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Asthma and Lower Airway Disease

Mepolizumab Effectiveness in Severe Asthma With/Without Chronic Rhinosinusitis With Nasal Polyps: Real-World Pooled Analysis

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ABSTRACT

Background: Severe asthma with an eosinophilic phenotype (SAEP) and chronic rhinosinusitis with nasal polyps (CRSwNP) are predominantly type 2-driven diseases, characterised by eosinophilic inflammation and substantial disease burden. Mepolizumab, a humanised monoclonal antibody that targets interleukin-5, a key cytokine in type 2 inflammation, is an effective, approved treatment both in SAEP and CRSwNP. We aimed to analyse real-world evidence of mepolizumab effectiveness in patients with comorbid SAEP and CRSwNP.

Methods: This study pooled five existing, predominantly European cohorts to describe the impact of mepolizumab on the rate of clinically significant exacerbations (CSEs) and other outcomes in adults with SAEP without and with comorbid CRSwNP (SAEP[−]CRSwNP and SAEP[+]CRSwNP, respectively).

Results: Overall, 1037 patients were included. Baseline characteristics were similar in both cohorts. Mepolizumab was associated with a reduction from baseline in the annual rate of CSEs at 12-months post-initiation (SAEP[−]CRSwNP: 72.7%; SAEP[+]CRSwNP: 79.7%), irrespective of baseline blood eosinophil count (BEC). When patients with SAEP[+]CRSwNP were compared with patients with SAEP[−]CRSwNP, a 30.0% incremental benefit in the reduction of CSEs was observed. At 12-months post-initiation, mepolizumab was also associated with a reduction in oral corticosteroid use and BEC, and

Abbreviations: ACT, Asthma Control Test; aRR, annual rate ratio; BEC, blood eosinophil count; BMI, body mass index; CRSwNP, chronic rhinosinusitis with nasal polyps; CSEs, clinically significant exacerbations; ED, emergency department; EGPA, eosinophilic granulomatosis with polyangiitis; FeNO, fractional exhaled nitric oxide; FVC, forced vital capacity; I^2, heterogeneity index; IgE, immunoglobulin E; IL, interleukin; IPD, individual patient data; Liège-BSAR, Belgium Severe Asthma Registry (Liège); MEPOLYP, real-world effectiveness of MEpolizumab in patients with severe eosinophilic asthma and comorbid chronic rhinosinusitis with or without nasal POLYPs; OCS, oral corticosteroid; ppb, parts per billion; REALITI-A, REAL world effectiveness of mepolizumab In paTIent care – Asthma study; REDES, REal worlD Effectiveness and Safety of Mepolizumab; RELIght, A two-year REal-LIfe study of mepolizumab in patients with severe eosinophilic asTHma in Greece; SAEP, Severe asthma with an eosinophilic phenotype; SD, standard deviation.

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an improvement in lung function and Asthma Control Test (ACT) scores in both cohorts. Post-mepolizumab initiation, ≥ 3 clinical remission criteria were fulfilled by 47.2% and 52.3% of patients with SAEP[−]CRSwNP and SAEP[+]CRSwNP, respectively.

Conclusions: The results provide a greater understanding of mepolizumab's effectiveness, demonstrating a substantial improvement in asthma outcomes, irrespective of baseline BEC and the presence of comorbid CRSwNP.

1 | Introduction

Of the estimated 262 million patients with asthma globally [1], approximately 7.7% have severe asthma [2]. It is estimated that up to 93% of patients with severe asthma have an eosinophilic phenotype (severe asthma with an eosinophilic phenotype [SAEP]) [3]. Elevated blood eosinophil count (BEC) may be indicative of type 2 inflammation and correlates with asthma severity and frequency of exacerbations, accelerated lung function decline, substantial airway obstruction and remodelling, and high levels of cytokine production and release (e.g., interleukin [IL]-4, IL-5 and IL-13) [3, 4]. SAEP is associated with substantial physical and emotional impact, including frequent exacerbations, symptom burden, anxiety, and depression [4, 5].

Patients with SAEP are reported to have significant comorbidities, including chronic rhinosinusitis with nasal polyps (CRSwNP) [6]. Both SAEP and CRSwNP share underlying core pathophysiological mechanisms driven by chronic type 2 inflammation, which can lead to elevated local eosinophil infiltration and higher BEC than those without comorbid disease [7–10]. Comorbid CRSwNP has been reported in 10.7%–40.6% of patients with SAEP [11, 12]. It is associated with significant treatment challenges and substantial disease burden, including frequent exacerbations, poor asthma control, increased airway obstruction, greater eosinophilic inflammation, higher treatment costs, and high nasal polyp recurrence rates; all of these can negatively impact health-related quality of life, compared with patients without comorbid disease [11–13]. The burden of disease associated with SAEP with comorbid CRSwNP (SAEP[+]CRSwNP) is reported to be greater than in those without comorbid CRSwNP (SAEP[−]CRSwNP) [14–16].

Mepolizumab is a humanised monoclonal antibody that specifically targets IL-5, a key cytokine in type 2 airway inflammation. Mepolizumab is approved for the treatment of uncontrolled SAEP and has been shown, in clinical and real-world studies, to reduce rates of clinically significant asthma exacerbations (CSEs), oral corticosteroid (OCS) use, and peripheral BEC, with long-term tolerability [12, 17–20]. Mepolizumab is also approved for the treatment of CRSwNP. In clinical and real-world studies, mepolizumab has demonstrated reductions in nasal polyp size, the requirement for nasal surgeries, OCS use, and BEC, resulting in improvements in nasal symptoms and patient quality of life [17, 21–26].

There remains limited published real-world data on the effectiveness of mepolizumab on reducing CSEs in patients with SAEP[+]CRSwNP in a real-world setting. The MEPOLYP (Real-world effectiveness of MEpolizumab in patients with severe eosinophilic asthma and comorbid chronic rhinosinusitis with or without nasal POLYPs) study aimed to further describe patient characteristics and clinical effectiveness of mepolizumab in a large population of patients with SAEP[−]CRSwNP and SAEP[+]CRSwNP.

2 | Materials and Methods

2.1 | Study Design

MEPOLYP was an observational, multi-country, retrospective pooled analysis examining real-world use and effectiveness of mepolizumab in patients with SAEP[−]CRSwNP or SAEP[+]CRSwNP in published cohorts with predominantly European data (Liège-BSAR: Belgium Severe Asthma Registry [Liège-BSAR], Swiss Severe Asthma Registry [SSAR], REAL world effectiveness of mepolizumab In paTIent care—Asthma study [REALITI-A], REal worlD Effectiveness and Safety of Mepolizumab [REDES], A two-year REal-LIfe study of mepolizumab in patients with severe eosinophilic asTHma in Greece [RELIght]; shown in Figure 1 and is detailed further in Table S1) [12, 20, 27–29].

Endpoints were compared 12 months post- versus 12 months pre-mepolizumab initiation. Baseline information was captured from data available at the index date or the most recent data available in the 12-month pre-mepolizumab period (excluding BEC, which was assessed in a 6-month pre-mepolizumab period). The index date was defined as the first prescription record of mepolizumab during the patient identification period. The patient identification period was from 2 December 2015 (date of mepolizumab approval for SAEP in the European Union) until the last follow-up visit of the last patient in the cohorts. Patients were followed for up to 24 months and were expected to have a minimum follow-up of 12 months post-mepolizumab initiation (Figure S1).

2.2 | Study Population

Patients included in the MEPOLYP analysis were aged ≥ 18 years at the index date, had a clinical diagnosis of SAEP, were treated with mepolizumab, provided informed consent, had relevant healthcare records available for at least 12 months pre-index and at least 12 months post-index, and were included in existing registries or prospective studies (Figure 1). Definitions for diagnosis of CRSwNP are included in the Appendix S1: Supplementary Methods.

