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Matching-Adjusted Indirect Comparison of Benralizumab vs. Interleukin-5 Inhibitors: Systematic Review

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Take-home message (117-character [including spaces] summary):

In an indirect treatment comparison with matched populations, benralizumab and mepolizumab had comparable efficacy.

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Article type: Original research

Key words: Benralizumab, mepolizumab, reslizumab, interleukin-5, interleukin-5 receptor, matching-adjusted indirect comparison

ABSTRACT (200 words; 200-word max)

The relative efficacy of benralizumab, an interleukin-5 receptor alpha–directed cytolytic monoclonal antibody that directly depletes eosinophils vs. other IL-5–targeted treatments for patients with severe, uncontrolled asthma, is not yet fully characterized.

We performed a matching-adjusted indirect comparison (MAIC) of benralizumab vs. mepolizumab and reslizumab. Trials were selected through systematic review and evaluation of trial methods. Benralizumab patient-level data were weighted to match treatment effect–modifying patient characteristics of comparator trials before indirect efficacy comparisons.

After matching adjustment, benralizumab and mepolizumab reduced exacerbations vs. placebo by 52% and 49%, respectively (rate ratio [RR]: 0.94; 95% confidence interval [CI]: 0.78–1.13; N=1,524) and reduced the rate of exacerbations requiring hospitalisation/emergency department visit by 52% and 52%, respectively (RR: 1.00; 95% CI: 0.57–1.75; N=1,524). Benralizumab and mepolizumab similarly improved prebronchodilator forced expiratory volume in 1 second at 32 weeks (difference=0.03 L; 95% CI: −0.06–0.12; N=1,443). Benralizumab and reslizumab patient populations were too dissimilar to generate a sufficient effective sample size to produce a reliable estimate for MAIC.

MAIC is a robust way to indirectly compare efficacies of treatments from trials with heterogeneous patient populations. When baseline patient characteristics were matched across asthma trials, benralizumab and mepolizumab yielded similar efficacy.

INTRODUCTION

Patients with severe asthma have frequent exacerbations and hospitalisations [1,2], a substantial cost burden [3,4], and residual symptoms despite use of high-dosage inhaled corticosteroids (ICS) plus a second controller medication [2,5]. The anti–interleukin (IL)-5 monoclonal antibodies, reslizumab [6] and mepolizumab [7], and the IL-5 receptor alpha (IL-5Rα)–directed

cytolytic monoclonal antibody, benralizumab [8], have demonstrated efficacy for patients with severe, uncontrolled asthma with an eosinophilic phenotype [9–13].

Data on the comparative efficacy of treatments would be valuable for clinicians making decisions about patients who are potential candidates for IL-5Rα or anti–IL-5 treatments. However, these biologics have not been compared in head-to-head clinical trials, limiting interpretations regarding their relative benefits and harms. In lieu of direct comparisons, indirect treatment comparisons (ITCs), including network meta-analyses (NMAs), can be performed to estimate effects using a common comparator, such as standard-of-care treatment and/or placebo. Meta-analyses have also been used to indirectly compare the efficacy and safety of benralizumab, mepolizumab, and reslizumab, and concluded that no treatment was clearly superior [14,15].

One important limitation in the interpretation of recent attempts at indirect comparison of IL-5Rα or anti–IL-5 therapies [16] is that the studies used aggregate data sources that may lead to biased estimates, because they do not take into account important between-trial differences. A key requirement of ITCs (and NMAs) is that included studies have sufficiently similar designs, treatment durations, and patient baseline characteristics to justify cross-study comparisons. Baseline asthma severity, eosinophil count, and exacerbation history, for example, are all important modulators of asthma treatment efficacy. If these differ across trials for each IL-5Rα or anti–IL-5 monoclonal antibody development program because of different inclusion/exclusion criteria, the indirect comparison estimate may be erroneous or biased.

Matching-adjusted indirect comparisons (MAICs) are a form of population-adjusted ITC that attempt to reduce bias in treatment comparisons by matching patient-level data from the clinical trials of one treatment to aggregate data reported for comparator trials [17]. Treatment effect–modifying variables that differ across studies, such as baseline exacerbation history, are used to weight the patient-level data to reflect the characteristics of the comparator's patient population. Patients who had exacerbation rates similar to the aggregate of the comparator population are weighted more heavily when modelling study outcomes, similar to a propensity score. Patients who are quite different from the comparator population would have less weight on the outcome. This matching adjustment simulates the results as if the treatments being compared were both tested in the same patient population [17].

MAIC analyses have been conducted for biologics across a variety of therapeutic areas, including haemophilia [18], psoriasis [19], and multiple myeloma [20]. The objective of this study was to perform a MAIC of benralizumab vs. IL-5–directed monoclonal antibodies for the treatment of patients with severe, uncontrolled asthma and with an eosinophilic phenotype.

METHODS

Overview

This MAIC analysis was conducted according to the National Institute for Health and Care Excellence (NICE) Technical Support Document (TSD) guidance [21] for a robust, population-adjusted ITC and required identification of randomised controlled studies of IL-5Rα/anti–IL-5 treatments with similar study methods. First, studies were identified through systematic review.

We then applied stringent requirements for MAIC analysis, which required narrowing the selection of trials, as described below. To perform matching of the benralizumab population to the comparator treatment populations, we used several steps to identify variables that were known to modify treatment effects. Patients in the benralizumab population were then weighted to reflect the treatment effect–modifying characteristics in the comparator populations. To evaluate the success of the weighting techniques, we compared the benralizumab population's adjusted baseline characteristics with the comparator's characteristics, as reported in the literature. Relative treatment effects could then be evaluated across comparators in ITCs.

Study Selection and Data Extraction

Further details on the methods for the systematic review are detailed in **Appendix 1**. The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) [22], and the requirements of health technology appraisal organizations in the United Kingdom, Germany, France and the United States. MEDLINE®, EMBASE®, MEDLINE® In-Process, and CENTRAL databases were searched using a combination of medical subject headings (MeSH) and free-text terms to identify English-language articles of relevant studies of biologics in moderate-to-severe uncontrolled asthma. Searches were conducted from database inception to August 2016 (search date). Conference abstracts were included and identified via EMBASE® or hand searching of relevant conference website.

All studies included the following outcomes, which were chosen to reflect their clinical significance in severe asthma, inclusion as primary endpoints in severe asthma trials, and

availability of data across trials: annual rate of clinically significant exacerbations, annual rate of exacerbations requiring emergency department (ED) visit or hospitalisation, and prebronchodilator forced expiratory volume in 1 second (FEV_1). Because definitions of exacerbation might differ, we included only trials in which the definition of exacerbation included worsening of asthma symptoms leading to use of systemic corticosteroids and an urgent care/ED visit or hospitalisation.

Citations identified through literature searches were screened for inclusion on the following prospectively defined criteria: randomised controlled trials comparing IL-5Rα/anti–IL-5 treatments with placebo for patients with severe, uncontrolled asthma receiving medium- or high-dosage ICS plus an additional controller medication. Two independent reviewers performed screening and data extraction activities with discrepancies reconciled by a third independent reviewer.

Assessment of Risk of Bias

The risk of bias was assessed using National Institute for Health and Care Excellence (NICE) check-list [23]. Sources of clinical heterogeneity were summarized and assessed. Each study was graded as having a high, low, or unclear risk of bias.

Data Analysis

Exacerbation rate outcomes were estimated as rate ratios for monoclonal antibody treatments vs. placebo. Change in FEV_1 was estimated as the mean difference between monoclonal antibody treatments and placebo. Studies were evaluated in detail for differences in study methods,

presence of potential treatment effect–modifying patient characteristics, and availability of variables and outcomes of interest in the treatment comparisons. Variables that we believed made findings uninterpretable because of between-trial variability were identified through elicitation of opinion from asthma experts, a literature review, and univariate and multivariate analyses of SIROCCO [9] and CALIMA data [11]. Eligibility criteria were then refined to increase the face validity of comparisons.

All analyses were conducted using SAS Version 9.1 and R Version 3.0.3.

Matching-Adjusted Indirect Comparison Analyses

To enable valid treatment comparison across trials, we used matching procedures to weight benralizumab patient characteristics to reflect the comparator populations. An anchoring method was used for the population-adjusted indirect comparisons, further described in **Appendix 1, Figure S2**. Matching variables were selected for their clinical and statistical importance in explaining variability in the outcomes of interest and their demonstrated imbalance between the SIROCCO/CALIMA [9,11] and comparator populations, as described in **Appendix 1**.

