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Anti-IL-5 therapies for asthma (Review)

Farne HA, Wilson A, Milan S, Banchoff E, Yang F, Powell CVE

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[Intervention Review]

Anti-IL-5 therapies for asthma

Hugo A Farne[1], Amanda Wilson[2], Stephen Milan[3], Emma Banchoff[4], Freda Yang[5], Colin VE Powell[6]

[1]Imperial College, London, UK. [2]School of Nursing and Midwifery, University of Technology Sydney, Sydney, Australia. [3]Health Innovation Campus and Centre for Health Futures, Lancaster University, Lancaster, UK. [4]University of Michigan, Ann Arbor, USA. [5]Chelsea and Westminster Hospital NHS Foundation Trust, London, UK. [6]Department of Emergency Medicine, Sidra Medciine, Doha, Qatar

Contact: Hugo A Farne, hugo.farne@gmail.com.

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ABSTRACT

Background

This is the second update of previously published reviews in the Cochrane Library (2015, first update 2017). Interleukin-5 (IL-5) is the main cytokine involved in the proliferation, maturation, activation and survival of eosinophils, which cause airway inflammation and are a classic feature of asthma. Studies of monoclonal antibodies targeting IL-5 or its receptor (IL-5R) suggest they reduce asthma exacerbations, improve health-related quality of life (HRQoL) and lung function in appropriately selected patients, justifying their inclusion in the latest 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 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.

Search methods

We searched CENTRAL, MEDLINE, Embase, and two trials registers, manufacturers' websites, and reference lists of included studies. The most recent search was 7 February 2022.

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

Main results

Seventeen studies on about 7600 participants met the inclusion criteria. Six used mepolizumab, five used reslizumab, and six used benralizumab. One study using 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. One was in children aged 6 to 17 years; nine others included children over 12 years but did not report results by age group separately. We deemed the overall risk of bias to be low, with all studies contributing data of robust methodology. We considered the certainty of the evidence for all comparisons to be high overall using the GRADE scheme, except for intravenous (IV) mepolizumab and subcutaneous (SC) reslizumab because these are not currently licensed delivery routes.

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 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) score of 1.5 or more), except for reslizumab SC. The rate ratios for these effects were 0.45 (95% confidence interval (CI) 0.36 to 0.55; high-certainty evidence) for mepolizumab SC, 0.53 (95% CI 0.44 to 0.64; moderate-certainty evidence) for mepolizumab IV, 0.43 (95% CI 0.33 to 0.55; high-certainty evidence) for reslizumab IV, and 0.59 (95% CI 0.52 to 0.66; high-certainty evidence) for benralizumab SC. Non-eosinophilic participants treated with benralizumab also showed a significant reduction in exacerbation rates, an effect not seen with reslizumab IV, albeit in only one study. No data were available for non-eosinophilic participants treated with mepolizumab.

There were improvements in validated HRQoL scores with all anti-IL-5 agents in severe eosinophilic asthma. This met the minimum clinically important difference (MCID) for the broader St. George's Respiratory Questionnaire (SGRQ; 4-point change) for benralizumab only, but the improvement in the ACQ and Asthma Quality of Life Questionnaire (AQLQ), which focus on asthma symptoms, fell short of the MCID (0.5 point change for both ACQ and AQLQ) for all of the interventions. The evidence for an improvement in HRQoL scores in non-eosinophilic participants treated with benralizumab and reslizumab was weak, but the tests for subgroup difference were negative.

All anti-IL-5 treatments produced small improvements in mean pre-bronchodilator forced expiratory flow in one second (FEV_1) of between 0.08 L and 0.15 L in eosinophilic participants, which may not be sufficient to be detected by patients.

There were no excess serious adverse events with any anti-IL-5 treatment; in fact, there was a reduction in such events with benralizumab, likely arising from fewer asthma-related hospital admissions. 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 (42/2026 (2.1%) benralizumab versus 11/1227 (0.9%) placebo).

The implications for efficacy or adverse events are unclear.

Authors' conclusions

Overall this analysis supports the use of anti-IL-5 treatments as an adjunct to standard care in people with severe eosinophilic asthma and poor symptom 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. The studies did not report safety concerns for mepolizumab or reslizumab, or any 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), comparing anti-IL-5 treatments to each other and, in patients meeting relevant eligibility criteria, to other biological (monoclonal antibody) therapies. 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

Key messages

• The asthma medicines mepolizumab, reslizumab and benralizumab reduced asthma attacks in selected individuals with severe asthma (those with high numbers of an inflammatory cell called an eosinophil in their blood).

• There were small improvements in quality of life questionnaire scores and breathing tests, but these may be too small to be detected by patients.

Review question

We considered in this review whether taking the medicines mepolizumab, reslizumab or benralizumab in addition to standard treatment (such as inhaled steroids and combination inhalers) are better than a placebo (a dummy medicine) 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. It affects around 350 million people worldwide. Mepolizumab, reslizumab and benralizumab are 'anti-IL-5' treatments that may help to reduce asthma symptoms.

Study characteristics

Seventeen studies compared mepolizumab, reslizumab or benralizumab to a placebo in about 7600 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 (the numbers of a type of inflammatory cell called eosinophils), and unwanted effects.

Key results

We found that participants with severe asthma, who had high numbers of eosinophils in their 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 medicines can be added to standard treatment for people with severe asthma. 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 are confident that participants in the studies were randomly placed into different treatment groups, that neither they nor the study team were aware of the treatment they were receiving, and that the small number who did not complete the study did not affect the findings.

This plain language summary is up to date as of 7 February 2022.

SUMMARY OF FINDINGS

Summary of findings 1. Mepolizumab subcutaneous (SC) compared to placebo for asthma

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)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with mepolizumab (SC)				
Rate of clinically significant exacerbations requiring systemic corticosteroids Follow-up: range 24-52 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- 52 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: 0-6 (lower is better) Follow-up: range 24-52 weeks	The mean change in the placebo group ranged from −0.4 to −0.5 units[c]	The mean in the intervention group was 0.38 units fewer (0.50 fewer to 0.26 fewer)	-	1231 (3 RCTs)	⊕⊕⊕⊕ High	A change of ≥ 0.5 points is considered the MCID
Health-related quality of life (SGRQ) Scale from: 0-100 (lower is better) Follow-up: range 24-52 weeks	The mean change in the placebo group ranged from −7.9 to −9.0 units[c]	The mean change in the intervention group was 6.4 units fewer (8.9 fewer to 4.0 fewer)	-	1231 (3 RCTs)	⊕⊕⊕⊕ High	A change of ≥ 4 points is considered the MCID
Pre-bronchodilator FEV_1 Follow-up: range 24-52 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)[c]	The mean difference from placebo was a further 0.09 L (0.05 L to 0.14 L)	-	1231 (3 RCTs)	⊕⊕⊕⊕ High	

Serious adverse events Follow-up: range 24-52 weeks	95 per 1000	65 per 1000 (44 to 96)	Risk ratio 0.68 (0.46 to 1.01)	1231 (3 RCTs)	⊕⊕⊕⊕ High
Clinically significant adverse events leading to discontinuation Follow-up: range 24-52 weeks	15 per 1000	9 per 1000 (3 to 28)	Risk ratio 0.60 (0.19 to 1.85)	1231 (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; **CI:** confidence interval; **FEV_1**: forced expiratory volume in 1 second; **MCID**: minimum clinically important difference; **SC**: subcutaneous; **SGRQ**: St. George's Respiratory Questionnaire

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: 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 certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: 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: 1.21 and 1.74.
[b]Rounded mean of the rate in the placebo group of the two studies: 0.10 and 0.20.
[c]Mean change in placebo taken from Chupp 2017 and Ortega 2014. Moore 2022 did not provide the mean change for each group.

Summary of findings 2. Mepolizumab intravenous (IV) compared to placebo for asthma

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)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with mepolizumab (IV)				

Rate of clinically significant exacerbations requiring systemic corticosteroids Follow-up: range 32-52 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)	⊕⊕⊕⊕ High	
Rate of exacerbations requiring emergency department treatment or admission Follow-up: range 32-52 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)	⊕⊕⊕⊕ High	
Health-related quality of life (AQLQ) Scale from: 1-7 (higher is better) Follow-up: range 32-52 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)	-	369 (2 RCTs)	⊕⊕⊕⊕ High	A change of ≥ 0.5 points is considered the MCID
Health-related quality of life (ACQ) Scale from: 0-6 (lower is better) Follow-up: range 32-52 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)	⊕⊕⊕⊕ High	A change of ≥ 0.5 points is considered the MCID
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)	⊕⊕⊕⊕ High	
Serious adverse events Follow-up: range 32-52 weeks	167 per 1000	99 per 1000 (62 to 157)	Risk ratio 0.59 (0.37 to 0.94)	751 (3 RCTs)	⊕⊕⊕⊕ High	
Clinically significant adverse events leading to discontinuation Follow-up: range 32-52 weeks	26 per 1000	19 per 1000 (5 to 77)	Risk ratio 0.72 (0.18 to 2.92)	751 (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; **IV**: intravenous; **MCID**: minimum clinically significant difference; **MD**: mean difference

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: 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 certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: 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.

Summary of findings 3. Reslizumab intravenous (IV) compared to placebo for asthma

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)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with reslizumab (IV)				
Rate of clinically significant 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: 1-7 (higher is better) Follow-up: range 16-52 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)	-	1164 (3 RCTs)	⊕⊕⊕⊕ High	A change of ≥ 0.5 points is considered the MCID
Health-related quality of life (ACQ) Scale from: 0 to 6 (lower is better)	The mean change in the placebo group ranged	MD -0.25 lower (−0.33 lower to −0.17 lower)	-	1652 (4 RCTs)	⊕⊕⊕⊕ High	A change of ≥ 0.5 points is

Follow-up: range 16 weeks to 52 weeks	from −0.368 to −0.80 units					considered the MCID
Pre-bronchodilator FEV_1 (L) Follow-up: range 16-52 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 16-52 weeks	91 per 1000	72 per 1000 (51 to 102)	Risk ratio 0.79 (0.56 to 1.12)	1656 (4 RCTs)	⊕⊕⊕⊕ High	
Clinically significant adverse events leading to discontinuation Follow-up: range 16-52 weeks	58 per 1000	38 per 1000 (25 to 59)	Risk ratio 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; **IV**: intravenous **MCID**: minimum clinically significant difference; **MD**: mean difference

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: 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 certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Summary of findings 4. Reslizumab subcutaneous (SC) compared to placebo for asthma

Reslizumab (SC) compared with placebo for asthma

Patient or population: people with asthma

Settings: community

Intervention: reslizumab (SC)

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk for placebo	Risk with reslizumab (SC)				
Rate of clinically significant exacerbations requiring systemic corticosteroids Follow-up: 52 weeks	The mean rate in the placebo group was 0.79 events per participant per year	The mean rate in the intervention group was 0.2 fewer events per participant per year (0.38 fewer to 0.06 more)	Rate ratio 0.79 (0.56 to 1.11)	464 (1 RCT)	⊕⊕⊕⊕ High	
Rate of exacerbations requiring emergency department treatment or admission Follow-up: 52 weeks	The mean rate in the placebo group was 0.05 events per participant per year	The mean rate in the intervention group was 0.003 fewer events per participant per year (0.03 fewer to 0.05 more)	Rate ratio 0.94 (0.43 to 2.05)	464 (1 RCT)	⊕⊕⊕⊕ High	
Health-related quality of life (AQLQ) Scale from: 1-7 (higher is better) Follow-up: 52 weeks	The mean change in the placebo group was 1.06	MD 0.08 higher (-0.11 to 0.27)	-	464 (1 RCT)	⊕⊕⊕⊕ High	A change of ≥ 0.5 points is considered the MCID
Health-related quality of life (ACQ) Scale from: 0 to 6 (lower is better) Follow up: 52 weeks	The mean change in the placebo group was -1.14	MD -0.09 lower (-0.27 to 0.09)	-	464 (1 RCT)	⊕⊕⊕⊕ High	A change of ≥ 0.5 points is considered the MCID
Health-related quality of life (SGRQ) Scale from: 0 to 100 (lower is better) Follow up: 32 weeks	The mean change in the placebo group was -13.1 points	MD -3.3 lower (-6.02 to -0.58 lower)	-	464 (1 RCT)	⊕⊕⊕⊕ High	A change of ≥ 4 points is considered the MCID
Pre-bronchodilator FEV_1 (L) Follow-up: 52 weeks	The mean change in the placebo group was 0.23 L	MD 0.14 higher (0.06 to 0.22)	-	46 4 (1 RCT)	⊕⊕⊕⊕ High	
Serious adverse events Follow-up: 52 weeks	82 per 1000	80 per 1000 (41 to 151)	Risk ratio 0.97 (0.53 to 1.79)	464 (1 RCT)	⊕⊕⊕⊕ High	
Clinically significant adverse events leading to discontinuation Follow-up: 52 weeks	4 per 1000	19 per 1000 (2 to 166)	Risk ratio 4.87 (0.57 to 41.4)	464 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **MCID**: minimum clinically important difference; **SC**: subcutaneous; **SGRQ**: St. George's Respiratory Questionnaire

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: 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 certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded because of imprecision.

Summary of findings 5. Benralizumab subcutaneous (SC) compared to placebo for asthma

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)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with benralizumab (SC)				
Rate of clinically significant exacerbations requiring systemic corticosteroids Follow-up: range 24-56 weeks	The mean rate in the placebo group was 1.2 events per participant per year[a]	The mean rate in the intervention groups was 0.49 fewer events per participant per year (0.58 fewer to 0.41 fewer)	Rate ratio 0.59 (0.52 to 0.66)	3112 (4 RCTs)	⊕⊕⊕⊕ High	
Rate of exacerbations requiring emergency department treatment or admission Follow-up: range 48-56 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[c]	There is greater heterogeneity (I^2 = 43%) owing to inclusion of participants with less severe asthma

						in FitzGerald 2016 (a larger proportion who had only suffered 1 exacerbation the previous year, with correspondingly less potential for exacerbation)
Health-related quality of life (AQLQ) Scale from: 1-7 (higher is better) Follow-up: range 48-56 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)[d]	-	1541 (3 RCTs)	⊕⊕⊕⊕ High	A change of ≥ 0.5 points is considered the MCID
Health-related quality of life (ACQ) Scale from: 0-6 (lower is better) Follow up: range 24-56 weeks	The mean change in the placebo group ranged from −1.19 to −0.76 units	MD -0.26 lower (-0.34 lower to -0.17 lower)[e]	-	2791 (4 RCTs)	⊕⊕⊕⊕ High	A change of ≥ 0.5 points is considered the MCID
Pre-bronchodilator FEV_1 (L) Follow-up: range 24-56 weeks	The mean change in the placebo group ranged from -0.01 L to 0.239 L	MD 0.11 L higher (0.08 L higher to 0.15 L higher)	-	2786 (4 RCTs)	⊕⊕⊕⊕ High	
Serious adverse events Follow-up: range 24-56 weeks	130 per 1000	109 per 1000 (81 to 121)	Risk ratio 0.76 (0.62 to 0.93)	3304 (5 RCTs)	⊕⊕⊕⊕ High	
Clinically significant adverse events leading to discontinuation Follow-up: range 48-56 weeks	9 per 1000	18 per 1000 (9 to 36)	Risk ratio 2.04 (1.03 to 4.03)	3253 (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; **IV**: intravenous; **MCID**: minimum clinically significant difference; **MD**: mean difference

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: 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 certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: 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]One point deducted to reflect the level of heterogeneity on this outcome.

BACKGROUND

This is the second update of previously published reviews in the Cochrane Library (2015, updated 2017), 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 characterised by symptoms of breathlessness, chest tightness, wheeze, and cough. These symptoms are due to variable airflow obstruction secondary to bronchial hyperresponsiveness and airway inflammation. These symptoms are variably and intermittently present in the natural course of the disease, with periods of acutely increased symptomatology called exacerbations.

An estimated 350 million people worldwide currently suffer from asthma, with numbers increasing (GBD Study 2017). 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 now recognised as a heterogeneous 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 or allergic asthma is generally considered the most common phenotype, representing roughly half of all people with asthma (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 is particularly important because they have severe asthma 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 these so called 'type 2 cytokines' have subsequently been developed and investigated for their potential in treating 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 airway eosinophil counts, for example following reduction in the dose of maintenance ICS, cause 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 (trade name Fasenra; 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 reduce eosinophil counts in sputum, a sample from the lower airways, and blood in a dose-dependent manner (Wang 2009). Benralizumab binds IL-5Rα to inhibit its activation and induces eosinophil apoptosis by natural killer cells via antibody-dependent cell-mediated cytotoxicity (Kolbeck 2010). Benralizumab has also been shown to reduce sputum and blood eosinophil counts (Busse 2010).

All three have marketing licences 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 blood eosinophil count but who may have an isolated elevation of eosinophils in the airways (i.e. sputum eosinophilia) or have an eosinophilia that has been suppressed by 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 Initiative for Asthma (GINA)'s 2021 clinical consensus statement; GINA 2021), 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). Reslizumab and benralizumab were subsequently approved by the US Food & Drug Administration and European Medicines Agency, so the scope of the updated review was broadened to consider all anti-IL-5 therapies (Farne 2017). 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) reported as full text, 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.

We excluded individuals with respiratory comorbidities such as cystic fibrosis, and current smokers. We included former smokers provided they had a smoking history of less than 10 pack years.

Types of interventions

We included studies that compared anti-IL-5 therapy with placebo, in addition to current standard 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, specifically 75 mg intravenous (IV) or 100 mg subcutaneous (SC) injections of mepolizumab, 3 mg/kg IV or 110 mg reslizumab SC, and 20 to 30 mg benralizumab SC. These are the licensed doses except 75 mg IV mepolizumab (only licensed for SC administration), 110 mg reslizumab SC (only licensed for IV administration) and 20 mg SC benralizumab (30 mg is the licensed dose). However, for benralizumab, we included the 20 mg dose used in the three previous phase 2a dose-ranging studies (Castro 2015a; Castro 2015b; Park 2016).

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 and oral corticosteroids (ICS and OCS respectively), oral aminophyllines and macrolide antibiotics. We excluded studies that initiated a reduction in standard asthma management (e.g. oral corticosteroids) as part of the protocol, as we felt that they were too dissimilar for meaningful comparison.

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 studies to identify appropriate outcome measures (Reddel 2009). These recommend that clinical studies 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). The joint ATS/ERS statement notes that exacerbation frequency, symptoms and lung function 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 studies, 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 as a secondary outcome, a measure that is readily available in hospitals and clinics.

Primary outcomes

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

Secondary outcomes

1. Asthma exacerbation requiring emergency department treatment or 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, defined as those prompting treatment discontinuation
6. Blood eosinophil counts

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

Search methods for identification of studies

Electronic searches

We identified studies from the following databases and trials registries:

1. Cochrane Airways Register, through the Cochrane Register of Studies (CRS) all years to 7 February 2022;
2. Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 2) via the Cochrane Register of Studies, all years to 7 February 2022;
3. MEDLINE Ovid SP 1946 to 7 February 2022;
4. Embase Ovid SP 1974 to 7 February 2022;
5. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov), all years to 7 February 2022;
6. World Health Organization International Clinical Trials Registry Platform (trialsearch.who.int/), all years to 7 February 2022.

Database search strategies are detailed in Appendix 1. The search strategies were developed and executed by the Cochrane Airways Information Specialist in collaboration with the review authors. 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, March 2017, September 2020, March 2021 and February 2022.

Searching other resources

We checked the bibliographies of all primary studies and review articles for additional references. We searched relevant manufacturers' websites for study 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) on 27 September 2021.

Data collection and analysis

Selection of studies

For this review update we used Cochrane's Screen4Me workflow to help assess the search results. Screen4Me comprises three components: known assessments - a service that matches records in the search results to records that have already been screened in Cochrane Crowd and have been labelled as 'RCT' or as 'Not an RCT'; the RCT classifier — a machine-learning model that distinguishes RCTs from non-RCTs (Marshall 2018); and if appropriate, Cochrane Crowd - Cochrane's citizen science platform where 'the crowd' help to identify and describe health evidence (Noel-Storr 2020).

Following this initial assessment, two review authors (HF, CP) independently screened titles and abstracts of all the potential studies identified in the search using Covidence software to select potentially relevant studies that met the inclusion criteria. The same two review authors (HF, CP) independently screened the full text of these studies to identify studies for inclusion and exclusion, and they recorded reasons for excluding the ineligible studies. Any disagreement was resolved 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 clinical study so that each clinical 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), and a Characteristics of excluded studies table.

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 for the 2017 review; EB, FY for the additional studies in the 2022 review) extracted the following study characteristics from the 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 study and notable conflicts of interest of study authors

The same review authors independently extracted outcome data from included studies. We noted in the Characteristics of included studies if outcome data were not reported in a usable way. We planned to resolve disagreements by consensus or by involving a third author (SJM), but this was not necessary. We transferred the data into Review Manager 5 (RevMan 5; Review Manager 2020). 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 for the 2017 review; this role was fulfilled by one of the authors of the 2022 review (EB). Another review author (SJM) spot-checked study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two review authors (HF, AW for the 2017 review; EB, FY for the additional studies in the 2022 review) 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 following 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 description of the study

under Included studies. 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 from that for a patient-reported pain scale). Where information on risk of bias related to unpublished data or correspondence with a study author, we noted this under the study description in Included studies .

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 Differences between protocol and 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 study arms were reported in a single study (Bjermer 2016; Castro 2014a; Park 2016; Pavord 2012a), we only included the arms with doses likely to be used clinically, that is, 75 mg IV or 100 mg mepolizumab SC, 3 mg/kg IV or 110 mg reslizumab SC, 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 and reslizumab 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 study arms are reported in a single study, 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 (placebo) group to avoid double-counting.

Unit of analysis issues

We did not identify any cross-over studies or cluster-randomised studies for inclusion in this version of the review. If cross-over studies are identified in the future, we will seek data from a paired analysis from the study report or authors in order to appropriately include data in the review using the inverse variance method. If we identify cluster-randomised studies 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 study, then we will impute it from similar studies.

Dealing with missing data

We contacted study authors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when we identified a study only as an abstract). If this was not possible and we thought that the missing data would 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

We assessed statistical heterogeneity between studies 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 statistic 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 (Deeks 2022).

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 studies 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.

We combined data on outcomes at 6 months and 12 months. We also described data for other time points, where they were reported.

Subgroup analysis and investigation of heterogeneity

Provided we had included sufficient studies, 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 (e.g. 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 Review Manager 2020.

Sensitivity analysis

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

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

Summary of findings and assessment of the certainty of the evidence

We created summary of findings tables using the following outcomes.

1. Rate of clinically significant exacerbations requiring systemic corticosteroids
2. Rate of exacerbations requiring emergency department treatment or admission
3. HRQoL (as measured by a validated questionnaire: e.g. ACQ, AQLA, SGRQ)
4. Measures of lung function (e.g. FEV_1)
5. Serious adverse events
6. Clinically significant adverse events leading to discontinuation

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty 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 chapter 8 (Higgins 2011) and Chapter 14 (Schünemann 2022) of the *Cochrane Handbook for Systematic Reviews of Interventions* using GRADEpro GDT software. We have justified all decisions to downgrade or upgrade the certainty of the evidence using footnotes, and we have made comments to aid the reader's understanding of the review where necessary.

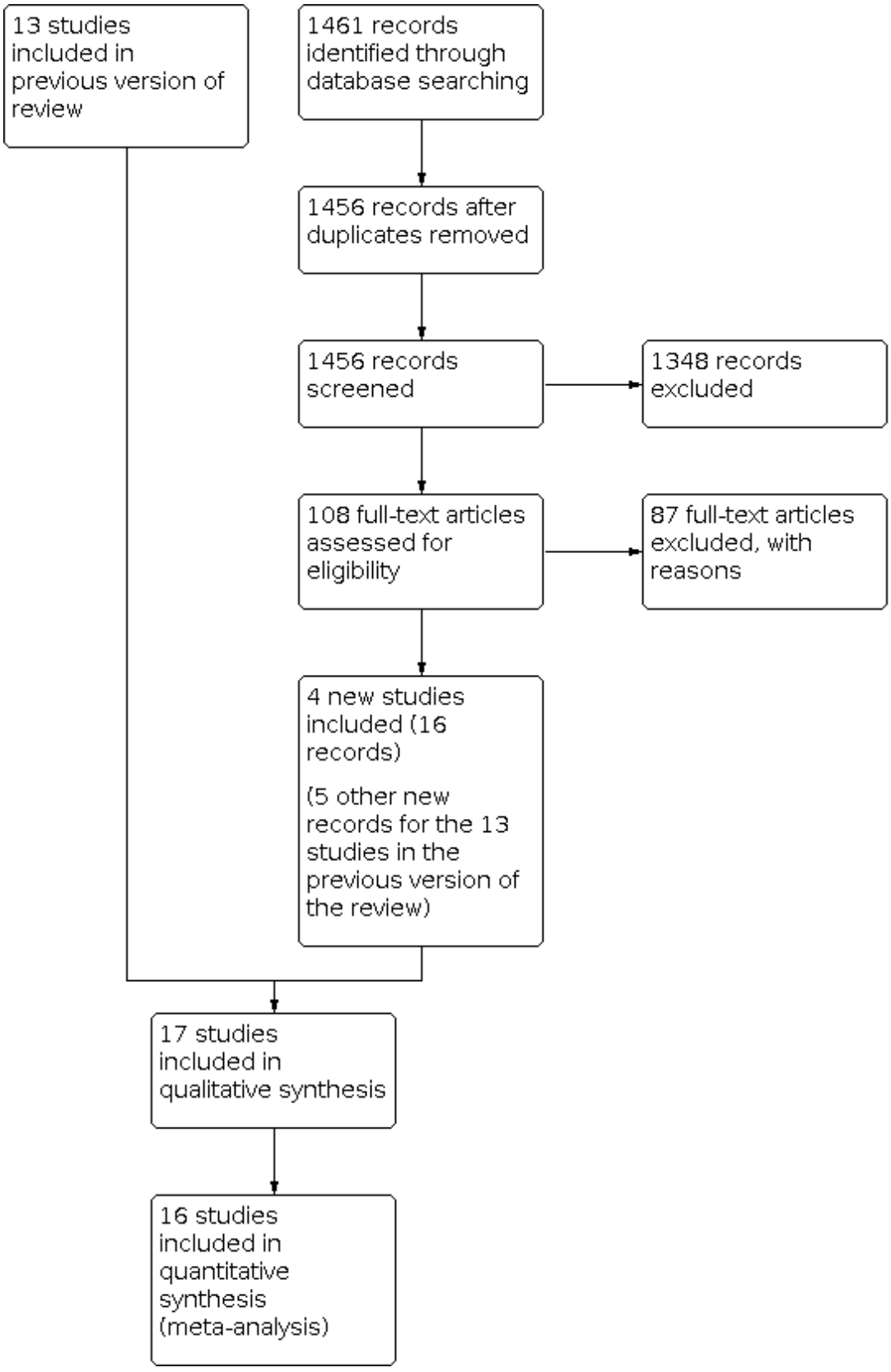
RESULTS

Description of studies

Results of the search

We identified 1461 records (Figure 1) in updated database searches, after duplicates were removed and following initial assessment by Cochrane Screen4Me (Noel-Storr 2020), for this review. The latest search was run on 7 February 2022.

