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To cite this article: Elliot Israel,, Giorgio Walter Canonica,, Guy Brusselle,, Shibing Yang,, Peter H. Howarth,, Amber L. Martin,, Maria Koufopoulou,, Steven G. Smith, & Rafael Alfonso-Cristancho, (2021): Real-life effectiveness of mepolizumab in severe asthma: a systematic literature review, Journal of Asthma, DOI: [10.1080/02770903.2021.2008431](https://doi.org/10.1080/02770903.2021.2008431)

To link to this article: <https://doi.org/10.1080/02770903.2021.2008431>



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Published online: 24 Dec 2021.



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Real-life effectiveness of mepolizumab in severe asthma: a systematic literature review

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ABSTRACT

Objective: The efficacy and safety of mepolizumab in patients with severe eosinophilic asthma in randomized controlled trials is well established. Following approval of mepolizumab as add-on therapy for severe eosinophilic asthma in multiple regions worldwide, it is now important to determine its impact in real-world settings in which patients are not subject to stringent eligibility criteria. This systematic literature review assessed published evidence of clinical outcomes, safety, and healthcare resource use among patients with severe asthma receiving mepolizumab in real-world settings.

Data sources: Searches were conducted in Embase, MEDLINE, and MEDLINE In-Process via Ovid.

Study selections: Eligible studies were observational, and enrolled ≥ 10 patients with asthma who received mepolizumab 100 mg subcutaneously. Data extracted included annualized exacerbation rate, mean daily oral corticosteroid (OCS) dose, proportion of patients using OCS, several measures of lung function, patient-reported asthma control and health-related quality of life (HRQoL), safety, and economic burden.

Results: Twenty-three articles (22 unique studies; 2,040 patients with severe asthma on mepolizumab) were identified. Mepolizumab use was associated with a reduction in annualized exacerbation rates (requiring OCS) of 54–97% ($p < 0.05$ in all studies), reduced mean/median daily OCS doses, and OCS discontinuation during follow-up (27–84% of patients). Improvements in lung function, asthma control, and HRQoL were also observed. The most commonly reported adverse events included headache and arthralgia; discontinuation of mepolizumab due to adverse events occurred in 0–10.6% of patients.

Conclusion: Findings show that patients with severe asthma consistently demonstrate clinically relevant benefits with mepolizumab treatment in a real-world setting.

ARTICLE HISTORY

Received 7 July 2021

Revised 8 November 2021

Accepted 16 November 2021

KEYWORDS

Therapy; treatment; management/control; quality of life

Introduction

Asthma is a heterogeneous respiratory condition affecting more than 339 million people globally (1). Patients with severe asthma typically have poorly controlled disease and experience frequent asthma exacerbations, impaired lung function and reduced health-related quality of life (HRQoL), despite standard of care therapy, which consists of medium to high doses of inhaled corticosteroids (ICS) plus one or more additional controller medications (such as a long-acting beta agonist [LABA]) (2–4). Patients whose symptoms persist despite optimization (i.e. good adherence and correct inhaler technique) of

medium to high dose ICS/LABA treatment should be considered for add-on therapy such as biologics that target the inflammatory signaling pathways seen in asthma (4).

A subset of patients with severe asthma have severe eosinophilic asthma, characterized by elevated levels of eosinophils in the blood and/or airways (3). Mepolizumab is a humanized monoclonal antibody that binds to and neutralizes interleukin (IL)-5, thus inhibiting IL-5 signaling and blocking eosinophil proliferation, activation, and survival (5,6). It is approved as an add-on therapy for patients with severe eosinophilic asthma and eosinophilic granulomatosis with polyangiitis in multiple regions

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 Supplemental data for this article can be accessed at [publisher's website](https://www.tandfonline.com/doi/suppl/10.1080/02770903.2021.2008431).

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worldwide, and for patients with hypereosinophilic syndrome in the US (7–9). Randomized controlled trials (RCTs) (10–13) and real-world studies (14–16) have demonstrated that compared with placebo, mepolizumab reduces exacerbations and oral corticosteroid (OCS) dependence, in addition to improving lung function, asthma control and HRQoL in patients with severe eosinophilic asthma. As real-world use of mepolizumab increases, the population of patients with access to mepolizumab is more diverse than those included in the mepolizumab RCTs, which have strict eligibility criteria that often lead to the exclusion of patients with respiratory comorbidities and other characteristics, such as a recent smoking history and lack of adherence to controller medications, frequently found in the real-world severe asthma population (11,13,17–19). It is therefore of clinical interest to fully understand the extent to which the clinical benefits associated with mepolizumab are observed in routine clinical practice.

The aim of this systematic literature review (SLR) was to assess the published evidence relating to a broad range of clinical outcomes, safety, and health-care resource utilization (HCRU) among patients with severe asthma receiving add-on therapy with mepolizumab in a real-world setting.

Methods

This SLR was conducted and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (20). All SLR methodology followed the established best methods used in systematic review research (21,22).

Search strategy

The SLR was designed to identify studies reporting data on the effectiveness and safety of mepolizumab in patients with asthma in a real-world setting. Systematic literature searches were conducted in Embase, MEDLINE and MEDLINE In-Process via Ovid, using a combination of free-text terms and medical subject headings for asthma combined with terms for mepolizumab (Supplementary Table 1). Searches were limited to articles published in the English language and publications reporting the results of clinical trials were excluded. A hand search of conference proceedings for several key 2018, 2019, and 2020 meetings (as available) was also conducted. This included the following congresses: American Academy of Allergy, Asthma, and Immunology (2018,

2019); American College of Allergy, Asthma, and Immunology (2018, 2019); American College of Chest Physicians (2018, 2019); American Thoracic Society (2018, 2019, 2020); British Thoracic Society (2018, 2019); European Academy of Allergy and Clinical Immunology (2018, 2019); European Respiratory Society (2018, 2019); International Society for Pharmacoeconomics and Outcomes Research (2018, 2019).

Study selection and data extraction

The eligibility criteria for abstracts and full-text articles were based on the Population, Intervention, Comparison, Outcomes, and Study (PICOS) design framework, and are described in full in [Supplementary Table 2](#). Briefly, eligible publications were published prior to 10 July, 2020 (with no lower limit applied to the publication date) and reported data from observational studies (prospective and retrospective cohort studies, registry and claims database analyses, cross-sectional studies) that enrolled ≥ 10 patients ≥ 6 years of age with asthma who had been treated with the approved dose of mepolizumab (100 mg, administered subcutaneously). Eligible publications also had to include data on at least one outcome of interest, including clinical outcomes (such as exacerbation frequency or lung function), disease control or HRQoL outcomes, or economic outcomes ([Supplementary Table 2](#)). The data could be from the overall study population, or for subgroups of patients stratified by baseline blood eosinophil count. Other subgroups (such as patients deemed to be treatment responders/ non-responders) were not included, owing to inconsistent definitions of treatment response across studies.

Any duplicate publications identified across databases were removed from the initial search results and all remaining unique publications were screened using Distiller Systematic Review software. Titles/abstracts and then full-text publications were screened for inclusion by two independent investigators and any discrepancies between investigators were resolved by a third investigator. Once all abstracts and full-text articles meeting the eligibility criteria were identified, data from these publications were extracted by a single investigator into a data extraction template. The data were then independently validated by a second, senior investigator.

Data synthesis

The results of the SLR were summarized qualitatively and no statistical analyses were planned. With regards

Table 1. Patient baseline characteristics.

Author, year	Study design, study name	Country	Sample size	Mean age (years)	Mean disease duration (years)	Females (%)	Smoking status	NP	Rhinitis	GERD	Patients on mOCS at baseline % (n/N)	Mean mOCS dose (mg/day) at baseline (SD)
Prospective studies												
Farah, 2019 (23)	Prospective cohort	Australia	20	60	NR	40.0%	Current: 0% Never: 80%	NR	NR	NR	NR	NR
Pertsov, 2021 (15)	Prospective cohort	Israel	61	57.46	NR	57.4%	NR	NR	NR	NR	52.5% (32/61)	Median: 20 (IQR: 6.25–4)
Harvey, 2020 (24)	Prospective cohort	Australia	309	59.55	27.52	57.60%	Current: 0.6% Never: 61.2% Ex-smoker: 38.2%	34.0%	Allergic: 63%	52.0%	47% (NR)	Median: 10 (IQR: 5.0–12.5)
Langton, 2020 (25)	Prospective observational study	Australia	47	61.3	NR	55.30%	NR	NR	NR	NR	40% (19/47)	11.1 (7.5)
Schleich, 2020 (26)	Prospective study	Belgium	116	54	NR	64%	Current: 8% Never: 64% Ex-smoker: 28%	62.9%	Rhinosinusitis: 62.9%	58%	25% (NR)	Median: 8
Retrospective studies												
Drick, 2018 (27)	Retrospective cohort	Germany	42	Median: 51	NR	45.0%	Current: 2% Never: 50% Former: 48%	NR	NR	NR	57% (23/42)	Median (IQR): 5 (5–10)
Pelaia, 2018 (28)	Retrospective cohort	Italy	14	56.79	NR	78.6%	NR	NR	NR	NR	100% (14/14)	24.11 (10.36)
Bagnasco, 2019 (29)	Retrospective cohort	Italy	138	58	30	56.5%	Former: 16%	59%	65%	31%	80.4% (111/138)	10.1 (9.4)
Caminati, 2019 (30)	Retrospective cohort	Italy	69	55.1	NR	60.9%	NR	61%	NR	NR	70.5% (43/61)	8.5 (8.8)
Lombardi, 2019 (31)	Retrospective cohort	Italy	143	67.1	NR	53.2%	NR	52%	NR	NR	NR	NR
Montero-Perez, 2019 (32)	Retrospective cohort	Spain	23	Median: 51	NR	88.0%	NR	NR	NR	NR	65.22% (15/23)	14.8
Cameli, 2020 (33)	Retrospective cohort	Italy	26	56.4	NR	34.7%	Current: 7.69% Never: 42.31% Former: 50.00%	53.80%	Allergic: 30.7%	26.90%	22.2% (6/26)	NR
d'Ancona, 2020 (34)	Retrospective cohort	UK	91	53.7	NR	54.9%	Current: 3.3% Former: 27.5%	NR	NR	NR	100% (91/91)	Median: 10
Kavanagh, 2020 (35)	Retrospective cohort	UK	99	53.47	NR	52.5%	Current: 4.5% Never: 59.6% Ex-smoker: 36.0%	46.5%	NR	NR	68.7% (68/99)	Median (IQR): 10 (10–15)
Llanos, 2020 (14)	Retrospective cohort	US	346	49.3	NR	61.6%	NR	21.7%	Allergic: 66.5	NR	35.3% (NR)	NR
Numata, 2020 (36)	Retrospective observational study	Japan	24	56	NR	58%	Never smoker: 62.5% Past smoker: 37.5%	NR	Allergic: 75% Chronic rhinosinusitis: 71%	NR	54% (13/24)	7
Pelaia, 2020 (37)	Retrospective cohort	Italy	88	54.51	Median: 20	64.77	Current: 26.14%	60.23%	Chronic rhinosinusitis: 78.41%	37.50%	76% (67/88)	NR
Sousa, 2020 (38)	Retrospective and cohort	Portugal	10	NR	NR	90.0%	NR	NR	NR	NR	NR	NR
Spasato, 2020 (39)	Retrospective cohort	Italy	134	58.3	NR	54.5%	Current: 4.5% Past: 32.1%	52.3%	59%	NR	74% (NR)	NR
Taille, 2020 (40)	Retrospective cohort	France	146	58.2	13.4	45.20%	Current: 7.6% Never: 53.1%	38.7%	Allergic: 17.5	38.7	92.8 (128/138)	20.6 (16.5)
van Toor, 2021 (16)	Retrospective cohort MOMENT	Netherlands	78	54	NR	69.2%	Current: 2.6% Never: 65.4%	30.8%	49%	7.7%	NR	NR
Yilmaz, 2020 (41)	Retrospective cohort	Turkey	16	48.6	12.9	81%	Former: 32.1% Current: 6% Never: 88% Ex-smoker: 6%	100%	Chronic rhinosinusitis: 100%	NR	100% (16/16)	9.2 (5.2)

GERD, gastroesophageal reflux disease; IQR, interquartile range; mOCS, maintenance OCS; NP, nasal polyps; NR, not reported; OCS, oral corticosteroids; SD, standard deviation; UK, United Kingdom; US, United States.