2.3 | Data Sources

Data sources included existing cohorts of patients with SAEP from Spain, Italy, Belgium, Greece, United Kingdom, Germany,

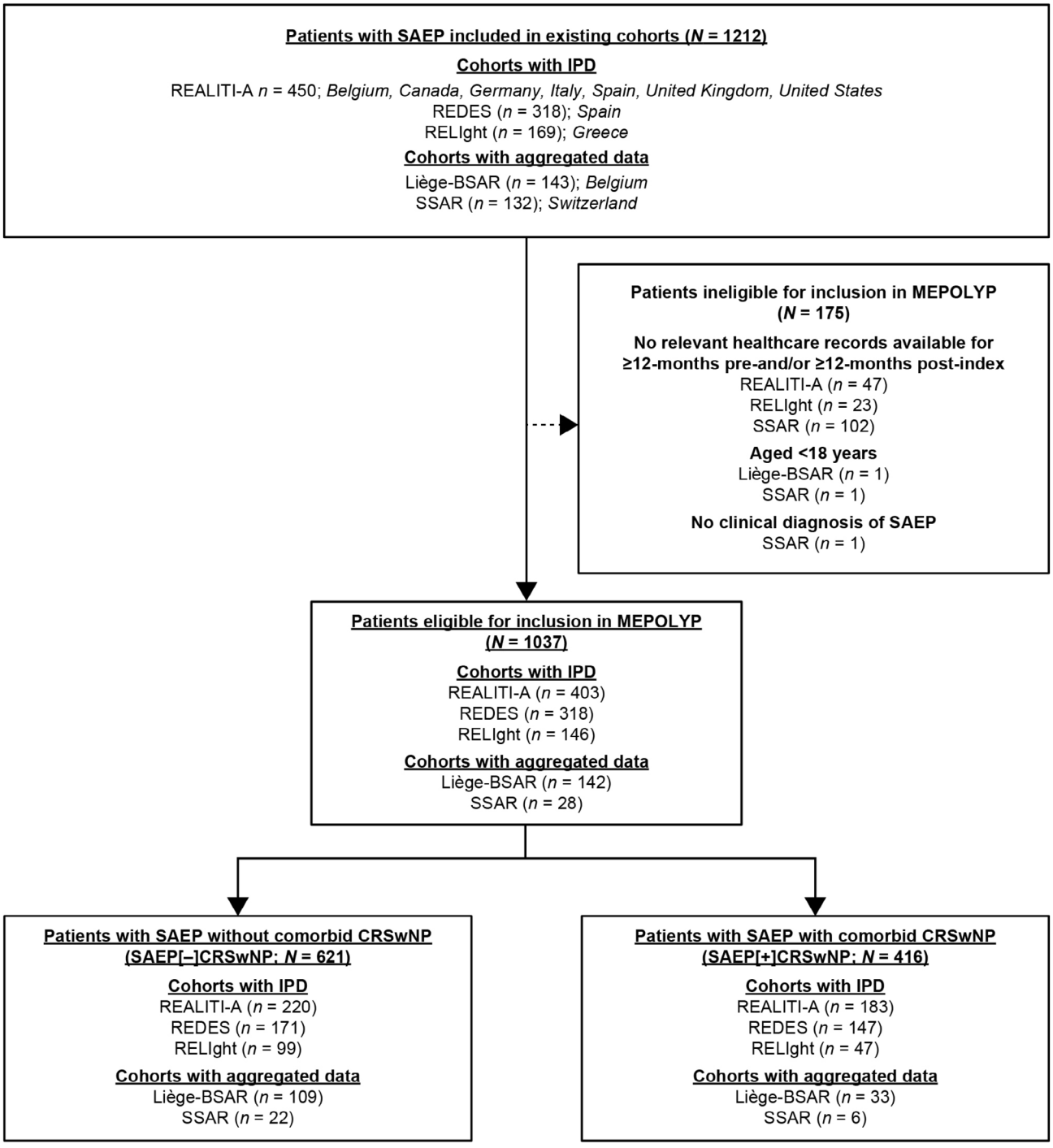


FIGURE 1 | Existing cohorts of patients with SAEP describing real-world effectiveness of mepolizumab included in the MEPOLYP analysis. Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; IPD, individual patient data; Liège-BSAR: Belgium Severe Asthma Registry (Liège); MEPOLYP, Real-world effectiveness of MEpolizumab in patients with severe eosinophilic asthma and comorbid chronic rhinosinusitis with or without nasal POLYPs; REALITI-A, REAL world effectiveness of mepolizumab in paTIent care—Asthma study; REDES, REal worlD Effectiveness and Safety of Mepolizumab; RELIght, A two-year REal-LIfe study of mepolizumab in patients with severe eosinophilic asTHma in Greece; REDES, REal worlD Effectiveness and Safety of Mepolizumab; SAEP, severe asthma with an eosinophilic phenotype; SSAR: Swiss Severe Asthma Registry.

United States, Switzerland, and Canada (Figure 1; listed in order of highest number of patients included). Of the 1037 patients included, only 54 were not from Europe (35 patients from the United States and 19 patients from Canada were included in the REALITI-A study).

Pooled individual patient data from the REALITI-A, REDES, and RELIght cohorts that provided raw data were combined with aggregated data from the Liège-BSAR and SSAR cohorts. Patients from Belgium and Spain were included in two data sources each. To avoid duplications, patient data were only

included from the larger existing cohort (Belgium: $n = 17$ patients included in REALITI-A excluded from Liège-BSAR; Spain: in case of duplication, only data from REDES were included).

2.4 | Study Endpoints

All endpoints were assessed and described separately in the SAEP[−]CRSwNP and SAEP[+]CRSwNP cohorts (Table 1).

The primary endpoint was the change in rate of CSEs (defined according to the European Respiratory Society/American Thoracic Society consensus [30] as a deterioration in asthma requiring the use of systemic corticosteroids and/or emergency department [ED] visit and/or hospitalisation) 12-months post- versus pre- mepolizumab initiation in patients with SAEP[−]CRSwNP or SAEP[+]CRSwNP. Secondary and exploratory endpoints relating to CSEs, exacerbations, OCS use, lung function, asthma control, BEC, and clinical remission are described in Table 1.

Patient demographics, clinical and disease-related characteristics at mepolizumab initiation, and pre-mepolizumab initiation asthma treatment patterns (e.g., OCS, ICS, inhaled treatments) were described as a secondary endpoint (Table 1).

2.5 | Data Analysis

All patients who met the eligibility criteria were considered as the enrolled population for evaluating demographic, clinical, and disease characteristics. Patients with at least one subcutaneous dose of mepolizumab 100 mg (approved dose for patients with SAEP) were considered as the analysis set; all endpoints were evaluated in the analysis set.

Data were analysed using SAS software (SAS Institute, North Carolina, USA), version 9.3 or higher, and cohort-level pooling methods were implemented in R version 4.2.1.

Further details on pooling methodology and data analysis are provided in the Appendix S1: Supplementary Methods.

2.6 | Ethics and Consent

This study complied with all applicable laws regarding patient privacy. Where data had already been collected in registries, no direct subject contact or primary collection of individual human subject data occurred. Where additional patient data were required, individual consent was obtained prior to the use of pre-existing patient data. Informed consent was confirmed from all data cohorts. The consent form was approved by an Ethics Committee and/or Institutional Review Board, which was compliant with the General Data Protection Regulation and any local requirements. Patients who did not provide informed consent were excluded from this analysis.

