Journal of Asthma and Allergy

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ORIGINAL RESEARCH

Benralizumab in Severe Eosinophilic Asthma and Chronic Rhinosinusitis with Nasal Polyps: The Real-World, Multi-Country RANS Observational Study

Tham T Le[1], Benjamin Emmanuel[1], Rohit Katial[2], Trung N Tran[1], Justin Joseph Kwiatek[1], David S Cohen[1], Shoshana R Daniel[3], Yunhui Cao[1], Vivian H Shih[1], Maria Gil Melcón[4], Gilles Devouassoux[5], Girolamo Pelaia[6] On behalf of the RANS Study Investigators

[1]BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, MD, USA; [2]Center for Clinical Immunology, National Jewish Health & University of Colorado School of Medicine, Denver, CO, USA; [3]Market Access Consulting, Fortrea Inc., Durham, NC, USA; [4]Otorhinolaryngology and Head and Neck Surgery Department, University Hospital of Salamanca, Salamanca, Spain; [5]Department of Pulmonology, Hospices Civils de Lyon (HCL), Hôpital de la Croix-Rousse, Lyon, and F-CRIN INSERM Network CRISALIS, Toulouse, France; [6]Department of Health Sciences, University "Magna Graecia" of Catanzaro, Catanzaro, Italy

Correspondence: Girolamo Pelaia, University "Magna Graecia" of Catanzaro, Viale Europa, 88100 Catanzaro, Italy, Tel +39 961 3647171, Fax +39 961 3647193, Email pelaia@unicz.it

Purpose: Real-world evidence of benralizumab effectiveness on nasal polyps (NP) and asthma outcomes in patients with severe eosinophilic asthma (SEA) and comorbid chronic rhinosinusitis with NP are limited. The objective of this study was to assess NP and asthma outcomes in benralizumab-treated patients with SEA and comorbid NP in a real-world setting.

Patients and Methods: RANS was a retrospective, multi-country observational study (ClinicalTrials.gov: NCT05180357) using medical chart reviews of adults with SEA and comorbid NP. Total NP Score (NPS), SinoNasal Outcome Test-22 (SNOT-22) total score, annualized exacerbation rate (AER), and 6-item Asthma Control Questionnaire (ACQ-6) and Asthma Control Test (ACT) scores during the 12 months pre-index (baseline) and post-index (follow-up) were measured. Clinically meaningful improvement from baseline following treatment, in terms of total NPS (≥1-point reduction), SNOT-22 total (≥8.9-point reduction), ACQ-6 (≥0.5-point reduction) or ACT (≥3-point increase) scores, were reported.

Results: A total of 233 patients were included. Baseline mean (standard deviation [SD]) NPS and SNOT-22 total scores were 3.8 (2.4) and 47.5 (22.6), respectively. The mean change (95% confidence interval [CI]) from baseline was –1.2 (–1.7, –0.6) for NPS, and –19.8 (–23.6, –15.9) for SNOT-22. The AER (95% CI) was 1.2 (0.96, 1.41) at baseline and 0.2 (0.13, 0.28) at follow-up. Mean (SD) ACQ-6 and ACT scores were 1.6 (1.3) and 15.0 (5.2) at baseline and 0.8 (1.0) and 22.0 (3.9) at follow-up, respectively. The proportion of patients who achieved clinically meaningful improvements in NPS, SNOT-22 total, ACQ-6, and ACT scores was 49.1%, 67.6%, 56.6%, and 81.1%, respectively.

Conclusion: In this real-world study, improvements in NP and asthma outcomes in patients with SEA and comorbid NP were observed during the 12 months following benralizumab initiation.

Keywords: exacerbations, comorbidity, biologics, patient-reported outcomes, SinoNasal Outcome Test-22, Nasal Polyps Score

Introduction

Chronic rhinosinusitis with nasal polyps (NP) is one of the most common comorbidities in patients with severe asthma.[1] A combination of NP and severe asthma causes a significant and substantial disease burden on health-related quality of life (HRQoL).[2,3] The management of asthma and comorbid NP is challenging, with patients having a higher risk of asthma exacerbations, and has, therefore, become an area of focus for novel targeted therapies.[2,4] The presence of NP is a strong indicator of the eosinophilic phenotype in severe asthma.[3,5]

Received: 25 August 2023
Accepted: 8 March 2024
Published: 5 April 2024

Benralizumab is a monoclonal antibody that binds directly to the IL-5 receptor-α on eosinophils and attracts natural killer cells to induce rapid and near-complete depletion of blood and tissue eosinophils in most patients via apoptosis.[6–8] The presence of NP is predictive of a response to benralizumab, including reductions in exacerbations and improvement in lung function.[3,5,9] In a previous Phase III study (OSTRO), benralizumab reduced symptoms and NP Score (NPS) in patients with severe NP who were symptomatic despite intranasal corticosteroid treatment and who had a history of surgery for NPs and/or systemic corticosteroid (SCS) use.[10] Benralizumab also produced meaningful improvements in HRQoL, lung function, and asthma outcomes in patients with severe eosinophilic asthma (SEA) and comorbid NP in the Phase 3b ANDHI study.[11] The effects of benralizumab were enhanced in the subgroup of NP patients who had comorbid asthma in the OSTRO study.[10] However, the SEA population was likely under-represented in the OSTRO study due to a low proportion of patients with frequent asthma exacerbations. Real-world evidence of benralizumab effectiveness on NP outcomes in patients with SEA and comorbid NP needs further examination.

The RANS study was conducted to improve our understanding of the use of biologics in the management of patients with SEA and comorbid NP. The objective of this retrospective, observational, international study was to describe NP and asthma outcomes in patients with SEA and comorbid NP treated with benralizumab in a real-world setting.

