



Comparative effectiveness of mepolizumab and omalizumab in severe asthma: An indirect treatment comparison



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ARTICLE INFO

Article history:

Received 6 September 2016

Received in revised form

24 November 2016

Accepted 16 December 2016

Available online 21 December 2016

Keywords:

Mepolizumab

Omalizumab

Severe asthma

Exacerbations

Lung function

Tolerability

ABSTRACT

Background: Severe asthma is a heterogeneous disease. Patients with both eosinophilic and allergic asthma phenotypes may be eligible for treatment with mepolizumab and omalizumab. Evidence on the relative effectiveness of these treatments in this 'overlap' population would be informative for clinical and payer decision making.

Methods: A systematic literature review and indirect treatment comparison (Bayesian framework) were performed to assess the comparative effectiveness and tolerability of mepolizumab and omalizumab, as add-ons to standard of care. Studies included in the primary analysis were double-blind, randomized controlled trials, ≥ 12 weeks' duration enrolling patients with severe asthma with a documented exacerbation history and receiving high-dose inhaled corticosteroids plus ≥ 1 additional controller. Two populations were examined: patients potentially eligible for 1) both treatments (Overlap population) and 2) either treatment (Trial population).

Results: In the Overlap population, no differences between treatments in clinically significant exacerbations and exacerbations requiring hospitalization were found, although trends favored mepolizumab (rate ratio [RR]:0.66 [95% credible intervals (CrI):0.37,1.19]; 0.19[0.02,2.32], respectively). In the Trial population, mepolizumab treatment produced greater reductions in clinically significant exacerbations (RR:0.63 [95% CrI:0.45,0.89]) but not exacerbations requiring hospitalization compared with omalizumab (RR:0.58 [95% CrI: 0.16,2.13]), although the trend favored mepolizumab. Both treatments had broadly comparable effects on lung function, and similar tolerability profiles.

Conclusions: Whilst this analysis has limitations due to a restricted evidence base and residual heterogeneity, it showed that in patients with severe asthma, mepolizumab seems to be at least as effective as omalizumab and that the tolerability profiles of the two treatments did not meaningfully differentiate.

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Abbreviations: CrI, credible interval; HRQoL, health related quality of life; ITC, indirect treatment comparison; MEPO, mepolizumab; OCS, oral corticosteroid; OMA, omalizumab; RCT, randomized controlled trial; RR, rate ratio; SoC, standard of care; SCS, systemic corticosteroid.

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1. Introduction

Severe asthma is characterized by frequent exacerbations, hospitalizations and poor symptom control, despite the regular use of intensive maintenance therapies [1,2]. Severe asthma is a heterogeneous disease with several phenotypes, including allergic and/or persistent eosinophilic asthma [2,3]. Owing to the significant unmet need in this patient population, novel targeted therapies have been developed for different phenotypes of severe asthma, with the aim of reducing the rate of clinical exacerbations [4]. For example,

mepolizumab (GSK, London, UK) is an anti-interleukin (IL)-5 mAb approved as an add-on treatment in patients with severe eosinophilic asthma [5,6]; omalizumab (Genentech, Inc., South San Francisco, CA), an anti-immunoglobulin E (IgE) monoclonal antibody (mAb) [7–9] is licensed as an add-on treatment for patients with moderate-to-severe (US) or severe (EU) allergic asthma.

In clinical trials, both mepolizumab and omalizumab were efficacious at reducing exacerbation rates in their respective patient populations when compared with placebo [10–13]. It is estimated that approximately one third of patients with severe asthma who are eligible for treatment with one biologic (mepolizumab or omalizumab) may also be eligible for treatment with the other biologic, hence for these patients the clinician has to make a choice between mepolizumab and omalizumab treatment [14,15]. Information on the relative effectiveness and tolerability profiles of the two treatments in this 'overlap' population would therefore be useful for both clinical and payer decision making. Since there are currently no published comparisons of mepolizumab and omalizumab in patients with severe asthma, we conducted a systematic literature review and indirect treatment comparison (ITC) to assess the comparative effectiveness and tolerability of mepolizumab and omalizumab, as add-on therapy to standard of care (SoC), in patients with severe asthma.

2. Methods

2.1. Data sources

A systematic literature review was conducted on August 5, 2014, and updated on July 8, 2015, to identify published randomized controlled trials (RCTs) of mepolizumab or omalizumab in severe asthma (GSK ID: HO-14-13436). Further details of the search strategy including databases and search terms can be found in [Supplementary Appendix A](#). This was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines based on a pre-defined PICOS (Population; Intervention; Comparator; Outcomes; and Study Design) framework.

The main objective of this systematic literature review was to collect all publicly available RCTs to support an ITC of mepolizumab and omalizumab in severe asthma. Due to the broad evidence base of severe asthma studies and the clinical and methodological heterogeneity, further pre-defined PICOS inclusion and exclusion criteria were applied to the studies identified from the systemic literature review to generate the evidence base for the ITC analysis (GSK ID 200277/HO-13-9058). The quality of RCTs was evaluated based on criteria outlined in [Supplementary Appendix A](#) and the results of this assessment are shown in [Table S1](#). The additional ITC eligibility criteria imposed a minimum appropriate level of comparability among the studies.

2.2. Eligibility criteria for inclusion in the indirect treatment comparison

2.2.1. Population

In order to be included in this ITC, studies were required to enroll patients meeting the following criteria: ≥ 12 years of age, with severe asthma (patients receiving ≥ 1000 $\mu\text{g/day}$ beclomethasone dipropionate equivalent plus ≥ 1 additional controller, and with a documented history of exacerbations). This population definition was then further refined to incorporate treatment eligibility for mepolizumab and omalizumab, as far as data availability allowed. Two populations were defined, 1) the Overlap population, which aimed to include patients eligible for both mepolizumab AND omalizumab, and 2) the Trial population, which aimed to

include patients eligible for either mepolizumab OR omalizumab ([Table 1](#)).

Mepolizumab eligibility was defined as severe eosinophilic asthma (blood eosinophil count ≥ 150 cells/ μL at treatment initiation or ≥ 300 cells/ μL in the prior 12 months) and a history of exacerbations. Omalizumab eligibility was defined as allergic asthma with a pre-treatment serum IgE versus body weight combination that met EU omalizumab prescribing criteria (baseline IgE levels ≥ 30 – ≤ 1500 IU/mL [patients ≥ 12 years of age with IgE < 76 IU/mL should have unequivocal *in vitro* reactivity to perennial allergen]; weight ≥ 20 kg– ≤ 150 kg; maximum dose 600 mg subcutaneous [SC] every 2 weeks). Detailed study and population inclusion criteria are shown in [Table 1](#) and [Fig. S1](#).

In order to accurately identify the Overlap population, treatment eligibility criteria would need to be applied to individual patient-level data from all included studies. However, patient-level data were only available for the mepolizumab studies. Therefore, it was necessary to make an assumption that patients enrolled in omalizumab trials that met the disease severity criteria also fulfilled the eligibility requirements for mepolizumab. However, the omalizumab RCTs identified by the systematic literature review had lower or undefined exacerbation history requirements, compared with a requirement for at least 2 exacerbations in the previous year in the mepolizumab RCTs. Consequently, if the exacerbation history requirement had been set to ≥ 2 exacerbations in the previous year, all the omalizumab trials would have been excluded from the analyses. Therefore, the exacerbation history requirement was relaxed in the Overlap population when compared with the inclusion criteria in the mepolizumab RCTs, while remaining strict enough to help identify mepolizumab and omalizumab eligible RCT populations of similar disease severity (according to exacerbation history).

2.2.2. Intervention

Eligible interventions for inclusion in the ITC were mepolizumab 100 mg SC and omalizumab as per the EU prescribing criteria. Detailed study and population inclusion criteria are shown in [Table 1](#) and [Fig. S1](#).

2.2.3. Comparator

It was anticipated that the common comparator for mepolizumab and omalizumab, would be placebo, in addition to SoC. If eligible studies examined omalizumab versus SoC alone, the SoC alone data were combined with placebo in the meta-analysis (ie., treated as a single common comparator for the active interventions). This was considered necessary due to the very small number of studies expected to be otherwise eligible for the ITC.

2.2.4. Outcomes

The primary pre-specified endpoints were the rate of clinically significant exacerbations (defined as exacerbations requiring systemic corticosteroid [SCS] treatment or at least a doubling of existing dose for maintenance oral corticosteroid [OCS] and/or hospitalization and/or an emergency department visit) and the rate of exacerbations requiring hospitalization. Pre-specified secondary endpoints included the change from baseline in health-related quality of life (HRQoL), measured by the St George's Respiratory Questionnaire or Asthma Quality of Life Questionnaire; change from baseline in lung function, defined as % predicted pre-bronchodilator forced expiratory volume in 1 s (FEV₁), or post-bronchodilator FEV₁, or FEV₁% predicted, or morning peak expiratory flow (PEF; L/min) when these data were unavailable; change from baseline in asthma control measured by the Asthma Control Questionnaire; and the proportion of patients with any adverse events (AEs), serious AEs (SAEs), withdrawals due to AEs or fatal

Table 1
Study and population inclusion criteria for the ITC.

ITC population	Disease criteria		Treatment eligibility criteria ^{a, b}			
			MEPO eligibility		OMA eligibility	
	Disease and current treatment	Exacerbation history	MEPO RCTs (IPD available)	OMA RCTs (aggregate RCT data only)	MEPO RCTs (IPD available)	OMA RCTs (aggregate RCT data only)
Overlap population	Severe asthma patients aged ≥ 12 years taking ≥ 1000 $\mu\text{g/day}$ BDP-equivalent ICS plus ≥ 1 additional controller	≥ 2 exacerbations (requiring SCS) OR ≥ 1 severe exacerbation (requiring hospitalization) in previous 12 months	Required Based on blood eosinophil count inclusion criteria in MEPO RCTs: blood eosinophil count ≥ 150 cells/ μL at treatment initiation or ≥ 300 cells/ μL in prior 12 months	Required Based on OMA RCTs that included patients meeting disease criteria	Required Sub-group of MEPO patients that met EU OMA license criteria: based on weight, IgE levels and positive RAST	Required OMA RCTs that included patients meeting EU OMA license
Trial population	Patient population eligible for either MEPO or OMA	≥ 1 exacerbation (requiring SCS or asthma hospitalization or asthma ED visit) in the previous 12 months	Required (As per Overlap population)	Not required in this scenario	Not required in this scenario	Required (As per Overlap population)

BDP, beclomethasone dipropionate; ED, emergency department; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IPD, individual patient-level data; ITC, indirect treatment comparison; MEPO, mepolizumab; OMA, Omalizumab; RAST, radioallergosorbent test; RCT, randomized controlled trial; SCS, systemic corticosteroids.

^a Criteria additional to disease criteria.

^b Definition of treatment eligibility differs for MEPO and OMA studies, due to data availability. MEPO eligibility in OMA studies was proxied using exacerbation history requirements at enrollment as imposed by the disease severity criteria.

AEs. These pre-specified endpoints were only analyzed if data were available in the trials meeting the criteria for inclusion in the Overlap population.

2.2.5. Study design

Eligible studies for the primary analysis were double-blind, parallel-group RCTs of ≥ 12 weeks duration. Where a protocol-driven change in inhaled corticosteroid/OCS maintenance dosage was implemented, only those data from periods prior to the dose change were included in the ITC. Eligible studies were required to have data for ≥ 1 pre-defined efficacy or tolerability endpoint available for extraction or calculation.

2.3. ITC methods

The primary analysis of each pre-specified endpoint was conducted using Bayesian network meta-analysis to indirectly compare mepolizumab (100 mg SC injection) and omalizumab (SC, licensed dose range per IgE level/weight) via a common comparator of placebo. The posterior distribution of the treatment effects (rate ratios [RR], odds ratios [OR], or mean difference with corresponding 95% credible intervals [CrIs]) were estimated through Gibbs sampling using either fixed- or random-effects models. Non-informative prior distributions were assigned for all treatment effects. Meta-regression to adjust for study-level covariates was planned but not performed due to an insufficient number of studies included. Analyses were performed using WinBUGS 1.4.0 (MRC Biostatistics Unit, Cambridge Institute of Public Health, Cambridge, UK). A detailed description is provided in [Supplementary Appendix 2](#).

2.4. Additional analyses

A Frequentist network meta-analysis was also conducted. Details of this are provided in [Supplementary Appendix B](#).

Sensitivity analyses were also conducted to assess the impact of study design and mepolizumab dose/formulation. In these analyses, PICOS ITC inclusion criteria remained the same as described above except that open-label omalizumab studies were included and mepolizumab 100 mg SC data were pooled with the

bioequivalent mepolizumab 75 mg intravenous (IV) data.

Analyses were also conducted on a third ITC population, the Extended overlap population, to assess the impact of exacerbation history requirement on analysis results. Population criteria are defined in [Table S3](#).

3. Results

3.1. Included studies

The systematic literature review identified seven mepolizumab publications corresponding to three distinct RCTs and 29 omalizumab publications, corresponding to 19 distinct RCTs ([Table S2](#)). Upon application of the ITC inclusion/exclusion criteria (PICOS), of the 22 identified RCTs, one mepolizumab study (MENZA [12]) and three omalizumab studies (INNOVATE [16], Chanez et al., 2010 [17] and EXTRA [18]) were eligible for inclusion in the primary ITC analysis ([Fig. 1](#)). MENSA and INNOVATE were eligible for inclusion in both the Overlap and Trial populations; EXTRA was only eligible for inclusion in the Trial population analysis. Key characteristics of the included studies are shown in [Table 2](#).

