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Anti-IL-5 therapies for chronic obstructive pulmonary disease (Review)

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[Intervention Review]

Anti-IL-5 therapies for chronic obstructive pulmonary disease

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ABSTRACT

Background

Exacerbations of chronic obstructive pulmonary disease (COPD) are a major cause of hospital admissions, disease-related morbidity and mortality. COPD is a heterogeneous disease with distinct inflammatory phenotypes, including eosinophilia, which may drive acute exacerbations in a subgroup of patients. Monoclonal antibodies targeting interleukin 5 (IL-5) or its receptor (IL-5R) have a role in the care of people with severe eosinophilic asthma, and may similarly provide therapeutic benefit for people with COPD of eosinophilic phenotype.

Objectives

To assess the efficacy and safety of monoclonal antibody therapies targeting IL-5 signalling (anti-IL-5 or anti-IL-5Rα) compared with placebo in the treatment of adults with COPD.

Search methods

We searched the Cochrane Airways Trials Register, CENTRAL, MEDLINE, Embase, clinical trials registries, manufacturers' websites, and reference lists of included studies. Our most recent search was 23 September 2020.

Selection criteria

We included randomised controlled trials comparing anti-IL-5 therapy with placebo in adults with COPD.

Data collection and analysis

Two review authors independently extracted data and analysed outcomes using a random-effects model.The primary outcomes were exacerbations requiring antibiotics or oral steroids, hospitalisations due to exacerbation of COPD, serious adverse events, and quality of life. We used standard methods expected by Cochrane. We used the GRADE approach to assess the certainty of the evidence.

Main results

Six studies involving a total of 5542 participants met our inclusion criteria. Three studies used mepolizumab (1530 participants), and three used benralizumab (4012 participants). The studies were on people with COPD, which was similarly defined with a documented history of COPD for at least one year. We deemed the risk of bias to be generally low, with all studies contributing data of robust methodology.

Mepolizumab 100 mg reduces the rate of moderate or severe exacerbations by 19% in those with an eosinophil count of at least 150/µL (rate ratio (RR) 0.81, 95% confidence interval (CI) 0.71 to 0.93; participants = 911; studies = 2, high-certainty evidence). When participants with lower eosinophils are included, mepolizumab 100 mg probably reduces the exacerbation rate by 8% (RR 0.92, 95% CI 0.82 to 1.03; participants = 1285; studies = 2, moderate-certainty evidence). Mepolizumab 300 mg probably reduces the rate of exacerbations by 14% in

participants all of whom had raised eosinophils (RR 0.86, 95% CI 0.70 to 1.06; participants = 451; studies = 1, moderate-certainty evidence); the evidence was uncertain for a single small study of mepolizumab 750 mg. In participants with high eosinophils, mepolizumab probably reduces the rate of hospitalisation by 10% (100 mg, RR 0.90, 95% CI 0.65 to 1.24; participants = 911; studies = 2, moderate-certainty evidence) and 17% (300 mg, RR 0.83, 95% CI 0.51 to 1.35; participants = 451; studies = 1, moderate-certainty evidence). Mepolizumab 100 mg increases the time to first moderate or severe exacerbation compared to the placebo group, in people with the eosinophilic phenotype (hazard ratio (HR) 0.78, 95% CI 0.66 to 0.92; participants = 981; studies 2, high-certainty evidence). When participants with lower eosinophils were included this difference was smaller and less certain (HR 0.87, 95% CI 0.75 to 1.0; participants = 1285; studies 2, moderate-certainty evidence). Mepolizumab 300 mg probably increases the time to first moderate or severe exacerbation in participants who all had eosinophilic phenotype (HR 0.77, 95% CI 0.60 to 0.99; participants = 451; studies = 1, moderate-certainty evidence).

Benralizumab 100 mg reduces the rate of severe exacerbations requiring hospitalisation in those with an eosinophil count of at least 220/µL (RR 0.63, 95% CI 0.49 to 0.81; participants = 1512; studies = 2, high-certainty evidence). Benralizumab 10 mg probably reduces the rate of severe exacerbations requiring hospitalisation in those with an eosinophil count of at least 220/µL (RR 0.68, 95% CI 0.49 to 0.94; participants = 765; studies = 1, moderate-certainty evidence).

There was probably little or no difference between the intervention and placebo for quality of life measures. Where there were differences the mean difference fell below the pre-specified minimum clinically significant difference.

Treatment with mepolizumab and benralizumab appeared to be safe. All pooled analyses showed that there was probably little or no difference in serious adverse events, adverse events, or side effects between the use of a monoclonal antibody therapy compared to placebo.

Authors' conclusions

We found that mepolizumab and benralizumab probably reduce the rate of moderate and severe exacerbations in the highly selected group of people who have both COPD and higher levels of blood eosinophils. This highlights the importance of disease phenotyping in COPD, and may play a role in the personalised treatment strategy in disease management.

Further research is needed to elucidate the role of monoclonal antibodies in the management of COPD in clinical practice. In particular, it is not clear whether there is a threshold blood eosinophil level above which these drugs may be effective. Studies including cost effectiveness analysis may be beneficial given the high cost of these therapies, to support use if appropriate.

PLAIN LANGUAGE SUMMARY

Mepolizumab or benralizumab for people with chronic obstructive pulmonary disease (COPD)

Background to the question

Chronic obstructive pulmonary disease (COPD) is a lung condition in which people can experience severe difficulties with breathing and an associated reduction in their quality of life.

For people with COPD, episodes in which the condition of patients seriously worsens are a major concern. We examined the findings of clinical trials to see whether mepolizumab or benralizumab, two new drugs, are better than placebo (dummy treatment) for people with COPD, and whether they reduce the number of episodes when the condition of patients seriously worsens.

Study characteristics

Six clinical studies compared either mepolizumab or benralizumab to placebo in a total of 5542 people with COPD. We examined the findings of the studies in terms of episodes when patients' conditions flared up requiring additional treatment, patient quality of life, patient performance in breathing tests, and side effects of the medication.

Main results

Three studies used mepolizumab, and the other three studies used benralizumab.

Mepolizumab 100 mg reduced the rate of flare-ups in a group of people with both COPD and higher levels of blood eosinophils (a type of white blood cells involved in inflammatory and allergic reactions). When mepolizumab is given in a higher dose (300 mg or 750 mg) the rate of flare-ups is probably reduced.

Benralizumab at a dose of 100mg resulted in a clear reduction in the number of episodes requiring admission to hospital, and when given at a lower dose (10mg) probably reduces flare-ups requiring hospitalisation. This is in people with COPD and higher levels of blood eosinophils.

Further studies comparing mepolizumab or benralizumab to a placebo may provide more clarity on the role of these drugs for COPD.

Quality of the evidence

The included studies were for the most part very well-designed and robust, and the evidence was generally of high quality.

SUMMARY OF FINDINGS

Summary of findings 1. Mepolizumab 100 mg compared with placebo for chronic obstructive pulmonary disease

Mepolizumab 100 mg compared with placebo for chronic obstructive pulmonary disease

Patient or population: individuals with COPD

Settings: outpatient

Intervention: mepolizumab 100 mg

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Mepolizumab 100 mg				
Rate of moderate or severe exacerbations Eosinophilic phenotype	1.60 moderate or severe exacerbations per year	1.30 (1.14 to 1.49) moderate or severe exacerbations per year	Rate ratio 0.81 (0.71 to 0.93)	911 (2 RCTs)	⊕⊕⊕⊕ **High**	
Rate of moderate or severe exacerbations All participants	1.51 moderate or severe exacerbations per year	1.39 (1.24 to 1.56) moderate or severe exacerbations per year	Rate ratio 0.92 (0.82 to 1.03)	1285 (2 RCTs)	⊕⊕⊕⊖ **Moderate** [a]	
Time to first moderate or severe exacerbation Eosinophilic phenotype	-	-	Hazard ratio 0.78 (0.66 to 0.92)	981 (2 RCTs)	⊕⊕⊕⊕ **High**	
Time to first moderate or severe exacerbation All participants	-	-	Hazard ratio 0.87 (0.75 to 1.0)	1285 (2 RCTs)	⊕⊕⊕⊖ **Moderate** [a]	
Rate of exacerbations with ED visit or hospitalisations Eosinophilic phenotype	0.27 exacerbations per year with ED visit	0.24 (0.18 to 0.33) exacerbations per year with ED visit	Rate ratio 0.90 (0.65 to 1.24)	911 (2 RCTs)	⊕⊕⊕⊖ **Moderate** [a]	
Rate of exacerbations with ED visit or hospitalisations	0.27 exacerbations per year with ED visit	0.25 (0.19 to 0.33) exacerbations per year with ED visit	Rate ratio 0.94 (0.72 to 1.22)	1285 (2 RCTs)	⊕⊕⊕⊖ **Moderate** [a]	

All participants						
Serious adverse events	199 serious adverse events out of 645 participants	172 serious adverse events out of 640 participants	Odds ratio 0.82 (0.65 to 1.05)	1285 (2 RCTs)	⊕⊕⊕⊖ **Moderate** [b]	
Health-related quality of life: change in SGRQ total score Scale: 0 to 100 (lower is better) Eosinophilic phenotype	-	The MD was −0.90 lower (−2.91 to 1.10).	-	911 (2 RCTs)	⊕⊕⊕⊖ **Moderate** [b]	A change of ≥ 4 is considered the minimum clinically significant difference.
Health-related quality of life: change in SGRQ total score Scale: 0 to 100 (lower is better) All participants	-	The MD was −0.30 lower (−2.00 to 1.41).	-	1285 (2 RCTs)	⊕⊕⊕⊖ **Moderate** [b]	A change of ≥ 4 is considered the minimum clinically significant difference.

*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).

CI: confidence interval; **COPD**: chronic obstructive pulmonary disease; **ED**: emergency department; **MD**: mean difference; **RCT**: randomised controlled trial; **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 once due to imprecision. There is high heterogeneity between the two studies.
[b]Downgraded once due to imprecision. The confidence intervals include the possibility of a small or no effect and important benefit or harm.

Summary of findings 2. Mepolizumab 300 mg compared with placebo for chronic obstructive pulmonary disease

Mepolizumab 300 mg compared with placebo for chronic obstructive pulmonary disease

Patient or population: individuals with COPD

Settings: outpatient

Intervention: mepolizumab 300 mg

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Mepolizumab 300 mg				
Rate of moderate or severe exacerbations Eosinophilic phenotype	1.49 moderate or severe exacerbations per year	1.28 (1.04 to 1.58) moderate or severe exacerbations per year	Rate ratio 0.86 (0.70 to 1.06)	451 (1 RCT)	⊕⊕⊕⊖ **Moderate** [a]	
Time to first moderate or severe exacerbation Eosinophilic phenotype	-	-	Hazard ratio 0.77 (0.60 to 0.99)	451 (1 RCT)	⊕⊕⊕⊖ **Moderate** [a]	
Rate of exacerbations with ED visit or hospitalisations Eosinophilic phenotype	0.28 exacerbations with ED visit per year	0.23 (0.14 to 0.38) exacerbations with ED visit per year	Rate ratio 0.83 (0.51 to 1.35)	451 (1 RCT)	⊕⊕⊕⊖ **Moderate** [a]	
Serious adverse events	68 serious adverse events out of 226 participants	60 serious adverse events out of 225 participants	Odds ratio 0.84 (0.56 to 1.27)	451 (1 RCT)	⊕⊕⊕⊖ **Moderate** [a]	
Health-related quality of life: change in SGRQ total score Scale: 0 to 100 (lower is better) Eosinophilic phenotype	-	The MD was −0.10 lower (−2.80 to 2.60).	-	451 (1 RCT)	⊕⊕⊕⊖ **Moderate** [a]	A change of ≥ 4 is considered the minimum clinically significant difference.

*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).

CI: confidence interval; **COPD**: chronic obstructive pulmonary disease; **ED**: emergency department; **MD**: mean difference; **RCT**: randomised controlled trial; **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 once as this is a single study. The true effect is likely to be close to the estimate of the effect, but further studies could be substantially different.

Summary of findings 3. Mepolizumab 750 mg compared with placebo for chronic obstructive pulmonary disease

Mepolizumab 750 mg compared with placebo for chronic obstructive pulmonary disease

Patient or population: individuals with COPD

Settings: outpatient

Intervention: mepolizumab 750 mg

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Mepolizumab 750 mg				
Number of participants experiencing an exacerbation within 6 months	7 out 10	4 out of 8	Odds ratio 0.43 (0.06 to 2.97)	18 (1 RCT)	⊕⊕⊖⊖ **Low** [a]	
Number of participants experiencing an exacerbation in 4-month follow-up period	1 out of 10	4 out of 8	Odds ratio 9.00 (0.75 to 108.31)	18 (1 RCT)	⊕⊕⊖⊖ **Low** [a]	
Serious adverse events	1 participant out of 10	2 participants out of 8	Odds ratio 3.00 (0.22 to 40.93)	18 (1 RCT)	⊕⊕⊖⊖ **Low** [a]	
Heath-related quality of life (CRQ at 6 months)	Mean 102.11 (SD 15.55)	MD 1.14 higher (−17.28 to 19.56)	-	18 (1 RCT)	⊕⊕⊖⊖ **Low** [a]	A higher score indicates better health-related quality of life.
Lung function (FEV_1) (litres post-bronchodilator) at 6 months	Mean 1.33 (SD 0.71)	MD 0.25 higher (−0.36 to 0.86)	-	18 (1 RCT)	⊕⊕⊖⊖ **Low** [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).

CI: confidence interval; **COPD**: chronic obstructive pulmonary disease; **CRQ**: Chronic Respiratory Disease Questionnaire; **FEV_1**: forced expiratory volume in 1 second; **MD**: mean difference; **RCT:** randomised controlled trial; **SD:** standard deviation

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 twice due to imprecision. The study is very small with few participants, and consequently wide confidence intervals.

Summary of findings 4. Benralizumab 10 mg compared with placebo for chronic obstructive pulmonary disease

Benralizumab 10 mg compared with placebo for chronic obstructive pulmonary disease

Patient or population: individuals with COPD

Settings: outpatient

Intervention: benralizumab 10 mg

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Benralizumab 10 mg				
Rate of moderate or severe exacerbations Eosinophils ≥ 220/µL	1.17 moderate or severe exacerbations per year	0.99 (0.83 to 1.19) moderate or severe exacerbations per year	Rate ratio 0.85 (0.71 to 1.02)	765 (1 RCT)	⊕⊕⊕⊖ **Moderate** [a]	
Rate of moderate or severe exacerbations Eosinophils < 220/µL	1.18 moderate or severe exacerbations per year	1.23 (0.97 to 1.56) moderate or severe exacerbations per year	Rate ratio 1.04 (0.82 to 1.32)	365 (1 RCT)	⊕⊕⊕⊖ **Moderate** [a]	
Rate of severe exacerbations requiring hospitalisation	0.32 severe exacerbations requiring hospitalisation per year	0.22 (0.16 to 0.30) severe exacerbations requiring hospitalisation per year	Rate ratio 0.68 (0.49 to 0.94)	765 (1 RCT)	⊕⊕⊕⊖ **Moderate** [a]	

Eosinophils ≥ 220/µL						
Serious adverse events	158 serious adverse events out of 568 participants	144 serious adverse events out of 561 participants	Odds ratio 0.90 (0.69 to 1.17)	1129 (1 RCT)	⊕⊕⊕⊖ **Moderate** [a]	
Heath-related quality of life, change in SGRQ total score Scale: 0 to 100 (lower is better) Eosinophils ≥ 220/µL	-	The MD was −0.87 lower (−3.23 to 1.49).	-	680 (1 RCT)	⊕⊕⊕⊖ **Moderate** [a]	A change of ≥ 4 is considered the minimum clinically significant difference.
Lung function (FEV_1) Eosinophils ≥ 220/µL	-	The MD was 0.01 higher (−0.04 to 0.05).	-	669 (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).

CI: confidence interval; **COPD**: chronic obstructive pulmonary disease; **FEV_1**: forced expiratory volume in 1 second; **MD**: mean difference; **RCT:** randomised controlled trial; **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 once as this is a single study. The true effect is likely to be close to the estimate of the effect, but further studies could be substantially different.

Summary of findings 5. Benralizumab 30 mg compared with placebo for chronic obstructive pulmonary disease

Benralizumab 30 mg compared with placebo for chronic obstructive pulmonary disease
Patient or population: individuals with COPD
Settings: outpatient
Intervention: benralizumab 30 mg
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Benralizumab 30 mg				
Rate of moderate or severe exacerbations Eosinophils ≥ 220/µL	1.20 moderate or severe exacerbations per year	1.20 (1.07 to 1.37) moderate or severe exacerbations per year	Rate ratio 1.00 (0.89 to 1.13)	1523 (2 RCTs)	⊕⊕⊕⊖ **Moderate** [a]	
Rate of moderate or severe exacerbations Eosinophils < 220/µL	1.24 moderate or severe exacerbations per year	1.33 (1.13 to 1.57) moderate or severe exacerbations per year	Rate ratio 1.07 (0.91 to 1.27)	711 (2 RCTs)	⊕⊕⊕⊖ **Moderate** [a]	
Rate of severe exacerbations requiring hospitalisation Eosinophils ≥ 220/µL	0.29 severe exacerbations requiring hospitalisation per year	0.28 (0.22 to 0.35) severe exacerbations requiring hospitalisation per year	Rate ratio 0.96 (0.75 to 1.22)	1523 (2 RCTs)	⊕⊕⊕⊖ **Moderate** [a]	
Serious adverse events	334 serious adverse events out of 1118 participants	328 serious adverse events out of 1117 participants	Odds ratio 0.98 (0.81 to 1.17)	2235 (2 RCTs)	⊕⊕⊕⊖ **Moderate** [a]	
Heath-related quality of life, change in SGRQ total score Scale: 0 to 100 (lower is better) Eosinophils ≥ 220/µL	-	The MD was −1.42 lower (−3.13 to 0.29).	-	1333 (2 RCTs)	⊕⊕⊕⊖ **Moderate** [a]	A change of ≥ 4 is considered the minimum clinically significant difference.
Lung function (FEV_1) Eosinophils ≥ 220/µL	-	There was no MD −0.00 (−0.03 to 0.03).	-	1312 (2 RCTs)	⊕⊕⊕⊖ **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).

CI: confidence interval; **COPD**: chronic obstructive pulmonary disease; **FEV_1**: forced expiratory volume in 1 second; **MD**: mean difference; **RCT:** randomised controlled trial; **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 once due to imprecision. The confidence intervals include the possibility of a small or no effect and important benefit or harm.

Summary of findings 6. Benralizumab 100 mg compared with placebo for chronic obstructive pulmonary disease

Benralizumab 100 mg compared with placebo for chronic obstructive pulmonary disease

Patient or population: individuals with COPD

Settings: outpatient

Intervention: benralizumab 100 mg

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Benralizumab 100 mg				
Rate of moderate or severe exacerbations	1.18 moderate or severe exacerbations per year	1.11 (1.00 to 1.22) moderate or severe exacerbations per year	Rate ratio 0.94 (0.85 to 1.03)	2314 (3 RCTs)	⊕⊕⊕⊖ **Moderate** [a]	
Rate of moderate or severe exacerbations Eosinophils ≥ 220/µL	1.20 moderate or severe exacerbations per year	1.06 (0.94 to 1.2) moderate or severe exacerbations per year	Rate ratio 0.88 (0.78 to 1.00)	1512 (2 RCTs)	⊕⊕⊕⊖ **Moderate** [a]	
Rate of moderate or severe exacerbations Eosinophils < 220/µL	1.24 moderate or severe exacerbations per year	1.26 (1.08 to 1.49) moderate or severe exacerbations per year	Rate ratio 1.02 (0.87 to 1.20)	720 (2 RCTs)	⊕⊕⊕⊖ **Moderate** [a]	
Rate of severe exacerbations requiring hospitalisation Eosinophils ≥ 220/µL	0.29 severe exacerbations requiring hospitalisation per year	0.18 (0.14 to 0.23) severe exacerbations requiring hospitalisation per year	Rate ratio 0.63 (0.49 to 0.81)	1512 (2 RCTs)	⊕⊕⊕⊕ **High**	
Serious adverse events	343 serious adverse events out of 1168 participants	318 serious adverse events out of 1165 participants	Odds ratio 0.90 (0.75 to 1.08)	2333 (3 RCTs)	⊕⊕⊕⊖ **Moderate** [a]	

Heath-related quality of life, change in SGRQ total score Scale: 0 to 100 (lower is better)	-	The MD was −1.45 lower (−2.84 to −0.07).	-	1433 (3 RCTs)	⊕⊕⊕⊕ **High**	A change of ≥ 4 is considered the minimum clinically significant difference.
Heath-related quality of life, change in SGRQ total score Scale: 0 to 100 (lower is better) Eosinophils ≥ 220/µL	-	The MD was −1.47 lower (−2.89 to −0.05).	-	1351 (2 RCTs)	⊕⊕⊕⊕ **High**	A change of ≥ 4 is considered the minimum clinically significant difference.
Lung function (FEV_1)	-	The MD was 0.03 higher (−0.00 to 0.06).	-	1425 (3 RCTs)	⊕⊕⊕⊕ **High**	
Lung function (FEV_1) Eosinophils ≥ 220/µL	-	The mean difference was 0.02 higher (−0.01 to 0.05).	-	1334 (2 RCTs)	⊕⊕⊕⊖ **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).