Table 2. Exacerbation data.

Author, year and country		Definition of exacerbation/ subgroup	Annualized exacerbation rate					Proportion of patients with an exacerbation during follow-up			
			Sample size	Timepoint for follow-up (months)	Mean (SD)/ median ER at baseline, events/year	Mean (SD)/median ER at follow-up, events/year	Mean (p-value) change in ER from baseline to follow-up	% change in mean ER from baseline to follow-up	Timepoint	Patients experiencing exacerbation, % (n/N)	
Prospective studies											
Harvey, 2020 (24) Australia	Exacerbation requiring OCS	309	12	4.16 (NR)	1.41 (NR)	-2.75 (<0.001)	-66	-	-		
	Exacerbation requiring hospitalization		12	0.57 (NR)	0.26 (NR)	-0.31 (<0.001)	-54	-	-		
	Exacerbation resulting in unscheduled doctor visits		12	1.35 (NR)	0.23 (NR)	-1.12 (<0.001)	-83	-	-		
	Exacerbation requiring ED		12	0.38 (NR)	0.17 (NR)	-0.21 (<0.01)	-56	-	-		
Langton, 2020 (25) Australia	Exacerbation requiring OCS use	47	12	2.80 (2.3)	0.90 (1.1)	-1.9 (<0.001)	-67.86	-	-		
Pertsov, 2021 (15) Israel	Exacerbation requiring an ED visit, OCS prescribed by a GP (if patient not on mOCS) or OCS prescribed by a GP at a dose ≥ 2 times the maintenance dose	61	12	3.14 (2.28)	0.85 (1.06)	-2.29 (<0.001)	-72.93	Baseline 12 months	85.2% (52/61) 13.1% (8/61)		
Retrospective studies											
Pelaia, 2018 (28) Italy	NR	14	6	3.64 (1.86)	1 (0.78)	-2.64 (<0.001)	-72.53	-	-		
Bagnasco, 2019 (29) Italy	NR, Overall study population	138	12	3.8 (2.5)	0.7 (0.11)	-3.1 (<0.0001)	-81.58	-	-		
	NR, Patients with <500 EOS/μL		12	3.61 (2.55)	0.78 (1.09)	-2.83 (<0.0001)	-78.39	-	-		
	NR, Patients with > 500 EOS/μL		12	3.89 (2.52)	0.72 (1.16)	-3.17 (<0.0001)	-81.49	-	-		
	NR, Patients with >400 EOS/μL		12	3.83 (2.49)	0.73 (1.15)	-3.10 (<0.0001)	-80.94	-	-		
Caminati, 2019 (30) Italy	Patients experiencing relapse	69	12	4.9 (3.4)	0.6 (1.4)	-4.30 (<0.0001)	-87.76	Baseline 12 months	94.1% (64/68) 40.0% (26/65)		
Montero-Perez, 2019 (32) Spain	NR	25	12	Median: 4.5 (NR)	Median: 0.58 (NR)	Median diff: -3.92 (NR)	-87.11	-	-		
Cameli, 2020 (33) Italy	Moderate-to-severe exacerbation rate with no hospitalizations or ED visits	26	6	3.8 (2.7)	0.4 (0.5)	-3.4 (0.0009)	-89.47	-	-		
d'Ancona, 2020 (34) UK	NR	91	12	2.7 (2.7)	1.4 (1.8)	-1.4 (NR)	-48.15	-	-		
Kavanagh, 2020 (35) UK	Worsening in asthma control that required ≥ 3 days of oral prednisolone treatment (or a doubling or more of prednisolone dose if already taking mOCS)	99	12	4.04 (2.7)	1.86 (2.17)	-2.18 (<0.001)	-53.96	Baseline 12 months	100% (99/99) 64% (NR/NR)		

(Continued)

Table 2. (Continued)

Author, year and country	Definition of exacerbation/ subgroup	Sample size	Timepoint for follow-up (months)	Annualized exacerbation rate			Mean (SD)/median ER at follow-up, events/year	Mean (SD)/median ER at baseline, events/year	% change in mean ER from baseline to follow-up	Mean (p-value) change in ER from baseline to follow-up	Proportion of patients with an exacerbation during follow-up	
				Mean (SD)/ median ER at follow-up, events/year	Mean (SD)/ median ER at baseline, events/year	% change in mean ER from baseline to follow-up					Timepoint	Patients experiencing exacerbation, % (n/N)
Llanos, 2020 (14) USA	Outpatient or ED visit with a diagnosis of asthma in any position (ICD-9: 493.xx, ICD-10: J45.xx) and ≥ 1 prescription of SCS; IM, IV, or oral) within ± 5 days of the encounter	346	12	2.68 (2.14)	1.65 (1.96)	-38.43	-1.03 (<0.001)	-38.43	-	-	Baseline 12 months	84.4% (292/346) 64.5% (223/346)
Numata, 2020 (36) Japan	Asthma exacerbations requiring hospitalization	346	12	0.11 (0.43)	0.03 (0.23)	-72.73	-0.08 (0.004)	-72.73	-	-	Baseline 12 months	7.5% (26/346) 2.6% (9/346)
	Exacerbations of asthma symptoms requiring SCS, EOS < 400 cells/ μ L	NR	12	NR	NR	-65.2	NR	-65.2	-	-	-	-
	Exacerbations of asthma symptoms requiring SCS, EOS ≥ 400 cells/ μ L	NR	12	NR	NR	-71	NR	-71	-	-	-	-
Sposato, 2020 (39) Italy	Moderate/severe exacerbations, requiring SCS for at least 3 days	134	Mean (SD): 10.9 ($\pm$ 3.7)	3.8 (1.9)	0.8 (1.1)	-78.95	-3 (<0.0001)	-78.95	-	-	-	-
Taille, 2020 (40) France	Definition 1 Disease worsening requiring an ED visit, hospitalization and/or use of OCS for ≥ 48 h or an increase of $\geq 50\%$ in daily OCS dose	146	24	5.8 (4.4)	0.8 (0.9)	-86.21	-5 (NR)	-86.21	-	-	-	-
Overall study population	Definition 2 Exacerbations requiring hospitalization	146	24	0.6 (1.5)	0.1 (0.4)	-83.33	-0.5 (NR)	-83.33	-	-	-	-
	Overall study population	146	24	0.5 (0.9)	0.1 (0.3)	-80.00	-0.4 (NR)	-80.00	-	-	-	-
	Definition 3 Exacerbations requiring an ED visit	146	24	0.5 (0.9)	0.1 (0.3)	-80.00	-0.4 (NR)	-80.00	-	-	-	-
Overall study population	Definition 1 EOS 300–500 cells/ μ L	11	24	6.9 (5.1)	0.7 (0.6)	-89.86	-6.2 (NR)	-89.86	-	-	-	-
	Definition 2 300–500 cells/ μ L	11	24	1.5 (3)	0.1 (0.3)	-93.33	-1.4 (NR)	-93.33	-	-	-	-
	Definition 3 EOS 300–500 cells/ μ L	11	24	0.7 (1.1)	0 (NA)	-100.00	-0.7 (NR)	-100.00	-	-	-	-
Overall study population	Definition 1 EOS 500–700 cells/ μ L	13	24	5.3 (3.8)	1.5 (1.1)	-71.70	-3.8 (NR)	-71.70	-	-	-	-
	Definition 2 EOS 500–700 cells/ μ L	13	24	0.5 (0.8)	0.4 (1)	-20.00	-0.1 (NR)	-20.00	-	-	-	-
	Definition 3 EOS 500–700 cells/ μ L	13	24	0.4 (0.8)	0.3 (0.6)	-25.00	-0.1 (NR)	-25.00	-	-	-	-
Overall study population	Definition 1 EOS ≥ 700 cells/ μ L	36	24	5.8 (3.9)	0.6 (0.7)	-89.66	-5.2 (NR)	-89.66	-	-	-	-
	Definition 2 EOS ≥ 700 cells/ μ L	36	24	0.5 (1)	0 (NA)	-100.00	-0.5 (NR)	-100.00	-	-	-	-
	Definition 3 EOS ≥ 700 cells/ μ L	36	24	0.5 (1.1)	0 (NA)	-100.00	-0.5 (NR)	-100.00	-	-	-	-

(Continued)

Table 2. (Continued)

Author, year and country	Definition of exacerbation/ subgroup	Sample size	Timepoint for follow-up (months)	Annualized exacerbation rate				Proportion of patients with an exacerbation during follow-up	
				Mean (SD)/ median ER at baseline, events/year	Mean (SD)/median ER at follow-up, events/year	Mean (p-value) change in ER from baseline to follow-up	% change in mean ER from baseline to follow-up	Timepoint	Patients experiencing exacerbation, % (n/N)
van Toor, 2021 (16) Netherlands	Severe exacerbations defined as any severe peak of symptoms that required an increase in dose of mOCS for ≥ 3 days, a cycle of OCS, a visit to the ED, hospitalization, mechanical ventilation, or ICU admission	78	12	4.6 (NR)	1.4 (NR)	-3.2 (0.001)	-69.57	-	-
Yilmaz, 2020 (41) Turkey	Severe asthma exacerbations requiring hospitalization	78	12	0.77 (NR)	0.35 (NR)	-0.42 (0.001)	-54.55	-	-
	Worsening of asthma symptoms requiring OCS at least 3 days a week or an increase in the OCS dose	16	6	2.1 (2.7)	0.07 (0.26)	-2.03 (0.012)	-96.67	-	-

ED, emergency department; EOS, eosinophil; ER, exacerbation rate; GP, general practitioner; ICD, International Classification of Diseases; ICU, intensive care unit; ID, identification; IM, intramuscular; IV, intravenous; mOCS, maintenance OCS; NA, not applicable; NR, not reported; OCS, oral corticosteroid; SCS, systemic corticosteroid; SD, standard deviation; UK, United Kingdom; US, United States.

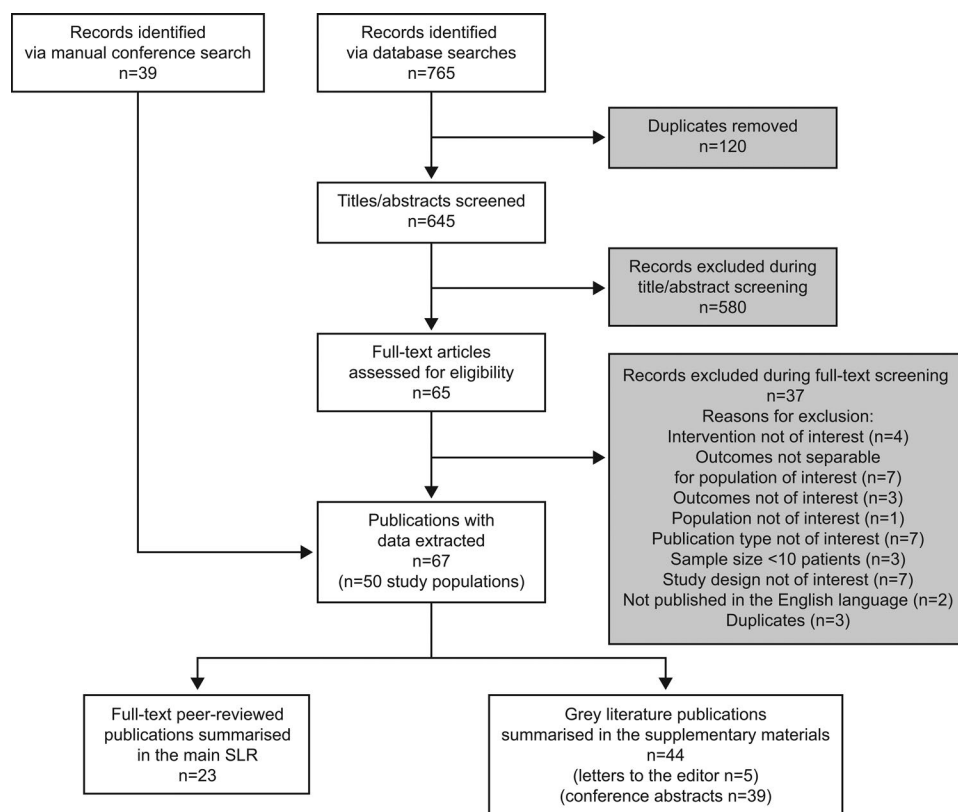


Figure 1. Study attrition. SLR, systematic literature review.

to safety data, adverse events (AEs) that occurred during the follow-up period of the included studies were captured by reported event type. The results reported in this publication focus on the available evidence from full-text, peer-reviewed journal articles, with the findings of gray literature (including letters to the editor and congress abstracts) summarized only briefly. For all key outcomes of interest, results have been summarized for prospective and retrospective studies, separately.