Sufficient data were available to conduct the ITC primary analysis on three of the pre-specified efficacy endpoints and four of the pre-specified safety endpoints. The efficacy endpoints were the rate of clinically significant exacerbations, rate of exacerbations requiring hospitalization, and the change from baseline in % predicted FEV₁. Although asthma control and QoL were pre-specified as efficacy endpoints for the ITC, feasibility assessment demonstrated there was insufficient data in the included studies for endpoint analysis. The feasibility assessment also concluded that it would be appropriate to analyze summary safety endpoints, rather than individual AE rates. The summary safety endpoints available in the included studies were the proportion of patients with any AE, any SAE, withdrawals due to AEs and fatal AEs.

3.2. Efficacy

3.2.1. Exacerbations

Mepolizumab and omalizumab reduced the rate of clinically significant exacerbations and exacerbations requiring

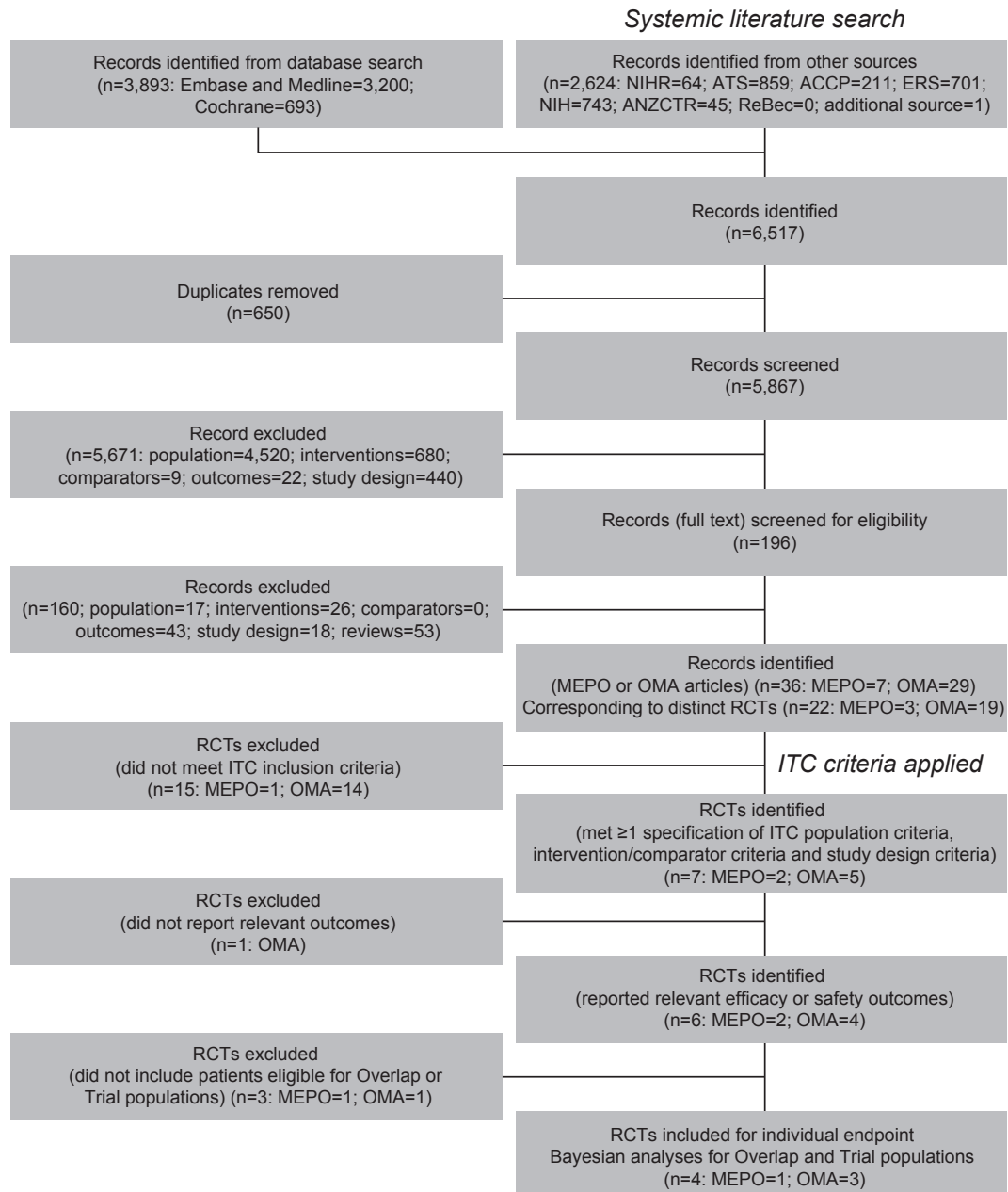


Fig. 1. Systematic literature search and application of ITC inclusion and exclusion criteria to identified RCTs.

ACCP, American College of Chest Physicians; ATS, American Thoracic Society; ANZCTR, Australian New Zealand Clinical Trials Registry; ERS, European Respiratory Society; ITC, indirect treatment comparison; MEPO, mepolizumab; NIH, National Institutes for Health; NIHR, National Institute for Health Research; OMA, omalizumab; ReBec, Registro Brasileiro de Ensaios Clínicos; RCTs, randomized controlled trials

hospitalization versus placebo and SoC in both the Overlap and Trial population analyses (Figs. 2 and 3). For the Overlap population, no difference was found between mepolizumab and omalizumab. However, trends in favor of mepolizumab were observed, with median estimated RRs of 0.66 (95% CrI: 0.37, 1.19; Fig. 2A) for the rate of clinically significant exacerbations and 0.19 (95% CrI: 0.02, 2.32; Fig. 2B) for the rate of exacerbations requiring hospitalization. Results of the Trial population analysis showed that mepolizumab was associated with an estimated median RR of 0.63 (95% CrI: 0.45, 0.89; Fig. 3A) corresponding to a reduction of 37% in the rate of clinically significant exacerbations versus omalizumab. No difference between treatments was observed for the rate of exacerbations resulting in hospitalization; however, the median RR

of 0.58 (0.16, 2.13) favored mepolizumab over omalizumab (Fig. 3B).

3.2.2. Lung function

Mepolizumab and omalizumab improved % predicted FEV₁ versus placebo and SoC in both populations (Figs. 2 and 3). The results of the ITC indicated that mepolizumab and omalizumab were broadly similar in terms of their effects on change in % predicted FEV₁ (Figs. 2C and 3C), with the point estimate favoring omalizumab in the Overlap population (mean difference: −0.98 [95% CrI: −6.35, 4.36]; Fig. 2C) and mepolizumab in the Trial population (mean difference: 0.24 [95% CrI: −3.61, 4.10; Fig. 3C]).

Table 2

Key characteristics of double-blind, randomized controlled trials included in the ITC.

	Study duration (weeks)	Treatment arms ^a	Key inclusion criteria	Number of patients	Included in Overlap population ^b analysis	Included in Trial population ^c analysis
Mepolizumab-included studies						
MENSA [12] ^d	32	• Mepolizumab 100 mg SC every 4 weeks (n = 194) • Placebo (n = 191)	• Blood eosinophil counts ≥ 150 cells/μL at 527 initiation of treatment or ≥ 300 cells/μL in previous 12 months • ≥ 2 asthma exacerbation in previous 12 months	✓		✓
Omalizumab-included studies						
INNOVATE [16] ^d	28	• Omalizumab administered every 2 or 4 weeks to provide dose of ≥ 0.016 mg/kg per IU/mL of IgE (n = 209) • Placebo (n = 210)	• Persistent allergic asthma despite high doses of corticosteroids and long-acting β_2 agonists • ≥ 2 asthma exacerbation (or 1 severe exacerbation) in previous 12 months	419	✓	✓
Chanez et al., 2010 [9] ^e	16	• Omalizumab administered every 2 or 4 weeks as per EU prescribing information [9] (n = 20) • Placebo (n = 11)	• Persistent allergic asthma despite high doses of corticosteroids and long-acting β_2 agonists • ≥ 2 severe asthma exacerbations in previous 12 months	31	✓	✓
EXTRA [18] ^f	48	• Omalizumab ≥ 0.008 mg/kg per IU/mL of IgE every 2 weeks or ≥ 0.016 mg/kg of IgE every 4 weeks (n = 427) • Placebo (n = 421)	• Severe allergic asthma despite high doses of corticosteroids and long-acting β_2 agonists • ≥ 1 asthma exacerbation in previous 12 months	848	–	✓

IgE, immunoglobulin E; ITC, indirect treatment comparison; SCS, systemic corticosteroids.

^a For patients included in the base case meta-analysis only.^b Including patients potentially eligible for both mepolizumab and omalizumab.^c Including all patients eligible for mepolizumab regardless of their eligibility for omalizumab.^d Provided data for all efficacy and safety endpoints in the primary Bayesian network meta-analysis of the Overlap and Trial populations.^e Provided data for all safety endpoints in the primary Bayesian network meta-analysis of the Overlap and Trial populations.^f Provided data for exacerbations and safety endpoints in the primary Bayesian network meta-analysis of the Trial population.

3.3. Safety

Both mepolizumab and omalizumab were broadly comparable to placebo in terms of their overall safety profile based on the endpoints assessed. In general, there was no difference between mepolizumab and omalizumab on the likelihood of AEs and SAEs in either population (Figs. 2 and 3). There was a lower likelihood of withdrawal due to AEs with mepolizumab, compared with omalizumab in both populations (Figs. 2 and 3). Due to the low incidence of fatal AEs, the analysis of fatal AEs could only be carried out in the Trial population. No difference in the rate of fatal AEs was found (data not shown).

3.4. Additional analyses

Overall, the additional analyses were broadly consistent with the main analyses described above (e.g. Frequentist vs Bayesian [Table S4]; sensitivity analyses including additional data from mepolizumab 75 mg IV data and eligible open-label omalizumab RCTs vs the primary analysis [Table S5] and Extended overlap populations vs Overlap and Trial population analyses [Table S6]).

4. Discussion

There are now several treatments available for severe asthma, including mepolizumab and omalizumab, which target the persistent eosinophilic and allergic phenotypes, respectively [5,8]. Approximately half of patients with severe asthma may exhibit both phenotypes [19] and about one third of patients with severe asthma may be eligible for both biologic treatments [14]. Consequently, it is important to determine the comparative efficacy and tolerability of mepolizumab and omalizumab in these patients in order to assist clinical and payer decision making. Indeed, a recent review article of treatments for severe asthma has highlighted the need for comparisons [20]. Although head-to-head studies would

be the preferred method to investigate relative treatment effects, in the absence of these studies, an ITC can be conducted. This analysis evaluated the comparative efficacy and tolerability of mepolizumab and omalizumab in patients with severe asthma and a history of exacerbations.

The evidence base for this ITC was identified through a systematic literature review conducted according to accepted methodology (ie., PRISMA guidelines) and further refined by the application of PICOS framework eligibility criteria. These studies provided the evidence base for a Bayesian network meta-analysis of the rate of clinically significant exacerbations, exacerbations requiring hospitalization, % predicted FEV₁, and four safety endpoints.

Compared with omalizumab, mepolizumab treatment was associated with greater reductions in the rate of clinically significant exacerbations in the Trial population than omalizumab, with a trend in favor of mepolizumab in the Overlap population. Trends in favor of mepolizumab were also shown in the rate of exacerbations requiring hospitalization. Changes in lung function and safety profiles were broadly comparable between the two treatments. Overall results were similar when exacerbation history requirements were varied between the Overlap and Trial populations, and that the tolerability profiles of both treatments were largely comparable. Results of the Frequentist analysis and sensitivity analyses (including additional data from mepolizumab 75 mg IV and omalizumab open-label trials) were consistent with the primary analysis, providing support for these results and the study conclusions. However, while it is difficult to make definitive conclusions based on this analysis, these results suggest that mepolizumab may be at least as effective as omalizumab.

