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Anti-IL5 therapies for asthma (Review)

Farne HA, Wilson A, Powell C, Bax L, Milan SJ

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[Intervention Review]

Anti-IL5 therapies for asthma

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ABSTRACT

Background

This review is the first update of a previously published review in The Cochrane Library (Issue 7, 2015). Interleukin-5 (IL-5) is the main cytokine involved in the activation of eosinophils, which cause airway inflammation and are a classic feature of asthma. Monoclonal antibodies targeting IL-5 or its receptor (IL-5R) have been developed, with recent studies suggesting that they reduce asthma exacerbations, improve health-related quality of life (HRQoL) and lung function. These are being incorporated into asthma guidelines.

Objectives

To compare the effects of therapies targeting IL-5 signalling (anti-IL-5 or anti-IL-5Rα) with placebo on exacerbations, health-related qualify of life (HRQoL) measures, and lung function in adults and children with chronic asthma, and specifically in those with eosinophilic asthma refractory to existing treatments.

Search methods

We searched the Cochrane Airways Trials Register, clinical trials registries, manufacturers' websites, and reference lists of included studies. The most recent search was March 2017.

Selection criteria

We included randomised controlled trials comparing mepolizumab, reslizumab and benralizumab versus placebo in adults and children with asthma.

Data collection and analysis

Two authors independently extracted data and analysed outcomes using a random-effects model. We used standard methods expected by Cochrane.

Main results

Thirteen studies on 6000 participants met the inclusion criteria. Four used mepolizumab, four used reslizumab, and five used benralizumab. One study in benralizumab was terminated early due to sponsor decision and contributed no data. The studies were predominantly on people with severe eosinophilic asthma, which was similarly but variably defined. Eight included children over 12 years but these results were not reported separately. We deemed the risk of bias to be low, with all studies contributing data being of robust

methodology. We considered the quality of the evidence for all comparisons to be high overall using the GRADE scheme, with the exception of intravenous mepolizumab because this is not currently a licensed delivery route.

All of the anti-IL-5 treatments assessed reduced rates of 'clinically significant' asthma exacerbation (defined by treatment with systemic corticosteroids for three days or more) by approximately half in participants with severe eosinophilic asthma on standard of care (at least medium-dose inhaled corticosteroids (ICS)) with poorly controlled disease (either two or more exacerbations in the preceding year or Asthma Control Questionnaire (ACQ) 1.5 or more). Non-eosinophilic participants treated with benralizumab also showed a significant reduction in exacerbation rates, but no data were available for non-eosinophilic participants, and mepolizumab or reslizumab.

We saw modest improvements in validated HRQoL scores with all anti-IL-5 agents in severe eosinophilic asthma. However these did not exceed the minimum clinically important difference for ACQ and Asthma Quality of Life Questionnaire (AQLQ), with St. George's Respiratory Questionnaire (SGRQ) only assessed in two studies. The improvement in HRQoL scores in non-eosinophilic participants treated with benralizumab, the only intervention for which data were available in this subset, was not statistically significant, but the test for subgroup difference was negative.

All anti-IL-5 treatments produced a small but statistically significant improvement in mean pre-bronchodilator forced expiratory flow in one second (FEV_1) of between 0.08 L and 0.11 L.

There were no excess serious adverse events with any anti-IL-5 treatment, and indeed a reduction in favour of mepolizumab that could be due to a beneficial effect on asthma-related serious adverse events. There was no difference compared to placebo in adverse events leading to discontinuation with mepolizumab or reslizumab, but significantly more discontinued benralizumab than placebo, although the absolute numbers were small (36/1599 benralizumab versus 9/998 placebo).

Mepolizumab, reslizumab and benralizumab all markedly reduced blood eosinophils, but benralizumab resulted in almost complete depletion, whereas a small number remained with mepolizumab and reslizumab. The implications for efficacy and/or adverse events are unclear.

Authors' conclusions

Overall our study supports the use of anti-IL-5 treatments as an adjunct to standard of care in people with severe eosinophilic asthma and poor control. These treatments roughly halve the rate of asthma exacerbations in this population. There is limited evidence for improved HRQoL scores and lung function, which may not meet clinically detectable levels. There were no safety concerns regarding mepolizumab or reslizumab, and no excess serious adverse events with benralizumab, although there remains a question over adverse events significant enough to prompt discontinuation.

Further research is needed on biomarkers for assessing treatment response, optimal duration and long-term effects of treatment, risk of relapse on withdrawal, non-eosinophilic patients, children (particularly under 12 years), and comparing anti-IL-5 treatments to each other and, in people eligible for both, to anti-immunoglobulin E. For benralizumab, future studies should closely monitor rates of adverse events prompting discontinuation.

PLAIN LANGUAGE SUMMARY

Mepolizumab, reslizumab or benralizumab for people already taking inhaled steroids and long-acting $beta_2$-agonists for their asthma

Review question

We considered in this review whether taking the new drugs mepolizumab, reslizumab or benralizumab in addition to standard treatment (e.g. inhaled steroids and combination inhalers) are better than a placebo for people with asthma.

Background

Asthma is an inflammatory lung condition characterised by the narrowing of the airways, breathlessness, a tight chest and reduced quality of life. By the year 2025, there may be up to 400 million people with asthma worldwide. Mepolizumab, reslizumab and benralizumab are new 'anti-IL-5' treatments that may help to reduce asthma symptoms.

Study characteristics

Thirteen studies compared mepolizumab, reslizumab or benralizumab to a placebo in 6000 people with asthma, most with severe disease. We summarised the results as they related to the occurrence of asthma attacks requiring additional treatment, quality of life, breathing tests, effects on a blood biomarker, and side effects.

Key results

We found that participants with severe asthma, who had high numbers of a certain type of inflammatory cell (eosinophils) in the blood, benefited from taking mepolizumab, reslizumab or benralizumab through reduced asthma attacks. There were small improvements in quality of life and breathing tests, but these may be too small to be detected by patients. We agree with international guidelines that say that these treatments can be added to standard treatment for people with severe asthma. However, we think that further research is needed to clarify some aspects, such as how to assess treatment response and how long to give treatment for.

Quality of the evidence

The evidence included in this review is provided by very well-designed studies. We consider these studies to be at low risk of bias in the following important respects: the procedure that determined who received which treatment, the blinding processes and the clarity of detail concerning participants who did not complete the study. Overall the evidence was high to moderate quality.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Mepolizumab (SC) compared to placebo for asthma

Patient or population: people with asthma
Setting: community
Intervention: mepolizumab (SC)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with mepolizumab (SC)				
Rate of exacerbations requiring systemic corticosteroids Follow-up: range 24 to 32 weeks	The mean rate in the placebo group was 1.48 events per participant per year[a]	The mean rate in the intervention group was 0.81 fewer events per participant per year (95% CI 0.66 fewer to 0.94 fewer)	Rate ratio 0.45 (0.36 to 0.55)	936 (2 RCTs)	⊕⊕⊕⊕ High	
Rate of exacerbations requiring emergency department treatment or admission Follow-up: range 24 to 32 weeks	The mean rate in the placebo group was 0.15 events per patient per year[b]	The mean rate in the intervention group was 0.10 fewer events per participant per year (95% CI 0.05 fewer to 0.12 fewer)	Rate ratio 0.36 (0.20 to 0.66)	936 (2 RCTs)	⊕⊕⊕⊕ High	
Health-related quality of life (ACQ) Scale from: 0 to 6 (lower is better) Follow-up: range 24 to 32 weeks	The mean change in the placebo group ranged from −0.4 to −0.5 units	The mean in the intervention group was -0.42 units fewer (-0.56 fewer to -0.28 fewer)	-	936 (2 RCTs)	⊕⊕⊕◯ Moderate[c]	A change of ≥ 0.5 is considered the minimum clinically significant difference

Health-related quality of life (SGRQ) Scale from: 0 to 100 (lower is better) Follow-up: range 24 to 32 weeks	The mean change in the placebo group ranged from −7.9 to −9.0 units	The mean change in the intervention group was -7.4 units fewer (-9.5 fewer to -5.29 fewer)	-	936 (2 RCTs)	⊕⊕⊕⊕ High	A change of ≥ 4 is considered the minimum clinically significant difference
Pre-bronchodilator FEV_1 (L) Follow-up: range 24 to 32 weeks	The mean change in the placebo group ranged from 0.086 L (± 0.031 L) to 0.120 L (0.047 to 0.192 L)	The mean difference from placebo was a further 0.11 L (0.06 L to 0.17 L)	-	936 (2 RCTs)	⊕⊕⊕⊕ High	
Adverse events leading to discontinuation Follow-up: range 24 to 32 weeks	15 per 1000	7 per 1000 (2 to 27)	Risk ratio 0.45 (0.11 to 1.80)	936 (2 RCTs)	⊕⊕⊕◯ Moderate[d]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

ACQ: Asthma Control Questionnaire; **CI:** confidence interval; **FEV_1** : forced expiratory volume in 1 second; **RR:** risk ratio; **SC**: subcutaneous; **SGRQ**: St. George's Respiratory Questionnaire

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Rounded mean of the rate in the placebo group of the two studies: 1.21 and 1.74.
[b] Rounded mean of the rate in the placebo group of the two studies: 0.10 and 0.20.
[c] The mean difference (-0.42) is smaller than the minimum clinically significant difference (a reduction of 0.5 points).
[d] The 95% CI crosses the line of no effect, thus we downgraded the quality of evidence to moderate because of imprecision.

BACKGROUND

This review is the first update of a previously published review in The Cochrane Library (Issue 7, 2015), evaluating the effects of therapies targeting IL-5 signalling (anti-IL-5 or anti-IL-5Rα) with placebo on asthma.

Description of the condition

Asthma is a chronic inflammatory condition affecting the airways in the lungs. It is defined by symptoms of breathlessness, chest tightness, wheeze, and cough. These symptoms are a consequence of variable airway hyperresponsiveness, with subsequent bronchoconstriction and airflow obstruction. These symptoms are variably and intermittently present in the natural course of the disease, with periods of acutely increased symptomatology called exacerbations.

A recent global estimate suggested 300 million people currently live with asthma, and predicted this to increase to 400 million by 2025 (WHO 2007). Asthma causes a significant degree of morbidity and mortality: every year in the UK alone there are an estimated 2.7 million GP consultations, 121,000 hospital attendances, 93,900 admissions, and over 1000 deaths (Mukherjee 2016). The annual cost in the UK has been estimated at GBP 1.1 billion. Current treatments, such as inhaled corticosteroids (ICS) and bronchodilators are well established, yet despite these almost half of people living with asthma experience an exacerbation each year (Price 2014).

Asthma is increasingly recognised as a heterogenous disease comprised of a number of different clinical phenotypes and molecular endotypes, although the precise definition of these remains a work in progress (Wenzel 2012). 'Atopic asthma' is generally considered the most common phenotype, representing roughly half of all asthmatics (Woodruff 2009). Atopic asthma is thought to be driven by an excess of 'type 2 inflammation': an elevated number of type 2 helper T (Th2) cells and the cytokines they secrete, interleukin 4 (IL-4), IL-5 and IL-13. A separate pathophysiological mechanism, in which type 2 innate lymphoid cells (ILC2s) produce large amounts of IL-5 and IL-13 (and to a lesser degree, IL-4), is hypothesised to be important in a subgroup of asthma sufferers with eosinophilia but no allergies (Brusselle 2013). This group are particularly important because they have severe disease that is largely resistant to ICS, and so have a high burden of disease.

The cytokines IL-4, IL-5 and IL-13 produce many of the classic features of atopic asthma, for example, eosinophilia (IL-5 controls the proliferation, survival and recruitment of eosinophils), raised immunoglobulin E (IgE) levels (the result of B cell class switching in response to IL-4 and IL-13), mucus hypersecretion and airway hyperresponsiveness (both a potential consequence of IL-13) (Chung 2015). Treatments targeting so called 'type 2 cytokines' have subsequently been developed and investigated for their potential in asthma.

Description of the intervention

One of the core pathological features of asthma is eosinophilic infiltration of the bronchial mucosa and airways (Kay 2015). Pro-inflammatory mediators secreted by eosinophils cause damage to the epithelium, initiating vasodilatation, smooth muscle contraction and increased mucous secretion, which in turn is associated with increased airway hyperresponsiveness, asthma symptoms and airway narrowing (Liu 2013). Thus increased eosinophil counts, for example following reduction in the dose of maintenance ICS, are associated with increased symptoms and asthma exacerbations (Jatakanon 2000).

The proliferation, maturation, activation, recruitment and survival of eosinophils is under the control of IL-5 (Lopez 1986), with the IL-5 receptor being selectively expressed on eosinophils and basophils. Elevated levels of IL-5 mRNA are seen in the bronchial biopsies of people with asthma and correlate with disease severity (Humbert 1997). IL-5 signalling is therefore an attractive target in asthma, and has yielded three monoclonal antibodies: mepolizumab (trade name Nucala; GlaxoSmithKline), reslizumab (trade names Cinqair or Cinqaero; Teva) and benralizumab (MedImmune/AstraZeneca). Mepolizumab and reslizumab both target IL-5, whereas benralizumab binds the alpha chain of the IL-5 receptor (IL-5Rα), found on eosinophils and basophils.

How the intervention might work

Mepolizumab and reslizumab bind IL-5 and interfere with its ligation to the IL-5 receptor on eosinophils and basophils. Both have been shown to reduce serum eosinophils (Wang 2009).

Benralizumab binds IL-5Rα to inhibit its activation. In addition it appears to induce eosinophil and basophil apoptosis (Kolbeck 2010). Benralizumab has also been shown to be effective in reducing serum eosinophil counts (Busse 2010).

Mepolizumab and reslizumab have marketing licenses for use in people with 'eosinophilic' asthma (variably defined) and it is logical that these drugs would be most effective in this subgroup of patients. Anti-IL-5 therapies might also theoretically be effective in patients with more relaxed definitions of eosinophilia, or in those defined as 'non-eosinophilic' based on their serum eosinophil count but who may have an isolated elevation of eosinophils in the airways (i.e. sputum eosinophilia), or whose eosinophils may be suppressed due to ICS treatment, or both.

Why it is important to do this review

As anti-IL-5 therapies become incorporated into national and international guidelines (e.g. the Global Initiatve for Asthma

(GINA)'s 2017 guidelines, GINA 2017) and clinical practice, it is important that the evidence is reviewed and made available in the Cochrane Library. The first Cochrane Review focused on mepolizumab, at the time the only anti-IL-5 agent licensed (Powell 2015).

Since then reslizumab has been approved by the US Food & Drug Administration and European Medicines Agency. With phase 3 clinical trials of benralizumab recently being reported as having met their primary endpoints, it seems likely that benralizumab will also be approved soon. These anti-IL-5 agents are likely to compete directly with each other and so the scope of this review has been broadened to consider all anti-IL-5 therapies. They are compared to each other rather than pooled as there are potentially important differences in dose, route of administration (subcutaneous versus intravenous), and in the case of benralizumab, a significant difference in the mechanism of action that uniquely induces eosinophil and basophil apoptosis - which could improve efficacy, but equally increase the incidence of adverse events.

OBJECTIVES

To compare the effects of therapies targeting IL-5 signalling (anti IL-5 or anti-IL-5Rα) with placebo on exacerbations, health-related quality of life (HRQoL) measures, and lung function in adults and children with chronic asthma, and specifically in those with eosinophilic asthma refractory to existing treatments.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs). We included studies reported as full text, those published as abstracts only and unpublished data.

Types of participants

We included both adults and children with a diagnosis of asthma. We focused on collating data from people who had been reported as having eosinophilic asthma to analyse these individuals as a subgroup. We examined individual articles in order to determine how this group should be defined.

Individuals with respiratory comorbidities such as cystic fibrosis were excluded, as were current smokers.

Types of interventions

We included trials comparing anti-IL-5 therapy with placebo, in addition to current standard of care for asthma (ICS, with or without a second controller such as a long-acting beta$_2$ agonist (LABA), provided the treatment period was 16 weeks or longer.

In the case of dose-ranging studies, we included data only for participants on doses likely to be used clinically, that is, 75 mg intravenous (IV) or 100 mg subcutaneous (SC) injections of mepolizumab, 3 mg/kg IV reslizumab, 20 to 30 mg SC benralizumab. For mepolizumab SC and reslizumab IV, these are the licensed doses. For benralizumab, we took the 30 mg dose used in the two phase 3 studies (Bleecker 2016; FitzGerald 2016), which is likely to be the licensed dose, and included the 20 mg dose in the three previous phase 2a dose-ranging studies (Castro 2015a; Castro 2015b; Park 2016).

Studies that initiated a reduction in standard asthma management (e.g. corticosteroids) as part of the protocol were excluded, as this is unlikely to reflect clinical practice in the majority of cases.

We planned to include the following co-interventions provided they were not part of the randomised treatment: leukotriene antagonists (LTRA), inhaled bronchodilators (including LABA), inhaled (ICS) and oral corticosteroids (OCS), oral aminophylline and macrolide antibiotics.

Types of outcome measures

We referred to the joint American Thoracic Society (ATS) and European Respiratory Society (ERS) statement on standardising endpoints for asthma clinical trials to identify appropriate outcome measures (Reddel 2009). These recommend that clinical trials should assess outcomes relevant to both goals of asthma management: current control of asthma symptoms, and reduced risk of exacerbations and other adverse outcomes (e.g. accelerated lung function decline, treatment side effects). Moreover the authors note that these aspects are often discordant, thus endpoints assessing each need to be considered.

Exacerbations are responsible for most of the morbidity, mortality and healthcare costs related to asthma, and therefore considered the primary outcome measure. The ATS/ERS statement defines severe exacerbations as including either use of systemic corticosteroids for at least three days, or emergency department treatment or admission requiring systemic corticosteroids (definitions in terms of changes from baseline in lung function, symptoms, or short-acting β2 agonist use are not validated).

Lung function, specifically low pre-bronchodilator forced expiratory flow in one second (FEV_1) (the most commonly reported lung function measure in clinical trials), is a strong independent predictor of asthma exacerbations (Osborne 2007), and is objective and reproducible. However lung function and symptoms correlate poorly over time in individual patients, so it is recommended that both are monitored. There is no gold standard score for assessing asthma symptoms, with several validated and regularly used

including the Asthma Control Questionnaire (ACQ) (Juniper 1999), Asthma Control Test (ACT) (Nathan 2004), Asthma Quality of Life Questionnaire (AQLQ) (Juniper 1992), and the St George's Respiratory Questionnaire (SGRQ) (Jones 1991). We considered any one of these an adequate measure of symptoms and health-related quality of life (HRQoL).

Identifying potential patient safety issues are a priority in the evaluation of new drugs. We consider the decision to discontinue study medication because of an adverse event to be a useful clinical marker of severity with real-world applicability, and have included this alongside serious adverse events, which would likely outweigh any potential benefits of the intervention.

Anti-IL-5 treatments should result in a reduction in eosinophils. Moreover as discussed earlier, increased eosinophil counts are associated with symptoms and exacerbations (Jatakanon 2000). We have therefore included eosinophil counts in the peripheral blood, a measure that is readily available in hospitals and clinics, as a secondary outcome.

Primary outcomes

1. 'Clinically significant' asthma exacerbation, as defined by treatment with a course (three days or more) of systemic corticosteroids (with or without hospital admission)

Secondary outcomes

1. Asthma exacerbation requiring hospital admission
2. HRQoL (as measured by a validated questionnaire e.g. ACQ, AQLQ, SGRQ)
3. Measures of lung function (e.g. FEV_1)
4. Serious adverse events
5. 'Clinically significant' adverse events, as defined by those that prompted discontinuation of the intervention and withdrawal from the study
6. Eosinophil counts in peripheral blood

Reporting one or more of the outcomes listed here in the trial was not an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Trials Register, which is maintained by the Information Specialist for the Group. The Cochrane Airways Trials Register contains studies identified from several sources:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies Online (crso.cochrane.org);
2. weekly searches of MEDLINE Ovid SP 1946 to date;
3. weekly searches of Embase Ovid SP 1974 to date;
4. Monthly searches of PsycINFO Ovid SP;
5. Monthly searches of CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature);
6. Monthly searches of AMED EBSCO (Allied and Complementary Medicine);
7. handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register are identified through search strategies based on the scope of Cochrane Airways. Details of these strategies, as well as a list of handsearched conference proceedings are in Appendix 1. See Appendix 2 for search terms used to identify studies for this review.

We also conducted a search of ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en).

We searched all databases from their inception to the present and imposed no restriction on language of publication. The search was first conducted in November 2013 and was updated in November 2014 and March 2017.

Searching other resources

We checked the bibliographies of all primary studies and review articles for additional references. We searched relevant manufacturers' websites for trial information (clinical trials registers on the GlaxoSmithKline (manufacturer of mepolizumab) and AstraZeneca (benralizumab) websites; the Teva (reslizumab) website does not have a clinical trials register).

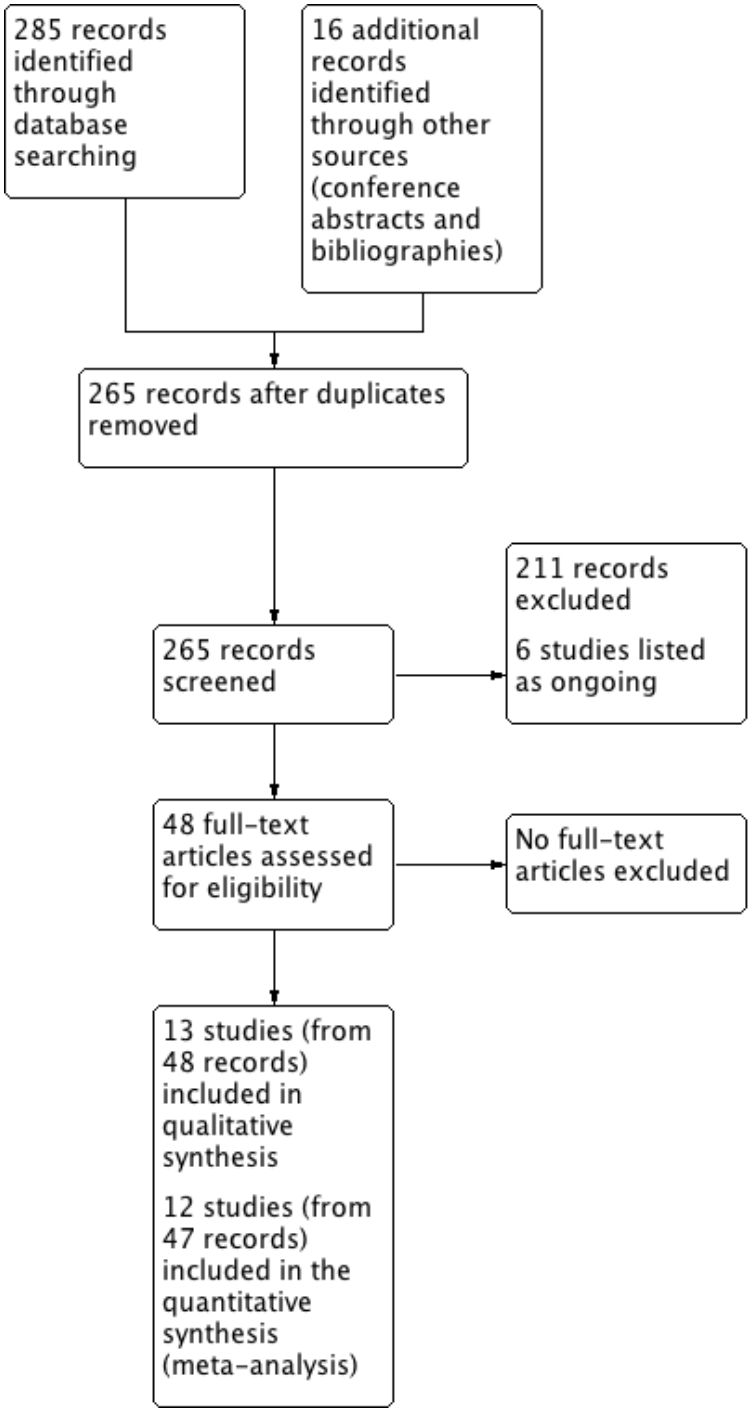
We searched for errata and retractions relevant to the included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and planned to report the date this was done within the review if this was an issue.

Data collection and analysis

Selection of studies

Two review authors (HF, CP) independently screened titles and abstracts of all the potential studies identified in the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports/publications, and two review authors (HF, CP) independently screened the full text and identified studies for inclusion, identifying and recording reasons for excluding the ineligible studies. We planned to resolve any disagreement through discussion or, if required, by consulting a third review author (SJM); however, this was not necessary. We identified and excluded duplicates and collated multiple reports of the same study so that each study rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009) (Figure 1) and a 'Characteristics of excluded studies' table.

Figure 1. Study flow diagram



Data extraction and management

We used a data collection form to record study characteristics and outcome data that had been piloted on at least one study in the review. Two review authors (HF, AW) extracted the following study characteristics from included studies.

1. Methods: study design, total duration of study, details of any run-in period, number of study centres and location, study setting, withdrawals and date of study
2. Participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria
3. Interventions: intervention, comparator, concomitant medications and excluded medications
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported
5. Notes: funding for trial and notable conflicts of interest of trial authors

Two review authors (HF, AW) independently extracted outcome data from included studies. We noted in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We planned to resolve disagreements by consensus or by involving a third author (CP), but this was not necessary. One review author (HF) transferred data into Review Manager 5 (RevMan 5) (RevMan 2014). We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. The data extracted were additionally checked by the Cochrane Airways' statistician. A second review author (SJM) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (HF, AW) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to resolve any disagreements by discussion or by involving another review author (SJM), but this was not necessary. We assessed the risk of bias according to the domains:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective outcome reporting;
7. other bias.

We graded each potential source of bias as high, low or unclear, and provided a quotation from the study report together with a justification for this judgement in the 'Risk of bias' table. We summarised the risk of bias judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes where necessary (e.g. for an unblinded outcome assessment, risk of bias for all-cause mortality may be very different than that for a patient-reported pain scale). Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table. When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

We conducted the review according to this published protocol and have reported any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We analysed dichotomous data as rate ratios and risk ratios, and continuous data as mean differences or standardised mean differences, which are presented with 95% confidence intervals. We entered data presented on a scale with a consistent direction of effect. We have undertaken meta-analyses only where this was meaningful (i.e. if the treatments, participants and underlying clinical question were sufficiently similar for pooling to make sense).

Where multiple trial arms were reported in a single trial (Bjermer 2016; Castro 2014a; Park 2016; Pavord 2012a), we only included the arms with doses likely to be used clinically, that is, 75 mg intravenous (IV) or 100 mg subcutaneous (SC) injections of mepolizumab, 3 mg/kg IV reslizumab, 20 to 30 mg SC benralizumab. We considered four-weekly and eight-weekly dosing schedules to be equally clinically valid and therefore pooled these data (Bleecker 2016; FitzGerald 2016). Mepolizumab can be administered by different routes (IV or SC); for the purpose of this review we considered these separately.

In future updates of this review, we will narratively describe skewed data reported as medians and interquartile ranges. Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) are combined in the same meta-analysis, we will halve the control group to avoid double-counting.

Unit of analysis issues

We did not identify any cross-over studies or cluster-randomised trials for inclusion in this version of the review. If cross-over trials are identified in the future, we will seek data from a paired analysis from the trial report or authors in order to appropriately include data in the review using the inverse variance method. If we identify cluster-randomised trials in the future, then analyses will be at the level of the individual while allowing for the clustering in the data by using the intracluster correlation coefficient. If this is not reported in the trial, then we will impute it from similar studies.

Dealing with missing data

We contacted investigators in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study was identified as an abstract only). If this was

not possible and the missing data were thought to introduce serious bias, we planned to explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Assessment of heterogeneity

Statistical heterogeneity between studies was assessed visually by inspection of the forest plots and using the Chi^2 test (a P value less than 0.10 was considered significant due to the low power of the test). We also calculated the I^2 statistic (Higgins 2003); this describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). Values of I^2 range from 0% to 100%, with 0% representing no heterogeneity and 100% representing considerable heterogeneity. For this review, we defined heterogeneity as reported using the I^2 statistic as follows.

1. 0% to 40%: heterogeneity might not be important.
2. 30% to 60%: may represent moderate heterogeneity.
3. 50% to 90%: may represent substantial heterogeneity.
4. 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

If we are able to pool more than 10 trials for future versions, we will create and examine a funnel plot to explore possible small study biases and publication bias.

Data synthesis

In view of the considerable clinical heterogeneity between the included studies, we used a random-effects model.

Data on outcomes were combined at 6 months and 12 months. Where data for other time points were reported, these were also described.

Subgroup analysis and investigation of heterogeneity

Provided sufficient studies were included, we planned to carry out subgroup analyses according to:

1. eosinophilic individuals versus non-eosinophilic individuals (as eosinophilia may be a prescribing requirement e.g. NICE 2017); and
2. age (0 to 5 years, 6 to 16 years, 17 years and older).

Using the outcomes:

1. 'clinically significant' asthma exacerbations;
2. HRQoL (as measured by a validated questionnaire); and
3. measures of lung function (e.g. FEV_1).

We used the formal test for subgroup interactions in RevMan 2014.

Sensitivity analysis

We planned to carry out the following sensitivity analyses if sufficient studies were included:

1. excluding studies with an overall high risk of bias;
2. excluding cross-over trials and cluster-randomised trials.

'Summary of findings' table

We created 'Summary of findings' tables using the following outcomes.

1. Asthma exacerbations
2. HRQoL (as measured by a validated questionnaire)
3. Measures of lung function (e.g. FEV_1)
4. Adverse events

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence as it related to the studies that contributed data to the meta-analyses for the prespecified outcomes. We used methods and recommendations described in Section 8.5 (Higgins 2011) and Chapter 12 (Schünemann 2011) of the *Cochrane Handbook for Systematic Reviews of Interventions* using GRADEpro GDT software (GRADEpro GDT 2015). We have justified all decisions to downgrade or upgrade the quality of studies using footnotes, and we have made comments to aid the reader's understanding of the review where necessary.

RESULTS

Description of studies

Results of the search

We identified 301 records in our literature searches (Figure 1):

1. 159 in database searches for the original mepolizumab review (last search April 2015)
2. 126 in updated database searches for this review (in August 2016 and March 2017)
3. 13 relevant studies reported in conference abstracts and two in study bibliographies in September 2016, and
4. A further study in April 2017 (identified on reviewing the ongoing studies and finding one had completed and published).

After removing duplicates, 265 records remained.

Thirteen (13) studies met our inclusion criteria ('Characteristics of included studies' table), and six others were included in the ongoing studies category ('Characteristics of ongoing studies' table). The thirteen studies included had 48 records:

1. The four included studies comparing mepolizumab versus placebo had 16 records: two for Chupp 2017, four for Haldar 2009, eleven for Ortega 2014 and six for Pavord 2012a.
2. The four included studies comparing reslizumab versus placebo had 16 records: five for Castro 2015a; three for Castro 2015b; four for Bjermer 2016, and three for Corren 2016.