Data adjustments

SIROCCO/CALIMA [9,11] individual patient data were weighted based on the relevant aggregate baseline characteristics from the mepolizumab or reslizumab studies. Variables were adjusted by estimating a logistic propensity score model that was conditional on the treatment-effect modifiers identified previously for comparison with either mepolizumab or reslizumab. Individuals were weighted by the inverse of their propensity score [21].

Effective sample size

After matching, and as part of the treatment comparison for each outcome, we evaluated effective sample size (ESS). A small ESS is an indication that the weighted population (i.e., from the benralizumab trials) and nonweighted population (i.e., from the mepolizumab or reslizumab trials) have little overlap, which may result in unstable, invalid estimates [21].

Treatment Comparisons

The final step was to estimate the relative treatment effects of benralizumab and the comparator included in the MAIC using standard ITC methodologies [24]. For the MAIC analysis, treatment differences of each intervention against placebo were used to derive the anchored ITCs for each outcome, rate of exacerbations, rate of exacerbations resulting in hospitalisation or ED visits, and change in FEV_1.

Sensitivity analysis

The mepolizumab MUSCA trial [25] was not included in the systematic review because it was unpublished at the time. However, MUSCA data were included in a set of sensitivity analyses at Week 24 (**Appendix 1**).

RESULTS

Study Selection and Variability Assessment

This systematic review identified 32 studies. **Figure 1** presents the flow of studies for eligibility in the systematic review and ITC. We identified important variability across study methods,

including patient selection criteria (such as disease severity, exacerbation history, and eosinophil count), primary outcome measure, sample size, study length, ICS dosage during the studies, and oral corticosteroid (OCS) background. Therefore, additional criteria were applied to narrow the studies, treatment arms, or patients included in the analysis. Only Phase III studies with a primary endpoint of reduction in asthma exacerbations were included.

For each pairwise treatment comparison, we established a standard ICS dosage. For the benralizumab vs. mepolizumab comparison, only patients who received high-dosage ICS (fluticasone propionate [FP] ≥880 μg/d) were included; patients in the benralizumab trials who received smaller dosages were excluded. Because no reslizumab studies used high-dosage ICS, we widened the criterion for the benralizumab vs. reslizumab comparison. Reslizumab Study 3082 and Study 3083 [10] were included, in which patients received medium- to high-dosage ICS. For this analysis only, patients in the benralizumab CALIMA study [11] who received medium- to high-dosage ICS were also included.

Evidence Networks for MAIC Analysis

The evidence networks generated for the placebo-anchored comparison of benralizumab vs. mepolizumab included the benralizumab SIROCCO [9] and CALIMA [11] trials and the mepolizumab MENSA [12] and DREAM [13] trials. The evidence network for the placebo-anchored comparison of benralizumab vs. reslizumab included the benralizumab SIROCCO [9] and CALIMA [11] trials and the reslizumab Study 3082 and Study 3083 trials [10] (**Appendix 2, Figure S3**). In studies with several treatment arms, only active treatment arms that used licensed (European and United States) dosages were included. Mepolizumab 75 mg administered

intravenously every 4 weeks is bioequivalent to the approved dosage of 100 mg administered subcutaneously every 4 weeks. Therefore, these two dosages were pooled. Data for benralizumab were obtained by pooling the individual patient data from the SIROCCO and CALIMA trials (patients who received FP ≥880 μg/d for the mepolizumab comparison and patients who received FP ≥500 μg/d for the reslizumab comparison). Aggregate data for mepolizumab were pooled from the clinical study reports for MENSA and DREAM (mepolizumab 75-mg data pooled from MENSA and DREAM; mepolizumab 100-mg data from MENSA). Aggregate results for reslizumab came from publications of Study 3082 and Study 3083 [10]. Study details for benralizumab, mepolizumab, and reslizumab are presented in **Appendix 2, Table S4**.

Benralizumab vs. Mepolizumab Comparison

Baseline characteristics and effective sample size

For the benralizumab vs. mepolizumab comparison, 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.

For change in FEV_1 for benralizumab vs. mepolizumab, the main analysis was conducted from baseline to Week 32 because each of the four trials included had FEV_1 data at Week 32. Because the MENSA trial was shorter than the other trials (DREAM: 32 weeks vs. 52 weeks; SIROCCO: 48 weeks; CALIMA: 56 weeks), two additional analyses of change in FEV_1 were conducted, one evaluating change from baseline to the end of each trial and the other evaluating change from baseline to the end of each trial after excluding the MENSA study from the analysis.

After adjustment for the mepolizumab MENSA/DREAM population characteristics, benralizumab SIROCCO/CALIMA baseline characteristics were well-matched to the mepolizumab population for the analyses of exacerbations (**Table 3**) and the analyses of change in FEV_1 at Week 32 (**Table 4**), end of each study (**Appendix 2, Table S5**), and end of each study excluding MENSA (**Appendix 2, Table S6**).

As a result of matching, the benralizumab population ESS decreased from 959 to 639 in the exacerbation comparison. When the benralizumab population was matched for the FEV_1 comparisons, ESS was reduced from 863 to 559 (32-week comparison), from 838 to 540 (end-of-study comparison), and 838 to 402 (end-of-study comparison excluding MENSA). These adjusted ESSs were adequate for robust MAIC analyses according to the NICE TSD [21].

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 52% (RR=0.48) after matching adjustment to the mepolizumab patient population (**Table 5**). Mepolizumab reduced the exacerbation rate in MENSA/DREAM by 49% (RR=0.51) vs. placebo.

Indirect comparison of benralizumab vs. mepolizumab after the matching adjustment indicated that benralizumab had a comparable reduction in clinically significant exacerbations compared with mepolizumab (6% greater exacerbation reduction, RR=0.94 [95% CI: 0.78–1.13] after

adjustment). The two treatments were not statistically significantly different in their effects on exacerbations either before or after the matching adjustment (**Figure 2**).

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

Benralizumab treatment reduced the rate of clinically significant exacerbations leading to ED visit/hospitalisation vs. placebo by 35% (RR=0.65) in SIROCCO/CALIMA before matching adjustment to the mepolizumab patient population and by 52% (RR=0.48) after matching adjustment (**Table 5**). Mepolizumab reduced the exacerbation rate in MENSA/DREAM by 52% (RR=0.48) 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 (RR=1.0) (**Figure 2**).

Prebronchodilator forced expiratory volume in 1 second

Before and after matching, benralizumab demonstrated a small improvement compared with mepolizumab in change in prebronchodilator FEV_1 at all time points (**Table 5**). For example, from baseline to Week 32 for benralizumab, after matching, the improvement was 0.10 L (95% CI: 0.04–0.17) vs. 0.07 L (95% CI: 0.02–0.13) for mepolizumab. The extent of FEV_1 improvement associated with benralizumab treatment was comparable before and after matching for analyses at 32 weeks, end of the studies, and end of the studies excluding MENSA (**Figure 2**).

Sensitivity analyses

In the set of sensitivity analyses that included the MUSCA trial, relative efficacy results for exacerbations and FEV_1 were similar to those of the main MAIC analyses (**Appendix 2, Table S7 and S8**).

Benralizumab vs. Reslizumab Comparison

For the benralizumab vs. reslizumab comparison, 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.

Matching the benralizumab SIROCCO/CALIMA data set to the reslizumab population resulted in a 99% reduction in the ESS, from 1,668 to 20 (**Table 6**), indicating very little overlap in the treatment characteristics of the patient populations. The small ESS of 20 patients was not sufficient to support a robust MAIC between benralizumab and reslizumab.

DISCUSSION

Our study compared exacerbation and lung function outcomes of benralizumab treatment against outcomes for other IL-5–directed biologics for severe, uncontrolled asthma. Results of the comparison between benralizumab and mepolizumab demonstrated that efficacy was comparable in reducing the annual rate of clinically significant exacerbations and exacerbations leading to ED/hospitalisation and improving prebronchodilator FEV_1. In most comparisons, benralizumab was numerically better than mepolizumab after matching adjustment balanced baseline

characteristics between the two populations, although there were no significant differences. This analysis extends findings from recent systematic review methods [26] and expands upon evidence from a recent ITC of IL-5–directed monoclonal antibody treatments by Cabon et al 2017 [15] that did not include the key benralizumab Phase III SIROCCO [9] and CALIMA [11] trials used in our analysis and did not adjust for differences in baseline patient characteristics. Cabon et al 2017 [15] also included heterogeneity across studies that was restricted in our analysis, such as treatment arms with monoclonal antibody dosages not licensed in Europe and the United States and widely varying treatment duration and patient selection criteria.