However, the literature search revealed heterogeneity in trial design, disease severity, exacerbation history and phenotype of the patients enrolled in the identified omalizumab and mepolizumab RCTs. Heterogeneity in the ITC was reduced by the application of stricter inclusion criteria, which sought to harmonize study designs

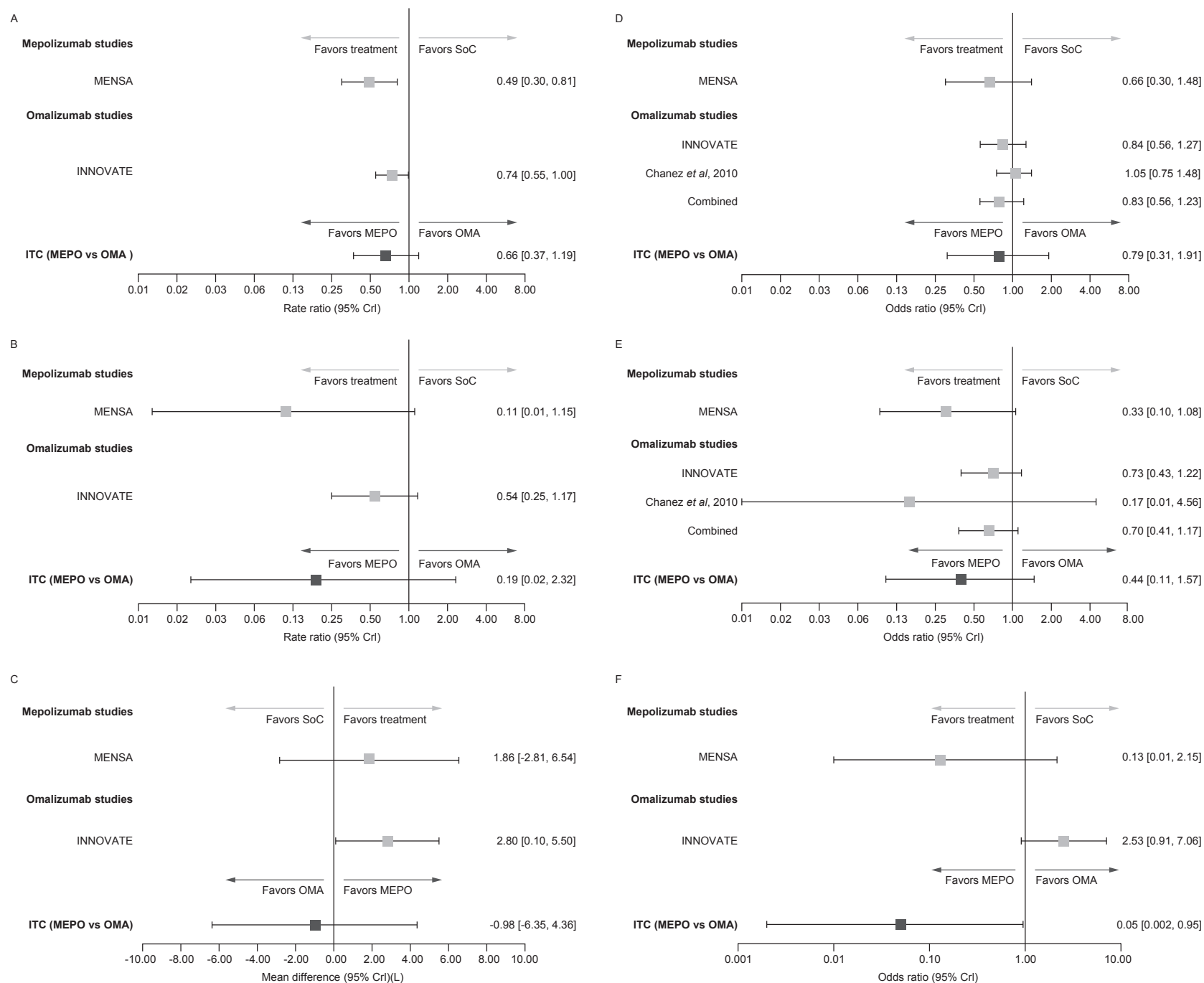


Fig. 2. Results of the Bayesian analysis for Overlap population: A) clinically significant exacerbations; B) exacerbations requiring hospitalization; C) change in % predicted FEV₁; D) adverse events; E) serious adverse events; F) withdrawals due to adverse events.

Overlap population: including patients potentially eligible for both mepolizumab and omalizumab.

CrI, credible interval; ITC, indirect treatment comparison; MEPO, mepolizumab; OMA, omalizumab; SoC, standard of care.

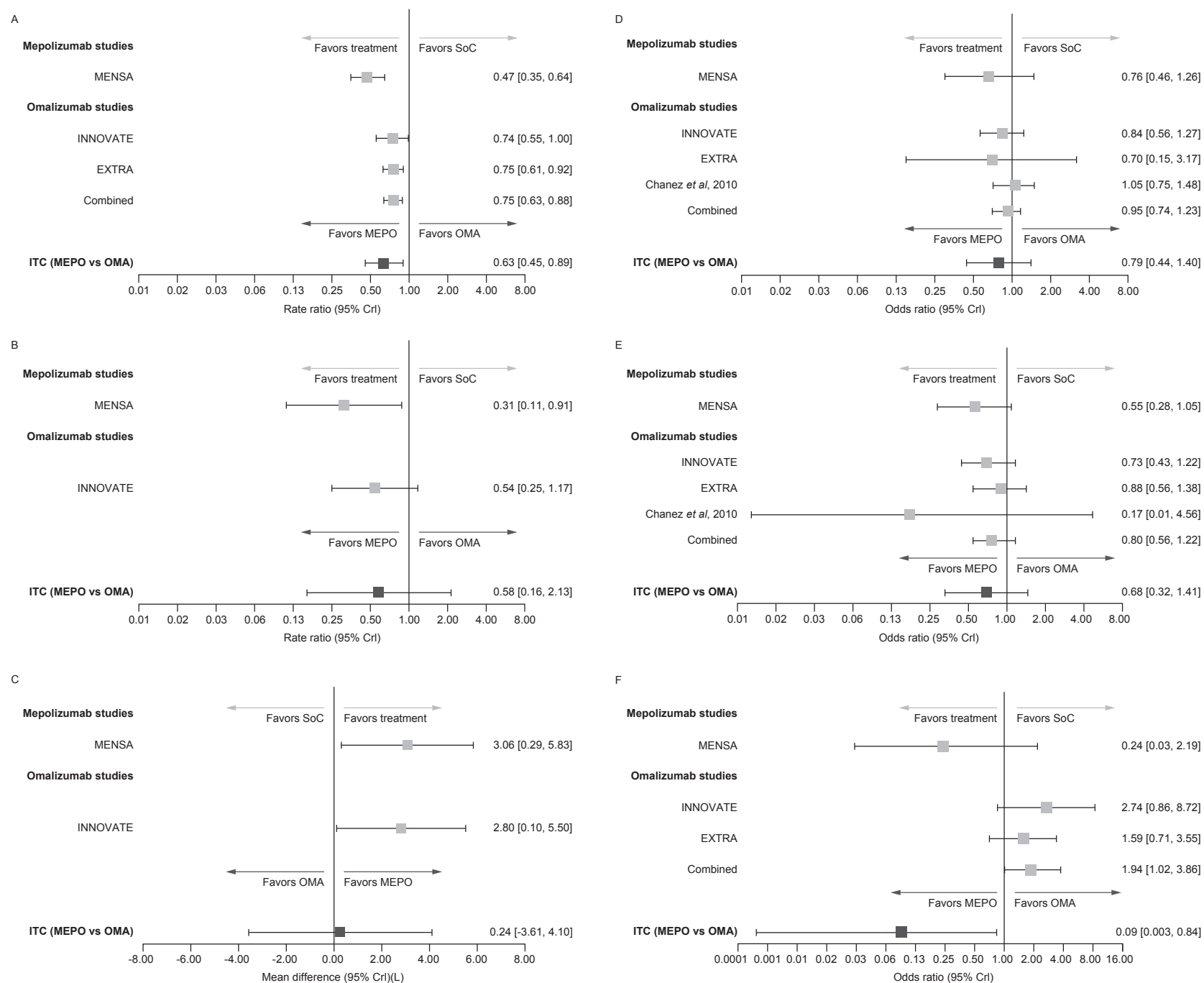


Fig. 3. Results of the Bayesian analysis for Trial population: A) clinically significant exacerbations; B) exacerbations requiring hospitalization; C) change in % predicted FEV₁; D) adverse events; E) serious adverse events; F) withdrawals due to adverse events.

CrI, credible interval; ITC, indirect treatment comparison; MEPO, mepolizumab; OMA, omalizumab; SoC, standard of care.

Overlap population: including patients potentially eligible for both mepolizumab and omalizumab.

and patient populations, and ensure a more valid treatment comparison. Consequently, only the mepolizumab MENSA and the omalizumab INNOVATE trials met the eligibility criteria for the Overlap population analysis [12,16]. Whilst these two studies are pivotal regulatory trials, they provide a limited evidence base.

Despite the attempts to reduce heterogeneity through the ITC inclusion criteria, it is possible that some heterogeneity remained, since it was not possible to identify the true Overlap population. Mepolizumab targets a specific asthma population with eosinophilic inflammation and a history of frequent exacerbations [5,6]. In contrast, omalizumab targets a more heterogeneous population of patients with allergic moderate-to-severe disease, without any specific requirement for previous exacerbations [8,9]. No omalizumab RCTs were identified that enrolled patients with the same exacerbation history as the mepolizumab MENSA trial [12], potentially biasing analysis results towards mepolizumab. The impact of differences in patient exacerbation histories was explored through the analysis of the Overlap and Extended overlap populations. Relaxing the criteria around exacerbation history had little impact on the results. The small number of eligible studies precluded the application of meta-regression to further reduce any residual heterogeneity.

The lack of individual patient-level data prevented the identification of patients from omalizumab studies with blood eosinophil counts that met mepolizumab eligibility requirements. However, the potential impact of this missing information on the assumptions of the ITC can be informed to some extent by a recently published post hoc subgroup analysis of the INNOVATE trial [21]. The results of this analysis indicate that in patients with blood eosinophil counts ≥ 300 cells/ μ L, the rate of clinically significant exacerbations was reduced by 39% with omalizumab compared with placebo [21]. Similarly, in a subgroup of patients from the MENSA and DREAM trials with blood eosinophil counts ≥ 300 cells/ μ L, the rate of clinically significant exacerbations was reduced by 59% with mepolizumab (pooled data from the 100 mg SC and 75 mg IV doses) compared with placebo [22]. These data suggest that if eosinophil data for patients treated with omalizumab had been available, it is unlikely that their incorporation would have altered the conclusions of this analysis.

Although this analysis sought to assess a broad range of endpoints, not all of these outcomes could be assessed. For example, asthma control and HRQoL could not be included in the analysis; different measures were used in the mepolizumab and omalizumab trials, preventing comparison. However, the included efficacy endpoints of clinically significant exacerbations and exacerbations requiring hospitalizations are very relevant endpoints for patients, payers, and clinicians. These endpoints represent an acute loss of asthma control that has a significant impact on the patients' health status, as well as being costly to healthcare systems [23–26]. Although, it was not possible to analyze a full range of safety endpoints, there were sufficient data to include any on-treatment AEs, SAEs, and AEs leading to discontinuation or withdrawals. The results from these endpoints should be evaluated while bearing in mind the heterogeneity in study designs and patient populations between ITC included studies. In particular, differences in the length of time between clinical visits may influence patient recall of AEs, and the existence of an extension study for the mepolizumab population may have influenced the rate of withdrawals. Additionally, the average patient age was greater in the mepolizumab MENSA trial [12] (~50 years of age) than in the omalizumab INNOVATE and EXTRA trials (43–45 years of age) [16,18]; consequently, the number of asthma comorbidities in these patients may have differed, suggesting that the comparison of treatment AE profiles between RCTs should be interpreted with caution. Despite these limitations, this analysis provided evidence on the relative

tolerability of mepolizumab and omalizumab and suggested their tolerability profiles did not meaningfully differentiate.

In summary, this ITC compared the efficacy and tolerability of mepolizumab and omalizumab. Restrictions in terms of data availability led to a number of study limitations, which have been acknowledged and which were partially tested by additional scenarios and sensitivity analyses. These additional analyses supported the results from the primary analysis, which suggested that in patients with severe asthma eligible to receive both treatments, mepolizumab seems to be at least as efficacious as omalizumab at reducing exacerbations and improving lung function, and that the tolerability profiles of the two treatments do not seem to meaningfully differentiate.

Role of the funding source

This study was funded by GlaxoSmithKline (GSK; 200227). The study was conducted in accordance with GSK policy that all results, regardless of study outcome should be published in a timely manner. Authors were in full editorial control of publication target journal, content and conclusions and accepted full responsibility for final approval of a manuscript describing this GSK sponsored research. The planning and development of publications is a scientific and medical function and GSK did not permit commercial staff to participate in the design, conduct or publication of human subject research. As agreed by authors before the preparation of the manuscript began, authors were provided with open and transparent access to data supporting publications including access to data tables, final study reports, case report forms and raw data as needed. The manuscript was prepared in line with Good Publication Practices: GSK does not pay for authorship of peer-reviewed articles or presentations, although GSK may reimburse reasonable expenses associated with authorship or congress presentations (e.g. travel expenses related to attendance at author meetings or congress presentations). Notable exceptions are the use of professional medical writers: If the authors request medical writing support, this is fully disclosed in the conflict of interests section in the manuscript. The decision to submit for publication was that of the authors alone. The sponsor did not place any restrictions on access to the data or on the statements made in the manuscript. The corresponding author had final responsibility for the decision to submit for publication.

Editorial support (in the form of writing assistance, including development of the initial draft based on author direction, assembling tables and figures, collating authors comments, grammatical editing and referencing) was provided by Alex Lowe, PhD and Elizabeth Hutchinson, PhD, at Fishawack Indicia Ltd, UK, and was funded by GSK.

Author contributions

GS, DP, NBG, RA-C, JWIL, SMC contributed to the study concept and design, in data acquisition, analysis and interpretation. ESB, JWex, and FCA contributed to the study concept and design and analysis and interpretation. All authors were involved in preparation and review of the manuscript and approved the final version to be submitted.

Conflict of interest

SMC, NBG, DP, JWIL, ESB, FCA and RA-C are all employees of GSK and own stock in GSK. JWex has no conflicts to declare. GS was an employee of GSK during the conduct of the study and owns stock in GSK.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmed.2016.12.009>.

