

Update on immunogenicity in severe asthma: Experience with mepolizumab

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Clinical Implications

- Few patients receiving mepolizumab developed antimepolizumab antibodies during the phase III clinical program. Antimepolizumab antibodies had no impact on the efficacy and safety of mepolizumab, with no indication of serious acute hypersensitivity reactions and no loss of efficacy.

TO THE EDITOR:

Immunogenicity testing is a key component for supporting clinical safety and efficacy during the development of biologics. Inherently, biologics (monoclonal antibodies [mAbs]) create the potential for presentation of foreign epitopes, which may generate antidrug antibodies (ADAs) or cell-based immune responses,¹ potentially increasing the risk of treatment failure and adverse events (AEs). Mepolizumab is a humanized mAb that binds to and inactivates IL-5 and is indicated for the treatment of 2 eosinophilic disorders: severe eosinophilic asthma and eosinophilic granulomatosis with polyangiitis. The immunogenicity of mepolizumab in severe eosinophilic asthma was investigated throughout its clinical development program, and a comprehensive assessment of data from the pivotal registration and extension studies is provided here.

We used data from 5 studies: 3 randomized, double-blind, placebo-controlled studies (DREAM [NCT01000506],² MENSA [NCT01691521],³ and SIRIUS [NCT01691508])⁴ and 2 open-label extension studies (a 52-week extension of MENSA and SIRIUS: COSMOS [NCT01842607]⁵ and an extension of DREAM spanning up to 4.5 years: COLUMBA [NCT01691859]).⁶ For further details of the included studies, see this article's Online Repository at www.jaci-inpractice.org. At enrollment, patients were 12 years or older, with a history of 2 or more asthma exacerbations in the previous year (DREAM, MENSA) or dependency on daily prednisone (SIRIUS), and evidence of eosinophilic airway inflammation. Treatment was given at 4-week intervals, in addition to standard care (high-dose inhaled corticosteroids plus ≥ 1 additional controller medication with or without daily oral corticosteroids). Patients received intravenous infusions of mepolizumab at doses of 75, 250, or 750 mg, or subcutaneous mepolizumab 100 mg (Table I).

A tiered testing approach was used to detect ADAs: screening, confirmation, and titration analysis, which used a bridging ligand-binding assay format with electrochemiluminescence detection. For screening, serum samples were diluted with an anti-IL-5-blocking antibody to reduce false-positive responses and then incubated with biotin- and ruthenium drug conjugates

in which the ADA forms a detectable bridge.⁷ A 5% false-positive statistical screening cutoff point was calculated on the basis of repeated assay responses from predose patients (DREAM: 1.57 relative electrochemiluminescence [RECL]; COLUMBA: 1.11 RECL; SIRIUS: 1.08 RECL; MENSA: 1.07 RECL; COSMOS: 1.07 RECL).⁸ For samples with RECL equal to or above the screening cutoff point, confirmation analysis was conducted (eg, the screening assay that includes sample incubation with drug before addition of drug conjugates, which then evaluates the reduction of assay response as the ADA binds free drug rather than form a bridge with drug conjugates). Samples that displayed inhibition equal to or above the 1% false-positive statistical cutoff point (43.18%) were considered ADA positive and titer values were then obtained to evaluate degree of binding. These samples were also analyzed in a neutralization assay, an indirect ligand-binding assay whereby neutralizing antibodies prevent drug binding its target and subsequent detection. Where applicable, critical reagents were bridged in qualifying assays to allow cross-study comparisons, and the same validated assays were used for these clinical studies.

A total of 1327 patients participated across the 3 primary studies; 915 received mepolizumab and 412 received placebo. Data for each study are reported in Table I. Few patients tested positive for mepolizumab ADAs at any point during the studies in the binding assay (<1% to 9%; Table I). Five patients receiving placebo had false-positive ADA results recorded. In the DREAM study in which patients received mepolizumab at doses of 75, 250, and 750 mg IV, there was no increase in the number of patients testing positive or increase in antibody titer with higher doses (Table I). Only a patient (in the SIRIUS study) tested positive for neutralizing antibodies; pharmacokinetic samples were below the limit of quantification during the follow-up period, and no AEs were reported as related to treatment in this patient.

