REVIEW ARTICLE

From DREAM to REALITI-A and beyond: Mepolizumab for the treatment of eosinophil-driven diseases

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Abstract

Effective treatment of inflammatory diseases is often challenging owing to their heterogeneous pathophysiology. Understanding of the underlying disease mechanisms is improving and it is now clear that eosinophils play a complex pathophysiological role in a broad range of type 2 inflammatory diseases. Standard of care for these conditions often still includes oral corticosteroids (OCS) and/or cytotoxic immune therapies, which are associated with debilitating side effects. Selective, biological eosinophil-reducing agents provide treatment options that improve clinical symptoms associated with eosinophilic inflammation and reduce OCS use. Mepolizumab is a humanized monoclonal antibody that binds to and neutralizes interleukin-5, the major cytokine involved in eosinophil proliferation, activation, and survival. Mepolizumab is approved for the treatment of severe eosinophilic asthma, eosinophilic granulomatosis with polyangiitis and hypereosinophilic syndrome. Additionally, the efficacy of add-on mepolizumab has been observed in patients with severe chronic rhinosinusitis with nasal polyposis and

chronic obstructive pulmonary disease with an eosinophilic phenotype. Here, we review the development, approval, and real-world effectiveness of mepolizumab for the treatment of patients with severe eosinophilic asthma, from the DREAM to REALITI-A studies, and describe how knowledge from this journey extended to the use of mepolizumab and other biologics across a broad spectrum of eosinophilic diseases.

1 | INTRODUCTION

Elevated eosinophil counts are implicated in several type 2 inflammatory diseases that occur at various sites throughout the body (Figure 1).[1,2] Over the last 20 years, our understanding of diseases driven by elevated eosinophil counts has advanced through the development of eosinophil-depleting medicines. One such compound is mepolizumab, a humanized monoclonal antibody that binds to and neutralizes interleukin (IL)-5,[3,4] the major cytokine involved in the proliferation, maturation, activation, recruitment, and survival of eosinophils (Figure 2).[2] Mepolizumab was first studied in patients with asthma in the late 1990s[5] and was approved as a first-in-class, add-on treatment for adults with severe eosinophilic asthma in 2015 (Figure 3).[6] Since then, mepolizumab has been approved for pediatric and adult patients (aged ≥ 6 years) with severe eosinophilic asthma, for adult patients with eosinophilic granulomatosis with polyangiitis (EGPA), and for patients aged ≥ 12 years with hypereosinophilic syndrome (HES) (Figure 3).[4] Other eosinophil-targeting monoclonal antibodies approved as add-on therapies in patients with severe eosinophilic asthma include reslizumab (IL-5 antagonist monoclonal antibody for patients aged ≥ 18 years) and benralizumab (IL-5 receptor alpha-directed cytolytic monoclonal antibody for patients aged ≥ 12 years) (Figure 2).[7,8] Furthermore, the IL-4 receptor alpha antagonist, dupilumab, has been approved for use in moderate-to-severe asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP) and moderate-to-severe atopic dermatitis, and
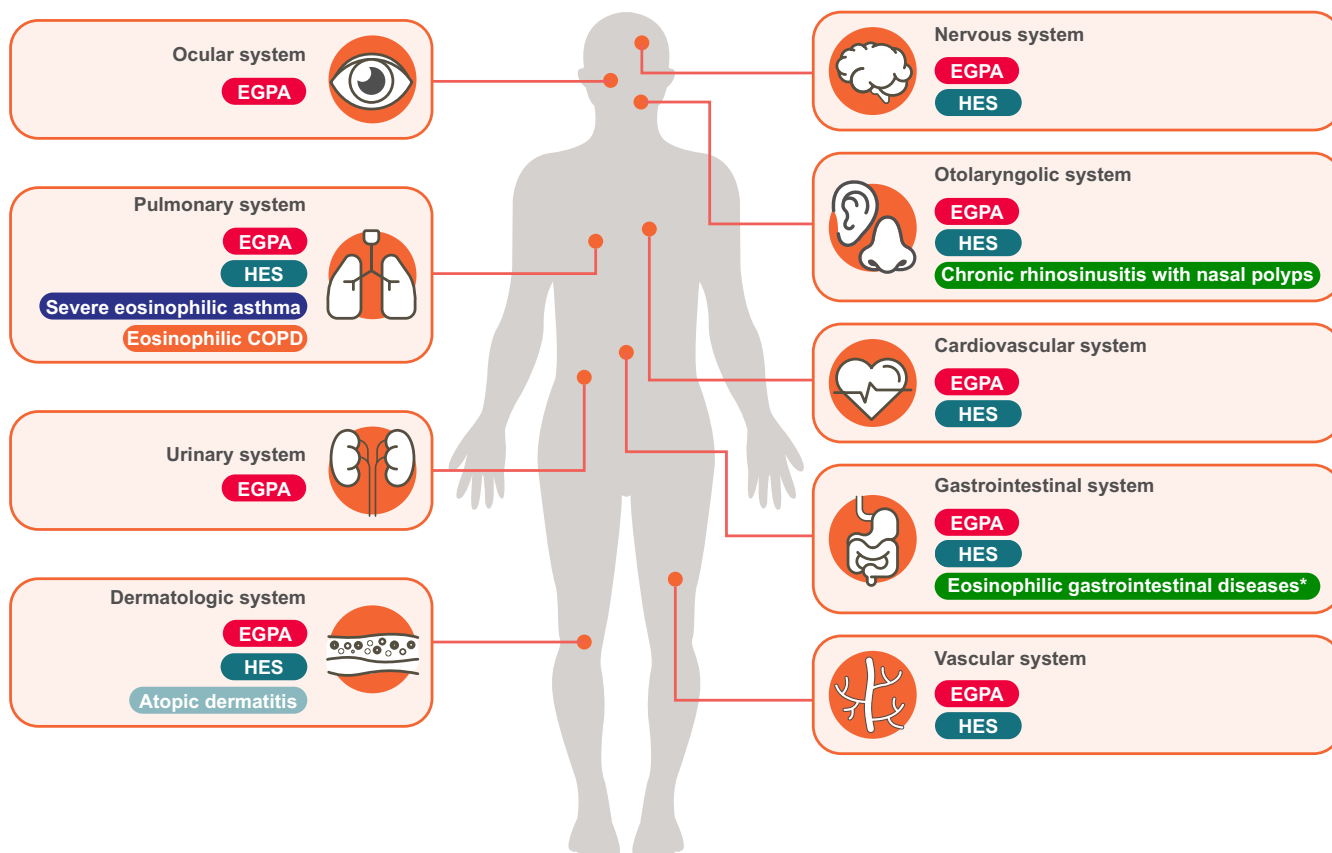