Materials and Methods

Study Design

RANS is a retrospective, observational, multi-country study (NCT05180357) using medical chart reviews of all adults with SEA and comorbid NP who initiated benralizumab in France, Italy, Japan, Spain, and the USA (Supplementary Table 1) between February 2018 and March 2022. The index date was defined as the day of the first benralizumab dose; the baseline period was up to 12 months prior to the index date, and the follow-up period was up to 12 months post-index (Supplementary Figure 1). Patients were censored at the time of switching to another asthma (non-benralizumab) biologic therapy during follow-up. Patient data including demographics, clinical characteristics, medication history, biologic treatment, and NP and asthma clinical outcomes (asthma exacerbations, patient-reported outcomes, and lung function, if available) were abstracted from patient medical charts using a pre-approved electronic case report form. No personal identifiable data were collected, and data from all participating centers were combined into a single anonymized dataset for analysis.

The study was performed in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, Good Pharmacoepidemiology Practices, and all applicable legislation on non-interventional studies and/or observational studies. Ethical approval was provided by the appropriate Institutional Review Board (IRB) and/or Independent Ethics Committee for each clinical site (see Supplementary Table 2).

Study Participants

Patients were eligible for inclusion in the study if they were currently or previously receiving benralizumab for SEA, had a physician-confirmed diagnosis and an evaluation of NP using NPS and/or Sino-Nasal Outcome Test-22 (SNOT-22) before and after the first benralizumab injection, and had a follow-up period of ≥5 months from the first benralizumab injection or ≥4 consecutive injections of benralizumab. Patients were excluded if they had received any other biologics during the 12 months prior to treatment with benralizumab, or if they had previously or were currently receiving any biologics for the treatment of asthma or NP in a clinical trial. The latter criterion did not apply to a small number of patients (n=26) who had previously received biologic treatment from Phase 4, open-label, single-arm interventional studies that provided biologic treatment as part of standard of care (according to approved labeling in that country).

Outcome Measures

The main outcomes included total NPS, SNOT-22 total score, annualized asthma exacerbation rate (AER), and 6-item Asthma Control Questionnaire (ACQ-6) and/or Asthma Control Test (ACT) scores, which were collected up to 12 months pre- and post-index date (ie, during the 12-month baseline and follow-up periods). NPS and/or SNOT-22 scores before and after first benralizumab injection were measured in all patients as part of the study inclusion criteria. The total NPS was the sum of left and right nostril scores (range: 0–8) with higher scores indicating heavier bilateral NP burden. SNOT-22 total scores were

calculated as the sum of all 22 responses (range: 0 to 110) with higher scores indicating poorer HRQoL. Asthma exacerbation was defined as a worsening of asthma leading to one of the following: (1) use of SCS for ≥3 days or a temporary increase in a stable background dosage of oral corticosteroids (OCS); (2) emergency department or urgent care visit (<24 hours) due to asthma that required SCS; (3) or inpatient admission to hospital (≥24 hours) due to asthma. The mean ACQ-6 scores were calculated as the average of all six responses and range from 0 (totally controlled) to 6 (severely uncontrolled). ACT scores were calculated as the sum of all five responses and range from 5 (poorly controlled asthma) to 25 (well-controlled asthma). Within-patient clinically meaningful improvement in total NPS and SNOT-22 total score, ACQ-6, and ACT scores were defined as follows: total NPS (reduction of ≥1 point),[12,13] SNOT-22 total score (reduction of ≥8.9 points),[14] ACQ-6 score (reduction of ≥0.5 points),[15] and ACT score (increase of ≥3 points).[16]

Demographic Characteristics

Baseline demographics, clinical characteristics, and background treatments among patients with SEA and comorbid NP receiving benralizumab were collected during the baseline period. Demographics included age, gender, body mass index, smoking status, and type of hospital. Clinical characteristics included key asthma, NP, OCS-related comorbidities, blood eosinophil count, fractional exhaled nitric oxide (FeNO), lung function, age of onset of asthma, and age at NP diagnosis. Considered OCS-related comorbidities were glaucoma, cataracts, obstructive sleep apnea, renal failure, depression, anxiety, type I/type II diabetes mellitus, osteoporosis/osteopenia/history of fractures, circulatory systems disease (heart failure, myocardial infarction, stroke, hypertension, other), and pneumonia. Information on background treatments included NP surgery and SCS use (for asthma only and for NP only).

Statistical Analysis

All analyses were descriptive in nature. All patients with available data were analyzed for each endpoint. Continuous variables were summarized by providing the number of patients, and mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables were summarized by providing frequency counts and percentages. For total NPS, SNOT-22 total score, and ACQ-6 and ACT scores, the baseline value was derived as the latest existing and non-missing assessment prior to or on the index date. Mean changes from baseline in total NPS and SNOT-22 total score were calculated and provided for patients who had both baseline and follow-up measures. The AER is presented as the annualized rate at baseline and follow-up (95% confidence interval [CI]). Within-patient clinically meaningful improvement in total NPS and SNOT-22 total, ACQ-6, and ACT scores from baseline to follow-up is presented as the percentage of patients who satisfied the criterion for that specific endpoint.

Subgroup Analyses

NPS was assessed in patients with baseline NPS <5 versus ≥5, blood eosinophil count ≥300 cells/μL, and according to history of NP surgery (no baseline NP surgery and no NP surgery/NP surgery at any time pre-index) and country. Baseline, follow-up, and change from baseline in the SNOT-22 total score were analyzed in patients with no previous NP surgery, blood eosinophil count ≥300 cells/μL, and according to baseline SNOT-22 score (8–20 [mild], >20–50 [moderate], ≤50 [mild/moderate], and >50 [severe]), history of NP surgery (no baseline NP surgery and no NP surgery/NP surgery at any time pre-index), and country. Only subgroups with a minimum of 20 patients were assessed.

Results

Patients

A total of 233 patients (France n=31 [13.3%]; Italy n=97 [41.6%]; Spain n=51 [21.9%]; Japan n=16 [6.9%]; USA n=38 [16.3%]) meeting inclusion criteria were included. The mean (SD) age was 56.0 (12.6) years and 53.6% were female. The mean (SD) pre-bronchodilator forced expiratory volume in 1 second was 2.2 (0.8) liters and mean (SD) blood eosinophil count (capped at 2000) was 726.5 (465.8) cells/μL (Table 1). In total, 24 (10.3%) patients had NP surgery during the baseline period and 129 (55.4%) had a lifetime history of NP surgery prior to index; 14 (6.0%) patients had NP surgery during follow-up. Asthma-, NP-, and eosinophil-related comorbidities were observed in 88.8% (n=207) of patients at baseline (Table 2). A total of 22.3% (n=52) of

Table 1 Baseline (12-Month Pre-Index Period) Demographics and Characteristics

Characteristic		N=233
Age, years	Mean (SD)	56.0 (12.6)
Sex, n (%)	Female	125 (53.6)
Race, n (%)	White Asian Black or African American Other[a] Not reported	175 (75.1) 19 (8.2) 4 (1.7) 2 (0.9) 33 (14.2)
Smoking status, n (%) [n=229]	Never Former Current	148 (64.6) 79 (34.5) 2 (0.9)
BMI category, n (%) [n=207]	Underweight (<18.5 kg/m^2) Normal (18.5 to <25.0 kg/m^2) Overweight (25.0 to <30.0 kg/m^2) Obese (≥30 kg/m^2) Moderately obese (30.00–34.99 kg/m^2) Severely obese (≥35.00 kg/m^2)	3 (1.4) 94 (45.4) 68 (32.9) 42 (20.3) 28 (66.7) 14 (33.3)
Type of hospital[b], n (%)	University hospital Private clinic or hospital Non-university specialty hospital Other public hospital	196 (84.1) 21 (9.0) 14 (6.0) 2 (0.9)
Pre-bronchodilator forced expiratory volume in 1 second, L [n=189]	Mean (SD) Median (range)	2.2 (0.8) 2.1 (0.6, 4.5)
Blood eosinophil count [n=176]	Mean (SD), cells/μL[c] Median (range), cells/μL[c] ≥300 cells/μL, n (%)	726.5 (465.8) 621.5 (0, 2000) 152 (86.4)
FeNO[d] [n=87]	Mean (SD), ppb Median (range), ppb ≥25 ppb, n (%)	64.1 (51.1) 54.0 (5.0, 274.0) 67 (77.0)
Total immunoglobulin E in peripheral blood [n=129]	Mean (SD), IU/mL Median (range), IU/mL ≥100 IU/mL, n (%)	420.4 (566.5) 219.0 (11.0, 3368.0) 98 (76.0)
Age at asthma diagnosis, years [n=208]	Mean (SD) Median (range), years	40.2 (15.3) 40.0 (4.0, 77.0)
Age at rhinitis diagnosis, years [n=127]	Mean (SD) Median (range), years	43.3 (14.5) 44.0 (4.0, 77.0)
Time since first appearance of nasal polyps symptoms, years[e] [n=199]	Mean (SD) Median (range), years	10.3 (10.4) 7.0 (0, 50.0)
Nasal polyp surgery prior to index, n (%)	In the 12 months pre-index At any time pre-index	24 (10.3) 129 (55.4)

Notes: [a]Included patients with multiple races. [b]Relevant physician specialties across countries included allergy/immunology, otolaryngology, and pulmonology; the actual specialties were: France – pulmonology, Spain – allergy/immunology, pulmonology, Italy, Japan, and USA – allergy/immunology, otolaryngology, and pulmonology. [c]Blood eosinophil count capped at 2000 cells/μL. [d]Excluded FeNO average results (n=12) reported in case report form based on average of multiple successful FeNO measurements. [e]Index date minus date of first appearance of symptoms.

Abbreviations: BMI, body mass index; FeNO, fractional exhaled nitric oxide; SD, standard deviation.

Table 2 Baseline (12-Month Pre-Index Period) Disease-Related Comorbidities Reported in ≥1% of Patients

Characteristic, n (%)	N=233
Asthma-, nasal polyp- and eosinophil-related comorbidities[a]	207 (88.8)
Asthma[b]	195 (83.7)
Nasal polyps[b]	154 (66.1)
Chronic sinusitis	38 (16.3)
Allergic rhinitis	31 (13.3)
Rhinitis	18 (7.7)
Allergy	10 (4.3)
Aspirin-exacerbated respiratory disease	7 (3.0)
NSAID-exacerbated respiratory disease	7 (3.0)
Bronchiectasis	6 (2.6)
Chronic obstructive pulmonary disease	4 (1.7)
Gastroesophageal reflux	4 (1.7)
Eosinophilic esophagitis	3 (1.3)
Oral corticosteroid-related comorbidities[a]	52 (22.3)
Osteoporosis	17 (7.3)
Obstructive sleep apnea syndrome	9 (3.9)
Sleep apnea syndrome	9 (3.9)
Osteopenia	6 (2.6)
Depression	5 (2.1)
Anxiety	5 (2.1)
Pneumonia	4 (1.7)
Cataract	3 (1.3)

Notes: Percentages add to >100% as more than one comorbidity may be reported per person. [a]Only conditions with prevalence ≥1% are reported. [b]Asthma and nasal polyp diagnosis in the 12 months pre-index.
Abbreviation: NSAID, non-steroidal anti-inflammatory drug.

patients had OCS-related comorbidities. Baseline SCS use was reported for 95 (40.8%) patients for asthma use only and for 17 (7.3%) patients for NP use only (Supplementary Table 3).

NP Outcomes

The mean total NPS (SD) at baseline and follow-up was 3.8 (2.4) and 3.0 (2.1), respectively (Figure 1). The mean change from baseline (95% CI) to follow-up was –1.2 (–1.7, –0.6). When analyzed according to 3-month follow-up windows, the mean change from baseline in total NPS was consistent across the study period (Figure 1). Clinically meaningful improvement (reduction of ≥1 point) in the total NPS during follow-up was observed in 49.1% (28/57) of patients (Figure 2A).

Clinically meaningful improvement (reduction of ≥8.9 points) in the SNOT-22 total score during follow-up was observed in 67.6% (71/105) of patients (Figure 2B). Within the first 6 months, 54.8% (17/31) of patients achieved a clinically meaningful reduction in NPS and 48.8% (21/43) in SNOT-22 score. The mean SNOT-22 total scores (SD) at baseline and follow-up were 47.5 (22.6) and 28.9 (21.1), respectively (Figure 3). The mean SNOT-22 total score change from baseline (95% CI) to the 12 months follow-up was –19.8 (–23.6, –15.9). By follow-up window, the mean change from baseline (95% CI) in SNOT-22 total score was –10.9 (–23.6, 1.8) at >0 to <3 months and the reduction increased to –18.7 (–27.1, –10.4) at ≥3 to <6 months and was then generally consistent throughout the remainder of the study duration (Figure 3).

NP Subgroup Analyses

Patients with a baseline total NPS ≥5 had larger improvements from baseline in total NPS during the follow-up (Supplementary Table 4), compared with the overall patient population (baseline: 6.3 vs 3.8 and follow-up: 4.1 vs 3.0,

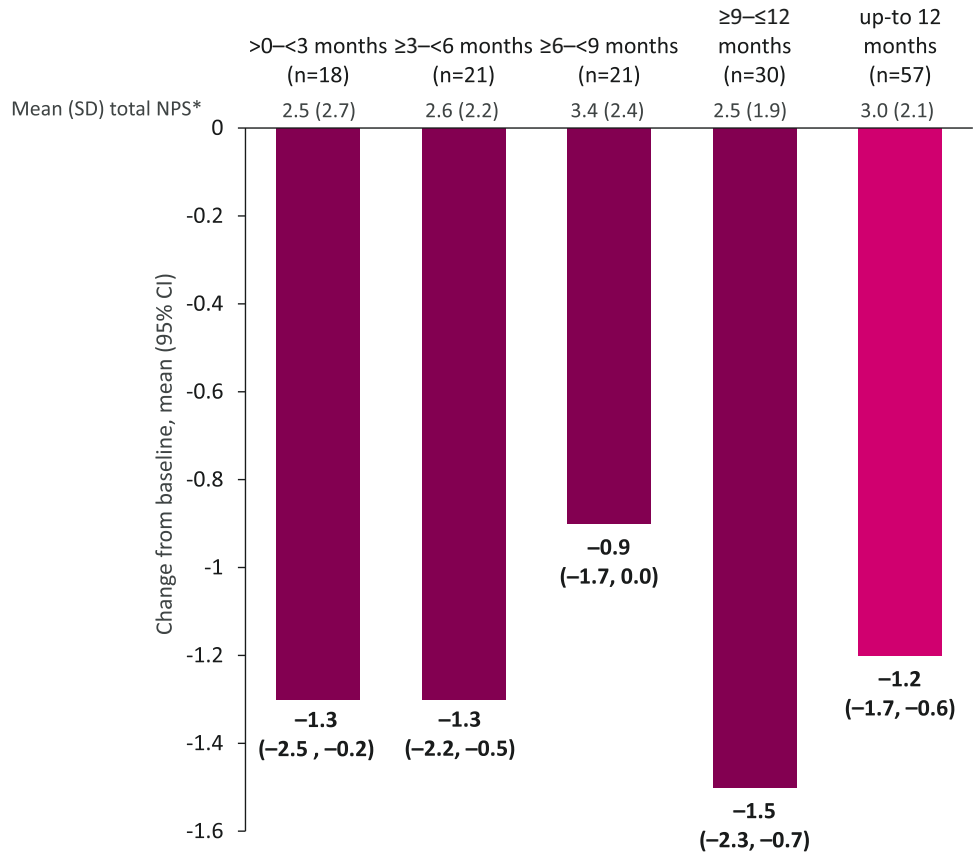

Figure 1 Mean change in total NPS from baseline following benralizumab initiation. Changes from baseline were evaluated in the subset of patients who had both baseline and follow-up available data. *All data. Baseline (n=91) 3.8 (2.4); >0–<3 months, n=20; ≥3–<6 months, n=22; ≥6–<9 months, n=21; ≥9–≤12 months, n=35; up to 12 months, n=63.
Abbreviations: CI, confidence interval; NPS, Nasal Polyp Score; SD, standard deviation.

respectively). Patients with no previous NP surgery and those with a baseline blood eosinophil count ≥300 cells/μL had comparable improvements to the overall patient population. During follow-up, 66.7% (16/24) of patients with a baseline total NPS ≥5 had a clinically meaningful improvement in the total NPS, as did 36.4% (12/33) of those with a baseline total NPS <5. Clinically meaningful improvement in total NPS was seen in 46.8% (22/47) of patients with no baseline NP surgery (in the 12 months pre-index), as with 46.7% (14/30) of patients with and 48.0% (12/25) without NP surgery at any time pre-index, and 53.3% (24/45) of those with a baseline blood eosinophil count ≥300 cells/μL. In patients with a baseline SNOT-22 score >50, greater reductions from baseline were observed versus those with a baseline SNOT-22 score ≤50 (baseline: 32.5 vs 66.4 and follow-up: 21.0 vs 36.8) (Supplementary Table 5). Clinically meaningful improvement in the SNOT-22 total score was seen in 68.4% (65/95) of patients with no baseline NP surgery, 66.7% (36/54) of patients with and 72.9% (35/48) without NP surgery at any time pre-index, and 69.8% (60/86) of those with baseline blood eosinophil count ≥300 cells/μL. In subgroup analyses by country, clinically meaningful improvement in the SNOT-22 total score during follow-up was observed in 72.7% (16/22) and 71.9% (41/57) of patients in France and Italy, respectively, while 56.5% (13/23) of patients in Spain achieved clinically meaningful improvement in total NPS (Supplementary Table 6).

Asthma Outcomes

There was an 84% reduction in the AER from baseline to follow-up (1.2 [95% CI 1.0, 1.4] to 0.2 [95% CI 0.1, 0.3]; Figure 4A). Overall, 49.1% (111/226) and 86.3% (195/226) of patients had zero exacerbations during the baseline and follow-up periods, respectively. Fewer patients had ≥1 exacerbation during follow-up versus baseline (13.7% [31/226] vs 50.9% [115/226]) (Figure 4B). At baseline, the mean (SD) ACQ-6 and ACT scores were 1.6 (1.3) and 15.0 (5.2), respectively (Figures 4C and D). During follow-up, mean (SD) scores were 0.8 (1.0) for ACQ-6 with a mean change from baseline of –0.8 (95% CI –1.1, –0.4)

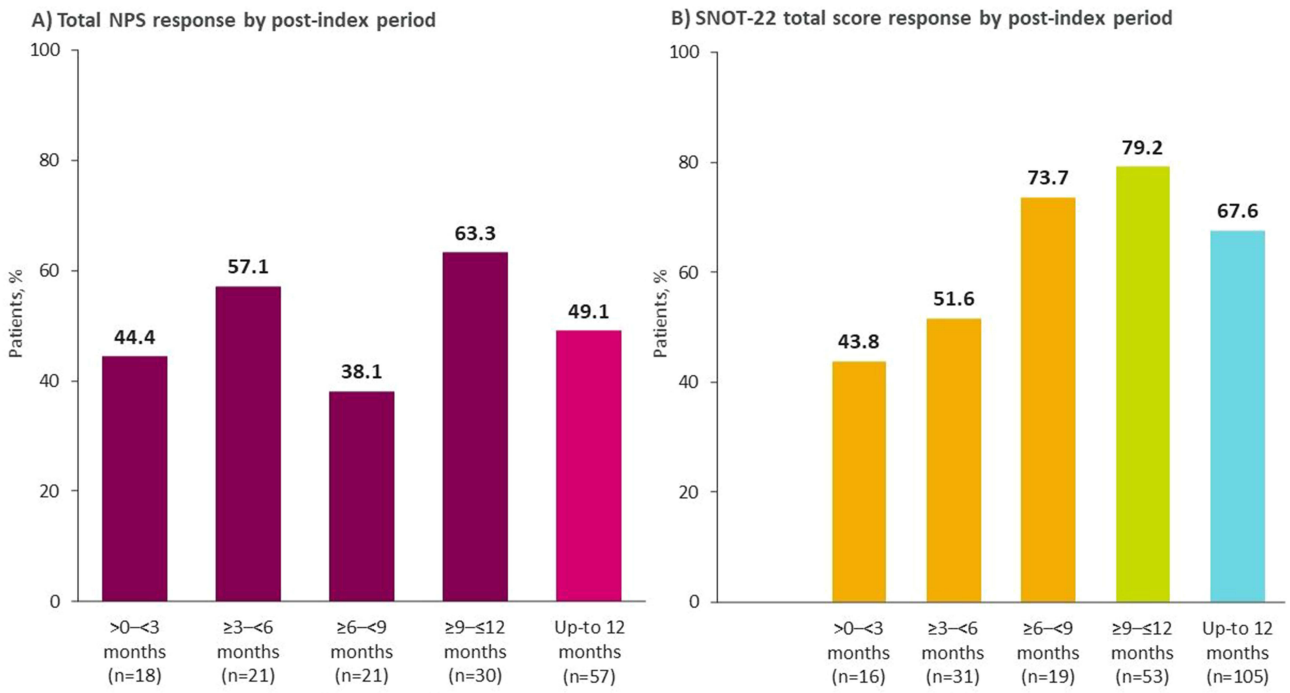

Figure 2 Percentage of patients with clinically meaningful improvement in (**A**) NPS, and (**B**) SNOT-22 total score, following benralizumab initiation. Improvement was defined as total NPS reduction ≥1 point; SNOT-22 total score reduction ≥8.9 points. Within the first 6 months, 54.8% (17/31) of patients achieved clinically meaningful reduction in NPS and 48.8% (21/43) in SNOT-22 score.
Abbreviations: NPS, Nasal Polyp Score; SNOT-22, SinoNasal Outcome Test-22.

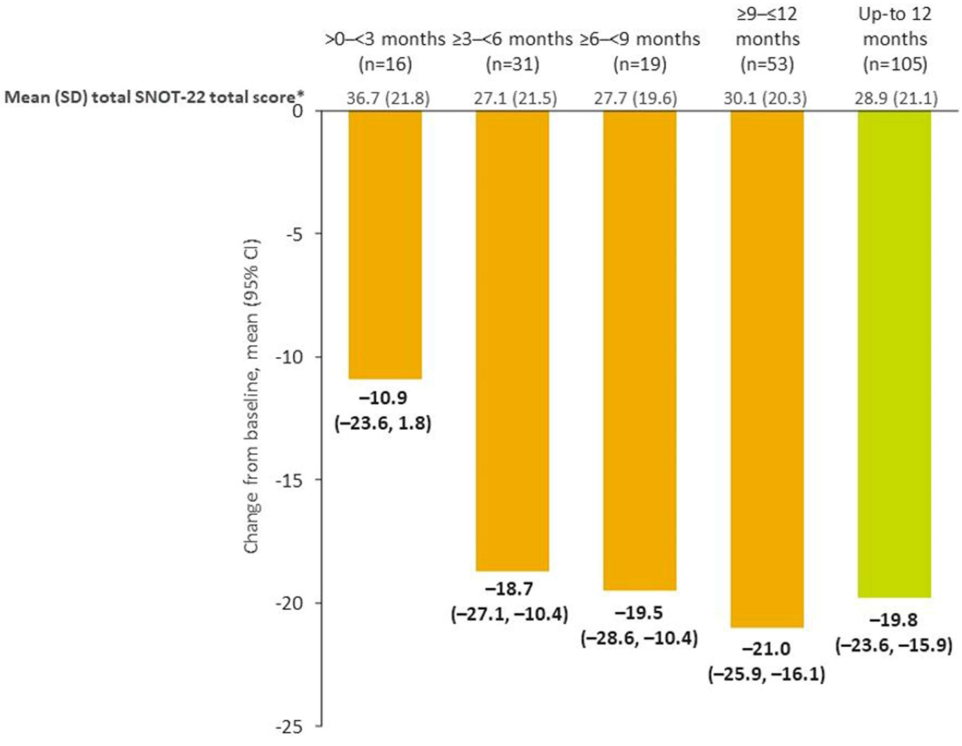

Figure 3 Mean change in SNOT-22 total score from baseline following benralizumab initiation. *All data. Baseline (n=161) 47.5 (22.6); >0–<3 months, n=18; ≥3–<6 months, n=34; ≥6–<9 months, n=22; ≥9–≤12 months, n=54; up to 12 months, n=114.
Abbreviations: CI, confidence interval; SNOT-22, SinoNasal Outcome Test-22; SD, standard deviation.

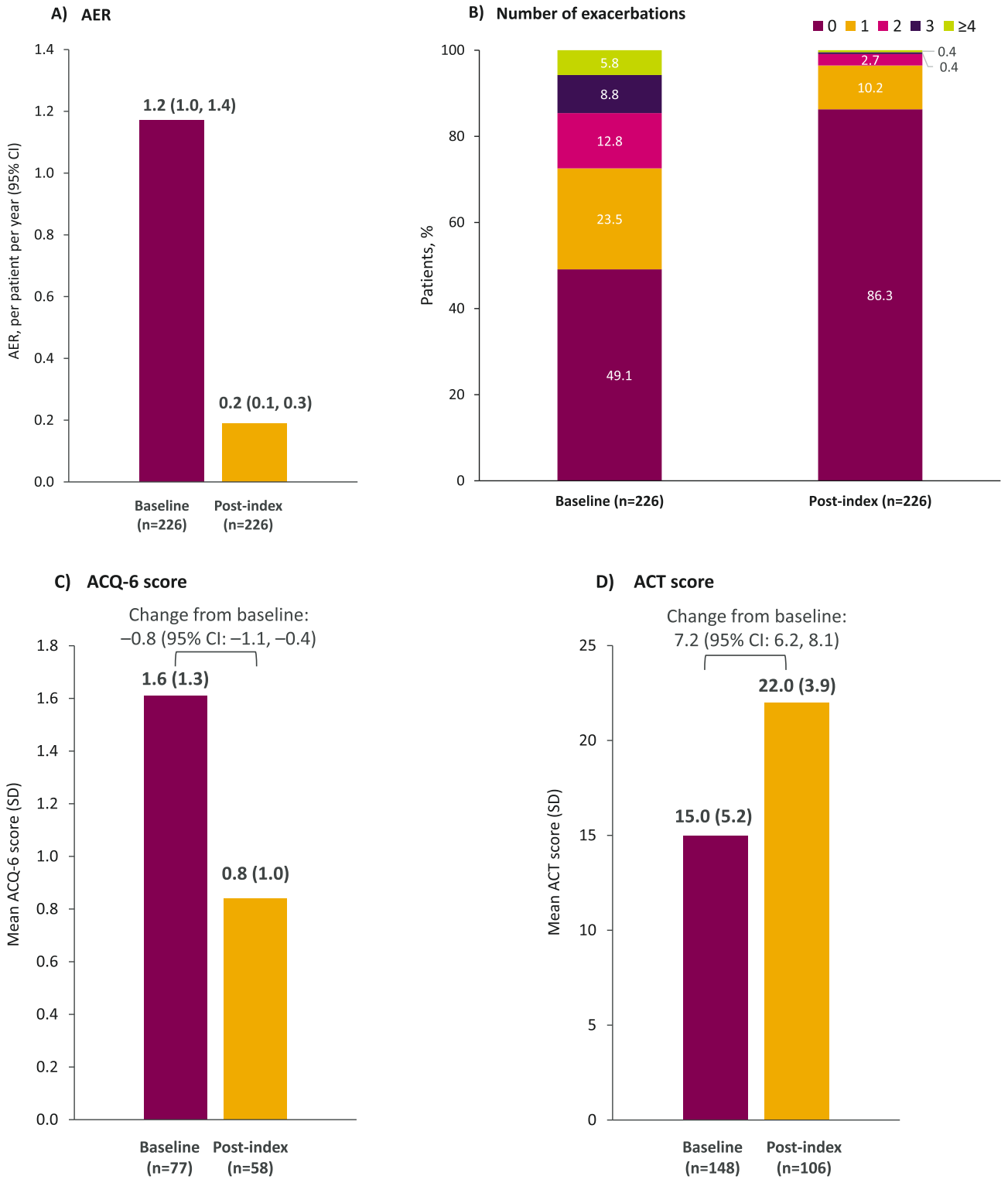

Figure 4 Asthma outcomes at baseline (12-month pre-index period) and following benralizumab initiation: (**A**) AER, (**B**) patients with exacerbations, (**C**) mean ACQ-6 score, and (**D**) mean ACT score. Changes from baseline were evaluated in the subset of patients who had both baseline and follow-up available data.
Abbreviations: AER, annualized exacerbation rate; ACQ-6, 6-item Asthma Control Questionnaire; ACT, Asthma Control Test; CI, confidence interval; SD, standard deviation.

and 22.0 (3.9) for ACT with a mean change from baseline of 7.2 (95% CI 6.2, 8.1). At baseline, 51.9% (40/77) and 22.3% (33/148) of patients had asthma control, defined as an ACQ-6 score <1.5 and an ACT score ≥20, respectively, which increased to 75.9% (44/58) and 80.5% (95/118), respectively, during follow-up (Figure 5). During follow-up, 56.6% (30/53) and 81.1% (81/106) of