CI: confidence interval; **COPD**: chronic obstructive pulmonary disease; **FEV_1**: forced expiratory volume in 1 second; **MD**: mean difference; **RCT:** randomised controlled trial; **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 once due to imprecision. The confidence intervals include the possibility of a small or no effect and important benefit or harm.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is a prevalent respiratory disease, affecting 251 million people worldwide and accounting for 5% of all deaths globally. It is projected to become the third-leading cause of death by 2030 (WHO 2019a; WHO 2019b). In the UK, 4.5% of the population aged over 40 have a diagnosis of COPD, which poses a substantial socio-economic burden (BLF 2019). COPD is a progressive disease that involves a spectrum of clinical features including dyspnoea, wheeze, cough and/or sputum production. Chronic exposure to noxious particles or gases, most commonly tobacco smoke, drives COPD development. Hallmarks of the disease are airway inflammation (bronchitis), airflow limitation, and lung parenchymal destruction (emphysema) (GOLD 2019; GOLD 2020). Unlike in asthma, the other common chronic airways disease, airflow obstruction in COPD is not fully reversible.

Exacerbations of COPD, characterised by acute worsening of symptoms beyond usual day-to-day variability, often require changes in treatment and are a major cause of hospitalisation and disease-related morbidity and mortality.

COPD is a heterogeneous disease with distinct inflammatory phenotypes. Whilst neutrophils, macrophages, and B lymphocytes are the predominant inflammatory cell types in some patients (Hogg 2004), a significant proportion of patients demonstrate airway eosinophilia (Singh 2014). Phenotypic clusters have also been identified during acute exacerbations, with up to 40% showing an eosinophil-predominant T helper type 2 (Th2) inflammatory profile (Shironjit 2006). Inflammatory phenotypes of COPD have clinical and therapeutic implications. Not only is blood eosinophilia significantly associated with increased severe exacerbation rates (Couillard 2017), the use of inhaled and systemic corticosteroids have demonstrated increased efficacies in preventing and treating COPD exacerbations in those with eosinophilia (Bafadhel 2012; Bafadhel 2014; Pascoe 2015). This may suggest that eosinophilia plays a role in the pathogenesis of COPD and may drive acute exacerbations in a subgroup of patients.

Description of the intervention

Corticosteroids suppress inflammation non-specifically and are effective in many individuals with asthma or COPD; a notable proportion, however, are poorly responsive. Moreover, frequent or continuous systemic corticosteroid use carries the risk of added morbidity, such as adrenal suppression, hyperglycaemia, osteoporosis, and skin thinning.

In the search for more targeted treatments, monoclonal antibody (MAb) technology has been employed, with anti-interleukin 5 (anti-IL-5) a commonly used MAb. The appeal of this approach is that MAbs can offer high affinity and specificity for targets not amenable to small-molecule drugs. They have revolutionised the management of other conditions, particularly certain connective tissue diseases, inflammatory bowel disease, and cancers (Adegbola 2018; Bittner 2018). In all cases, biomarkers are needed which can predict therapeutic responses, for example eosinophils, which infiltrate the airways. MAbs can then be directed against immune pathways which may contribute to the presence of eosinophils, such as IL-5.

Th2 cells and eosinophils are implicated in both COPD and asthma. Mediators including IL-3, IL-5, and IL-13 are prominent in Th2-type inflammation, where they promote eosinophil maturation. IL-5 is particularly key for the differentiation, proliferation, and activation of eosinophils. Th2 cells can also drive airway inflammation via an immunoglobulin E (IgE) and mast cell mechanism. Several biologic drugs targeting Th2-type inflammation have demonstrated efficacy as an adjunct to corticosteroids in the management of severe eosinophilic or atopic asthma, with acceptable side effect profiles (Farne 2017; Normansell 2014). Consequently, a number of these drugs have been approved for use in this context, namely omalizumab (anti-IgE), mepolizumab (anti-IL-5), reslizumab (anti-IL-5), and benralizumab (anti-IL-5 receptor).

There may also be useful drug targets outside the Th2-eosinophil pathway, although to date these have not shown such efficacy in airway diseases (Durham 2016; Nixon 2017).

How the intervention might work

Eosinophilic inflammation has been implicated in a proportion of individuals with COPD, most prominently during exacerbations (Singh 2014; Siva 2007; Vedel-Krogh 2016). This process has been effectively targeted in severe eosinophilic asthma, therefore it is reasonable to expect that MAbs directed against similar targets in COPD patients with eosinophilic phenotypes may provide therapeutic benefit.

Why it is important to do this review

Whilst COPD is an irreversible disease, management of the condition is directed at slowing or halting the decline in lung function, preventing and aborting exacerbations, and optimising quality of life. Monoclonal antibody therapies have proven to be a useful tool for asthma. A recent Cochrane Review supports the use of anti-IL-5 treatments as an adjunct to standard treatment in people with severe eosinophilic asthma, with treatments roughly halving asthma exacerbations (Farne 2017). Given the number of pathological similarities between asthma and COPD, it may be that anti-IL-5 treatments can also benefit at least a subset of COPD patients. Anti-IL-5 treatments have not been approved for use in COPD, and they are not mentioned in guidelines, but as there is an emerging literature in this field, it is important to establish whether or not they have a role to play (Tan 2018). COPD is such a common condition that any additional treatments have the potential to benefit a large number of individuals. Exacerbations are a major determinant of both quality of life and healthcare usage. These drugs reduce exacerbations of asthma (Farne 2017); if they also reduced exacerbations of COPD in those with eosinophils it would be advantageous for both patients and healthcare systems.

OBJECTIVES

To assess the efficacy and safety of monoclonal antibody therapies targeting IL-5 signalling (anti-IL-5 or anti-IL-5Rα) compared with placebo in the treatment of adults with COPD.

METHODS

Criteria for considering studies for this review

Types of studies

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

Types of participants

We included adults (≥ 40 years old) with a diagnosis of COPD as defined by GOLD 2020. We recorded study authors' definitions of the severity of COPD. We did not exclude participants with comorbidities. Where possible, we excluded participants with a substantial asthma component to their disease, either with a label of 'asthma COPD overlap syndrome' (Pavord 2015), or excessive variation in lung function, defined by a variation of more than 12% and 200 mL in forced expiratory volume in one second (FEV_1), either between tests or with a bronchodilator at trial entry (GINA 2019).

Types of interventions

We included studies comparing anti-IL-5 therapy with placebo. Specifically, we considered anti-IL-5 therapies developed for use in other airway diseases such as those directed against various IL-5 targets. We included studies that allowed participants to continue using their inhaled therapies including inhaled corticosteroids (ICS), long-acting $beta_2$-agonist (LABA), and long-acting muscarinic antagonist (LAMA) or combination inhalers, as long as these co-interventions were not part of the randomised treatment.

Types of outcome measures

Primary outcomes

1. All exacerbations
2. Hospitalisations due to COPD exacerbation
3. Serious adverse events
4. Quality of life (as measured on a validated scale, e.g. St George's Respiratory Questionnaire (SGRQ) or Chronic Respiratory Disease Questionnaire (CRQ))

Secondary outcomes

1. Measures of pulmonary function such as FEV_1, and forced vital capacity (FVC)
2. Exercise performance: six-minute walk test and other measures
3. Self-rated symptom score/symptoms of breathlessness such as:
   a. inhaled rescue medication used during the treatment period and concomitant medication usage, including antibiotics and steroids;
   b. number of days (or nights) participant experienced symptoms;
   c. COPD Assessment Test (CAT) score; or
   d. COPD Control Questionnaire (CCQ) score.
4. Mortality
5. Adverse events/side effects

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 searches of the following databases and trial registries:

1. Cochrane Airways Trials Register, via the Cochrane Register of Studies, all years to 23 September 2020 (Cochrane Airways 2019);
2. Cochrane Central Register of Controlled Trials (CENTRAL), via the Cochrane Register of Studies, all years to 23 September 2020;
3. MEDLINE Ovid SP 1946 to 23 September 2020;
4. Embase Ovid SP 1974 to 23 September 2020;
5. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov)
6. World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch)

The database search strategies are listed in Appendix 1. The search strategy was developed in MEDLINE by the Cochrane Airways Information Specialist, in collaboration with the review authors, and then adapted for use in the other databases.

The Cochrane Airways Information Specialist searched all databases and trials registries from their inception to September 2020, using no restriction on language or type of publication. We identified handsearched conference abstracts and grey literature through the Cochrane Airways Trials Register and the CENTRAL database in the Cochrane Library.

Searching other resources

We checked the reference lists of all primary studies and review articles for additional references. We searched relevant manufacturers' websites for study information.

We searched on PubMed for errata or retractions from included studies published in full text on 19 June 2020.

Data collection and analysis

Selection of studies

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 been labelled as an RCT or as Not an RCT; the RCT classifier – a machine learning model that distinguishes RCTs from non-RCTs; and if appropriate, Cochrane Crowd (crowd.cochrane.org), Cochrane's citizen science platform where the Crowd help to identify and describe health evidence. More detailed information about the Screen4Me components can be found in the following publications: Marshall 2018, McDonald 2017, Noel-Storr 2018, Thomas 2017.

Following this initial assessment, two review authors (RW and TD) independently screened the titles and abstracts identified by the search results and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports of all potentially eligible studies, and two review authors (IC and PB) independently screened them for inclusion and recorded the reasons for exclusion of ineligible

studies. Any disagreements were resolved through discussion or by consulting a third person/review author (RW, TD, or SM) if required. We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and Characteristics of excluded studies table (Moher 2009).

Data extraction and management

We used a data collection form for study characteristics and outcome data that had been piloted on at least one study in the review. Two review authors (SM and TD) 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: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for studies and notable conflicts of interest of trial authors.

Two review authors (SM and EB) independently extracted outcome data from the included studies. We noted in the Characteristics of included studies table if outcome data were not reported in a useable way. Any disagreements were resolved by consensus or by involving a third person/review author (RW, TD, or SM). Two review authors (SM and EB) transferred data into the Review Manager 5 file (Review Manager 2020). We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (TD) spot-checked study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two review authors (SM and TD) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements were resolved by discussion or by involving another review author (IC, PB, or RW). 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 judged each potential source of bias as high, low, or unclear and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table in Characteristics of 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 unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale).

When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

Measures of treatment effect

We analysed dichotomous data as odds ratios (OR) and continuous data as the inverse variance for rate ratios (RR) and hazard ratios (HR), mean difference (MD), or standardised mean difference (SMD). Where we combined data from rating scales in a meta-analysis, we ensured that they were entered with a consistent direction of effect (e.g. lower scores always indicate improvement).

We undertook meta-analyses only where this was meaningful, that is if the treatments, participants, and the underlying clinical question were similar enough for pooling to make sense.

We planned to describe reported skewed data narratively (e.g. as medians and interquartile ranges for each group); however, this was not an issue with the reported data.

Where multiple trial arms were reported in a single study, we included only the relevant arms. If we combined two comparisons (e.g. drug A versus placebo and drug B versus placebo) in the same meta-analysis, we either combined the active arms or halved the control group to avoid double-counting.

If adjusted analyses were available (analysis of variance (ANOVA) or analysis of covariance (ANCOVA)), we would use these as a preference in our meta-analyses. If both change-from-baseline scores and endpoint scores were available for continuous data, we used change-from-baseline scores. If a study reported outcomes at multiple time points, we preferentially used 12-month data but reported other time points where appropriate.

We used intention-to-treat (ITT), or 'full analysis set' analyses where they were reported (i.e. where data have been imputed for participants who were randomly assigned but did not complete the study) instead of completer or per-protocol analyses.

Unit of analysis issues

For dichotomous outcomes we used participants, rather than events, as the unit of analysis (i.e. number of people admitted to hospital, rather than number of admissions per person). Where RRs were reported in a study, we analysed them on this basis. We planned to only meta-analyse data from cluster-RCTs if the available data had been adjusted to account for the clustering; however, the need to do so did not arise as no cluster-RCTs were included in the review.

Dealing with missing data

We contacted investigators or study sponsors in order to verify key study characteristics and to obtain missing numerical outcome data where possible (e.g. when a study was identified as an abstract only). Where this was not possible, and we considered the missing data to introduce serious bias, we took this into consideration in the GRADE rating for the affected outcomes.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity amongst the studies in each analysis. Where we identified substantial heterogeneity we reported it and explored the possible causes by prespecified subgroup analysis.

Assessment of reporting biases

We were not able to pool more than 10 studies, therefore we did not create and examine a funnel plot to explore possible small-study and publication biases.

Data synthesis

We used a random-effects model, reported with 95% CIs, and performed a sensitivity analysis with a fixed-effect model. We synthesised and reported dichotomous and continuous data separately for each outcome (e.g. hospitalisation/no hospitalisation or duration of hospitalisation). We also analysed ORs and reported them separately. For a given outcome measure, we combined effect estimates, such as differences at endpoint and change from baseline. We planned to combine outcomes measured using different scales (e.g. health-related quality of life) by employing SMDs in the analyses; however, this was not necessary with the available data.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses.

1. Baseline serum eosinophil counts (> 0.3 versus ≤ 0.3 × 10^9 per litre of blood)
2. Baseline COPD severity using GOLD 2020 classification

We planned to use our primary outcomes in the subgroup analyses.

We would have used the formal test for subgroup interactions in Review Manager 5 (Review Manager 2020); however, due to the limited number of included studies, no subgroup analyses were carried out.

Sensitivity analysis

We planned to carry out the following sensitivity analyses, removing the following from the primary outcome analyses.

1. A comparison of available-case analysis to true ITT analyses, where the ITT analyses are imputed.
2. A comparison based on the 'Risk of bias' assessment, where trials are judged to be at high risk of bias for any of the six 'Risk of bias' domains.

However, due to the limited number of included studies, no sensitivity analyses were carried out.

Summary of findings and assessment of the certainty of the evidence

We created a 'Summary of findings' table using the following outcomes: all exacerbations, hospitalisations due to COPD, serious adverse events, lung function (FEV_1), and quality of life. We used the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data for the prespecified outcomes. We used the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), employing GRADEpro GDT software (GRADEpro GDT). We justified all decisions to downgrade the quality of studies using footnotes and made comments to aid the reader's understanding of the review where necessary.

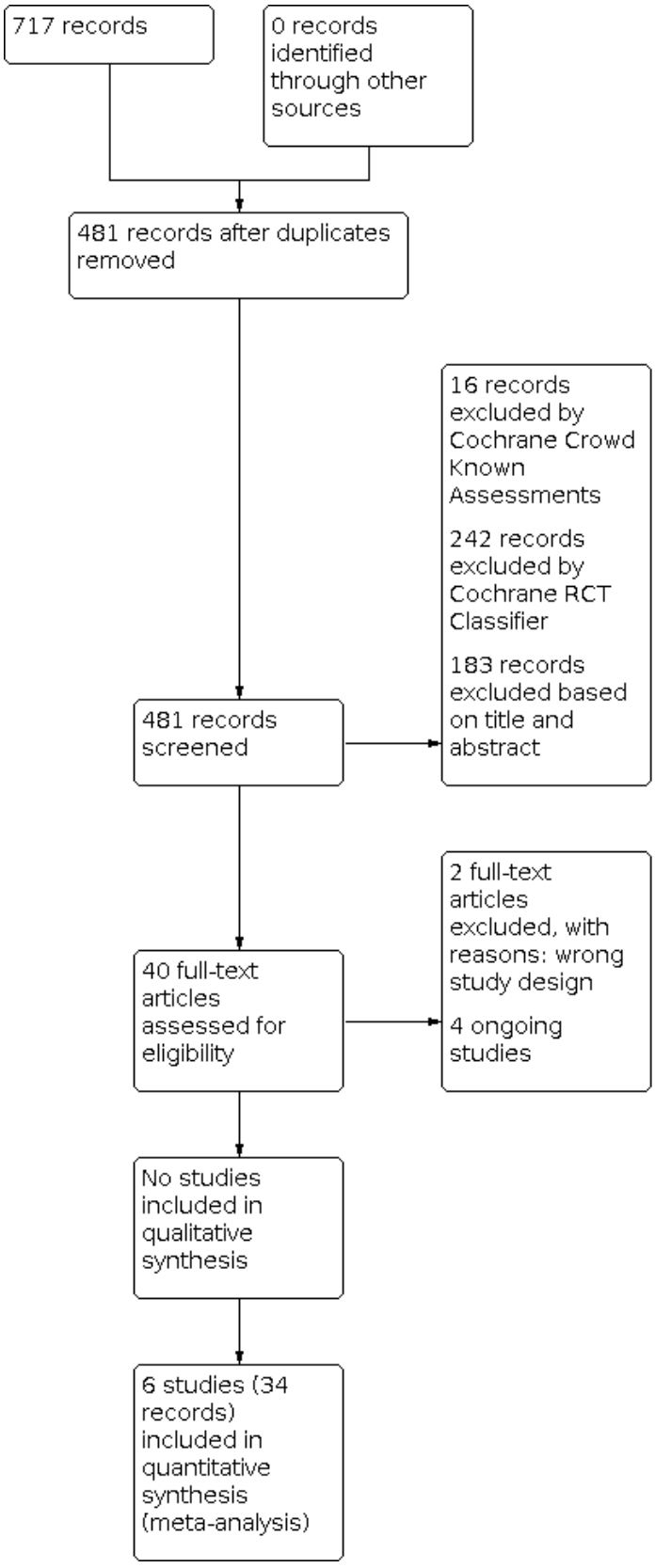
RESULTS

Description of studies

Results of the search

We identified 717 records in our literature searches (Figure 1), the last search being conducted in September 2020. We screened the 481 records that remained after removal of duplicates for eligibility. We excluded 183 records on the basis of title and abstract screening, 242 records were excluded by Cochrane RCT Classifier, and 16 records were excluded by Cochrane Crowd Known Assessments.

Figure 1. Study flow diagram.



Six studies met our inclusion criteria (Characteristics of included studies), and four others were included as ongoing studies (Characteristics of ongoing studies). The six included studies included had 34 records, as follows.

1. The three included studies comparing mepolizumab versus placebo had 16 records: four for Dasgupta 2016, six for NCT02105948 (METREX), and six for NCT02105961 (METREO).
2. The three included studies comparing benralizumab versus placebo had 18 records: nine for Brightling 2014, five for NCT02138916 (GALATHEA), and four for NCT02155660 (TERRANOVA).

There are four ongoing studies (see Characteristics of ongoing studies), two comparing benralizumab versus placebo NCT04053634 and NCT04098718 (the ABRA study), and two comparing mepolizumab versus placebo NCT04075331 and NCT04133909 (the MATINEE study).

We found no studies looking at reslizumab.

The definition used for exacerbation of COPD varied slightly amongst the included studies. GOLD 2020 defines three levels of severity of exacerbation depending on the treatment required: mild exacerbations no more than short-acting bronchodilators, moderate exacerbations need antibiotics or oral steroids, or both, and severe exacerbations result in hospital attendance.

In NCT02138916 (GALATHEA) and NCT02155660 (TERRANOVA), exacerbations were defined as "a symptomatic worsening ... resulting in the use of systemic glucocorticoids, the use of antibiotics, or hospitali[s]ation or COPD-related death". This definition of (any) exacerbation maps to moderate and severe exacerbations using the GOLD 2020 definitions. Brightling 2014, NCT02105948 (METREX), and NCT02105961 (METREO) used definitions that approximate the GOLD 2020 definition, but only recorded moderate and severe exacerbations. Dasgupta 2016 does not define exacerbation.

In this review, we have used the terms 'moderate and severe exacerbations' and 'severe exacerbation' where we believe the working definition used is sufficiently close to the GOLD 2020 definition to be practically equivalent.

Included studies

Mepolizumab

We included three studies comparing mepolizumab versus placebo (see Characteristics of included studies table), involving a total of 1530 participants distributed as follows: Dasgupta 2016 n = 19; NCT02105948 (METREX) n = 837; and NCT02105961 (METREO) n = 674. Mepolizumab was administered intravenously (IV) in Dasgupta 2016 (at a dose of 750 mg). In NCT02105948 (METREX) administration was subcutaneous (SC) (at a dose of 100 mg), and in NCT02105961 (METREO) administration was SC (at a dose of 100 mg or 300 mg). In NCT02105948 (METREX) and NCT02105961 (METREO), administration was every 4 weeks for up to 52 weeks, whilst in Dasgupta 2016 it was once a month.

The three studies only included participants with frequent exacerbations of COPD, with at least one "major" exacerbation in the previous year (Dasgupta 2016), or two moderate exacerbations (NCT02105948 (METREX); NCT02105961 (METREO)). Diagnosis in all three studies was in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) definition, with a documented history of COPD for at least one year. Dasgupta 2016 specified FEV_1/FVC < 70% and FEV_1 < 60% of predicted normal values calculated using National Health and Nutrition Examination Survey (NHANES) III reference equations at screening visit. In addition, NCT02105948 (METREX) and NCT02105961 (METREO) specified a measured post-salbutamol FEV_1 > 20% and ≤ 80% of predicted normal values calculated using NHANES III reference equations. Participants in Dasgupta 2016 were current or former smokers, whereas in NCT02105948 (METREX) and NCT02105961 (METREO) participation was independent of smoking status and smoking history.

Dasgupta 2016 would have allowed > 12% FEV_1 reversibility with prednisone as a surrogate for sputum eosinophilia. All participants were meant to have less than 12% FEV_1 reversibility with a bronchodilator. In the event, all participants had more than 3% sputum eosinophilia, and the prednisone surrogate was not used (Milan 2020 [pers comm]), so we considered this study as meeting our inclusion criteria. It appears that some individuals were included in this study despite not meeting the bronchodilator reversibility criteria.

Benralizumab

We included three studies comparing benralizumab versus placebo (see Characteristics of included studies table), involving a total of 4012 participants distributed as follows: Brightling 2014 n = 101; NCT02138916 (GALATHEA) n = 1656; and NCT02155660 (TERRANOVA) n = 2255. Benralizumab was administered SC in Brightling 2014 (at a dose of 100 mg), SC in NCT02138916 (GALATHEA) (at a dose of 30 mg or 100 mg), and SC in NCT02155660 (TERRANOVA) (at a dose of 10 mg, 30 mg, or 100 mg). Administration was every four weeks for the first three doses and then every eight weeks for the next five doses in Brightling 2014. In NCT02138916 (GALATHEA) and NCT02155660 (TERRANOVA), administration was every four weeks for the first three doses and every eight weeks thereafter, with the last dose administered at week 48.

The studies included participants with a diagnosis of COPD and a documented history of one or more annualised incidence rate of moderate or severe acute exacerbations of chronic obstructive pulmonary disease (Brightling 2014), or two or more moderate or one or more severe exacerbations in the previous year (NCT02138916 (GALATHEA); NCT02155660 (TERRANOVA)). NCT02138916 (GALATHEA) and NCT02155660 (TERRANOVA) specified a post-bronchodilator FEV_1 > 20% and ≤ 65%. All participants were current or former smokers with ≥ 10 pack-year exposure.

Excluded studies

Of the full-text studies assessed for eligibility, three were ongoing studies and two were excluded with reasons (one was not a randomised trial, and the other was an aggregation of two studies investigating modulation of blood inflammatory markers) (see Characteristics of excluded studies).

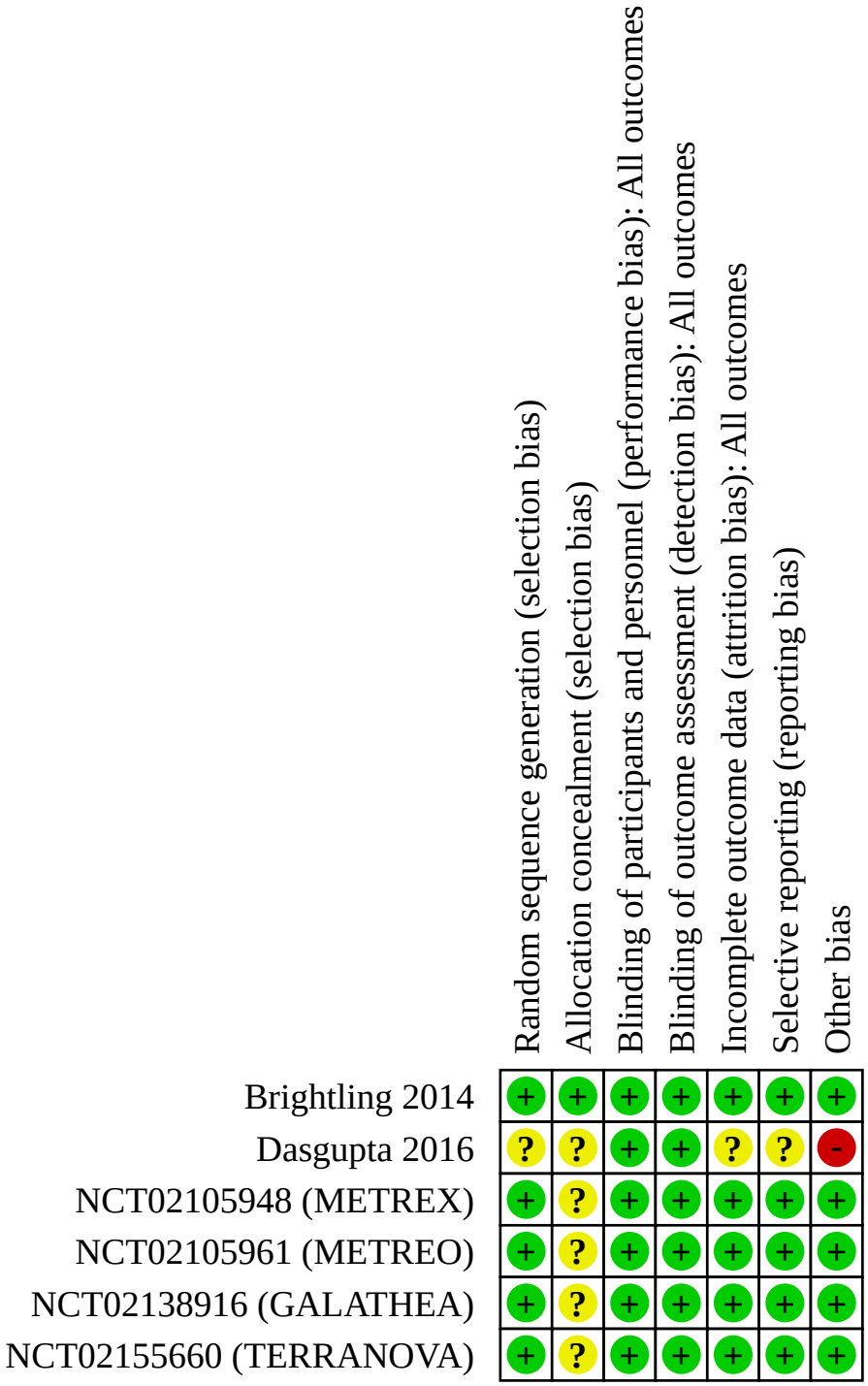
Risk of bias in included studies

We assessed the risk of bias using the 'Risk of bias' tool described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Allocation

We determined one study to be at low risk of selection bias across two domains (Brightling 2014). Four studies provided details on random sequence generation, and although it is highly likely that the allocation concealment was adequate, we were unable to find any details on this in the trial reports (NCT02105948 (METREX); NCT02105961 (METREO); NCT02138916 (GALATHEA); NCT02155660 (TERRANOVA)). One study presented no details on either random sequence generation or allocation concealment and was judged to be at unclear risk of bias for both domains (Figure 2) (Dasgupta 2016).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Blinding

We assessed all six studies as at low risk of performance and detection bias.

Incomplete outcome data

We assessed five studies as at low risk of attrition bias. One study provided no information about incomplete outcome data (Dasgupta 2016).

Selective reporting

We assessed five studies as at low risk of reporting bias. Information for one study was insufficient to permit a judgement (Dasgupta 2016).

Other potential sources of bias

It is likely that Dasgupta 2016 included people with asthma. The inclusion criteria for this study required < 12% FEV_1 reversibility to a bronchodilator, but it appears that a number of participants were included (particularly in the placebo arm) despite having greater than 12% reversibility.

Effects of interventions

See: **Summary of findings 1** Mepolizumab 100 mg compared with placebo for chronic obstructive pulmonary disease; **Summary of findings 2** Mepolizumab 300 mg compared with placebo for chronic obstructive pulmonary disease; **Summary of findings 3** Mepolizumab 750 mg compared with placebo for chronic obstructive pulmonary disease; **Summary of findings 4** Benralizumab 10 mg compared with placebo for chronic obstructive pulmonary disease; **Summary of findings 5** Benralizumab 30 mg compared with placebo for chronic obstructive pulmonary disease; **Summary of findings 6** Benralizumab 100 mg compared with placebo for chronic obstructive pulmonary disease

Mepolizumab 100 mg versus placebo

Primary outcomes

All exacerbations

The two trials NCT02105961 (METREO) and NCT02105948 (METREX) providing data to this comparison reported their results for participants with higher levels of blood eosinophils (defined as ≥ 150 cells per mm^3 at screening or ≥ 300 cells per mm^3 in the year before trial entry) separately and their total sample. To reflect the information in these studies we have followed the same rationale here.

With regard to rate of moderate or severe exacerbations, we found evidence that participants with higher blood eosinophils had a lower rate of exacerbations when receiving mepolizumab 100 mg compared to those receiving placebo (rate ratio (RR) 0.81, 95% confidence interval (CI) 0.71 to 0.93; participants = 911; studies = 2, Analysis 1.1, high-certainty evidence). There was probably a smaller reduction in the exacerbation rate with the inclusion of participants with lower blood eosinophils (RR 0.92, 95% CI 0.82 to 1.03; participants = 1285; studies = 2, Analysis 1.1, moderate-certainty evidence).

Data were also available for the time to first moderate or severe exacerbation. The eosinophilic-phenotype participants receiving mepolizumab 100 mg experienced a longer duration to first moderate or severe exacerbation than those in the placebo group (hazard ratio (HR) 0.78, 95% CI 0.66 to 0.92; participants = 981; studies = 2, Analysis 1.2, high-certainty evidence). Evidence for a reduction within the total sample was less certain (HR 0.87, 95% CI 0.75 to 1.00; participants = 1285; studies = 2, Analysis 1.2, moderate-certainty evidence) (Summary of findings 1).

Hospitalisations due to COPD exacerbation

Mepolizumab 100 mg probably reduces the rate of exacerbations leading to an emergency department visit or hospitalisation for the higher eosinophil participants (RR 0.90, 95% CI 0.65 to 1.24; participants = 911; studies = 2, Analysis 1.3, moderate-certainty evidence), and there was a similar result within the total sample (RR 0.94, 95% CI 0.72 to 1.22; Analysis 1.3, moderate-certainty evidence). We are not confident about these results due to high statistical heterogeneity between the two studies (Summary of findings 1).

Serious adverse events

There was probably a reduction in serious adverse events between mepolizumab 100 mg and placebo groups (odds ratio (OR) 0.82, 95% CI 0.65 to 1.05; participants = 1285; studies = 2, Analysis 1.4, moderate-certainty evidence). Although both studies were large with a robust methodology, the confidence intervals include the possibility of benefit or harm (Summary of findings 1).

Quality of life

In the higher blood eosinophil participants, there was probably only a small difference in St George's Respiratory Questionnaire (SGRQ) total scores between mepolizumab 100 mg and placebo groups (mean difference (MD) −0.90, 95% CI −2.91 to 1.10; participants = 911; studies = 2, Analysis 1.5, moderate-certainty evidence). The minimal important difference on this scale is a change of four units. We found similar results for the total sample of participants (MD −0.30, 95% CI −2.00 to 1.41; participants = 1285; studies = 2, Analysis 1.5, moderate-certainty evidence). Although both studies were large with a robust methodology, the confidence intervals include the possibility of benefit or harm (Summary of findings 1).

Secondary outcomes

Measures of pulmonary function

NCT02105961 (METREO) and NCT02105948 (METREX) did not include these specific measures of pulmonary function as an outcome measure.

Exercise performance

NCT02105961 (METREO) and NCT02105948 (METREX) did not include these specific measures of exercise performance as an outcome measure.

Self-rated symptom score/symptoms of breathlessness

NCT02105961 (METREO) and NCT02105948 (METREX) did not include any self-rated symptom score/symptoms of breathlessness or number of days (or nights) that participants experienced symptoms as outcome measures.

COPD Assessment Test score

The COPD Assessment Test scores revealed evidence of a small difference between mepolizumab 100 mg and placebo groups for participants with higher blood eosinophils (MD −0.95, 95% CI −1.80 to −0.10; participants = 911; studies = 2, Analysis 1.6) indicating a benefit in favour of mepolizumab 100 mg. A similar benefit was observed for the total sample of participants (MD −0.78, 95% CI −1.50 to −0.06; participants = 1285; studies = 2, Analysis 1.6). The minimum important difference on this scale was a change of two units.

COPD Control Questionnaire score

NCT02105961 (METREO) and NCT02105948 (METREX) did not include COPD Control Questionnaire (CCQ) score as an outcome measure.

Mortality

There was uncertainty between mepolizumab 100 mg and placebo groups with regard to mortality (OR 0.77, 95% CI 0.42 to 1.39; participants = 1285; studies = 2; I^2 = 15%, Analysis 1.7).

Adverse events/side effects

We are uncertain if there is a difference between mepolizumab 100 mg and placebo groups with regard to adverse events/side effects (OR 0.97, 95% CI 0.77 to 1.21; participants = 1285; studies = 2; I^2 = 63%, Analysis 1.8); the statistical heterogeneity for this outcome was high.

Mepolizumab 300 mg versus placebo

Primary outcomes

All exacerbations

Only one study contributed data for this outcome (NCT02105961 (METREO)). All participants in this study had higher levels of blood eosinophils using the same definition of higher eosinophils as the mepolizumab 100 mg versus placebo comparison above.

There was probably a reduction in the rate of moderate or severe exacerbations for mepolizumab 300 mg versus placebo for the study participants (RR 0.86, 95% CI 0.70 to 1.06; participants = 451; studies = 1, Analysis 2.1, moderate-certainty evidence).

There was probably a difference favouring mepolizumab 300 mg in terms of the time to first moderate or severe exacerbation (HR 0.77, 95% CI 0.60 to 0.99; participants = 451; studies = 1, Analysis 2.2, moderate-certainty evidence). The analysis included only one study, which has a robust methodology (Summary of findings 2).

Hospitalisations due to COPD exacerbation

Mepolizumab 300 mg probably reduces the rate of hospitalisations due to COPD exacerbation when compared with placebo (RR 0.83, 95% CI 0.51 to 1.35; participants = 451; studies = 1, Analysis 2.3, moderate-certainty evidence) (Summary of findings 2).

Serious adverse events

There was probably a difference between mepolizumab 300 mg and placebo groups in the number of participants experiencing serious adverse events (OR 0.84, 95% CI 0.56 to 1.27; participants = 451; studies = 1, Analysis 2.4, moderate-certainty evidence), with fewer serious adverse events in the intervention group (Summary of findings 2).

Quality of life

There was probably little or no difference in SGRQ total scores between mepolizumab 300 mg and placebo groups (MD −0.10, 95% CI −2.80 to 2.60; participants = 451; studies = 1; Analysis 2.5, moderate-certainty evidence) (Summary of findings 2).

Secondary outcomes

Measures of pulmonary function

NCT02105961 (METREO) did not include these specific measures of pulmonary function as an outcome measure.

Exercise performance

NCT02105961 (METREO) did not include these specific measures of exercise performance as an outcome measure.

Self-rated symptom score/symptoms of breathlessness

NCT02105961 (METREO) did not include any self-rated symptom score/symptoms of breathlessness or number of days (or nights) participants experienced symptoms as outcome measures.

COPD Assessment Test score

There was probably little or no difference between mepolizumab 300 mg and placebo groups in CAT scores (MD −0.40, 95% CI −1.50 to 0.70; participants = 451; studies = 1, Analysis 2.6). The minimum important difference on this scale was a change of two units.

COPD Control Questionnaire score

NCT02105961 (METREO) did not include the CCQ score as an outcome measure.

Mortality

There was considerable uncertainty between mepolizumab 300 mg and placebo groups with regard to mortality (OR 0.89, 95% CI 0.34 to 2.35; participants = 451; studies = 1, Analysis 2.7).

Adverse events/side effects

We are uncertain if there is a difference between mepolizumab 300 mg and placebo groups in adverse events/side effects (OR 1.01, 95% CI 0.69 to 1.48; participants = 451; studies = 1, Analysis 2.8).

Mepolizumab 750 mg versus placebo

Primary outcomes

All exacerbations

Only one trial involving 19 participants compared mepolizumab 750 mg versus placebo (Dasgupta 2016). There is great uncertainty between mepolizumab 750 mg and placebo groups in the number of participants experiencing an exacerbation within six months (OR 0.43, 95% CI 0.06 to 2.97; participants = 18; studies = 1, Analysis 3.1, low-certainty evidence). Similarly, there is great uncertainty between mepolizumab 750 mg and placebo groups in the number of participants experiencing an exacerbation in the four-month follow-up period (OR 9.00, 95% CI 0.75 to 108.31; participants = 18; studies = 1, Analysis 3.2, low-certainty evidence) (Summary of findings 3).

Hospitalisations due to COPD exacerbation

Dasgupta 2016 did not include data relating to hospitalisations as a specific outcome measure.

Serious adverse events

Data for this outcome were obtained through correspondence with the study authors. We are uncertain if there is a difference between the two study arms with regard to serious adverse events (OR 3.00, 95% CI 0.22 to 40.93; participants = 18; studies = 1, Analysis 3.3, low-certainty evidence) (Summary of findings 3).

Quality of life

We are uncertain if there is a difference between mepolizumab 750 mg and placebo groups with regard to health-related quality of life (HRQoL) (measured with the Chronic Respiratory Disease Questionnaire (CRQ)) at three months (MD 6.92, 95% CI −11.28 to 25.12; participants = 18; studies = 1, Analysis 3.4, low-certainty evidence). There is also great uncertainty between groups in HRQoL at six months (MD 1.14, 95% CI −17.28 to 19.56; participants = 18; studies = 1, Analysis 3.5, low-certainty evidence) (Summary of findings 3).

Secondary outcomes

Measures of pulmonary function

Post-bronchodilator FEV_1 was assessed at three and six months. We are uncertain if there is a difference between mepolizumab 750 mg and placebo groups at three months (MD 0.26, 95% CI −0.35 to 0.87; participants = 18; studies = 1, Analysis 3.6) or six months (MD 0.25, 95% CI −0.36 to 0.86; participants = 18; studies = 1, Analysis 3.7).

FVC was similarly assessed at three and six months. In both cases, we are uncertain if there is a difference between the two groups: the FVC % post-bronchodilator at three months for mepolizumab 750 mg was median 82.50 (interquartile range (IQR) 43 to 90) versus placebo median 64.50 (IQR 31 to 94). At six months, the authors observed median 75.50 (IQR 46 to 87) for mepolizumab 750 mg versus median 66.50 (IQR 31 to −84) for placebo.

Exercise performance

Dasgupta 2016 did not include these specific measures of exercise performance as an outcome measure.

Self-rated symptom score/symptoms of breathlessness

Dasgupta 2016 did not include any self-rated symptom score/symptoms of breathlessness or number of days (or nights) participants experienced symptoms as an outcome measure.

COPD Assessment Test score

The CAT was measured at three and six months. The scores were mepolizumab 750 mg median 13 (IQR 6 to 23) versus placebo median 22 (IQR 0 to 27) at three months, and mepolizumab 750 mg median 14 (IQR 3 to 29) versus placebo median 23 (IQR 4 to 39) at six months. The minimum important difference on this scale was a change of two units. These results are uncertain, as the quality of evidence is low due to the limited number of participants (Summary of findings 3).

COPD Control Questionnaire score

Dasgupta 2016 did not include the CCQ questionnaire as an outcome measure.

Mortality

Dasgupta 2016 did not include mortality as an outcome measure.

Adverse events/side effects

Data for this outcome were obtained through correspondence with the study authors. We are uncertain if there is a difference between the two study arms for adverse events (OR 0.78, 95% CI 0.04 to 14.75; participants = 18; studies = 1, Analysis 3.8, low-certainty evidence) (Summary of findings 3).

Benralizumab 10 mg versus placebo

Primary outcomes

All exacerbations

Data for this comparison were available only from NCT02155660 (TERRANOVA). The data in this trial were reported separately for participants with eosinophils ≥ 220/µL and for those with eosinophils < 220/µL. To remain consistent with the reporting of that trial, we followed the same strategy. Regarding moderate of severe exacerbations for participants with eosinophils ≥ 220/µL, benralizumab 10 mg probably reduces the exacerbation rate (RR 0.85, 95% CI 0.71 to 1.02; participants = 765; studies = 1, Analysis 4.1, moderate-certainty evidence); however, there was probably little or no difference between groups for those with eosinophils < 220/µL (RR 1.04, 95% CI 0.82 to 1.32; participants = 365; studies = 1, Analysis 4.1, moderate-certainty evidence).

The annual EXAcerbations of Chronic pulmonary disease Tool (EXACT-PRO) exacerbation rate was also reported for participants with eosinophils ≥ 220/µL in NCT02155660 (TERRANOVA) (RR 0.98, 95% CI 0.81 to 1.19; participants = 765; studies = 1, Analysis 4.2, moderate-certainty evidence), indicating there was probably little or no difference between benralizumab 10 mg and placebo for this outcome.

Hospitalisations due to COPD exacerbation

However, regarding the rate of severe exacerbations requiring hospitalisation, there was probably a difference favouring benralizumab 10 mg versus placebo (RR 0.68, 95% CI 0.49 to 0.94; participants = 765; studies = 1, Analysis 4.3, moderate-certainty evidence) (Summary of findings 4).

Serious adverse events

Serious adverse events were reported for the complete sample in NCT02155660 (TERRANOVA), and there was probably little or no difference between benralizumab 10 mg and placebo groups for this outcome (OR 0.90, 95% CI 0.69 to 1.17; participants = 1129; studies = 1, Analysis 4.4, moderate-certainty evidence) (Summary of findings 4).

Quality of life

The SGRQ total score for participants with baseline ≥ 220/µL was reported in NCT02155660 (TERRANOVA). The data revealed little or no difference between benralizumab and placebo for this outcome (MD −0.87, 95% CI −3.23 to 1.49; participants = 680; studies = 1, Analysis 4.5, moderate-certainty evidence) (Summary of findings 4).

Secondary outcomes

Measures of pulmonary function

Data were reported for FEV_1 for participants with baseline ≥ 220/µL in NCT02155660 (TERRANOVA). There was probably little or no difference between benralizumab and placebo for this outcome (MD 0.01, 95% CI −0.04 to 0.05; participants = 669; studies = 1, Analysis 4.6, moderate-certainty evidence) (Summary of findings 4).

Exercise performance

No separate data were available for this outcome.

Self-rated symptom score/symptoms of breathlessness

Total rescue medication use for participants with baseline ≥ 220/µL was reported in NCT02155660 (TERRANOVA). There was probably a slight difference between groups favouring benralizumab for this outcome (MD −0.59 puffs per day, 95% CI −1.11 to −0.07; participants = 619; studies = 1, Analysis 4.7).

Data for nights with awakenings for participants with baseline ≥ 220/µL were also available from NCT02155660 (TERRANOVA), and there was probably little or no difference between the two treatment arms for this outcome (MD −0.04, 95% CI −0.09 to 0.01; participants = 638; studies = 1, Analysis 4.8).

COPD Assessment Test score

There was probably little or no difference between benralizumab and placebo groups for participants with baseline ≥ 220/µL on the CAT score (MD 0.18, 95% CI −0.82 to 1.18; participants = 682; studies = 1, Analysis 4.9). The minimum important difference on this scale was a change of two units.

COPD Control Questionnaire score

No data were available for this outcome.

Mortality

Mortality data were reported for the complete sample in NCT02155660 (TERRANOVA), and there was probably little difference between benralizumab 10 mg and placebo groups for this outcome (OR 0.90, 95% CI 0.46 to 1.76; participants = 1129; studies = 1, Analysis 4.10).

Adverse events/side effects

Adverse events were reported for the complete sample in NCT02155660 (TERRANOVA), and there was probably little or no difference between benralizumab 10 mg and placebo groups for this outcome (OR 0.96, 95% CI 0.76 to 1.21; participants = 1129; studies = 1, Analysis 4.11).

Benralizumab 30 mg versus placebo

Primary outcomes

All exacerbations

The rate of moderate or severe exacerbations reported in NCT02155660 (TERRANOVA) and NCT02138916 (GALATHEA) for participants in the eosinophils ≥ 220/µL category indicated that there was probably little or no difference between benralizumab 30 mg and placebo groups for this outcome (RR 1.00, 95% CI 0.89 to 1.13; participants = 1523; studies = 2 Analysis 5.1, moderate-certainty evidence). Similarly, the data for participants in the eosinophils < 220/µL subgroup indicated that there was probably little or no difference between benralizumab 30 mg and placebo groups for this outcome (RR 1.07, 95% CI 0.91 to 1.27; participants = 711; studies = 2, Analysis 5.1, moderate-certainty evidence). Data for the EXACT-PRO exacerbation rate for participants in the eosinophils ≥ 220/µL category also indicated that there was probably little or no difference between benralizumab 30 mg and placebo groups (RR 1.03, 95% CI 0.90 to 1.17; participants = 1522; studies = 2, Analysis 5.2, moderate-certainty evidence). Although the studies were large with a robust methodology, the confidence intervals include the possibility of a small or no effect and some benefit or harm (Summary of findings 5).

Hospitalisations due to COPD exacerbation

There was similarly probably little or no difference between benralizumab 30 mg and placebo in rate of severe exacerbations for participants in the eosinophils ≥ 220/µL category (RR 1.01, 95% CI 0.77 to 1.33; participants = 1523; studies = 2, Analysis 5.3, moderate-certainty evidence). This was also the case with regard to rate of severe exacerbations requiring hospitalisation for participants in the eosinophils ≥ 220/µL subgroup (RR 0.96, 95% CI 0.75 to 1.22; participants = 1523; studies = 2, Analysis 5.4, moderate-certainty evidence) (Summary of findings 5).

Serious adverse events

There was similarly probably little or no difference between benralizumab 30 mg and placebo in serious adverse events (OR 0.98, 95% CI 0.81 to 1.17; participants = 2235; studies = 2; I^2 = 79%, Analysis 5.5, moderate-certainty evidence). There was high statistical heterogeneity between the two studies, although they both have a robust methodology (Summary of findings 5).

Quality of life

Mean change from baseline in SGRQ total score for participants with baseline ≥ 220/µL was reported in both NCT02155660 (TERRANOVA) and NCT02138916 (GALATHEA). There was probably only a small difference between benralizumab 30 mg and placebo for this outcome (MD −1.42, 95% CI −3.13 to 0.29; participants = 1333; studies = 2, Analysis 5.6, moderate-certainty evidence). The minimal important difference on this scale was a change of four units. Although both studies were large with a robust methodology, the confidence intervals include the possibility of a small or no effect and some benefit or harm (Summary of findings 5).

Secondary outcomes

Measures of pulmonary function

Data on FEV_1 performance were available from both NCT02155660 (TERRANOVA) and NCT02138916 (GALATHEA) relating to participants with baseline ≥ 220/µL. There was probably no difference between benralizumab 30 mg and placebo groups for this outcome (MD −0.00, 95% CI −0.03 to 0.03; participants = 1312; studies = 2, Analysis 5.7, moderate-certainty evidence).

Exercise performance

No separate data were available for this outcome.

Self-rated symptom score/symptoms of breathlessness

Both NCT02155660 (TERRANOVA) and NCT02138916 (GALATHEA) provided data on inhaled rescue medication used during the treatment period; however, this was reported only for participants

with baseline ≥ 220/µL. A small difference between benralizumab 30 mg versus placebo was indicated, favouring benralizumab (MD −0.40 puffs per day, 95% CI −0.77 to −0.03; participants = 1216; studies = 2; I^2 = 0%, Analysis 5.8).

The number of nights participants experienced symptoms was reported in both trials as a measure of nights with awakenings for participants with baseline ≥ 220/µL. A small difference favouring benralizumab was indicated (MD −0.06, 95% CI −0.09 to −0.02; participants = 1242; studies = 2; I^2 = 11%, Analysis 5.9).

COPD Assessment Test score

The CAT score was reported in both trials for participants with baseline eosinophils ≥ 220/µL. No evidence of a difference between benralizumab 30 mg and placebo was observed for this outcome (MD −0.18, 95% CI −0.90 to 0.55; participants = 1338; studies = 2; I^2 = 0%, Analysis 5.10). The minimum important difference on this scale was a change of two units.

COPD Control Questionnaire score

No data were available relating to CCQ score.

Mortality

We are uncertain if there is a difference in mortality between benralizumab 30 mg and placebo groups (OR 1.13, 95% CI 0.70 to 1.84; participants = 2235; studies = 2; I^2 = 0%, Analysis 5.11).

Adverse events/side effects

There was probably little or no difference between benralizumab 30 mg and placebo groups in adverse events (OR 0.94, 95% CI 0.80 to 1.12; participants = 2235; studies = 2; I^2 = 51%, Analysis 5.12).

Benralizumab 100 mg versus placebo

Primary outcomes

All exacerbations

The rate of moderate or severe exacerbations was reported in Brightling 2014, NCT02155660 (TERRANOVA), and NCT02138916 (GALATHEA), with no certain difference observed between benralizumab 100 mg and placebo groups (RR 0.94, 95% CI 0.85 to 1.03; participants = 2314; studies = 3, Analysis 6.1, moderate-certainty evidence).

The annual EXACT-PRO exacerbation rate was also reported for participants in the eosinophils ≥ 220/µL category in NCT02155660 (TERRANOVA) and NCT02138916 (GALATHEA), with no certain difference indicated between benralizumab 100 mg and placebo groups (RR 0.95, 95% CI 0.82 to 1.09; participants = 1509; studies = 2, Analysis 6.2, moderate-certainty evidence). Although both studies were large with a robust methodology, the confidence intervals include the possibility of a small or no effect and important benefit or harm (Summary of findings 6).

Hospitalisations due to COPD exacerbation

There was probably a small difference favouring benralizumab 100 mg versus placebo in absolute number of participants experiencing exacerbations (OR 0.39, 95% CI 0.07 to 2.13; participants = 82; studies = 1; Analysis 6.3, moderate certainty evidence) (Brightling 2014). However, with regard to rate of exacerbations for participants in the eosinophils ≥ 220/µL category in NCT02155660 (TERRANOVA) and NCT02138916 (GALATHEA), there was a clear advantage with benralizumab 100 mg versus placebo (RR 0.63, 95% CI 0.49 to 0.81; participants = 1512; studies = 2, Analysis 6.4, high-certainty evidence) (Summary of findings 6).

Serious adverse events

Three studies reported this outcome (Brightling 2014; NCT02138916 (GALATHEA); NCT02155660 (TERRANOVA)). There was probably little or no difference between benralizumab 100 mg and placebo groups (OR 0.90, 95% CI 0.75 to 1.08; participants = 2333; studies = 3, Analysis 6.5, moderate-certainty evidence) (Summary of findings 6).

Quality of life

There may be little or no difference between benralizumab 100 mg and placebo in change in SGRQ total score in Brightling 2014 (MD −1.08, 95% CI −7.34 to 5.18; participants = 82; studies = 1, Analysis 6.6). However, for participants in the eosinophils ≥ 220/µL category in NCT02155660 (TERRANOVA) and NCT02138916 (GALATHEA), there was a small difference in change in SGRQ total score favouring benralizumab 100 mg versus placebo (MD −1.47, 95% CI −2.89 to −0.05; participants = 1351; studies = 2, Analysis 6.6, high-certainty evidence), although this difference was not greater than the minimum clinically significant difference of four units (Summary of findings 6).

Secondary outcomes

Measures of pulmonary function such as FEV_1, and FVC

NCT02155660 (TERRANOVA) and NCT02138916 (GALATHEA) reported FEV_1 data only for participants with baseline eosinophils ≥ 220/µL. There was no certain difference between benralizumab 100 mg and placebo groups for this outcome (MD 0.02, 95% CI −0.01 to 0.05; participants = 1334; studies = 2; I^2 = 0%, Analysis 6.7).

However, in Brightling 2014, FEV_1 data were reported for the complete sample. A difference was observed favouring the benralizumab arm (MD 0.19, 95% CI 0.05 to 0.33; participants = 91; studies = 1, Analysis 6.7).

Exercise performance

No separate data were available for this outcome.

Self-rated symptom score/symptoms of breathlessness

Data on inhaled rescue medication used during the treatment period were reported for participants with baseline eosinophils ≥ 220/µL in both NCT02155660 (TERRANOVA) and NCT02138916 (GALATHEA). A small difference favouring benralizumab 100 mg versus placebo was indicated (MD −0.49, 95% CI −0.83 to −0.15; participants = 1237; studies = 2; I^2 = 0%, Analysis 6.8).

Data relating to the proportion of nights participants were awake were also provided by NCT02155660 (TERRANOVA) and NCT02138916 (GALATHEA) for those with baseline eosinophils ≥ 220/µL. There was probably a small difference favouring benralizumab for this outcome (MD −0.03, 95% CI −0.07 to 0.00; participants = 1263; studies = 2; I^2 = 0%, Analysis 6.9). The minimum important difference on this scale was a change of two units.

COPD Assessment Test score

Data were also available for participants with baseline eosinophils ≥ 220/µL in NCT02155660 (TERRANOVA) and NCT02138916

(GALATHEA), indicating probably a small difference favouring benralizumab on this measure (MD −0.60, 95% CI −1.29 to 0.10; participants = 1358; studies = 2; I^2 = 66%, Analysis 6.10).

COPD Control Questionnaire score

No data were available for this outcome.

Mortality

Three studies reported this outcome (Brightling 2014; NCT02138916 (GALATHEA); NCT02155660 (TERRANOVA)), with probably no difference observed between benralizumab 100 mg and placebo groups (OR 0.94, 95% CI 0.57 to 1.55; participants = 2333; studies = 3; I^2 = 0%, Analysis 6.11).

Adverse events/side effects

Data from three studies revealed that there was probably no difference between study arms for this outcome (OR 1.06, 95% CI 0.90 to 1.26; participants = 2333; studies = 3; I^2 = 64%, Analysis 6.12) (Brightling 2014; NCT02138916 (GALATHEA); NCT02155660 (TERRANOVA)).

DISCUSSION

Summary of main results

Six studies met the inclusion criteria for this review (Brightling 2014; Dasgupta 2016; NCT02105948 (METREX); NCT02105961 (METREO); NCT02138916 (GALATHEA); NCT02155660 (TERRANOVA)). Three studies compared mepolizumab to placebo (Dasgupta 2016; NCT02105948 (METREX); NCT02105961 (METREO)), and three compared benralizumab to placebo (Brightling 2014; NCT02138916 (GALATHEA); NCT02155660 (TERRANOVA)). No head-to-head trials were identified. All studies included only participants with frequent exacerbations of COPD.

For our primary outcome, rate of moderate or severe exacerbations, mepolizumab 100 mg reduces exacerbations by 19% in those with an eosinophil count of at least 150/µL, based on high-certainty evidence. With the inclusion of participants with lower eosinophils, mepolizumab 100 mg probably reduces the exacerbation rate by 8%, based on moderate-certainty evidence. Mepolizumab 300 mg also probably reduces the rate of exacerbations by 14% in participants all of whom had raised eosinophils. The evidence in a single small study of mepolizumab 750 mg was very uncertain.

Participants receiving mepolizumab 100 mg experienced a longer duration to first moderate or severe exacerbation than those in the placebo group, but only those with the eosinophilic phenotype; within the total sample this difference was smaller and less certain. The certainty of the evidence for the eosinophilic group was high. There was also a small increase in time to first moderate or severe exacerbation in all participants receiving mepolizumab 300 mg, based on moderate-certainty evidence.

The COPD Assessment Test (CAT score), a questionnaire designed to measure the impact of COPD on a person's life, revealed a modest benefit in favour of the mepolizumab 100 mg group for all participants, including the eosinophilic phenotype participants. There was probably little or no difference between mepolizumab 300 mg and placebo groups in CAT scores. This difference may be due to measurement imprecision, with the mepolizumab 100 mg data based on two studies with high heterogeneity (NCT02105948 (METREX); NCT02105961 (METREO)), and the mepolizumab 300 mg data having wide confidence intervals (NCT02105961 (METREO)).

For all other outcomes where mepolizumab was compared to placebo, there were no certain differences between the intervention and placebo.

Benralizumab 100 mg reduces the rate of severe exacerbation requiring hospitalisation in participants with an eosinophil count of at least 220/µL, based on high-certainty evidence. Benralizumab 10 mg probably reduces the rate of severe exacerbations in those with an eosinophil count of at least 220/µL, based on moderate-certainty evidence.

For participants in the eosinophils ≥ 220/µL category in NCT02155660 (TERRANOVA) and NCT02138916 (GALATHEA), there was an improvement in the St George's Respiratory Questionnaire (SGRQ) total score in favour of benralizumab 100 mg; however, the difference fell below the minimum clinically significant difference.

Self-rated symptom score/symptoms of breathlessness, such as inhaled rescue medication used during the treatment period and concomitant medication usage, including antibiotics and steroids, showed a treatment advantage for benralizumab SC 30 mg and 100 mg. The number of nights participants experienced symptoms, as a measure of nights with awakenings, was also reported in NCT02155660 (TERRANOVA) and NCT02138916 (GALATHEA), with a difference favouring benralizumab 30 mg, and a probable benefit of benralizumab 100 mg.

No clinically meaningful changes in lung function were seen. The included trials were conducted in populations selected for fixed airflow obstruction, so it would be surprising if large changes in pulmonary physiological measurements were observed.

Treatment with mepolizumab SC and benralizumab SC appeared to be safe. All pooled analyses showed that there was probably little or no difference in serious adverse events, adverse events, or side effects between the use of a monoclonal antibody therapy compared to placebo.

Anti-IL-5 therapies appear to be safe in individuals with COPD, and have demonstrated some modest efficacy in the reduction of exacerbation rates and disease-related symptoms. Nevertheless, these efficacies were more certain in those participants with higher blood eosinophil levels. (Note that the definition of higher blood eosinophils differed between the mepolizumab and the benralizumab trials, but in both cases included participants with blood eosinophils at the higher end of the normal range as well as those with true blood eosinophilia).

Overall completeness and applicability of evidence

The participant demographics are representative of individuals with COPD, with mean age between 63 to 67 years. The aim of this review was to assess the efficacy and safety of monoclonal antibody therapies targeting IL-5 signalling (anti-IL-5 or anti-IL-5Rα) compared with placebo in the treatment of adults with COPD. Whilst exacerbation rate, hospitalisation, health-related quality of life, and adverse events were consistently reported in all studies, other outcome measures such as exercise tolerance, self-rated symptoms, and lung function were not.

We identified four studies that are ongoing and have yet to be completed.

There are a number of monoclonal antibody therapies approved for use in the context of eosinophilic or atopic asthma. We did not find evidence in COPD for monoclonal antibodies other than mepolizumab (anti-IL-5) and benralizumab (anti-IL-5 receptor). The information does not lend itself to a direct dose response interpretation as there is no evidence of greater effects at higher doses.

Certainty of the evidence

We applied the GRADE system and judged the certainty of the evidence for most comparisons to be at least moderate. Although we are more certain about the benefits for participants with higher levels of blood eosinophils in reducing the rate of severe exacerbations, we cannot deduce that the intervention does not work in those with lower levels of blood eosinophils; we are less certain about this group due to the wider confidence intervals which include the possibility of a small or no effect and important benefit or harm. The limitations in some of the included studies are noted in the Results, Figure 2, and Characteristics of included studies. A funnel plot was not feasible due to the small number of included studies, therefore a formal assessment of publication bias using such methods was not possible. Nevertheless, our search strategy was comprehensive and robust, and included searching conference abstracts and ongoing studies to find unpublished studies.

Potential biases in the review process

Our review adhered as closely as possible to our published protocol (Donovan 2019). In order to align with the GOLD 2020 definition, we have used different labels for two of our primary outcomes compared with our protocol (Donovan 2019): "severe exacerbation" is functionally identical to "hospitalisations due to COPD exacerbation", and the switch from "any exacerbation" to "moderate or severe exacerbation" allows meaningful comparisons between the two drugs.

As with most systematic reviews, there remains the possibility that we may have failed to identify unpublished trials contributing positive or negative results, and we are aware of the potential for publication bias. Six trials meeting our inclusion criteria were identified through comprehensive and systematic database searches, and two review authors independently evaluated all the identified studies to endeavour to address any study selection bias or errors.

Agreements and disagreements with other studies or reviews

We are not aware of any other systematic reviews addressing this question.

The results of NCT02105948 (METREX) and NCT02105961 (METREO) were published together, along with both pre-planned and post hoc analyses of their combined data (Pavord 2017). These analyses found a 23% reduction in the rate of moderate or severe exacerbations in participants with baseline blood eosinophil counts greater than 300 cells per microlitre treated with mepolizumab compared with placebo. This reduction was possibly confined to exacerbations that required treatment with corticosteroids, rather than those requiring antibiotics alone (Pavord 2018). This reduction in exacerbation rate is consistent with our review (19% reduction in exacerbation rate in those with an eosinophilic phenotype treated with mepolizumab 100 mg), although we did not specifically examine the treatments chosen for exacerbations.

A Cochrane Review found that both mepolizumab and benralizumab reduced exacerbation rates in severe asthma by around 50% (Farne 2017). Whilst we did find some evidence of a reduction in exacerbations in COPD with a eosinophilic phenotype with these drugs, the decrease was far more modest, not consistent across drug doses, and in the case of benralizumab, confined to exacerbations severe enough to require hospitalisation.

AUTHORS' CONCLUSIONS

Implications for practice

Mepolizumab and benralizumab may have a small role as add-on therapies in a highly selected group of chronic obstructive pulmonary disease (COPD) patients who have both higher levels of blood eosinophils and frequent moderate to severe exacerbations. In this group, these treatments appear to modestly reduce the rate of severe exacerbations (and for mepolizumab, possibly moderate exacerbations). The included studies did not compare frequent with infrequent exacerbators, and our conclusions here relate only to the former reflecting the samples in the included studies; we are not in a position to comment on infrequent exacerbators. Importantly, there were no safety concerns or an excess of serious adverse events. Lung function and health-related quality of life were not improved.

Implications for research

Based on the available evidence, it seems unlikely that interleukin 5 (IL-5) or its receptor (IL-5R) therapies will be of use for the majority of people with COPD. Given the mechanisms of action of these drugs, they would only be expected to be of benefit in those with type 2 inflammation. The cut-off points used to define higher levels of blood eosinophils were relatively low (150 to 220/µL), so even the high-eosinophil groups may have included substantial numbers of participants with only modest degrees of type 2 inflammation. Future trials of anti-IL-5 therapies in COPD should target those with true peripheral blood eosinophilia.

Without direct comparisons between benralizumab versus mepolizumab from head-to-head trials there is considerable uncertainty to guide practice. Whilst a network meta-analysis could potentially illuminate this issue, in the absence of such studies, the differing definitions of eosinophilia in the included studies are a major barrier to this.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Brightling 2014

Study characteristics	
Methods	Multicentre, phase 2a, randomised, double-blind, placebo-controlled study Study locations: Canada, Denmark, Germany, Poland, Spain, the United Kingdom, the United States
Participants	421 participants were screened, and 101 participants with a diagnosis of COPD were randomised into the following 2 study arms. Benralizumab 100 mg: 51 participants, mean age 62.9 years (SD 8.2); females 16 (31.4%) Placebo: 50 participants, mean age 64.6 years (SD 7.5); females 21 (42%) Inclusion criteria: • Participants aged 40 to 85 years at the time of screening. • Written informed consent obtained from the participant prior to performing any protocol-related procedures. • Documented history of 1 or more annualised incidence rate of moderate or severe AECOPD. • Current smoker or ex-smoker with a tobacco history of ≥ 10 pack-years. • Adequate contraception from screening through end of trial. • Able to read and write. Exclusion criteria:

Brightling 2014 *(Continued)*

- Any condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of participant safety or study results.
- Pregnant, breastfeeding, or lactating women.
- Known history of allergy or reaction to any component of the investigational product formulation.
- History of anaphylaxis to any other biologic therapy.
- Donation or transfusion of blood, plasma, or platelets within the past 3 months prior to screening.
- Other significant pulmonary disease which in the opinion of the investigator or medical monitor might compromise the interpretation of the study.
- Fever > 37.0 °C (98.6 °F) at screening.
- Receipt of any novel investigational medicinal product within 3 months before the first dose of investigational product in this study and through the end of the study.
- Seropositive for hepatitis A, hepatitis B surface antigen, hepatitis C, or HIV 1 or 2 (HIV-1 or HIV-2).
- History of alcohol or drug abuse within the past year that required treatment which the investigator or medical monitor felt would compromise interpretation of the study data.
- Past or current malignancy within the past 5 years except adequately treated non-invasive basal cell and squamous cell carcinoma of the skin and cervical carcinoma in situ treated with apparent success more than 1 year prior to screening.
- Patients participating in, or scheduled for, an intensive COPD rehabilitation programme (patients who were in the maintenance phase of a rehabilitation programme were eligible to take part).
- Current diagnosis of asthma according to GINA guidelines.
- Previous treatment with MEDI-563.

Interventions	Benralizumab (MEDI-563) 100 mg versus placebo matched to benralizumab (MEDI-563). In both intervention and control arms of the study: injection subcutaneously every 4 weeks for the first 3 doses and then every 8 weeks for the next 5 doses (Day 1, 29, 57, 113, 169, 225, 281, and 337).
Outcomes	Primary outcome measures: • Annualised incidence rate of moderate or severe AECOPD. Time Frame: Day 1 up to 393 Secondary outcome measures: • Number of Participants Reporting TEAEs and TESAEs. Time Frame: Day 1 up to 561 • Number of Participants Hospitalised Due to AECOPD. Time Frame: Day 1 up to 393 • Percentage of Participants Hospitalised Due to AECOPD. Time Frame: Day 1 up to 393 • Annual incidence rate of hospitalisation due to ECOPD. Time Frame: Day 1 up to 393 • Change From Baseline in COPD-Specific SGRQ-C Total and Domain Scores at Day 393. Time Frame: Baseline, Day 393 • Percentage of Participants With Improvement in SGRQ-C Total Score. Time Frame: Day 393 • Change From Baseline in CRQ-SAS Domain Scores at Day 393. Time Frame: Baseline, Day 393 • Percentage of Participants With a 0.5-Point Improvement in CRQ-SAS Domain Scores at Day 393. Time Frame: Day 393 • Change From Baseline in BODE Scores at Day 393. Time Frame: Baseline, Day 393
Notes	Principal Investigator: Rene van der Merwe, MBChB. MedImmune LLC Sponsor: MedImmune LLC. Collaborator: AstraZeneca

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned (1:1), via computer-generated permuted block randomisation (block size of 4) with a central telephone and web-based system, to receive 100 mg benralizumab or matched placebo, subcutaneously.

Brightling 2014 *(Continued)*

Allocation concealment (selection bias)	Low risk	All other study site personnel, participants, and sponsors, including data analysts, were masked to treatment allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel were blinded (clearly stated in clinicaltrials.gov/ct2/show/nct01227278).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators were blinded (clearly stated in clinicaltrials.gov/ct2/show/nct01227278).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete outcome data were comprehensively reported.
Selective reporting (reporting bias)	Low risk	No apparent indication of selective outcome reporting.
Other bias	Low risk	No other apparent sources of bias.

Dasgupta 2016

Study characteristics	
Methods	Phase 3, randomised, double-blind, placebo-controlled study Study location: Firestone Institute of Respiratory Health, St Joseph's Hospital, Hamilton, Ontario, Canada, L8N 4A6
Participants	19 participants aged 40 to 80 years with a diagnosis of COPD with eosinophilic bronchitis were randomised into 2 study arms. 1 participant (from placebo group) left the study just after randomisation because of severe exacerbation requiring hospitalisation, therefore the study was conducted in 18 participants. Mepolizumab 750 mg: 8 participants, mean age 65.1 years (SD 6.3); females 4 (50%). Placebo: 10 participants, mean age 66.9 years (SD 5.9); females 1 (10%). Inclusion criteria: • Diagnosis: an established clinical history of COPD in accordance with the definition by the ATS/ERS as follows: COPD is a preventable and treatable disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences. • Sputum eosinophils > 3% at randomisation and on at least 1 occasion in the past 2 years. If these historic data are not available, documented improvement in FEV_1 of at least 12% with a course of prednisone in the past 2 years will be used as a surrogate for the presence of airway eosinophilia. • FEV_1/FVC < 70% and FEV_1 < 60% of predicted normal values calculated using NHANES III reference equations at screening visit. • At least 1 major exacerbation requiring prednisone in the preceding 12 months. If patients are currently well controlled by optimising their sputum cell counts (eosinophils < 2%), they should have documented history of exacerbations when their eosinophilia was uncontrolled. • A signed and dated written informed consent prior to study participation. • Smoking history: current or former cigarette smokers with a history of cigarette smoking of greater than 10 pack-years (number of pack years = (number of cigarettes per day/20) x number of years

Dasgupta 2016 *(Continued)*

	smoked (e.g. 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years)). Former smokers are defined as those who have stopped smoking for at least 6 months prior to screening visit. • Male or female adults. A female is eligible to enter and participate in the study if she is either of non-childbearing potential, or is of childbearing age and has a negative pregnancy test at screening and agrees to acceptable contraceptive methods used consistently and correctly. Exclusion criteria: • Current asthma (12% reversibility to a bronchodilator). • Sputum eosinophils < 3% on fluticasone (or equivalent) of 250 µg twice a day. • Inability to use salmeterol or tiotropium. • Significant comorbidity that prevents participation in the study. • Known bronchiectasis or immune deficiency disorders that would predispose the individual to recurrent infections. • Pregnancy or intent to become pregnant and lactating females. • Drug or alcohol abuse: a known or suspected history of alcohol or drug abuse within 2 years prior to screening visit.
Interventions	Mepolizumab 750 mg versus placebo. Mepolizumab (an anti-IL-5, given once a month intravenously at a dose of 750 mg). The placebo consisted of 100 mL normal saline solution (0.9%, 154 mmol/L sodium chloride).
Outcomes	Primary outcome measures: • Percentage decrease of sputum eosinophils from baseline. Time Frame: 6 months Secondary outcome measures: • Proportion of participants with a major exacerbation. Time Frame: 6 months
Notes	Principal Investigator: Parameswaran Nair, MD, PhD, FRCP. Associate Professor of Medicine, Division of Respiratory, McMaster University Sponsor: McMaster University

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information in the trial report to permit a judgement.
Allocation concealment (selection bias)	Unclear risk	Insufficient information in the trial report to permit a judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This is clearly stated in clinicaltrials.gov/show/NCT01463644.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This is clearly stated in clinicaltrials.gov/show/NCT01463644.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information in the trial report to permit a judgement.

Dasgupta 2016 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information in the trial report to permit a judgement.
Other bias	High risk	The inclusion criteria for this study required < 12% FEV_1 reversibility to a bronchodilator. It appears that some participants were entered despite not meeting this criterion, therefore it is likely that some people in this study had current asthma.

NCT02105948 (METREX)

Study characteristics	
Methods	Multicentre, phase 3, randomised, placebo-controlled, double-blind, parallel-group study. Study locations: Australia, Belgium, Canada, the Czech Republic, Estonia, France, Greece, Italy, Mexico, Norway, Peru, Poland, the Russian Federation, Spain, Sweden, the United States Study duration: 52 weeks A 4-arm study: mepolizumab 100 mg - high stratum versus placebo - high stratum; and mepolizumab 100 mg - low stratum versus placebo - low stratum.
Participants	837 participants aged at least 40 years with frequent exacerbations of COPD. Unselected participants in the mITT population with an eosinophilic phenotype were stratified according to blood eosinophil count (≥ 150 per cubic millimetre at screening or ≥ 300 per cubic millimetre during the previous year). Mepolizumab 100 mg - high stratum: 233 participants, mean age 65.2 years (SD 8.36); females 84 (36.1%) Placebo - high stratum: 229 participants, mean age 65.3 years (SD 8.53); females 79 (34.5%) Mepolizumab 100 mg - low stratum: 184 participants, mean age 66.1 years (SD 9.14); females 76 (41.3%) Placebo - low stratum: 190 participants, mean age 65.2 years (SD 8.62); females 77 (40.5%) Inclusion criteria: • COPD diagnosis: participants with a clinically documented history of COPD for at least 1 year in accordance with ATS/ERS definition. • Severity of COPD: participants must present with the following: a measured pre- and post-salbutamol FEV_1/FVC ratio of < 0.70 at Visit 1 to confirm the diagnosis of COPD; a measured post-salbutamol FEV_1 > 20% and ≤ 80% of predicted normal values calculated using NHANES III reference equations at Visit 1. • History of exacerbations: a well-documented history (e.g. medical record verification) in the 12 months prior to Visit 1 of: at least 2 moderate COPD exacerbations (defined as the use of systemic corticosteroids (IM, IV, or oral) and/or treatment with antibiotics) or at least 1 severe COPD exacerbation (defined as having required hospitalisation). Note: at least 1 exacerbation must have occurred whilst the participant was taking ICS plus LABA plus LAMA. Note: prior use of antibiotics alone does not qualify as a moderate exacerbation unless the use was specifically for the treatment of worsening symptoms of COPD. • Concomitant COPD therapy: a well-documented requirement for optimised standard of care background therapy that includes ICS plus 2 additional COPD medications (i.e. triple therapy) for the 12 months prior to Visit 1 and meets the following criteria: immediately prior to Visit 1, minimum of 3 months of use of an ICS (at a dose ≥ 500 µg/day fluticasone propionate dose equivalent plus); or LABA and LAMA. • For participants who are not continually maintained on ICS plus LABA plus LAMA for the entire 12 months prior to Visit 1, use of the following is allowed (but not in the 3 months immediately prior to Visit 1): ICS at a dose ≥ 500 µg/day fluticasone propionate dose equivalent plus a LABA or LAMA and use

NCT02105948 (METREX) *(Continued)*

of at least 1 other class of COPD medication suggested by the 2013 GOLD guidelines for patients who are prone to exacerbation (i.e. phosphodiesterase-4-inhibitors, methylxanthines, or a combination of SABA and SAMA). Note: participants must be willing to stay on their standard COPD medication for the duration of the study.

- Informed consent: able to give written informed consent prior to participation in the study, which will include the ability to comply with the requirements and restrictions listed in the consent form. Participants must be able to read, comprehend, and write at a level sufficient to complete study-related materials.
- Gender: male or eligible female: to be eligible for entry into the study females of childbearing potential must commit to consistent and correct use of an acceptable method of birth control from the time of consent, for the duration of the trial, and for 4 months after last study drug administration.
- Age: at least 40 years of age at Visit 1.
- Smoking status: participants with confirmed COPD are eligible to participate independent of their smoking status and smoking history, i.e. current smokers, never-smokers, or ex-smokers can be enrolled into the study. Current smokers are defined as those with a history of cigarette smoking of ≥ 10 pack-years (number of pack years = (number of cigarettes per day/20) x number of years smoked (e.g. 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years)). Former smokers are defined as those who met the definition of a current smoker but had stopped smoking for at least 6 months prior to Visit 1. Never-smokers are those who did not meet the definition of a current or former smoker.
- French participants: in France, participants are eligible for inclusion in study only if they were either affiliated to or a beneficiary of a social security category.

Exclusion criteria:

- Participants having asthma: current and former smokers: participants with a current diagnosis of asthma (those with a prior history are eligible if they meet inclusion criteria for a current diagnosis of COPD). Never-smokers: participants with any history of asthma. Other respiratory disorders: the investigator must judge that COPD is the primary diagnosis accounting for the clinical manifestations of the lung disease. Participants with alpha-1-antitrypsin deficiency as the underlying cause of COPD are excluded. Participants with active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, primary pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases are excluded. Participants are also excluded if maintenance use of bi-level positive airway pressure is required for the treatment of respiratory disorder.
- COPD stability: participants with pneumonia, exacerbation, lower respiratory infection within the 4 weeks prior to Visit 1.
- Lung resection: participants with lung volume reduction surgery within the 12 months prior to Visit 1.
- Pulmonary rehabilitation programme: participation in the acute phase of a pulmonary rehabilitation programme within 4 weeks prior to Visit 1. Participants who are in the maintenance phase of a pulmonary rehabilitation programme are not excluded.
- Oxygen: participants receiving treatment with oxygen more than 4.0 L/min. Whilst breathing supplemental oxygen, participants should demonstrate an oxyhaemoglobin saturation ≥ 89%.
- 12-lead ECG finding: an abnormal and significant ECG finding from the 12-lead ECG conducted at Visit 1 if considered to be clinically significant by the Investigator. 12-lead ECGs will be over-read by a centralised independent cardiologist to assist in consistent evaluation of participant eligibility. Results from the 12-lead ECG over-read must be received prior to assessing eligibility at Visit 2.
- Unstable or life-threatening cardiac disease: participants with any of the following are excluded: myocardial infarction or unstable angina in the last 6 months; unstable or life-threatening cardiac arrhythmia requiring intervention in the last 3 months; NYHA Class IV heart failure.
- Other diseases/abnormalities: participants with (historical or) current evidence of clinically significant, neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease), or haematological abnormalities that are uncontrolled. 'Significant' is defined as any disease that, in the opinion of the investigator, would put the safety of the participant at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study.
- Eosinophilic disease: participants with other conditions that could lead to elevated eosinophils such as hypereosinophilic syndromes including eosinophilic granulomatosis with polyangiitis (EGPA, also known as Churg-Strauss syndrome), or eosinophilic oesophagitis.
- Parasitic infection: participants with a pre-existing helminthes infestation within 6 months prior to Visit 1 are also excluded.

NCT02105948 (METREX) *(Continued)*

- Malignancy: a current malignancy or previous history of cancer in remission for less than 12 months prior to Visit 1 (participants that had localised carcinoma of the skin or cervix which was resected for cure are not excluded). Note for South Korea: Korean participants with a diagnosis of malignancy within 5 years of Visit 1 are excluded.
- Immunodeficiency: a known immunodeficiency (e.g. HIV) other than that explained by the use of corticosteroids taken for COPD.
- Liver disease: unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice), cirrhosis, and known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). Chronic stable hepatitis B and C are acceptable if participant otherwise meets entry criteria (e.g. presence of hepatitis B surface antigen or positive hepatitis C test result within 3 months of screening).
- Monoclonal antibodies: participants who have received any monoclonal antibody within 5 half-lives of Visit 1.
- Investigational medications: participants who have received an investigational drug within 30 days of Visit 1, or within 5 drug half-lives of the investigational drug, whichever is longer (this also includes investigational formulations of a marketed product).
- Hypersensitivity: participants with a known allergy or intolerance to another monoclonal antibody or biologic including history of anaphylaxis to another biologic.
- Inability to read: in the opinion of the investigator, any participant who is unable to read and/or would not be able to complete study-related materials.
- Non-compliance: participants at risk of non-compliance, or unable to comply with the study procedures. Any infirmity, disability, or geographic location that would limit compliance for scheduled visits.
- Questionable validity of consent: participants with a history of psychiatric disease, intellectual deficiency, poor motivation, or other conditions that would limit the validity of informed consent to participate in the study.
- Drug or alcohol abuse: a known or suspected history of alcohol or drug abuse within 2 years prior to Visit 1.
- Previous participation: participants who have previously participated in any study of mepolizumab.
- Affiliation with Investigator Site: is an investigator, sub-investigator, study co-ordinator, employee of a participating investigator or study site, or immediate family member of the aforementioned that is involved in this study.

Interventions	Mepolizumab 100 mg versus placebo. Each participant received 100 mg mepolizumab SC injection or placebo every 4 weeks (13 administrations during 52-week treatment period) along with optimised standard of care background therapy. Placebo: sterile 0.9% sodium chloride solution Salbutamol MDI was issued for use as rescue medication throughout the study.
Outcomes	Primary outcome measures: • Rate of Moderate or Severe Exacerbations in Participants in the High Stratum. Time Frame: from randomisation to Week 52 • Rate of Moderate or Severe Exacerbations in the mITT Population. Time Frame: from randomisation to Week 52 Secondary outcome measures • Time to First Moderate/Severe Exacerbation in Participants in the High Stratum. Time Frame: from randomisation to Week 52 • Rate of COPD Exacerbations Requiring an ED Visit and/or Hospitalisation in Participants in the High Stratum. Time Frame: from randomisation to Week 52 • Change From Baseline in Mean Total SGRQ Score in Participants in the High Stratum. Time Frame: baseline and Week 52 • Change From Baseline in Mean CAT Score in Participants in the High Stratum. Time Frame: baseline and Week 52

NCT02105948 (METREX) *(Continued)*

- Time to First Moderate/Severe Exacerbation in the mITT Population. Time Frame: from randomisation to Week 52
- Rate of COPD Exacerbations Requiring ED Visit and/or Hospitalisation in the mITT Population. Time Frame: from randomisation to Week 52
- Change From Baseline in Mean Total SGRQ Score in the mITT Population. Time Frame: baseline and Week 52
- Change From Baseline in Mean CAT Score in the mITT Population. Time Frame: baseline and Week 52

Notes	Principal Investigator: GSK Clinical Trials Sponsor: GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using a centralised, computer-generated, permuted-block design with fixed block size of 6; separate schedules were generated for each country.
Allocation concealment (selection bias)	Unclear risk	It is highly likely that the allocation concealment was adequate, but no details provided in the trial report.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participant, investigator, outcomes assessor masked (confirmed in clinicaltrials.gov/ct2/show/results/NCT02105948).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participant, investigator, outcomes assessor masked (confirmed in clinicaltrials.gov/ct2/show/results/NCT02105948).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data sensitivity analyses conducted indicating robustness of primary efficacy results.
Selective reporting (reporting bias)	Low risk	No apparent indication of selective outcome reporting
Other bias	Low risk	No apparent indication of other sources of bias.

NCT02105961 (METREO)

Study characteristics

Methods	Multicentre, phase 3, randomised, placebo-controlled, double-blind, parallel-group study Study locations: Argentina, Australia, Canada, Chile, Denmark, Germany, Japan, Republic of Korea, the Netherlands, Romania, Slovakia, Taiwan, Ukraine, the United Kingdom, the United States Study duration: 52 weeks
Participants	674 participants aged at least 40 years with COPD. All participants had a blood eosinophil count of at least 150 per cubic millimetre at screening or at least 300 per cubic millimetre during the previous year. Mepolizumab 300 mg: 225 participants, mean age 64.8 years (SD 8.96); females 67 (29.8%)

NCT02105961 (METREO) *(Continued)*

Mepolizumab 100 mg: 223 participants, mean age 64.8 (SD 9.06); females 91 (40.8%)

Placebo: 226 participants, mean age 65.8 years (SD 8.64); females 70 (31.0%)

Inclusion criteria:

- COPD diagnosis: participants with a clinically documented history of COPD for at least 1 year in accordance with ATS/ERS definition.
- Severity of COPD: participants must present with the following: a measured pre- and post-salbutamol FEV_1/FVC ratio of < 0.70 at Visit 1 to confirm the diagnosis of COPD; a measured post-salbutamol FEV_1 > 20% and ≤ 80% of predicted normal values calculated using NHANES III reference equations at Visit 1.
- History of exacerbations: a well-documented history (e.g. medical record verification) in the 12 months prior to Visit 1 of at least 2 moderate COPD exacerbations. 'Moderate' is defined as the use of systemic corticosteroids (IM, IV, or oral) and/or treatment with antibiotics; or at least 1 severe COPD exacerbation. 'Severe' is defined as having required hospitalisation. Note: at least 1 exacerbation must have occurred while the participant was taking ICS plus LABA or LAMA. Prior use of antibiotics alone does not qualify as a moderate exacerbation unless the use was specifically for the treatment of worsening symptoms of COPD.
- Concomitant COPD therapy: a well-documented requirement for optimised standard of care background therapy that includes ICS plus 2 additional COPD medications (i.e. triple therapy) for the 12 months prior to Visit 1 and meets the following criteria: immediately prior to Visit 1, minimum of 3 months of use of an inhaled corticosteroid at a dose ≥ 500 µg/day fluticasone propionate dose equivalent plus LABA and LAMA.
- For participants who are not continually maintained on ICS plus LABA plus LAMA for the entire 12 months prior to Visit 1, use of following is allowed (but not in the 3 months immediately prior to Visit 1): ICS at a dose ≥ 500 µg/day fluticasone propionate dose equivalent plus a LABA or LAMA and use of at least 1 other class of COPD medication (i.e. phosphodiesterase-4-inhibitors, methylxanthines, or a combination of short acting $beta_2$-agonist and short-acting muscarinic antagonist).
- Informed consent: able to give written informed consent prior to participation in the study, which will include the ability to comply with the requirements and restrictions listed in the consent form. Participants must be able to read, comprehend, and write at a level sufficient to complete study-related materials.
- Gender: male or eligible female; to be eligible for entry into the study females of childbearing potential must commit to consistent and correct use of an acceptable method of birth control from the time of consent, for the duration of the trial, and for 4 months after last study drug administration.
- Age: at least 40 years of age at Visit 1.
- Smoking status: participants with confirmed COPD are eligible to participate independent of their smoking status and smoking history, i.e. current smokers, never-smokers, or ex-smokers can be enrolled into the study. Current smokers are defined as those with a history of cigarette smoking of ≥ 10 pack-years (number of pack-years = (number of cigarettes per day/20) x number of years smoked (e.g. 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years)). Former smokers are defined as those who meet the definition of a current smoker but have stopped smoking for at least 6 months prior to Visit 1. Never-smokers are those who do not meet the definition of a current or former smoker.
- French participants: In France, participants are eligible for inclusion only if either affiliated to or a beneficiary of a social security category.

Exclusion criteria:

- Participants with asthma: current and former smokers: participants with a current diagnosis of asthma (those with a prior history are eligible if they meet inclusion criteria for a current diagnosis of COPD); never-smokers: participants with any history of asthma.
- Other respiratory disorders: the investigator must judge that COPD is the primary diagnosis accounting for the clinical manifestations of the lung disease. Participants with $alpha_1$-antitrypsin deficiency as the underlying cause of COPD are excluded. Participants with active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, primary pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases are also excluded. Participants are excluded if maintenance use of bi-level positive airway pressure is required for the treatment of respiratory disorder.
- COPD stability: participants with pneumonia, exacerbation, lower respiratory infection within the 4 weeks prior to Visit 1.
- Lung resection: participants with lung volume reduction surgery within the 12 months prior to Visit 1.

NCT02105961 (METREO) *(Continued)*

- Pulmonary rehabilitation programme: participation in the acute phase of a pulmonary rehabilitation programme within 4 weeks prior to Visit 1. Participants who are in the maintenance phase of a pulmonary rehabilitation programme are not excluded.
- Oxygen: participants receiving treatment with oxygen more than 4.0 L/min. Whilst breathing supplemental oxygen, participants should demonstrate an oxyhaemoglobin saturation ≥ 89%.
- 12-lead ECG finding: an abnormal and significant ECG finding from the 12-lead ECG conducted at Visit 1, if considered to be clinically significant by the Investigator. 12-lead ECGs will be over-read by a centralised independent cardiologist to assist in consistent evaluation of participant eligibility. Results from the 12-lead ECG over-read must be received prior to assessing eligibility at Visit 2.
- Unstable or life-threatening cardiac disease: participants with any of the following are excluded: myocardial infarction or unstable angina in the last 6 months; unstable or life-threatening cardiac arrhythmia requiring intervention in the last 3 months; NYHA Class IV heart failure.
- Other diseases/abnormalities: participants with (historical or) current evidence of clinically significant, neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease), or haematological abnormalities that are uncontrolled. 'Significant' is defined as any disease that, in the opinion of the investigator, would put the safety of the participant at risk through participation, or that would affect the efficacy or safety analysis if the disease/condition exacerbated during the study.
- Eosinophilic disease: participants with other conditions that could lead to elevated eosinophils such as hypereosinophilic syndromes including eosinophilic granulomatosis with polyangiitis (EGPA, also known as Churg-Strauss syndrome) or eosinophilic oesophagitis.
- Parasitic infection: participants with a pre-existing helminthes infestation within 6 months prior to Visit 1 are also excluded.
- Malignancy: a current malignancy or previous history of cancer in remission for less than 12 months prior to Visit 1 (participants who had localised carcinoma of the skin or cervix which was resected for cure are not excluded). Participants in South Korea with a diagnosis of malignancy within 5 years of Visit 1 are excluded.
- Immunodeficiency: a known immunodeficiency (e.g. HIV) other than that explained by the use of corticosteroids taken for COPD.
- Liver disease: unstable liver disease (defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice), cirrhosis, and known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). Chronic stable hepatitis B and C are acceptable if participant otherwise meets entry criteria (e.g. presence of hepatitis B surface antigen or positive hepatitis C test result within 3 months of screening).
- Monoclonal antibodies: participants who have received any monoclonal antibody within 5 half-lives of Visit 1.
- Investigational medications: participants who have received an investigational drug within 30 days of Visit 1, or within 5 drug half-lives of the investigational drug, whichever is longer (this also includes investigational formulations of a marketed product).
- Hypersensitivity: participants with a known allergy or intolerance to another monoclonal antibody or biologic including history of anaphylaxis to another biologic.
- Inability to read: in the opinion of the investigator, any participant who is unable to read and/or would not be able to complete study-related materials.
- Non-compliance: participants at risk of non-compliance, or unable to comply with the study procedures. Any infirmity, disability, or geographic location that would limit compliance for scheduled visits.
- Questionable validity of consent: participants with a history of psychiatric disease, intellectual deficiency, poor motivation, or other conditions that would limit the validity of informed consent to participate in the study.
- Drug or alcohol abuse: a known or suspected history of alcohol or drug abuse within 2 years prior to Visit 1.
- Previous participation: participants who have previously participated in any study of mepolizumab.
- Affiliation with Investigator Site: is an investigator, sub-investigator, study co-ordinator, employee of a participating investigator or study site, or immediate family member of the aforementioned that is involved in this study.

Interventions	3 arm trial: mepolizumab 100 mg versus mepolizumab 300 mg versus placebo.

NCT02105961 (METREO) *(Continued)*

	Each participant received 100 mg or 300 mg mepolizumab SC injection or placebo every 4 weeks (13 administrations during 52-week treatment period) along with their baseline standard of care COPD medication. Placebo: sterile 0.9% sodium chloride solution Salbutamol MDI was issued for use as rescue medication throughout the study.
Outcomes	Primary outcome measures: • Rate of Moderate or Severe Exacerbations. Time Frame: from randomisation to Week 52 Secondary outcome measures: • Time to First Moderate/Severe Exacerbation. Time Frame: from randomisation to Week 52 • Rate of COPD Exacerbations Requiring ED Visits and/or Hospitalisations. Time Frame: from randomisation to Week 52 • Change From Baseline in Mean Total SGRQ Score. Time Frame: baseline and Week 52 • Change From Baseline in Mean CAT Score. Time Frame: baseline and Week 52
Notes	Principal Investigator: GSK Clinical Trials Sponsor: GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using a centralised, computer-generated, permuted-block design with fixed block size of 6; separate schedules were generated for each country.
Allocation concealment (selection bias)	Unclear risk	It is highly likely that the allocation concealment was adequate, but no details provided in the trial report.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participant, investigator, and outcomes assessor were masked (confirmed in clinicaltrials.gov/ct2/show/results/NCT02105961).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participant, investigator, and outcomes assessor were masked (confirmed in clinicaltrials.gov/ct2/show/results/NCT02105961).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data sensitivity analyses conducted indicating robustness of primary efficacy results.
Selective reporting (reporting bias)	Low risk	No apparent indication of selective outcome reporting.
Other bias	Low risk	No apparent indication of other sources of bias.

NCT02138916 (GALATHEA)

Study characteristics

NCT02138916 (GALATHEA) *(Continued)*

Methods	Multicentre, phase 3, randomised, placebo-controlled, double-blind, parallel-group study A 3-arm study: benralizumab 30 mg versus benralizumab 100 mg versus placebo. Study locations: Austria, Canada, the Czech Republic, Germany, Hungary, Italy, Japan, Republic of Korea, the Netherlands, Poland, Romania, the Russian Federation, South Africa, Spain, Switzerland, the United Kingdom, the United States Duration of study: 56 weeks
Participants	1656 participants aged at least 40 to 85 years with moderate to very severe COPD. Benralizumab 30 mg: 554 participants, mean age 65.9 years (SD 7.77); females 172 (31.0%) Benralizumab 100 mg: 552 participants, mean age 65.3 years (SD 8.05); females 180 (32.6%) Placebo: 550 participants, mean age 65.2 years (SD 8.22); females 175 (31.8%) Inclusion criteria: • Informed consent. • Participants aged 40 to 85 years. • Moderate to very severe COPD with post-bronchodilator FEV_1 > 20% and ≤ 65%. • ≥ 2 moderate or ≥ 1 severe COPD exacerbation(s) requiring treatment or hospitalisation within 2 to 52 weeks prior to Visit 1. • mMRC score ≥ 1 at Visit 1. • Treatment with double or triple therapy throughout the year prior to Visit 1, constant 2 weeks prior to Visit 1. • Tobacco history of ≥ 10 pack-years. • Women of childbearing potential must use a highly effective form of birth control from Visit 1 until 16 weeks after their last dose, and negative serum pregnancy test result at Visit 1. • Male participants who are sexually active must be surgically sterile 1 year prior to Visit 1 or use an adequate method of contraception from the first IP dose until 16 weeks after their last dose. • Compliance with maintenance therapy during run-in ≥ 70%. • Blood eosinophils due to participant's stratification and cap for blood eosinophil levels. When any eosinophil cohort is full, participants in the completed cohort will not be randomised and will be withdrawn from the study. Exclusion criteria: • Clinically important pulmonary disease other than COPD or another diagnosed pulmonary or systemic disease associated with elevated peripheral eosinophil counts. • Any disorder or major physical impairment that is not stable by Investigator opinion and/or could affect: participant safety; study findings or their interpretation; or participant's ability to complete the entire study duration. • Unstable ischaemic heart disease, arrhythmia, cardiomyopathy, or other relevant cardiovascular disorder that in Investigator's judgement may put the participant at risk or negatively affect the study outcome. • Treatment with systemic corticosteroids and/or antibiotics, and/or hospitalisation for a COPD exacerbation within 2 weeks prior to Visit 1 or during the enrolment and run-in period. • Acute upper or lower respiratory infection requiring antibiotics or antiviral medication within 2 weeks prior to Visit 1 or during the enrolment and run-in period. • Pneumonia within 8 weeks prior to Visit 1 or during the enrolment and run-in period. • Pregnant, breastfeeding, or lactating women. • Risk factors for pneumonia. • History of anaphylaxis to any other biologic therapy. • Long-term oxygen therapy with signs and/or symptoms of cor pulmonale, right ventricular failure.

NCT02138916 (GALATHEA) *(Continued)*

- Use of immunosuppressive medication within 2 weeks prior to Visit 1 and/or during the enrolment and run-in period.
- Receipt of any investigational non-biologic product within 30 days or 5 half-lives prior to Visit 1.
- Evidence of active tuberculosis without an appropriate course of treatment.
- Lung volume reduction surgery within the 6 months prior to Visit 1. History of partial or total lung resection (single lobe or segmentectomy is acceptable).
- Asthma as a primary or main diagnosis according to GINA guidelines or other accepted guidelines.
- Previous treatment with benralizumab.
- Helminth parasitic infection diagnosed within 24 weeks prior to Visit 1.

Interventions	3-arm trial: benralizumab 30 mg versus benralizumab 100 mg versus placebo Each participant received 30 mg or 100 mg benralizumab or placebo subcutaneously on study week 0 until study week 48 inclusive. Participants were randomised to receive benralizumab 30 mg or 100 mg or placebo by SC injection every 8 weeks throughout the 56-week study.
Outcomes	Primary outcome measures: • Annual COPD Exacerbation Rate Over 56 Weeks Treatment Comparison for participants With Baseline EOS ≥ 220/µL. Time Frame: From first IP to Week 56 Secondary outcome measures: • Annual COPD Exacerbation Rate Over 56 Weeks Treatment Comparison for participants With Baseline EOS < 220/µL. Time Frame: from first IP to Week 56 • Mean Change From Baseline to Week 56 in Pre-bronchodilator FEV_1 (L) Value for participants With Baseline EOS ≥ 220/µL. Time Frame: first IP up to end of treatment Week 56 • Mean Change From Baseline in SGRQ Total Score for participants With Baseline EOS ≥ 220/µL. Time Frame: first IP up to Week 56 • Mean Change From Baseline in CAT Total Score for participants With Baseline EOS ≥ 220/µL. Time Frame: first IP up to Week 56 • Mean Change From Baseline in E-RS:COPD Total Score for participants With Baseline EOS ≥ 220/µL. Time Frame: first IP up to Week 56 • Mean Change From Baseline in Total Rescue Medication Use (Number of Puffs Per Day) for participants With Baseline EOS ≥ 220/µL. Time Frame: first IP up to Week 56 • Mean Change From Baseline in Proportion of Nights Awakenings Due to Respiratory Symptoms for participants With Baseline EOS ≥ 220/µL. Time Frame: first IP up to Week 56 • Number of Participants by Number of COPD Exacerbations Based on EXACT-PRO for participants With Baseline EOS ≥ 220/µL. Time Frame: immediately following first IP up to Week 56 • Severity of EXACT-PRO for participants With Baseline EOS ≥ 220/µL. Time Frame: immediately following first IP up to Week 56 • Duration of EXACT-PRO for participants With Baseline EOS ≥ 220/µL. Time Frame: immediately following first IP up to Week 56 • Annual EXACT-PRO Exacerbation Rate Over 56 Weeks Treatment Comparison for participants With Baseline EOS ≥ 220/µL. Time Frame: immediately following first IP up to Week 56 • Number of Participants Having at Least 1 COPD Exacerbation for participants With Baseline EOS ≥ 220/µL. Time Frame: immediately following first IP up to week 56 • Time to First COPD Exacerbation. Time Frame: immediately following first IP up to Week 56 • Annual COPD Exacerbation Rate Associated With ED visit or Hospitalisation Over 56 Weeks Treatment Comparison for participants With Baseline EOS ≥ 220/µL. Time Frame: immediately following first IP up to Week 56 • Number of Participants who Had COPD-related Healthcare Encounter for participants With Baseline EOS ≥ 220/µL. Time Frame: immediately following first IP up to Week 56 • Duration of Study Treatment Administration. Time Frame: from first dose date to last dose date, 48 weeks per protocol

NCT02138916 (GALATHEA) *(Continued)*

- Serum Concentration of Benralizumab. Time Frame: pre-first dose and pre-dose at end of treatment (Week 56)
- Immunogenicity of Benralizumab. Time Frame: pre-treatment until end of follow-up, Week 60 per protocol

Notes	Principal Investigator: Gerard Criner, MD. Temple University School of Medicine, 3401 North Broad Street, Suite 745 PP, Philadelphia, PA 19140 Sponsor: AstraZeneca. Collaborator: MedImmune LLC

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Detailed account of stratification of eligible participants.
Allocation concealment (selection bias)	Unclear risk	Unable to find confirmation on this point in the trial reports.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and personnel is explicit in clinicaltrials.gov/ct2/show/NCT02138916.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As detailed in clinicaltrials.gov/ct2/show/NCT02138916.
Incomplete outcome data (attrition bias) All outcomes	Low risk	As detailed in clinicaltrials.gov/ct2/show/NCT02138916.
Selective reporting (reporting bias)	Low risk	No indication of selective outcome reporting.
Other bias	Low risk	No indication of other sources of bias.

NCT02155660 (TERRANOVA)

Study characteristics

Methods	Multicentre, phase 3, randomised, placebo-controlled, double-blind, parallel-group study A 4-arm study: benralizumab 10 mg versus benralizumab 30 mg versus benralizumab 100 mg versus placebo. Study locations: Argentina, Australia, Belgium, Brazil, Bulgaria, Chile, Colombia, Croatia, Denmark, France, Israel, Mexico, New Zealand, Norway, Peru, the Philippines, Poland, Serbia, Slovenia, Sweden, Taiwan, Thailand, Turkey, Ukraine, the United States, Vietnam Study duration: 56 weeks
Participants	2255 participants aged at least 40 to 85 years with moderate to very severe COPD Benralizumab 10 mg: 562 participants, mean age 64.7 years (SD 8.47); females 196 (34.9%) Benralizumab 30 mg: 562 participants, mean age 65.6 years (SD 8.61); females 194 (34.5%)

NCT02155660 (TERRANOVA) *(Continued)*

Benralizumab 100 mg: 562 participants, mean age 65.0 years (SD 8.23); females 207 (36.8%)

Placebo: 568 participants, mean age 65.3 years (SD 8.44); females 209 (36.8%)

Inclusion criteria:

- Informed consent.
- Participants aged 40 to 85 years.
- Moderate to very severe COPD with post-bronchodilator FEV_1 > 20% and ≤ 65%.
- ≥ 2 moderate or ≥ 1 severe COPD exacerbation(s) requiring treatment or hospitalisation within 2 to 52 weeks prior to Visit 1.
- mMRC score ≥ 1 at Visit 1.
- Treatment with double or triple therapy throughout the year prior to Visit 1, constant 2 weeks prior to Visit 1.
- Tobacco history of ≥ 10 pack-years.
- Women of childbearing potential must use a highly effective form of birth control from Visit 1 until 16 weeks after their last dose, and negative serum pregnancy test result at Visit 1.
- Male participants who are sexually active must be surgically sterile 1 year prior to Visit 1 or use an adequate method of contraception from the first IP dose until 16 weeks after their last dose.
- Compliance with maintenance therapy during run-in ≥ 70%.
- Blood eosinophils due to participant's stratification and cap for blood eosinophil levels. When any eosinophil cohort is full, participants in the completed cohort will not be randomised and will be withdrawn from the study.

Exclusion criteria:

- Clinically important pulmonary disease other than COPD or another diagnosed pulmonary or systemic disease associated with elevated peripheral eosinophil counts.
- Any disorder or major physical impairment that is not stable by Investigator opinion and/or could affect: participant safety; study findings or their interpretation; or participant's ability to complete the entire study duration.
- Unstable ischaemic heart disease, arrhythmia, cardiomyopathy, or other relevant cardiovascular disorder that in Investigator's judgement may put the participant at risk or negatively affect the study outcome.
- Treatment with systemic corticosteroids and/or antibiotics, and/or hospitalisation for a COPD exacerbation within 2 weeks prior to Visit 1 or during the enrolment and run-in period.
- Acute upper or lower respiratory infection requiring antibiotics within 2 weeks prior to Visit 1 or during the enrolment and run-in period.
- Pneumonia within 8 weeks prior to Visit 1 or during the enrolment and run-in period.
- Pregnant, breastfeeding, or lactating women.
- Risk factors for pneumonia.
- History of anaphylaxis to any other biologic therapy.
- Long-term oxygen therapy with signs and/or symptoms of cor pulmonale, right ventricular failure.
- Use of immunosuppressive medication within 2 weeks prior to Visit 1 and/or during the enrolment and run-in period.
- Receipt of any investigational non-biologic product within 30 days or 5 half-lives prior to Visit 1.
- Evidence of active tuberculosis without an appropriate course of treatment.
- Lung volume reduction surgery within the 6 months prior to Visit 1. History of partial or total lung resection (single lobe or segmentectomy is acceptable).
- Asthma as a primary or main diagnosis according to the GINA guidelines or other accepted guidelines.
- Previous treatment with benralizumab.
- Helminth parasitic infection diagnosed within 24 weeks prior to Visit 1.

Interventions	4-arm trial: benralizumab 10 mg versus benralizumab 30 mg versus benralizumab 100 mg versus placebo

NCT02155660 (TERRANOVA) *(Continued)*

	Each participant received 10 mg, 30 mg, or 100 mg benralizumab or placebo subcutaneously on study week 0 until study week 48 inclusive. Participants were randomised to receive benralizumab 10 mg, benralizumab 30 mg, benralizumab 100 mg, or placebo by SC injection every 8 weeks throughout the 56-week study.
Outcomes	Primary outcome measures: • Annual COPD Exacerbation Rate Over 56 Weeks Treatment Comparison for participants With Baseline EOS ≥ 220/µL. Time Frame: immediately following the first IP dose through Week 56 Secondary outcome measures: • Annual COPD Exacerbation Rate Over 56 Weeks Treatment Comparison for participants With Baseline EOS < 220/µL. Time Frame: immediately following the first IP dose through Week 56 • Mean Change From Baseline to Week 56 in pre-bronchodilator FEV_1 (L) Value for participants With Baseline EOS ≥ 220/µL. Time Frame: first IP up to end of treatment Week 56 • Mean Change From Baseline in SGRQ Total Score for participants With Baseline EOS ≥ 220/µL. Time Frame: first IP up to Week 56 • Mean Change From Baseline in CAT Total Score for participants With Baseline EOS ≥ 220/µL. Time Frame: first IP up to Week 56 • Mean Change From Baseline in E-RS:COPD Total Score for participants With Baseline EOS ≥ 220/µL. Time Frame: first IP up to Week 56 • Mean Change From Baseline in Total Rescue Medication Use (Number of Puffs Per Day) for participants With Baseline EOS ≥ 220/µL. Time Frame: first IP up to Week 56 • Mean Change From Baseline in Proportion of Nights With Awakenings Due to Respiratory Symptoms for participants With Baseline EOS ≥ 220/µL. Time Frame: first IP up to Week 56 • Number of Participants by Number of COPD Exacerbations Based on EXACT-PRO for participants With Baseline EOS ≥ 220/µL. Time Frame: immediately following first IP up to Week 56 • Severity of EXACT-PRO for participants With Baseline EOS ≥ 220/µL. Time Frame: immediately following first IP up to Week 56 • Duration of COPD Exacerbation Based on EXACT-PRO Score for participants With Baseline EOS ≥ 220/µL. Time Frame: immediately following first IP up to Week 56 • Annual EXACT-PRO Exacerbation Rate Over 56 Weeks Treatment Comparison for participants With Baseline EOS ≥ 220/µL. Time Frame: immediately following the first IP dose through Week 56 • Number of Participants Having at Least 1 COPD Exacerbation for participants With Baseline EOS ≥ 220/µL. Time Frame: immediately following first IP dose up to Week 56 • Time to First COPD Exacerbation. Time Frame: immediately following IP dose to Week 56 • Annual COPD Exacerbation Rate Associated With ED visit or Hospitalisation Over 56 Weeks Treatment Comparison for participants With Baseline EOS ≥ 220/µL. Time Frame: immediately following the first IP dose through Week 56 • Number of Participants who Had COPD-related Healthcare Encounter for participants With Baseline EOS ≥ 220/µL. Time Frame: immediately following first IP dose up to Week 56 • Duration of Study Treatment Administration. Time Frame: from first dose date to last dose date, 48 weeks per protocol • Serum Concentration of Benralizumab. Time Frame: pre-first dose and pre-dose at end of treatment (Week 56) • Immunogenicity of Benralizumab. Time Frame: pre-treatment until end of follow-up, Week 60 per protocol
Notes	Principal Investigator: Bartolome R Celli, MD. Brigham and Women's Hospital, Pulmonary Division, 75 Francis Street, PBB Clinics 3, Boston, MA 02115 Sponsor: AstraZeneca. Collaborator: MedImmune LLC

Risk of bias

Bias	Authors' judgement	Support for judgement

NCT02155660 (TERRANOVA) *(Continued)*

Random sequence generation (selection bias)	Low risk	Detailed account of stratification of eligible participants.
Allocation concealment (selection bias)	Unclear risk	Unable to find confirmation on this point in the trial reports.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As indicated in clinical trial information (clinicaltrials.gov/ct2/show/NCT02155660).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As indicated in clinical trial information (clinicaltrials.gov/ct2/show/NCT02155660).
Incomplete outcome data (attrition bias) All outcomes	Low risk	As indicated in clinical trial information (clinicaltrials.gov/ct2/show/NCT02155660).
Selective reporting (reporting bias)	Low risk	All endpoints reported.
Other bias	Low risk	No apparent indication of other sources of bias.

AECOPD: acute exacerbation of chronic obstructive pulmonary disease; **anti-IL-5:** anti-interleukin 5; **ATS**: American Thoracic Society; **BODE**: body mass index obstruction dyspnoea exercise capacity; **CAT**: COPD Assessment Test; **COPD**: chronic obstructive pulmonary disease; **CRQ-SAS**: Chronic Respiratory Questionnaire Self-Administered Standardized Format; **ECG**: electrocardiogram; **ECOPD:** exacerbation of chronic obstructive pulmonary disease; **ED:** emergency department; **EGPA**: eosinophilic granulomatosis with polyangiitis; **EOS**: elevated blood eosinophils; **E-RS:COPD**: Evaluating Respiratory Symptoms in Chronic Obstructive Pulmonary Disease; **ERS**: European Respiratory Society; **EXACT-PRO:** EXAcerbations of Chronic pulmonary disease Tool; **FEV_1**: forced expiratory volume in 1 second; **FVC**: forced vital capacity; **GINA**: Global Initiative for Asthma; **GOLD**: Global Initiative for Chronic Obstructive Lung Disease; **ICS**; inhaled corticosteroid; **IM**: intramuscular; **IP**: investigational product; **IV**: intravenous; **LABA**: long-acting $beta_2$-agonist; **LAMA**: long-acting muscarinic antagonist; **MDI:** metered dose inhaler; **mMRC**: modified Medical Research Council Scale; **mITT**: modified intention-to-treat; **NHANES**: National Health and Nutrition Examination Survey; **NYHA**: New York Heart Association; **PEFR**: peak expiratory flow rate; **RCT**: randomised controlled trial; **SABA**: short-acting $beta_2$-agonist; **SAMA:** short-acting muscarinic antagonist; **SC**: subcutaneous; **SD**: standard deviation; **SGRQ**: St George's Respiratory Questionnaire; **SGRQ-C**: St George's Respiratory Questionnaire for COPD patients; **TB**: active tuberculosis; **TEAE**: treatment-emergent adverse events; **TESAE**: treatment-emergent serious adverse events

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

Study	Reason for exclusion
Condreay 2019	Investigation of genetic associations with frequency of moderate or severe COPD exacerbations (or both) in COPD participants receiving mepolizumab. Not a randomised trial
Sridhar 2019	Aggregation of 2 studies investigating modulation of blood inflammatory markers

COPD: chronic obstructive pulmonary disease

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

NCT04053634

Study name	Efficacy and safety of benralizumab in moderate to very severe chronic obstructive pulmonary disease (COPD) with a history of frequent exacerbations (RESOLUTE)

NCT04053634 *(Continued)*

Methods	Multicentre, randomised, double-blind, chronic-dosing, parallel-group, placebo-controlled phase 3 study Study locations: Argentina, Austria, Brazil, Canada, Chile, Colombia, the Czech Republic, Denmark, Germany, Hungary, Italy, Japan, Republic of Korea, the Philippines, Poland, Spain, Sweden, Turkey, the United Kingdom, the United States
Participants	Patients with a history of ≥ 2 moderate and/or severe COPD exacerbations in the previous year. Estimated enrolment: 868 participants Inclusion criteria: • Provision of informed consent. • Age 40 to 85 years. • Male and/or female. • Current or former smoker with a tobacco history of ≥ 10 pack-years. • History of moderate to very severe COPD with a post-bronchodilator $FEV_1/FVC < 0.70$ and $FEV_1 \leq$ 65% of predicted normal value. • Documented history of 2 or more COPD exacerbations that required treatment with systemic corticosteroids or hospitalisation (or both) within 52 weeks prior to enrolment. Exacerbations treated with antibiotics alone are excluded unless accompanied by treatment with systemic corticosteroids or hospitalisation (or both). Hospitalisation is defined as an inpatient admission ≥ 24 hours. Previous exacerbations should be confirmed to have occurred whilst on stable triple therapy for COPD. • Documented use of triple (ICS/LABA/LAMA) background therapy for COPD throughout the year (52 weeks) prior to enrolment. ICS dose should be equivalent to ≥ 500 µg of fluticasone propionate daily. Total cumulative duration of not being on triple background therapy must not exceed 2 months. Stable therapy/doses for the last 3 months prior to randomisation. • Blood eosinophil count ≥ 300/µL at screening and documented historical eosinophil count of ≥ 150/µL within 52 weeks of enrolment (or repeated testing during run-in). • CAT total score ≥ 15 at Visit 1. • Negative pregnancy test for females of childbearing potential at Visit 1. • Women of childbearing potential must agree to use a highly effective method of birth control from randomisation throughout the study and 16 weeks after last dose of IP. Exclusion criteria: • Clinically important pulmonary disease other than COPD. • Current diagnosis of asthma, prior history of asthma or asthma-COPD overlap. • Radiological findings of a respiratory disease other than COPD contributing to respiratory symptoms. Solitary pulmonary nodules without appropriate follow-up or findings of acute infection. • Another pulmonary or systemic disease associated with elevated peripheral eosinophil counts. • Any unstable disorder that could affect participant safety, study findings, or the participant's ability to complete the study. • Any clinically significant abnormal findings in physical examination, vital signs, ECG, laboratory tests that could affect participant safety, study findings, or the participant's ability to complete the study. • Cor pulmonale or right ventricular failure (or both). • Long-term treatment with oxygen > 4.0 L/min and/or oxyhaemoglobin saturation < 89% whilst breathing supplemental oxygen. • Use of any NIPPV device. Note: use of CPAP or BiPAP for sleep apnoea syndrome is allowed. • Known immunodeficiency disorder, including positive HIV-1/2 testing. • Active liver disease. Chronic stable hepatitis B and C (including positive HBsAg or hepatitis C antibody testing), or other stable chronic liver disease is acceptable. • ALT or AST ≥ 3 times the upper limit of normal, confirmed by repeated testing during the run-in period.

NCT04053634 *(Continued)*

- Helminth parasitic infection within 24 weeks prior to enrolment, not treated or failed to respond to standard of care therapy.
- Alcohol or drug abuse within the past year, which may compromise the study data.
- Malignancy, current or within the past 5 years, except for adequately treated non-invasive basal cell and squamous cell carcinoma of the skin and cervical carcinoma-in-situ treated with apparent success more than 1 year prior to Visit 1. Suspected malignancy or undefined neoplasms.
- Evidence of active tuberculosis, as judged by investigator. Patients with a recent (within 2 years) first-time or newly positive PPD or QuantiFERON test need to complete an appropriate course of treatment before enrolment. Evaluation will be according to the local standard of care.
- Participation, or planned participation, in intensive COPD rehabilitation programme (maintenance phase of a rehabilitation is allowed).
- History of surgical or endoscopic lung volume reduction within the 6 months prior to enrolment. History of partial or total lung resection (single lobe or segmentectomy is acceptable).
- Scheduled major surgical procedure during the study. Minor elective procedures are allowed.
- History of anaphylaxis to benralizumab or any other biologic therapy.
- Receipt of blood products or immunoglobulins within 30 days prior to randomisation.
- Receipt of any marketed or investigational biologic product within 4 months or 5 half-lives prior to randomisation, whichever is longer.
- Receipt of live attenuated vaccines 30 days prior to randomisation.
- Chronic use of immunosuppressive medication or expected need for chronic use during the study.
- Chronic use of antibiotics if duration of treatment is < 9 months prior to randomisation. Chronic macrolide or other antibiotic therapy is allowed provided the patient has been on stable dose/regimen for ≥ 9 months prior to randomisation and has had ≥ 2 COPD exacerbations whilst on stable therapy.
- Receipt of any investigational non-biologic product within 30 days or 5 half-lives prior to enrolment.
- Receipt of benralizumab within 12 months prior to enrolment.
- Known history of allergy or reaction to any component of the IP formulation.

Interventions	Benralizumab versus placebo Benralizumab solution for injection in accessorised prefilled syringe or matching placebo will be administered SC every 4 weeks for the first 3 doses - Weeks 0, 4, and 8, and then every 8 weeks until the end of treatment.
Outcomes	Primary outcome measure: • Annualised rate of moderate or severe COPD exacerbations. Time Frame: over first 56 weeks Secondary outcome measures: • Annualised rate of severe COPD exacerbations. Time Frame: minimum of 1 year and an average of 2 years • Annualised rate of COPD exacerbations that are associated with an emergency room/emergency department visit or a hospitalisation. Time Frame: minimum of 1 year and an average of 2 years • Time to first COPD exacerbation. Time Frame: during first 56 weeks • Change from baseline in SGRQ total and domain scores. Time Frame: up to 56 weeks • Change from baseline in E-RS:COPD total and domain scores. Time Frame: up to 56 weeks • Change from baseline in pre-dose/pre-bronchodilator FEV_1. Time Frame: up to 56 weeks • All-cause and respiratory-related mortality rate. Time Frame: minimum of 1 year and an average of 2 years • Annual rate of hospitalisations due to COPD. Time Frame: minimum of 1 year and an average of 2 years • Serum benralizumab concentration as a measure of pharmacokinetics. Time Frame: up to 56 weeks • Anti-drug antibodies as a measure of immunogenicity. Time Frame: up to 56 weeks • Change from baseline in CAT total score. Time Frame: up to 56 weeks

NCT04053634 *(Continued)*

- Length of hospital stay. Time Frame: minimum of 1 year and an average of 2 years
- ICU days. Time Frame: minimum of 1 year and an average of 2 years
- Annual rate of hospitalisations and emergency department visits combined. Time Frame: minimum of 1 year and an average of 2 years
- Annual rate of unscheduled outpatient visits including unscheduled visits to study sites. Time Frame: minimum of 1 year and an average of 2 years
- Annual rate of unscheduled healthcare encounters. Time Frame: minimum of 1 year and average of 2 years

Additional predefined outcome measures:

- Annualised rate of COPD-related events. Time Frame: up to 56 weeks
- Severity, frequency, and duration of EXACT-PRO defined events. Time Frame: up to 56 weeks
- Clinically important deterioration. Time Frame: up to 56 weeks
- Onset of effect of benralizumab. Time Frame: up to 48 weeks
- Total dose and number of days on systemic corticosteroids. Time Frame: minimum of 1 year and average of 2 years
- EQ-5D-5L. Time Frame: minimum of 1 year and average of 2 years
- Change and per cent change from baseline in peripheral blood eosinophil levels. Time Frame: minimum of 1 year and average of 2 years
- Safety and tolerability of benralizumab in participants with moderate to very severe COPD. Time Frame: minimum of 1 year and average of 2 years

Starting date	August 2019
Contact information	AstraZeneca Clinical Study Information Center
Notes	Sponsor: AstraZeneca

NCT04075331

Study name	Mepolizumab for COPD Hospital Eosinophilic Admissions Pragmatic Trial (COPD-HELP)
Methods	Single-centre, double-blinded, randomised, placebo-controlled trial Study location: Leicestershire, UK
Participants	Patients admitted to hospital for a severe exacerbation of eosinophilic COPD. Estimated enrolment: 238 participants Inclusion criteria: • Symptoms typical of COPD when stable (baseline eMRC dyspnoea grade 2 or more). • A clinician-defined exacerbation of COPD requiring admission to hospital. • Serum eosinophil count of ≥ 300 cells/μL either at time of admission or at any one time in the preceding 12 months. • Smoking pack-years > 10 years. • Age ≥ 40 years. • Established on ICS prior to this admission. • Willing and able to consent to participate in trial. • Able to understand written and spoken English. Exclusion criteria:

NCT04075331 *(Continued)*

- COPD patients without eosinophilia (defined as persistently < 300 cells/μL within the last 12 months).
- Other conditions that may be the cause of eosinophilia (such as hypereosinophilic syndrome, eosinophilic granulomatosis, eosinophilic oesophagitis, or parasitic infection).
- Patients whose treatment is considered palliative (life expectancy < 6 months).
- Other respiratory conditions including active lung cancer, interstitial lung disease, primary pulmonary hypertension, or any other conditions that in the view of the investigator will affect the trial.
- Known history of anaphylaxis or hypersensitivity to mepolizumab or any of the excipients (sucrose, sodium phosphate dibasic heptahydrate, polysorbate 80).
- Unstable or life-threatening cardiac disease including myocardial infarction or unstable angina in the last 6 months, unstable or life-threatening cardiac arrhythmia requiring intervention in the last 3 months, and NYHA Class IV heart failure.
- Decompensated liver disease or cirrhosis.
- Pregnant, breastfeeding, or lactating women. Women of childbearing potential must agree to use appropriate methods of birth control and have a negative blood serum pregnancy test performed after randomisation but prior to first dosing with randomised treatment.
- Participation in an interventional clinical trial within 3 months of Visit 1 or receipt of any investigational medicinal product within 3 months or 5 half-lives.
- Known blood borne infection (e.g. HIV, hepatitis B or C).

Interventions	Mepolizumab 100 mg versus placebo Both mepolizumab and placebo are delivered SC. The placebo is saline solution for subcutaneous injection.
Outcomes	Primary outcome measure: • Time from randomisation to next hospital readmission or death (all cause). Time Frame: 48 weeks Secondary outcome measures: • Time from randomisation to first hospital readmission or death due to a respiratory cause. Time Frame: 48 weeks • Total number of hospital readmissions all-cause over 48 weeks. Time Frame: 48 weeks • Total number of moderate exacerbations over 48 weeks. Time Frame: 48 weeks • Time from randomisation to treatment failure. Time Frame: 48 weeks • Time from randomisation to death (all-cause). Time Frame: 48 weeks • Time from randomisation to death (respiratory cause). Time Frame: 48 weeks • Time from randomisation to first hospital readmission (all-cause). Time Frame: 48 weeks • Time from randomisation to first hospital readmission (respiratory cause). Time Frame: 48 weeks • Length of index hospital admission. Time Frame: 48 weeks • eMRC. Time Frame: Weeks 0, 4, 8, 12, 24, 36, 48 • SGRQ. Time Frame: Weeks 0, 4, 8, 12, 24, 36, 48 • CAT. Time Frame: Weeks 0, 4, 8, 12, 24, 36, 48 • Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS). Time Frame: Weeks 0, 4, 8, 12, 24, 36, 48 • London Chest Activities of Daily Living Questionnaire (LCADL). Time Frame: Weeks 0, 4, 8, 12, 24, 36, 48 • Post-bronchodilator lung function (FEV_1). Time Frame: Weeks 0, 4, 8, 12, 24, 36, 48 • Post-bronchodilator lung function (FVC). Time Frame: Weeks 0, 4, 8, 12, 24, 36, 48 • Lung function (oscillometry). Time Frame: Weeks 0, 4, 8, 12, 24, 36, 48 • Short physical performance battery (SPPB). Time Frame: Weeks 0, 4, 8, 12, 24, 36, 48 • Physical activity using accelerometry. Time Frame: Weeks 0, 4, 8, 12, 24, 36, 48 • Handgrip strength. Time Frame: Weeks 0, 4, 8, 12, 24, 36, 48 • Total serum eosinophil count (inflammatory markers). Time Frame: Weeks 0, 4, 8, 12, 24, 36, 48

NCT04075331 *(Continued)*

	• Percentage sputum eosinophil count (inflammatory markers). Time Frame: Weeks 0, 4, 8, 12, 24, 36, 48 • AEs. Time Frame: 48 weeks • SAEs. Time Frame: 48 weeks • Heart rate (bpm). Time Frame: Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 • Blood pressure (systolic/diastolic mmHg). Time Frame: Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 • Temperature (°C). Time Frame: Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48
Starting date	February 2020
Contact information	Neil Greening +44 (0)116 258 3474; neil.greening@leicester.ac.uk
Notes	Sponsor: University of Leicester. Collaborators: Leicester Clinical Trials Unit and GlaxoSmithKline

NCT04098718

Study name	Acute Exacerbations Treated With BenRAlizumab (The ABRA Study) (ABRA)
Methods	Randomised, double-blinded, randomised, placebo-controlled, phase 2 study Study location: UK
Participants	Patients with a diagnosis of COPD or asthma (or both COPD and asthma) Estimated enrolment: 158 participants Inclusion criteria: • Participant is willing and able to give written informed consent for participation in the trial. • Male or female, aged ≥ 18 years or above. • Diagnosis made in primary or secondary care of: COPD with current or historic evidence of spirometry confirming airflow obstruction (FEV_1/FVC ratio < 0.7) and a smoking pack-year history of ≥ 10. Or, asthma with current or historic evidence of spirometry confirming variable airflow limitation (any one of airflow reversibility FEV_1 change > 200 mL; and/or FEV_1% change of 12%; and/or Pc20 ≤ 8; and/or peak flow diurnal variation; and/or variable FEV_1/FVC ratio) and a smoking pack-year history < 10. Or, COPD and asthma (as defined above). • History of at least 1 exacerbation requiring oral/intravenous corticosteroids in the previous 12 months. • Prior (within 2 years) evidence of eosinophilic inflammation; including an elevated exhaled nitric oxide (FENO) ≥ 25 ppb; and/or peripheral blood eosinophil count ≥ 250 cells/µL; and/or sputum eosinophils ≥ 3% of the total cell count. • Female participants of childbearing potential unless surgically sterile and/or at least 2 years post-menopause must agree to use effective measures of birth control (including sexual abstinence, vasectomised sexual partner, female sterilisation by tubal ligation, any effective intrauterine device, Depo-Provera injections, oral or transdermal contraceptive) from study recruitment to 16 weeks of the last dose of IMP. • Male participants who are sexually active with partner(s) of childbearing potential must use an adequate method of contraception (condom) or be surgically sterile from the first dose of IMP until 16 weeks after this dose. • In the Investigator's opinion, is able and willing to comply with all trial requirements Exclusion criteria: • Known allergy to IP (benralizumab or prednisolone).