FIGURE 1 Sites of eosinophilic diseases. *Eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis. COPD, chronic obstructive pulmonary disease; EGPA, eosinophilic granulomatosis with polyangiitis; HES, hypereosinophilic syndrome
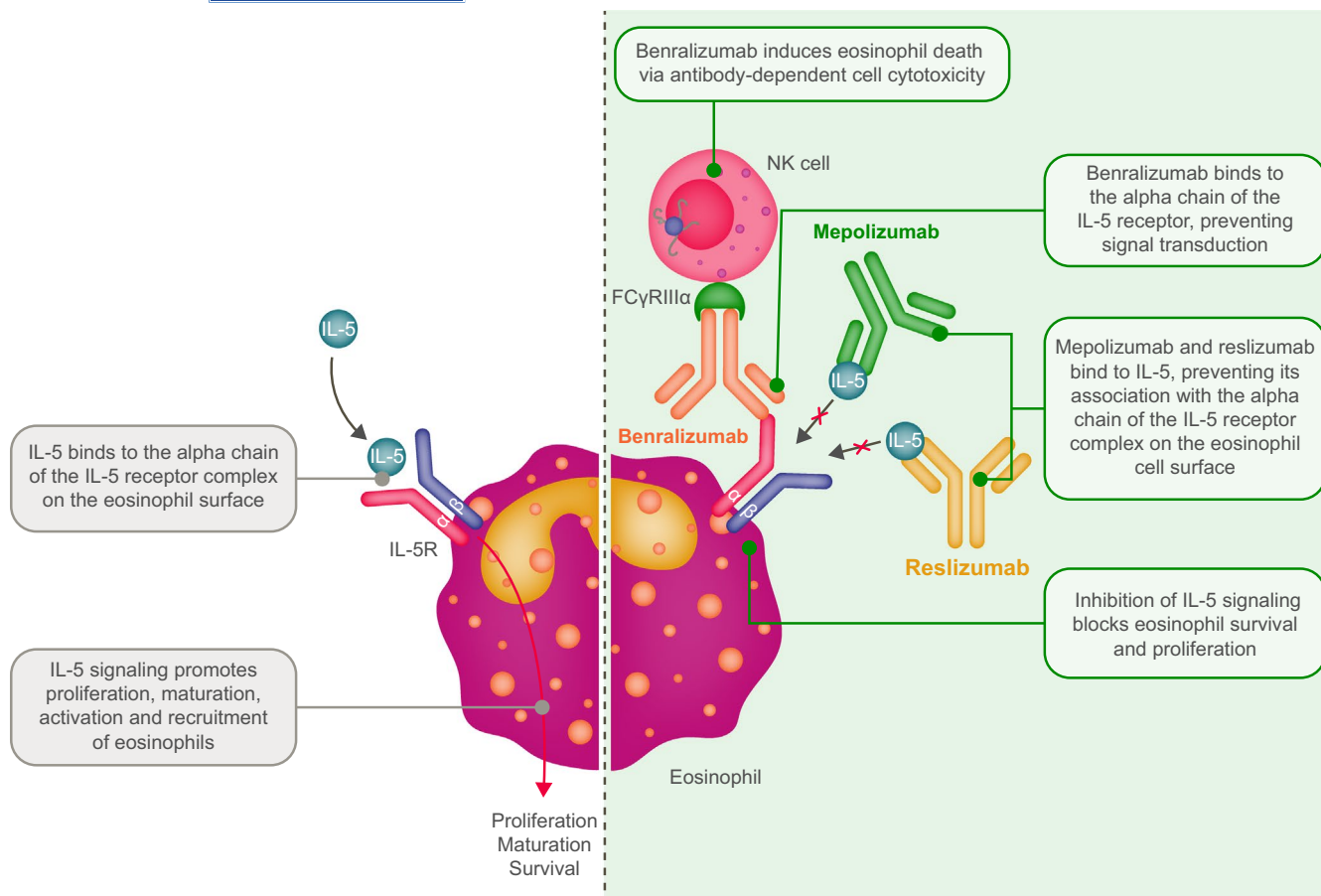
FIGURE 2   Mechanisms of action of anti-IL-5/anti-IL-5-receptor antibodies. IL, interleukin

the anti-immunoglobulin (Ig) E antibody, omalizumab, has been approved for use in moderate-to-severe, persistent, allergic asthma, nasal polyps, and chronic idiopathic urticaria.[9,10]

Early studies demonstrated the association of blood and tissue eosinophilia with bronchial asthma,[11] and the relationship between elevated eosinophil counts in blood and sputum and disease severity.[12] This was supported during the clinical development of mepolizumab, which showed that mepolizumab induces sustained, significant reductions in blood eosinophil counts with improved clinical outcomes in patients with severe asthma who had an eosinophilic phenotype.[13–16] Furthermore, blood eosinophil count was identified as a treatable trait and was established as a validated pharmacodynamic and predictive biomarker for response to mepolizumab in patients with severe eosinophilic asthma.[13,17–19]

Experience has shown that an understanding of pathobiology in one disease can be extended to other diseases, in which biological pathways overlap. Moreover, in-depth knowledge of a disease with a relatively straightforward pathogenesis may benefit from understanding and identification of treatment options in diseases with more complex underlying mechanisms. Indeed, this has occurred in other fields. For example, tocilizumab, a humanized monoclonal antibody that targets the IL-6 receptor, was first approved in Castleman disease and later approved for other IL-6-related

diseases, such as rheumatoid arthritis, and is now being evaluated for the treatment of severe COVID-19 pneumonia.[20–22] Overall, discovery of the importance of eosinophils during the development of mepolizumab for asthma, along with the confirmation that neutralizing IL-5 results in eosinophil reduction and disease control in HES, paved the way for mepolizumab treatment in other eosinophilic disorders.[6,23]

2 | SEVERE EOSINOPHILIC ASTHMA WAS THE FIRST DISEASE APPROVED FOR ANTI-IL-5 TREATMENTS (MEPOLIZUMAB) THAT SPECIFICALLY REDUCE EOSINOPHIL COUNTS

Eosinophils are derived in the bone marrow and reside in a range of tissues in healthy individuals.[24,25] They are multifunctional cells involved in the modulation of innate and adaptive immune responses as well as tissue homeostasis, remodeling, and repair.[24,26,27] Eosinophils express several membrane receptors that are critical to their function, including IL-5 receptor alpha, that binds IL-5 to facilitate eosinophil differentiation, maturation, homing and survival, and CC chemokine receptor 3, which binds the eotaxins
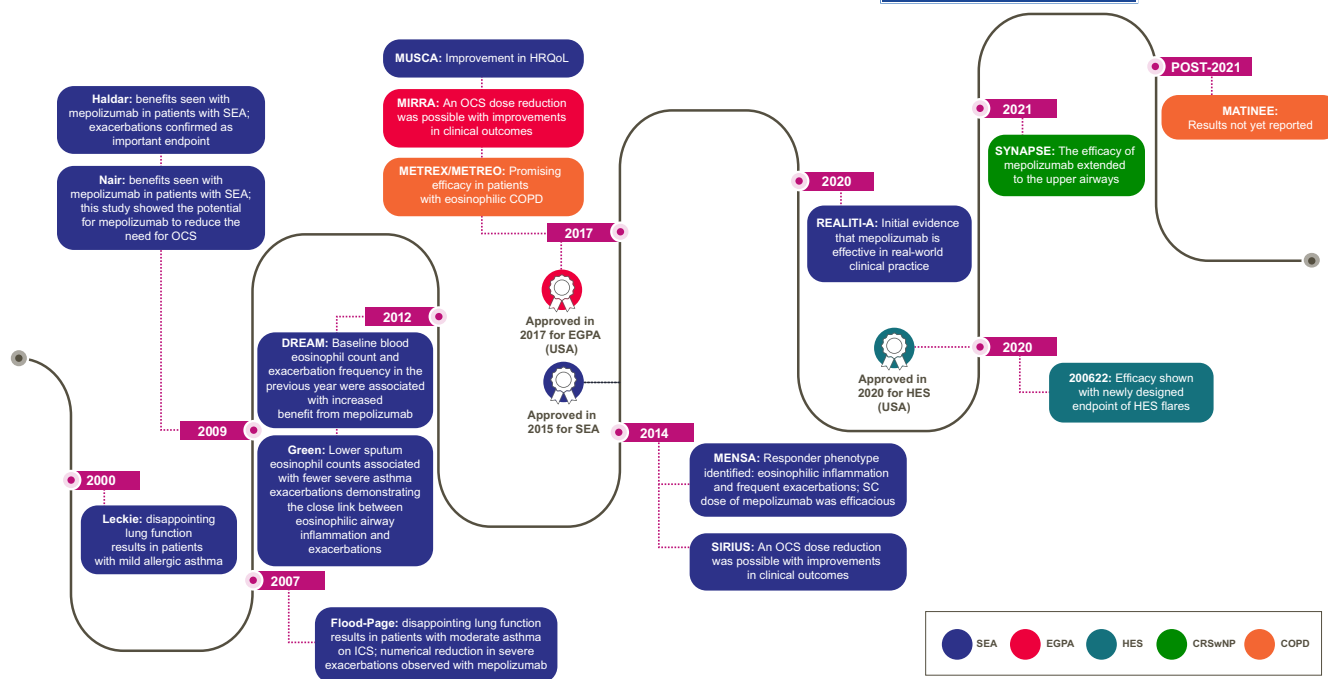
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FIGURE 3 Timeline of the Phase III trials and approvals of mepolizumab in eosinophil-driven diseases and the key takeaways. COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyposis; DREAM, Dose Ranging Efficacy And safety with Mepolizumab in severe asthma; EGPA, eosinophilic granulomatosis with polyangiitis; HES, hypereosinophilic syndrome; HRQoL, health-related quality of life; ICS, inhaled corticosteroids; MATINEE, Mepolizumab as Add-on Treatment IN participants with COPD characterized by frequent Exacerbations and Eosinophil level; MENSA, MEpolizumab as adjunctive therapy iN patients with Severe Asthma; METREO, MEpolizumab vs. placebo as add-on TReatment for frequently exacerbating COPD patients characterized by EOsinophil level; METREX, MEpolizumab vs. placebo as add-on TReatment for frequently EXacerbating COPD patients; MIRRA, Mepolizumab In Relapsing or Refractory EGPA; MUSCA, Mepolizumab adjUnctive therapy in subjects with Severe eosinophiliC Asthma; OCS, oral corticosteroids; REALITI-A, REAL world effectiveness of mepolizumab In paTIent care—Asthma; SC, subcutaneous; SEA, severe eosinophilic asthma; SIRIUS, SteroId ReductIon with mepolizUmab Study; SYNAPSE, StudY in NAsal Polyps patients to assess the Safety and Efficacy of mepolizumab

responsible for migration of eosinophils into target tissues.[28–30] In addition to cytokines, enzymes, and growth factors, eosinophils contain specific cytoplasmic granule proteins that are released into target tissues upon activation.[31]