Aggregated outcomes data in tabular form were produced to avoid subject identification. This was conducted in accordance with the Declaration of Helsinki and in compliance with the applicable laws and regulatory requirements in the countries where the pooled analysis was conducted.

3 | Results

3.1 | Demographic and Clinical Characteristics

A total of 1037 patients were included in the pooled analysis; further details on the number of patients included from each data source are provided in Figure 1. Overall, 94.8% of patients were from Europe.

Patient baseline demographics were similar in both the SAEP[−]CRSwNP ($N = 621$) and SAEP[+]CRSwNP ($N = 416$) cohorts (mean age 55.7 years and 55.2 years; mean body mass index (BMI) 29.2 kg/m^2 and 27.4 kg/m^2, respectively); however, there was a greater proportion of females in the SAEP[−]CRSwNP cohort than in the SAEP[+]CRSwNP cohort (70.5% vs. 59.4%, respectively) (Table 2). Comorbidities reported in > 20% of patients (in at least one cohort) were obesity (60.5% and 29.0%), gastroesophageal reflux (28.5% and 32.1%), allergic rhinitis (28.2% and 29.2%), anxiety (20.9% and 16.0%) and bronchiectasis (14.0% and 21.6%) in the SAEP[−]CRSwNP and SAEP[+]CRSwNP cohorts, respectively. Mean (standard deviation [SD]) BEC was 583.3 cells/μL (558.1) for patients in the SAEP[−]CRSwNP cohort and 725.1 cells/μL (712.7) for patients in the SAEP[+]CRSwNP cohort. In both cohorts, at least 95% of patients had received asthma/CRSwNP-related treatment pre-mepolizumab initiation, and 39.2% and 38.4% of patients in the SAEP[−]CRSwNP and SAEP[+]CRSwNP cohorts, respectively, were using maintenance OCS at index (mean [SD] maintenance dose at baseline; 8.0 mg/day [9.6] and 6.7 mg/day [7.2], respectively; Table 3).

3.2 | Exacerbations

At baseline, patients with SAEP[−]CRSwNP had a mean (SD) of 4.4 (3.6) CSEs and patients with SAEP[+]CRSwNP had a mean (SD) of 4.2 (3.3) CSEs (Table 2). At 12 months post-initiation, mepolizumab was associated with a reduction from baseline in the annual rate of CSEs in both cohorts (Table 3; SAEP[−]CRSwNP: 72.7% [95% confidence interval (CI) 67.8, 76.9]; SAEP[+]CRSwNP: 79.7% [95% CI 74.4, 83.8]). At 24 months post-initiation, the reduction in CSEs from baseline was similar to the reduction at 12 months in both cohorts (Table 3). When assessed by baseline BEC value, mepolizumab was effective in reducing the rate of CSEs observed in patients with SAEP[−]CRSwNP and SAEP[+]CRSwNP, irrespective of baseline BEC (Figure 2A,B). The annual rate of CSEs decreased as the quartile of baseline BEC increased (Table S2). A significantly higher response was found with increasing baseline BEC values for patients with SAEP[−]CRSwNP ($p = 0.0005$; Figure 2A). A non-significant trend was also found for patients with SAEP[+]CRSwNP, with a high response observed even in those with low baseline BEC ($p = 0.1599$; Figure 2B).

When the change in the annual rate of CSEs from 12-months pre-initiation to 12-months post-initiation was compared statistically

TABLE 1 | Endpoints included within the MEPOLYP analysis.

Outcome	Endpoint	Description
CSEs[a]	Primary	Reduction in rate of CSEs between the 12-month post- and pre- mepolizumab initiation periods, including the effect of baseline BEC on response
	Exploratory	Reduction in rate of CSEs between the 24-month follow-up period and the 12-month pre-initiation period
		Reduction in rate of CSEs from 12-months post- versus 12-months pre-initiation whilst controlling for baseline demographic and clinical characteristics, and treatment distribution between cohorts
Exacerbations[b]	Secondary	Reduction in rate of asthma exacerbations that required ED visits or hospitalisation between the 12-month post- and pre- mepolizumab initiation periods
		Reduction in rate of asthma exacerbations that required hospitalisation between the 12-month post- and pre- mepolizumab initiation periods
OCS dose	Secondary	Reduction in daily OCS maintenance dose at 6- and 12-months post-mepolizumab initiation and the 12-month pre-initiation period
Lung function	Secondary	Improvement in FEV_1 values at 6-, 12-, 18- and 24-months post-mepolizumab initiation with the pre-mepolizumab treatment period (using the historical value nearest to the index date in the pre-initiation period) with FEV_1 values
		Improvement in % predicted FEV_1 values at 6, 12, 18 and 24 months
Asthma control	Secondary	Improvement in ACT scores at 6- and 12-months post-mepolizumab initiation versus the pre-mepolizumab treatment period (using the historical score nearest to the index date in the pre-initiation period) with ACT
BEC	Exploratory	Reduction in peripheral BECs in the 12-month post-initiation period compared with 6-months pre-initiation
		Reduction in rate of CSEs by quartiles of peripheral BEC at baseline for each cohort
Clinical remission[c]	Exploratory	Clinical remission in patients who achieved a CSE reduction (as assessed in the primary endpoint) in the 12-month post-mepolizumab initiation period[d]
	Exploratory	Patients who achieved clinical remission and the proportion of patients who satisfied two, three or all four criteria of clinical remission
Patient demographics, clinical and disease-related characteristics	Secondary	Patient demographic, clinical and disease characteristics at initiation of mepolizumab
Pre-mepolizumab initiation asthma treatment patterns	Secondary	Pre-mepolizumab initiation asthma treatment patterns

Abbreviations: ACQ-5, Asthma Control Questionnaire-5; ACT, Asthma Control Test; BEC, blood eosinophil count; CSE, clinically significant exacerbation; ED, emergency department; FEV_1, forced expiratory volume in 1 second; MEPOLYP, real-world effectiveness of MEpolizumab in patients with severe eosinophilic asthma and comorbid chronic rhinosinusitis with or without nasal POLYPs; OCS, oral corticosteroids.

[a]CSEs were defined according to the European Respiratory Society/American Thoracic Society consensus [30] as a deterioration in asthma requiring the use of systemic corticosteroids and/or ED visit and/or hospitalisation.

[b]Exacerbations were defined as a worsening of asthma requiring the use of systemic corticosteroids for at least three consecutive days (or for patients on a stable maintenance dose, an increase in the use of systemic corticosteroids).

[c]Clinical remission was defined as (1) no asthma exacerbations during the 12-month period (exacerbations defined as a worsening of asthma requiring the use of systemic corticosteroids for at least three consecutive days [or for patients on a stable maintenance dose, an increase in the use of systemic corticosteroids]); (2) no OCS use for asthma during the 12-month period; (3) Asthma Control Questionnaire-5 (ACQ-5) < 1.5 or ACT ≥ 20, assessed at the end of the 12-month period; (4) lung function stabilisation (no decline of lung function measured using FEV_1 from pre-initiation period ≥ 100 mL at 12 months) [31].

[d]Patients who discontinued treatment before 12 months in the post-mepolizumab initiation period were not included.