3. The five included studies for benralizumab versus placebo had 16 records: three for Bleecker 2016; six for Castro 2014a; three for FitzGerald 2016; three for Park 2016, and one for NCT01947946 2013.

The remaining 211 records were excluded for various reasons ('Characteristics of excluded studies' table). In particular, Nair 2009 and Bel 2014 were excluded as the dose of prednisolone was reduced four weeks after the first dose of mepolizumab.

Included studies

Table 1 compares the design, numbers, interventions and participant groups in the included trials.

Mepolizumab

We included four studies comparing mepolizumab versus placebo ('Characteristics of included studies' table), involving 1809 total participants distributed as follows: Chupp 2017 n = 551; Haldar 2009 n = 61; Ortega 2014 n = 576, and Pavord 2012a n = 621. Mepolizumab was administered intravenously (IV) in Haldar 2009 (at a dose of 750 mg) and Pavord 2012a (at doses of 75 mg, 250 mg and 750 mg), subcutaneously (SC) in Chupp 2017, and via both routes (75 mg IV or 100 mg SC) in Ortega 2014 over a range of treatment periods. For Pavord 2012a, we only included the arm dosed at 75 mg, as this is considered comparable to the 100 mg SC dose that is licensed (according to manufacturer's evidence submission to the UK's National Institute for Health and Care Excellence in November 2015).

The studies only included participants with severe eosinophilic asthma. In all four studies severe disease was defined as requiring high-dose ICS and a second controller medication plus a history of at least two exacerbations in the preceding 12 months. In addition Chupp 2017 and Ortega 2014 required that participants had impaired lung function despite treatment with an FEV_1 of less than 80%. Eosinophilia was defined as a serum eosinophil count of 150 cells or more per μL at screening or 300 cells or more per μL at some time during the previous year (Chupp 2017; Ortega 2014), or either a sputum eosinophil count of 3% or more (Haldar 2009) and/or a blood eosinophil count of 300 cells or more per μL (Pavord 2012a). The blood eosinophil thresholds used in Chupp 2017 and Ortega 2014 were identified as those that best predicted response to mepolizumab in a secondary analysis of previous studies (Ortega 2014; Pavord 2012a).

Reslizumab

Four studies comparing reslizumab versus placebo were included ('Characteristics of included studies' table), involving 1764 total participants distributed as follows: Bjermer 2016 n = 315, Castro 2015a n = 489; Castro 2015b n = 464; and Corren 2016 n = 496. Reslizumab was administered intravenously in all four studies over a range of treatment periods at a dose of 3.0 mg/kg, with an additional arm at a dose of 0.3 mg/kg in Bjermer 2016, which was not included as it is 10 times lower than the licensed dose of 3.0 mg/kg.

All the participants had moderate to severe asthma, defined as requiring medium-dose ICS. In addition they had inadequate symptom control, with an ACQ of 1.5 or more. In addition Castro 2015a and Castro 2015b required a history of at least one exacerbation in the preceding 12 months. Three studies of reslizumab (Bjermer 2016; Castro 2015a; Castro 2015b) required that participants had a blood eosinophil count of 400 cells or more per μL, which has been shown to be predictive of a sputum eosinophil count of 3% or more in studies of participants with paired blood and sputum samples (Farooqui 2009; Van Veen 2009). Corren 2016 included participants with a range of eosinophil counts.

Benralizumab

We included five studies comparing benralizumab versus placebo ('Characteristics of included studies' table), involving 3232 total participants distributed as follows: Bleecker 2016 n = 1204; Castro 2014a n = 606; FitzGerald 2016 n = 1306, NCT01947946 2013 n = 13 and Park 2016 n = 103. The benralizumab was administered subcutaneously in all studies, with dosage varying from 2 mg to 100 mg every four or eight weeks over a range of treatment periods. We only included participants dosed with 20 mg or 30 mg benralizumab in the analysis, as the other doses are unlikely to be licensed and therefore used clinically. NCT01947946 2013 was terminated due to sponsor decision after randomising 13 participants and contributes no data to the review.

The severity of asthma among participants varied from moderate to severe, defined as a requirement for maintenance therapy with medium- or high-dose ICS plus LABA. Participants also had poor asthma control, determined by a history of at least two exacerbations in the previous 12 months and an ACQ of 1.5 or above in the studies contributing data. All five benralizumab trials included participants regardless of eosinophilia, but results were stratified by blood eosinophil count using a threshold of 300 cells or more per μL.

Excluded studies

We excluded 187 studies from the review (from 211 references). Of these: 117 (61%) because anti-IL-5 therapy had not been included in the study; 32 (17%) were not randomised placebo-controlled studies; 14 (8%) had a treatment period of less than 16 weeks; 11 (6%) were conducted on participants without a diagnosis of asthma; 9 (5%) were an aggregation of trials, and 4 (2%) because the focus was on steroid reduction. (See 'Characteristics of excluded studies' table).

Risk of bias in included studies

Details of our 'Risk of bias' assessments are available in the 'Characteristics of included studies' table, and a summary of our assessment can be seen in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

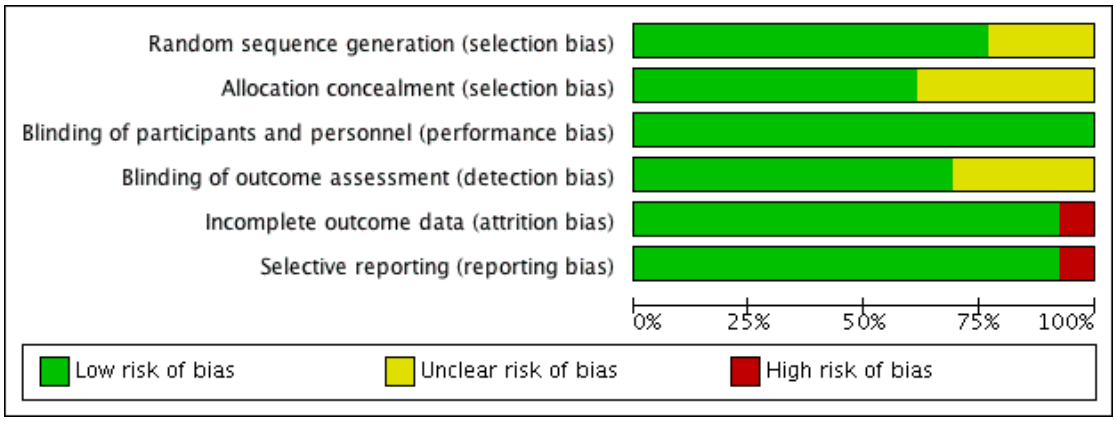
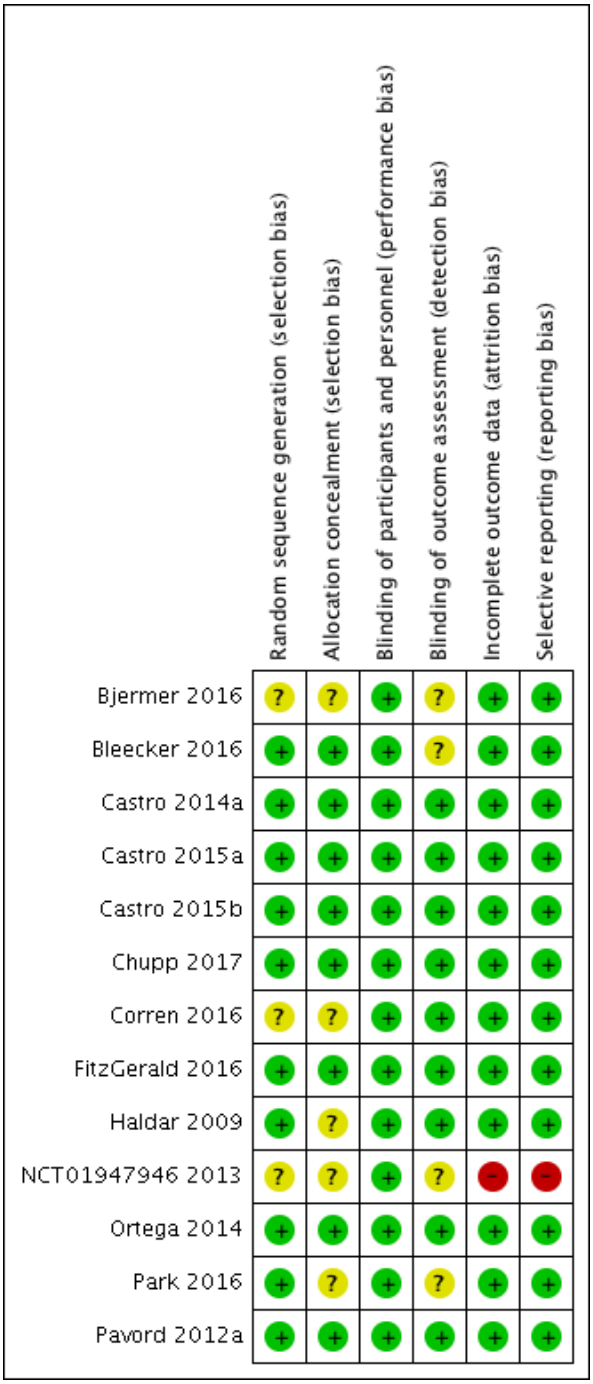


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

We deemed the majority of studies to be at low risk of bias for both random sequence generation and allocation concealment. Three studies (Bjermer 2016; Corren 2016; NCT01947946 2013) presented no details on either random sequence generation or allocation concealment, whereas a further two (Haldar 2009; Park 2016) presented no details on allocation concealment only (Figure 3).

Blinding

We determined that all 13 studies were at low risk of performance bias, and nine were at low risk of detection bias; the risk of detection bias was unclear for four studies (Bjermer 2016; Bleecker 2016; NCT01947946 2013; Park 2016) (Figure 3).

Incomplete outcome data

We considered all 12 studies contributing data to be at low risk of attrition bias (Figure 3). One study, in which no participant completed the trial, was deemed to be at high risk (NCT01947946 2013).

Selective reporting

We considered the risk of reporting bias to be low in 12 studies (Figure 3) and high in the terminated study (NCT01947946 2013).

Other potential sources of bias

We did not note any other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Mepolizumab subcutaneous (SC) compared to placebo for asthma; **Summary of findings 2** Mepolizumab intravenous (IV) compared to placebo for asthma; **Summary of findings 3** Reslizumab intravenous (IV) compared to placebo for asthma; **Summary of findings 4** Benralizumab subcutaneous (SC) compared to placebo for asthma

Mepolizumab (SC) versus placebo

The data for this comparison come from two studies, Chupp 2017 and Ortega 2014, with a combined 936 participants with severe eosinophilic asthma. In both studies this was defined as a serum eosinophil count of 300 cells or more per μL in the preceding 12 months or 150 cells or more per μL at screening. Our confidence in the results below is high, as both studies were large with a robust methodology.

Primary Outcomes

'Clinically significant' asthma exacerbation (as defined by treatment with a course of systemic corticosteroids, with or without hospital attendance or admission)

The meta-analysis produced a statistically significant effect favouring mepolizumab, versus placebo, from the two studies contributing data to this outcome Chupp 2017; Ortega 2014 (rate ratio 0.45, 95% confidence interval (CI) 0.36 to 0.55; participants = 936; studies = 2) (Analysis 1.1).

Secondary outcomes

Exacerbations requiring emergency department treatment or admission

The rate of exacerbations requiring emergency department treatment or admission from the two studies (Chupp 2017; Ortega 2014) contributing to this outcome was significantly lower in the mepolizumab condition (rate ratio 0.36, 95% CI 0.20 to 0.66; participants = 936; studies = 2) (Analysis 1.2); and the rate of exacerbations requiring admission in the same two studies similarly favoured mepolizumab versus placebo (rate ratio 0.31, 95% CI 0.13 to 0.73; participants = 936; studies = 2) (Analysis 1.3).

HRQoL (as measured by a validated questionnaire e.g. ACQ, AQLQ, SGRQ)

Two studies (Chupp 2017; Ortega 2014) contributed HRQoL data measured by the ACQ instrument, indicating a statistically significant effect in favour of mepolizumab versus placebo (mean difference (MD) -0.42, 95% CI -0.56 to -0.28; participants = 936; studies = 2) (Analysis 1.4), but this did not meet the minimum clinically important difference (MCID) of 0.5 points in the ACQ. However there was a statistically and clinically significant improvement in the SGRQ in these studies (MD -7.40, 95% CI -9.50 to -5.29; participants = 936; studies = 2) (Analysis 1.5); the MCID is -4 points for the SGRQ). The SGRQ is a 50-item questionnaire with questions covering three domains: symptoms, activity, and impacts (psycho-social). The ACQ has between five and seven items (there are three variations) focused on asthma symptoms and airflow limitation (the seven-item ACQ includes short-acting bronchodilator use for symptom relief and FEV_1).

Thus the intervention may have had broader effects on activity and psycho-social aspects that were not captured by the ACQ.
In a responder analysis, Chupp 2017 found 59% of participants experienced an improvement greater than the MCID of 0.5 points in the ACQ, versus 42% of participants on placebo (P = 0.0014), and 73% had an improvement of greater than the MCID of 4 points in the SGRQ, versus 55% in the placebo arm (P < 0.0001).

Measures of lung function (e.g. FEV_1)

We observed a statistically significant increase of 110 mL in pre-bronchodilator FEV_1 in the mepolizumab condition of the aggregated studies (Chupp 2017; Ortega 2014) (MD 0.11 L, 95% CI 0.06 to 0.17; participants = 936; studies = 2) (Analysis 1.6). This is a relatively modest increase; although there is no universally accepted MCID for FEV_1 in asthma, variability within a single testing session can be up to 0.12 L (data from a mixed pool of respiratory patients, Enright 2004).

Serious adverse events

Overall there were statistically fewer serious adverse events in the mepolizumab condition when we combined data from Chupp 2017 and Ortega 2014 (risk ratio 0.63, 95% CI 0.41 to 0.97; participants = 936; studies = 2) (Analysis 1.7). This may be due to a reduction in asthma-related serious adverse events (e.g. exacerbations requiring hospitalisation, which were significantly reduced), although neither study achieved statistical significance alone and therefore this was not commented on by the investigators. It is also possible that the inclusion of asthma-related serious adverse effects, which were reduced, could mask a relatively smaller increase in non-asthma-related serious adverse effects; in future it would be useful for this to be separated.

'Clinically significant' adverse events (defined as those prompting participants to stop the intervention)

There was no significant statistical difference between the two conditions with respect to this outcome (risk ratio 0.45, 95% CI 0.11 to 1.80; participants = 936; studies = 2; I^2 = 0%) (Analysis 1.8).

Serum eosinophil counts

Insufficient data were available to analyse this outcome. However Ortega 2014 reported a decrease in serum eosinophil counts by week 4, with a maximal drop of 86% by week 12 that was maintained during the study.

Mepolizumab (IV) versus placebo

The data for this comparison come from three studies (Haldar 2009; Ortega 2014; Pavord 2012a) with a combined 751 participants, all with severe eosinophilic asthma; there were no subgroups with non-eosinophilic participants. Our confidence in the results is moderate, as IV delivery is not currently a licenced delivery route for mepolizumab, and although the results for exacerbations mirror those with mepolizumab SC, those for HRQoL measures do not.

Primary Outcomes

'Clinically significant' asthma exacerbation (as defined by treatment with a course of systemic corticosteroids, with or without hospital attendance or admission)

The rate of 'clinically significant' exacerbations was significantly lower in the mepolizumab condition (rate ratio 0.53, 95% CI 0.44 to 0.64; participants = 751; studies = 3 (Haldar 2009; Ortega 2014; Pavord 2012a)) (Analysis 2.1).

Secondary outcomes

Exacerbations requiring emergency department treatment or admission

The rate of exacerbations requiring emergency department treatment or admission was significantly lower in the mepolizumab condition (rate ratio 0.52, 95% CI 0.31 to 0.87; participants = 690; studies = 2 (Ortega 2014; Pavord 2012a)) (Analysis 2.2). The rate of exacerbations requiring admission favoured the intervention group but this did not reach statistical significance (rate ratio 0.61, 95% CI 0.33 to 1.13; participants = 690; studies = 2 (Ortega 2014; Pavord 2012a)) (Analysis 2.3).
These findings are consistent with results from a smaller trial (participants = 61; Haldar 2009), which reported three admissions for asthma exacerbations in the mepolizumab group (n = 29) compared to 11 in the placebo group (n = 32; P = 0.07). However there was no significant difference between mepolizumab versus placebo in terms of people experiencing one or more exacerbations in this smaller trial (Haldar 2009; risk ratio 0.82, 95% CI 0.61 to 1.09; participants = 61; studies = 1) (Analysis 2.4).

HRQoL (as measured by a validated questionnaire e.g. ACQ, AQLQ, SGRQ)

There was no significant difference between mepolizumab and placebo for HRQoL when measured using the AQLQ instrument (MD 0.21, 95% CI -0.06 to 0.47; participants = 369; studies = 2 (Haldar 2009; Pavord 2012a)) (Analysis 2.5). Similarly there

was no statistically reliable difference between the two conditions when measuring HRQoL using the ACQ in these studies (MD -0.11, 95% CI -0.32 to 0.09; participants = 369; studies = 2) (Analysis 2.6). However, we observed a statistically significant benefit favouring mepolizumab in HRQoL using the SGRQ in a single study (MD -6.40, 95% CI -9.65 to -3.15; participants = 382; studies = 1 (Ortega 2014)) (Analysis 2.7). These results conflict with those with mepolizumab SC, but in those cases where statistical significance was not reached, the trend was in favour of mepolizumab and so it may be that the effect is relatively small and this outcome is therefore underpowered.

Measures of lung function (e.g. FEV_1)

We observed a statistically significant benefit favouring mepolizumab in pre-bronchodilator FEV_1 (litres) (MD 0.08, 95% CI 0.02 to 0.15; participants = 690; studies = 2 (Ortega 2014; Pavord 2012a)) (Analysis 2.8). This increase is comparable, but slightly smaller, than that for mepolizumab SC and, at an individual participant level, would be considered within the normal range of variability at a single session (Enright 2004).

Serious adverse events

Significantly fewer serious adverse events occurred in the mepolizumab condition (risk ratio 0.59, 95% CI 0.37 to 0.94; participants = 751; studies = 3 (Haldar 2009; Ortega 2014; Pavord 2012a); I^2 = 27%) (Analysis 2.9). As with mepolizumab SC, this may be due to a reduction in asthma-related serious adverse events but as the individual studies did not report a clear effect, there is no comment by the investigators.

'Clinically significant' adverse events (defined as those prompting discontinuation)

For this outcome there was no significant difference between mepolizumab versus placebo (risk ratio 0.72, 95% CI 0.18 to 2.92; participants = 751; studies = 3 (Haldar 2009; Ortega 2014; Pavord 2012a); I^2 = 24%) (Analysis 2.10).

Serum eosinophil counts

We included a single small study (Haldar 2009) in the analysis as it was the only one to report serum eosinophil counts. This reported a significant benefit favouring mepolizumab (MD -170.00, 95% CI -230.00 to -110.00; participants = 61; studies = 1 (Haldar 2009)) (Analysis 2.11).

Ortega 2014 also reported a decrease in serum eosinophil counts by week 4, with a maximal drop of 83% by week 12 that was maintained during the study, but did not provide absolute counts that could be included.

Reslizumab (IV) versus placebo

The data for this comparison come from four studies (Bjermer 2016; Castro 2015a; Castro 2015b; Corren 2016) with a combined 1652 participants. One of these studies included participants with non-eosinophilic asthma (Corren 2016). Our confidence in the results as applied to eosinophilic participants is high, as the studies were large and had a robust methodology. Where data were available for non-eosinophilic participants we have compared the effect estimate with that for eosinophilic participants using the test for subgroup difference.

Primary Outcomes

'Clinically significant' asthma exacerbation (as defined by treatment with a course of systemic corticosteroids, with or without hospital attendance or admission)

There were significantly fewer 'clinically significant' asthma exacerbations in the reslizumab condition (rate ratio 0.43, 95% CI 0.33 to 0.55; participants = 953; studies = 2 (Castro 2015a; Castro 2015b)) (Analysis 3.1). This only included eosinophilic participants; there were no data for non-eosinophilic participants.

Secondary outcomes

Exacerbations requiring emergency department treatment or admission

There was no significant difference between reslizumab versus placebo on this outcome (rate ratio 0.67, 95% CI 0.39 to 1.17; participants = 953; studies = 2 (Castro 2015a; Castro 2015b)) (Analysis 3.2). This only included eosinophilic participants; there were no data for non-eosinophilic participants.

HRQoL (as measured by a validated questionnaire e.g. ACQ, AQLQ, SGRQ)

Participants in the reslizumab condition experienced a significantly better HRQoL measured by the AQLQ instrument (MD 0.28, 95% CI 0.17 to 0.39; participants = 1164; studies = 3 (Bjermer 2016; Castro 2015a; Castro 2015b)) (Analysis 3.3), although this failed to meet the MCID of 0.5 points or more. This only included eosinophilic participants; there were no data for non-eosinophilic participants.

We found the same effect when using the ACQ (MD -0.25, 95% CI -0.33 to -0.17; participants = 1652; studies = 4 (Bjermer 2016; Castro 2015a; Castro 2015b; Corren 2016)) (Analysis 3.4), again, lower than the MCID of -0.5 points or more. In this analysis data were available (in only one study, Corren 2016) from non-eosinophilic participants and for that particular group there was

no significant difference between reslizumab versus placebo on this outcome. However, the formal test for subgroup difference was not significant (P = 0.19, I^2 = 41.1%).

Measures of lung function (e.g. FEV_1)

We noted a clear, statistically significant increase in pre-bronchodilator FEV_1 with reslizumab treatment (MD 0.11 L, 95% CI 0.07 to 0.15; participants = 1652; studies = 4 (Bjermer 2016; Castro 2015a; Castro 2015b; Corren 2016)) (Analysis 3.5). For this outcome data from non-eosinophilic participants were available (again in only one study, Corren 2016) and for that subgroup we observed no significant difference between reslizumab versus placebo. As in the ACQ data, there was a significant benefit only in eosinophilic participants. However, as before, the formal test for subgroup differences was not significant (P = 0.13, I^2 = 56.3%). Again it is worth noting that the absolute difference of 0.11 L is relatively modest, although there is no consensus around a MCID in FEV_1 in asthma.

Serious adverse events

There was no significant difference in the number of serious adverse events occurring in the two conditions (risk ratio 0.79, 95% CI 0.56 to 1.12; participants = 1656; studies = 4 (Bjermer 2016; Castro 2015a; Castro 2015b; Corren 2016); I^2 = 0%) (Analysis 3.6).

There was a reduction favouring the treatment group with the pooled mepolizumab trials, which may have been due to a reduction in asthma-related serious adverse events (the pooled studies showed significantly fewer asthma exacerbations requiring hospital admission, which would qualify as a serious adverse event). However there was no significant difference in the rate of hospitalisations due to asthma exacerbations in studies of reslizumab, which may explain the discrepancy in serious adverse events compared to mepolizumab.

'Clinically significant' adverse events (defined as those prompting discontinuation)

There was no significant difference between reslizumab versus placebo on this outcome (risk ratio 0.66, 95% CI 0.43 to 1.02; participants = 1659; studies = 4 (Bjermer 2016; Castro 2015a; Castro 2015b; Corren 2016); I^2 = 0%) (Analysis 3.7).

Serum eosinophil counts

The serum eosinophil counts were significantly reduced in the reslizumab condition (MD -476.83, 95% CI -499.32 to -454.34; participants = 1656; studies = 4 (Bjermer 2016; Castro 2015a; Castro 2015b; Corren 2016)) (Analysis 3.8). This only included eosinophilic participants; note that a reduction in eosinophils amongst participants whose eosinophil counts are within the normal range to start with is not necessarily desirable or achievable.

Benralizumab (SC) versus placebo

The data for this comparison come from four studies (Bleecker 2016; Castro 2014a; FitzGerald 2016; Park 2016) with a combined 2648 participants. All four studies included participants with an eosinophilic and non-eosinophilic phenotype, with more complete data presented for eosinophilic participants. In addition two studies had additional treatment arms for four-weekly and eight-weekly dosing regimens (Bleecker 2016; FitzGerald 2016), which we have shown separately in the meta-analyses with the placebo group split across them (and adjusted accordingly). Our confidence in the results is high, as the studies were large and had a robust methodology. However limited data were available on non-eosinophilic subgroups, and these were variably consistent with the findings in eosinophilic subgroups.

Primary Outcomes

'Clinically significant' asthma exacerbation (as defined by treatment with a course of systemic corticosteroids, with or without hospital attendance or admission)

Significantly fewer 'clinically significant' asthma exacerbations occurred in the benralizumab condition (rate ratio 0.62, 95% CI 0.55 to 0.70; participants = 2456; studies = 3 (Bleecker 2016; Castro 2014a; FitzGerald 2016)) (Analysis 4.1). We observed this effect in both eosinophilic and non-eosinophilic participants, with a slightly larger effect for the eosinophilic subgroup (eosinophilic: rate ratio 0.59, 95% CI 0.51 to 0.68 versus non-eosinophilic: rate ratio 0.69, 95% CI 0.56 to 0.85) but the test for subgroup difference was non-significant (P = 0.22, I^2 = 33.9%).

Secondary outcomes

Exacerbations requiring emergency department treatment or admission

There were significantly fewer exacerbations requiring emergency department treatment or admission for participants in the benralizumab condition (rate ratio 0.68, 95% CI 0.47 to 0.98; participants = 1537; studies = 2 (Bleecker 2016; FitzGerald 2016)) (Analysis 4.2). This only included eosinophilic participants; there were no data for non-eosinophilic participants. However there was a considerable degree of heterogeneity (I^2 = 43%), despite the Bleecker 2016 and FitzGerald 2016 studies having the same design. Both studies noted heterogeneity in the exacerbation history of their participants, FitzGerald 2016 specifically commenting that participants recruited in Eastern Europe and South America had fewer exacerbations in the year before study entry than

those recruited elsewhere. These would therefore have less scope for a reduction in exacerbation. FitzGerald 2016 noted that participants who had had three or more exacerbations in the previous year had the greatest effects of benralizumab treatment, at rates comparable to the Bleecker 2016 study.

HRQoL (as measured by a validated questionnaire e.g. ACQ, AQLQ, SGRQ)

HRQoL (AQLQ mean difference) was significantly better in the benralizumab condition (MD 0.23, 95% CI 0.11 to 0.35; participants = 1541; studies = 3 (Bleecker 2016; Castro 2014a; FitzGerald 2016)) (Analysis 4.3); on this particular outcome data were available only from eosinophilic participants. However a similar significant advantage in favour of benralizumab was also observed with both eosinophilic and non-eosinophilic participants when measuring HRQoL with the ACQ instrument (MD -0.20, 95% CI -0.29 to -0.11; participants = 2359; studies = 3 (Bleecker 2016; Castro 2014a; FitzGerald 2016)) (Analysis 4.4). When taking the non-eosinophilic subgroup only this fell short of statistical significance (MD -0.14, 95% CI -0.30 to 0.02), although the test for subgroup difference was non-significant (P = 0.36, I^2 = 0%). Neither difference reached the MCID of 0.5 points or more on either the AQLQ or ACQ scale.

Measures of lung function (e.g. FEV_1)

Pre-bronchodilator FEV_1 was significantly superior in the benralizumab condition (MD 0.10, 95% CI 0.05 to 0.14; participants = 2355; studies = 3 (Bleecker 2016; Castro 2014a; FitzGerald 2016)) (Analysis 4.5). However on closer inspection it was apparent that only eosinophilic participants had experienced this benefit, with a significant test for subgroup difference between eosinophilic and non-eosinophilic participants (P = 0.02, I^2 = 82.0%). This improvement of 0.10 L is of a similar magnitude to that seen with mepolizumab and reslizumab, and is relatively modest.

Serious adverse events

There was no significant difference in the number of serious adverse events occurring in the two conditions (risk ratio 0.81, 95% CI 0.66 to 1.01; participants = 2648; studies = 4 (Bleecker 2016; Castro 2014a; FitzGerald 2016; Park 2016); I^2 = 0%)(Analysis 4.6), based on eosinophilic and non-eosinophilic participants (including a subgroup of participants whose eosinophil status was not defined).

This is slightly surprising given that the pooled analysis for mepolizumab showed a reduction in serious adverse events compared to placebo, which may have been due to a reduction in asthma-related serious adverse events such as exacerbations requiring admission, which was also seen with benralizumab (significantly fewer exacerbations requiring admission or emergency department treatment). However the size of the effect on asthma exacerbations requiring admission or emergency department treatment was smaller with benralizumab (rate ratio 0.68, 95% CI 0.47 to 0.98) than mepolizumab (rate ratio 0.36, 95% CI 0.20 to 0.66 for mepolizumab SC; rate ratio 0.52, 95% CI 0.31 to 0.87 for mepolizumab IV). The dilution of this by including other adverse events may have been sufficient to make it non-significant. Indeed examining the rate ratios suggests that this is the case both for mepolizumab, where the 95% CIs are nearer to 1 than it is for the asthma exacerbation outcomes, and benralizumab, where the upper CI is 1.01. Equally it is possible that benralizumab results in relatively greater numbers of non-asthma-related serious adverse events than mepolizumab (or reslizumab), given its different mechanism of action. It will be important in future to distinguish asthma-related from non-asthma-related serious adverse events and, if licensed, to monitor real-world data.

'Clinically significant' adverse events (defined as those prompting discontinuation)

There were significantly fewer 'clinically significant' adverse events in the placebo condition (risk ratio 2.15, 95% CI 1.02 to 4.57; participants = 2597; studies = 3 (Bleecker 2016; Castro 2014a; FitzGerald 2016); I^2 = 0%) (Analysis 4.7), based on eosinophilic and non-eosinophilic participants (including a subgroup of participants whose eosinophil status was not defined). The individual studies did not find a statistically significant effect and thus there was no comment by the investigators. However benralizumab has a different mechanism of action resulting in a much larger reduction in eosinophils, which could result in an increase in adverse events. This is an area for further research.

Serum eosinophil levels (% change from baseline)

The serum eosinophil levels were significantly reduced in the benralizumab condition (MD -104.74, 95% CI -116.12 to -93.35; participants = 2295; studies = 2 (Bleecker 2016; FitzGerald 2016)) (Analysis 4.8). This included both eosinophilic and non-eosinophilic participants. This is shown as a percentage change rather than absolute number, which was not available. There was also a marked reduction in serum eosinophils in Castro 2014a, with mean values of 46 to 56 cells per μL in participants with 300 or more cells per μL at baseline, and in Park 2016, to around 0 cells per μL from a mean of 564 to 824 cells per μL (these data were shown graphically and could not be extracted for inclusion in the meta-analysis).