The role of eosinophils in asthma pathogenesis was highlighted in the 1980s, when it was noted that they secrete proteins that damage bronchial epithelium when in an activated state.[11] Blood and airway eosinophils in humans with asthma were later shown to correlate with asthma severity,[12] and treatment directed at normalizing sputum eosinophil counts was shown to markedly reduce severe asthma exacerbations.[32] Analyses of IL-5 knockout mice and a mouse model of asthma also showed that IL-5 and eosinophilia play a pivotal role in the development of lung inflammation in asthma[33,34]; in vitro experiments confirmed IL-5 as a useful target in eosinophil-driven diseases.[23]

Establishing the clinical efficacy of eosinophil-reducing treatment in patients was not straightforward; while mepolizumab treatment was shown to reduce markers of airway remodeling in patients with mild atopic asthma,[35] early trials of mepolizumab in a mild allergic asthma population in 2000 and in a moderate asthma population in 2007 were considered unsuccessful in terms of clinical improvement[36,37]; early trials of reslizumab in patients with severe persistent

asthma were also unsuccessful.[38] Although mepolizumab reduced blood and sputum eosinophil counts in the two early studies, there were no significant clinical improvements in the endpoints commonly assessed in asthma at the time, such as lung function and asthma symptoms.[36,37] At that point in the development of mepolizumab, patients had been selected based on clinical and physiological characteristics, not on the presence of eosinophilic inflammation, and it is now clear that the outcomes in these studies were not closely associated with eosinophilic airway inflammation.[36,37] However, while there was no difference in lung function for patients treated with mepolizumab versus placebo in Flood-Page et al., there was a numerical reduction in the percentage of patients with severe exacerbations with mepolizumab.[37] This suggested that mepolizumab might reduce exacerbations in patients with severe asthma.

Increasing knowledge surrounding the link between exacerbations, eosinophilic airway inflammation, and asthma symptoms led to the discovery that eosinophilic airway inflammation correlated more closely with asthma exacerbations and oral corticosteroid (OCS) responsiveness than with asthma symptoms and variable airflow limitation.[23,39,40] An exploratory investigation was then conducted with mepolizumab in patients with refractory asthma, sputum eosinophils >3% despite high-dose inhaled corticosteroid treatment,

and at least two exacerbations requiring rescue prednisolone treatment in the previous 12 months.[41] Reductions in blood and sputum eosinophil counts seen among patients corresponded with a 43% reduction ($p = .02$) in exacerbations versus placebo and a 0.35-point improvement ($p = .02$) in asthma quality of life questionnaire (AQLQ) score; however, there were no statistically significant differences between the groups in lung function or asthma symptoms (measured monthly).[41] In another, small, exploratory study in patients with persistent sputum eosinophilia and continued symptoms despite maintenance OCS therapy, published concurrently, mepolizumab reduced blood and sputum eosinophil counts to within normal limits, versus placebo, and permitted a reduction in maintenance OCS dose without any increase in asthma exacerbations.[42] The development of mepolizumab therefore required a fundamental rethink of the way asthma was viewed. Of particular importance was the recognition that eosinophilic airway inflammation and airway reversibility to bronchodilators (ie, the definition of asthma) are relatively independent treatable traits, and the realization that eosinophilic airway inflammation is associated particularly with asthma exacerbations.[23]

The target population that would benefit from mepolizumab treatment was identified in 2012 based on data from the DREAM (Dose Ranging Efficacy And safety with Mepolizumab in severe asthma; NCT01000506) clinical trial; this trial showed that mepolizumab was efficacious in patients with severe asthma, evidence of eosinophilic inflammation, and a history of exacerbations.[13] In addition, it was shown that baseline peripheral blood eosinophil count and exacerbation frequency in the previous year were associated with response to mepolizumab (Table 1; Figure 3).[13] The correlation between blood eosinophil count and mepolizumab response was confirmed in the Phase III MENSA (MEpolizumab as adjunctive therapy iN patients with Severe Asthma; NCT01691521) trial (Table 1; Figure 3), in which a direct relationship between baseline blood eosinophil count and reduction in exacerbation rates was shown.[14] Importantly, clinically relevant reductions in exacerbation rates (54% in DREAM and 53% in MENSA) were observed at baseline blood eosinophil counts of ≥150 cells/μl.[17] As patient stratification improved throughout the development of mepolizumab, there was more clear evidence of treatment benefits in lung function and asthma symptoms.[43] Taken together, in patients with severe eosinophilic asthma, mepolizumab treatment was shown to reduce exacerbations, increase forced expiratory volume in 1 s (FEV_1) and improve both asthma control and quality of life in the DREAM, MENSA, and MUSCA (Mepolizumab adjUnctive therapy in subjects with Severe eosinophiliC Asthma; NCT02281318) trials,[13,14,43] and to have an OCS-sparing effect in the SIRIUS (SteroId ReductIon with mepolizUmab Study; NCT01691508) trial (Table 1; Figure 3).[44] Clinical benefit with mepolizumab treatment has now been clearly demonstrated in randomized controlled trials in patients with a blood eosinophil count of ≥150 cells/μl despite standard of care treatment including inhaled and/or systemic corticosteroids.[14,17,44] With increasing use in clinical practice, the improvements with mepolizumab noted in clinical trials are now being confirmed in the real world.[45–48] For example, in an initial analysis from the large prospective REALITI-A (REAL world effectiveness of

mepolizumab In paTIent care—Asthma) study ($n = 368$), there was an 83% reduction in blood eosinophil count and a significant 69% reduction in the rate of clinically significant exacerbations in the 12 months following initiation of mepolizumab treatment.[45] Furthermore, a clinically meaningful 52% median reduction in daily maintenance OCS dose was shown in the 12 months post versus the 12 months pre-mepolizumab treatment initiation.

The clinical benefits associated with targeting the IL-5 pathway in patients with asthma have been further supported by the results of clinical trials with intravenous (IV) reslizumab and subcutaneous (SC) benralizumab, both of which have shown reduced exacerbations and improved lung function and quality of life in patient populations similar to those included in the mepolizumab trials.[49–53] An OCS-sparing effect has also been shown with reslizumab[54] and benralizumab.[55] Trials with benralizumab also confirmed the relationship between baseline blood eosinophil counts ≥ 150 cells/μl and response to treatment.[56]

3 | MEPOLIZUMAB TREATMENT IN THE RARE DISEASE EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS CONFIRMED THAT THE IL-5 PATHWAY COULD BE TARGETED IN OTHER EOSINOPHIL-DRIVEN DISEASES

EGPA (also known as Churg-Strauss syndrome) is a rare, complex inflammatory disease defined by an eosinophil-rich granulomatosis often involving the respiratory tract, and necrotizing eosinophilic vasculitis predominantly affecting small to medium-sized vessels; it is associated with asthma, marked blood or tissue eosinophilia, sinusitis/nasal polyps, neuropathy, and in 30%–40% of patients, antineutrophil cytoplasmic antibodies (ANCA).[57–59] Along with T and B cells, eosinophils are key inflammatory cells involved in causing tissue damage in EGPA.[59] Historically, conventional treatment was with OCS, with or without additional immunosuppressive drugs,[59] but many patients experienced corticosteroid-related side effects or relapses during OCS tapering.[60] As a result, healthcare resource utilization and burden of disease and treatment were high.[61]

Since eosinophils contribute to the pathophysiology of EGPA, and with severe eosinophilic asthma being a key feature of the disease,[57] mepolizumab was postulated as a potential treatment option for patients with EGPA. In 2010, early data on the use of mepolizumab in patients with EGPA were published in a case report and in a pilot trial.[62,63] Following the promising early findings shown in these publications, which showed reductions in OCS and exacerbation rates with mepolizumab, recruitment of patients with relapsing or refractory EGPA (regardless of ANCA status) who were receiving standard of care therapy began in 2014 for the Phase III MIRRA (Mepolizumab In Relapsing or Refractory EGPA; NCT02020889) trial.[64] In this 136 patient study, add-on mepolizumab therapy (300 mg SC), versus placebo, led to a reduction in blood eosinophil count and more accrued time in remission, reduced the rate of relapse, and allowed