TABLE 2 | Baseline demographics and clinical characteristics of patients with SAEP[−]CRSwNP and SAEP[+]CRSwNP pre-mepolizumab initiation.

	n	SAEP[−]CRSwNP (*N* = 621)	*n*	SAEP[+]CRSwNP (*N* = 416)
Baseline demographics				
Age, years, mean (SD)	621	55.7 (13.3)	416	55.2 (12.2)
Sex, female, *n* (%)	621	438 (70.5)	416	247 (59.4)
Smoking status at baseline, *n* (%)	621		416	
Never smoked		379 (61.0)		255 (61.3)
Ex-smoker		210 (33.8)		145 (34.9)
Current		26 (4.2)		5 (1.2)
Unknown		6 (1.0)		11 (2.6)
BMI, kg/m^2, mean (SD)	618	29.2 (6.9)	414	27.4 (5.6)
Country, *n* (%)	621		416	
Spain		171 (27.5)		147 (35.3)
Belgium		125 (20.1)		46 (11.1)
Greece		99 (15.9)		47 (11.3)
Italy		69 (11.1)		109 (26.2)
United Kingdom		68 (11.0)		30 (7.2)
United States		31 (5.0)		4 (1.0)
Germany		26 (4.2)		18 (4.3)
Switzerland		22 (3.5)		6 (1.4)
Canada		10 (1.6)		9 (2.2)
Clinical characteristics				
Comorbidities, *n* (%)[a]				
Obesity (BMI > $30\,kg/m^2$)	618	374 (60.5)	414	120 (29.0)
Gastroesophageal reflux disease	606	173 (28.5)	399	128 (32.1)
Allergic rhinitis	401	113 (28.2)	233	68 (29.2)
Anxiety	484	101 (20.9)	344	55 (16.0)
Depression	507	98 (19.3)	350	38 (10.9)
Atopic dermatitis	512	83 (16.2)	383	35 (9.1)
Bronchiectasis	193	27 (14.0)	153	33 (21.6)
Diabetes	338	44 (13.0)	206	17 (8.3)
COPD	518	37 (7.1)	365	11 (3.0)
EGPA	271	10 (3.7)	147	5 (3.4)
Vasculitis	211	3 (1.4)	178	7 (3.9)
Hypereosinophilic syndrome	513	4 (0.8)	365	8 (2.2)
Eosinophilic oesophagitis	212	1 (0.5)	176	3 (1.7)
Lung function, mean (SD)				
FEV_1 (pre-bronchodilator), mL	237	1830.6 (712.3)	225	2034.7 (825.1)

(Continues)

TABLE 2 | (Continued)

	n	SAEP[−]CRSwNP (*N* = 621)	*n*	SAEP[+]CRSwNP (*N* = 416)
FEV_1 (post-bronchodilator), mL	379	1845.2 (727.3)	209	2208.5 (829.8)
% predicted FEV_1, %	382	68.1 (22.3)	214	74.9 (20.8)
FEV_1/FVC ratio	369	66.2 (15.3)	212	65.8 (19.1)
Biomarkers, mean (SD)				
FeNO, ppb	382	50.8 (45.7)	247	59.3 (46.6)
BEC, cells/μL	532	583.3 (558.1)	384	725.1 (712.7)
Total IgE, kU/L	424	539.7 (1668.1)	291	383.1 (751.4)
Asthma history				
Allergy diagnosis, *n* (%)	414	148 (35.7)	341	118 (34.6)
Allergic asthma diagnosis, *n* (%)	181	112 (61.9)	157	89 (56.7)
CSEs in the pre-initiation period, mean (SD)	605	4.4 (3.6)	409	4.2 (3.3)
Pre-mepolizumab initiation treatment history, *n* (%)				
Use of asthma/CRSwNP-related treatment	608	571 (93.9)	415	398 (95.9)
Use of maintenance OCS	618	242 (39.2)	414	159 (38.4)
Daily OCS dose, mg/day, mean (SD)	123	3.6 (9.2)	39	1.8 (6.9)
Daily maintenance OCS dose at baseline, mg/day, mean (SD)	238	8.0 (9.6)	159	6.7 (7.2)
Use of ICS[b]	558	530 (95.0)	392	383 (97.7)
Prior polypectomy	500	0 (0.0)	369	296 (80.2)

Abbreviations: BEC, blood eosinophil count; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyps; CSE, clinically significant exacerbation; EGPA, eosinophilic granulomatosis with polyangiitis; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids; IgE, immunoglobulin E; OCS, oral corticosteroids; ppb, parts per billion; SAEP, severe asthma with an eosinophilic phenotype; SD, standard deviation.
[a]Comorbidities were prespecified and assessed during the entire pre-initiation period, where data were available.
[b]Assessed independently to 'use of asthma/CRSwNP-related treatment'.

between cohorts (controlled for age, BMI, BEC, sex and smoking status at index), a 30.0% (95% CI 18.0, 40.3) incremental benefit of mepolizumab in reducing CSEs was observed for patients with SAEP[+]CRSwNP compared with SAEP[−]CRSwNP (Figure 3).

For each cohort, there was a reduction in the mean number of cohort-specific CSEs when comparing the 12- and 24-month post-mepolizumab periods with the 12-month pre-mepolizumab period (Figure S2A,B). Although a reduction from the pre-mepolizumab period remained at 24 months post-mepolizumab, there was an increase in the mean number of CSEs compared with 12 months in all individual existing cohorts excluding SSAR, for which no 24-month data were available, and Liège-BSAR, for which a further reduction in CSEs was observed at 24 compared with 12 months.

At 12-months post-initiation, mepolizumab was associated with both a reduction in the annual rate of exacerbations requiring ED visit or hospitalisation (SAEP[−]CRSwNP: 68.6% [95% CI 43.7, 82.5]; SAEP[+]CRSwNP: 84.0% [95% CI 77.2, 88.7]), and a reduction in the annual rate of exacerbations requiring hospitalisation (SAEP[−]CRSwNP: 62.1% [95% CI 18.5, 82.4]; SAEP[+]CRSwNP: 75.4% [95% CI 58.5, 85.4]), for both cohorts (Table 3).

3.3 | OCS Dose

There was a decrease in OCS maintenance dose for both cohorts at 6- and 12-months post-mepolizumab initiation, versus the pre-initiation period. The mean difference in OCS maintenance dose at 6 and 12 months, respectively, was −3.14 mg/day (95% CI −6.74, 0.47; 39.15% reduction) and −4.37 mg/day (95% CI −8.33, −0.42; 54.48% reduction) for patients with SAEP[−]CRSwNP, and −2.35 mg/day (95% CI −5.09, 0.39; 34.77% reduction) and −3.26 mg/day (95% CI −6.84, 0.32; 48.24% reduction) for patients with SAEP[+]CRSwNP (Table 3).

3.4 | Lung Function

At baseline, patients with SAEP[−]CRSwNP and SAEP[+]CRSwNP had mean (SD) pre- and post-bronchodilator forced expiratory volume in 1 second; (FEV_1) of 1830.6 mL (712.3) and 1845.2 mL (727.3), and 2034.7 mL (825.1) and 2208.5 mL (829.8), respectively (Table 2). Following initiation of mepolizumab, improvements in FEV_1 were observed at 6, 12, 18, and 24 months in both cohorts (Table 3). For patients with SAEP[−]CRSwNP, the mean difference in FEV_1 at 6 and 12 months, respectively, was 120.99 mL

TABLE 3 | Clinical outcomes post-mepolizumab initiation versus pre-mepolizumab initiation in patients with SAEP[−]CRSwNP and SAEP[+]CRSwNP.