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Mepolizumab (IV) compared to placebo for asthma

Patient or population: people with asthma
Setting: community
Intervention: mepolizumab (IV)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with mepolizumab (IV)				
Rate of clinically significant exacerbations Follow-up: range 32 weeks to 52 weeks	The mean rate in the placebo group was 2.51 events per participant per year[a]	The mean rate in the intervention groups was 1.18 fewer events per participant per year (1.41 fewer to 0.90 fewer)	Rate ratio 0.53 (0.44 to 0.64)	751 (3 RCTs)	⊕⊕⊕◯ Moderate[c]	
Rate of exacerbations requiring emergency department treatment or admission Follow-up: range 32 weeks to 52 weeks	The mean rate in the placebo group was 0.32 events per participant per year[b]	The mean rate in the intervention groups was 0.15 fewer events per participant per year (0.22 fewer to 0.04 fewer)	Rate ratio 0.52 (0.31 to 0.87)	690 (2 RCTs)	⊕⊕⊕◯ Moderate[c]	
Health-related quality of life (AQLQ) Scale from: 1 to 7 (higher is better) Follow-up: range 32 weeks to 52 weeks	The mean change in the placebo group ranged from 0.18 to 0.71 units	MD 0.21 higher (-0.06 lower to 0.47 higher)	-	677 (2 RCTs)	⊕⊕⊕◯ Moderate[c]	A change of ≥ 0.5 is considered the minimum clinically significant difference

Health-related quality of life (ACQ) Scale from: 0 to 6 (lower is better) Follow-up: range 32 weeks to 52 weeks	The mean change in the placebo group ranged from −0.59 to −0.50 units	MD -0.11 lower (-0.32 lower to 0.09 higher)	-	369 (2 RCTs)	⊕⊕⊕◯ Moderate[c]	A change of ≥ 0.5 is considered the minimum clinically significant difference
Pre-bronchodilator FEV_1 (L) Follow-up: range 32 weeks to 52 weeks	The mean change in the placebo group ranged from 0.060 L (± 0.038 L) to 0.086 L (± 0.031 L)	MD 0.08 L (0.02 L higher to 0.15 L higher)	-	690 (2 RCTs)	⊕⊕⊕◯ Moderate[c]	
Adverse events leading to discontinuation Follow-up: range 32 weeks to 52 weeks	26 per 1000	19 per 1000 (5 to 77)	RR 0.72 (0.18 to 2.92)	751 (3 RCTs)	⊕⊕⊕◯ Moderate[c]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

ACQ: Asthma Control Questionnaire; **AQLQ**: Asthma Quality of Life Questionnaire; **CI:** confidence interval; **FEV_1** : forced expiratory volume in 1 second; **MD**: mean difference; **IV**: intravenous; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Rounded mean of the rate in the placebo group of the three studies: 1.74, 2.40 and 3.4.
[b]Rounded mean of the rate in the placebo group of the two studies: 0.20 and 0.43.
[c]The intravenous route is not currently licenced for mepolizumab; one point deducted for indirectness.

Reslizumab (IV) compared to placebo for asthma

Patient or population: people with asthma
Setting: community
Intervention: reslizumab (IV)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with reslizumab (IV)				
Rate of exacerbations requiring systemic corticosteroids Follow-up: 52 weeks	The mean rate in the placebo group was 1.54 events per participant per year	The mean rate in the intervention groups was 0.93 fewer events per participant per year (1.09 fewer to 0.73 fewer)	Rate ratio 0.43 (0.33 to 0.55)	953 (2 RCTs)	⊕⊕⊕⊕ High	
Rate of exacerbations requiring emergency department treatment or admission Follow-up: 52 weeks	The mean rate in the placebo group was 0.12 events per participant per year	The mean rate in the intervention groups was 0.04 fewer events per participant per year (0.07 fewer to 0.02 more)	Rate ratio 0.67 (0.39 to 1.17)	953 (2 RCTs)	⊕⊕⊕⊕ High	
Health-related quality of life (AQLQ) Scale from: 1 to 7 (higher is better) Follow -p: range 16 weeks to 52 weeks	The mean change in the placebo group ranged from 0.779 to 0.89 units	MD 0.28 higher (0.17 higher to 0.39 higher)[a]	-	1164 (3 RCTs)	⊕⊕⊕⊕ High	A change of ≥ 0.5 is considered the minimum clinically significant difference
Health-related quality of life (ACQ) Scale from: 0 to 6 (lower is better) Follow-up: range 16	The mean change in the placebo group ranged from −0.368 to −0.80 units	MD -0.25 lower (-0.33 lower to -0.17 lower)[b]	-	1652 (4 RCTs)	⊕⊕⊕⊕ High	A change of ≥ 0.5 is considered the minimum clinically significant difference

weeks to 52 weeks					
Pre-bronchodilator FEV_1 (L) Follow-up: range 16 weeks to 52 weeks	The mean change in the placebo group ranged from 0.002 L (± 0.1216 L) to 0.215 (± 0.0484 L)	MD 0.11 L higher (0.07 L higher to 0.15 L higher)	-	1652 (4 RCTs)	⊕⊕⊕⊕ High
Serious adverse events Follow-up: range 16 weeks to 52 weeks	91 per 1000	72 per 1000 (51 to 102)	RR 0.79 (0.56 to 1.12)	1656 (4 RCTs)	⊕⊕⊕⊕ High
Adverse events leading to discontinuation Follow-up: range 16 weeks to 52 weeks	58 per 1000	38 per 1000 (25 to 59)	RR 0.66 (0.43 to 1.02)	1659 (4 RCTs)	⊕⊕⊕⊕ High

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

ACQ: Asthma Control Questionnaire; **AQLQ**: Asthma Quality of Life Questionnaire; **CI:** confidence interval; **FEV_1** : forced expiratory volume in 1 second; **MD**: mean difference; **IV**: intravenous; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] The mean difference (0.28) is smaller than the minimum clinically significant difference (a reduction of 0.5 points).
[b] The mean difference (-0.25) is smaller than the minimum clinically significant difference (a reduction of 0.5 points)

Benralizumab (SC) compared to placebo for asthma

Patient or population: people with asthma
Setting: community
Intervention: benralizumab (SC)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with benralizumab (SC)				
Rate of exacerbations requiring systemic corticosteroids Follow-up: range 48 weeks to 56 weeks	The mean rate in the placebo group was 0.98 events per participant per year[a]	The mean rate in the intervention groups was 0.37 fewer events per participant per year (0.44 fewer to 0.29 fewer)	Rate ratio 0.62 (0.55 to 0.70)	2456 (3 RCTs)	⊕⊕⊕⊕ High	
Rate of exacerbations requiring emergency department treatment or admission Follow-up: range 48 weeks to 56 weeks	The mean rate in the placebo group was 0.11 events per participant per year[b]	The mean rate in the intervention groups was 0.04 fewer events per participant per year (0.06 fewer to 0.002 fewer)	Rate ratio 0.68 (0.47 to 0.98)	1537 (2 RCTs)	⊕⊕⊕◯ Moderate[e]	There is greater heterogeneity (I^2 = 43%) owing to inclusion of less severe participants in FitzGerald 2016 (a larger proportion who had only suffered one exacerbation the previous year, with correspondingly less potential for exacerbation)
Health-related quality of life (AQLQ) Scale from: 1 to 7 (higher is better) Follow-up: range 48 weeks to 56 weeks	The mean change in the placebo group ranged from 0.98 to 1.31 units	MD 0.23 higher (0.11 higher to 0.35 higher)[c]	-	1541 (3 RCTs)	⊕⊕⊕⊕ High	A change of ≥ 0.5 is considered the minimum clinically significant difference

Health-related quality of life (ACQ) Scale from: 0 to 6 (lower is better) Follow up: range 48 weeks to 56 weeks	The mean change in the placebo group ranged from −1.19 to −0.76 units	MD -0.20 lower (-0.29 lower to -0.11 lower)[d]	-	2359 (3 RCTs)	⊕⊕⊕⊕ High	A change of ≥ 0.5 is considered the minimum clinically significant difference
Pre-bronchodilator FEV_1 (L) Follow-up: range 48 weeks to 56 weeks	The mean change in the placebo group ranged from -0.01 L to 0.239 L	MD 0.10 L higher (0.05 L higher to 0.14 L higher)	-	2355 (3 RCTs)	⊕⊕⊕⊕ High	
Serious adverse events Follow-up: range 48 weeks to 56 weeks	135 per 1000	109 per 1000 (89 to 136)	RR 0.81 (0.66 to 1.01)	2648 (4 RCTs)	⊕⊕⊕⊕ High	
Adverse events leading to discontinuation Follow-up: range 48 weeks to 56 weeks	9 per 1000	19 per 1000 (9 to 41)	RR 2.15 (1.02 to 4.57)	2597 (3 RCTs)	⊕⊕⊕⊕ High	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

ACQ: Asthma Control Questionnaire; **AQLQ**: Asthma Quality of Life Questionnaire; **CI:** confidence interval; **FEV_1** : forced expiratory volume in 1 second; **MD**: mean difference; **IV**: intravenous; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Rounded mean of the rate in the placebo group of the eosinophilic and non-eosinophilic arms (as applicable) or the three studies: 1.33, 1.21, 0.68, 0.49, 0.93, 1.21.
[b] Rounded mean of the rate in the placebo group of the two studies: 0.18 and 0.04.
[c] The mean difference (0.23) is less than the minimum clinically significant difference (≥ 0.5).

[d] The mean difference (-0.2) is less than the minimum clinically significant difference (≥ -0.5)
[e] One point deducted to reflect the level of heterogeneity on this outcome.

DISCUSSION

Summary of main results

Thirteen studies met the inclusion criteria for this systematic review (Bjermer 2016; Bleecker 2016; Castro 2014a; Castro 2015a; Castro 2015b; Chupp 2017; Corren 2016; FitzGerald 2016; Haldar 2009; NCT01947946 2013; Ortega 2014; Park 2016; Pavord 2012a). Five studies included adult participants only (Castro 2014a; Corren 2016; Haldar 2009; NCT01947946 2013; Park 2016) while the remaining eight (Bjermer 2016; Bleecker 2016; Castro 2015a; Castro 2015b; Chupp 2017; FitzGerald 2016; Pavord 2012a; Ortega 2014) included participants aged 12 years and over. Results in adolescents were not reported separately and thus we could not perform a subgroup analysis on this population.

The results suggest that treatments targeting IL-5 or the IL-5 receptor reduce 'clinically significant' asthma exacerbation rates by approximately half in participants with severe eosinophilic asthma already on standard of care therapy with a history of poor control ('clinically significant' exacerbations defined as episodes requiring at least three days' treatment with systemic corticosteroids; standard of care defined as at least medium-dose ICS; poor control defined as either two or more exacerbations in the preceding 12 months or an ACQ score of 1.5 or more). The effect size was largest with reslizumab and mepolizumab SC, although the study design and populations studied differed across trials and no head-to-head trials were performed. In addition, treatment with mepolizumab SC and benralizumab significantly reduced rates of exacerbations requiring emergency department attendance or hospital admission, with mepolizumab IV and reslizumab also showing a non-significant trend towards this. Non-eosinophilic participants experienced a significant, albeit smaller, reduction in asthma exacerbation rates when treated with benralizumab (with the test for subgroup difference non-significant); no data were available for mepolizumab or reslizumab treatment in participants with non-eosinophilic asthma. Whether this finding will be replicated with mepolizumab and reslizumab is uncertain.

Mepolizumab SC, reslizumab and benralizumab all produced modest improvements in validated HRQoL scores (e.g. ACQ, AQLQ) in severe eosinophilic asthma. However these did not exceed the MCID for ACQ and AQLQ. Improvements in the SGRQ did reach the MCID but came from only two studies (Chupp 2017; Ortega 2014). This may be due to differences between the different tools used. The SGRQ is a longer (50-item) questionnaire with three domains (symptoms, activity, and psychosocial impact); the ACQ is much shorter (five to seven items) and focuses on asthma symptoms and airflow limitation; however the AQLQ is more like the SGRQ, with 32 items in four domains (symptoms, activity, emotional function, environmental stimuli). It is therefore not entirely clear why there were differences between the SGRQ and the AQLQ in particular, although an analysis of the results by question domain might be illuminating in that regard.

We saw no improvement in HRQoL scores in those treated with mepolizumab IV or non-eosinophilic participants treated with benralizumab (data not available for mepolizumab or reslizumab), although in both cases there was a non-significant trend in this direction. The effect size was largest with mepolizumab, although again the study designs and populations enrolled differed with no head-to-head studies to assess this.

All anti-IL-5 interventions produced a small but statistically significant improvement in mean pre-bronchodilator FEV_1 of between 0.08 L and 0.11 L. There is no agreed definition of a MCID in FEV_1 in asthma, but the reproducibility of FEV_1 values in a single session in participants with a range of respiratory conditions is up to 0.12 L (Enright 2004) suggesting that the increase with anti-IL-5 is modest.

Treatment with mepolizumab (SC and IV) and reslizumab appeared to be safe, although there remain safety concerns over benralizumab. Pooling the results of the clinical trials of mepolizumab (SC and IV), but not benralizumab or reslizumab, showed a small but statistically significant reduction in severe adverse events in favour of the active treatment group. This may well be attributable to the impact of the study drug on asthma-related adverse events, particularly those leading to hospital admission that would be classed as serious adverse events (although the split of asthma- and non-asthma-related adverse events was not provided). When considering adverse events prompting participants to discontinue the study drug, there was a small but significant increase with benralizumab compared to placebo, which was not the case for mepolizumab (SC or IV) or reslizumab. This may be due to the different mechanism of action of benralizumab; further research is needed.

There were marked reductions in blood eosinophil levels with all anti-IL-5 treatments. Benralizumab resulted in almost complete depletion of eosinophils from the peripheral circulation, in both eosinophilic and non-eosinophilic participants, unlike mepolizumab and reslizumab where a small number of residual eosinophils remained. This is attributed to a difference in its mechanism of action (anti-IL-5 receptor rather than anti-IL-5). It is unclear whether this translates into greater clinical efficacy or greater risk of adverse events (e.g. parasitic or helminth infections) or both.

Overall our study supports the use of anti-IL-5 treatments as an adjunct to standard of care (at least medium-dose ICS) in people with severe eosinophilic asthma and a history of poor control (either two or more exacerbations in the preceding 12 months or an ACQ score of 1.5 or more).

Overall completeness and applicability of evidence

A reduction in asthma exacerbations is considered to be one of the key goals of asthma management (GINA 2017). Asthma exacerbations are of major clinical significance as they are the primary cause of morbidity and mortality in asthma, and drive increased healthcare utilisation and cost (Zeiger 2016). This is particularly the case for those with severe asthma, who continue to suffer from frequent exacerbations despite existing treatment options and therefore have a high unmet need (Custovic 2013).

We found evidence of a reduction in the rate of clinically significant exacerbations in adults with severe eosinophilic asthma with poor control given anti-IL-5 treatment, with low heterogeneity between studies. Secondary outcomes included safety data showing that anti-IL-5 treatments are well tolerated.

Whilst statistically significant improvements in symptoms (as assessed by validated HRQoL scores) and lung function (FEV_1) were evident with anti-IL-5 interventions, these changes were modest and likely to be below levels that would be clinically detected by patients. There were also large reductions in blood eosinophil levels, but a relationship between these and symptoms is not established and thus this may also be of limited direct relevance to patients.

The included studies did not directly compare the different anti-IL-5 treatments, however, the effect sizes versus placebo were similar. Pragmatically, mepolizumab is given subcutaneously every four weeks, reslizumab is given by intravenous infusion necessitating a healthcare setting, whereas benralizumab can be given subcutaneously every eight weeks. Thus there are practical advantages to benralizumab treatment.

Given the mechanism of action of anti-IL-5 agents, the studies were predominantly conducted in participants with severe eosinophilic asthma and poor control. None extended beyond a year. It is therefore not possible to draw any conclusions about those with milder or better-controlled (e.g. ACQ less than 1.5 with no exacerbations) disease, non-eosinophilic asthma, nor about the long-term effects of treatment. Eosinophilic and severe asthma were variably defined. Most studies considered blood eosinophil counts, although others used sputum eosinophil counts which are not readily available in most hospitals or clinics (Haldar 2009; Pavord 2012a). The thresholds used to determine eosinophilia in blood counts varied, with the mepolizumab studies considering 150 cells or more per μL at screening or 300 cells or more per μL in the previous year, benralizumab studies using a cut-off of 300 or more cells per μL and reslizumab 400 cells or more per μL. All the included studies defined severe asthma as a requirement to be on stable treatment with at least medium-dose ICS, but most specified high-dose ICS, often with additional controller medication(s). In addition all studies restricted participants to those with uncontrolled asthma. This was either defined in terms of exacerbation history (usually at least two in the previous 12 months; e.g. the studies of mepolizumab), ACQ score (1.5 or more; e.g. the studies of reslizumab), or both (e.g. the studies of benralizumab). Given this heterogeneity, it is unclear exactly how best to select patients for anti-IL-5 treatment, although current evidence suggests that a measure of eosinophilia, treatment with at least medium-dose ICS, and a history of poor control, defined as either two or more exacerbations in the last 12 months or an ACQ score of 1.5 or more, are necessary.

The evidence on mepolizumab IV is of limited applicability as it is currently only available subcutaneously.

In summary, anti-IL-5 agents represent a new treatment option for severe eosinophilic asthma with poor control, a patient population with a high, unmet need.

Quality of the evidence

Using the GRADE system, we considered the quality of the evidence for all comparisons to be high overall, with the exception of mepolizumab IV, which is not currently a licensed delivery route (so we would regard this as indirect evidence). We are aware of the limitations in some of the studies and have detailed them in the Results section, Figure 2 and Figure 3. We did not formally assess publication bias through the construction of a funnel plot due to the small number of included studies. However, our search strategy was thorough, including searching conference abstracts and ongoing studies, in order to identify unpublished studies.

Potential biases in the review process

This review and update was based on a published protocol (Powell 2013). We acknowledge the potential for publication bias in this review, as it is possible that we failed to identify unpublished trials that may have provided positive or negative outcomes, which in turn could have altered the treatment benefits. However, to the best of our knowledge, we identified a significant number of trials meeting our inclusion criteria through comprehensive and systematic database searches. We tried to address any study selection bias by having two review authors who independently evaluated all the identified studies. We also ensured that the assessment of each trial was consistently in line with the inclusion criteria.

Agreements and disagreements with other studies or reviews

This review is an update on a previous Cochrane Review of mepolizumab in asthma (Powell 2015), which noted one previous review with similar findings (Liu 2013). Since then, several reviews have been published on the topic:

1. Wang 2016, which considered all anti-IL-5 treatments, but also included studies with a treatment duration of less than 16 weeks and those with concomitant oral steroid reduction, and which did not include Chupp 2017;
2. Cabon 2017, which also assessed all anti-IL-5 treatments and included studies with a treatment duration of less than 16

weeks or concomitant oral steroid reduction. However fewer studies were included as the search was up to September 2015;

3. Yancey 2017, which only included studies of mepolizumab in asthma;

4. Li 2017, which only included studies of reslizumab in asthma;

Our findings are consistent with these reviews, despite the application of more rigorous inclusion criteria (in terms of treatment duration and allowed concomitant treatments, that is, standard of care rather than oral steroid reduction) and inclusion of an additional recent trial (Chupp 2017). All the reviews highlight the need for further research in this area.

AUTHORS' CONCLUSIONS

Implications for practice

The currently available studies provide evidence to support the use of anti-IL-5 treatments in adults with severe eosinophilic asthma, which is now being incorporated into national and international guidelines (e.g. GINA 2017). These treatments appear to roughly halve the rate of asthma exacerbations in this patient population, for whom exacerbations are particularly troublesome (Custovic 2013). Importantly there were no safety concerns regarding mepolizumab or reslizumab, and no excess serious adverse events with benralizumab, although a question over adverse events significant enough to prompt discontinuing this treatment. There is limited evidence for improvement in health-related quality-of-life scores and lung function, which may not meet clinically detectable levels.

Whilst the majority of studies included children over the age of 12, these did not provide sufficient evidence to reach a conclusion about efficacy and safety in this population.

Implications for research

Further research is needed to identify biomarkers for assessing treatment response, what the optimal duration of treatment is, the long-term effects of treatment and risk of relapse on withdrawal, the impact of eosinophil-depleting treatment on parasitic or helminth infections, and to clarify how best to define the people who will benefit from this treatment, considering the availability of tests (e.g. sputum cell differentials) and thresholds (for blood eosinophil counts). Research is also needed in people with non-eosinophilic asthma and younger age groups, both under 12 years old, in whom there have been no trials, and 12 years to 18 years old, for whom data has not been reported separately.

With regards to benralizumab in particular, future trials and observational studies should closely monitor the incidence of adverse events leading to discontinuation.

There will be some people who are eligible for more than one anti-IL-5 agent and potentially also treatment with anti-immunoglobulin E. At present there are no direct comparisons from head-to-head trials, leaving the clinician faced with such patients in an evidence-free quandary. A network meta-analysis could provide much needed guidance, but ultimately high-quality head-to-head trials are required.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bjermer 2016

Methods	Parallel, double-blind RCT with a 16-week treatment phase
Participants	315 participants (42 male) with moderate-severe asthma, with airway reversibility, blood eosinophilia, ACQ score of at least 1.5, and taking ICS 1. Main inclusion/exclusion criteria: i) blood eosinophils $\geq$ 400 cells/μL during 2-4 week screening period ii) ACQ-7 score $\geq$ 1.5 iii) maintenance treatment with medium-dose ICS (maintenance OCS not allowed) 2. Age in years, mean: reslizumab 0.3 mg/kg, 44.5; reslizumab 3 mg/kg, 43.0; placebo, 44.2 3. Males (%): reslizumab 0.3 mg/kg, 43; reslizumab 3 mg/kg, 42; placebo, 41 4. Baseline mean FEV_1 % predicted: reslizumab 0.3 mg/kg, 69; reslizumab 3 mg/kg, 70; placebo, 71 5. Allocation, N: reslizumab 0.3 mg/kg, 104; reslizumab 3 mg/kg, 106; placebo, 105
Interventions	IV infusion of reslizumab 0.3 mg/kg, reslizumab 3.0 mg/kg, or placebo once every 4 weeks (total of 4 doses)
Outcomes	Primary outcome 1. pre-bronchodilator spirometry (FEV_1). Secondary outcomes 1. FVC, forced expiratory flow at 25%-75% of FVC (FEF 25%-75%) 2. Asthma symptoms (ACQ, ACQ-6, ACQ-5), Asthma Symptom Utility Index (ASUI20), Asthma Quality of Life Questionnaire (AQLQ21), 3. Rescue inhaler use 4. Blood eosinophil levels
Notes	68 locations across 13 countries Funded by Teva Branded Pharmaceutical Products R&D, Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated, no clarification available from study authors
Allocation concealment (selection bias)	Unclear risk	Not stated, no clarification available from study authors
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind

Bjermer 2016 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated, no clarification available from study authors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Slightly more withdrawals in placebo group (20/105, 19%) than treatment arms (12-17%)
Selective reporting (reporting bias)	Low risk	All outcomes reported

Bleecker 2016

Methods	Randomised, double-blind, parallel-group, placebo-controlled trial run over 48 weeks
Participants	1204 participants with symptomatic asthma were randomised to 1 of 3 groups (benralizumab 30 mg 4 weeks, benralizumab 30 mg 8 weeks, or placebo) 1. Main inclusion/exclusion criteria: i) $\geq$ 2 exacerbations in the previous 12 months ii) ACQ-6 score $\geq$ 1.5 at enrolment iii) FEV_1 < 80% (if 12-17 years old, < 90%) iv) maintenance treatment with high-dose ($\geq$ 500 μg/d FP or equivalent) ICS/LABA for $\geq$ 12 months for adults > 18 years, or at least medium-dose ($\geq$ 250 μg/d FP or equivalent) ICS/LABA for children (12-17 years) 2. Age mean (SD) years: benralizumab 30 mg every 4 weeks, 50 (13.4); benralizumab 30 mg every eight weeks, 48 (14.5); placebo, 49 (14.9) 3. Males (%): benralizumab 30 mg every four weeks, 124 (31%); benralizumab 30 mg every eight weeks, 146 (37%); placebo, 138 (34%) 4. Baseline mean (SD) FEV_1 % predicted: benralizumab 30 mg every four weeks, 57 (14.1); benralizumab 30 mg every eight weeks, 56 (14.6); placebo, 57 (15.0) 5. Allocation: benralizumab 30 mg every 4 weeks, 399; benralizumab 30 mg every eight weeks, 398; placebo, 407
Interventions	SC benralizumab 30 mg/mL every 4 weeks or every 8 weeks versus placebo
Outcomes	Primary outcomes 1. Annual asthma exacerbation rate. Secondary outcomes 1. Pre-bronchodilator FEV_1 2. Total asthma symptom score, 3. Time to first asthma exacerbation 4. Asthma exacerbations associated with visit to ED, urgent care centre or admission to hospital 5. Post-bronchodilator FEV_1 6. ACQ-6, AQLQ(S)+12 7. Blood eosinophils

Bleecker 2016 (*Continued*)

Notes	Multi-centre trial in 374 centres from 17 countries Funded by AstraZeneca and Kyowa Hakko Kirin

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Each participant was assigned a unique enrolment number and randomisation code by an interactive web-based voice response system
Allocation concealment (selection bias)	Low risk	The identity of the treatment allocation was not made available to the participants, investigators involved in participant treatment or clinical assessment, or study funder
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind (participant, caregiver and investigator)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated, no clarification available from study authors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal rates were relatively low (10.1%-12.8%)
Selective reporting (reporting bias)	Low risk	Unless otherwise specified, all results were presented for participants with baseline blood eosinophilia

Castro 2014a

Methods	Randomised, controlled, double-blind, dose-ranging trial
Participants	606 participants with uncontrolled asthma randomised and 535 completed 1. Main inclusion/exclusion criteria: i) 2-6 exacerbations in the previous 12 months ii) ACQ-6 score $\geq$ 1.5 at least twice during screening iii) morning pre-bronchodilator FEV_1 40%-90% iv) maintenance treatment with medium- to high-dose ICS in combination with LABA for $\geq$ 12 months 2. Age mean (SD) years: eosinophilic benralizumab 2 mg, 47 (12.8); eosinophilic benralizumab 20 mg, 47 (13.2); eosinophilic benralizumab 100 mg, 48 (12.9); eosinophilic placebo, 46 (11.7); non-eosinophilic benralizumab 100 mg, 50 (11.5); non-eosinophilic placebo, 50 (12.3).

	3. Males (%): eosinophilic benralizumab 2 mg, 23 (28%); eosinophilic benralizumab 20 mg, 33 (41%); eosinophilic benralizumab 100 mg, 22 (27%); eosinophilic placebo, 27 (33%); non-eosinophilic benralizumab 100 mg, 42 (30%); non-eosinophilic placebo, 42 (30%) 4. Baseline mean (SD) FEV_1 % predicted: eosinophilic benralizumab 2 mg, 65 (15%); eosinophilic benralizumab 20 mg, 64 (15%); eosinophilic benralizumab 100 mg, 66 (16%); eosinophilic placebo, 65 (15%); non-eosinophilic benralizumab 100 mg, 69 (15%); non-eosinophilic placebo, 67 (15%) 5. Allocation: eosinophilic benralizumab 2 mg, 81; eosinophilic benralizumab 20 mg, 81; eosinophilic benralizumab 100 mg, 80; eosinophilic placebo, 80; non-eosinophilic benralizumab 100 mg, 140; non-eosinophilic placebo, 142
Interventions	6 arms: benralizumab 2 mg or benralizumab 20 mg or benralizumab 100 mg or placebo delivered by 2 SC injections every 4 weeks for the first 3 doses (weeks 1, 4, and 8), then every 8 weeks (weeks 16, 24, 32, and 40)
Outcomes	Primary outcomes 1. Annual exacerbation rate in eosinophilic participants. Secondary outcomes in eosinophilic individuals 1. Change from baseline, in FEV_1, 2. ACQ-6 3. Overall symptom score 4. AQLQ
Notes	52-year multi-national study with sites in 10 countries. The study protocol was developed by MedImmune and the corresponding author. The investigators collected and had full access to all study data, which were analysed by the funding source. The analysis was done solely by MedImmune; however, study authors helped determine which analyses were done and could request further ad-hoc analyses. The report was written by the study authors with a medical writer funded by the funding source. The corresponding author had final responsibility for decision to submit for publication Funding: MedImmune

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Interactive web/voice-response system for random assignment
Allocation concealment (selection bias)	Low risk	Allocation concealment was ensured by the vendor systems and no study personnel or site had access to the system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, treating physicians, study investigators, and study statisticians were masked to treatment allocation

Castro 2014a (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	The withdrawal rates were even across groups
Selective reporting (reporting bias)	Low risk	Results for most but not all listed primary and secondary outcomes were reported (e.g. symptoms score, AQLQ - shown in supplementary material in graphs only)

Castro 2015a

Methods	Double-blind, placebo-controlled, parallel-group study
Participants	489 participants with moderate-severe asthma (medium dose of ICS, inadequate control ACQ $\geq$ 1.5, and at least 1 exacerbation in the past 12 months) 1. Main inclusion/exclusion criteria: i) blood eosinophils $\geq$ 400 cells/μL during 2-4 week screening period ii) ACQ-7 score $\geq$ 1.5 iii) maintenance treatment with medium-dose ICS (i.e. $\geq$ 440 μg/d FP or equivalent daily); ± additional controller or maintenance OCS 2. Age: reslizumab, mean (IQR) 48 (38-57) years; placebo, mean (IQR) 49 (38-57) years 3. Males (%): reslizumab, 103 (42); placebo, 83 (34) 4. Baseline mean (SD) FEV_1 % predicted: reslizumab, 64% placebo, 65% 5. 245 allocated to reslizumab, 244 to placebo
Interventions	IV infusion of reslizumab 3 mg/kg or matching placebo every 4 weeks (13 doses with last dose in week 48)
Outcomes	Primary outcomes (per protocol) 1. HRQoL (as measured by a validated questionnaire) 2. Asthma exacerbation as defined by a hospital admission or treatment OCS 3. Serious adverse events Secondary outcomes (per protocol): 1. Measures of lung function: FEV_1, PEFR 2. Asthma symptoms 3. Adverse events/side effects 4. Eosinophil counts in peripheral blood, sputum or bronchioalveolar lavage fluid
Notes	128 clinical research centres. The research was funded by Teva Branded Pharmaceutical Products R&D. Teva employees were involved in the study design, data collection and analysis, and in the writing of this manuscript. All study authors had full access to all study data and had final responsibility for the decision to submit for publication
Risk of bias	

Castro 2015a (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done with use of interactive response technology with computerised central randomisation
Allocation concealment (selection bias)	Low risk	The funder's clinical personnel involved in the study were also masked to the study drug identity until the database was locked for analysis and the treatment assignment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators remained masked to treatment assignment during the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and investigators remained masked to treatment assignment during the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	The withdrawal rates were relatively low and even across the groups (11%-14%)
Selective reporting (reporting bias)	Low risk	All primary and secondary outcome measures were reported.