Of the 77 patients testing positive for ADAs across the 5 studies, 39 (51%) were transient positive (tested positive at 1 visit only [excluding the last visit]). Of the 38 persistent positive patients (tested positive at ≥ 2 time points), 18 were ADA negative at their last visit. Although 3 of these patients were positive at their last visit only, 12 had decreasing titer values and 5 had increasing titer values. The difference between titer values from the 39 transient positive patients (median titer [range], 16 [2-1280]) and the 38 persistent positive patients (median titer [range], 16 [2-640]) was minimal. As a result, a clinically relevant titer value was not determined.

At baseline, the geometric mean blood eosinophil count was 260 and 240 cells/ μ L in patients who tested ADA negative and ADA positive, respectively. At final visit, corresponding values were 40 and 50 cells/ μ L, respectively. Blood eosinophil counts were not affected by the presence of ADAs. Of the 33 patients across the randomized studies who tested positive for ADAs, 27 experienced AEs. There was no pattern to the AEs observed in these patients, and the rate of AEs did not differ from that in the overall study population. AEs evaluated as potential systemic allergic reactions were uncommon ($\leq 2\%$ of events) and were not considered related to the study drug in patients who were ADA positive. There was no indication of serious acute hypersensitivity reactions or serum sickness-like reactions associated with positive ADA status (Table I).

TABLE I. Number of patients with antimepolizumab antibodies on at least 1 postbaseline visit in each study (binding antibody assay)

Study	Patient population	Postbaseline sample collection	Treatment	No. of patients in treatment group	No. of patients with available sample	No. (%) of patients with ADA	Antibody titer, median (range)	No. (%) of patients with NAb	Condensed safety summary*
DREAM 52 wk	Age ≥ 12 y; asthma with evidence of eosinophilic inflammation; ≥ 2 asthma exacerbations in the previous year	Week 16 Week 72	Mepolizumab 750 mg IV	156	150	1 (<1)	32 (32-32)	0	Hypersensitivity possibly related to investigational product was reported in ≤ 2 ($\leq 1\%$) patients in each mepolizumab treatment group and 3 (2%) patients receiving placebo. Five (3%) patients in both the placebo and mepolizumab 75-mg groups reported injection-site reactions. Urticaria was experienced by 6 patients (2 in the 750-mg group, 3 in the 250-mg group, and 1 in the placebo group). None of these AEs occurred in patients with a positive binding assay result. No serious life-threatening anaphylactic reactions were reported.
			Mepolizumab 250 mg IV	152	149	2 (1)	34 (4-64)	0	
			Mepolizumab 75 mg IV	153	147	3 (2)	4 (4-8)	0	
			Placebo	155	148	2 (1)	6 (4-8)	0	
MENSA 32 wk	Age ≥ 12 y; asthma with evidence of eosinophilic airway inflammation; ≥ 2 asthma exacerbations in the previous year	Week 16 Week 32 Week 40†	Mepolizumab 75 mg IV	191	187	7 (4)	32 (8-128)	0	Eleven patients reported systemic reactions (3 in the SC group and 4 in the IV and placebo groups). All 11 patients had negative ADA and NAb results. Injection-site reactions were more frequent in the SC group (9%) than in the IV group or the placebo group (both 3%). No cases of anaphylaxis were reported.
			Mepolizumab 100 mg SC	194	191	9 (5)	32 (2-320)	0	
			Placebo	191	188	3 (2)	32 (8-32)	0	

