

Anti-IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: Indirect treatment comparison

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Background: Three anti-IL-5 pathway-directed therapies are approved for use in patients with severe eosinophilic asthma (SEA); however, no head-to-head comparison data are available.

Objective: We sought to compare the efficacy of licensed doses of mepolizumab, benralizumab, and reslizumab in patients with SEA, according to baseline blood eosinophil counts.

Methods: This indirect treatment comparison (ITC) used data from a Cochrane review and independent searches. Eligible studies were randomized controlled trials in patients aged 12 years or greater with SEA. End points included annualized rate of clinically significant exacerbations and change from baseline in Asthma Control Questionnaire score and FEV₁. An ITC was performed in patients with Asthma Control Questionnaire scores of 1.5 or greater and stratified by baseline blood eosinophil count.

Results: Eleven studies were included. All treatments significantly reduced the rate of clinically significant

exacerbations and improved asthma control versus placebo in all blood eosinophil count subgroups. Mepolizumab reduced clinically significant exacerbations by 34% to 45% versus benralizumab across subgroups (rate ratio ≥ 400 cells/ μ L: 0.55 [95% CI, 0.35-0.87]; ≥ 300 cells/ μ L: 0.61 [95% CI, 0.37-0.99]; and ≥ 150 cells/ μ L: 0.66 [95% CI, 0.49-0.89]; all $P < .05$) and by 45% versus reslizumab in the 400 cells/ μ L or greater subgroup (rate ratio, 0.55 [95% CI, 0.36-0.85]; $P = .007$). Asthma control was significantly improved with mepolizumab versus benralizumab (all subgroups: $P < .05$) and versus reslizumab in the 400 cells/ μ L or greater subgroup ($P = .004$). Benralizumab significantly improved lung function versus reslizumab in the 400 cells/ μ L or greater subgroup ($P = .025$).

Conclusions: This ITC of the licensed doses suggests that mepolizumab was associated with significantly greater improvements in clinically significant exacerbations and asthma control compared with reslizumab or benralizumab in patients with similar blood eosinophil counts. (J Allergy Clin Immunol 2018;■■■:■■■-■■■.)

Key words: Benralizumab, indirect treatment comparison, mepolizumab, network meta-analysis, reslizumab, severe eosinophilic asthma

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Severe eosinophilic asthma (SEA) is a clinically recognized phenotype of severe asthma characterized by recurrent exacerbations, poor disease control, and eosinophilic inflammation.¹ Eosinophil proliferation, maturation, and activation are controlled by the cytokine IL-5.² Moreover, IL-5 levels are correlated with asthma severity.³ Three anti-IL-5 pathway-directed therapies have been developed and approved for use in patients with SEA. Mepolizumab^{4,5} and reslizumab^{6,7} are mAbs that target IL-5, and the mAb benralizumab^{8,9} binds to the IL-5 receptor. All 3 therapies have demonstrated statistically significant reductions in exacerbation rates compared with placebo in patients with SEA in phase III randomized controlled trials.¹⁰⁻¹⁴ Additionally, mepolizumab and benralizumab significantly reduced dependency on oral corticosteroid (OCS) use,^{15,16} mepolizumab improved health-related quality of life compared with placebo,¹⁷ and reslizumab and benralizumab significantly improved pulmonary function versus placebo.^{18,19} Current Global Initiative for Asthma (GINA) treatment guidelines recommend add-on anti-IL-5 therapy as an option for patients with SEA at GINA step 5.²⁰ However, there is a need for more clinical data on the relative efficacy of the 3 anti-IL-5 therapies, in particular subgroups of patients with SEA, to help guide physicians in clinical decision making.

Recently, an indirect treatment comparison (ITC)²¹ and a Cochrane analysis²² reviewed the efficacy of the 3 anti-IL-5

Abbreviations used

ACQ:	Asthma Control Questionnaire
ED:	Emergency department
GINA:	Global Initiative for Asthma
ITC:	Indirect treatment comparison
ITT:	Intent-to-treat
OCS:	Oral corticosteroid
Q4W:	Every 4 weeks
Q8W:	Every 8 weeks
RR:	Rate ratio
SAE:	Serious adverse event
SEA:	Severe eosinophilic asthma

pathway-directed biologics versus placebo in patients with asthma across licensed and unlicensed doses of each treatment entity. The analyses supported use of anti-IL-5 pathway-directed treatments as an adjunct to standard of care in patients with SEA with poor disease control. However, these analyses did not take into account baseline blood eosinophil counts or patient-reported asthma control (as assessed by the Asthma Control Questionnaire [ACQ]) of patients included in the various clinical trials.^{21,22} This is important because the clinical characteristics of patients included in the clinical trials for mepolizumab, reslizumab, and benralizumab differed, particularly in relation to baseline blood eosinophil counts.^{10,12,13} Given that higher baseline blood eosinophil counts have been associated with more beneficial responses for all 3 treatments,^{11,13,19} there is limited clinical value in comparisons across different baseline blood eosinophil counts. Furthermore, the previous 2 reviews included both licensed and unlicensed routes of administration. Thus there remains a need for a robust and clinically relevant indirect comparison of the 3 anti-IL-5 pathway-directed treatments licensed for SEA that assesses efficacy at distinct baseline blood eosinophil count thresholds and only considers data on licensed doses and formulations.

In this study we compared the licensed formulations of anti-IL-5 pathway-directed treatments in patients with SEA and similar baseline characteristics, in particular baseline blood eosinophil counts and ACQ scores. On this background, we hypothesized that the efficacy of all 3 treatments would be influenced by patients' baseline blood eosinophil counts; therefore, by taking this variable into account, our analysis would produce more clinically informative results than those previously published. An ITC was used to compare the efficacy of mepolizumab, reslizumab, and benralizumab.

METHODS

Data source

The primary data source for this ITC was the recently published Cochrane review of anti-IL-5 pathway-directed therapies developed in severe asthma.²² The search strategy used for conducting the systematic review, which was undertaken to identify randomized placebo-controlled trials comparing mepolizumab, reslizumab, or benralizumab in adults and adolescents with asthma, is detailed within the Cochrane report (Cochrane searches carried out in March 2017). For this ITC, additional searches were carried out in January 2018 to identify any additional publications or relevant data sets (eg, subgroup analyses) since March 2017 (see the [Methods](#) section in this article's Online Repository at www.jacionline.org).

Eligibility criteria for study inclusion

Studies eligible for inclusion in this ITC were required to meet a predefined Population, Intervention, Comparator, Outcomes, Study Design (PICOS) framework. The populations consisted of patients with SEA aged 12 years or greater. Only those assessing approved doses or formulations of licensed anti-IL-5 pathway-directed treatments were included (100 mg of mepolizumab administered subcutaneously every 4 weeks [Q4W], 3 mg/kg reslizumab Q4W, and 30 mg of benralizumab every 8 weeks [Q8W; 3 × 4 weekly doses followed by 8 weekly dosing]) to ensure interventions reflected availability within clinical practice. The comparators included placebo only. The outcomes included in the analysis were clinically significant exacerbations, defined as an exacerbation requiring treatment with OCSs/systemic corticosteroids (for patients on maintenance OCSs, a ≥2-fold increase in dose was required) or requiring an emergency department (ED) visit or hospitalization; exacerbations requiring an ED visit/hospitalization; ACQ score (any version); and change from baseline prebronchodilator FEV₁. Finally, all included studies had a randomized, double-blind, controlled study design. There were no restrictions on study timeframe or duration.

Data collection and outcome measures

Data from eligible studies were extracted by a study member (Q.S.) and reviewed independently by a different member (N.B.G.). Information extracted from publications included treatment effects for study end points relevant to this ITC for the overall populations and for any subgroup analyses performed and key inclusion/exclusion criteria defining the patient population included in the studies (blood eosinophils, exacerbation history, ACQ score, inhaled corticosteroid dose, OCS use and dose, and lung function).

The analyses assessed the annualized rate of exacerbations (primary end point: clinically significant exacerbations and exacerbations requiring ED visit/hospitalization) and change from baseline at the end of the study in ACQ score (all versions; primary end point) and change from baseline at the end of the study in prebronchodilator FEV₁ (secondary end point).

Subgroup selection

Baseline blood eosinophil counts were selected before treatment comparisons as a clinical characteristic of interest to be used when defining subgroups. The rationale for this was 2-fold: (1) there was evidence to support that blood eosinophil counts influence the efficacy outcomes of all 3 anti-IL-5 pathway-directed biologics (more favorable treatment effect estimates are expected in patients with higher blood eosinophil counts) and (2) randomized controlled trials for the 3 biologics have used different blood eosinophil count inclusion criteria, as presented in [Table I](#). Selection of blood eosinophil count thresholds was based on the inclusion criteria used in the mepolizumab, benralizumab, and reslizumab clinical development programs (≥150, ≥300, and ≥400 cells/μL, respectively).

Additional subgroups were deemed of clinical interest if there was compelling evidence of a demographic or clinical characteristic fulfilling all 3 of the following criteria: (1) evidence that the characteristic acts as an effect modifier²³ for any of the 3 biologic agents, (2) a difference in distribution of characteristics between the included studies across treatments, and (3) data available to perform comparisons. As a result of this assessment, exacerbation history was also included as a subgroup of interest. Further details are available in [Tables E1 to E8](#) in this article's Online Repository at www.jacionline.org.

Treatment comparisons

After data extraction from included studies, analyses were feasible in the following subgroups: 150 cells/μL or greater (mepolizumab and benralizumab studies), 300 cells/μL or greater (mepolizumab and benralizumab studies), 400 cells/μL or greater (mepolizumab, benralizumab, and reslizumab studies), 3 or more exacerbations in the previous year (mepolizumab and benralizumab [≥300 cells/μL] studies), and 4 or more exacerbations in the previous year (mepolizumab, benralizumab [≥300 cells/μL], and reslizumab [≥400 cells/μL] studies). Comparisons based on

TABLE I. Key differences in inclusion criteria among included studies by treatment assessed

Characteristic	Mepolizumab	Reslizumab	Benralizumab
Baseline blood eosinophil count	≥150 cells/μL at baseline or ≥300 cells/μL in past year	≥400 cells/μL	≥300 cells/μL*
Exacerbation history	≥2 Exacerbations in past year	≥1 Exacerbation in past year†	≥2 Exacerbations in past year
ICS	High	Medium-high (≥440 μg/d fluticasone)	High*
Maintenance OCS use	Allowed, any dose	Allowed but ≤10 mg/d prednisolone	Allowed, any dose
Predicted FEV ₁ (%)	<80% (<90% for age <18 y) at screening	None	<80% (<90% for age <18 y) at screening and baseline
ACQ score	None	ACQ-7 score ≥1.5 at screening and baseline	ACQ-6 score ≥1.5 at screening

ICS, Inhaled corticosteroid.

*Inclusion criteria for benralizumab studies were wider for blood eosinophil count and ICS dose; however, the primary publications reported results for the 300 cells/μL or greater and high-ICS dose patient populations. Additional subgroup analyses for patients with baseline blood eosinophil counts of 150 cells/μL or greater were reported in the benralizumab pooled analysis of the phase 3 trials only and subsequently included in this study.