	n	SAEP[−]CRSwNP (*N* = 621)	*n*	SAEP[+]CRSwNP (*N* = 416)
Exacerbations				
Reduction in annual rate of CSEs at 12 months, % (95% CI)[a]	584		401	
Reduction in annual rate		72.7 (67.8, 76.9)		79.7 (74.4, 83.8)
I^2, % (95% CI)		51.9 (0.0, 82.3)		34.2 (0.0, 75.2)
Reduction in annual rate of CSEs at 24 months, % (95% CI)[a]	316		183	
Reduction in annual rate		69.8 (47.1, 82.8)		72.9 (49.1, 85.3)
I^2, % (95% CI)		91.1 (80.4, 96.0)		85.7 (58.2, 95.1)
Reduction in annual rate of exacerbations requiring ED visit or hospitalisation at 12 months, % (95% CI)[a]	475		352	
Reduction in annual rate		68.6 (43.7, 82.5)		84.0 (77.2, 88.7)
I^2, % (95% CI)		77.7 (27.7, 93.1)		0.0 (0.0, 89.6)
Reduction in annual rate of exacerbations requiring hospitalisation at 12 months, % (95% CI)[a]	475		352	
Reduction in annual rate		62.1 (18.5, 82.4)		75.4 (58.5, 85.4)
I^2, % (95% CI)		74.8 (16.4, 92.4)		0.0 (0.0, 89.6)
OCS dose				
Reduction in OCS maintenance dose at 6 months[a,b]	228		155	
Mean difference (95% CI), mg/day		−3.14 (−6.74, 0.47)		−2.35 (−5.09, 0.39)
I^2, % (95% CI)		94.4 (87.0, 97.6)		93.8 (85.1, 97.4)
% reduction		−39.15		−34.77
Reduction in OCS maintenance dose at 12 months[a,b]	216		145	
Mean difference (95% CI), mg/day		−4.37 (−8.33, −0.42)		−3.26 (−6.84, 0.32)
I^2, % (95% CI)		95.0 (88.8, 97.8)		96.0 (91.5, 98.1)
% reduction		−54.48		−48.24
Lung function				
Improvement in mean FEV_1, mL at 6 months[c]	302		156	
Mean difference (95% CI), mL		120.99 (74.10, 167.88)		169.08 (46.07, 292.09)
I^2, % (95% CI)		3.1 (0.0, 85.2)		73.7 (26.3, 90.6)
% improvement		6.56		7.66
Improvement in mean FEV_1, % predicted at 6 months[d,e]				
IPD pooled results, % (95% CI)	210	4.60 (2.43, 6.77)	130	8.09 (5.07, 11.10)
% improvement		6.53		10.83
Improvement in mean FEV_1, mL at 12 months[c]	330		165	
Mean difference (95% CI), mL		152.59 (96.09, 209.08)		233.84 (118.46, 349.22)
I^2, % (95% CI)		36.4 (0.0, 76.2)		69.9 (23.3, 88.2)
% improvement		8.27		10.59

(Continues)

TABLE 3 | (Continued)

	n	SAEP[−]CRSwNP (*N* = 621)	*n*	SAEP[+]CRSwNP (*N* = 416)
Improvement in mean FEV_1, % predicted at 12 months[d,e]				
IPD pooled results, % (95% CI)	229	6.21 (3.98, 8.44)	141	11.18 (8.23, 14.13)
% improvement		8.82		14.96
Improvement in mean FEV_1 at 18 months[d,e]	111		76	
Mean difference (95% CI), mL		255.82 (176.15, 335.48)		357.51 (246.69, 468.34)
% improvement		13.78		16.36
Improvement in mean FEV_1, % predicted at 18 months[d,e]				
IPD pooled results, % (95% CI)	230	6.10 (3.80, 8.40)	142	10.90 (7.77, 14.03)
% improvement		8.66		14.59
Improvement in mean FEV_1 at 24 months[d,e]	97		65	
Mean difference (95% CI), mL		275.20 (186.38, 364.03)		353.20 (221.43, 484.96)
% improvement		14.83		16.16
Improvement in mean FEV_1, % predicted at 24 months[d,e]				
IPD pooled results, % (95% CI)	230	6.14 (3.80, 8.48)	142	10.62 (7.41, 13.83)
% improvement		8.72		14.21
Asthma control				
Improvement in ACT at 6 months[f]	317		191	
Mean difference (95% CI)		5.50 (4.78, 6.23)		6.01 (5.28, 6.74)
I^2, % (95% CI)		45.2 (0.0, 83.8)		0.0 (0.0, 89.6)
% improvement		40.78		41.61
Improvement in ACT at 12 months[g]	338		197	
Mean difference (95% CI)		6.02 (5.15, 6.89)		5.77 (4.54, 7.00)
I^2, % (95% CI)		57.7 (0.0, 86.0)		56.8 (0.0, 85.7)
% improvement		44.64		39.95
BEC				
Reduction in peripheral blood eosinophils at 12 months	446		316	
Mean difference (95% CI), cells/μL		−461.47 (−513.27, −409.67)		−618.01 (−688.98, −547.04)
I^2, % (95% CI)		29.8 (0.0, 74.4)		0.0 (0.0, 84.7)
% reduction		79.73		85.10

Abbreviations: ACT, Asthma Control Test; BEC, blood eosinophil count; CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; CSE, clinically significant exacerbation; ED, emergency department; FEV_1, forced expiratory volume in 1 second; I^2, heterogeneity index; IPD, individual patient data; Liège-BSAR, Belgium Severe Asthma Registry (Liège); OCS, oral corticosteroids; REALITI-A, REAL world effectiveness of mepolizumab In paTIent care; REDES, REal worlD Effectiveness and Safety of Mepolizumab; RELIght, A two-year REal-LIfe study of mepolizumab in patients with severe eosinophilic asTHma in Greece; SAEP, severe asthma with an eosinophilic phenotype; SSAR, Swiss Severe Asthma Registry.

[a]Random effect model.

[b]Only data from REALITI-A, REDES, and Liège-BSAR were included.

[c]Post-bronchodilator FEV_1 values were used for REALITI-A, REDES, and RELIght, whereas pre-bronchodilator FEV_1 values were used for BSAR and SSAR due to missing post-bronchodilator FEV_1 values.

[d]Post-bronchodilator FEV_1 values recorded in the 3 months prior to the timepoint of interest were used.

[e]No data from Liège-BSAR and SSAR were included.

[f]No data from REALITI-A and SSAR were included.

[g]No data from REALITI-A were included.