References

- [1] G.I.F. Asthma, GINA Report, Global Strategy for Asthma Management and Prevention, 2015 (accessed February 2016), <http://www.ginasthma.org/documents/4>.
- [2] K.F. Chung, S.E. Wenzel, J.L. Brozek, et al., International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma, *Eur. Respir. J.* 43 (2014) 343–373.
- [3] S. Wenzel, Severe asthma: from characteristics to phenotypes to endotypes, *Clin. Exp. Allergy* 42 (2012) 650–658.
- [4] K. Al Efraji, J.M. FitzGerald, Current and emerging treatments for severe asthma, *J. Thorac. Dis.* 7 (2015) E522–E525.
- [5] GSK, NUCALA® Highlights of Prescribing Information, 2015 (accessed May 2016), https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL.PDF.
- [6] GSK, NUCALA® Summary of Product Characteristics, 2015 (accessed May 2016), https://www.google.co.uk/search?q=Summary+of+product+characteristics&ie=utf-8&oe=utf-8&client=firefox-b-ab&gfe_rd=cr&ei=Ttl-V6nsCOjS8Afxkb6IDw#q=Summary+of+product+characteristics.
- [7] J.G. Ayres, B. Higgins, E.R. Chilvers, et al., Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma, *Allergy* 59 (2004) 701–708.
- [8] Genetech, XOLAIR® Highlights of Prescribing Information, 2003 (accessed May 2016), http://www.gene.com/download/pdf/xolair_prescribing.pdf.
- [9] Genetech, XOLAIR® Summary of Product Characteristics, 2009 (accessed May 2016), http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000606/WC500057298.pdf.
- [10] E.H. Bel, S.E. Wenzel, P.J. Thompson, et al., Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma, *N. Engl. J. Med.* 371 (2014) 1189–1197.
- [11] W. Busse, J. Corren, B.Q. Lanier, et al., Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma, *J. Allergy. Clin. Immunol.* 108 (2001) 184–190.
- [12] H.G. Ortega, M.C. Liu, I.D. Pavord, et al., Mepolizumab treatment in patients with severe eosinophilic asthma, *N. Engl. J. Med.* 371 (2014) 1198–1207.
- [13] M. Soler, J. Matz, R. Townley, et al., The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics, *Eur. Respir. J.* 18 (2001) 254–261.
- [14] GSK, 201722_Clinical-Study-Result-Summary, 2016 (accessed August 2016), http://www.gsk-clinicalstudyregister.com/search/?study_ids=201722#.
- [15] R.Y. Suruki, N. Gunsoy, J. Shin, et al., The identification and description of severe asthma patients in a cross-sectional study—the IDEAL study, *J. Allergy. Clin. Immunol.* 137 (Supplement) (2016) AB103.
- [16] M. Humbert, R. Beasley, J. Ayres, et al., Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE, *Allergy* 60 (2005) 309–316.
- [17] P. Chanez, C. Contin-Bordes, G. Garcia, et al., Omalizumab-induced decrease of Fc ϵ RI expression in patients with severe allergic asthma, *Respir. Med.* 104 (2010) 1608–1617.
- [18] N.A. Hanania, O. Alpan, D.L. Hamilos, et al., Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial, *Ann. Intern. Med.* 154 (2011) 573–582.
- [19] T.N. Tran, R.S. Zeiger, S.P. Peters, et al., Overlap of atopic, eosinophilic, and TH2-high asthma phenotypes in a general population with current asthma, *Ann. Allergy. Asthma. Immunol.* 116 (2016) 37–42.
- [20] M.F. Patterson, L. Borish, J.L. Kennedy, The past, present, and future of monoclonal antibodies to IL-5 and eosinophilic asthma: a review, *J. Asthma. Allergy* 8 (2015) 125–134.
- [21] M. Manga, M. Humbert, R. Djukanovic, et al., Blood eosinophils and serum IgE predict response to omalizumab in patients with severe allergic asthma: innovate trial post-hoc analysis, *J. Allergy. Clin. Immunol.* 137 (Supplement) (2016) AB1–AB412.
- [22] H.G. Ortega, S.W. Yancey, B. Mayer, et al., Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies, *Lancet. Respir. Med.* 4 (2016) 549–556.
- [23] S. Cockle, L. Nelsen, M. Kimel, F. Albers, P. Jones, Impact of asthma exacerbations on health status in patients with severe asthma, *J. Allergy. Clin. Immunol.* 137 (Supplement) (2016) AB8.
- [24] M. Filipowski, A. Bozek, R. Kozłowska, D. Czyżewski, J. Jarzab, The influence of hospitalizations due to exacerbations or spontaneous pneumothoraces on the quality of life, mental function and symptoms of depression and anxiety in patients with COPD or asthma, *J. Asthma* 51 (2014) 294–298.
- [25] M. Kupczyk, A. ten Brinke, P.J. Sterk, et al., Frequent exacerbators—a distinct phenotype of severe asthma, *Clin. Exp. Allergy* 44 (2014) 212–221.
- [26] R.S. Zeiger, M. Schatz, A.A. Dalal, et al., Utilization and costs of severe uncontrolled asthma in a managed-care setting, *J. Allergy Clin. Immunol. I Pract.* 4 (2016) 120–129.

Supplementary Appendix A.

Systematic literature review methods

Randomized controlled trials

Search strategy

All databases were searched without time frame or language limitations imposed, with the exception of conference abstracts. Conference abstracts were only searched from 2012 until the date of search. It was assumed that abstracts published earlier than 3 years at the relevant conferences would have been published as full-text articles. It was expected that the mepolizumab RCT data would be most extensively detailed in clinical study reports. Therefore, the relevant data from the clinical study reports were added to the identified systematic literature review results after the search and selection phase as the primary source of mepolizumab clinical trial data. The following databases were searched:

Search engine (website)	Databases	Limits
ProQuest (www.proquest.com/)	• Medline® • EMBASE® • MEDLINE® In-Process • PASCAL	No limits
Cochrane (www.cochrane.org/)	• CDSR • DARE • CENTRAL • HTA	No limits
NIHR (http://www.hta.ac.uk/erg/index.asp)	• ERG reports • Manufacturers submissions	No limits
Conference abstracts (http://www.thoracic.org/) (http://ersnet.org/) (http://www.chestnet.org/)	• ATS • ERS • ACCP	Time limit (years): 2012–2014 (2015 conference abstracts not yet available)
Clinical trial registries (https://clinicaltrials.gov/ct2/home) (http://www.anzctr.org.au/) (http://www.ensaioclinicos.gov.br/)	• NIH ClinicalTrials.gov Register • ANZCTR • ReBec	No limits

ACCP, American College of Chest Physicians; ATS, American Thoracic Society; ANZCTR, Australian New Zealand Clinical Trials Registry; CDSR, Cochrane - systematic reviews; CENTRAL, Cochrane - central register of controlled trials; DARE, Database of Abstracts of Reviews of Effects; ERG, Evidence Review Group; ERS, European Respiratory Society; HTA, Health Technology Assessments Database; NIH, National Institutes for Health; NIHR, National Institute for Health Research; ReBec, Registro Brasileiro de Ensaios Clínicos.

Search terms and study eligibility criteria

The search strategy combined search terms (free-text, Emtree/MESH terms and brand names) for asthma and relevant treatments (mepolizumab and omalizumab, reslizumab, benralizumab, tralokinumab, lebrikizumab, dupilumab, tiotropium, and maintenance OCS). If a more extensive search was possible in the available search engines these terms were additionally combined with search terms (free-text, Emtree/Medical Subject Headings terms) for RCTs. The following search terms:

Search engine (database)	Search no. (search terms)
ProQuest (Medline® EMBASE® MEDLINE® in progress)	Asthma: #1: TI,AB(asthma) OR EMB("asthma") OR MESH("asthma"); #2: TI,AB(mepolizumab OR bosatria) OR EMB("mepolizumab"); #3: TI,AB(omalizumab OR xolair OR "rhumab-e25") OR EMB("omalizumab"); #4: TI,AB(reslizumab OR cinquil) OR EMB("reslizumab"); #5 TI,AB(benralizumab) OR EMB("benralizumab"); #6: TI,AB(tralokinumab) OR EMB("tralokinumab") #7: TI,AB(lebrikizumab) OR EMB("lebrikizumab"); #8: TI,AB(dupilumab) OR EMB("dupilumab") #9: TI,AB(tiotropium OR spiriva OR tiova) OR EMB("tiotropium") #10: (TI,AB(oral) OR EMB.EXACT("oral drug administration") OR MESH.EXACT.EXPLODE("Administration, Oral")) AND (TI,AB(steroid* OR glucocorticoid* OR corticosteroid* OR glucocosteroid* OR cyclocosteroid* OR beclomethasone OR beclometasone OR beclamet OR beclocort OR becotide OR betamethasone OR betadexamethasone OR flubenisolone OR celeston* OR cellestoderm OR betnelan OR oradexon OR dexamethasone OR dexameth OR dexone OR dexametasone OR decadron OR dexasone OR hexadecadron OR hexadrol OR methylfluorprednisolone OR millicorten OR flunisolide OR fluticasone OR hydrocortisone OR cortisol OR cortifair OR cortril OR hyrocortone OR cortef OR epicortisol OR efcortisol OR methylprednisolone OR medrol OR metripred OR urbason OR mometasone OR prednisolone OR prednisolon OR precortisyl OR deltacortril OR deltastab OR prednesol OR deltasone OR prednisone OR prednison OR cortan OR paramethasone OR triamcinolone OR aristocort OR volon OR deflazacort OR atolone OR kenacort OR orasone OR panasol OR prednicen OR azathioprine OR imuran OR "oral gold" OR terbutaline OR brethine OR bricanyl OR ciclosporin OR neoral OR sandimmune OR methotrexate OR maxtrex OR panafcortelone OR ciclesonide OR alvesco OR budesonide OR budelin OR pulmicort OR qvar OR "clenil modulate" OR asmabec OR becodisks OR flixotide OR asmanex) OR EMB.EXACT.EXPLODE("corticosteroid") OR MESH.EXACT.EXPLODE("Adrenal Cortex Hormones")) #11: #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 Asthma & treatment: #12: #1 AND #11; Study design (RCT): #13: (TI,AB(randomi*ed controlled trial) OR TI,AB(clinical AND (stud* OR trial*) AND (control OR blind OR random OR randomi*ed))) OR (randomi*ed AND (EMB.EXACT.EXPLODE("controlled clinical trial") OR MESH.EXACT.EXPLODE("Controlled Clinical Trial")) OR (EMB.EXACT.EXPLODE("randomized controlled trial") OR MESH.EXACT.EXPLODE("Randomized Controlled Trial")) Asthma & treatment & study design: #14: #12 AND #13

Cochrane (CDSR, DARE, CENTRAL, HTA)	Asthma: #1: asthma:ti,ab,kw #2: MeSH descriptor: [Asthma] #3: #1 OR #2 Treatment: #4: mepolizumab:ti,ab,kw OR bosatria:ti,ab,kw #5: omalizumab:ti,ab,kw OR xolair:ti,ab,kw OR “rhumab-25”:ti,ab,kw #6: reslizumab:ti,ab,kw OR cinquil:ti,ab,kw #7: benralizumab:ti,ab,kw #8: tralokinumab:ti,ab,kw #9: lebrikizumab:ti,ab,kw, #10: dupilumab:ti,ab,kw, #11: tiotropium:ti,ab,kw or spiriva:ti,ab,kw OR tiova:ti,ab,kw, #12: oral:ti,ab and (steroid* or glucocorticoid* or corticosteroid* or glucocosteroid* or cyclocosteroid* or beclomethasone or beclometasone or beclamet or beclocort or becotide or betamethasone or betadexamethasone or flubenisolone or celeston* or cellestoderm or betnelan or oradexon or dexamethasone or dexameth or dexone or dexametasone or decadron or dexasone or hexadecadron or hexadrol or methylfluorprednisolone or millicorten or flunisolide or fluticasone or hydrocortisone or cortisol or cortifair or cortril or hyrocortone or cortef or epicortisol or efcortesol or methylprednisolone or medrol or metripred or urbason or mometasone or prednisolone or prednisolon or precortisyl or deltacortril or deltastab or prednesol or deltasone or prednisone or prednison or cortan or paramethasone or triamcinolone or aristocort or volon or deflazacort or atolone or kenacort or orasone or panasol or prednicen or azathioprine or imuran or "oral gold" or terbutaline or brethine or bricanyl or ciclosporin or neoral or sandimmune or methotrexate or maxtrex or panafcortelone or ciclesonide or alvesco or budesonide or budelin or pulmicort or qvar or "clenil modulate" or asmabec or becodisks or flixotide or asmanex):ti,ab,kw #13: #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 Asthma and treatment: #14: #3 AND #10 Study design (RCT): #15: (randomi*ed controlled trial):ti,ab,kw or (clinical and (stud* or trial*) and (control or blind or random or randomi*ed)):ti,ab,kw or MeSH descriptor: [Randomized Controlled Trial] or (randomi*ed) and MeSH descriptor:[Controlled Trial]) Asthma & treatment & study design: #16: #14 AND #15
NIHR (ERG reports Manufacturers submissions)	Asthma: #1: asthma
Conference abstracts (ATS, ERS, ACCP)	ATS #1: All abstracts from 2012, 2013, 2014,; ERS : #1: All abstracts from 2012, 2013; ACCP: #1: All abstracts from 2012, 2013, 2014

**Clinical trial registries (NIH
ClinicalTrials.gov Register,
ANZCTR, ReBec)**

NIH: #1: asthma AND (mepolizumab OR bosatria) **#2:** asthma AND (omalizumab OR xolair) **#3:** asthma AND (reslizumab OR cinquil) **#4:** asthma AND benralizumab **#5:** asthma AND tralokinumab **#6:** asthma AND lebrikizumab **#7:** asthma AND dupilumab **#8:** asthma AND (tiotropium OR spiriva OR tiova) **#9:** asthma AND oral AND (steroid OR corticosteroid) **#10:** asthma AND (prednisolone OR prednisolon OR prednisone OR prednison)

ANZCTR: #1: mepolizumab **#2:** bosatria **#3:** omalizumab **#4:** xolair **#5:** reslizumab **#6:** cinquil **#7:** benralizumab **#8:** tralokinumab **#9:** lebrikizumab **#10:** dupilumab **#11:** tiotropium **#12:** Spiriva **#13:** tiova **#14:** asthma(as health condition) AND steroid **#15:** asthma(as health condition) AND prednisolone **#16:** asthma(as health condition) AND prednisone

ReBec: #1: mepolizumab **#2:** bosatria **#3:** omalizumab **#4:** xolair **#5:** reslizumab **#6:** cinquil **#7:** benralizumab **#8:** tralokinumab **#9:** lebrikizumab **#10:** dupilumab **#11:** tiotropium **#12:** Spiriva **#13:** tiova **#14:** steroid **#15:** prednisolone OR prednisolon **#16:** prednisone OR prednison

AB, search in abstract; ATS, American Thoracic Society; ANZCTR, Australian New Zealand Clinical Trials Registry; CDSR, Cochrane - systematic reviews; CENTRAL, Cochrane - central register of controlled trials; DARE, Database of Abstracts of Reviews of Effects; ERG, Evidence Review Group; ERS, European Respiratory Society; EMB, search as Emtree term; HTA, Health Technology Assessments Database; kw, search in keywords; MESH, search as Mesh term; NIH, National Institutes for Health; NIHR, National Institute for Health Research; ReBec, Registro Brasileiro de Ensaios Clinicos, TI, search in title.