Ethics

Only publicly available summary-level data were included in this SLR; ethical approval was therefore not required.

Results

Characteristics of the included studies

The electronic database searches identified 645 unique titles and abstracts; 580 of these were excluded during eligibility screening. The remaining 65 abstracts were retrieved for full-text review, and following screening, 67 publications reporting data in 50 unique study populations met the criteria for inclusion. Among

these, 23 full-text peer-reviewed articles reported data from 22 unique study populations and 44 gray literature publications reported data from 28 unique study populations (Figure 1).

The 22 unique study populations included in the full-text publications (14–16,23–41) included a total of 2,040 patients and were conducted in Italy ($n=7$) (28–31,33,37,39), Australia ($n=3$) (23–25), United Kingdom ($n=2$) (34,35), United States ($n=1$) (14), France ($n=1$) (40), Netherlands ($n=1$) (16), Spain ($n=1$) (32), Germany ($n=1$) (27), Belgium ($n=1$) (26), Portugal ($n=1$) (38), Japan ($n=1$) (36), Turkey ($n=1$) (41) and Israel ($n=1$) (15). Most ($n=12$) studies were conducted at a single centre (15,16,23,25–28,33–36,41), while five enrolled patients across multiple centers (29,32,37,38,40) and five analyzed data from database/registry sources (14,24,30,31,39). Full study details are described in [Supplementary Table 3](#). Details of the gray literature publications identified by this SLR are described in [Supplementary Table 4](#).

Findings of studies reported in full-text peer-reviewed publications

Patient characteristics

Patient baseline characteristics from the 22 studies reported in full-text publications are shown in [Table 1](#). The mean/median age of recruited patients ranged from 49 (14) to 67 (31) years across the studies and the

Table 3. OCS data.

Author, year and country	Sample size	Timepoint for follow-up in months	Patients receiving mOCS at baseline, % (n/N)	Patients receiving mOCS at follow-up, % (n/N)	Proportion of patients who discontinued mOCS at follow-up	Mean (SD)/median OCS dose at baseline, mg/day	Mean (SD)/ median OCS dose at follow-up, mg/day	Mean change in OCS dose (p-value) from baseline to follow-up, mg/day	% change in dose from baseline to follow-up
Prospective studies									
Harvey, 2020 (24) Australia	309	6	47% (NR)	30% (NR)	36.3%	10 (NR)	7.5 (NR)	-2.5 (0.001)	-25.00
Pertzov, 2021 (15) Israel	61	Median (range): 13.5 (3–36)	52.5% (32/61)	16.3% (10/61) Patients who are still on maintenance OCS and did not decrease dose by more than 50%	NR	Median: 20 (IQR: 6.25–40)	Median: 5 (IQR: 0–9.37)	-15 (NR)	-75.00
Langton, 2020 (25) Australia	47	12	40% (19/47)	29.78% (14/47)	26.0% (5/19)	11.1 (7.5)	7.1 (11.4)	-4 (0.07)	-36.04
Schleich, 2020 (26) Belgium	116	30	25% (NR)	NR	NR	Median: 8	Median: 2.1	-5.9 (NR)	-73.75
Retrospective studies									
Drick, 2018 (27)	42	Median (IQR): 12 (7–15)	57% (23/42)	31% (13/42)	24.0%	Median (IQR): 5 (5–10)	Median (IQR): 5 (4–12.5)	0 (NR)*	0*
Germany	14	6	100% (14/14)	21.4% (3/14)	78.6%	24.11 (10.36)	1.78 (3.82)	-22 (<0.0001)	-92.62
Pelaia, 2018 (28) Italy	138	12	80.4% (111/138)	27.5% (38/138)	66.0%	10.1 (9.4)	2.0 (4.2)	-8.1 (<0.001)	-81.00
Bagnasco, 2019 (29)	41	12				10.46 (10.17)	2.62 (4.9)	-7.84 (<0.001)	-74.95
Overall population	97	12				9.97 (9.1)	1.79 (3.9)	-8.18 (<0.001)	-82.05
EOS <500 cells/ μ L	109	12				9.66 (8.92)	1.75 (3.8)	-7.91 (<0.001)	-81.88
EOS >500 cells/ μ L	69	6	70.5% (43/61)	32.2% (19/59)	57.1%	8.5 (8.8)	1.4 (2.2)	-7.1 (NR)	-83.53
Caminati, 2019 (30) Italy	25	12	65.22% (15/23)	47.8% (11/23)	26.7%	14.8 (NR)	10	-4.8 (NR)	-32.43
Montero-Perez, 2019 (32) Spain	26	6	22.2% (6/26)	7.7% (2/26)	66.7%	3 (4.8)	0.3 (1.1)	-2.7 (0.0211)*	-90.00*
Cameli, 2020 (33) Italy	91	12	100%	NR	52.0%	Median: 10	NR	-8.4 (NR)	NR
d'Ancona, 2020 (34) UK	99	12	68.7% (68/99)	NR	57.0% (NR)	Median (IQR): 10 (10–15)	Median (IQR): 0 mg (0–10)	-10 (<0.001)	-100
Kavanagh 2020 (35) UK	346	12	36.7% (127/346)	24.6% (85/346)	NR	-	-	-	-
Llanos, 2020 (14) US	527	12	42.1% (NR)	27.5% (NR)	NR	-	-	-	-
November 2015 to September 2017									
Numata, 2020 (36) Japan	12	12	-	-	-	NR	NR	NR	-44.8
EOS <400 cells/ μ L	NR					NR	NR	NR	-88.9
EOS $\geq$ 400 cells/ μ L	NR					NR	NR	NR	

(Continued)

Table 3. (Continued)

Author, year and country	Sample size	Timepoint for follow-up in months	Patients receiving mOCS at baseline, % (n/N)	Patients receiving mOCS at follow-up, % (n/N)	Proportion of patients who discontinued mOCS at follow-up	Mean (SD)/median OCS dose at baseline, mg/day	Mean (SD)/median OCS dose at follow-up, mg/day	Mean change in OCS dose (p-value) from baseline to follow-up, mg/day	% change in OCS dose from baseline to follow-up
Pelaia, 2020 (37) Italy	88	12	76% (67/88)	12% (11/88)	83.6%	Median: 3	Median: 0	-3 (<0.0001)*	-100*
Sposato, 2020 (39) Italy	134	Mean (SD): 10.9 (3.7)	74% (NR)	43% (NR)	46.4%	-	-	-	-
Taille, 2020 (40) France	146	24	92.8 (128/138)	34.3 (44/128)	65.3%	20.6 (16.5)	7.8 (17.0)	-12.8 (NR)	-62.14
	11	24	100% (11/11)	48 (11/23)	52.0%	19.0 (12.4)	13.0 (16.5)	-6 (NR)	-31.58
	13	24	100% (13/13)	46 (13/28)	54.0%	21.4 (16.3)	9.1 (11.8)	-12.3 (NR)	-57.48
	36	24	100% (36/36)	59 (36/61)	41.0%	20.1 (16.2)	7.6 (21.2)	-12.5 (NR)	-62.19
van Toor, 2021 (16) Netherlands	78	12	51.3% (40/78)	15.4% (NR)	NR				
Yilmaz, 2020 (41) Turkey	16	6	100% (16/16)	60% (9/15)	40.0%	9.2 (5.2)	1.3 (1.4)	-7.9 (<0.001)	-85.87

*These publications were not included in the SLR reporting of mean/% change in OCS dose, since they did not specify whether the included patients were using mOCS at baseline and/or still receiving mepolizumab at the follow-up timepoint. EOS, eosinophil; IQR, interquartile range; mOCS, maintenance OCS; NR, not reported; OCS, oral corticosteroid; SD, standard deviation; UK, United Kingdom.

proportion of female patients ranged from 35% (33) to 90% (38). Eighteen studies reported information on maintenance oral corticosteroid (mOCS) use at baseline, with between 22.2% (33) and 100% (28,34,41) of patients using mOCS; three studies enrolled only patients with OCS-dependent asthma (28,34,41). Fourteen studies reported smoking status, with the proportion of patients who never smoked ranging from 42% (33) to 88% (41) and the proportion of current smokers ranging from 0% (23) to 26% (37). Eight studies reported mean baseline blood eosinophil counts, ranging from 647 (28) to 1,228 cells/ μ L (36); two studies reported median (interquartile range) baseline blood eosinophil counts of 630 (400–900) (15) and 590 (400–830) (24) cells/ μ L (Supplementary Table 5). Among the two studies enrolling only patients with OCS-dependent asthma and with blood eosinophil count data available, mean baseline blood eosinophil counts were 580 (41) and 647 (28) cells/ μ L. Across the few studies that reported asthma-related comorbidities, 22% (14) to 100% (41) of patients had nasal polyps (study reporting the upper range recruited only patients with comorbid nasal polyps), 18% (40) to 100% (41) of patients had allergic rhinitis/chronic rhinosinusitis, and 8% (16) to 58% (26) had gastroesophageal reflux disease.

Exacerbations

A total of 16 studies (three prospective and 13 retrospective) reported annualized exacerbation rates. Although the definitions of an exacerbation varied across the studies, common factors across the definitions used included worsening asthma symptoms requiring emergency department (ED) or hospital visits, treatment with systemic corticosteroids, and/or increases in mOCS doses. Three studies (28,32,34) did not provide a definition for exacerbations. The exacerbation definition(s) adopted by each study as well as changes in exacerbation rate with mepolizumab are described in Table 2.

Three prospective studies, all with 12 months of follow-up data, reported statistically significant ($p < 0.001$) reductions in OCS-requiring exacerbations with mepolizumab. These studies reported reductions from baseline to follow-up of 66% (4.16 vs 1.41 events/year) (24), 68% (2.80 vs 0.90 events/year) (25) and 73% (3.14 vs 0.85 events/year) (15), with one study also reporting a 54% reduction in the annualized rate of exacerbations requiring hospitalization (0.57 vs 0.26 events/year at baseline vs follow-up; $p < 0.001$) (24) (Figure 2A and 2B). The findings of the prospective studies were supported by data from the 13 retrospective studies, which included between 6 and 24 months

of follow-up data (Table 2). Six of the retrospective studies reported the rate of exacerbations requiring at least treatment with OCS (14,16,35,39–41), showing reductions of 54% (4.04 vs 1.86 events/year at baseline vs follow-up; $p < 0.001$) (35) to 97% (2.10 vs 0.07 events/year at baseline vs follow-up; $p = 0.012$) (41) (Figure 2A). Three retrospective studies also reported reductions in the rate of exacerbations requiring hospitalization of 55% (0.77 vs 0.35 events/year at baseline vs follow-up; $p = 0.001$) (16), 73% (0.11 vs 0.03 events/year at baseline vs follow-up; $p = 0.004$) (14), and 83% (0.6 vs 0.1 events/year at baseline vs follow-up; p values not reported) (40) events/year (Figure 2B). Two of the retrospective studies presented results in subgroups according to baseline blood eosinophil count (29,40). In both studies, exacerbation rates were reduced with mepolizumab across all blood eosinophil count groups; of note, the majority of patients from both studies (80% and 93%) were receiving mOCS at baseline.