SIRIUS 24 wk	Age ≥12 y; severe eosinophilic asthma with evidence of eosinophilic airway inflammation; dependent on daily prednisone	Week 16 Week 24 Week 32†	Mepolizumab 100 mg SC	69	69	6 (9)	24 (16-640)	1 (1)	Seven patients (4 in the mepolizumab group and 3 in the placebo group) had systemic reactions; 6 (4 in the mepolizumab group and 2 in the placebo group) had local injection-site reactions. No cases of anaphylaxis were reported.
			Placebo	66	66	0	—	0	
COSMOS 52 wk	Patients from MENSA or SIRIUS; receiving inhaled corticosteroid and another controller	Week 52 Week 60‡	Mepolizumab 100 mg SC	651	646	31 (5)	16 (2-1280)	0	Systemic and local-site reactions were reported in 13 (2%) and 29 (4%) patients, respectively. There were no reports of anaphylaxis considered related to treatment with mepolizumab.
COLUMBA Up to 4.5 y	Patients from DREAM; receiving asthma controller medication	Week 4 Week 24 Every 24 wk‡§	Mepolizumab 100 mg SC	347	346	27 (8)	32 (2-160)	0	Eight (2%) patients experienced allergic/hypersensitivity systemic reactions and 1 (<1%) patient experienced a nonallergic systemic reaction. There were no reports of mepolizumab-related anaphylaxis.
Integrated		—	Mepolizumab 750 mg IV	156	150	1 (<1)	32 (32-32)	0	—
			Mepolizumab 250 mg IV	152	149	2 (1)	34 (4-64)	0	
			Mepolizumab 75 mg IV	344	334	10 (3)	24 (4-128)	0	
			Mepolizumab 100 mg SC	263	260	15 (6)	32 (2-640)	1 (<1)	
			All mepolizumab doses	915	893	28 (3)	32 (2-640)	1 (<1)	
			Placebo	412	402	5 (1)	8 (4-32)	0	

IV, Intravenous; *NAb*, neutralizing antibody; SC, subcutaneous.

*Safety summary includes AEs that could be indicative of an immunogenic reaction, eg, hypersensitivity reactions, urticaria, anaphylaxis, and injection-site reactions.

†For those patients who did not enter the open-label extension.

‡Samples were also collected in patients switching from IV to SC formulation, at first and second visits where new formulation was received.

§Samples were also collected 4 wk after the last dose.

||Integrated data from randomized trials (DREAM, MENSA, and SIRIUS).

TABLE II. Immunogenicity results from pivotal phase 3 trials of biologics indicated for the treatment of severe asthma

Biologic	Target	Study	Patient population	Study duration	Treatment	N	ADA response	Condensed safety summary*
Benralizumab	IL-5 R α	Bleecker et al ⁹ NCT01928771 (SIROCCO)	Age 12-75 y; asthma diagnosis for ≥ 1 y; ≥ 2 exacerbations while on high-dose ICS plus LABA in the previous year	48 wk	Benralizumab 30 mg SC Q4W	400	13% (105 of 797)	Hypersensitivity AEs were experienced by 13 (3%) patients on benralizumab Q4W, 11 (3%) patients on benralizumab Q8W, and 11 (3%) patients on placebo. Six patients reported hypersensitivity AEs deemed to be treatment- related (urticaria [n = 5] and allergic granulomatous angiitis [n = 1]). Injection- site reactions were similar between groups (2%-4%). “There was no suggestion that positive ADA response was associated with hypersensitivity or affected efficacy outcomes.”
					Benralizumab 30 mg SC Q8W†	398		
					Placebo SC	407	NR	
		FitzGerald et al ¹⁰ NCT01914757 (CALIMA)	Age 12-75 y; severe asthma uncontrolled by medium/ high-dose ICS plus LABA; ≥ 2 exacerbations in the previous year	56 wk	Benralizumab 30 mg SC Q4W	425	15% (127 of 866)	Hypersensitivity AEs were experienced by 43 (3%) patients. The most common hypersensitivity AE was urticaria (n = 22). Numbers of injection-site reactions and hypersensitivity were similar between all treatment groups. Injection- site reactions were similar between groups (2%-3%).
					Benralizumab 30 mg SC Q8W†	441		
					Placebo SC	440	NR	