After the searches were performed, the hits from all databases were combined in one Excel file and used to remove duplicate records and to record the reasons for inclusion and exclusion. Duplicates were identified using Excel functions to match titles and authors from different data sources. The eligibility of all articles was assessed based on pre-specified inclusion and exclusion criteria applied by two independent researchers in two rounds. For the first selection round, the title and abstract were evaluated. For the second selection round, full text articles were evaluated if eligibility remained uncertain after the previous selection round. The eligibility of non-English publications was assessed based on their English abstracts. For publications without English abstracts, articles were screened by individuals in the wider search team who spoke the language, or by using an online translation tool. In case of discrepancies between the two researchers with respect to the final selection of RCTs, a third reviewer was consulted who would make the final decision on inclusion. Eligibility criteria are shown below:

Topic	Inclusion criteria	Exclusion criteria
Population	- Patients with asthma with the following characteristics: - Age >12 years) - Severe (or refractory/difficult-to-treat/persistent/treatment-resistant/uncontrolled) asthma - Patients with and without eosinophilic and allergic asthma subtypes were included	- Non-humans - Healthy subjects - Other (respiratory) diseases besides asthma - Age ≤12 years - Mild/moderate asthma^a - Studies including patients with severe asthma, but not reporting results for this (sub)population
Intervention	- Active arm, BSC (ICS/LABA) with: - Mepolizumab - Omalizumab - Reslizumab - Benralizumab - Tralokinumab - Lebrikizumab - Dupilumab - Tiotropium - Maintenance OCS	- Studies not investigating one of the following treatments in the active arm: - Mepolizumab - Omalizumab - Reslizumab - Benralizumab - Tralokinumab - Lebrikizumab - Dupilumab - Tiotropium - Maintenance OCS - Studies investigating the impact of acute OCS treatment
Comparators	- Comparator arm: - Placebo - BSC - Active comparator (mepolizumab, omalizumab, reslizumab, benralizumab, tralokinumab, lebrikizumab, dupilumab, tiotropium, maintenance OCS)	Studies not investigating placebo, BSC or relevant active comparator in the comparator arm
Outcomes	- Publications reporting at least one of the following outcomes: - Exacerbations - Lung function - Asthma control - Symptoms	Publications without at least one of the relevant endpoints

	- o Steroid sparing rescue medication use (OCS/ICS) - o Hospitalizations - o HRQoL (utilities) - o Safety and tolerability	
Study design	• Double-blind, single-blind and open-label RCTs^b reporting efficacy and/or safety results (without restriction to date or language or study duration) • Systematic reviews including references to relevant RCTs^b	• Non-randomized clinical trials, case reports • Systematic reviews discussing only other trial designs besides RCTs or not discussing relevant outcomes • Posters which report no new/different study outcomes than the full publication reporting on the same trial
Language	• Publications in all languages were included	• Not applicable
Timeframe	• Conference proceedings from the last 3 years (2012–2014) • No time limit was applied to all other publications and reports	• Conference proceedings older than 3 years (<2012)

^aStudies with mild and/or moderate asthma patients were excluded in this review. Studies with patients with moderate/severe asthma were included, if the majority of the patients had severe asthma (see protocol deviations); ^bRCT data were only extracted from publications that report primary results. Systematic reviews were screened for references to relevant RCTs, but data were not extracted from this source.

BSC, best standard care; HRQoL, health-related quality of life; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; OCS, oral corticosteroid; RCT, randomized controlled trial.

Data extraction

An empty Excel data extraction file was developed for one formal review round before the data-extraction process was started. One researcher extracted the data and a second researcher independently checked the data extraction forms, in accordance with Centre for Review and Dissemination guidelines.[55] The second reviewer verified the data extraction file for accuracy and completeness, by checking if all data presented in the Excel file corresponded directly with what was presented in the selected articles. Thus the second reviewer did not only review a sample, but checked all articles.

If article data were presented in a 2D graph, xyExtract software was used to obtain an accurate estimate of the presented values.

Identified articles were categorized according to the clinical study reference number. Thus in cases where multiple articles report data from a single study - with no difference in design, methodology or patient population - these publications were treated as duplicates and all data from the identified articles were reported under the clinical trial reference number in the data extraction file. In cases where a subsequent publication provides pooled data across studies, this was treated as a new study (ie, not included under the clinical trial reference number of pooled studies), and data were extracted separately.

Reported data for all different subpopulations were inserted in the data extraction file. Relevant subpopulations were eosinophilic asthma (including low and high eosinophil levels) and different degrees of severe asthma. The different degrees could be defined in terms of the number, type and severity of exacerbations, including hospitalization for an asthma exacerbation, or according to

published severity guidelines,[1, 56] or according to concomitant treatment received such as maintenance OCS.

If case outcomes at different time points were reported, all published data were included in the data-extraction file. In the Excel file a clear differentiation between primary and secondary outcomes was made. Data from online supplements or appendices were also included.

Quality assessment

After the data-extraction process was completed, a critical appraisal of the quality of the selected RCTs was performed by a single researcher as per National Institute for Health and Care Excellence guidelines.[57] Quality assessment was performed by assessing the following questions, adapted from Centre for Reviews and Dissemination (2008) Systematic Reviews[55]:

Trial no. (acronym)	Answers per trial
Was randomization carried out appropriately?	(yes/no/not clear/N/A)
Was the concealment of treatment allocation adequate?	(yes/no/not clear/N/A)
Were the groups similar at the outset of the study in terms of prognostic factors?	(yes/no/not clear/N/A)
Were the care providers, participants and outcome assessors blind to treatment allocation?	(yes/no/not clear/N/A)
Were there any unexpected imbalances in drop-outs between groups?	(yes/no/not clear/N/A)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	(yes/no/not clear/N/A)
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	(yes/no/not clear/N/A)
N/A, not applicable.	

Supplementary Appendix B.

Indirect treatment comparison methods

Bayesian modelling

Model specification and assumptions for each outcome type are detailed in the table below.

For the between-trial standard deviation (σ), a uniform distribution with a range of 0 to 0.5–5 was used. The upper limit of this uniform distribution was determined by comparing the posterior distribution of σ to the prior distribution of σ to ensure that it was sufficiently different from the prior. If not sufficiently different, this would indicate that the prior is dominating the data and no posterior updating has taken place. In cases where the prior and posterior could not be discerned, the upper limit was set to 0.5. Uninformative priors were used for all other parameters.

Posterior distributions were estimated through Gibbs sampling using 3 chains of 50,000 iterations including a burn-in of 20,000. Estimates (expressed as rate ratio, odds ratio, or mean difference depending on type of analysis) along with their 95% credible interval (CrI) were reported.

Convergence assessment was based on visual inspection of trace and autocorrelation plots and on the Gelman-Rubin-Brooks diagnostic $\hat{R} < 1.2$. The accuracy of the posterior estimates was assessed using the Monte Carlo error (< 5% of the posterior SD) for each parameter.

To select between fixed- or random-effects, the model with smallest deviance Information Criterion (DIC) and residual deviance was chosen.

	A) Rate data (exacerbation rates)	B) Continuous data (lung function)	C) Binary outcomes (yes/no) (safety data)
Model	A normal distribution for the continuous measure of the treatment effect of arm k relative to arm 1 in study j, y_{jk}, with with variance σ_{jk}^2 such that: $y_{jk} \sim \text{Normal}(\theta_{jk}, 1/\sigma_{jk}^2)$ $\theta_{jk} = \delta_{j,bk}$ $k = B, C, D$, if k is after b $\delta_{j,bk} \sim \text{Normal}(d_{bk}, \sigma^2) = \text{Normal}(d_{Ak} - d_{Ab}, \sigma^2)$ $d_{AA} = 0$	A normal distribution for the continuous measure of the treatment difference of arm k relative to arm 1 in study j, y_{jk}, with variance σ_{jk}^2 such that: $y_{jk} \sim \text{Normal}(\theta_{jk}, 1/\sigma_{jk}^2)$ $\theta_{jk} = \delta_{j,bk}$ $k = B, C, D$, if k is after b $\delta_{j,bk} \sim \text{Normal}(d_{bk}, \sigma^2) = \text{Normal}(d_{Ak} - d_{Ab}, \sigma^2)$ $d_{AA} = 0$	The number of subjects with an event was assumed to follow a Binomial distribution $r_{jk} \sim \text{Binomial}(p_{jk}, n_{jk})$ The probabilities of success p_{jk} were modelled on the logit scale: $r_{jk} \sim \text{Binomial}(p_{jk}, n_{jk})$ $\text{logit}(p_{jk}) = \begin{cases} \mu_{jb} & b = A, B, C, \text{ if } k = b \\ \mu_{jb} + \delta_{jbk} & k = B, C, D, \text{ if } k \text{ is after } b \end{cases}$ $\delta_{jbk} \sim \text{Normal}(d_{bk}, \sigma^2) = \text{Normal}(d_{Ak} - d_{Ab}, \sigma^2)$ $d_{AA} = 0$
Priors	$d_{Ak} \sim \text{Normal}(0, 0.0001)$ $FE \rightarrow \sigma = 0$ $RE \rightarrow \sigma \sim \text{Uniform}(0.05 - 5)$	$d_{Ak} \sim \text{Normal}(0, 0.0001)$ $FE \rightarrow \sigma = 0$ $RE \rightarrow \sigma \sim \text{Uniform}(0.05 - 5)$	$\mu_{jb} \sim \text{Normal}(0, 0.0001)$ $d_{Ak} \sim \text{Normal}(0, 0.0001)$ $FE \rightarrow \sigma = 0$ $RE \rightarrow \sigma \sim \text{Uniform}(0.05 - 5)$
j = study, b = control group (can be treatment A, B, C, k = treatment group (can be B, C, D), y_{jk} = effect estimate for treatment k in study j (log of rate-ratio for (A), treatment difference for (B)), θ_{jk} = the underlying outcome for treatment k in study j, μ_{jb} = odds of an event for 'baseline' treatment b in study j, σ^2 = constant variance of relative effects for each treatment versus reference treatment A across studies as a reflection of heterogeneity, δ_{jbk} = difference for treatment k relative to comparator b in study j (log of rate-ratio for (A), treatment difference for (B), log of odds ratio for (C)), σ_{jk}^2 = variance of effect estimate for treatment k in study j, d_{bk} = pooled difference treatment b relative to reference treatment k (log of rate-ratio for (A), treatment difference for (B), log of odds ratio for (C)), d_{Ak} = pooled difference treatment k relative to reference treatment A (log of rate-ratio for (A), treatment difference for (B), log of odds ratio for (C)), d_{Ab} = pooled difference treatment b relative to reference treatment A (log of rate-ratio for (A), treatment difference for (B), log of odds ratio for (C)), r_{jk} = number of events observed for the treatment k in study j, n_{jk} = number of subjects for treatment k in study j, and p_{jk} = probability of an event for treatment k in study j.			

Frequentist modelling

The Bucher method was applied as only two active treatments were indirectly compared (as shown in (a) below). The Bucher method requires evidence from each treatment to be combined separately before calculating the ITC estimate and uncertainty. Heterogeneity was assessed via test for heterogeneity where a p-value of ≤ 0.1 was interpreted as some evidence of heterogeneity. In these instances, random-effects methods were used.