To conduct a standard ITC of published aggregate data, which is typically performed when researchers do not have access to individual patient data, the contributing studies should have homogeneous methods because differences across studies may result in biased comparisons of outcomes. Our assessment indicated considerable variation across studies of monoclonal antibody treatments for severe asthma, including differences in inclusion/exclusion criteria, baseline patient characteristics, and outcome definitions, that would likely bias standard ITCs. Therefore, we used the MAIC approach, in which individual patient data for one treatment are adjusted to match important aggregate baseline characteristics from the comparator trial. The re-weighted, matching-adjusted data can then be used to provide an estimate of the outcomes that might have occurred if the comparator trial had included a benralizumab arm. Use of individual patient data for adjustment offers more information on patient-level associations than aggregate-level adjustments applied to standard ITCs, making MAIC a more powerful tool than meta-regression in adjusting for the impact of treatment effect modifiers [17]. In situations with few trials and no head-to-head data, as with the current study of relatively new therapies, MAIC may

be a particularly helpful approach to address evidence gaps and aid decision making by payers and health technology assessment authorities [17].

When methods differ between studies, the placebo effect size may also differ. For example, the placebo group's annual exacerbation event rate was greater in the pooled MENSA/DREAM studies than in the pooled SIROCCO/CALIMA studies (2.0 and 1.27 events per year, respectively). This difference might occur because of procedural differences between studies, such as permitted concomitant treatments. However, when the SIROCCO/CALIMA data were matched to the MENSA/DREAM patient population characteristics in our MAIC analysis, the placebo group's annual exacerbation event rate in SIROCCO/CALIMA increased from 1.27 to 1.63 (**Appendix 2**), suggesting that at least part of this difference in the placebo effects for benralizumab vs. mepolizumab was because of patient population differences. Inspection of patient baseline characteristics in each pooled data set (**Table 1**) also suggested that patients taking mepolizumab had somewhat more severe asthma than patients taking benralizumab, as indicated by differences in baseline eosinophil count, prior exacerbations, and the percentage of patients using OCS at baseline.

Because the trial patient populations from the benralizumab (SIROCCO [9], CALIMA [11]) and reslizumab (Study 3082 and Study 3083 [10]) trials had limited overlap in their sample characteristics, MAIC analysis was not possible, and no conclusion could be drawn about the relative efficacy of these two treatments using this methodology. Although we selected similar trials of benralizumab and reslizumab for indirect comparison, the patient populations were still different enough that robust MAIC could not be accomplished. The most notable difference in

the baseline characteristics of the two studies was the number of exacerbations in the previous year. Whereas almost every patient in the benralizumab population had ≥2 exacerbations in the previous year, approximately 60% of patients in the reslizumab population had only one exacerbation in the previous year. This indicates a difference in disease severity, as specified in the inclusion criteria; SIROCCO/CALIMA enrolled patients with severe asthma, whereas the two reslizumab studies enrolled patients with less severe asthma. A recent ITC analysis [16] used the same four Phase III studies used in our analysis to evaluate comparative efficacy for several asthma outcomes, including the exacerbation and FEV_1 outcomes we analysed. However, they used no matching adjustment to balance population characteristics. Their NMA suggests a numeric advantage for reslizumab for several efficacy outcomes, with a statistically significant advantage in reduction of clinically significant exacerbations. Given that exacerbation history was an important characteristic in which the benralizumab and reslizumab populations differed, our analysis suggests caution in drawing conclusions about relative efficacies from these trials.

Limitations

MAIC analysis has several advantages over traditional ITC, but it also has limitations. Although we balanced treatment effect–modifying patient characteristics that were measured in the trials, there may have been unmeasured differences between trials that were not matched.

Another limitation is the occurrence of extreme weights for some patients during matching adjustment, which can lead to decreased statistical power to detect differences between treatments. ESS is a reliable indicator in such cases, and we did not perform MAIC when the ESS was insufficient for the benralizumab vs. reslizumab comparison. All other comparisons had sufficient ESS.

To limit heterogeneity across studies, the current analysis included only trials with exacerbations as a key endpoint. OCS sparing is another important endpoint for patients with severe, uncontrolled asthma; however, trials evaluating OCS sparing effects have important study design differences that warrant separate analysis. A MAIC analysis of the OCS-sparing properties of benralizumab vs. IL-5 inhibitors could not be adequately addressed here but will be described in a future report.

The MUSCA trial [25] was unpublished at the time of this analysis. It was not retrospectively included in the MAIC analysis because it differed from the other benralizumab and mepolizumab studies in several ways, including study design and choice of health-related quality of life as the primary endpoint. Despite these differences, the MUSCA trial was included in a sensitivity analysis, and the overall pattern of significance did not change.

Conclusions

MAIC is an accepted method for comparing treatments in lieu of head-to-head trials and is less subject to biases than standard ITC. To our knowledge, this is the first MAIC comparing monoclonal antibodies for the treatment of severe asthma. The MAIC demonstrated that, after adjustment for baseline population characteristics that differed across benralizumab vs. mepolizumab trials, reduction in asthma exacerbation rates were similar, and improvements in FEV_1 were slightly better but not statistically significant at all time points tested. Comparisons with reslizumab could not be performed because of insufficient ESS.

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DISCLOSURES

Authors S. Golam, L. Lindner, and X. Xu are full-time employees of AstraZeneca. N. Molinari has nothing to declare. M.K. Siddiqui is an employee of PARAXEL International and performed the analysis on behalf of AstraZeneca. A. Bourdin received personal fees, nonfinancial support, and other support from AstraZeneca; grants, personal fees, and other support from GSK; grants, personal fees, nonfinancial support, and other support from Boehringer Ingelheim; personal fees, nonfinancial support, and other support from Novartis; personal fees and other support from Teva; personal fees and other support from Regeneron; personal fees, nonfinancial support, and

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REFERENCES

1. Chastek B, Korrer S, Nagar SP, *et al*. Economic burden of illness among patients with severe asthma in a managed care setting. *J Manag Care Spec Pharm* 2016; 22: 848–861.
2. Lang DM. Severe asthma: epidemiology, burden of illness, and heterogeneity. *Allergy Asthma Proc* 2015; 36: 418–424.
3. Kerkhof M, Tran TN, Soriano JB, *et al*. Healthcare resource use and costs of severe, uncontrolled eosinophilic asthma in the UK general population. *Thorax* 2018; 73: 116–124.
4. Nunes C, Pereira AM, Morais-Almeida M. Asthma costs and social impact. *Asthma Res Pract* 2017; 3: 1.
5. Ivanova JI, Bergman R, Birnbaum HG, *et al*. Effect of asthma exacerbations on health care costs among asthmatic patients with moderate and severe persistent asthma. *J Allergy Clin Immunol* 2012; 129: 1229–1235.
6. Teva Pharmaceutical Industries Ltd. CINQAIR® (reslizumab) label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761033lbl.pdf. Date last updated: March 2016. Date last accessed: March 23 2018.

7. GlaxoSmithKline LLC. NUCALA® (mepolizumab) label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125526Orig1s000Lbl.pdf. Date last updated: November 2015. Date last accessed: April 13 2018.
8. AstraZeneca. FASENRA™ (benralizumab) label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761070s000lbl.pdf. Date last accessed: April 13 2018.
9. Bleecker ER, FitzGerald JM, Chanez P, *et al*. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet* 2016; 388: 2115–2127.
10. Castro M, Zangrilli J, Wechsler ME, *et al*. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015; 3: 355–366.
11. FitzGerald JM, Bleecker ER, Nair P, *et al*. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016; 388: 2128–2141.
12. Ortega H, Liu MC, Pavord ID, *et al*. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014; 371: 1198–1207.
13. Pavord ID, Korn S, Howarth P, *et al*. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012; 380: 651–659.

14. Cockle SM, Stynes G, Gunsoy NB, *et al*. Comparative effectiveness of mepolizumab and omalizumab in severe asthma: An indirect treatment comparison. *Respir Med* 2017; 123: 140–148.

15. Cabon Y, Molinari N, Marin G, *et al*. Comparison of anti-interleukin-5 therapies in patients with severe asthma: global and indirect meta-analyses of randomized placebo-controlled trials. *Clin Exp Allergy* 2017; 47: 129–138.

16. Casale T, Mesana L, Pacou M, *et al*. Reslizumab vs benralizumab in patients with inadequately controlled asthma: a Bayesian network meta-analysis. *Eur Respir J* 2017; 50: OA2903.

17. Signorovitch JE, Sikirica V, Erder MH, *et al*. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. *Value Health* 2012; 15: 940–947.

18. Pocoski J, Li N, Ayyagari R, *et al*. Matching-adjusted indirect comparisons of efficacy of BAY 81-8973 vs two recombinant factor VIII for the prophylactic treatment of severe hemophilia A. *J Blood Med* 2016; 7: 129–137.