Reslizumab	IL-5	Nair et al ¹¹ NCT02075255 (ZONDA)	Adults with asthma; blood eosinophil count ≥ 150 cells/mm ³ ; treated with medium/high-dose ICS plus LABA for ≥ 12 mo and high-dose ICS plus LABA for ≥ 6 mo; oral glucocorticoid therapy for ≥ 6 continuous months directly before enrollment	28 wk	Benralizumab 30 mg SC Q4W	72	5 (7%) 4 of 5 NAb positive	In patients with an ADA response, 1 of 5 patients in the Q4W group and 3 of 7 patients in the Q8W group had an increase from baseline in blood eosinophil count. Hypersensitivity AEs were experienced by ≤ 2 patients in each treatment group. One patient in the placebo and benralizumab Q8W groups, respectively, experienced urticaria, and 2 patients in the placebo and benralizumab Q4W groups both experienced local injection-site reactions.
					Benralizumab 30 mg SC Q8W†	73	7 (19%) 6 of 7 NAb positive	
					Placebo SC	75	6 (8%) 3 of 6 NAb positive	
					Reslizumab 3.0 mg/kg IV Q4W	477	3% (15 of 477)	
Reslizumab	IL-5	Castro et al ¹² NCT01287039 NCT01285323	Age 12-75 y; asthma inadequately controlled by medium/high-dose ICS; blood eosinophil count ≥ 400 cells/ μ L; ≥ 1 exacerbation in the previous year	52 wk	Placebo IV	476	NR	Anaphylactic reactions were experienced by 2 patients in the reslizumab group in study 2 (judged to be treatment-related); these patients were discontinued from the study. Both patients were negative for ADA. The frequency of injection-site reactions was low and similar between placebo and reslizumab groups. ADA responses were generally transient and low titer. The safety profile was similar between patients ADA positive and the overall population.

(continued)

TABLE II. (Continued)

Biologic	Target	Study	Patient population	Study duration	Treatment	N	ADA response	Condensed safety summary*
Omalizumab	IgE	Solèr et al ^{13,†}	Age 12-75 y; symptomatic allergic asthma despite ICS	52 wk (28-wk trial +24-wk extension)	Omalizumab SC§	274 (trial)	0	Urticaria was experienced by 2 patients receiving omalizumab and 5 patients receiving placebo during the core study. None of these events were severe. Injection-site reactions were associated with 11.8% of omalizumab vs 7.7% of placebo injections in the core study and 5.3% of omalizumab vs 4.3% of placebo injections in the extension. No AEs were suggestive of immunologic reactions during the extension.
		Buhl et al ^{14,†}				254 (extension)		
					Placebo SC	272 (trial)	NR	Urticaria was experienced by 4 patients receiving omalizumab and 8 patients receiving placebo. Local injection-site reactions were similar in the omalizumab (8.6%) and placebo (6.5%) groups. No clinically relevant laboratory test abnormalities were observed.
		Busse et al ^{15,†}	Age 12-75 y; asthma diagnosis for ≥ 1 y; symptomatic despite ICS	28 wk	Omalizumab SC§	268	0	
					Placebo SC	257	0	

ICS, Inhaled corticosteroid; *IL-5 R α* , IL-5 receptor α ; *IV*, intravenous; *LABA*, long-acting β_2 -agonists; *NAb*, neutralizing antibody; *NR*, not reported; *Q4W*, every 4 wk; *Q8W*, every 8 wk; *SC*, subcutaneous.

*Safety summary includes AEs reported in the publication that could be indicative of an immunogenic reaction, eg, hypersensitivity reactions, urticaria, anaphylaxis, and injection-site reactions.

†First 3 doses 4 wks apart.

‡Trial not registered with clinicaltrials.gov.

§Omalizumab administered every 2-4 wk, dose dependent on body weight and serum total IgE.

The results from the combined analysis reported here demonstrate the low immunogenic response elicited by mepolizumab during its clinical trial program. Table II reports immunogenicity data from the pivotal trials of other biologics indicated for the treatment of severe asthma. Importantly, direct comparisons of ADA responses cannot be made across clinical studies used to evaluate different biologics, because there is no standardization across different ADA analytical detection methods.