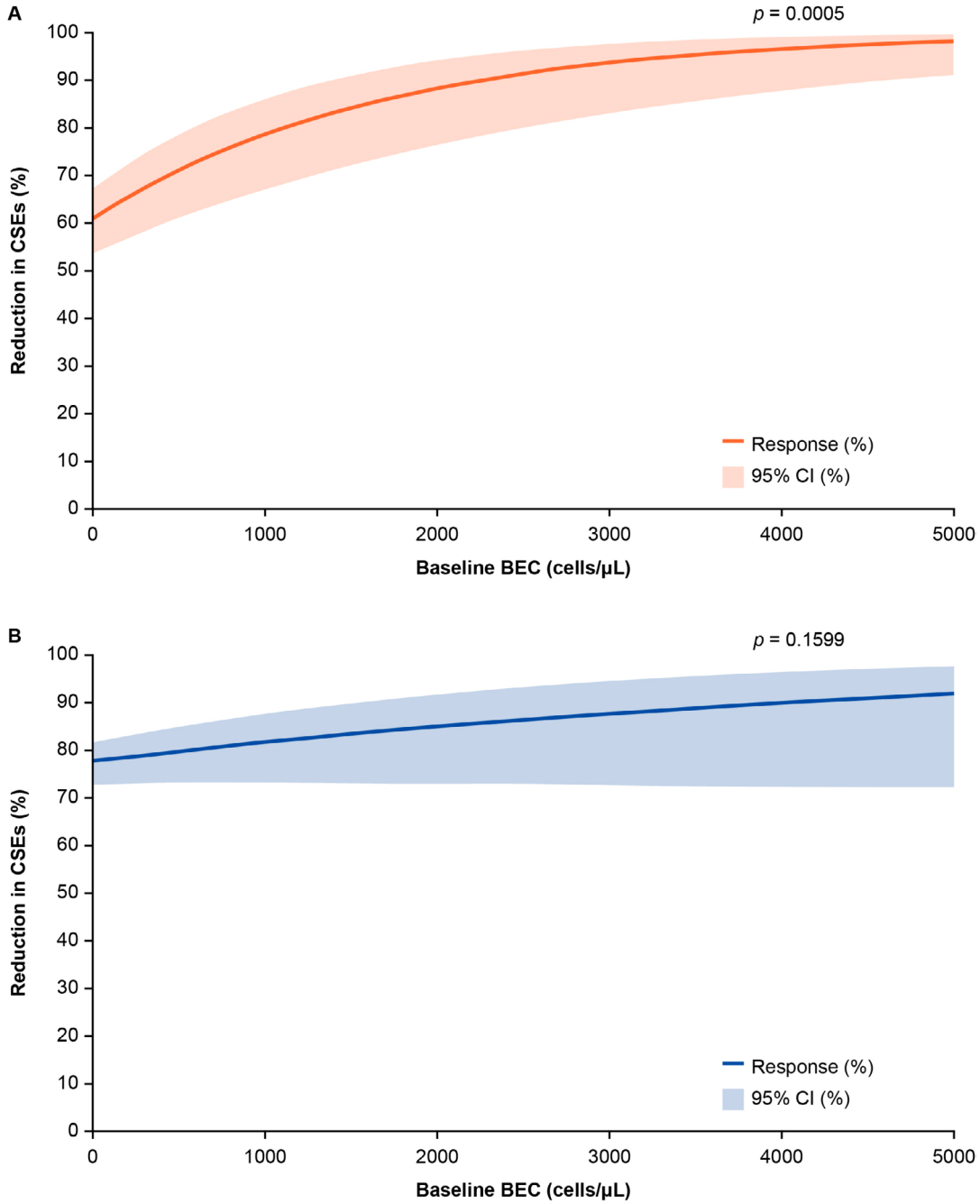


FIGURE 2 | Change in rate of CSEs by baseline peripheral BEC for patients with (A) SAEP[−]CRSwNP and (B) SAEP[+]CRSwNP. Abbreviations: BEC, blood eosinophil count; CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; CSE, clinically significant exacerbation; SAEP, severe asthma with an eosinophilic phenotype.

(95% CI 74.10, 167.88; 6.56% increase) and 152.59 mL (95% CI 96.09, 209.08; 8.27% increase); improvements continued to be observed at 18 and 24 months. For patients with SAEP[+]CRSwNP, the mean difference in FEV_1 at 6 and 12 months, respectively, was 169.08 mL (95% CI 46.07, 292.09; 7.66% increase) and 233.84 mL (95% CI 118.46, 349.22; 10.59% increase). Improvement was also observed at 18- and 24 months post-mepolizumab initiation.

3.5 | Asthma Control

Similar to other outcomes, Asthma Control Test (ACT) score increased 6- and 12-months, respectively, post-mepolizumab in both cohorts (Table 3; SAEP[−]CRSwNP: mean difference 5.50 [95% CI 4.78, 6.23; 40.78% increase] and 6.02 [95% CI 5.15, 6.89; 44.64% increase]; SAEP[+]CRSwNP: mean difference 6.01 [95% CI 5.28, 6.74; 41.61% increase] and 5.77 [95% CI 4.54, 7.00; 39.95% increase]).

3.6 | BEC

At 12 months post-mepolizumab initiation, there was a reduction in BEC in both cohorts (Table 3; SAEP[−]CRSwNP: mean difference −461.47 cells/μL [95% CI −513.27, −409.67; 79.73% reduction]; SAEP[+]CRSwNP: mean difference −618.01 cells/μL [95% CI −688.98, −547.04; 85.10% reduction]). A high percent

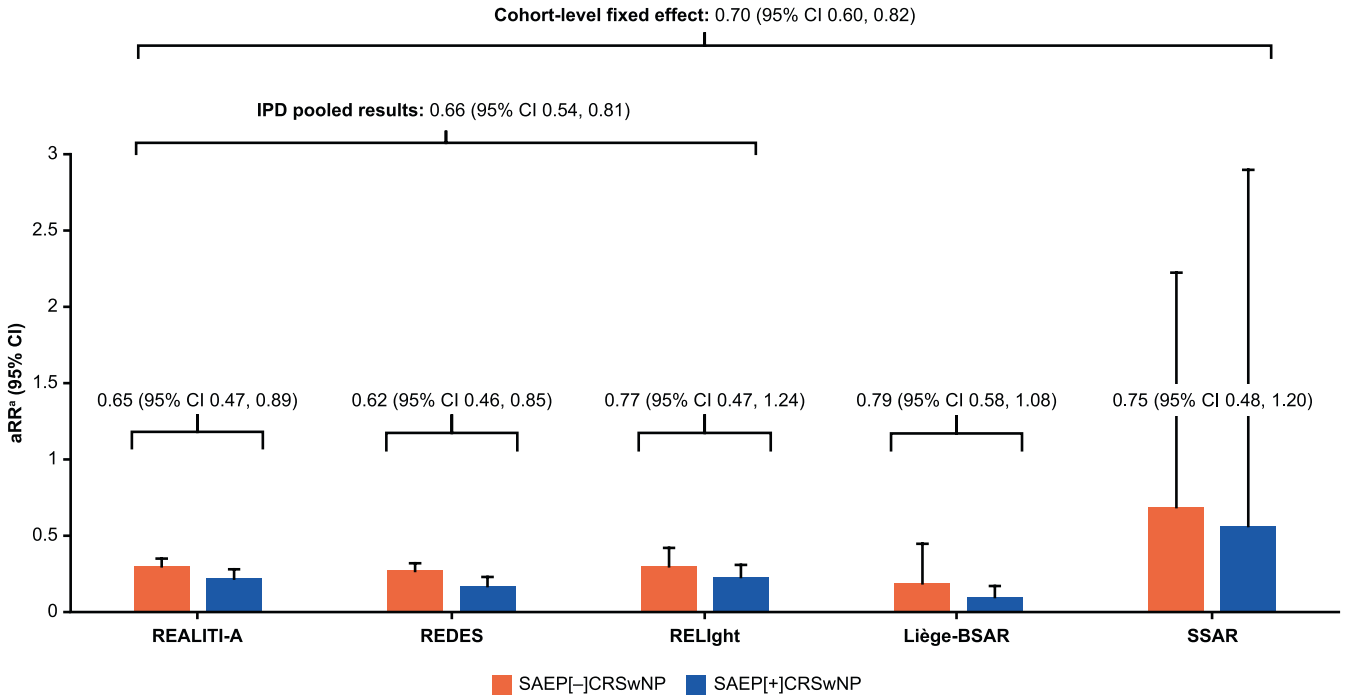


FIGURE 3 | Between-cohort statistical comparison of reduction in CSEs from 12-months pre-initiation to 12-months post-mepolizumab initiation in patients with SAEP[−]CRSwNP versus patients with SAEP[+]CRSwNP. Abbreviations: aRR, annual rate ratio; CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; CSE, clinically significant exacerbation; Liège-BSAR, Belgium Severe Asthma Registry (Liège); IPD, individual patient data; REALITI-A, REAL world effectiveness of mepolizumab In paTIent care —Asthma study; REDES, REal worlD Effectiveness and Safety of Mepolizumab; RELIght, a two-year REal-LIfe study of mepolizumab in patients with severe eosinophilic asTHma in Greece; SAEP, severe asthma with an eosinophilic phenotype; SSAR, Swiss Severe Asthma Registry. [a]: Cohort-specific annual rate ratio.

reduction in BEC was observed 12-months post-mepolizumab initiation for all baseline peripheral BEC values (Table S3), with a greater reduction observed in those with higher baseline BEC (% reduction in patients with SAEP[−]CRSwNP with ≥150 cells/μL vs. patients with ≥700 cells/μL at baseline: −79.46% vs. −82.32%; patients with SAEP[+]CRSwNP with ≥150 cells/μL vs. patients with ≥700 cells/μL at baseline: −83.79% vs. −86.16%).