Calculation for each type of outcome is specified as follows:

	Rate data (exacerbation rates)	Continuous data (lung function)	Binary outcomes (yes/no) (safety data)
Combining data for each treatment	Inverse-variance weighting (fixed effects) or DerSimonian and Laird (DSL) (random effects) applied to effect estimate (rate ratio, RR) and standard error (SE) of $\ln(RR)$.	Inverse-variance weighting (fixed effects) or DSL (random effects) applied to effect estimate (mean difference versus placebo, μ) and standard error (SE).	Mantel-Haenszel (fixed effects or random effects) applied to 2x2 contingency tables. Studies where no events were observed in both arms were excluded from analysis. For studies with a zero cell, treatment arm continuity correction (TACC) was applied, defined as $TCC=k/(R+k)$, $CCC=R/(R+k)$ where $TCC+CCC=k$; TCC =Treatment group Continuity Correction; CCC =Control group Continuity Correction; R =Ratio of group sizes (Treatment vs. Control group), and k =Proportionality constant. Where there was a zero cell in every study for one treatment, the PETO method was used.
Indirect estimate	$RR_{AB} = \frac{RR_{AC}}{RR_{BC}}$ $SE(\ln(RR_{AB})) = \sqrt{SE(\ln(RR_{AC}))^2 + SE(\ln(RR_{BC}))^2}$	$\mu_{AB} = \mu_{AC} - \mu_{BC}$ $SE(\mu_{AB}) = \sqrt{SE(\mu_{AC})^2 + SE(\mu_{BC})^2}$	$OR_{AB} = \frac{OR_{AC}}{OR_{BC}}$ $SE(\ln(OR_{AB})) = \sqrt{SE(\ln(OR_{AC}))^2 + SE(\ln(OR_{BC}))^2}$
RR = Rate ratio, A = Active treatment 1, B = Active treatment 2, C = Common comparator, SE = standard error, μ = Mean difference, OR = Odds ratio			

Supplementary data

Table S1. Quality assessment of systematic literature review results

Study	Randomization (Was randomization carried out appropriately?)	Concealment (Was the concealment of treatment allocation adequate?)	Similar groups (Were the groups similar at the outset of the study in terms of prognostic factors?)	Blinding (Were the care providers, participants and outcome assessors blind to treatment allocation?)	Drop-outs (Were there any unexpected imbalances in drop-outs between groups?)	Outcomes (Is there any evidence to suggest that the authors measured more outcomes than they reported?)	ITT (Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?)
Pavord 2012[1]	yes	yes	yes	yes	no	no	yes
Dotter 2014[2]	yes	yes	yes	yes	no	no	yes
Haldar 2009[3]	yes	not clear	yes	yes	no	no	yes
Nair 2009[4]	no	yes	yes	yes	no	no	yes
Bel 2014[5]	yes	yes	yes	yes	no	no	yes
Ortega 2014[6]	yes	yes	yes	yes	no	no	yes
Nair 2014[7]	yes	yes	yes	yes	no	no	yes
Holgate 2004[8]	not clear	not clear	yes	not clear	no	no	yes
Humbert 2005[9]	yes	not clear	yes	yes	no	no	yes
Sthoeger 2007[10]	yes	not clear	not clear	not clear	no	no	no
Humbert 2008[11]	yes	not clear	yes	yes	no	yes	yes
Hanania 2011[12]	yes	not clear	yes	yes	no	no	yes
Hanania 2013 [13]	yes	not clear	yes	yes	no	no	yes
Bardelas 2012[14]	not clear	yes	yes	not clear	no	no	yes
Busse 2001[15]	not clear	not clear	yes	not clear	yes	no	yes
Finn 2003[16]	not clear	not clear	yes	not clear	yes	yes	yes

Study	Randomization (Was randomization carried out appropriately?)	Concealment (Was the concealment of treatment allocation adequate?)	Similar groups (Were the groups similar at the outset of the study in terms of prognostic factors?)	Blinding (Were the care providers, participants and outcome assessors blind to treatment allocation?)	Drop-outs (Were there any unexpected imbalances in drop-outs between groups?)	Outcomes (Is there any evidence to suggest that the authors measured more outcomes than they reported?)	ITT (Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?)
Lanier 2003[17]	not clear	not clear	yes	not clear	yes	yes	yes
Garcia 2013[18]	not clear	yes	yes	yes	no	no	yes
Mohamed 2013[19]	not clear	not clear	not clear	not clear	not clear	no	not clear
Chanez 2010[20]	not clear	yes	yes	yes	no	no	yes
Massanari 2010[21]	not clear	yes	yes	yes	yes	no	yes
Ohta 2009[22]	not clear	not clear	yes	not clear	yes	no	yes
Ayres 2004[23]	not clear	no	yes	no	not clear	yes	yes
Niven 2008[24]	not clear	no	yes	no	not clear	no	no
Bousquet 2011[25]	yes	no	yes	no	yes	no	yes
Siergiejko 2011[26]	yes	no	yes	no	not clear	no	yes
Hoshino 2012[27]	not clear	no	yes	no	no	no	yes
Rubin 2012[28]	not clear	no	yes	no	no	yes	yes
Solèr 2001[29]	not clear	not clear	yes	not clear	yes	no	yes
Buhl 2002[30]	not clear	not clear	yes	not clear	yes	yes	yes
Buhl 2002[31]	not clear	not clear	yes	not clear	yes	yes	yes
Milgrom 1999[32]	not clear	not clear	yes	not clear	no	no	no
eXplore (NCT00670930)[33]	not clear	yes	not clear	not clear	no	no	yes
Bousquet 2004[34]	not clear	not clear	no	not clear	yes	no	no
Busse 2013[35]	yes	yes	yes	yes	no	no	yes
Vignola 2004[36]	not clear	not clear	yes	not clear	yes	no	yes

Study	Randomization (Was randomization carried out appropriately?)	Concealment (Was the concealment of treatment allocation adequate?)	Similar groups (Were the groups similar at the outset of the study in terms of prognostic factors?)	Blinding (Were the care providers, participants and outcome assessors blind to treatment allocation?)	Drop-outs (Were there any unexpected imbalances in drop-outs between groups?)	Outcomes (Is there any evidence to suggest that the authors measured more outcomes than they reported?)	ITT (Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?)
Piper 2013[37]	yes	not clear	yes	not clear	no	no	yes
Corren 2011[38]	yes	yes	yes	yes	no	no	yes
Hanania 2014[39]	not clear	not clear	not clear	not clear	not clear	no	not clear
Castro 2011[40]	yes	yes	yes	yes	yes	no	yes
Mathur 2011[41]	not clear	not clear	not clear	not clear	not clear	not	not clear
Wenzel 2013[42]	not clear	not clear	yes	yes	yes	no	yes
Corren 2013[43]	not clear	not clear	not clear	not clear	not clear	no	not clear
Bernstein 2013[44]	not clear	not clear	not clear	not clear	not clear	no	not clear
Kerstjens 2012[45]	yes	yes	yes	yes	no	no	yes
Dahl 2013[46]	not clear	not clear	not clear	not clear	not clear	no	not clear
Dahl 2014[47]	not clear	not clear	not clear	not clear	not clear	no	not clear
Vandewalker 2013[48]	not clear	not clear	yes	not clear	no	no	yes
Kerstjens 2011[49]	yes	yes	yes	yes	not clear	no	not clear
Bel 2014[50]	yes	yes	yes	yes	not clear	no	not clear
Castro 2014[51]	yes	yes	no	yes	no	yes	yes
Castro 2015[52]	not clear	not clear	not clear	yes	not clear	no	not clear
Castro 2015[53]	yes	not clear	yes	yes	no	yes	yes
Feshchenko 2014[54]	not clear	not clear	not clear	yes	not clear	no	not clear
Hanania 2015[55]	yes	not clear	yes	yes	no	yes	not clear
Ohta 2014 [56]	not clear	not clear	not clear	yes	no	no	not clear

Study	Randomization (Was randomization carried out appropriately?)	Concealment (Was the concealment of treatment allocation adequate?)	Similar groups (Were the groups similar at the outset of the study in terms of prognostic factors?)	Blinding (Were the care providers, participants and outcome assessors blind to treatment allocation?)	Drop-outs (Were there any unexpected imbalances in drop-outs between groups?)	Outcomes (Is there any evidence to suggest that the authors measured more outcomes than they reported?)	ITT (Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?)
Kerstjens 2014[57]	not clear	not clear	not clear	yes	not clear	no	not clear
Kerstjens 2014[58]	not clear	not clear	not clear	yes	not clear	no	not clear
Maspero 2014[59]	not clear	not clear	not clear	yes	not clear	no	not clear
Nowak 2015[60]	yes	not clear	no	yes	yes	no	yes
Price 2014[61]	not clear	not clear	not clear	yes	not clear	no	not clear
Price 2014[62]	not clear	not clear	not clear	yes	not clear	no	not clear
Tashkin 2014[63]	yes	not clear	not clear	yes	not clear	no	not clear
Murphy 2014[64]	not clear	not clear	not clear	yes	not clear	no	not clear

ITT, Intent-to-treat,

Table S2. Assessment of systematic literature search retrieved RCTs for ITC inclusion

MEPO studies retrieved by SLR ^a														
Study name/reference	Outcome of eligibility Assessment: ITC inclusion			Details of eligibility assessment per base case ITC inclusion criteria: MEPO studies										
				Population/intervention				Comparator		Study design		Outcomes		
	Prima ry analys is	+ open- label studies	+ MEPO 75 mg IV data	MEPO- eligible ^b patients treated with:		OMA- eligible ^c patients	Patients aged ≥12 years	Current Tx of ≥1000 µg BDP- equiv. ICS/day ≥1 controller	Exac. history (≥1 in previous year) ^d	Placebo plus SoC, or SoC alone	RCT	Stable dosing regime n	Double- blind	≥1 ITC- relevant endpoint
				100 mg SC	75 mg IV									
‘MENZA’ Ortega, 2014[6]	YES	YES	YES	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
‘DREAM’ Pavord, 2012[1]	NO	NO	YES	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nair, 2009[4]	NO	NO	NO	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Haldar, 2009[3]	NO	NO	NO	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
‘SIRIUS’ Bel, 2014[5]	NO	NO	NO	Yes	No	Yes	Yes	Yes	Yes - subset only	Yes	Yes	No	Yes	Yes
Bel, 2015[50]	NO	NO	NO	Secondary publication; assessment identical to main publication										
Nair, 2014[7]	NO	NO	NO	Editorial, assessment identical to primary publications										

OMA studies retrieved by SLR

Study name/reference	Outcome of eligibility			Details of eligibility assessment per base case ITC inclusion criteria: OMA studies								
	Assessment: ITC inclusion				Population/intervention			Comparator		Study design		Outcomes
	Primary analysis	+ open-label studies	+ MEPO 75 mg IV data	OMA-eligible ^c patients	Patients aged ≥12 years	Current Tx of ≥1000 µg BDP-equiv. ICS/day	Exac. history (≥1 in previous year) ^d	Placebo plus SoC, or SoC alone	RCT	Stable dosing regimen	Double-blind	≥1 ITC-relevant endpoint
‘INNOVATE’ Humbert, 2005[9]	YES	YES	YES	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sthoeger, 2007[10]	YES	YES	YES			Secondary publication; assessment identical to main publication						
Humbert, 2008[11]	YES	YES	YES			Secondary publication; assessment identical to main publication						
Chanez, 2010[20]	YES	YES	YES	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
‘EXTRA’ Hanania 2011[12]	YES	YES	YES	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hanania, 2013[13]	YES	YES	YES			Secondary publication; assessment identical to main publication						
Bousquet, 2011[25]	NO	YES	YES	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Siergiejko, 2011[26]	NO	YES	YES			Secondary publication; assessment identical to main publication						
Holgate, 2004[8]	NO	NO	NO	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Ayres, 2004[23]	NO	NO	NO	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Niven, 2008[24]	NO	YES	YES	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Bardelas, 2012[14]	NO	NO	NO	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Busse, 2001[15]	NO	NO	NO	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Finn, 2003[16]	NO	NO	NO			Secondary publication; assessment identical to main publication						

Lanier, 2003[17]	NO	NO	NO	<i>Secondary publication; assessment identical to main publication</i>								
Garcia, 2013[18]	NO	NO	NO	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hoshino, 2012[27]	NO	NO	NO	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Massanari, 2010[21]	NO	NO	NO	Yes	Yes	No	No	Yes	Yes	No	Yes	No
Ohta, 2009[22]	NO	NO	NO	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Rubin, 2012[28]	NO	NO	NO	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Solèr, 2001[29]	NO	NO	NO	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Buhl, 2002[30]	NO	NO	NO	<i>Secondary publication; assessment identical to main publication</i>								
Buhl, 2002[31]	NO	NO	NO	<i>Secondary publication; assessment identical to main publication</i>								
Bousquet, 2004[34]	NO	NO	NO	<i>Secondary publication; assessment identical to main publication</i>								
Mohamed, 2013[19]	NO	NO	NO	<i>Secondary publication; assessment identical to main publications^e</i>								
Milgrom, 1999[32]	NO	NO	NO	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes
eXplore (NCT00670930)[33]	NO	NO	NO	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No
Busse, 2013[35]	NO	NO	NO	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Vignola, 2004[36]	NO	NO	NO	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes

Yes = pass base-case ITC inclusion criterion; No = fail primary ITC analysis inclusion criterion.

^aPrimary mepolizumab studies were also informed by clinical study reports; ^bMepolizumab eligibility was defined as severe eosinophilic asthma (blood eosinophil count ≥ 150 cells/ μ L at treatment initiation or ≥ 300 cells/ μ L in the prior 12 months) and a history of exacerbations; ^cOMA eligibility is based on patients fulfilling the criteria for ≥ 1 OMA license; for MEPO studies, this criterion is necessary only for the Overlap population; ^dthis is the less restrictive exacerbation history criteria applied for the Trial population. To identify studies included in the Overlap population a stricter criterion of ≥ 2 OCS-treated exacerbation or ≥ 1 severe exacerbation resulting in hospitalization in previous 12 months was applied. This criterion is used to identify 'MEPO eligible' populations at the study level in OMA studies; ^eMohamed 2013 is a pooled analysis of two excluded studies; Busse 2001 and Solèr 2001.