A consideration when interpreting ADA results is that the presence of the biologic can interfere with the assay. The presence of drug at a concentration above the drug tolerance threshold of the assay can impair assay sensitivity, which may lead to underreporting of ADA-positive cases. Therefore, the ADA assays (screening, confirmation, and titration) were validated with sufficient drug tolerance at the anticipated trough levels, and samples collected before the next dose administration. Assay sensitivity is a useful validation parameter; however, it is dependent on the quality and purity of the positive control. ADA rates are not standalone results, but need to be evaluated in the context of other study parameters such as pharmacokinetic and pharmacodynamic profiles and AEs to obtain an understanding of the overall impact of immunogenicity.¹⁶

In summary, following extensive testing in phase III trials, mepolizumab has been shown to be well tolerated with minimal potential to elicit immunogenicity. Excluding the single report of neutralizing antibodies, ADAs did not impact pharmacokinetic or pharmacodynamic profiles and did not correlate with the incidence of any specific AEs.

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REFERENCES

1. Yin L, Chen X, Vicini P, Rup B, Hickling TP. Therapeutic outcomes, assessments, risk factors and mitigation efforts of immunogenicity of therapeutic protein products. *Cell Immunol* 2015;295:118-26.
2. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380:651-9.
3. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014;371:1198-207.
4. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014;371:1189-97.
5. Lugogo N, Domingo C, Chanez P, Leigh R, Gilson MJ, Price RG, et al. Long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma: a multi-center, open-label, phase IIIb study. *Clin Ther* 2016;38:2058-2070.e1.
6. Khatri S, Moore W, Gibson PG, Leigh R, Bourdin A, Maspero J, et al. Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. *J Allergy Clin Immunol* 2019;143:1742-51.e7.
7. Liao K, Meyer E, Lee TN, Loercher A, Sikkema D. Inhibition of interleukin-5 induced false positive anti-drug antibody responses against mepolizumab through the use of a competitive blocking antibody. *J Immunol Methods* 2017; 441:15-23.
8. Koren E, Zuckerman LA, Mire-Sluis AR. Immune responses to therapeutic proteins in humans—clinical significance, assessment and prediction. *Curr Pharm Biotechnol* 2002;3:349-60.
9. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomized, multicentre, placebo-controlled phase 3 trial. *Lancet* 2016;388:2115-27.
10. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomized, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016;388:2128-41.
11. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med* 2017;376:2448-58.
12. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomized, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015;3:355-66.
13. Soler M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001;18:254-61.
14. Buhl R, Soler M, Matz J, Townley R, O'Brien J, Noga O, et al. Omalizumab provides long-term control in patients with moderate-to-severe allergic asthma. *Eur Respir J* 2002;20:73-8.
15. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001; 108:184-90.
16. Koren E, Smith HW, Shores E, Shankar G, Finco-Kent D, Rup B, et al. Recommendations on risk-based strategies for detection and characterization of antibodies against biotechnology products. *J Immunol Methods* 2008;333:1-9.

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Further details of included studies

DREAM (NCT01000506) was a phase 2b, randomized, double-blind, placebo-controlled trial of mepolizumab as an add-on therapy to standard of care in patients with severe eosinophilic asthma (defined as a peripheral blood eosinophil level ≥ 300 cells/ μ L or sputum eosinophils $\geq 3\%$ or exhaled nitric oxide ≥ 50 ppb), 12 years or older, with 2 or more exacerbations in the previous year. Patients were required to have a well-documented requirement for high-dose inhaled corticosteroids (≥ 880 μ g/d fluticasone propionate or equivalent in adults), with or without maintenance oral corticosteroids (OCSs), plus an additional controller for at least 12 months before screening. Patients were randomized to receive intravenous mepolizumab at 75, 250, or 750 mg or placebo every 4 weeks for 52 weeks. The primary outcome measure was the rate of clinically significant asthma exacerbations, defined as episode of acute asthma requiring use of systemic corticosteroids and/or hospitalization and/or emergency department (ED) visit. Secondary outcomes included frequency of exacerbations requiring hospitalization or ED visit, mean change from baseline in prebronchodilator FEV₁ over the study period, and mean change from baseline in the Asthma Control Questionnaire score. The study was conducted from November 9, 2009, to December 5, 2011.