†Data for the end point of exacerbations requiring ED visits/hospitalizations were reported in the reslizumab pooled analysis. Patients had 2 or more exacerbations in the past year and GINA step 4/5 therapy.

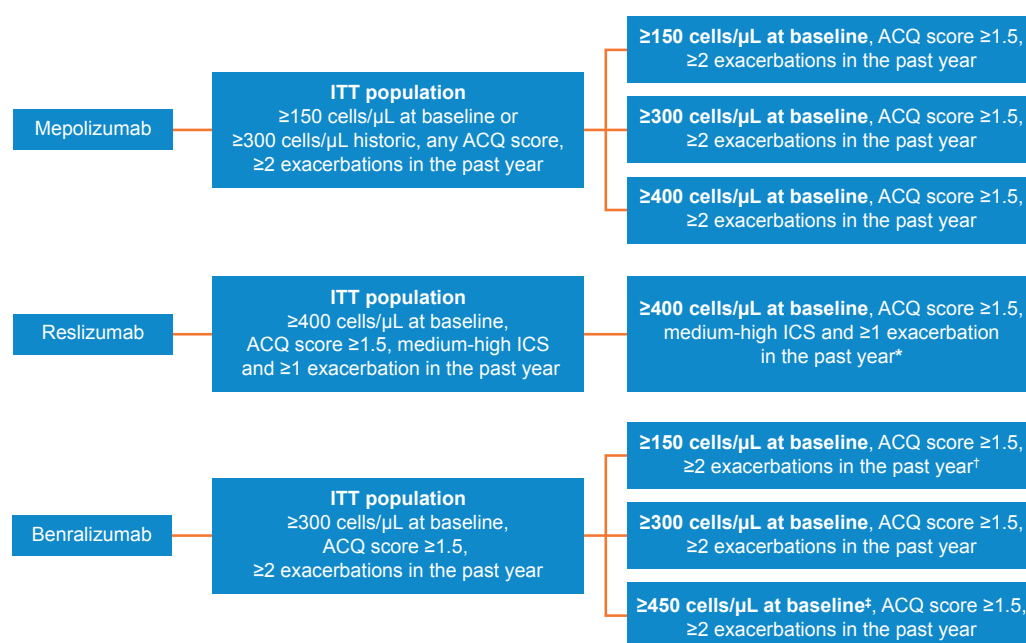


FIG 1. Overview of patients' baseline characteristics in the ITT populations and baseline blood eosinophil count subgroups used in the ITC. *Data for the end point of exacerbations requiring ED visits/hospitalizations were reported in the published reslizumab pooled analysis; patients had 2 or more exacerbations in the past year and GINA step 4/5 therapy. †Data for the 150 cells/μL or greater subgroup were reported in the published benralizumab pooled analysis only. ‡Because of the lack of available subgroup data for benralizumab, it was only possible to define a 450 cells/μL or greater subgroup. ICS, Inhaled corticosteroid; ITT, intent to treat.

eosinophil thresholds could be performed across all end points. Because of data availability, comparisons based on exacerbation history could only be performed for the clinically significant exacerbations end point (full assessment is available in the [Methods](#) section in this article's Online Repository).

Benralizumab and reslizumab studies excluded patients with ACQ scores of less than 1.5 points at baseline, and therefore for mepolizumab treatment effects to be comparable, estimates were obtained by using individual patient data excluding patients with ACQ scores of less than 1.5 points at baseline from mepolizumab studies. [Fig 1](#) shows an overview of patient inclusion criteria in the intent-to-treat (ITT) populations for each treatment and the baseline blood eosinophil count subgroups defined for this analysis.

Because all treatments were compared with a placebo plus standard-of-care control in the included studies, mepolizumab, reslizumab, and benralizumab could only be compared by using an ITC. Indirect treatment effect estimates were produced by using the Bucher method.²⁴ Inverse variance weighting and DerSimonian and Laird²⁵ methods were used for fixed- and random-effects meta-analyses of each treatment versus placebo, respectively. I^2 values, associated 95% CIs, and P values from pairwise comparisons were calculated. I^2 values of greater than 50% were considered indicative of heterogeneity between studies, and in such cases random-effects estimates were used for that given treatment effect. More details on the methods of the indirect treatment effect estimates are presented in the [Methods](#) section in this article's Online Repository.

TABLE II. Summary of baseline characteristics in included studies

	Mepolizumab studies				Reslizumab studies	
	MENSA (n = 576)*		MUSCA (n = 551)		Castro et al, 2011 (n = 106)	
	MEPO, 100 mg SC	PBO	MEPO, 100 mg SC	PBO	RESLI, 3 mg/kg Q4W	PBO
Treatment allocation, no.	194	191	274	277	53	53
Age (y), mean	51	49	49.8	52.1	44.9	45.8
Female sex, no. (%)	116 (60)	107 (56)	149 (54)	176 (64)	34 (64)	29 (55)
Baseline prebronchodilator FEV ₁						
L, mean (SD)	1.73 (0.66)	1.86 (0.63)	1.8 (0.6)	1.7 (0.6)	2.1 (0.60)	2.3 (0.75)
Percent predicted, mean (SD)§	59.3 (17.5)	62.4 (18.1)	55.5 (14.4)	55.2 (14.6)	66.0 (15.2)	69.3 (16.4)
Baseline ACQ score, mean (SD)	2.26 (1.27)	2.28 (1.19)	2.2 (1.1)	2.2 (1.2)	2.8 (0.79)	2.5 (0.73)
Blood eosinophil count, mean cells/μL	290**	320**	300**	350**	500†	500†
Mean (SD) no. of exacerbations in 12 mo before screening	3.8 (2.7)††	3.6 (2.80)††	2.9 (1.9)	2.7 (1.5)	NA	NA
Patients experiencing ≥1 exacerbation in 12 mo before baseline, no. (%)	33 (17)‡‡	35 (18)‡‡	87 (32)§§	92 (33)§§	NA	NA

BENRA, Benralizumab; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2 -agonist; *MEPO*, mepolizumab; *NA*, data not available; *PBO*, placebo; *RESLI*, reslizumab; *SC*, subcutaneous.

*Remaining patients received unlicensed doses or regimens (75 mg of mepolizumab administered intravenously, 0.3 mg/kg reslizumab, or benralizumab Q4W) and were therefore not included in the analysis.

†Median reported.

‡No SD data are available.

§Spirometric equations used to calculate percent predicted FEV₁ were not provided in the respective publications.

||ACQ-5.

¶ACQ-7.

#ACQ-6.

**Geometric mean reported.

††Severe exacerbations.

‡‡Exacerbations requiring hospitalization.

§§Exacerbations requiring ED visits/hospitalizations in the 12 months before screening.

P-scores were also calculated to rank treatments based on efficacy. P-scores range from 0 to 1,²⁶ with a higher P-score indicating a higher ranking treatment compared with other treatments in the ITC.

Unadjusted comparison

An unadjusted comparison was also performed as a sensitivity analysis for the ITC, in which the ITT populations for all treatments, uncontrolled for baseline blood eosinophil counts or ACQ scores, were used to compare the effect of treatment on the 4 end points; this analysis is referred to as the unadjusted comparison.

RESULTS

Included studies and patients

Results of the systematic literature search have previously been reported.²² From the Cochrane review, 9 studies were identified as eligible for inclusion in this ITC: 2 for mepolizumab (MENSA [NCT01691521] and MUSCA [NCT02281318]),^{10,17} 2 for benralizumab (SIROCCO [NCT01928771] and CALIMA [NCT01914757]),^{13,14} and 5 for reslizumab (Castro et al, 2011 [NCT00587288]; NCT01270464; NCT01508936; NCT01287039; and NCT01285323).^{12,18,19,27} Additional searches identified 11 further articles, 2 of which presented subgroup analyses relevant for this ITC that were not reported in the primary publications. First, a pooled analysis of the 2 benralizumab studies, SIROCCO and CALIMA,²⁸ provided data for patients with

baseline blood eosinophil counts of 150 cells/μL or greater. Second, a pooled analysis of the 2 reslizumab studies (NCT01287039 and NCT01285323)²⁹ provided more closely matched patient data for the end point exacerbations requiring hospitalizations/ED visits (all patients had GINA step 4/5 therapy and ≥2 exacerbations in the prior year). Both pooled analyses were included in the ITC. The remaining 9 articles were excluded: 6 meta-analyses of existing data, 1 review paper, 1 meta-analysis that reported results for subgroups not relevant to this ITC, and 1 report of a clinical trial of benralizumab that did not use the licensed dose. A summary of the key differences in the inclusion criteria of the included studies stratified by treatment is shown in Table I.

Across all studies, 3723 patients received either 100 mg of mepolizumab administered subcutaneously Q4W, 3 mg/kg reslizumab Q4W, 30 mg of benralizumab Q8W or placebo. Of the 385 and 551 patients in MENSA and MUSCA, respectively, who received either 100 mg of mepolizumab administered subcutaneously Q4W or placebo, 257 (67%) and 390 (71%) patients had baseline ACQ-5 scores of 1.5 or greater and were subsequently included in the treatment comparison analyses by baseline blood eosinophil thresholds. Baseline demographic characteristics are summarized in Table II. The mean age of patients was similar across studies, ranging from 43.0 to 52.1 years. Baseline blood eosinophil counts varied with mean, median, and geometric mean values ranging from 277 to 696 cells/μL across studies.

Reslizumab studies								Benralizumab studies (patients receiving high-dose ICSs plus LABAs, with baseline blood eosinophil counts ≥ 300 cells/ μ L)			
NCT01270464 (n = 315)*		NCT01508936 (n = 496)		NCT01287039 (n = 489)		NCT01285323 (n = 464)		SIROCCO (n = 809)*		CALIMA (n = 728)*	
RESLI, 3 mg/kg Q4W	PBO	RESLI, 3 mg/kg Q4W	PBO	RESLI, 3 mg/kg Q4W	PBO	RESLI, 3 mg/kg Q4W	PBO	BENRA, 30 mg Q8W	PBO	BENRA, 30 mg Q8W	PBO
106	105	398	98	245	244	232	232	267	267	239	248
43.0	44.2	44.9	45.1	49 [†]	48 [†]	48 [†]	48 [†]	47.6	48.6	49.6	48.5
61 (58)	62 (59)	261 (66)	54 (55)	142 (58)	161 (66)	144 (62)	150 (65)	174 (65)	180 (67)	138 (58)	145 (58)
2.19 [†]	2.22 [†]	2.10 [†]	2.18 [†]	1.89 (0.73)	1.93 (0.80)	2.13 (0.78)	2.00 (0.67)	1.66 (0.57)	1.65 (0.58)	1.76 (0.62)	1.82 (0.65)
70.4 [†]	71.1 [†]	66.8 [†]	66.5 [†]	63.6 (18.6)	65.0 (19.8)	70.4 (21.0)	68.0 (18.9)	55.5 (14.6)	56.4 (14.6)	57.0 (14.2)	58.2 (13.9)
2.59 [†] ¶	2.47 [†] ¶	2.56 [¶]	2.56 [¶]	2.66 (0.85)¶	2.76 (0.88)¶	2.57 (0.89)¶	2.61 (0.79)¶	2.81 (0.89)#	2.90 (0.95)#	2.80 (0.95)#	2.75 (0.94)#
592	601	281	277	696	624	610	688	500 [†]	500 [†]	500 [†]	510 [†]
NA	NA	NA	NA	1.9 (1.6)	2.1 (2.3)	1.9 (1.6)	2.0 (1.8)	NA	NA	NA	NA
NA (57)	NA (54)	166 (42)	37 (38)	NA	NA	NA	NA	NA	NA	NA	NA

Exacerbations

Compared with placebo, all treatments significantly reduced the rate of clinically significant exacerbations in each baseline blood eosinophil count threshold subgroup; however, only mepolizumab and reslizumab significantly reduced the rate of exacerbations requiring ED visit/hospitalization (see Figs E1 and E2 in this article's Online Repository at www.jacionline.org).

When comparing treatments against one another, mepolizumab significantly reduced the rate of clinically significant exacerbations compared with benralizumab (rate ratio [RR], 0.55 [95% CI, 0.35-0.87]; $P = .011$) and reslizumab (RR, 0.55 [95% CI, 0.36-0.85]; $P = .007$) among patients with baseline blood eosinophil counts of 400 cells/ μ L or greater; there was no difference in exacerbation reduction between reslizumab and benralizumab (Fig 2). In patients with baseline blood eosinophil counts of 150 cells/ μ L or greater and 300 cells/ μ L or greater, mepolizumab significantly reduced the rate of clinically significant exacerbations compared with benralizumab (RR, 0.66 [95% CI, 0.49-0.89; $P = .006$] and 0.61 [95% CI, 0.37-0.99; $P = .047$], respectively; Fig 2). For exacerbations requiring ED visits/hospitalizations, no significant differences were observed between any 2 treatments in any subgroup assessed (Fig 3).

Among patients with baseline blood eosinophil counts of 400 cells/ μ L or greater, for the end point of clinically significant exacerbations, mepolizumab ranked first (P-score = 0.997), followed by reslizumab (P-score = 0.504) and benralizumab

(P-score = 0.499); however, for exacerbations requiring ED visit/hospitalization, reslizumab ranked higher than mepolizumab (P-scores = 0.810 vs 0.681). All treatment rankings and P-scores for both exacerbation end points are shown in Table E9 in this article's Online Repository at www.jacionline.org.

Results for the additional subgroup analyses of mepolizumab and benralizumab conducted among patients with blood eosinophil counts of 300 cells/ μ L or greater, further stratified by exacerbation history, were in line with results observed for all patients with blood eosinophil counts of 300 cells/ μ L or greater (see the Results section and Tables E10-E13 in this article's Online Repository at www.jacionline.org).

Patient-reported asthma control

All treatments significantly improved patient-reported asthma control compared with placebo across all blood eosinophil count thresholds (see Fig E3 in this article's Online Repository at www.jacionline.org).

In patients with baseline blood eosinophil counts of 400 cells/ μ L or greater, mepolizumab was associated with significant improvements in change from baseline in ACQ scores compared with benralizumab (difference, -0.36 [95% CI, -0.66 to -0.05]; $P = .023$) and reslizumab (difference, -0.39 [95% CI, -0.66 to -0.12]; $P = .004$; Fig 4). There was no significant difference in change from baseline in ACQ score between reslizumab and

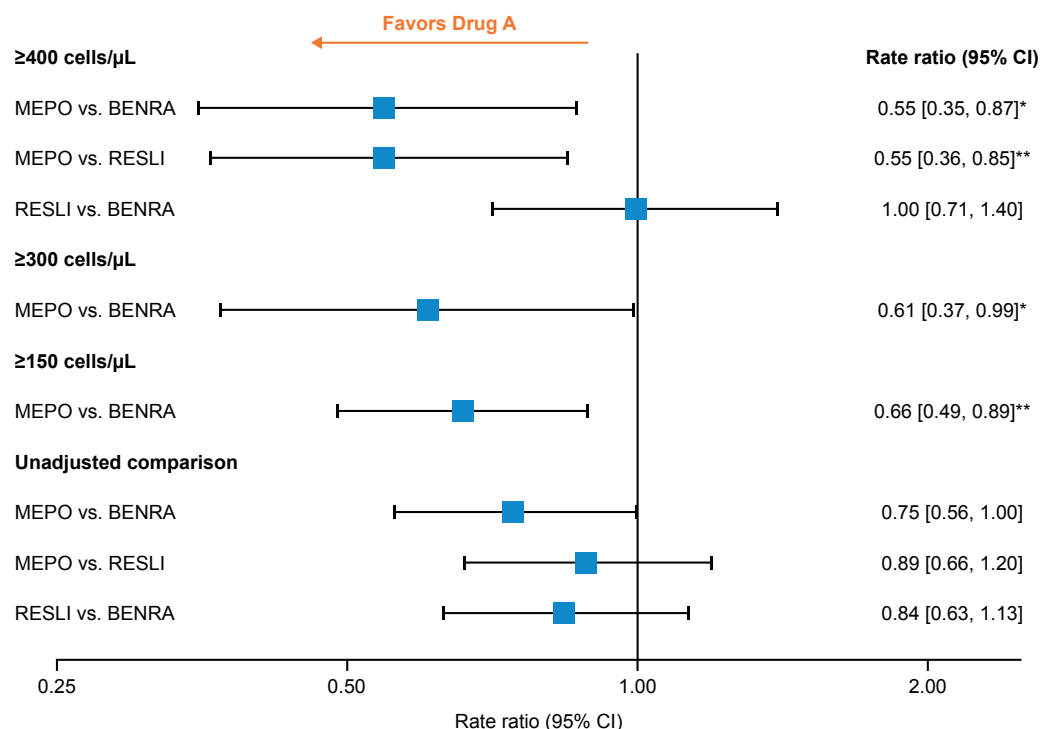


FIG 2. ITC of the rate of clinically significant exacerbations by baseline blood eosinophil count subgroups and in the ITT population. * $P < .05$ and ** $P < .01$. Comparisons are presented as drug A versus drug B. Not all comparisons were possible at each blood eosinophil count threshold because of a lack of data from included studies. I^2 values: 400 cells/μL or greater, 0% (MEPO vs PBO), NA (BENRA vs PBO), and 0% (RESLI vs PBO); 300 cells/μL or greater, 0% (MEPO vs PBO) and 73% (BENRA vs PBO); 150 cells/μL or greater, 0% (MEPO vs PBO) and NA (BENRA vs PBO); and unadjusted comparison, 0% (MEPO vs PBO), 73% (BENRA vs PBO), and 0% (RESLI vs PBO). BENRA, Thirty milligrams of benralizumab Q8W; MEPO, 100 mg of mepolizumab administered subcutaneously; NA, not applicable; RESLI, 3 mg/kg reslizumab.

benralizumab. In subgroups with baseline blood eosinophil counts of 150 cells/μL or greater and 300 cells/μL or greater, mepolizumab treatment was associated with significant improvements in change from baseline in ACQ scores compared with benralizumab (difference, -0.33 [95% CI, -0.54 to -0.11 ; $P = .003$] and -0.40 [95% CI, -0.76 to -0.03 ; $P = .035$], respectively; Fig 4).

For patient-reported asthma control, among patients with baseline blood eosinophil counts of 400 cells/μL or greater, mepolizumab ranked first (P-score = 0.995), followed by benralizumab (P-score = 0.552) and reslizumab (P-score = 0.453; see Table E9).

Lung function

Mepolizumab, benralizumab, and reslizumab all significantly improved lung function compared with placebo in all eosinophil count subgroups (see Fig E4 in this article's Online Repository at www.jacionline.org).

At all eosinophil count thresholds, there were no significant differences in change from baseline in prebronchodilator FEV₁ between mepolizumab and benralizumab. Additionally, among patients with baseline blood eosinophil counts of 400 cells/μL or greater, no significant differences were observed between mepolizumab and reslizumab; however, benralizumab was associated with a significant improvement in change from baseline in

FEV₁ compared with reslizumab (difference, 0.11 [95% CI, 0.01-0.20; $P = .025$]; Fig 5).

For prebronchodilator FEV₁, among patients with baseline blood eosinophil counts of 400 cells/μL or greater, benralizumab ranked highest (P-score = 0.915), followed by mepolizumab (P-score = 0.697) and reslizumab (P-score = 0.389). Mepolizumab ranked higher than benralizumab in patients with baseline blood eosinophil counts of 300 cells/μL or greater (P-score = 0.910 vs 0.590) and 150 cells/μL or greater (P-score = 0.808 vs 0.692; see Table E9).

Unadjusted comparison

The ITT populations from all studies were included in the unadjusted comparison. Compared with placebo, all treatments resulted in significant improvements in the rate of clinically significant exacerbations and changes from baseline in ACQ score and prebronchodilator FEV₁ (see Figs E1, E3, and E4). Additionally, as seen in the analysis by blood eosinophil count threshold, mepolizumab significantly reduced the rate of exacerbations requiring ED visits/hospitalizations compared with placebo (see Fig E2).

In the ITC no significant differences were observed between any 2 treatments for any end point when using the ITT population (Figs 2-5).

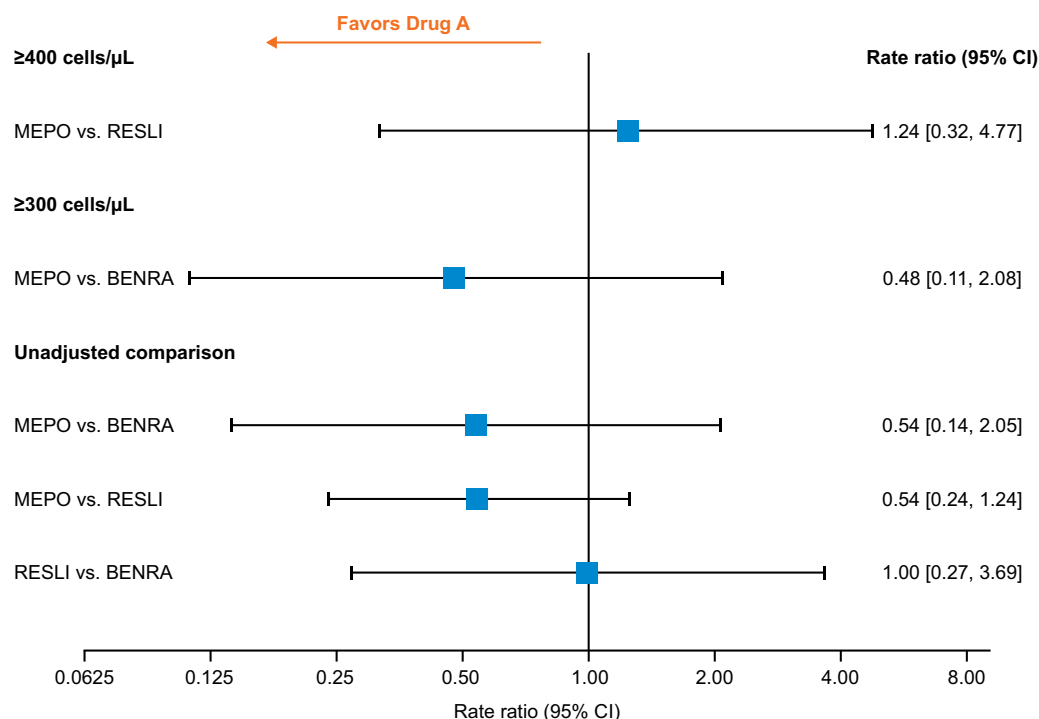


FIG 3. ITCs of the rate of exacerbations requiring ED visits/hospitalizations by baseline blood eosinophil count subgroup and in the ITT population. Comparisons are presented as drug A versus drug B. Not all comparisons were possible at each blood eosinophil count threshold because of a lack of data from included studies. P values: 400 cells/μL or greater, 12% (MEPO vs PBO) and NA (RESLI vs PBO); 300 cells/μL or greater, 0% (MEPO vs PBO) and 86% (BENRA vs PBO); unadjusted comparison, 0% (MEPO vs PBO), 86% (BENRA vs PBO), and 0% (RESLI vs PBO). *BENRA*, Thirty milligrams of benralizumab Q8W; *MEPO*, 100 mg of mepolizumab administered subcutaneously; *NA*, not applicable; *PBO*, placebo; *RESLI*, 3 mg/kg reslizumab.

DISCUSSION

This ITC of the 3 available anti-IL-5 pathway-directed therapies for SEA focused on the licensed formulations of each treatment and clinical end points that are common to all 3 biologics, taking baseline blood eosinophil counts and ACQ scores into consideration. Mepolizumab significantly reduced the rate of clinically significant exacerbations by 34% to 45% compared with benralizumab across all baseline blood eosinophil count thresholds and by 45% compared with reslizumab in the 400 cells/μL or greater subgroup. Furthermore, mepolizumab was associated with significant improvements in patient-reported asthma control, as assessed by ACQ score, compared with reslizumab and benralizumab in the 400 cells/μL or greater subgroup and benralizumab in the 150 cells/μL or greater and 300 cells/μL or greater subgroups. A significant improvement in lung function of 110 mL (as assessed by change from baseline in prebronchodilator FEV₁) was observed for benralizumab versus reslizumab in patients with baseline blood eosinophil counts of 400 cells/μL or greater. Of note, when treatment comparisons used the ITT populations and did not take into account differences in baseline blood eosinophil count or ACQ score, there were no significant differences among the 3 treatments. Therefore, accounting for baseline characteristics, as in the current study, improved the accuracy of the comparative efficacy of the treatments,³⁰ thus allowing clinicians and patients to make more informed decisions about the available treatment options.

Asthma exacerbations are a primary cause of morbidity and mortality in patients with asthma and drive health care use and costs.³¹ The significant improvement in the rate of clinically significant exacerbations observed with all 3 treatments versus placebo in the ITT population seen here is in accordance with previous meta-analyses of anti-IL-5 pathway-directed therapies in patients with severe asthma.^{21,22} However, our analysis reports on an ITC between the 3 licensed formulations of the anti-IL-5 pathway-directed therapies in baseline blood eosinophil count subgroups, which has not previously been conducted. This ITC demonstrates a statistically significant improvement in clinically significant exacerbations with mepolizumab compared with benralizumab in all baseline blood eosinophil count subgroups and compared with reslizumab in the subgroup of patients with a baseline blood eosinophil count of 400 cells/μL or greater (data for subgroups with baseline blood eosinophil counts of ≥ 150 cells/μL and ≥ 300 cells/μL were not available for reslizumab). These differences were observed despite inherent between-study variation in the mode of action of the study drugs, study drug preparation, dosing regimens, mode of delivery, and background standard of care, thus providing evidence that the peripheral blood eosinophil count determines differences in efficacy within and between the treatments. Given the well-documented importance of baseline blood eosinophil counts in individualizing treatment for patients with severe asthma,³² these results are of considerable interest clinically.

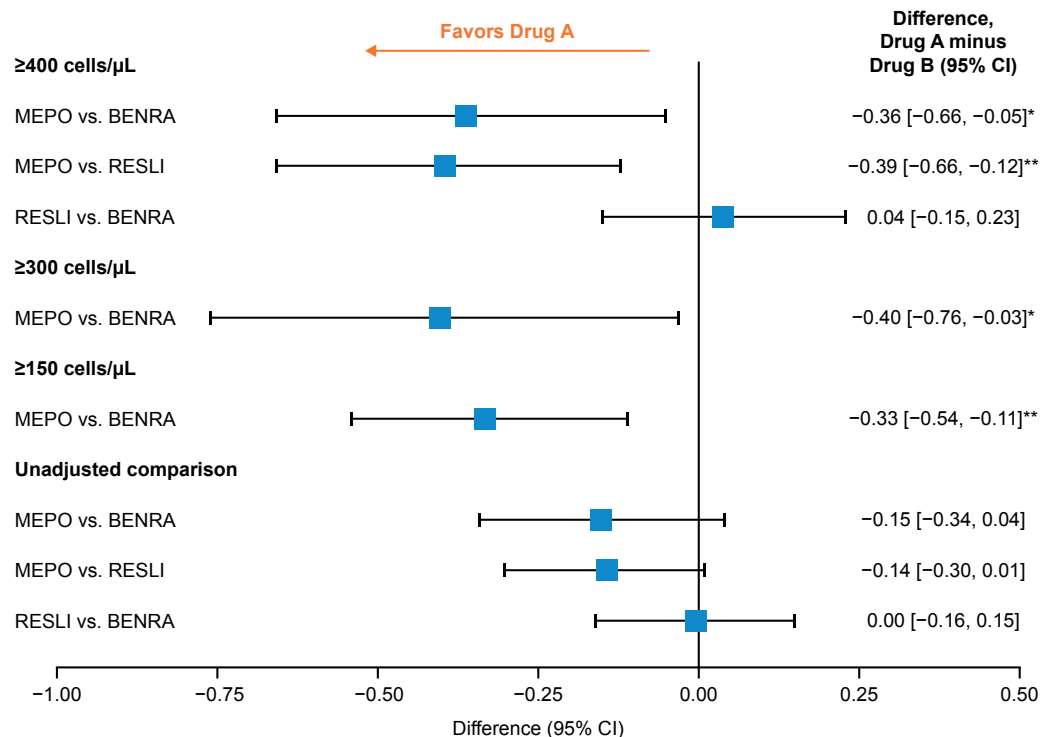


FIG 4. ITCs of the change from baseline in ACQ score by baseline blood eosinophil count subgroups and in the ITT population. * $P < .05$ and ** $P < .01$. Comparisons are presented as drug A versus drug B. Not all comparisons were possible at each blood eosinophil count threshold because of a lack of data from included studies. I^2 values: 400 cells/ μ L or greater, 28% (MEPO vs PBO), NA (BENRA vs PBO), and 0% (RESLI vs PBO); 300 cells/ μ L or greater, 60% (MEPO vs PBO) and 0% (BENRA vs PBO); 150 cells/ μ L or greater, 0% (MEPO vs PBO) and NA (BENRA vs PBO); unadjusted comparison, 0% (MEPO vs PBO), 0% (BENRA vs PBO), and 0% (RESLI vs PBO). BENRA, Thirty milligrams of benralizumab Q8W; MEPO, 100 mg of mepolizumab administered subcutaneously; NA, not applicable; PBO, placebo; RESLI, 3 mg/kg reslizumab.

In addition, when comparisons used the unadjusted population, which did not take baseline blood eosinophil counts into consideration, no statistically significant differences were observed between the 3 treatments with regard to reducing clinically significant exacerbations. The fact that there were no differences between treatments, despite the aforementioned between-study variability in dosing, further highlights the importance of considering blood eosinophil counts when comparing the efficacy of anti-IL-5 pathway-directed asthma treatments.

The aim of this analysis was to provide relevant information based on comparative phenotypic characteristics for clinicians and formulary/health technology assessment assessors to help inform treatment choices for patients with SEA. Further information about the relationship between blood eosinophil counts and the effect of treatment on other important asthma-related outcomes, such as patient-reported asthma symptoms and quality of life, is important to consider. Our results are in keeping with previous publications,^{14,17,18,22} showing statistically significant improvements in ACQ scores with mepolizumab, benralizumab, and reslizumab versus placebo in all subgroups assessed. In the ITC mepolizumab resulted in significant improvements in asthma control compared with benralizumab and reslizumab in patients with baseline blood eosinophil counts of 400 cells/ μ L or greater (data for reslizumab were not available in the ≥ 300 cells/ μ L and ≥ 150 cells/ μ L subgroups). Mepolizumab was also associated with significantly improved asthma control compared with

benralizumab in patients with blood eosinophil counts of 300 cells/ μ L or greater and 150 cells/ μ L or greater. Given the importance of improving asthma control in patients with SEA who experience persistent symptoms, these results are informative for clinicians considering the various anti-IL-5 pathway-directed treatment options.

Overall, the results of this ITC suggest that mepolizumab has greater efficacy than benralizumab and reslizumab at all blood eosinophil count thresholds assessed for clinically significant exacerbations and ACQ scores but not for exacerbations requiring ED visits/hospitalizations. The lack of statistically significant differences observed between treatments for exacerbations requiring ED visits/hospitalizations is possibly because these are infrequent events, and as such, there might have been insufficient data to determine statistically significant differences between treatments for this end point.

The anti-IL-5 pathway-directed treatments included in this analysis not only differ with respect to their clinical efficacy but also their dosing regimens and possible mechanisms of action. Mepolizumab and reslizumab are anti-IL-5 antibodies administered at 100 mg Q4W subcutaneously and 3 mg/kg Q4W intravenously, respectively, whereas benralizumab is an anti-IL-5 receptor antibody administered at 30 mg Q8W subcutaneously (after 3 doses every 4 weeks). Furthermore, the magnitude of the depletion of blood eosinophils varied between the 3 treatments (potentially reflecting the differences in mechanism

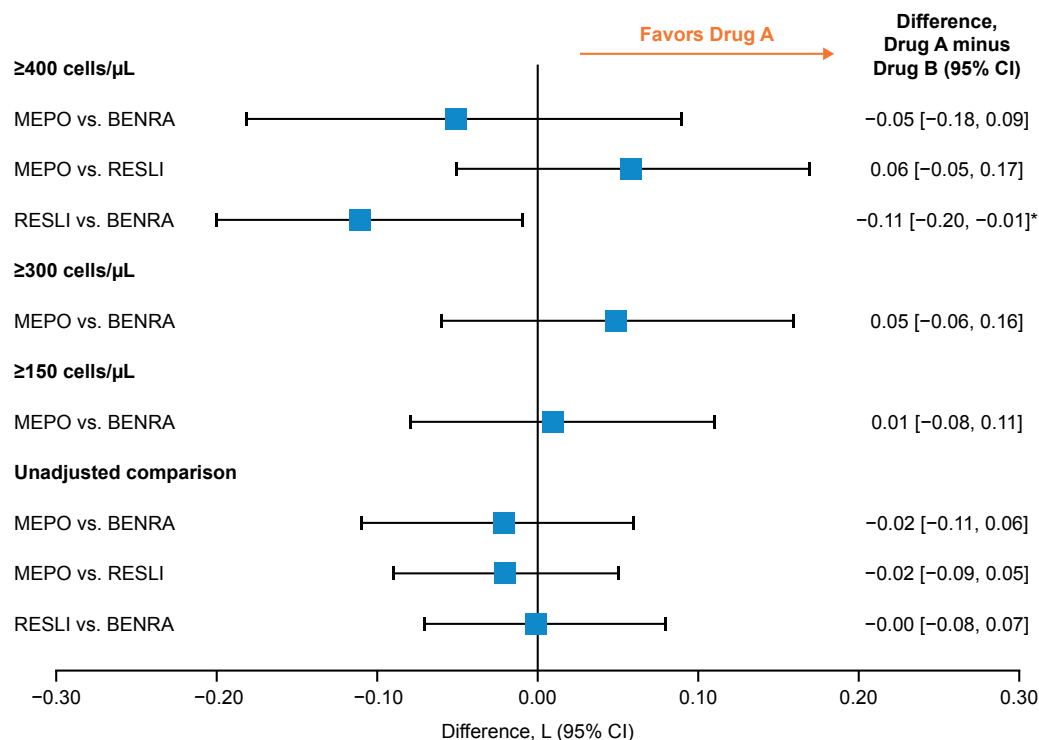


FIG 5. ITCs of the change from baseline in prebronchodilator FEV₁ (in liters) by baseline blood eosinophil count subgroups and in the ITT population. * $P < .05$. Comparisons are presented as drug A versus drug B. Not all comparisons were possible at each blood eosinophil count threshold because of a lack of data from included studies. I^2 values: 400 cells/μL or greater, 0% (MEPO vs PBO), NA (BENRA vs PBO), and 13% (RESLI vs PBO); 300 cells/μL or greater, 0% (MEPO vs PBO) and 0% (BENRA vs PBO); 150 cells/μL or greater, 0% (MEPO vs PBO) and NA (BENRA vs PBO); unadjusted comparison, 0% (MEPO vs PBO), 0% (BENRA vs PBO), and 13% (RESLI vs PBO). BENRA, Thirty milligrams of benralizumab Q8W; MEPO, 100 mg of mepolizumab administered subcutaneously; NA, not applicable; PBO, placebo; RESLI, 3 mg/kg reslizumab.

of action between anti-IL-5 and anti-IL-5 receptor therapies),^{10-12,15,18,27,33} However, recent animal data suggest that a specific eosinophil subtype present in the eosinophil population might contribute to homeostatic immune processes, therefore targeting complete depletion of eosinophils might not be desirable.³⁴ Additionally, the results of the current study suggest that the near-complete depletion of blood eosinophils with benralizumab does not improve exacerbation or asthma control outcomes compared with reslizumab and mepolizumab. In fact, there were significant improvements in clinically significant exacerbation rates with mepolizumab compared with benralizumab when patient populations were closely matched.

The strengths of this analysis support the clinical relevance of these results. First, the comparison included only the licensed formulations of each anti-IL-5 pathway-directed treatment, with the aim of evaluating the clinical effects of the 3 treatments available in clinical practice. Second, comparisons were carried out on patient populations grouped by baseline blood eosinophil count, which is known to influence treatment effect,^{11,13,19,35} and matched according to baseline ACQ score (and in one analysis, exacerbation history), an approach that should allow like-for-like comparisons between treatments. As such, this study improves understanding of expected treatment benefits based on patients' blood eosinophil counts and can therefore help treating physicians make clinical decisions that are better tailored to patients' clinical characteristics.

Despite these strengths, our results should be interpreted with caution. The included studies were conducted in different cohorts of patients, different regions over different periods of time, and within different health care delivery systems. These considerations should be noted when interpreting the relative efficacies shown here because all these factors can have an effect on observed treatment effects. For example, the definition of standard of care will have differed between the included trials, which might have influenced the observed treatment effects. Despite this, it must be noted that considerable overlap exists between the different study populations, particularly when inclusion criteria for blood eosinophil counts and ACQ scores were matched.

The variation in study duration, ranging from 15 to 56 weeks, might have affected treatment comparisons. A detailed assessment of the potential influence of study duration on treatment effect estimates is provided in this article's Online Repository at www.jacionline.org. In short, although the change from baseline in each treatment changed through time, the treatment differences (between treatment and placebo) remained consistent from approximately 16 weeks onward in the individual studies, meaning that differences in change from baseline ACQ score and FEV₁ reported from 15 weeks and up to 56 weeks could be compared without further correction.^{10,12-14,17,18,27} The effect measures used in this analysis (eg, RR for exacerbations rather than dichotomous outcomes, such as percentage of patients with ≥ 1

exacerbation) were also appropriate for combining results from studies of different durations.

Furthermore, there was no evidence of heterogeneity when combining studies of different durations. Therefore the bias potentially caused by variations in study duration is likely to be small. Slight variation in the definition of clinically significant exacerbations also existed between studies. It was not possible to conduct a meta-regression analysis adjusting for within-study and between-study variation in blood eosinophil counts or other baseline covariates because of the small number of studies included in the ITC and the inconsistency of data reporting between included studies (eg, geometric mean blood eosinophil counts vs nongeometric means).

A further limitation of the study was that the patient populations from the reslizumab studies could not be closely matched with regard to their exacerbation history or inhaled corticosteroid use. Closer matching of exacerbation history is of particular importance given the effect of exacerbation history on treatment efficacy.¹¹ Nonetheless, for the end point of exacerbations requiring ED visits/hospitalizations, we were able to match patient subgroups by the presence of 2 or more historic exacerbations and the use of GINA step 4/5 therapy.

An additional limitation is the use of different versions of the ACQ in different clinical trials (ACQ-7 in the reslizumab trials, ACQ-6 in the benralizumab trials, and ACQ-5 in the mepolizumab trials). However, validation studies have been published showing that all ACQ versions have similar psychometric properties and produce similar results.^{36,37} For the assessment of lung function, comparisons were based on FEV₁ in liters because percent predicted FEV₁ was not available for the majority of the benralizumab or reslizumab studies. Because this analysis did not use normalized lung function values (ie, percent predicted FEV₁), it does not account for potential differences in baseline lung function. Furthermore, the variations between the included studies described above prevented closer matching of patient populations.

Finally, safety data and other clinical outcomes, such as the OCS-sparing effect and health-related quality of life, were not within the scope of this ITC because OCS-sparing data were not available for all 3 biologics and different questionnaires were used for assessment of quality of life (St George's Respiratory Questionnaire for mepolizumab and Asthma Quality of Life Questionnaire for benralizumab and reslizumab), which did not allow for a matched comparison. A safety analysis was carried out in the recent Cochrane review and found that there were no excess serious adverse events (SAEs) with any anti-IL-5 pathway-directed treatment and that there was a reduction of SAEs in favor of mepolizumab versus placebo that might be attributable to a beneficial effect on asthma-related SAEs.²² Despite these limitations, our analysis provides robust clinically relevant data and in the absence of head-to-head comparisons is the only ITC of the approved doses of mepolizumab, benralizumab, and reslizumab to date that compares treatments in patients with similar baseline blood eosinophil counts and ACQ scores.

In summary, this ITC of licensed formulations of available anti-IL-5 pathway-directed therapies in patients with SEA, in which treatments were compared in patient populations with similar baseline blood eosinophil counts and asthma control, shows that mepolizumab, reslizumab, and benralizumab all significantly reduced clinically significant exacerbations and improved asthma control and lung function versus placebo.

Significant reductions in exacerbations requiring ED visits/hospitalizations were also seen with mepolizumab versus placebo across all baseline blood eosinophil thresholds assessed and with reslizumab versus placebo among patients with 2 or more historic exacerbations and GINA step 4/5 therapy but not with benralizumab versus placebo; differences between treatments did not reach statistical significance when compared indirectly. In the unadjusted ITT analysis, in which differences in baseline blood eosinophil counts were not accounted for, there were no significant differences among the 3 treatments for the end points analyzed; however, our analysis shows the importance of considering differences in characteristics known to affect treatment efficacy when comparing anti-IL-5 pathway-directed therapies. Indeed, when differences in baseline blood eosinophil counts were accounted for, results from this study suggest that mepolizumab was associated with significantly greater reductions in asthma exacerbations and significantly greater improvement in asthma control at all baseline blood eosinophil thresholds assessed compared with reslizumab or benralizumab.

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Clinical implications: Mepolizumab induced significantly greater asthma exacerbation reductions and asthma control improvements versus reslizumab and benralizumab at all baseline blood eosinophil count thresholds, informing treatment decisions for patients with SEA.

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METHODS

Details of additional searches carried out in January 2018

For this ITC, any publications from ongoing studies identified by the Cochrane report that might have been published since March 2017 were also searched. European Medicines Agency, US Food and Drug Administration, and National Institute for Health and Care Excellence documents, as well as [ClinicalTrials.gov](https://www.clinicaltrials.gov) postings, were checked to identify any additional published subgroup analyses. In addition, any published meta-analyses for reslizumab and benralizumab using individual patient data potentially investigating subgroups were identified by searching PubMed. The following search terms were used to search PubMed: pooled[Title/Abstract] OR meta[Title/Abstract] OR combined[Title/Abstract] AND benralizumab[Title/Abstract] OR reslizumab[Title/Abstract]. There were no date, language, or article-type restrictions on the literature search.

Subgroup feasibility assessment

Subgroup analyses were selected based on identification of characteristics that have been shown to influence the effect of treatment on outcomes, which are termed effect modifiers.

When using data from randomized clinical trials, randomization should ensure balance across baseline characteristics between treatment groups. Effect modifiers influence the observed treatment effects; however, if there are no differences between studies in these effect modifiers, then results can be compared between studies. Therefore baseline characteristics of interest in which comparisons between the 3 investigated biologics would be of clinical interest had:

1. confirmed effect modification in 1 or more of the included treatments;
2. a difference between the included studies across treatments in baseline characteristics; and
3. available estimates of treatment effects for benralizumab and reslizumab.

This evaluation process is presented in [Table E1](#).

Blood eosinophil counts and exacerbation history were the subgroups in which all the conditions for being explored further were met (ie, there were confirmed effect modification and differences across studies between the treatments, and data were available for performing analyses). Because effect modification by blood eosinophil count is driven by the biologic mechanism for all 3 treatments and there are known variations in entry criteria for blood eosinophils among the studies conducted for the 3 treatments, the assessment of data availability was performed by using thresholds of relevance to the 3 biologics:

- Mepolizumab studies included patients with blood eosinophil counts of 150 cells/ μ L or greater at initiation or 300 cells/ μ L or greater any time in the past year. Based on this, a first threshold was set to 150 cells/ μ L or greater.
- Benralizumab studies included patients regardless of eosinophil counts; however, primary analyses were focused on patients with 300 cells/ μ L or greater at initiation. Based on this, a second threshold was set to 300 cells/ μ L or greater.
- Reslizumab studies included patients with 400 cells/ μ L or greater at initiation. Based on this, a third threshold was set to 400 cells/ μ L or greater.

A comparison across multiple outcomes could only be performed based on blood eosinophil count thresholds, where results for exacerbation reduction, change from baseline in ACQ score, and change from baseline in prebronchodilator FEV₁ were available ([Table E2](#)). Data for patients with 450 cells/ μ L or greater were available for benralizumab; although this was greater than the set threshold of 400 cells/ μ L or greater, this was considered close enough to enable a comparison accounting for blood eosinophil count. Comparisons based on subgroups by exacerbation history could only be informed by data relating to the primary analysis populations for benralizumab and reslizumab and only by comparing mepolizumab

with reslizumab and mepolizumab with benralizumab separately. *A priori*, it is also expected that these subgroups represent a very small subset of the patient population, particularly for mepolizumab, considering the patient population will already be subset based on eosinophil count and ACQ score. This means that comparisons performed on these subsets of patients are subject to high uncertainty and low power to detect clinically meaningful differences.

Considering that (1) blood eosinophil counts are the only confirmed effect modifier across all treatments, (2) a reasonable number of patients are available to perform comparisons, and (3) results are available for multiple end points, enabling a holistic comparison across subgroups and end points, comparisons based on blood eosinophil count thresholds are presented in the main body of the article. Results by the remaining subgroups, which can only be performed on a single end point and are based on a small proportion of the overall patient population, are presented in this supplementary document.

Additional subgroup analyses

Additional analyses were performed in the following subgroups based on data availability.

- For mepolizumab and benralizumab only: patients with blood eosinophil counts of 300 cells/ μ L or greater, ACQ scores of 1.5 or greater, and 3 or more exacerbations in the previous year and patients with blood eosinophil counts of 300 cells/ μ L or greater, ACQ scores of 1.5 or greater, and 4 or more exacerbations in the previous year.
- For mepolizumab and reslizumab only: patients with blood eosinophil counts of 400 cells/ μ L or greater, ACQ scores of 1.5 or greater, and 4 or more exacerbations in the previous year.

Indirect treatment effect estimates

The indirect treatment effect of drug A versus drug B (μ_{AB}) was estimated by using the combined treatment effects and associated SEs of each drug against placebo (C) obtained from the pairwise comparisons (mean difference for ACQ score and FEV₁ and log RR for exacerbations) of A versus C (μ_{AC} , $SE(\mu_{AB})$) and B versus C (μ_{BC} , $SE(\mu_{BC})$), as follows:

$$\begin{aligned}\mu_{AB} &= \mu_{AC} - \mu_{BC} \\ \text{var}(\mu_{AB}) &= \text{var}(\mu_{AC}) + \text{var}(\mu_{BC}) \\ SE(\mu_{AB}) &= \sqrt{SE(\mu_{AC})^2 + SE(\mu_{BC})^2}.\end{aligned}$$

Assessment of study duration

The duration of studies included in the ITC ranged from 15 to 56 weeks ([Table E3](#)).^{E1-E8}

Differences in study duration among included studies can potentially bias results. Therefore an assessment of the potential effect of differences in study duration was carried out to determine the extent of bias that could be expected. This assessment was carried out separately for each end point and was composed of the following evaluation:

1. Evaluation of individual study results by time: Where individual study results were available by time point, the variability of the end point measure was assessed qualitatively.
2. Evaluation of heterogeneity between studies: The I^2 statistic indicates the level of homogeneity between different treatment effects. In general, a statistic of 50% or less indicates that the treatment effects observed in different studies are consistent (ie, there is no evidence of heterogeneity). A statistic of greater than 50% indicates some evidence of heterogeneity. The presence of heterogeneity is not necessarily indicative of bias from study duration alone. However, if heterogeneity is present and the studies included present with different study duration, it could be hypothesized that this heterogeneity can be affected by different study durations.

End point 1: Exacerbations (clinically significant exacerbations and exacerbations requiring ED visits/hospitalizations). In all included studies the analysis of exacerbations took into account the amount of follow-up time contributed by each patient to estimate treatment effects. Therefore the treatment effect estimate, expressed as an RR, is dissociated with time; that is, the treatment effect would remain unchanged regardless of the length of study.

Table E4 summarizes estimates of heterogeneity across studies for each treatment. There was no evidence of heterogeneity among the mepolizumab and reslizumab studies. A high degree of heterogeneity was observed among benralizumab studies; however, these studies were of comparable length, and therefore the observed heterogeneity is unlikely to be due to study duration.

In addition, one published meta-analysis of mepolizumab studies, which combined data from 2 studies of 32 (MENSA) and 52 (DREAM) weeks' duration, reported consistent findings across studies within all investigated subgroups.^{E9}

As a result of this assessment, it was found to be very unlikely that study duration would affect comparisons when using estimates of the RR for the included treatments. Therefore further adjustment for study duration was not deemed necessary.

End point 2: Change from baseline ACQ score. Evidence regarding the time dependency of the treatment difference in change from baseline ACQ score was consistent across the 3 treatments.

For reslizumab, the primary publication of study 1 and study 2, which were of 52 weeks' duration, reported the treatment difference in change from baseline ACQ score results for weeks 16 and 52 (Table E5).

Results between weeks 16 and 52 were consistent, with one study reporting slightly more favorable results at week 16 and the other for week 52. For both studies combined, week 52 results yielded slightly more favorable results than week 16.

For benralizumab, the SIROCCO and CALIMA studies did not report treatment differences for other time points than the end of the study. However, Appendices 13 and 11 of SIROCCO and CALIMA publications, respectively, present a figure of change from baseline in total asthma symptom score by study visit. Although a downward trend is observed within each treatment through time, the difference between treatments remains consistent from approximately week 16. Of note, however, a slight increase in separation between 30 mg of benralizumab Q8W and placebo is observed after week 42. Although total asthma symptoms and ACQ scores are not the same measure, the 2 measures are expected to be strongly correlated because they measure similar concepts.

For mepolizumab, the MENSA and MUSCA studies, of 32 and 24 weeks' duration, respectively, consistently showed similar treatment differences in the change from baseline ACQ score from week 16 onward (Fig E4: MENSA and Fig 4: MUSCA).^{E1,E2} Results from DREAM, a 52-week study that investigated mepolizumab but that did not include the 100-mg subcutaneous dose, also show no clear further differentiation between treatments from week 16 onward (Fig 3, D).^{E10}

Table E6 summarizes estimates of heterogeneity across studies for each treatment. There was no evidence of heterogeneity among the mepolizumab and reslizumab studies.

As a result of this assessment, it was found unlikely that study duration would have a large effect on comparisons when using estimates of treatment difference in the change from baseline ACQ score for the included treatments. Based on benralizumab and reslizumab data, the likely effect would be that results from studies with longer follow-up (up to 56 weeks) would yield slightly more favorable treatment differences versus shorter studies. Therefore further adjustment for study duration was not deemed necessary.

End point 3: Change from baseline prebronchodilator FEV₁. Evidence regarding the time dependency of the treatment

difference in change from baseline prebronchodilator FEV₁ score was consistent across the 3 treatments.

For reslizumab, the primary publication of study 1 and study 2, which were of 52 weeks' duration, reported the treatment difference in change from baseline prebronchodilator FEV₁ results for weeks 16 and 52. Results between week 16 and week 52 were very consistent (Table E7).

For benralizumab, Fig 3 in the SIROCCO and CALIMA primary publications show the change from baseline FEV₁ at each study visit. Although an upward trend was observed across time within each treatment arm, the difference between treatment arms remained consistent from week 8 onward, with 1 study (SIROCCO) showing slight increases in the difference between treatments from weeks 40 to 48.

For mepolizumab, the MENSA and MUSCA studies, of 32 and 24 weeks' duration, respectively, consistently showed similar treatment differences in the change from baseline prebronchodilator FEV₁ from week 16 onward (Fig 2: MENSA; Fig 4, MUSCA).^{E1,E2}

Table E8 summarizes estimates of heterogeneity across studies for each treatment. There was no evidence of heterogeneity among the mepolizumab and reslizumab studies.

As a result of this assessment, it was found unlikely that study duration would have a large effect on comparisons when using estimates of treatment difference in the change from baseline FEV₁ for the included treatments. Therefore further adjustment for study duration was not deemed necessary.

RESULTS

Additional subgroup analyses for mepolizumab and benralizumab

Mepolizumab and benralizumab both significantly reduced the rate of clinically significant exacerbations compared with placebo among all additional subgroups investigated (Table E10).

Among patients with blood eosinophil counts of 300 cells/ μ L or greater, ACQ scores of 1.5 or greater, and 3 or more exacerbations in the previous year, mepolizumab significantly reduced the rate of clinically significant exacerbations by 39% (95% CI, 1-62; $P = .045$) compared with benralizumab (Table E10). Among patients with blood eosinophil counts of 300 cells/ μ L or greater, ACQ scores of 1.5 or greater, and 4 or more exacerbations in the previous year, mepolizumab significantly reduced the rate of clinically significant exacerbations by 50% (95% CI, 6-73; $P = .030$) compared with benralizumab (Table E10).

The P-score for mepolizumab and benralizumab for each additional analysis subgroup is presented in Table E11. P-scores for mepolizumab ranged from 0.989 to 0.992 across the considered populations compared with a range of 0.511 to 0.508 for benralizumab, indicating a very high probability of superiority for mepolizumab compared with benralizumab.

Additional subgroup analyses for mepolizumab and reslizumab

Mepolizumab and reslizumab both significantly reduced the rate of clinically significant exacerbations compared with placebo in all subgroups investigated (Table E12).

Among patients with blood eosinophil counts of 400 cells/ μ L or greater, ACQ scores of 1.5 or greater, and 4 or more exacerbations in the previous year, mepolizumab significantly reduced the rate of clinically significant exacerbations by 60% (95% CI, 7-83; $P = .034$; P-score = 0.987) compared with reslizumab (P-score = 0.513; Tables E12 and E13).