Castro 2015b

Methods	Double-blind, placebo-controlled, parallel-group study
Participants	464 participants with moderate-severe asthma (medium does of ICS, inadequate control ACQ $\geq$1.5 and at least 1 exacerbation in the past 12 months) 1. Main inclusion/exclusion criteria: i) blood eosinophils $\geq$ 400 cells/μL during 2-4 week screening period ii) ACQ-7 score $\geq$ 1.5 iii) maintenance treatment with medium-dose ICS (i.e. $\geq$ 440 μg/day FP or equivalent daily); ± additional controller or maintenance OCS 2. Age: reslizumab, mean (IQR) 48 (37-57) years; placebo, mean (IQR) 48 (40-57) years 3. Males (%): reslizumab, 88 (38); placebo, 82 (35) 4. Baseline mean (SD) FEV_1 % predicted: reslizumab, 68% placebo, 70% 5. Allocation: to reslizumab 232; to placebo, 232
Interventions	IV infusion of reslizumab 3 mg/kg or matching placebo every 4 weeks (13 doses with last dose in week 48)
Outcomes	Primary outcomes (per protocol): 1. HRQoL (as measured by a validated questionnaire 2. Asthma exacerbation as defined by a hospital admission or treatment OCS

Castro 2015b (*Continued*)

	3. Serious adverse events Secondary outcomes (per protocol): 1. Measures of lung function: FEV_1, PEFR; asthma symptoms 2. Adverse events/side effects 3. Eosinophil counts in peripheral blood, sputum or bronchioalveolar lavage fluid
Notes	Funding: Teva Branded Pharmaceutical Products R&D. Teva employees were involved in the study design, data collection and analysis, and in the writing of this manuscript. All study authors had full access to all the data in the study and had final responsibility for the decision to submit for publication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was done with use of interactive response technology with computerised central randomisation
Allocation concealment (selection bias)	Low risk	The funder's clinical personnel involved in the study were also masked to the study drug identity until the database was locked for analysis and the treatment assignment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators remained masked to treatment assignment during the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and investigators remained masked to treatment assignment during the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	The withdrawal rates were relatively low and even across the groups (11%-14%)
Selective reporting (reporting bias)	Low risk	All primary and secondary outcome measures were reported

Chupp 2017

Methods	Multicentre, placebo-controlled, double-blind, parallel-group study
Participants	551 participants with severe eosinophilic asthma Males (%): mepolizumab 125 (46); placebo, 101 (36) • Main inclusion/exclusion criteria: ◦ blood eosinophils $\geq$ 150 cells/μL at screening or $\geq$ 300 cells/μL in previous 12 months ◦ $\geq$ 2 exacerbations in previous 12 months

Chupp 2017 (*Continued*)

	○ FEV_1 < 80% ○ maintenance treatment with high-dose ICS for ≥ 12 months; + additional controller for ≥ 3 months; ± maintenance OCS
Interventions	Mepolizumab 100 mg SC every 4 weeks for a period of 24 weeks (total of 6 doses) along with their respective standard care of treatment, versus placebo (0.9% sodium chloride) SC every 4 weeks for a period of 24 weeks (total of 6 doses) along with their respective standard care of treatment
Outcomes	Primary outcomes 1. Mean change from baseline in SGRQ score at week 24 Secondary outcomes 1. Mean change from baseline in clinic pre-bronchodilator FEV_1 at week 24 2. Percentage of participants achieving a 4-point or greater reduction from baseline in SGRQ score at week 24 3. Mean change from baseline in 5-item ACQ-5 score at week 24
Notes	Funding: GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using an interactive voice-response system and a centralised, computer-generated, permuted-block design of block size six
Allocation concealment (selection bias)	Low risk	Participants, investigators, other site staff, and the entire study team including those assessing outcomes data were masked to treatment assignment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators remained masked to treatment assignment during the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and investigators remained masked to treatment assignment during the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the treatment arm 5 participants were withdrawn from the study: 2 withdrew consent, 2 experienced an adverse event and 1 was lost to follow-up. In the placebo arm 14 participants were withdrawn from study: 6 withdrew consent, 2 experienced an adverse event, 2 withdrew due to poor efficacy, 2 were lost to follow-up and 2 were

Chupp 2017 (*Continued*)

		withdrawn on a physician's decision
Selective reporting (reporting bias)	Low risk	No indication of reporting bias

Corren 2016

Methods	Parallel, double-blind
Participants	496 participants with moderate-severe asthma (based on at least medium-dose ICS, inadequate control ACQ ≥ 1.5) 1. Main inclusion/exclusion criteria: i) ACQ-7 score ≥ 1.5 ii) maintenance treatment with medium-dose ICS; maintenance OCS not allowed 2. Age: reslizumab, mean 44.9; placebo, mean 45.1 3. Males: reslizumab, 137; placebo, 44 4. Baseline mean (SD) FEV_1, % predicted: reslizumab, 66.8% placebo, 66.5% 5. Allocation: to reslizumab, 398; to placebo, 98
Interventions	IV reslizumab 3.0 mg/kg or placebo once every 4 weeks (total of 4 doses)
Outcomes	Primary outcomes 1. HRQoL (as measured by a validated questionnaire) 2. Asthma exacerbation as defined by a hospital admission or treatment with oral corticosteroids 3. Serious adverse events. Secondary outcomes 1. FEV_1 2. PEFR 3. Asthma symptoms 4. Adverse events/side effects 5. Eosinophil counts in peripheral blood, sputum or bronchioalveolar lavage fluid
Notes	66 study locations across the USA Funding: Teva Branded Pharmaceutical Products R&D, Inc

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated, no clarification available from study authors
Allocation concealment (selection bias)	Unclear risk	Not stated, no clarification available from study authors
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind

Corren 2016 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts comparable in each group (16/98, 16%, placebo vs 58/398, 15%, reslizumab)
Selective reporting (reporting bias)	Low risk	All primary and secondary outcomes reported with numbers, except blood eosinophil counts only shown as a chart

FitzGerald 2016

Methods	Multicentre, randomised, double-blind, parallel-group, placebo-controlled trial
Participants	1306 participants with moderate-severe (medium-high-dose ICS + LABA, ≥ 2 asthma exacerbations last 12 months, FEV_1 < 80% predicted), ACQ-6 ≥ 1.5 at enrolment 1. Main inclusion/exclusion criteria: i) ≥ 2 exacerbations in the previous 12 months ii) ACQ-6 score ≥ 1.5 at enrolment iii) FEV_1 < 80% iv) maintenance treatment with medium- (≥ 250 μg/day FP or equivalent) to high-dose (≥ 500 μg/day FP or equivalent) ICS/LABA for ≥ 12 months; high-dose ICS/LABA for ≥ 3 months 2. Age mean (SD) years: eosinophil ≥ 300 cells per μL benralizumab 30 mg every 4 weeks, 50 (13.1); eosinophil ≥ 300 cells per μL benralizumab 30 mg Q8W. 50 (13.0); eosinophil ≥ 300 cells per μL placebo, 49 (14.1); eosinophil < 300 cells per μL benralizumab 30 mg every four weeks, 52 (12.2); eosinophil < 300 cells per μL benralizumab 30 mg Q8W, 51 (13.8); eosinophil < 300 cells per μL placebo, 52 (14.4) 3. Males (%): eosinophil ≥ 300 cells per μL benralizumab 30 mg every four weeks, 82 (34); eosinophil ≥ 300 cells per μL benralizumab 30 mg Q8W, 101 (42); eosinophil ≥ 300 cells per μL placebo, 103 (42); eosinophil < 300 cells per μL benralizumab 30 mg every four weeks, 45 (39); eosinophil < 300 cells per μL benralizumab 30 mg Q8W, 38 (30); eosinophil < 300 cells per μL placebo, 46 (38). 4. Baseline mean (SD) FEV_1 % predicted: eosinophil ≥ 300 cells per μL benralizumab 30 mg every four weeks, 59 (13.7); eosinophil ≥ 300 cells per μL benralizumab 30 mg Q8W, 57 (14.2); eosinophil ≥ 300 cells per μL placebo, 58 (13. 9); eosinophil < 300 cells per μL benralizumab 30 mg every four weeks, 57 (16.2); eosinophil < 300 cells per μL benralizumab 30 mg Q8W, 57 (15.2); eosinophil < 300 cells per μL placebo, 56 (16.3) 5. Allocation: eosinophil ≥ 300 cells per μL benralizumab 30 mg every four weeks, 241; eosinophil ≥ 300 cells per μL benralizumab 30 mg Q8W, 239; eosinophil ≥ 300 cells per μL placebo, 248; eosinophil < 300 cells per μL benralizumab 30 mg every four weeks, 116; eosinophil < 300 cells per μL benralizumab 30 mg Q8W, 125; eosinophil < 300 cells per μL placebo, 122
Interventions	56 weeks (final follow-up at 60 weeks). SC benralizumab 30 mg every 4 weeks for 56 weeks or every 4 weeks for 3 doses then 8 weeks thereafter for 56 weeks

Outcomes	Primary outcomes 1. Annual asthma exacerbations Secondary outcomes 1. Pre-bronchodilator FEV_1 2. Total asthma symptom score 3. Time to first asthma exacerbation 4. Annual rate of asthma exacerbations associated with an ED visit, urgent care visit, or admission to hospital 5. Post-bronchodilator FEV_1 6. ACQ-6 score 7. AQLQ(S)+12 score 8. EQ-5D-5L visual analogue scale (to rate current health status) 9. Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire 10. Use of healthcare resources 11. Participant and clinician assessment of response to treatment 12. PK parameter and anti-drug antibodies 13. Safety and tolerability of intervention
Notes	Funding: AstraZeneca and Kyowa Hakko Kirin. 303 clinical research centres in 11 countries

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were assigned to treatment groups using an interactive web-based voice-response system. Randomisation was stratified by ICS dosage at enrolment (high or medium), geographic region, age group (adult or adolescent), and peripheral blood eosinophil count at enrolment (< 300 cells per μL or $\geq$ 300 cells per μL)
Allocation concealment (selection bias)	Low risk	The study investigator assigned randomisation codes sequentially in each stratum as participants became eligible for randomisation, until each stratum was full
Blinding of participants and personnel (performance bias) All outcomes	Low risk	To preserve blinding, participants and study centre staff were masked to treatment allocation, placebo solution was visually matched with benralizumab solution, and both placebo and benralizumab were provided in accessorised (needle guards and finger phalanges), prefilled syringes

FitzGerald 2016 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	The withdrawal rates were relatively low: placebo 11.1% (49/440); benralizumab 30 mg every four weeks 9.6% (41/425); benralizumab 30 mg every eight weeks 13.4% (59/441)
Selective reporting (reporting bias)	Low risk	Results for all listed primary and secondary outcomes were reported

Haldar 2009

Methods	Randomised, double-blind, placebo-controlled, parallel-group trial
Participants	61 participants had refractory eosinophilic asthma and a history of recurrent severe exacerbations 1. Main inclusion/exclusion criteria: i) ≥ 3% sputum eosinophils on at least 1 occasion in previous 2 years despite high-dose corticosteroid treatment ii) ≥ 2 exacerbations in previous 12 months iii) maintenance treatment with high-dose ICS 2. Age: mepolizumab, mean 48 (range from 21-63); placebo, mean 50 (range from 24-72) 3. Males: mepolizumab, 14; placebo, 18 4. Baseline mean (SD) FEV_1, % predicted after bronchodilator use: mepolizumab, 78.1% (± 20.9%); placebo, 77.6% (± 24.1%) 5. Baseline mean (SD) FEV_1/FVC ratio: mepolizumab, 72.2% (± 9.6%), placebo, 67.7% (± 13.5%) 6. 29 allocated to receive mepolizumab 750 mg, 32 to receive placebo
Interventions	Intravenous mepolizumab (750 mg) versus matched placebo (150 mL of 0.9% saline) at monthly intervals for 1 year
Outcomes	Reported as: "[P]rimary outcome measure was the number of severe exacerbations per participant during the 50-week treatment phase. Secondary outcomes included a change in asthma symptoms, scores on the Asthma Quality of Life Questionnaire (AQLQ, in which scores range from 1 to 7, with lower values indicating more severe impairment and a change of 0.5 unit considered to be clinically important), forced expiratory volume in 1 second (FEV_1) after use of a bronchodilator, airway hyperresponsiveness, and eosinophil counts in the blood and sputum."
Notes	Single centre trial conducted at Institute for Lung Health, Leicester, UK Supported by GlaxoSmithKline

Risk of bias

Haldar 2009 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reported as: "Stratified randomisation with use of the minimisation method, which was performed by an independent clinician. Participants were randomly assigned with the use of the minimisation method to receive 12 infusions of either 750 mg of mepolizumab delivered intravenously or matched placebo (150 mL of 0.9% saline) at monthly intervals between visits 3 and 14. The criteria used for minimisation were the frequency of exacerbations in the previous 12 months, the baseline eosinophil count in the sputum and the number of participants taking oral corticosteroids."
Allocation concealment (selection bias)	Unclear risk	Details not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as double blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Reported as double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reported as: "A total of 61 of the 63 participants (one required and operation and one withdrew consent) who were screened started treatment and constituted the modified intention-to-treat population. Thirty-two participants were randomly assigned to receive placebo. Overall, 94.9% of treatment visits were completed. Participants who withdrew completed a mean of 4.6 treatment visits (38.3%)."
Selective reporting (reporting bias)	Low risk	No apparent indication of reporting bias

NCT01947946 2013

Methods	Multicentre, randomised, double-blind, parallel-group, placebo-controlled, phase 3 efficacy and safety study

Participants	13 participants with uncontrolled asthma taking medium-dose ICS plus long-acting beta$_2$ agonist (LABA) 1. Main inclusion criteria: i) aged from 18-75 years, inclusively ii) history of physician-diagnosed asthma requiring treatment with medium-dose ICS (> 250 μg fluticasone dry powder formulation equivalents total daily dose) and a LABA, for at least 12 months prior to first visit iii) Documented treatment with medium-dose ICS (> 250 μg and $\leq$ 500 μg fluticasone dry powder formulation equivalents total daily dose) and LABA for at least 3 month prior to first visit 2. Age mean (SD) years: benralizumab 30 mg every 4 weeks 58.7 (15.70); benralizumab 30 mg every 8 weeks 57.8 (6.38); placebo: 49.6 (6.35) 3. Males n (15): benralizumab 30 mg every 4 weeks 2 (67) benralizumab 30 mg every 8 weeks: 4 (80); placebo: 5 (100) 4. Baseline lung function not reported 5. Allocation: benralizumab 30 mg every 4 weeks 3; benralizumab 30 mg every 8 weeks: 5; placebo: 5
Interventions	Fixed 30 mg dose of benralizumab every 4 weeks or fixed 30 mg dose of benralizumab, every 4 weeks for the first 3 doses and then every 8 weeks thereafter versus placebo
Outcomes	Primary outcomes 1. Asthma exacerbations over planned 48-week study period Secondary outcomes 1. Not stated
Notes	Study terminated due to sponsor decision after recruitment of 13 participants. No participant completed the study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised but no further details
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as double blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Reported as double blind, but blinding of outcome assessment not specifically described
Incomplete outcome data (attrition bias) All outcomes	High risk	Study terminated due to decision of sponsor after recruitment of 13 participants. No

NCT01947946 2013 (*Continued*)

		reason given for decision to terminate
Selective reporting (reporting bias)	High risk	Study terminated due to decision of sponsor after recruitment of 13 participants. No reason given for decision to terminate. Original secondary outcomes listed removed from trial registration. Outcomes could not be incorporated into meta-analysis

Ortega 2014

Methods	Randomised, double-blind, double-dummy, phase 3 study
Participants	576 participants with recurrent asthma exacerbations and evidence of eosinophilic inflammation despite high doses of inhaled glucocorticoids to 1 of 3 study groups 1. Main inclusion/exclusion criteria: i) blood eosinophils $\geq$ 150 cells/μL at screening or $\geq$ 300 cells/μL in previous 12 months ii) $\geq$ 2 exacerbations in previous 12 months iii) FEV_1 < 80% iv) maintenance treatment with high-dose ICS for $\geq$ 12 months; plus additional controller for $\geq$ 3 months; ± maintenance OCS 2. Age mean (range) years: mepolizumab 75 mg 50 (13-82); mepolizumab 100 mg 51 (12-81); placebo, 49 (12-76) 3. Males (43%): mepolizumab 75 mg, 106 (55); mepolizumab 100 mg, 116 (60); placebo, 107 (56) 4. Baseline mean (SD) FEV_1 % predicted: mepolizumab 75 mg, 61.4 ± 18.3; mepolizumab 100 mg, 59.3 ± 17.5; placebo, 62.4 ± 18.1 5. Allocation: mepolizumab 75 mg, 191; mepolizumab 100 mg, 194; placebo, 191
Interventions	Mepolizumab in a 75 mg intravenous dose versus mepolizumab in a 100 mg subcutaneous dose versus placebo every 4 weeks for 32 weeks
Outcomes	Primary outcomes 1. Number of clinically significant exacerbations of asthma per year Secondary outcomes: 1. Number of clinically significant exacerbations requiring hospitalisation (including intubation and admittance to an intensive care unit) or ED visits per year 2. Mean change from baseline in clinic pre-bronchodilator FEV_1 at week 32 3. Mean change from baseline in the SGRQ total score at week 32
Notes	32-week treatment intervention, with 1-6 weeks run-in and 8-week follow-up. Conducted in Baltimore, Middlesex, Ghent, Vancouver, Parma, Marseille and Paris Funding: GlaxoSmithKline

Risk of bias

Ortega 2014 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised computer-generated permuted block schedule
Allocation concealment (selection bias)	Low risk	Treatment allocations will be concealed via the RandAll system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Mepolizumab and placebo were identical in appearance and were administered by a staff member who was unaware of the study group assignments
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study drugs were prepared by staff members who were aware of the study group assignments but were not involved in study assessments
Incomplete outcome data (attrition bias) All outcomes	Low risk	6% (placebo), 8% (IV), 5% (SC) did not complete the study
Selective reporting (reporting bias)	Low risk	All outcome measures reported

Park 2016

Methods	Parallel
Participants	103. 38 males. (age 53.2, 55.6, 51.4, 50.8 Moderate/severe (based on ICS dose (medium/high), exacerbation history, and ACQ $\geq$ 1.5 on at least 2 occasions) participants also had to demonstrate post-bronchodilator FEV_1 reversibility $\geq$ 12% and $\geq$ 200 mL, or a positive response to methacholine challenge ($PC_{20} \leq$ 8 mg/mL) 1. Main inclusion/exclusion criteria: i) 2-6 exacerbations in the previous 12 months ii) ACQ-6 score $\geq$ 1.5 at least twice during screening iii) morning pre-bronchodilator FEV_1 40%-90% iv) maintenance treatment with medium- to high-dose ICS in combination with LABA for $\geq$ 12 months 2. Age mean (SD) years: benralizumab 2 mg, 53 (11.3); benralizumab 20 mg, 56 (8.9); benralizumab 100 mg, 51 (13.8); placebo, 51 (11.8) 3. Males n (%): benralizumab 2 mg, 13 (50); benralizumab 20 mg, 6 (24); benralizumab 100 mg, 10 (39); placebo, 9 (35) 4. Baseline mean (SD) FEV_1 % predicted: benralizumab 2 mg, 65 (14.1); benralizumab 20 mg, 71 (13.2); benralizumab 100 mg, 68 (15.8); placebo, 69 (16.3) 5. Allocation: benralizumab 2 mg, 26; benralizumab 20 mg, 25; benralizumab 100 mg, 26; placebo, 26
Interventions	Subcutaneous doses given at weeks 1, 4, 8, 16, 24, 32, 40. Benralizumab 2 mg, 20 mg or 100 mg subcutaneously

Park 2016 (*Continued*)

Outcomes	Primary outcomes 1. Annual exacerbation rate Secondary outcomes 1. Lung function 2. ACQ-6 3. FeNO Exploratory endpoints included blood eosinophil counts.
Notes	32 sites in South Korea and Japan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eosinophilic participants were randomised using a central, interactive web-response system
Allocation concealment (selection bias)	Unclear risk	Not stated, no clarification available from study authors
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study medication was administered … in a blinded fashion
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated, no clarification available from study authors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates relatively high but even across groups (19.2% for placebo vs 16.0%-23.1% for treatment groups)
Selective reporting (reporting bias)	Low risk	All outcomes reported

Pavord 2012a

Methods	Multicentre, double-blind, placebo-controlled trial
Participants	621 participants with severe asthma despite receiving high doses of standard asthma medications 1. Main inclusion/exclusion criteria: i) $\geq$ 3% sputum eosinophils or blood eosinophil $\geq$ 300 cells/μL ii) $\geq$ 2 exacerbations in previous 12 months iii) maintenance treatment with high-dose ICS (i.e. $\geq$ 880 μg/d FP or equivalent daily); + additional controller; ± maintenance OCS 2. Age mean (SD) years: mepolizumab 750 mg, 48.6 (11.1); mepolizumab 250 mg, 49 (11.6); mepolizumab 75 mg, 50.2 (10.8); placebo, 46.4 (11.3) 3. Males n (%): mepolizumab 750 mg, 93 (60%); mepolizumab 250 mg, 93 (61%); mepolizumab 75 mg, 104 (68%); placebo, 97 (63%)

Pavord 2012a (*Continued*)

	4. Baseline mean (SD) FEV_1 % predicted: mepolizumab 750 mg, 61% (16); mepolizumab 250 mg, 59% (17); mepolizumab 75 mg, 60% (16); placebo, 59% (15) 5. Allocation: mepolizumab 750 mg, 156; mepolizumab 250 mg, 152; mepolizumab 75 mg, 154; placebo, 159
Interventions	13 total intravenous infusions of mepolizumab (750 mg), mepolizumab (250 mg), mepolizumab (75 mg) or placebo given every 4 weeks
Outcomes	Primary outcomes 1. Frequency of clinically significant exacerbations of asthma Secondary outcomes 1. Time to first clinically significant exacerbation requiring oral or systemic corticosteroids, hospitalisation, and/or ED visits 2. Frequency of exacerbations requiring hospitalisation (including intubation and admittance to an ICU) or ED visits 3. Time to first exacerbation requiring hospitalisation or ED visit 4. Frequency of investigator-defined exacerbations 5. Time to first investigator-defined exacerbation 6. Mean change from baseline in clinic pre-bronchodilator FEV_1 over the 52-week treatment period 7. Mean change from baseline in clinic post-bronchodilator FEV_1 over the 52-week treatment period 8. Mean change from baseline in ACQ score
Notes	52-week study conducted at 81 centres in 13 countries (Argentina, Australia, Canada, Chile, France, Germany, South Korea, Poland, Romania, Russia, Ukraine, the UK and the USA) Supported by GlaxoSmithKline

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central telephone-based system and computer-generated randomly permuted block schedule stratified by whether treatment with OCS was required
Allocation concealment (selection bias)	Low risk	Mepolizumab and placebo were prepared by unmasked site staff who were not involved in study assessments
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Mepolizumab and placebo were prepared by unmasked site staff who were not involved in study assessments. Both treatments were identical in appearance and were given to participants by a masked member of the site staff

Pavord 2012a (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data analysts were masked to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for with information on reasons for having withdrawn. Some participants not included in results due to 'poor efficacy'
Selective reporting (reporting bias)	Low risk	No apparent indication of reporting bias

ACQ: Asthma Control Questionnaire; **ALT**: alanine aminotransferase; **Alk Phos**: alkaline phosphatase; **AQLQ**: Asthma Quality of Life Questionnaire; **AST**: aspartate aminotransferase; **ECP**: eosinophil cationic protein; **ED**: emergency department; **FeNO**: exhaled fraction of nitric oxide; **FEV_1** : Forced expiratory volume in 1 second; **FP**: fluticasone propionate; **FVC**: forced vital capacity; **HRQoL**: health-related quality of life; **ICS**: inhaled corticosteroid; **ICU**: intensive care unit; **IL**: interleukin; **IQR**: interquartile range; **IV**: intravenous; **JACQ**: Juniper Asthma Control Questionnaire; **OCS**: oral corticosteroids; **PC_{20}** : histamine provocative concentration causing a 20% drop in FEV_1;**PEFR**: peak expiratory flow rate; **SC**: subcutaneous; **SD**: standard deviation; **SGRQ**: St. George's Respiratory Questionnaire; **ULN**: Upper Limit of Normal; **VC**: vital capacity.

[a] **QTc(F)**: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle, corrected for the heart rate using Fredericia's formula.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Albers 2016	Post-hoc analysis of observational study
Alvarez-Cuesta 1994	Intervention used in study (cat extract immunotherapy) is not anti-IL-5 therapy
Armentia 1992	Intervention used in study (immunotherapy) is not anti-IL-5 therapy
Austin 2016	Aggregation of two clinical trials
Ayres 2004	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Bel 2014	Focus of trial is on steroid reduction and therefore does not meet our predefined inclusion criteria
Berger 2003	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Blanken 2012	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Blanken 2013	Intervention used in study (pavilizumab) is not anti-IL-5 therapy

(*Continued*)

Boulet 1997	Intervention used in study (anti-IgE antibody e25) is not anti-IL-5 therapy
Bousquet 2004	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Bousquet 2011	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Brightling 2014	Intervention used in study (tralokinumab) is not anti-IL-5 therapy
Brown 2007	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Brusselle 2016	Aggregation of two clinical trials
Bryant 1975a	Not a RCT
Bryant 1975b	Not a RCT
Buhl 2000a	Intervention used in study (rhumab-25) is not anti-IL-5 therapy
Buhl 2000b	Intervention used in study (rhumab-25) is not anti-IL-5 therapy
Buhl 2002	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Bush 1985	Intervention used in study (soybean oil) is not anti-IL-5 therapy
Busse 2001	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Busse 2008	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Busse 2015	Intervention used in study (tralokinumab) is not anti-IL-5 therapy
Buttner 2003	Treatment < 16 weeks
Caffarelli 2000	Intervention used in study (immunotherapy) is not anti-IL-5 therapy
Canvin 2016	Aggregation of two clinical trials
Castro 2011	< 16 weeks in length
Castro 2014b	Intervention used in study (dupilumab) is not anti-IL-5 therapy
Chandra 1989	Intervention used in study (various foods) is not anti-IL-5 therapy
Chervinsky 2003	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Clavel 1998	Intervention used in study (immunotherapy) is not anti-IL-5 therapy
Corren 2003	Intervention used in study (omalizumab) is not anti-IL-5 therapy

(*Continued*)

Corren 2010	Intervention used in study (il-4ralpha antagonist) is not anti-IL-5 therapy
Cullell-Young 2002	Not a RCT
Dasgupta 2016	Participants did not have a diagnosis of asthma (COPD patients)
De Boever 2014	Intervention used in study (anti-IL-13 mab) is not anti-IL-5 therapy
Djukanovic 2004	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Ebner 1989	Intervention used in study (immunotherapy) is not anti-IL-5 therapy
Eckman 2010	Intervention used in study (immunotherapy) is not anti-IL-5 therapy
El-Nawawy 2000	Not a RCT
EUCTR2012-004385-17-BE	The study participants did not have asthma
EUCTR2014-002666-76-GB	Treatment period < 16 weeks
EUCTR2014-003162-25-DE	The study participants did not have asthma
EUCTR2015-001152-29-BE	Not an RCT and endpoints are not applicable as this is a long-term access programme
EUCTR2015-003697-32-NL	Not placebo-controlled. Single treatment arm only
EUCTR2016-001831-10-NL	No placebo arm/single treatment arm and treatment duration < 16 weeks
EUCTR2016-002405-19-DE	Participants do not have a diagnosis of asthma, no placebo arm, treatment duration < 16 weeks
Fahy 1997	Intervention used in study (anti-IgE) is not anti-IL-5 therapy
Fahy 1999	Intervention used in study (anti-IgE) is not anti-IL-5 therapy
Ferrguson 2016	Treatment duration < 16 weeks in length
Finn 2003	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Flood-Page 2003	Treatment < 16 weeks
Flood-Page 2007	Treatment < 16 weeks
Frew 1998	Intervention used in study (anti-IgE) is not anti-IL-5 therapy
Garcia 2013	Intervention used in study (omalizumab) is not anti-IL-5 therapy

(*Continued*)

Gauvreau 2011	Intervention used in study (anti-IL-13) is not anti-IL-5 therapy
Gauvreau 2014a	Intervention used in study (anti-tslp) is not anti-IL-5 therapy
Gauvreau 2014b	Intervention used in study (ox40l antagonism) is not anti-IL-5 therapy
Gauvreau 2014c	Intervention used in study (quilizumab) is not anti-IL-5 therapy
Gauvreau 2015a	Intervention used in study (ligelizumab) is not anti-IL-5 therapy
Gauvreau 2015b	Intervention used in study (ligelizumab) is not anti-IL-5 therapy
Gevaert 2013	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Gordon 1972	Intervention used in study is not anti-IL-5 therapy
Greenberg 1991	Participants do not have a diagnosis of asthma
Gunsoy 2016	Not a randomised, placebo-controlled trial
Han 2009	Intervention used in study (jade screen powder) is not anti-IL-5 therapy
Hanania 2011	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Hanania 2013	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Hanania 2014	Intervention used in study (lebrikizumab) is not anti-IL-5 therapy
Hanania 2015	Intervention used in study (lebrikizumab) is not anti-IL-5 therapy
Harris 2016	Intervention used in study (quilizumab) is not anti-IL-5 therapy
Hendeles 2015	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Hill 1982	Intervention used in study (immunotherapy) is not anti-IL-5 therapy
Hodsman 2013	Intervention used in study (anti-IL-13) is not anti-IL-5 therapy
Holgate 2004	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Hoshino 2012	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Humbert 2005	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Humbert 2008	Intervention used in study (omalizumab) is not anti-IL-5 therapy

(*Continued*)

Humbert 2009	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Jacquemin 1995	Intervention used in study (immunotherapy) is not anti-IL-5 therapy
Jutel 2005	Intervention used in study (immunotherapy) is not anti-IL-5 therapy
Kang 1988	Intervention used in study (immunotherapy) is not anti-IL-5 therapy
Kips 2003	Treatment < 16 weeks
Kon 2001	Intervention used in study (anti-cd4) is not anti-IL-5 therapy
Kopp 2009	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Kopp 2013	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Kulus 2010	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Lanier 2003	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Lanier 2009	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Laviolette 2013	Treatment < 16 weeks
Leckie 2000	Treatment < 16 weeks
Leynadier 2004	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Li 2016	Review article, not a RCT
Lizaso 2008	Intervention used in study (immunotherapy) is not anti-IL-5 therapy
Lugogo 2016	Not a randomised, placebo-controlled trial
Maspero 2016	Combined secondary analysis of two trials: NCT01287039 and NCT01285323
Massanari 2009	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Massanari 2010	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Metzger 1998	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Milgrom 1999	Intervention used in study (anti-IgE) is not anti-IL-5 therapy
Milgrom 2001	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Modlin 1977	Participants do not have diagnosis of asthma