BDP, beclomethasone dipropionate; IV, intravenous; ICS, inhaled corticosteroid; ITC, indirect treatment comparison; MEPO, mepolizumab; OMA, omalizumab; RCT, randomized clinical trial; SC, subcutaneous; SLR, systematic literature review; SoC, standard of care; TX, treatment.

Table S3. Study and population inclusion criteria for the ITC Overlap and Extended overlap population

ITC population	Disease criteria		Treatment eligibility criteria ^{a, b}			
	Disease and current treatment	Exacerbation history	MEPO eligibility		OMA Eligibility	
			MEPO RCTs (IPD available)	OMA RCTs (aggregate RCT data only)	MEPO RCTs (IPD available)	OMA RCTs (aggregate RCT data only)
<u>Overlap population</u> Patient population that is eligible for both MEPO and OMA	Severe asthma patients aged ≥12 years taking ≥1,000 µg/day BDP-equivalent ICS plus ≥1 additional controller	≥2 exacerbations (requiring SCS) OR ≥1 severe exacerbation (requiring hospitalization) in previous 12 months	Required Based on blood eosinophil count inclusion criteria in MEPO RCTs: blood eosinophil count ≥150 cells/µL at treatment initiation or ≥300 cells/µL in prior 12 months	Required Based on OMA RCTs that included patients meeting disease criteria	Required Sub-group of MEPO patients that met EU OMA license criteria: based on weight, IgE levels and positive RAST	Required OMA RCTs that included patients meeting EU OMA license
<u>Extended overlap population</u> Patient population that reduces RCT exacerbation history requirements from the Overlap Population		≥1 exacerbation in the previous 12 months (defined as treatment with SCS or asthma hospitalization or asthma ED visit)	Required (As per Overlap population)	Required (As per Overlap population)	Required (As per Overlap population)	Required (As per Overlap population)

^aCriteria additional to disease criteria; ^bdefinition of treatment eligibility differs for MEPO and OMA studies, due to data availability. MEPO eligibility in OMA studies was proxied using exacerbation history requirements at enrollment.

BDP, beclomethasone dipropionate; ED, emergency department; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IPD, individual patient-level data; ITC, indirect treatment comparison; MEPO, mepolizumab; OMA, Omalizumab; RAST, radioallergosorbent test; RCT, randomized controlled trial; SCS, systemic corticosteroids.

Table S4. Summary of the results of the Frequentist analysis for Overlap and Trial population^a

ITC population	ITC outcome	Favors MEPO	Favors OMA
		Point estimate (95% CrI)	Point estimate (95% CrI)
<u>Overlap population</u>	Rate of clinically significant exacerbations	RR 0.67 (0.37, 1.120)	–
	Rate of exacerbations requiring hospitalization	RR 0.20 (0.02, 2.40)	–
	Change from baseline in % predicted FEV ₁	–	Mean Diff. -0.94 (-6.31, 4.44)
	Proportion of patients with any AE	OR 0.79 (0.32, 1.94)	–
	Proportion of patients with any SAE	OR 0.46 (0.13, 1.71)	–
	Proportion of patients withdrawing due to an AE	OR 0.07 (0.0, 1.122)	–
	Proportion of patients with fatal AE	Analysis could not be conducted	
<u>Trial population</u>	Rate of clinically significant exacerbations	RR 0.64 (0.45, 0.90)	–
	Rate of exacerbations requiring hospitalization	RR 0.58 (0.16, 2.17)	–
	Change from baseline in % predicted FEV ₁	Mean Diff. 0.26 (-3.61, 4.13)	–
	Proportion of patients with any AE	OR 0.79 (0.45, 1.40)	–
	Proportion of patients with any SAE	OR 0.68 (0.33, 1.43)	–
	Proportion of patients withdrawing due to an AE	OR 0.13 (0.01, 1.25)	–
	Proportion of patients with fatal AE	OR 1.0 (0.0, 256.5)	

^aITC inclusion criteria – study design: parallel-group RCT; double-blind study; RCT duration ≥ 12 weeks; where a protocol-driven change in ICS/OCS maintenance dosage is implemented, only those data from periods prior to the change may be included in the ITC; at least one pre-defined and comparable outcome can be extracted or calculated from the available RCT data; interventions/comparators: MEPO 100 mg SC plus SoC; OMA doses compatible with local licensed/reimbursed OMA prescribing criteria; SoC, or placebo plus SoC; AE, adverse event; CrI, credible interval; Diff., difference; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; ITC, indirect treatment comparison; MEPO, mepolizumab; OCS, oral corticosteroid; OMA, omalizumab; OR, odds ratio; RCT, randomized controlled trial; RR, rate ratio; SAE, serious adverse event; SC, subcutaneous; SoC, standard of care.

Table S5. Summary of the results of the Bayesian sensitivity analysis^a for Overlap and Trial population

ITC population	ITC outcome	Favors MEPO	Favors OMA
		Point estimate (95% CrI)	Point estimate (95% CrI)
<u>Overlap population</u>	Rate of clinically significant exacerbations	RR 0.97 (0.66, 1.43)	–
	Rate of exacerbations requiring hospitalization	–	RR 1.35 (0.34, 5.33)
	Change from baseline in % predicted FEV ₁	–	Mean Diff. -0.13 (-4.29, 4.03)
	Proportion of patients with any AE	–	OR 1.56 (0.77, 3.12)
	Proportion of patients with any SAE	OR 0.91 (0.36, 2.32)	–
	Proportion of patients withdrawing due to an AE	OR 0.13 (0.0, 1, 1.12)	–
	Proportion of patients with fatal AE	Analysis could not be conducted	
<u>Trial population</u>	Rate of clinically significant exacerbations	RR 0.80 (0.41, 1.61)	–
	Rate of exacerbations requiring hospitalization	–	RR 1.11 (0.47, 2.65)
	Change from baseline in % predicted FEV ₁	Mean Diff. 0.65 (-2.65, 3.96)	–
	Proportion of patients with any AE	OR 0.93 (0.35, 2.71)	–
	Proportion of patients with any SAE	OR 0.67 (0.39, 1.15)	–
	Proportion of patients withdrawing due to an AE	OR 0.15 (0.03, 0.56)	–
	Proportion of patients with fatal AE	OR 0.6 (0.004, 88.53)	

^aITC inclusion criteria – parallel-group RCT; double-blind or open-label RCTs; RCT duration ≥ 12 weeks; where a protocol-driven change in ICS/OCS maintenance dosage is implemented, only those data from periods prior to the change may be included in the ITC; at least one pre-defined and comparable outcome can be extracted or calculated from the available data; interventions/comparators: MEPO 100 mg SC plus SoC; MEPO 75 mg IV plus SoC; OMA doses compatible with local licensed/reimbursed OMA prescribing criteria; SoC, or placebo plus SoC.

AE, adverse event; CrI, credible interval; Diff., difference; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; ITC, indirect treatment comparison; IV, intravenous; MEPO, mepolizumab; OCS, oral corticosteroid; OMA, omalizumab; OR, odds ratio; RCT, randomized controlled trial; RR, rate ratio; SAE, serious adverse event; SC, subcutaneous; SoC, standard of care.

Table S6. Summary of the results of the Bayesian analysis^a for the Extended overlap population

ITC population	ITC outcome	Favors MEPO	Favors OMA
		Point estimate (95% CrI)	Point estimate (95% CrI)
<u>Extended overlap population</u>	Rate of clinically significant exacerbations	RR 0.66 (0.39, 1.11)	–
	Rate of exacerbations requiring hospitalization	RR 0.19 (0.02, 2.32)	–
	Change from baseline in % predicted FEV ₁	–	Mean Diff. -0.98 (-6.35, 4.36)
	Proportion of patients with any AE	OR 0.68 (0.28, 1.60)	–
	Proportion of patients with any SAE	OR 0.38 (0.09, 1.28)	–
	Proportion of patients withdrawing due to an AE	OR 0.07 (0.00, 1.17)	–
	Proportion of patients with fatal AE	Analysis could not be conducted	

^aITC inclusion criteria – study design: parallel-group RCT; double-blind study; RCT duration ≥ 12 weeks; where a protocol-driven change in ICS/OCS maintenance dosage is implemented, only those data from periods prior to the change may be included in the ITC; at least one pre-defined and comparable outcome can be extracted or calculated from the available RCT data; interventions/comparators: MEPO 100 mg SC plus SoC; OMA doses compatible with local licensed/reimbursed OMA prescribing criteria; SoC, or placebo plus SoC; AE, adverse event; CrI, credible interval; Diff., difference; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; ITC, indirect treatment comparison; MEPO, mepolizumab; OCS, oral corticosteroid; OMA, omalizumab; OR, odds ratio; RCT, randomized controlled trial; RR, rate ratio; SAE, serious adverse event; SC, subcutaneous; SoC, standard of care.

Figure S1. Conceptual diagram of overlap and trial ITC populations

This is an illustrative diagram, not intended to accurately represent the relative size of the patient groups identified.

ITC, indirect treatment comparison; MEPO, mepolizumab; OMA, omalizumab; SCS, systemic corticosteroids.

References

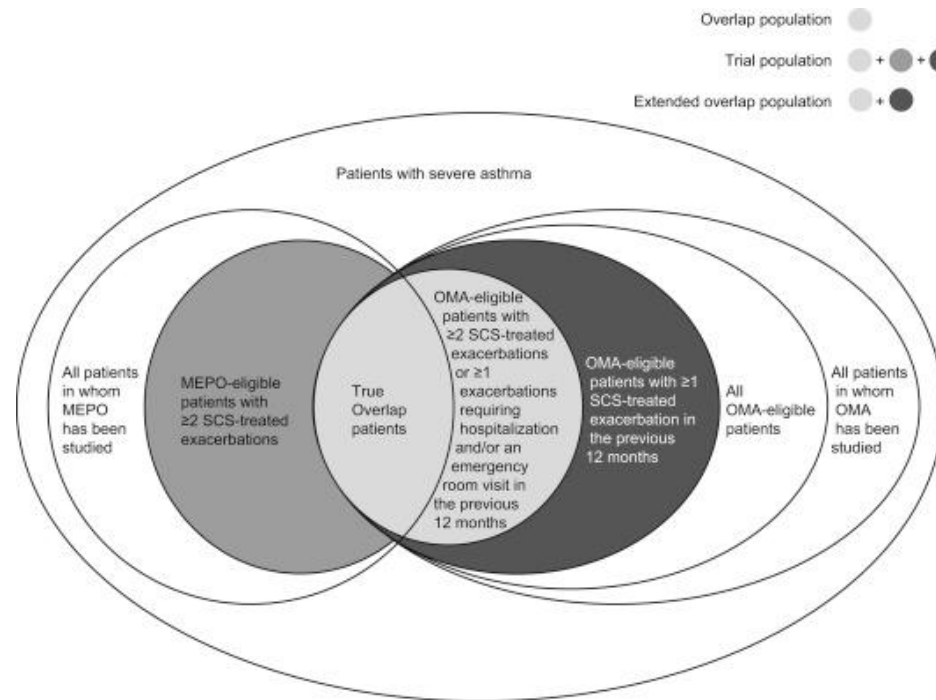
1. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, Ortega H, Chanez P: **Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial.** *Lancet* 2012, **380**:651-659.
2. **MEA115575: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study of Mepolizumab Adjunctive Therapy to Reduce Steroid Use in Subjects with Severe Refractory Asthma** [<https://www.gsk-clinicalstudyregister.com/study/115575#ps>]
3. Halder P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, Marshall RP, Bradding P, Green RH, Wardlaw AJ, Pavord ID: **Mepolizumab and exacerbations of refractory eosinophilic asthma.** *N Engl J Med* 2009, **360**:973-984.
4. Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, Hargreave FE, O'Byrne PM: **Mepolizumab for prednisone-dependent asthma with sputum eosinophilia.** *N Engl J Med* 2009, **360**:985-993.
5. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, Ortega HG, Pavord ID: **Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma.** *N Engl J Med* 2014, **371**:1189-1197.
6. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, Humbert M, Katz LE, Keene ON, Yancey SW, et al: **Mepolizumab treatment in patients with severe eosinophilic asthma.** *N Engl J Med* 2014, **371**:1198-1207.
7. Nair P: **Anti-interleukin-5 monoclonal antibody to treat severe eosinophilic asthma.** *N Engl J Med* 2014, **371**:1249-1251.
8. Holgate ST, Chuchalin AG, Hebert J, Lotvall J, Persson GB, Chung KF, Bousquet J, Kerstjens HA, Fox H, Thirlwell J, Cioppa GD: **Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma.** *Clin Exp Allergy* 2004, **34**:632-638.
9. Humbert M, Beasley R, Ayres J, Slavin R, Hebert J, Bousquet J, Beeh KM, Ramos S, Canonica GW, Hedegcock S, et al: **Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE.** *Allergy* 2005, **60**:309-316.
10. Stohger ZM, Eliraz A, Asher I, Berkman N, Elbirt D: **The beneficial effects of Xolair (omalizumab) as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available treatment (GINA 2002 step IV)--the Israeli arm of the INNOVATE study.** *Isr Med Assoc J* 2007, **9**:472-475.
11. Humbert M, Berger W, Rapatz G, Turk F: **Add-on omalizumab improves day-to-day symptoms in inadequately controlled severe persistent allergic asthma.** *Allergy* 2008, **63**:592-596.
12. Hanania NA, Alpan O, Hamilos DL, Condemi JJ, Reyes-Rivera I, Zhu J, Rosen KE, Eisner MD, Wong DA, Busse W: **Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial.** *Ann Intern Med* 2011, **154**:573-582.
13. Hanania NA, Wenzel S, Rosen K, Hsieh HJ, Mosesova S, Choy DF, Lal P, Arron JR, Harris JM, Busse W: **Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study.** *Am J Respir Crit Care Med* 2013, **187**:804-811.
14. Bardelas J, Figliomeni M, Kianifard F, Meng X: **A 26-week, randomized, double-blind, placebo-controlled, multicenter study to evaluate the effect of omalizumab**