Figure 1.



After removing additional duplicates, 1456 records remained.

Seventeen studies from 72 records met our inclusion criteria (see Characteristics of included studies).

There are no ongoing studies and no studies awaiting classification.

We excluded 289 records for various reasons (see Characteristics of excluded studies). In particular, we excluded records relating to the Bel 2014, Nair 2009 and Nair 2017a studies because their protocols included maintenance oral steroid dose reduction (as specified in Types of interventions).

Included studies

Table 1 compares the design, numbers, interventions and participant groups in the included studies. See Characteristics of included studies for details of each study.

Mepolizumab

We included six studies that compared mepolizumab versus placebo, involving a total of 2294 participants distributed as follows: Chupp 2017 n = 551; Haldar 2009 n = 61; Jackson 2022 n = 290; Moore 2022 n = 195; 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 Moore 2022 and Chupp 2017 (at a dose of 100 mg) and Jackson 2022 (at doses of 40 mg for 6 to 11 year-olds and 100 mg for 12 to 17 year-olds), 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 (NICE STA)).

The studies only included participants with eosinophilic asthma. Chupp 2017, Haldar 2009, Ortega 2014, and Pavord 2012a defined severe disease 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 blood 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). Jackson 2022 used a minimum cut-off of 150 cells or more per µL for inclusion in the study. Moore 2022 recruited severe eosinophilic patients who had earlier been enrolled in Pavord 2012a, Ortega 2014 or Bel 2014, which had the same blood eosinophil and disease severity criteria as Ortega 2014 but was excluded from the meta-analysis as the intervention included steroid reduction. The intervention group for Moore 2022 continued mepolizumab, while the control group switched to placebo.

Reslizumab

We included five studies that compared reslizumab versus placebo, involving a total of 2232 participants distributed as follows: Bernstein 2020 n = 468, Bjermer 2016 n = 315, Castro 2015a n = 489; Castro 2015b n = 464; and Corren 2016 n = 496. Reslizumab was administered subcutaneously in Bernstein 2020 at a dose of 110 mg every 4 weeks. Reslizumab was administered intravenously in the remaining four studies over a range of treatment periods at a dose of 3 mg/kg, with an additional arm at a dose of 0.3 mg/kg in Bjermer 2016, which we did not include as it is 10 times lower than the licensed dose of 3 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. Castro 2015a and Castro 2015b furthermore required a history of at least one exacerbation in the preceding 12 months, and Bernstein 2020 required at least two exacerbations during the same time period. Three studies of reslizumab (Bjermer 2016; Castro 2015a; Castro 2015b), required participants to have 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). Bernstein 2020 required a blood eosinophil count of 300 cells or more per µL at screening. Corren 2016 included participants with a range of eosinophil counts.

Benralizumab

We included six studies that compared benralizumab versus placebo, involving a total of 3888 participants distributed as follows: Bleecker 2016 n = 1204; Castro 2014a n = 606; FitzGerald 2016 n = 1306, Harrison 2020 n = 656, NCT01947946 n = 13 and Park 2016 n = 103. All studies administered benralizumab subcutaneously, 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 30 mg is the licensed dose and therefore we considered these the most clinically relevant. NCT01947946 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. Harrison 2020 required a blood eosinophil count of 300 cells or more per µL at screening, but also accepted levels of 150 if other requirements were met. The remaining five studies 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 287 studies from the review: 115 (40%) because anti-IL-5 therapy had not been included in the study; 66 (23%) were an aggregation of studies; 37 (13%) were not randomised placebo-controlled studies; 21 (7%) had a treatment period of less than 16 weeks; 20 (7%) were conducted on participants without a diagnosis of asthma; 15 (5%) were a post hoc analysis focusing on a specific subgroup (not specified in our protocol); 12 (4%) because the focus

was on steroid reduction and 1 study (< 1%) was terminated early because of recruitment issues. (See Characteristics of excluded studies).

Risk of bias in included studies

Details of our risk of bias assessments are available in the Characteristics of included studies, 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

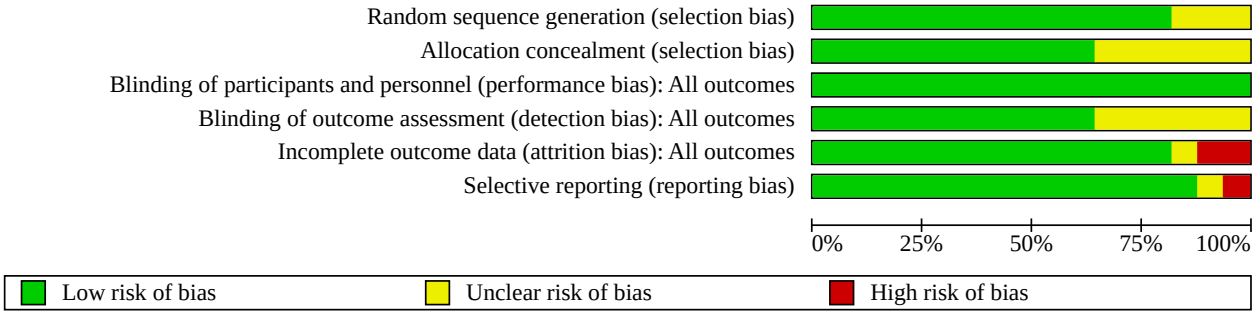
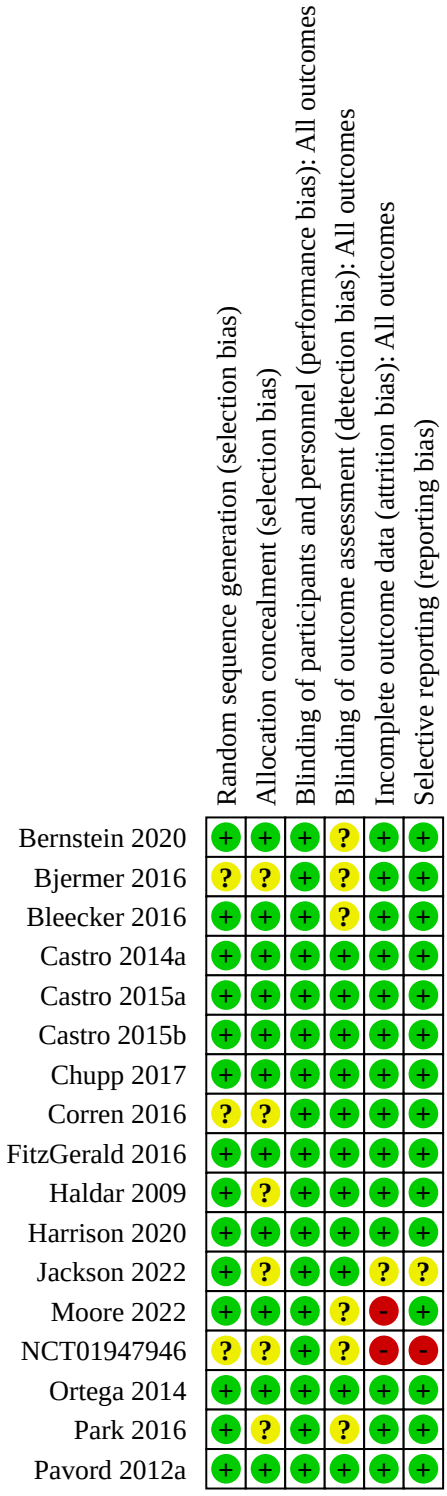


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



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), presented no details on either random sequence generation or allocation concealment and were therefore judged as being unclear risk of bias, whereas a further three (Haldar 2009; Jackson 2022; Park 2016), presented no details on allocation concealment so we judged them as unclear risk of bias for that domain (Figure 3).

Blinding

We determined that all studies were at low risk of performance bias, and 11 were at low risk of detection bias; the risk of detection bias was unclear for six studies (Bernstein 2020; Bjermer 2016; Bleecker 2016; Moore 2022; NCT01947946; Park 2016Figure 3).

Incomplete outcome data

We considered 14 studies to be at low risk of attrition bias, with similar dropout rates in the different study arms ranging from 5% to 20% for the placebo and 2% to 23% for the treatment groups (Figure 3). We rated one study high risk due to substantial attrition (Moore 2022). We also deemed NCT01947946 to be high risk because no participants completed the study. There was insufficient information on a further study that has only been published in abstract form thus far, so we judged that study as unclear risk of bias (Jackson 2022).

Selective reporting

We considered the risk of reporting bias to be low in 15 studies (Figure 3), unclear in one study with insufficient data (Jackson 2022), and high in the terminated study (NCT01947946).

Other potential sources of bias

We did not note any other potential sources of bias.

Effects of interventions

See: **Summary of findings 1** 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** Reslizumab subcutaneous (SC) compared to placebo for asthma; **Summary of findings 5** Benralizumab subcutaneous (SC) compared to placebo for asthma

Mepolizumab (SC) versus placebo

The data for this comparison come from four studies, with a combined total of 1521 participants with severe eosinophilic asthma (Chupp 2017; Jackson 2022; Moore 2022; Ortega 2014). Severe eosinophilia was defined as a blood eosinophil count of 300 cells or more per µL in the preceding 12 months or 150 cells or more per µL at screening, historically in the case of Moore 2022, which recruited participants already on mepolizumab from previous studies (Chupp 2017; Ortega 2014; Moore 2022). Jackson 2022 used a threshold of 150 eosinophils per µL. Our confidence in the results below is moderate to high, as the studies had a robust methodology. Chupp 2017 and Ortega 2014 were large studies, whilst the other two were more modest. Moore 2022 (n = 295) had substantial attrition from the blinded study arms (the study assessed cessation versus continuation of long-term mepolizumab treatment, randomising participants on mepolizumab to placebo or continued mepolizumab; n = 84/151 in the placebo arm and n = 45/144 in the mepolizumab arm were switched to open-label mepolizumab), but was otherwise methodologically sound. Jackson 2022 (n = 290) only had conference abstracts and a Clinicaltrials.gov registry entry available at the time of the search.

Primary outcomes

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

Mepolizumab SC resulted in a large reduction in clinically significant asthma exacerbations compared to placebo (rate ratio 0.45, 95% CI 0.36 to 0.55; 2 studies, 936 participants; high-certainty evidence; Analysis 1.1). Jackson 2022 also examined this outcome but the information published to date does not include participant numbers for each arm and thus we omitted this study from the meta-analysis. Like the other two studies, Jackson 2022 found a reduction in clinically significant exacerbations in the intervention group (rate ratio 0.73, 95% CI 0.56 to 0.95). Moore 2022 also examined clinically significant exacerbations but used a Cox proportional hazards model to estimate and compare the time to first exacerbation between the intervention and placebo groups. This study found that stopping mepolizumab SC treatment likely resulted in a shorter time to clinically significant exacerbations (hazard ratio 1.61, 95% CI 1.17 to 2.22).

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), that contributed to this outcome was reduced in those receiving mepolizumab SC (rate ratio 0.36, 95% CI 0.20 to 0.66; 2 studies, 936 participants; high-certainty evidence; Analysis 1.4); and the rate of exacerbations requiring admission in the same two studies was similarly reduced in mepolizumab SC participants versus those receiving placebo (rate ratio 0.31, 95% CI 0.13 to 0.73; 2 studies, 936 participants; high-certainty evidence; Analysis 1.3). Moore 2022 found no evidence for an effect of mepolizumab SC on time to exacerbations requiring emergency department treatment or admission (hazard ratio 1.33, 95% CI 0.50 to 3.54; 295 participants).

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

Three studies (Chupp 2017; Moore 2022; Ortega 2014), contributed HRQoL data measured by the ACQ instrument, indicating a moderate effect in favour of mepolizumab SC versus placebo (mean difference (MD) −0.38, 95% CI −0.50 to −0.26; 1231 participants; moderate-certainty evidence; Analysis 1.5), but this did not meet the minimum clinically important difference (MCID) of 0.5 points in the ACQ. However, mepolizumab SC reduced SGRQ scores by a clinically meaningful improvement in these studies (MD −6.37, 95% CI −8.76 to −3.98; I^2 = 36%; 3 studies, 1231 participants; high-certainty evidence; Analysis 1.6); 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). 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 treated with mepolizumab SC 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). This is consistent with a post-hoc responder analysis of the Ortega 2014 study, where 57% of the mepolizumab SC group achieved an improvement in the ACQ above the MCID compared to 45% of the placebo group (Llanos-Ackert 2017).

Moore 2022 reported time to a 0.5-point increase on the ACQ-5 instrument, finding that stopping mepolizumab SC likely increased the time to a score increase compared to placebo (hazard ratio 1.52, 95% CI 1.13 to 2.04; 295 participants).

Measures of lung function (e.g. FEV_1)

In a pooled analysis of three studies (Chupp 2017; Moore 2022; Ortega 2014), there was an increase of 90 mL in pre-bronchodilator FEV_1 in the mepolizumab SC group (MD 0.09, 95% CI 0.05 to 0.14; 3 studies, 1231 participants; high-certainty evidence; Analysis 1.7). 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 participants (Enright 2004)).

Serious adverse events

There was some slight evidence for fewer serious adverse events in participants receiving mepolizumab SC when the studies were pooled (risk ratio 0.68, 95% CI 0.46 to 1.01; 3 studies, 1231 participants; high-certainty evidence; Analysis 1.8). This may be due to a reduction in asthma-related serious adverse events (e.g. exacerbations requiring hospitalisation, which did decline), with Chupp 2017 reporting fewer serious adverse events with mepolizumab SC (15/273 (5%) on mepolizumab SC versus 22/278 (8%) on placebo) noting that 12 of these were asthma-related: three (1%) with mepolizumab SC and nine (3%) with placebo. There were no reports of anaphylaxis after mepolizumab.

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

There was no evidence for a difference between the two groups with respect to adverse events prompting treatment discontinuation (rate ratio 0.60, 95% CI 0.19 to 1.85; 3 studies, 1231 participants; high-certainty evidence; Analysis 1.9).

Blood eosinophil counts

Insufficient data were available to analyse this outcome. However, Ortega 2014 reported a decrease in blood eosinophil counts by week 4, with a maximal drop of 86% by week 12 that was maintained during the study. Those participants who continued mepolizumab SC treatment in the Moore 2022 study had consistently lower eosinophil counts than those in the placebo group, a difference that persisted through the entire treatment period (stopping versus continuing mepolizumab: 6.19, 95% CI 4.89 to 7.83).

Mepolizumab (IV) versus placebo

The data for this comparison come from three studies (Haldar 2009; Ortega 2014; Pavord 2012a), with a combined total of 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)

All three studies reported the rate of clinically significant exacerbations, which were likely reduced in participants receiving mepolizumab IV compared to placebo (rate ratio 0.53, 95% CI 0.44 to 0.64; 3 studies, 751 participants; high-certainty evidence; Analysis 2.1).

Secondary outcomes

Exacerbations requiring emergency department treatment or admission

Two studies reported the rate of exacerbations requiring emergency department treatment or admission (Ortega 2014; Pavord 2012a). Mepolizumab IV probably reduces the rate of such exacerbations (rate ratio 0.52, 95% CI 0.31 to 0.87; I^2 = 5%; 2 studies, 690 participants; high-certainty evidence; Analysis 2.2). For exacerbations requiring admission, there is little to no evidence for an effect of mepolizumab IV (rate ratio 0.61, 95% CI 0.33 to 1.13; 2 studies, 690 participants; Analysis 2.3).

These findings are consistent with results from the third, smaller study (Haldar 2009; 61 participants), which reported three admissions for asthma exacerbations in the mepolizumab IV group (n = 29) compared to 11 in the placebo group (n = 32; P = 0.07), albeit we have low confidence in this finding (risk ratio 0.82, 95% CI 0.61 to 1.09; 61 participants; Analysis 2.4).

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

Two of the studies (Haldar 2009; Pavord 2012a), used the AQLQ and ACQ questionnaires, whereas the third used the SGRQ only (Ortega 2014). There is little to no evidence for a difference between mepolizumab IV and placebo for HRQoL when measured using the AQLQ instrument (MD 0.21, 95% CI −0.06 to 0.47; I^2 = 53%; 2 studies, 369 participants; high-certainty evidence; Analysis 2.5). Similarly, there is little evidence for a difference between the two groups when measuring HRQoL using the ACQ in these studies (MD −0.11, 95% CI −0.32 to 0.09; 2 studies, 369 participants; high-certainty evidence; Analysis 2.6). However, mepolizumab IV likely reduces SGRQ scores (MD −6.40, 95% CI −9.65 to −3.15; 1 study, 382 participants; Analysis 2.7). These results conflict with those for mepolizumab SC, but in cases with insufficient evidence to conclude an effect, 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)

Two studies contributed lung function data (Ortega 2014; Pavord 2012a). Mepolizumab IV slightly increases pre-bronchodilator FEV_1 (litres) (MD 0.08 L, 95% CI 0.02 to 0.15; 2 studies, 690 participants; high-certainty evidence; 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

Fewer serious adverse events occurred in the mepolizumab IV group (risk ratio 0.59, 95% CI 0.37 to 0.94; I^2 = 27%; 3 studies, 751 participants; high-certainty evidence; 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 study authors.

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

All three studies reported this outcome, finding no evidence for a difference between mepolizumab IV and placebo (risk ratio 0.72, 95% CI 0.18 to 2.92; I^2 = 24%; 3 studies, 751 participants; high-certainty evidence; Analysis 2.10).

Blood eosinophil counts

Only one small study (Haldar 2009), reported blood eosinophil counts. Mepolizumab IV likely reduces counts (MD −170.00, 95% CI −230.00 to −110.00; 1 study, 61 participants; Analysis 2.11). Ortega 2014 also reported a decrease in blood 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 total of 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)

Two studies reported this outcome (Castro 2015a; Castro 2015b), with the pooled data showing that reslizumab IV reduces clinically significant asthma exacerbations compared to placebo (rate ratio 0.43, 95% CI 0.33 to 0.55; 2 studies, 953 participants; high-certainty evidence; Analysis 3.1). This analysis only included eosinophilic participants; there were no data for non-eosinophilic participants.

Secondary outcomes

Exacerbations requiring emergency department treatment or admission

The same two studies included data on the exacerbations requiring emergency department treatment or admission, with no evidence for a difference between the treatment groups (rate ratio 0.67, 95% CI 0.39 to 1.17; 2 studies, 953 participants; high-certainty evidence; Analysis 3.2). Again only eosinophilic participants were included.

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

Three of the four studies used the AQLQ instrument (Bjermer 2016; Castro 2015a; Castro 2015b), and all four used ACQ. While reslizumab IV slightly improves HRQoL as measured by AQLQ scores, the MCID of 0.5 points or more is not reached (MD 0.28, 95% CI 0.17 to 0.39; 3 studies, 1164 participants; high-certainty evidence; Analysis 3.3). This analysis only included eosinophilic participants; there were no data for non-eosinophilic participants. Similarly, reslizumab IV slightly reduces ACQ scores, though falls short of the MCID of −0.5 points (MD −0.25, 95% CI −0.33 to −0.17; 4 studies, 1652 participants; high-certainty evidence; Analysis 3.4). Only one study (Corren 2016), reported data from non-eosinophilic participants, finding no evidence for a difference between reslizumab IV and placebo. Furthermore, there was no evidence for subgroup differences between eosinophilic and non-eosinophilic participants (P = 0.19, I^2 = 41.1%).

Measures of lung function (e.g. FEV_1)

We noted a clear increase in pre-bronchodilator FEV_1 with reslizumab IV treatment, with data contributed by all four reslizumab IV studies (MD 0.11 L, 95% CI 0.07 to 0.15; I^2 = 21%; 4 studies, 1652 participants; high-certainty evidence; Analysis 3.5). The absolute difference of 0.11 L is relatively modest, although there is no consensus around a MCID in FEV_1 in asthma. For this outcome, data from non-eosinophilic participants were available (again in only one study, Corren 2016), and for that subgroup we observed no evidence for a difference between reslizumab IV versus placebo. The formal test for subgroup differences yielded a P-value of 0.13 (I^2 = 56.3%).

Serious adverse events

There is little to no effect of reslizumab IV on serious adverse events compared to placebo (risk ratio 0.79, 95% CI 0.56 to 1.12; I^2 = 0%; 4 studies, 1656 participants; high-certainty evidence; Analysis 3.6). We note that there was also no difference in the rate of hospitalisations due to asthma exacerbations between reslizumab IV and placebo (Analysis 3.2), which would have counted as serious adverse events. This may explain the difference in effect compared to mepolizumab SC.

Anaphylaxis was reported in three participants after receiving reslizumab (0.13%). One participant experienced breathlessness, wheezing and flushing shortly after the infusion, but did not have haemodynamic compromise (Corren 2016). All participants were treated for anaphylaxis with standard management at the study site and tested negative for antibodies to reslizumab.

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

There was a slight difference between reslizumab IV and placebo for this outcome, which was seen in all the reslizumab IV studies (risk ratio 0.66, 95% CI 0.43 to 1.02; 4 studies, 1659 participants; high-certainty evidence; Analysis 3.7).

Blood eosinophil counts

The blood eosinophil counts were reduced in the reslizumab IV treatment group across all four studies (MD −476.83, 95% CI −499.32 to −454.34; I^2 = 15%; 4 studies, 1656 participants; Analysis 3.8). This analysis 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.

Reslizumab (SC) versus placebo

The data for this comparison come from a single study (Bernstein 2020), which randomised 468 patients. Many of the analyses for this study were stratified by blood eosinophil count, using 300 to less than 400 cells/µL and 400 cells or more per µL as the two analytical groups. However all participants had blood eosinophil counts of 300 or more cells/µL and participants who were truly non-eosinophilic were excluded. The meta-analyses for this comparison therefore use all participants. The additional results of the two subgroups (300 to < 400 cells/µL and ≥ 400 cells/µL) are discussed narratively, though we did not conduct a formal test of subgroup differences.

A further 177 participants were randomised as part of a second study reported in the same publication, but this study involved oral steroid dose reduction and was therefore excluded from this review.

Primary outcomes

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

There was no evidence for a difference in clinically significant asthma exacerbations between reslizumab SC and placebo (rate ratio 0.79, 95% CI 0.56 to 1.11; 464 participants; high-certainty evidence; Analysis 4.1). In prespecified subgroup analyses, those with a blood eosinophil count of 400 cells or more per µL and treated with reslizumab SC experienced a lower rate of clinical asthma exacerbations (rate ratio 0.64, 95% CI 0.43 to 0.95; 373 participants), with no effect of treatment in a smaller group with more modest blood eosinophilia of 300 to less than 400 cells/µL (rate ratio 1.78, 95% CI 0.69 to 4.58; 90 participants). The threshold blood eosinophil count of 400 cells or more per µL is the same as that used in the studies of reslizumab IV, which did find reductions in clinically significant asthma exacerbations (Bjermer 2016; Castro 2015a; Castro 2015b; Corren 2016).

Secondary outcomes

Exacerbations requiring emergency department treatment or admission

There was no difference in the rate of clinical asthma exacerbations requiring emergency department treatment or hospitalisation between the two groups (rate ratio 0.94, 95% CI 0.43 to 2.05; 464 participants; high-certainty evidence; Analysis 4.2). Subgroup analyses were not reported for this outcome.

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

There was no observed effect of reslizumab SC on ACQ scores (MD −0.09, 95% CI −0.27 to 0.09; 464 participants; high-certainty evidence; Analysis 4.4). Subgroup analysis confirmed no effect on either the higher blood eosinophil group with 400 cells or more per µL (MD −0.12, 95% CI −0.32 to 0.08; 373 participants) or the subgroup with 300 to less than 400 eosinophils/µL (MD 0.05, 95% CI −0.38 to 0.48; 90 participants). Similarly, there was no clear benefit of reslizumab SC on AQLQ scores in the overall population (MD 0.08, 95% CI −0.11 to 0.27; 464 participants; high-certainty evidence) or in the subgroups with blood eosinophil counts of either 400 cells or more per µL (MD 0.08, 95% CI −0.14 to 0.30; 373 participants) or 300 to less than 400 cells/µL (MD 0.05, 95% CI −0.38 to 0.48; 90 participants; Analysis 4.3). Participants on reslizumab SC experienced a slight benefit in SGRQ score at week 32 (MD −3.30, 95% CI −6.02 to −0.58; 464 participants; high-certainty evidence), but this was below the MCID and did not persist to week 52 (Analysis 4.5).