(*Continued*)

Moss 1987	Intervention used in study (immunotherapy) is not anti-IL-5 therapy
Nair 2009	Focus of trial is on steroid reduction and therefore does not meet our predefined inclusion criteria
Nair 2016	All participants do not have a diagnosis of asthma
NCT00783289 2008	Treatment duration < 16 weeks
NCT00802438	Non randomised study
NCT01290887 2011	Study does not include a placebo arm
NCT01366521	Phase 2 study comparing three doses of mepolizumab. This trial does not have a placebo arm
NCT01471327	Focus of study was on tolerability, pharmacokinetics and pharmacodynamics of single dose SB-240563 administered intravenously to Japanese healthy male participants. People with asthma were not included in the study
NCT01691859	This study does not include a placebo group. Multi-centre, open-label, long-term safety study with total sample receiving 100 mg mepolizumab administered subcutaneously (no control group)
NCT01842607	This study does not include a placebo group. Multi-centre, open-label, long-term safety study with total sample receiving 100 mg mepolizumab administered subcutaneously (no control group)
NCT02075255 2014	Focus of trial is on oral steroid reduction
NCT02135692	This study does not include a placebo group. Multi-center, open-label, long-term study of subcutaneously (SC) administered mepolizumab 100 mg in addition to standard of care (SOC), in participants with severe eosinophilic asthma
NCT02258542 2014	Not a RCT (an extension study with no placebo arm)
NCT02293265	Aim of study is to provide a 'reliable description of the severe asthma patient landscape with respect to the potential eligibility for treatment with mepolizumab, omalizumab, and reslizumab'. No pharmaceutical intervention in study
NCT02417961 2015	Not a RCT
NCT02501629 2015	Focus of trial is on oral steroid reduction
NCT02559791	Not placebo-controlled - single treatment arm only
NCT02808819 2016	Not a RCT
NCT02814643 2016	Treatment duration < 16 weeks
NCT02869438	Treatment duration < 16 weeks

(*Continued*)

NCT02937168	Treatment duration < 16 weeks
NCT02968914	Not a placebo-controlled trial
NCT03014674	Not a placebo-controlled trial and treatment duration < 16 weeks
NCT03021304	No placebo arm/single treatment arm, treatment duration < 16 weeks
Newbold 2016	Not a RCT
Niven 2008	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Noga 2003	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Noga 2008	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Noonan 2013	Intervention used in study (lebrikizumab) is not anti-IL-5 therapy
Nowak 2015	Treatment < 16 weeks
Oba 2004	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Oh 2013	Intervention used in study (anti-IL-9) is not anti-IL-5 therapy
Ohashi 1997	Participants do not have a diagnosis of asthma
Ohman 1984	Intervention used in study (immunotherapy) is not anti-IL-5 therapy
Ohta 2009	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Ong 2005	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Park 1998	Not a RCT
Parker 2010	Intervention used in study (anti-IL-9) is not anti-IL-5 therapy
Pauli 1984	Intervention used in study (immunotherapy) is not anti-IL-5 therapy
Pavord 2012b	Posthoc analysis of Pavord 2012a and Ortega 2014 stratified by prior use of anti-IgE therapy
Pelaia 2016	Study is not a RCT
Pham 2016	An analysis of sera collected from asthma patients enrolled in two clinical studies: NCT00659659 and NCT00783289
Piper 2012	Intervention used in study (tralokinumab) is not anti-IL-5 therapy

(*Continued*)

Piper 2013	Intervention used in study (tralokinumab) is not anti-IL-5 therapy
Pouliquen 2015	Study has no placebo arm or clinical endpoints
Pouliquen 2016	Aggregation of two clinical trials
Prazma 2016	Study is not a randomised, placebo controlled trial
Prieto 2006	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Pui 2010	Intervention used in study (air/diesel exhaust +/- antioxidant) is not anti-IL-5 therapy
Ranade 2015	Intervention used in study (tralokinumab) is not anti-IL-5 therapy
Rose 2009	Intervention used in study (pneumococcal vaccine) is not anti-IL-5 therapy
Sakamoto 1984	Not a RCT
Scheerens 2011	Intervention used in study (lebrikizumab) is not anti-IL-5 therapy
Scheerens 2012	Intervention used in study (lebrikizumab) is not anti-IL-5 therapy
Scheerens 2014	Intervention used in study (lebrikizumab) is not anti-IL-5 therapy
Siergiejko 2011	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Silk 1998	Intervention used in study (pneumococcal vaccine) is not anti-IL-5 therapy
Silkoff 2004	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Simoes 2007	Intervention used in study (pavilizumab) is not anti-IL-5 therapy
Singh 2010	Intervention used in study (anti-IL-13) is not anti-IL-5 therapy
Slavin 2009	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Soler 2001	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Sorkness 2013	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Sthoeger 2007	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Sugaya 1994	Intervention used in study (influenza vaccine) is not anti-IL-5 therapy
Swanson 2014	Intervention used in study (dupilumab) is not anti-IL-5 therapy
Szymaniak 1998	Not a RCT

(*Continued*)

Tanaka 1993	Intervention used in study (influenza vaccine) is not anti-IL-5 therapy
Terr 1969	Study predates monoclonal treatments
Van Rensen 2009	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Vignola 2004	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Virchow 2016	Aggregation of two clinical trials
Wang 2015	Pharmacometrics assessment of phase IIb data to characterize the exposure-response relationship with Benralizumab in adults with asthma
Wark 2003	Intervention used in study (itraconazole) is not anti-IL-5 therapy
Weinstein 2016	Combined secondary analysis of two trials: NCT01287039 and NCT01285323
Wenzel 2009	Intervention used in study (golimumab) is not anti-IL-5 therapy
Wenzel 2013a	Intervention used in study (dupilumab) is not anti-IL-5 therapy
Wenzel 2013b	Interventionused in study (dupilumab) is not anti-IL-5 therapy
Wenzel 2014	Intervention used in study (dupilumab) is not anti-IL-5 therapy
Yan 2015	Participants do not have a diagnosis of asthma
Zetterstrom 1972	Participants do not all have diagnosis of asthma
Zhu 2013	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Zielen 2013	Intervention used in study (omalizumab) is not anti-IL-5 therapy

RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

EUCTR2005-001932-61-GB

Trial name or title	Mepolizumab and exacerbation frequency in refractory eosinophilic asthma. A randomised, double blind, placebo controlled, parallel group trial
Methods	Randomised, double-blind, placebo-controlled, parallel-group trial

EUCTR2005-001932-61-GB (*Continued*)

Participants	Target recruitment = 60 participants with refractory eosinophilic asthma Principal inclusion criteria 1. Refractory asthma as defined by the American Thoracic Society guidelines 2. Symptoms and objective evidence of variable airflow obstruction as indicated by one or more of the following: i) > 15% increase in FEV_1 following 200 μg inhaled salbutamol ii) > 20% within-day variability in PEFR noted on any day following assessment twice-daily over 2 weeks iii) and/or a concentration of methacholine causing 20% fall in FEV_1 of < 8 mg/mL documented at any time during previous assessments at Glenfield Hospital 3. A history of $\geq$ 2 asthma exacerbations in the previous 12 months requiring oral corticosteroids on at least 3 consecutive days, emergency care visit and treatment or hospitalisation 4. Evidence of eosinophilic airway inflammation - a sputum eosinophil count of > 3% in last 2 years
Interventions	Mepolizumab IV Placebo
Outcomes	Main objective To investigate whether mepolizumab effectively suppresses the presence of eosinophils in sputum and whether this translates into a fall in the frequency of asthma exacerbations in a cohort of refractory asthmatics who otherwise require a high dose of inhaled corticosteroids and, in some cases, regular oral corticosteroids to control their asthma Secondary objectives To assess the effects of mepolizumab on: 1. long-term changes in airway structure and function (airway remodelling) after 12 months' treatment using bronchial biopsy material and CT scans 2. asthma symptoms and quality of life, analysed using diary cards and validated questionnaires 3. exhaled nitric oxide levels 4. concentration of methacholine required to cause a fall in FEV_1 by 20% from baseline 5. Hospital admission rates over the 12 months 6. Obtain blood samples for pharmacogenomic analysis by GSK (N.B. This does not form part of the data collection/analysis of this study)
Starting date	Date of competent authority/ethics committee decision 2005-11-16
Contact information	(No contact details listed) Sponsored by University Hospitals of Leicester www.clinicaltrialsregister.eu/ctr-search/trial/2005-001932-61/GB
Notes	Non-commercial

NCT01520051

Trial name or title	Mepolizumab treatment for rhinovirus-induced asthma exacerbations (MATERIAL)
Methods	Randomised, double-blind trial

NCT01520051 (*Continued*)

Participants	People with mild allergic asthma with viral airway infections Target recruitment = 48 participants Inclusion criteria 1. Age: from 18-50 years 2. History of episodic chest tightness and wheezing 3. Intermittent or mild persistent asthma according to the criteria of the Global Initiative for Asthma 4. Non-smoking or stopped smoking > 12 months ago and ≤ 5 pack-years 5. Clinically stable, no history of exacerbations within 6 weeks prior to the study 6. Steroid-naïve or those not currently on corticosteroids and who have not taken any corticosteroids by any dosing routes within 2 weeks prior to the study. Occasional usage of inhaled short-acting beta$_2$-agonists as rescue medication is allowed, prior to and during the study 7. Baseline FEV_1 > 80% of predicted 8. Airway hyperresponsiveness, indicated by a positive acetyl-beta-methylcholine bromide (MeBr) challenge with PC_{20} < 9.8 mg/mL 9. Positive skin prick test (SPT) to one or more of the 12 common aeroallergen extracts, defined as a wheal with an average diameter over 3 mm 10. No other clinically significant abnormality on medical history and clinical examination Exclusion criteria: 1. Presence of antibodies directed against RV16 in serum (titre > 4), measured at visit 1 2. History of clinical significant hypotensive episodes or symptoms of fainting, dizziness, or light-headedness 3. Women who are pregnant, lactating or who have a positive urine pregnancy test at visit 1 4. Chronic use of any other medication for treatment of lung disease other than short-acting beta$_2$-agonists 5. Participation in any clinical investigational drug treatment protocol in previous 3 months 6. Ongoing use of tobacco products of any kind or previous usage with ≥ 6 total pack-years 7. Concomitant disease or condition which could interfere with the conduct of the study, or for which the treatment might interfere with the conduct of the study, or which would, in the opinion of the investigator, pose an unacceptable risk to the participant 8. People with young children (< 2 years)
Interventions	3 monthly intravenous infusions of 750 mg versus 3 monthly intravenous infusions with saline
Outcomes	Primary outcome measures 1. FEV_1 1 day prior and 6 days after RV16 challenge 2. Questionnaire to score asthma and common cold complaints during 14 days following viral infection Secondary outcome measures: 1. Viral load on day 6 after viral infection 2. Sputum eosinophils before and after mepolizumab infusion 3. Cell influx in bronchoalveolar lavage fluid 6 days after viral infection 4. Pro-inflammatory cytokines in bronchoalveolar lavage fluid 6 days after viral infection 5. Antibody production 6 weeks after infection
Starting date	January 2012
Contact information	Suzanne Bal +31 205668043 s.m.bal@amc.uva.nl Koenraad van der Sluijs +31 205668224 kvandersluijs@amc.uva.nl Principal Investigator: René Lutter, Academisch Medisch Centrum - Universiteit van Amsterdam (AMC-UvA)

NCT01520051 (*Continued*)

Notes	Also known as "MATERIAL" study. Clinicaltrials.gov website notes "The recruitment status of this study is unknown. The completion date has passed and the status has not been verified in more than two years." Estimated study completion date March 2014

NCT02452190

Trial name or title	A 52-week double-blind, placebo-controlled, parallel-group efficacy and safety study of reslizumab 110 mg fixed, subcutaneous dosing in patients with uncontrolled asthma and elevated blood eosinophils
Methods	Double-blind, placebo-controlled, parallel-group study
Participants	469 participants with unstable asthma Inclusion criteria 1. Male or female, ≥ 12 years, with a diagnosis of asthma 2. FEV_1 reversibility according to standard American Thoracic Society (ATS) or European Respiratory Society (ERS) protocol 3. Required an inhaled corticosteroid 4. Required an additional asthma controller medication besides inhaled corticosteroids 5. History of asthma exacerbation
Interventions	Reslizumab will be administered subcutaneously in a dose of 110 mg every 4 weeks versus placebo
Outcomes	The primary objective of this study is to determine the effect of reslizumab (110 mg) administered subcutaneously every 4 weeks on clinical asthma exacerbations in adults and adolescents with asthma and elevated blood eosinophils who are inadequately controlled on standard-of-care asthma therapy Primary outcome measures 1. Frequency of clinical asthma exacerbations (time frame: 52 weeks) 2. Spirometry Secondary outcome measures 1. Change in FEV_1 (time frame: baseline, week 52) 2. Change in Asthma Quality of Life Questionnaire (time frame: 52 weeks) 3. Change in Asthma Control Questionnaire (time frame: baseline, week 52) 4. Percentage of participants with adverse events (time frame: 52 weeks) 5. Change in total asthma symptom scores (time frame: baseline, 52 weeks) 6. Asthma control days (time frame: 52 weeks) 7. Change in St. George's Respiratory Questionnaire (time frame: baseline, week 32) 8. Time to first clinical asthma exacerbation (time frame: 52 weeks) 9. Frequency of exacerbations requiring hospitalisation or emergency department visits (time frame: 52 weeks) 10. Frequency of moderate exacerbations (time frame: 52 weeks)
Starting date	September 2015
Contact information	Study Director: Teva Medical Expert, MD

NCT02452190 (*Continued*)

Notes	Estimated study completion date: January 2018 Responsible party: Teva Branded Pharmaceutical Products, R&D Inc. International multicentre study with 200 centres

NCT02555371

Trial name or title	Cessation versus continuation of long-term mepolizumab in severe eosinophilic asthma patients
Methods	Multi-center, randomised, double-blind, placebo-controlled, parallel-group study
Participants	300 participants 1. Asthma is currently being treated with a controller medication and the participant has been on a controller medication for the past 12 weeks. Participants will be expected to continue controller therapy for the duration of the study. 2. Male or eligible female participants
Interventions	Mepolizumab 100 mg versus placebo
Outcomes	Primary outcome measures 1. Time to first clinically significant exacerbation)(time frame: up to 52 week)] Secondary outcome measures • Ratio to baseline in blood eosinophil count (time frame: baseline (week 0) and up to week 52) • Time to a decrease in asthma control, defined as an increase from baseline in Asthma Control Questionnaire-5 (ACQ-5) score of $\geq$ 0.5 units • Time to first exacerbation requiring hospitalisation or ED visit (time frame: up to 52 weeks)
Starting date	January 2016
Contact information	US GSK Clinical Trials Call Center GSKClinicalSupportHD@gsk.com
Notes	Estimated study completion date: January 2019

NCT02594332

Trial name or title	A randomised, double-blind, placebo-controlled, mono-center study to evaluate the effects of mepolizumab on airway physiology in patients with eosinophilic asthma: the MEMORY Study
Methods	Randomised, double-blind, placebo-controlled, mono-centre study
Participants	29 participants with severe eosinophilic asthma Inclusion criteria • Men or women at least 18 years • Physician-diagnosis of asthma and evidence of asthma as documented by either reversibility of airflow obstruction ($FEV_1 \geq$ 12% or 200 mL) demonstrated at visit 1 or visit 2 • ICS dose must be $\geq$ 1000 μg/d BDP or equivalent daily with or without maintenance oral corticosteroids • Treatment in the past 12 months with an additional controller medication for at least 3 successive

	months, e.g. long-acting beta$_2$-agonist (LABA), leukotriene receptor antagonist (LTRA), or theophylline • Persistent airflow obstruction as indicated by a pre-bronchodilator FEV_1 < 80% predicted recorded at visit 1 or < 90% for participants on oral corticosteroids • An elevated peripheral blood eosinophil level of ≥ 300/μL that is related to asthma or ≥ 150/μL in participants treated with oral corticosteroids as maintenance therapy demonstrated at visit 1 or in the previous 12 months • Confirmed history of ≥ 2 exacerbations requiring treatment with systemic corticosteroids (intramuscular, intravenous, or oral), in the 12 months prior to visit 1, despite the use of high-dose inhaled corticosteroids. For participants receiving maintenance corticosteroids, the corticosteroid treatment for the exacerbations must have been a two-fold increase or greater in the dose.
Interventions	Mepolizumab 100 mg SC every 4 weeks for 13 injections and placebo
Outcomes	Primary outcome measures 1. Mean change from baseline in pre- and post-bronchodilator FVC at visit 10 (week 24) and at time of response 2. Mean change from baseline in pre- and post-bronchodilator FEV_1 at visit 10 (week 24) and at time of response 3. Mean change from baseline in pre- and post-bronchodilator RV at visit 10 (week 24) and at time of response 4. Mean change from baseline in pre- and post-bronchodilator TLC at visit 10 (week 24) and at time of response 5. Mean change from baseline in pre- and post-bronchodilator airway resistance at visit 10 (week 24) and at time of response 6. Mean change from baseline in pre- and post-bronchodilator IC at visit 10 (week 24) and at time of response 7. Mean change from baseline in pre- and post-bronchodilator CO diffusion capacity at visit 10 (week 24) and at time of response Secondary outcome measures 1. Mean change from baseline in pre- and post-bronchodilator FVC over the 48-week treatment period at prespecified time points (1, 3, 6, 9 and 12 months) 2. Mean change from baseline in pre- and post-bronchodilator FEV_1 over the 48-week treatment period at prespecified time points (1, 3, 6, 9 and 12 months) 3. Mean change from baseline in pre- and post-bronchodilator RV over the 48-week treatment period at prespecified time points (1, 3, 6, 9 and 12 months) 4. Mean change from baseline in pre- and post-bronchodilator TLC over the 48-week treatment period at prespecified time points (1, 3, 6, 9 and 12 months) 5. Mean change from baseline in pre- and post-bronchodilator airway resistance over the 48-week treatment period at prespecified time points (1, 3, 6, 9 and 12 months) 6. Mean change from baseline in pre- and post-bronchodilator (IC) over the 48-week treatment period at prespecified time points (1, 3, 6, 9 and 12 months) 7. Mean change from baseline in pre- and post-bronchodilator CO diffusion capacity over the 48-week treatment period at prespecified time points (1, 3, 6, 9 and 12 months) 8. Exercise tolerance in a subgroup of patients: Mean change from baseline in exercise endurance time (time frame: 1, 3, 6, 9 and 12 months) 9. Exercise tolerance in a subgroup of participants: mean change from baseline in IC (time frame: 1, 3, 6, 9 and 12 months) 10. Exercise tolerance in a subgroup of participants: mean change from baseline in exertional dyspnoea and leg discomfort (Borg CR10 Scale®) (time frame: 1, 3, 6, 9 and 12 months)

NCT02594332 (*Continued*)

	11. Time to clinical response and time to change of baseline parameters of clinical response: sense of smell (time frame: 52 weeks) 12. Time to clinical response and time to change of baseline parameters of clinical response: sense of taste (time frame: 52 weeks) 13. Time to clinical response and time to change of baseline parameters of clinical response: lung volume (time frame: 52 weeks) 14. Time to clinical response and time to change of baseline parameters of clinical response: CO diffusion capacity (time frame: 52 weeks) 15. Time to clinical response and time to change of baseline parameters of clinical response: FEV_1 reversibility (time frame: 52 weeks) 16. Time to clinical response and time to change of baseline parameters of clinical response: exhaled NO (eNO) (time frame: 52 weeks) 17. Time to clinical response and time to change of baseline parameters of clinical response: blood eosinophils (time frame: 52 weeks) 18. Time to clinical response and time to change of baseline parameters of clinical response: eosinophilic cationic protein (time frame: 52 weeks) 19. Time to clinical response and time to change of baseline parameters of clinical response: blood periostin (time frame: 52 weeks) 20. Mean change from baseline in Asthma Control Questionnaire (ACQ) (time frame: 52 weeks) 21. Mean change from baseline in Asthma Quality of Life Questionnaire (AQLQ) (time frame: 52 weeks) 22. Mean change from baseline in St. George's Respiratory Questionnaire (SGRQ) (time frame: 52 weeks) 23. Mean change from baseline in Dyspnoe Index (BDI/TDI) (time frame: 52 weeks) 24. Mean change from baseline in fatigue (time frame: 52 weeks) 25. Mean change from baseline in number of days off school/work over the 48-week treatment period (time frame: 48 weeks) 26. Time to first clinically significant exacerbation requiring oral or systemic corticosteroids, hospitalisation, and/or ED visits (time frame: 52 weeks) 27. Frequency of clinically significant exacerbations (time frame: 52 weeks) 28. Time to first exacerbation requiring hospitalisation or ED visit (time frame: 52 weeks) 29. Frequency of exacerbations requiring hospitalisation (including intubation and admittance to ICU) or ED visits (time frame: 52 weeks) 30. GETE rating by physician and participant at time of response and over the 52-week treatment period at pre-specified time points (1, 3, 6, 9 and 12 months) (time frame: 1, 3, 6, 9 and 12 months) 31. Mean change in proportion of participants with nasal polyps, chronic sinusitis and loss of smell and taste (time frame: 52 weeks) 32. Clinical response to mepolizumab in relation to asthma parameters which potentially predict clinical response (time frame: 52 weeks) 33. Routine safety assessment (adverse events and serious adverse events reporting, withdrawals, pregnancy, haematological and clinical chemistry parameters, ECG and vital signs (pulse rate and systolic and diastolic blood pressure)) (time frame: 52 weeks)
Starting date	November 2015
Contact information	PI Dr. Stephanie Korn, Johannes Gutenberg University Mainz
Notes	GlaxoSmithKline collaborator Estimated study completion date August 2018

NCT02821416

Trial name or title	A double-bind, randomised, parallel group, placebo-controlled multi-centre study to evaluate the effect of benralizumab on allergen-induced inflammation in mild, atopic asthmatics
Methods	Randomised, double-blind, parallel-group, placebo-controlled study
Participants	Estimated enrolment 42 participants with mild atopic asthma Inclusion criteria 1. Female or male aged 18-65 years, inclusively, at the time of enrolment 2. Mild, stable, allergic asthma and asthma therapy limited to inhaled, short-acting beta 2 agonists (not more than twice weekly) 3. Positive skin-prick test to at least one common aeroallergen
Interventions	Benralizumab administered subcutaneously compared with placebo administered subcutaneously Allergen challenge (all participants)
Outcomes	Primary outcome measures 1. Change in percent of eosinophils in sputum 7 h post allergen challenge 2. Maximal percentage decrease in FEV_1 3-7 h post allergen challenge Secondary outcome measures 1. Change in percent of basophil numbers in induced sputum 2. Maximal percentage decrease in FEV_1 0-2 h post allergen challenge 3. Area under the curve of time-adjusted percent decrease in FEV_1 curve in early asthmatic response 4. Change in eosinophil and basophil numbers in endobronchial biopsies 5. Change in eosinophils, eosinophil progenitor cells and basophils in bone marrow aspirates 6. Change in eosinophils and basophils in blood 7. Change in eosinophils and basophils in induced sputum, blood and bone marrow aspirates 8. Change in eosinophils and basophils in endobronchial biopsies 9. Methacholine PC20 Other outcome measures: 1. Safety and tolerability of benralizumab assessed by the reporting of adverse events/serious adverse events and physical examination/vital signs 2. Safety and tolerability of benralizumab assessed by ECG and clinical chemistry/haematology/urinalysis
Starting date	October 2016
Contact information	AstraZeneca Clinical Study Information Center 1-877-240-9479 information.center@astrazeneca.com
Notes	Still recruiting April 2017 Estimated completion date February 2019

BDP: beclomethasone dipropionate; **CO:** carbon monoxide; **ECG**: electrocardiogram; **ED**: emergency department; **eNO:** exhaled nitric oxide; **FEV_1** : Forced expiratory volume in 1 second; **FVC**: forced vital capacity; **GETE**: global evaluation of treatment effectiveness; **IC**: inspiratory capacity; **ICU**: intensive care unit; **NO:** nitric oxide; **PC_{20}** : histamine provocative concentration causing a 20% drop in FEV_1: **RV**: residual volume; **TLC**: total lung capacity;

DATA AND ANALYSES

Comparison 1. Mepolizumab (SC) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rate of exacerbations requiring systemic corticosteroids	2	936	Rate Ratio (Random, 95% CI)	0.45 [0.36, 0.55]
1.1 Eosinophilic	2	936	Rate Ratio (Random, 95% CI)	0.45 [0.36, 0.55]
2 Rate of exacerbations requiring emergency department treatment or admission	2	936	Rate Ratio (Random, 95% CI)	0.36 [0.20, 0.66]
2.1 Eosinophilic	2	936	Rate Ratio (Random, 95% CI)	0.36 [0.20, 0.66]
3 Rate of exacerbations requiring admission	2	936	Rate Ratio (Random, 95% CI)	0.31 [0.13, 0.73]
3.1 Eosinophilic	2	936	Rate Ratio (Random, 95% CI)	0.31 [0.13, 0.73]
4 Health-related quality of life (ACQ)	2	936	Mean Difference (Random, 95% CI)	-0.42 [-0.56, -0.28]
4.1 Eosinophilic	2	936	Mean Difference (Random, 95% CI)	-0.42 [-0.56, -0.28]
5 Health-related quality of life (SGRQ)	2	936	Mean Difference (Random, 95% CI)	-7.40 [-9.50, -5.29]
5.1 Eosinophilic	2	936	Mean Difference (Random, 95% CI)	-7.40 [-9.50, -5.29]
6 Pre-bronchodilator FEV_1 (litres)	2	936	Mean Difference (Random, 95% CI)	0.11 [0.06, 0.17]
6.1 Eosinophilic	2	936	Mean Difference (Random, 95% CI)	0.11 [0.06, 0.17]
7 Serious adverse events	2	936	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.41, 0.97]
7.1 Eosinophilic	2	936	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.41, 0.97]
8 Adverse events leading to discontinuation	2	936	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.11, 1.80]
8.1 Eosinophilic	2	936	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.11, 1.80]

Comparison 2. Mepolizumab (IV) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rate of clinically significant exacerbations	3	751	Rate Ratio (Random, 95% CI)	0.53 [0.44, 0.64]
1.1 Eosinophilic	3	751	Rate Ratio (Random, 95% CI)	0.53 [0.44, 0.64]
2 Rate of exacerbations requiring emergency department treatment or admission	2	690	Rate Ratio (Random, 95% CI)	0.52 [0.31, 0.87]
2.1 Eosinophilic	2	690	Rate Ratio (Random, 95% CI)	0.52 [0.31, 0.87]
3 Rate of exacerbations requiring admission	2	690	Rate Ratio (Random, 95% CI)	0.61 [0.33, 1.13]
3.1 Eosinophilic	2	690	Rate Ratio (Random, 95% CI)	0.61 [0.33, 1.13]

4 People with one or more exacerbations	1	61	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.61, 1.09]
4.1 Eosinophilic	1	61	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.61, 1.09]
5 Health-related quality of life (AQLQ)	2	369	Mean Difference (Random, 95% CI)	0.21 [-0.06, 0.47]
5.1 Eosinophilic	2	369	Mean Difference (Random, 95% CI)	0.21 [-0.06, 0.47]
6 Health-related quality of life (ACQ)	2	369	Mean Difference (Fixed, 95% CI)	-0.11 [-0.32, 0.09]
6.1 Eosinophilic	2	369	Mean Difference (Fixed, 95% CI)	-0.11 [-0.32, 0.09]
7 Health-related quality of life (SGRQ)	1	382	Mean Difference (Random, 95% CI)	-6.4 [-9.65, -3.15]
7.1 Eosinophilic	1	382	Mean Difference (Random, 95% CI)	-6.4 [-9.65, -3.15]
8 Pre-bronchodilator FEV_1 (litres)	2	690	Mean Difference (Random, 95% CI)	0.08 [0.02, 0.15]
8.1 Eosinophilic	2	690	Mean Difference (Random, 95% CI)	0.08 [0.02, 0.15]
9 Serious adverse events	3	751	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.37, 0.94]
9.1 Eosinophilic	3	751	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.37, 0.94]
10 Adverse events leading to discontinuation	3	751	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.18, 2.92]
10.1 Eosinophilic	3	751	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.18, 2.92]
11 Serum eosinophil level (cells/microlitre)	1		Mean Difference (Fixed, 95% CI)	-170.0 [-228.00, -110.00]
11.1 Eosinophilic	1		Mean Difference (Fixed, 95% CI)	-170.0 [-228.00, -110.00]

Comparison 3. Reslizumab (IV) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rate of exacerbations requiring systemic corticosteroids	2	953	Rate Ratio (Fixed, 95% CI)	0.43 [0.33, 0.55]
1.1 Eosinophilic	2	953	Rate Ratio (Fixed, 95% CI)	0.43 [0.33, 0.55]
2 Rate of exacerbations requiring emergency department treatment or admission	2	953	Rate Ratio (Fixed, 95% CI)	0.67 [0.39, 1.17]
2.1 Eosinophilic	2	953	Rate Ratio (Fixed, 95% CI)	0.67 [0.39, 1.17]
3 Health-related quality of life (AQLQ)	3	1164	Mean Difference (Fixed, 95% CI)	0.28 [0.17, 0.39]
3.1 Eosinophilic	3	1164	Mean Difference (Fixed, 95% CI)	0.28 [0.17, 0.39]
4 Health-related quality of life (ACQ)	4	1652	Mean Difference (Fixed, 95% CI)	-0.25 [-0.33, -0.17]
4.1 Eosinophilic	4	1260	Mean Difference (Fixed, 95% CI)	-0.27 [-0.36, -0.19]
4.2 Non-eosinophilic	1	392	Mean Difference (Fixed, 95% CI)	-0.12 [-0.33, 0.09]
5 Pre-bronchodilator FEV_1 (litres)	4	1652	Mean Difference (Fixed, 95% CI)	0.11 [0.07, 0.15]
5.1 Eosinophilic	4	1260	Mean Difference (Fixed, 95% CI)	0.12 [0.08, 0.16]
5.2 Non-eosinophilic	1	392	Mean Difference (Fixed, 95% CI)	0.03 [-0.07, 0.14]
6 Serious adverse events	4	1656	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.56, 1.12]
6.1 Eosinophilic	3	1160	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.51, 1.22]

6.2 Eosinophil status unknown	1	496	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.34, 2.88]
7 Adverse events leading to discontinuation	4	1659	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.43, 1.02]
7.1 Eosinophilic	3	1163	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.37, 1.20]
7.2 Eosinophil status unknown	1	496	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.35, 1.23]
8 Serum eosinophil level (cells/microlitre)	4	1656	Mean Difference (Fixed, 95% CI)	-476.83 [-499.32, -454.34]
8.1 Eosinophilic	4	1656	Mean Difference (Fixed, 95% CI)	-476.83 [-499.32, -454.34]

Comparison 4. Benralizumab (SC) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rate of exacerbations requiring systemic corticosteroids	3	2456	Rate Ratio (Fixed, 95% CI)	0.62 [0.55, 0.70]
1.1 Eosinophilic	3	1698	Rate Ratio (Fixed, 95% CI)	0.59 [0.51, 0.68]
1.2 Non-eosinophilic	2	758	Rate Ratio (Fixed, 95% CI)	0.69 [0.56, 0.85]
2 Rate of exacerbations requiring emergency department treatment or admission	2	1537	Rate Ratio (Fixed, 95% CI)	0.68 [0.47, 0.98]
2.1 Eosinophilic	2	1537	Rate Ratio (Fixed, 95% CI)	0.68 [0.47, 0.98]
3 Health-related quality of life (AQLQ mean difference)	3	1541	Mean Difference (Fixed, 95% CI)	0.23 [0.11, 0.35]
3.1 Eosinophilic	3	1541	Mean Difference (Fixed, 95% CI)	0.23 [0.11, 0.35]
4 Health-related quality of life (ACQ mean difference)	3	2359	Mean Difference (Fixed, 95% CI)	-0.20 [-0.29, -0.11]
4.1 Eosinophilic	3	1604	Mean Difference (Fixed, 95% CI)	-0.23 [-0.34, -0.12]
4.2 Non-eosinophilic	2	755	Mean Difference (Fixed, 95% CI)	-0.14 [-0.30, 0.02]
5 Pre-bronchodilator FEV_1 (litres)	3	2355	Mean Difference (Fixed, 95% CI)	0.10 [0.05, 0.14]
5.1 Eosinophilic	3	1617	Mean Difference (Fixed, 95% CI)	0.13 [0.08, 0.19]
5.2 Non-eosinophilic	2	738	Mean Difference (Fixed, 95% CI)	0.03 [-0.03, 0.10]
6 Serious adverse events	4	2648	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.66, 1.01]
6.1 Eosinophilic	2	1537	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.60, 1.06]
6.2 Non-eosinophilic	2	758	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.57, 1.27]
6.3 Eosinophil status unknown	2	353	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.37, 1.51]
7 Adverse events leading to discontinuation	3	2597	Risk Ratio (M-H, Random, 95% CI)	2.15 [1.02, 4.57]
7.1 Eosinophilic	2	1537	Risk Ratio (M-H, Random, 95% CI)	2.70 [0.86, 8.49]
7.2 Non-eosinophilic	2	758	Risk Ratio (M-H, Random, 95% CI)	1.81 [0.54, 6.05]
7.3 Eosinophil status unknown	1	302	Risk Ratio (M-H, Random, 95% CI)	1.82 [0.31, 10.69]
8 Serum eosinophil level (% change from baseline)	2	2295	Mean Difference (Fixed, 95% CI)	-104.74 [-116.12, -93.35]

8.1 Eosinophilic	2	1537	Mean Difference (Fixed, 95% CI)	-101.74 [-113.27, -90.21]
8.2 Non-eosinophilic	2	758	Mean Difference (Fixed, 95% CI)	-216.81 [-287.35, -146.28]

Analysis 1.1. Comparison 1 Mepolizumab (SC) versus placebo, Outcome 1 Rate of exacerbations requiring systemic corticosteroids.