- on asthma control in patients with persistent allergic asthma. *J Asthma* 2012, **49**:144-152.
15. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, van As A, Gupta N: **Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma.** *J Allergy Clin Immunol* 2001, **108**:184-190.
 16. Finn A, Gross G, van Bavel J, Lee T, Windom H, Everhard F, Fowler-Taylor A, Liu J, Gupta N: **Omalizumab improves asthma-related quality of life in patients with severe allergic asthma.** *J Allergy Clin Immunol* 2003, **111**:278-284.
 17. Lanier BQ, Corren J, Lumry W, Liu J, Fowler-Taylor A, Gupta N: **Omalizumab is effective in the long-term control of severe allergic asthma.** *Ann Allergy Asthma Immunol* 2003, **91**:154-159.
 18. Garcia G, Magnan A, Chiron R, Contin-Bordes C, Berger P, Taille C, Devouassoux G, de Blay F, Couderc LJ, Didier A, et al: **A proof-of-concept, randomized, controlled trial of omalizumab in patients with severe, difficult-to-control, nonatopic asthma.** *Chest* 2013, **144**:411-419.
 19. Mohamed Z, ., Aby-Hussein S, ., Abu-Hussein A, ., Ahmed M, . **The Effect of Omalizumab in Treatment of Inadequate Controlled Severe Persistent Asthma Patient.** *CHEST* 2013, **144**:76A.
 20. Chanez P, Contin-Bordes C, Garcia G, Verkindre C, Didier A, De Blay F, de Lara MT, Blanco P, Moreau JF, Robinson P, et al: **Omalizumab-induced decrease of Fc ϵ RI expression in patients with severe allergic asthma.** *Respir Med* 2010, **104**:1608-1617.
 21. Massanari M, Nelson H, Casale T, Busse W, Kianifard F, Geba GP, Zeldin RK: **Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma.** *J Allergy Clin Immunol* 2010, **125**:383-389.
 22. Ohta K, Miyamoto T, Amagasaki T, Yamamoto M: **Efficacy and safety of omalizumab in an Asian population with moderate-to-severe persistent asthma.** *Respirology* 2009, **14**:1156-1165.
 23. Ayres JG, Higgins B, Chilvers ER, Ayre G, Blogg M, Fox H: **Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma.** *Allergy* 2004, **59**:701-708.
 24. Niven R, Chung KF, Panahloo Z, Blogg M, Ayre G: **Effectiveness of omalizumab in patients with inadequately controlled severe persistent allergic asthma: an open-label study.** *Respir Med* 2008, **102**:1371-1378.
 25. Bousquet J, Siergiejko Z, Swiebocka E, Humbert M, Rabe KF, Smith N, Leo J, Peckitt C, Maykut R, Peachey G: **Persistency of response to omalizumab therapy in severe allergic (IgE-mediated) asthma.** *Allergy* 2011, **66**:671-678.
 26. Siergiejko Z, Swiebocka E, Smith N, Peckitt C, Leo J, Peachey G, Maykut R: **Oral corticosteroid sparing with omalizumab in severe allergic (IgE-mediated) asthma patients.** *Curr Med Res Opin* 2011, **27**:2223-2228.
 27. Hoshino M, Ohtawa J: **Effects of adding omalizumab, an anti-immunoglobulin E antibody, on airway wall thickening in asthma.** *Respiration* 2012, **83**:520-528.
 28. Rubin AS, Souza-Machado A, Andradre-Lima M, Ferreira F, Honda A, Matozo TM: **Effect of omalizumab as add-on therapy on asthma-related quality of life in severe allergic asthma: a Brazilian study (QUALITX).** *J Asthma* 2012, **49**:288-293.
 29. Soler M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, Thirlwell J, Gupta N, Della Cioppa G: **The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics.** *Eur Respir J* 2001, **18**:254-261.
 30. Buhl R, Hanf G, Soler M, Bensch G, Wolfe J, Everhard F, Champain K, Fox H, Thirlwell J: **The anti-IgE antibody omalizumab improves asthma-related quality of life in patients with allergic asthma.** *Eur Respir J* 2002, **20**:1088-1094.

31. Buhl R, Soler M, Matz J, Townley R, O'Brien J, Noga O, Champain K, Fox H, Thirlwell J, Della Cioppa G: **Omalizumab provides long-term control in patients with moderate-to-severe allergic asthma.** *Eur Respir J* 2002, **20**:73-78.
32. Milgrom H, Fick RB, Jr., Su JQ, Reimann JD, Bush RK, Watrous ML, Metzger WJ: **Treatment of allergic asthma with monoclonal anti-IgE antibody. rhuMAb-E25 Study Group.** *N Engl J Med* 1999, **341**:1966-1973.
- 33.
34. Bousquet J, Wenzel S, Holgate S, Lumry W, Freeman P, Fox H: **Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma.** *Chest* 2004, **125**:1378-1386.
35. Busse W, Spector S, Rosen K, Wang Y, Alpan O: **High eosinophil count: a potential biomarker for assessing successful omalizumab treatment effects.** *J Allergy Clin Immunol* 2013, **132**:485-486 e411.
36. Vignola AM, Humbert M, Bousquet J, Boulet LP, Hedgecock S, Blogg M, Fox H, Surrey K: **Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR.** *Allergy* 2004, **59**:709-717.
37. Piper E, Brightling C, Niven R, Oh C, Faggioni R, Poon K, She D, Kell C, May RD, Geba GP, Molfino NA: **A phase II placebo-controlled study of tralokinumab in moderate-to-severe asthma.** *Eur Respir J* 2013, **41**:330-338.
38. Corren J, Lemanske RF, Hanania NA, Korenblat PE, Parsey MV, Arron JR, Harris JM, Scheerens H, Wu LC, Su Z, et al: **Lebrikizumab treatment in adults with asthma.** *N Engl J Med* 2011, **365**:1088-1098.
39. Hanania NA, Noonan MJ, Corren J, Korenblat P, Zheng Y, Putnam W, Murray E, Abelardo C, Scheerens H, Maciucia R, et al: **Efficacy and Safety of Lebrikizumab in Severe Uncontrolled Asthma: Results from the Lute and Verse Phase II Randomized, Double-Blind, Placebo-Controlled Trials.** *Journal of Allergy and Clinical Immunology* 2014, **133**:AB402.
40. Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, Wilkins HJ, Henkel T, Nair P: **Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study.** *Am J Respir Crit Care Med* 2011, **184**:1125-1132.
41. Mathur S, Castro M, Hargreave F, Xie F, Wilkins HJ, Henkel T, Nair P: **Efficacy of Reslizumab in Patients with Poorly Controlled Eosinophilic Asthma: Subgroup Analysis of Patients with Nasal Polyyps.** *Journal of Allergy and Clinical Immunology* 2011, **127**:AB84.
42. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, Wang L, Kirkesseli S, Rocklin R, Bock B, et al: **Dupilumab in persistent asthma with elevated eosinophil levels.** *N Engl J Med* 2013, **368**:2455-2466.
43. Corren J: **Tiotropium as Add-On Therapy to ICS+LABA in Patients With Symptomatic Severe Asthma: Spirometric Assessment Over 24 Hours.** In *CHEST*, vol. 144; 2013.
44. JA B: **Once-Daily Tiotropium Is Well Tolerated as Add-On to Standard Treatment for Patients With Symptomatic Asthma Despite Receiving Inhaled Corticosteroids and Long-Acting β_2 -Agonists.** *CHEST* 2013, **144**.
45. Kerstjens HA, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, Sigmund R, Seibold W, Moroni-Zentgraf P, Bateman ED: **Tiotropium in asthma poorly controlled with standard combination therapy.** *N Engl J Med* 2012, **367**:1198-1207.
46. Dahl R PP, Engel M et al: **Once-daily tiotropium improves lung function and reduces risk of asthma exacerbation/worsening in patients with symptomatic asthma, regardless of allergic status.** *Allergy* 2013, **68**.

47. Dahl R, Doherty DE, Corren J, Karpel J, Kerstjens HAM, Engel M, Moroni-Zentgraf P, Schmidt H, Hashimoto S: **Once-Daily Tiotropium Respimat[®] Improves Lung Function In Patients With Severe Symptomatic Asthma Independent Of Leukotriene Modifier Use.** *Journal of Allergy and Clinical Immunology*, **133**:AB5.
48. Vandewalker ML, Engel M, Schmidt H, Siebold W, Moroni-Zentgraf P, Kerstjens H, Bateman ED, Tashkin DP: **Efficacy of Tiotropium in Patients with Asthma in Relation to Allergic Status.** *Journal of Allergy and Clinical Immunology* 2013, **131**:AB1.
49. Kerstjens HA, Disse B, Schroder-Babo W, Bantje TA, Gahlemann M, Sigmund R, Engel M, van Noord JA: **Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial.** *J Allergy Clin Immunol* 2011, **128**:308-314.
50. Bel EH, Wenzel S, Thompson PJ, Prazma CM, Keene ON, Yancey SW, Ortega H, Pavord ID: **Late-breaking abstract: Oral corticosteroid-sparing effect of mepolizumab in severe eosinophilic asthma: The SIRIUS study.** *Eur Respir J* 2014, **44**.
51. Castro M, Wenzel SE, Bleecker ER, Pizzichini E, Kuna P, Busse WW, Gossage DL, Ward CK, Wu Y, Wang B, 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.
52. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle G, Bardin PG, Murphy KR, Maspero JF, O'Brien C, Korn S: **Reslizumab Treatment for Moderate to Severe Asthma with Elevated Blood Eosinophil Levels.** *Journal of Allergy and Clinical Immunology*, **135**:AB381.
53. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, Murphy K, Maspero JF, O'Brien C, Korn S: **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.
54. Feshchenko Y, Iashyna L, Moskalenko S, M. P: **Clinical-functional effectiveness of different regimens of basic treatment in severe bronchial asthma patients.** *Allergy* 2014, **69**:517.
55. Hanania NA, Noonan M, Corren J, Korenblat P, Zheng Y, Fischer SK, Cheu M, Putnam WS, Murray E, Scheerens H, et al: **Lebrikizumab in moderate-to-severe asthma: pooled data from two randomised placebo-controlled studies.** *Thorax* 2015, **70**:748-756.
56. Ohta K IM, Tohda Y et al: **Once-Daily Tiotropium Respimat[®] Is Well Tolerated And Efficacious Over 52 Weeks In Japanese Patients With Symptomatic Asthma Receiving Inhaled Corticosteroids (ics) ± Long-Acting -Agonist (laba): A Randomized , Double-Blind , Placebo-Controlled Study.** *American Journal of Respiratory and Critical Care Medicine* 2014, **189**.
57. Kerstjens HAM EM, Dahl R et al: **Tiotropium Respimat[®] Add-On Therapy To Inhaled Corticosteroids (ics) ± Long-Acting ±2-Agonists (labas) In Patients With Symptomatic Severe Asthma : Efficacy By Level Of Airway Obstruction.** *American Journal of Respiratory and Critical Care Medicine* 2014, **189**.
58. Kerstjens HAM BE, Casale T et al. : **Tiotropium as add-on therapy to inhaled corticosteroids for patients with symptomatic asthma: Lung function and safety.** In *Respiratory Society Annual Congress* 2013.
59. Maspero J BL, Lemire C et al: **A randomized phase 3 study assessing patient-reported outcomes and safety of reslizumab in patients with asthma with elevated eosinophils.** *Annals of Allergy, Asthma & Immunology* 2014, **113**.

60. Nowak RM, Parker JM, Silverman RA, Rowe BH, Smithline H, Khan F, Fiening JP, Kim K, Molfino NA: **A randomized trial of benralizumab, an antiinterleukin 5 receptor alpha monoclonal antibody, after acute asthma.** *Am J Emerg Med* 2015, **33**:14-20.
61. Price D, Engel M, Moroni-Zentgraf P, Schmidt H, Dahl R, Paggiaro P, Vandewalker M, Kerstjens H, Kaplan A: **S91 Once-daily tiotropium Respimat® add-on to ICS + LABA improves symptom control and reduces exacerbations in patients with symptomatic asthma.** *Thorax* 2014, **69**:A49-A50.
62. Price D, Bateman E, Paggiaro P, Kaplan A, Engel M, Schmidt H, Moroni-Zentgraf P, Kerstjens H: **S92 Efficacy Of Once-daily Tiotropium Respimat® 5 µg From Five Phase Iii Trials In Adults With Symptomatic Asthma.** *Thorax* 2014, **69**:A50.
63. Tashkin D, Moroni-Zentgraf P, Engel M, Schmidt H, Kerstjens H: **ONce-daily tiotropium respimat add-on to ics+laba reduces risk of severe exacerbation and asthma worsening in patients with asthma, independent of degree of airflow obstruction.** *Chest* 2014, **146**:18A-18A.
64. Murphy K BG, Berger WE et al: **Once-daily tiotropium respimat® add-on inhaled corticosteroids ± long-acting â2-agonists improves lung function and asthma control and reduces risk of asthma worsening in patients with moderate or severe asthma.** *Annals of allergy, asthma & immunology* 2014, **113**.



Supplementary Figure.

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Respiratory Medicine, Volume 123, 2017, 140–148

<http://dx.doi.org/10.1016/j.rmed.2016.12.009>