The proportion of patients with exacerbations (any definition) before and after mepolizumab initiation was reported by one prospective (15) and three retrospective (14,30,35) studies (Table 2). The prospective study reported an 85% relative risk reduction from baseline to follow-up in the proportion of patients with ≥ 1 exacerbation (85% in the 12 months preceding vs 13% in the 12 months following mepolizumab initiation). The three retrospective studies all reported reductions from baseline to follow-up in the proportion of patients with ≥ 1 exacerbation, ranging from 24% (14) to 85% (15); one of these also showed a 65% relative risk reduction in the proportion of patients with an exacerbation requiring hospitalization (14).

Reduction in maintenance OCS

Eighteen studies enrolled patients who were receiving mOCS at baseline, and 16 (three prospective (15,24,25) and 13 retrospective (14,16,27–30,32,33,35,37,39–41)) of these reported either the percentage of patients who remained on mOCS following mepolizumab initiation or the proportion of patients who discontinued mOCS use during the follow-up period (Table 3).

In the three prospective studies, 40% (25) to 53% (15) of patients were receiving mOCS at baseline; after 6 months to 1 year of follow-up, the two studies with data available showed that 36% (24) and 26% (25) of the patients who were using mOCS at baseline had discontinued mOCS (Figure 2C; Table 3). Among the retrospective studies, 22% (33) to 100% (41) of patients were receiving mOCS at baseline. Among those studies with follow-up data available at 6 months

($n = 4$) (28,30,33,41), 12 months ($n = 5$) (29,32,34,35,37), and 24 months ($n = 1$) (40), 40% (41) to 79% (28) of the patients receiving mOCS at baseline had discontinued mOCS after 6 months of mepolizumab treatment, 27% (32) to 84% (37) had discontinued mOCS after 12 months, and 65% (40) had discontinued mOCS after 24 months (Figure 2C; Table 3). There was no clear association between the duration of follow-up and the degree of reduction in mOCS use.

Three prospective (15,24,25) and eight retrospective (26,28–30,32,35,40,41) studies reported mOCS doses at baseline and at follow-up, among patients who were using mOCS at baseline. In the prospective studies, reductions from baseline in mOCS dose ranged from 2.5 mg/day ($p = 0.001$) (24) to 15 mg/day (p values not recorded) (15) during follow-up, translating to a 25% (24) to 75% (15) reduction from baseline in mOCS dose with mepolizumab (Figure 2D; Table 3). In the retrospective studies, reductions from baseline in mOCS dose ranged from 4.8 mg/day (p values not recorded) (32) to 22 mg/day ($p < 0.0001$) (28) during follow-up, translating to a 32% (32) to 100% (35) reduction from baseline mOCS dose with mepolizumab (Figure 2D; Table 3).

Lung function

Of nine studies (two prospective (15,23) and seven retrospective (28,29,33,35,37,39,41)) reporting changes in FEV₁ from baseline to follow-up, both prospective studies and the majority ($n = 6$ (28,29,33,37,39,41)) of the retrospective studies reported improvements in forced expiratory volume in 1 s (FEV₁) with mepolizumab (Figure 2E; Supplementary Table 6). Mean changes in FEV₁ ranged from +0.15 (15) to +0.27 L (23) in the prospective studies and –0.03 (35) to +0.40 L (33) in the retrospective studies. Results were statistically significant ($p < 0.05$) in all but two (35,41) of the studies in which statistical analyses were reported.

Of the 10 studies (two prospective (24,25) and eight retrospective (16,30,33–36,39,41)) with available data, both prospective studies and six retrospective studies (16,30,33,36,39,41) reported improvements in % predicted FEV₁ with mepolizumab (Supplementary Table 5). The remaining two retrospective studies reported reductions in % predicted FEV₁ of 1.5% ($p = 0.438$) (35) and 2.3% (p values not reported) (34). Improvements from baseline ranged from 6.1% (24) to 6.3% (25) in the prospective studies and 3.2% (36) to 8.1% (30) in the retrospective studies; statistical significance ($p < 0.05$) was shown in the one prospective study and two of the five retrospective studies

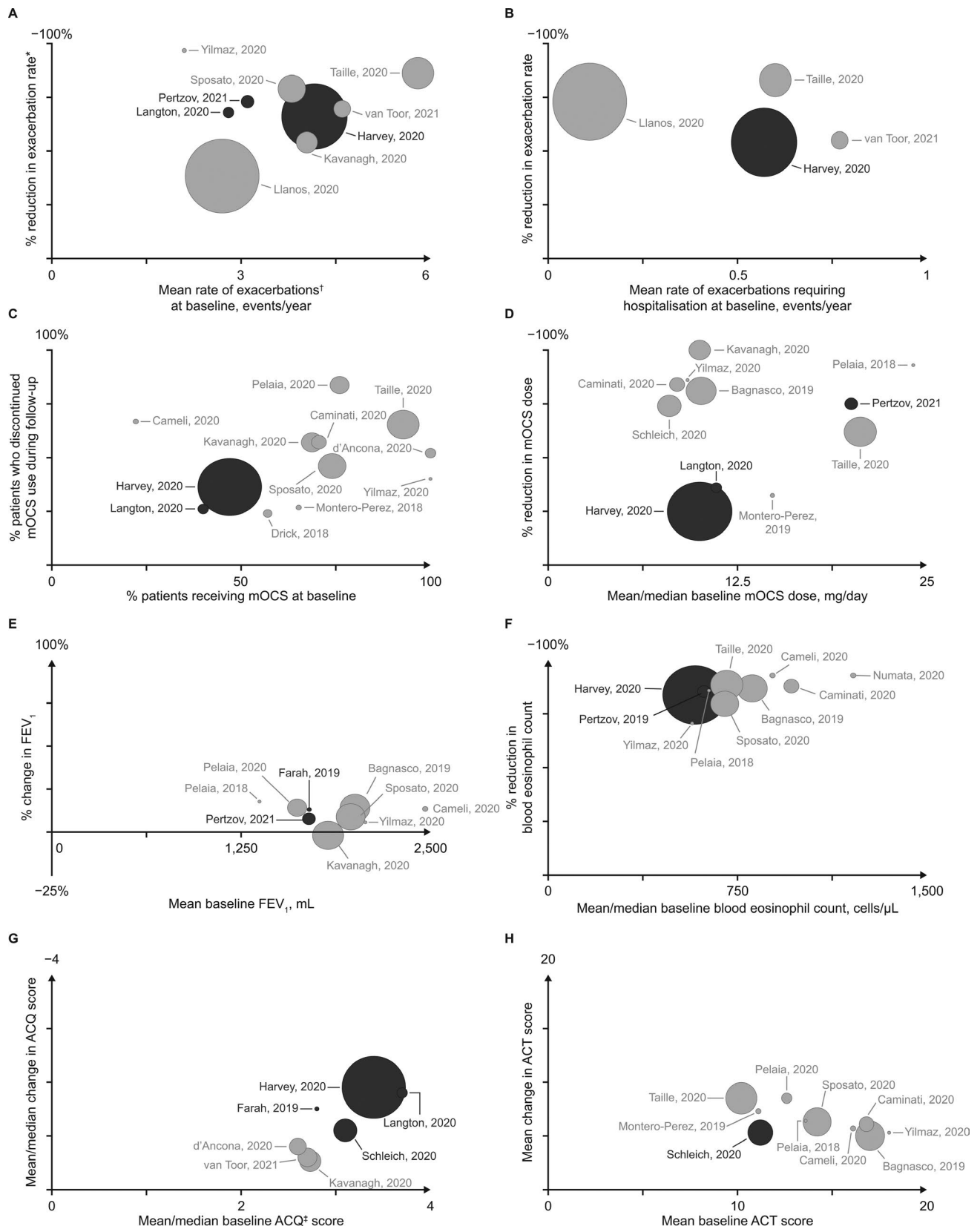


Figure 2. Summary of study outcomes.

Darker spheres indicate prospective studies and paler spheres indicate retrospective studies; sphere size is proportional to study patient population size; for studies reporting statistical analyses, statistical significance information was extracted and has been reported in [Tables 2 and 3](#) (exacerbation and OCS data), and supplementary Tables 5–7 (FEV₁, blood eosinophil count, ACQ and ACT data).

*Exacerbations defined as worsening of asthma that required at least treatment with OCS; [†]Farah (2019), Harvey (2020) and Langton (2020) reported ACQ-5 score, d'Ancona (2020), Kavanagh (2020) and van Toor (2020) reported ACQ-6 score, Schleich (2020) did not disclose the version of the ACQ used.

ACT, asthma control test; ACQ-5, asthma control questionnaire – 5 item; ACQ-6, asthma control questionnaire – 6 item; FEV₁, forced expiratory volume in 1 second; mOCS, maintenance oral corticosteroids.

that showed improvements and reported statistical analyses ([16,25,34,35,39](#)).

Three studies (one prospective ([23](#)) and two retrospective ([29,33](#))) evaluated mean changes in forced vital capacity (FVC); an improvement from baseline to follow-up in FVC was observed with mepolizumab in all three studies (mean change from baseline in the prospective study: +0.15 L [no *p* values reported]; mean change from baseline in the retrospective studies: +0.16 L [*p* < 0.0001] and +0.03 L [*p* = 0.7857]; [Supplementary Table 5](#)). All five studies with FEV₁/FVC data (one prospective ([23](#)) and four retrospective ([28,29,33,36](#))) reported improvements following 6 or 12 months of mepolizumab treatment, with mean FEV₁/FVC ratios of 61% (mean change of 6%) in the prospective study and 66–72% ([28,33](#)) (mean change of 2.1–4.8% ([28,36](#))) in the retrospective studies ([Supplementary Table 5](#)).

Blood eosinophil counts

Ten studies (two prospective ([15,24](#)) and eight retrospective ([28–30,33,36,39–41](#))) reported the impact of mepolizumab on blood eosinophil counts. All studies reported lower mean blood eosinophil counts following mepolizumab treatment, with post-treatment mean (SD) absolute blood eosinophil counts ranging from 75–177 cells/μL. Percentage reductions from baseline to follow-up in blood eosinophil counts ranged from 83% ([24](#)) to 84% ([15](#)) in the prospective studies and 69% ([41](#)) to 92% ([36](#)) in the retrospective studies ([Figure 2F](#); [Supplementary Table 6](#)). Reductions were statistically significant in both prospective studies and in all six of the retrospective studies that reported statistical analyses ([28,29,33,36,39,41](#)).

Asthma control and HRQoL

All 16 studies reporting Asthma Control Questionnaire (ACQ) or Asthma Control Test (ACT) scores (four prospective ([23–26](#)) and 12 retrospective ([26,28–30,32–35,37,39–41](#))) showed improvements with mepolizumab ([Figure 2G and 2H](#); [Supplementary](#)

[Table 7](#)). Among the included studies, mean baseline ACQ and ACT scores ranged from 2.6 ([16](#)) to 3.7 ([25](#)) and 10.2 ([40](#)) to 18.0 ([41](#)) points, respectively. Mean changes in ACQ score from baseline to follow-up ranged from –1.1 ([26](#)) to –1.9 ([24](#)) points among the prospective studies (*n* = 4) and –0.5 ([35](#)) to –0.8 ([16](#)) points among the retrospective studies (*n* = 3) with ACQ data available. These differences were all equal to or greater than the established minimal clinically important difference (MCID) of 0.5 points ([42](#)). Changes were statistically significant (*p* < 0.001) in all five studies that reported statistical analyses ([16,24–26,35](#)). With regards to ACT score, mean changes from baseline to follow-up were 5.31 points (*p* < 0.0001) ([26](#)) in one prospective study and 5.00 ([29](#)) to 8.53 ([37](#)) points in nine retrospective studies with data available. These differences all exceeded the established MCID of 3 points ([43](#)). Changes were statistically significant (*p* ≤ 0.006) in the eight retrospective studies that reported statistical analyses ([28–30,33,37,39,41](#)).

Three studies (two prospective ([24,26](#)) and one retrospective ([35](#))) showed that mepolizumab had a statistically significant (*p* < 0.001) beneficial impact on Asthma Quality of Life Questionnaire (AQLQ) or mini-AQLQ score. Mean baseline scores ranged from 3.48 ([26](#)) to 4.05 ([35](#)) points; the prospective studies reported AQLQ improvements of 1.5 ([24](#)) and 1.24 ([26](#)) points, and the retrospective study reported a 0.86-point improvement ([35](#)) in mini-AQLQ score ([Supplementary Table 7](#)). One retrospective study ([33](#)) also reported Sino-nasal Outcome Test-22 scores among 26 patients with severe eosinophilic asthma, and showed a statistically significant improvement of 16.9 points (from a mean baseline score of 40.5 points) following mepolizumab treatment, almost double the MCID of 8.9 points ([44](#)) ([Supplementary Table 7](#)).