3.7 | Clinical Remission

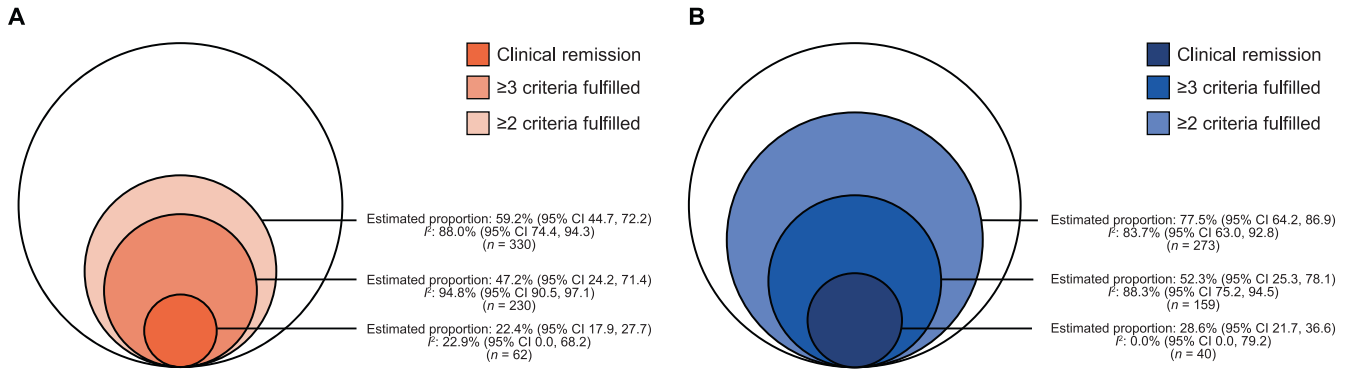
Clinical remission was assessed in patients who achieved a reduction in CSEs by 12 months post-mepolizumab initiation. Overall, >60% of patients from both cohorts achieved at least one criterion of clinical remission (Figure 4; excludes 'no exacerbations' for patients with SAEP[−]CRSwNP).

Overall, 22.4% and 28.6% of patients achieved clinical remission 12 months post-mepolizumab initiation with SAEP[−]CRSwNP and SAEP[+]CRSwNP, respectively. At least three criteria of clinical remission were fulfilled by 47.2% and 52.3%, and at least two criteria of clinical remission were fulfilled by 59.2% and 77.5% of patients with SAEP[−]CRSwNP and SAEP[+]CRSwNP, respectively (Figure 4).

4 | Discussion

This multi-country, retrospective pooled analysis examined the real-world effectiveness of mepolizumab in existing cohorts of patients with SAEP[−]CRSwNP or SAEP[+]CRSwNP. Patient characteristics were similar to those reported in previous real-world studies of patients with SAEP [3]. As reported in previous clinical trials and real-world studies [17, 20, 32], mepolizumab was effective in reducing the rate of CSEs (by 72.7% and 79.7% at 12 months in patients with SAEP[−]CRSwNP and SAEP[+]CRSwNP, respectively, with reductions remaining similar at 24 months). A clinical and functional response was seen irrespective of baseline BEC. The BEC-independent effectiveness of mepolizumab is of interest, given the now greater understood, broad effects of IL-5 on a range of immune and structural cell populations beyond eosinophilic inflammation [10].

Whilst this analysis did not aim to compare outcomes between patients with SAEP[−]CRSwNP and SAEP[+]CRSwNP, an exploratory analysis that adjusted for all control variables to compare the primary endpoint between cohorts demonstrated a 30.0% incremental benefit in the reduction of CSEs for patients with SAEP[+]CRSwNP compared with patients with SAEP[−]CRSwNP. Due to demographic and clinical characteristic differences between the patient populations, this exploratory between-cohort comparison was only possible for the primary endpoint. However, this additional benefit of mepolizumab is encouraging as it could further reduce disease burden and OCS use in patients with SAEP[+]CRSwNP [33], for whom the impact of SAEP is reported to be greater than those with SAEP[−]CRSwNP [14–16]. Higher response in patients with SAEP[+]CRSwNP may be due to the shared pathophysiological mechanisms of both SAEP and CRSwNP [7–9].



Individual criteria for clinical remission achieved, *n* (%)	*n*	SAEP[–]CRSwNP (*n* = 559)[a]
No exacerbations[b]	549	269 (49.0)
No OCS use for asthma[b]	539	331 (61.4)
ACQ-5 <1.5 or ACT ≥20[c]	520	317 (61.0)
No FEV_1 decline from baseline ≥100 mL[c]	305	192 (63.0)

Individual criteria for clinical remission achieved, *n* (%)	*n*	SAEP[+]CRSwNP (*n* = 385)[a]
No exacerbations[b]	383	237 (61.9)
No OCS use for asthma[b]	379	228 (60.2)
ACQ-5 <1.5 or ACT ≥20[c]	357	259 (72.5)
No FEV_1 decline from baseline ≥100 mL[c]	152	97 (63.8)

FIGURE 4 | Clinical remission criteria in patients with (A) SAEP[–]CRSwNP and (B) SAEP[+]CRSwNP who achieved a reduction in CSEs. Abbreviations: ACQ-5, Asthma Control Questionnaire-5; ACT, Asthma Control Test; CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; CSE, clinically significant exacerbation; FEV_1, forced expiratory volume in 1 s; I^2, heterogeneity index; OCS, oral corticosteroids; SAEP, severe asthma with an eosinophilic phenotype. [a]: Total number of patients who achieved a reduction in CSEs in each cohort; [b]During the 12-month post-mepolizumab initiation period; [a]At 12-months post-mepolizumab initiation.

Mepolizumab was also associated with a reduction in maintenance OCS dose and BEC levels and improved lung function (FEV_1) and asthma control (ACT) in patients with SAEP[–]CRSwNP and SAEP[+]CRSwNP. Long-term use of OCS is associated with adverse effects, and patients with type 2-driven diseases, such as SAEP and CRSwNP, are often chronic users of OCS requiring high doses to achieve symptom control [34, 35]. Due to high OCS use globally, there is a movement towards patient and healthcare professional education to reduce OCS use [34–37]. Biologic treatment of severe asthma has been shown in clinical and real-world studies to reduce the regular use of OCS. Our findings reported clinically meaningful reductions in OCS maintenance dose 6- and 12-months post-mepolizumab initiation.

Consistent with other published clinical trials and real-world studies, improvements in FEV_1 post-mepolizumab initiation were reported for both patients with SAEP[–]CRSwNP and SAEP[+]CRSwNP [17, 32]. A systematic literature review has demonstrated that patients with severe uncontrolled asthma experience more frequent symptoms than those with controlled disease [38]; this analysis encouragingly showed that initiation of mepolizumab was associated with an improvement in asthma control (ACT scores) at both 6- and 12-months post-mepolizumab initiation in both patients with SAEP[–]CRSwNP and SAEP[+]CRSwNP.