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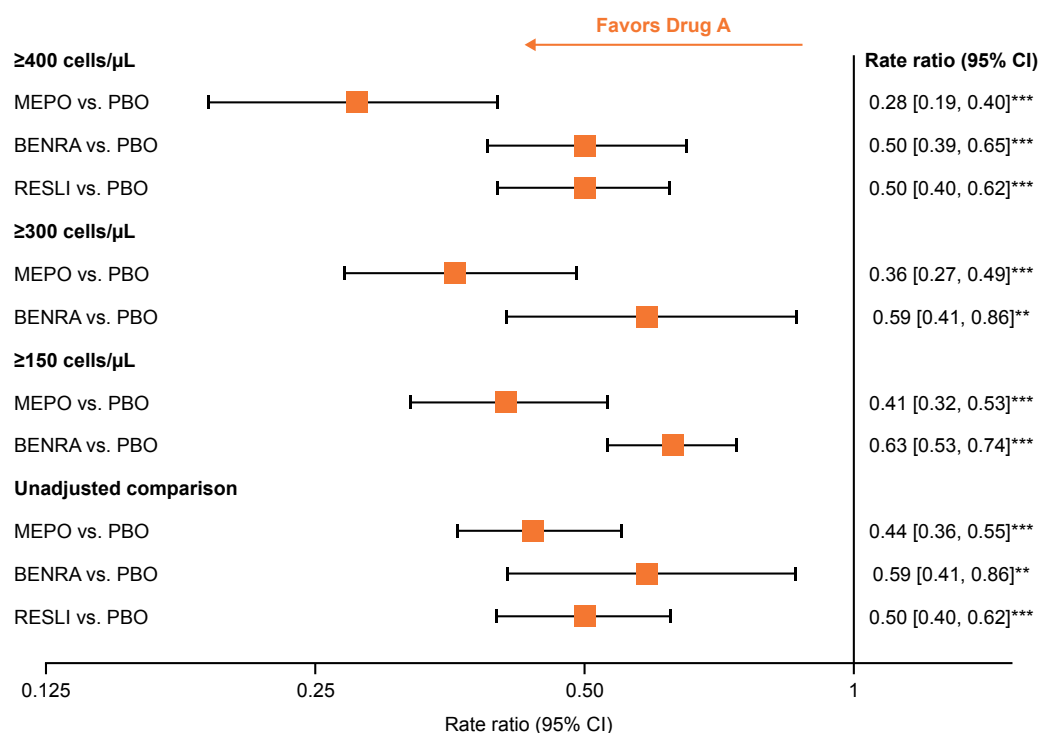


FIG E1. Treatment comparison with placebo on the rate of clinically significant exacerbations in baseline blood eosinophil count subgroups and the ITT population. ** $P < .01$ and *** $P < .001$. Comparisons are presented as drug versus placebo. Not all comparisons were possible at each blood eosinophil count threshold because of a lack of data from included studies. *BENRA*, Thirty milligrams of benralizumab Q8W; *MEPO*, 100 mg of mepolizumab administered subcutaneously; *PBO*, placebo; *RESLI*, 3 mg/kg reslizumab; *SC*, subcutaneous.

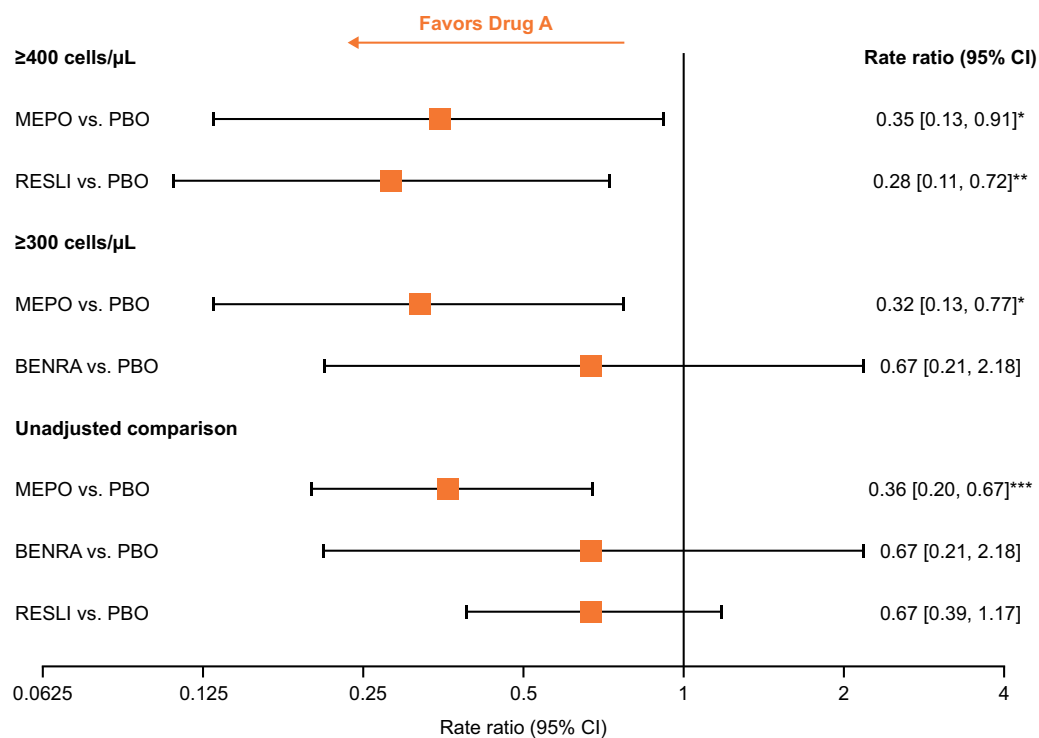


FIG E2. Treatment comparison with placebo on the rate of exacerbations requiring ED visits/hospitalizations in baseline blood eosinophil count subgroups and the ITT population. * $P < .05$, ** $P < .01$, and *** $P = .001$. Comparisons are presented as drug versus placebo. Not all comparisons were possible at each blood eosinophil count threshold because of a lack of data from included studies. *BENRA*, Thirty milligrams of benralizumab Q8W; *MEPO*, 100 mg of mepolizumab administered subcutaneously; *PBO*, placebo; *RESLI*, 3 mg/kg reslizumab; *SC*, subcutaneous.

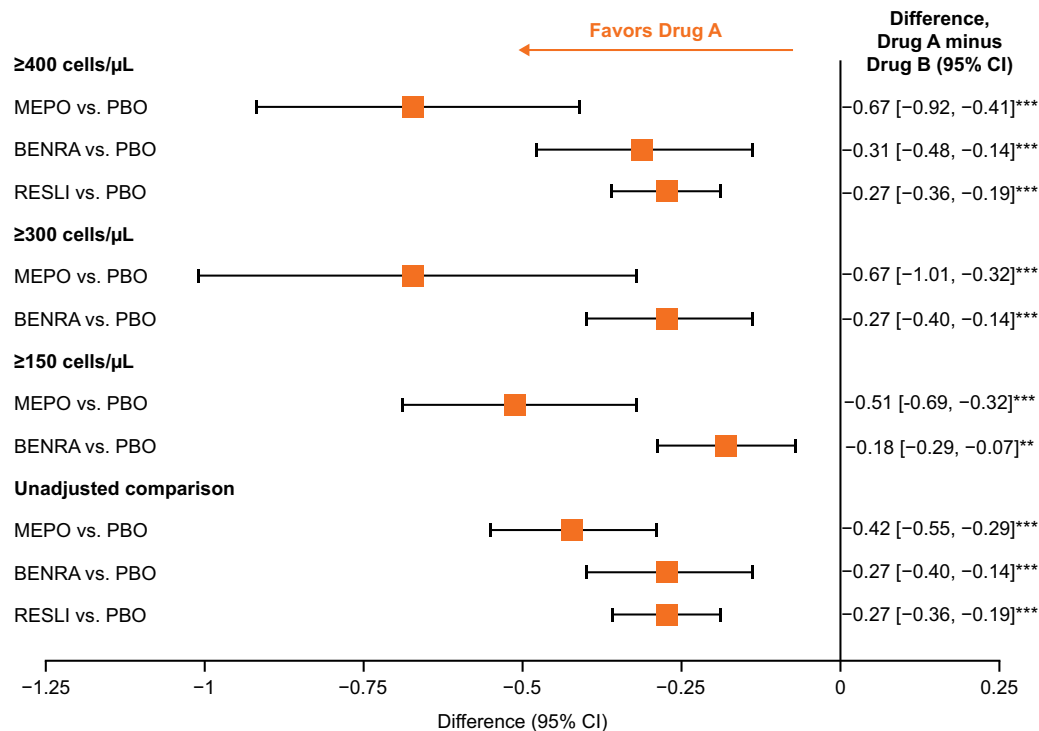


FIG E3. Treatment comparison with placebo on change from baseline in ACQ score in baseline blood eosinophil count subgroups and the ITT population. ** $P < .01$ and *** $P < .001$. Comparisons are presented as drug versus placebo. Not all comparisons were possible at each blood eosinophil count threshold because of a lack of data from included studies. *BENRA*, Thirty milligrams of benralizumab Q8W; *MEPO*, 100 mg of mepolizumab administered subcutaneously; *PBO*, placebo; *RESLI*, 3 mg/kg reslizumab 3; *SC*, subcutaneous.

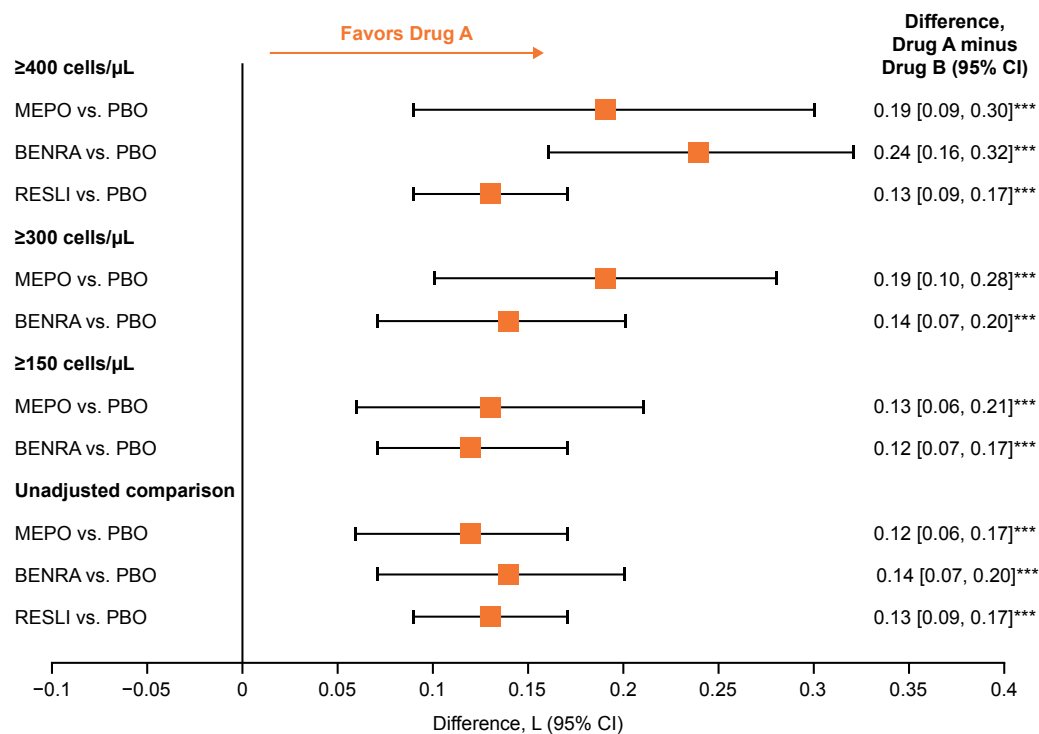


FIG E4. Treatment comparison with placebo on change from baseline in prebronchodilator FEV₁ (liters) in baseline blood eosinophil count subgroups and the ITT population. *** $P < .001$. Comparisons are presented as drug versus placebo. Not all comparisons were possible at each blood eosinophil count threshold because of a lack of data from included studies. *BENRA*, Thirty milligrams of benralizumab Q8W; *MEPO*, 100 mg of mepolizumab administered subcutaneously; *PBO*, placebo; *RESLI*, 3 mg/kg reslizumab; *SC*, subcutaneous.

TABLE E1. Subgroup feasibility assessment

Characteristics	Conclusive evidence of effect modification	Difference between studies	Data availability	
			Benralizumab	Reslizumab
Age	No	NA	Not assessed	Not assessed
Sex	No	NA	Not assessed	Not assessed
Race	No	NA	Not assessed	Not assessed
BMI	No	NA	Not assessed	Not assessed
Smoking history	No	NA	Not assessed	Not assessed
Maintenance OCS use	No*	NA	Primary population only	Primary population only
Eosinophil counts	Yes	Yes	Available (≥ 0 , ≥ 150 , ≥ 300 , ≥ 450)	Not available (primary population ≥ 400)
ACQ score	Yes	Yes	Not available (primary population ≥ 1.5)	Not available (primary population ≥ 1.5)
FEV ₁ (% predicted)	No	NA	Not assessed	Not assessed
FEV ₁ reversibility	No	NA	Not assessed	Not assessed
Exacerbation history	Yes	Yes	Yes (=2, =3, ≥ 3 , ≥ 4)	Yes (=1, =2, =3, ≥ 4)

BMI, Body mass index; *NA*, not applicable because there was no evidence of effect modification.

*For maintenance OCS use, there was no conclusive evidence of effect modification: there was conflicting evidence of effect modification by maintenance OCS use between studies and treatments where results in similar directions would be expected to be plausible. Evidence from exacerbation reduction studies was not deemed of interest for informing clinical practice because OCS doses were maintained constant in the included trials to avoid interference with exacerbation reduction, whereas in clinical practice this dose would be reduced. Regional differences between studies among OCS users would make comparisons among OCS users extremely challenging to interpret because clinical practice differs considerably between countries with regards to OCS use and dose. Note: Data availability for mepolizumab was not assessed because individual data were available to perform additional analysis.

TABLE E2. End points available for assessment

Subgroup	Blood eosinophil count threshold								
	≥150			≥300			≥400		
	Mepolizumab	Benralizumab	Reslizumab	Mepolizumab	Benralizumab	Reslizumab	Mepolizumab	Benralizumab	Reslizumab
Blood eosinophils	Exacerbations ACQ FEV ₁ ED/hospitalization	Exacerbations ACQ FEV ₁	NR	Exacerbations ACQ FEV ₁ ED/hospitalization	Exacerbations ACQ FEV ₁ ED/hospitalization	NR	Exacerbations ACQ FEV ₁ ED/hospitalization	Exacerbations ACQ FEV ₁ (≥450)	Exacerbations ACQ FEV ₁ ED/hospitalization
Exacerbation history ≥3	Exacerbations ACQ FEV ₁ ED/hospitalization	NR	NR	Exacerbations ACQ FEV ₁ ED/hospitalization	Exacerbations ACQ FEV ₁ ED/hospitalization	NR	Exacerbations ACQ FEV ₁ ED/hospitalization	NR	NR
Exacerbation history ≥4	Exacerbations ACQ FEV ₁ ED/hospitalization	NR	NR	Exacerbations ACQ FEV ₁ ED/hospitalization	Exacerbations ACQ FEV ₁ ED/hospitalization	NR	Exacerbations ACQ FEV ₁ ED/hospitalization	NR	Exacerbations

History of 2 or more exacerbations was an entry criterion for mepolizumab and benralizumab studies but not for reslizumab studies. Data on history of 2 or more exacerbations were not available for reslizumab.
 NR, Not reported.

TABLE E3. Duration of mepolizumab studies included in the ITC

Treatment	Study	Duration (wk)
Mepolizumab	MENSA ^{E1}	32
Mepolizumab	MUSCA ^{E2}	24
Reslizumab	Study 1 ^{E3}	52
Reslizumab	Study 2 ^{E3}	52
Reslizumab	Castro et al, 2011 ^{E4}	15
Reslizumab	NCT01508936 ^{E5}	16
Reslizumab	NCT01270464 ^{E6}	16
Benralizumab	SIROCCO ^{E7}	48
Benralizumab	CALIMA ^{E8}	56

TABLE E4. Estimates of heterogeneity across studies for exacerbations

Treatment	Included studies	Range of duration (wk)	I^2 (ITT)
Mepolizumab	MENSA, MUSCA	24–32	0%
Reslizumab	Study 1, study 2*	52	0%
Benralizumab	SIROCCO, CALIMA	48–56	73% to 86%

*Other reslizumab studies were not included in this analysis because they did not have clinically significant exacerbations or exacerbations requiring ED visit/hospitalization as end points.

TABLE E5. Duration of reslizumab studies included in the ITC

	Study 1	Study 2	Pooled data
Week 16	−0.27	−0.20	−0.23
Week 52	−0.26	−0.24	−0.25

TABLE E6. Estimates of heterogeneity across studies for ACQ score

Treatment	Included studies	Range of duration (wk)	I^2 (ITT)
Mepolizumab	MENSA, MUSCA	24–32	0%
Reslizumab	Study 1; study 2; Castro et al, 2011; NCT01508936; NCT01270464	15–52	0%
Benralizumab	SIROCCO, CALIMA	48–56	0%

TABLE E7. Treatment difference in change from baseline
prebronchodilator FEV₁ at weeks 16 and 52

	Study 1	Study 2	Pooled data
Week 16	0.14	0.09	0.12
Week 52	0.13	0.09	0.11

TABLE E8. Estimates of heterogeneity across studies for prebronchodilator FEV₁

Treatment	Included studies	Range of duration (wk)	<i>I</i> ² (ITT)
Mepolizumab	MENSA, MUSCA	24–32	0%
Reslizumab	Study 1; study 2; Castro et al, 2011; NCT01508936; NCT01270464	15–52	13%
Benralizumab	SIROCCO, CALIMA	48–56	0%

TABLE E9. Summary of treatment ranks and P-scores for mepolizumab, reslizumab, and benralizumab for each end point by baseline blood eosinophil count subgroup and in the ITT population

	Treatment rank (P-score)		
	1	2	3
Clinically significant exacerbations			
≥400 cells/μL	MEPO (0.997)	RESLI (0.504)	BENRA (0.499)
≥300 cells/μL	MEPO (0.998)	BENRA (0.510)	—
≥150 cells/μL	MEPO (0.998)	BENRA*	—
Unadjusted comparison	MEPO (0.917)	RESLI (0.699)	BENRA (0.384)
Exacerbations requiring ED visits/hospitalizations			
≥400 cells/μL	RESLI† (0.810)	MEPO (0.681)	—
≥300 cells/μL	MEPO (0.956)	BENRA (0.455)	—
Unadjusted comparison	MEPO (0.952)	RESLI (0.483)	BENRA (0.477)
Asthma control score			
≥400 cells/μL	MEPO (0.995)	BENRA (0.552)	RESLI (0.453)
≥300 cells/μL	MEPO (0.991)	BENRA (0.501)	—
≥150 cells/μL	MEPO (0.999)	BENRA*	—
Unadjusted comparison	MEPO (0.970)	RESLI (0.519)	BENRA (0.511)
Prebronchodilator FEV ₁			
≥400 cells/μL	BENRA (0.915)	MEPO (0.697)	RESLI (0.389)
≥300 cells/μL	MEPO (0.910)	BENRA (0.590)	—
≥150 cells/μL	MEPO (0.808)	BENRA*	—
Unadjusted comparison	BENRA (0.744)	RESLI (0.716)	MEPO (0.540)

P-scores indicate the probability that a treatment is superior to the average treatment. A P-score of 0.5 indicates that the treatment is no different from the average of the treatments, whereas a P-score >0.5 indicates that the treatment is superior to the average treatment. Treatments can be ranked according to P-scores, whereby the treatment with the highest P-score can be ranked as best.

BENRA, Thirty milligrams of benralizumab Q8W; *MEPO*, 100 mg of mepolizumab administered subcutaneously; *RESLI*, 3 mg/kg reslizumab.

*Data for the 150 cells/μL or greater subgroup were reported in the published benralizumab pooled analysis only.

†Data for the end point of exacerbations requiring ED visits/hospitalizations were reported in the published reslizumab pooled analysis. Patients had 2 or more exacerbations in the past year and GINA step 4/5 therapy.

TABLE E10. Treatment comparison on the rate of clinically significant exacerbations by exacerbation history (mepolizumab compared with benralizumab)

	Clinically significant exacerbations, RR (95% CI)	
	≥3 Exacerbations in prior year	≥4 Exacerbations in prior year
MEPO vs PBO	0.28 (0.19-0.41)†	0.23 (0.14-0.37)†
BENRA vs PBO	0.46 (0.35-0.61)†	0.46 (0.31-0.68)†
MEPO vs BENRA	0.61 (0.38-0.99)*	0.50 (0.27-0.94)*

All patients had baseline blood eosinophil counts of 300 cells/ μ L or greater plus ACQ score of 1.5 or greater.

BENRA, Thirty milligrams of benralizumab Q8W; *MEPO*, 100 mg of mepolizumab administered subcutaneously; *PBO*, placebo.

* $P < .05$ and † $P < .001$.

TABLE E11. P-scores for mepolizumab and benralizumab by patient population

	Mepolizumab, 100 mg SC	Benralizumab, 30 mg Q8W
Blood eosinophil count ≥300 cells/μL, ACQ score ≥1.5, and ≥3 exacerbations in prior year	0.989	0.511
Blood eosinophils ≥300 cells/μL, ACQ score ≥1.5, and ≥4 exacerbations in prior year	0.992	0.508

P-scores indicate the probability that a treatment is superior to the average treatment. A P-score of 0.5 indicates that the treatment is no different from the average of the treatments, whereas a P-score >0.5 indicates that the treatment is superior to the average treatment. Treatments can be ranked according to P-scores, whereby the treatment with the highest P-score can be ranked as best.

SC, Subcutaneous.

TABLE E12. Treatment comparison on the rate of clinically significant exacerbations by exacerbation history (mepolizumab compared with reslizumab)

	Clinically significant exacerbations, RR (95% CI)
	≥ 4 Exacerbations in prior year
MEPO vs PBO	0.14 (0.07-0.29)†
RESLI vs PBO	0.36 (0.22-0.58)†
MEPO vs RESLI	0.40 (0.17-0.93)*

All patients had baseline blood eosinophil counts of 400 cells/ μ L or greater plus ACQ scores of 1.5 or greater.

MEPO, 100 mg of mepolizumab administered subcutaneously; PBO, placebo; RESLI, 3 mg/kg reslizumab.

* $P < .05$ and † $P < .001$.

TABLE E13. P-scores for mepolizumab and reslizumab by patient population

	Mepolizumab, 100 mg SC	Reslizumab, 3 mg/kg
Blood eosinophil count ≥400 cells/μL, ACQ score ≥1.5, and ≥4 exacerbations in prior year	0.987	0.513

P-scores indicate the probability that a treatment is superior to the average treatment. A P-score of 0.5 indicates that the treatment is no different from the average of the treatments, whereas a P-score >0.5 indicates that the treatment is superior to the average treatment. Treatments can be ranked according to P-scores, whereby the treatment with the highest P-score can be ranked as best.
SC, Subcutaneous.