Measures of lung function (e.g. FEV_1)

Pre-bronchodilator FEV_1 improved with reslizumab SC versus placebo (MD 0.14, 95% CI 0.06 to 0.22; 464 participants; high-certainty evidence; Analysis 4.6). The same was seen in the subgroup with a blood eosinophil count 400 cells or more per µL (MD 0.15, 95% CI 0.05 to 0.25; 373 participants), though the 300 to less than 400 cells/µL subgroup had a weaker effect in the same direction (MD 0.13, 95% CI −0.05 to 0.31; 90 participants). The increases were modest for both groups but may have reached a clinically important difference, although this benchmark has not yet been established for FEV_1 in asthma.

Serious adverse events

There was no difference in serious adverse events between the groups (risk ratio 0.97, 95% CI 0.53 to 1.79, high-certainty evidence; Analysis 4.7).

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

There was no difference in adverse events prompting discontinuation (risk ratio 4.87, 95% CI 0.57 to 41.40; 468 participants; moderate-certainty evidence; Analysis 4.8).

Blood eosinophil counts

Reslizumab SC treatment reduced blood eosinophil counts (MD −0.49, 95% CI −0.58 to −0.40; Analysis 4.9).

Benralizumab (SC) versus placebo

The data for this comparison come from five studies (Bleecker 2016; Castro 2014a; FitzGerald 2016; Harrison 2020; Park 2016), with a combined total of 3304 participants. Four of the five studies included participants with an eosinophilic and non-eosinophilic phenotype (Bleecker 2016; Castro 2014a; FitzGerald 2016; Park 2016), 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), 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, which 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)

Benralizumab reduced clinically significant asthma exacerbations in all studies (rate ratio 0.59, 95% CI 0.52 to 0.66; I^2 = 21%; 4 studies, 3112 participants; high-certainty evidence; Analysis 5.1). We observed this effect in both eosinophilic and non-eosinophilic participants, with a stronger effect for the eosinophilic subgroup (eosinophilic: rate ratio 0.55, 95% CI 0.48 to 0.63; 4 studies, 2354 participants; versus non-eosinophilic: rate ratio 0.69, 95% CI 0.56 to 0.85; 2 studies, 758 participants). However, there was no evidence for a subgroup difference (P = 0.08; I^2 = 68.4%).

Secondary outcomes

Exacerbations requiring emergency department treatment or admission

Two studies (Bleecker 2016; FitzGerald 2016), reported exacerbations requiring emergency department treatment or admission, finding that benralizumab likely decreased these exacerbations versus placebo (rate ratio 0.68, 95% CI 0.47 to 0.98; I^2 = 43%; 2 studies, 1537 participants; moderate-certainty evidence; Analysis 5.2). This analysis only included eosinophilic participants; there were no data for non-eosinophilic participants available. However, there was a considerable degree of heterogeneity (I^2 = 43%), despite Bleecker 2016 and FitzGerald 2016 having the same study 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 had less scope for a reduction in exacerbation rate. FitzGerald 2016 noted that participants who had had three or more exacerbations in the previous year saw the greatest effects of benralizumab treatment, at rates comparable to Bleecker 2016.

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

Three studies included data on AQLQ scores (Bleecker 2016; Castro 2014a; FitzGerald 2016), four on ACQ scores (Bleecker 2016; Castro 2014a; FitzGerald 2016; Harrison 2020), and one on SGRQ scores (Harrison 2020). AQLQ mean difference was better in the benralizumab group (MD 0.23, 95% CI 0.11 to 0.35; 3 studies, 1541 participants; high-certainty evidence; Analysis 5.3); for this particular outcome data were available only from eosinophilic participants. However, we observed a similar advantage in favour of benralizumab in combined eosinophilic and non-eosinophilic participants when measuring HRQoL using the ACQ instrument (MD −0.26, 95% CI −0.34 to −0.17; I^2 = 37%; 4 studies, 2791 participants; high-certainty evidence; Analysis 5.4). When analysing the non-eosinophilic subgroup only, however, the evidence for this effect was weak (MD −0.14, 95% CI −0.30 to 0.02; 2 studies, 755 participants). There was also no strong evidence for subgroup differences (P = 0.09, I^2 = 64.3%). Neither the AQLQ and ACQ differences reached the MCID of 0.5 points or more. The one study that measured SGRQ scores found a strong improvement with benralizumab versus placebo among eosinophilic participants, exceeding the MCID of 4 points (MD −11.16, 95% CI −15.10 to −7.22; 1 study, 406 participants; Analysis 5.5).

One study (Harrison 2020), undertook a responder analysis, which found that 73% and 80% of participants receiving benralizumab experienced an improvement in excess of the MCID in the ACQ and SGRQ respectively, compared to 67% and 68% of participants on placebo (P = 0.019 and P = 0.001 respectively).

Measures of lung function (e.g. FEV_1)

Pre-bronchodilator FEV_1 was superior in the benralizumab group (MD 0.11, 95% CI 0.08 to 0.15; I^2 = 35%; 4 studies, 2786 participants; high-certainty evidence; Analysis 5.6; Bleecker 2016; Castro 2014a; FitzGerald 2016; Harrison 2020). However, only eosinophilic participants experienced this benefit: there was strong evidence for a difference between the two subgroups (P = 0.004; I^2 = 88.2%). The observed improvement of 0.11 L is relatively modest and of a similar magnitude to that seen with the mepolizumab and reslizumab interventions.

Serious adverse events

Serious adverse events were reduced in the benralizumab group across the five pooled studies (risk ratio 0.76, 95% CI 0.62 to 0.93; 5 studies, 3304 participants; high-certainty evidence; Analysis 5.7). Two of the largest studies reported a reduced incidence of serious adverse events with benralizumab (FitzGerald 2016; Harrison 2020); the authors noted that the most commonly reported serious adverse event was worsening asthma, as did the authors of the other large study (Bleecker 2016). This was consistent with the effect of the treatment. There were no reports of anaphylaxis after benralizumab.

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

There were more clinically significant adverse events in the benralizumab group, pooled across all studies except Park 2016, which did not report this outcome (risk ratio 2.04, 95% CI 1.03 to 4.03; 4 studies, 3253 participants; high-certainty evidence; Analysis 5.8), based on eosinophilic and non-eosinophilic participants (including a subgroup of participants whose eosinophil status was not defined). The individual studies did not find evidence for an effect and thus there was no comment by the investigators. However, benralizumab has a different mechanism of action resulting in a larger reduction in eosinophils, which could result in an increase in adverse events. This is an area for further research.

Blood eosinophil levels (% change from baseline)

Although four studies included data on blood eosinophil levels, two provided this as a percentage change from baseline (Bleecker 2016; FitzGerald 2016), whilst the other two provided absolute counts (Castro 2014a; Park 2016). All found marked reductions in blood eosinophil levels with benralizumab. The pooled results of the studies showing this as a percentage change, which includes both eosinophilic and non-eosinophilic participants, are shown in Analysis 5.9 (MD −104.74, 95% CI −116.12 to −93.35; I^2 = 36%; 2 studies, 2295 participants). In this analysis, there was strong evidence for subgroup differences (P = 0.002; I^2 = 90%). Castro 2014a reported mean values of 46 to 56 cells per µL in participants with 300

or more cells per µL at baseline, whereas Park 2016 saw reductions to around 0 cells per µL from a mean of 564 to 824 cells per µL (these data were shown graphically and we could not extract them for inclusion in the meta-analysis).

DISCUSSION

Summary of main results

Seventeen studies met the inclusion criteria for this systematic review (Bernstein 2020; Bjermer 2016; Bleecker 2016; Castro 2014a; Castro 2015a; Castro 2015b; Chupp 2017; Corren 2016; FitzGerald 2016; Haldar 2009; Harrison 2020; Jackson 2022; Moore 2022; NCT01947946; Ortega 2014; Park 2016; Pavord 2012a). Seven studies included adult participants only (Bernstein 2020; Castro 2014a; Corren 2016; Haldar 2009; Harrison 2020; Moore 2022; NCT01947946; Park 2016), one included six to 17 year-olds only (Jackson 2022), and the remaining nine (Bernstein 2020; Bjermer 2016; Bleecker 2016; Castro 2015a; Castro 2015b; Chupp 2017; FitzGerald 2016; Ortega 2014; Pavord 2012a), recruited participants aged 12 years and over. Results in adolescents were not reported separately in the latter studies, and thus we could not perform a subgroup analysis on the paediatric population. However the results from the single study in children and adolescents, not yet published in full, are consistent with those in adults (Jackson 2022).

The results indicate 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 care with a history of poor control ('clinically significant' exacerbations defined as episodes requiring at least three days' treatment with systemic corticosteroids; standard 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 comparable across the drugs and formulations, with the exception of reslizumab SC, which was relatively ineffective, although the study design and populations studied differed across studies and no head-to-head studies were performed. In addition, treatment with mepolizumab and benralizumab reduced rates of exacerbations requiring emergency department attendance or hospital admission. Non-eosinophilic participants experienced a smaller reduction in asthma exacerbation rates when treated with benralizumab, but there was no evidence for a subgroup difference. 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, as no studies to assess this are underway.

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. 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. Improvements in the SGRQ did reach the MCID but came from only four studies, in mepolizumab (Chupp 2017; Moore 2022; Ortega 2014), and benralizumab (Harrison 2020). This may be due to differences between the questionnaires: the SGRQ is a 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 found little to no evidence of improvement in ACQ and AQLQ scores in those treated with mepolizumab IV or ACQ scores in non-eosinophilic participants treated with benralizumab (data were not available for mepolizumab or reslizumab).

All anti-IL-5 interventions produced an improvement in mean pre-bronchodilator FEV_1 of between 0.08 L and 0.15 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 drugs is modest and may not be noticed by participants.

Treatment with mepolizumab and reslizumab (both SC and IV) appeared to result in few adverse events, although there remain minor safety concerns over benralizumab. The pooled results of the benralizumab studies showed some evidence for a reduction in severe adverse events. This was most likely due to the reduction in asthma exacerbations requiring hospital admission that would be classed as severe adverse events. However, when considering adverse events prompting participants to discontinue the study drug, whilst mepolizumab and reslizumab treatment were no different to placebo, there were more discontinuations with benralizumab versus placebo, although the absolute numbers were small (42/2026 (2.1%) benralizumab versus 11/1227 (0.9%) placebo). A meta-analysis of eight benralizumab placebo-controlled randomised studies in asthma, including those excluded from this review because the treatment duration was less than 16 weeks or the protocol involved oral corticosteroid dose reduction, found that the excess non-severe adverse events in those treated with benralizumab related to headache and pyrexia, with no excess of hypersensitivity, injection-site reactions, nasopharyngitis, rhinitis, upper respiratory tract infection, influenza, cough, nausea, back pain or arthralgia (Liu 2019). This may be due to the different mechanism of action of benralizumab; further research is needed.

All anti-IL-5 treatments produced marked reductions in blood eosinophil levels. 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 few residual eosinophils remained. This is attributed to the ability of benralizumab to induce apoptosis of eosinophils. It is unclear whether this translates into greater clinical efficacy, a greater risk of adverse events, or both.

A single study (Bernstein 2020), assessed reslizumab SC, and found it did not reduce clinically significant asthma exacerbations in a population with blood eosinophil counts of 400 cells or more per µL. However, in a prespecified analysis, there was a reduction in exacerbation rates in a subgroup with blood eosinophil counts of 400 cells or more per µL, the same threshold as used in the reslizumab IV studies. Moreover, the study authors noted that the fixed SC dose used, 110 mg, was roughly equivalent to 1 mg/kg reslizumab IV for an average 70 kg man after accounting for bioavailability, compared to the licensed 3 mg/kg reslizumab IV dose. Thus the findings with reslizumab SC do not entirely

contradict the results for the other formulations and drugs in this class.

Overall the evidence in this review supports the use of anti-IL-5 treatments as an adjunct to standard 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 one of the primary goals of asthma management (GINA 2021). 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 adverse event data showing that anti-IL-5 treatments are well tolerated. In addition, the few studies measuring the SGRQ, a broader HRQoL score, found significant improvements with anti-IL-5 interventions that exceeded the MCID. Statistically significant but more modest improvements, likely below levels that would be clinically detected by patients, were evident in the narrower AQLQ and ACQ scores, focusing on asthma symptoms, and lung function (FEV_1). 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 relevance to patients. The evidence on mepolizumab IV and reslizumab SC is of limited applicability as these drugs are not currently available in these formulations.

The included studies did not directly compare the different anti-IL-5 treatments, however the effect sizes versus placebo were similar. No head-to-head studies exist, although indirect treatment comparisons and network meta-analyses have been published with differing results (Busse 2019a; Calzetta 2019; Casale 2019; Edris 2019; Edris 2021; He 2018; Iftikhar 2018; Ramonell 2020; Yan 2019), all limited by the differences in eligibility criteria and outcome measures across the studies. A single study comparing biologicals in asthma, omalizumab versus mepolizumab is ongoing (NCT03476109). Pragmatically, reslizumab is given by intravenous infusion necessitating a healthcare setting whereas mepolizumab and benralizumab are given subcutaneously, every four weeks and eight weeks respectively. Thus, there are practical advantages to mepolizumab and particularly 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. It is therefore not possible to draw conclusions about those with milder or better-controlled disease (e.g. ACQ less than 1.5 with no exacerbations) or non-eosinophilic asthma. 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 (except Jackson 2022: 150 cells or more per µL), reslizumab studies using a cut-off of 400 cells or more per µL (except Bernstein 2020's study of reslizumab SC: 300 cells or more per µL), and benralizumab studies 300 cells or more per µL (except Harrison 2020: 150 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.

None of the included studies extended beyond a year, although several open-label extension studies have since confirmed that the favourable safety profile of these drugs persists for at least between 1.5 and 3.5 years (Bourdin 2021; Busse 2019b; Fitzgerald 2019; Khatri 2019; Khurana 2019; Lugogo 2016; Murphy 2017). One study assessed the need for ongoing anti-IL-5 treatment, comparing cessation to continuation of long-term mepolizumab (Moore 2022), finding that the clinical benefits are only sustained if treatment is continued.

The potential for anti-IL-5 treatments to enable a reduction in maintenance OCS in patients requiring this has been documented in several RCTs (Bel 2014; Bernstein 2020; Nair 2009; Nair 2017a). These studies incorporated differing OCS weaning regimens and we therefore considered them too heterogeneous for inclusion in the meta-analysis, but have nonetheless consistently documented significant OCS-sparing effects.

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 certainty of the evidence for all comparisons to be high overall, except for mepolizumab IV and reslizumab SC, which are not currently licensed delivery routes for these drugs (we therefore regard this as indirect evidence). We are aware of the limitations in some studies and have detailed them in the Results, 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 studies 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 studies 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 study was consistently in line with the inclusion criteria.

Agreements and disagreements with other studies or reviews

This review is the second update of a previous Cochrane Review, of which the first iteration focused solely on mepolizumab in asthma (Powell 2015, updated in Farne 2017). The previous version noted other reviews with similar findings (Cabon 2017; Li 2017; Liu 2013; Wang 2016; Yancey 2017a). Since then, several systematic reviews have assessed anti-IL-5 therapies versus placebo for treating asthma.

1. Agache 2020: a meta-analysis of benralizumab, mepolizumab, reslizumab and also dupilumab and omalizumab to placebo, including studies incorporating OCS dose reduction
2. Calzetta 2019: a network meta-analysis that compared mepolizumab, reslizumab and benralizumab (and other biologicals) to placebo, as well as each other
3. Edris 2019 a network meta-analysis that compared mepolizumab, reslizumab and benralizumab (and other biologicals) to placebo, as well as each other
4. Edris 2021: a network meta-analysis that compared mepolizumab, reslizumab and benralizumab (and other biologicals) to placebo, as well as each other
5. He 2018: a network meta-analysis that compared mepolizumab, reslizumab and benralizumab to placebo, as well as each other
6. Henriksen 2018: a meta-analysis and indirect comparison of mepolizumab and reslizumab (not benralizumab), including a study incorporating OCS dose reduction
7. Iftikhar 2018: a network meta-analysis that compared mepolizumab, reslizumab and benralizumab (and other biologicals) to placebo, as well as each other
8. Ramonell 2020: a network meta-analysis that compared benralizumab, mepolizumab, reslizumab and also dupilumab to placebo, as well as each other

Our findings are consistent with these reviews, despite the inclusion of additional recent studies (Bernstein 2020; Harrison 2020; Jackson 2022; Moore 2022). All the reviews highlight the need for further research in this area, particularly direct head-to-head comparisons of the different treatments.

Real-world, observational studies of people with severe asthma receiving anti-IL-5 therapies have reported efficacy consistent with, and sometimes superior to, that seen in RCTs and in this review. The largest, an ongoing observational study of more than1800 adults with severe asthma in the USA, reported an annualised exacerbation rate of 0.62 per patient year in those receiving any biologic (including but not only anti-IL-5) compared to 0.88 in those on maintenance systemic corticosteroids and 0.91 in those not receiving biologics or maintenance systemic corticosteroids (Trevor 2021). In the 261 participants who started biologics during the study period, exacerbation rates fell by 43% in those treated with anti-IgE compared to 62% in those starting another biological (breakdown by treatment not provided but likely to be overwhelmingly anti-IL-5/-IL-5Rα, rather than the more recently licensed anti-IL-4Rα drug dupilumab). Similar findings were reported for emergency department attendances and hospital admissions. Other outcomes (e.g. ACQ, lung function) were not analysed.

A systematic review and meta-analysis of mepolizumab treatment for severe asthma identified 13 studies with 1457 participants and found improvements after 6 to 12 months' treatment in: exacerbations and hospital admissions, quantified in events per patient year; ACQ and ACT scores in excess of the MCID (1.03 and 6.52 points respectively); and 0.23 L in FEV_1 (Li 2021). Real-world reports of benralizumab are similarly consistent with the RCTs (e.g. Kavanagh 2021; Pelaia 2021).

AUTHORS' CONCLUSIONS

Implications for practice

The studies that are currently available provide evidence to support the use of anti-IL-5 treatments in adults with severe eosinophilic asthma, which have been incorporated into national and international guidelines (e.g. Global Initiative for Asthma's 2021 clinical consensus statement, GINA 2021). These treatments appear to roughly halve the rate of asthma exacerbations in this patient population, for whom exacerbations are particularly troublesome (Custovic 2013). Importantly, no concerns about safety were reported for mepolizumab or reslizumab, and there were no excess serious adverse events with benralizumab, although there was a small but significant incidence of adverse events prompting discontinuation of benralizumab. 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 years, these did not provide sufficient data to reach a conclusion about efficacy and safety in this population. The initial findings of Jackson 2022, a study in those aged 6 to 17 years, only available in abstract form, suggest similar efficacy to adults but the full results are eagerly awaited.

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, in whom there has been only one incompletely published study, and 12 to 18 years old, for whom data have not been reported separately.

With regard to benralizumab in particular, future studies 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 (omalizumab) and the newer treatments, anti-IL-4 receptor α subunit (blocking IL-4 and IL-13 signalling; dupilumab), and anti-thymic stromal lymphopoietin (TSLP;

tezepelumab). At present there are no direct comparisons from head-to-head studies, leaving the clinician faced with such patients in an evidence-free quandary. The variability in enrolment criteria present an obstacle to conducting a network meta-analysis. High-quality, head-to-head studies are required; one is indeed underway comparing omalizumab and mepolizumab (NCT03476109), more will be needed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Bernstein 2020

Study characteristics	
Methods	Double-blind, placebo-controlled, parallel-group study
Participants	468 participants with unstable asthma 1. Main inclusion/exclusion criteria: a. male or female, ≥ 12 years, with a diagnosis of asthma b. ACQ-6 score of at least 1.5 c. ≥ 2 asthma exacerbations requiring systemic corticosteroids in past year d. blood eosinophil count of ≥ 300 cells/μL during screening e. FEV_1 reversibility of ≥ 12% to inhaled short-acting β agonist at screening or documentation within 12 months of signing informed consent f. receiving ICS g. required an additional asthma controller medication besides ICSs h. history of asthma exacerbation 2. Mean age, years (SD): reslizumab 110 mg every 4 weeks, 46.9 (17.6); placebo, 44.8 (17.7) 3. Male, n (%): reslizumab 110 mg every 4 weeks, 90 (38%); placebo, 102 (44%) 4. Baseline mean (SD) FEV_1 % predicted: reslizumab 110 mg every 4 weeks: 64.4 (18.3); placebo, 65 (19.7) 5. Allocation: reslizumab 110 mg every 4 weeks, 236; placebo, 232
Interventions	Reslizumab will be administered SC in a dose of 110 mg every 4 weeks vs placebo
Outcomes	The primary objective of this study is to determine the effect of reslizumab (110 mg) administered SC every 4 weeks on clinical asthma exacerbations in adults and adolescents with asthma and elevated blood eosinophils who are inadequately controlled on standard care asthma therapy Primary outcomes 1. Frequency of clinical asthma exacerbations (time frame: 52 weeks) 2. Spirometry Secondary outcomes 1. Change in FEV_1 (time frame: baseline, week 52) 2. Change in AQLQ (time frame: 52 weeks) 3. Change in AQLQ (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 SGRQ (time frame: baseline, week 32) 8. Time to first clinical asthma exacerbation (time frame: 52 weeks) 9. Frequency of exacerbations requiring hospitalisation or ED visits (time frame: 52 weeks) 10. Frequency of moderate exacerbations (time frame: 52 weeks)
Notes	Estimated study completion date: January 2018

Bernstein 2020 *(Continued)*

	Responsible party: Teva Branded Pharmaceutical Products, R&D Inc. International multicentre study with 201 centres.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reported as: "Participants were assigned using an interactive web response system (IWRS)."
Allocation concealment (selection bias)	Low risk	Reported as: "Patients and investigators were masked to treatment assignment."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as: "Patients and investigators were masked to treatment assignment."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information on outcome assessor blindness
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up was < 10% in both groups.
Selective reporting (reporting bias)	Low risk	All primary and secondary outcomes reported, with additional outcomes presented in supplement

Bjermer 2016

Study characteristics	
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: a. blood eosinophils ≥ 400 cells/µL during 2 to 4-week screening period b. ACQ-7 score ≥ 1.5 c. maintenance treatment with medium-dose ICS (maintenance OCS not allowed) 2. Mean age, years: reslizumab 0.3 mg/kg, 44.5; reslizumab 3 mg/kg, 43.0; placebo, 44.2 3. Male, n: 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

Bjermer 2016 *(Continued)*

	1. FVC, FEF 25%-75% 2. Asthma symptoms (ACQ, ACQ-6, ACQ-5), ASUI, AQLQ 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
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

Study characteristics

Methods	Randomised, double-blind, parallel-group, placebo-controlled study 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: a. ≥ 2 exacerbations in the previous 12 months b. ACQ-6 score ≥ 1.5 at enrolment c. FEV_1 < 80% (if 12-17 years old, < 90%) d. maintenance treatment with high-dose (≥ 500 µg/d FP or equivalent) ICS/LABA for ≥ 12 months for adults > 18 years, or at least medium-dose (≥ 250 µg/d FP or equivalent) ICS/LABA for children (12-17 years) 2. Mean age, years (SD): benralizumab 30 mg every 4 weeks, 50 (13.4); benralizumab 30 mg every 8 weeks, 48 (14.5); placebo, 49 (14.9) 3. Male, n (%): benralizumab 30 mg every 4 weeks, 124 (31%); benralizumab 30 mg every 8 weeks, 146 (37%); placebo, 138 (34%)

Bleecker 2016 *(Continued)*

4. Baseline mean (SD) FEV_1 % predicted: benralizumab 30 mg every 4 weeks, 57 (14.1); benralizumab 30 mg every 8 weeks, 56 (14.6); placebo, 57 (15.0)
5. Allocation: benralizumab 30 mg every 4 weeks, 399; benralizumab 30 mg every 8 weeks, 398; placebo, 407

Interventions	Benralizumab SC 30 mg/mL every 4 weeks or every 8 weeks vs 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
Notes	Multi-centre study 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

Study characteristics

Castro 2014a *(Continued)*

Methods	Double-blind, dose-ranging RCT
Participants	606 participants with uncontrolled asthma randomised and 535 completed 1. Main inclusion/exclusion criteria: a. 2-6 exacerbations in the previous 12 months b. ACQ-6 score ≥ 1.5 at least twice during screening c. morning pre-bronchodilator FEV_1 40%-90% d. maintenance treatment with medium- to high-dose ICS in combination with LABA for ≥ 12 months 2. Mean age, years (SD): 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. Male, n (%): 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% (SD 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-week 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.