MENSA (NCT01691521) was a phase 3a, randomized, double-blind, placebo-controlled trial of mepolizumab as an add-on therapy to standard of care in patients 12 years or older with severe asthma. Patients had a history of 2 or more exacerbations in the previous year and evidence of eosinophilic inflammation (defined as ≥ 150 cells/ μ L at screening or ≥ 300 cells/ μ L in the previous 12 months). Patients were required to have a well-documented requirement for high-dose inhaled corticosteroids (≥ 880 μ g/d fluticasone propionate or equivalent in adults), with or without maintenance OCSs, for at least 12 months before screening. Patients received mepolizumab 100 mg subcutaneous (SC) or 75 mg intravenous or placebo every 4 weeks for 32 weeks. The primary outcome measure was rate of clinically significant asthma exacerbations as defined by worsening of asthma, which required use of systemic corticosteroids and/or hospitalization and/or ED visits. Secondary outcomes included frequency of exacerbations requiring hospitalization or ED visit, frequency of exacerbations requiring hospitalization, mean change from baseline in prebronchodilator FEV₁ at week 32, and mean change from baseline in St. George's Respiratory Questionnaire at week 32. At baseline, 144 of 576 patients were on maintenance/daily OCS therapy, with a mean prednisone-equivalent dose of 13.2 mg/d, and doses ranging from 1 to 80 mg. The study was conducted from October 8, 2012, to January 18, 2014.

SIRIUS (NCT01691508) was a phase 3a, randomized, double-blind placebo-controlled trial of mepolizumab as an add-on therapy to standard of care in patients 12 years or older with severe, OCS-dependent asthma and an eosinophil count of

greater than or equal to 150 cells/ μ L at screening or greater than or equal to 300 cells/ μ L in the previous 12 months. Patients were randomized 1:1 to receive mepolizumab 100 mg SC or placebo every 4 weeks for 24 weeks. Included patients were taking 5.0 to 35 mg of prednisone or equivalent daily at screening and switched to prednisone/prednisolone at equivalent dose for the study duration. The study included an OCS-optimization phase before mepolizumab initiation, ensuring patients entered the treatment phase on the lowest dose of OCS that would manage their symptoms. The OCS-optimization phase lasted 3 to 10 weeks and the lowest effective dose was determined as the OCS dose just before symptom emergence (increase in the 5-item Asthma Control Questionnaire score) or an exacerbation. OCS dose was decreased weekly using a protocol-defined optimization titration schedule. The primary outcome measure was reduction in OCS dose during weeks 20 to 24 compared with post-OCS-optimization baseline dose. Secondary outcomes included the proportion of patients with greater than or equal to 50% reduction in daily OCS use, proportion of patients achieving a reduction in OCS dose to less than or equal to 5.0 mg, and proportion of patients achieving a total reduction in OCS dose. The study was conducted from October 29, 2012, to December 12, 2013.

COSMOS (NCT01842607) was a phase 3a, open-label, long-term safety study of mepolizumab in addition to standard of care in patients who completed either MENSA or SIRIUS and who were being treated with an inhaled corticosteroid and another asthma controller medication throughout either study. Patients were expected to continue on controller therapy throughout the duration of this study. Mepolizumab 100 mg SC was administered every 4 weeks for 48 weeks. The primary outcome measure was the frequency of AEs. Secondary outcomes included annualized rate of exacerbations, prebronchodilator FEV₁, and frequency of positive ADAs and neutralizing antibodies. The study was conducted from May 27, 2013, to March 13, 2015.

COLUMBA (NCT01691859) was a phase 3a, open-label, long-term safety study of mepolizumab in addition to standard of care in patients with severe eosinophilic asthma who participated in the DREAM study and who had been receiving an asthma controller medication for 12 or more weeks before enrollment in this study. Patients received mepolizumab 100 mg SC every 4 weeks until a protocol-defined stopping criterion was met, such as mepolizumab becoming commercially available. Patients continued to receive standard-of-care asthma therapy for the duration of the study, which could be adjusted at the discretion of their physician. The primary end point was the frequency of all AEs, including serious AEs, and AEs of special interest. Secondary end points included electrocardiogram parameters, laboratory data, vital signs, and immunogenicity to mepolizumab (frequency of positive ADAs and neutralizing antibodies). The study was conducted from September 2012 to May 2017.

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