Review: Anti-IL5 therapies for asthma

Comparison: 1 Mepolizumab (SC) versus placebo

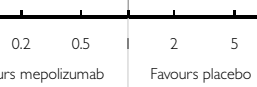
Outcome: 1 Rate of exacerbations requiring systemic corticosteroids

Study or subgroup	Mepolizumab N	Placebo N	log [Rate Ratio] (SE)	Rate Ratio IV,Random,95% CI	Weight	Rate Ratio IV,Random,95% CI
1 Eosinophilic						
Chupp 2017	274	277	-0.8675 (0.1549)		48.2 %	0.42 [0.31, 0.57]
Ortega 2014	194	191	-0.755 (0.1495)		51.8 %	0.47 [0.35, 0.63]
Total (95% CI)	**468**	**468**			**100.0 %**	**0.45 [0.36, 0.55]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.27$, df = 1 (P = 0.60); $I^2 = 0.0\%$

Test for overall effect: Z = 7.52 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Mepolizumab (SC) versus placebo, Outcome 2 Rate of exacerbations requiring emergency department treatment or admission.

Review: Anti-IL5 therapies for asthma

Comparison: 1 Mepolizumab (SC) versus placebo

Outcome: 2 Rate of exacerbations requiring emergency department treatment or admission

Study or subgroup	Mepolizumab N	Placebo N	log [Rate Ratio] (SE)	Rate Ratio IV,Random,95% CI	Weight	Rate Ratio IV,Random,95% CI
1 Eosinophilic						
Chupp 2017	274	277	-1.1394 (0.5004)		37.2 %	0.32 [0.12, 0.85]
Ortega 2014	194	191	-0.9416 (0.3854)		62.8 %	0.39 [0.18, 0.83]
Total (95% CI)	**468**	**468**			**100.0 %**	**0.36 [0.20, 0.66]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.10$, df = 1 (P = 0.75); $I^2 = 0.0\%$

Test for overall effect: Z = 3.33 (P = 0.00088)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Mepolizumab (SC) versus placebo, Outcome 3 Rate of exacerbations requiring admission.

Review: Anti-IL5 therapies for asthma

Comparison: 1 Mepolizumab (SC) versus placebo

Outcome: 3 Rate of exacerbations requiring admission

Study or subgroup	Mepolizumab N	Placebo N	log [Rate Ratio] (SE)	Rate Ratio IV,Random,95% CI	Weight	Rate Ratio IV,Random,95% CI
1 Eosinophilic						
Chupp 2017	274	277	-1.1712 (0.7073)		37.6 %	0.31 [0.08, 1.24]
Ortega 2014	194	191	-1.1712 (0.5494)		62.4 %	0.31 [0.11, 0.91]
Total (95% CI)	**468**	**468**			**100.0 %**	**0.31 [0.13, 0.73]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 1 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 2.70 (P = 0.0069)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Mepolizumab (SC) versus placebo, Outcome 4 Health-related quality of life (ACQ).

Review: Anti-IL5 therapies for asthma

Comparison: 1 Mepolizumab (SC) versus placebo

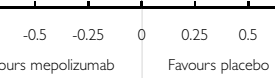
Outcome: 4 Health-related quality of life (ACQ)

Study or subgroup	Mepolizumab N	Placebo N	Mean Difference (SE)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Eosinophilic						
Chupp 2017	274	277	-0.4 (0.102)		47.4 %	-0.40 [-0.60, -0.20]
Ortega 2014	194	191	-0.44 (0.0969)		52.6 %	-0.44 [-0.63, -0.25]
Total (95% CI)	**468**	**468**			**100.0 %**	**-0.42 [-0.56, -0.28]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.08$, df = 1 (P = 0.78); $I^2 = 0.0\%$

Test for overall effect: Z = 5.99 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1 Mepolizumab (SC) versus placebo, Outcome 5 Health-related quality of life (SGRQ).

Review: Anti-IL5 therapies for asthma

Comparison: 1 Mepolizumab (SC) versus placebo

Outcome: 5 Health-related quality of life (SGRQ)

Study or subgroup	Mepolizumab N	Placebo N	Mean Difference (SE)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Eosinophilic						
Chupp 2017	274	277	-7.7 (1.4286)		56.6 %	-7.70 [-10.50, -4.90]
Ortega 2014	194	191	-7 (1.6327)		43.4 %	-7.00 [-10.20, -3.80]
Total (95% CI)	**468**	**468**			**100.0 %**	**-7.40 [-9.50, -5.29]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.10$, df = 1 (P = 0.75); $I^2 = 0.0\%$

Test for overall effect: Z = 6.88 (P < 0.00001)

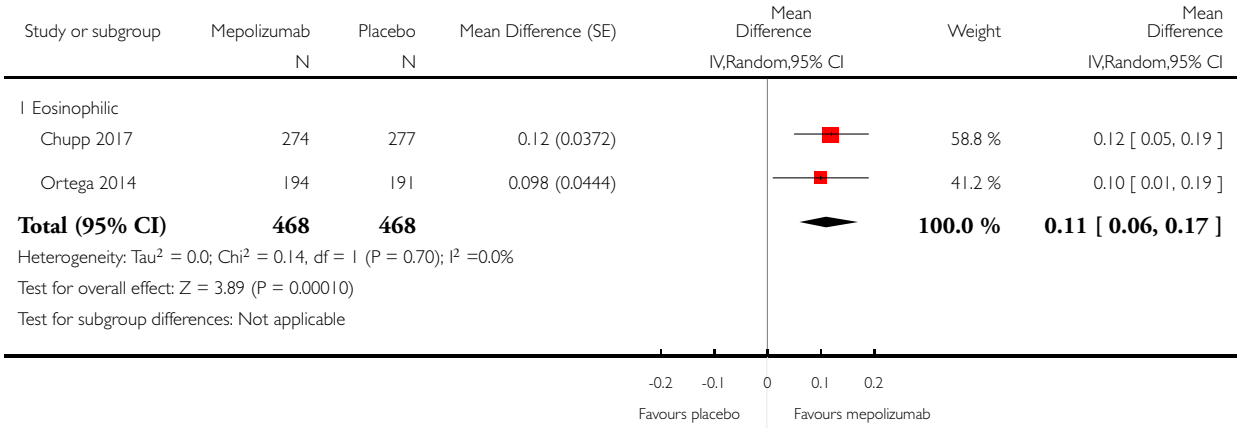
Test for subgroup differences: Not applicable

Analysis 1.6. Comparison 1 Mepolizumab (SC) versus placebo, Outcome 6 Pre-bronchodilator FEV1 (litres).

Review: Anti-IL5 therapies for asthma

Comparison: 1 Mepolizumab (SC) versus placebo

Outcome: 6 Pre-bronchodilator FEV_1 (litres)

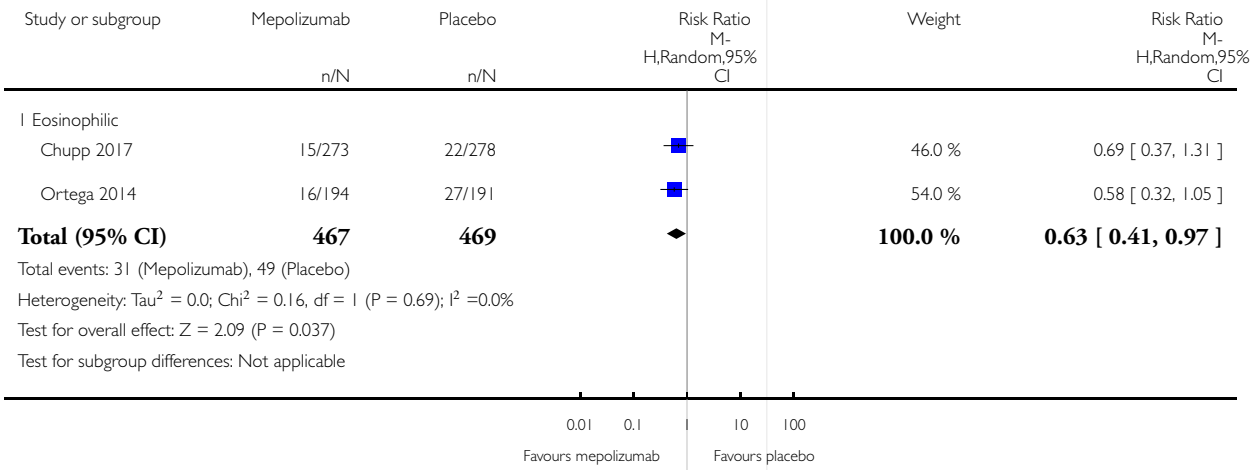


Analysis 1.7. Comparison 1 Mepolizumab (SC) versus placebo, Outcome 7 Serious adverse events.

Review: Anti-IL5 therapies for asthma

Comparison: 1 Mepolizumab (SC) versus placebo

Outcome: 7 Serious adverse events



Analysis 1.8. Comparison 1 Mepolizumab (SC) versus placebo, Outcome 8 Adverse events leading to discontinuation.

Review: Anti-IL5 therapies for asthma

Comparison: 1 Mepolizumab (SC) versus placebo

Outcome: 8 Adverse events leading to discontinuation

Study or subgroup	Mepolizumab n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Eosinophilic					
Chupp 2017	2/273	3/278		60.0 %	0.68 [0.11, 4.03]
Ortega 2014	1/194	4/191		40.0 %	0.25 [0.03, 2.18]
Total (95% CI)	**467**	**469**		**100.0 %**	**0.45 [0.11, 1.80]**

Total events: 3 (Mepolizumab), 7 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.50$, df = 1 (P = 0.48); $I^2 = 0.0\%$

Test for overall effect: Z = 1.13 (P = 0.26)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Mepolizumab (IV) versus placebo, Outcome 1 Rate of clinically significant exacerbations.

Review: Anti-IL5 therapies for asthma

Comparison: 2 Mepolizumab (IV) versus placebo

Outcome: 1 Rate of clinically significant exacerbations

Study or subgroup	Mepolizumab N	Placebo N	log [Rate Ratio] (SE)	Rate Ratio IV,Random,95% CI	Weight	Rate Ratio IV,Random,95% CI
1 Eosinophilic						
Pavord 2012a	153	155	-0.6539 (0.1443)		43.8 %	0.52 [0.39, 0.69]
Ortega 2014	191	191	-0.6349 (0.1492)		40.9 %	0.53 [0.40, 0.71]
Haldar 2009	29	32	-0.5621 (0.2443)		15.3 %	0.57 [0.35, 0.92]
Total (95% CI)	**373**	**378**			**100.0 %**	**0.53 [0.44, 0.64]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.11$, df = 2 (P = 0.95); $I^2 = 0.0\%$

Test for overall effect: Z = 6.62 (P < 0.00001)

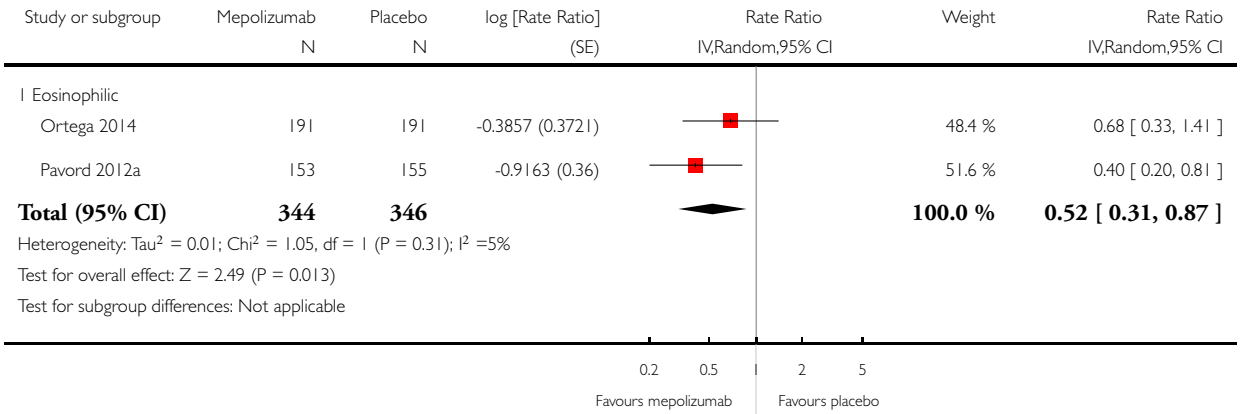
Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Mepolizumab (IV) versus placebo, Outcome 2 Rate of exacerbations requiring emergency department treatment or admission.

Review: Anti-IL5 therapies for asthma

Comparison: 2 Mepolizumab (IV) versus placebo

Outcome: 2 Rate of exacerbations requiring emergency department treatment or admission

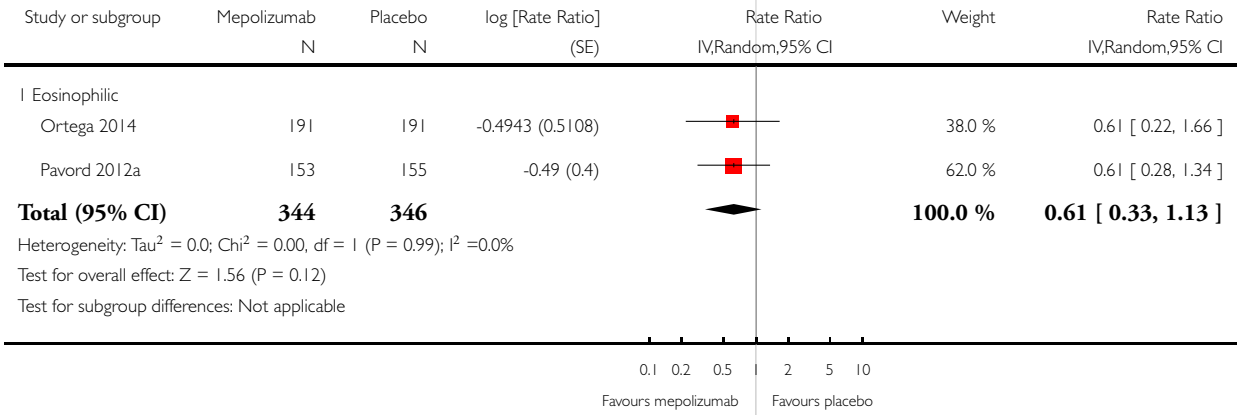


Analysis 2.3. Comparison 2 Mepolizumab (IV) versus placebo, Outcome 3 Rate of exacerbations requiring admission.

Review: Anti-IL5 therapies for asthma

Comparison: 2 Mepolizumab (IV) versus placebo

Outcome: 3 Rate of exacerbations requiring admission

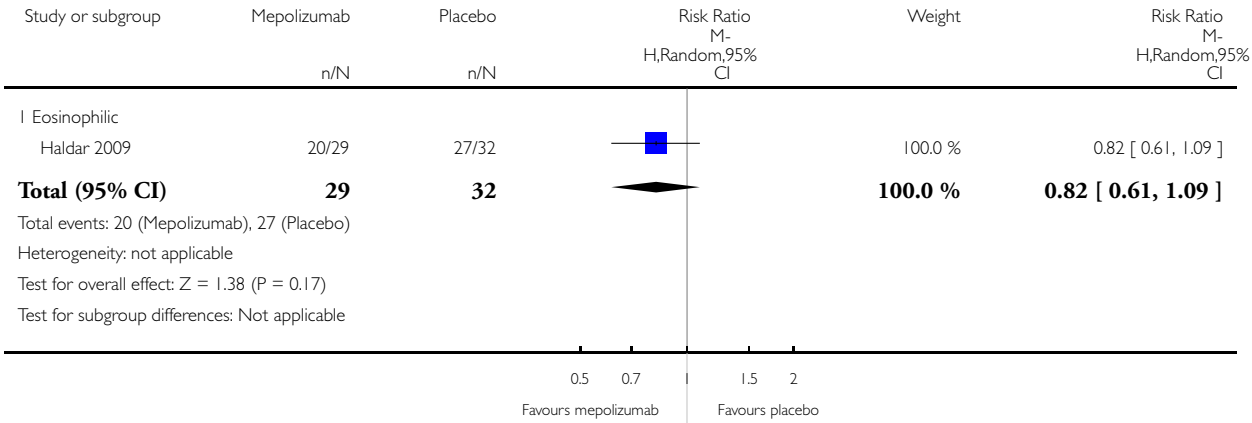


Analysis 2.4. Comparison 2 Mepolizumab (IV) versus placebo, Outcome 4 People with one or more exacerbations.

Review: Anti-IL5 therapies for asthma

Comparison: 2 Mepolizumab (IV) versus placebo

Outcome: 4 People with one or more exacerbations



Analysis 2.5. Comparison 2 Mepolizumab (IV) versus placebo, Outcome 5 Health-related quality of life (AQLQ).

Review: Anti-IL5 therapies for asthma

Comparison: 2 Mepolizumab (IV) versus placebo

Outcome: 5 Health-related quality of life (AQLQ)

Study or subgroup	Mepolizumab N	Placebo N	Mean Difference (SE)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Eosinophilic						
Haldar 2009	29	32	0.35 (0.14)		46.8 %	0.35 [0.08, 0.62]
Pavord 2012a	153	155	0.08 (0.1225)		53.2 %	0.08 [-0.16, 0.32]
Total (95% CI)	**182**	**187**			**100.0 %**	**0.21 [-0.06, 0.47]**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 2.11$, df = 1 (P = 0.15); $I^2 = 53\%$

Test for overall effect: Z = 1.53 (P = 0.13)

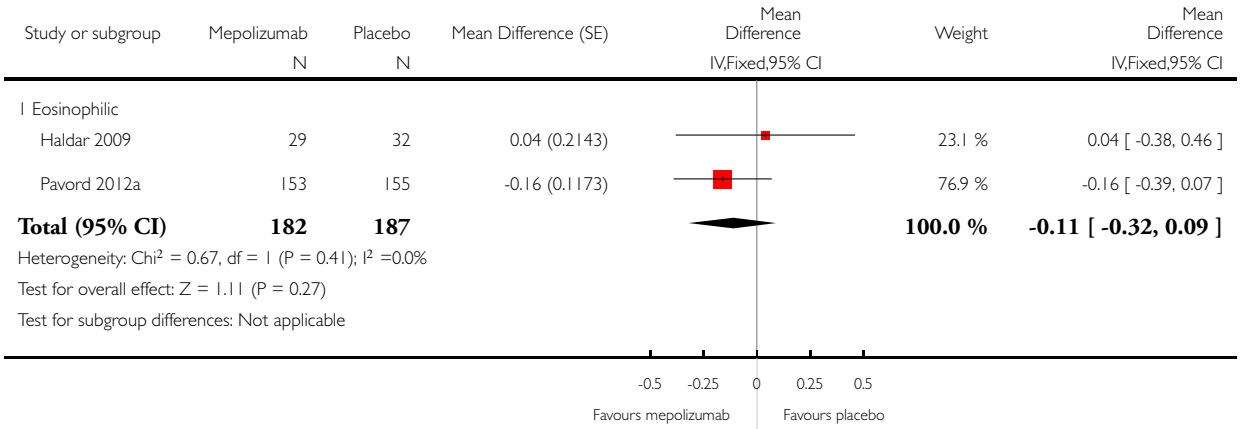
Test for subgroup differences: Not applicable

Analysis 2.6. Comparison 2 Mepolizumab (IV) versus placebo, Outcome 6 Health-related quality of life (ACQ).

Review: Anti-IL5 therapies for asthma

Comparison: 2 Mepolizumab (IV) versus placebo

Outcome: 6 Health-related quality of life (ACQ)

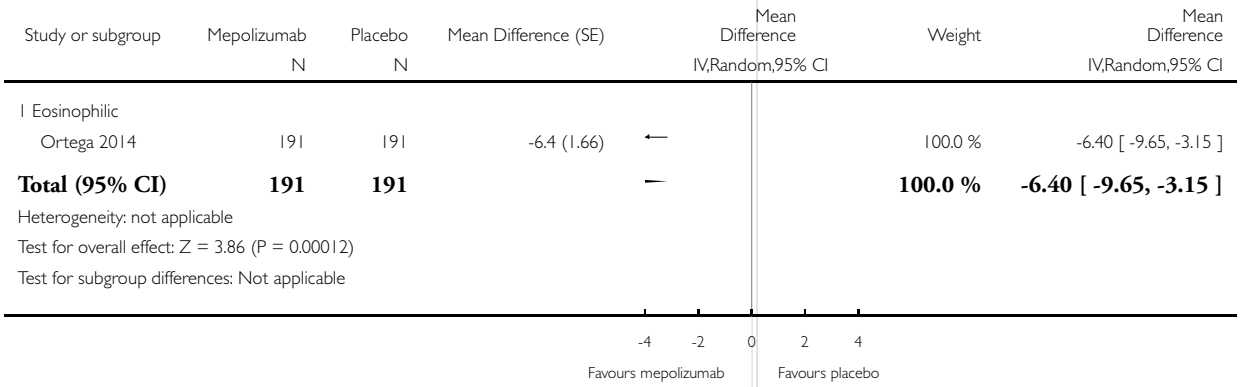


Analysis 2.7. Comparison 2 Mepolizumab (IV) versus placebo, Outcome 7 Health-related quality of life (SGRQ).

Review: Anti-IL5 therapies for asthma

Comparison: 2 Mepolizumab (IV) versus placebo

Outcome: 7 Health-related quality of life (SGRQ)

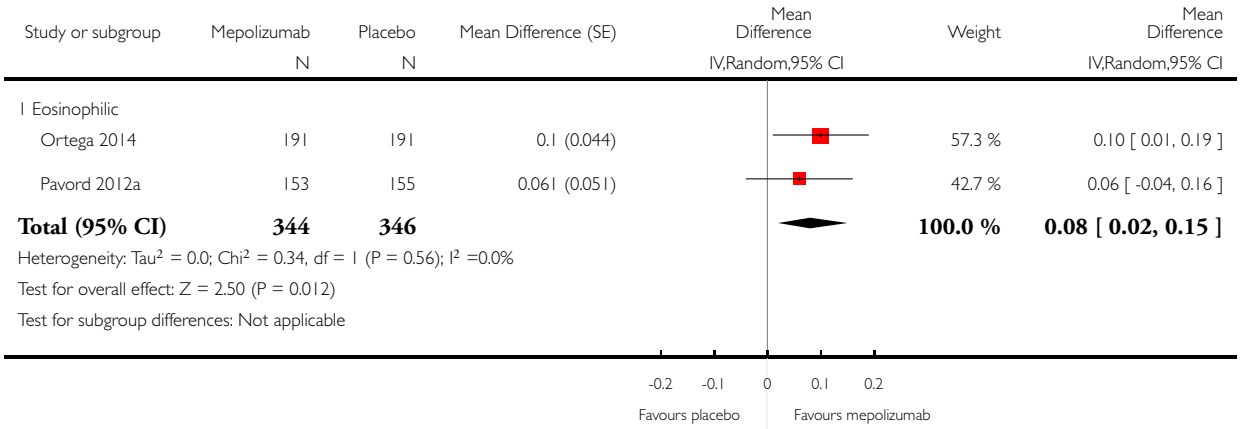


Analysis 2.8. Comparison 2 Mepolizumab (IV) versus placebo, Outcome 8 Pre-bronchodilator FEV1 (litres).

Review: Anti-IL5 therapies for asthma

Comparison: 2 Mepolizumab (IV) versus placebo

Outcome: 8 Pre-bronchodilator FEV_1 (litres)



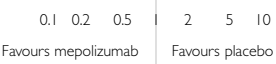
Analysis 2.9. Comparison 2 Mepolizumab (IV) versus placebo, Outcome 9 Serious adverse events.

Review: Anti-IL5 therapies for asthma

Comparison: 2 Mepolizumab (IV) versus placebo

Outcome: 9 Serious adverse events

Study or subgroup	Mepolizumab n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Eosinophilic					
Haldar 2009	3/29	11/32		14.2 %	0.30 [0.09, 0.97]
Ortega 2014	14/191	27/191		39.6 %	0.52 [0.28, 0.96]
Pavord 2012a	20/153	25/155		46.2 %	0.81 [0.47, 1.40]
Total (95% CI)	**373**	**378**		**100.0 %**	**0.59 [0.37, 0.94]**
Total events: 37 (Mepolizumab), 63 (Placebo)					
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 2.72$, df = 2 (P = 0.26); $I^2 = 27\%$					
Test for overall effect: Z = 2.20 (P = 0.028)					
Test for subgroup differences: Not applicable					

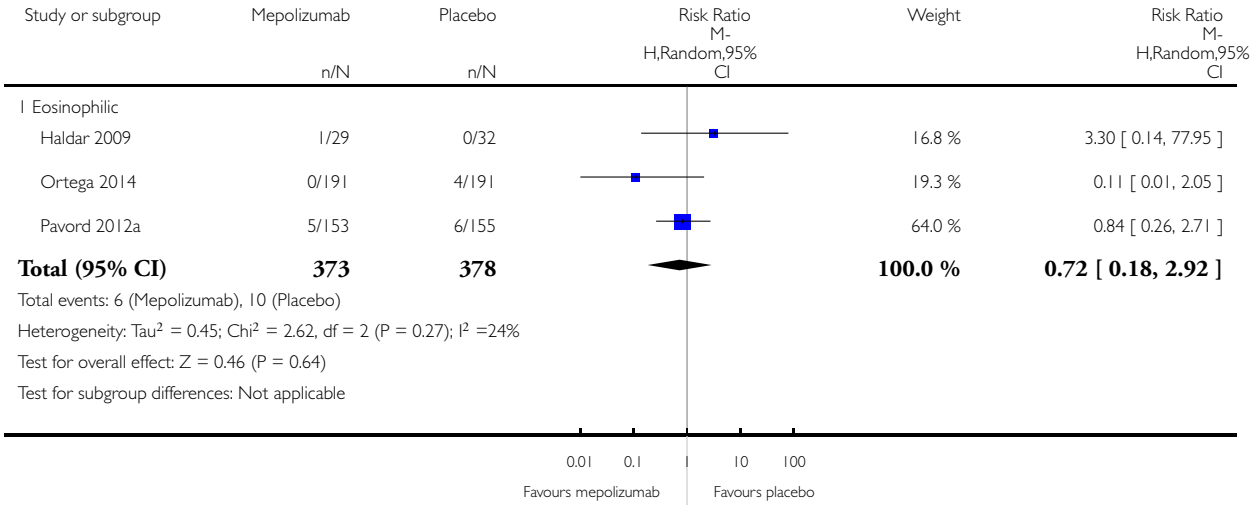


Analysis 2.10. Comparison 2 Mepolizumab (IV) versus placebo, Outcome 10 Adverse events leading to discontinuation.