Castro 2014a *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, treating physicians, study investigators, and study statisticians were masked to treatment allocation.
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

Study characteristics	
Methods	Double-blind, placebo-controlled, parallel-group study
Participants	489 participants with moderate-severe asthma (medium dose of ICS, inadequate control ACQ ≥ 1.5, and at least 1 exacerbation in the past 12 months) 1. Main inclusion/exclusion criteria: a. blood eosinophils ≥ 400 cells/µL during 2 to 4-week screening period b. ACQ-7 score ≥ 1.5 c. maintenance treatment with medium-dose ICS (i.e. ≥ 440 µg/d FP or equivalent daily); ± additional controller or maintenance OCS 2. Mean age, years (IQR): reslizumab, 48 (38-57); placebo, 49 (38-57) 3. Male, n (%): reslizumab, 103 (42); placebo, 83 (34) 4. Baseline mean 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

Castro 2015a *(Continued)*

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

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

Study characteristics

Methods	Double-blind, placebo-controlled, parallel-group study
Participants	464 participants with moderate-severe asthma (medium dose of ICS, inadequate control ACQ ≥ 1.5 and at least 1 exacerbation in the past 12 months) 1. Main inclusion/exclusion criteria: a. blood eosinophils ≥ 400 cells/µL during 2 to 4-week screening period b. ACQ-7 score ≥ 1.5 c. maintenance treatment with medium-dose ICS (i.e. ≥ 440 µg/day FP or equivalent daily); ± additional controller or maintenance OCS 2. Mean age, years (IQR): reslizumab, 48 (37-57); placebo, 48 (40-57) 3. Male, n (%): reslizumab, 88 (38); placebo, 82 (35) 4. Baseline mean 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

Study characteristics	
Methods	Multicentre, placebo-controlled, double-blind, parallel-group study

Participants	551 participants with severe eosinophilic asthma
	
	Male (%): mepolizumab 125 (46); placebo, 101 (36)
	
	• Main inclusion/exclusion criteria:
	  ○ blood eosinophils ≥ 150 cells/μL at screening or ≥ 300 cells/μL in previous 12 months
	  ○ ≥ 2 exacerbations in previous 12 months
	  ○ FEV_1 < 80%
	  ○ maintenance treatment with high-dose ICS for ≥ 12 months; + additional controller for ≥ 3 months; ± maintenance OCS

Chupp 2017 *(Continued)*

Interventions	Mepolizumab 100 mg SC every 4 weeks for a period of 24 weeks (total of 6 doses) along with their respective standard care 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 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 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 withdrawn on a physician's decision.
Selective reporting (reporting bias)	Low risk	No indication of reporting bias

Corren 2016

Study characteristics

Methods	Parallel, double-blind
Participants	496 participants with moderate-severe asthma (based on at least medium-dose ICS, inadequate control ACQ ≥ 1.5)

Corren 2016 *(Continued)*

	1. Main inclusion/exclusion criteria: a. ACQ-7 score ≥ 1.5 b. maintenance treatment with medium-dose ICS; maintenance OCS not allowed 2. Mean age, years: reslizumab, 44.9; placebo, 45.1 3. Male, n: reslizumab, 137; placebo, 44 4. Baseline mean FEV_1, % predicted: reslizumab, 66.8; placebo, 66.5 5. Allocation: to reslizumab, 398; to placebo, 98
Interventions	Reslizumab IV 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
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

Study characteristics	
Methods	Multicentre, randomised, double-blind, parallel-group, placebo-controlled study
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: a. ≥ 2 exacerbations in the previous 12 months b. ACQ-6 score ≥ 1.5 at enrolment c. FEV_1 < 80% d. 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, years (SD): eosinophil ≥ 300 cells/µL benralizumab 30 mg every 4 weeks, 50 (13.1); eosinophil ≥ 300 cells/µL benralizumab 30 mg every 8 weeks. 50 (13.0); eosinophil ≥ 300 cells/µL placebo, 49 (14.1); eosinophil < 300 cells/µL benralizumab 30 mg every 4 weeks, 52 (12.2); eosinophil < 300 cells/µL benralizumab 30 mg every 8 weeks, 51 (13.8); eosinophil < 300 cells/µL placebo, 52 (14.4) 3. Male, n (%): eosinophil ≥ 300 cells/µL benralizumab 30 mg every 4 weeks, 82 (34); eosinophil ≥ 300 cells/µL benralizumab 30 mg every 8 weeks, 101 (42); eosinophil ≥ 300 cells/µL placebo, 103 (42); eosinophil < 300 cells/µL benralizumab 30 mg every 4 weeks, 45 (39); eosinophil < 300 cells/µL benralizumab 30 mg every 8 weeks, 38 (30); eosinophil < 300 cells/µL placebo, 46 (38). 4. Baseline mean (SD) FEV_1 % predicted: eosinophil ≥ 300 cells/µL benralizumab 30 mg every 4 weeks, 59 (13.7); eosinophil ≥ 300 cells/µL benralizumab 30 mg every 8 weeks, 57 (14.2); eosinophil ≥ 300 cells/µL placebo, 58 (13.9); eosinophil < 300 cells/µL benralizumab 30 mg every 4 weeks, 57 (16.2); eosinophil < 300 cells/µL benralizumab 30 mg every 8 weeks, 57 (15.2); eosinophil < 300 cells/µL placebo, 56 (16.3) 5. Allocation: eosinophil ≥ 300 cells/µL benralizumab 30 mg every 4 weeks, 241; eosinophil ≥ 300 cells/µL benralizumab 30 mg every 8 weeks, 239; eosinophil ≥ 300 cells/µL placebo, 248; eosinophil < 300 cells/µL benralizumab 30 mg every 4 weeks, 116; eosinophil < 300 cells/µL benralizumab 30 mg every 8 weeks, 125; eosinophil < 300 cells/µL placebo, 122
Interventions	56 weeks (final follow-up at 60 weeks). Benralizumab SC 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. Pharmacokinetic parameter s and anti-drug antibodies 13. Safety and tolerability of intervention
Notes	Funding: AstraZeneca and Kyowa Hakko Kirin. 303 clinical research centres in 11 countries

FitzGerald 2016 *(Continued)*

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/μL or ≥ 300 cells/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.
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 4 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

Study characteristics

Methods	Randomised, double-blind, placebo-controlled, parallel-group study
Participants	61 participants had refractory eosinophilic asthma and a history of recurrent severe exacerbations. 1. Main inclusion/exclusion criteria: a. ≥ 3% sputum eosinophils on at least 1 occasion in previous 2 years despite high-dose corticosteroid treatment b. ≥ 2 exacerbations in previous 12 months c. maintenance treatment with high-dose ICS 2. Mean age, years (range): mepolizumab, 48 (21-63); placebo, 50 (24-72) 3. Male, n: 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	Mepolizumab IV (750 mg) vs 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/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 in-

Haldar 2009 *(Continued)*

	dicating 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 study conducted at Institute for Lung Health, Leicester, UK Supported by GlaxoSmithKline

Risk of bias

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

Harrison 2020

Study characteristics

Methods	Multicentre, randomised, double-blind, parallel-group, placebo-controlled, phase 3b study
Participants	656 participants aged 18-75 with severe eosinophilic asthma

Harrison 2020 *(Continued)*

1. Main inclusion/exclusion criteria:
   a. history of physician-diagnosed asthma requiring treatment
   b. history of at least 2 asthma exacerbations in previous 12 months, despite treatment with medium-dose to high-dose ICS plus another asthma controller
   c. use of a high-dose ICS plus another asthma controller for 3 months prior to enrolment
   d. ACQ-6 of at least 1.5 at screening
   e. Blood eosinophils of at least 300 cells/μL (or at least 150 with at least 1 of the following: maintenance OCS use at study entry, history of nasal polyposis, ≥ 3 exacerbations in the previous year, FVC of < 65% predicted, or ≥ 18 years at asthma diagnosis)
   f. Documented prebronchodilator FEV_1 < 80%, ACQ-6 of at least 1.5, FEV1 ≥ 12%, and PEF variability ≥ 10%
2. Exclusion: other pulmonary disease or disorder, alcohol abuse, current malignancy
3. Age mean, years (SD): benralizumab 30 mg, 52.5 (12.7); placebo, 53.3 (12.5)
4. Male, n (%): benralizumab 30 mg, 164 (38%); placebo, 93 (41%)
5. Baseline mean (SD) prebronchodilator FEV_1 % predicted: benralizumab 30 mg, 54 (14.2); placebo, 55.9 (13.6)
6. Baseline mean (SD) post-bronchodilator FEV_1 % of predicted: benralizumab 30 mg, 68 (16.44); placebo, 68.6 (15.24)
7. Blood eosinophil count, median (range): benralizumab 30 mg, 390 (40-7970); placebo, 390 (20-5600)

Interventions	Benralizumab SC every 8 weeks at 30 mg (1st 3 doses given 4 weeks apart) for 24 weeks vs matched placebo. Patients were randomised 2:1 intervention to placebo
Outcomes	Primary 1. Annualised exacerbation rate Secondary 1. Time to first asthma exacerbation 2. Mean change from baseline of SGRQ score 3. Mean weekly PEF change from baseline 4. FEV_1 % predicted 5. ACQ-6
Notes	Study conducted from July 2017-September 2019 at 221 research centres across Europe and North America. Supported by AstraZeneca. NCT03170271

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by a web-based system.
Allocation concealment (selection bias)	Low risk	Treatment group assignment as well as kit allocation was performed by a web-based system.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study

Harrison 2020 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Reported as: "...eosinophil, basophil, and monocyte counts were removed from any central laboratory reports sent to investigative sites to prevent unintentional unblinding of treatment allocation post-dose."
Incomplete outcome data (attrition bias) All outcomes	Low risk	92.3% of participants completed intervention, and 95.2% of participants completed placebo
Selective reporting (reporting bias)	Low risk	No evidence of reporting bias

Jackson 2022

Study characteristics	
Methods	Randomised, parallel-group, placebo-controlled study
Participants	290 total participants (age 6-17 years) Main inclusion criteria: 1. at least 2 exacerbations in the previous year 2. blood eosinophils ≥ 150 cells/μL
Interventions	Mepolizumab administered SC every 4 weeks, 40 mg for 6-11 year-olds and 100 mg for 12-17 year-olds for 52 weeks
Outcomes	Primary 1. Asthma exacerbations treated with systemic corticosteroids Secondary 1. Time to first exacerbation 2. Lung function 3. Quality of life 4. Composite Asthma Severity Index (CASI)
Notes	Conference abstract. NCT03292588

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Allocation is random
Allocation concealment (selection bias)	Unclear risk	Details not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	ClinicalTrials.gov reports triple masking (participant, care provider, investigator)

Jackson 2022 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	ClinicalTrials.gov reports triple masking (participant, care provider, investigator)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not provided
Selective reporting (reporting bias)	Unclear risk	Challenging to assess reporting bias from a short abstract

Moore 2022

Study characteristics	
Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group study
Participants	195 adults with severe eosinophilic asthma who had previous long-term treatment with mepolizumab 1. Main inclusion/exclusion criteria: a. completion of either COLUMBA (NCT01691859) or COSMEX (NCT02135692) study b. continuous mepolizumab treatment for ≥ 3 years (no treatment gaps ≥ 12 weeks) c. remained on asthma controller medication/therapy 2. Mean age, years (SD): mepolizumab 100 mg every 4 weeks, 56.6 (11.53); placebo: 55.7 (11.42) 3. Male, n (%): mepolizumab 100 mg every 4 weeks, 57 (40); placebo, 65 (43) 4. Baseline mean (SD) prebronchodilator FEV_1 % predicted: mepolizumab 100 mg, 61.6 (19.08); placebo, 65.5 (19.64) 5. Baseline blood eosinophil count, cells / µL,geometric mean (SD): mepolizumab 100 mg, 50 (0.881); placebo, 40 (0.870) 6. Allocation: mepolizumab, 144; placebo, 151
Interventions	Mepolizumab SC 100 mg every 4 weeks for 52 weeks vs placebo (but can switch to open-label mepolizumab after a severe exacerbation). Placebo is discontinuation from previous mepolizumab treatment
Outcomes	Primary 1. Percentage of participants with 1st clinically significant exacerbation in Part C (primary) 2. Time to 1st clinically significant exacerbation (requiring systemic corticosteroids, ED visit or hospitalisation) Secondary 1. Ratio to baseline in blood eosinophil count in Part C 2. Percentage of participants with ≥ 0.5 point increase in ACQ-5 score from baseline in Part C 3. Time to decrease in asthma control (ACQ-5 score increase from baseline ≥ 0.5 points) 4. Percentage of participants with exacerbation requiring ED visit/hospitalisation 5. Time to first exacerbation requiring ED visit/hospitalisation
Notes	Study conducted from January 2016-July 2019 at 75 centres in 14 countries Supported by GlaxoSmithKline. NCT02555371
Risk of bias	

Moore 2022 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by an interactive response technology system.
Allocation concealment (selection bias)	Low risk	Reported as: "[Treatement] will be administered by a designated blinded member of the site staff. Once prepared, mepolizumab and placebo will be identical in appearance."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as: "The blinding of all those involved in the evaluation of the study treatment (e.g. physician/nurse as well as the subject) shall be maintained at all times."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Reported as: "The blinding of all those involved in the evaluation of the study treatment (e.g. physician/nurse as well as the subject) shall be maintained at all times." Biomarker results will be masked to outcome assessors to protect unblinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 41% of the placebo group and 67% of the intervention group finished the randomised study.
Selective reporting (reporting bias)	Low risk	All outcomes reported

NCT01947946

Study characteristics	
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 LABA 1. Main inclusion criteria: a. aged from 18-75 years, inclusive b. 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 c. Documented treatment with medium-dose ICS (> 250 µg and ≤ 500 µg fluticasone dry powder formulation equivalents total daily dose) and LABA for at least 3 month prior to first visit 2. Mean age, years (SD): 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. Male, 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

NCT01947946 *(Continued)*

	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 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 study registration. Outcomes could not be incorporated into meta-analysis

Ortega 2014

Study characteristics

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: a. blood eosinophils ≥ 150 cells/μL at screening or ≥ 300 cells/μL in previous 12 months b. ≥ 2 exacerbations in previous 12 months c. FEV_1 < 80% d. maintenance treatment with high-dose ICS for ≥ 12 months; plus additional controller for ≥ 3 months; ± maintenance OCS 2. Mean age, years (range): mepolizumab 75 mg, 50 (13-82); mepolizumab 100 mg, 51 (12-81); placebo, 49 (12-76) 3. Male, n (%): mepolizumab 75 mg, 85 (45); mepolizumab 100 mg, 78 (40); placebo, 84 (44) 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)

Ortega 2014 *(Continued)*

	5. Allocation: mepolizumab 75 mg, 191; mepolizumab 100 mg, 194; placebo, 191
Interventions	Mepolizumab in a 75 mg IV dose vs mepolizumab in a 100 mg SC dose vs placebo every 4 weeks for 32 weeks
Outcomes	Primary outcomes 1. Number of clinically significant exacerbations of asthma/year Secondary outcomes 1. Number of clinically significant exacerbations requiring hospitalisation (including intubation and admittance to an ICU) or ED visits/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 week run-in and 8-week follow-up. Conducted in Baltimore, Middlesex, Ghent, Vancouver, Parma, Marseille and Paris Funding: GlaxoSmithKline

Risk of bias

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

Study characteristics

Methods	Parallel
Participants	103: 38 male (age 53.2, 55.6, 51.4, 50.8)

Park 2016 *(Continued)*

	Moderate/severe (based on ICS dose (medium/high), exacerbation history, and ACQ ≥ 1.5 on at least 2 occasions) participants also had to demonstrate post-bronchodilator FEV_1 reversibility ≥ 12% and ≥ 200 mL, or a positive response to methacholine challenge (PC_{20} ≤ 8 mg/mL) 1. Main inclusion/exclusion criteria: a. 2-6 exacerbations in the previous 12 months b. ACQ-6 score ≥ 1.5 at least twice during screening c. morning pre-bronchodilator FEV_1 40%-90% d. maintenance treatment with medium- to high-dose ICS in combination with LABA for ≥ 12 months 2. Mean age, years (SD): benralizumab 2 mg, 53 (11.3); benralizumab 20 mg, 56 (8.9); benralizumab 100 mg, 51 (13.8); placebo, 51 (11.8) 3. Male, 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	SC doses given at weeks 1, 4, 8, 16, 24, 32, 40. Benralizumab 2 mg, 20 mg or 100 mg SC
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)

Park 2016 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes reported

Pavord 2012a

Study characteristics	
Methods	Multicentre, double-blind, placebo-controlled study
Participants	621 participants with severe asthma despite receiving high doses of standard asthma medications 1. Main inclusion/exclusion criteria: a. ≥ 3% sputum eosinophils or blood eosinophil ≥ 300 cells/μL b. ≥ 2 exacerbations in previous 12 months c. maintenance treatment with high-dose ICS (i.e. ≥ 880 μg/d FP or equivalent daily); + additional controller; ± maintenance OCS 2. Mean age, years (SD): 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. Male, n (%): mepolizumab 750 mg, 93 (60); mepolizumab 250 mg, 93 (61%); mepolizumab 75 mg, 104 (68%); placebo, 97 (63%) 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 IV 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**

Pavord 2012a *(Continued)*

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
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; **ASUI**: Asthma Symptom Utility Index; **ECP**: eosinophil cationic protein; **ED**: emergency department; **EQ-5D-5L:** Euroquol 5-dimension, 5-level healthcare instrument; **FEF:** forced expiratory flow; **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; **LABA**: long-acting beta2-agonist; **OCS**: oral corticosteroids; **PC_{20}**: histamine provocative concentration causing a 20% drop in FEV_1;**PEFR**: peak expiratory flow rate; **RCT:** randomised controlled trial; **SC**: subcutaneous; **SD**: standard deviation; **SGRQ**: St. George's Respiratory Questionnaire; **ULN**: Upper Limit of Normal; **VC**: vital capacity.

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

Study	Reason for exclusion
Albers 2016	Post-hoc analysis of observational study
Albers 2020	Data pooled from 2 studies, also post hoc analysis looking at participants grouped by prior omalizumab use, which is not a subgroup prespecified in our protocol
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 2 clinical trials
Austin 2016a	Not an RCT (analysis of the characteristics of patients that entered 2 trials of mepolizumab)
Ayres 2004	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Bardford 2018	Post hoc analysis of mepolizumab study (MUSCA, Chupp 2017), looking at participants grouped by prior omalizumab use, which is not a subgroup prespecified in our protocol.
Bel 2014	Focus of trial is on steroid reduction and therefore does not meet our predefined inclusion criteria

Study	Reason for exclusion
Berger 2003	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Bernstein 2020a	Not asthma (wrong disease group)
Bjermer 2017	Only pooled data (from > 1 RCT) presented
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
Bleecker 2018a	Data pooled from 2 studies
Bleecker 2018b	Only pooled data (from > 1 RCT) presented
Boulet 1997	Intervention used in study (anti-IgE antibody e25) is not anti-IL-5 therapy
Bourdin 2018	Post hoc analysis of reslizumab study looking at patients grouped by presence or absence of allergen-specific IgE, which is not a subgroup prespecified in our protocol.
Bourdin 2020	This is not an RCT (it is a type of meta-analysis of other RCTs)
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 2 clinical trials
Brusselle 2017	Data pooled from 2 studies, also post hoc analysis looking at participants grouped by baseline step 4/5 therapy, which is not a subgroup prespecified in our protocol.
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

Study	Reason for exclusion
Canvin 2016	Aggregation of 2 clinical trials
Carr 2017	Data pooled from 2 studies
Carr 2019	Only pooled data (from > 1 RCT) presented
Castro 2011	< 16 weeks in length
Castro 2014	Intervention used in study (dupilumab) is not anti-IL-5 therapy
Castro 2018	Data pooled from 2 studies, also post hoc analysis looking at participants grouped by whether screening and baseline eosinophils > 400 or not, which is not a subgroup prespecified in our protocol
Chandra 1989	Intervention used in study (various foods) is not anti-IL-5 therapy
Chanez 2017	Only pooled data (from > 1 RCT) presented
Chanez 2017a	Only pooled data (from > 1 RCT) presented
Chanez 2018	Open-label extension not an RCT
Chanez 2019	Post hoc analysis of reslizumab study comparing participants who didn't have a blood eosinophil response to reslizumab to those who did, which is not a subgroup prespecified in our analysis
Chauhan 2017	Only pooled data (from > 1 RCT) presented
Chervinsky 2003	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Chipps 2017	Pooled data only (from SIROCCO (Bleecker 2016) and CALIMA FitzGerald 2016) studies; data are already in the analysis)
Chipps 2018	Only pooled data (from > 1 RCT) presented
Chipps 2019	Only pooled data (from > 1 RCT) presented
Chipps 2020	Only pooled data (from > 1 RCT) presented
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
Corren 2010	Intervention used in study (il-4r alpha 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
DuBuske 2018	Data pooled from 2 studies
Ebner 1989	Intervention used in study (immunotherapy) is not anti-IL-5 therapy

Study	Reason for exclusion
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
EUCTR2015-001152-29-BE	Not an RCT and endpoints are not applicable as this is a long-term access programme
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
EUCTR2017-003958-16-NL	Treatment duration < 16 weeks (12 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
Ferguson 2016a	Benralizumab for mild to moderate, persistent asthma: the BISE phase III study - duration < 16 weeks (12 weeks)
Ferguson 2016b	Treatment duration < 16 weeks in length
Ferguson 2017	Study duration < 16 weeks (12 weeks)
Finn 2003	Intervention used in study (omalizumab) is not anti-IL-5 therapy
FitzGerald 2017a	Post hoc analysis of CALIMA (FitzGerald 2016), benralizumab study looking at the subset of patients from Japan, which is not a subgroup prespecified in our protocol.
FitzGerald 2017b	Only pooled data (from > 1 RCT) presented
FitzGerald 2018	Only pooled data (from > 1 RCT) presented
Fitzgerald 2019	2-year safety study including 1 year in RCT (3 studies pooled) and 1 year open-label extension
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
Garin 2019	Only pooled data (from > 1 RCT) presented
Gauvreau 2011	Intervention used in study (anti-IL-13) is not anti-IL-5 therapy
Gauvreau 2014a	Intervention used in study (quilizumab) is not anti-IL-5 therapy
Gauvreau 2014b	Intervention used in study (anti-tslp) is not anti-IL-5 therapy
Gauvreau 2014c	Intervention used in study (OX40L antagonist) is not anti-IL-5 therapy
Gauvreau 2015a	Intervention used in study (ligelizumab) is not anti-IL-5 therapy

Study	Reason for exclusion
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
Gibson 2021	Wrong study design
Goldman 2017	Only pooled data (from > 1 RCT) presented
Gopalan 2017a	Data pooled from 2 studies
Gopalan 2017b	Data pooled from 2 studies
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
Hickey 2019	Only pooled data (from > 1 RCT) presented
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
Howarth 2020	Study focused on nasal polyps rather than asthma
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
Humbert 2009	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Humbert 2017	Post hoc analysis looking at participants in a reslizumab trial (BREATH) grouped by omalizumab eligibility, which is not a subgroup prespecified in our protocol
Humbert 2019	Data pooled from 2 mepolizumab studies (MENSA, MUSCA), post hoc analysis looking at participants grouped by omalizumab eligibility, which is not a subgroup prespecified in our protocol

Study	Reason for exclusion
Iino 2019	Study in eosinophilic otitis media not asthma
Jackson 2019	Pooled data only from trials that are already included (Bleecker 2016; FitzGerald 2016)
Jacobs 2018	Pooled data only from trials that are already included (Castro 2015a; Castro 2015b)
Jacquemin 1995	Intervention used in study (immunotherapy) is not anti-IL-5 therapy
Jimenez 2019	Aggregation of 5 studies
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
Katial 2019	Subgroup analysis by subgroups not relevant to our protocol
Katial 2020	Post hoc analysis of benralizumab study looking at patients grouped by high or low FeNO, which is not a subgroup prespecified in our protocol
Kim 2020	Pooled data only: mepolizumab IV (Pavord 2012a), and mepolizumab SC (Ortega 2014)
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
Korenblat 2018	Only pooled data (from > 1 RCT) presented
Kreindler 2019	Pooled data only from trials that are already included (Bleecker 2016; FitzGerald 2016)
Kuang 2018	Not asthma (hypereosinophilic syndrome)
Kuang 2019	Not asthma (hypereosinophilic syndrome)
Kulus 2010	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Lam 2018	Not a RCT (cost-effectiveness analysis incorporating multiple inputs, including but not only data from 2 RCTs)
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

Study	Reason for exclusion
Lugogo 2016	Not a randomised, placebo-controlled trial
Lugogo 2020	The intervention includes a reduction in standard asthma management (OCS maintenance), and as per our protocol, we have excluded such studies as the heterogeneity in study design makes them too dissimilar to compare
Manning 2018	Only pooled data (from > 1 RCT) presented
Maselli 2017	Trial involves OCS dose reduction (1 of our exclusion criteria)
Maspero 2016	Combined secondary analysis of 2 trials
Maspero 2018	Pooled data from 2 trials (Bleecker 2016; FitzGerald 2016)
Maspero 2019	Only pooled data (from > 1 RCT) presented
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
Mathur 2019	Pooled data from 2 trials (Bleecker 2016; FitzGerald 2016)
Mathur 2020	Only pooled data (from > 1 RCT) presented
Maunoury 2018	Not a RCT
Menzies-Gow 2019a	Trial involves OCS dose reduction (one of our exclusion criteria)
Menzies-Gow 2019b	Trial involves OCS dose reduction (one of our exclusion criteria)
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
Moran 2020	Not an RCT (observational study of patients with asthma and COPD)
Moss 1987	Intervention used in study (immunotherapy) is not anti-IL-5 therapy
Murphy 2018	Only pooled data (from > 1 RCT) presented
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
Nair 2017a	Trial involves OCS dose reduction (1 of our exclusion criteria)
Nair 2017b	Substudy of a trial involving OCS dose reduction (one of our exclusion criteria)
Nair 2017c	Trial involves OCS dose reduction (one of our exclusion criteria)
Nair 2020	Only pooled data (from > 1 RCT) presented

Study	Reason for exclusion
NCT00783289	Treatment duration < 16 weeks
NCT00802438	Not RCT
NCT01290887	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 IV to Japanese healthy male participants. People with asthma were not included in the study.
NCT01520051	Duration < 16 weeks, additional intervention (experimental rhinovirus infection)
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 SC (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 SC (no control group)
NCT02020889	The study participants did not have asthma
NCT02075255	Focus of trial is on oral steroid reduction
NCT02135692	This study does not include a placebo group. Multi-centre, open-label, long-term study of SC administered mepolizumab 100 mg in addition to standard care, in participants with severe eosinophilic asthma
NCT02258542	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
NCT02377427	Treatment period < 16 weeks
NCT02417961	Not a RCT
NCT02501629	Focus of trial is on oral steroid reduction
NCT02559791	Not placebo-controlled - single treatment arm only
NCT02594332	Study terminated (recruitment problems)
NCT02654145	Not placebo-controlled. Single treatment arm only
NCT02808819	Not an RCT
NCT02814643	Treatment duration < 16 weeks
NCT02821416	Duration < 16 weeks, additional intervention (allergen challenge)
NCT02869438	Treatment duration < 16 weeks
NCT02937168	Treatment duration < 16 weeks