NCT04098718 *(Continued)*

- Clinically important and significant pulmonary disease other than asthma or COPD (e.g. lung cancer, pulmonary fibrosis, bronchiectasis as primary respiratory problem, active pulmonary tuberculosis, cystic fibrosis, obesity hypoventilation syndrome).
- Another clinically significant pulmonary or systemic disease associated with an elevated peripheral blood eosinophil count (e.g. allergic bronchopulmonary aspergillosis, eosinophilic granulomatosis with polyangitis, hyper-eosinophilic syndrome, and helminth infection).
- Unstable ischaemic heart disease, arrhythmia, cardiomyopathy, heart failure, significant renal or hepatic impairment, uncontrolled hypertension, or ECG abnormality as defined by the investigator, which in the judgement of the investigator may put the individual at risk or negatively affect the outcome of the study.
- Confirmed (radiological) diagnosis of pneumonia 8 weeks prior to Exacerbation Visit, based on the last date of antibiotic treatment or hospitalisation date.
- An ALT or AST level that is persistently ≥ 1.5 times the upper limit of normal.
- Regular use of immunosuppressive medication (including but not limited to maintenance daily prednisolone (> 10 mg per day), hydrocortisone, azathioprine, or weekly methotrexate).
- Established use (greater than 3 months) of long-term oxygen therapy (i.e. receiving oxygen therapy for > 15 hours per day).
- The presence of hypercapnic ventilatory failure or the requirement of nocturnal non-invasive ventilation therapy (or both).
- Scheduled elective surgery or other procedures requiring general anaesthesia during the trial.
- Participant with life expectancy of less than 6 months.
- Any other unstable significant disease or disorder which, in the opinion of the Investigator, could either put the individual at risk because of participation in the trial, or could influence the result of the trial or the individual's ability to participate in the trial.
- Receipt of any licenced (e.g. omalizumab, mepolizumab, or benralizumab) or other monoclonal antibody or polyclonal antibody therapy (e.g. gamma globulin) within 6 months.
- History of known immunodeficiency disorder (including HIV-1 or HIV-2).
- Positive hepatitis B surface antigen, or positive hepatitis C virus antibody serology or a known medical history of hepatitis B or C.
- History of drug or alcohol abuse in the previous 12 months, which in the opinion of the investigator may compromise study data interpretation.
- Current (or within 5 years) history of solid organ or haematological malignancy.
- Female participant who is pregnant, lactating, or breastfeeding.

Additional exclusion criteria on day of exacerbation (Visit 2):

- Fever recorded as > 38 °C measured using the tympanic temperature and/or a suspected pulmonary bacterial infection (chest radiograph demonstrating consolidation).
- Type 2 respiratory failure necessitating non-invasive or invasive ventilation.
- Any clinically significant abnormal findings in physical examination, vital signs, haematology, clinical chemistry or urinalysis, which in the opinion of the investigator, could put the individual at risk because of their participation, or could influence the results of the study or the ability of the individual to complete the duration of the study.
- An alternative cause for the increase in symptoms that are unrelated to an exacerbation such as:
  * suspicion or clinical evidence of pneumonia;
  * high probability and suspicion of pulmonary embolism;
  * suspicion or clinical evidence of a pneumothorax;
  * primary ischaemic event: ST or non-ST elevation myocardial infarct and left ventricular failure (i.e. not an exacerbation of asthma and/or COPD).
- Treatment with oral corticosteroids and/or hospitalisation for an exacerbation of asthma and/or COPD in the previous 4 weeks prior to randomisation.
- More than 12 hours of oral corticosteroid treatment for a current exacerbation.
- Pregnancy or a positive urinary βHCG.
- Donation of blood, plasma, or platelets within 90 days prior to Visit 2.
- Receipt of blood products within 30 days prior to Visit 2.

NCT04098718 *(Continued)*

	• Individuals who have participated in another research trial involving an investigational product in the past 4 weeks or 5 half-lives prior to Visit 2. • Treatment with allergy immunotherapy, actively or within 90 days prior to Visit 2.
Interventions	4-arm study: standard care prednisolone 30 mg given daily for 5 days to treat an exacerbation versus benralizumab as a single 100 mg SC injection and oral placebo tablet daily for 5 days versus benralizumab as a single 100 mg SC injection and oral prednisolone 30 mg daily for 5 days versus placebo SC injection and oral prednisolone 30 mg daily for 5 days
Outcomes	Primary outcome measures: • Change from baseline in respiratory visual analogue scale symptom scores with benralizumab treatment with and without prednisolone. Time Frame: Day 0 to 28 • Rate of treatment non-response with benralizumab treatment with and without prednisolone. Time Frame: Day 7 • Rate of treatment non-response with benralizumab treatment with and without prednisolone. Time Frame: Day 28 • Rate of treatment non-response with benralizumab treatment with and without prednisolone. Time Frame: Day 90 Secondary outcome measures: • Evaluate the effect of benralizumab on time to next exacerbation. Time Frame: Day 28, 90, and 360 • Evaluate the effect of benralizumab on quality of life questionnaire. Time Frame: Day 0, 7, 14, 28, and 90 • Evaluate the effect of benralizumab on breathlessness. Time Frame: Day 0, 7, 14, 28, and 90 • Evaluate the effect of benralizumab on CAT. Time Frame: Day 0, 7, 14, 28, and 90 • Evaluate the effect of benralizumab on ACQ-6. Time Frame: Day 0, 7, 14, 28, and 90 • Evaluate the effect of benralizumab on AQLQ. Time Frame: Day 0, 7, 14, 28, and 90 • Evaluate the effect of benralizumab on ACT. Time Frame: Day 0, 7, 14, 28, and 90 • Evaluate the effect of benralizumab on spirometry. Time Frame: Day 0, 7, 14, 28, and 90 • Evaluate the effect of prednisolone on respiratory symptoms. Time Frame: Day 0 and 28 • Evaluate the effect of prednisolone on rates of treatment non-response. Time Frame: Day 7 and 28 • Evaluate the effect of prednisolone on time to next exacerbation. Time Frame: Day 28 and 90 • Evaluate the effect of prednisolone on quality of life questionnaire. Time Frame: Day 0, 7, 14, and 28 • Evaluate the effect of prednisolone on breathlessness. Time Frame: Day 0, 7, 14, and 28 • Evaluate the effect of prednisolone on CAT. Time Frame: Day 0, 7, 14, and 28 • Evaluate the effect of prednisolone on ACQ-6. Time Frame: Day 0, 7, 14, and 28 • Evaluate the effect of prednisolone on AQLQ. Time Frame: Day 0, 7, 14, and 28 • Evaluate the effect of prednisolone on ACT. Time Frame: Day 0, 7, 14, and 28 • Evaluate the effect of prednisolone on spirometry. Time Frame: Day 0, 7, 14, and 28 Additional predefined outcome measures: • Sputum eosinophil count. Time Frame: Day 0, 7, 14, 28, and 90 • Sputum neutrophil count. Time Frame: Day 0, 7, 14, 28, and 90
Starting date	October 2019
Contact information	Mona Bafadhel, PhD, MBChB. Nuffield Department of Medicine, University of Oxford, UK
Notes	Sponsor: University of Oxford

NCT04133909

Study name	Mepolizumab as Add-on Treatment IN Participants With COPD Characterized by Frequent Exacerbations and Eosinophil Level (MATINEE)
Methods	Multicentre, randomised, double-blind, parallel-group, placebo-controlled phase 3 study Study locations: Argentina, Australia, Belgium, Canada, Denmark, France, Germany, Hungary, Israel, Republic of Korea, Mexico, the Netherlands, New Zealand, Poland, Spain, the United Kingdom, the United States
Participants	Inclusion criteria: • Participant must be at least 40 years of age at Screening Visit 1. • Participants with a peripheral blood eosinophil count of ≥ 300 cells/µL from the haematology sample collected at Screening Visit 0. Participants with a documented historical blood eosinophil count of ≥ 150 cells/µL in the 12 months prior to Screening Visit 0 that meet the following: it must have been measured between 12 months and 1 month prior to Screening Visit 0, and it must not have been measured within 14 days of a COPD exacerbation. Participants with no documented historical blood eosinophil count of ≥ 150 cells/µL must meet this threshold at the Screening Visit 1 assessment. • Participants with a clinically documented history of COPD for at least 1 year in accordance with the definition by the ATS or ERS. • Participants must present with a measured pre- and post-salbutamol FEV_1/FVC ratio of < 0.70 at Screening Visit 1 to confirm the diagnosis of COPD and with a measured post-salbutamol FEV_1 > 20% and ≤ 80% of predicted normal values calculated using NHANES III reference equations at Screening Visit 1. • Participants must have a well-documented history (e.g. medical record verification) in the 12 months prior to Screening Visit 1 of 2 or more moderate COPD exacerbations that were treated with systemic corticosteroids (IM, IV, or oral) with or without antibiotics or at least 1 severe COPD exacerbation requiring hospitalisation. • Participants must have a well-documented requirement for optimised standard of care background therapy that includes ICS plus 2 additional COPD medications (ICS-based triple therapy) for the 12 months prior to Screening Visit 1 and meet the following criteria: immediately prior to Screening Visit 1, minimum of 3 months of use of 1) inhaled corticosteroid at a dose ≥ 500 µg per day fluticasone propionate dose equivalent plus 2) LABA and 3) LAMA unless documentation of safety or intolerance issues related to LABA or LAMA. For participants who are not continually maintained on ICS plus LABA plus LAMA for the entire 12 months prior to Visit 1, use of the following is allowed (but not in the 3 months immediately prior to Visit 1): inhaled corticosteroid at a dose ≥ 500 µg per day fluticasone propionate dose equivalent plus inhaled LABA or inhaled LAMA and PDE4 inhibitors, methylxanthines, or scheduled daily use of SABA and/or SAMA. • Current or former cigarette smokers with a history of cigarette smoking of ≥ 10 pack-years at Screening (Visit 1) calculated as (number of pack years = (number of cigarettes per day/20) multiplied by number of years smoked (e.g. 20 cigarettes per day for 10 years or 10 cigarettes per day for 20 years)). • Contraceptive use for female participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. • A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies: she is not a WOCBP, or she is a WOCBP and using a contraceptive method that is highly effective, with a failure rate of < 1%, during the intervention period and for at least 16 weeks after the last dose of study intervention. The principal investigator should evaluate the effectiveness of the contraceptive method in relation to the first dose of study intervention. • A WOCBP must have a negative highly sensitive pregnancy urine test within 24 hours before the first dose of study intervention. If a urine test cannot be confirmed as negative (e.g. an ambiguous result), a serum pregnancy test is required. In such cases, the WOCBP must be excluded from participation if the serum pregnancy result is positive. • Participants capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form and in this protocol. Exclusion criteria:

NCT04133909 *(Continued)*

- Participants with a past history or concurrent diagnosis of asthma are excluded regardless of whether they have active or inactive disease.
- The Investigator must judge that COPD is the primary diagnosis accounting for the clinical manifestations of the lung disease. Participants with alpha$_1$-antitrypsin deficiency as the underlying cause of COPD are excluded. Participants with active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, primary pulmonary hypertension, interstitial lung diseases, or other active pulmonary diseases are also excluded.
- Participants with pneumonia, COPD exacerbation, or lower respiratory tract infection within the 4 weeks prior to Screening Visit 1.
- Participants with lung volume reduction surgery within the 12 months prior to Screening Visit 1.
- Participation in the acute phase of a pulmonary rehabilitation programme within 4 weeks prior to Screening Visit 1. Participants who are in the maintenance phase of a pulmonary rehabilitation programme are not excluded.
- Participants receiving treatment with oxygen more than 2 L/min at rest over 24 hours. For participants receiving oxygen treatment, they should demonstrate an oxyhaemoglobin saturation ≥ 89% whilst breathing supplemental oxygen.
- Participants with a QT interval, from the ECG conducted at Screening Visit 1, corrected with Fridericia's formula (QTcF) > 450 ms (or QTcF > 480 ms in participants with bundle branch block). Fridericia's formula must be used to determine eligibility and discontinuation for an individual participant. Participants are excluded if an abnormal ECG finding from the 12-lead ECG conducted at Screening Visit 1 is considered to be clinically significant and would impact the individual's participation during the study, based on the evaluation of the Investigator.
- Participants with any of the following are excluded: myocardial infarction or unstable angina in the 6 months prior to Screening Visit 1; unstable or life-threatening cardiac arrhythmia requiring intervention in the 3 months prior to Screening Visit 1; NYHA Class IV heart failure.
- Participants with historical or current evidence of clinically significant, neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease), or haematological abnormalities that are uncontrolled. 'Significant' is defined as any disease that, in the opinion of the Investigator, would put the safety of the participant at risk through participation, or which could affect the efficacy or safety analysis if the disease/condition exacerbated during the study.
- Participants with other conditions that could lead to elevated eosinophils such as hypereosinophilic syndromes including eosinophilic granulomatosis with polyangiitis (also known as Churg-Strauss syndrome) or eosinophilic oesophagitis.
- Participants with a known, pre-existing parasitic infestation within 6 months prior to Screening Visit 1.
- A current malignancy or previous history of cancer in remission for less than 12 months prior to Screening Visit 1 (participants with localised carcinoma of the skin or cervix which was resected for cure are not excluded).
- Participants with a known immunodeficiency (e.g. HIV) other than that explained by the use of corticosteroids taken for COPD.
- Participants with cirrhosis or current unstable liver disease per investigator assessment defined as the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice. Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C (e.g. presence of HbsAg) or positive hepatitis C antibody test result) is acceptable if the participant otherwise meets entry criteria.
- Participants who have received interventional product in previous mepolizumab studies are excluded.
- Participants who have received any monoclonal antibody within 5 half-lives of Screening Visit 1.
- Participants who have received an investigational drug within 30 days of Visit 1, or within 5 drug half-lives of the investigational drug, whichever is longer (this also includes investigational formulations of a marketed product).
- Participants who have received short-term oral corticosteroids treatment within 30 days of Visit 1.
- Participants with a known allergy or sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator or Medical Monitor, con-

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	traindicates participation in the study, or intolerance to another monoclonal antibody or biologic including history of anaphylaxis to another biologic. • Participants at risk of non-compliance, or unable to comply with the study procedures. Any infirmity, disability, or geographic location that would limit compliance for scheduled visits. • Participants with conditions that would limit the validity of informed consent to participate in the study, e.g. uncontrolled psychiatric disease or intellectual deficiency. • Participants with a known or suspected history of alcohol or drug abuse within 2 years prior to Visit 1.
Interventions	This study is designed to confirm the benefits of mepolizumab treatment on moderate or severe exacerbations in COPD participants given as an add on to their optimised maintenance COPD therapy. The maximum duration of participation is approximately 57 weeks, consisting of 2 screening visits, run-in period, and a 52-week intervention period. 800 to 1000 participants will be randomised in 1:1 ratio to receive mepolizumab 100 mg or placebo every 4 weeks for a total of 13 doses.
Outcomes	Primary outcome measure: • Annualised rate of moderate or severe exacerbations. Time Frame: up to Week 52 Secondary outcome measures: • Time to first moderate or severe exacerbation. Time Frame: up to Week 52 • Number of CAT responders. Time Frame: up to Week 52 • Number of SGRQ total score responders. Time Frame: up to Week 52 • Number of E-RS:COPD responders. Time Frame: up to Week 52 • Annualised rate of exacerbations requiring ED visit or hospitalisation. Time Frame: up to Week 52
Starting date	October 2019
Contact information	GSKClinicalSupportHD@gsk.com
Notes	Sponsor: GlaxoSmithKline

ACQ-6: Asthma Control Questionnaire; **ACT**: Asthma Control Test; **ADA**: anti-drug antibodies; **AE**: acute exacerbation;**AECOPD**: acute exacerbation of chronic obstructive pulmonary disease; **ALT**: alanine aminotransferase; **APFS**: accessorised prefilled syringe; **AST**: aspartate transaminase; **AQLQ**: Asthma Quality of Life Questionnaire; **ATS**: American Thoracic Society; **βHCG:** beta human chorionic gonadotropin; **BiPAP**: bi-level positive airway pressure; **BODE**: body mass index obstruction dyspnoea exercise capacity; **bpm**: beats per minute; **CAT**: COPD Assessment Test; **COPD**: chronic obstructive pulmonary disease; **CPAP**: continuous positive airway pressure; **CRQ-SAS**: Chronic Respiratory Questionnaire Self-Administered Standardized Format; **ECG**: electrocardiogram; **ED:** emergency department; **EGPA**: eosinophilic granulomatosis with polyangiitis; **eMCR:** extended Medical Research Council; **EOS**: elevated blood eosinophils; **E-RS:COPD**: Evaluating Respiratory Symptoms in Chronic Obstructive Pulmonary Disease; **ERS**: European Respiratory Society; **EXACT-PRO:** EXAcerbations of Chronic pulmonary disease Tool; **FENO**: fractional exhaled nitric oxide; **FEV_1**: forced expiratory volume in 1 second; **FVC**: forced vital capacity; **GINA**: Global Initiative for Asthma; **HBsAg**: hepatitis B surface antigen; **ICS**; inhaled corticosteroid; **ICU**: intensive care unit; **IM**: intramuscular; **IMP**: progestogen-only implant; **IP**: investigational product; **IV**: intravenous; **LABA**: long-acting beta$_2$-agonist; **LAMA**: long-acting muscarinic antagonist; **LCADL**: London Chest Activities of Daily Living Questionnaire; **mMRC**: modified Medical Research Council Scale; **mITT**: modified intention-to-treat; **NHANES**: National Health and Nutrition Examination Survey; **NIPPV**: non-invasive positive pressure ventilation device; **NYHA**: New York Heart Association; **Pc20:** The provocative concentration of methacholine that results in a 20% drop in FEV1; **PEFR**: peak expiratory flow rate; PDE4: Phosphodiesterase-4; **PPB**: parts-per-billion; **PPD:** purified protein derivative; **RCT**: randomised controlled trial; **SABA**: short-acting beta$_2$-agonist; **SAE**: serious acute exacerbation; **SAMA:** short-acting muscarinic antagonist; **SC**: subcutaneous; **SD**: standard deviation; **SGRQ**: St George's Respiratory Questionnaire; **SGRQ-C**: St George's Respiratory Questionnaire for COPD patients; **SPPB**: short physical performance battery; **TB**: active tuberculosis; **TEAE**: treatment-emergent adverse events; **TESAE**: treatment-emergent serious adverse events; **WEMWBS**: Warwick-Edinburgh Mental Wellbeing Scale; **WOCBP**: women of childbearing potential

HISTORY

Protocol first published: Issue 9, 2019
Review first published: Issue 12, 2020

CONTRIBUTIONS OF AUTHORS

The review authors contributed to the following sections.

TD: Methods, Data collection, and Analysis sections
SM: Background, Methods, Data collection, Analysis, and Methods sections
RW: Methods, Data collection, and Analysis sections
EB: Analysis and Methods sections
PB: Background and Methods sections
IC: Methods section

Contributions of the editorial team

Chris Cates (Co-ordinating Editor): checked the methods and the data; edited the review; advised on methodology; approved the review prior to publication.
Han Ni (Contact Editor): edited the review and advised on content.
Emma Dennett (Managing Editor): co-ordinated the editorial process; advised on content; edited the review.
Emma Jackson (Assistant Managing Editor): conducted peer review; edited the references and other sections of the review.
Elizabeth Stovold (Information Specialist): designed the search strategy and conducted the searches.

DECLARATIONS OF INTEREST

TD: none known.
SM: none known.
RW: I work in a clinically relevant speciality (respiratory medicine).
EB: none known.
PB: I work in a clinically relevant speciality (respiratory medicine).
IC: I work in a clinically relevant speciality (respiratory medicine). I have been involved as a local investigator for a GSK-sponsored drug trial of inhaled nemiralisib for COPD, but did not directly receive funding for this.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We used Cochrane's Screen4Me workflow to help assess the search results, which was not in the published protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibodies, Monoclonal, Humanized [adverse effects] [*therapeutic use]; Bias; Disease Progression; Eosinophils; Hospitalization [statistics & numerical data]; Interleukin-5 [*antagonists & inhibitors]; Pulmonary Disease, Chronic Obstructive [*drug therapy]; Randomized Controlled Trials as Topic; Receptors, Interleukin-5 [*antagonists & inhibitors]

MeSH check words

Humans