Review: Anti-IL5 therapies for asthma

Comparison: 2 Mepolizumab (IV) versus placebo

Outcome: 10 Adverse events leading to discontinuation

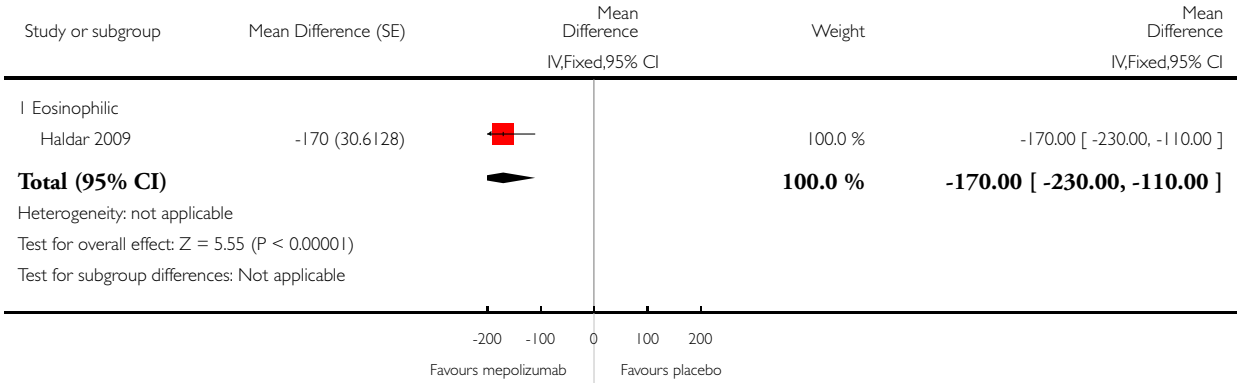


Analysis 2.11. Comparison 2 Mepolizumab (IV) versus placebo, Outcome 11 Serum eosinophil level (cells/microlitre).

Review: Anti-IL5 therapies for asthma

Comparison: 2 Mepolizumab (IV) versus placebo

Outcome: 11 Serum eosinophil level (cells/microlitre)

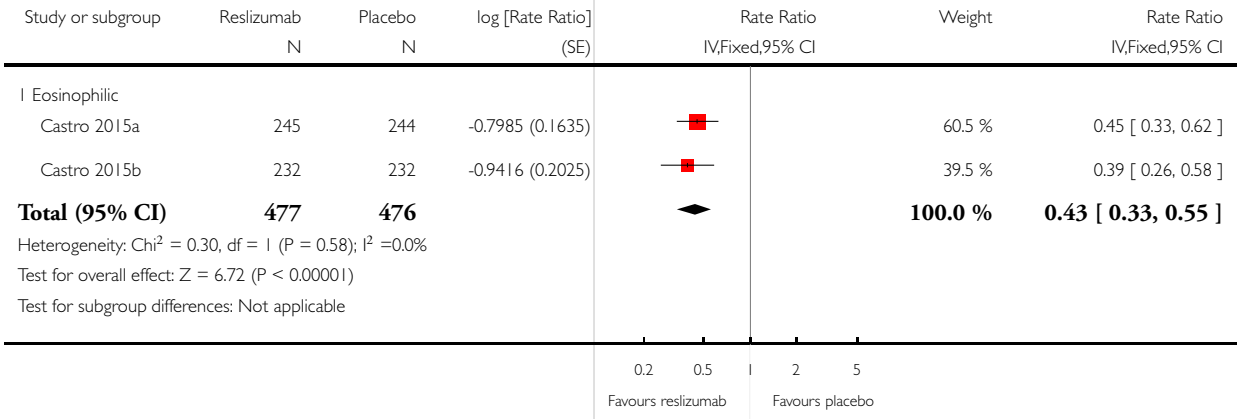


Analysis 3.1. Comparison 3 Reslizumab (IV) versus placebo, Outcome 1 Rate of exacerbations requiring systemic corticosteroids.

Review: Anti-IL5 therapies for asthma

Comparison: 3 Reslizumab (IV) versus placebo

Outcome: 1 Rate of exacerbations requiring systemic corticosteroids



Analysis 3.2. Comparison 3 Reslizumab (IV) versus placebo, Outcome 2 Rate of exacerbations requiring emergency department treatment or admission.

Review: Anti-IL5 therapies for asthma

Comparison: 3 Reslizumab (IV) versus placebo

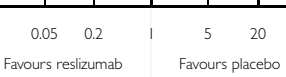
Outcome: 2 Rate of exacerbations requiring emergency department treatment or admission

Study or subgroup	Reslizumab N	Placebo N	log [Rate Ratio] (SE)	Rate Ratio IV,Fixed,95% CI	Weight	Rate Ratio IV,Fixed,95% CI
1 Eosinophilic						
Castro 2015a	245	244	-0.4155 (0.3689)		59.2 %	0.66 [0.32, 1.36]
Castro 2015b	232	232	-0.3711 (0.4448)		40.8 %	0.69 [0.29, 1.65]
Total (95% CI)	**477**	**476**			**100.0 %**	**0.67 [0.39, 1.17]**

Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.94); I^2 =0.0%

Test for overall effect: Z = 1.40 (P = 0.16)

Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3 Reslizumab (IV) versus placebo, Outcome 3 Health-related quality of life (AQLQ).

Review: Anti-IL5 therapies for asthma

Comparison: 3 Reslizumab (IV) versus placebo

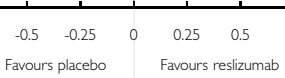
Outcome: 3 Health-related quality of life (AQLQ)

Study or subgroup	Reslizumab N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Eosinophilic						
Bjermer 2016	106	105	0.359 (0.1587)		12.3 %	0.36 [0.05, 0.67]
Castro 2015a	245	244	0.3 (0.0842)		43.8 %	0.30 [0.13, 0.47]
Castro 2015b	232	232	0.23 (0.0842)		43.8 %	0.23 [0.06, 0.40]
Total (95% CI)	**583**	**581**			**100.0 %**	**0.28 [0.17, 0.39]**

Heterogeneity: Chi^2 = 0.65, df = 2 (P = 0.72); I^2 =0.0%

Test for overall effect: Z = 4.96 (P < 0.00001)

Test for subgroup differences: Not applicable



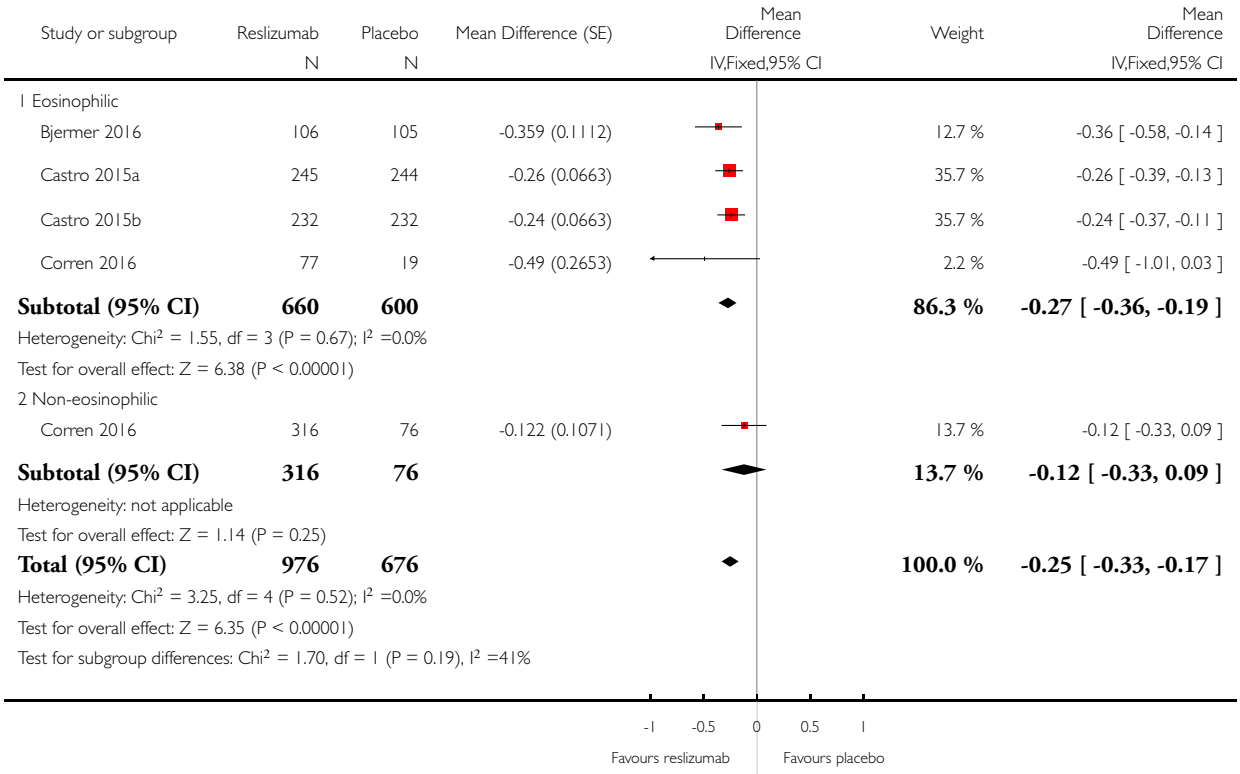
Analysis 3.4. Comparison 3 Reslizumab (IV) versus placebo, Outcome 4 Health-related quality of life (ACQ).

Review: Anti-IL5 therapies for asthma

Comparison: 3 Reslizumab (IV) versus placebo

Outcome: 4 Health-related quality of life (ACQ)

Study or subgroup	Reslizumab N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Eosinophilic						
Bjermer 2016	106	105	-0.359 (0.1112)		12.7 %	-0.36 [-0.58, -0.14]
Castro 2015a	245	244	-0.26 (0.0663)		35.7 %	-0.26 [-0.39, -0.13]
Castro 2015b	232	232	-0.24 (0.0663)		35.7 %	-0.24 [-0.37, -0.11]
Corren 2016	77	19	-0.49 (0.2653)		2.2 %	-0.49 [-1.01, 0.03]
Subtotal (95% CI)	**660**	**600**			**86.3 %**	**-0.27 [-0.36, -0.19]**
Heterogeneity: Chi^2 = 1.55, df = 3 (P = 0.67); I^2 =0.0%						
Test for overall effect: Z = 6.38 (P < 0.00001)						
2 Non-eosinophilic						
Corren 2016	316	76	-0.122 (0.1071)		13.7 %	-0.12 [-0.33, 0.09]
Subtotal (95% CI)	**316**	**76**			**13.7 %**	**-0.12 [-0.33, 0.09]**
Heterogeneity: not applicable						
Test for overall effect: Z = 1.14 (P = 0.25)						
Total (95% CI)	**976**	**676**			**100.0 %**	**-0.25 [-0.33, -0.17]**
Heterogeneity: Chi^2 = 3.25, df = 4 (P = 0.52); I^2 =0.0%						
Test for overall effect: Z = 6.35 (P < 0.00001)						
Test for subgroup differences: Chi^2 = 1.70, df = 1 (P = 0.19), I^2 =41%						



Analysis 3.5. Comparison 3 Reslizumab (IV) versus placebo, Outcome 5 Pre-bronchodilator FEV1 (litres).

Review: Anti-IL5 therapies for asthma

Comparison: 3 Reslizumab (IV) versus placebo

Outcome: 5 Pre-bronchodilator FEV_1 (litres)

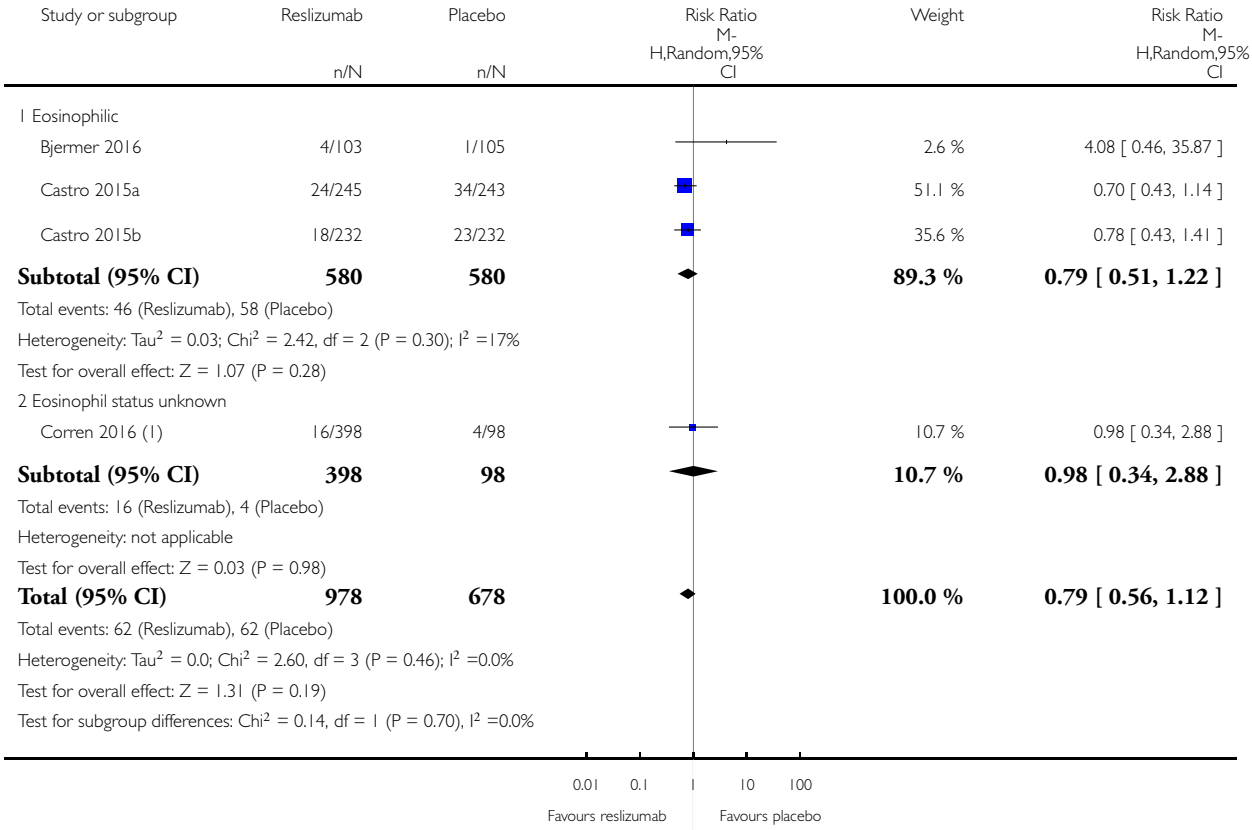
Study or subgroup	Reslizumab N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Eosinophilic						
Bjermer 2016	106	105	0.16 (0.0505)		14.2 %	0.16 [0.06, 0.26]
Castro 2015a	245	244	0.126 (0.0316)		36.3 %	0.13 [0.06, 0.19]
Castro 2015b	232	232	0.09 (0.0321)		35.1 %	0.09 [0.03, 0.15]
Corren 2016	77	19	0.27 (0.1337)		2.0 %	0.27 [0.01, 0.53]
Subtotal (95% CI)	**660**	**600**			**87.6 %**	**0.12 [0.08, 0.16]**
Heterogeneity: Chi^2 = 2.80, df = 3 (P = 0.42); I^2 =0.0%						
Test for overall effect: Z = 5.92 (P < 0.00001)						
2 Non-eosinophilic						
Corren 2016	316	76	0.033 (0.0541)		12.4 %	0.03 [-0.07, 0.14]
Subtotal (95% CI)	**316**	**76**			**12.4 %**	**0.03 [-0.07, 0.14]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						
Total (95% CI)	**976**	**676**			**100.0 %**	**0.11 [0.07, 0.15]**
Heterogeneity: Chi^2 = 5.08, df = 4 (P = 0.28); I^2 =21%						
Test for overall effect: Z = 5.76 (P < 0.00001)						
Test for subgroup differences: Chi^2 = 2.29, df = 1 (P = 0.13), I^2 =56%						

Analysis 3.6. Comparison 3 Reslizumab (IV) versus placebo, Outcome 6 Serious adverse events.

Review: Anti-IL5 therapies for asthma

Comparison: 3 Reslizumab (IV) versus placebo

Outcome: 6 Serious adverse events



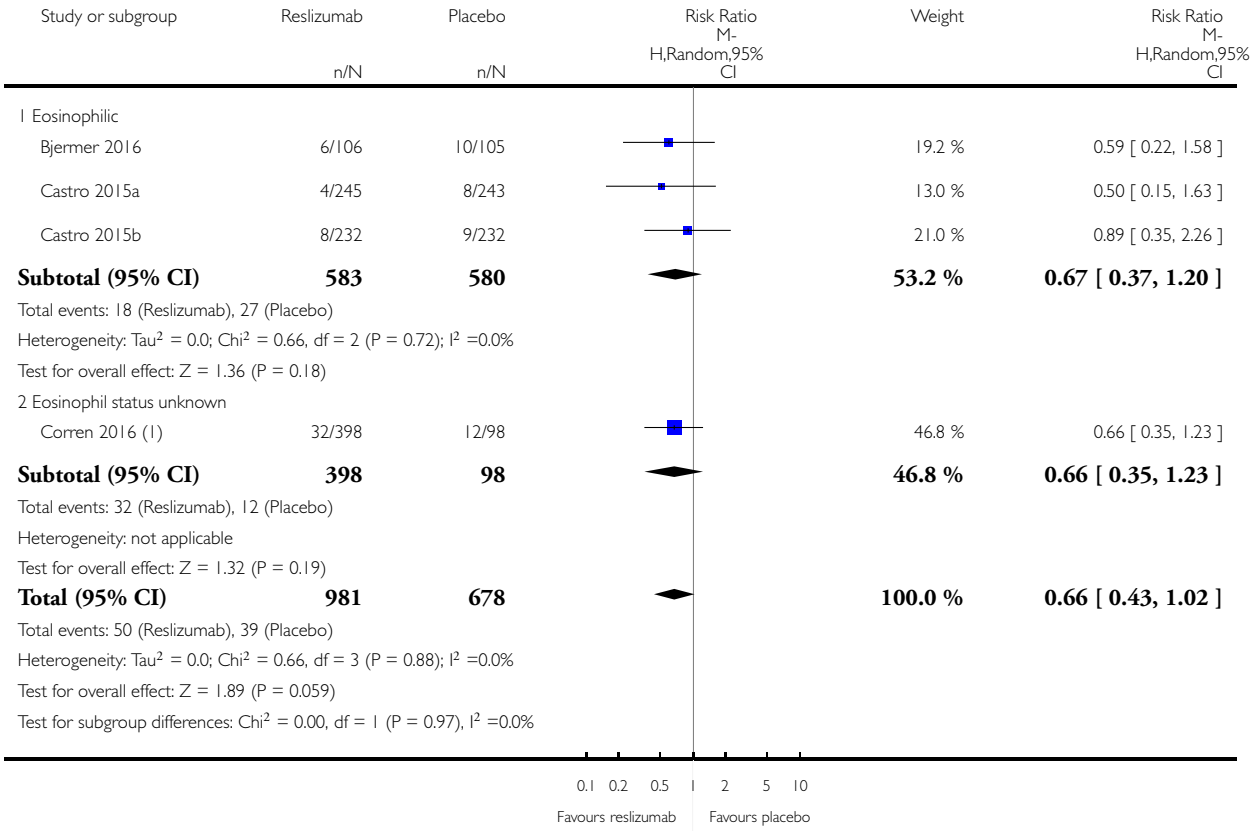
(1) Note: Corren 2016 does not separate out adverse events by eosinophilic / non-eosinophilic so pooled group shown

Analysis 3.7. Comparison 3 Reslizumab (IV) versus placebo, Outcome 7 Adverse events leading to discontinuation.

Review: Anti-IL5 therapies for asthma

Comparison: 3 Reslizumab (IV) versus placebo

Outcome: 7 Adverse events leading to discontinuation



(1) Note: Corren 2016 does not separate out adverse events by eosinophilic / non-eosinophilic so pooled group shown

Analysis 3.8. Comparison 3 Reslizumab (IV) versus placebo, Outcome 8 Serum eosinophil level (cells/microlitre).

Review: Anti-IL5 therapies for asthma

Comparison: 3 Reslizumab (IV) versus placebo

Outcome: 8 Serum eosinophil level (cells/microlitre)

Study or subgroup	Reslizumab N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Eosinophilic						
Bjermer 2016	106	105	-494 (24.4902)		22.0 %	-494.00 [-542.00, -446.00]
Castro 2015a	245	244	-455 (18.3677)		39.0 %	-455.00 [-491.00, -419.00]
Castro 2015b	232	232	-489 (18.3677)		39.0 %	-489.00 [-525.00, -453.00]
Corren 2016 (1)	395	97	-260 (0)			Not estimable
Total (95% CI)	**978**	**678**			**100.0 %**	**-476.83 [-499.32, -454.34]**

Heterogeneity: Chi² = 2.34, df = 2 (P = 0.31); I² =15%

Test for overall effect: Z = 41.56 (P < 0.00001)

Test for subgroup differences: Not applicable

(1) Note: Corren 2016 does not separate out eosinophil count by eosinophilic / non-eosinophilic so pooled group shown

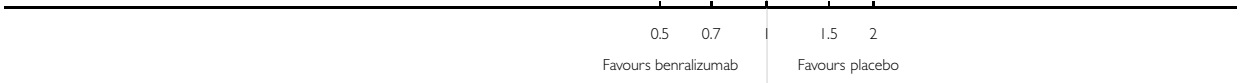
Analysis 4.1. Comparison 4 Benralizumab (SC) versus placebo, Outcome 1 Rate of exacerbations requiring systemic corticosteroids.

Review: Anti-IL5 therapies for asthma

Comparison: 4 Benralizumab (SC) versus placebo

Outcome: 1 Rate of exacerbations requiring systemic corticosteroids

Study or subgroup	Benralizumab N	Placebo N	log [Rate Ratio] (SE)	Rate Ratio IV,Fixed,95% CI	Weight	Rate Ratio IV,Fixed,95% CI
1 Eosinophilic						
Bleecker 2016 (1)	275	133	-0.7133 (0.1755)		12.3 %	0.49 [0.35, 0.69]
Bleecker 2016 (2)	275	134	-0.5978 (0.1685)		13.4 %	0.55 [0.40, 0.77]
Castro 2014a (3)	70	83	-0.5621 (0.1523)		16.4 %	0.57 [0.42, 0.77]
FitzGerald 2016 (4)	239	124	-0.3285 (0.1798)		11.8 %	0.72 [0.51, 1.02]
FitzGerald 2016 (5)	241	124	-0.4463 (0.1669)		13.6 %	0.64 [0.46, 0.89]
Subtotal (95% CI)	**1100**	**598**			**67.5 %**	**0.59 [0.51, 0.68]**
Heterogeneity: Chi^2 = 2.80, df = 4 (P = 0.59); I^2 =0.0%						
Test for overall effect: Z = 7.10 (P < 0.00001)						
2 Non-eosinophilic						
Bleecker 2016 (6)	131	70	-0.1863 (0.2132)		8.4 %	0.83 [0.55, 1.26]
Bleecker 2016 (7)	124	70	-0.3567 (0.2103)		8.6 %	0.70 [0.46, 1.06]
FitzGerald 2016 (8)	116	61	-0.4463 (0.2201)		7.8 %	0.64 [0.42, 0.99]
FitzGerald 2016 (9)	125	61	-0.5108 (0.2229)		7.7 %	0.60 [0.39, 0.93]
Subtotal (95% CI)	**496**	**262**			**32.5 %**	**0.69 [0.56, 0.85]**
Heterogeneity: Chi^2 = 1.27, df = 3 (P = 0.74); I^2 =0.0%						
Test for overall effect: Z = 3.43 (P = 0.00061)						
Total (95% CI)	**1596**	**860**			**100.0 %**	**0.62 [0.55, 0.70]**
Heterogeneity: Chi^2 = 5.58, df = 8 (P = 0.69); I^2 =0.0%						
Test for overall effect: Z = 7.79 (P < 0.00001)						
Test for subgroup differences: Chi^2 = 1.51, df = 1 (P = 0.22), I^2 =34%						



(1) 8 weekly treatment. Control (placebo) arm halved and SE inflated by 1.225.

(2) 4 weekly treatment. Control (placebo) arm halved and SE inflated by 1.225.

(3) 20 mg benralizumab treatment arm only (doses of 2 mg and 100 mg not considered clinically relevant). Rate reduction in original paper provided with 80% confidence interval. The total width of the 80% confidence interval has been divided by 2.56 to give SE.

(4) 8 weekly treatment. Control (placebo) arm halved and SE inflated by 1.225.

(5) 4 weekly treatment. Control (placebo) arm halved and SE inflated by 1.225.

(6) 8 weekly treatment. Control (placebo) arm halved and SE inflated by 1.225.

(7) 4 weekly treatment. Control (placebo) arm halved and SE inflated by 1.225.

(8) 4 weekly treatment. Control (placebo) arm halved and SE inflated by 1.225.

(9) 8 weekly treatment. Control (placebo) arm halved and SE inflated by 1.225.

Analysis 4.2. Comparison 4 Benralizumab (SC) versus placebo, Outcome 2 Rate of exacerbations requiring emergency department treatment or admission.

Review: Anti-IL5 therapies for asthma

Comparison: 4 Benralizumab (SC) versus placebo

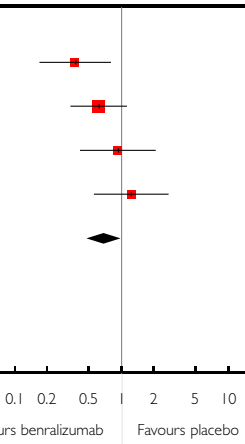
Outcome: 2 Rate of exacerbations requiring emergency department treatment or admission

Study or subgroup	Benralizumab N	Placebo N	log [Rate Ratio] (SE)	Rate Ratio IV,Fixed,95% CI	Weight	Rate Ratio IV,Fixed,95% CI
1 Eosinophilic						
Bleecker 2016 (1)	267	133	-0.9943 (0.3844)		23.4 %	0.37 [0.17, 0.79]
Bleecker 2016 (2)	275	134	-0.4943 (0.3124)		35.5 %	0.61 [0.33, 1.13]
FitzGerald 2016 (3)	241	124	-0.0726 (0.4134)		20.3 %	0.93 [0.41, 2.09]
FitzGerald 2016 (4)	239	124	0.207 (0.4082)		20.8 %	1.23 [0.55, 2.74]
Total (95% CI)	**1022**	**515**			**100.0 %**	**0.68 [0.47, 0.98]**

Heterogeneity: Chi^2 = 5.31, df = 3 (P = 0.15); I^2 =43%

Test for overall effect: Z = 2.04 (P = 0.041)

Test for subgroup differences: Not applicable



(1) 8 weekly treatment. Control (placebo) arm halved and SE inflated by 1.225.

(2) 4 weekly treatment. Control (placebo) arm halved and SE inflated by 1.225.

(3) 4 weekly treatment. Control (placebo) arm halved and SE inflated by 1.225.

(4) 8 weekly treatment. Control (placebo) arm halved and SE inflated by 1.225.

Analysis 4.3. Comparison 4 Benralizumab (SC) versus placebo, Outcome 3 Health-related quality of life (AQLQ mean difference).

Review: Anti-IL5 therapies for asthma

Comparison: 4 Benralizumab (SC) versus placebo

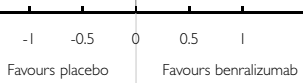
Outcome: 3 Health-related quality of life (AQLQ mean difference)

Study or subgroup	Benralizumab N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Eosinophilic						
Bleecker 2016 (1)	261	127	0.18 (0.119)		26.8 %	0.18 [-0.05, 0.41]
Bleecker 2016 (2)	252	127	0.3 (0.1249)		24.4 %	0.30 [0.06, 0.54]
Castro 2014a (3)	34	37	0.44 (0.293)		4.4 %	0.44 [-0.13, 1.01]
FitzGerald 2016 (4)	233	120	0.16 (0.1309)		22.2 %	0.16 [-0.10, 0.42]
FitzGerald 2016 (5)	230	120	0.24 (0.1308)		22.2 %	0.24 [-0.02, 0.50]
Total (95% CI)	**1010**	**531**			**100.0 %**	**0.23 [0.11, 0.35]**

Heterogeneity: Chi^2 = 1.30, df = 4 (P = 0.86); I^2 =0.0%

Test for overall effect: Z = 3.73 (P = 0.00020)

Test for subgroup differences: Not applicable



(1) 4 weekly treatment.

(2) 8 weekly treatment.

(3) 20mg benralizumab treatment arm only (doses of 2mg and 100mg not considered clinically relevant). Treatment difference in original paper provided with 80% confidence interval. The total width of the 80% confidence interval has been divided by 2.56 to give SE.

(4) 4 weekly treatment.

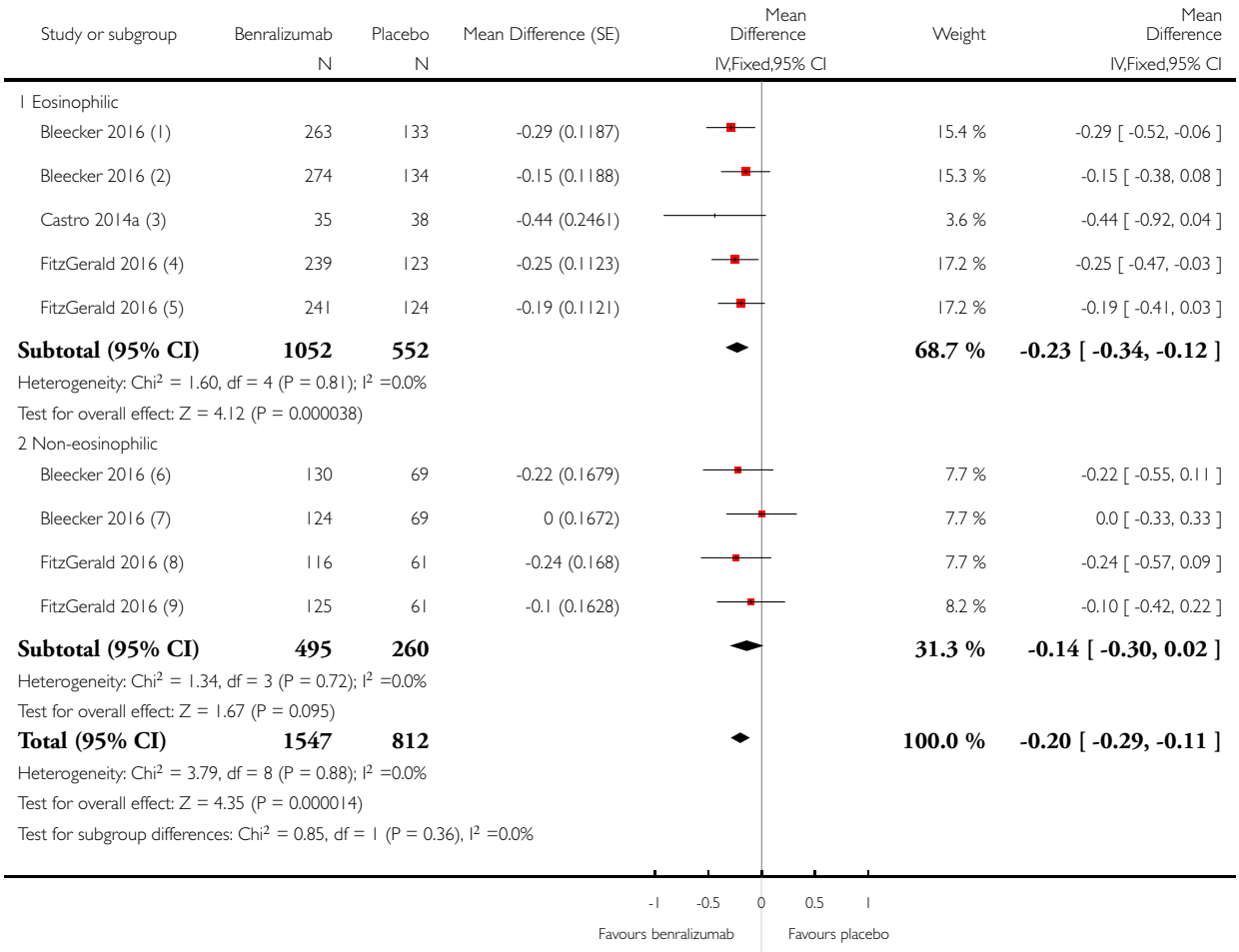
(5) 8 weekly treatment.

Analysis 4.4. Comparison 4 Benralizumab (SC) versus placebo, Outcome 4 Health-related quality of life (ACQ mean difference).

Review: Anti-IL5 therapies for asthma

Comparison: 4 Benralizumab (SC) versus placebo

Outcome: 4 Health-related quality of life (ACQ mean difference)



(1) 8 weekly treatment.

(2) 4 weekly treatment.

(3) 20mg benralizumab treatment arm only (doses of 2mg and 100mg not considered clinically relevant). Treatment difference in original paper provided with 80% confidence interval. The total width of the 80% confidence interval has been divided by 2.56 to give SE.

(4) 8 weekly treatment.

(5) 4 weekly treatment.

(6) 8 weekly treatment.

(7) 4 weekly treatment.

(8) 4 weekly treatment.

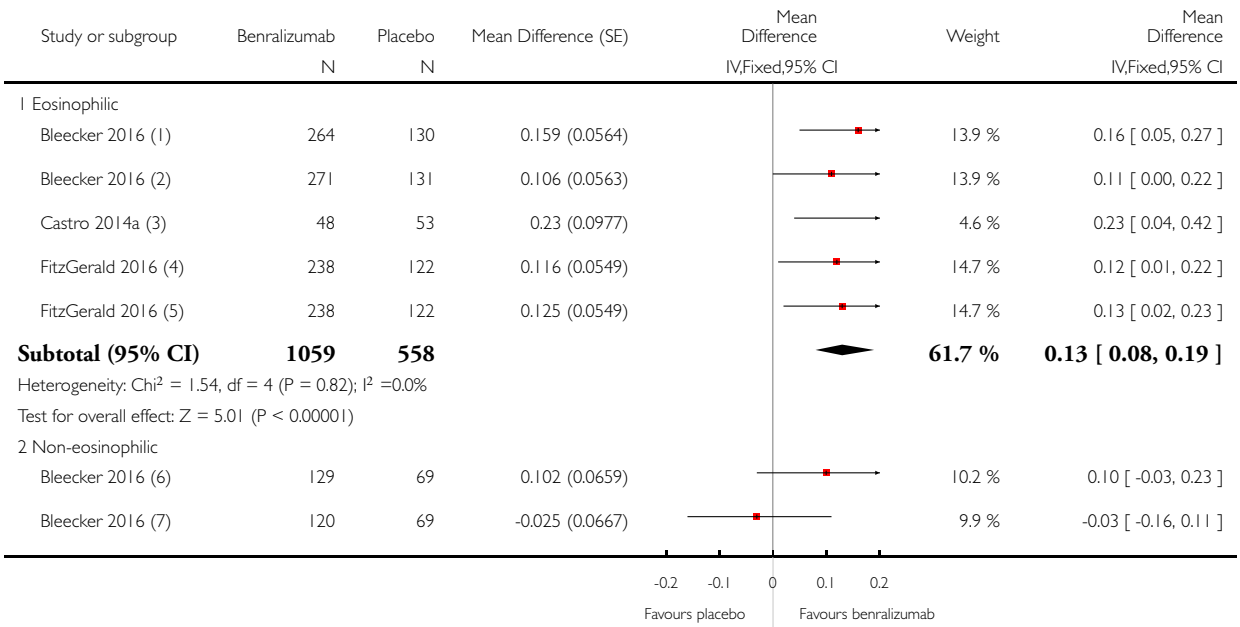
(9) 8 weekly treatment.

Analysis 4.5. Comparison 4 Benralizumab (SC) versus placebo, Outcome 5 Pre-bronchodilator FEV1 (litres).

Review: Anti-IL5 therapies for asthma

Comparison: 4 Benralizumab (SC) versus placebo

Outcome: 5 Pre-bronchodilator FEV_1 (litres)



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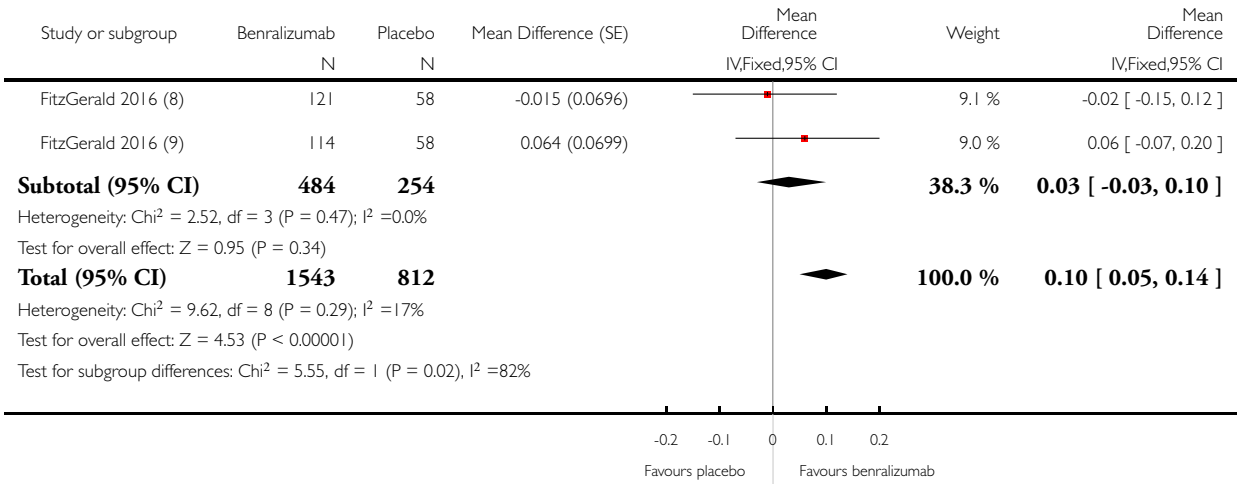


(1) 8 weekly treatment.

(2) 4 weekly treatment.

(3) 20mg benralizumab treatment arm only (doses of 2mg and 100mg not considered clinically relevant). Treatment difference in original paper provided with 80% confidence interval. The total width of the 80% confidence interval has been divided by 2.56 to give SE. FEV_1 not specified as pre- or post-bronchodilator but assumed to be pre.

(4) 8 weekly treatment.

(5) 4 weekly treatment.

(6) 8 weekly treatment.

(7) 4 weekly treatment.

(8) 8 weekly treatment.

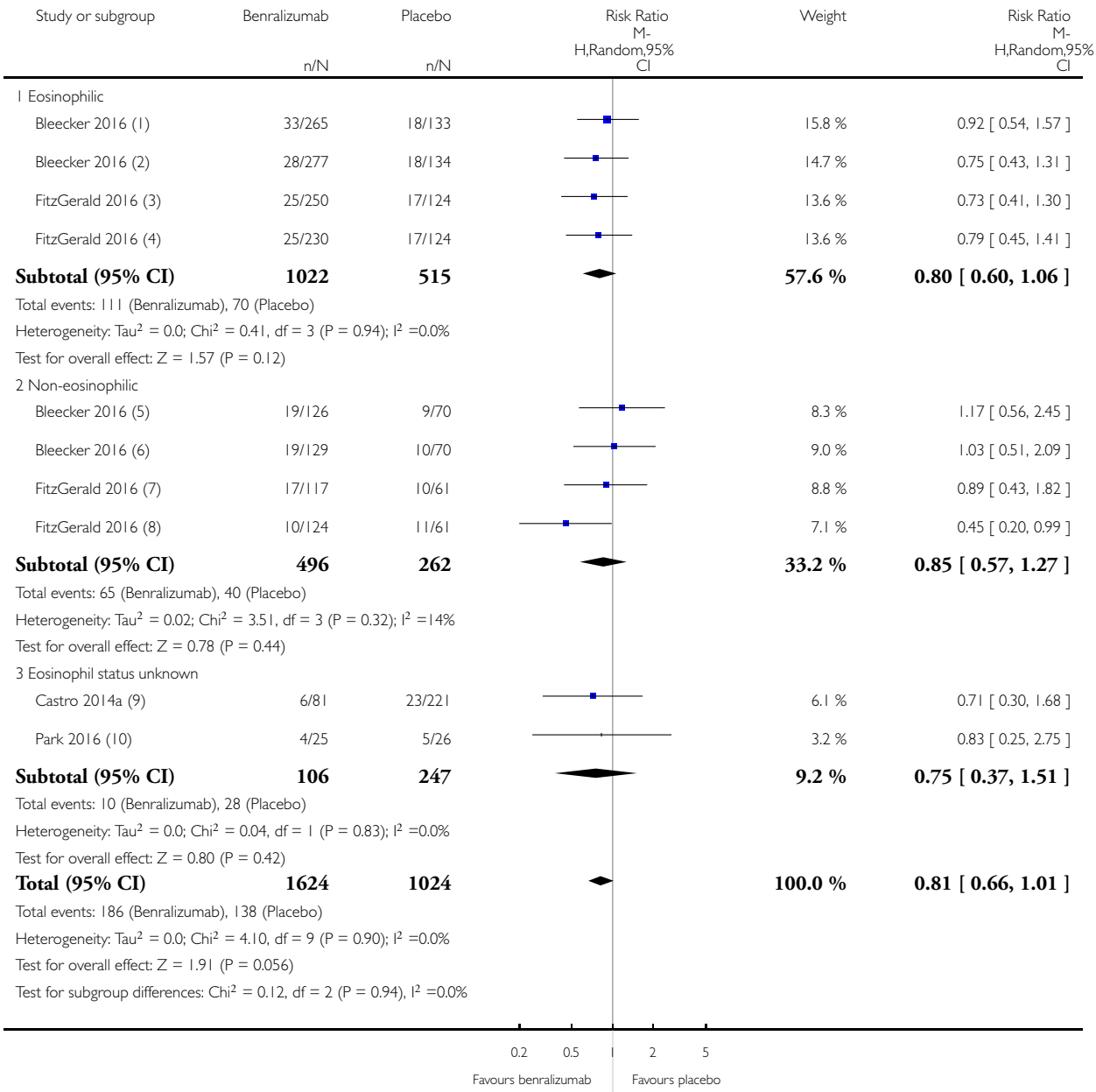
(9) 4 weekly treatment.

Analysis 4.6. Comparison 4 Benralizumab (SC) versus placebo, Outcome 6 Serious adverse events.

Review: Anti-IL5 therapies for asthma

Comparison: 4 Benralizumab (SC) versus placebo

Outcome: 6 Serious adverse events



(1) 8 weekly treatment.

(2) 4 weekly treatment.

(3) 4 weekly treatment.

(4) 8 weekly treatment.

(5) 4 weekly treatment.

(6) 8 weekly treatment.

(7) 4 weekly treatment.

(8) 8 weekly treatment.

(9) 20mg benralizumab treatment arm only (doses of 2mg and 100mg not considered clinically relevant).

(10) 20mg benralizumab treatment arm only (doses of 2mg and 100mg not considered clinically relevant).

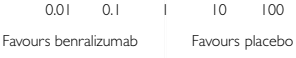
Analysis 4.7. Comparison 4 Benralizumab (SC) versus placebo, Outcome 7 Adverse events leading to discontinuation.

Review: Anti-IL5 therapies for asthma

Comparison: 4 Benralizumab (SC) versus placebo

Outcome: 7 Adverse events leading to discontinuation

Study or subgroup	Benralizumab n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Eosinophilic					
Bleecker 2016 (1)	6/265	1/133		12.7 %	3.01 [0.37, 24.76]
Bleecker 2016 (2)	3/277	1/134		11.1 %	1.45 [0.15, 13.82]
FitzGerald 2016 (3)	5/250	1/124		12.4 %	2.48 [0.29, 21.00]
FitzGerald 2016 (4)	6/230	0/124		6.9 %	7.03 [0.40, 123.85]
Subtotal (95% CI)	**1022**	**515**		**43.1 %**	**2.70 [0.86, 8.49]**
Total events: 20 (Benralizumab), 3 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.76$, df = 3 (P = 0.86); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.70 (P = 0.089)					
2 Non-eosinophilic					
Bleecker 2016 (5)	6/126	0/70		6.9 %	7.27 [0.42, 127.13]
Bleecker 2016 (6)	2/129	1/70		10.0 %	1.09 [0.10, 11.76]



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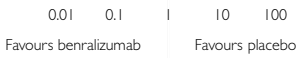
Study or subgroup	Benralizumab n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
FitzGerald 2016 (7)	4/124	1/61		12.0 %	1.97 [0.22, 17.23]
FitzGerald 2016 (8)	2/117	1/61		10.0 %	1.04 [0.10, 11.27]
Subtotal (95% CI)	**496**	**262**		**38.8 %**	**1.81 [0.54, 6.05]**
Total events: 14 (Benralizumab), 3 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.39$, df = 3 (P = 0.71); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.96 (P = 0.33)					
3 Eosinophil status unknown					
Castro 2014a (9)	2/81	3/221		18.0 %	1.82 [0.31, 10.69]
Subtotal (95% CI)	**81**	**221**		**18.0 %**	**1.82 [0.31, 10.69]**
Total events: 2 (Benralizumab), 3 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.66 (P = 0.51)					
Total (95% CI)	**1599**	**998**		**100.0 %**	**2.15 [1.02, 4.57]**
Total events: 36 (Benralizumab), 9 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.42$, df = 8 (P = 0.97); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.00 (P = 0.046)					
Test for subgroup differences: $Chi^2 = 0.26$, df = 2 (P = 0.88), $I^2 = 0.0\%$					



(1) 4 weekly treatment.

(2) 8 weekly treatment.

(3) 4 weekly treatment.

(4) 8 weekly treatment.

(5) 4 weekly treatment.

(6) 8 weekly treatment.

(7) 8 weekly treatment.

(8) 4 weekly treatment.

(9) 20mg benralizumab treatment arm only (doses of 2mg and 100mg not considered clinically relevant).

Analysis 4.8. Comparison 4 Benralizumab (SC) versus placebo, Outcome 8 Serum eosinophil level (% change from baseline).

Review: Anti-IL5 therapies for asthma

Comparison: 4 Benralizumab (SC) versus placebo

Outcome: 8 Serum eosinophil level (% change from baseline)

Study or subgroup	Benralizumab N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Eosinophilic						
Bleecker 2016 (1)	265	133	-99.6 (8.7538)		44.0 %	-99.60 [-116.76, -82.44]
Bleecker 2016 (2)	277	134	-102.2 (8.764)		43.9 %	-102.20 [-119.38, -85.02]
FitzGerald 2016 (3)	239	124	-106.8 (26.7247)		4.7 %	-106.80 [-159.18, -54.42]
FitzGerald 2016 (4)	241	124	-112.3 (26.681)		4.7 %	-112.30 [-164.59, -60.01]
Subtotal (95% CI)	**1022**	**515**			**97.4 %**	**-101.74 [-113.27, -90.21]**
Heterogeneity: Chi^2 = 0.26, df = 3 (P = 0.97); I^2 =0.0%						
Test for overall effect: Z = 17.29 (P < 0.00001)						
2 Non-eosinophilic						
Bleecker 2016 (5)	126	70	-206.1 (53.1424)		1.2 %	-206.10 [-310.26, -101.94]
Bleecker 2016 (6)	129	70	-210.5 (52.4414)		1.2 %	-210.50 [-313.28, -107.72]
FitzGerald 2016 (7)	125	61	-329.6 (192.1639)		0.1 %	-329.60 [-706.23, 47.03]
FitzGerald 2016 (8)	116	61	-327.8 (191.2175)		0.1 %	-327.80 [-702.58, 46.98]
Subtotal (95% CI)	**496**	**262**			**2.6 %**	**-216.81 [-287.35, -146.28]**
Heterogeneity: Chi^2 = 0.74, df = 3 (P = 0.86); I^2 =0.0%						
Test for overall effect: Z = 6.02 (P < 0.00001)						
Total (95% CI)	**1518**	**777**			**100.0 %**	**-104.74 [-116.12, -93.35]**
Heterogeneity: Chi^2 = 10.95, df = 7 (P = 0.14); I^2 =36%						
Test for overall effect: Z = 18.03 (P < 0.00001)						
Test for subgroup differences: Chi^2 = 9.96, df = 1 (P = 0.00), I^2 =90%						

(1) 8 weekly treatment.

(2) 4 weekly treatment.

(3) 8 weekly treatment.

(4) 4 weekly treatment.

(5) 8 weekly treatment.

(6) 4 weekly treatment.

(7) 8 weekly treatment.

(8) 4 weekly treatment.

ADDITIONAL TABLES

Table 1. Comparisons of study characteristics

Study (Number of Participants)	Design, follow-up (weeks)	Baseline asthma severity	Baseline treatment	Intervention (route)	Primary and secondary outcomes
Chupp 2017 (551)	RCT, double-blind, placebo-controlled (24)	Blood eosinophils ≥ 150 cells/μL at screening or ≥ 300 cells/μL in previous 12 months; and ≥ 2 exacerbations in previous 12 months; and FEV_1 < 80%	High-dose ICS for ≥ 12 months; + additional controller for ≥ 3 months; ± maintenance OCS	Mepolizumab 100 mg (SC) or placebo every 4 weeks for 24 weeks (last dose at 20 weeks)	- SGRQ - Mean change from baseline pre-bronchodilator FEV_1 - Proportion of SGRQ total score responders at week 24 - Mean change from baseline in ACQ-5
Haldar 2009 (61)	RCT, double-blind, placebo-controlled, parallel-group (50)	≥ 3% sputum eosinophils; and ≥ 2 exacerbations in previous 12 months	High-dose ICS	Mepolizumab 75 (IV) or matched placebo (150 mL of 0.9% saline) at monthly intervals for 1 y	- Severe exacerbations per person - Change in AQLQ - post-bronchodilator FEV_1 - Airway hyperresponsiveness - Blood/sputum eosinophil counts
Ortega 2014 (576)	RCT, double-blind, double-dummy, phase 3 (32)	Blood eosinophils ≥ 150 cells/μL at screening or ≥ 300 cells/μL in previous 12 months; and ≥ 2 exacerbations in previous 12 months; and FEV_1 < 80%	High-dose ICS for ≥ 12 months; + additional controller for ≥ 3 months; ± maintenance OCS	Mepolizumab 75 mg (IV) or 100 mg (SC) or placebo every 4 weeks for 32 weeks	- Exacerbations per y - Mean change from baseline pre-bronchodilator FEV_1 - Mean change from baseline SGRQ total score
Pavord 2012a (621)	Multicentre, double-blind, placebo-controlled (52)	≥ 3% sputum eosinophils or blood eosinophil ≥ 300 cells/μL; and ≥ 2 exacerbations in previous 12 months	High-dose ICS (i.e. ≥ 880 μg/d FP or equivalent daily); + additional controller; ± maintenance OCS	Mepolizumab 75 mg, 250 mg or 750 mg (IV) or placebo every 4 weeks for 13 doses	- Time to first clinically significant exacerbation - Frequency of exacerbations requiring hospitalisation - Time to first exacerbation requiring hospitalisation or ED visit - Mean change from baseline pre-bron-

Table 1. Comparisons of study characteristics (*Continued*)

					chodilator FEV_1 - Mean change from baseline post-bronchodilator FEV_1 - Mean change from baseline ACQ
Bjermer 2016 (315)	RCT, double-blind, placebo-controlled, parallel-group, fixed-dosage, multicentre phase 3 (16)	Blood eosinophils ≥ 400 cells/μL during 2-4 weeks screening period; and ACQ-7 score ≥ 1.5	Medium-dose ICS; maintenance OCS not allowed	Reslizumab 0.3 mg/kg or 3 mg/kg (IV) or placebo every 4 weeks for 4 doses	- Pre-bronchodilator FEV_1, FVC, FEF_{25-75} - ACQ, ACQ-6, ACQ-5 - ASUI - AQLQ - Rescue inhaler use - Blood eosinophil levels
Castro 2015a (489) and Castro 2015b (464)	2 x duplicate RCT double-blind, placebo-controlled, parallel-group, multicentre, phase 3 (52)	Blood eosinophils ≥ 400 cells/μL during 2-4 week screening period; and ACQ-7 score ≥ 1.5	Medium-dose ICS (i.e. ≥ 440 μg/day FP or equivalent daily); ± additional controller or maintenance OCS	Reslizumab 3 mg/kg (IV) or matching placebo every 4 weeks for 13 doses (last dose week 48)	- Annual frequency of exacerbations - Change in FEV_1 from baseline over 16 weeks - ACQ-7 score - ASUI score - Rescue use of SABA - Blood eosinophil count - AQLQ total score at weeks 16, 32 and 52
Corren 2016 (496)	RCT double-blind, placebo-controlled, multicentre phase 3 (16)	ACQ-7 score ≥ 1.5 (no selection based on blood eosinophils)	Medium-dose ICS; maintenance OCS not allowed	Reslizumab 3 mg/kg (IV) or matching placebo every 4 weeks for 4 doses	- Change in FEV_1 from baseline - ACQ-7 score - Rescue (SABA) use within previous 3 days - FVC - Blood eosinophils
Bleecker 2016 (1204)	RCT double-blind, parallel-group, placebo-controlled multicentre (52)	≥ 2 exacerbations in the previous 12 months; and ACQ-6 score ≥ 1.5 at enrolment; and FEV_1 < 80% (if 12-17 years old, < 90%)	Adults (> 18 y) high-dose (≥ 500 μg/d FP or equivalent) ICS/LABA for ≥ 12 months Children (12-17 y) at least medium-	Benralizumab 30 mg (SC) or placebo either every 4 weeks or every 4 weeks for the first 3 doses then every 8 weeks or placebo for	- Annual exacerbation rate - Pre-bronchodilator FEV_1 - Total asthma symptom score - Time to first exac-

Table 1. Comparisons of study characteristics (*Continued*)

			dose (≥ 250 μg/day FP or equivalent) ICS/LABA	48 weeks	erbation - Annual rate of exacerbations requiring ED visit or hospital admission - Post-bronchodilator FEV_1 - ACQ-6 - AQLQ(S)+12 score
Castro 2014a (606)	RCT double-blind, placebo-controlled, multicentre dose-ranging (52)	2-6 exacerbations in the previous 12 months; and ACQ-6 score ≥ 1.5 at least twice during screening; and morning pre-bronchodilator FEV_1 40%-90%	Medium- to high-dose ICS in combination with LABA for ≥ 12 months	Benralizumab 2 mg, 20 mg or 100 mg (SC) or placebo every 4 weeks for the first 3 doses, then every 8 weeks (total 7 doses)	- Annual exacerbation rate - Change from baseline in FEV_1 - Mean ACQ-6 score - Overall symptom score - Mean AQLQ score
FitzGerald 2016 (1306)	RCT, double-blind, parallel-group, placebo-controlled multicentre (56)	≥ 2 exacerbations in the previous 12 months; and ACQ-6 score ≥ 1.5 at enrolment; and FEV_1 < 80%	Medium- (≥ 250 μg/d FP or equivalent) to high-dose (≥ 500 μg/d FP or equivalent) ICS/LABA for ≥ 12 months; high-dose ICS/LABA for ≥ 3 months	Benralizumab 30 mg (SC) or placebo either every 4 weeks or every 4 weeks for the first 3 doses then every 8 weeks or placebo	- Annual exacerbation rate for participants with blood eosinophils ≥ 300 cells/μL - Pre-bronchodilator FEV_1 - Total asthma symptom score - Time to first exacerbation - Annual rate of exacerbations requiring ED visit or hospital admission - Post-bronchodilator FEV_1 - ACQ-6 - AQLQ(S)+12 score
NCT01947946 2013 (13)	RCT double-blind, parallel-group, placebo-controlled multicentre (48)	Uncontrolled asthma taking medium-dose ICS plus LABA	Medium-dose ICS (>250ug and ≤500ug fluticasone dry powder formulation equivalents total daily dose) and	Benralizumab 30 mg (SC) or placebo either every 4 weeks or every 4 weeks for the first 3 doses then every 8 weeks or placebo	Asthma exacerbations over 48-week treatment period

Table 1. Comparisons of study characteristics (*Continued*)

			LABA for at least 3 month prior to first visit		
Park 2016 (103)	RCT double-blind, placebo-controlled, dose-ranging multi-centre (52)	2-6 exacerbations in the previous 12 months; and ACQ-6 score $\geq$ 1.5 at least twice during screening; and morning pre-bronchodilator FEV_1 40%-90%	Medium- to high-dose ICS in combination with LABA for $\geq$ 12 months	Benralizumab 2 mg, 20 mg or 100 mg (SC) or placebo every 4 weeks for the first 3 doses, then every 8 weeks (total 7 doses)	- Annual exacerbation rate - Lung function - ACQ-6 - FeNO - Blood eosinophil counts

ACQ: Asthma Control Questionnaire; **AQLQ**: Asthma Quality of Life Questionnaire; **ASUI**: Asthma Symptom Utility Index; **BDP**: beclomethasone dipropionate; **b**: day; **ECP**: eosinophil cationic protein; **ED**: emergency department; **FEF_{25-75}** : forced expiratory flow at 25% to 75% of FVC; **FeNO**: exhaled fraction of nitric oxide; **FEV_1** : Forced expiratory volume in 1 second; **FVC**: forced vital capacity; **FP**; fluticasone propionate; **ICS**; inhaled corticosteroid; **IV**: intravenous; **LABA**: long-acting $beta_2$ agonist**OCS**; oral corticosteroid; **PC_{20}** : histamine provocative concentration causing a 20% drop in FEV_1; **PEFR**: peak expiratory flow rate; **RCT**: randomised controlled trial; **SABA**: short-acting $beta_2$-agonists; **SC**: subcutaneous; **SGRQ**: St George's Respiratory Questionnaire; **y**: year

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Trials Register

Electronic searches: core databases

Database	Frequency of search
CENTRAL (the Cochrane Library)	Monthly
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly

(*Continued*)

AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the Register

Asthma search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.

16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Appendix 2. Search strategy for Cochrane Airways Trials Register

#1 AST:MISC1
#2 MeSH DESCRIPTOR Asthma Explode All
#3 asthma*:ti,ab
#4 #1 or #2 or #3
#5 MeSH DESCRIPTOR Antibodies, Monoclonal
#6 MeSH DESCRIPTOR Antibodies, Monoclonal, Humanized
#7 mepolizumab*
#8 SB24056 or SB-24056
#9 human* NEAR2 monoclonal* NEAR2 antibod*
#10 Bosatria or Nucala

#11 benralizumab*

#12 MEDI-563

#13 reslizumab*

#14 Cinquil or Cinqair

#15 CEP-38072

#16 "anti-interleukin 5"

#17 "anti-IL5"

#18 "anti-IL- 5"

#19 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18

#20 #4 AND #19
[In search line #1, MISC1 denotes the field where the reference has been coded for condition, in this case, asthma]

WHAT'S NEW

Last assessed as up-to-date: 29 March 2017.

Date	Event	Description
29 March 2017	New search has been performed	New literature search run
29 March 2017	New citation required and conclusions have changed	Scope broadened to encompass all Anti IL 5 therapies (reslizumab and benralizumab), rather than mepolizumab alone Review substantively redrafted Inclusion criteria applied more strictly resulting in exclusion of five (out of eight) mepolizumab studies Search updated leading to the inclusion of 10 new studies (one mepolizumab, four reslizumab and five benralizumab) Groups on doses of the trial medications that are not clinically relevant (e.g. 10 times higher or lower) have been excluded from the analysis Outcomes revised to focus on validated symptom scores, only a pre-bronchodilator measure of lung function, subgroups for eosinophilia or otherwise New author team

CONTRIBUTIONS OF AUTHORS

On the current version of this review, SM, HF and CP contributed to the rewriting of the Background and Methods sections. HF and CP independently selected trials for the review, HF and AW extracted the data, and HF entered the data into the RevMan 2014 file with cross-checking by Christopher Cates, the Cochrane Airways Group statistician. HF, SM and AW wrote the Results section, and HF, CP and SM co-authored the Discussion and Conclusions.

On the previous version (Powell 2015), SM, KD, NW and CP contributed to the writing of the protocol. NW and CP independently selected trials for the review, NW and LB extracted the data, and KD entered the data into the RevMan 2014 file with cross-checking by SM. KD and SM wrote the Results section, and NW, LB, CP, KD and SM coauthored the Discussion and Conclusions.

DECLARATIONS OF INTEREST

HF: none known.

AW: none known.

CP: none known.

LB: none known.US Food & Drug Administration

SM: none known.

SOURCES OF SUPPORT

Internal sources

- The authors declare that no such funding was received for this systematic review, Other.

External sources

- The authors declare that no such funding was received for this systematic review, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We initially planned to use a fixed-effect model for meta-analysis, but we agreed with a peer reviewer who suggested that a random-effects model was more appropriate in view of the substantial clinical heterogeneity between the trials.

The scope was broadened to encompass all anti-IL-5 therapies, that is, including reslizumab and benralizumab in addition to mepolizumab. Since the previous review, reslizumab has been licensed and benralizumab has entered phase 3 clinical trials with a licensing decision due from the US Food & Drug Administration and European Medicines Agency in 2017. These agents are all designed for the same patients and are therefore comparable.

Data from study arms on doses not deemed clinically relevant (e.g. 10 times more or less than the dose that has marketing approval) was excluded. Similarly studies where an additional intervention was the withdrawal of systemic corticosteroid were also excluded.

Outcomes were revised to focus on validated symptom scores (i.e. excluding non-validated scores, as these cannot be readily compared across studies) and only a pre-bronchodilator measure of lung function (as per American Thoracic Society/European Respiratory Society guidelines on standardising endpoints for clinical asthma trials). Subgroups were set as eosinophilic or otherwise, as these agents are primarily designed for eosinophilic asthma.

The original protocol stated that included trials should be a minimum of 16 weeks in duration; we have clarified that there should be a minimum of 16 weeks treatment.

Congenital heart disease had been listed as an exclusion criteria previously but this was removed as there was no reason why these conditions in particular should be excluded.

The number of studies identified was insufficient to conduct subgroup analyses or formally assess for reporting bias.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibodies, Monoclonal, Humanized [*administration & dosage]; Asthma [*therapy]; Disease Progression; Injections, Intravenous; Injections, Subcutaneous; Quality of Life

MeSH check words

Adolescent; Adult; Child; Humans