TABLE 1 Phase III[a] mepolizumab clinical trials, primary endpoints, and key inclusion/exclusion criteria across eosinophilic-driven diseases

Eosinophilic-driven disease and studies	ITT/mITT/ treated population, n	Key criteria for patient population (full details are in the publications)	Treatment dosages	Primary and secondary endpoint results
Severe eosinophilic asthma				
DREAM[13] Pavord, et al. 2012	616	• Aged 12–74 years with asthma • Receiving high-dose ICS with a second controller • ≥2 exacerbations requiring systemic corticosteroid treatment in the previous year • Eosinophilic inflammation	Mepolizumab 75 mg IV Mepolizumab 250 mg IV Mepolizumab 750 mg IV Placebo Every 4 weeks for 52 weeks Treatment was plus SoC	**Primary** **Rate of clinically significant exacerbations/patient/year[b]:** reduced vs. placebo by: • 48% (95% CI 31, 61; $p < .001$), mepolizumab 75 mg IV • 39% (19, 54; $p < .001$), mepolizumab 250 mg IV • 52% (36, 64; $p < .001$), mepolizumab 750 mg IV **Secondary** **Mean pre-bronchodilator FEV$_1$:** improved vs. placebo by: • 61 ml (95% CI −39, 161), mepolizumab 75 mg IV • 81 ml (−19, 180), mepolizumab 250 mg IV • 56 ml (−43, 155), mepolizumab 750 mg IV **Mean ACQ score:** improved vs. placebo by: • −0.16 (95% CI −0.39, 0.07), mepolizumab 75 mg IV • −0.27 (−0.51, 0.04), mepolizumab 250 mg IV • −0.20 (−0.43, 0.03), mepolizumab 750 mg IV **Mean AQLQ score:** improved vs. placebo by: • 0.08 (95% CI −0.16, 0.32), mepolizumab 75 mg IV • 0.05 (−0.19, 0.29), mepolizumab 250 mg IV • 0.22 (−0.02, 0.46), mepolizumab 750 mg IV **Geometric mean FeNO:** ratio to placebo: • 0.97 (95% CI 0.82, 1.15), mepolizumab 75 mg IV • 0.90 (0.76, 1.06), mepolizumab 250 mg IV • 0.96 (0.81, 1.13), mepolizumab 750 mg IV

TABLE 1 (Continued)

Eosinophilic-driven disease and studies	ITT/mITT/ treated population, n	Key criteria for patient population (full details are in the publications)	Treatment dosages	Primary and secondary endpoint results
MENSA[14] Ortega, et al. 2014	576	• Aged 12–82 years with asthma • Receiving high-dose ICS with a second controller • ≥2 exacerbations requiring systemic corticosteroid treatment in the previous year • Blood eosinophil count ≥150 cells/µl at screening or ≥300 cells/µl during the previous year	Mepolizumab 75 mg IV Mepolizumab 100 mg SC Placebo Every 4 weeks for 32 weeks Treatment was plus SoC	**Primary** **Rate of clinically significant exacerbations/patient/year[b]:** reduced vs. placebo by: • 47% (95% CI 28, 60; $p < .001$), mepolizumab 75 mg IV • 53% (95% CI 36, 65; $p < .001$), mepolizumab 100 mg SC **Secondary** **Mean pre-bronchodilator FEV$_1$:** improved vs. placebo by: • 100 ml (95% CI 13, 187; $p = .02$), mepolizumab 75 mg IV • 98 ml (95% CI 11, 184; $p = .03$), mepolizumab 100 mg SC **Mean ACQ score:** improved vs. placebo by: • −0.42 (95% CI −0.61, −0.23; $p < .001$), mepolizumab 75 mg IV • −0.44 (95% CI −0.63, −0.25; $p < .001$), mepolizumab 100 mg SC **Mean SGRQ score:** improved vs. placebo by: • −6.4 (95% CI −9.7, −3.2; $p < .001$), mepolizumab 75 mg IV • −7.0 (−10.2, −3.8; $p < .001$), mepolizumab 100 mg SC
SIRIUS[44] Bel, et al. 2014	135	• Aged ≥12 years with asthma • Receiving high-dose ICS with a second controller • 6-month history of maintenance treatment with systemic corticosteroids before study entry • Blood eosinophil count ≥150 cells/µl during the optimization phase or ≥300 cells/µl during the previous year	Mepolizumab 100 mg SC Placebo Every 4 weeks for 20 weeks Treatment was plus SoC	**Primary** **Daily OCS dose reduction category (90–100%; 75–<90%; 50–<75%; >0–<50%):** mepolizumab vs. placebo: overall OR of 2.39 (95% CI 1.25, 4.56; $p = .008$) **Other** **Clinically significant exacerbations/patient/year[b]:** reduced by 32% vs. placebo (RR 0.68 [95% CI 0.47, 0.99]; $p = .04$) **Mean ACQ-5 score:** improved vs. placebo by −0.52 (95% CI −0.87, −0.17; $p = .004$) **Mean SGRQ score:** improved vs. placebo by −5.8 (95% CI −10.6, −1.0; $p = .02$) **Mean pre-bronchodilator FEV$_1$:** improved vs. placebo by 114 ml ($p = .15$)

TABLE 1 (Continued)

Eosinophilic-driven disease and studies	ITT/mITT/ treated population, n	Key criteria for patient population (full details are in the publications)	Treatment dosages	Primary and secondary endpoint results
MUSCA[43] Chupp, et al. 2017	551	• Aged ≥12 years with asthma • Receiving high-dose ICS with a second controller • ≥2 exacerbations requiring SCS treatment in the previous year • Blood eosinophil count ≥150 cells/µl at screening or ≥300 cells/µl during the previous year	Mepolizumab 100 mg SC Placebo Every 4 weeks for 24 weeks Treatment was plus SoC	**Primary** **Mean SGRQ total score:** improved vs. placebo by −7.7 (95% CI −10.5, −4.9; $p < .0001$)[c] **Secondary** **Mean ACQ-5 score:** improved vs placebo by −0.4 (95% CI −0.6, −0.2; $p < .0001$) **Mean pre-bronchodilator FEV$_1$:** improved vs placebo by 120 ml (95% CI 47, 192; $p = .001$) **Rate of clinically significant exacerbations/patient/year:** 58% reduction vs. placebo (RR 0.42 [95% CI 0.31, 0.56; $p < .0001$])
REALITI-A[a] Harrison, et al. 2020[45]	368	• Aged ≥18 years with asthma • Newly prescribed mepolizumab treatment in the real world (physician decision) • Relevant medical records for ≥12 months pre-enrollment	Mepolizumab 100 mg SC as prescribed in clinical practice (every 4 weeks) Treatment was plus SoC	**Rate of clinically significant asthma exacerbations/patient/year**[b] during the 12-month mepolizumab follow-up period vs. the pre-mepolizumab treatment period: relative reduction of 69% (RR 0.31 [95% CI 0.27, 0.35]; $p < .001$) **Other** **Median daily maintenance OCS dose:** the median percent reduction during treatment up to Weeks 53–56 was 52% (95% CI 50.0, 75.0)
EGPA				
MIRRA[64] Wechsler, et al. 2017	136	• Aged ≥18 years with a diagnosis of relapsing or refractory EGPA[d] for ≥6 months prior to the study • EGPA was defined as a history or presence of asthma, a blood eosinophil count of 10% or absolute eosinophil count ≥1000 cells/µl and ≥2 criteria typical of EGPA[d] • Receiving a stable dose of prednisolone or prednisone (≥7.5–≤50.0 mg/day, with or without additional immunosuppressive therapy) for ≥4 weeks before the baseline visit	Mepolizumab 300 mg SC Placebo Every 4 weeks for 52 weeks Treatment was plus SoC	**Co-primary** **Total accrued weeks of remission**[e]: 28% of the patients in the mepolizumab group vs. 3% in the placebo group had remission for ≥24 weeks **Proportion of patients who had remission:** 32% patients in the mepolizumab group vs. 3% patients in the placebo group had remission at both Week 36 and week 48 (OR 16.74 [95% CI 3.61, 77.56]; $p < .001$).