Study	Reason for exclusion
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
NCT03476109	No placebo comparator
NCT04617171	Treatment of participants with acute asthma exacerbation, not chronic asthma
NCT04710134	Ineligble study design
Nelsen 2019	Pooled data from 2 trials (Chupp 2017; Ortega 2014), and a 3rd observational study
Newbold 2016	Not an RCT
Newbold 2017	Pooled data from 2 trials (Bleecker 2016; FitzGerald 2016)
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
O'Quinn 2019	Only pooled data (from > 1 RCT) presented
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
Ohta 2017	Post hoc analysis of CALIMA (FitzGerald 2016), benralizumab study looking at the subset of patients from Japan, which is not a subgroup prespecified in our protocol
Ong 2005	Intervention used in study (omalizumab) is not anti-IL-5 therapy
Ortega 2018a	Only pooled data (from > 1 RCT) presented
Ortega 2018b	Only pooled data (from > 1 RCT) presented
Panettieri 2017	Post hoc analysis of reslizumab study looking at participants who had an FEV_1 < 50%, which is not a subgroup prespecified in our analysis
Park 1998	Not an RCT

Study	Reason for exclusion
Park 2018	Post hoc analysis of SIROCCO (Bleecker 2016), benralizumab study looking at the subset of patients from Korea, which is not a subgroup prespecified in our protocol
Park 2019	Post hoc analysis of SIROCCO (Bleecker 2016) benralizumab study looking at the subset of patients from Korea, which is not a subgroup prespecified in our protocol
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 2012	Posthoc analysis of Pavord 2012a and Ortega 2014 stratified by prior use of anti-IgE therapy
Pelaia 2016	Study is not an RCT
Pham 2016	An analysis of sera collected from asthma patients enrolled in 2 clinical studies
Piper 2012	Intervention used in study (tralokinumab) is not anti-IL-5 therapy
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 2 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
Roskos 2018	Pooled data from 2 trials (Bleecker 2016; FitzGerald 2016)
Roufosse 2020	Not asthma (hypereosinophilic syndrome)
Sakamoto 1984	Not an 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
Shaw 2019	Trial involves oral corticosteroid dose reduction (one of our exclusion criteria).
Shrimanker 2018	Only pooled data (from > 1 RCT) presented
Shrimanker 2019	Only pooled data (from > 1 RCT) presented
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

Study	Reason for exclusion
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
Steinfeld 2020	Not asthma (hypereosinophilic syndrome)
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 an RCT
Tanaka 1993	Intervention used in study (influenza vaccine) is not anti-IL-5 therapy
Terr 1969	Study predates monoclonal treatments
Vanlandingham 2019	Only pooled data (from > 1 RCT) presented
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 2 clinical trials
Virchow 2017	Only pooled data (from > 1 RCT) presented
Virchow 2019	Only pooled data (from > 1 RCT) presented
Virchow 2020	Only pooled data (from > 1 RCT) presented
Virchow 2020a	Only pooled data (from >1 RCT) presented
Wang 2015	Pharmacometrics assessment of phase IIb data to characterise the exposure-response relationship with benralizumab in adults with asthma
Wang 2017	Only pooled data (from > 1 RCT) presented
Wark 2003	Intervention used in study (itraconazole) is not anti-IL-5 therapy
Wechsler 2017	Pooled data from 2 trials (Castro 2015a; Castro 2015b)
Wechsler 2017a	Only pooled data (from > 1 RCT) presented
Wechsler 2019	Only pooled data (from > 1 RCT) presented

Study	Reason for exclusion
Wechsler 2020	Post hoc analysis of reslizumab studies looking at participants who had ≥ 2 or ≥ 3 exacerbations, which is not a subgroup prespecified in our analysis
Weinstein 2016	Combined secondary analysis of 2 trials
Wenzel 2009	Intervention used in study (golimumab) is not anti-IL-5 therapy
Wenzel 2013	Interventionused in study (dupilumab) is not anti-IL-5 therapy
Wenzel 2013a	Intervention used in study (dupilumab) is not anti-IL-5 therapy
Wenzel 2014	Intervention used in study (dupilumab) is not anti-IL-5 therapy
Xu 2017	Pooled data from 2 trials (Bleecker 2016; FitzGerald 2016)
Xu 2018	Pooled data from 2 trials (Bleecker 2016; FitzGerald 2016)
Yan 2015	Participants do not have a diagnosis of asthma
Yancey 2017	Analysis of subgroup not relevant to our protocol (participants with ≥ 3 exacerbations and eosinophils ≥ 300/µL)
Yancey 2020	Analysis of subgroup not relevant to our protocol
Zangrilli 2019	Pooled data from 2 trials (Bleecker 2016; FitzGerald 2016)
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

COPD: chronic obstructive pulmonary disease; **FeNO**: exhaled fraction of nitric oxide; **IV:** intravenous; **OCS:** oral corticosteroid; **RCT**: randomised controlled trial; **SC:** subcutaneous

DATA AND ANALYSES

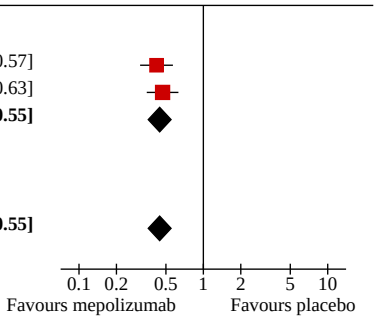
Comparison 1. Mepolizumab (SC) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Rate of exacerbations requiring systemic corticosteroids	2	936	Rate Ratio (IV, Random, 95% CI)	0.45 [0.36, 0.55]
1.1.1 Eosinophilic	2	936	Rate Ratio (IV, Random, 95% CI)	0.45 [0.36, 0.55]
1.2 At least one clinically significant exacerbation	1	295	Odds Ratio (M-H, Random, 95% CI)	0.59 [0.37, 0.93]
1.2.1 Eosinophilic	1	295	Odds Ratio (M-H, Random, 95% CI)	0.59 [0.37, 0.93]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Rate of exacerbations requiring admission	2	936	Rate Ratio (IV, Random, 95% CI)	0.31 [0.13, 0.73]
1.3.1 Eosinophilic	2	936	Rate Ratio (IV, Random, 95% CI)	0.31 [0.13, 0.73]
1.4 Rate of exacerbations requiring ED treatment or admission	2	936	Rate Ratio (IV, Random, 95% CI)	0.36 [0.20, 0.66]
1.4.1 Eosinophilic	2	936	Rate Ratio (IV, Random, 95% CI)	0.36 [0.20, 0.66]
1.5 Health-related quality of life (ACQ)	3	1231	Mean Difference (IV, Random, 95% CI)	-0.38 [-0.50, -0.26]
1.5.1 Eosinophilic	3	1231	Mean Difference (IV, Random, 95% CI)	-0.38 [-0.50, -0.26]
1.6 Health-related quality of life (SGRQ)	3	1231	Mean Difference (IV, Random, 95% CI)	-6.37 [-8.76, -3.98]
1.6.1 Eosinophilic	3	1231	Mean Difference (IV, Random, 95% CI)	-6.37 [-8.76, -3.98]
1.7 Pre-bronchodilator FEV_1 (litres)	3	1231	Mean Difference (IV, Random, 95% CI)	0.09 [0.05, 0.14]
1.7.1 Eosinophilic	3	1231	Mean Difference (IV, Random, 95% CI)	0.09 [0.05, 0.14]
1.8 Serious adverse events	3	1231	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.46, 1.01]
1.8.1 Eosinophilic	3	1231	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.46, 1.01]
1.9 Adverse events leading to discontinuation	3	1231	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.19, 1.85]
1.9.1 Eosinophilic	3	1231	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.19, 1.85]

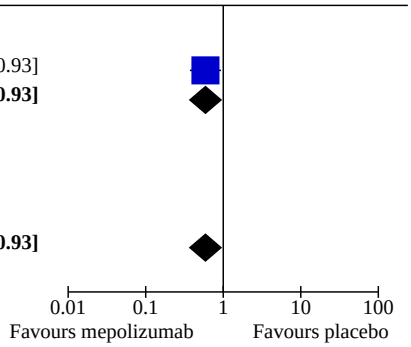
Analysis 1.1. Comparison 1: Mepolizumab (SC) versus placebo, Outcome 1: Rate of exacerbations requiring systemic corticosteroids

Study or Subgroup	log[Rate Ratio]	SE	Mepolizumab Total	Placebo Total	Weight	Rate Ratio IV, Random, 95% CI
1.1.1 Eosinophilic						
Chupp 2017	-0.8675	0.1549	274	277	48.2%	0.42 [0.31 , 0.57]
Ortega 2014	-0.755	0.1495	194	191	51.8%	0.47 [0.35 , 0.63]
Subtotal (95% CI)			**468**	**468**	**100.0%**	**0.45 [0.36 , 0.55]**
Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 1 (P = 0.60); I² = 0%						
Test for overall effect: Z = 7.52 (P < 0.00001)						
Total (95% CI)			**468**	**468**	**100.0%**	**0.45 [0.36 , 0.55]**
Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 1 (P = 0.60); I² = 0%						
Test for overall effect: Z = 7.52 (P < 0.00001)						
Test for subgroup differences: Not applicable						



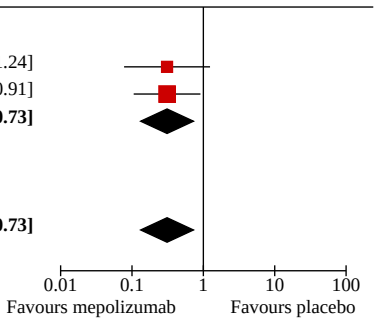
Analysis 1.2. Comparison 1: Mepolizumab (SC) versus placebo, Outcome 2: At least one clinically significant exacerbation

Study or Subgroup	Mepolizumab Events	Mepolizumab Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
1.2.1 Eosinophilic						
Moore 2022	66	144	89	151	100.0%	0.59 [0.37 , 0.93]
Subtotal (95% CI)		**144**		**151**	**100.0%**	**0.59 [0.37 , 0.93]**
Total events:	66		89			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.25 (P = 0.02)						
Total (95% CI)		**144**		**151**	**100.0%**	**0.59 [0.37 , 0.93]**
Total events:	66		89			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.25 (P = 0.02)						
Test for subgroup differences: Not applicable						

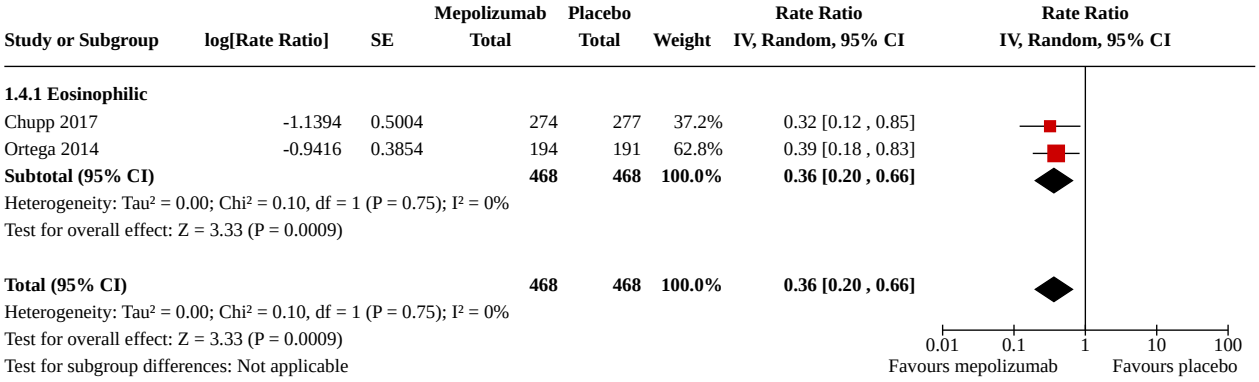


Analysis 1.3. Comparison 1: Mepolizumab (SC) versus placebo, Outcome 3: Rate of exacerbations requiring admission

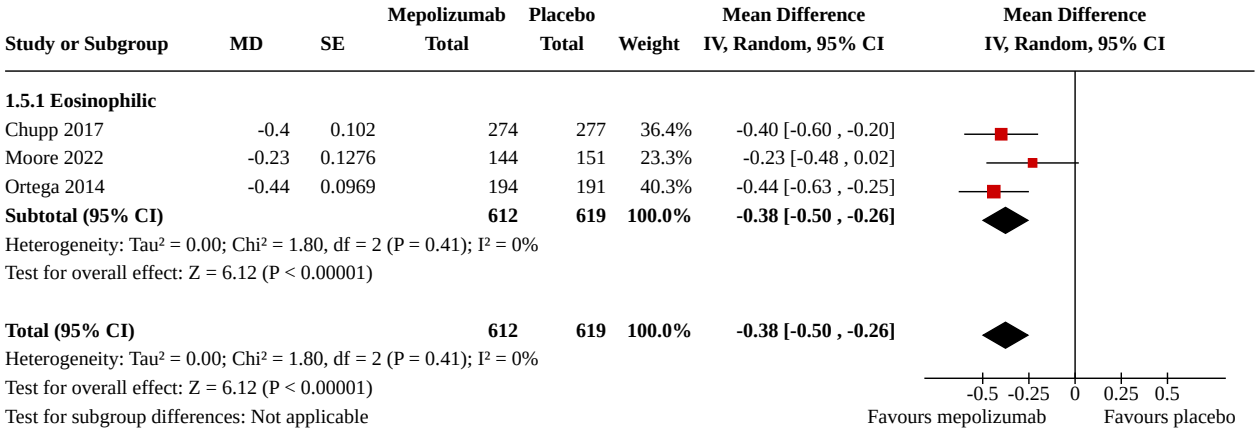
Study or Subgroup	log[Rate Ratio]	SE	Mepolizumab Total	Placebo Total	Weight	Rate Ratio IV, Random, 95% CI
1.3.1 Eosinophilic						
Chupp 2017	-1.1712	0.7073	274	277	37.6%	0.31 [0.08 , 1.24]
Ortega 2014	-1.1712	0.5494	194	191	62.4%	0.31 [0.11 , 0.91]
Subtotal (95% CI)			**468**	**468**	**100.0%**	**0.31 [0.13 , 0.73]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 2.70 (P = 0.007)						
Total (95% CI)			**468**	**468**	**100.0%**	**0.31 [0.13 , 0.73]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 2.70 (P = 0.007)						
Test for subgroup differences: Not applicable						



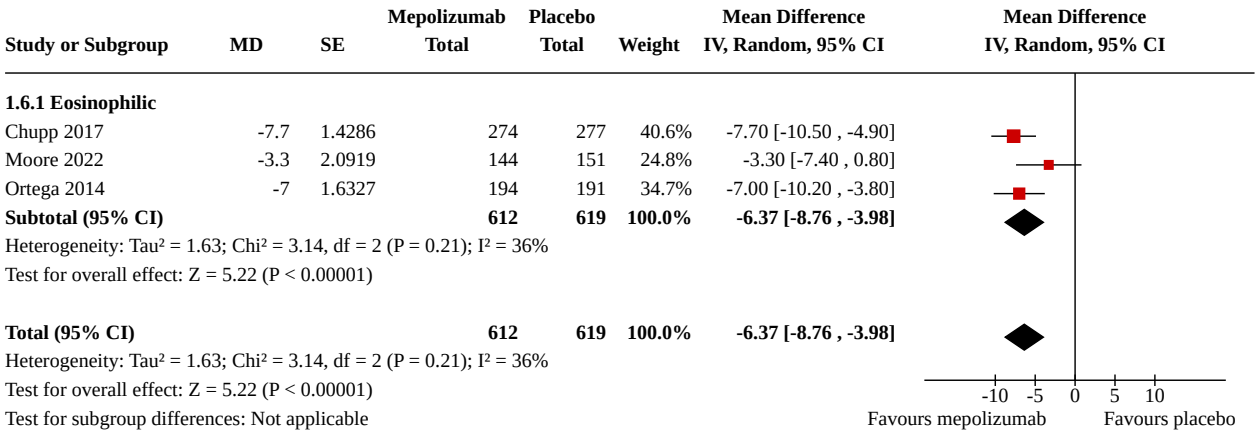
Analysis 1.4. Comparison 1: Mepolizumab (SC) versus placebo, Outcome 4: Rate of exacerbations requiring ED treatment or admission



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

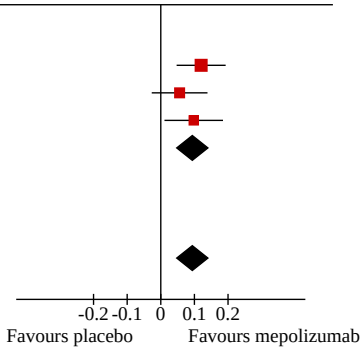


Analysis 1.6. Comparison 1: Mepolizumab (SC) versus placebo, Outcome 6: Health-related quality of life (SGRQ)



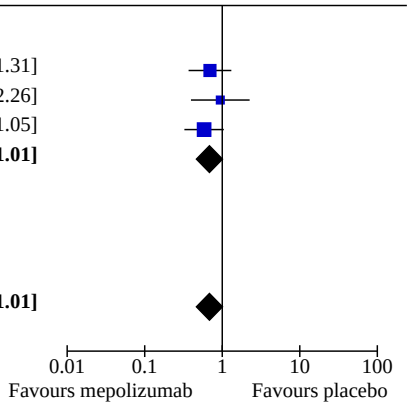
Analysis 1.7. Comparison 1: Mepolizumab (SC) versus placebo, Outcome 7: Pre-bronchodilator FEV $_1$ (litres)

Study or Subgroup	MD	SE	Mepolizumab Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
1.7.1 Eosinophilic						
Chupp 2017	0.12	0.0372	274	277	40.4%	0.12 [0.05 , 0.19]
Moore 2022	0.056	0.0423	144	151	31.2%	0.06 [-0.03 , 0.14]
Ortega 2014	0.098	0.0444	194	191	28.4%	0.10 [0.01 , 0.19]
Subtotal (95% CI)			**612**	**619**	**100.0%**	**0.09 [0.05 , 0.14]**
Heterogeneity: Tau² = 0.00; Chi² = 1.30, df = 2 (P = 0.52); I² = 0%						
Test for overall effect: Z = 3.97 (P < 0.0001)						
Total (95% CI)			**612**	**619**	**100.0%**	**0.09 [0.05 , 0.14]**
Heterogeneity: Tau² = 0.00; Chi² = 1.30, df = 2 (P = 0.52); I² = 0%						
Test for overall effect: Z = 3.97 (P < 0.0001)						
Test for subgroup differences: Not applicable						



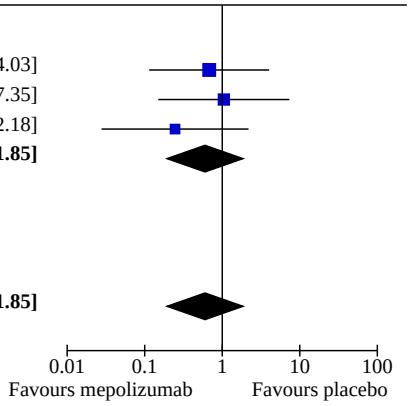
Analysis 1.8. Comparison 1: Mepolizumab (SC) versus placebo, Outcome 8: Serious adverse events

Study or Subgroup	Mepolizumab Events	Mepolizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Eosinophilic						
Chupp 2017	15	273	22	278	36.9%	0.69 [0.37 , 1.31]
Moore 2022	9	144	10	151	19.6%	0.94 [0.39 , 2.26]
Ortega 2014	16	194	27	191	43.5%	0.58 [0.32 , 1.05]
Subtotal (95% CI)		**611**		**620**	**100.0%**	**0.68 [0.46 , 1.01]**
Total events:	40		59			
Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 2 (P = 0.67); I² = 0%						
Test for overall effect: Z = 1.93 (P = 0.05)						
Total (95% CI)		**611**		**620**	**100.0%**	**0.68 [0.46 , 1.01]**
Total events:	40		59			
Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 2 (P = 0.67); I² = 0%						
Test for overall effect: Z = 1.93 (P = 0.05)						
Test for subgroup differences: Not applicable						



Analysis 1.9. Comparison 1: Mepolizumab (SC) versus placebo, Outcome 9: Adverse events leading to discontinuation

Study or Subgroup	Mepolizumab Events	Mepolizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 Eosinophilic						
Chupp 2017	2	273	3	278	39.9%	0.68 [0.11 , 4.03]
Moore 2022	2	144	2	151	33.4%	1.05 [0.15 , 7.35]
Ortega 2014	1	194	4	191	26.6%	0.25 [0.03 , 2.18]
Subtotal (95% CI)		**611**		**620**	**100.0%**	**0.60 [0.19 , 1.85]**
Total events:	5		9			
Heterogeneity: Tau² = 0.00; Chi² = 0.99, df = 2 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.89 (P = 0.37)						
Total (95% CI)		**611**		**620**	**100.0%**	**0.60 [0.19 , 1.85]**
Total events:	5		9			
Heterogeneity: Tau² = 0.00; Chi² = 0.99, df = 2 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.89 (P = 0.37)						
Test for subgroup differences: Not applicable						



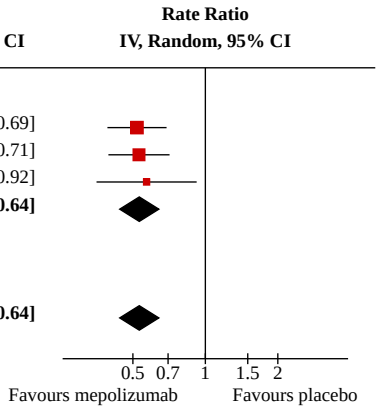
Comparison 2. Mepolizumab (IV) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Rate of clinically significant exacerbations	3	751	Rate Ratio (IV, Random, 95% CI)	0.53 [0.44, 0.64]
2.1.1 Eosinophilic	3	751	Rate Ratio (IV, Random, 95% CI)	0.53 [0.44, 0.64]
2.2 Rate of exacerbations requiring emergency department treatment or admission	2	690	Rate Ratio (IV, Random, 95% CI)	0.52 [0.31, 0.87]
2.2.1 Eosinophilic	2	690	Rate Ratio (IV, Random, 95% CI)	0.52 [0.31, 0.87]
2.3 Rate of exacerbations requiring admission	2	690	Rate Ratio (IV, Random, 95% CI)	0.61 [0.33, 1.13]
2.3.1 Eosinophilic	2	690	Rate Ratio (IV, Random, 95% CI)	0.61 [0.33, 1.13]
2.4 People with one or more exacerbations	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.4.1 Eosinophilic	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.5 Health-related quality of life (AQLQ)	2	369	Mean Difference (IV, Random, 95% CI)	0.21 [-0.06, 0.47]
2.5.1 Eosinophilic	2	369	Mean Difference (IV, Random, 95% CI)	0.21 [-0.06, 0.47]
2.6 Health-related quality of life (ACQ)	2	369	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.32, 0.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.6.1 Eosinophilic	2	369	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.32, 0.09]
2.7 Health-related quality of life (SGRQ)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.7.1 Eosinophilic	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.8 Pre-bronchodilator FEV_1 (litres)	2	690	Mean Difference (IV, Random, 95% CI)	0.08 [0.02, 0.15]
2.8.1 Eosinophilic	2	690	Mean Difference (IV, Random, 95% CI)	0.08 [0.02, 0.15]
2.9 Serious adverse events	3	751	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.37, 0.94]
2.9.1 Eosinophilic	3	751	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.37, 0.94]
2.10 Adverse events leading to discontinuation	3	751	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.18, 2.92]
2.10.1 Eosinophilic	3	751	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.18, 2.92]
2.11 Blood eosinophil level (cells/µL)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.11.1 Eosinophilic	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

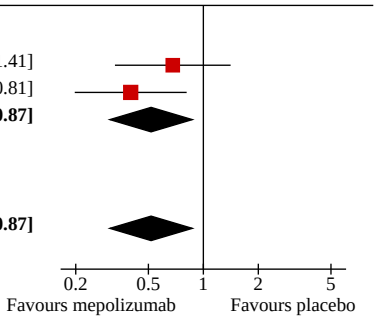
Analysis 2.1. Comparison 2: Mepolizumab (IV) versus placebo, Outcome 1: Rate of clinically significant exacerbations

Study or Subgroup	log[Rate Ratio]	SE	Mepolizumab Total	Placebo Total	Weight	Rate Ratio IV, Random, 95% CI
2.1.1 Eosinophilic						
Pavord 2012a	-0.6539	0.1443	153	155	43.8%	0.52 [0.39 , 0.69]
Ortega 2014	-0.6349	0.1492	191	191	40.9%	0.53 [0.40 , 0.71]
Haldar 2009	-0.5621	0.2443	29	32	15.3%	0.57 [0.35 , 0.92]
Subtotal (95% CI)			**373**	**378**	**100.0%**	**0.53 [0.44 , 0.64]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.11$, df = 2 (P = 0.95); $I^2 = 0\%$						
Test for overall effect: Z = 6.62 (P < 0.00001)						
Total (95% CI)			**373**	**378**	**100.0%**	**0.53 [0.44 , 0.64]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.11$, df = 2 (P = 0.95); $I^2 = 0\%$						
Test for overall effect: Z = 6.62 (P < 0.00001)						
Test for subgroup differences: Not applicable						



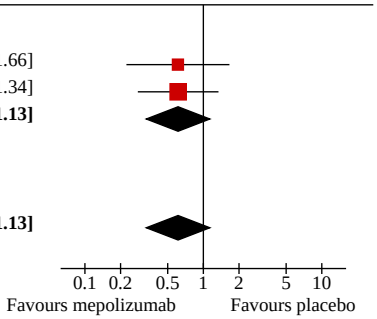
Analysis 2.2. Comparison 2: Mepolizumab (IV) versus placebo, Outcome 2: Rate of exacerbations requiring emergency department treatment or admission