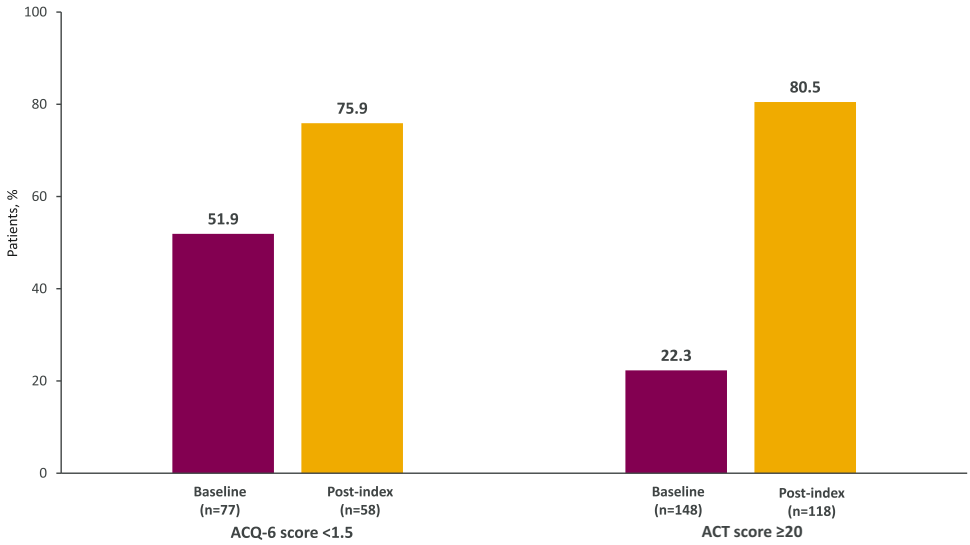

Figure 5 Percentage of patients with controlled asthma at baseline (12-month pre-index period) and during follow-up. Controlled asthma defined as ACQ-6 score <1.5 (well-controlled/partly controlled) or ACT score ≥20 (well-controlled).
Abbreviations: ACQ-6, 6-item Asthma Control Questionnaire; ACT, Asthma Control Test.

patients achieved clinically meaningful improvements in ACQ-6 and ACT scores, respectively. The use of SCS was reported for 28 (12.0%) patients for asthma only and for 11 (4.7%) patients for NP only during follow-up (Supplementary Table 3).

Discussion

The RANS study data show that patients with SEA and comorbid NP experienced improvements in both NP and asthma outcomes during the 12 months following benralizumab initiation. Among patients with a mean change in total NPS from baseline (n=57), nearly one-half had clinically meaningful improvements in the total NPS and two-thirds had clinically meaningful improvements in the SNOT-22 total score. In subgroup analyses, improvements in total NPS and SNOT-22 total score following benralizumab initiation were greater among patients with total baseline NPS ≥5 or SNOT-22 score >50, suggesting an increased benefit of benralizumab in patients with SEA with higher NP disease burden. In addition, the percentage of patients with clinically meaningful improvement in SNOT-22 total score was higher among those with no prior NP surgeries at any time pre-index, compared with those with prior surgeries. Improvements in NPS or SNOT-22 total score were similar among those with high baseline blood eosinophil counts compared with the main analyses, potentially due to the high percentage of patients with SCS use in this cohort.

Interestingly, the percentage of patients with a clinically meaningful improvement in total NPS was slightly higher in the first 6 months (54.8% [17/31]) than over the 12-month follow-up period, while the percentage of patients achieving clinically meaningful improvement in SNOT-22 in the first 6 months (48.8% [21/43]) was lower than over the 12-month follow-up period. These results suggest that the NP-related quality-of-life benefit of benralizumab treatment lags behind the physiological benefit, supporting the suggestion from the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) that treatment with biologics should be maintained, ideally for at least 12 months, to observe expected treatment benefits on NP outcomes.[17] This finding also reinforces the importance of incorporating patient education and expectation management into treatment conversations particularly around the expected timeline of symptom relief and improvements in quality of life.

The treatment effect on NP outcomes observed with benralizumab in RANS was somewhat larger than that reported in the Phase III OSTRO trial in patients with NP, with and without comorbid asthma, in terms of both the improvement in total NPS and the percentage of patients achieving NPS response.[10] This larger treatment effect in RANS may be the result of differences in the patient populations included in the two studies, such as lower baseline NP severity but greater asthma severity with higher eosinophil counts in RANS than in OSTRO. However, the limitations of the RANS study, as discussed below, may also have driven this larger treatment effect.

Treatment with benralizumab was shown to improve asthma outcomes in the RANS study. The percentage of patients with ≥1 asthma exacerbation decreased from 50.9% to 13.7%, with a sizable 84% reduction in AER (from 1.2 to 0.2) from baseline to follow-up. The mean ACQ-6 score decreased from baseline (1.61) to follow-up by –0.8 (95% CI –1.1, –0.4), whereas the mean ACT score increased from baseline (15.0) to follow-up by 7.2 (95% CI 6.2, 8.1). The AER results marginally improved versus the effect observed in patients with SEA in the Phase III CALIMA (28–40% AER reduction) and SIROCCO (17–51% AER reduction) trials,[18,19] and are consistent with prior literature suggesting that the presence of NP is predictive of enhanced treatment response with benralizumab.[3,5,9]

The results of the RANS study are also consistent with results of other real-world studies in patients with SEA and comorbid NP with benralizumab as standard-of-care treatment.[20–24] Country-specific, small-cohort, real-world evidence studies in Italy (n=10 and n=34)[20,24] and the USA (n=23)[23] indicated improvements in NP and asthma outcomes in patients with SEA and comorbid NP who were treated with benralizumab as standard of care for at least 4 months (Italy: mean [SD] SNOT-22 total score decreased from 61.1 [17.2] to 26.3 [19.7] and from 58.6 [18.0] to 44.0 [19.8]; Italy: mean [SD] exacerbations decreased from 4.7 [3.8] to 0.35 [1.37]; USA: mean [SD] SNOT-22 total score decreased from 46.35 [24.96] to 25.79 [23.84]).[20,23,24] In real-world, observational multicenter and/or binational studies (n=79 and n=16), the benefits of benralizumab treatment for 24 weeks to 6 months were further demonstrated on NPS (mean [SD] decrease from 5.5 [1] to 3.0 [2.0]) and SNOT-22 score (median [interquartile range] decrease from 46 [39.5–64.5] to 32 [19–46]) in patients with SEA and NP with or without chronic rhinosinusitis.[21,22] These results are consistent with the decrease from baseline to follow-up observed in this study in SNOT-22 total score in the patient subgroups (≥20 patients) from Italy (from 50.2 to 27.7) and France (from 49.9 to 34.0) and in total NPS in those from Spain (from 4.4 to 3.3).

This study supports our understanding of the NP response to benralizumab specifically in patients with SEA, who are under-represented in stand-alone NP clinical trials. Therefore, the findings from this real-world study on the benefits of benralizumab help inform clinical considerations around biologic treatment of severe asthma in the context of comorbid NP.

The strength of this retrospective, observational study is that it was based on real-world chart reviews during the 12 months following benralizumab initiation and includes a large number of patients from multiple countries. The main limitation of RANS, as a single-arm study, is the lack of a comparison group; as treatment with biologic therapies is often initiated at the time of disease worsening, it is possible that the improvements observed in this real-world study may represent regression to the mean, potentially confounding the effect of benralizumab, which cannot be elucidated without a comparable patient cohort. Furthermore, patients who switched to an alternative biologic therapy were censored, whereas those who continued to use benralizumab were analyzed, meaning that the efficacy of benralizumab could potentially have been overestimated. However, during the follow-up period, only five out of 233 patients (2.1%) permanently discontinued benralizumab treatment with none switching to another biologic therapy, and as this was a small proportion of the total study population, these cases are unlikely to have significantly impacted the overall results or conclusions. The remaining limitations are frequently inherent in retrospective analyses based on chart reviews. The study findings may not be representative of the overall population of patients with SEA and comorbid NP treated with benralizumab, as RANS included only participating hospitals and participating patients for whom NP clinical and symptomatic outcomes were recorded before and during benralizumab treatment. While no confirmation of SEA diagnosis was required for inclusion, all patients received benralizumab per local country regulations. Additionally, changes from baseline in total NPS and SNOT-22 total score were examined in relatively few patients at 12 months' follow-up (24% [57/233] and 45% [105/233], respectively). Data captured were limited to information available in medical records with missing data, providing what had been recorded at the time of consultation and depending on recording information provided by participating centers from different countries. Despite data checks and monitoring, there may be potential inconsistencies of entered data; however, data were reported for clean patient forms only. Finally, confounders were not adjusted for, and country-specific data could not be presented for all countries.

Future studies should extend the examination of benralizumab effects in patients with NP but without comorbid asthma.

Conclusion

In conclusion, improvements in both asthma and NP outcomes were seen during the 12-month period following benralizumab initiation in this real-world study, supporting the clinical effects of benralizumab in patients with SEA and comorbid NP.

Abbreviations

ACT, Asthma Control Test; ACQ-6, 6-item Asthma Control Questionnaire; AER, annualized exacerbation rate; CI, confidence interval; EUFOREA, European Forum for Research and Education in Allergy and Airway Diseases; FeNO, fractional exhaled nitric acid; HRQoL, health-related quality of life; NP, nasal polyps; NPS, Nasal Polyp Score; OCS, oral corticosteroid; SCS, systemic corticosteroid; SD, standard deviation; SEA, severe eosinophilic asthma; SNOT-22, SinoNasal Outcome Test-22.

Data Sharing Statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Acknowledgments

We would like to thank all patients for their participation, and the RANS study principal investigators and other staff at the study sites (Supplementary Table 1); Dr James Kreindler as previous Senior Global Medical Affair Lead for the RANS study; and Joseph Gaab for support with programming and analysis.

This study was supported by AstraZeneca. The authors would like to thank Susanne Ulm and Anna Mett of inScience Communications, Springer Healthcare Ltd, UK, for providing medical writing support, in accordance with Good Publication Practice guidelines, which was funded by AstraZeneca.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. All authors have drafted or substantially revised or critically reviewed the article. All authors have agreed on the journal to which the article will be submitted. All authors reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage. All authors agree to take responsibility and be accountable for the contents of the article.

Disclosure

Tham T. Le, Benjamin Emmanuel, David S. Cohen, Trung N. Tran, Yunhui Cao and Vivian H. Shih are employees of, and own stock in, AstraZeneca. Rohit Katial and Justin J. Kwiatek are former employees of AstraZeneca, Denver, CO, USA, and Justin J. Kwiatek is an employee of GlaxoSmithKline, Upper Providence, PA, USA since June 2023. Shoshana Daniel is an employee of Fortrea Inc. Maria Gil Melcón reports consultancy fees from AstraZeneca, GlaxoSmithKline, Novartis, and Sanofi Genzyme, and participation at medical meetings for AstraZeneca, GlaxoSmithKline, Novartis, and Sanofi Genzyme. Gilles Devouassoux reports consultancy fees from ALK, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Menarini, Mundipharma, Novartis Pharma, Sanofi, and Vivisol; participation at medical meetings for AGIR à dom, ALK, AstraZeneca, Boehringer Ingelheim, Chiesi, CIPLA, GlaxoSmithKline, Meda, MSD, Menarini, Novartis Pharma, Orkyn, Sanofi, Takeda, and TEVA; PI for clinical trials from AB Science, ALK, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Gossamer, Lilly, Novartis Pharma, Regeneron, Roche, Sanofi, Teva, Vitalair, and Zambon; and research grants from AGIR à dom, ALLP, Chiesi, GlaxoSmithKline, MSD, Novartis Pharma, Orkyn, Takeda, and Vivisol. Girolamo Pelaia reports advisory board fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Guidotti, Insmed, Lusofarmaco, Menarini, Neopharmed Gentili, Novartis, Sanofi, and Zambon. The authors report no other conflicts of interest in this work.

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