Safety and treatment discontinuation

Across 10 studies with available data (three prospective ([24–26](#)) and seven retrospective ([16,27,33,35,37,40,41](#))), the overall rate of mepolizumab discontinuation ranged

from 7% (6 months of follow-up) (26) to 26% (12 months of follow-up) (25) in the prospective studies and from 0% (7–15 months of follow-up) (27) to 33% (24 months of follow-up) (40) in the retrospective studies (Supplementary Table 8). Treatment discontinuation due to AEs was uncommon, occurring in 2% (24) to 11% (25) of patients in the prospective studies (12 months of follow-up) and 0% (27,37) to 6% (41) of patients in the retrospective studies (6–24 months of follow-up). Fifteen studies (three prospective (24–26) and 12 retrospective (16,27–33,37,38,40,41)) reported the proportions of patients with AEs whilst receiving mepolizumab treatment. Reported AEs in order of frequency included headache (0–40%), arthralgia (0–35%), fatigue (0–30%), dizziness (0–26%), injection-site reactions (0–7%), urticaria or hypersensitivity reactions (0–5%), and cardiac events (0–1%) (Supplementary Table 9).

Economic outcomes: HCRU and cost

Two retrospective studies presented data on HCRU before and after mepolizumab treatment. Both of these studies, one from Italy (29) and one from the US (14), reported a statistically significant decrease in the mean number of hospitalizations in the 12 months following versus the 12 months preceding mepolizumab initiation. The US study also reported a significant reduction from baseline to follow-up in mean exacerbation-related costs per patient (\$5,178 vs \$2,383; $p < 0.001$) and a numerical reduction in the mean number of OCS pharmacy claims during the follow-up period (3.9 claims) compared with the baseline period (5.5 claims) (14).

Findings from the gray literature

Results reported in the gray literature generally supported those of the full-text peer-reviewed publications. Where data were available, overall improvements in exacerbation rates, mOCS use, lung function, blood eosinophil count, and asthma control were observed. Rates of mepolizumab discontinuation reported in the gray literature were also similar to those reported in the full-text peer-reviewed publications.

Discussion

Across the current respiratory treatment landscape, there is an important need for real-world studies with high external validity to support the efficacy results of RCTs (45). This SLR aimed to provide a broad picture of the full range of clinical impacts seen with

mepolizumab in a real-world setting, in order to determine whether the clinical benefits shown in RCTs of mepolizumab in severe eosinophilic asthma, namely reduced exacerbation rates, reduced OCS use, improved asthma control, and improved HRQoL (10–13), are also seen in more diverse, real-world populations. Our findings indicate that patients with severe asthma receiving mepolizumab treatment in real-world clinical practice experience important health benefits, including reductions in exacerbations, OCS use and blood eosinophil counts, plus improvements in lung function, asthma control and HRQoL.

The observational real-world studies identified by the SLR included a heterogeneous patient population, with a broader spectrum of disease severity, comorbidities and concomitant medications compared with those typically enrolled in RCTs. Compared with patients enrolled in previous mepolizumab RCTs (10–13,46,47), the patients included in real-world studies were generally older, with more severe asthma and a larger number of comorbid conditions. Overall, 40–93% of patients included in this SLR were using mOCS prior to mepolizumab initiation, compared with 23–33% in the RCTs of mepolizumab in patients with severe asthma (where mOCS use was not a requirement for patient eligibility) (11–13). Although definitions varied, the annualized rate of exacerbations requiring at least OCS treatment was similar in the real-world literature prior to mepolizumab initiation compared with previous RCTs (2.1–5.8 events/year in this SLR vs 2.7–3.8 events/year in RCTs). Only a few of the studies included in this SLR reported on asthma-specific comorbidities; among these, the proportion of patients with comorbidities was high, and generally exceeded the proportion reported in a recent open-label extension study of mepolizumab (22% to 100% in this SLR vs 7% in RCT with nasal polyps; 49% to 100% in this SLR vs 12% in RCT with chronic rhinosinusitis) (47). This is expected, since interventional studies in patients with severe asthma typically exclude those with comorbidities associated with respiratory symptoms, such as chronic obstructive pulmonary disease. The studies identified by this SLR included a wide selection of geographic locations, with publications from the United States, Japan, Australia, and multiple European countries. Although no studies from China (where mepolizumab is not licensed) or South America were identified as meeting the eligibility criteria, the geographical spread of the available data appears to be sufficiently representative of real-world use of mepolizumab.

Despite the range of differences between the real-world populations included in this SLR and the

populations included in RCTs of mepolizumab in patients with severe asthma, the clinical benefits shown in real-world settings were consistent with those shown previously in RCTs. These included a significant reduction in asthma exacerbations, which is a primary goal of asthma treatment, and indeed, reductions in exacerbation rates were among the most important efficacy results of the landmark mepolizumab RCTs. The SLR also demonstrated mepolizumab treatment to have a significant OCS-sparing effect in clinical practice, with 24–84% of patients able to discontinue OCS use completely with mepolizumab. Reducing OCS dependence is another key goal of asthma treatment, owing to multiple negative side effects associated with long-term OCS use (48). The real-world data reported here build on the results of a formal OCS-sparing trial, which reported 23% of patients receiving mepolizumab to have reduced their mOCS use by 90–100% by study end (10). It should be noted that the ability to reduce OCS was not at the expense of loss of disease control; moreover, irrespective of their improvements in disease control with mepolizumab, some patients may not have been able to discontinue mOCS entirely due to adrenal insufficiency (49). Finally, the published real-world evidence also indicated that geometric mean absolute blood eosinophil counts were reduced to levels within the identified normal range following mepolizumab initiation (50). Despite variations in the assessment tools used, improvements in asthma control and HRQoL were also observed with mepolizumab therapy. It is important to consider that since mepolizumab specifically targets IL-5, patients who had any respiratory comorbidities that were not associated with eosinophilia may have experienced smaller improvements in their asthma control than those without (24). Together the data from the large number of studies included in the SLR demonstrate that the broad range of clinical benefits shown with mepolizumab in patients with severe asthma during RCTs was mirrored in the real-world population of patients with asthma receiving mepolizumab.

In the SLR studies with available safety data, headache was the most commonly reported AE, followed by injection site reactions and arthralgia. These AEs were reported in the mepolizumab clinical trials, where headache was often also the most commonly reported AE (11–13,46,47). Mepolizumab discontinuation rates due to AEs were typically low in the studies identified by the SLR, and broadly similar to those reported in RCTs (10,11,47,51).

With regards to the impact of mepolizumab on economic burden, only one study reporting

exacerbation-related costs and two studies reporting exacerbation-related HCRU were identified by the SLR. The findings of these studies associated mepolizumab treatment with substantial reductions in exacerbation-related costs for patients with severe uncontrolled asthma, compared with baseline values. In addition, hospitalizations due to asthma exacerbations were significantly decreased following mepolizumab treatment.

There are several limitations that must be considered when interpreting the findings of this SLR. Firstly, differences in study design may limit comparison of the data from real-world studies with those from RCTs. For example, restrictions in OCS tapering protocols may have prevented patients from substantially tapering or discontinuing OCS in the RCT setting; conversely, RCTs with rapid reduction algorithms may have reduced OCS use more quickly than in real-world clinical practice. Second, the absence of a control group in the included studies makes them prone to bias; however, the general consistency of the extracted data does not suggest that the results were confounded. Moreover, results of the single-centre clinical studies included in this SLR ($n=12$) are likely to be less generalizable to real-world clinical practice than those of the multi-centre registry/national database studies ($n=5$) (52). Third, SLRs are by nature limited to published data (and in this case those published in the English language) only. In addition, the risk of bias within individual studies was not assessed. Finally, we observed considerable heterogeneity in study design, patient cohort, sample size and outcome definitions across the included studies. In particular, the small sample size of some of the studies included in this SLR may have resulted in a lack of power to identify statistical differences in specific outcomes. Furthermore, the definitions of exacerbation varied across the studies, as did the patient reported outcomes instruments used to assess HRQoL. Owing to this between-study heterogeneity, the SLR did not pool results to perform meta-analyses. Nonetheless, the data identified by this SLR consistently demonstrated clinical benefits in patients with severe asthma receiving mepolizumab treatment. Notably, since the search was conducted in July 2020, several additional real-world studies of mepolizumab have been published, all of which report clinical benefits with mepolizumab (53–55) and therefore support the findings of this SLR.

Conclusions

Despite substantial heterogeneity observed in the available literature, mepolizumab was consistently

associated with clinically relevant benefits in eligible patients with severe asthma receiving treatment in real-world clinical practice. It is therefore reasonable to conclude that the benefits of mepolizumab demonstrated in previous RCTs extend to patients with heterogeneous demographics and characteristics, treated in a real-world setting.

Acknowledgements

This study was funded by GlaxoSmithKline (GSK; ID: 213095). Analyses were performed by Evidera, funded by GSK; employees did not receive funding for manuscript development. Editorial support (in the form of writing assistance, including development of the initial draft from the author discussions, assembling tables and figures, collating authors comments, grammatical editing and referencing) was provided by Bianca Paris, PhD, at Fishawack Indicia Ltd, UK, part of Fishawack Health, and was funded by GSK.

Author contributions

SY, PHH, ALM, MK, SGS and RAC all contributed to the conception or design of this study and were involved in the acquisition of data. All authors were involved in the data analysis and interpretation, contributed to the development of the manuscript, and approved the final version for submission. All authors agree to be accountable for all aspects of the work.

Disclosure of interest

EI reports consultancy fees from AB Science, Allergy and Asthma Network, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Equillium, Genentech, GSK, Merck, NHLBI, Novartis, Pneuma Respiratory, PPS Health, Regeneron, Sanofi Genzyme, Sienna Biopharmaceuticals and Teva; receipt of study drug/equipment from Boehringer Ingelheim, Circassia, Genentech, GSK and Teva; clinical research grants from AstraZeneca, Avillion, Circassia, Gossamer Bio, NIH, Novartis and PCORI; advisory board participation for Novartis; royalties from UpToDate and stock options from Vorso; he was a co-ordinating committee member for the National Asthma Education Prevention Program. GWC reports research grants and fees from A.Menarini, Alk-Abello, Allergy Therapeutics, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Genentech, Guidotti-Malesci, GSK, Hal Allergy, Mylan, Merck, Merck Sharp & Dome, Mundipharma, Novartis, Regeneron, Roche, Sanofi-Aventis, Sanofi-Genzyme, Stallergenes-Greer, UCB Pharma, Uriach Pharma, Valeas and Vibor-Pharma. GB has received honoraria for lectures from AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, Novartis, Teva and Sanofi; he is a member of advisory boards for Amgen, AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, Novartis, Sanofi/Regeneron and Teva. SY, PHH, SGS and RAC are employees

of GSK and hold stocks/shares. ALM is an employee of Evidera and MK is a former employee of Evidera and a current employee of Xcenda UK Ltd; as Evidera employees, they did not receive any direct payments or honoraria for their services.

Funding

This work was funded by GlaxoSmithKline (GSK ID: 213095).

Data availability statement

Data recorded in the data extraction template for this systematic literature review are available upon reasonable request from GlaxoSmithKline

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Supplementary Materials

Real-life effectiveness of mepolizumab in patients with severe asthma: a systematic literature review

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Supplementary Table 1. Search strategies

#	Category	Search terms	Search yield
MEDLINE search strategy via Ovid (searched on 10 July, 2020)			
1	Indication	Exp Asthma/	127,599
2		Asthma.mp.	173,163
3		1 or 2	173,468
4	Intervention	Mepolizumab.mp.	660
5		Nucala.mp.	16
6		Bosatria.mp.	1
7		(SB-240563 or SB240563).af.	8
8		4 or 5 or 6 or 7	663
9	Indication + intervention	3 and 8	463
10	Language limits	9 limited to English language	433
11	Study design	10 not (exp Randomized Controlled Trial/ or exp Random Allocation/ or exp Double-Blind Method/ or exp Single-Blind Method/ or exp Cross-Over Studies/ or (rct or controlled trial or cross over or crossover or placebo or (doubl\$ adj3 blind\$) or (singl\$ adj3 blind\$) or (open adj3 label\$) or factorial\$ or assign\$ or allocate\$ or controlled study or major clinical study or clinical article).ti,ab. or (randomised or randomized or trial or clinical trial).ti.)	342
Embase search strategy via Ovid (searched on 10 July, 2020)			
1	Indication	Exp Asthma/	257,194
2		Asthma.mp.	287,983
3		1 or 2	288,918
4	Intervention	Mepolizumab.mp.	2,649
5		Nucala.mp.	86
6		Bosatria.mp.	35
7		(SB-240563 or SB240563).af.	87
8		4 or 5 or 6 or 7	2,649
9	Indication + intervention	3 and 8	1,992
10	Language limits	9 limited to English language	1,926
11	Study design	10 not (exp Randomized Controlled Trial/ or exp Random Allocation/ or exp Double-Blind Method/ or exp Single-Blind Method/ or exp Cross-Over Studies/ or (rct or controlled trial or cross over or crossover or placebo or (doubl\$ adj3 blind\$) or (singl\$ adj3 blind\$) or (open adj3 label\$) or factorial\$ or assign\$ or allocate\$ or controlled study or major clinical study or clinical article).ti,ab. or (randomised or randomized or trial or clinical trial).ti.)	1,637
12	Publication type*	11 limited to limit (article or article in press)	423

*Embase indexes conference abstracts, so this limit was applied to limit the search to published full-text articles; a separate manual search was conducted for conference abstracts of interest.

Supplementary Table 2. PICOS-T eligibility criteria

PICOS	Inclusion criteria	Exclusion criteria
Population	Patients aged ≥ 6 years with asthma eligible for treatment with mepolizumab	Studies of patients without asthma
Interventions/ comparators	Patients treated with mepolizumab 100 mg SC*	Studies where none of the patients were receiving mepolizumab, or included only patients who switched from other interventions to mepolizumab (e.g., benralizumab)
Outcomes	For the overall population, or subgroups of patients stratified per EOS levels at baseline. Clinical outcomes - Exacerbations (all definitions, e.g. severe, hospitalised) - Annual exacerbation rate - Proportion of patients experiencing exacerbations - Lung function - Change/improvement in FEV₁ (measured in L and % predicted; mean or median values) - Change/improvement in FVC (mean or median values) - Change/improvement in FEV₁/FVC (mean or median values) - Change/improvement in blood EOS (mean or median values) - Reductions in daily dosage of OCS % of patients discontinuing maintenance OCS among those on maintenance OCS at baseline - Adherence to mepolizumab - Mepolizumab discontinuation rates - Overall - Due to AEs - AEs (i.e. injection-site reactions, dizziness, headache, arthralgia, cardiac events, urticaria, or hypersensitivity reactions and fatigue) reported with mepolizumab	- Studies investigating in-vitro, animal, foetal, molecular, genetic, pathologic, or pharmacokinetic/pharmacodynamic outcomes - Studies that do not report at least one of the outcomes of interest as noted under the inclusion criteria - Studies that do not report data for the overall population, and only report data for subgroups other than patients with specific EOS levels at baseline

Outcomes (continued)	HRQoL outcomes, mean change, including but not limited to the following measures: • Disease specific questionnaires: ○ AQLQ ○ ACQ ○ ACT ○ SGRQ • Generic questionnaires: ○ EQ-5D ○ SF-36 Economic outcomes • Asthma-exacerbation related costs ○ Total (sum of direct and indirect costs) ○ Direct (overall and itemised as available) ▪ Indirect (overall and itemised available) • Healthcare resource use ○ Physician visits ○ Specialist visits ○ Emergency department visits ○ Hospitalisations ○ Inpatient length of stay	
Study design	Observational studies (e.g., prospective and retrospective cohort studies, registry and claims database analysis, cross-sectional studies) enrolling at least 10 patients	• Clinical trials (RCTs, single-arm trials, and non-randomised trials) • Narrative publications, systematic reviews[†], case studies or case reports (<10 patients), and editorials • Protocols for RCTs or for other primary study types • Long-term extension studies of mepolizumab

Time period	1 January, 1946 through to 10 July, 2020	Studies published before 1946 or after 10 July, 2020
Language	Studies published in English	Studies published in languages other than English

*When dose was not reported it was assumed to be 100mg SC; [†] Publications of systematic reviews were used for citation chasing and will be subsequently excluded at full-text level. ACQ, asthma control questionnaire; ACT asthma control test; AE, adverse event; AQLQ, asthma quality of life questionnaire; EQ-5D, EuroQol-5 dimension; FEV₁, forced expiratory volume in 1 second, FVC, forced vital capacity; OCS, oral corticosteroids; RCT, randomised controlled trial; SC, subcutaneous; SF-36, 36-Item Short Form Survey; SGRQ, St George's respiratory questionnaire.

Supplementary Table 3. Details of the full-text studies included in the systematic literature review

Author, year and country	Study design	Setting/ source	Patient inclusion criteria	Patient accrual years	Study sample size	Reports data for overall population or subgroups?
Prospective studies						
Farah, 2019[1] Australia	Prospective cohort	Hospital-based airways clinic	All patients fulfilled nationally approved pre-specified criteria and were managed by a pulmonologist for at least 1 year prior to commencing mepolizumab. All patients had poorly controlled asthma despite receiving high-dose ICS and LABA combination therapy and had a history of at least one severe asthma exacerbation.	NR	20	Overall population
Pertsov, 2021[2] Israel	Prospective cohort	Rabin Medical Centre	Patients >18 years of age with severe eosinophilic asthma treated with mepolizumab.	Mar 2016 to May 2018	61	Overall population
Harvey, 2020[3] Australia	Prospective cohort	Post-marketing surveillance registry (AMR- ACTRN12618001497 291)	Patients treated with mepolizumab for severe uncontrolled eosinophilic asthma and enrolled through centres of the Australasian Severe Asthma Network	Jan 2017 to Apr 2019	309	EOS ≤600 cells/μL EOS >600 cells/μL
Langton, 2020[4] Australia	Prospective cohort	Severe Asthma Clinic (University teaching hospital in Victoria, Australia)	Patients with uncontrolled asthma despite optimised inhaled triple therapy including high-dose ICS	Jan 2017 to NR	47	Overall population
Schleich, 2020[5] Belgium	Prospective cohort	Asthma clinic (University asthma clinic of Liege)	Patients with severe eosinophilic asthma, diagnosed according to GINA. Patients had blood EOS >300 cells/μL, airway obstruction (FEV1 <80%) and had received at least two courses of systemic steroids within the last year.	Oct 2016 to Apr 2018	116	Overall population
Retrospective studies						
Drick, 2018[6] Germany	Retrospective cohort	Asthma out-patient clinic	Patients with severe eosinophilic asthma treated with mepolizumab for at least 6 months. All patients were treated with high-dose ICS/LABA, partially with a second or third controller and partially with additional OCS therapy.	NR	42	Overall population

Author, year and country	Study design	Setting/ source	Patient inclusion criteria	Patient accrual years	Study sample size	Reports data for overall population or subgroups?
			Documentation of EOS counts of ≥ 300 cells/ μL in peripheral blood within the past 12 months had to be present.			
Pelaia, 2018[7] Italy	Retrospective cohort	Respiratory Unit of "Magna Græcia" University Hospital	Patients with severe persistent asthma, characterised by an inadequate symptom control, despite a continuous therapy with high ICS dosages associated with LABA. All patients received an additional regular bronchodilator treatment, consisting of an inhaled LAMA. Every participant was treated continuously or near continuously with OCS. In spite of such a very intense inhaled and systemic therapy, the asthmatic patients enrolled in this study experienced frequent daily symptoms and/or nocturnal awakenings, as well as recurrent asthma exacerbations. Each recruited patient had EOS counts in peripheral blood of at least 150 cells/ μL at baseline and at least 300 cells/ μL within the past 12 months, respectively. With regard to lung function, FEV_1 was $<80\%$ of the predicted value, and improved of at least 12% and 200 mL within 30 minutes after inhalation of 400 μg of salbutamol.	Jun 2017 to Jan 2018	14	Overall population
Bagnasco, 2019[8] Italy	Retrospective cohort	Severe asthma clinics	Patients with severe uncontrolled asthma and a EOS count above 300 cells/ μL on at least one occasion during the last year, and more than 150 cells/ μL before the first mepolizumab injection. All patients were on the maximum inhaled treatment as per guidelines and on the minimum dose of OCS achievable to maintain the control.	May 2017 to Dec 2018	138	Overall population and EOS subgroups (<500 EOS/ μL , >500 EOS/ μL , >400 EOS/ μL)
Caminati, 2019[9] Italy	Retrospective cohort	RINOVA database of patients from allergy and respiratory medicine units	Patients with 1) confirmed diagnosis of severe asthma according to the ERS/ATS definition, 2) eligibility for mepolizumab treatment, according to the prescription requirements established by the European Regulatory Agency (EOS >150 cells/ μL when recruited and at least 300 cells/ μL within the 12 months prior to treatment start)	NR	69	Overall population
Lombardi, 2019[10] Italy	Retrospective cohort	Severe asthma centres (database study)	Patients who received at least one dose of mepolizumab	Mar 2017 to NR	143	Overall population

Author, year and country	Study design	Setting/ source	Patient inclusion criteria	Patient accrual years	Study sample size	Reports data for overall population or subgroups?
Montero-Perez, 2019[11] Spain	Retrospective cohort	Public hospitals	Every patient prescribed mepolizumab in three public hospitals of a province of Spain with more than 500,000 inhabitants since its introduction into the hospital was included in the study.	Oct 2017 to Oct 2018	25	Overall population
Cameli, 2020[12] Italy	Retrospective cohort	Clinical setting (Centre for Lung Diseases at Siena Regional Referral Centre for Rare Interstitial Lung Diseases)	Patients with severe eosinophilic asthma according to ERS/ATS guidelines.	Oct 2018 to Jan 2020	26	Overall population
d'Ancona, 2020[13] UK	Retrospective cohort	Guy's Severe Asthma Centre, in Guy's and St. Thomas' Hospitals	Patients that met NICE inclusion criteria for initiation of mepolizumab: all had confirmed severe asthma requiring ≥ 5 mg prednisolone daily for at least 6 months and had a EOS count of ≥ 300 cells/ μ L in the preceding 12 months.	Apr 2017 to Jun 2018	91	Overall population
Kavanagh, 2020[14] UK	Retrospective cohort	Tertiary asthma centre; Guys Severe Asthma Centre.	Patients with severe asthma, an EOS count of ≥ 300 cells/ μ L in the preceding 12 months, and a minimum of 4 exacerbations in the prior year and/or were on mOCS therapy	Apr 2017 to Nov 2017	99	Overall population
Llanos, 2020[15] USA	Retrospective cohort	Data from the IBM Watson Health MarketScan® Commercial Claims Database GSK ID: 209017, HO-18-19168	Patients ≥ 12 years with a diagnosis of severe asthma during the baseline period, and a minimum of two doses of mepolizumab in the first 180 days of the follow-up period.	Nov 2015 to Mar 2017	346	Overall population
Numata, 2020[16] Japan	Retrospective cohort	Hospital setting (Jikei University Hospital)	Patients with severe eosinophilic asthma, who had at least two exacerbations requiring OCS treatment in the previous year, blood EOS count $150/\text{mm}^3$ or greater at screening or $300/\text{mm}^3$ or greater in the previous year, or received OCS maintenance therapy (regardless of the number of exacerbations and blood EOS counts).	Jul 2016 to Dec 2019	24	EOS < 400 cells/ μ L EOS ≥ 400 cells/ μ L

Author, year and country	Study design	Setting/ source	Patient inclusion criteria	Patient accrual years	Study sample size	Reports data for overall population or subgroups?
Pelaia, 2020[17] Italy	Retrospective cohort	Four asthma clinics	Adults with severe persistent eosinophilic asthma, treated with mepolizumab. All patients met the ERS/ATS criteria that define severe uncontrolled asthma. All patients had EOS counts in peripheral blood of at least 150 cells/ μ L at baseline and at least 300 cells/ μ L within the past 12 months. They were treated with high dosages of ICS/LABA combinations. Furthermore, all recruited patients used an inhaled LAMA, and a large majority of them needed a permanent or near continuous intake of OCS.	NR	88	Overall population
Sousa, 2020[18] Portugal	Retrospective and descriptive analysis	Portuguese Pharmacovigilance System	Spontaneous reports of suspected adverse drug reactions involving biologicals that have been approved and are prescribed for the treatment of severe asthma in Portugal	Feb 2006 to Oct 2018	10	Overall population
Sposato, 2020[19] Italy	Retrospective cohort	Severe asthma centres (database study)	All patients had a diagnosis of severe asthma fulfilling all the diagnostic criteria established by guidelines (ERS/ATS). They had been poorly controlled even while using high ICS doses, OCS, long-acting bronchodilators and anti-leukotrienes (montelukast) which made it necessary to add mepolizumab, as recommended by step 5 of GINA asthma guidelines. All patients had to be adherent to inhaled treatments and had to use devices correctly. Mepolizumab was prescribed to patients who had an EOS count above 300/ μ L on at least one occasion during the previous year and more than 150/ μ L before the first mepolizumab injection.	May 2017 to Dec 2018	134	Overall population
Taille, 2020[20] France	Retrospective cohort	Medical records from the Temporary Authorisation for Utilisation for the treatment of severe eosinophilic asthma in France (GSK ID: 207943; HO-17-18317)	Patients with severe eosinophilic asthma who received mepolizumab treatment under Temporary Authorisation for Utilisation	Jun 2015, to Feb 2018	146	EOS <300 cells/ μ L EOS 300–500 cells/ μ L EOS 500–700 cells/ μ L EOS $\geq$ 700 cells/ μ L

Author, year and country	Study design	Setting/ source	Patient inclusion criteria	Patient accrual years	Study sample size	Reports data for overall population or subgroups?
van Toor, 2021[21] Netherlands	Retrospective cohort	Tertiary referral centre for severe asthma MOMENT	Patients ≥18 years of age, with severe eosinophilic asthma and who were treated with at least one dose of mepolizumab	Aug 2018 to Apr 2019	78	Overall population
Yilmaz, 2020[22] Turkey	Retrospective cohort	Single centre	Adult patients with OCS-dependent SEA-CRSwNP phenotype according to GINA step 5 (uncontrolled, partially controlled, or, in cases where OCS side effects developed, even in cases of controlled asthma). All patients were treated with high-dose ICS and a LABA, along with a second controller montelukast in addition to regular OCS therapy at least 6 months before mepolizumab treatment.	2018 to 2019	16	Overall population

ATS, American Thoracic Society; EOS, eosinophil; ERS, European Respiratory Society; FEV₁, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; GSK, GlaxoSmithKline; ICS, inhaled corticosteroid; ID, identification; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; mOCS, maintenance oral corticosteroid; NA, not available; NICE, National Institute for Health and Care Excellence; NR, not reported; OCS, oral corticosteroid; SEA-CRSwNP, severe eosinophilic asthma with chronic rhinosinusitis with nasal polyps.

Supplementary Table 4. Details of the studies presented only in conference abstracts or letters to the editor

Author, year and country	Study design	Setting/ Source (Study Name)	Patient inclusion criteria	Patient accrual years	Study sample size	Reports data for overall population or subgroups?
Arakawa, 2018[23] Japan	Prospective cohort	NR	Patients with severe eosinophilic asthma scheduled to receive mepolizumab	NR	12	Overall population
Benjamin, 2018[24] USA	Retrospective cohort	Allergy/ immunology clinic Single centre	Patients treated with mepolizumab for asthma	NR	28	Overall population
Bjerrum, 2018[25] Denmark	Retrospective cohort	Real-life clinical setting Single centre	Patients with severe, eosinophilic asthma	Jun 2016 to Dec 2017	47	Overall population
d'Ancona, 2018[26] NR	Prospective cohort	Type of care facility unclear (data sources: primary care prescription records, patient-reported usage and nurse recorded doses)	Patients with severe eosinophilic asthma requiring mOCS or recurrent short courses of OCS, who were commenced on mepolizumab	NR	104	Overall population
Gittins, 2018[27] UK	Prospective cohort	Routine clinical practice Single centre Oxford cohort	Patients with severe eosinophilic asthma	NR	50	Overall population

Author, year and country	Study design	Setting/ Source (Study Name)	Patient inclusion criteria	Patient accrual years	Study sample size	Reports data for overall population or subgroups?
Randolph, 2018[28] USA	Retrospective cohort	Allergy/ immunology private practice Single centre	Patients with moderate to severe asthma in a currently two provider allergy/immunology private practice initiated on mepolizumab over a 1–2-year period were followed for their clinical control and exacerbation rate in the year prior to and time on mepolizumab.	NR	16	Overall population
Roxas, 2018 [29] UK	Retrospective cohort	Guy's Severe Asthma Centre Single centre	Adult patients with severe eosinophilic asthma treated with mepolizumab	NR	38	Overall population
Seccombe, 2018[30] NR	Prospective cohort	NR	Patients with severe eosinophilic asthma	NR	12	Overall population
Strauss, 2018[31] USA	Retrospective cohort	Asthma clinic NR	Patients with severe eosinophilic asthma. They all required a high daily dose of ICS with a LABA, montelukast, and, at times, additional controller medications, and they had at least 2 exacerbations requiring a burst of prednisone during the past year.	NR	36	Overall population
Strauss, 2018[32] USA	Retrospective cohort	NR	Patients with severe eosinophilic asthma, EOS count >150 cells/mcL, treated with daily prednisone ranging from 7mg to 25mg per day with daily ICS/LABA, two inhalations twice a day and frequent use of inhaled	NR	13	Overall population

Author, year and country	Study design	Setting/ Source (Study Name)	Patient inclusion criteria	Patient accrual years	Study sample size	Reports data for overall population or subgroups?
			albuterol.			
Hahn, 2019[33] USA	Retrospective cohort	Patients with commercial and Medicare Advantage insurance. NR	Patients ≥12 years of age, had asthma diagnosis during baseline, ≥ 2 doses of mepolizumab in the first 180 days of follow-up, and no evidence of another asthma biologic treatment at baseline or follow-up.	NR	201	Overall population Clinical trial-like cohort
Hernandez-Martin, 2019[34] Spain	Retrospective cohort	Difficult to control asthma unit from Hospital La Paz Single centre	Patients with uncontrolled severe eosinophilic asthma treated with mepolizumab. All patients were treated with GINA Step-5 therapy.	NR	16	Overall population
Iribarren, 2019[35] Spain	Retrospective cohort	Asthma unit Single centre	Patients with uncontrolled eosinophilic severe persistent asthma.	Jan 2017 to Sep 2018	16	Overall population
Kroes, 2019[36] Netherlands	Retrospective cohort	NR Single centre	Patients with severe asthma.	NR	20	Overall population

Author, year and country	Study design	Setting/ Source (Study Name)	Patient inclusion criteria	Patient accrual years	Study sample size	Reports data for overall population or subgroups?
Masciopinto, 2019[37] Italy	Retrospective cohort	NR	Patients with severe eosinophilic asthma.	NR	27	Overall population
McDowell, 2019[38] UK	Retrospective cohort	Routine clinical care NR	Patients with severe OCS-dependent asthma cohort commencing mepolizumab in routine clinical care.	NR	22	Overall population
Mitchell, 2019[39] UK	Retrospective cohort	NR	Patients with severe eosinophilic asthma.	Jun 2017 to Jan 2019	39	Overall population
Ordóñez Pinilla, 2019[40] NR	Retrospective cohort	NR	Patients with uncontrolled severe asthma (ATS/ERS criteria of uncontrolled severe asthma) treated with either mepolizumab or reslizumab.	NR	24	Overall population
Pelaia, 2019[41] NR	Observational study	NR Single centre	Patients with severe eosinophilic asthma, receiving add-on therapy with mepolizumab.	NR	16	Overall population

Author, year and country	Study design	Setting/ Source (Study Name)	Patient inclusion criteria	Patient accrual years	Study sample size	Reports data for overall population or subgroups?
Pennington, 2019[42] USA	Retrospective cohort	Single large academic medical centre (REDCap)	Patients with severe persistent eosinophilic asthma, aged ≥ 18 years, who completed at least 12 study visits	NR	48	Overall population
Pereira, 2019[43] Portugal	Retrospective cohort	Outpatient pneumology/asthma clinic Multicentre	Patients from the outpatient pneumology/asthma clinic of 2 tertiary referral hospitals with severe eosinophilic asthma with at least 6 months of treatment with mepolizumab	NR	20	Overall population
Pereira Coutinho, 2019[44] Portugal	Retrospective cohort study	NR Single centre	Patients treated with mepolizumab for more than 6 months	NR	10	Overall population
Sharma, 2019[45] USA	Retrospective chart review	Electronic medical records from the Comprehensive Lung Clinical of UPMC Single centre	Severe eosinophilic asthma patients treated with mepolizumab (100mg monthly) in the Comprehensive Lung Clinical of UPMC between 2015 and 2019.	2015 to 2019	107	Overall population
Tavernier, 2019[46] UK	Retrospective cohort	Manchester severe asthma clinic Single centre	Patients treated by Manchester severe asthma team who had undergone a synacthen test.	April 2017 to NR	51	Overall population

Author, year and country	Study design	Setting/ Source (Study Name)	Patient inclusion criteria	Patient accrual years	Study sample size	Reports data for overall population or subgroups?
Wright, 2019[47] NR	Prospective case-control	Asthma clinic Single centre	Patients with severe asthma	NR	24	Overall population
Yang, 2019[48] UK	Retrospective cohort	Severe asthma clinic Single centre	Patients with severe eosinophilic asthma	NR	33	Overall population
Antonicelli, 2020[49] Italy	Prospective cohort	NR	Patients with severe eosinophilic asthma, candidates for mepolizumab therapy	NR	18	Overall population
Chaudhuri, 2020[50] International	Prospective cohort	NR Multicentre (REALITI-A)	Patients with severe eosinophilic asthma	NR	368	Overall population and four subgroups: UK cohort only; baseline EOS <150, ≥150–300, and ≥300 cells/μL

ATS, American Thoracic Society; EOS, eosinophil; ERS, European Respiratory Society; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; mOCS, maintenance oral corticosteroid; NR, not reported; OCS, oral corticosteroid.