Study or Subgroup	log[Rate Ratio]	SE	Mepolizumab Total	Placebo Total	Weight	Rate Ratio IV, Random, 95% CI
2.2.1 Eosinophilic						
Ortega 2014	-0.3857	0.3721	191	191	48.4%	0.68 [0.33 , 1.41]
Pavord 2012a	-0.9163	0.36	153	155	51.6%	0.40 [0.20 , 0.81]
Subtotal (95% CI)			**344**	**346**	**100.0%**	**0.52 [0.31 , 0.87]**
Heterogeneity: Tau² = 0.01; Chi² = 1.05, df = 1 (P = 0.31); I² = 5%						
Test for overall effect: Z = 2.49 (P = 0.01)						
Total (95% CI)			**344**	**346**	**100.0%**	**0.52 [0.31 , 0.87]**
Heterogeneity: Tau² = 0.01; Chi² = 1.05, df = 1 (P = 0.31); I² = 5%						
Test for overall effect: Z = 2.49 (P = 0.01)						
Test for subgroup differences: Not applicable						



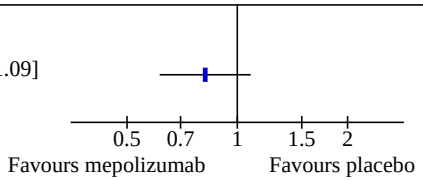
Analysis 2.3. Comparison 2: Mepolizumab (IV) versus placebo, Outcome 3: Rate of exacerbations requiring admission

Study or Subgroup	log[Rate Ratio]	SE	Mepolizumab Total	Placebo Total	Weight	Rate Ratio IV, Random, 95% CI
2.3.1 Eosinophilic						
Ortega 2014	-0.4943	0.5108	191	191	38.0%	0.61 [0.22 , 1.66]
Pavord 2012a	-0.49	0.4	153	155	62.0%	0.61 [0.28 , 1.34]
Subtotal (95% CI)			**344**	**346**	**100.0%**	**0.61 [0.33 , 1.13]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 1.56 (P = 0.12)						
Total (95% CI)			**344**	**346**	**100.0%**	**0.61 [0.33 , 1.13]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 1.56 (P = 0.12)						
Test for subgroup differences: Not applicable						



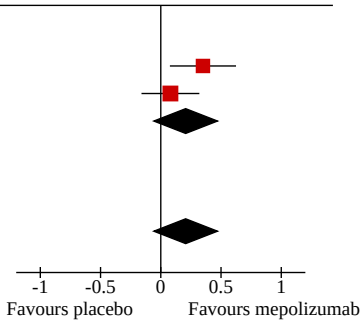
Analysis 2.4. Comparison 2: Mepolizumab (IV) versus placebo, Outcome 4: People with one or more exacerbations

Study or Subgroup	Mepolizumab Events	Mepolizumab Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
2.4.1 Eosinophilic					
Haldar 2009	20	29	27	32	0.82 [0.61 , 1.09]



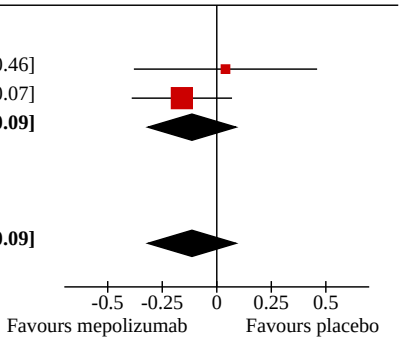
Analysis 2.5. Comparison 2: Mepolizumab (IV) versus placebo, Outcome 5: Health-related quality of life (AQLQ)

Study or Subgroup	MD	SE	Mepolizumab Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
2.5.1 Eosinophilic						
Haldar 2009	0.35	0.14	29	32	46.8%	0.35 [0.08 , 0.62]
Pavord 2012a	0.08	0.1225	153	155	53.2%	0.08 [-0.16 , 0.32]
Subtotal (95% CI)			**182**	**187**	**100.0%**	**0.21 [-0.06 , 0.47]**
Heterogeneity: Tau² = 0.02; Chi² = 2.11, df = 1 (P = 0.15); I² = 53%						
Test for overall effect: Z = 1.53 (P = 0.13)						
Total (95% CI)			**182**	**187**	**100.0%**	**0.21 [-0.06 , 0.47]**
Heterogeneity: Tau² = 0.02; Chi² = 2.11, df = 1 (P = 0.15); I² = 53%						
Test for overall effect: Z = 1.53 (P = 0.13)						
Test for subgroup differences: Not applicable						



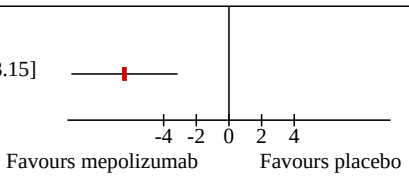
Analysis 2.6. Comparison 2: Mepolizumab (IV) versus placebo, Outcome 6: Health-related quality of life (ACQ)

Study or Subgroup	MD	SE	Mepolizumab Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
2.6.1 Eosinophilic						
Haldar 2009	0.04	0.2143	29	32	23.1%	0.04 [-0.38 , 0.46]
Pavord 2012a	-0.16	0.1173	153	155	76.9%	-0.16 [-0.39 , 0.07]
Subtotal (95% CI)			**182**	**187**	**100.0%**	**-0.11 [-0.32 , 0.09]**
Heterogeneity: Chi² = 0.67, df = 1 (P = 0.41); I² = 0%						
Test for overall effect: Z = 1.11 (P = 0.27)						
Total (95% CI)			**182**	**187**	**100.0%**	**-0.11 [-0.32 , 0.09]**
Heterogeneity: Chi² = 0.67, df = 1 (P = 0.41); I² = 0%						
Test for overall effect: Z = 1.11 (P = 0.27)						
Test for subgroup differences: Not applicable						



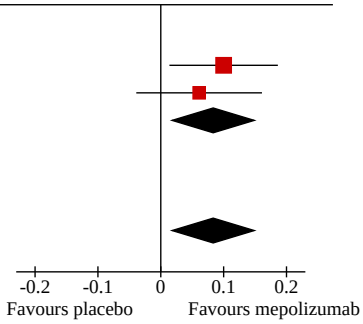
Analysis 2.7. Comparison 2: Mepolizumab (IV) versus placebo, Outcome 7: Health-related quality of life (SGRQ)

Study or Subgroup	MD	SE	Mepolizumab Total	Placebo Total	Mean Difference IV, Random, 95% CI
2.7.1 Eosinophilic					
Ortega 2014	-6.4	1.66	191	191	-6.40 [-9.65 , -3.15]



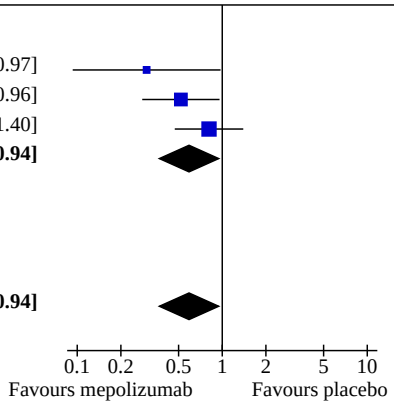
Analysis 2.8. Comparison 2: Mepolizumab (IV) versus placebo, Outcome 8: Pre-bronchodilator FEV $_1$ (litres)

Study or Subgroup	MD	SE	Mepolizumab Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
2.8.1 Eosinophilic						
Ortega 2014	0.1	0.044	191	191	57.3%	0.10 [0.01 , 0.19]
Pavord 2012a	0.061	0.051	153	155	42.7%	0.06 [-0.04 , 0.16]
Subtotal (95% CI)			**344**	**346**	**100.0%**	**0.08 [0.02 , 0.15]**
Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 2.50 (P = 0.01)						
Total (95% CI)			**344**	**346**	**100.0%**	**0.08 [0.02 , 0.15]**
Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 2.50 (P = 0.01)						
Test for subgroup differences: Not applicable						



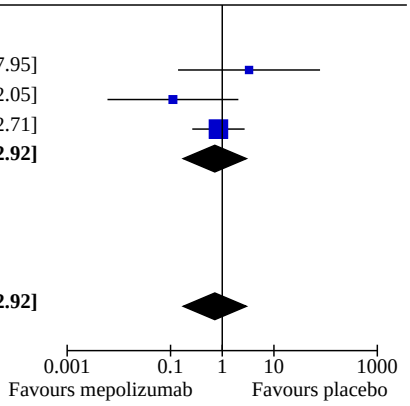
Analysis 2.9. Comparison 2: Mepolizumab (IV) versus placebo, Outcome 9: Serious adverse events

Study or Subgroup	Mepolizumab Events	Mepolizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.9.1 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]
Subtotal (95% CI)		**373**		**378**	**100.0%**	**0.59 [0.37 , 0.94]**
Total events:	37		63			
Heterogeneity: Tau² = 0.05; Chi² = 2.72, df = 2 (P = 0.26); I² = 27%						
Test for overall effect: Z = 2.20 (P = 0.03)						
Total (95% CI)		**373**		**378**	**100.0%**	**0.59 [0.37 , 0.94]**
Total events:	37		63			
Heterogeneity: Tau² = 0.05; Chi² = 2.72, df = 2 (P = 0.26); I² = 27%						
Test for overall effect: Z = 2.20 (P = 0.03)						
Test for subgroup differences: Not applicable						



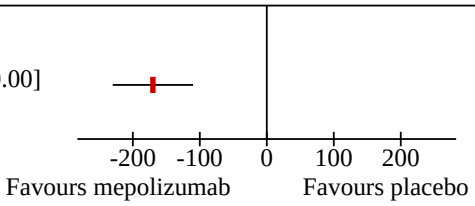
Analysis 2.10. Comparison 2: Mepolizumab (IV) versus placebo, Outcome 10: Adverse events leading to discontinuation

Study or Subgroup	Mepolizumab Events	Mepolizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.10.1 Eosinophilic						
Haldar 2009	1	29	0	32	16.8%	3.30 [0.14 , 77.95]
Ortega 2014	0	191	4	191	19.3%	0.11 [0.01 , 2.05]
Pavord 2012a	5	153	6	155	64.0%	0.84 [0.26 , 2.71]
Subtotal (95% CI)		**373**		**378**	**100.0%**	**0.72 [0.18 , 2.92]**
Total events:	6		10			
Heterogeneity: Tau² = 0.45; Chi² = 2.62, df = 2 (P = 0.27); I² = 24%						
Test for overall effect: Z = 0.46 (P = 0.64)						
Total (95% CI)		**373**		**378**	**100.0%**	**0.72 [0.18 , 2.92]**
Total events:	6		10			
Heterogeneity: Tau² = 0.45; Chi² = 2.62, df = 2 (P = 0.27); I² = 24%						
Test for overall effect: Z = 0.46 (P = 0.64)						
Test for subgroup differences: Not applicable						



Analysis 2.11. Comparison 2: Mepolizumab (IV) versus placebo, Outcome 11: Blood eosinophil level (cells/µL)

Study or Subgroup	MD	SE	Mean Difference IV, Fixed, 95% CI
2.11.1 Eosinophilic			
Haldar 2009	-170	30.6128	-170.00 [-230.00 , -110.00]



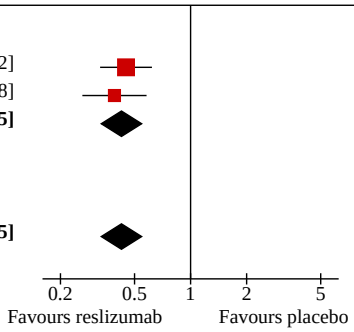
Comparison 3. Reslizumab (IV) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Rate of exacerbations requiring systemic corticosteroids	2	953	Rate Ratio (IV, Fixed, 95% CI)	0.43 [0.33, 0.55]
3.1.1 Eosinophilic	2	953	Rate Ratio (IV, Fixed, 95% CI)	0.43 [0.33, 0.55]
3.2 Rate of exacerbations requiring emergency department treatment or admission	2	953	Rate Ratio (IV, Fixed, 95% CI)	0.67 [0.39, 1.17]
3.2.1 Eosinophilic	2	953	Rate Ratio (IV, Fixed, 95% CI)	0.67 [0.39, 1.17]
3.3 Health-related quality of life (AQLQ)	3	1164	Mean Difference (IV, Fixed, 95% CI)	0.28 [0.17, 0.39]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3.1 Eosinophilic	3	1164	Mean Difference (IV, Fixed, 95% CI)	0.28 [0.17, 0.39]
3.4 Health-related quality of life (ACQ)	4	1652	Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.33, -0.17]
3.4.1 Eosinophilic	4	1260	Mean Difference (IV, Fixed, 95% CI)	-0.27 [-0.36, -0.19]
3.4.2 Non-eosinophilic	1	392	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.33, 0.09]
3.5 Pre-bronchodilator FEV_1 (litres)	4	1652	Mean Difference (IV, Fixed, 95% CI)	0.11 [0.07, 0.15]
3.5.1 Eosinophilic	4	1260	Mean Difference (IV, Fixed, 95% CI)	0.12 [0.08, 0.16]
3.5.2 Non-eosinophilic	1	392	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.07, 0.14]
3.6 Serious adverse events	4	1656	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.56, 1.12]
3.6.1 Eosinophilic	3	1160	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.51, 1.22]
3.6.2 Eosinophil status unknown	1	496	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.34, 2.88]
3.7 Adverse events leading to discontinuation	4	1659	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.43, 1.02]
3.7.1 Eosinophilic	3	1163	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.37, 1.20]
3.7.2 Eosinophil status unknown	1	496	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.35, 1.23]
3.8 Blood eosinophil level (cells/µL)	4	1656	Mean Difference (IV, Fixed, 95% CI)	-476.83 [-499.32, -454.34]
3.8.1 Eosinophilic	4	1656	Mean Difference (IV, Fixed, 95% CI)	-476.83 [-499.32, -454.34]

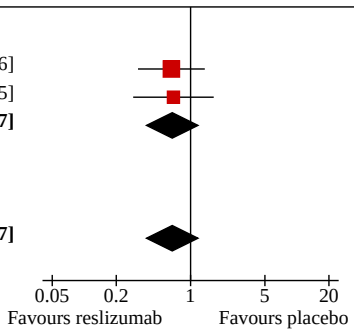
Analysis 3.1. Comparison 3: Reslizumab (IV) versus placebo, Outcome 1: Rate of exacerbations requiring systemic corticosteroids

Study or Subgroup	log[Rate Ratio]	SE	Reslizumab Total	Placebo Total	Weight	Rate Ratio IV, Fixed, 95% CI
3.1.1 Eosinophilic						
Castro 2015a	-0.7985	0.1635	245	244	60.5%	0.45 [0.33 , 0.62]
Castro 2015b	-0.9416	0.2025	232	232	39.5%	0.39 [0.26 , 0.58]
Subtotal (95% CI)			**477**	**476**	**100.0%**	**0.43 [0.33 , 0.55]**
Heterogeneity: Chi² = 0.30, df = 1 (P = 0.58); I² = 0%						
Test for overall effect: Z = 6.72 (P < 0.00001)						
Total (95% CI)			**477**	**476**	**100.0%**	**0.43 [0.33 , 0.55]**
Heterogeneity: Chi² = 0.30, df = 1 (P = 0.58); I² = 0%						
Test for overall effect: Z = 6.72 (P < 0.00001)						
Test for subgroup differences: Not applicable						



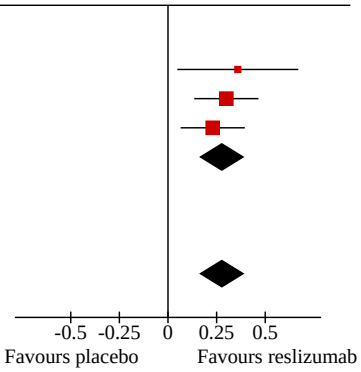
Analysis 3.2. Comparison 3: Reslizumab (IV) versus placebo, Outcome 2: Rate of exacerbations requiring emergency department treatment or admission

Study or Subgroup	log[Rate Ratio]	SE	Reslizumab Total	Placebo Total	Weight	Rate Ratio IV, Fixed, 95% CI
3.2.1 Eosinophilic						
Castro 2015a	-0.4155	0.3689	245	244	59.2%	0.66 [0.32 , 1.36]
Castro 2015b	-0.3711	0.4448	232	232	40.8%	0.69 [0.29 , 1.65]
Subtotal (95% CI)			**477**	**476**	**100.0%**	**0.67 [0.39 , 1.17]**
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%						
Test for overall effect: Z = 1.40 (P = 0.16)						
Total (95% CI)			**477**	**476**	**100.0%**	**0.67 [0.39 , 1.17]**
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%						
Test for overall effect: Z = 1.40 (P = 0.16)						
Test for subgroup differences: Not applicable						



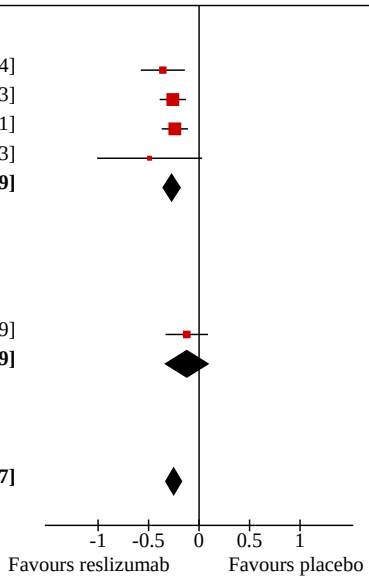
Analysis 3.3. Comparison 3: Reslizumab (IV) versus placebo, Outcome 3: Health-related quality of life (AQLQ)

Study or Subgroup	MD	SE	Reslizumab Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
3.3.1 Eosinophilic						
Bjermer 2016	0.359	0.1587	106	105	12.3%	0.36 [0.05 , 0.67]
Castro 2015a	0.3	0.0842	245	244	43.8%	0.30 [0.13 , 0.47]
Castro 2015b	0.23	0.0842	232	232	43.8%	0.23 [0.06 , 0.40]
Subtotal (95% CI)			**583**	**581**	**100.0%**	**0.28 [0.17 , 0.39]**
Heterogeneity: Chi² = 0.65, df = 2 (P = 0.72); I² = 0%						
Test for overall effect: Z = 4.96 (P < 0.00001)						
Total (95% CI)			**583**	**581**	**100.0%**	**0.28 [0.17 , 0.39]**
Heterogeneity: Chi² = 0.65, df = 2 (P = 0.72); I² = 0%						
Test for overall effect: Z = 4.96 (P < 0.00001)						
Test for subgroup differences: Not applicable						



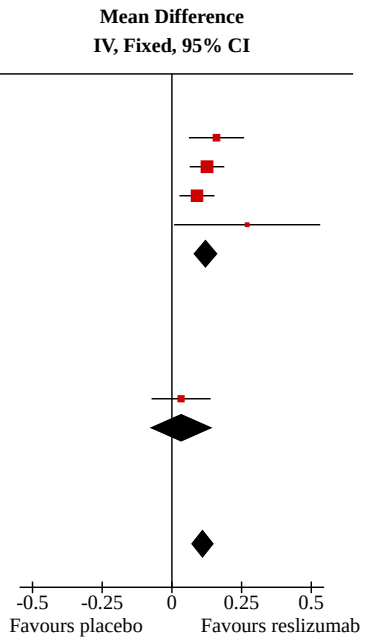
Analysis 3.4. Comparison 3: Reslizumab (IV) versus placebo, Outcome 4: Health-related quality of life (ACQ)

Study or Subgroup	MD	SE	Reslizumab Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
3.4.1 Eosinophilic						
Bjermer 2016	-0.359	0.1112	106	105	12.7%	-0.36 [-0.58 , -0.14]
Castro 2015a	-0.26	0.0663	245	244	35.7%	-0.26 [-0.39 , -0.13]
Castro 2015b	-0.24	0.0663	232	232	35.7%	-0.24 [-0.37 , -0.11]
Corren 2016	-0.49	0.2653	77	19	2.2%	-0.49 [-1.01 , 0.03]
Subtotal (95% CI)			**660**	**600**	**86.3%**	**-0.27 [-0.36 , -0.19]**
Heterogeneity: Chi² = 1.55, df = 3 (P = 0.67); I² = 0%						
Test for overall effect: Z = 6.38 (P < 0.00001)						
3.4.2 Non-eosinophilic						
Corren 2016	-0.122	0.1071	316	76	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: Chi² = 3.25, df = 4 (P = 0.52); I² = 0%						
Test for overall effect: Z = 6.35 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.70, df = 1 (P = 0.19), I² = 41.1%						



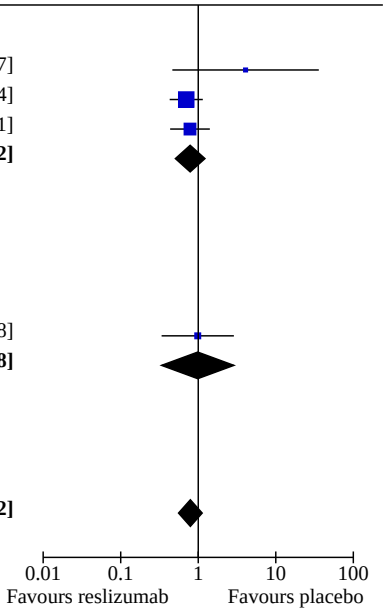
Analysis 3.5. Comparison 3: Reslizumab (IV) versus placebo, Outcome 5: Pre-bronchodilator FEV $_1$ (litres)

Study or Subgroup	MD	SE	Reslizumab Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
3.5.1 Eosinophilic						
Bjermer 2016	0.16	0.0505	106	105	14.2%	0.16 [0.06 , 0.26]
Castro 2015a	0.126	0.0316	245	244	36.3%	0.13 [0.06 , 0.19]
Castro 2015b	0.09	0.0321	232	232	35.1%	0.09 [0.03 , 0.15]
Corren 2016	0.27	0.1337	77	19	2.0%	0.27 [0.01 , 0.53]
Subtotal (95% CI)			**660**	**600**	**87.6%**	**0.12 [0.08 , 0.16]**
Heterogeneity: Chi² = 2.80, df = 3 (P = 0.42); I² = 0%						
Test for overall effect: Z = 5.92 (P < 0.00001)						
3.5.2 Non-eosinophilic						
Corren 2016	0.033	0.0541	316	76	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: Chi² = 5.08, df = 4 (P = 0.28); I² = 21%						
Test for overall effect: Z = 5.76 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.29, df = 1 (P = 0.13), I² = 56.3%						



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

Study or Subgroup	Reslizumab Events	Reslizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.6.1 Eosinophilic						
Bjermer 2016	4	103	1	105	2.6%	4.08 [0.46 , 35.87]
Castro 2015a	24	245	34	243	51.1%	0.70 [0.43 , 1.14]
Castro 2015b	18	232	23	232	35.6%	0.78 [0.43 , 1.41]
Subtotal (95% CI)		**580**		**580**	**89.3%**	**0.79 [0.51 , 1.22]**
Total events:	46		58			
Heterogeneity: Tau² = 0.03; Chi² = 2.42, df = 2 (P = 0.30); I² = 17%						
Test for overall effect: Z = 1.07 (P = 0.28)						
3.6.2 Eosinophil status unknown						
Corren 2016 (1)	16	398	4	98	10.7%	0.98 [0.34 , 2.88]
Subtotal (95% CI)		**398**		**98**	**10.7%**	**0.98 [0.34 , 2.88]**
Total events:	16		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.03 (P = 0.98)						
Total (95% CI)		**978**		**678**	**100.0%**	**0.79 [0.56 , 1.12]**
Total events:	62		62			
Heterogeneity: Tau² = 0.00; Chi² = 2.60, df = 3 (P = 0.46); I² = 0%						
Test for overall effect: Z = 1.31 (P = 0.19)						
Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.70), I² = 0%						

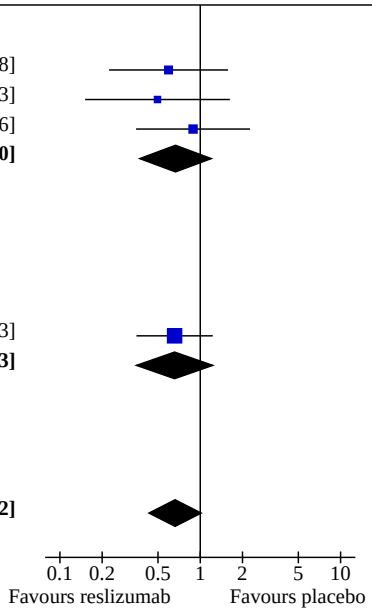


Footnotes

(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

Study or Subgroup	Reslizumab Events	Reslizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.7.1 Eosinophilic						
Bjermer 2016	6	106	10	105	19.2%	0.59 [0.22 , 1.58]
Castro 2015a	4	245	8	243	13.0%	0.50 [0.15 , 1.63]
Castro 2015b	8	232	9	232	21.0%	0.89 [0.35 , 2.26]
Subtotal (95% CI)		**583**		**580**	**53.2%**	**0.67 [0.37 , 1.20]**
Total events:	18		27			
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 2 (P = 0.72); I² = 0%						
Test for overall effect: Z = 1.36 (P = 0.18)						
3.7.2 Eosinophil status unknown						
Corren 2016 (1)	32	398	12	98	46.8%	0.66 [0.35 , 1.23]
Subtotal (95% CI)		**398**		**98**	**46.8%**	**0.66 [0.35 , 1.23]**
Total events:	32		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.32 (P = 0.19)						
Total (95% CI)		**981**		**678**	**100.0%**	**0.66 [0.43 , 1.02]**
Total events:	50		39			
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 3 (P = 0.88); I² = 0%						
Test for overall effect: Z = 1.89 (P = 0.06)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%						

