with an increased future risk of exacerbations [1] and irreversible airflow obstruction [6]. We also found that treating severe eosinophilic asthma with anti-IL-5 was associated with attenuated lung function decline [26] but longer-term follow-up studies are needed to confirm the impact of depletion of sputum eosinophils on lung function decline over time. In the MEX trial [27], half of the exacerbations observed in patients with severe eosinophilic asthma treated with mepolizumab were associated with ongoing sputum eosinophilic inflammation.

Large asthma cohort studies of patients not treated with biological therapies have found that $F_{ENO}$ consistently correlates with sputum eosinophil counts [28]. The present study highlights the fact that eosinophils and $F_{ENO}$ may be independent biomarkers. In a study confirming the observed effect with mepolizumab [29], there was a dissociation between sputum eosinophils and $F_{ENO,}$ demonstrating that NO synthesis in the airways is driven by molecular and cellular paths other than the one involving IL-5 and eosinophils.

In this real-life study, super-responders were characterised by the presence of more intense sputum type-2 inflammation and non-current smoking status. We previously showed that patients presenting with intense type-2 inflammation at baseline were more prone to reach asthma remission with anti-IL-5 treatments [30]. To our knowledge, this is the first study looking at induced sputum in real life in a large population of patients treated with benralizumab. Moreover, patients presenting with severe asthma and comorbid CRSwNP in this study had greater improvement in asthma outcomes than those without CRSwNP. This result is consistent with the high responsiveness of a subgroup of patients with eosinophilic asthma and CRSwNP to a previously studied biological treatment [31].

The pulmonologists in PROMISE decided to continue benralizumab in 81% of patients after 6 months. Most of the patients who discontinued benralizumab had no reduction in exacerbations rate and/or a reduction in OCS dose by half. Only two patients decided to stop benralizumab because of side effects.

Our study has some limitations. A limited number of patients was included in our real-life study. To deal with multiple statistical testing, we compared p-values to adapted cut-offs using the Bonferroni correction and still found significant results. Moreover, our study was not placebo-controlled.

In conclusion, patients with severe eosinophilic asthma receiving benralizumab in real life in Liege, Belgium, showed improvement in all clinical outcomes, similar to what has been reported in RCTs. We found an important and sustained reduction in exacerbation rate and in mOCS dose, a marked improvement in asthma control and quality of life, and stable lung function. Moreover, we found a significant reduction in blood and sputum eosinophil counts without any impact on $F_{ENO}$.

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Ethics statement: The database used for this study was approved by the Ethics Committee of CHU Liege B70720096732 (2009/161) and each patient gave informed consent.

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## References


1 Schleich FN, Chevremont A, Paulus V, *et al.* Importance of concomitant local and systemic eosinophilia in uncontrolled asthma. *Eur Respir J* 2014; 44: 97–108.
2 Schleich F, Brusselle G, Louis R, *et al.* Heterogeneity of phenotypes in severe asthmatics. The Belgian Severe Asthma Registry (BSAR). *Respir Med* 2014; 108: 1723–1732.
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.
4 Schleich F, Bougard N, Moermans C, *et al.* Cytokine-targeted therapies for asthma and COPD. *Eur Respir Rev* 2023; 32: 220193.
5 Rådinger M, Lötvall J. Eosinophil progenitors in allergy and asthma – do they matter? *Pharmacol Ther* 2009; 121: 174–184.
6 Graff S, Bricmont N, Moermans C, *et al.* Clinical and biological factors associated with irreversible airway obstruction in adult asthma. *Respir Med* 2020; 175: 106202.
7 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 $\beta_2$-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet* 2016; 388: 2115–2127.
8 FitzGerald JM, Bleecker ER, Nair P, *et al.* Benralizumab, an anti-interleukin-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.
9 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.
10 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* 2022; 10: 47–58.
11 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2018. Available from: http://ginasthma.org/
12 Juniper EF, Guyatt GH, Epstein RS, *et al.* Evaluation of impairment of health-related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax* 1992; 47: 76–83.
13 Juniper EF, O'Byrne PM, Guyatt GH, *et al.* Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999; 14: 902–907.
14 Nathan RA, Sorkness CA, Kosinski M, *et al.* Development of the Asthma Control Test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004; 113: 59–65.
15 Delvaux M, Henket M, Lau L, *et al.* Nebulised salbutamol administered during sputum induction improves bronchoprotection in patients with asthma. *Thorax* 2004; 59: 111–115.
16 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.
17 Thomson NC, Chaudhuri R, Livingston E. Asthma and cigarette smoking. *Eur Respir J* 2004; 24: 822–833.
18 Klein DK, Silberbrandt A, Frøssing L, *et al.* Impact of former smoking exposure on airway eosinophilic activation and autoimmunity in patients with severe asthma. *Eur Respir J* 2022; 60: 2102446.
19 Menzella F, Bargagli E, Aliani M, *et al.* ChAracterization of ItaliaN severe uncontrolled Asthmatic patieNts Key features when receiving benralizumab in a real-life setting: the observational rEtrospective ANANKE study. *Respir Res* 2022; 23: 36.
20 Kavanagh JE, Hearn AP, Dhariwal J, *et al.* Real-world effectiveness of benralizumab in severe eosinophilic asthma. *Chest* 2021; 159: 496–506.
21 Padilla-Galo A, Levy-Abitbol RC, Olveira C, *et al.* Real-life experience with benralizumab during 6 months. *BMC Pulm Med* 2020; 20: 184.
22 Vitale C, Maglio A, Pelaia C, *et al.* Effectiveness of benralizumab in OCS-dependent severe asthma: the impact of 2 years of therapy in a real-life setting. *J Clin Med* 2023; 12: 985.

23 Louis R, Harrison TW, Chanez P, *et al.* Severe asthma standard-of-care background medication reduction with benralizumab: ANDHI in practice substudy. *J Allergy Clin Immunol Pract* 2023; 11: 1759–1770.

24 d'Ancona G, Kavanagh JE, Dhariwal J, *et al.* Adherence to inhaled corticosteroids and clinical outcomes following a year of benralizumab therapy for severe eosinophilic asthma. *Allergy* 2021; 76: 2238–2241.

25 Schleich F, Graff S, Nekoee H, *et al.* Real-world experience with mepolizumab: does it deliver what it has promised? *Clin Exp Allergy* 2020; 50: 687–695.

26 Graff S, Brusselle G, Hanon S, *et al.* Anti-interleukin-5 therapy is associated with attenuated lung function decline in severe eosinophilic asthma patients from the Belgian Severe Asthma Registry. *J Allergy Clin Immunol Pract* 2022; 10: 467–477.

27 McDowell PJ, Diver S, Yang F, *et al.* The inflammatory profile of exacerbations in patients with severe refractory eosinophilic asthma receiving mepolizumab (the MEX study): a prospective observational study. *Lancet Respir Med* 2021; 9: 1174–1184.

28 Schleich FN, Seidel L, Sele J, *et al.* Exhaled nitric oxide thresholds associated with a sputum eosinophil count ⩾3% in a cohort of unselected patients with asthma. *Thorax* 2010; 65: 1039–1044.

29 Haldar P, Brightling CE, Hargadon B, *et al.* Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009; 360: 973–984.

30 Moermans C, Brion C, Bock G, *et al.* Sputum type 2 markers could predict remission in severe asthma treated with anti-IL-5. *Chest* 2023; 163: 1368–1379.

31 Weinstein SF, Katial RK, Bardin P, *et al.* Effects of reslizumab on asthma outcomes in a subgroup of eosinophilic asthma patients with self-reported chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol Pract* 2019; 7: 589–596.