TABLE 1 (Continued)

Eosinophilic-driven disease and studies	ITT/mITT/ treated population, n	Key criteria for patient population (full details are in the publications)	Treatment dosages	Primary and secondary endpoint results
HES				
200622[82] Roufosse, et al. 2020	108	• Aged ≥12 years with a diagnosis of FIP1L1-PDGFRA–negative HES[f] for ≥6 months • History of ≥2 flares within the last 12 months and a blood eosinophil count ≥1000 cells/µl • Stable background HES therapy for ≥4 weeks	Mepolizumab 300 mg SC Placebo Every 4 weeks for 32 weeks Treatment was in addition to existing background HES therapy (whether chronic or episodic)	**Primary** **Proportion of patients who experienced an HES flare[g]:** was 50% lower for patients receiving mepolizumab vs. placebo ($n = 15/54$ [28%] vs. $n = 30/54$ [56%]; $p = .002$).
CRSwNP				
SYNAPSE[101] Han, et al. 2021	407	• Aged ≥18 years with recurrent, refractory severe bilateral NP symptoms • Eligible for repeat nasal surgery • Had ≥1 nasal surgery in the last 10 years • Received stable maintenance therapy for ≥8 weeks before screening, with symptoms of CRS for ≥12 weeks before screening	Mepolizumab 100 mg SC Placebo Every 4 weeks (by safety syringe) for 52 weeks Treatment was plus SoC, including intranasal corticosteroids	**Co-primary** **Median change from baseline in total endoscopic NP score[h]:** • Improved vs. placebo −0.73 (95% CI −1.11, −0.34; $p < .0001$) **Median change from baseline in nasal obstruction VAS score[h]:** • Improved vs placebo: −3.14 (−4.09, −2.18; $p < .0001$) **Key secondary** **Time to first nasal surgery up to Week 52:** • Lower risk vs. placebo: Hazard ratio 0.43 (95% CI: 0.25, 0.76; $p = .0032$)
COPD				
METREX/METREO[121] Pavord, et al. 2017	836/674	• Aged ≥40 years and diagnosed with COPD for ≥1 year • History of COPD exacerbations in the last year (≥2 moderate or ≥1 severe exacerbations) • Receiving background ICS-based therapy in the year before screening • Receiving triple inhaled therapy comprising a high-dose ICS, LABA, and LAMA for ≥3 months before screening • METREO: Eosinophilic phenotype • METREX: Eosinophilic and non-eosinophilic phenotype	METREX: mepolizumab 100 mg SC or placebo METREO: mepolizumab 100 mg SC, mepolizumab 300 mg SC or placebo In both trials, treatment was administered every 4 weeks, for 52 weeks Treatment was plus SoC	**Primary** **Rate of moderate/severe exacerbations reduced vs. placebo by:** • METREX (eosinophilic phenotype): 18% (RR 0.82; [95% CI 0.68, 0.98]; $p = .04$), mepolizumab 100 mg SC • METREO: 20% (RR 0.80 [95% CI 0.65, 0.98]; $p = .07$), mepolizumab 100 mg SC • METREO: 14% (RR 0.86 [95% CI 0.70, 1.05]; $p = .14$), mepolizumab 300 mg SC

TABLE 1 (Continued)

Eosinophilic-driven disease and studies	ITT/mITT/treated population, n	Key criteria for patient population (full details are in the publications)	Treatment dosages	Primary and secondary endpoint results
MATINEE[124] ClinicalTrials.gov, 2020. https://clinicaltrials.gov/ct2/show/NCT04133909	Target: 800	• Aged ≥40 years • History of COPD exacerbations in the last year (≥2 moderate or ≥1 severe exacerbations) • Patients with COPD with an eosinophilic phenotype (blood eosinophil count ≥300 cells/μl at screening and ≥150 cells/μl during the previous year)	Mepolizumab 100 mg SC Placebo Every 4 weeks for 52 weeks Treatment s plus SoC (ICS plus 2 additional COPD medications [ie, ICS-based triple therapy])	**Primary** **Annualized rate of moderate/severe exacerbations** Primary endpoint: rate of moderate or severe exacerbations Study not yet completed

Abbreviations: BVAS, Birmingham Vasculitis Activity Score; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyposis; ED, emergency department; EGPA, eosinophilic granulomatosis with polyangiitis; FeNO, an exhaled nitric oxide concentration; FEV_1, forced expiratory volume in 1 s; HES, hypereosinophilic syndrome; HRQOL, health-related quality of life; ICS, inhaled corticosteroids; ITT, intent-to-treat; IV, intravenous; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic-receptor antagonist; MCID, minimal clinically important difference; mITT, modified intent-to-treat; NP, nasal polyposis; OCS, oral corticosteroids; OR, odds ratio; RR, rate ratio; SC, subcutaneous; SCS, systemic corticosteroid(s); SoC, standard of care; VAS, visual analog scale.

[a]All trials are Phase III except for the REALITI-A study, which was a real-world study.

[b]Clinically significant exacerbations were defined as the worsening of asthma requiring systemic corticosteroids for ≥3 days (or a doubling [or more] of the existing maintenance dose of OCS for ≥3 days if patients were on maintenance OCS) or an ED visit or hospital admission.

[c]A reduction in SGRQ is indicative of improvement. The SGRQ is scored from 0 to 100, with higher scores indicating worse HRQOL. The MCID is a 4-point reduction in score.[43]

[d]Criteria typical of EGPA included histopathological evidence of eosinophilic vasculitis, perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation; neuropathy; pulmonary infiltrates; sinonasal abnormality; cardiomyopathy; glomerulonephritis; alveolar hemorrhage; palpable purpura; or antineutrophil cytoplasmic antibody positivity.

[e]Defined as a BVAS of 0 and the receipt of prednisolone or prednisone ≤4.0 mg/day during the 52-week period. The BVAS version 3 has a scale of 0–63, with higher scores indicating greater disease activity.

[f]HES diagnosis was based on organ system involvement and/or dysfunction that could be directly related to a blood eosinophil count more than 1500 cells/μl on ≥2 occasions, and/or tissue eosinophilia, without a discernible secondary cause.

[g]HES flares during the treatment period were defined as either of the following: physician-documented change in clinical signs or symptoms of a HES-related clinical manifestation that required an increase in maintenance OCS dose by ≥10 mg prednisone equivalent/day for 5 days or an increase in/addition of any cytotoxic and/or immunosuppressive HES therapy; 2 receipt of ≥2 courses of blinded OCS during the treatment period, blinded OCS was administered for approx. Two weeks if the blood eosinophil count exceeded a predefined threshold (2 × baseline value [randomization] or baseline value +2500 cells/μl).

[h]Co-primary endpoints. Total endoscopic NP score was the sum of left and right nostril scores ranging from 0 (no polyps) to 4 (large polyps causing complete obstruction of the inferior meatus) giving a total score of up to 8. VAS scores ranged from 0.0 to 10.0.

patients to decrease their OCS use (Table 1).[64] Based on these findings, mepolizumab 300 mg SC was approved for EGPA in the USA in 2017 (Figure 3).[65] Notably, not all patients in the mepolizumab group in MIRRA achieved protocol-defined remission (a Birmingham Vasculitis Activity Score of 0 [scale: 0–63] and a prednisolone/prednisone dose of ≤4.0 mg/day over a 52-week period). However, a post hoc analysis using a composite endpoint comprising remission, OCS reduction, and/or being relapse free for the treatment period showed that mepolizumab provided clinical benefit in up to 87% of patients with EGPA beyond the remission-based primary endpoints.[66] Early evidence of efficacy for other anti-IL-5 treatments, reslizumab, and benralizumab has also been shown in recent small studies (≤10 patients).[67–69] A Phase III trial of benralizumab in EGPA is currently underway (MANDARA; NCT04157348).[70]

Overall, the clinical benefits associated with eosinophil reduction in patients with EGPA confirmed that eosinophils contribute to EGPA disease pathology and supported the use of mepolizumab in eosinophil-driven diseases beyond severe eosinophilic asthma.

4 | MEPOLIZUMAB TREATMENT FOR THE RARE DISEASE HYPEREOSINOPHILIC SYNDROME HIGHLIGHTED THE IMPORTANCE OF IDENTIFYING THE APPROPRIATE ENDPOINT TO ASSESS EFFICACY

HES is a rare, heterogeneous group of disorders defined by the presence of persistent eosinophil counts in blood and/or tissues (≥1500 cells/μl in the blood), and evidence of a major role for eosinophils in end-organ damage.[71] In the absence of validated biomarkers, an elevated blood eosinophil count is generally considered

to be a surrogate marker for tissue eosinophilia and organ damage in patients with HES; a reduction in the blood eosinophil count is therefore a therapeutic objective, to reverse and prevent further damage.[72–74] Since the underlying mechanisms resulting in eosinophilia vary across the HES subtypes (reviewed elsewhere[6]), differences in clinical presentation, prognosis, and responses to therapy occur among patients with HES.[71,75–78] Treatment options for HES are limited, with the standard of care generally comprising systemic corticosteroids and cytotoxic/immunosuppressive therapy, similar to patients with EGPA.[59,74]

The potential of mepolizumab for the treatment of HES was shown as early as 2003/2004 in a small case series and an open-label, non-controlled trial, in which it was shown to reduce blood eosinophil counts and have an OCS-sparing effect.[79,80] It subsequently became available for compassionate use in 2005 (NCT00244686).[73,81] In 2008, a randomized, double-blind, placebo-controlled, trial evaluating the efficacy of mepolizumab versus placebo in OCS-dependent (20–60 mg/day) patients with HES without the *FIP1L1-PDGFRA* fusion gene (GSK ID: MHE100185; NCT00086658) demonstrated that 4-weekly mepolizumab infusions (750 mg IV) resulted in a higher proportion of patients able to taper to ≤10 mg/day prednisone (odds ratio 8.0; 95% CI 2.7, 23.8; $p < .001$) versus placebo.[72] Other endpoints assessed in this trial showed further benefits of mepolizumab treatment; there was a significantly lower daily prednisone dose at the end of the study (Week 36) with mepolizumab versus placebo (6.2 mg vs. 21.8 mg) and a significantly higher proportion of patients stopping prednisone completely during the treatment period with mepolizumab versus placebo (47% vs. 5%).[72]

Despite the clinical success demonstrated in the NCT00086658 trial, the development of mepolizumab in HES was halted temporarily owing to absence of established efficacy endpoints deemed suitable by regulatory agencies; efficacy could not be based solely on reductions in OCS.[6] Given the heterogeneous range of symptoms experienced by patients with HES, the assessment of response and change in symptoms through an established clinical efficacy endpoint posed a challenge.[6,82]

After further regulatory discussion, another trial was subsequently designed to investigate clinical improvements with mepolizumab in HES using a clinical endpoint based on disease flares, inspired by the benefits shown in the severe asthma and EGPA trials. The Phase III mepolizumab HES trial (GSK ID: 200622, NCT02836496) assessed the 300 mg SC dose, which was a lower dose and different administration route than assessed in the previous HES trial (750 mg IV).[82] In this trial, HES flares were defined as (1) a HES-related clinical manifestation, based on a physician-documented change in clinical signs or symptoms, requiring an increase in the maintenance OCS dose by ≥10 mg prednisone equivalent/day for 5 days or an increase in/addition of any cytotoxic and/or immunosuppressive HES therapy; or (2) receipt of ≥2 courses of blinded rescue OCS treatment (triggered by a predefined marked rise in the blood eosinophil count) during the treatment period.[82] This was the first trial to show that treatment (ie, mepolizumab) could reduce disease flares

in addition to decreasing blood eosinophil count in patients with *FIP1L1-PDGFRA*-negative HES; there was a 50% reduction in the proportion of patients who experienced a flare or withdrew during the study (28% vs. 56%), a 66% reduction in risk of a first flare and a 66% reduction in annualized flare rate with mepolizumab versus placebo (Table 1; Figure 3).[82] The Phase III mepolizumab trial was also designed to assess daily symptoms that were self-reported as most bothersome to patients using a HES daily symptom questionnaire, as an exploratory endpoint.[83] This pragmatic approach, reflecting the goals of individual patients to reduce the symptoms they found to be most disruptive to their lives, demonstrated that mepolizumab, versus placebo, improved the most bothersome HES symptoms as rated by patients.

A post hoc analysis of data from the mepolizumab HES compassionate use/expanded access program, collecting data over more than 10 years, suggested peak absolute eosinophil count, OCS sensitivity, pulmonary involvement, HES clinical subtype, and serum IL-5 levels may be associated with a response to mepolizumab treatment in severe HES.[75] Whether these findings apply to the larger patient population for which mepolizumab is now approved at monthly 300 mg SC dosing remains to be explored. In terms of other anti-IL-5 therapies, a small Phase II trial (NCT02130882) has shown that 4-weekly benralizumab (30 mg SC) was able to reduce blood eosinophil counts with associated improvements in clinical symptoms in patients with *FIP1L1-PDGFRA*-negative HES.[84]

Overall, findings from the Phase III mepolizumab trial and subsequent approval for treatment of HES in the USA have provided physicians with a well-tolerated efficacious treatment for this rare, debilitating disease.

5 | MEPOLIZUMAB TREATMENT FOR CHRONIC RHINOSINUSITIS WITH NASAL POLYPS SHOWED THAT BENEFIT COULD BE EXTENDED TO THE UPPER AIRWAYS

CRSwNP is a heterogeneous disease of the upper airways characterized by chronic local eosinophilic inflammation[85,86] and symptoms of nasal blockage, loss of smell (anosmia), nasal discharge, facial pain/pressure, and sneezing as a result of nasal mucosal thickening and the formation of nasal polyps.[86,87] It often involves type 2 inflammation and is a frequent comorbidity in patients with severe eosinophilic asthma.[88–90] IL-5 was implicated in the pathogenesis of NP in 1997 when it was found in significant amounts in the NP tissue samples from patients with asthma undergoing polypectomy.[91] Neutralization of IL-5 led to a reduction in eosinophilia in the NP tissues.[91] Later, in 2010, IL-5 was found to significantly predict comorbid asthma in patients with NP.[89,92] In addition, IL-4/IL-13 are now known to be involved in the differentiation of nasal polyp basal cells.[93]

In patients with CRSwNP, treatment with systemic corticosteroids can temporarily reduce NP size and improve symptoms

while on treatment, but is associated with adverse effects; additionally, patients who have surgery frequently experience recurrence of NPs.[87,94] Data from the Severe Asthma Network in Italy (SANI) registry have shown that patients with severe asthma and comorbid CRSwNP have worse outcomes in terms of number of exacerbations, number of days on OCS, and likelihood of a need for long-term OCS use, compared with those patients with severe asthma without CRSwNP.[95] Similarly, the presence of asthma increases disease burden in patients with CRS.[96,97] In patients with severe eosinophilic asthma receiving anti-IL-5 therapies, improvements in nasal symptoms in addition to asthma outcomes have been shown,[98–100] and the presence of NPs has been shown to predict a positive response to mepolizumab in this population.[48] Based on this knowledge, mepolizumab was investigated as a treatment option in patients with recurrent, refractory severe CRSwNP who had a high symptom burden and previous NP surgeries and were eligible for repeat nasal surgery despite treatment with intranasal corticosteroids.[101] In the Phase III SYNAPSE (StudY in NAsal Polyps patients to assess the Safety and Efficacy of mepolizumab; NCT03085797) study, mepolizumab 100 mg SC reduced the occurrence of surgery and corticosteroid use and improved symptoms in this population, while also reducing the blood eosinophil count, when compared with placebo (Table 1).[101] These effects were not dissimilar to those seen in CRSwNP populations with dupilumab and omalizumab in the SINUS (NCT02912468 and NCT02898454) and POLYP (NCT03280550 and NCT03280537) studies.[90,102] Notably, these populations differed from the SYNAPSE population in their surgical history, with 63% and 60% of patients in SINUS and POLYP, respectively, having had ≥1 prior nasal surgery at enrollment compared with 100% of those in SYNAPSE. Both dupilumab and omalizumab have recently been approved for the treatment of patients with CRSwNP.[9,10] Additionally, there is early evidence for the efficacy of benralizumab in patients with CRSwNP, and the Phase III OSTRO (NCT03401229) and ORCHID (NCT04157335) studies are currently evaluating benralizumab in this population.[103–105]

The identification of biomarkers, such as blood or tissue eosinophils, total immunoglobulin E (IgE), and fractional exhaled nitric oxide (FeNO), in patients with CRSwNP will help tailor treatment to endotype.[106] Interestingly, preliminary clinical research suggests that pre-operative blood eosinophil count in patients with CRSwNP may have potential in clinical phenotyping, and help predict the recurrence of NP in this population.[107,108]

6 | MEPOLIZUMAB TREATMENT MAY ALSO PROVIDE CLINICAL BENEFIT TO PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is another heterogenous respiratory disease, in which eosinophils may contribute to pathogenesis.[109–112] Approximately 55% of patients with COPD have eosinophil-associated COPD and eosinophilic inflammation is associated with an increased risk of COPD exacerbations, which can be minimized by long term, consistent treatment with inhaled corticosteroids (ICS).[113–117] The use of ICS in patients with COPD may be guided by the recommended biomarker of baseline blood eosinophil count,[114] and the COPD Biomarker Qualification Consortium have proposed to the US Food and Drug Administration that blood eosinophil count should be assessed as a drug development tool.[115,118,119] An eosinophilic phenotype in patients with COPD therefore represents a treatable trait,[111] and such patients have shown a good response to treatment of acute exacerbations with OCS.[109,110] Furthermore, treatment directed at normalizing sputum eosinophil count reduces the number of severe exacerbations in patients with COPD.[120] Together, these findings suggest eosinophils play a pathogenic role in exacerbations of COPD and provide a strong rationale for therapies that specifically inhibit eosinophilic inflammation.

The Phase III METREX (MEpolizumab vs. placebo as add-on TReatment for frequently EXacerbating COPD patients; NCT02105948) and METREO (MEpolizumab vs. placebo as add-on TReatment for frequently exacerbating COPD patients characterized by EOsinophil level; NCT02105961) trials investigated the effect of mepolizumab in patients with COPD who had exacerbations despite receiving ICS-based triple maintenance therapy; the primary endpoint was the annual rate of moderate or severe exacerbations.[121] Both trials examined outcomes in patients with COPD with an eosinophilic phenotype (defined as a blood eosinophil count of ≥150 cells/μl at screening or ≥300 cells/μl within the previous year).[121] In addition, the METREX trial included a cohort of patients without an eosinophilic phenotype. In METREX and METREO, in patients with an eosinophilic COPD phenotype, mepolizumab reduced the annual rate of moderate or severe exacerbations by 18% and 20%, respectively, for mepolizumab 100 mg SC versus placebo (Table 1).[121] This is consistent with results observed in the benralizumab Phase III COPD trials.[122] In contrast, COPD exacerbations were not significantly reduced versus placebo in the non-eosinophilic populations in METREX. Of note, in METREX and METREO, there was a clear blood eosinophil count-dependent suppressive effect on exacerbations treated with OCS but no effect on exacerbations treated with antibiotics alone.[123] Better stratification of exacerbation endpoints may be key to the successful clinical development of eosinophil-targeting therapies in COPD.[121]

Overall, the findings from the METREX and METREO trials suggested that mepolizumab treatment may represent precision treatment in the management of COPD and led to the identification of a potentially treatable trait, the COPD eosinophilic phenotype (Figure 3).[121] A new multicenter, randomized, placebo-controlled, double-blind, parallel-group Phase III trial, MATINEE (Mepolizumab as Add-on Treatment IN participants with COPD characterized by frequent Exacerbations and Eosinophil level; NCT04133909), began in 2019 and is currently recruiting patients with COPD (>40 years; former or current smokers) with an eosinophilic phenotype (blood eosinophil count ≥300 cells/μl at screening) who have experienced either ≥2 moderate COPD exacerbations in the previous year despite

TABLE 2 Summary of safety data from long-term asthma trials and other non-asthma Phase III trials

	COSMOS (open label[a])[125]	COLUMBA (open label[b])[16]	COSMEX (open label[c])[15]	MIRRA[64]	
	Mepo 100 mg SC every 4 weeks for 52 weeks plus asthma SoC (N = 651)	Mepo 100 mg SC every 4 weeks plus asthma SoC (N = 347)	Mepo 100 mg SC every 4 weeks plus asthma SoC (N = 339)	Mepo 300 mg SC (N = 68) Every 4 weeks for 52 weeks plus EGPA SoC	Placebo (N = 68)
Any on-treatment AEs	558 (86)	326 (94)	315 (93)	66 (97)	64 (94)
Treatment-related AE	123 (19)	97 (28)	51 (15)	35 (51)	24 (35)
Leading to study withdrawal	11 (<2)	19 (5)	4 (1)	2 (3)	1 (1)
Any on-treatment SAE, n (%)	94 (14)	79 (23)	84 (25)	12 (18)	18 (26)
Treatment-related SAE	2 (<1)	2 (<1)	3 (0.9)	3 (4)	3 (4)
Any fatal SAE	0	6 (2)[e]	2 (<1)[e]	1 (1)[e]	0
Any systemic reaction	13 (2)	9 (3)	2 (0.6)	4 (6)	1 (1)
Local injection-site reaction	29 (4)	42 (12)	14 (4)	10 (15)	9 (13)
Immunogenicity (presence of anti-mepolizumab antibodies) in patients tested	31 (5)	1/346 (8)	6/335 (2)	0	0
Serious infections	–	17 (5)	20 (6)	–	–
Malignancies	–	6 (2)	8 (2)	–	–

Note: Data are given as number (%) of patients unless otherwise noted.

Abbreviations: AE, adverse event; COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyposis; EGPA, eosinophilic granulomatosis with polyangiitis; HES, hypereosinophilic syndrome; IV, intravenous; mepo, mepolizumab; NP, nasal polyposis; SAE, serious adverse event; SC, subcutaneous; SoC, standard of care.

[a]Eligible patients in the COSMOS open-label extension study had completed either the MENSA or SIRIUS double-blind studies and were treated with mepolizumab regardless of treatment allocation in the prior studies.

[b]Eligible patients in the COLUMBA open-label extension study had to have been randomized and received at least 2 doses of treatment (mepolizumab or placebo) in the DREAM study had received an asthma controller medication for ≥12 weeks before enrollment in COLUMBA. Mepolizumab treatment was administered until a protocol-defined stopping criterion was met.

[c]Patients were enrolled from the COSMEX open-label extension study and had to have the most severe forms of severe eosinophilic asthma (eg, a history of life-threatening or seriously debilitating asthma, the full definitions of which are noted in the COSMEX publication), have been receiving ICS controller therapy for the last 8 months, and had to have previously demonstrated a protocol-defined clinical benefit with mepolizumab treatment. The study completed after all patients met a protocol-defined discontinuation criterion.

[d]The METREX safety population with an eosinophilic phenotype included patients with blood eosinophil count of ≥150 cells/μl at screening or ≥300 cells/μl within the previous year.

[e]Fatalities were not considered related to mepolizumab treatment.

ICS-based triple therapy or ≥1 severe COPD exacerbation requiring hospitalization.[124]

7 | MEPOLIZUMAB HAS A TOLERABLE AND ACCEPTABLE SAFETY PROFILE ACROSS THE EOSINOPHIL-DRIVEN DISEASE SPECTRUM

Mepolizumab has demonstrated a consistent safety profile, broadly similar to that of placebo, in clinical trials of patients with a broad spectrum of eosinophil-driven diseases (Table 2).[13–15,43,44,64,82,101] The most frequently reported adverse events with mepolizumab in these trials were nasopharyngitis and headache; the incidence of serious drug-related adverse events was low (≤1%).[13,14,43,44] The favorable long-term safety and tolerability profile of mepolizumab 100 mg SC in severe eosinophilic asthma has also been demonstrated in the COSMOS (NCT01842607),[125] COLUMBA (NCT01691859),[16] and COSMEX (COSMOS EXtension; NCT02135692)[15] extension studies, which followed patients for up to 4.8 years after starting treatment. These findings were consistent with previous randomized controlled trials that compared mepolizumab with placebo.[13,14,43,44] An open-label extension study also demonstrated the long-term safety of mepolizumab treatment for patients with HES, finding that mepolizumab 750 mg IV was well tolerated over a mean duration of 4.8 years of treatment.[126] Additionally, Kuang et al. confirmed that long-term treatment with mepolizumab in patients with HES (≥5 years) does not increase the risk of malignancy and confers improvement in OCS-related comorbidities.[75] Overall, the safety profiles for benralizumab and reslizumab are similar to the safety profile of mepolizumab.[49–53,55,67–69]

200622[82]		SYNAPSE[101] (safety population)		METREX[121] (safety population with an eosinophilic phenotype[d])		METREO[121] (safety population)		
Mepo 300 mg SC (N = 54)	Placebo (N = 54)	Mepo 100 mg SC (N = 206)	Placebo (N = 201)	Mepo 100 mg SC (N = 233)	Placebo (N = 229)	Mepo 100 mg SC (N = 223)	Mepo 300 mg SC (N = 225)	Placebo (N = 226)
Every 4 weeks for 32 weeks plus HES SoC		Every 4 weeks for 52 weeks plus CRSwNP SoC		Every 4 weeks for 52 weeks plus COPD SoC				
48 (89)	47 (87)	169 (82)	168 (84)	190 (82)	189 (83)	191 (86)	196 (87)	185 (82)
12 (22)	7 (13)	30 (15)	19 (9)	–	–	–	–	–
1 (2)	2 (4)	0	1 (<1)	7 (3)	10 (4)	7 (3)	13 (6)	18 (8)
10 (19)	8 (15)	12 (6)	13 (6)	65 (28)	80 (35)	57 (26)	60 (27)	68 (30)
0	0	0	1 (<1)	–	–	–	–	–
1 (2)[e]	0	0	1 (<1)	6 (3)[e]	8 (3)	4 (2)[e]	8 (4)[e]	9 (4)
1 (2)	0	2 (<1)	1 (<1)	3 (1)	4 (2)	3 (1)	5 (2)	4 (2)
4 (7)	2 (4)	5 (2)	2 (<1)	7 (3)	7 (3)	6 (3)	11 (5)	10 (4)
1 (<1)	0	6 (3)	3 (<1)	14/395 (4)	2/395 (2)	13/220 (6)	4/220 (2)	3/217 (1)
–	–	–	–	–	–	–	–	–
1 (2)	0	–	–	–	–	–	–	–

8 | FUTURE DIRECTIONS

There are case reports and analyses in the literature on the varying impact of mepolizumab in several diseases, including allergic bronchopulmonary aspergillosis, Kimura's disease, chronic spontaneous urticaria, eosinophilic esophagitis, atopic dermatitis, idiopathic chronic eosinophilic pneumonia, and bronchiectasis not related to other pathologies.[127–133] Furthermore, genetic evidence associating eosinophil numbers and autoimmune diseases including rheumatoid arthritis and celiac disease may support investigation of IL-5-targeting treatments in these areas.[134] As such, anti-IL-5 therapies may have potential in other eosinophilic disorders beyond those discussed in this review.

Inflammatory diseases are heterogeneous in nature and pathophysiology is not always driven exclusively by eosinophils, as seen in asthma.[10] As such, prolonged OCS therapy remains a key component of the treatment of chronic eosinophil-driven diseases.[112,135–137] However, there are significant risks associated with long-term use of OCS[138]; therefore, early initiation of targeted biologic treatment is essential to reduce OCS use,[44,64,82,101] and achieve the best results for patients. This is especially true for patients with EGPA[139] or HES,[140] since serious, irreparable damage, and remodeling may develop during the disease course.[141] This is also true for patients with severe asthma, as eosinophil-driven changes to the airways are associated with reduced lung function.[142] Further analysis of treatable traits across the eosinophilic disease spectrum will help to facilitate early, targeted treatment. Although there are some real-world reports on the use of mepolizumab during pregnancy and the post-partum period, there are limited data on this subject.[126,143] Of note, an ongoing study (GSK ID: 200870) monitoring the outcome of

exposure to mepolizumab during planned and unplanned pregnancies, expected to be completed in 2023, will provide much-needed data on efficacy and safety among pregnant women.

Different dosing strategies across the different diseases could also be investigated in the future studies so that treatment can be personalized to the patient and their condition. Novel long-acting IL-5 monoclonal antibodies, such as Depemokimab, which is currently being investigated for the treatment of patients with severe eosinophilic asthma in the SWIFT (NCT04719832 and NCT04718103) and NIMBLE (NCT04718389) trials,[70,144] may be important in this regard. The impact of stopping versus continuing mepolizumab therapy after continuous treatment for ≥3 years in patients with severe eosinophilic asthma was investigated in asthma in the COMET study (GSK ID: 201810, NCT02555371).[145] This study showed that patients need to continue with biologic therapy in order to continue deriving clinical benefit and prevent worsening in clinical outcomes including lung function. This concept was supported by small, early trials of mepolizumab cessation in patients with EGPA, in which the majority of patients experienced relapses when switched to methotrexate therapy following induction of remission with mepolizumab.[146,147] This will be an important area of research as the use of mepolizumab expands into other eosinophilic diseases.

Further insights into the cost-effectiveness of biologic treatments in asthma and other eosinophilic diseases are also needed. In asthma, it is suggested that biologic therapy is directed to those patients most likely to respond in order to improve cost-effectiveness.[148] This would involve the use of biomarkers to identify such patients prior to treatment, as well as close monitoring of individuals following treatment initiation to assess treatment response. As work to identify biomarkers that are useful in this regard is ongoing, continued assessment of cost-effectiveness is needed to support treatment decision-making.

It is known that eosinophil biology is complex, with roles in both maintaining health and contributing to disease.[149] In a healthy population, the blood eosinophil count can vary; however, the "normal" blood eosinophil count in healthy individuals is lower than generally perceived, as several highly prevalent factors, such as atopy, allergy rhinitis, and smoking, can elevate counts.[150] In patients with mild asthma, there is now convincing and consistent evidence that high blood eosinophil counts are associated with increased exacerbation risk, even if they initially present with mild symptoms and normal lung function.[151,152] In addition, an association between blood eosinophilia and lung function decline has been identified, independent of asthma and smoking, meaning that eosinophilia is a risk factor for airflow obstruction even in individuals without disease symptoms.[151] Whether reducing eosinophils in these healthy individuals may be beneficial is an interesting consideration. In addition, the consequences of long-term eosinophil reduction in patients with eosinophilic diseases will be an important topic for future research.

9 | CONCLUSIONS

Inflammatory diseases often have heterogeneous pathogenic mechanisms and phenotypes. Several important lessons have been learned from the mepolizumab clinical development program. First, it has highlighted the importance of identifying target populations with the relevant phenotypes that will respond to a particular therapy, information that should be used in clinical practice to accurately phenotype patients and direct treatment accordingly. Second, it has emphasized the importance of using the appropriate endpoint to assess treatment efficacy; indeed, early studies in which mepolizumab did not demonstrate clinical benefits provided valuable information enabling the refinement of clinical study designs, which ultimately allowed the full clinical potential of mepolizumab and the other IL-5 targeting antibodies to be uncovered. Persistence in the goal of identifying the appropriate target patient population was of the utmost importance in this regard. Finally, data on the safety and impact of mepolizumab treatment in clinical trials and real-world settings demonstrate its clinical benefits across the eosinophil-driven disease spectrum, providing valuable insights into the importance of eosinophils in these chronic inflammatory diseases. These insights may contribute to the further development of mepolizumab and extend to other rare/orphan eosinophilic-driven diseases and provide a template of success for developing medicines in general.

CONFLICT OF INTEREST
Ian Pavord reports that he has received speaker's honoraria for sponsored meetings from AstraZeneca, Boehringer Ingelheim, Aerocrine, Almirall, Novartis, Teva, Chiesi, Sanofi/Regeneron, and GSK; and payments for organizing educational events from AstraZeneca, GSK, Sanofi/Regeneron, and Teva. He has received honoraria for attending advisory panels with Genentech, Sanofi/Regeneron, AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Teva, Merck, Circassia, Chiesi, and Knopp; and payments to support FDA approval meetings from GSK. He has received sponsorship to attend international scientific meetings from Boehringer Ingelheim, GSK, AstraZeneca, Teva, and Chiesi. He has received a grant from Chiesi to support a Phase II clinical trial in Oxford. He is co-patent holder of the rights to the Leicester Cough Questionnaire; and has received payments for its use in clinical trials from Merck, Bayer, and Insmed. In 2014–15, he was an expert witness for a patent dispute involving AstraZeneca and Teva. Elisabeth H Bel reports grants from GSK and Teva; and personal fees from AstraZeneca, GSK, Sanofi/Regeneron, Sterna Biologicals, and Chiesi. Arnaud Bourdin has received grants from Boehringer Ingelheim and AstraZeneca; has participated in clinical research projects (as an investigator) with GSK, AstraZeneca, Boehringer Ingelheim, Chiesi, Novartis, and Sanofi; and has received personal fees from GSK, AstraZeneca, Regeneron-Sanofi, Novartis,

AUTHORS' CONTRIBUTIONS

RC, NM, JS, and SWY involved in the conception of the work. AB, FR, MEW, IP, JKH, EHB, AP, and MCL involved in the acquisition of data. All authors contributed to the analysis or interpretation of data, drafted the work or revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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