Recent analyses of the Liège-BSAR cohort have demonstrated that high sputum type-2 biomarkers and CRSwNP were predictors of clinical remission and super-response to treatments targeting IL-5 pathways [39, 40]. Other real-world studies have demonstrated that elevated BEC is associated with poor asthma control and lung function and an increased risk of exacerbations [41]. Whilst the results of this study corroborate evidence that increased BEC is associated with an increased response to anti-IL-5 treatments [33], this analysis highlights the effectiveness of mepolizumab in patients with type 2-driven diseases, irrespective of baseline BEC. Whilst a reduction in OCS dose can result in an increase in BEC [34], this analysis shows that the initiation of mepolizumab reduced both OCS dose and BEC in patients with SAEP[–]CRSwNP and SAEP[+]CRSwNP, which aligns with other real-world studies of mepolizumab in patients with SAEP [36] or CRSwNP [23].

Clinical remission on treatment, broadly defined as low or no disease activity [31], is increasingly considered as an achievable goal of asthma management. Although not an endpoint of the original cohorts, when the four criteria for on-treatment clinical remission were assessed in patients who had achieved a reduction in CSEs, at least two, at least three, and all four clinical remission criteria were fulfilled by 59.2%, 47.2%, and 22.4% of patients with SAEP[–]CRSwNP, respectively, and by 77.5%, 52.3%, and 28.6% of patients with SAEP[+]CRSwNP, respectively. These values are broadly in line with those reported by Pavord et al. in a post hoc analysis of the REDES study ($N = 318$) [42], but are slightly lower than those reported by Bagnasco et al. in a retrospective real-world study of patients from Italy ($N = 71$) [43]. The latter could be due to patient population, differences in definitions of lung function and disease control, and only inclusion of patients who had achieved a reduction in CSEs by 12 months post-mepolizumab initiation [43]. Given clinical remission is increasingly considered a clinically relevant treatment goal, future studies in patients with SAEP should consider inclusion of clinical remission as a study endpoint.

There are several limitations that should be considered for this analysis. Firstly, missing data from the existing cohorts could be considered a study limitation and may limit sub-analyses; for example, correlation between outcomes and comorbidities, specific patient characteristics, or type 2 inflammation biomarkers. Furthermore, whilst reflective of real-world studies,

some of the cohorts included a greater number of patients than others, and there were several differences in baseline characteristics between the existing cohorts. Missing and variable data could have introduced selection and information bias and reduced generalisability to the overall patient population using mepolizumab. An additional limitation due to the sourcing of data from real-world cohorts is potential inconsistencies in definitions or recording of data, for example, CSEs or ED visits, or in clinical practices of the recording physicians. These differences may also occur between countries. We also note as a limitation that this analysis did not assess upper respiratory tract symptoms to better evaluate the impact of mepolizumab in patients with SAEP[+]CRSwNP, specifically. Future studies could consider using a validated questionnaire to better evaluate the impact of mepolizumab in patients with SAEP[+]CRSwNP, specifically. Furthermore, it should be noted that the original aim of the existing cohorts was to examine outcomes following initiation of mepolizumab in patients with SAEP; therefore, diagnoses of SAEP[+]CRSwNP may not have been accurately recorded, which could have led to underestimation of patient numbers. Finally, as published data focused on outcomes pertaining to patients with SAEP, CRSwNP-specific characteristics such as disease severity and level of control, and outcomes such as Sino-Nasal Outcome Test-22, visual analogue scale loss of smell, polypectomy or endoscopic sinus surgery, could not be calculated. Future research could further assess these outcomes.

A key strength of this study is that by pooling existing real-world data, a robust analysis on a large population of patients was feasible; furthermore, the use of healthcare records for at least 12 months prior to index date provided internal validity, with patients acting as their own controls. This methodology highlighted improvements in multiple endpoints post-mepolizumab initiation, reinforcing the real-world effectiveness of mepolizumab in patients with type 2-driven diseases.

5 | Conclusions

This pooled analysis of existing predominantly European cohorts of patients with SAEP demonstrated that mepolizumab was effective at reducing rates of CSEs and maintenance OCS dose, with improvements in lung function and symptom control. Clinical benefit was seen in patients with SAEP[−]CRSwNP and SAEP[+]CRSwNP, with a 30.0% higher incremental benefit in the reduction of CSEs observed in patients with SAEP[+]CRSwNP.

This study increases understanding of baseline disease severity and treatment patterns for patients with SAEP[−]CRSwNP and SAEP[+]CRSwNP, and the effectiveness of mepolizumab in these populations, in a real-world setting.

Author Contributions

All authors had access to the pooled analysis data, take responsibility for the accuracy of the analysis, contributed to data interpretation, reviewed and contributed to the content of the manuscript, and had authority in the decision to submit the manuscript.

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Ethics Statement

This study complied with all applicable laws regarding patient privacy. Where data had already been collected in registries, no direct subject contact or primary collection of individual human subject data occurred. Where additional patient data were required, individual consent was obtained prior to the use of pre-existing patient data. Informed consent (stored confirmation) was confirmed from all data cohorts. The consent form was approved by an Ethics Committee and/or Institutional Review Board, which was in compliance with the General Data Protection Regulation and any local requirements. Patients who did not provide informed consent were excluded from this analysis. Outcomes were produced in tabular form, and aggregate analyses were made to omit subject identification. This was conducted in accordance with the Declaration of Helsinki and in compliance with the applicable laws and regulatory requirements in the countries where the pooled analysis was conducted.

Conflicts of Interest

Some material discussed herein has been presented at ERS 2024, Vienna, Austria: Palomares I, Loukides S, Schleich F, et al. Eur Resp J 2024; 64 (suppl 68): PA3929: doi.org/10.1183/13993003.congress-2024.PA3929. F. Schleich reports consulting fees from AstraZeneca, Chiesi, GSK and TEVA; and payment or honoraria from AstraZeneca, Chiesi and GSK; and support for attending meetings/travel from AstraZeneca and Chiesi. S. Loukides reports consulting fees from GSK; payment or honoraria from AstraZeneca and GSK; participation on a Drug Safety Monitoring Board or Advisory Board for GSK; and holding of an unpaid position as President of the Hellenic Thoracic Society. R. Chaudhuri reports receiving grants or contracts from AstraZeneca for an investigator-led study; payment or honoraria from AstraZeneca, Chiesi, GSK, Sanofi and TEVA; support for attending meetings/travel from Chiesei, GSK and Sanofi; and participation on a Drug Safety Monitoring Board or Advisory Board for AstraZeneca, Celltrion Healthcare and GSK. J. D. Leuppi reports unrestricted grants from AstraZeneca, GSK, OM Pharma and Sanofi; and payment or honoraria for lectures from AstraZeneca, GSK, OM Pharma and Sanofi. E. Heffler reports a research grant from Chiesi; consulting fees from Almirall, Apogee Therapeutics, AstraZeneca, Bosch, Celltrion Healthcare, Chiesi, GSK, Lofarma, Novartis, Regeneron and Sanofi; and support for attending meetings or travel from AstraZeneca, GSK and Sanofi. C. Domingo reports consulting fees, payment or honoraria, payment for expert testimony, and support for attending meetings or travel from ALK, GSK, Novartis, Sanofi, not on the original submitted file AstraZeneca, Asac Pharmaceutical Immunology, Immunotek and MSD. C. Micheletto has received payment or honoraria from AstraZeneca, Berlin Chemie, Boehringer Ingelheim, Chiesi, GSK, Guidotti, Lusofarmaco, Menarini, Roche, Sanofi and Zambon; support for attending meetings or travel from AstraZeneca, Menarini and Sanofi; and is President of the Italian Thoracic Society and member of the Regional Drug Commission. T. Paulsson, N. Gaw, K. Kallinikou and I. Palomares are employees of GSK and hold financial equities in GSK. C. Vossen, F. Guelfucci, J. Menon and A. Ngami are employees of Syneos Health, which received funding from GSK to conduct this study.

Data Availability Statement

For requests for access to anonymised subject level data, please contact Corresponding Author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.