Supplementary Table 5. Lung function outcomes

Study			FEV ₁			FEV ₁ % predicted			FEV ₁ /FVC (%)			FVC		
Author, year	Sample size	Follow-up (months)	Mean (SD) at baseline	Mean (SD) at follow-up	Mean change (p-value) from baseline	Mean (SD) at baseline	Mean (SD) at follow-up	Mean change (p-value) from baseline	Mean (SD) at baseline	Mean (SD) at follow-up	Mean change (p-value) from baseline	Mean (SD) at baseline	Mean (SD) at follow-up	Mean change (p-value) from baseline
Prospective studies														
Farah, 2019[1]	20	6	1.72 (0.63)	1.99 (0.82)	0.27 (NR)	-	-	-	55 (14)	61 (18)	6 (NR)	3.11 (0.8)	3.26 (0.8)	0.15 (NR)
Pertzov, 2021[2]	61	Median (range): 13.5 (3–36)	1.72 (0.78)	1.87* (0.85)	0.15 (0.043)	-	-	-	-	-	-	-	-	-
Harvey, 2020[3]	Overall population	309	12	-	-	56.9 (17.78)	63 (21.5)	6.1 (NR)	-	-	-	-	-	-
	EOS ≤600 cells/μL	178	12	-	-	56.52 (18.34)	59.7 (NR)	3.18 (NR)	-	-	-	-	-	-
	EOS >600 cells/μL	131	12	-	-	57.45 (17.03)	65.47 (NR)	8.02 (NR)	-	-	-	-	-	-
Langton, 2020[4]	47	12	-	-	-	50.2 (17.9)	56.5 (20.7)	6.3 (0.003)	-	-	-	-	-	-
Retrospective studies														
Pelaia, 2018[7]	14	6	1.39 (0.45)	1.70 (0.46)	0.31 (<0.01)	-	-	-	61.46 (8.99)	66.26 (8.58)	4.8 (<0.01)	-	-	-
Bagnasco, 2019[8]	138	12	2.03 (0.78)	2.36 (0.88)	0.34 (0.001)	-	-	-	65 (11)	69 (11)	4 (0.02)	3.16 (1.05)	3.32 (1.04)	0.16 (<0.0001)
Cameli, 2020[12]	26	6	2.5 (0.9)	2.9 (1)	0.4 (0.0278)	86.5 (22.9)	92.9 (22.6)	6.4 (0.3929)	69.7 (11.6)	72.4 (10.4)	2.7 (0.1327)	3.6 (1)	3.9 (1.1)	0.3 (0.7857)
Numata, 2020[16]	24	12	-	-	-	77.8 (26.8)	80.3 (21.1)	3.21 (0.84)	66.6 (14)	68 (13.1)	2.10 (0.16)	-	-	-
Kavanagh, 2020[14]	99	12	1.85 (0.72)	1.82 (0.72)	-0.03 (0.551)	64.74 (21.32)	63.21 (21.55)	-1.53 (0.438)	-	-	-	-	-	-
Pelaia, 2020[17]	88	12	1.64 (NR)	1.92 (NR)	0.28 (<0.0001)				-	-	-	-	-	-
Sposato, 2020[19]	134	Mean (SD): 10.9 (3.7)	2 (0.8)	2.21 (0.8)	0.21 (<0.0001)	72 (21)	78 (20)	6 (<0.0001)	-	-	-	-	-	-
Yilmaz, 2020[22]	16	6	2.092 (0.995)	2.232 (0.875)	0.14 (0.533)	80 (30.7)	84.6 (26)	4.6 (0.392)	-	-	-	-	-	-
Caminati, 2019[9]	69	6	-	-	-	71.3 (18.9)	79.4 (19.1)	8.1 (NR)	-	-	-	-	-	-
d'Ancona, 2020[13]	91	12	-	-	-	65.80 (22.2)	NR	-2.30%	-	-	-	-	-	-
van Toor, 2021[21]	78	12	-	-	-	75.9 (17.3)	NR	3.7 (0.034)	-	-	-	-	-	-

*Mean of last 3 months of treatment. FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; NR, not reported; SD, standard deviation.

Supplementary Table 6. Blood eosinophil counts

Author, year	Sample size	Follow-up timepoint (months)	Mean blood EOS count/ μ L (SD) at baseline	Mean blood EOS count/ μ L (SD) at follow-up	Mean change in blood EOS (p-value) from baseline	% change in mean blood EOS
Prospective studies						
Pertzov, 2021[2]	61	Median (range): 13.5 (3–36)	Median (IQR): 630 (400–900)	Median (IQR): 100 (64–200) (mean of first 3 months of treatment)	–530 (<0.001)	–84.13
Harvey, 2020[3]	309	12	Median (IQR): 590 (400–830)	Median (IQR): 100 (40–100)	–490 (<0.001)	–83.05
Retrospective studies						
Pelaia, 2018[7]	14	6	647.1 (274.7)	98.6 (40.3)	–548.5 (<0.0001)	–84.76
Bagnasco, 2019[8]	138	12	822 (NR)	117 (NR)	–705 (<0.0001)	–85.77
Caminati, 2019[9]	69	6	983 (1,201.3)	130.5 (192.3)	–852.5 (NR)	–86.72
Cameli, 2020[12]	26	6	904.4 (628.7)	75 (54.8)	–829.4 (<0.0001)	–91.71
Numata, 2020[16]	24	12	1,228 (2,360)	99 (131)	–1,129	–91.94 (<0.0001)
Sposato, 2020[19]	134	Mean (SD): 10.9 (3.7)	712 (731)	151 (384)	–561 (<0.0001)	–78.79
Taille, 2020[20]	146	24	721.7 (500)	92 (72.3)	–629.7 (NR)	–87.25
Yilmaz, 2020 [22]	16	6	580 (607)	177 (137)	–403 (0.019)	–69.48

EOS, eosinophil; IQR, interquartile range; NR, not reported; SD, standard deviation.

Supplementary Table 7. Patient-reported disease control and HRQoL outcomes

Study			Asthma control				HRQoL				
Author, year		Sample size	Timepoint for follow-up (months)	Tool	Mean (SD)/ median score at baseline	Mean (SD)/ median score at follow-up	Mean (p-value) change from baseline to follow-up	Tool	Mean (SD) score at baseline	Mean (SD) score at follow-up	Mean (p-value) change from baseline to follow-up
Prospective studies											
Farah, 2019[1]		20	6	ACQ-5	2.8 (1.1)	1.3 (1.3)	−1.5 (NR)	-	-	-	-
Harvey, 2020[3]	Overall study population	309	12	ACQ-5	Median (IQR): 3.4 (3.0–4.2)	Median (IQR): 1.5 (0.6-2.3)	−1.9 (<0.001)	AQLQ	Median (IQR): 3.8 (3.1–4.8)	Median (IQR): 5.3 (4.5–6.6)	1.5 (<0.001)
	EOS ≤600 cells/μL	178	12	ACQ-5	Median: 3.4 (NR)	Median: 1.1 (NR)	−2.3 (NR)	AQLQ	3.77 (1.18)	3.77 (1.18)	3.77 (1.18)
	EOS >600 cells/μL	131	12	ACQ-5	Median: 3.6 (NR)	Median: 1.23 (NR)	−2.37 (NR)	AQLQ	3.8 (1.12)	5.4 (NR)	1.6 (NR)
Langton, 2020[4]		47	12	ACQ-5	3.7 (1)	1.9 (1.3)	−1.8 (<0.001)	-	-	-	-
Schleich, 2020[5]		116	6	ACQ*	3.09 (1.32)	NR	−1.13 (<0.0001)	AQLQ	3.48 (1.29)	NR	1.24 (<0.0001)
				ACT	11.2 (5.3)	NR	5.31 (<0.0001)				
Retrospective studies											
Pelaia, 2018[7]		14	6	ACT	13.64 (3)	20.07 (1.94)	6.43 (<0.0001)	-	-	-	-
Bagnasco, 2019[8]	Overall study population	138	12	ACT	17 (5)	22 (3)	5 (<0.0001)	-	-	-	-
	EOS <500 cells/μL	41	12	ACT	17 (5.3)	22 (2.8)	5 (<0.0001)	-	-	-	-
	EOS > 500 cells/μL	97	12	ACT	17 (4.7)	22 (2.6)	5 (<0.0001)	-	-	-	-
	EOS >400 cells/μL	109	12	ACT	17 (4.7)	23 (2.6)	6 (<0.0001)	-	-	-	-
Caminati, 2019[9]		69	6	ACT	16.8 (4.8)	22.9 (3.3)	6.1 (<0.001)	-	-	-	-

Study			Asthma control				HRQoL			
Author, year	Sample size	Timepoint for follow-up (months)	Tool	Mean (SD)/ median score at baseline	Mean (SD)/ median score at follow-up	Mean (p-value) change from baseline to follow-up	Tool	Mean (SD) score at baseline	Mean (SD) score at follow-up	Mean (p-value) change from baseline to follow-up
Montero-Perez, 2019[11]	25	12	ACT	11.1 (NR)	18.4 (NR)	7.3 (NR)	-	-	-	-
Cameli, 2020[12]	26	6	ACT	16.1 (4.8)	21.8 (3.5)	5.7 (0.0016)	SNOT-22	40.5 (21.9)	23.6 (13.2)	-16.9 (0.0179)
d'Ancona, 2020[13]	91	12	ACQ-6	2.69 (1.33)	NR	-0.63 (NR)	-	-	-	-
Kavanagh, 2020[14]	99	12	ACQ-6	2.73 (1.27)	2.2 (1.42)	-0.53 (<0.001)	Mini-AQLQ	4.05 (1.34)	4.91 (1.54)	0.86 (<0.001)
Pelaia, 2020[17]	88	12	ACT	12.55 (3.72)	21.08 (3.36)	8.53 (<0.0001)	-	-	-	-
Sposato, 2020[19]	134	Mean (SD): 10.9 (3.7)	ACT	14.2 (4.4)	20.5 (1.94)	6.3 (<0.0001)	-	-	-	-
Taille, 2020[20]	146	24	ACT	10.2 (4.5)	18.7 (NR)	8.5 (NR)	-	-	-	-
van Toor, 2021[21]	78	12	ACQ-6	2.56 (0.96)	NR	-0.8 (<0.001)	-	-	-	-
Yilmaz, 2020[22]	16	6	ACT	18 (5.7)	23.3 (3)	5.3 (0.006)	-	-	-	-

*Version of the ACQ test used was not reported in this publication. ACQ, Asthma Control Questionnaire; AQLQ, Asthma quality of life questionnaire; EOS, eosinophil; HRQoL, health-related quality of life; IQR, interquartile range; NR, not reported; SD, standard deviation.

Supplementary Table 8. Treatment discontinuation

Author, year and country	Sample size	Timepoint for follow-up in months	Patients who discontinued treatment (overall)	Patients who discontinued treatment (due to AEs)
Prospective studies				
Harvey, 2020 [3]	309	12	15.21%	1.94%
Langton, 2020 [4]	47	12	25.50%	10.60%
Schleich, 2020[5]	116	6	6.90%	NR
		18	12.07%	NR
		30	14.66%	NR
Retrospective studies				
Drick, 2018[6]	42	Median (IQR): 12 (7–15)	0%	0%
Cameli, 2020 [12]	26	6	7.69%	NR
Kavanagh, 2020[14]	99	12	13.13%	NR
Pelaia, 2020[17]	88	12	NR	0%
Taille, 2020[20]	146	24	32.89%	0.08%
van Toor, 2021[21]	78	12	24.4%	NR
Yilmaz, 2020[22]	16	6	6.25%	6.25%

AE, adverse event; IQR, interquartile range; NR, not reported.

Supplementary Table 9. Safety data

Author, year and country	Sample size	Timepoint for follow-up in months	Injection site reactions	Dizziness	Headache	Cardiac events	Arthralgia	Urticaria or hypersensitivity reactions	Fatigue
Prospective studies									
Harvey, 2020[3]	309	12	3.3%	NR	9.9%	NR	0.3%	2.3%	NR
Langton, 2020 [4]	47	12	NR	NR	4.3%	NR	4.3%	NR	NR
Schleich, 2020 [5]	116	6	0%	NR	40%	NR	5%	NR	30%
Retrospective studies									
Drick, 2018 [6]	42	Median (IQR): 12 (7–15)	5%	NR	7%	NR	5%	NR	NR
Pelaia, 2018[7]	14	6	7.1%	NR	NR	NR	NR	NR	NR
Bagnasco, 2019[8]	138	12	4.3%	0.7%	0.7%	Paroxysmal SVT: 0.7%	0.7%	0.7%	NR
Caminati, 2019 [9]	69	6	0%	0%	0%	0%	0%	0%	0%
Lombardi, 2019 [10]	143	Mean: 8.5	NR	NR	NR	NR	NR	0.7%	NR
Montero-Perez, 2019 [11]	25	12	4.3%	26.1%	34.7%	NR	34.7%	4.3%	8.6%
Cameli, 2020 [12]	26	6	0%	0%	19.2%	0%	0%	0%	0%
Pelaia, 2020 [17]	88	12	0%	0%	0%	0%	0%	0%	0%
Sousa, 2020 [18]	10	NA	NR	NR	5%	NR	20%	5%	5%
Taille, 2020 [20]	146	24	0.01%	NR	9.6%	0.7%	NR	NR	8.2%
van Toor, 2021 [21]	78	12	NR	NR	9%	Paroxysmal atrial fibrillation 1.3% Palpitations 1.3%	Knee pain 1.3%	NR	3.9%
Yilmaz, 2020 [22]	16	6	NR	NR	NR	NR	6.3%	NR	NR

AE, adverse event; IQR, interquartile range; NR, not reported; SVT, supraventricular tachycardia.

Studies included in the SLR

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