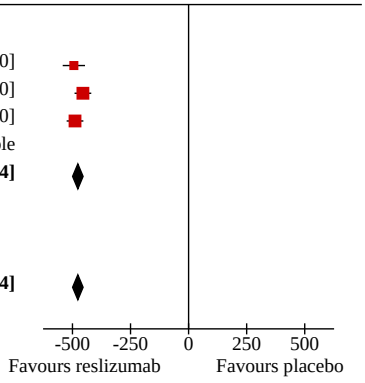


Footnotes

(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: Blood eosinophil level (cells/µL)

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



Footnotes

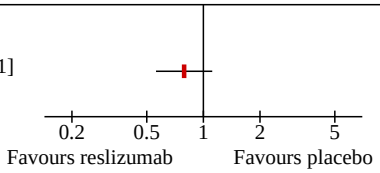
(1) Note: Corren 2016 does not separate out eosinophil count by eosinophilic / non-eosinophilic so pooled group shown

Comparison 4. Reslizumab (SC) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Rate of exacerbations requiring systemic corticosteroids	1		Rate Ratio (IV, Fixed, 95% CI)	Totals not selected
4.1.1 Eosinophilic	1		Rate Ratio (IV, Fixed, 95% CI)	Totals not selected
4.2 Rate of exacerbations requiring emergency department treatment or admission	1		Rate Ratio (IV, Fixed, 95% CI)	Totals not selected
4.2.1 Eosinophilic	1		Rate Ratio (IV, Fixed, 95% CI)	Totals not selected
4.3 Health-related quality of life (AQLQ mean difference)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.3.1 Eosinophilic	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.4 Health-related quality of life (ACQ mean difference)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.4.1 Eosinophilic	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.5 Health-related quality of life (SGRQ mean difference)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.5.1 Eosinophilic	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.6 Pre-bronchodilator FEV_1 (litres)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.6.1 Eosinophilic	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.7 Serious adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.7.1 Eosinophilic	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.8 Adverse events leading to discontinuation	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.8.1 Eosinophilic	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.9 Blood eosinophil level (cells × 10^9/litre)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.9.1 Eosinophilic	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

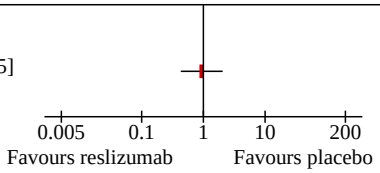
Analysis 4.1. Comparison 4: Reslizumab (SC) versus placebo, Outcome 1: Rate of exacerbations requiring systemic corticosteroids

Study or Subgroup	log[Rate Ratio]	SE	Reslizumab Total	Placebo Total	Rate Ratio IV, Fixed, 95% CI
4.1.1 Eosinophilic					
Bernstein 2020	-0.2357	0.1756	234	230	0.79 [0.56 , 1.11]



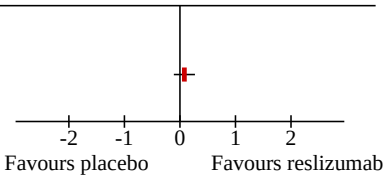
Analysis 4.2. Comparison 4: Reslizumab (SC) versus placebo, Outcome 2: Rate of exacerbations requiring emergency department treatment or admission

Study or Subgroup	log[Rate Ratio]	SE	Reslizumab Total	Placebo Total	Rate Ratio IV, Fixed, 95% CI
4.2.1 Eosinophilic					
Bernstein 2020	-0.0619	0.399	234	230	0.94 [0.43 , 2.05]



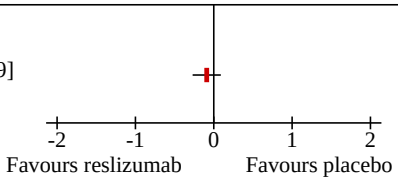
Analysis 4.3. Comparison 4: Reslizumab (SC) versus placebo, Outcome 3: Health-related quality of life (AQLQ mean difference)

Study or Subgroup	MD	SE	Reslizumab Total	Placebo Total	Mean Difference IV, Fixed, 95% CI
4.3.1 Eosinophilic					
Bernstein 2020	0.08	0.0969	234	230	0.08 [-0.11 , 0.27]



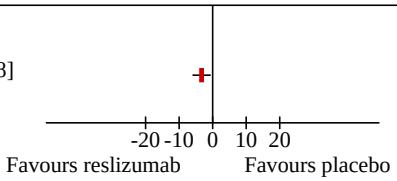
Analysis 4.4. Comparison 4: Reslizumab (SC) versus placebo, Outcome 4: Health-related quality of life (ACQ mean difference)

Study or Subgroup	MD	SE	Reslizumab Total	Placebo Total	Mean Difference IV, Fixed, 95% CI
4.4.1 Eosinophilic					
Bernstein 2020	-0.09	0.0918	234	230	-0.09 [-0.27 , 0.09]



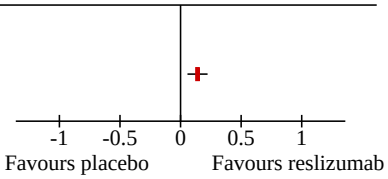
Analysis 4.5. Comparison 4: Reslizumab (SC) versus placebo, Outcome 5: Health-related quality of life (SGRQ mean difference)

Study or Subgroup	MD	SE	Reslizumab Total	Placebo Total	Mean Difference IV, Fixed, 95% CI
4.5.1 Eosinophilic					
Bernstein 2020	-3.3	1.3878	234	230	-3.30 [-6.02 , -0.58]



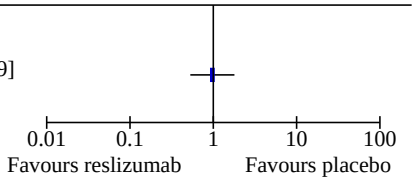
Analysis 4.6. Comparison 4: Reslizumab (SC) versus placebo, Outcome 6: Pre-bronchodilator FEV $_1$ (litres)

Study or Subgroup	MD	SE	Reslizumab Total	Placebo Total	Mean Difference IV, Fixed, 95% CI
4.6.1 Eosinophilic					
Bernstein 2020	0.14	0.0423	234	230	0.14 [0.06 , 0.22]



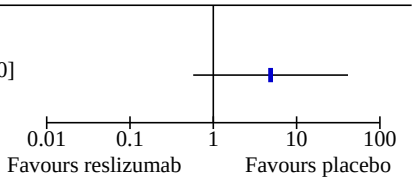
Analysis 4.7. Comparison 4: Reslizumab (SC) versus placebo, Outcome 7: Serious adverse events

Study or Subgroup	Reslizumab Events	Reslizumab Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
4.7.1 Eosinophilic					
Bernstein 2020	19	237	19	231	0.97 [0.53 , 1.79]

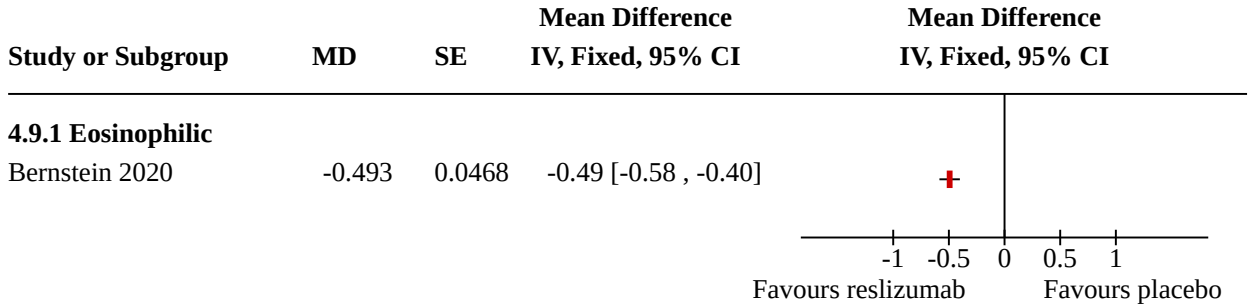


Analysis 4.8. Comparison 4: Reslizumab (SC) versus placebo, Outcome 8: Adverse events leading to discontinuation

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio M-H, Random, 95% CI
4.8.1 Eosinophilic					
Bernstein 2020	5	237	1	231	4.87 [0.57 , 41.40]



Analysis 4.9. Comparison 4: Reslizumab (SC) versus placebo, Outcome 9: Blood eosinophil level (cells × 10^9/litre)



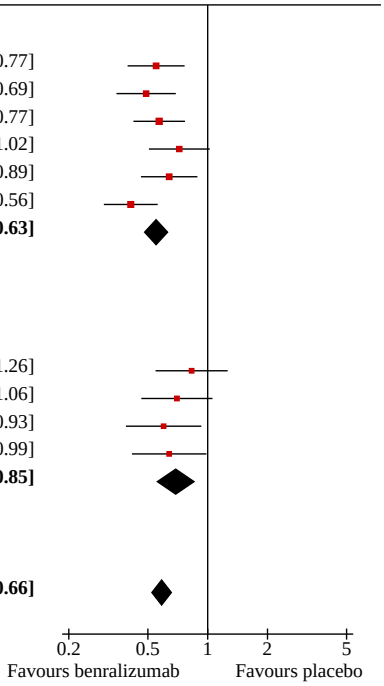
Comparison 5. Benralizumab (SC) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Rate of exacerbations requiring systemic corticosteroids	4	3112	Rate Ratio (IV, Fixed, 95% CI)	0.59 [0.52, 0.66]
5.1.1 Eosinophilic	4	2354	Rate Ratio (IV, Fixed, 95% CI)	0.55 [0.48, 0.63]
5.1.2 Non-eosinophilic	2	758	Rate Ratio (IV, Fixed, 95% CI)	0.69 [0.56, 0.85]
5.2 Rate of exacerbations requiring emergency department treatment or admission	2	1537	Rate Ratio (IV, Fixed, 95% CI)	0.68 [0.47, 0.98]
5.2.1 Eosinophilic	2	1537	Rate Ratio (IV, Fixed, 95% CI)	0.68 [0.47, 0.98]
5.3 Health-related quality of life (AQLQ mean difference)	3	1541	Mean Difference (IV, Fixed, 95% CI)	0.23 [0.11, 0.35]
5.3.1 Eosinophilic	3	1541	Mean Difference (IV, Fixed, 95% CI)	0.23 [0.11, 0.35]
5.4 Health-related quality of life (ACQ mean difference)	4	2791	Mean Difference (IV, Fixed, 95% CI)	-0.26 [-0.34, -0.17]
5.4.1 Eosinophilic	4	2036	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.40, -0.20]
5.4.2 Non-eosinophilic	2	755	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.30, 0.02]
5.5 Health-related quality of life (SGRQ mean difference)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.5.1 Eosinophilic	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.6 Pre-bronchodilator FEV_1 (litres)	4	2786	Mean Difference (IV, Fixed, 95% CI)	0.11 [0.08, 0.15]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.6.1 Eosinophilic	4	2048	Mean Difference (IV, Fixed, 95% CI)	0.15 [0.11, 0.19]
5.6.2 Non-eosinophilic	2	738	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.03, 0.10]
5.7 Serious adverse events	5	3304	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.62, 0.93]
5.7.1 Eosinophilic	3	2193	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.56, 0.93]
5.7.2 Non-eosinophilic	2	758	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.57, 1.27]
5.7.3 Eosinophil status unknown	2	353	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.37, 1.51]
5.8 Adverse events leading to discontinuation	4	3253	Risk Ratio (M-H, Random, 95% CI)	2.04 [1.03, 4.03]
5.8.1 Eosinophilic	3	2193	Risk Ratio (M-H, Random, 95% CI)	2.26 [0.89, 5.73]
5.8.2 Non-eosinophilic	2	758	Risk Ratio (M-H, Random, 95% CI)	1.81 [0.54, 6.05]
5.8.3 Eosinophil status unknown	1	302	Risk Ratio (M-H, Random, 95% CI)	1.82 [0.31, 10.69]
5.9 Blood eosinophil level (% change from baseline)	2	2295	Mean Difference (IV, Fixed, 95% CI)	-104.74 [-116.12, -93.35]
5.9.1 Eosinophilic	2	1537	Mean Difference (IV, Fixed, 95% CI)	-101.74 [-113.27, -90.21]
5.9.2 Non-eosinophilic	2	758	Mean Difference (IV, Fixed, 95% CI)	-216.81 [-287.35, -146.28]

Analysis 5.1. Comparison 5: Benralizumab (SC) versus placebo, Outcome 1: Rate of exacerbations requiring systemic corticosteroids

Study or Subgroup	log[Rate Ratio]	SE	Benralizumab Total	Placebo Total	Weight	Rate Ratio IV, Fixed, 95% CI
5.1.1 Eosinophilic						
Bleecker 2016 (1)	-0.5978	0.1685	275	134	11.6%	0.55 [0.40 , 0.77]
Bleecker 2016 (2)	-0.7133	0.1755	275	133	10.7%	0.49 [0.35 , 0.69]
Castro 2014a (3)	-0.5621	0.1523	70	83	14.3%	0.57 [0.42 , 0.77]
FitzGerald 2016 (2)	-0.3285	0.1798	239	124	10.2%	0.72 [0.51 , 1.02]
FitzGerald 2016 (1)	-0.4463	0.1669	241	124	11.9%	0.64 [0.46 , 0.89]
Harrison 2020 (4)	-0.8916	0.1591	427	229	13.1%	0.41 [0.30 , 0.56]
Subtotal (95% CI)			**1527**	**827**	**71.8%**	**0.55 [0.48 , 0.63]**
Heterogeneity: Chi² = 6.97, df = 5 (P = 0.22); I² = 28%						
Test for overall effect: Z = 8.81 (P < 0.00001)						
5.1.2 Non-eosinophilic						
Bleecker 2016 (2)	-0.1863	0.2132	131	70	7.3%	0.83 [0.55 , 1.26]
Bleecker 2016 (1)	-0.3567	0.2103	124	70	7.5%	0.70 [0.46 , 1.06]
FitzGerald 2016 (2)	-0.5108	0.2229	125	61	6.7%	0.60 [0.39 , 0.93]
FitzGerald 2016 (1)	-0.4463	0.2201	116	61	6.8%	0.64 [0.42 , 0.99]
Subtotal (95% CI)			**496**	**262**	**28.2%**	**0.69 [0.56 , 0.85]**
Heterogeneity: Chi² = 1.27, df = 3 (P = 0.74); I² = 0%						
Test for overall effect: Z = 3.43 (P = 0.0006)						
Total (95% CI)			**2023**	**1089**	**100.0%**	**0.59 [0.52 , 0.66]**
Heterogeneity: Chi² = 11.40, df = 9 (P = 0.25); I² = 21%						
Test for overall effect: Z = 9.29 (P < 0.00001)						
Test for subgroup differences: Chi² = 3.16, df = 1 (P = 0.08), I² = 68.4%						

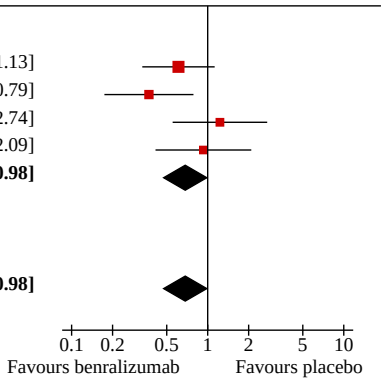


Footnotes

(1) 4 weekly treatment. Control (placebo) arm halved and SE inflated by 1.225.
(2) 8 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% con
(4) For subgroup with blood eosinophil count >300 cells/μL (consistent with other studies)

Analysis 5.2. Comparison 5: Benralizumab (SC) versus placebo, Outcome 2: Rate of exacerbations requiring emergency department treatment or admission

Study or Subgroup	log[Rate Ratio]	SE	Benralizumab Total	Placebo Total	Weight	Rate Ratio IV, Fixed, 95% CI
5.2.1 Eosinophilic						
Bleecker 2016 (1)	-0.4943	0.3124	275	134	35.5%	0.61 [0.33 , 1.13]
Bleecker 2016 (2)	-0.9943	0.3844	267	133	23.4%	0.37 [0.17 , 0.79]
FitzGerald 2016 (2)	0.207	0.4082	239	124	20.8%	1.23 [0.55 , 2.74]
FitzGerald 2016 (1)	-0.0726	0.4134	241	124	20.3%	0.93 [0.41 , 2.09]
Subtotal (95% CI)			**1022**	**515**	**100.0%**	**0.68 [0.47 , 0.98]**
Heterogeneity: Chi² = 5.31, df = 3 (P = 0.15); I² = 43%						
Test for overall effect: Z = 2.04 (P = 0.04)						
Total (95% CI)			**1022**	**515**	**100.0%**	**0.68 [0.47 , 0.98]**
Heterogeneity: Chi² = 5.31, df = 3 (P = 0.15); I² = 43%						
Test for overall effect: Z = 2.04 (P = 0.04)						
Test for subgroup differences: Not applicable						

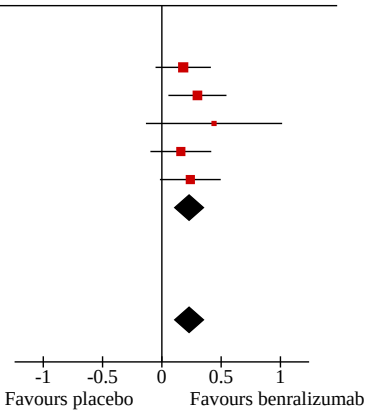


Footnotes

(1) 4 weekly treatment. Control (placebo) arm halved and SE inflated by 1.225.
(2) 8 weekly treatment. Control (placebo) arm halved and SE inflated by 1.225.

Analysis 5.3. Comparison 5: Benralizumab (SC) versus placebo, Outcome 3: Health-related quality of life (AQLQ mean difference)

Study or Subgroup	MD	SE	Benralizumab Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
5.3.1 Eosinophilic						
Bleecker 2016 (1)	0.18	0.119	261	127	26.8%	0.18 [-0.05 , 0.41]
Bleecker 2016 (2)	0.3	0.1249	252	127	24.4%	0.30 [0.06 , 0.54]
Castro 2014a (3)	0.44	0.293	34	37	4.4%	0.44 [-0.13 , 1.01]
FitzGerald 2016 (1)	0.16	0.1309	233	120	22.2%	0.16 [-0.10 , 0.42]
FitzGerald 2016 (2)	0.24	0.1308	230	120	22.2%	0.24 [-0.02 , 0.50]
Subtotal (95% CI)			**1010**	**531**	**100.0%**	**0.23 [0.11 , 0.35]**
Heterogeneity: Chi² = 1.30, df = 4 (P = 0.86); I² = 0%						
Test for overall effect: Z = 3.73 (P = 0.0002)						
Total (95% CI)			**1010**	**531**	**100.0%**	**0.23 [0.11 , 0.35]**
Heterogeneity: Chi² = 1.30, df = 4 (P = 0.86); I² = 0%						
Test for overall effect: Z = 3.73 (P = 0.0002)						
Test for subgroup differences: Not applicable						



Footnotes

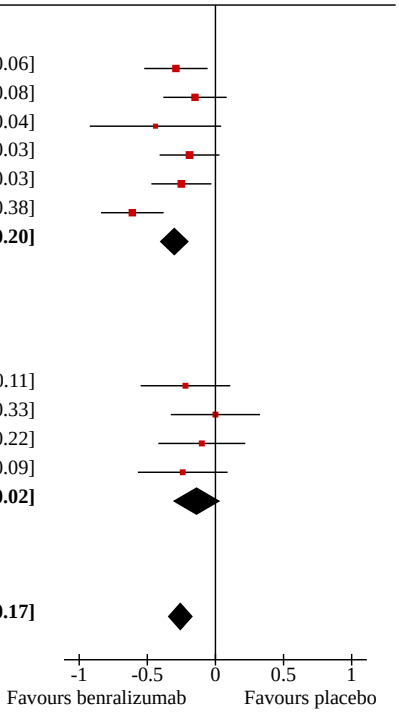
(1) 4 weekly treatment.

(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

Analysis 5.4. Comparison 5: Benralizumab (SC) versus placebo, Outcome 4: Health-related quality of life (ACQ mean difference)

Study or Subgroup	MD	SE	Benralizumab Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
5.4.1 Eosinophilic						
Bleecker 2016 (1)	-0.29	0.1187	263	133	13.3%	-0.29 [-0.52 , -0.06]
Bleecker 2016 (2)	-0.15	0.1188	274	134	13.3%	-0.15 [-0.38 , 0.08]
Castro 2014a (3)	-0.44	0.2461	35	38	3.1%	-0.44 [-0.92 , 0.04]
FitzGerald 2016 (2)	-0.19	0.1121	241	124	14.9%	-0.19 [-0.41 , 0.03]
FitzGerald 2016 (1)	-0.25	0.1123	239	123	14.8%	-0.25 [-0.47 , -0.03]
Harrison 2020 (4)	-0.61	0.1173	277	155	13.6%	-0.61 [-0.84 , -0.38]
Subtotal (95% CI)			**1329**	**707**	**73.0%**	**-0.30 [-0.40 , -0.20]**
Heterogeneity: Chi² = 10.07, df = 5 (P = 0.07); I² = 50%						
Test for overall effect: Z = 5.96 (P < 0.00001)						
5.4.2 Non-eosinophilic						
Bleecker 2016 (1)	-0.22	0.1679	130	69	6.6%	-0.22 [-0.55 , 0.11]
Bleecker 2016 (2)	0	0.1672	124	69	6.7%	0.00 [-0.33 , 0.33]
FitzGerald 2016 (1)	-0.1	0.1628	125	61	7.1%	-0.10 [-0.42 , 0.22]
FitzGerald 2016 (2)	-0.24	0.168	116	61	6.6%	-0.24 [-0.57 , 0.09]
Subtotal (95% CI)			**495**	**260**	**27.0%**	**-0.14 [-0.30 , 0.02]**
Heterogeneity: Chi² = 1.34, df = 3 (P = 0.72); I² = 0%						
Test for overall effect: Z = 1.67 (P = 0.09)						
Total (95% CI)			**1824**	**967**	**100.0%**	**-0.26 [-0.34 , -0.17]**
Heterogeneity: Chi² = 14.21, df = 9 (P = 0.12); I² = 37%						
Test for overall effect: Z = 5.96 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.80, df = 1 (P = 0.09), I² = 64.3%						



Footnotes

(1) 8 weekly treatment.

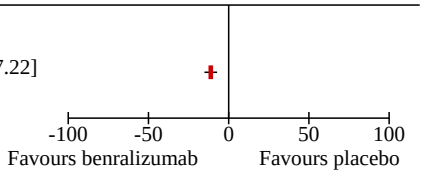
(2) 4 weekly treatment.

(3) 20mg benralizumab treatment arm only (doses of 2mg and 100mg not considered clinically relevant). Treatment difference in original paper provided wit

(4) For subgroup with blood eosinophil count >300 cells/µL (consistent with other studies)

Analysis 5.5. Comparison 5: Benralizumab (SC) versus placebo, Outcome 5: Health-related quality of life (SGRQ mean difference)

Study or Subgroup	MD	SE	Benralizumab Total	Placebo Total	Mean Difference IV, Fixed, 95% CI
5.5.1 Eosinophilic					
Harrison 2020 (1)	-11.16	2.0102	260	146	-11.16 [-15.10 , -7.22]

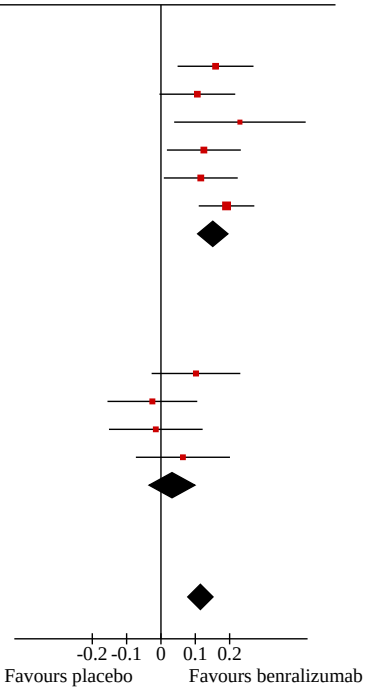


Footnotes

(1) For subgroup with blood eosinophil count >300 cells/µL (consistent with other studies)

Analysis 5.6. Comparison 5: Benralizumab (SC) versus placebo, Outcome 6: Pre-bronchodilator FEV $_1$ (litres)

Study or Subgroup	MD	SE	Benralizumab Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
5.6.1 Eosinophilic						
Bleecker 2016 (1)	0.159	0.0564	264	130	11.0%	0.16 [0.05 , 0.27]
Bleecker 2016 (2)	0.106	0.0563	271	131	11.1%	0.11 [-0.00 , 0.22]
Castro 2014a (3)	0.23	0.0977	48	53	3.7%	0.23 [0.04 , 0.42]
FitzGerald 2016 (2)	0.125	0.0549	238	122	11.6%	0.13 [0.02 , 0.23]
FitzGerald 2016 (1)	0.116	0.0549	238	122	11.6%	0.12 [0.01 , 0.22]
Harrison 2020 (4)	0.191	0.0413	278	153	20.6%	0.19 [0.11 , 0.27]
Subtotal (95% CI)			**1337**	**711**	**69.6%**	**0.15 [0.11 , 0.19]**
Heterogeneity: Chi² = 2.88, df = 5 (P = 0.72); I² = 0%						
Test for overall effect: Z = 6.72 (P < 0.00001)						
5.6.2 Non-eosinophilic						
Bleecker 2016 (1)	0.102	0.0659	129	69	8.1%	0.10 [-0.03 , 0.23]
Bleecker 2016 (2)	-0.025	0.0667	120	69	7.9%	-0.03 [-0.16 , 0.11]
FitzGerald 2016 (1)	-0.015	0.0696	121	58	7.2%	-0.01 [-0.15 , 0.12]
FitzGerald 2016 (2)	0.064	0.0699	114	58	7.2%	0.06 [-0.07 , 0.20]
Subtotal (95% CI)			**484**	**254**	**30.4%**	**0.03 [-0.03 , 0.10]**
Heterogeneity: Chi² = 2.52, df = 3 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.95 (P = 0.34)						
Total (95% CI)			**1821**	**965**	**100.0%**	**0.11 [0.08 , 0.15]**
Heterogeneity: Chi² = 13.90, df = 9 (P = 0.13); I² = 35%						
Test for overall effect: Z = 6.13 (P < 0.00001)						
Test for subgroup differences: Chi² = 8.50, df = 1 (P = 0.004), I² = 88.2%						



Footnotes

(1) 8 weekly treatment.