19. Signorovitch JE, Wu EQ, Yu AP, *et al*. Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. *Pharmacoeconomics* 2010; 28: 935–945.

20. Van Sanden S, Ito T, Diels J, *et al*. Comparative efficacy of daratumumab monotherapy and pomalidomide plus low-dose dexamethasone in the treatment of multiple myeloma: A matching adjusted indirect comparison. *Oncologist* 2018; 23: 279–287.

21. Phillippo DM, Ades AE, Dias S, *et al*. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. December 2016.

22. Hutton B, Salanti G, Caldwell DM, *et al*. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015; 162: 777–784.

23. NICE STA. Specification for manufacturer/sponsor submission of evidence. June 2012. http://www.nice.org.uk/aboutnice/howwework/devnicetech/SpecificationForManufacturerSponsorSubmissionOfEvidence.jsp?domedia¼1&mid¼97E2DC44-19B9-E0B5-D4F73F1DB153AA86. Date last accessed: June 2017.

24. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997; 50: 683–691.

25. Chupp GL, Bradford ES, Albers FC, *et al*. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *Lancet Respir Med* 2017; 5: 390–400.

26. Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev* 2017; 9: CD010834.

27. Nair P, Wenzel S, Rabe K, *et al*. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med* 2017; 376: 2448–2458.

28. Castro M, Wenzel SE, Bleecker ER, *et al*. Benralizumab, an anti-interleukin 5 receptor alpha monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. *Lancet Respir Med* 2014; 2: 879–890.

29. Park HS, Kim MK, Imai N, *et al*. A Phase 2a study of benralizumab for patients with eosinophilic asthma in South Korea and Japan. *Int Arch Allergy Immunol* 2016; 169: 135–145.

30. Nowak RM, Parker JM, Silverman RA, *et al*. A randomized trial of benralizumab, an antiinterleukin 5 receptor alpha monoclonal antibody, after acute asthma. *Am J Emerg Med* 2015; 33: 14–20.

31. Bel E, Wenzel S, Thompson P, *et al*. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014; 371: 1189–1197.

32. Haldar P, Brightling C, Hargadon B. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009; 360: 973–984.

33. Nair P, Pizzichini M, Kjarsgaard M, Inman M. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009; 360: 985–993.

34. Castro M, Mathur S, Hargreave F, *et al*. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med* 2011; 184: 1125–1132.

35. Jacobs J, Murphy K, Bjermer L, Zangrilli J, Garin M. Long-term effect of reslizumab on asthma-related quality of life (AQLQ) in asthma patients (PTS) previously enrolled in reslizumab safety and efficacy studies. *Ann Allergy Asthma Immunol* 2015; 115: A57.

TABLES

Table 1. Comparison of baseline characteristics of patients included in benralizumab (SIROCCO, CALIMA) and mepolizumab (MENSA, DREAM) studies

	SIROCCO		CALIMA (only high-dosage ICS subgroup)		MENSA			DREAM	
Characteristics	Benralizumab Q8W N=398	Placebo N=407	Benralizumab Q8W N=364	Placebo N=370	Mepolizumab 100 mg SC N=194	Mepolizumab 75 mg IV N=191	Placebo N=191	Mepolizumab 75 mg IV N=153	Placebo N=155
Age [years], mean (SD)	47.6 (14.5)	48.7 (14.9)	50.1 (13.3)	49.8 (14.3)	51.2 (14.55)	50.0 (14.03)	49.2 (14.26)	50.2 (11.3)	46.4 (10.8)
Sex, % male	36.7	33.9	38.2	40.3	40.0	45.0	44.0	32.0	37.0
Race, %									
Whites	72.1	74.2	85.2	86.8	77.0	79.0	77.0	91.0	90.0
Blacks	3.8	3.9	3.6	3.2	4.0	3.0	2.0	3.0	4.0
Asians	12.6	12.3	11.0	10.0	18.0	17.0	20.0	5.0	6.0
Others	11.6	9.6	0.3	0.0	1.0	1.0	1.0	1.0	0.0
BMI, mean (SD)	28.21 (6.18)	28.93 (7.07)	29.0 (6.5)	29.25 (6.54)	27.60 (5.58)	27.68 (5.68)	28.04 (5.58)	28.4 (6.0)	28.3 (6.1)
FEV_1 predicted [%], mean	56.1[a]	56.6[a]	56.9	57.5	59.3	61.4	62.4	60[a]	59[a]
Morning PEF [L/min], mean	233.12	230.83	241.85	242.16	255.3	268.6	277	-	-
FEV_1/FVC, %	65	66	64	65	63	64	64	68	67
FEV_1 prebronch, L	1.68	1.66	1.72	1.76	1.73	1.85	1.86	1.81[a]	1.90[a]
Reversibility, %	27.2	25.5	25.1	27.2	27.9[a]	25.4[a]	27.4[a]	22.6[b]	26.8[b]
ACQ score[c]	2.8	2.87	2.82	2.73	2.26	2.12	2.28	2.2	2.5
Exacerbations in previous year									
Mean	2.8	3	2.7	2.8	3.8	3.5	3.6	>3[d]	>3[d]
2 exacerbations, %	63.3	60	62.9	63.5	38	43	47	46	42
≥3 exacerbations, %	36.68	40	36.81	36.49	61.86	57.07	52.88	54	57
Never smokers, %	82.2	80.6	78.02[a]	78.92[a,e]	74[a,e]	73[a]	70[a]	80[a]	78[a]
OCS use, %	17.8	16.2	10.71[a]	11.08[a,e]	27[a,e]	25[a]	23[a]	30.07[a]	29.03[a]
EOS ≥300 cells/µL, %	67.08	65.6	65.6	67.02	51.5	53.4	55.4	56.2	45.16

Characteristics	SIROCCO		CALIMA (only high-dosage ICS subgroup)		MENSA			DREAM	
EOS <300 cells/µL, %	32.9	34.3	34.3	32.9	47.4	45.02	43.4	43.7	54.8
EOS count [cells/µL], mean	469.8	456.5	463.4	490.8	290[f]	280[f]	320[f]	250[f]	280[f]
IgE concentration	-	-	-	-	149.72[f]	180.32[f]	150.12[f]	-	-
Atopic status, %	61.3	56.5	61.5	63.0	-	-	-	51.0	52.0
Nasal polyps, %	19.0	19.0	16.8	18.1	14.4	16.7	17.2	7.0	10.0

Highlighted cells indicate differences across benralizumab and mepolizumab trials. For cells with no data listed, none were available.

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

[b]Data reported at screening visit.

[c]ACQ-6 in SIROCCO, CALIMA, and DREAM; ACQ-5 in MENSA.

[d]Calculated from the reported frequency of exacerbations.

[e]Calculated from the reported subgroup data.

[f]Geometric means.

ACQ, Asthma Control Questionnaire; EOS, eosinophil; BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IV, intravenous; OCS, oral corticosteroid; PEF, peak expiratory flow; Q8W, every 8 weeks (first three doses every 4 weeks); SC, subcutaneous; SD, standard deviation.

Table 2. Comparison of baseline characteristics of patients included in benralizumab (SIROCCO, CALIMA) and reslizumab (Study 3082 and Study 3083) studies

	SIROCCO (high-dosage ICS)		CALIMA (medium- to high-dosage ICS)		Study 3082 (medium- to high-dosage ICS)		Study 3083 (medium- to high-dosage ICS)		Study 3082 and Study 3083 (Pooled) (medium- to high-dosage ICS)	
Characteristics	Benralizumab Q8W N=398	Placebo N=407	Benralizumab Q8W N=441	Placebo N=440	Reslizumab 3 mg/kg N=245	Placebo N=244	Reslizumab 3 mg/kg N=232	Placebo N=232	Reslizumab 3 mg/kg N=477	Placebo N=476
Age [years], mean (SD)	47.6 (14.5)	48.7 (14.9)	49.0 (14.3)	48.8 (15.1)	46.6[a] (13.8)	46.7[a] (14.8)	46.4[a] (13.8)	47.5[a] (13.6)	-	-
Sex, % male	36.7	33.9	38.1	40.0	42.0	34.0	38.0	35.0	40.04	34.45
BMI, mean (SD)	28.21 (6.18)	28.93 (7.07)	29.0 (6.5)	29.25 (6.54)	27.7 (6.3)	28 (6.2)	27 (5.1)	27 (5.3)	-	-
FEV_1 predicted [%], mean	56.1[b]	56.6[b]	57.9	58.0	63.6	65.0	70.4	68.0	-	-
Reversibility [%], mean	27.2	25.5	24.6	27.3	26.1	26.3	28.1	28.7	-	-
ACQ score, mean[c]	2.8	2.87	2.82	2.73	2.66	2.76	2.57	2.61	-	-
Never smokers, %	82.2	80.6	78.9	79.3	-	-	-	-	-	-
OCS use, %	17.8	16.2	10.0	8.9	19.0	19.0	12.0	12.0	-	-
EOS count [cells/µL], mean	469.8	456.5	465.1	487.5	696.0	624.0	610.0	688.0	-	-
Exacerbations in previous year										
Mean	2.8	3	2.7	2.8	1.9	2.1	1.9	2.0	-	-
1 exacerbation,%	0.0	0.0	0.2[d]	0.0	-	-	-	-	58.07	59.24
2 exacerbations,%	63.3	60.0	65.1	65.5	-	-	-	-	18.03	22.48
≥3 exacerbations, %	19.8	18.7	21.1	21.1	-	-	-	-	9.22	7.56
≥4 exacerbations, %	16.9	21.3	13.6	13.4	-	-	-	-	14.05	10.08
Omalizumab use, %	7.0	7.6	2.7	3.8	-	-	-	-	-	-
Nasal polyps, %	19.0[b]	19.0[b]	16.8	18.1	-	-	-	-	-	-

Highlighted cells indicate differences across benralizumab and reslizumab studies. For cells with no data listed, none were available.

[a]Extracted from reslizumab NICE STA; all other data for reslizumab trials are extracted from publications.

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

[c]ACQ-5 in benralizumab trials and ACQ-7 in reslizumab trials.

[d]One patient in CALIMA had one exacerbation in the past year.

ACQ, Asthma Control Questionnaire; BMI, body mass index; EOS, eosinophil; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; NICE, National Institute for Health and Care Excellence; OCS, oral corticosteroid; STA, single technology appraisal; Q8W, every 8 weeks (first three doses every 4 weeks).

Table 3. Baseline characteristics of patients before and after matching for the analysis of annual rate of clinically significant exacerbations and annual rate of exacerbations leading to ED visit or hospitalisation

	SIROCCO/CALIMA (before adjustment)[a]	MENSA/DREAM (aggregate reported data)	SIROCCO/CALIMA (after adjustment)
Baseline characteristics	Benralizumab Q8W, placebo N=959	Mepolizumab 75 mg IV, mepolizumab 100 mg SC, placebo N=884	Benralizumab Q8W, placebo Effective sample size=639
Eosinophil count, %			
≥300 cells/µL	67.05	52.45	52.75
<300 cells/µL	32.95	47.55	47.25
Maintenance oral corticosteroid use, %			
Yes	15.22	26.58[b]	30.18
No use	84.78	73.42[b]	69.82
IgE count, %			
<30 IU/mL	11.55	13.29	14.66
≥30–≤700 IU/mL	71.19	70.35	70.02
>700 IU/mL	17.27	16.35	15.32
Sex, %			
Male	36.60	40.05	39.2
Female	63.40	59.95	60.8
Exacerbations in the previous year, %			
2	61.63	42.99	42.69
>2	38.38	56.79	57.31
Nasal polyps, %			
No	81.33	86.83	83.44
Yes	18.67	13.17	16.56
BMI, mean (SD)	29.89 (6.27)	27.98 (5.912)	28.37 (6.13)

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

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

BMI, body mass index; ED, emergency department; FP, fluticasone propionate; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IPD, individual patient data; IV, intravenous; Q8W, every 8 weeks (first three doses every 4 weeks); SC, subcutaneous; SD, standard deviation.

Table 4. Comparison of baseline characteristics of patients before and after matching for the analysis of change from baseline prebronchodilator FEV_1 at 32 weeks

Baseline characteristics	SIROCCO/CALIMA[a] (before adjustment) Benralizumab Q8W, placebo N=863	MENSA/DREAM (aggregate reported data) Mepolizumab 75 mg IV, mepolizumab 100 mg SC, placebo N=884	SIROCCO/CALIMA (after adjustment) Benralizumab Q8W, placebo Effective sample size=559
Eosinophil count, %			
≥300 cells/µL	68.02	52.45	52.43
<300 cells/µL	31.98	47.55	47.57
Maintenance OCS use, %			
Yes	15.06	26.58[b]	30.24
No	84.94	73.42[b]	69.76
IgE count, %			
<30 IU/mL	11.40	13.29	14.62
≥30–≤700 IU/mL	71.09	70.35	70.01
>700 IU/mL	17.51	16.35	15.37
Sex, %			
Male	37.43	40.05	39.08
Female	62.57	59.95	60.92
Exacerbations in previous year, %			
2	62.34	42.99	42.82
>2	37.66	56.79	57.18
Nasal polyps, %			
No	81.23	86.83	83.09
Yes	18.77	13.17	16.91
BMI, mean (SD)	28.89 (6.27)	27.98 (5.912)	28.38 (6.15)

[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 5. Benralizumab vs. mepolizumab: 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 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)	0.51 (0.44–0.58)	0.48 (0.43–0.55)
Annualised rate of exacerbations resulting in ED visit or hospitalisation	0.65 (0.46–0.93)	0.48 (0.31–0.73)	0.48 (0.33–0.68)
Change in prebronchodilator FEV_1, L		Mean (95% CI)	
From baseline to Week 32	0.11 (0.05–0.18)	0.07 (0.02–0.13)	0.10 (0.04–0.17)
From baseline to end of study[b]	0.11 (0.05–0.18)	0.09 (0.04–0.14)	0.11 (0.04–0.17)
From baseline to end of study, excluding data from MENSA	0.11 (0.05–0.18)	0.06 (–0.04–0.16)[c]	0.09 (0.03–0.14)[d]

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

[b]End of study was at the following time points: SIROCCO, 48 weeks; CALIMA, 56 weeks; MENSA, 32 weeks; DREAM, 52 weeks.

[c]This comparison excludes MENSA. Comparison includes DREAM mepolizumab 75 mg IV vs. placebo.

[d]This comparison included matching adjustment to DREAM only.

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

Table 6. Baseline characteristics of SIROCCO/CALIMA before and after matching to the population of reslizumab Study 3082 and Study 3083

Baseline characteristics	SIROCCO/CALIMA (before adjustment)	Study 3082 and Study 3083 (aggregate reported data)	SIROCCO/CALIMA (after adjustment)
	Benralizumab Q8W, placebo (medium- to high-dosage ICS) N=1,668	Reslizumab 3 mg/kg, placebo (medium- to high-dosage ICS) N=953	Effective sample size=20
Sex, %			
Male	37.35	37.25	37.25
Female	62.65	62.75	62.75
OCS use at baseline, %			
No use	86.69	84.50	84.50
Used OCS	13.31	15.50	15.50
EOS count, mean (SD)	456.22 (402.28)	654.68 (628.74)	654.68 (247.39)
Exacerbations in previous year, mean (SD)	2.76 (1.53)	1.98 (1.85)	1.98 (0.73)

Data for Study 3082 and Study 3083 were extracted from publications.

EOS, eosinophil; ICS, inhaled corticosteroid; OCS, oral corticosteroid; SD, standard deviation; Q8W, every 8 weeks (first three doses every 4 weeks).

FIGURES

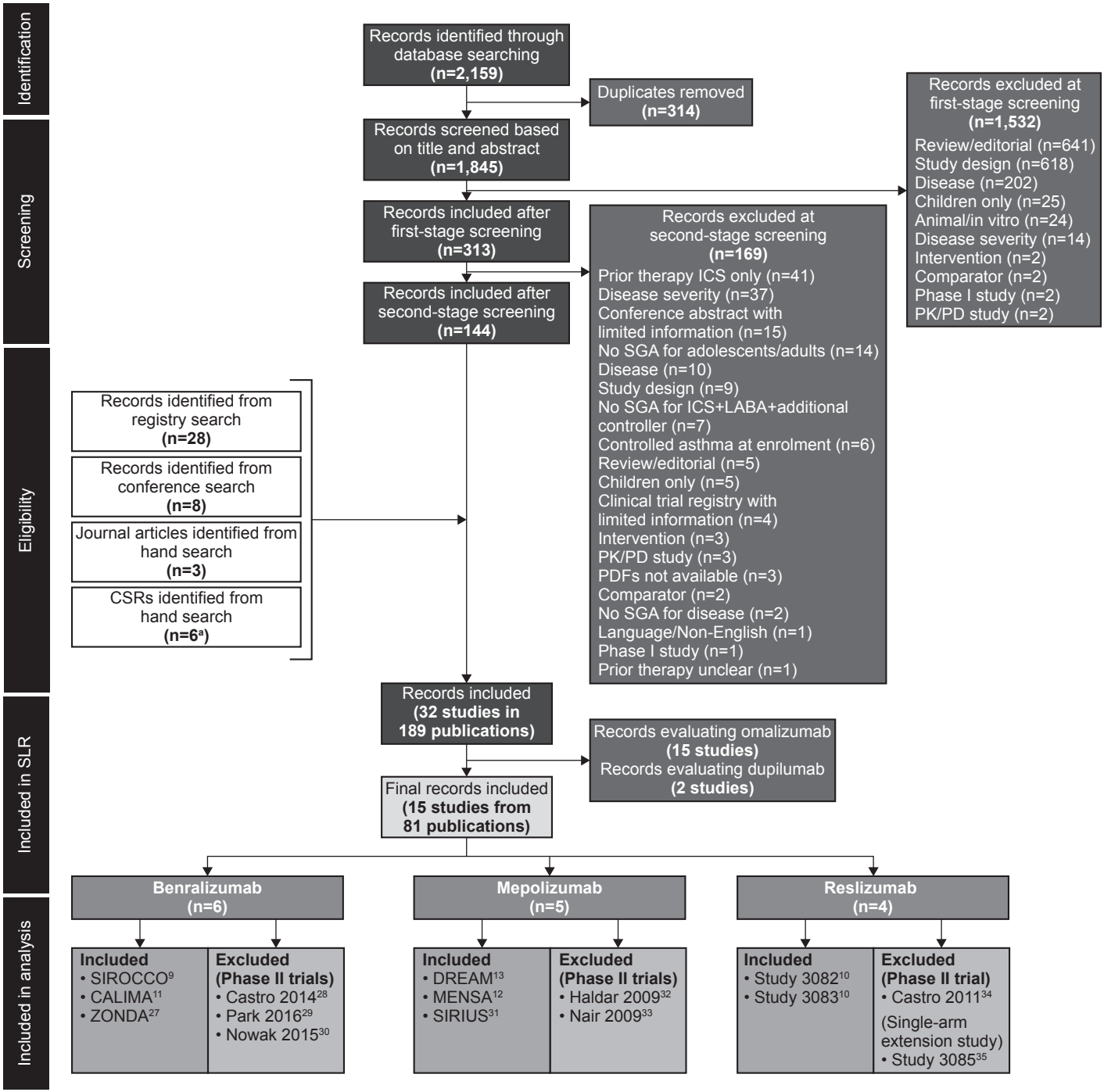
Figure 1. Flow of citations for inclusion in MAIC

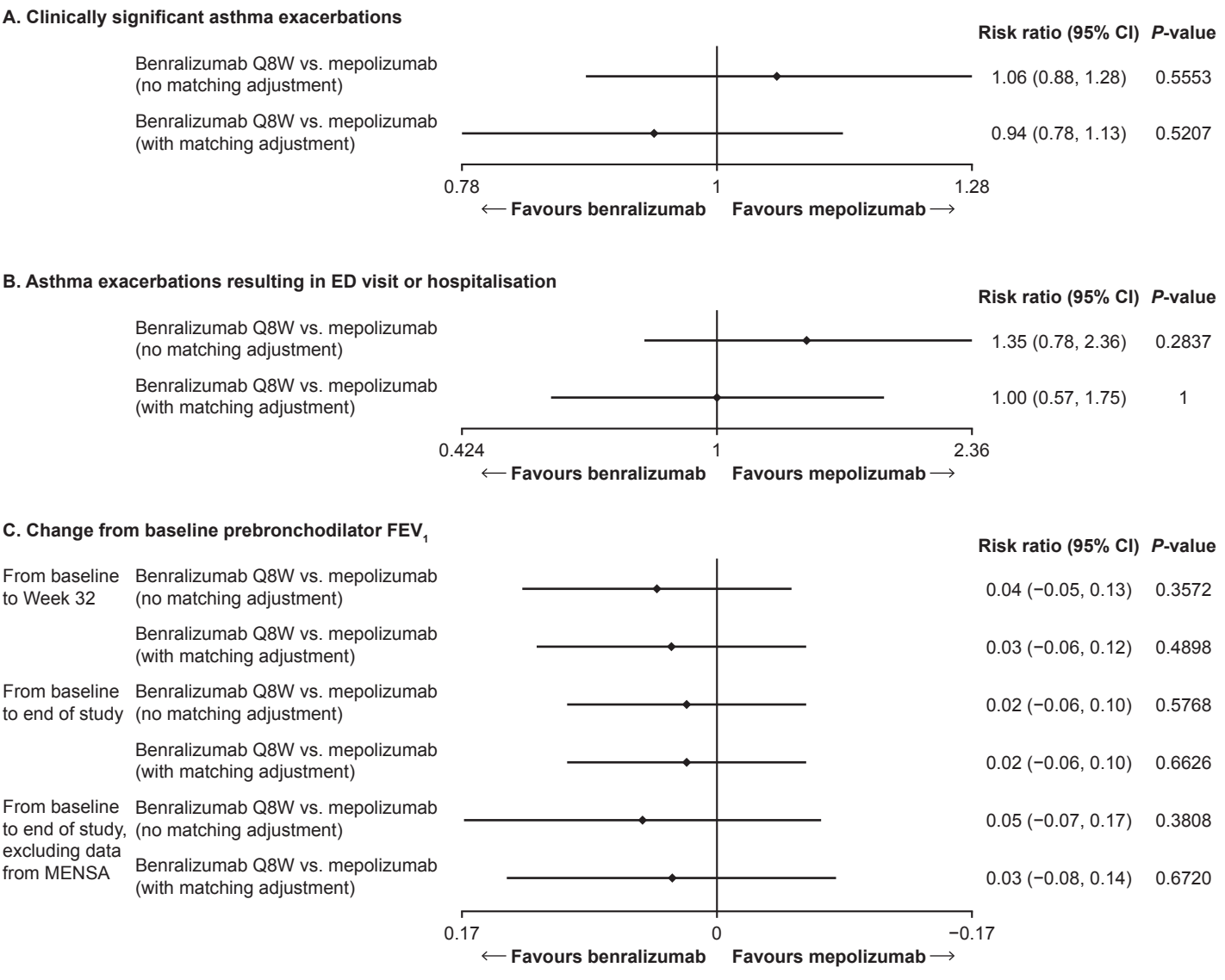
[a]Includes benralizumab clinical study reports (SIROCCO, CALIMA, ZONDA).

CSR, clinical study report; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; MAIC, matching-adjusted indirect comparison; PD, pharmacodynamics; PK, pharmacokinetics; SGA, subgroup analysis.

Figure 2. Risk ratios from indirect treatment comparisons of benralizumab and mepolizumab for clinically significant asthma exacerbations (A), asthma exacerbations resulting in ED visit or hospitalisation (B), and change from baseline prebronchodilator FEV_1 (C)

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


Identification
Screening
Eligibility
Included in SLR
Included in analysis
Records identified through database searching (n=2,159)
Duplicates removed (n=314)
Records screened based on title and abstract (n=1,845)
Records excluded at first-stage screening (n=1,532)
Review/editorial (n=641)
Study design (n=618)
Disease (n=202)
Children only (n=25)
Animal/in vitro (n=24)
Disease severity (n=14)
Intervention (n=2)
Comparator (n=2)
Phase I study (n=2)
PK/PD study (n=2)
Records included after first-stage screening (n=313)
Records excluded at second-stage screening (n=169)
Prior therapy ICS only (n=41)
Disease severity (n=37)
Conference abstract with limited information (n=15)
No SGA for adolescents/adults (n=14)
Disease (n=10)
Study design (n=9)
No SGA for ICS+LABA+additional controller (n=7)
Controlled asthma at enrolment (n=6)
Review/editorial (n=5)
Children only (n=5)
Clinical trial registry with limited information (n=4)
Intervention (n=3)
PK/PD study (n=3)
PDFs not available (n=3)
Comparator (n=2)
No SGA for disease (n=2)
Language/Non-English (n=1)
Phase I study (n=1)
Prior therapy unclear (n=1)
Records included after second-stage screening (n=144)
Records identified from registry search (n=28)
Records identified from conference search (n=8)
Journal articles identified from hand search (n=3)
CSRs identified from hand search (n=6[a])
Records included (32 studies in 189 publications)
Records evaluating omalizumab (15 studies)
Records evaluating dupilumab (2 studies)
Final records included (15 studies from 81 publications)
Benralizumab (n=6)
Mepolizumab (n=5)
Reslizumab (n=4)
Included
• SIROCCO[9]
• CALIMA[11]
• ZONDA[27]
Excluded (Phase II trials)
• Castro 2014[28]
• Park 2016[29]
• Nowak 2015[30]
Included
• DREAM[13]
• MENSA[12]
• SIRIUS[31]
Excluded (Phase II trials)
• Haldar 2009[32]
• Nair 2009[33]
Included
• Study 3082[10]
• Study 3083[10]
Excluded (Phase II trial)
• Castro 2011[34]
(Single-arm extension study)
• Study 3085[35]


A. Clinically significant asthma exacerbations
Risk ratio (95% CI)
P-value
Benralizumab Q8W vs. mepolizumab (no matching adjustment)
1.06 (0.88, 1.28)
0.5553
Benralizumab Q8W vs. mepolizumab (with matching adjustment)
0.94 (0.78, 1.13)
0.5207
0.78
1
1.28
← Favours benralizumab
Favours mepolizumab →
B. Asthma exacerbations resulting in ED visit or hospitalisation
Risk ratio (95% CI)
P-value
Benralizumab Q8W vs. mepolizumab (no matching adjustment)
1.35 (0.78, 2.36)
0.2837
Benralizumab Q8W vs. mepolizumab (with matching adjustment)
1.00 (0.57, 1.75)
1
0.424
1
2.36
← Favours benralizumab
Favours mepolizumab →
C. Change from baseline prebronchodilator FEV1
Risk ratio (95% CI)
P-value
From baseline to Week 32
Benralizumab Q8W vs. mepolizumab (no matching adjustment)
0.04 (−0.05, 0.13)
0.3572
Benralizumab Q8W vs. mepolizumab (with matching adjustment)
0.03 (−0.06, 0.12)
0.4898
From baseline to end of study
Benralizumab Q8W vs. mepolizumab (no matching adjustment)
0.02 (−0.06, 0.10)
0.5768
Benralizumab Q8W vs. mepolizumab (with matching adjustment)
0.02 (−0.06, 0.10)
0.6626
From baseline to end of study, excluding data from MENSA
Benralizumab Q8W vs. mepolizumab (no matching adjustment)
0.05 (−0.07, 0.17)
0.3808
Benralizumab Q8W vs. mepolizumab (with matching adjustment)
0.03 (−0.08, 0.14)
0.6720
0.17
0
−0.17
← Favours benralizumab
Favours mepolizumab →

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

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
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
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

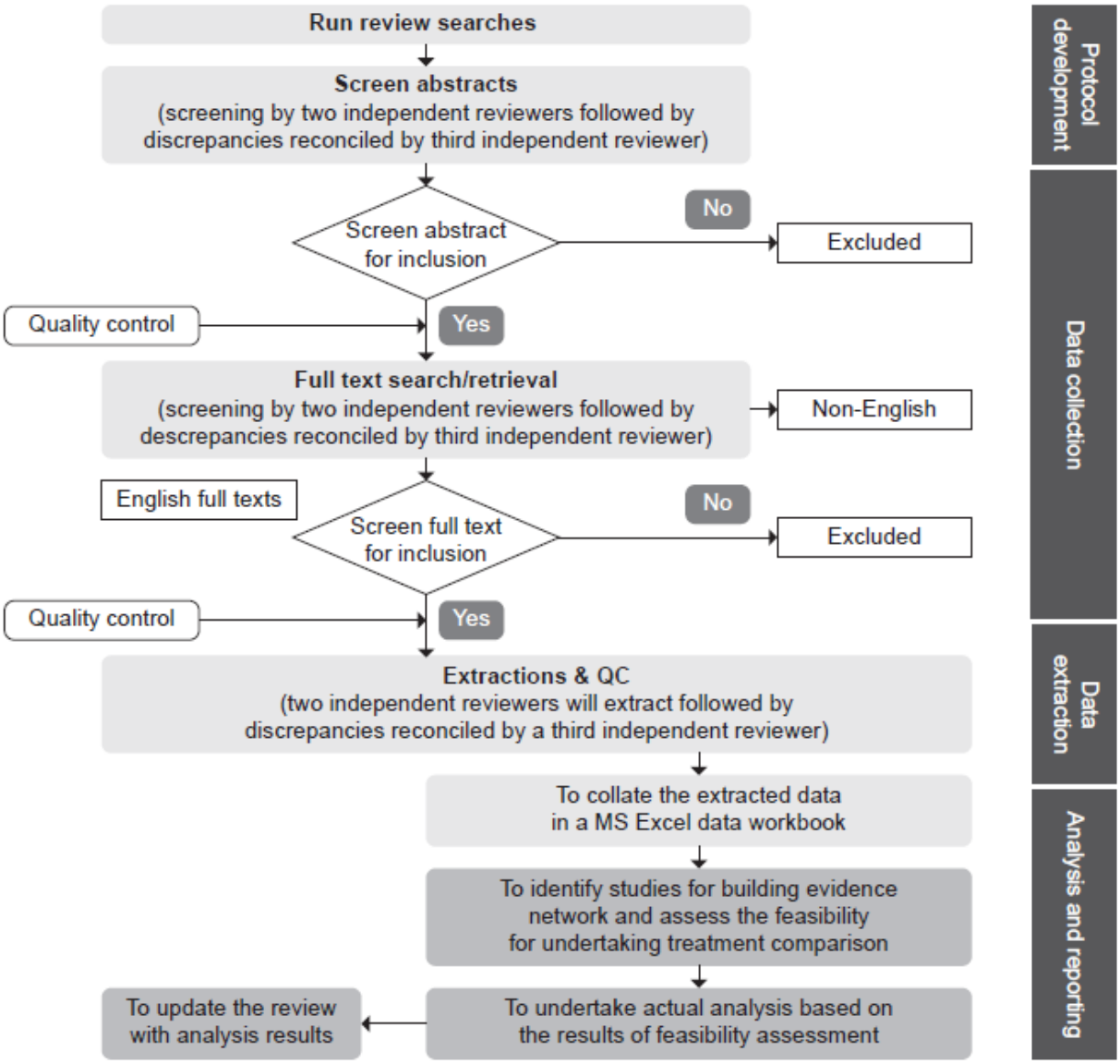
Table S2. Eligibility criteria applied to the search results

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)

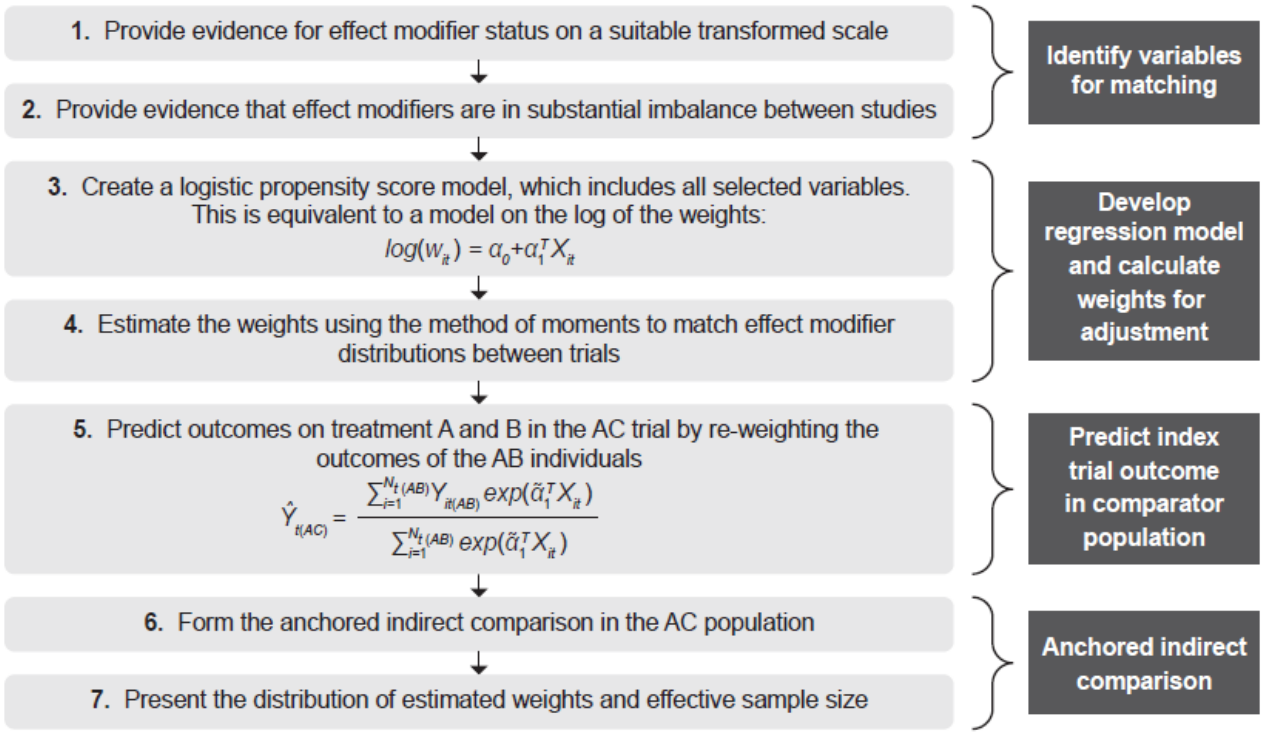
ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CS, corticosteroid; ER, emergency room; EQ-5D, EuroQOL 5D; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene 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]

Study	Study phase	Sample size	Interventions	Primary results publication
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.

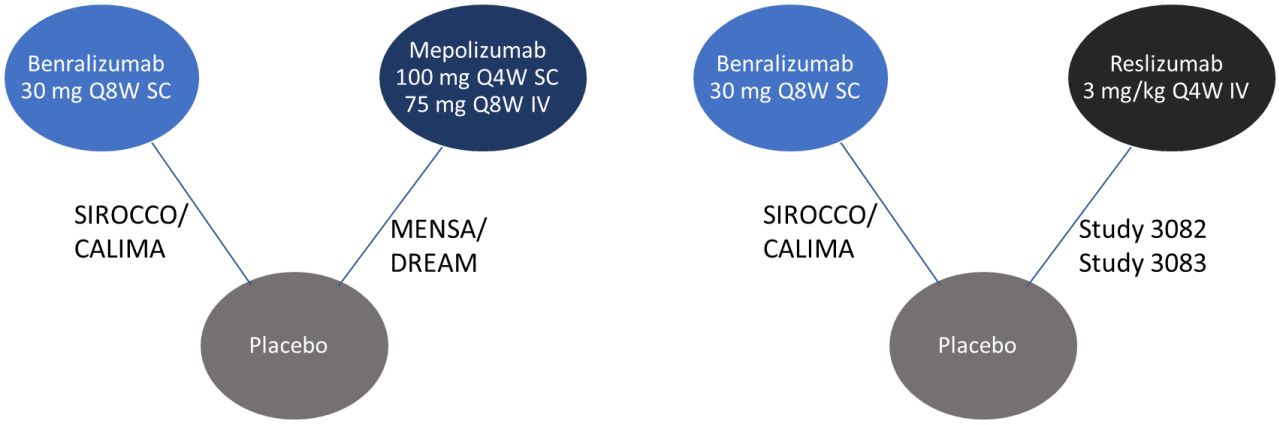
Table S8. Benralizumab vs. mepolizumab analysis including MUSCA study: Matched and unmatched treatment comparisons of clinically significant asthma exacerbations and asthma exacerbations resulting in ED visit or hospitalisation, and change from baseline in prebronchodilator FEV_1

	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

1. Chupp GL, Bradford ES, Albers FC, *et al*. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *Lancet Respir Med* 2017; 5: 390–400.
2. ClinicalTrials.gov. Efficacy and safety study of benralizumab added to high-dose inhaled corticosteroid plus LABA in patients with uncontrolled asthma (NCT01928771). https://ClinicalTrials.gov/show/NCT01928771. Date last updated: May 3 2017. Date last accessed: March 20 2018.
3. Bleecker ER, FitzGerald JM, Chanez P, *et al*. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet* 2016; 388: 2115–2127.
4. ClinicalTrials.gov. Efficacy and safety study of benralizumab in adults and adolescents inadequately controlled on inhaled corticosteroid plus long-acting β2 agonist (NCT01914757). https://ClinicalTrials.gov/show/NCT01914757. Date last updated: January 25 2017. Date last accessed: March 20 2018.
5. FitzGerald JM, Bleecker ER, Nair P, *et al*. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016; 388: 2128–2141.

6. ClinicalTrials.gov. Efficacy and safety study of benralizumab to reduce OCS use in patients with uncontrolled asthma on high dose inhaled corticosteroid plus LABA and chronic OCS therapy (NCT02075255). https://ClinicalTrials.gov/show/NCT02075255. Date last updated: October 17 2017. Date last accessed: March 20 2018.
7. Nair P, Wenzel S, Rabe K, *et al*. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med* 2017; 376: 2448–2458.
8. ClinicalTrials.gov. Study to evaluate the efficacy and eafety of MEDI-563 in adults with uncontrolled asthma. https://ClinicalTrials.gov/show/NCT01238861. Date last updated: November 17 2016. Date last accessed: March 20 2018.
9. Castro M, Wenzel SE, Bleecker ER, *et al*. Benralizumab, an anti-interleukin 5 receptor alpha monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. *Lancet Respir Med* 2014; 2: 879–890.
10. ClinicalTrials.gov. A Phase IIa study of KHK4563 (NCT01412736). https://ClinicalTrials.gov/show/NCT01412736. Date last updated: December 23 2014. Date last accessed: March 20 2018.
11. Park HS, Kim MK, Imai N, *et al*. A Phase 2a study of benralizumab for patients with eosinophilic asthma in South Korea and Japan. *Int Arch Allergy Immunol* 2016; 169: 135–145.
12. ClinicalTrials.gov. Efficacy and safety study of benralizumab added to medium-dose inhaled corticosteroid plus LABA in patients with uncontrolled asthma (NCT01947946). https://ClinicalTrials.gov/show/NCT01947946. Date last updated: November 24 2015. Date last accessed: March 20 2018.

13. ClinicalTrials.gov. A Phase 2 study to evaluate the safety and efficacy of intravenously administered MEDI-563 (NCT00768079). https://ClinicalTrials.gov/show/NCT00768079. Date last updated: July 18 2016. Date last accessed: March 20 2018.

14. Nowak RM, Parker JM, Silverman RA, *et al*. A randomized trial of benralizumab, an antiinterleukin 5 receptor alpha monoclonal antibody, after acute asthma. *Am J Emerg Med* 2015; 33: 14–20.

15. ClinicalTrials.gov. Efficacy and safety study of mepolizumab adjunctive therapy in subjects with severe uncontrolled refractory asthma (NCT01691521). https://ClinicalTrials.gov/show/NCT01691521. Date last updated: October 6 2017. Date last accessed: March 21 2018.

16. Ortega H, Liu MC, Pavord ID, *et al*. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014; 371: 1198–1207.

17. ClinicalTrials.gov. Dose ranging efficacy and safety with mepolizumab in severe asthma (NCT01000506). https://ClinicalTrials.gov/show/NCT01000506. Date last updated: January 24 2018. Date last accessed: March 22 2018.

18. Pavord ID, Korn S, Howarth P, *et al*. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012; 380: 651–659.

19. ClinicalTrials.gov. Mepolizumab steroid-sparing study in subjects with severe refractory asthma (NCT01691508). https://ClinicalTrials.gov/show/NCT01691508. Date last updated: March 23 2017. Date last accessed: March 22 2018.

20. Bel E, Wenzel S, Thompson P, *et al*. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014; 371: 1189–1197.

21. ISRCTN.com. Mepolizumab and exacerbation frequency in refractory eosinophilic asthma: a randomised, double blind, placebo controlled trial (ISRCTN75169762). http://www.isrctn.com/ISRCTN75169762. Date last updated: October 3 2009. Date last accessed: March 22 2018.

22. Haldar P, Brightling C, Hargadon B. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009; 360: 973–984.

23. ClinicalTrials.gov. The prednisone-sparing effect of anti-IL-5 antibody (SB-240563) (NCT00292877). https://ClinicalTrials.gov/show/NCT00292877. Date last updated: January 24 2011. Date last accessed: March 22 2018.

24. Nair P, Pizzichini M, Kjarsgaard M, Inman M. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009; 360: 985–993.

25. ClinicalTrials.gov. A study to evaluate the efficacy and safety of reslizumab (3.0 mg/kg) in the reduction of clinical asthma exacerbations in patients (12-75 years of age) with eosinophilic asthma (NCT01287039). https://ClinicalTrials.gov/show/NCT01287039. Date last updated: June 27 2016. Date last accessed: March 22 2018.

26. Castro M, Zangrilli J, Wechsler ME, *et al*. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015; 3: 355–366.

27. ClinicalTrials.gov. A study to evaluate the efficacy and safety of reslizumab in patients with eosinophilic asthma (NCT01285323).

https://ClinicalTrials.gov/show/NCT01285323. Date last updated: June 27 2016. Date last accessed: March 22 2018.

28. ClinicalTrials.gov. Efficacy and safety study of reslizumab to treat poorly controlled asthma (NCT00587288). https://ClinicalTrials.gov/show/NCT00587288. Date last updated: August 17 2016. Date last accessed: March 22 2018.

29. Castro M, Mathur S, Hargreave F, *et al*. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med* 2011; 184: 1125–1132.