Canonica et al. World Allergy Organization Journal (2026) 19:101159
http://doi.org/10.1016/j.waojou.2025.101159

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

Clinical remission in patients with severe eosinophilic asthma treated with benralizumab over 24 months: Post hoc analysis of the ANANKE study

Giorgio Walter Canonica, MD[a,b]*, Gianenrico Senna, MD[c], Luisa Brussino, MD[d], Maria Aliani, MD[e], Elena Altieri, MD[f], Pietro Bracciale, MD[g], Maria Filomena Caiaffa, MD[h], Paolo Cameli, MD[i], Marco Caminati, MD[j,k], Cristiano Caruso, MD[l,m], Stefano Centanni, MD[n], Fausto De Michele, MD[o], Stefano Del Giacco, MD[p], Fabiano Di Marco, MD[q], Laura Malerba, MD[r], Francesco Menzella, MD[s], Paola Rogliani, MD[t,u], Micaela Romagnoli, MD[v], Pietro Schino, MD[w], Jan Walter Schroeder, MD[x], Alessandra Vultaggio, MD[y], Maria D'Amato, MD[z] and Girolamo Pelaia, MD[aa]

ABSTRACT

Background: Clinical remission is an emerging treatment goal in severe eosinophilic asthma (SEA). While benralizumab, an anti-IL-5Rα monoclonal antibody, has demonstrated efficacy in SEA, its ability to induce clinical remission in real-life settings over extended follow-up remains underexplored.

Methods: This post hoc analysis of the multicenter, retrospective ANANKE study evaluated clinical remission over 24 months in 167 Italian patients with SEA treated with benralizumab. Remission was defined according to the Severe Asthma Network Italy (SANI) criteria. Complete clinical remission (cCR) required the absence of oral corticosteroid (OCS) use and the presence of 3 criteria: no symptoms, no exacerbations, and stable lung function. Partial clinical remission (pCR) required the absence of OCS use and 2 of the 3 criteria. Outcomes were assessed at 3, 12, and 24 months.

Results: The proportion of patients achieving clinical remission increased over time: 87.2% at 3 months (40.4% pCR, 46.8% cCR), 95.0% at 12 months (17.5% pCR, 77.5% cCR), and 96.1% at 24 months (23.5% pCR, 72.6% cCR). No baseline demographic or clinical characteristics were found to significantly predict remission status. Blood eosinophil counts declined from a mean of 476.7 to 5.2 cells/μL at 24 months.

Conclusion: In this real-world Italian cohort, benralizumab was associated with rapid and sustained clinical remission in patients with SEA over 24 months. The high remission rates observed early and maintained throughout treatment support the role of benralizumab as a disease-modifying therapy and reinforce clinical remission as a meaningful therapeutic goal in SEA.

Keywords: Severe eosinophilic asthma, Benralizumab, Clinical remission

[a]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele MI, Italy
*Corresponding author. Pulmonology Unit, Ospedale "S. Valentino", AULSS 2 Marca Trevigiana, Montebelluna TV, Italy. E-mail: giorgio_walter.canonica@hunimed.eu
Full list of author information is available at the end of the article

http://doi.org/10.1016/j.waojou.2025.101159

Received 28 August 2025; Received in revised from 19 November 2025; Accepted 7 December 2025
Online publication date xxx

INTRODUCTION

Clinical remission is emerging as a treatment goal in severe asthma.[1,2] An improved understanding of asthma pathophysiology has led to more targeted therapies, resulting in a shift in asthma management from traditional treatment goals of symptom control and relief to a treat-to-target approach.[1] Disease-modifying anti-asthmatic drugs (DMAADs) play a crucial role in this transformation, offering the potential to modulate the underlying disease mechanisms and support the achievement of remission.[1,3]

The global burden of severe asthma continues to rise, in part due to the increasing prevalence of obesity and exposure to urban and environmental risk factors.[4] Severe eosinophilic asthma (SEA), a significant subset of severe asthma, is characterized by high levels of eosinophils in the blood or sputum.[5,6] This condition is associated with frequent exacerbations, impaired lung function, and an increased reliance on oral corticosteroids (OCS),[7] resulting in significant morbidity, lower quality of life,[8] and increased healthcare costs.[9] Therefore, achieving remission in SEA patients could improve their quality of life and reduce healthcare costs. From a patient's perspective, clinical remission is strongly associated with avoiding oral corticosteroids and achieving meaningful symptom control, rather than focusing solely on lung function or reducing exacerbations. Bonini et al found that patients prioritize OCS use and Asthma Control Test (ACT) scores as key indicators of remission, emphasizing the need for patient-centered definitions of treatment success to improve adherence and satisfaction in asthma management.[10]

Various definitions of clinical remission in the treatment of severe asthma have been proposed.[11–13] One of the first frameworks to define clinical remission in asthma was introduced by Menzies-Gow et al,[11] who identified 4 key pillars: the absence of significant symptoms, lung function stabilization, no use of systemic corticosteroids, and patient/provider agreement on remission status. This work laid the foundation for subsequent definitions and discussions on asthma remission. Furthermore, Lommatzsch et al emphasized the role of DMAADs in achieving remission due to their ability to control symptoms and alter the underlying pathophysiology of asthma. The authors argued for a paradigm shift in asthma management, moving beyond symptom relief toward a more comprehensive disease-modifying strategy.[3]

Building on these concepts, the Severe Asthma Network Italy (SANI) defines complete clinical remission (cCR) as requiring no OCS and meeting 3 criteria: absence of symptoms, absence of exacerbations, and stable lung function. Partial clinical remission (pCR) is defined similarly but only requires 2 of the 3 criteria in the absence of OCS.[12] Recent work by Canonica et al has refined the practical application of these remission criteria, proposing a structured approach to patient management that takes into account different levels of disease control. Their framework guides treatment adjustments based on remission status, helping to optimize therapeutic decisions for patients with severe asthma.[2]

Benralizumab, a monoclonal antibody against IL-5 receptor alpha (IL-5R-α), is a targeted biological treatment for SEA.[14] By depleting eosinophils,[14,15] benralizumab has demonstrated substantial efficacy in phase 3 randomized controlled trials (RCTs), where it significantly reduced exacerbation rates, improved lung function and symptoms, and reduced daily OCS usage compared to placebo.[16–18] Moreover, the MELTEMI study has demonstrated a durable response to benralizumab for up to 5 years and a favorable safety profile.[19] Several real-world studies have reinforced data from pivotal studies.[20–23] In a recent 36-month, real-life, Italian multicenter study of benralizumab in 108 patients with SEA, benralizumab induced partial or complete clinical remission in 84.3% of enrolled patients.[24] The exacerbation rate was reduced by 89%. This study demonstrated, for the first time in clinical practice, the ability of benralizumab to optimize ICS and other asthma controllers, as previously observed in the SHAMAL study.[24] A more recent real-world study further explored the long-term efficacy of benralizumab in inducing clinical remission in a small cohort of 23 patients with SEA followed for 48 months. The proportion of patients achieving

clinical remission progressively increased over time, reaching 86.9% after 12 months and 91.3% at both 24 and 48 months. Notably, the proportion of patients in complete remission also rose with prolonged treatment duration, supporting the sustained and incremental benefit of benralizumab in real-life clinical practice.[25] SHAMAL, a phase IV, randomized controlled trial of 168 patients, was the first RCT to demonstrate a reduction in ICS in patients with severe asthma; nearly all patients (92%) had well-controlled disease with benralizumab and were able to reduce their dose of ICS.[26] The XALOC-1 programme, a large, multinational, retrospective analysis, assessed over 1000 patients with SEA treated for up to 96 weeks. Clinical remission, defined as no exacerbations, no maintenance OCS use, and well-controlled asthma (ACT $\geq$20 or ACQ-6 $\leq$ 0.75), was achieved by approximately one-third of patients at 96 weeks. Lower baseline OCS use, lower BMI, and higher peak eosinophil counts were associated with a greater likelihood of remission, highlighting the importance of early intervention and tailored treatment strategies.[27,28]

The ANANKE study is a real-world study that examined the baseline characteristics of a large SEA population treated with benralizumab for up to 96 weeks.[20,29] In line with the results obtained from RCTs, benralizumab treatment reduced the annualized exacerbation rate (AER) and OCS dosage and improved lung function.

While several studies highlight the benefits of biologics in SEA management, only a few have used clinical remission as a defined endpoint. Furthermore, the definitions of remission vary across studies. Therefore, to evaluate the effectiveness of benralizumab in a patient population with SEA, we performed a post hoc analysis of the ANANKE study using the SANI definition of clinical remission.[12] This is the first post-hoc analysis of the ANANKE real-world cohort assessing benralizumab through the SANI clinical remission framework over 24 months. Despite the increasing focus on remission as a treatment goal in severe asthma, published data specifically applying the SANI criteria to benralizumab remain scarce, especially for long-term follow-up exceeding 12 months, highlighting the need for real-world evidence on the durability of clinical remission.

METHODS

Study design

ANANKE (NCT04272463) is an observational, multi-center, retrospective cohort study conducted in Italy, as described previously.[29] Benralizumab was administered to patients with severe eosinophilic asthma (SEA) in accordance with standard clinical practice or as part of the Italian Sampling Program, with the initiation date defined as the "index date." Enrolment occurred at least 3 months after the index date. The index date corresponds to the first benralizumab administration and was used as a reference for all follow-up assessments. Patients were required to have received at least 3 benralizumab doses ($\geq$3 months of therapy) to ensure a minimal therapeutic exposure for evaluating clinical outcomes, consistent with pharmacodynamic evidence of eosinophil depletion.

The present study's observation period was extended to 96 weeks, in contrast to the 48 weeks of the original study design. Patients, therefore, consented to participate in the extended study and signed the necessary privacy and informed consent forms. Data were collected at the index date and then at 3, 12, and 24 months. The ANANKE study adhered to the ethical principles of the Declaration of Helsinki and complied with Italian regulations and policies governing clinical practice. The study received approval from the ethics committees/institutional review boards at all participating sites.

Patient population

Inclusion and exclusion criteria were described previously.[29] The study included adult patients (aged 18 years or older) treated with benralizumab. The patients had severe eosinophilic asthma, necessitating stable high-dose inhaled corticosteroids (ICS) and a long-acting β2 agonist, with or without additional asthma controllers. To be eligible, patients had to have started benralizumab and received at least 1 injection at least 3 months before enrollment. Additionally, they were required to sign an informed consent and privacy form at the enrolment visit, and their hospital medical charts needed to be available from the start of their

benralizumab treatment. Patients were excluded if they received benralizumab during the observation period as part of a clinical experimental trial.

Furthermore, participants in studies that required specific patient management strategies not aligned with the standard clinical practice of the site were also excluded. The present study included patients with clinical remission data available at 96 weeks. Due to the retrospective design of the study and the extended observation period of 96 weeks, as opposed to the 48 weeks of the original study, some patients had to be excluded because of missing 96-week data, withdrawal before completing 3 injections, or incomplete follow-up information.

Outcome measures

The primary endpoint of this analysis is clinical remission, both partial and complete, as defined by SANI.[12] Complete clinical remission (cCR) is achieved when there is no need for OCS, and all 3 of the following criteria are met: the absence of asthmatic symptoms, the absence of exacerbations or attacks, and lung function stability. Partial clinical remission (pCR) is achieved when OCS is not needed, and 2 of the 3 abovementioned criteria are met.[12] Stable lung function was defined as no clinically meaningful decline in FEV1 over time (FEV1 $\geq$ 150 mL), according to SANI criteria. Severe asthma was classified according to the ERS/ATS 2014[30] and GINA 2024 definitions.[31]

The data at the index date were collected throughout the 12 months before the start of benralizumab treatment. They consisted of age, gender, body mass index (BMI), tobacco usage, age at asthma diagnosis, duration of asthma and SEA, diagnosis of atopy, diagnosis of concomitant illnesses, BEC, blood level of serum immunoglobulin E (IgE), respiratory parameters, control of asthma symptoms, use of asthma controllers, any and severe AER. Any AER accounted for all the clinically significant asthma exacerbations determined by a physician. Severe AER included all exacerbations that further deteriorated asthma symptoms, requiring either: a) systemic corticosteroids, administered for at least 3 days, or a transient increment in the dosage of maintenance OCS; b) a visit to the emergency department (shorter than 24 h) during which systemic corticosteroids were administered; or c) hospitalization (longer than 24 h). Additionally, secondary endpoints were recorded at 3, 12, and 24 months, when available. They included changes in BEC, treatment with OCS, and dosage.

Statistical analyses

Statistical analyses were described previously.[29] For descriptive analyses, continuous variables were presented as means with standard deviations (SD) or medians with ranges or interquartile ranges (IQR), and categorical variables were expressed as the number of subjects (n) and percentage values. To assess the association of demographic and clinical variables on pCR and cCR, a mixed-effects Cox model was used. The hazard ratios associated with pCR and cCR were calculated, along with their 95% confidence intervals, for each factor using the Cox Proportional-Hazards model. The center variability was considered a random effect in all mixed-effect Cox models. The likelihood ratio test was used for statistical significance, and p-values were not adjusted for multiple comparisons.

Differences with a p-value less than 0.05 were considered significant. Data were acquired and analyzed in the R v4.4.1 software environment.

RESULTS

The ANANKE study enrolled 218 patients from December 2019 to July 2020. Of these, 167 (76.6%) were eligible for the present analysis. Of the 218 patients initially enrolled, 51 were excluded due to missing 96-week data, withdrawal before receiving 3 benralizumab doses, or incomplete follow-up information. Baseline characteristics of the excluded patients were comparable to those of the analyzed population, minimizing selection bias. Table 1 summarises the study participants' baseline demographic, biochemical, and clinical characteristics. Briefly, 167 patients (103 (61.68%) females, mean age 56.28 years) participated in this study. The mean age at diagnosis of severe asthma was 53.54 years.

Blood eosinophil count was >450 cells/μL in 79 (47.31%) patients.

Benralizumab promoted clinical remission

Fig. 1 shows the number of patients who achieved CR, and partial or complete CR, at 3, 12, and 24 months compared to baseline. Three months after the index date, 41 (87.2%) patients had achieved CR (40.4% pCR and 46.8% cCR). At 12 months, 38 (95.0%) patients had achieved CR (17.5% pCR and 77.5% cCR). The number of CR rose to 49 (96.1%) at 24 months (23.5% pCR and 72.6% cCR). The percentage of patients who did not achieve CR fell from 12.8% at 3 months to 5.0% at 12 months and 3.9% at 24 months. We also calculated the number of patients who achieved clinical remission at each time point compared to the previous **(Supplementary Fig. 1)**. These results were similar, with 77.78% of patients in cCR at 24 months (16.67% pCR and 61.11% cCR).

To determine whether baseline demographic and clinical parameters affected clinical remission outcomes, we performed a mixed Cox regression analysis. We found no significant effects of any of the parameters on CR outcome, neither cCR nor pCR **(Supplementary Tables 1 and 2)**.

Benralizumab reduced blood eosinophil count

Patients experienced a significant and rapid reduction of blood eosinophil count over time. The baseline blood eosinophil count declined from a mean of 476.7 (586.9) to 15.8 (74.0) after just 3 months and remained low at all time points, reaching 5.2 (17.4) at 24 months (Fig. 2).

DISCUSSION

This is the first post-hoc analysis of the ANANKE real-world cohort that has applied the SANI clinical remission criteria to evaluate 24-month sustained remission with benralizumab. Although clinical remission is increasingly recognized as a meaningful treatment goal in severe asthma, evidence specifically using the SANI criteria to assess benralizumab remains limited, particularly for long-term follow-up beyond 1 year.

This study highlights the potential of benralizumab to induce a rapid and durable clinical remission in patients with SEA. Notably, the majority (87.2%) of patients achieved clinical remission within the first 3 months. The percentage of patients achieving clinical remission continued to increase and was sustained over 24 months, with nearly all (96.1%) patients reaching complete or partial remission. These results emphasize the clinical utility of remission as a therapeutic goal.

The study further supports the importance of a standardized definition of clinical remission. By applying the SANI criteria, the analysis provides a framework for evaluating treatment outcomes, ensuring consistency across clinical and real-world settings. Pini et al[24] used the SANI definition in a real-life multicenter study on 108 patients with SEA. At 24 months, benralizumab induced clinical remission in 90.0% of enrolled patients, with 12.5% achieving pCR and 77.5% achieving cCR. These numbers align with our findings. Quarato et al[25] reported results from a smaller real-world cohort of 23 SEA patients followed for 48 months, showing a progressive increase in clinical remission rates over time (86.9% at 12 months and 91.3% at both 24 and 48 months), with a growing proportion of patients achieving complete remission. Although based on a limited sample size, these findings further support the long-term and sustained effectiveness of benralizumab in maintaining clinical remission.

However, the lack of a consensus definition of remission remains a challenge, as emphasized by Jackson et al,[28] who noted that varying criteria for asthma symptom control and remission endpoints complicate cross-study comparisons and highlight the need for more standardized definitions in real-world research.

The discontinuation of OCS observed in this study reinforces the strong corticosteroid-sparing effect of benralizumab in patients achieving clinical remission. These findings are consistent with previous real-world and clinical trials and align with the therapeutic goals outlined in the SANI remission criteria. The ability of benralizumab to

Characteristic	Overall
Age, years	
<45	26 (15.57%)
≥ 45	141 (84.43%)
Gender	
Male	64 (38.32%)
Female	103 (61.68%)
BMI *(n = 150)*	
Under/normal-weight	79 (52.67%)
Overweight	52 (34.67%)
Obese	19 (12.67%)
Smoking habit *(n = 160)*	
Non-smoker	112 (70.00%)
Previous smoker	43 (26.88%)
Current smoker	5 (3.13%)
Asthma duration *(n = 166)*	
≤ 10 years	68 (40.96%)
> 10 years	98 (59.04%)
Age at severe asthma diagnosis, years	53.54 (13.00)
Age at severe asthma diagnosis, years	
≤40	24 (14.37%)
41-50	35 (20.96%)
51-60	51 (30.54%)
61-70	43 (25.75%)
> 70	14 (8.38%)
Severe asthma duration, years	
≤ 1	95 (56.89%)
> 1 and ≤ 2	20 (11.98%)
> 2	52 (31.14%)
IgE	
No	66 (39.52%)
Yes	101 (60.48%)
IgE, ng/mL *(n = 99)*	1137.76 (1711.18)
Atopy *(n = 99)*	
No	11 (11.11%)
Yes	88 (88.89%)
Blood eosinophil count (BEC), cells/μL	
≤ 450	88 (52.69%)
> 450	79 (47.31%)
OCS, mg/day *(n = 154)*	
≤ 10	141 (91.56%)
> 10	13 (8.44%)

(continued)

Characteristic	Overall
Pre-FEV1/FVC predicted *(n = 124)*	
≥ 70	92 (74.19%)
< 70	32 (25.81%)

Table 1. (Continued) Baseline patient demographic, biochemical, and clinical characteristics. Data refer to n = 167 patients unless otherwise specified and are expressed as the number of subjects (percentage) or mean (SD), as appropriate. ***Abbreviations:*** *BMI, body mass index; BEC, blood eosinophil count; IgE, immunoglobulin E; OCS, oral corticosteroids; AER, annual exacerbation rate; BD, bronchodilator; pre-BD FEV1, pre-bronchodilator forced expiratory volume in 1 s; pre-BD FVC, pre-bronchodilator forced vital capacity; FeNo, fractional exhaled nitric oxide; ACT, asthma control test*

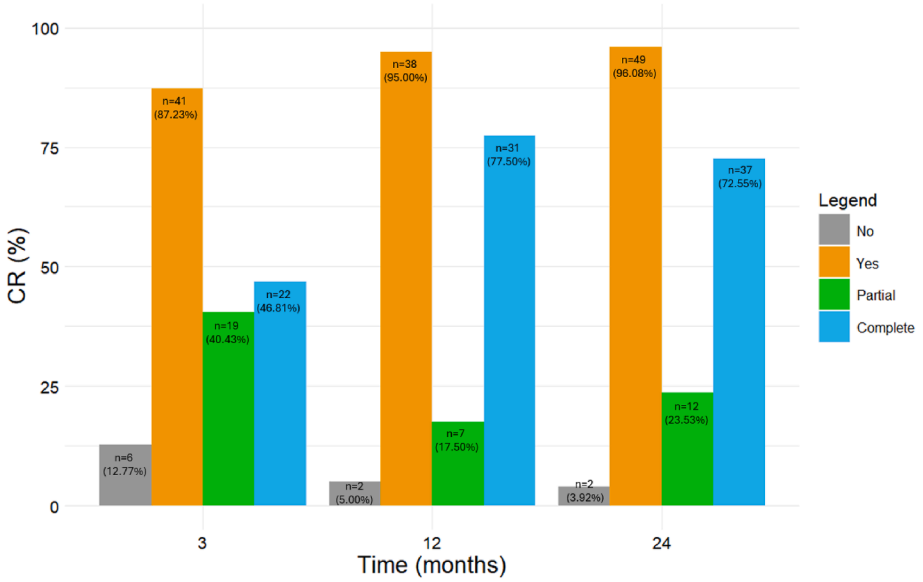

Fig. 1 Clinical remission. Number and percentage of patients who achieved and did not achieve CR (either pCR or cCR) at 3, 12, and 24 months during the treatment with benralizumab (from baseline)

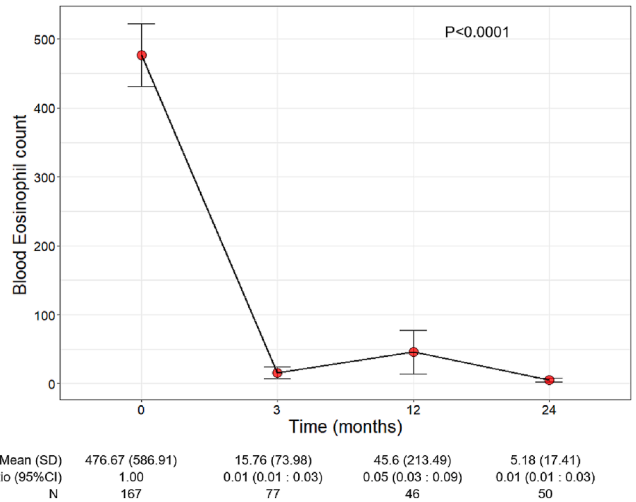

Fig. 2 Blood eosinophil count. Blood eosinophil count from benralizumab treatment start up to 24 months

rapidly and persistently deplete eosinophils is central to this effect. As an anti-IL-5 receptor α monoclonal antibody, benralizumab induces apoptosis of eosinophils, resulting in profound eosinophil depletion. This rapid control of type 2 inflammation plays a crucial role in reducing the

need for systemic corticosteroids, thereby mitigating their long-term adverse effects.

Vultaggio et al[32] have recently reviewed the immunomodulatory potential of benralizumab, noting its sustained suppression of eosinophilic inflammation as a key factor in achieving long-term disease control and facilitating corticosteroid sparing in patients with SEA. This immunological impact supports the concept of benralizumab as a DMAAD, capable of altering the inflammatory trajectory of SEA beyond symptom management.

Furthermore, Canonica et al[33] confirmed, in a comprehensive analysis of the SANI registry, the utility of clinical remission as a pragmatic endpoint for evaluating biologic therapies, including benralizumab. They reported that approximately 60% of the patients on benralizumab achieved complete clinical remission at 12 months. The alignment between our findings and those from Canonica et al underscores the robustness of the SANI remission framework and its relevance for guiding real-life asthma management.

Together, these results highlight that the observed OCS reduction is not simply a downstream effect but is deeply linked to the mechanism of benralizumab in eosinophilic-driven asthma, offering a rationale for its inclusion in remission-oriented treatment strategies. This effect was also observed in the MANDARA trial, a phase 3 non-inferiority randomized trial comparing benralizumab to metalizumab in patients with eosinophilic granulomatosis with polyangiitis (EGPA).[34] Mepolizumab is a monoclonal antibody that inhibits eosinophil activation and differentiation by binding interleukin-5.[35] In this study, benralizumab was found to be non-inferior to mepolizumab for inducing remission in patients with relapsing or refractory EGPA. A complete withdrawal of OCS was achieved in 41% of patients who received benralizumab and in 26% of those who received mepolizumab during weeks 48 through 52. This underlines the OCS-sparing effect of benralizumab across different diseases driven by eosinophilic inflammation.

The study has limitations. The retrospective nature of the analysis introduces potential biases, including patient selection and missing data. The number of evaluable patients decreased over time due to varying availability of follow-up visits or missing data at later time points, as expected in real-world retrospective studies. Additionally, while extending the observation period to 96 weeks provides valuable insights, the lack of a control group limits the ability to attribute outcomes solely to benralizumab. Future prospective studies with controlled designs are warranted to confirm these results and further explore long-term outcomes. The exclusion of 51 patients due to incomplete data could have introduced a degree of selection bias; however, the demographic and baseline characteristics of the excluded patients were comparable to those of the analyzed patients, which limited the potential impact.

CONCLUSION

This post hoc analysis of the ANANKE study confirms the effectiveness of benralizumab in inducing a rapid and sustained clinical remission in patients with severe eosinophilic asthma (SEA) over a prolonged 24-month period. A substantial proportion of patients reached either partial or complete clinical remission as defined by the SANI criteria, with high rates of remission observed early and maintained throughout follow-up. The rapid and sustained depletion of eosinophils observed with benralizumab underscores its potent anti-inflammatory and immunomodulatory effects. It supports the concept of benralizumab as a DMAAD, capable of not only controlling symptoms but also modulating the underlying immunological mechanisms of eosinophilic asthma.

Taken together, these data emphasize the importance of adopting clinical remission as a realistic and actionable treatment goal in SEA and position benralizumab as a valid therapeutic option.

Abbreviations

ACT, asthma control test; AER, annualized exacerbation rate; BEC, blood eosinophil count; cCR, complete clinical remission; CR, clinical remission; DMAAD, disease-modifying anti-asthmatic drug; EGPA, eosinophilic granulomatosis with polyangiitis; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; IL-5, interleukin-5; OCS, oral corticosteroids;

pCR, partial clinical remission; RCT, randomized controlled trial; SA, severe asthma; SD, standard deviation; SEA, severe eosinophilic asthma.

Acknowledgments
Support for medical writing was provided by Lisa Mathiasen, PhD, CMPP™, MWC®, and statistical analysis by Fabio Gallo, on behalf of EDRA SpA.

Funding
AstraZeneca SpA, Italy, provided financial support for the article's preparation. The company participated in the study design, data collection, and analysis.

Availability of data and materials
The datasets used in the current study are available from the corresponding author upon reasonable request.

Authors' contributions
All authors contributed equally to the conception and design of the study, data collection, manuscript drafting, critical revision, and final approval of the submitted version. All authors agree to be accountable for all aspects of the work.

Ethics approval and consent to participate
This study followed the ethical principles outlined in the Declaration of Helsinki and the regulations and guidelines governing medical practice and ethics in Italy. All patients provided informed consent before enrolling in the study and signed additional and amended study informed consent and privacy forms for the extended observation period. Ethical approval was provided by the ethics committees/institutional review boards at each participating site.

Declaration of competing interest
PC has received grants and fees as a speaker from AstraZeneca-MedImmune, Sanofi, and GlaxoSmithKline (GSK) in the last 3 years. GWC reports research or clinical trials grants paid to his institution from Menarini, AstraZeneca, GSK, Sanofi Genzyme and fees for lectures or advisory board participation from Menarini, AstraZeneca, CellTrion, Chiesi, Faes Farma, Firma, Genentech, Guidotti-Malesci, GSK, HAL Allergy, Innovacaremd, Novartis, OM-Pharma, Red Maple, Sanofi-Aventis, Sanofi-Genzyme, Stallergenes-Greer, and Uriach Pharma. SDG declares fees from AstraZeneca, Chiesi, GSK, Novartis, Sanofi, Menarini; unrestricted grants from AstraZeneca, GSK, Novartis, and Sanofi. FDM declares personal fees and support for research from AstraZeneca, Boehringer Ingelheim, Chiesi, Eurodrugs Laboratories, Laboratori Guidotti, GlaxoSmithKline, Levante Pharma, Menarini, Sanofi, Zambon. PR reports grants/research support to her institution from Arcede Pharma, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Sanofi, Verona Pharma and Zambon and honoraria or consultation fees from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Menarini Group, Novartis, Pfizer, Recipharm, Regeneron, Roche and Sanofi. JWS declares personal fees and support for research from AstraZeneca, GSK, Sanofi, Stallergenes. The authors MA, EA, PB, LB, MF, MC, CC, SC, MD, FDM, LM, FM, GP, MR, PS, GS, and AV, declared no competing interests.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2025.101159.

Declaration of Generative AI and AI-assisted technologies in the writing process
Nothing to disclose.

Author details
[a]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele MI, Italy. [b]Personalized Medicine Center: Asthma and Allergology, Humanitas Research Hospital, Rozzano MI, Italy. [c]Allergy Unit - Pederzoli Hospital, Peschiera del Garda VR Italy. [d]Dipartimento di Scienze Mediche, Università degli Studi di Torino, SCDU Immunologia e Allergologia, AO Ordine Mauriziano Umberto I, Torino, Italy. [e]UO Pneumologia e Pneumologia Riabilitativa, ICS Maugeri, IRCCS Bari, Bari, Italy. [f]Reparto di Pneumologia, P.O. Garbagnate Milanese, Garbagnate Milanese MI, Italy. [g]Reparto di Pneumologia, Ospedale Ostuni, Ostuni BR, Italy. [h]Cattedra e Scuola di Allergologia e Immunologia Clinica, Dipartimento di Scienze Mediche, Università di Foggia, Foggia, Italy. [i]Respiratory Diseases Unit, Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy. [j]Allergy Unit and Asthma Center, Verona University Hospital, Verona, Italy. [k]Department of Medicine, University of Verona, Verona, Italy. [l]UOSD Allergy and Clinical Immunology, Fondazione Policlinico A. Gemelli, IRCCS, Rome, Italy. [m]UOC Internal Medicine, Ospedale Isola Tiberina - Gemelli Isola, Rome, Italy. [n]Respiratory Unit, ASST Santi Paolo e Carlo, Department of Health Sciences, Università degli Studi di Milano, Milano, Italy. [o]UOC Pneumologia e Fisiopatologia Respiratoria, AORN A. Cardarelli, Napoli, Italy. [p]Dipartimento di Scienze Mediche e Sanità Pubblica, Università degli Studi di Cagliari, Monserrato, Cagliari, Italy. [q]Department of Health Sciences, Università degli Studi di Milano, Pneumologia, ASST Papa Giovanni XXIII, Bergamo, Italy. [r]Medical Affairs R&I, AstraZeneca, Milano, Italy. [s]Pulmonology Unit, Ospedale "S. Valentino", AULSS 2 Marca Trevigiana, Montebelluna TV, Italy. [t]Division of Respiratory Medicine, University Hospital "Fondazione Policlinico Tor Vergata", Rome, Italy. [u]Unit of Respiratory Medicine, Department of Experimental Medicine, University of Rome "Tor Vergata", Roma, Italy. [v]UOC Pneumologia, AULSS 2 Marca Trevigiana, Treviso, Italy. [w]Fisiopatologia Respiratoria, Ospedale Generale Regionale, Ente Ecclesiastico "F. Miulli", Acquaviva delle Fonti BA, Italy. [x]Allergy and Clinical Immunology, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy. [y]Dipartimento di Medicina Sperimentale e Clinica, Università degli Studi di Firenze, Firenze, Italy. [z]UOSD Malattie Respiratorie "Federico II", Ospedale Monaldi, AO Dei Colli, Napoli, Italy. [aa]Dipartimento di Scienze della Salute, Università Magna Graecia, Catanzaro, Italy.

REFERENCES

1. Lommatzsch M, et al. Pioneering a paradigm shift in asthma management: remission as a treatment goal. *Lancet Respir Med*. 2024;12(2):96–99.
2. Canonica GW, et al. SANI clinical remission definition: a useful tool in severe asthma management. *J Asthma*. 2024:1–8.
3. Lommatzsch M, et al. Disease-modifying anti-asthmatic drugs. *Lancet*. 2022;399(10335):1664–1668.
4. Wang Z, et al. Global, regional, and national burden of asthma and its attributable risk factors from 1990 to 2019: a systematic analysis for the Global Burden of Disease Study 2019. *Respir Res*. 2023;24(1):169.
5. Coumou H, Westerhof GA, de Nijs SB, Amelink M, Bel EH. Diagnosing persistent blood eosinophilia in asthma with single blood eosinophil or exhaled nitric oxide level. *Respir Med*. 2018;141:81–86.
6. Bakakos A, Loukides S, Usmani OS, Bakakos P. Biologics in severe asthma: the overlap endotype - opportunities and challenges. *Expert Opin Biol Ther*. 2020;20(12):1427–1434.
7. de Groot JC, et al. Clinical profile of patients with adult-onset eosinophilic asthma. *ERJ Open Res*. 2016;2(2).
8. Schleich FN, et al. Importance of concomitant local and systemic eosinophilia in uncontrolled asthma. *Eur Respir J*. 2014;44(1):97–108.
9. Kerkhof M, et al. Healthcare resource use and costs of severe, uncontrolled eosinophilic asthma in the UK general population. *Thorax*. 2018;73(2):116–124.
10. Bonini M, et al. Asthma remission one, none and one-hundred thousand: the relevance of the patient's view. *J Asthma*. 2024:1–10.
11. Menzies-Gow A, et al. An expert consensus framework for asthma remission as a treatment goal. *J Allergy Clin Immunol*. 2020;145(3):757–765.
12. Canonica GW, et al. Severe Asthma Network Italy Definition of Clinical Remission in Severe Asthma: A Delphi Consensus. *J Allergy Clin Immunol Pract*. 2023;11(12):3629–3637.
13. Álvarez-Gutiérrez FJ, et al. Spanish Consensus on Remission in Asthma (REMAS). *Arch Bronconeumol*. 2024;60(8):503–509.
14. Kolbeck R, et al. MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. *J Allergy Clin Immunol*. 2010;125(6):1344–1353.e1342.
15. Pham TH, Damera G, Newbold P, Ranade K. Reductions in eosinophil biomarkers by benralizumab in patients with asthma. *Respir Med*. 2016;111:21–29.
16. Bleecker ER, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β(2)-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2115–2127.
17. FitzGerald JM, et al. Benralizumab, an anti-interleukin-5 receptor α 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(10056):2128–2141.
18. Nair P, et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. *N Engl J Med*. 2017;376(25):2448–2458.
19. Korn S, et al. Integrated Safety and Efficacy Among Patients Receiving Benralizumab for Up to 5 Years. *J Allergy Clin Immunol Pract*. 2021;9(12):4381–4392.e4384.
20. Vultaggio A, et al. Long-term effectiveness of benralizumab in severe eosinophilic asthma patients treated for 96-weeks: data from the ANANKE study. *Respir Res*. 2023;24(1):135.
21. Nolasco S, 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.e4374.
22. Sposato B, et al. Severe asthma and long-term Benralizumab effectiveness in real-life. *Eur Rev Med Pharmacol Sci*. 2022;26(20):7461–7473.
23. Pelaia C, 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.
24. Pini L, et al. Unlocking the Long-Term Effectiveness of Benralizumab in Severe Eosinophilic Asthma: A Three-Year Real-Life Study. *J Clin Med*. 2024;13(10).
25. Quarato CMI, et al. Long-Term Clinical Remission on Benralizumab Treatment in Severe Eosinophilic Asthma: A Four-Year Real-Life Study. *J Clin Med*. 2025;14(6).
26. Jackson DJ, et al. Reduction of daily maintenance inhaled corticosteroids in patients with severe eosinophilic asthma treated with benralizumab (SHAMAL): a randomised, multicentre, open-label, phase 4 study. *Lancet*. 2024;403(10423):271–281.
27. Pelaia G, et al. XALOC-1: Clinical Remission Over 2 Years With Benralizumab in Severe Eosinophilic Asthma. *Chest*. 2025;168(1):19–32.
28. Jackson DJ, et al. Benralizumab in severe eosinophilic asthma by previous biologic use and key clinical subgroups: real-world XALOC-1 programme. *Eur Respir J*. 2024;64(1).
29. Menzella F, 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(1):36.
30. Chung KF, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43(2):343–373.
31. Global Initiative for Asthma (GINA). *Difficult-to-treat and severe asthma in adolescent and adult patients, v5.0*. 2024. Available from ginasthma.org.
32. Vultaggio A, et al. Benralizumab: from tissue distribution to eosinophilic cytotoxicity up to potential immunoregulation. *Expert Opin Biol Ther*. 2024:1–11.
33. Canonica GW, et al. Biologics as well as inhaled anti-asthmatic therapy achieve clinical remission: Evidence from the Severe

Asthma Network in Italy (SANI). *World Allergy Organ J*. 2025;18(1), 101016.

34. Wechsler ME, et al. Benralizumab versus Mepolizumab for Eosinophilic Granulomatosis with Polyangiitis. *N Engl J Med*. 2024;390(10):911–921.

35. Menzies-Gow A, et al. Anti-IL-5 (mepolizumab) therapy induces bone marrow eosinophil maturational arrest and decreases eosinophil progenitors in the bronchial mucosa of atopic asthmatics. *J Allergy Clin Immunol*. 2003;111(4):714–719.