Matching-Adjusted Indirect Comparison of Benralizumab vs. Mepolizumab and Reslizumab: Systematic Review

APPENDICES

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APPENDIX 1: METHODS

Systematic Review

This systematic review was conducted in accordance with the University of York Centre for Reviews and Dissemination standards and Cochrane standards. The purpose of the review was to identify randomised controlled trials that evaluated efficacy, safety, and tolerability of biologic treatments for patients with severe, uncontrolled asthma receiving medium- or high-dosage inhaled corticosteroids (ICS) plus an additional controller medication. A full protocol was developed for searching, screening, extracting information, and evaluating the data; the protocol was not registered.

Data sources included biomedical databases, conference proceedings, bibliographies, and clinical trial registries. Databases were searched from study inception to 3 August 2016, and included Embase®, MEDLINE®, MEDLINE® In-Process, and Cochrane Central Register of Controlled Trials (CENTRAL) (**Table S1**). On 18 July 2016, the past 3 years of the American Thoracic Society, European Respiratory Society, and American College of Chest Physician conference proceedings were searched for studies that were not yet published in journals as full-text articles. The online clinical trial registries included ClinicalTrials.gov, the World Health Organization Indicator Metadata Registry, the Australian New Zealand Clinical Trials Registry, the European Union Clinical Trials Register, and PharmNet.Bund Klinische Prüfungen and Arzneimittel-Informationssystem. Manufacturer websites also were searched for unpublished data, such as clinical study reports.

Predefined eligibility criteria (specific patient populations, interventions, treatment comparators, outcomes, and study designs [**Table S2**]) were applied to the search results. Eligible studies were identified by the systematic application of criteria by two independent reviewers, with discrepancies adjudicated by a third reviewer. Methods for selection, extraction, and feasibility analyses are depicted in **Figure S1**.

Selection of Treatment Modifiers for MAIC Analysis

We identified potential treatment effect modifiers through the following multi-step process: open elicitation of opinions from asthma experts, literature search for variables that modified treatment effects in studies of severe asthma, univariate and multivariate analysis of SIROCCO and CALIMA data to determine statistical predictors of outcomes of interest, and assessment of methods and baseline characteristics for trials included in the MAIC to determine which predictor variables were different across comparator trial populations.

Benralizumab vs. mepolizumab modifiers. Although the benralizumab and mepolizumab trial designs were similar overall, they varied in their definition of ICS dosage and eosinophil count required at baseline as well as treatment duration (SIROCCO, 48 weeks; CALIMA, 56 weeks; MENSA, 32 weeks; DREAM, 52 weeks). The populations also differed in baseline eosinophil count, prior history of exacerbations, and the percentage of patients using OCS at baseline. Based on their clinical and statistical importance in explaining variability in the outcomes of interest, the following variables were selected for matching: eosinophil count (≥300 cells/μL vs. <300 cells/μL), IgE count (<30 IU/mL vs. >30–≤700 IU/mL vs. >700 IU/mL), exacerbations in the previous 12 months (two vs. more than two), presence of nasal polyps, mean body mass index, sex, and maintenance OCS use.

Benralizumab vs. reslizumab modifiers. The study inclusion criteria for benralizumab vs. reslizumab differed in terms of disease severity, medium-dosage ICS definition and dosage at baseline, exacerbation history in the previous year, and baseline eosinophil count. A comparison of baseline characteristics for the two populations demonstrated that number of exacerbations in the prior year was greater for the benralizumab studies and baseline eosinophil count was greater in the reslizumab studies. Based on their clinical and statistical importance in explaining variability in the outcomes of interest, the following variables were selected for matching: mean baseline eosinophil count, mean number of exacerbations in the previous 12 months, sex, and maintenance OCS use.

Benralizumab vs. Mepolizumab: Sensitivity Analyses

The mepolizumab MUSCA trial [1] was not included in the systematic review because it was not published at the time. Therefore, it was not included in the main benralizumab vs. mepolizumab matching-adjusted indirect comparison (MAIC) analysis. However, MUSCA was included in sensitivity analyses of exacerbations and prebronchodilator forced expiratory volume in 1 second (FEV_1) at Week 24.

Table S1. Database search strategies

Database searched: Embase® and MEDLINE® (Embase.com) on 17 June 2016 (without dupilumab).

	Search history	Facet	Hits
1	'asthma'/syn OR 'asthma/de' OR 'severe persistent asthma'/syn OR 'asthma bronchiale' OR 'asthma, bronchial' OR 'asthmatic' OR 'asthmatic subject' OR 'bronchial asthma' OR 'bronchus asthma' OR 'childhood asthma' OR 'chronic asthma' OR 'lung allergy' OR 'inadequately controlled asthma' OR asthma* NEAR/4 (severe OR uncontrol*)	Disease	261,101
2	'prospective study'/exp OR 'randomization'/de OR 'controlled study'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'clinical trial' OR 'clinical trials' OR 'controlled clinical trial' OR 'controlled clinical trials' OR 'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials' OR 'randomisation' OR 'randomization' OR random* OR rct OR 'random allocation' OR 'random assignment' OR 'randomly allocated' OR 'randomly assigned' OR 'allocated randomly' OR 'assigned randomly' OR allocated NEAR/2 random OR assign* NEAR/2 random* OR randomi* OR (single OR double OR triple OR treble) NEAR/1 (blind* OR mask*) OR placebo* OR 'prospective study'/de OR nrct OR 'n rct' OR n?rct OR non NEAR/2 random* OR 'controlled clinical trial'/exp OR 'intervention study'/exp OR (clinical NEXT/1 trial*):ab,ti OR 'major clinical study'/exp OR compar*:ab,ti OR group*:ab,ti OR 'cohort analysis'/exp OR 'longitudinal study'/exp OR 'retrospective study'/exp OR 'follow up'/exp OR cohort*:ab,ti OR (('follow up' OR followup) NEXT/1 (study OR studies)):ab,ti OR 'open study'/exp OR (case* NEXT/1 control*):ab,ti OR 'clinical trial'/exp OR 'clinical article'/exp OR 'survival'/exp OR 'case control study'/exp NOT ('letter'/de OR 'abstract report'/de OR 'case report' OR 'case study'/de)	Study design	12,573,022
3	'biologic agent' OR 'omalizumab'/syn OR 'hu 901' OR 'hu901' OR 'monoclonal antibody e 25' OR 'monoclonal antibody e25' OR 'olizumab' OR 'xolair' OR 'mepolizumab'/syn OR 'bosatria' OR 'nucala' OR 'sb 240563' OR 'sb-240563' OR 'sb240563' OR 'reslizumab'/syn OR 'reslizumab' OR 'sch 55700' OR 'sch55700' OR 'benralizumab'/syn OR 'medi 563' OR 'medi563' OR CINQAIR OR CINQAERO	Interventions	6,926
4	#1 AND #2 AND #3	Combined search	2,601
5	#4 AND [animals]/lim NOT ([humans]/lim AND [animals]/lim)	Animal studies	16

	Search history	Facet	Hits
6	#4 AND ([conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [review]/lim)	Review/editorial	1,042
7	#5 OR #6	Animal studies and reviews	1,058
8	#4 NOT #7	Evidence excluding animal studies and reviews	1,543

Database searched: Cochrane Central Register of Controlled Trials (CENTRAL) on 17 June 2016 (without dupilumab).

	Search history	Facet	Hits
1	MeSH descriptor: [Asthma] explode all trees	Disease	9,789
2	"asthma" or "severe asthma" or "uncontrolled asthma" or "severe persistent asthma" or "inadequately controlled asthma" or "poorly controlled asthma" or "severe allergic asthma" or "asthma bronchiale" or or "asthma, bronchial" or "asthmatic" or "asthmatic subject" or "bronchial asthma" or "bronchus asthma" or "childhood asthma" or "chronic asthma" or "lung allergy" or "moderate to severe asthma"		21,009
3	asthma* near/4 (severe or uncontrol* or persistent)		3,978
4	#1 OR #2 OR #3		27,030
5	"biologic agent" OR "omalizumab" OR "hu 901" OR "hu901" OR "monoclonal antibody e 25" OR "monoclonal antibody e25" OR "olizumab" OR "xolair" OR "mepolizumab" OR "bosatria" OR "nucala" OR "sb 240563" OR "sb-240563" OR "sb240563" OR "reslizumab" OR "sch 55700" OR "sch55700" OR "benralizumab" OR "medi 563" OR "medi563" OR CINQAIR OR CINQAERO	Intervention	687
6	#4 AND #5	Combined	496
7	#6 in Trials (word variations were searched)	Limited to trials	441

Database searched: MEDLINE® In-Process (https://www.ncbi.nlm.nih.gov/pubmed) on 17 June 2016 (without dupilumab).

	Search history	Facet	Hits
1	Asthma OR "severe asthma" OR "uncontrolled asthma" OR "severe persistent asthma" OR "inadequately controlled asthma" OR "poorly controlled asthma" OR "severe allergic asthma" OR "asthma bronchiale" OR "asthma, bronchial" OR "asthmatic" OR "asthmatic subject" OR "bronchial asthma" OR "bronchus asthma" OR "childhood asthma" OR "chronic asthma" OR "lung allergy" OR asthma* near/4 (severe or uncontrol* or persistent) OR "moderate to severe asthma"	Disease	160,619
2	"biologic agent" OR "omalizumab" OR "hu 901" OR "hu901" OR "monoclonal antibody e 25" OR "monoclonal antibody e25" OR "olizumab" OR "xolair" OR "mepolizumab" OR "bosatria" OR "nucala" OR "sb 240563" OR "sb-240563" OR "sb240563" OR "reslizumab" OR "sch 55700" OR "sch55700" OR "benralizumab" OR "medi 563" OR "medi563" OR CINQAIR OR CINQAERO	Intervention	2,196
3	#1 AND #2	Combined	1,153
4	#3 AND (inprocess[sb] OR pubstatusaheadofprint)	Trials in process	91

Database searched: Embase® and MEDLINE® (Embase.com) on 03 August 2016 (with dupilumab).

	Search history	Facet	Hits
1	'asthma'/syn OR 'asthma/de' OR 'severe persistent asthma'/syn OR 'asthma bronchiale' OR 'asthma, bronchial' OR 'asthmatic' OR 'asthmatic subject' OR 'bronchial asthma' OR 'bronchus asthma' OR 'childhood asthma' OR 'chronic asthma' OR 'lung allergy' OR 'inadequately controlled asthma' OR asthma* NEAR/4 (severe OR uncontrol*)	Disease	262,689

	Search history	Facet	Hits
2	'prospective study'/exp OR 'randomization'/de OR 'controlled study'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'clinical trial' OR 'clinical trials' OR 'controlled clinical trial' OR 'controlled clinical trials' OR 'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials' OR 'randomisation' OR 'randomization' OR random* OR rct OR 'random allocation' OR 'random assignment' OR 'randomly allocated' OR 'randomly assigned' OR 'allocated randomly' OR 'assigned randomly' OR allocated NEAR/2 random OR assign* NEAR/2 random* OR randomi* OR (single OR double OR triple OR treble) NEAR/1 (blind* OR mask*) OR placebo* OR 'prospective study'/de OR nrct OR 'n rct' OR n?rct OR non NEAR/2 random* OR 'controlled clinical trial'/exp OR 'intervention study'/exp OR (clinical NEXT/1 trial*):ab,ti OR 'major clinical study'/exp OR compar*:ab,ti OR group*:ab,ti OR 'cohort analysis'/exp OR 'longitudinal study'/exp OR 'retrospective study'/exp OR 'follow up'/exp OR cohort*:ab,ti OR (('follow up' OR followup) NEXT/1 (study OR studies)):ab,ti OR 'open study'/exp OR (case* NEXT/1 control*):ab,ti OR 'clinical trial'/exp OR 'clinical article'/exp OR 'survival'/exp OR 'case control study'/exp NOT ('letter'/de OR 'abstract report'/de OR 'case report' OR 'case study'/de)	Study design	12,682,199
3	'dupilumab'/syn OR 'regn 668' OR 'regn668' OR 'sar 231893' OR 'sar231893'	Interventions	200
4	#1 AND #2 AND #3	Combined search	112
5	#4 AND [animals]/lim NOT ([humans]/lim AND [animals]/lim)	Animal studies	0
6	#4 AND ([conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [review]/lim)	Review/editorial	57
7	#5 OR #6	Animal studies and reviews	57
8	#4 NOT #7	Evidence excluding animal studies and reviews	55

Database searched: Cochrane Central Register of Controlled Trials (CENTRAL) on 03 August 2016 (with dupilumab).

	Search history	Facet	Hits
1	MeSH descriptor: [Asthma] explode all trees	Disease	9,866

	Search history	Facet	Hits
2	"asthma" or "severe asthma" or "uncontrolled asthma" or "severe persistent asthma" or "inadequately controlled asthma" or "poorly controlled asthma" or "severe allergic asthma" or "asthma bronchiale" or "asthma, bronchial" or "asthmatic" or "asthmatic subject" or "bronchial asthma" or "bronchus asthma" or "childhood asthma" or "chronic asthma" or "lung allergy" or "moderate to severe asthma"		27,303
3	asthma* near/4 (severe or uncontrol* or persistent)		4,056
4	#1 OR #2 OR #3		27,323
5	'dupilumab'/syn OR 'regn 668' OR 'regn668' OR 'sar 231893' OR 'sar231893'	Intervention	36
6	#4 AND #5	Combined	21
7	#6 in Trials (word variations were searched)	Limited to trials	21

Database searched: MEDLINE® In-Process (https://www.ncbi.nlm.nih.gov/pubmed) on 03 August 2016 (with dupilumab).

	Search history	Facet	Hits
1	Asthma OR "severe asthma" OR "uncontrolled asthma" OR "severe persistent asthma" OR "inadequately controlled asthma" OR "poorly controlled asthma" OR "severe allergic asthma" OR "asthma bronchiale" OR "asthma, bronchial" OR "asthmatic" OR "asthmatic subject" OR "bronchial asthma" OR "bronchus asthma" OR "childhood asthma" OR "chronic asthma" OR "lung allergy" OR asthma* near/4 (severe or uncontrol* or persistent) OR "moderate to severe asthma"	Disease	161,773
2	'dupilumab'/syn OR 'regn 668' OR 'regn668' OR 'sar 231893' OR 'sar231893'	Intervention	55
3	#1 AND #2	Combined	32
4	#3 AND (inprocess[sb] OR pubstatusaheadofprint)	Trials in process	8

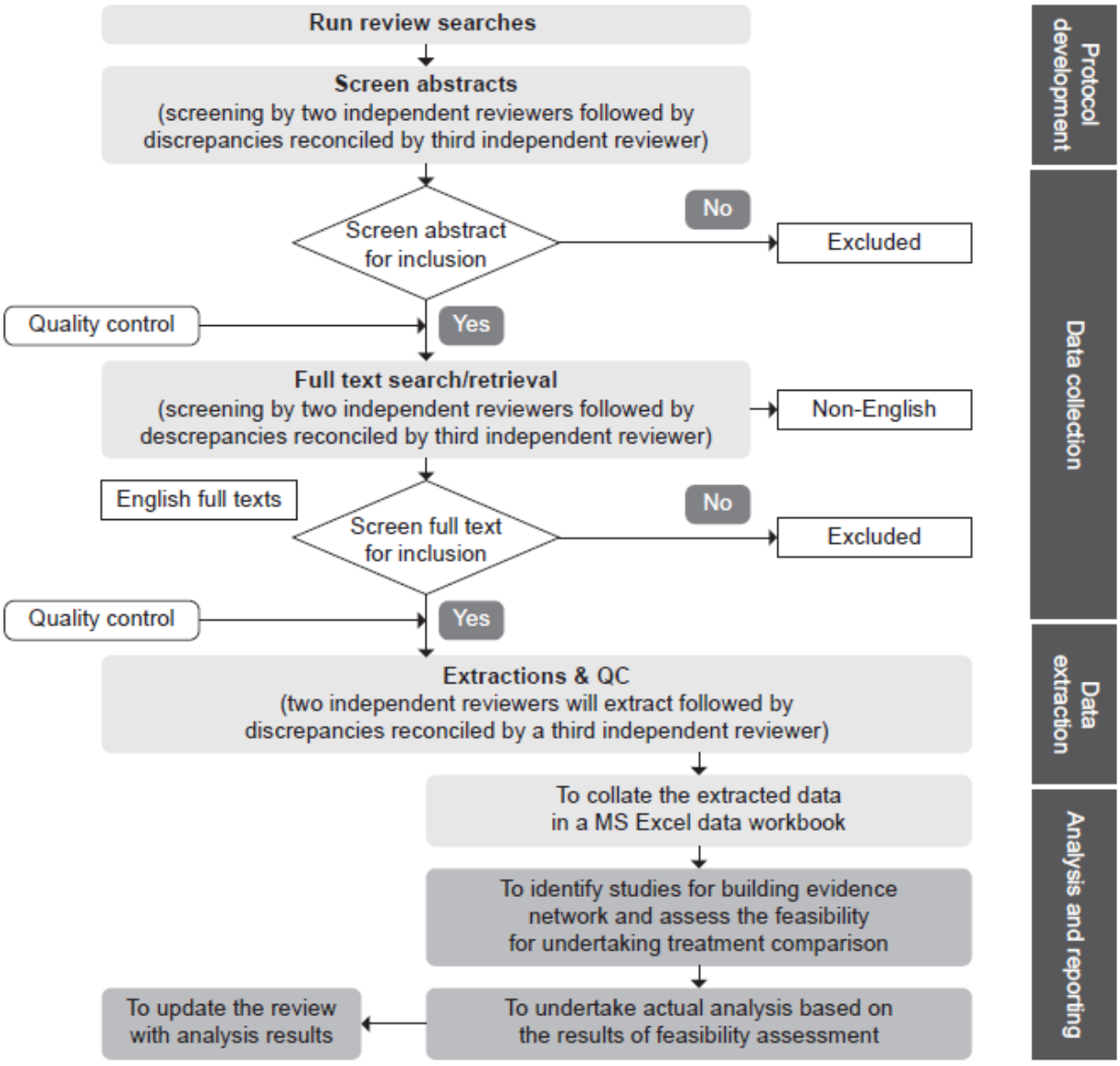
Table S2. Eligibility criteria applied to the search results

Eligibility criteria	
Patient population	Age: adults (≥18 years) and adolescents (≥12–18 years) Sex: any Race: any Disease: severe asthma that is uncontrolled despite treatment with medium- to high-dosage ICS plus ≥1 additional controller
Interventions	Biologics (approved and in development): Benralizumab Mepolizumab Omalizumab Reslizumab Dupilumab
Treatment comparators	Placebo/best supportive care Medium- or high-dosage ICS plus ≥1 additional controller Medium-dosage ICS plus 1 additional controller (e.g., LABA/LTRA/LAMA/theophylline) High-dosage ICS plus 1 additional controller (e.g., LABA/LTRA/LAMA/theophylline) High-dosage ICS plus 2 additional controllers (e.g., LABA+LAMA/LABA+LTRA) High-dosage ICS plus ≥1 additional asthma controller + OCS maintenance treatment
Outcomes of interest	Efficacy and quality-of-life outcomes: Prebronchodilator FEV_1 Postbronchodilator FEV_1 Peak expiratory flow Asthma exacerbation (overall exacerbation, exacerbations requiring systemic CS, ER visit and/or hospitalisation) Definition of exacerbation Number of patients with exacerbations Total number of exacerbations experienced over the duration of the study Mean rate of exacerbations per patient per year Time to first exacerbation Symptom-free days Asthma control measured by ACQ Asthma symptoms (overall, daytime, night-time symptom, night-time awakening) OCS-sparing efficacy AQLQ or mini-AQLQ SGRQ EQ-5D WPAI

	Safety outcomes: Any adverse events Any serious adverse events Any treatment-related adverse events Bronchitis Cardiac events Cough Dry mouth Hoarseness or dysphonia Mortality Nausea Oral candidiasis Pneumonia Palpitations Sinusitis Tremor Upper respiratory tract infections
	Tolerability: All withdrawals Withdrawal due to adverse events Withdrawal due to lack of efficacy
Study designs	RCTs
Language	Database to be searched irrespective of language English language studies were included in systematic review
Publication timeframe	Database inception to present date (searched on 3 August 2016) Conference proceedings for past 3 years (searched on 18 July 2016)

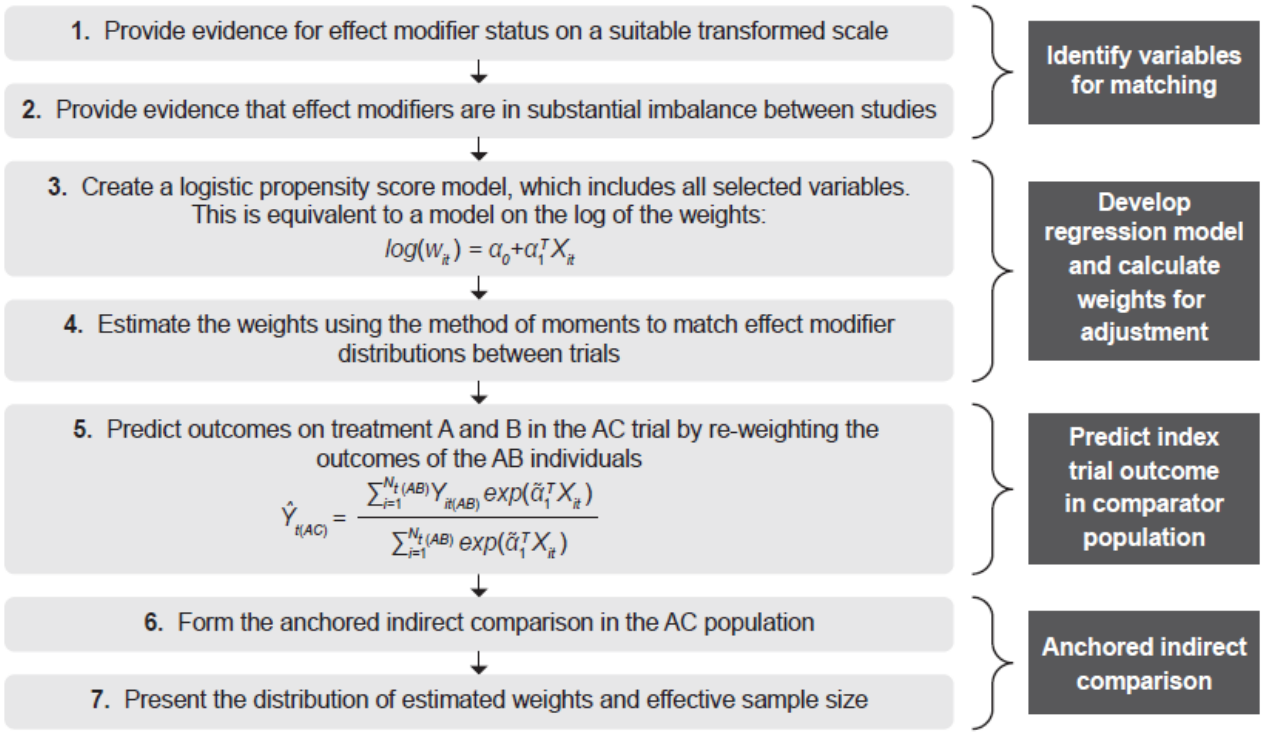
ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CS, corticosteroid; ER, emergency room; EQ-5D, EuroQOL 5D; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; RCT, randomised controlled trial; SGRQ, St. George's Respiratory Questionnaire; WPAI, Work Productivity and Activity Impairment.

Figure S1. Methods for conducting the systematic review



MS, Microsoft; QC, quality check.

Figure S2. Anchored methods for population-adjusted indirect comparisons



APPENDIX 2: RESULTS

Systematic Review

The database search identified 2,159 references (**Table S2; Figure 1**). Of these, 314 were removed as duplicates and 1,532 were excluded after an initial screen based on title and abstract. The remaining 313 references were evaluated as full-text articles. Of these, 144 references met the inclusion criteria for this review. A search of conference proceedings, bibliographies, and clinical trial registries identified an additional 45 articles. Thus, 189 references representing 32 clinical studies were identified by the systematic review (**Table S3**). Studies of omalizumab and dupilumab were removed. Fifteen studies remained; six evaluated benralizumab, five evaluated mepolizumab, and four evaluated reslizumab as add-on therapy for patients with severe, uncontrolled asthma.

Analysis of Placebo Event Rate Before and After Matching

Matching adjustment may change the size of the placebo effect in the adjusted data set. We evaluated the placebo effect before and after matching as one way to assess performance of the adjustment process. The placebo group exacerbation event rate was greater in MENSA/DREAM (pooled aggregate exacerbation rate=2.0) than in SIROCCO/CALIMA (pooled exacerbation rate=1.27 [95% confidence interval {CI}: 1.19–1.36]). The matching adjustment increased the placebo group's annual exacerbation event rate in SIROCCO/CALIMA from 1.27 to 1.63 (95% CI: 1.52–1.75), making it closer to the aggregate pooled annual exacerbation event rate of 2.0 for the placebo group in MENSA/DREAM.

Benralizumab vs. Mepolizumab: Sensitivity Analysis Including MUSCA

Baseline characteristics and effective sample size

The benralizumab SIROCCO/CALIMA baseline characteristics were well matched to the mepolizumab trial population following adjustment for the mepolizumab MENSA/DREAM/MUSCA population characteristics (**Table S6**). As a result of matching, the effective sample size (ESS) of the benralizumab population decreased from 959 to 770, which was considered adequate for robust MAIC analyses.

Annual rate of clinically significant exacerbations

Benralizumab treatment reduced the annual rate of clinically significant exacerbations vs. placebo by 46% (rate ratio [RR]=0.54) in SIROCCO/CALIMA before matching adjustment and by 49% (RR=0.51) after matching adjustment to the mepolizumab patient population (**Table S8**). Mepolizumab reduced the exacerbation rate in MENSA/DREAM/MUSCA by 52% (RR=0.48) vs. placebo.

Indirect comparison of benralizumab vs. mepolizumab indicated that the treatments were not statistically significantly different in their effects on exacerbations either before (RR=1.2, 95% CI: 0.92–1.36) or after (RR=1.05, 95% CI: 0.86–1.29) matching adjustment.

Annual rate of asthma exacerbations resulting in emergency department visit or hospitalisation

Benralizumab treatment reduced the rate of clinically significant exacerbations leading to emergency department (ED) visit/hospitalisation vs. placebo by 34% (RR=0.66) for patients in SIROCCO/CALIMA before matching adjustment to the mepolizumab patient population and by

45% (RR=0.55) after matching adjustment (**Table S7**). Mepolizumab reduced the exacerbation rate for patients in MENSA/DREAM by 55% (RR=0.45) vs. placebo.

Indirect comparison of benralizumab vs. mepolizumab after matching adjustment indicated comparable efficacy of benralizumab and mepolizumab for reducing exacerbations requiring ED visit or hospitalisation both before (RR=1.47, 95% CI: 0.86–2.49) and after (RR=1.22, 95% CI: 0.71–2.10) matching adjustment.

Prebronchodilator forced expiratory volume in 1 second

Before and after matching, benralizumab and mepolizumab demonstrated similar improvements in prebronchodilator FEV_1 from baseline to Week 24 (**Table S7**). Indirect comparison demonstrated comparable improvement in FEV_1 for benralizumab and mepolizumab before (RR=0.50, 95% CI: −0.05–0.10) and after (RR=0.61, 95% CI: −0.06–0.10) matching.

Table S3. Studies of IL-5–targeted treatments included by the systematic review

Benralizumab

Study	Study phase	Sample size	Interventions	Primary results publication
SIROCCO study NCT01928771 [2]	III	1,205	Benralizumab 30 mg SC Q4W Benralizumab 30 mg SC Q8W[a] Placebo	Bleecker, et al. (2016) [3]
CALIMA study NCT01914757 [4]	III	1,306	Benralizumab 30 mg SC Q4W Benralizumab 30 mg SC Q8W[a] Placebo	Fitzgerald, et al. (2016) [5]
ZONDA study NCT02075255 [6]	III	220	Benralizumab 30 mg SC Q4W Benralizumab 30 mg SC Q8W[a] Placebo	Nair, et al. (2017) [7]
NCT01238861 [8]	II	609	Benralizumab 2 mg SC Benralizumab 20 mg SC Benralizumab 100 mg SC Placebo	Castro, et al. (2014) [9]
NCT01412736 [10]	II	106	Benralizumab 2 mg SC Benralizumab 20 mg SC Benralizumab 100 mg SC Placebo	Park, et al. (2016) [11]
NCT01947946 [12]	III	13	Benralizumab 30 mg Q4W Benralizumab 30 mg Q8W Placebo	
NCT00768079 [13]	II	110	Benralizumab 0.3 mg/kg IV Benralizumab 1 mg/kg IV Placebo	Nowak, et al. (2015) [14]

Mepolizumab

Study	Study phase	Sample size	Interventions	Primary results publication
MENSA study NCT01691521 [15]	III	580	Mepolizumab 100 mg SC Mepolizumab 75 mg IV Placebo	Ortega, et al. (2014) [16]
DREAM study NCT01000506 [17]	IIb/III	621	Mepolizumab 75 mg IV Mepolizumab 250 mg IV Mepolizumab 750 mg IV Placebo	Pavord, et al. (2012) [18]
SIRIUS study NCT01691508 [19]	III	135	Mepolizumab 100 mg SC Placebo	Bel, et al. (2014) [20]
ISRCTN75169762 [21]	II	61	Mepolizumab 750 mg Placebo	Haldar, et al. (2009) [22]
NCT00292877 [23]	II	20	Mepolizumab 750 mg Placebo	Nair, et al. (2009) [24]

Reslizumab

Study	Study phase	Sample size	Interventions	Primary results publication
Study 3082 NCT01287039 [25]	III	489	Reslizumab 3 mg/kg Placebo	Castro, et al. (2015) [26]
Study 3083 NCT01285323 [27]	III	464	Reslizumab 3 mg/kg Placebo	Castro, et al. (2015) [26]
NCT00587288 [28]	II	106	Reslizumab 3 mg/kg Placebo	Castro, et al. (2011) [29]

[a]First three doses given Q4W.

IL, interleukin; IV, intravenously; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneously.

Table S4. Summary of study characteristics of benralizumab, mepolizumab, and reslizumab studies

Study characteristics	Benralizumab		Mepolizumab		Reslizumab	
	SIROCCO [3]	**CALIMA [5]**	**MENSA [16]**	**DREAM [18]**	**Study 3082 [26]**	**Study 3083 [26]**
Publication type	Journal and CSR	Journal and CSR	Journal and CSR	Journal and CSR	Journal	Journal
Interventions	Benralizumab 30 mg Q4W SC	Benralizumab 30 mg Q4W SC	Mepolizumab 75 mg Q4W IV	Mepolizumab 75 mg Q4W IV	Reslizumab 3.0 mg/kg IV	Reslizumab 3.0 mg/kg IV
	Benralizumab 30 mg Q8W SC	Benralizumab 30 mg Q8W SC	Mepolizumab 100 mg Q4W SC	Mepolizumab 250 mg Q4W IV	Placebo	Placebo
	Placebo	Placebo	Placebo	Mepolizumab 750 mg Q4W IV	-	-
	-	-	-	Placebo	-	-
Phase	III	III	III	IIb	III	III
Sample size	1205 (805)[a]	1306 (734)[a]	580	308	489	464
Method of randomisation	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate
Blinding status	Double-blind	Double-blind	Double-blind	Double-blind	Double-blind	Double-blind
Treatment duration	48 weeks	56 weeks	32 weeks	52 weeks	52 weeks	52 weeks
Primary outcome	• Annual rate ratio of asthma exacerbations for patients receiving high-dose ICS + LABA vs placebo with baseline blood EOS ≥300 cells/μL	• Annual rate ratio of asthma exacerbations for patients receiving high-dose ICS + LABA vs placebo with baseline blood EOS ≥300 cells/μL	• Rate of clinically significant exacerbations	• Rate of clinically significant exacerbations	• The frequency of clinical asthma exacerbations per patient during the 52 week treatment period, with events adjudicated by an independent review committee	• The frequency of clinical asthma exacerbations per patient during the 52 week treatment period, with events adjudicated by an independent review committee

The highlighted cells indicate differences across the trials.

*Number in parenthesis represents patients for benralizumab Q8W and placebo arms.

CSR, Clinical Study Report; EOS, eosinophils; ICS:, inhaled corticosteroids; IV, intravenous; LABA, Long-acting beta-2 agonist; Q4W, every four weeks; Q8W, every eight weeks; SC, subcutaneous;

Table S5. Comparison of baseline characteristics of patients before and after matching for the analysis of prebronchodilator FEV_1 change from baseline to the end of each study

	SIROCCO/CALIMA[a] (before adjustment)	MENSA/DREAM (aggregate reported data)	SIROCCO/CALIMA (after adjustment for MENSA/DREAM)
Baseline characteristics	Benralizumab Q8W, placebo N=838	Mepolizumab 75 mg IV, mepolizumab 100 mg SC, placebo N=884	Benralizumab Q8W, placebo Effective sample size=540
Eosinophil count, %			
≥300 cells/μL	67.66	52.45	52.72
<300 cells/μL	32.34	47.55	47.28
Maintenance OCS use, %			
Yes	14.68	26.58[b]	29.83
No	85.32	73.42[b]	70.17
IgE count, %			
≤30 IU/mL	11.00	13.29	14.15
>30–≤700 IU/mL	71.34	70.35	70.39
>700 IU/mL	17.65	16.35	15.45
Sex, %			
Male	36.99	40.05	39.25
Female	63.01	59.95	60.75
Exacerbations in previous year, %			
2	62.65	42.99	43.2
>2	37.35	56.79	56.8
Nasal polyps, %			
No	80.79	86.83	82.99
Yes	19.21	13.17	17.01
BMI, mean (SD)	28.84 (6.32)	27.98 (5.912)	28.36 (6.10)

[a]Includes only patients receiving FP ≥880 µg/d.

[b]Data are extracted from publications rather than clinical study reports.

BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FP, fluticasone propionate; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IV, intravenous; OCS, oral corticosteroid; Q8W, every 8 weeks (first three doses every 4 weeks); SC, subcutaneous; SD, standard deviation.

Table S6. Comparison of baseline characteristics of patients before and after matching for the analysis of prebronchodilator FEV_1 change from baseline to the end of each study (excluding MENSA trial)

	SIROCCO/CALIMA[a] (before adjustment)	DREAM (aggregate reported data)	SIROCCO/CALIMA (after adjustment for DREAM)
Baseline characteristics	Benralizumab Q8W, placebo N=838	Mepolizumab 75 mg IV, placebo N=256	Effective sample size=402
Eosinophil count, %			
≥300 cells/μL	67.66	41.88	40.56
<300 cells/μL	32.34	58.12	59.44
Maintenance OCS use, %			
Yes	14.68	30.84[b]	33.07
No	85.32	69.16[b]	66.93
IgE count, %			
≤30 IU/mL	11.00	12.34	14.60
>30–≤700 IU/mL	71.34	70.45	70.8
>700 IU/mL	17.65	16.88	14.6
Sex, %			
Male	36.99	34.74	32.9
Female	63.01	65.26	67.1
Exacerbations in previous year, %			
2	62.65	43.83	44.38
>2	37.35	55.84	55.62
Nasal polyps, %			
No	80.79	91.3	89.63
Yes	19.21	8.7	10.37
BMI, mean (SD)	28.84 (6.32)	28.35 (6.05)	29.12 (6.48)

[a]Includes only patients receiving FP ≥880 µg/d.

[b]Data are extracted from publications rather than clinical study reports.

BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FP, fluticasone propionate; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IV, intravenous; OCS, oral corticosteroid; Q8W, every 8 weeks (first three doses every 4 weeks); SC, subcutaneous; SD, standard deviation.

Table S7. Benralizumab vs. mepolizumab analysis including MUSCA study: Baseline characteristics of patients before and after matching

	SIROCCO/CALIMA (before adjustment)[a]	MENSA/DREAM/MUSCA (aggregate reported data)	SIROCCO/CALIMA (after adjustment)
Baseline characteristics	Benralizumab Q8W, placebo N=959	Mepolizumab 75 mg IV, mepolizumab 100 mg SC, placebo N=1435	Benralizumab Q8W, placebo Effective sample size=770
Eosinophil count, %			
≥300 cells/μL	67.05	54.28	55.00
<300 cells/μL	32.95	44.78	45.00
Maintenance oral corticosteroid use, %			
Yes	15.22	25.46[b]	25.46
No use	84.78	75.53[b]	75.53
Sex, %			
Male	36.60	40.43	40.43
Female	63.40	59.52	59.52
Exacerbations in the previous year, %			
2	61.63	51.23	51.00
>2	38.37	48.48	49.00
Nasal polyps, %			
No	81.33	84.38	84.38
Yes	18.67	15.61	15.61
BMI, mean (SD)	29.89 (6.27)	28.06 (6.10)	28.06 (5.79)

[a]Includes only patients receiving FP ≥880 μg/d.

[b]Data are extracted from publications rather than clinical study reports.

BMI, body mass index; FP, fluticasone propionate; IV, intravenous; Q8W, every 8 weeks (first three doses every 4 weeks); SC, subcutaneous; SD, standard deviation.

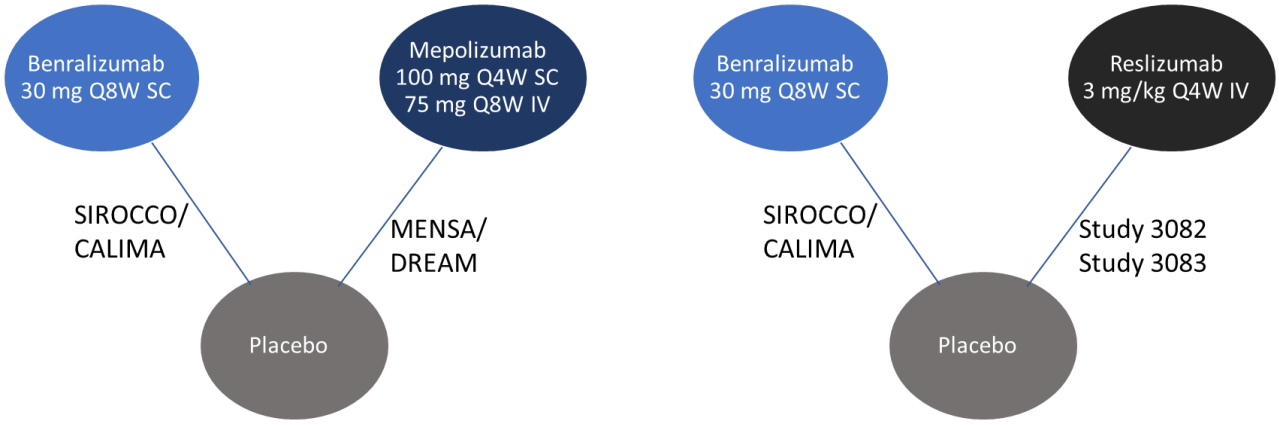
Table S8. Benralizumab vs. mepolizumab analysis including MUSCA study: Matched and unmatched treatment comparisons of clinically significant asthma exacerbations and asthma exacerbations resulting in ED visit or hospitalisation, and change from baseline in prebronchodilator FEV_1

	Treatment comparison		
Efficacy outcome	SIROCCO/CALIMA Benralizumab Q8W vs. placebo (no matching adjustment)[a]	MENSA/DREAM/ MUSCA Mepolizumab vs. placebo	SIROCCO/CALIMA Benralizumab Q8W vs. placebo (with matching adjustment)
Asthma exacerbations		RR (95% CI)	
Annualised rate of clinically significant exacerbations	0.54 (0.47–0.61)	0.48 (0.42–0.56)	0.51 (0.44–0.58)
Annualised rate of exacerbations resulting in ED visit or hospitalisation	0.66 (0.46–0.94)	0.45 (0.30–0.66)	0.55 (0.37–0.79)
Change in prebronchodilator FEV_1, L		Mean (95% CI)	
From baseline to Week 24	0.10 (0.04–0.17)	0.08 (0.03–0.12)	0.10 (0.03–0.16)

[a]Includes only patients receiving FP ≥880 μg/d.

CI, confidence interval; ED, emergency department; FEV_1, forced expiratory volume in 1 second; FP, fluticasone propionate; Q8W, every 8 weeks (first three doses every 4 weeks); RR, risk ratio.

Figure S3. Evidence networks for comparisons of benralizumab with mepolizumab and reslizumab for patients with severe, uncontrolled asthma



IV, intravenously; SC, subcutaneously; Q4W, every 4 weeks; Q8W, every 8 weeks (first three doses of benralizumab Q4W).

APPENDIX 3: REFERENCES

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