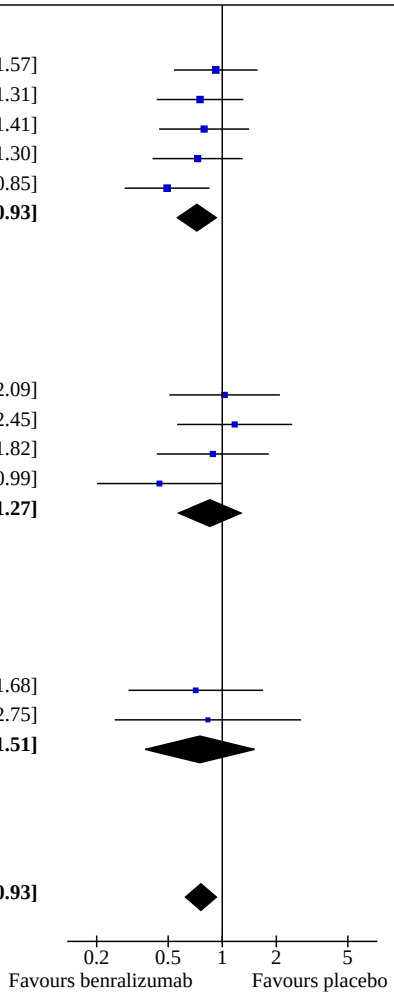
(2) 4 weekly treatment.

(3) 20mg benralizumab treatment arm only (doses of 2mg and 100mg not considered clinically relevant). Treatment difference in original paper provided with 80%

(4) For subgroup with blood eosinophil count >300 cells/μL (consistent with other studies)

Analysis 5.7. Comparison 5: Benralizumab (SC) versus placebo, Outcome 7: Serious adverse events

Study or Subgroup	Benralizumab Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
5.7.1 Eosinophilic						
Bleecker 2016 (1)	33	265	18	133	13.7%	0.92 [0.54 , 1.57]
Bleecker 2016 (2)	28	277	18	134	12.7%	0.75 [0.43 , 1.31]
FitzGerald 2016 (1)	25	230	17	124	11.8%	0.79 [0.45 , 1.41]
FitzGerald 2016 (2)	25	250	17	124	11.8%	0.73 [0.41 , 1.30]
Harrison 2020 (3)	23	427	25	229	13.3%	0.49 [0.29 , 0.85]
Subtotal (95% CI)		**1449**		**744**	**63.2%**	**0.72 [0.56 , 0.93]**
Total events:	134		95			
Heterogeneity: Tau² = 0.00; Chi² = 2.80, df = 4 (P = 0.59); I² = 0%						
Test for overall effect: Z = 2.56 (P = 0.01)						
5.7.2 Non-eosinophilic						
Bleecker 2016 (1)	19	129	10	70	7.8%	1.03 [0.51 , 2.09]
Bleecker 2016 (2)	19	126	9	70	7.2%	1.17 [0.56 , 2.45]
FitzGerald 2016 (2)	17	117	10	61	7.6%	0.89 [0.43 , 1.82]
FitzGerald 2016 (1)	10	124	11	61	6.1%	0.45 [0.20 , 0.99]
Subtotal (95% CI)		**496**		**262**	**28.8%**	**0.85 [0.57 , 1.27]**
Total events:	65		40			
Heterogeneity: Tau² = 0.02; Chi² = 3.51, df = 3 (P = 0.32); I² = 14%						
Test for overall effect: Z = 0.78 (P = 0.44)						
5.7.3 Eosinophil status unknown						
Castro 2014a (4)	6	81	23	221	5.3%	0.71 [0.30 , 1.68]
Park 2016 (4)	4	25	5	26	2.7%	0.83 [0.25 , 2.75]
Subtotal (95% CI)		**106**		**247**	**8.0%**	**0.75 [0.37 , 1.51]**
Total events:	10		28			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.80 (P = 0.42)						
Total (95% CI)		**2051**		**1253**	**100.0%**	**0.76 [0.62 , 0.93]**
Total events:	209		163			
Heterogeneity: Tau² = 0.00; Chi² = 6.92, df = 10 (P = 0.73); I² = 0%						
Test for overall effect: Z = 2.71 (P = 0.007)						
Test for subgroup differences: Chi² = 0.48, df = 2 (P = 0.79), I² = 0%						



Footnotes

(1) 8 weekly treatment.

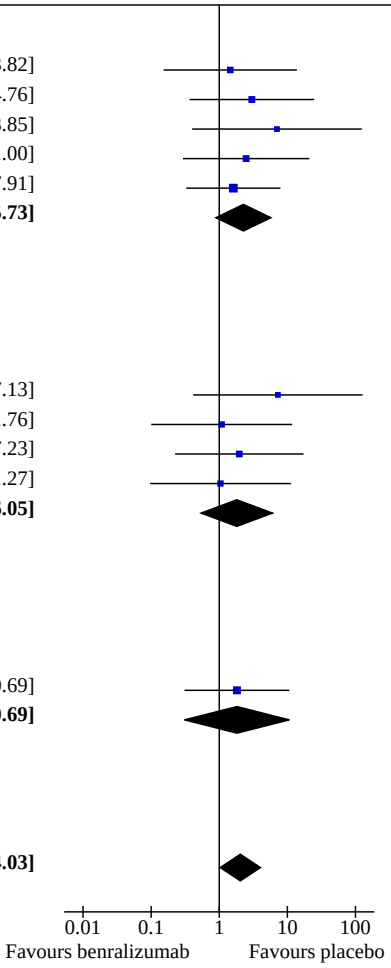
(2) 4 weekly treatment.

(3) Patients with blood eosinophil count >150 cells/μL (lower threshold than other studies, >300 cells/μL)

(4) 20mg benralizumab treatment arm only (doses of 2mg and 100mg not considered clinically relevant).

Analysis 5.8. Comparison 5: Benralizumab (SC) versus placebo, Outcome 8: Adverse events leading to discontinuation

Study or Subgroup	Benralizumab Events	Benralizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
5.8.1 Eosinophilic						
Bleecker 2016 (1)	3	277	1	134	9.1%	1.45 [0.15 , 13.82]
Bleecker 2016 (2)	6	265	1	133	10.4%	3.01 [0.37 , 24.76]
FitzGerald 2016 (1)	6	230	0	124	5.6%	7.03 [0.40 , 123.85]
FitzGerald 2016 (2)	5	250	1	124	10.1%	2.48 [0.29 , 21.00]
Harrison 2020 (3)	6	427	2	229	18.2%	1.61 [0.33 , 7.91]
Subtotal (95% CI)		**1449**		**744**	**53.5%**	**2.26 [0.89 , 5.73]**
Total events:	26		5			
Heterogeneity: Tau² = 0.00; Chi² = 1.04, df = 4 (P = 0.90); I² = 0%						
Test for overall effect: Z = 1.72 (P = 0.08)						
5.8.2 Non-eosinophilic						
Bleecker 2016 (2)	6	126	0	70	5.6%	7.27 [0.42 , 127.13]
Bleecker 2016 (1)	2	129	1	70	8.1%	1.09 [0.10 , 11.76]
FitzGerald 2016 (1)	4	124	1	61	9.8%	1.97 [0.22 , 17.23]
FitzGerald 2016 (2)	2	117	1	61	8.2%	1.04 [0.10 , 11.27]
Subtotal (95% CI)		**496**		**262**	**31.8%**	**1.81 [0.54 , 6.05]**
Total events:	14		3			
Heterogeneity: Tau² = 0.00; Chi² = 1.39, df = 3 (P = 0.71); I² = 0%						
Test for overall effect: Z = 0.96 (P = 0.33)						
5.8.3 Eosinophil status unknown						
Castro 2014a (4)	2	81	3	221	14.7%	1.82 [0.31 , 10.69]
Subtotal (95% CI)		**81**		**221**	**14.7%**	**1.82 [0.31 , 10.69]**
Total events:	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
Total (95% CI)		**2026**		**1227**	**100.0%**	**2.04 [1.03 , 4.03]**
Total events:	42		11			
Heterogeneity: Tau² = 0.00; Chi² = 2.52, df = 9 (P = 0.98); I² = 0%						
Test for overall effect: Z = 2.06 (P = 0.04)						
Test for subgroup differences: Chi² = 0.10, df = 2 (P = 0.95), I² = 0%						



Footnotes

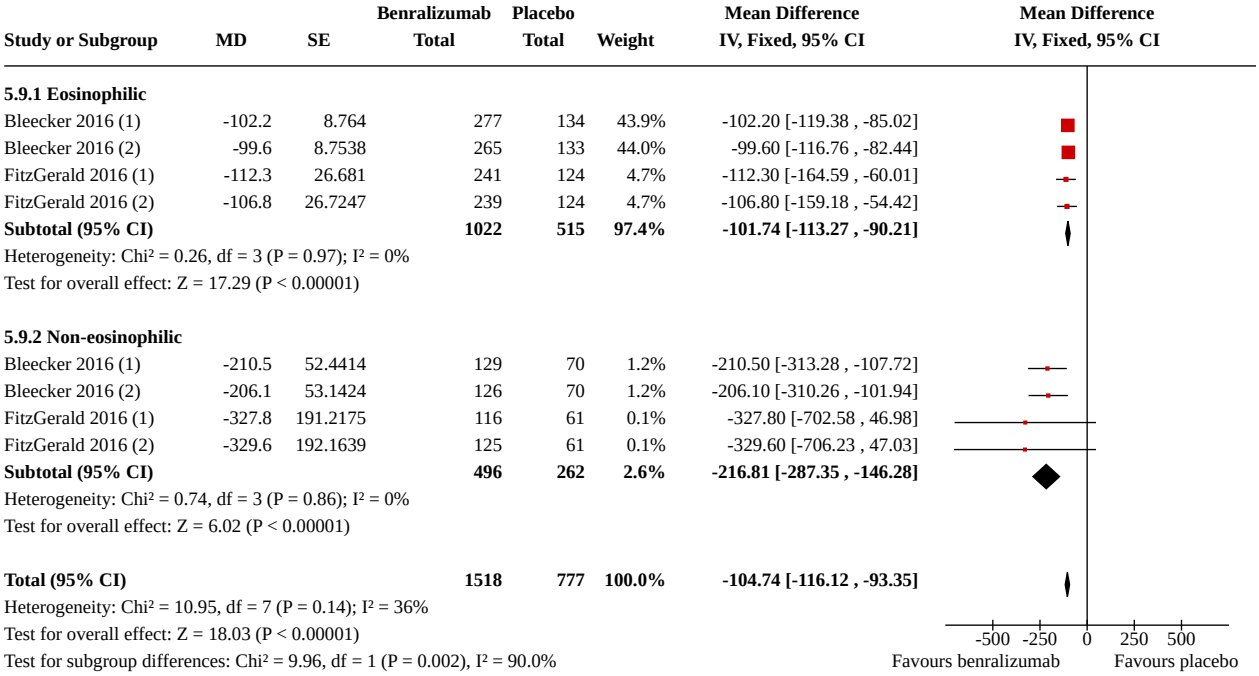
(1) 8 weekly treatment.

(2) 4 weekly treatment.

(3) Patients with blood eosinophil count >150 cells/μL (lower threshold than other studies, >300 cells/μL)

(4) 20mg benralizumab treatment arm only (doses of 2mg and 100mg not considered clinically relevant).

Analysis 5.9. Comparison 5: Benralizumab (SC) versus placebo, Outcome 9: Blood eosinophil level (% change from baseline)



Study or Subgroup	MD	SE	Benralizumab Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
5.9.1 Eosinophilic						
Bleecker 2016 (1)	-102.2	8.764	277	134	43.9%	-102.20 [-119.38 , -85.02]
Bleecker 2016 (2)	-99.6	8.7538	265	133	44.0%	-99.60 [-116.76 , -82.44]
FitzGerald 2016 (1)	-112.3	26.681	241	124	4.7%	-112.30 [-164.59 , -60.01]
FitzGerald 2016 (2)	-106.8	26.7247	239	124	4.7%	-106.80 [-159.18 , -54.42]
Subtotal (95% CI)			**1022**	**515**	**97.4%**	**-101.74 [-113.27 , -90.21]**
Heterogeneity: Chi² = 0.26, df = 3 (P = 0.97); I² = 0%						
Test for overall effect: Z = 17.29 (P < 0.00001)						
5.9.2 Non-eosinophilic						
Bleecker 2016 (1)	-210.5	52.4414	129	70	1.2%	-210.50 [-313.28 , -107.72]
Bleecker 2016 (2)	-206.1	53.1424	126	70	1.2%	-206.10 [-310.26 , -101.94]
FitzGerald 2016 (1)	-327.8	191.2175	116	61	0.1%	-327.80 [-702.58 , 46.98]
FitzGerald 2016 (2)	-329.6	192.1639	125	61	0.1%	-329.60 [-706.23 , 47.03]
Subtotal (95% CI)			**496**	**262**	**2.6%**	**-216.81 [-287.35 , -146.28]**
Heterogeneity: Chi² = 0.74, df = 3 (P = 0.86); I² = 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: Chi² = 10.95, df = 7 (P = 0.14); I² = 36%						
Test for overall effect: Z = 18.03 (P < 0.00001)						
Test for subgroup differences: Chi² = 9.96, df = 1 (P = 0.002), I² = 90.0%						

Footnotes

(1) 4 weekly treatment.

(2) 8 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
Bernstein 2020 (468)	RCT, double-blind, placebo-controlled, parallel-group (52)	ACQ-6 score ≥ 1.5; ≥ 2 exacerbations in the last year requiring systemic corticosteroids; blood eosinophils ≥ 300 cells/μL; and FEV_1 bronchodilator reversibility of < 12%	Medium-dose ICS for ≥ 3 months; + additional controller for ≥ 3 months; ± maintenance OCS	Reslizumab 110 mg (SC) or placebo every 4 weeks for 52 weeks (last dose at 48 weeks)	• Clinical asthma exacerbations during 52-week treatment period • Change from baseline pre-bronchodilator FEV_1 • Change from baseline in ACQ-6 at week 52 • Change from baseline in AQLQ+12 at week 52 • Change from baseline in SGRQ at week 32
Bjermer 2016 (315)	RCT, double-blind, placebo-controlled, parallel-group, fixed-dosage,	Blood eosinophils ≥ 400 cells/μL during 2-4-week 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

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

	multicentre phase 3 (16)				• Blood eosinophil levels
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 years) high-dose (≥ 500 µg/d FP or equivalent) ICS/LABA for ≥ 12 months Children (12-17 years) at least medium-dose (≥ 250 µg/day FP or equivalent) ICS/LABA	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 48 weeks	• Annual exacerbation rate • 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
Castro 2015a (489) and Castro 2015b (464)	2 duplicate RCTs, 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
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
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
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
FitzGerald 2016	RCT, double-blind, parallel-group,	≥ 2 exacerbations in the previous 12 months; and ACQ-6	Medium- (≥ 250 µg/d FP or equivalent) to high-	Benralizumab 30 mg (SC) or placebo either every	• Annual exacerbation rate for participants with blood eosinophils ≥ 300 cells/µL

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

(1306)	placebo-controlled multicentre (56)	score ≥ 1.5 at enrolment; and FEV_1 < 80%	dose (≥ 500 µg/d FP or equivalent) ICS/LABA for ≥ 12 months; high-dose ICS/LABA for ≥ 3 months	4 weeks or every 4 weeks for the first 3 doses then every 8 weeks or placebo	• 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
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 year	• Severe exacerbations per person • Change in AQLQ • Post-bronchodilator FEV_1 • Airway hyperresponsiveness • Blood/sputum eosinophil counts

Harrison 2020
(656)
	RCT, double-blind, placebo-controlled, parallel-group (24)	≥ 2 exacerbations in the last year requiring systemic corticosteroids; FEV_1 < 80%; blood eosinophils ≥ 300 cells/µL or ≥ 150 cells/µL and maintenance OCS or history of nasal polyps or ≥ 2 exacerbations in the last year or FVC < 65% or ≥ 18 years at asthma diagnosis; ACQ-6 score ≥ 1.5; bronchodilator reversibility ≥ 12% or airway hyperresponsiveness or PEF variability ≥ 10%	Medium-to-high-dose ICS + additional controller for ≥ 3 months; ± maintenance OCS	Benralizumab 30 mg (SC) or placebo every 8 weeks (first 3 doses every 4 weeks) for 24 weeks	• Annualised asthma exacerbation rate
					• Change from baseline to week 24 in
					  ◦ SGRQ
					  ◦ FEV_1
					  ◦ PEF
					  ◦ ACQ-6
					  ◦ PSIA
					  ◦ CGI-C
					  ◦ PGI-C
					  ◦ SNOT-22

Jackson 2022 (290)	RCT triple-blind, placebo-controlled	≥ 2 exacerbations in the previous 12 months; peripheral blood eosinophils ≥ 150 cells/µL	For those aged 6-11 years, treatment with at least medium- to high-dose ICS For those ≥ 12 years of age, treatment with at least medium- to high-dose ICS in combination with LABA	Mepolizumab 40 mg (SC) for 6-11 year-olds, 100 mg (SC) for 12-17 year-olds every 4 weeks	• Asthma exacerbations treated with systemic corticosteroids • Time to first exacerbation • Lung function • Quality of life • CASI
Moore 2022 (295)	Randomised, double-blind, placebo-controlled, par-	Patients who had received continuous mepolizumab treatment for ≥ 3 years (ini-	Mepolizumab ≥ 6 months + controller medication ≥ 12 weeks	Mepolizumab 100 mg (SC) or placebo every	• Percentage of patients with clinically significant exacerbations (requiring systemic

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

	allel-group, multicentre study (52)	tially as part of an RCT, Pavord 2012a, Ortega 2014, or Bel 2014)		4 weeks for 52 weeks	corticosteroids for ≥ 3 days) at 52 weeks • Change from baseline in blood eosinophil count • Percentage of participants with ≥ 0.5 point increase from baseline in ACQ-5 • Percentage of participants with exacerbations requiring hospitalisation or ED visit
NCT01947946 (13)	RCT double-blind, parallel-group, placebo-controlled multicentre (48)	Uncontrolled asthma taking medium-dose ICS plus LABA	Medium-dose ICS (> 250 µg and ≤ 500 µg fluticasone dry powder formulation equivalents total daily dose) and LABA for at least 3 months prior to first visit	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
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 year • Mean change from baseline pre-bronchodilator FEV_1 • Mean change from baseline SGRQ total score
Park 2016 (103)	RCT double-blind, placebo-controlled, dose-ranging multicentre (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 • Lung function • ACQ-6 • FeNO • Blood eosinophil counts
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-bronchodilator FEV_1 • Mean change from baseline post-bronchodilator FEV_1 • Mean change from baseline ACQ

ACQ: Asthma Control Questionnaire; **AQLQ:** Asthma Quality of Life Questionnaire; **ASUI:** Asthma Symptom Utility Index; **BDP:** beclomethasone dipropionate; **CASI:** Composite Asthma Severity Index; **CGI-C**: Clinician Global Impression of Change; **ECP:** eosinophil cationic protein; **ED:** emergency department; **FEF_{25-75}:** forced expiratory flow at 25% to 75% of FVC; **FeNO:** exhaled fraction of nitric

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

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; **PGI-C:** Patient Global Impression of Change; **PSIA:** Predominant Symptom and Impairment Assessment; **RCT:** randomised controlled trial; **SABA:** short-acting $beta_2$-agonists; **SC:** subcutaneous; **SGRQ:** St George's Respiratory Questionnaire; **SNOT-22:** Sino-Nasal Outcome Test-22

APPENDICES

Appendix 1. Database search strategies

Database/search platform/date of last search	Search strategy
Airways Register (via Cochrane Register of Studies) Date of most recent search: 7 February 2022	#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 human* NEAR2 monoclonal* NEAR2 antibod* #8 mepolizumab #9 SB24056 or SB-24056 #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
CENTRAL (via Cochrane Register of Studies) Date of most recent search: 7 February 2022	#1 AST:MISC1 #2 MeSH DESCRIPTOR Asthma Explode All #3 asthma*:ti,ab

(Continued)

	#4 #1 or #2 or #3
	#5 MeSH DESCRIPTOR Antibodies, Monoclonal
	#6 MeSH DESCRIPTOR Antibodies, Monoclonal, Humanized
	#7 human* NEAR2 monoclonal* NEAR2 antibod*
	#8 mepolizumab
	#9 SB24056 or SB-24056
	#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
MEDLINE (Ovid) ALL Date of most recent search: 7 February 2022	1 exp asthma/
	2 asthma*.tw.
	3 1 or 2
	4 Antibodies, Monoclonal, Humanized/tu [Therapeutic Use]
	5 mepolizumab.tw.
	6 (Bosatria or Nucala).tw.
	7 benralizumab.tw.
	8 MEDI-563.tw.
	9 reslizumab.tw.
	10 (Cinquil or Cinqair).tw.
	11 CEP-38072.tw.
	12 "anti-interleukin 5".tw.
	13 "anti-IL5".tw.
	14 "anti-IL-5".tw.
	15 or/4-14
	16 3 and 15
	17 (controlled clinical trial or randomized controlled trial).pt.

(Continued)

	18 (randomized or randomised).ab,ti.
	19 placebo.ab,ti.
	20 dt.fs.
	21 randomly.ab,ti.
	22 trial.ab,ti.
	23 groups.ab,ti.
	24 or/17-23
	25 Animals/
	26 Humans/
	27 25 not (25 and 26)
	28 24 not 27
	29 16 and 28
Embase (Ovid) Date of most recent search: 7 February 2022	1 exp asthma/
	2 asthma$.tw.
	3 1 or 2
	4 mepolizumab/
	5 mepolizumab.tw.
	6 (Bosatria or Nucala).tw.
	7 benralizumab.tw.
	8 MEDI-563.tw.
	9 benralizumab/
	10 reslizumab/
	11 (Cinquil or Cinqair).tw.
	12 CEP-38072.tw.
	13 "anti-interleukin 5".tw.
	14 "anti-IL5".tw.
	15 "anti-IL-5".tw.
	16 or/4-15
	17 Randomized Controlled Trial/
	18 randomization/
	19 controlled clinical trial/
	20 Double Blind Procedure/
	21 Single Blind Procedure/
	22 Crossover Procedure/

(Continued)

	23 (clinica$ adj3 trial$).tw. 24 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (mask$ or blind$ or method$)).tw. 25 exp Placebo/ 26 placebo$.ti,ab. 27 random$.ti,ab. 28 ((control$ or prospectiv$) adj3 (trial$ or method$ or stud$)).tw. 29 (crossover$ or cross-over$).ti,ab. 30 or/17-29 31 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ 32 human/ or normal human/ or human cell/ 33 31 and 32 34 31 not 33 35 30 not 34 36 16 and 35
ClinicalTrials.gov Date of most recent search: 7 February 2022	Study type: interventional Condition: asthma Intervention: mepolizumab or reslizumab or benralizumab
WHO trials portal Date of most recent search: 7 February 2022	Condition: asthma Intervention: mepolizumab or reslizumab or benralizumab

WHAT'S NEW

Date	Event	Description
7 February 2022	New search has been performed	New literature search run
7 February 2022	New citation required but conclusions have not changed	Three new studies involving ~1300 people added to the review.

HISTORY

Protocol first published: Issue 11, 2013
Review first published: Issue 7, 2015

Date	Event	Description
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

Date	Event	Description
		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
29 March 2017	New search has been performed	New literature search run

CONTRIBUTIONS OF AUTHORS

SM, HF and CP contributed to the rewriting of the Background and Methods sections. HF and CP independently selected studies for the review, HF, AW, EB and FY extracted the data, and EB entered the data into the Review Manager 2020 file with cross-checking by Christopher Cates, the Cochrane Airways Group statistician. HF, SM, EB and AW wrote the Results section, and HF, CP and SM co-authored the Discussion and Conclusions.

Contributions of editorial team

Rebecca Fortescue (Co-ordinating Editor) edited the review and advised on methodology.

Sally Spencer (Co-ordinating Editor): signed off the review prior to copyediting.

Alexander Mathiousdakis (Contact Editor): edited the review; advised on methodology, interpretation and content, assisted with sign-off of the review.

Emma Dennett (Deputy Co-ordinating Editor): co-ordinated the editorial process; advised on interpretation and content; edited the review. Emma also assisted the authors in screening a pre-publication search update in February 2022.

Emma Jackson (Managing Editor): co-ordinated peer review; edited the reference and other sections of the review.

Elizabeth Stovold (Information Specialist): designed the search strategy; ran the searches; edited the search methods section.

Data were checked by Emma Banchoff who was invited to join the author team after making a significant contribution to the review.

DECLARATIONS OF INTEREST

HF: none known

AW: none known

CP: none known

FY: none known

SM: none known

EB: none known

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Internal sources

- All, Other

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- Cochrane Airways, UK

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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 studies.

The scope was broadened to encompass all anti-IL-5 therapies, that is, including reslizumab and benralizumab in addition to mepolizumab. Since the protocol was written, reslizumab and benralizumab have also been licensed. 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) were 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 studies). Subgroups were set as eosinophilic or otherwise, as these agents are primarily designed for eosinophilic asthma.

The original protocol stated that included studies 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)

Adrenal Cortex Hormones [therapeutic use]; Antibodies, Monoclonal [therapeutic use]; *Asthma [drug therapy]; Chronic Disease; Disease Progression; *Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans