

GRADE Evidence profiles and Evidence to Decision Frameworks, Severe Asthma Task Force.

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Should a monoclonal anti-IL5 antibody be used in adults and children with severe asthma?

GRADE Evidence Profile: MEPOLIZUMAB

Bibliography^a: Bel 2014, Chupp 2017, Ortega 2014

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mepolizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life (change from baseline) (follow up: range 24 weeks to 32 weeks; assessed with: St George's Respiratory Questionnaire; Scale from: 0 to 100; higher scores indicate more limitations; MCID 4 units)												
3 ^{1,2,3}	randomised trials	not serious	not serious	not serious ^b	not serious	none	537	534	-	MD 7.14 lower (9.07 lower to 5.21 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Asthma control (change from baseline) (follow up: range 24 weeks to 32 weeks; assessed with: Asthma Control Questionnaire (ACQ-5); Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5)												
3 ^{1,2,3}	randomised trials	not serious	not serious	not serious ^b	serious ^c	none	537	534	-	MD 0.43 lower (0.56 lower to 0.31 lower)	⊕⊕⊕○ MODERATE	CRITICAL
Asthma symptoms (change from baseline) (follow up: 24 weeks; assessed with: Asthma symptom score; Scale from: 0 to 5; higher scores indicate more frequent symptoms and more limitations)												
1 ²	randomised trials	serious ^d	not serious	not serious ^e	not serious	none	266	259	-	MD 0.2 units lower (0.03 lower to 0.37 lower)	⊕⊕⊕○ MODERATE	CRITICAL
Lung function (Pre-bronchodilator FEV1 % predicted) (follow up: range 24 weeks to 32 weeks; MCID 10.38% ⁴)												
2 ^{1,3}	randomised trials	serious ^f	not serious	not serious ^b	not serious ^g	none	Graphs presenting results from Bel 2014 and Ortega 2014 showed the mepolizumab group had higher FEV1 % predicted than the placebo group at the end of the studies, however the 95% CI around the central estimate from each treatment arm overlap. This suggests the difference between groups in non-significant.			⊕⊕⊕○ MODERATE	IMPORTANT	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mepolizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Lung function (Pre-bronchodilator FEV1 litres, change from baseline) (follow up: range 24 weeks to 32 weeks; MCID 0.23 litre ⁴)												
2 ^{1,2}	randomised trials	not serious	not serious	not serious _b	not serious _h	none	468	468	-	MD 0.11 higher (0.06 higher to 0.17 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Lung function (Post-bronchodilator FEV1 litres, change from baseline) (follow up: range 24 weeks to 32 weeks; MCID 0.23 litre ⁴)												
3 ^{1,2,3}	randomised trials	serious ⁱ	not serious	not serious _b	not serious	none	Ortega 2014 reported the mean difference from placebo (95%CI) = 0.138 L (0.043 to 0.232 L), P = 0.004. Two studies reported a non-significant difference favouring mepolizumab: Bel 2014, (0.128 L, P = 0.06) and Chupp 2017 (data not shown).			⊕⊕⊕○ MODERATE	IMPORTANT	
Rate of any exacerbation (follow up: range 24 weeks to 32 weeks)												
3 ^{1,2,3}	randomised trials	not serious	not serious	not serious _b	not serious	none	537	534	Rate ratio 0.50 (0.39 to 0.65)	Incidence rate (events/patient/year): mepolizumab 0.92; placebo 1.69	⊕⊕⊕⊕ HIGH	CRITICAL
Time to first asthma exacerbation (follow up: 32 weeks)												
1 ¹	randomised trials	not serious	not serious	not serious ^j	not serious	none	Hazard ratio (95% CI) (mepolizumab/placebo) = 0.44 (0.32, 0.60), p <0.001. Number of patients: 194 (mepolizumab) and 191 (placebo).			⊕⊕⊕⊕ HIGH	CRITICAL	
Rate of exacerbations requiring emergency department visit or hospitalisation (follow up: range 24 weeks to 32 weeks)												
2 ^{1,2}	randomised trials	not serious	not serious	not serious _b	not serious	none	468	468	Rate ratio 0.36 (0.20 to 0.66)	Incidence rate (events/patient/year): mepolizumab 0.05; placebo 0.15	⊕⊕⊕⊕ HIGH	CRITICAL
Rate of exacerbations requiring hospitalisation (follow up: range 24 weeks to 32 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mepolizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
2 ^{1,2}	randomised trials	not serious	not serious	not serious ^b	not serious	none	468	468	Rate ratio 0.31 (0.13 to 0.73)	Incidence rate (events/patient/year): mepolizumab 0.02; placebo 0.07 (from Chupp 2017)	⊕⊕⊕⊕ HIGH	CRITICAL
Adverse events (follow up: range 24 weeks to 32 weeks)												
3 ^{1,2,3}	randomised trials	not serious	not serious	not serious ^b	not serious ^{k,l}	none	401/536 (74.8%)	426/535 (79.6%)	RR 0.93 (0.88 to 0.99) ^k	56 fewer per 1,000 (from 8 fewer to 96 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Drug-related adverse events (follow up: range 24 weeks to 32 weeks)												
3 ^{1,2,3}	randomised trials	not serious	not serious	not serious ^b	not serious ^l	none	91/536 (17.0%)	67/535 (12.5%)	RR 1.35 (1.01 to 1.80)	44 more per 1,000 (from 1 more to 100 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Serious adverse events (follow up: range 24 weeks to 32 weeks)												
3 ^{1,2,3}	randomised trials	not serious	not serious ^m	not serious ^b	not serious ⁿ	none	32/536 (6.0%)	62/535 (11.6%)	RR 0.50 (0.24 to 1.05)	58 fewer per 1,000 (from 88 fewer to 6 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Systemic steroids (absolute final dose) (follow up: 24 weeks)												
1 ³	randomised trials	not serious	not serious	not serious	serious ^o	none	Prednisone dose (mg) at study weeks 20-24 were: placebo group, mean (standard deviation, SD) = 10.5 (7.8); median (range) = 10.0 (0-30). Mepolizumab group, mean (SD) = 8.6 (11.9); median (range) = 3.1 (0-67). No statistical test comparing results from the two groups has been reported. ^p				⊕⊕⊕○ MODERATE	CRITICAL
Systemic steroid (percent reduction) (follow up: 24 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mepolizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
1 ³	randomised trials	not serious	not serious	not serious	serious ^o	none	Median percent reduction from baseline in daily oral glucocorticoid dose (95% CI): Placebo = 0.0 (-20.0 to 33.3), Mepolizumab = 50.0 (20.0 to 75.0), p = 0.007. ^q				⊕⊕⊕○ MODERATE	CRITICAL
Loss of work or school days, Intensive care unit admission, Non-invasive ventilation, Intubation, Comorbidities, Upper airway symptoms - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	

CI: Confidence interval; FEV1: forced expiratory volume in 1 second; MCID: minimal clinically important difference; MD: Mean difference; HR: Hazard Ratio; RR: Risk ratio

Explanations

- The participants included in the three studies have been considered by the Task Force to represent a population of severe asthmatics as defined by the ERS/ATS Guidelines on Severe Asthma 2014⁵.
- Chupp 2017 and Ortega 2014 inclusion criteria for participants 12-17 years of age required treatment with inhaled corticosteroids at lower doses than those recommended by the ERS/ATS Guidelines on Severe Asthma 2014⁵. The proportion of included participants 12-17 years of age was not specified, however we have assumed this proportion was small relative to each study's total population and therefore we have not downgraded for indirectness.
- The ends of the 95% confidence interval include appreciable clinical benefit (MCID = 0.5) and no benefit and could lead to different clinical decisions.
- This outcome has been planned by Bel 2014 and Ortega 2014, as specified in the study protocols, but has not been reported.
- Chupp 2017 inclusion criteria for participants 12-17 years of age required treatment with inhaled corticosteroids at lower doses than those recommended by the ERS/ATS Guidelines on Severe Asthma 2014⁵. The proportion of included participants 12-17 years of age was not specified, however we have assumed this proportion was small relative to the total study population and therefore we have not downgraded for indirectness.
- This outcome has been reported incompletely by Bel 2014 and Ortega 2014 so that results cannot be entered in a meta-analysis (high risk of selective outcome reporting bias).
- The results of the primary studies have been presented in graphical format only and cannot be entered in a meta-analysis. As we have downgraded the rating of risk of bias for this same reason, we have decided not to downgrade the rating of imprecision.
- Bel 2014 reported the mean difference in pre-bronchodilator FEV1 between the mepolizumab and placebo groups to be 0.114 liters (p = 0.15). These results have been reported incompletely so that they cannot be entered in the meta-analysis. However the sample size on Bel 2014 is the smallest among the three included studies and the effect estimate (0.114) is very close to that from Chupp 2017 and Ortega 2014, so we considered it unlikely that inclusion of Bel's results would change the pooled effect estimate significantly.
- This outcome has been reported incompletely by Bel 2014 and Chupp 2017 so that results cannot be entered in a meta-analysis (high risk of selective outcome reporting bias).
- Ortega 2014 inclusion criteria for participants 12-17 years of age required treatment with inhaled corticosteroids at lower doses than those recommended by the ERS/ATS Guidelines on Severe Asthma 2014⁵. The proportion of included participants 12-17 years of age was not specified, however we have assumed this proportion was small relative to the total study population and therefore we have not downgraded for indirectness.

- k. There was a high incidence of adverse events in both mepolizumab and placebo groups. The apparent benefit from mepolizumab might be explained by a reduction of asthma-related adverse events with the active drug.
- l. This judgement was based on an arbitrary clinical decision threshold of 15% increase or decrease in absolute effect.
- m. $I^2 = 57\%$ ($P=0.10$) may represent moderate heterogeneity. However the point estimates from the 3 studies have the same direction of effect and the 95% confidence intervals overlap. For these reasons we have not rated down for inconsistency.
- n. This judgement was based on an arbitrary clinical decision threshold of 10% increase or decrease in absolute effect.
- o. Single study including only 135 patients.
- p. The mean and median from the mepolizumab group are very different (8.6 and 3.1). We have performed data checks (http://handbook-5-1.cochrane.org/chapter_9/9_4_5_3_meta_analysis_of_skewed_data.htm) using the reported mean and standard deviations which indicate a skewed distribution. So we have not used the mean and standard deviation to calculate the mean difference in systemic steroid use.
- q. Bel 2014 reported the median difference and associated confidence intervals were calculated with the use of the Hodges–Lehman estimation. P values were calculated with the use of a Wilcoxon rank-sum test.

References

1. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014; 371: 1198-1207.
2. Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *Lancet Respir Med* 2017; 5: 390–400.
3. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014; 371: 1189-1197.
4. Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? *Eur Respir J* 1999; 14: 23-27.
5. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43: 343-373.

GRADE Evidence Profile: RESLIZUMAB

Bibliography: Bjermer 2016, Castro 2011, Castro 2015, Corren 2016

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reslizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life (change from baseline) (follow up: range 16 weeks to 52 weeks; assessed with: Asthma Quality of Life Questionnaire (AQLQ); Scale from: 1 to 7; higher values indicate better quality of life; MCID 0.5)												
3 ^{1,2}	randomised trials	not serious	not serious	serious ^a	not serious	none	576	577	-	MD 0.28 higher (0.17 higher to 0.39 higher)	⊕⊕⊕○ MODERATE	CRITICAL
Asthma control (change from baseline) (follow up: range 15 weeks to 52 weeks; assessed with: Asthma Control Questionnaire (ACQ-7); Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5)												
5 ^{1,2,3,4}	randomised trials	not serious	not serious	serious ^b	not serious	none	1024	727	-	MD 0.26 lower (0.33 lower to 0.18 lower)	⊕⊕⊕○ MODERATE	CRITICAL
Asthma control (change from baseline) (follow up: 15 weeks; assessed with: Asthma Control Questionnaire (ACQ-7); Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5)												
Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma ⁶												
1 ⁴	randomised trials	not serious	not serious	not serious	very serious ^c	none	53	53	-	MD 0.4 lower (0.79 lower to 0.01 lower)	⊕⊕○○ LOW	CRITICAL
Asthma symptoms (change from baseline) (follow up: range 16 weeks to 52 weeks; assessed with: Asthma Symptom Utility Index; Scale from: 0 to 1; lower scores indicate worse asthma symptoms; MCID 0.09 ⁷)												
3 ^{1,2}	randomised trials	not serious	not serious	serious ^a	not serious	none	578	579	-	MD 0.05 higher (0.04 higher to 0.06 higher)	⊕⊕⊕○ MODERATE	CRITICAL

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reslizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Lung function (Pre-bronchodilator FEV1 % predicted, change from baseline) (follow up: 15 weeks; MCID 10.38% ⁵)												
Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma ⁶												
1 ⁴	randomised trials	not serious	not serious	not serious	very serious ^d	none	52	52	-	MD 8.63 higher (3.88 higher to 13.38 higher)	⊕⊕○○ LOW	IMPORTANT
Lung function (Pre-bronchodilator FEV1 litres, change from baseline) (follow up: range 15 weeks to 52 weeks; MCID 0.23 litre ⁵)												
5 ^{1,2,3,4}	randomised trials	not serious	not serious	serious ^b	not serious	none	1024	726	-	MD 0.12 higher (0.07 higher to 0.17 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
Lung function (Pre-bronchodilator FEV1 litres, change from baseline) (follow up: 15 weeks; MCID 0.23 litre ⁵)												
Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma ⁶												
1 ⁴	randomised trials	not serious	not serious	not serious	very serious ^e	none	52	52	-	MD 0.24 higher (0.09 higher to 0.39higher)	⊕⊕○○ LOW	IMPORTANT
Exacerbations (patients with ≥1 exacerbation) (follow up: range 15 weeks to 52 weeks)												
3 ^{2,4}	randomised trials	not serious	not serious	serious ^f	not serious	none	155/530 (29.2%)	247/529 (46.7%)	RR 0.63 (0.53 to 0.76)	173 fewer per 1,000 (from219fewer to 112 fewer)	⊕⊕⊕○ MODERATE	CRITICAL
Exacerbations (patients with ≥1 exacerbation) (follow up: 15 weeks)												
Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma ⁶												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reslizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
1 ⁴	randomised trials	not serious	not serious	not serious	very serious ^{g,h}	none	4/53 (7.5%)	10/53 (18.9%)	RR 0.40 (0.13 to 1.20)	113 fewer per 1,000 (from 164 fewer to 38 more)	⊕⊕○○ LOW	CRITICAL
Rate of any exacerbation (follow up: 52 weeks)												
2 ²	randomised trials	not serious	not serious	serious ^f	not serious	none	477	476	Rate ratio 0.46 (0.37 to 0.58)	Incidence rate (events/patient/year): reslizumab 0.84; placebo 1.81	⊕⊕⊕○ MODERATE	CRITICAL
Time to first asthma exacerbation (follow up: 52 weeks)												
2 ²	randomised trials	not serious	not serious	serious ^f	not serious	none	477	476	HR 0.54 (0.44 to 0.66)	-	⊕⊕⊕○ MODERATE	CRITICAL
Rate of exacerbations requiring emergency department visit or hospitalisation (follow up: 52 weeks)												
2 ²	randomised trials	not serious	not serious	serious ^f	serious ^g	none	477	476	Rate ratio 0.67 (0.39 to 1.17)	Incidence rate (events/patient/year): reslizumab 0.08; placebo 0.12	⊕⊕○○ LOW	CRITICAL
Exacerbations requiring emergency department visit (patients with ≥1 exacerbation) (follow up: 15 weeks)												
<u>Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma⁶</u>												
1 ⁴	randomised trials	not serious	not serious	not serious	very serious ^{g,h}	none	3/53 (5.7%)	4/53 (7.5%)	Peto OR 0.74 (0.16 to 3.40)	19 fewer per 1,000 (from 63 fewer to 142 more)	⊕⊕○○ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reslizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Exacerbations requiring hospitalisation (patients with ≥1 exacerbation) (follow up: 15 weeks)												
Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma ⁶												
1 ⁴	randomised trials	not serious	not serious	not serious	very serious ^{g,h}	none	1/53 (1.9%)	0/53 (0.0%)	OR 3.00 (0.12 to 72.02)	NA	⊕⊕○○ LOW	CRITICAL
Adverse events (follow up: range 15 weeks to 52 weeks)												
5 ^{1,2,3,4}	randomised trials	not serious	not serious ⁱ	serious ^b	serious ^{j,k}	none	690/1028 (67.1%)	587/730 (80.4%)	RR 0.88 (0.81 to 0.96) ^k	96 fewer per 1,000 (from 153 fewer to 32 fewer)	⊕⊕○○ LOW	CRITICAL
Adverse events (follow up: 15 weeks)												
Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma ⁶												
1 ⁴	randomised trials	not serious	not serious	not serious	very serious ^{h,j}	none	38/53 (71.7%)	42/53 (79.2%)	RR 0.90 (0.73 to 1.13)	79 fewer per 1,000 (from 214 fewer to 103 more)	⊕⊕○○ LOW	CRITICAL
Drug-related adverse events (follow up: 16 weeks)												
2 ^{1,3}	randomised trials	serious ^l	serious ^m	serious ^a	not serious ⁿ	none	40/498 (8.0%)	24/202 (11.9%)	RR 0.78 (0.22 to 2.72)	26 fewer per 1,000 (from 93 fewer to 204 more)	⊕○○○ VERY LOW	CRITICAL
Serious adverse events (follow up: range 15 weeks to 52 weeks)												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reslizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
5 ^{1,2,3,4}	randomised trials	not serious	not serious	serious ^b	not serious ^o	none	64/1028 (6.2%)	63/730 (8.6%)	RR 0.81 (0.57 to 1.14)	16 fewer per 1,000 (from 37 fewer to 12 more)	⊕⊕⊕○ MODERATE	CRITICAL
Serious adverse events (follow up: 15 weeks) Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma⁶												
1 ⁴	randomised trials	not serious	not serious	not serious	very serious ^{g,h}	none	2/53 (3.8%)	1/53 (1.9%)	OR 1.97 (0.20 to 19.40)	18 more per 1,000 (from 15 fewer to 253 more)	⊕⊕○○ LOW	CRITICAL
Systemic steroids (absolute final dose), Systemic steroids (percent reduction), Loss of work or school days, Intensive care unit admission, Non-invasive ventilation, Intubation, Comorbidities, Upper airway symptoms - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	

CI: Confidence interval; FEV1: forced expiratory volume in 1 second; MCID: minimal clinically important difference; MD: Mean difference; OR: Odds ratio; RR: Risk ratio; HR: Hazard Ratio; NA: Not available

Explanations

- All studies included a mixed population of patients with moderate and severe asthma.
- All studies except one (Castro 2011) included a mixed population of patients with moderate and severe asthma.
- The ends of the 95% confidence interval include appreciable clinical benefit (MCID = 0.5) and no benefit and could lead to different clinical decisions. Results from single study including only 106 patients.
- The ends of the 95% confidence interval include appreciable clinical benefit (MCID = 10.38%) and no benefit and could lead to different clinical decisions. Single study including only 104 patients.
- The ends of the 95% confidence interval include appreciable clinical benefit (MCID = 0.23 L) and no benefit and could lead to different clinical decisions. Results from single study including only 104 patients.
- The two studies reported by Castro 2015 included a mixed population of patients with moderate and severe asthma.
- The ends of the 95% confidence interval include appreciable benefit and harm and could lead to different clinical decisions.
- Single study including only 106 patients.

i. $I^2 = 54\%$ ($P=0.07$) may represent moderate heterogeneity. However the point estimates from the 5 studies have the same direction of effect and 4 of 5 studies have overlapping 95% confidence intervals. For these reasons we have not rated down for inconsistency.

j. The ends of the 95% confidence interval include appreciable benefit and no benefit and could lead to different clinical decisions. This judgement was based on a arbitrary clinical decision threshold of 15% increase or decrease in absolute effect.

k. There was a high incidence of adverse events in both reslizumab and placebo groups. The apparent benefit from reslizumab might be explained by a reduction of asthma-related adverse events with the active drug.

l. High risk of selective outcome reporting bias because 5 studies have reported any adverse events but only 2 studies have reported drug-related adverse events.

m. There is considerable statistical heterogeneity ($I^2 = 83\%$, $P = 0.01$), the effect estimates point in different directions (one study suggests benefit and the other suggests harm) and the 95% confidence intervals show minimal overlap.

n. This judgement was based on a arbitrary clinical decision threshold of 15% increase or decrease in absolute effect.

o. This judgement was based on a arbitrary clinical decision threshold of 10% increase or decrease in absolute effect.

References

1. Bjerner L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for Inadequately Controlled Asthma With Elevated Blood Eosinophil Levels: A Randomized Phase 3 Study. *Chest* 2016; 150: 789-798.
2. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015; 3: 355-366.
3. Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 Study of Reslizumab in Patients With Poorly Controlled Asthma: Effects Across a Broad Range of Eosinophil Counts. *Chest* 2016; 150: 799-810.
4. Castro M, Mathur S, Hargreave F, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med* 2011; 184: 1125-1132.
5. Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? *Eur Respir J* 1999; 14: 23-27.
6. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43: 343-373.
7. Bime C, Wei CY, Holbrook JT, et al. Asthma Symptom Utility Index: Reliability, validity, responsiveness, and the minimal important difference in adult asthmatic patients. *J Allergy Clin Immunol* 2012; 130: 1078-1084.

GRADE Evidence Profile: BENRALIZUMAB

Bibliography: Bleecker 2016, Castro 2014, FitzGerald 2016, Nair 2017, Park 2016

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benralizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life (change from baseline) (follow up: range 28 weeks to 56 weeks; assessed with: Asthma Quality of Life Questionnaire (AQLQ); Scale from: 1 to 7; higher values indicate better quality of life; MCID 0.5)												
4 ^{1,2,3,4}	randomised trials	not serious	not serious	serious ^a	not serious	none	592	657	-	MD 0.32 higher (0.19 higher to 0.45 higher)	⊕⊕⊕○ MODERATE	CRITICAL
Quality of life (change from baseline) (follow up: 28 weeks; assessed with: Asthma Quality of Life Questionnaire (AQLQ); Scale from: 1 to 7; higher values indicate better quality of life; MCID 0.5)												
Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma ⁷												
1 ¹	randomised trials	not serious	not serious	not serious	very serious ^b	none	72	75	-	MD 0.45 higher (0.14 higher to 0.76 higher)	⊕⊕○○ LOW	IMPORTANT
Asthma control (change from baseline) (follow up: range 28 weeks to 56 weeks; assessed with: Asthma Control Questionnaire (ACQ-6); Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5)												
4 ^{1,2,3,4}	randomised trials	not serious	not serious	serious ^a	not serious	none	870	946	-	MD 0.29 lower (0.40 lower to 0.17 lower)	⊕⊕⊕○ MODERATE	CRITICAL
Asthma control (change from baseline) (follow up: 28 weeks; assessed with: Asthma Control Questionnaire (ACQ-6); Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5)												
Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma ⁷												
1 ¹	randomised trials	not serious	not serious	not serious	very serious ^b	none	73	74	-	MD 0.55 lower (0.86 lower to 0.24 lower)	⊕⊕○○ LOW	CRITICAL

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benralizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Asthma symptoms (change from baseline) (follow up: range 28 weeks to 56 weeks; assessed with: different symptom scores; lower scores indicate less frequent and/or severe symptoms)												
4 ^{1,2,3,4}	randomised trials	not serious	not serious	serious ^a	not serious	none	858	953	-	SMD 0.19 lower (0.28 lower to 0.09 lower)	⊕⊕⊕○ MODERATE	CRITICAL
Asthma symptoms (change from baseline) (follow up: 28 weeks; assessed with: Total asthma symptom score; lower scores indicate less frequent and/or severe symptoms)												
Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma ⁷												
1 ¹	randomised trials	not serious	not serious	not serious	very serious ^c	none	68	67	-	MD 0.18 lower (0.52 lower to 0.16 higher)	⊕⊕○○ LOW	CRITICAL
Lung function (FEV1 % of predicted) (follow up: 52 weeks; MCID 10.38% ⁶)												
1 ⁵	randomised trials	not serious	not serious	serious ^d	very serious ^e	none	25	26	-	MD 5.3 lower (17.63 lower to 7.03 higher)	⊕○○○ VERY LOW	IMPORTANT
Lung function (Pre-bronchodilator FEV1 litres, change from baseline) (follow up: range 28 weeks to 56 weeks; MCID 0.23 litre ⁶)												
4 ^{1,2,3,4}	randomised trials	not serious	not serious	serious ^a	not serious	none	879	982	-	MD 0.11 higher (0.06 higher to 0.16 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
Lung function (Pre-bronchodilator FEV1 litres, change from baseline) (follow up: 28 weeks; MCID 0.23 litre ⁶)												
Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma ⁷												
1 ¹	randomised trials	not serious	not serious	not serious	very serious ^f	none	69	73	-	MD 0.11 higher (0.03 lower to 0.26 higher)	⊕⊕○○ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benralizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Lung function(Post-bronchodilator FEV1 litres, change from baseline) (follow up: range 48 weeks to 56 weeks; MCID 0.23 litre ⁶)												
2 ^{2,4}	randomised trials	not serious	not serious	serious ^g	not serious	none	472	484	-	MD 0.1 higher (0.04 higher to 0.16 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
Exacerbations (patients with ≥1 exacerbation) (follow up: range 28 weeks to 56 weeks)												
2 ^{1,2}	randomised trials	not serious	serious ^h	serious ⁱ	serious ^j	none	112/312 (35.9%)	165/323 (51.1%)	RR 0.62 (0.36 to 1.06)	194 fewer per 1,000 (from 327 fewer to 31 more)	⊕○○○ VERY LOW	CRITICAL
Exacerbations (patients with ≥1 exacerbation) (follow up: 28 weeks)												
Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma ⁷												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^k	none	17/73 (23.3%)	39/75 (52.0%)	RR 0.45 (0.28 to 0.72)	286 fewer per 1,000 (from 374 fewer to 146 fewer)	⊕⊕⊕○ MODERATE	CRITICAL
Rate of any exacerbation (Age range 12-75 years; follow up: range 28 weeks to 56 weeks)												
4 ^{1,2,3,4}	randomised trials	not serious	not serious	serious ^a	not serious	none	905	935	Rate ratio 0.58 (0.47 to 0.73)	Incidence rate (events/patient/year): benralizumab 0.64; placebo 1.19	⊕⊕⊕○ MODERATE	CRITICAL
Rate of any exacerbation (Age range 12-17 years; follow up: range 48 weeks to 56 weeks)												
2 ^{2,4}	randomised trials	not serious	not serious	serious ^g	very serious ^{i,l}	none	16	19	Rate ratio 1.70 (0.50 to 5.81)	NA	⊕○○○ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benralizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Rate of any exacerbation (follow up: 28 weeks)												
Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma ⁷												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^k	none	73	75	Rate ratio 0.30 (0.17 to 0.53)	Incidence rate (events/patient/year): benralizumab 0.54; placebo 1.83	⊕⊕⊕○ MODERATE	CRITICAL
Time to first asthma exacerbation (follow up: range 28 weeks to 56 weeks)												
3 ^{1,2,4}	randomised trials	not serious	not serious	serious ^g	not serious	none	579	590	HR 0.57 (0.40 to 0.81)	-	⊕⊕⊕○ MODERATE	CRITICAL
Time to first asthma exacerbation (follow up: 28 weeks)												
Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma ⁷												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^k	none	73	75	HR 0.32 (0.18 to 0.57)	-	⊕⊕⊕○ MODERATE	CRITICAL
Rate of exacerbations requiring emergency department visit or hospitalisation (follow up: range 28 weeks to 56 weeks)												
3 ^{1,2,4}	randomised trials	not serious	serious ^m	serious ^g	serious ^j	none	579	590	Rate ratio 0.45 (0.14 to 1.47)	Incidence rate (events/patient/year): benralizumab 0.04; placebo 0.18	⊕○○○ VERY LOW	CRITICAL
Rate of exacerbations requiring emergency department visit or hospitalisation (follow up: 28 weeks)												
Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma ⁷												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benralizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^k	none	73	75	Rate ratio 0.07 (0.01 to 0.63)	Incidence rate (events/patient/year): benralizumab 0.02; placebo 0.32	⊕⊕⊕○ MODERATE	CRITICAL
Exacerbations requiring emergency department visit or hospitalisation (patients with ≥1 exacerbation) (follow up: 56 weeks)												
1 ²	randomised trials	not serious	not serious	serious ⁿ	serious ^j	none	20/239 (8.4%)	20/248 (8.1%)	RR 1.04 (0.57 to 1.88)	3 more per 1,000 (from 35 fewer to 71 more)	⊕⊕○○ LOW	CRITICAL
Adverse events (follow up: range 28 weeks to 68 weeks)												
5 1,2,3,4,5	randomised trials	not serious	not serious	serious ^o	not serious ^p	none	737/1001 (73.6%)	883/1169 (75.5%)	RR 0.96 (0.91 to 1.01) ^q	30 fewer per 1,000 (from 68 fewer to 8 more)	⊕⊕⊕○ MODERATE	CRITICAL
Adverse events (follow up: 28 weeks)												
<u>Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma⁷</u>												
1 ¹	randomised trials	not serious	not serious	not serious	very serious ^{k,r}	none	55/73 (75.3%)	62/75 (82.7%)	RR 0.91 (0.77 to 1.08) ^q	74 fewer per 1,000 (from 190 fewer to 66 more)	⊕⊕○○ LOW	CRITICAL
Drug-related adverse events (follow up: 48 weeks)												
1 ⁴	randomised trials	serious ^s	not serious	serious ^d	not serious ^p	none	47/354 (13.3%)	34/370 (9.2%)	RR 1.44 (0.95 to 2.19)	40 more per 1,000 (from 5 fewer to 109 more)	⊕⊕○○ LOW	CRITICAL
Serious adverse events (follow up: range 28 weeks to 68 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benralizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
5 1,2,3,4,5	randomised trials	not serious	not serious	serious ^o	not serious ^t	none	109/1001 (10.9%)	157/1169 (13.4%)	RR 0.79 (0.63 to 1.00)	28 fewer per 1,000 (from 50 fewer to 0 fewer)	⊕⊕⊕○ MODERATE	CRITICAL
Serious adverse events (follow up: 28 weeks)												
Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma ⁷												
1 ¹	randomised trials	not serious	not serious	not serious	very serious ^{k,u}	none	7/73 (9.6%)	14/75 (18.7%)	RR 0.51 (0.22 to 1.20)	91 fewer per 1,000 (from 146 fewer to 37 more)	⊕⊕○○ LOW	CRITICAL
Systemic steroids (absolute final dose) (follow up: 28 weeks)												
Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma ⁷												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^k	none	The median oral prednisone or prednisolone dose (range) at the final visit (week 28) was 10.0 mg/day (0.0 to 40.0) in patients who received placebo (n=75) and 5.0 mg/day (0.0 to 30.0) in patients who received benralizumab (n=73) . No statistical test comparing results from the two groups has been reported.			⊕⊕⊕○ MODERATE	CRITICAL	
Systemic steroids (percent reduction) (follow up: 28 weeks)												
Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma ⁷												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^k	none	The median prednisone or prednisolone dose reduction from baseline (range) at the final visit (week 28) was 25.0% (–150% to 100%) in the placebo group (n=75) and 75.0% (–50% to 100%) in the benralizumab group (n=73) (Wilcoxon rank-sum test P<0.001). Negative values indicate an increase in the final oral prednisone or prednisolone dose from baseline.			⊕⊕⊕○ MODERATE	CRITICAL	
Loss of work or school days, Intensive care unit admission, Non-invasive ventilation, Intubation, Comorbidities, Upper airway symptoms - not reported												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benralizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	

CI: Confidence interval; **FEV1:** forced expiratory volume in 1 second; **MCID:** minimal clinically important difference; **MD:** Mean difference; **SMD:** Standardised mean difference; **RR:** Risk ratio; **HR:** Hazard Ratio; **NA:** Not available

Explanations

- a. Three studies (Bleecker 2016, Castro 2014 and FitzGerald 2016) included a mixed population of patients with moderate and severe asthma.
- b. The ends of the 95% confidence interval include appreciable clinical benefit (MCID = 0.5) and no benefit and could lead to different clinical decisions. Results from single study with only 147 patients.
- c. The end of the 95% confidence interval could lead to different clinical decisions. Results from single study including only 135 patients.
- d. The study included a mixed population of patients with moderate and severe asthma.
- e. The ends of the 95% confidence interval include appreciable clinical harm (MCID = 10.38%) and no benefit and could lead to different clinical decisions. Results from single study with only 51 patients.
- f. The ends of the 95% confidence interval include appreciable clinical benefit (MCID = 0.23 ml) and no benefit and could lead to different clinical decisions. Results from single study with only 142 patients.
- g. Two studies (Bleecker 2016 and FitzGerald 2016) included a mixed population of patients with moderate and severe asthma.
- h. There is considerable statistical heterogeneity ($I^2 = 79\%$, $P = 0.03$) and the 95% confidence intervals show little overlap.
- i. One study (Bleecker 2016) included a mixed population of patients with moderate and severe asthma.
- j. The ends of the 95% confidence interval include appreciable clinical benefit and harm and could lead to opposite clinical decisions.
- k. Single study including only 148 patients.
- l. Two studies including only 35 patients aged 12-17 years.
- m. There is considerable statistical heterogeneity ($I^2 = 82\%$, $P = 0.004$) and the point estimates from individual studies vary widely.
- n. The study included a mixed population of patients with moderate and severe asthma
- o. Four studies (Bleecker 2016, Castro 2014, FitzGerald 2016 and Park 2016) included a mixed population of patients with moderate and severe asthma.
- p. This judgement was based on an arbitrary clinical decision threshold of 15% increase or decrease in absolute effect.
- q. There was a high incidence of adverse events in both benralizumab and placebo groups. The apparent benefit from benralizumab might be explained by a reduction of asthma-related adverse events with the active drug.

- r. The ends of the 95% confidence interval include appreciable clinical benefit and no benefit, assuming an arbitrary clinical decision threshold of 15% increase or decrease in absolute effect. This could lead to different clinical decisions.
- s. High risk of selective outcome reporting bias because 5 studies have reported any adverse events but only 1 study has reported drug-related adverse events.
- t. This judgement was based on an arbitrary clinical decision threshold of 10% increase or decrease in absolute effect.
- u. The ends of the 95% confidence interval include appreciable clinical benefit and no benefit, assuming an arbitrary clinical decision threshold of 10% increase or decrease in absolute effect. This could lead to different clinical decisions.

References

1. Nair P, Wenzel SE, Rabe KF, et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. *N Engl J Med* 2017; 376: 2448-2458.
2. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016; 388: 2128–2141.
3. Castro M, Wenzel SE, Bleecker ER, et al. Benralizumab, an anti-interleukin 5 receptor [alpha] monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. *Lancet Respir Med* 2014; 2: 878–890.
4. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β 2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet* 2016.; 388: 2115–2127.
5. Park HS, Kim MK, Imai N, et al. A Phase 2a Study of Benralizumab for Patients with Eosinophilic Asthma in South Korea and Japan. *Int Arch Allergy Immunol* 2016; 169:135-145.
6. Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? *Eur Respir J* 1999; 14: 23-27.
7. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43: 343-73.

Should an anti-interleukin 5 strategy versus no anti-interleukin 5 strategy be used for adults and children with severe asthma?

POPULATION:	Adults and children with severe asthma	BACKGROUND:	<p>By definition, patients with severe asthma have disease that is either unresponsive to traditional therapies with inhaled corticosteroids and bronchodilators or require these therapies to maintain adequate control. To address this unmet need for improved therapies, several biologic therapies have been designed to target the inflammatory signature typical of most patients with asthma. Interleukin 5 (IL5) is the principal cytokine driving eosinophilic inflammation in most of these patients. Monoclonal antibodies that target the IL5 cytokine or its receptor have been found to be efficacious in randomized controlled trials in improving asthma-related outcomes. These three drugs in this category are mepolizumab, reslizumab, and benralizumab, and will henceforth be referred to as the anti-IL5 strategy. This systematic review and meta-analysis synthesizes the data from randomized controlled trials and meta-analyses investigating the anti-IL5 strategy and provides treatment recommendations based on the results.</p>
INTERVENTION:	Anti-interleukin 5 strategy (monoclonal antibodies directed against the interleukin 5 or its receptor)		
COMPARISON:	No anti-interleukin 5 strategy		
MAIN OUTCOMES:	<p>Rate of exacerbations</p> <p>Time to first asthma exacerbation</p> <p>Asthma exacerbations requiring ER visits or hospitalization</p> <p>Lung function</p> <p>Asthma control</p> <p>Maintenance corticosteroid dose reduction</p> <p>Adverse events</p> <p>Serious adverse events</p> <p>Quality of life</p>		

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	<p>How substantial are the desirable anticipated effects?</p> <ul style="list-style-type: none"> ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know 	<p>Asthma exacerbations are a critically important outcome for the patients with asthma who experience these and the clinicians who care for them.</p> <p>Relative to participants assigned to placebo, those assigned to mepolizumab experienced a 50% reduction (95% CI 39-65%) (see evidence profiles) in their rates of asthma exacerbations; participants assigned to reslizumab and benralizumab demonstrated similar reductions in rates of asthma exacerbations [54% (95% CI 42-63%) and 42% (95% CI 27-53%), respectively]. Although a defined threshold for clinically meaningful reductions in asthma exacerbations has not been universally agreed upon, the effect sizes in reductions in asthma exacerbations for these three drugs are considered clinically substantial by most practitioners.</p> <p>Among adolescent participants (ages 12-17 years, n=35 between two trials), those assigned to benralizumab experienced a 1.7x increase (95% CI 0.50x-5.81x) in their rates of asthma exacerbations (very low quality evidence).</p> <p>Another critically important outcome in asthma includes asthma symptom scores. Although the evidence favors all anti-IL5 strategy drugs relative to placebo on these outcomes, their relative change was not as large compared to the improvement observed with asthma exacerbations.</p> <p>Relative to participants assigned to placebo, those assigned to mepolizumab experienced a 0.43-point decrease (i.e. improvement) in Asthma Control Questionnaire (ACQ) (95% CI 0.31-0.56-point decrease); participants assigned to reslizumab and benralizumab demonstrated similar improvements in ACQ scores [0.26 (95% CI 0.18-0.33-point decrease) and 0.29 (95% CI 0.17-0.40 point decreases), respectively]. Although these were statistically significant decreases in ACQ scores, on average these drugs did not surpass the 0.5-point decrease threshold traditionally assigned as the MCID in ACQ symptom score for trials in asthma.</p> <p>Meta-analytical results on other outcomes appear in the online supplement.</p>	<ul style="list-style-type: none"> ● The decision to consider changes in lung function [forced expiratory volume in the first second (FEV1)] as 'important' outcomes as opposed to 'critical' outcomes is due to their place relative to other critical outcomes. We understand that most clinicians would prescribe anti-IL5 strategy drugs due to their efficacy in reducing asthma exacerbations despite only modest improvements in lung function. ● Data from children or adolescents are unavailable for mepolizumab and reslizumab. There are data available on the effects of benralizumab on adolescents with severe asthma, but this subset of the cohort is small. The resulting confidence intervals around effect estimates are large, which makes the quality of the data for adolescents very low. As noted in the FDA approval statement, the decision to allow the use of benralizumab in adolescents was based on the impracticality of conducting a sufficiently powered study among severe asthmatic adolescents due to the low prevalence of this population; the similarities in pharmacokinetic and pharmacodynamic values for this drug, and the absence of major safety concerns for the population. More data are needed in order to have greater quality recommendations for adolescents. ● The meta-analysis for mepolizumab included only the trials that tested the FDA- and EMA-approved dose of 100mg administered subcutaneously. ● Taken together, however, the reduction in asthma exacerbations is substantial enough for this committee to judge the desirable effects of an anti-IL5 strategy as large, regardless of relatively smaller effects on lung function and symptom scores.

UNDESIRABLE EFFECTS	<p>How substantial are the undesirable anticipated effects?</p> <ul style="list-style-type: none"> ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know 	<p>In the RCTs analysed, the risk of a study participant developing either an adverse event or a serious adverse event was lower for those participants assigned to any of the 3 anti-IL5 strategy drugs compared to those assigned to placebo. Relative to placebo, the risk of developing an adverse event for a participant assigned to mepolizumab was 7% lower (95% CI 1-12% lower) and for those assigned to reslizumab it was 12% lower (95% CI 4-18% lower). This difference was not statistically significant for those assigned to benralizumab, but the direction of the effect was also toward a lower risk of adverse events (3% lower). Similarly, participants experienced a lower risk of serious adverse events (not statistically significant) when assigned to anti-IL5 strategy drugs.</p> <p>The lower risk of <i>total</i> adverse events is likely driven by the reduction in asthma exacerbations shown by these drugs.</p> <p>Data are available on <i>drug-related</i> adverse events from all 3 mepolizumab trials, but only from 2 of 5 reslizumab trials and 1 of 5 benralizumab trials. These data show that, relative to placebo, participants assigned to mepolizumab had a 35% greater relative risk of drug-related adverse events (95% CI 1-81% greater RR); those assigned to reslizumab had a 22% lower relative risk and those assigned to benralizumab had a 44% greater relative risk, however the effect for last two drugs was not statistically significant.</p>	<p>Research evidence reveals that the rates of adverse events with anti-IL5 therapies are not substantially different from placebo. Infrequent but severe adverse reactions, including hypersensitive reactions, can not be excluded since randomised clinical trials are not powered enough to detect them. Safety data from phase 3 extension studies have been recently published and are reassuring. Post-authorisation pharmacovigilance systems, including larger cohorts of patients receiving these treatments, are expected to provide additional real-life safety data.</p>
CERTAINTY OF EVIDENCE	<p>What is the overall certainty of the evidence of effects?</p> <ul style="list-style-type: none"> ● Very low ● Low ● Moderate ○ High ○ No included studies 	<p>Mepolizumab (population meets the definition of severe asthma defined by the ERS/ATS Guidelines): moderate quality of evidence.</p> <p>Benralizumab:</p> <p>--overall population (patients with moderate and severe persistent asthma): very low quality of evidence;</p> <p>--population that meets criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines: low quality of evidence</p> <p>Reslizumab:</p> <p>--overall population (patients with moderate and severe persistent asthma): low quality of evidence;</p> <p>--population that meets criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines: low quality of evidence</p>	<p>Our certainty assessment relies on study design (randomized controlled trials), risk of bias, inconsistency, indirectness, and imprecision.</p> <p>Further the certainty is based on the quality of evidence that is lowest among critical outcomes.</p> <p>The RCTs on all anti-IL5 strategy drugs were mainly designed to investigate changes in asthma exacerbations. Consequently, the certainty of the data for this critical outcome is high (mepolizumab and reslizumab) or moderate (benralizumab). However, the certainty of other outcomes such as respiratory symptoms was lower for all three drugs, and therefore downgraded the overall certainty of the evidence.</p>

VALUES	<p>Is there important uncertainty about or variability in how much people value the main outcomes?</p> <ul style="list-style-type: none"> ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes 	<p>No evidence identified.</p>	<p>There is no important uncertainty about how patients and the clinicians who care for them assess asthma exacerbations. On the other hand, asthma exacerbations is not the only critical outcome for patients and clinicians, who also consider the effect of interventions on other outcomes, such as changes in lung function, change in maintenance dose of systemic corticosteroids, asthma symptoms, and quality of life. Although the effect size of anti-IL5 strategy drugs is not uniform across these outcomes, these drugs tended to improve to varying degrees all asthma related outcomes. For instance, although the reduction in asthma exacerbation rates is greater in magnitude than the change in lung function for all 3 of these drugs, all 3 did improve lung function. Further, patients and clinicians rarely decide to prescribe these drugs based on only one of these outcomes in isolation.</p> <p>All three anti-IL5 strategy drugs are currently FDA and EMA approved in patients with severe eosinophilic asthma. Patients with asthma of greater severity are more likely to experience a greater rate of asthma exacerbations. Therefore, the decision to whether or not to prescribe these drugs is currently restricted to patients for whom the main outcome researched in the anti-IL5 strategy trials—asthma exacerbations—is likely to be important. Further, many pharmacy</p>

			formularies for physician groups and hospitals restrict these drugs to patients with severe asthma and a recent history of asthma exacerbations.
BALANCE OF EFFECTS	<p>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</p> <ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know 	All three anti-IL5 strategy drugs have been associated with large desirable effects and small undesirable effects.	As noted above, both serious and non-serious side effects were noted in clinical trials to have occurred more commonly in the placebo groups to which these drugs were compared. Thus, considering the substantial benefit in terms of reducing asthma exacerbations, the balance favors using an anti-IL5 strategy.
COST EFFECTIVENESS	<p>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</p> <ul style="list-style-type: none"> ● Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies 	The December 2018 report by the Institute for Clinical and Economic Review (ICER) states that anti-IL5 strategy drugs cost >\$340,000 per quality-adjusted life years (QALY) gained when compared to standard of care (ICER 2018). These figures far exceed the accepted threshold for a cost-effective intervention of \$150,000 per QALY gained.	Therefore, the alternative is favored over an anti-IL5 strategy from a cost-effectiveness standpoint.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	<p>What is the certainty of the evidence of resource requirements (costs)?</p> <ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate ● High ○ No included studies 	The manufacturers' listed annual net prices are \$29,500, \$28,900, and \$27,800 for mepolizumab, reslizumab, and benralizumab, respectively, after applying discounts and rebates (ICER 2018).	
EQUITY	<p>What would be the impact on health equity?</p> <ul style="list-style-type: none"> ○ Reduced ● Probably reduced 	No evidence identified.	In the US, racial and ethnic minorities, and individuals of lower socioeconomic status have been documented to have

	<ul style="list-style-type: none"> ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know 		<p>less access to specialty clinics and are less likely to use controller therapy for asthma. Since anti-IL5 strategy drugs are mainly prescribed by specialists it is likely that racial and ethnic minorities will be less likely to be prescribed one of these drugs. Other groups may thus experience greater reductions in asthma exacerbations due to access to these drugs, which will thus reduce health equity. Similarly, patients with severe asthma who live in regions with fewer specialists will be less likely to receive these drugs, thus reducing equity between areas with high and low access to specialty care.</p> <p>On the other hand, the manufacturers of these drugs have programs in place to reduce patients' out of pocket costs for these drugs, which may partly mitigate the decrease in equity posed by differences in access by socioeconomic status and race/ethnicity.</p>
ACCEPTABILITY	<p>Is the intervention acceptable to key stakeholders?</p> <ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know 	No evidence identified.	<p>Most patients with severe asthma welcome the possibility of relief from asthma through anti-IL5 strategy drugs.</p> <p>Health insurance companies and clinic administrations find anti-IL5 strategy drugs less acceptable due to their high cost.</p>
FEASIBILITY	<p>Is the intervention feasible to implement?</p> <ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know 	No evidence identified.	<p>The feasibility to implement is limited by the prescription of these drugs only by asthma specialists with the clinical resources to administer these drugs and monitor patients. Clinicians also need to have access to a laboratory that can document peripheral blood eosinophils in these patients. Patients without access to such clinicians would find it very difficult to receive these drugs.</p>

Should a measurement of a specific biomarker be used to guide initiation of treatment with a monoclonal anti-IL5 or IL5R α antibody in adults and children with severe asthma? (biomarkers being exhaled NO, peripheral or sputum eosinophils, and serum periostin)

GRADE Evidence Profile: MEPOLIZUMAB (according to baseline number of blood eosinophils)

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)		Certainty	What happens
			Difference		
Asthma control (ACQ-5 responders defined as patients achieving a ≥0.5-point reduction from baseline in ACQ-5 score) assessed with: Asthma Control Questionnaire (ACQ-5); Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5. Follow up: 24 weeks № of participants: 457 (1 RCT) ¹ Importance: CRITICAL	Percentage of patients treated with mepolizumab who achieved a ≥0.5-point reduction from baseline in ACQ-5 score compared to placebo were: Eosinophil ≥ 150/uL: 63% versus 41%, RR (95%CI) = 1.53 (1.27 to 1.84), Absolute effect = 217 more per 1,000 (from 110 more to 343 more), n=457. Eosinophil ≥ 300/uL: 63% versus 37%, RR (95%CI) = 1.68 (1.33 to 2.12), Absolute effect = 254 more per 1,000 (from 123 more to 418 more), n=322. Eosinophil ≥ 500/uL: 62% versus 37%, RR (95%CI) = 1.67 (1.23 to 2.28), Absolute effect = 249 more per 1,000 (from 86 more to 477 more), n=187.			⊕⊕⊕○ MODERATE b,c	There are significant increases in the number of patients treated with mepolizumab compared to placebo who achieve a reduction of at least 0.5 point in the ACQ-5 score. Increases are seen in patients with baseline blood eosinophil counts ≥150/uL, ≥300/uL and ≥500/uL. However there is appreciable overlap of the 95% CIs.

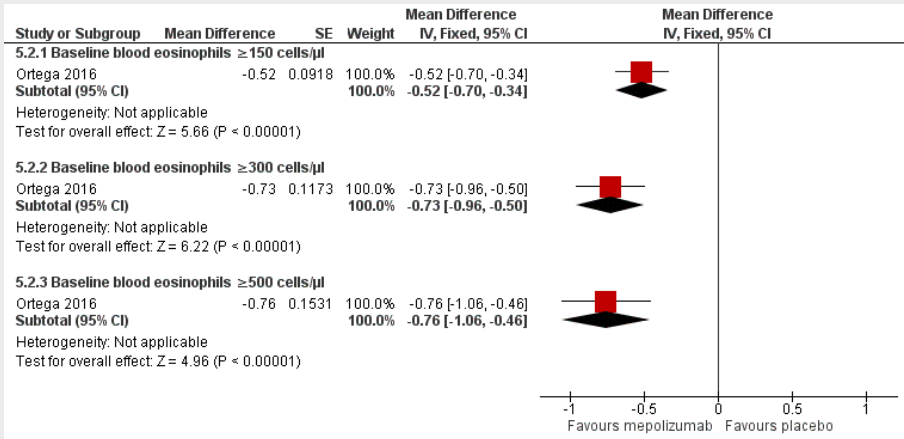
Study or Subgroup	Mepolizumab Events	Mepolizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
5.1.1 Baseline blood eosinophils ≥150 cells/μl							
Chupp 2017	139	222	96	235	100.0%	1.53 [1.27, 1.84]	
Subtotal (95% CI)		222		235	100.0%	1.53 [1.27, 1.84]	
Total events	139		96				
Heterogeneity: Not applicable Test for overall effect: Z = 4.54 (P < 0.00001)							
5.1.2 Baseline blood eosinophils ≥300 cells/μl							
Chupp 2017	98	156	62	166	100.0%	1.68 [1.33, 2.12]	
Subtotal (95% CI)		156		166	100.0%	1.68 [1.33, 2.12]	
Total events	98		62				
Heterogeneity: Not applicable Test for overall effect: Z = 4.41 (P < 0.0001)							
5.1.3 Baseline blood eosinophils ≥500 cells/μl							
Chupp 2017	58	93	35	94	100.0%	1.67 [1.23, 2.28]	
Subtotal (95% CI)		93		94	100.0%	1.67 [1.23, 2.28]	
Total events	58		35				
Heterogeneity: Not applicable Test for overall effect: Z = 3.30 (P = 0.0010)							

0.50.711.52

Favours placebo Favours mepolizumab

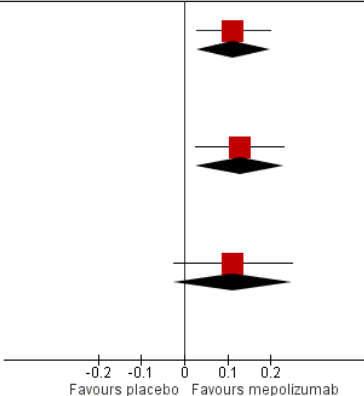
⊕⊕⊕○
MODERATE
b,c

There are significant increases in the number of patients treated with mepolizumab compared to placebo who achieve a reduction of at least 0.5 point in the ACQ-5 score. Increases are seen in patients with baseline blood eosinophil counts $\geq 150/\mu\text{L}$, $\geq 300/\mu\text{L}$ and $\geq 500/\mu\text{L}$. However there is appreciable overlap of the 95% CIs.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)		Difference	Certainty	What happens																																																																													
Asthma control (change from baseline) assessed with: Asthma Control Questionnaire (ACQ-5); Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5. Follow up: 32 weeks № of participants: 402 (1 RCT) ² Importance: CRITICAL	Mean change from baseline to week 32 in patients treated with mepolizumab compared to placebo were: Eosinophil ≥150/uL: Mean difference (95%CI) = -0.52 (-0.70 to -0.34), n=402. Eosinophil ≥300/uL: Mean difference (95%CI) = -0.73 (-0.96 to -0.50), n=274. Eosinophil ≥500/uL: Mean difference (95%CI) = -0.76 (-1.06 to -0.46), n=171. ^d	 <table><thead><tr><th>Study or Subgroup</th><th>Mean Difference</th><th>SE</th><th>Weight</th><th>Mean Difference IV, Fixed, 95% CI</th><th>Mean Difference IV, Fixed, 95% CI</th></tr></thead><tbody><tr><td colspan="6">5.2.1 Baseline blood eosinophils ≥150 cells/μl</td></tr><tr><td>Ortega 2016</td><td>-0.52</td><td>0.0918</td><td>100.0%</td><td>-0.52 [-0.70, -0.34]</td><td></td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>100.0%</td><td>-0.52 [-0.70, -0.34]</td><td></td></tr><tr><td colspan="6">Heterogeneity: Not applicable Test for overall effect: Z = 5.66 (P < 0.00001)</td></tr><tr><td colspan="6">5.2.2 Baseline blood eosinophils ≥300 cells/μl</td></tr><tr><td>Ortega 2016</td><td>-0.73</td><td>0.1173</td><td>100.0%</td><td>-0.73 [-0.96, -0.50]</td><td></td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>100.0%</td><td>-0.73 [-0.96, -0.50]</td><td></td></tr><tr><td colspan="6">Heterogeneity: Not applicable Test for overall effect: Z = 6.22 (P < 0.00001)</td></tr><tr><td colspan="6">5.2.3 Baseline blood eosinophils ≥500 cells/μl</td></tr><tr><td>Ortega 2016</td><td>-0.76</td><td>0.1531</td><td>100.0%</td><td>-0.76 [-1.06, -0.46]</td><td></td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>100.0%</td><td>-0.76 [-1.06, -0.46]</td><td></td></tr><tr><td colspan="6">Heterogeneity: Not applicable Test for overall effect: Z = 4.96 (P < 0.00001)</td></tr></tbody></table>		Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	5.2.1 Baseline blood eosinophils ≥150 cells/μl						Ortega 2016	-0.52	0.0918	100.0%	-0.52 [-0.70, -0.34]		Subtotal (95% CI)			100.0%	-0.52 [-0.70, -0.34]		Heterogeneity: Not applicable Test for overall effect: Z = 5.66 (P < 0.00001)						5.2.2 Baseline blood eosinophils ≥300 cells/μl						Ortega 2016	-0.73	0.1173	100.0%	-0.73 [-0.96, -0.50]		Subtotal (95% CI)			100.0%	-0.73 [-0.96, -0.50]		Heterogeneity: Not applicable Test for overall effect: Z = 6.22 (P < 0.00001)						5.2.3 Baseline blood eosinophils ≥500 cells/μl						Ortega 2016	-0.76	0.1531	100.0%	-0.76 [-1.06, -0.46]		Subtotal (95% CI)			100.0%	-0.76 [-1.06, -0.46]		Heterogeneity: Not applicable Test for overall effect: Z = 4.96 (P < 0.00001)						⊕○○○ VERY LOW b,c,e,f	There are significant improvements in asthma control assessed by the ACQ-5 in patients treated with mepolizumab compared to placebo at 32 weeks of follow up. Improvements are seen in patients with baseline blood eosinophil counts ≥150/uL, ≥300/uL and ≥500/uL. However the 95% CI of the subgroups ≥150 cells/uL and ≥500 cells/uL include a response below the MCID and there is appreciable overlap of the 95% CIs.
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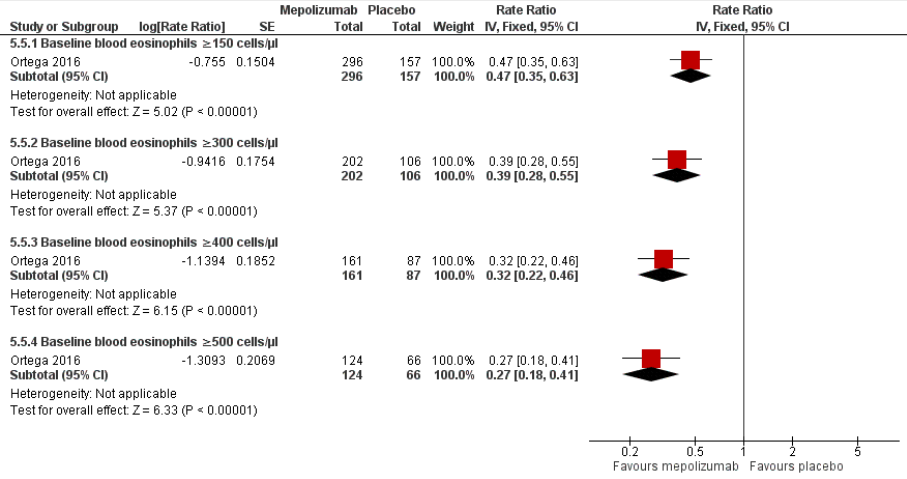
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Quality of life (change from baseline) assessed with: St George's Respiratory Questionnaire; Scale from: 0 to 100; higher scores indicate worse quality of life; MCID 4 units. Follow up: 32 weeks № of participants: 420 (1 RCT) ² Importance: CRITICAL	Mean change from baseline to week 32 in patients treated with mepolizumab compared to placebo were: Eosinophil ≥150/uL: Mean difference (95%CI) = -8.10 (-11.10 to -5.10), n=420. Eosinophil ≥300/uL: Mean difference (95%CI) = -10.40 (-14.10 to -6.70), n=288. Eosinophil ≥500/uL: Mean difference (95%CI) = -11.30 (-16.20 to -6.40), n=179. ^d	<table><thead><tr><th>Study or Subgroup</th><th>Mean Difference</th><th>SE</th><th>Weight</th><th>Mean Difference IV, Fixed, 95% CI</th></tr></thead><tbody><tr><td colspan="5">5.4.1 Baseline blood eosinophils ≥ 150 cells/μl</td></tr><tr><td>Ortega 2016</td><td>-8.1</td><td>1.5306</td><td>100.0%</td><td>-8.10 [-11.10, -5.10]</td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>100.0%</td><td>-8.10 [-11.10, -5.10]</td></tr><tr><td colspan="5">Heterogeneity: Not applicable Test for overall effect: Z = 5.29 (P < 0.00001)</td></tr><tr><td colspan="5">5.4.2 Baseline blood eosinophils ≥ 300 cells/μl</td></tr><tr><td>Ortega 2016</td><td>-10.4</td><td>1.8878</td><td>100.0%</td><td>-10.40 [-14.10, -6.70]</td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>100.0%</td><td>-10.40 [-14.10, -6.70]</td></tr><tr><td colspan="5">Heterogeneity: Not applicable Test for overall effect: Z = 5.51 (P < 0.00001)</td></tr><tr><td colspan="5">5.4.3 Baseline blood eosinophils ≥ 500 cells/μl</td></tr><tr><td>Ortega 2016</td><td>-11.3</td><td>2.5</td><td>100.0%</td><td>-11.30 [-16.20, -6.40]</td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>100.0%</td><td>-11.30 [-16.20, -6.40]</td></tr><tr><td colspan="5">Heterogeneity: Not applicable Test for overall effect: Z = 4.52 (P < 0.00001)</td></tr></tbody></table>			Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI	5.4.1 Baseline blood eosinophils ≥ 150 cells/μl					Ortega 2016	-8.1	1.5306	100.0%	-8.10 [-11.10, -5.10]	Subtotal (95% CI)			100.0%	-8.10 [-11.10, -5.10]	Heterogeneity: Not applicable Test for overall effect: Z = 5.29 (P < 0.00001)					5.4.2 Baseline blood eosinophils ≥ 300 cells/μl					Ortega 2016	-10.4	1.8878	100.0%	-10.40 [-14.10, -6.70]	Subtotal (95% CI)			100.0%	-10.40 [-14.10, -6.70]	Heterogeneity: Not applicable Test for overall effect: Z = 5.51 (P < 0.00001)					5.4.3 Baseline blood eosinophils ≥ 500 cells/μl					Ortega 2016	-11.3	2.5	100.0%	-11.30 [-16.20, -6.40]	Subtotal (95% CI)			100.0%	-11.30 [-16.20, -6.40]	Heterogeneity: Not applicable Test for overall effect: Z = 4.52 (P < 0.00001)					⊕⊕○○ LOW ^{b,c,e}	There are significant improvements in respiratory symptoms measured by the SGRQ in patients treated with mepolizumab compared to placebo at 32 weeks of follow up. Improvements are seen in patients with baseline blood eosinophil counts ≥150/uL, ≥300/uL and ≥500/uL, however there is appreciable overlap of the 95% CIs.
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Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)		Certainty	What happens
			Difference		
Lung function (Pre-bronchodilator FEV1 litres, change from baseline); MCID 0.23 liter ⁴ follow up: 32 weeks № of participants: 423 (1 RCT) ²	Mean change from baseline to week 32 in patients treated with mepolizumab compared to placebo were: Eosinophil ≥150/uL: Mean difference (95%CI) = 0.11 L (0.03 L to 0.20 L), n=423. Eosinophil ≥300/uL: Mean difference (95%CI) = 0.13 L (0.02 L to 0.23 L), n=290. Eosinophil ≥500/uL: Mean difference (95%CI) = 0.11 L (-0.02 L to 0.25 L), n=181. ^d			⊕○○○ VERY LOW b,c,e,f	There is a significant change in pre-BD FEV1 (litres) with mepolizumab compared to placebo in the subgroups of patients with blood eosinophil counts ≥150/uL and ≥300/uL at 32 weeks of follow up, whereas there are no differences in similar terms for those patients with blood eosinophils ≥500/uL at the same follow up. There is appreciable overlap of the 95% CIs.

Importance: IMPORTANT

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Lung function (Post-bronchodilator FEV1 litres, change from baseline); MCID 0.23 liter ⁴ follow up: 32 weeks № of participants: 386 (1 RCT) ² Importance: IMPORTANT	Mean change from baseline to week 32 in patients treated with mepolizumab compared to placebo were: Eosinophil ≥150/uL: Mean difference (95%CI) = 0.17 L (0.08 L to 0.27 L), n=386. Eosinophil ≥300/uL: Mean difference (95%CI) = 0.20 L (0.09 L to 0.31 L), n=268. Eosinophil ≥500/uL: Mean difference (95%CI) = 0.25 L (0.10 L to 0.39 L), n=166. ^d	<table><thead><tr><th>Study or Subgroup</th><th>Mean Difference</th><th>SE</th><th>Weight</th><th>Mean Difference IV, Fixed, 95% CI</th><th>Mean Difference IV, Fixed, 95% CI</th></tr></thead><tbody><tr><td colspan="6">5.8.1 Baseline blood eosinophils ≥150 cells/μl</td></tr><tr><td>Ortega 2016</td><td>0.172</td><td>0.0485</td><td>100.0%</td><td>0.17 [0.08, 0.27]</td><td rowspan="2"></td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>100.0%</td><td>0.17 [0.08, 0.27]</td></tr><tr><td colspan="6">Heterogeneity: Not applicable Test for overall effect: Z = 3.55 (P = 0.0004)</td></tr><tr><td colspan="6">5.8.2 Baseline blood eosinophils ≥300 cells/μl</td></tr><tr><td>Ortega 2016</td><td>0.202</td><td>0.0571</td><td>100.0%</td><td>0.20 [0.09, 0.31]</td><td rowspan="2"></td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>100.0%</td><td>0.20 [0.09, 0.31]</td></tr><tr><td colspan="6">Heterogeneity: Not applicable Test for overall effect: Z = 3.54 (P = 0.0004)</td></tr><tr><td colspan="6">5.8.3 Baseline blood eosinophils ≥500 cells/μl</td></tr><tr><td>Ortega 2016</td><td>0.247</td><td>0.074</td><td>100.0%</td><td>0.25 [0.10, 0.39]</td><td rowspan="2"></td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>100.0%</td><td>0.25 [0.10, 0.39]</td></tr><tr><td colspan="6">Heterogeneity: Not applicable Test for overall effect: Z = 3.34 (P = 0.0008)</td></tr></tbody></table> <div><div>-0.2-0.100.10.2</div><div>Favours placeboFavours mepolizumab</div></div>			Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	5.8.1 Baseline blood eosinophils ≥150 cells/μl						Ortega 2016	0.172	0.0485	100.0%	0.17 [0.08, 0.27]		Subtotal (95% CI)			100.0%	0.17 [0.08, 0.27]	Heterogeneity: Not applicable Test for overall effect: Z = 3.55 (P = 0.0004)						5.8.2 Baseline blood eosinophils ≥300 cells/μl						Ortega 2016	0.202	0.0571	100.0%	0.20 [0.09, 0.31]		Subtotal (95% CI)			100.0%	0.20 [0.09, 0.31]	Heterogeneity: Not applicable Test for overall effect: Z = 3.54 (P = 0.0004)						5.8.3 Baseline blood eosinophils ≥500 cells/μl						Ortega 2016	0.247	0.074	100.0%	0.25 [0.10, 0.39]		Subtotal (95% CI)			100.0%	0.25 [0.10, 0.39]	Heterogeneity: Not applicable Test for overall effect: Z = 3.34 (P = 0.0008)						⊕○○○ VERY LOW b,c,e,f	There is a significant change in post-BD FEV1 (litres) with mepolizumab compared to placebo in the subgroups of patients with blood eosinophil counts ≥150/uL, ≥300/uL and ≥500/uL at 32 weeks of follow up. However there is appreciable overlap of the 95% CIs.
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Exacerbation rate (mean exacerbation rate per patient per year); lower rates, greater reduction in exacerbations; Follow up: 32 weeks № of participants: 453 (1 RCT) ²	Annualised mean exacerbation rates per patient treated with mepolizumab compared to placebo were: Eosinophil ≥150/uL: 0.78 vs 1.65, Rate ratio (95%CI) = 0.47 (0.35 to 0.63), n=453. Eosinophil ≥300/uL: 0.78 vs 1.98, Rate ratio (95%CI) = 0.39 (0.28 to 0.55), n=308. Eosinophil ≥400/uL: 0.66 vs 2.06, Rate ratio (95%CI) = 0.32 (0.22 to 0.46), n=248. Eosinophil ≥500/uL: 0.58 vs 2.11, Rate ratio (95%CI) = 0.27 (0.18 to 0.41), n=190.					⊕⊕○○ LOW ^{b,c,e}	There is a significant reduction of exacerbation rates with mepolizumab compared to placebo in those patients with baseline blood eosinophil counts ≥150/uL, ≥300/uL, ≥400/uL and ≥500/uL. However there is overlap of the 95% CIs.

Importance: CRITICAL

Outcome N _e of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens																																																																																																																														
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Exacerbation rate (mean exacerbation rate per patient per year); lower rates, greater reduction in exacerbations; Follow up: 32 weeks N _e of participants: 569 (1 RCT) ² Importance: CRITICAL	Annualised mean exacerbation rates per patient treated with mepolizumab compared to placebo were: Eosinophil <150/uL: 1.19 vs 1.92, Rate ratio (95%CI) = 0.62 (0.37 to 1.05), n=116. Eosinophil 150 to <300/uL: 0.66 vs 1.02, Rate ratio (95%CI) = 0.64 (0.35 to 1.16), n=145. Eosinophil 300 to <500/uL: 1.01 vs 1.66, Rate ratio (95%CI) = 0.61 (0.35 to 1.07), n=118. Eosinophil ≥500/uL: 0.58 vs 2.11, Rate ratio (95%CI) = 0.27 (0.18 to 0.41), n=190. Test for subgroup differences, p=0.02.	<table border="1"> <thead> <tr> <th>Study or Subgroup</th> <th>log[Rate Ratio]</th> <th>SE</th> <th>Mepolizumab Total</th> <th>Placebo Total</th> <th>Weight</th> <th>Rate Ratio IV, Fixed, 95% CI</th> </tr> </thead> <tbody> <tr> <td colspan="7">5.6.1 Baseline blood eosinophils <150 cells/μl</td> </tr> <tr> <td>Ortega 2016</td> <td>-0.478</td> <td>0.2688</td> <td>84</td> <td>32</td> <td>100.0%</td> <td>0.62 [0.37, 1.05]</td> </tr> <tr> <td>Subtotal (95% CI)</td> <td></td> <td></td> <td>84</td> <td>32</td> <td>100.0%</td> <td>0.62 [0.37, 1.05]</td> </tr> <tr> <td colspan="7">Heterogeneity: Not applicable Test for overall effect: Z = 1.78 (P = 0.08)</td> </tr> <tr> <td colspan="7">5.6.2 Baseline blood eosinophils 150 to <300 cells/μl</td> </tr> <tr> <td>Ortega 2016</td> <td>-0.4463</td> <td>0.3034</td> <td>94</td> <td>51</td> <td>100.0%</td> <td>0.64 [0.35, 1.16]</td> </tr> <tr> <td>Subtotal (95% CI)</td> <td></td> <td></td> <td>94</td> <td>51</td> <td>100.0%</td> <td>0.64 [0.35, 1.16]</td> </tr> <tr> <td colspan="7">Heterogeneity: Not applicable Test for overall effect: Z = 1.47 (P = 0.14)</td> </tr> <tr> <td colspan="7">5.6.3 Baseline blood eosinophils 300 to <500 cells/μl</td> </tr> <tr> <td>Ortega 2016</td> <td>-0.4943</td> <td>0.2867</td> <td>78</td> <td>40</td> <td>100.0%</td> <td>0.61 [0.35, 1.07]</td> </tr> <tr> <td>Subtotal (95% CI)</td> <td></td> <td></td> <td>78</td> <td>40</td> <td>100.0%</td> <td>0.61 [0.35, 1.07]</td> </tr> <tr> <td colspan="7">Heterogeneity: Not applicable Test for overall effect: Z = 1.72 (P = 0.08)</td> </tr> <tr> <td colspan="7">5.6.4 Baseline blood eosinophils ≥500 cells/μl</td> </tr> <tr> <td>Ortega 2016</td> <td>-1.3093</td> <td>0.2069</td> <td>124</td> <td>66</td> <td>100.0%</td> <td>0.27 [0.18, 0.41]</td> </tr> <tr> <td>Subtotal (95% CI)</td> <td></td> <td></td> <td>124</td> <td>66</td> <td>100.0%</td> <td>0.27 [0.18, 0.41]</td> </tr> <tr> <td colspan="7">Heterogeneity: Not applicable Test for overall effect: Z = 6.33 (P < 0.00001)</td> </tr> <tr> <td colspan="7">Test for subgroup differences: Chi² = 9.99, df = 3 (P = 0.02), I² = 70.0%</td> </tr> </tbody> </table>			Study or Subgroup	log[Rate Ratio]	SE	Mepolizumab Total	Placebo Total	Weight	Rate Ratio IV, Fixed, 95% CI	5.6.1 Baseline blood eosinophils <150 cells/μl							Ortega 2016	-0.478	0.2688	84	32	100.0%	0.62 [0.37, 1.05]	Subtotal (95% CI)			84	32	100.0%	0.62 [0.37, 1.05]	Heterogeneity: Not applicable Test for overall effect: Z = 1.78 (P = 0.08)							5.6.2 Baseline blood eosinophils 150 to <300 cells/μl							Ortega 2016	-0.4463	0.3034	94	51	100.0%	0.64 [0.35, 1.16]	Subtotal (95% CI)			94	51	100.0%	0.64 [0.35, 1.16]	Heterogeneity: Not applicable Test for overall effect: Z = 1.47 (P = 0.14)							5.6.3 Baseline blood eosinophils 300 to <500 cells/μl							Ortega 2016	-0.4943	0.2867	78	40	100.0%	0.61 [0.35, 1.07]	Subtotal (95% CI)			78	40	100.0%	0.61 [0.35, 1.07]	Heterogeneity: Not applicable Test for overall effect: Z = 1.72 (P = 0.08)							5.6.4 Baseline blood eosinophils ≥500 cells/μl							Ortega 2016	-1.3093	0.2069	124	66	100.0%	0.27 [0.18, 0.41]	Subtotal (95% CI)			124	66	100.0%	0.27 [0.18, 0.41]	Heterogeneity: Not applicable Test for overall effect: Z = 6.33 (P < 0.00001)							Test for subgroup differences: Chi ² = 9.99, df = 3 (P = 0.02), I ² = 70.0%							⊕⊕○○ LOW ^{b,c,e}	There is a significant reduction of exacerbation rates with mepolizumab compared to placebo in those patients with baseline blood eosinophil counts ≥500/uL, but not in patients with eosinophil counts <150/uL, 150 to <300/uL and 300 to <500/uL. There are statistically significant differences between subgroups.
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CI: Confidence interval; RR: Risk ratio; MD: Mean difference; OR: Odds ratio

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

Explanations

a. The participants included in these analyses have been considered to represent a population of severe asthmatics as defined by the ERS/ATS Guidelines on Severe Asthma 2014³.

b. Potential risk of bias associated with selective outcome reporting bias (non-predefined post-hoc analyses).

- c. The inclusion criteria for participants 12-17 years of age required treatment with inhaled corticosteroids at a lower dose than that recommended by the ERS/ATS Guidelines on Severe Asthma (2014)³. The proportion of included participants 12-17 years of age was not specified. However we have assumed the proportion of included participants 12-17 years was small relative to the whole study population and therefore we have not downgraded for indirectness.
- d. The measure of effect was not clearly specified in Ortega 2016, but we have assumed it was presented as mean difference between change-from-baseline measures.
- e. Mepolizumab doses (100 mg SC and 75 mg IV) were combined for the analysis, as reported by Ortega 2016.
- f. The ends of the 95% confidence interval of at least one subgroup include appreciable benefit and no benefit and could lead to different clinical decisions.

References

1. Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *Lancet Respir Med* 2017; 5: 390–400.
2. Ortega HG, Yancey SW, Mayer B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *Lancet Respir Med* 2016; 4: 549-556.
3. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43: 343-373.
4. Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? *Eur Respir J* 1999; 14: 23-27.

GRADE Evidence Profile: BENRALIZUMAB (according to baseline number of blood eosinophils)

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Quality of life (change from baseline) assessed with: Asthma Quality of Life Questionnaire (AQLQ) follow up: range 28 weeks to 56 weeks; Scale from: 1 to 7; higher values indicate better quality of life; MCID 0.5) № of participants: 1194 (3 RCTs) 1,2,3 Importance: CRITICAL	Mean change from baseline in AQLQ score in patients treated with benralizumab compared to placebo were: Eosinophil <300/µL: Mean difference (95% CI) = 0.85 (-0.39 to 2.09), n=55 ; Eosinophil ≥300/µL: Mean difference (95% CI) = 0.29 (0.15 to 0.43), n=1047 . Test for subgroup differences, p=0.38.	<table border="1"> <thead> <tr> <th>Study or Subgroup</th> <th>Mean Difference</th> <th>SE</th> <th>Benralizumab Total</th> <th>Placebo Total</th> <th>Weight</th> <th>Mean Difference IV, Random, 95% CI</th> </tr> </thead> <tbody> <tr> <td colspan="7">6.1.1 Baseline blood eosinophils <300 cells/µL</td> </tr> <tr> <td>Castro 2014</td> <td>0.85</td> <td>0.635</td> <td>4</td> <td>51</td> <td>100.0%</td> <td>0.85 [-0.39, 2.09]</td> </tr> <tr> <td>Subtotal (95% CI)</td> <td></td> <td></td> <td>4</td> <td>51</td> <td>100.0%</td> <td>0.85 [-0.39, 2.09]</td> </tr> <tr> <td colspan="7">Heterogeneity: Not applicable Test for overall effect: Z = 1.34 (P = 0.18)</td> </tr> <tr> <td colspan="7">6.1.2 Baseline blood eosinophils ≥300 cells/µL</td> </tr> <tr> <td>Bleecker 2016</td> <td>0.3</td> <td>0.102</td> <td>252</td> <td>254</td> <td>49.3%</td> <td>0.30 [0.10, 0.50]</td> </tr> <tr> <td>Castro 2014</td> <td>0.44</td> <td>0.293</td> <td>34</td> <td>37</td> <td>6.0%</td> <td>0.44 [-0.13, 1.01]</td> </tr> <tr> <td>FitzGerald 2016</td> <td>0.25</td> <td>0.1071</td> <td>230</td> <td>240</td> <td>44.7%</td> <td>0.25 [0.04, 0.46]</td> </tr> <tr> <td>Subtotal (95% CI)</td> <td></td> <td></td> <td>516</td> <td>531</td> <td>100.0%</td> <td>0.29 [0.15, 0.43]</td> </tr> <tr> <td colspan="7">Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 2 (P = 0.82); I² = 0% Test for overall effect: Z = 3.99 (P < 0.0001)</td> </tr> <tr> <td colspan="7">Test for subgroup differences: Chi² = 0.78, df = 1 (P = 0.38), I² = 0%</td> </tr> </tbody> </table>			Study or Subgroup	Mean Difference	SE	Benralizumab Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI	6.1.1 Baseline blood eosinophils <300 cells/µL							Castro 2014	0.85	0.635	4	51	100.0%	0.85 [-0.39, 2.09]	Subtotal (95% CI)			4	51	100.0%	0.85 [-0.39, 2.09]	Heterogeneity: Not applicable Test for overall effect: Z = 1.34 (P = 0.18)							6.1.2 Baseline blood eosinophils ≥300 cells/µL							Bleecker 2016	0.3	0.102	252	254	49.3%	0.30 [0.10, 0.50]	Castro 2014	0.44	0.293	34	37	6.0%	0.44 [-0.13, 1.01]	FitzGerald 2016	0.25	0.1071	230	240	44.7%	0.25 [0.04, 0.46]	Subtotal (95% CI)			516	531	100.0%	0.29 [0.15, 0.43]	Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 2 (P = 0.82); I² = 0% Test for overall effect: Z = 3.99 (P < 0.0001)							Test for subgroup differences: Chi² = 0.78, df = 1 (P = 0.38), I² = 0%							⊕○○○ ○ VERY LOW ^{a,b,c}	There are significant improvements in asthma quality of life assessed by the AQLQ with benralizumab compared to placebo in patients with baseline blood eosinophil counts ≥300/µL but not <300/µL. There are no statistically significant differences between subgroups.														
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Lung function (Pre-bronchodilator FEV1 litres) follow up: range 28 to 56 weeks; MCID 0.23 litre ⁶ № of participants: 611 (3 RCTs) ^{1,2,3} Importance: IMPORTANT	Mean change from baseline in pre-bronchodilator FEV1 (litres) in patients treated with benralizumab compared to placebo were: Eosinophil <300/μL: Mean difference (95% CI) = 0.05 L (-0.03 to 0.14 L), n=611; Eosinophil ≥300/μL: Mean difference (95% CI) = 0.15 L (0.09 to 0.21 L), n=1108. Test for subgroup differences, p=0.07.	<table><thead><tr><th rowspan="2">Study or Subgroup</th><th rowspan="2">Mean Difference</th><th rowspan="2">SE</th><th colspan="2">Benralizumab</th><th colspan="2">Placebo</th><th rowspan="2">Weight</th><th rowspan="2">Mean Difference IV, Random, 95% CI</th><th rowspan="2">Mean Difference IV, Random, 95% CI</th></tr><tr><th>Total</th><th>Total</th><th>Total</th><th>Total</th></tr></thead><tbody><tr><td colspan="10">6.6.1 Baseline blood eosinophils <300 cells/μL</td></tr><tr><td>Bleecker 2016</td><td>0.102</td><td>0.0505</td><td></td><td>129</td><td></td><td>138</td><td>49.2%</td><td>0.10 [0.00, 0.20]</td><td rowspan="4"></td></tr><tr><td>Castro 2014</td><td>0.09</td><td>0.1301</td><td></td><td>10</td><td></td><td>97</td><td>9.8%</td><td>0.09 [-0.16, 0.34]</td></tr><tr><td>FitzGerald 2016</td><td>-0.015</td><td>0.0571</td><td></td><td>121</td><td></td><td>116</td><td>41.0%</td><td>-0.01 [-0.13, 0.10]</td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td></td><td>260</td><td></td><td>351</td><td>100.0%</td><td>0.05 [-0.03, 0.14]</td></tr><tr><td colspan="10">Heterogeneity: Tau² = 0.00; Chi² = 2.44, df = 2 (P = 0.30); I² = 18% Test for overall effect: Z = 1.26 (P = 0.21)</td></tr><tr><td colspan="10">6.6.2 Baseline blood eosinophils ≥300 cells/μL</td></tr><tr><td>Bleecker 2016</td><td>0.159</td><td>0.0464</td><td></td><td>264</td><td></td><td>261</td><td>43.6%</td><td>0.16 [0.07, 0.25]</td><td rowspan="3"></td></tr><tr><td>Castro 2014</td><td>0.23</td><td>0.0977</td><td></td><td>48</td><td></td><td>53</td><td>9.8%</td><td>0.23 [0.04, 0.42]</td></tr><tr><td>FitzGerald 2016</td><td>0.116</td><td>0.0449</td><td></td><td>238</td><td></td><td>244</td><td>46.6%</td><td>0.12 [0.03, 0.20]</td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td></td><td>550</td><td></td><td>558</td><td>100.0%</td><td>0.15 [0.09, 0.21]</td></tr><tr><td colspan="10">Heterogeneity: Tau² = 0.00; Chi² = 1.26, df = 2 (P = 0.53); I² = 0% Test for overall effect: Z = 4.76 (P < 0.00001)</td></tr><tr><td colspan="10">Test for subgroup differences: Chi² = 3.21, df = 1 (P = 0.07), I² = 68.9%</td></tr></tbody></table>				Study or Subgroup	Mean Difference	SE	Benralizumab		Placebo		Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI	Total	Total	Total	Total	6.6.1 Baseline blood eosinophils <300 cells/μL										Bleecker 2016	0.102	0.0505		129		138	49.2%	0.10 [0.00, 0.20]		Castro 2014	0.09	0.1301		10		97	9.8%	0.09 [-0.16, 0.34]	FitzGerald 2016	-0.015	0.0571		121		116	41.0%	-0.01 [-0.13, 0.10]	Subtotal (95% CI)				260		351	100.0%	0.05 [-0.03, 0.14]	Heterogeneity: Tau ² = 0.00; Chi ² = 2.44, df = 2 (P = 0.30); I ² = 18% Test for overall effect: Z = 1.26 (P = 0.21)										6.6.2 Baseline blood eosinophils ≥300 cells/μL										Bleecker 2016	0.159	0.0464		264		261	43.6%	0.16 [0.07, 0.25]		Castro 2014	0.23	0.0977		48		53	9.8%	0.23 [0.04, 0.42]	FitzGerald 2016	0.116	0.0449		238		244	46.6%	0.12 [0.03, 0.20]	Subtotal (95% CI)				550		558	100.0%	0.15 [0.09, 0.21]	Heterogeneity: Tau ² = 0.00; Chi ² = 1.26, df = 2 (P = 0.53); I ² = 0% Test for overall effect: Z = 4.76 (P < 0.00001)										Test for subgroup differences: Chi ² = 3.21, df = 1 (P = 0.07), I ² = 68.9%										⊕⊕○ ○ LOW ^{b,g}	There is a significant increase in pre-BD FEV1 (litres) with benralizumab compared to placebo in the subgroup of patients with blood eosinophil counts ≥300/uL, whereas there are no differences for those patients with blood eosinophils <300/uL. However there are no statistically significant differences between subgroups.
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Rate of any exacerbation follow up: range 28 weeks to 56 weeks № of participants: 1322 (3 RCTs) ^{1,2,3} Importance: CRITICAL	Annualised mean exacerbation rates per patient treated with mepolizumab compared to placebo were: Eosinophil <300/uL: Rate ratio (95%CI) = 0.71 (0.52 to 0.97), n=518. Eosinophil ≥300/uL: Rate ratio (95%CI) = 0.59 (0.47 to 0.73), n=1174. Test for subgroup differences, p=0.33.	<table border="1"> <thead> <tr> <th>Study or Subgroup</th> <th>log[Rate Ratio]</th> <th>SE</th> <th>Benralizumab Total</th> <th>Placebo Total</th> <th>Weight</th> <th>Rate Ratio IV, Random, 95% CI</th> </tr> </thead> <tbody> <tr> <td colspan="7">6.7.1 Baseline blood eosinophils <300 cells/μL</td> </tr> <tr> <td>Bleecker 2016</td> <td>-0.1863</td> <td>0.1741</td> <td>131</td> <td>140</td> <td>51.3%</td> <td>0.83 [0.59, 1.17]</td> </tr> <tr> <td>FitzGerald 2016</td> <td>-0.5108</td> <td>0.182</td> <td>125</td> <td>122</td> <td>48.7%</td> <td>0.60 [0.42, 0.86]</td> </tr> <tr> <td>Subtotal (95% CI)</td> <td></td> <td></td> <td>256</td> <td>262</td> <td>100.0%</td> <td>0.71 [0.52, 0.97]</td> </tr> <tr> <td colspan="7">Heterogeneity: Tau² = 0.02; Chi² = 1.66, df = 1 (P = 0.20); I² = 40%</td> </tr> <tr> <td colspan="7">Test for overall effect: Z = 2.12 (P = 0.03)</td> </tr> <tr> <td colspan="7">6.7.2 Baseline blood eosinophils ≥300 cells/μL</td> </tr> <tr> <td>Bleecker 2016</td> <td>-0.7133</td> <td>0.1433</td> <td>267</td> <td>267</td> <td>34.4%</td> <td>0.49 [0.37, 0.65]</td> </tr> <tr> <td>Castro 2014</td> <td>-0.5621</td> <td>0.1523</td> <td>70</td> <td>83</td> <td>32.1%</td> <td>0.57 [0.42, 0.77]</td> </tr> <tr> <td>FitzGerald 2016</td> <td>-0.3285</td> <td>0.1468</td> <td>239</td> <td>248</td> <td>33.5%</td> <td>0.72 [0.54, 0.96]</td> </tr> <tr> <td>Subtotal (95% CI)</td> <td></td> <td></td> <td>576</td> <td>598</td> <td>100.0%</td> <td>0.59 [0.47, 0.73]</td> </tr> <tr> <td colspan="7">Heterogeneity: Tau² = 0.02; Chi² = 3.56, df = 2 (P = 0.17); I² = 44%</td> </tr> <tr> <td colspan="7">Test for overall effect: Z = 4.72 (P < 0.00001)</td> </tr> <tr> <td colspan="7">Test for subgroup differences: Chi² = 0.94, df = 1 (P = 0.33), I² = 0%</td> </tr> </tbody> </table>			Study or Subgroup	log[Rate Ratio]	SE	Benralizumab Total	Placebo Total	Weight	Rate Ratio IV, Random, 95% CI	6.7.1 Baseline blood eosinophils <300 cells/μL							Bleecker 2016	-0.1863	0.1741	131	140	51.3%	0.83 [0.59, 1.17]	FitzGerald 2016	-0.5108	0.182	125	122	48.7%	0.60 [0.42, 0.86]	Subtotal (95% CI)			256	262	100.0%	0.71 [0.52, 0.97]	Heterogeneity: Tau² = 0.02; Chi² = 1.66, df = 1 (P = 0.20); I² = 40%							Test for overall effect: Z = 2.12 (P = 0.03)							6.7.2 Baseline blood eosinophils ≥300 cells/μL							Bleecker 2016	-0.7133	0.1433	267	267	34.4%	0.49 [0.37, 0.65]	Castro 2014	-0.5621	0.1523	70	83	32.1%	0.57 [0.42, 0.77]	FitzGerald 2016	-0.3285	0.1468	239	248	33.5%	0.72 [0.54, 0.96]	Subtotal (95% CI)			576	598	100.0%	0.59 [0.47, 0.73]	Heterogeneity: Tau² = 0.02; Chi² = 3.56, df = 2 (P = 0.17); I² = 44%							Test for overall effect: Z = 4.72 (P < 0.00001)							Test for subgroup differences: Chi² = 0.94, df = 1 (P = 0.33), I² = 0%							⊕⊕○ ○ LOW ^{b,g}	There are significant reductions in exacerbation rates with benralizumab compared to placebo in those patients with baseline blood eosinophil counts <300/μL and ≥300/ μL. However there are no statistically significant differences between subgroups.
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Adverse events follow up: range 48 weeks to 56 weeks № of participants: 1525 (2 RCTs) ^{1,3} Importance: IMPORTANT	<p>The proportion of patients treated with benralizumab who had any adverse event compared to placebo were: Eosinophil < 300/uL: 76.3% versus 79.8%, RR (95%CI) = 0.95 (0.87 to 1.04), Absolute effect = 40 fewer per 1,000 (from 104 fewer to 32 more), n=515. Eosinophil ≥ 300/uL: 73.6% versus 75.9%, RR (95%CI) = 0.98 (0.87 to 1.10), Absolute effect = 15 fewer per 1,000 (from 99 fewer to 76 more), n=1010. Test for subgroup differences, p=0.75.ⁿ</p> <table><thead><tr><th>Study or Subgroup</th><th>Benralizumab Events</th><th>Benralizumab Total</th><th>Placebo Events</th><th>Placebo Total</th><th>Weight</th><th>Risk Ratio M-H, Random, 95% CI</th></tr></thead><tbody><tr><td colspan="7">6.8.1 Baseline blood eosinophils <300 cells/μl</td></tr><tr><td>Bleecker 2016</td><td>96</td><td>129</td><td>108</td><td>140</td><td>45.2%</td><td>0.96 [0.84, 1.10]</td></tr><tr><td>FitzGerald 2016</td><td>97</td><td>124</td><td>101</td><td>122</td><td>54.8%</td><td>0.94 [0.84, 1.07]</td></tr><tr><td>Subtotal (95% CI)</td><td></td><td>253</td><td></td><td>262</td><td>100.0%</td><td>0.95 [0.87, 1.04]</td></tr><tr><td>Total events</td><td>193</td><td></td><td>209</td><td></td><td></td><td></td></tr><tr><td colspan="7">Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%</td></tr><tr><td colspan="7">Test for overall effect: Z = 1.02 (P = 0.31)</td></tr><tr><td colspan="7">6.8.2 Baseline blood eosinophils ≥300 cells/μl</td></tr><tr><td>Bleecker 2016</td><td>185</td><td>265</td><td>203</td><td>267</td><td>48.9%</td><td>0.92 [0.83, 1.02]</td></tr><tr><td>FitzGerald 2016</td><td>181</td><td>230</td><td>188</td><td>248</td><td>51.1%</td><td>1.04 [0.94, 1.14]</td></tr><tr><td>Subtotal (95% CI)</td><td></td><td>495</td><td></td><td>515</td><td>100.0%</td><td>0.98 [0.87, 1.10]</td></tr><tr><td>Total events</td><td>366</td><td></td><td>391</td><td></td><td></td><td></td></tr><tr><td colspan="7">Heterogeneity: Tau² = 0.00; Chi² = 2.88, df = 1 (P = 0.09); I² = 65%</td></tr><tr><td colspan="7">Test for overall effect: Z = 0.37 (P = 0.71)</td></tr><tr><td colspan="7">Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%</td></tr></tbody></table>	Study or Subgroup	Benralizumab Events	Benralizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	6.8.1 Baseline blood eosinophils <300 cells/μl							Bleecker 2016	96	129	108	140	45.2%	0.96 [0.84, 1.10]	FitzGerald 2016	97	124	101	122	54.8%	0.94 [0.84, 1.07]	Subtotal (95% CI)		253		262	100.0%	0.95 [0.87, 1.04]	Total events	193		209				Heterogeneity: Tau ² = 0.00; Chi ² = 0.05, df = 1 (P = 0.82); I ² = 0%							Test for overall effect: Z = 1.02 (P = 0.31)							6.8.2 Baseline blood eosinophils ≥300 cells/μl							Bleecker 2016	185	265	203	267	48.9%	0.92 [0.83, 1.02]	FitzGerald 2016	181	230	188	248	51.1%	1.04 [0.94, 1.14]	Subtotal (95% CI)		495		515	100.0%	0.98 [0.87, 1.10]	Total events	366		391				Heterogeneity: Tau ² = 0.00; Chi ² = 2.88, df = 1 (P = 0.09); I ² = 65%							Test for overall effect: Z = 0.37 (P = 0.71)							Test for subgroup differences: Chi ² = 0.10, df = 1 (P = 0.75), I ² = 0%							<p>⊕⊕○ ○ LOW _{k,l,m}</p>	<p>There is no significant increase in the incidence of adverse events with benralizumab compared to placebo in patients with baseline blood eosinophil counts <300/μL and ≥300/ μL. There are no statistically significant differences between subgroups.</p>
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Serious adverse events follow up: range 48 weeks to 56 weeks № of participants: 1525 (2 RCTs) ^{1,3} Importance: IMPORTANT	<p>The proportion of patients treated with benralizumab who had any serious adverse event compared to placebo were: Eosinophil < 300/uL: 11.5% versus 15.3%, RR (95%CI) = 0.73 (0.32 to 1.66), Absolute effect = 41 fewer per 1,000 (from 104 fewer to 101 more), n=515. Eosinophil ≥ 300/uL: 11.7% versus 13.6%, RR (95%CI) = 0.86 (0.62 to 1.19), Absolute effect = 19 fewer per 1,000 (from 52 fewer to 26 more), n=1010. Test for subgroup differences, p=0.71.</p> <table><tr><th>Study or Subgroup</th><th>Benralizumab Events</th><th>Benralizumab Total</th><th>Placebo Events</th><th>Placebo Total</th><th>Weight</th><th>Risk Ratio M-H, Random, 95% CI</th></tr><tr><td colspan="7">6.9.1 Baseline blood eosinophils <300 cells/μl</td></tr><tr><td>Bleecker 2016</td><td>19</td><td>129</td><td>19</td><td>140</td><td>52.9%</td><td>1.09 [0.60, 1.96]</td></tr><tr><td>FitzGerald 2016</td><td>10</td><td>124</td><td>21</td><td>122</td><td>47.1%</td><td>0.47 [0.23, 0.95]</td></tr><tr><td>Subtotal (95% CI)</td><td></td><td>253</td><td></td><td>262</td><td>100.0%</td><td>0.73 [0.32, 1.66]</td></tr><tr><td>Total events</td><td>29</td><td></td><td>40</td><td></td><td></td><td></td></tr><tr><td colspan="7">Heterogeneity: Tau² = 0.24; Chi² = 3.19, df = 1 (P = 0.07); I² = 69%</td></tr><tr><td colspan="7">Test for overall effect: Z = 0.75 (P = 0.45)</td></tr><tr><td colspan="7">6.9.2 Baseline blood eosinophils ≥300 cells/μl</td></tr><tr><td>Bleecker 2016</td><td>33</td><td>265</td><td>36</td><td>267</td><td>54.7%</td><td>0.92 [0.59, 1.44]</td></tr><tr><td>FitzGerald 2016</td><td>25</td><td>230</td><td>34</td><td>248</td><td>45.3%</td><td>0.79 [0.49, 1.29]</td></tr><tr><td>Subtotal (95% CI)</td><td></td><td>495</td><td></td><td>515</td><td>100.0%</td><td>0.86 [0.62, 1.19]</td></tr><tr><td>Total events</td><td>58</td><td></td><td>70</td><td></td><td></td><td></td></tr><tr><td colspan="7">Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%</td></tr><tr><td colspan="7">Test for overall effect: Z = 0.89 (P = 0.37)</td></tr><tr><td colspan="7">Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.71), I² = 0%</td></tr></table>	Study or Subgroup	Benralizumab Events	Benralizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	6.9.1 Baseline blood eosinophils <300 cells/μl							Bleecker 2016	19	129	19	140	52.9%	1.09 [0.60, 1.96]	FitzGerald 2016	10	124	21	122	47.1%	0.47 [0.23, 0.95]	Subtotal (95% CI)		253		262	100.0%	0.73 [0.32, 1.66]	Total events	29		40				Heterogeneity: Tau² = 0.24; Chi² = 3.19, df = 1 (P = 0.07); I² = 69%							Test for overall effect: Z = 0.75 (P = 0.45)							6.9.2 Baseline blood eosinophils ≥300 cells/μl							Bleecker 2016	33	265	36	267	54.7%	0.92 [0.59, 1.44]	FitzGerald 2016	25	230	34	248	45.3%	0.79 [0.49, 1.29]	Subtotal (95% CI)		495		515	100.0%	0.86 [0.62, 1.19]	Total events	58		70				Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%							Test for overall effect: Z = 0.89 (P = 0.37)							Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.71), I² = 0%							<p>⊕○○○ ○ VERY LOW ^{1,3,p}</p>	<p>There is no significant increase in the incidence of serious adverse events with benralizumab compared to placebo in patients with baseline blood eosinophil counts <300/μL and ≥300/ μL. There are no statistically significant differences between subgroups.</p>
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Systemic steroids (absolute final dose) follow up: 28 weeks № of participants: 148 (1 RCT) ⁵ <u>Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma⁷</u> Importance: CRITICAL	<p>The median oral glucocorticoid dose (range) at the final visit (week 28) in the subgroup with baseline blood eosinophils ≥150 to <300/μL was: 5.0 mg/day (0.0–15.0) in patients who received placebo (n=11) and 6.25 mg/day (0.0–30.0) in patients who received benralizumab (n=12). In the subgroup with baseline blood eosinophils ≥300/μL: 10.0 mg/day (0.0–40.0) in patients who received placebo (n=64) and 5.0 mg/day (0.0–25.0) in patients who received benralizumab (n=61). No statistical test comparing results has been reported.</p>	<p>⊕○○○ ○ VERY LOW ^{q,r}</p>	<p>Oral glucocorticoid dose is 5 mg/day less with benralizumab compared to placebo in the subgroup with baseline blood eosinophils ≥300/μL whereas in the subgroup with baseline blood eosinophils ≥150 to <300/μL oral glucocorticoid dose is 1.25 mg/day less with placebo. No statistical test available.</p>																																																																																																																

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
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Systemic steroids (percent reduction) follow up: 28 weeks № of participants: 148 (1 RCT) ⁵ <u>Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma⁷</u> Importance: CRITICAL		The median reduction in final oral glucocorticoid dose compared with baseline (range, %) in the subgroup with baseline blood eosinophils ≥ 150 to $<300/\mu\text{L}$ was: 50.0% (0.0–100) in patients who received placebo (n=11) and 57.5% (-50.0–100) in patients who received benralizumab (n=12). In the subgroup with baseline blood eosinophils $\geq 300/\mu\text{L}$: 0.0% (-150 to 100) in patients who received placebo (n=64) and 75.0% (-50.0 to 100) in patients who received benralizumab (n=61). No statistical test comparing results has been reported.			⊕○○ ○ VERY LOW ^{q,r}	There were similar oral glucocorticoid dose reduction with benralizumab or placebo in the subgroup with baseline blood eosinophils ≥ 150 to $<300/\mu\text{L}$ (50% and 57.7%) whereas in the subgroup with baseline blood eosinophils $\geq 300/\mu\text{L}$ the oral glucocorticoid dose reduction was 0% in placebo and 75% in benralizumab. No statistical test available.

CI: Confidence interval; FEV1: forced expiratory volume in 1 second; MCID: minimal clinically important difference; MD: Mean difference; SMD: Standardised mean difference; RCT: randomised controlled trial; RR: Risk ratio

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

Explanations

- Potential risk of bias associated with selective outcome reporting bias (ad hoc subgroup analysis in participants with blood eosinophil counts $<300/\mu\text{L}$ in Castro 2014).
- Three studies (Bleecker 2016, Castro 2014 and FitzGerald 2016) included a mixed population of patients with moderate and severe asthma.
- A single study reported results for the subgroup with blood eosinophils counts $<300/\mu\text{L}$. This analysis included only 55 patients (4 in benralizumab arm and 51 in placebo arm).
- Potential risk of bias associated with selective outcome reporting bias in participants with eosinophil counts $<300/\mu\text{L}$ (ad hoc subgroup analysis in Castro 2014; analysis not specified in protocols of Bleecker 2016 and FitzGerald 2016).
- The study included a mixed population of patients with moderate and severe asthma.
- For both subgroups the ends of the 95% confidence interval include appreciable clinical harm (MCID = 0.5) and no benefit and could lead to opposite clinical decisions. Results from single study with only 51 patients.

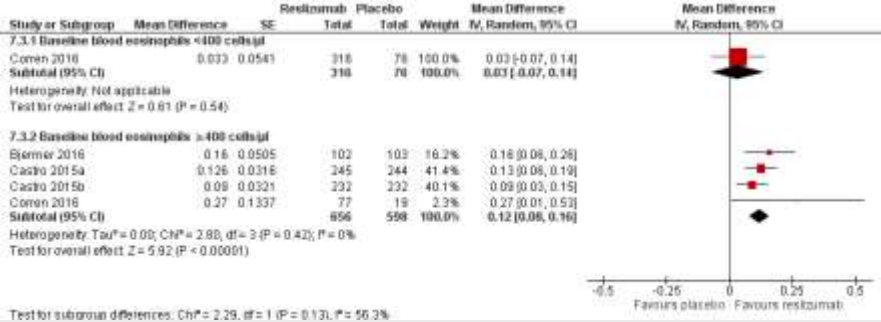
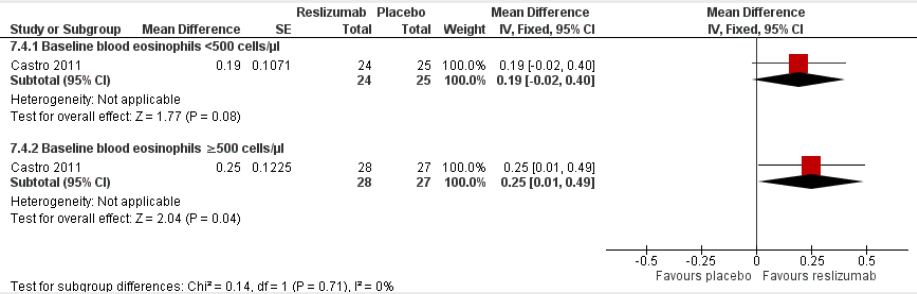
- g. Potential risk of bias associated with selective outcome reporting bias in participants with baseline blood eosinophil counts <300 cells/μl: ad hoc subgroup analysis in Castro 2014; additional analysis in patients with blood eosinophil counts <150/μL, 150-299/μL, 300-449/μL and ≥450/μL were stated in the protocol but not reported by Bleecker 2016 and FitzGerald 2016.
- h. For the subgroup with baseline blood eosinophils <300 cells/μl the ends of the 95% confidence interval include appreciable clinical benefit and no benefit and could lead to opposite clinical decision.
- i. FEV1% was not specified as pre- or post-bronchodilator in Park 2016 but we have assumed it to be pre-bronchodilator.
- j. For both subgroups the ends of the 95% confidence interval include appreciable clinical harm (MCID = 10.38%) and no benefit and could lead to opposite clinical decisions. Results from single study with only 51 patients.
- k. $I^2=65\%$ ($p=0.09$) may represent substantial statistical heterogeneity in the subgroup with baseline eosinophil count ≥300 cells/μl.
- l. The studies included a mixed population of patients with moderate and severe asthma.
- m. This judgement was based on a arbitrary clinical decision threshold of 15% increase or decrease in absolute effect.
- n. There was a high incidence of adverse events in both benralizumab and placebo groups. The apparent benefit from benralizumab might be explained by a reduction of asthma-related adverse events with the active drug.
- o. $I^2=69\%$ ($p=0.07$) may represent substantial statistical heterogeneity in the subgroup with baseline eosinophil count <300 cells/μl.
- p. This judgement was based on a arbitrary clinical decision threshold of 10% increase or decrease in absolute effect in the subgroup with baseline blood eosinophil count <300 cells/μl.
- q. Potential risk of bias associated with selective outcome reporting bias: the protocol for Nair 2017 specified that percentage reduction in oral glucocorticoid dose would be summarized by treatment group in patients with baseline blood eosinophil counts 150-299/μL, ≥300/μL, 300-450/μL and >450/μL separately. However results have not been reported for patients with 300-450 eosinophils/μL and >450 eosinophils/μL.
- r. 95% confidence intervals could not be obtained and data from single study including only 148 patients.

References

1. Fitzgerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016; 388: 2128–2141.
2. Castro M, Wenzel SE, Bleecker ER, et al. Benralizumab, an anti-interleukin 5 receptor [alpha] monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. *Lancet Respiratory Medicine* 2014; 2: 878–890.
3. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet* 2016; 388: 2115–2127..
4. Park HS, Kim MK, Imai N, Nakanishi T, Adachi M, Ohta K, Tohda Y. A Phase 2a Study of Benralizumab for Patients with Eosinophilic Asthma in South Korea and Japan. *Int Arch Allergy Immunol* 2016; 169:135-145.
5. Nair P, Wenzel SE, Rabe KF, et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. *New England Journal of Medicine* 2017; 376: 2448-2458.
6. Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? *Eur Respir J* 1999; 14: 23-27.
7. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43: 343-373.

GRADE Evidence Profile: RESLIZUMAB (according to baseline number of blood eosinophils)

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<p>Asthma control (change from baseline) assessed with: Asthma Control Questionnaire (ACQ-7); Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5 follow up: range 16 weeks to 52 weeks № of participants: 1645 (4 RCTs) ^{1,2,3}</p> <p>Importance: CRITICAL</p>	<p>Mean change from baseline in ACQ-7 score in patients treated with reslizumab compared to placebo were: Eosinophil <400/μL: Mean difference (95% CI) = -0.12 (-0.33 to 0.09), n=392; Eosinophil ≥400/μL: Mean difference (95% CI) = -0.27 (-0.36 to -0.19), n=1253. Test for subgroup differences, p=0.19.</p>	<table border="1"> <thead> <tr> <th>Study or Subgroup</th><th>Mean Difference</th><th>SE</th><th>Reslizumab Total</th><th>Placebo Total</th><th>Weight</th><th>Mean Difference IV, Random, 95% CI</th></tr> </thead> <tbody> <tr> <td colspan="7">7.1.1 Baseline blood eosinophils <400 cells/μL</td> </tr> <tr> <td>Corren 2016</td><td>-0.122</td><td>0.1071</td><td>316</td><td>76</td><td>100.0%</td><td>-0.12 [-0.33, 0.09]</td> </tr> <tr> <td>Subtotal (95% CI)</td><td></td><td></td><td>316</td><td>76</td><td>100.0%</td><td>-0.12 [-0.33, 0.09]</td> </tr> <tr> <td colspan="7">Heterogeneity: Not applicable Test for overall effect: Z = 1.14 (P = 0.25)</td> </tr> <tr> <td colspan="7">7.1.2 Baseline blood eosinophils ≥400 cells/μL</td> </tr> <tr> <td>Bjerner 2016</td><td>-0.359</td><td>0.1112</td><td>101</td><td>103</td><td>14.7%</td><td>-0.36 [-0.58, -0.14]</td> </tr> <tr> <td>Castro 2015a</td><td>-0.26</td><td>0.0663</td><td>245</td><td>244</td><td>41.4%</td><td>-0.26 [-0.39, -0.13]</td> </tr> <tr> <td>Castro 2015b</td><td>-0.24</td><td>0.0663</td><td>232</td><td>232</td><td>41.4%</td><td>-0.24 [-0.37, -0.11]</td> </tr> <tr> <td>Corren 2016</td><td>-0.49</td><td>0.2653</td><td>77</td><td>19</td><td>2.6%</td><td>-0.49 [-1.01, 0.03]</td> </tr> <tr> <td>Subtotal (95% CI)</td><td></td><td></td><td>655</td><td>598</td><td>100.0%</td><td>-0.27 [-0.36, -0.19]</td> </tr> <tr> <td colspan="7">Heterogeneity: Tau² = 0.00; Chi² = 1.55, df = 3 (P = 0.67); I² = 0% Test for overall effect: Z = 6.38 (P < 0.00001)</td> </tr> <tr> <td colspan="7">Test for subgroup differences: Chi² = 1.70, df = 1 (P = 0.19), I² = 41.1%</td> </tr> </tbody> </table>			Study or Subgroup	Mean Difference	SE	Reslizumab Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI	7.1.1 Baseline blood eosinophils <400 cells/μL							Corren 2016	-0.122	0.1071	316	76	100.0%	-0.12 [-0.33, 0.09]	Subtotal (95% CI)			316	76	100.0%	-0.12 [-0.33, 0.09]	Heterogeneity: Not applicable Test for overall effect: Z = 1.14 (P = 0.25)							7.1.2 Baseline blood eosinophils ≥400 cells/μL							Bjerner 2016	-0.359	0.1112	101	103	14.7%	-0.36 [-0.58, -0.14]	Castro 2015a	-0.26	0.0663	245	244	41.4%	-0.26 [-0.39, -0.13]	Castro 2015b	-0.24	0.0663	232	232	41.4%	-0.24 [-0.37, -0.11]	Corren 2016	-0.49	0.2653	77	19	2.6%	-0.49 [-1.01, 0.03]	Subtotal (95% CI)			655	598	100.0%	-0.27 [-0.36, -0.19]	Heterogeneity: Tau ² = 0.00; Chi ² = 1.55, df = 3 (P = 0.67); I ² = 0% Test for overall effect: Z = 6.38 (P < 0.00001)							Test for subgroup differences: Chi ² = 1.70, df = 1 (P = 0.19), I ² = 41.1%							<p>⊕⊕⊕○ MODERATE a</p>	<p>There are significant improvements in asthma control assessed by the ACQ-7 with reslizumab compared to placebo in patients with baseline blood eosinophil counts ≥400/μL but not <400/μL. However there are no statistically significant differences between subgroups.</p>
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Heterogeneity: Not applicable Test for overall effect: Z = 1.80 (P = 0.07)																																																																																																	
Total (95% CI)			53	53	100.0%	-0.26 [-0.64, 0.13]																																																																																											
Heterogeneity: Chi ² = 1.60, df = 1 (P = 0.21); I ² = 38% Test for overall effect: Z = 1.31 (P = 0.19) Test for subgroup differences: Chi ² = 1.60, df = 1 (P = 0.21), I ² = 37.5%																																																																																																	

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Lung function (Pre-bronchodilator FEV1 litres) follow up: range 16 weeks to 52 weeks MCID 0.23 litre ⁶ № of participants: 1646 (4 RCTs) ^{1,2,3} Importance: IMPORTANT	Mean change from baseline in pre-bronchodilator FEV1 (litres) in patients treated with reslizumab compared to placebo were: Eosinophil <400/μL: Mean difference (95% CI) = 0.03 L (-0.07 to 0.14 L), n=392; Eosinophil ≥400/μL: Mean difference (95% CI) = 0.12 L (0.08 to 0.16 L), n=1254. Test for subgroup differences, p=0.13.	 <table border="1"> <thead> <tr> <th>Study or Subgroup</th> <th>Mean Difference</th> <th>SE</th> <th>Reslizumab Total</th> <th>Placebo Total</th> <th>Weight</th> <th>Mean Difference IV, Random, 95% CI</th> </tr> </thead> <tbody> <tr> <td colspan="7">7.3.1 Baseline blood eosinophils <400 cells/μl</td> </tr> <tr> <td>Cohen 2016</td> <td>0.033</td> <td>0.0543</td> <td>316</td> <td>76</td> <td>100.0%</td> <td>0.03 [-0.07, 0.14]</td> </tr> <tr> <td>Subtotal (95% CI)</td> <td></td> <td></td> <td>316</td> <td>76</td> <td>100.0%</td> <td>0.03 [-0.07, 0.14]</td> </tr> <tr> <td colspan="7">Heterogeneity: Not applicable Test for overall effect: Z = 0.61 (P = 0.54)</td> </tr> <tr> <td colspan="7">7.3.2 Baseline blood eosinophils ≥400 cells/μl</td> </tr> <tr> <td>Biemer 2016</td> <td>0.16</td> <td>0.0505</td> <td>102</td> <td>103</td> <td>16.2%</td> <td>0.16 [0.06, 0.26]</td> </tr> <tr> <td>Castro 2015a</td> <td>0.126</td> <td>0.0316</td> <td>245</td> <td>244</td> <td>41.4%</td> <td>0.13 [0.06, 0.19]</td> </tr> <tr> <td>Castro 2015b</td> <td>0.08</td> <td>0.0321</td> <td>232</td> <td>232</td> <td>40.1%</td> <td>0.09 [0.03, 0.15]</td> </tr> <tr> <td>Cohen 2016</td> <td>0.27</td> <td>0.1337</td> <td>77</td> <td>19</td> <td>2.3%</td> <td>0.27 [0.01, 0.53]</td> </tr> <tr> <td>Subtotal (95% CI)</td> <td></td> <td></td> <td>656</td> <td>598</td> <td>100.0%</td> <td>0.12 [0.08, 0.16]</td> </tr> <tr> <td colspan="7">Heterogeneity: Tau² = 0.00; Chi² = 2.80, df = 3 (P = 0.42); I² = 0% Test for overall effect: Z = 5.92 (P < 0.00001)</td> </tr> <tr> <td colspan="7">Test for subgroup differences: Chi² = 2.29, df = 1 (P = 0.13), I² = 56.3%</td> </tr> </tbody> </table>			Study or Subgroup	Mean Difference	SE	Reslizumab Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI	7.3.1 Baseline blood eosinophils <400 cells/μl							Cohen 2016	0.033	0.0543	316	76	100.0%	0.03 [-0.07, 0.14]	Subtotal (95% CI)			316	76	100.0%	0.03 [-0.07, 0.14]	Heterogeneity: Not applicable Test for overall effect: Z = 0.61 (P = 0.54)							7.3.2 Baseline blood eosinophils ≥400 cells/μl							Biemer 2016	0.16	0.0505	102	103	16.2%	0.16 [0.06, 0.26]	Castro 2015a	0.126	0.0316	245	244	41.4%	0.13 [0.06, 0.19]	Castro 2015b	0.08	0.0321	232	232	40.1%	0.09 [0.03, 0.15]	Cohen 2016	0.27	0.1337	77	19	2.3%	0.27 [0.01, 0.53]	Subtotal (95% CI)			656	598	100.0%	0.12 [0.08, 0.16]	Heterogeneity: Tau ² = 0.00; Chi ² = 2.80, df = 3 (P = 0.42); I ² = 0% Test for overall effect: Z = 5.92 (P < 0.00001)							Test for subgroup differences: Chi ² = 2.29, df = 1 (P = 0.13), I ² = 56.3%							⊕⊕⊕○ MODERATE a	There is a significant increase in pre-BD FEV1 (litres) with reslizumab compared to placebo in the subgroup of patients with blood eosinophil counts ≥400/μL, whereas there are no differences for those patients with blood eosinophils <400/μL. However there are no statistically significant differences between subgroups.
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Lung function (Pre-bronchodilator FEV1 litres) follow up: 15 weeks MCID 0.23 litre ⁶ № of participants: 104 (1 RCT) ⁴ <u>Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma⁵</u> Importance: IMPORTANT	Mean change from baseline in pre-bronchodilator FEV1 (litres) in patients treated with reslizumab compared to placebo were: Eosinophil <500/μL: Mean difference (95% CI) = 0.19 L (-0.02 to 0.40 L), n=49; Eosinophil ≥500/μL: Mean difference (95% CI) = 0.25 L (0.01 to 0.49 L), n=55. Test for subgroup differences, p=0.71.	 <table border="1"> <thead> <tr> <th>Study or Subgroup</th> <th>Mean Difference</th> <th>SE</th> <th>Reslizumab Total</th> <th>Placebo Total</th> <th>Weight</th> <th>Mean Difference IV, Fixed, 95% CI</th> </tr> </thead> <tbody> <tr> <td colspan="7">7.4.1 Baseline blood eosinophils <500 cells/μl</td> </tr> <tr> <td>Castro 2011</td> <td>0.19</td> <td>0.1071</td> <td>24</td> <td>25</td> <td>100.0%</td> <td>0.19 [-0.02, 0.40]</td> </tr> <tr> <td>Subtotal (95% CI)</td> <td></td> <td></td> <td>24</td> <td>25</td> <td>100.0%</td> <td>0.19 [-0.02, 0.40]</td> </tr> <tr> <td colspan="7">Heterogeneity: Not applicable Test for overall effect: Z = 1.77 (P = 0.08)</td> </tr> <tr> <td colspan="7">7.4.2 Baseline blood eosinophils ≥500 cells/μl</td> </tr> <tr> <td>Castro 2011</td> <td>0.25</td> <td>0.1225</td> <td>28</td> <td>27</td> <td>100.0%</td> <td>0.25 [0.01, 0.49]</td> </tr> <tr> <td>Subtotal (95% CI)</td> <td></td> <td></td> <td>28</td> <td>27</td> <td>100.0%</td> <td>0.25 [0.01, 0.49]</td> </tr> <tr> <td colspan="7">Heterogeneity: Not applicable Test for overall effect: Z = 2.04 (P = 0.04)</td> </tr> <tr> <td colspan="7">Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.71), I² = 0%</td> </tr> </tbody> </table>			Study or Subgroup	Mean Difference	SE	Reslizumab Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI	7.4.1 Baseline blood eosinophils <500 cells/μl							Castro 2011	0.19	0.1071	24	25	100.0%	0.19 [-0.02, 0.40]	Subtotal (95% CI)			24	25	100.0%	0.19 [-0.02, 0.40]	Heterogeneity: Not applicable Test for overall effect: Z = 1.77 (P = 0.08)							7.4.2 Baseline blood eosinophils ≥500 cells/μl							Castro 2011	0.25	0.1225	28	27	100.0%	0.25 [0.01, 0.49]	Subtotal (95% CI)			28	27	100.0%	0.25 [0.01, 0.49]	Heterogeneity: Not applicable Test for overall effect: Z = 2.04 (P = 0.04)							Test for subgroup differences: Chi ² = 0.14, df = 1 (P = 0.71), I ² = 0%							⊕○○○ VERY LOW b,d	There is a significant increase in pre-BD FEV1 (litres) with reslizumab compared to placebo in the subgroup of patients with blood eosinophil counts ≥500/μL, whereas there are no differences for those patients with blood eosinophils <500/μL. However there are no statistically significant differences between subgroups.																					
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Rate of any exacerbation follow up: 52 weeks № of participants: 953 (2 RCTs) ² Importance: CRITICAL	Annualised mean exacerbation rates per patient treated with reslizumab compared to placebo were: Eosinophil ≥400/μL: 0.84 versus 1.81 events/patient/year, Rate ratio (95%CI) = 0.46 (0.37, 0.58), n=953. Eosinophil ≥500/μL: Rate ratio (95%CI) = 0.49 (0.37 to 0.65), n=567; Eosinophil ≥700/μL: Rate ratio (95%CI) = 0.41 (0.28 to 0.60), n=344. Exacerbation rates were not specified for the subgroups ≥500 and ≥700 eosinophils/μL	<table><thead><tr><th rowspan="2">Study or Subgroup</th><th rowspan="2">log[Rate Ratio]</th><th rowspan="2">SE</th><th>Reslizumab</th><th>Placebo</th><th rowspan="2">Weight</th><th>Rate Ratio</th><th>Rate Ratio</th></tr><tr><th>Total</th><th>Total</th><th>IV, Fixed, 95% CI</th><th>IV, Fixed, 95% CI</th></tr></thead><tbody><tr><td colspan="8">7.5.1 Baseline blood eosinophils ≥400 cells/μl</td></tr><tr><td>Castro 2015</td><td>-0.7695</td><td>0.1147</td><td>477</td><td>476</td><td>100.0%</td><td>0.46 [0.37, 0.58]</td><td rowspan="4"></td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>477</td><td>476</td><td>100.0%</td><td>0.46 [0.37, 0.58]</td></tr><tr><td colspan="7">Heterogeneity: Not applicable Test for overall effect: Z = 6.71 (P < 0.00001)</td></tr><tr><td colspan="8">7.5.2 Baseline blood eosinophils ≥500 cells/μl</td></tr><tr><td>Castro 2015</td><td>-0.7133</td><td>0.1442</td><td>281</td><td>286</td><td>100.0%</td><td>0.49 [0.37, 0.65]</td><td rowspan="4"></td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>281</td><td>286</td><td>100.0%</td><td>0.49 [0.37, 0.65]</td></tr><tr><td colspan="7">Heterogeneity: Not applicable Test for overall effect: Z = 4.95 (P < 0.00001)</td></tr><tr><td colspan="8">7.5.3 Baseline blood eosinophils ≥700 cells/μl</td></tr><tr><td>Castro 2015</td><td>-0.8916</td><td>0.1946</td><td>172</td><td>172</td><td>100.0%</td><td>0.41 [0.28, 0.60]</td><td rowspan="3"></td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>172</td><td>172</td><td>100.0%</td><td>0.41 [0.28, 0.60]</td></tr><tr><td colspan="7">Heterogeneity: Not applicable Test for overall effect: Z = 4.58 (P < 0.00001)</td></tr></tbody></table> <div> 0.5 0.7 1 1.5 2 Favours reslizumab Favours placebo</div>			Study or Subgroup	log[Rate Ratio]	SE	Reslizumab	Placebo	Weight	Rate Ratio	Rate Ratio	Total	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI	7.5.1 Baseline blood eosinophils ≥400 cells/μl								Castro 2015	-0.7695	0.1147	477	476	100.0%	0.46 [0.37, 0.58]		Subtotal (95% CI)			477	476	100.0%	0.46 [0.37, 0.58]	Heterogeneity: Not applicable Test for overall effect: Z = 6.71 (P < 0.00001)							7.5.2 Baseline blood eosinophils ≥500 cells/μl								Castro 2015	-0.7133	0.1442	281	286	100.0%	0.49 [0.37, 0.65]		Subtotal (95% CI)			281	286	100.0%	0.49 [0.37, 0.65]	Heterogeneity: Not applicable Test for overall effect: Z = 4.95 (P < 0.00001)							7.5.3 Baseline blood eosinophils ≥700 cells/μl								Castro 2015	-0.8916	0.1946	172	172	100.0%	0.41 [0.28, 0.60]		Subtotal (95% CI)			172	172	100.0%	0.41 [0.28, 0.60]	Heterogeneity: Not applicable Test for overall effect: Z = 4.58 (P < 0.00001)							⊕⊕○○ LOW ^{a,b}	There are significant reductions in exacerbation rates with reslizumab compared to placebo in those patients with baseline blood eosinophil counts ≥400/μL, ≥500/μL and ≥700/μL. However there is appreciable overlap of the 95% CIs.
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Adverse events follow up: range 16 weeks to 52 weeks № of participants: 1652 (4 RCTs) ^{1,2,3} Importance: IMPORTANT	<p>The proportion of patients treated with reslizumab who had any adverse event compared to placebo were: Eosinophil ≥ 400/μL: 75% versus 81.6%, RR (95%CI) = 0.92 (0.87 to 0.97), Absolute effect = 65 fewer per 1,000 (from 106 fewer to 24 fewer), n=1160. Unspecified baseline blood eosinophil counts: 54.9% versus 74.2%, RR (95%CI) = 0.74 (0.64 to 0.86), Absolute effect = 193 fewer per 1,000 (from 267 fewer to 104 fewer), n=492. Test for subgroup differences, p=0.008. ^{e,f}</p>	<table><tr><th>Study or Subgroup</th><th>Reslizumab Events Total</th><th>Placebo Events Total</th><th>Weight</th><th>Risk Ratio M-H, Random, 95% CI</th></tr><tr><td colspan="5">7.6.1 Baseline blood eosinophils ≥400 cells/μl</td></tr><tr><td>Bjermer 2016</td><td>61 103</td><td>66 105</td><td>7.0%</td><td>0.94 [0.76, 1.17]</td></tr><tr><td>Castro 2015a</td><td>197 245</td><td>206 243</td><td>49.9%</td><td>0.95 [0.87, 1.03]</td></tr><tr><td>Castro 2015b</td><td>177 232</td><td>201 232</td><td>43.1%</td><td>0.88 [0.81, 0.96]</td></tr><tr><td>Subtotal (95% CI)</td><td>580</td><td>580</td><td>100.0%</td><td>0.92 [0.87, 0.97]</td></tr><tr><td colspan="5">Total events 435 473</td></tr><tr><td colspan="5">Heterogeneity: Tau² = 0.00; Chi² = 1.54, df = 2 (P = 0.46); I² = 0%</td></tr><tr><td colspan="5">Test for overall effect: Z = 2.90 (P = 0.004)</td></tr><tr><td colspan="5">7.6.2 Unspecified baseline blood eosinophil count</td></tr><tr><td>Corren 2016</td><td>217 395</td><td>72 97</td><td>100.0%</td><td>0.74 [0.64, 0.86]</td></tr><tr><td>Subtotal (95% CI)</td><td>395</td><td>97</td><td>100.0%</td><td>0.74 [0.64, 0.86]</td></tr><tr><td colspan="5">Total events 217 72</td></tr><tr><td colspan="5">Heterogeneity: Not applicable</td></tr><tr><td colspan="5">Test for overall effect: Z = 4.00 (P < 0.0001)</td></tr></table> <p>Test for subgroup differences: Chi² = 7.13, df = 1 (P = 0.008), I² = 86.0%</p>				Study or Subgroup	Reslizumab Events Total	Placebo Events Total	Weight	Risk Ratio M-H, Random, 95% CI	7.6.1 Baseline blood eosinophils ≥400 cells/μl					Bjermer 2016	61 103	66 105	7.0%	0.94 [0.76, 1.17]	Castro 2015a	197 245	206 243	49.9%	0.95 [0.87, 1.03]	Castro 2015b	177 232	201 232	43.1%	0.88 [0.81, 0.96]	Subtotal (95% CI)	580	580	100.0%	0.92 [0.87, 0.97]	Total events 435 473					Heterogeneity: Tau² = 0.00; Chi² = 1.54, df = 2 (P = 0.46); I² = 0%					Test for overall effect: Z = 2.90 (P = 0.004)					7.6.2 Unspecified baseline blood eosinophil count					Corren 2016	217 395	72 97	100.0%	0.74 [0.64, 0.86]	Subtotal (95% CI)	395	97	100.0%	0.74 [0.64, 0.86]	Total events 217 72					Heterogeneity: Not applicable					Test for overall effect: Z = 4.00 (P < 0.0001)					<p>⊕⊕○○ LOW ^{a,g}</p>	<p>There are significant decreases in the incidence of adverse events with reslizumab compared to placebo in patients with baseline blood eosinophil counts ≥400/μL and with unspecified baseline blood eosinophil counts. There are statistically significant differences between subgroups.</p>
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Serious adverse events follow up: range 16 weeks to 52 weeks № of participants: 1652 (4 RCTs) ^{1,2,3} Importance: IMPORTANT	<p>The proportion of patients treated with reslizumab who had any serious adverse event compared to placebo were: Eosinophil ≥ 400/μL: 7.9% versus 10.0%, RR (95%CI) = 0.79 (0.51 to 1.22), Absolute effect = 21 fewer per 1,000 (from 49 fewer to 22 more), n=1160. Unspecified baseline blood eosinophil counts: 4.1% versus 4.1%, RR (95%CI) = 0.98 (0.34 to 2.87), Absolute effect = 1 fewer per 1,000 (from 27 fewer to 77 more), n=492. Test for subgroup differences, p=0.71.^e</p> <table><tr><th>Study or Subgroup</th><th>Reslizumab Events</th><th>Reslizumab Total</th><th>Placebo Events</th><th>Placebo Total</th><th>Weight</th><th>Risk Ratio M-H, Random, 95% CI</th></tr><tr><td colspan="7">7.7.1 Baseline blood eosinophils ≥400 cells/μL</td></tr><tr><td>Bjermer 2016</td><td>4</td><td>103</td><td>1</td><td>105</td><td>4.0%</td><td>4.08 [0.46, 35.87]</td></tr><tr><td>Castro 2015a</td><td>24</td><td>245</td><td>34</td><td>243</td><td>54.2%</td><td>0.70 [0.43, 1.14]</td></tr><tr><td>Castro 2015b</td><td>18</td><td>232</td><td>23</td><td>232</td><td>41.8%</td><td>0.78 [0.43, 1.41]</td></tr><tr><td>Subtotal (95% CI)</td><td></td><td>580</td><td></td><td>580</td><td>100.0%</td><td>0.79 [0.51, 1.22]</td></tr><tr><td>Total events</td><td>46</td><td></td><td>58</td><td></td><td></td><td></td></tr><tr><td colspan="7">Heterogeneity: Tau² = 0.03; Chi² = 2.42, df = 2 (P = 0.30); I² = 17%</td></tr><tr><td colspan="7">Test for overall effect: Z = 1.07 (P = 0.28)</td></tr><tr><td colspan="7">7.7.2 Unspecified baseline blood eosinophil count</td></tr><tr><td>Corren 2016</td><td>16</td><td>395</td><td>4</td><td>97</td><td>100.0%</td><td>0.98 [0.34, 2.87]</td></tr><tr><td>Subtotal (95% CI)</td><td></td><td>395</td><td></td><td>97</td><td>100.0%</td><td>0.98 [0.34, 2.87]</td></tr><tr><td>Total events</td><td>16</td><td></td><td>4</td><td></td><td></td><td></td></tr><tr><td colspan="7">Heterogeneity: Not applicable</td></tr><tr><td colspan="7">Test for overall effect: Z = 0.03 (P = 0.97)</td></tr><tr><td colspan="7">Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.71), I² = 0%</td></tr></table>	Study or Subgroup	Reslizumab Events	Reslizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	7.7.1 Baseline blood eosinophils ≥400 cells/μL							Bjermer 2016	4	103	1	105	4.0%	4.08 [0.46, 35.87]	Castro 2015a	24	245	34	243	54.2%	0.70 [0.43, 1.14]	Castro 2015b	18	232	23	232	41.8%	0.78 [0.43, 1.41]	Subtotal (95% CI)		580		580	100.0%	0.79 [0.51, 1.22]	Total events	46		58				Heterogeneity: Tau ² = 0.03; Chi ² = 2.42, df = 2 (P = 0.30); I ² = 17%							Test for overall effect: Z = 1.07 (P = 0.28)							7.7.2 Unspecified baseline blood eosinophil count							Corren 2016	16	395	4	97	100.0%	0.98 [0.34, 2.87]	Subtotal (95% CI)		395		97	100.0%	0.98 [0.34, 2.87]	Total events	16		4				Heterogeneity: Not applicable							Test for overall effect: Z = 0.03 (P = 0.97)							Test for subgroup differences: Chi ² = 0.14, df = 1 (P = 0.71), I ² = 0%							<p>⊕⊕⊕○ MODERATE a,h</p>	<p>There are no significant increases in the incidence of serious adverse events with reslizumab compared to placebo in patients with baseline blood eosinophil counts ≥400/μL and with unspecified baseline blood eosinophil counts. There are no statistically significant differences between subgroups.</p>
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GRADE Working Group grades of evidence

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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

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Explanations

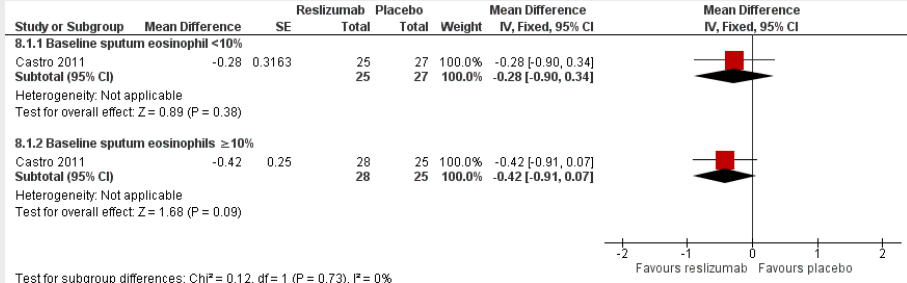
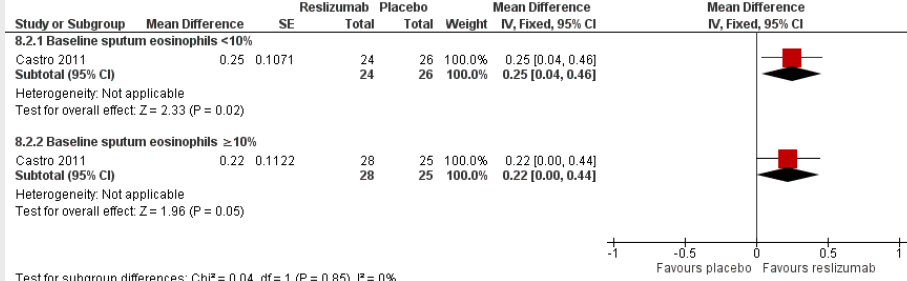
a. All studies included a mixed population of patients with moderate and severe asthma.

- b. Potential risk of bias associated with selective outcome reporting bias (post hoc subgroup analysis).
- c. For both subgroups the ends of the 95% confidence interval include appreciable clinical benefit (MCID 0.5) and no benefit and could lead to opposite clinical decisions. Results from single study with only 106 patients.
- d. For both subgroups the ends of the 95% confidence interval include appreciable clinical benefit (MCID 0.23 L) and no benefit and could lead to opposite clinical decisions. Results from single study with only 104 patients.
- e. The trial by Corren 2016, which provided results for the subgroup "Unspecified baseline blood eosinophil counts" reported that eosinophils ≥ 400 cells/ μ L were observed in 20% of patients at baseline, distributed similarly between treatment groups.
- f. There was a high incidence of adverse events in both reslizumab and placebo groups. The apparent benefit from reslizumab might be explained by a reduction of asthma-related adverse events with the active drug.
- g. This judgement was based on an arbitrary clinical decision threshold of 15% increase or decrease in absolute effect in the subgroup with unspecified baseline blood eosinophil counts.
- h. This judgement was based on an arbitrary clinical decision threshold of 10% increase or decrease in absolute effect.

References

1. Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 Study of Reslizumab in Patients With Poorly Controlled Asthma: Effects Across a Broad Range of Eosinophil Counts. *Chest* 2016; 150: 799-810.
2. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015; 3: 355-366.
3. Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for Inadequately Controlled Asthma With Elevated Blood Eosinophil Levels: A Randomized Phase 3 Study. *Chest* 2016; 150: 789-798.
4. Castro M, Mathur S, Hargreave F, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med* 2011; 184: 1125-1132.
5. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43: 343-373.
6. Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? *Eur Respir J* 1999; 14: 23-27.

GRADE Evidence Profile: RESLIZUMAB (according to baseline sputum eosinophils - %)

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens																																																																													
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Asthma control (change from baseline) assessed with: Asthma Control Questionnaire (ACQ-7); Scale from: 0 to 6; lower values indicate better asthma control; MCID 0.5 follow up: 15 weeks № of participants: 105 (1 RCT) ¹ <u>Study participants meet criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines on Severe Asthma³</u> Importance: CRITICAL	Mean change from baseline in ACQ-7 score in patients treated with reslizumab compared to placebo were: sputum eosinophils <10%: Mean difference (95% CI) = -0.28 (-0.90 to 0.34), n=52; sputum eosinophils ≥10%: Mean difference (95% CI) = -0.42 (-0.91 to 0.07), n=53. Test for subgroup differences, p=0.73.	 <table border="1"> <thead> <tr> <th>Study or Subgroup</th><th>Mean Difference</th><th>SE</th><th>Reslizumab Total</th><th>Placebo Total</th><th>Weight</th><th>Mean Difference IV, Fixed, 95% CI</th></tr> </thead> <tbody> <tr> <td>8.1.1 Baseline sputum eosinophil <10%</td><td></td><td></td><td></td><td></td><td></td><td></td></tr> <tr> <td>Castro 2011</td><td>-0.28</td><td>0.3163</td><td>25</td><td>27</td><td>100.0%</td><td>-0.28 [-0.90, 0.34]</td></tr> <tr> <td>Subtotal (95% CI)</td><td></td><td></td><td>25</td><td>27</td><td>100.0%</td><td>-0.28 [-0.90, 0.34]</td></tr> <tr> <td>Heterogeneity: Not applicable</td><td></td><td></td><td></td><td></td><td></td><td></td></tr> <tr> <td>Test for overall effect: Z = 0.89 (P = 0.38)</td><td></td><td></td><td></td><td></td><td></td><td></td></tr> <tr> <td>8.1.2 Baseline sputum eosinophils ≥10%</td><td></td><td></td><td></td><td></td><td></td><td></td></tr> <tr> <td>Castro 2011</td><td>-0.42</td><td>0.25</td><td>28</td><td>25</td><td>100.0%</td><td>-0.42 [-0.91, 0.07]</td></tr> <tr> <td>Subtotal (95% CI)</td><td></td><td></td><td>28</td><td>25</td><td>100.0%</td><td>-0.42 [-0.91, 0.07]</td></tr> <tr> <td>Heterogeneity: Not applicable</td><td></td><td></td><td></td><td></td><td></td><td></td></tr> <tr> <td>Test for overall effect: Z = 1.68 (P = 0.09)</td><td></td><td></td><td></td><td></td><td></td><td></td></tr> </tbody> </table> <p>Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.73), I² = 0%</p>			Study or Subgroup	Mean Difference	SE	Reslizumab Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI	8.1.1 Baseline sputum eosinophil <10%							Castro 2011	-0.28	0.3163	25	27	100.0%	-0.28 [-0.90, 0.34]	Subtotal (95% CI)			25	27	100.0%	-0.28 [-0.90, 0.34]	Heterogeneity: Not applicable							Test for overall effect: Z = 0.89 (P = 0.38)							8.1.2 Baseline sputum eosinophils ≥10%							Castro 2011	-0.42	0.25	28	25	100.0%	-0.42 [-0.91, 0.07]	Subtotal (95% CI)			28	25	100.0%	-0.42 [-0.91, 0.07]	Heterogeneity: Not applicable							Test for overall effect: Z = 1.68 (P = 0.09)							⊕○○○ VERY LOW ^{a,b}	There are no significant improvements in asthma control assessed by the ACQ-7 with reslizumab compared to placebo in patients with baseline sputum eosinophils <10% or ≥10%. There are no statistically significant differences between subgroups.
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BD: bronchodilator; CI: Confidence interval; FEV1: forced expiratory volume in 1 second; MCID: minimal clinically important difference; MD: Mean difference; RCT: randomised controlled trial

Outcome No of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
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GRADE Working Group grades of evidence

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Explanations

- Potential risk of bias associated with selective outcome reporting bias (post hoc subgroup analysis).
- For both subgroups the ends of the 95% confidence interval include appreciable clinical benefit (MCID 0.5) and no benefit and could lead to opposite clinical decisions. Results from single study with only 105 patients.
- For both subgroups the ends of the 95% confidence interval include appreciable clinical benefit (MCID 0.23 L) and no benefit and could lead to opposite clinical decisions. Results from single study with only 103 patients.

References

- Castro M, Mathur S, Hargreave F, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med* 2011; 184: 1125-1132.
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Should the level of eosinophils (in blood or sputum) be used to guide the initiation of a monoclonal anti-IL5 strategy in adults and children with severe asthma?

<p>POPULATION: Adults and children with severe asthma</p> <p>INTERVENTION: Use of Eosinophil level in blood or sputum identify patients for therapy with an anti-interleukin 5 strategy (monoclonal antibodies directed against the interleukin 5 or its receptor)</p> <p>COMPARISON: Treatment of all with anti-interleukin 5 strategy (monoclonal antibodies directed against the interleukin 5 or its receptor)</p> <p>MAIN OUTCOMES:</p> <ul style="list-style-type: none"> Respiratory symptoms Lung function Exacerbation rate Adverse events Serious adverse events 	<p>BACKGROUND: Patients with severe asthma are characterized by uncontrolled symptoms and signs despite treatment with high dose steroids and bronchodilators, or require these therapies to maintain control. IL-5 is the main cytokine involved in the activation of eosinophils which are a classic feature of atopic severe asthma. Monoclonal antibodies have been developed that bind the IL-5 cytokine or receptor. The three drugs in this category: mepolizumab, reslizumab and benralizumab have been shown to be efficacious in randomized controlled trials at improving outcomes. However, patients exposed to this therapy have variable therapeutic response to this class of drugs which may reflect differences in their underlying biology. This systematic review and meta-analysis investigates whether specific levels of eosinophilia in blood or sputum can be used as a biomarker to predict therapeutic response to monoclonal anti-IL5 therapies.</p>
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Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	<p>How substantial are the desirable anticipated effects?</p> <ul style="list-style-type: none"> ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know 	<p>Results from research evidence (studies)</p> <p>There were 13 RCT studies (PMID: 27056586; 27609408; 25306557; 25736990; 28395936; 27018175; 27609406; 28530840; 27177493; 27097165; 21852542) that performed either pre-specified or post hoc subgroup analyses evaluating different treatment responses based on baseline sputum or blood eosinophil levels. The results across anti-IL 5 medications and well as biomarker level and type varies substantially for outcomes.</p> <p>An important outcome for patients includes rate of exacerbation. Blood eosinophils were the most typically measured biomarker and was available for all the medications.</p> <p>In one study (PMID: 27177493), baseline serum eosinophils of $\geq 500/\mu\text{L}$ were associated with a significantly greater response to therapy for mepolizumab only. For this outcome, there was a 73% reduction in exacerbations amongst those with a blood eosinophil level of $\geq 500/\mu\text{L}$ compared to 36-39% non-statistically significant reduction in subgroups with eosinophil levels of 150 to <300 cells/μL and 300 to <500 cells/μL, respectively. Notably mepolizumab reduced exacerbation rates in all the subgroups defined by different baseline eosinophil thresholds (≥ 150, ≥ 300, ≥ 400 and ≥ 500 cells/μL).</p> <p>Blood eosinophil levels of greater than $300/\mu\text{L}$ were associated with improvement in quality of life after treatment with benralizumab but there was no significant difference between subgroups (PMID: 27609408; 25306557; 27609406).</p> <p>Sputum eosinophil level was only considered in one study of reslizumab. Sputum levels were categorized as $>$ or $\geq 10\%$. There were no differences found between groups.</p> <p>Higher blood sputum levels were associated with a greater improvement in asthma control; however the differences between levels were not significant.</p> <p>As per PICO1, all subjects at eosinophil levels $\geq 150/\mu\text{L}$ experienced a significant reduction in exacerbations.</p> <p>Notably, studies of iv mepolizumab were excluded since only subcutaneous mepolizumab have been approved by the FDA/EMA.</p>	<p>Panel considerations</p> <p>One single-blind, placebo controlled sequential trial (PMID: 28915080) assessed treatment response of weight-adjusted IV reslizumab in patients previously treated with 100-mg SC mepolizumab.</p> <p>They reported that persistently high levels of eosinophils (blood eos $>300/\mu\text{L}$ and sputum eos $>3\%$) after treatment with mepolizumab characterized non-responders. Treatment of this group with reslizumab lead to improvements in their symptoms and eosinophil levels.</p>

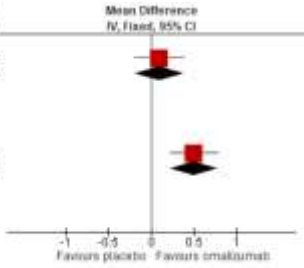
UNDESIRABLE EFFECTS	<p>How substantial are the undesirable anticipated effects?</p> <ul style="list-style-type: none"> ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know 	<p>There were 5 papers reporting results of six RCTs (PMID: 27609406, 27609408, 27056586, 25736990, 27018175) that assessed adverse events. There was no data in mepolizumab. The data suggested that overall there was no difference in adverse events amongst those with higher vs lower eosinophil counts for benralizumab. For Reslizumab, the fewest adverse events occurred in the group who had no data on eosinophil count. There was a slight reduction in the number of adverse events amongst those with an eosinophil count of $\geq 400/\mu\text{L}$ but it was 8% lower (95% CI: 3, 13%).</p>	<p>There was a high incidence of adverse events in both the active-drug (benralizumab and reslizumab) and placebo groups. The apparent benefit from the active-drugs might be explained by a reduction of asthma-related adverse events with the active drugs.</p>
CERTAINTY OF EVIDENCE	<p>What is the overall certainty of the evidence of effects?</p> <ul style="list-style-type: none"> ● Very low ○ Low ○ Moderate ○ High ○ No included studies 	<p>The level of evidence is very low.</p> <p>The evidence is based on pre-specified or post-hoc subgroup analyses of RCTs that tested whether baseline eosinophil levels were predictive of the therapeutic response to an anti-IL5 strategy. Therefore, there is a potential bias of selective outcome reporting bias. For studies of benralizumab, moderate and severe asthmatics were selected.</p>	
VALUES	<p>Is there important uncertainty about or variability in how much people value the main outcomes?</p> <ul style="list-style-type: none"> ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes 		<p>There is no uncertainty in how patients and clinicians value asthma exacerbations. However, there is some uncertainty the impact of measurement of eosinophil level at baseline in predicting outcomes. The data suggests that patients with severe asthma benefit from an anti-IL5 strategy and those with higher levels $>300\text{-}500/\mu\text{L}$ derive greater benefit than those with a level of $<150/\mu\text{L}$.</p> <p>Different patients may value the benefits / harms of the intervention differently (for instance more value to avoid harms compared to anticipated benefits).</p>

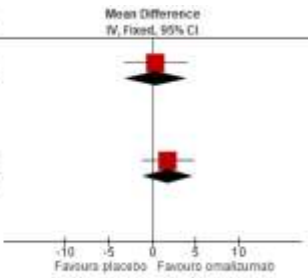
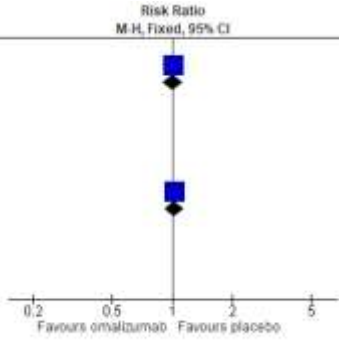
BALANCE OF EFFECTS	<p>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</p> <ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ Don't know 	<p>Most of the data presented suggests that patients with severe asthma benefit from an anti-IL5 strategy. Furthermore, there is some evidence that further benefit may be derived in patients with higher levels of baseline blood eosinophilia > 300 – 500/uL compared to those with an eosinophil level <150/uL.</p> <p>Only mepolizumab showed a significant reduction in asthma exacerbation amongst patients with an eosinophil level of ≥500/uL compared to other levels > 150/uL. However, even subjects with a eosinophil levels between 150 and 300/uL benefited from therapy compared to placebo.</p>	
COST EFFECTIVENESS	<p>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</p> <ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies 	No research evidence available.	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	<p>What is the certainty of the evidence of resource requirements (costs)?</p> <ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate ○ High ● No included studies 	No research evidence available on the cost of the intervention (studying eosinophil level).	Cost and feasibility differ based on the biomarker. Blood eosinophil levels are easily ascertained in most blood laboratories; sputum eosinophils are primarily available only in specialized centers.
EQUITY	<p>What would be the impact on health equity?</p> <ul style="list-style-type: none"> ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased 	No research evidence available.	<p>Consider:</p> <p>Blood eosinophils are very variable and can fluctuate dramatically with oral steroid treatment. In areas, where oral steroid therapy is more common than the use of</p>

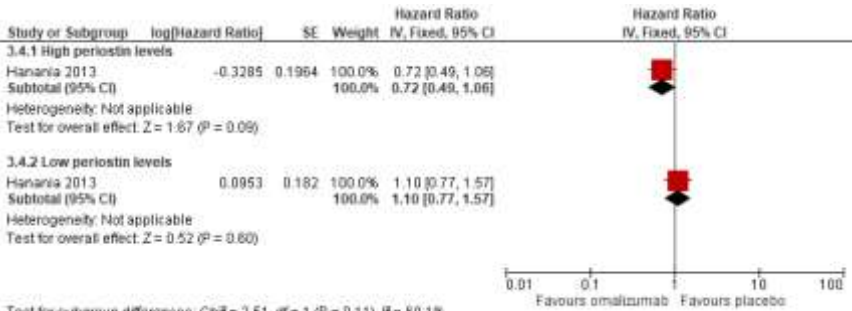
	<ul style="list-style-type: none"> ○ Increased ○ Varies ● Don't know 		<p>combination inhalers, blood eosinophils may be lower.</p> <p>Are there groups or settings that might be disadvantaged in relation to the problem or options that are considered?</p> <p>Are there plausible reasons for anticipating differences in the relative effectiveness of the option for disadvantaged groups or settings?</p> <p>Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the option or the importance of the problem for disadvantaged groups or settings?</p> <p>Are there important considerations that should be made when implementing the intervention (option) in order to ensure that inequities are reduced, if possible, and that they are not increased?</p>
ACCEPTABILITY	<p>Is the intervention acceptable to key stakeholders?</p> <ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know 	No research evidence available.	<p>There are no data on the acceptability of baseline eosinophil measurement. More data is required to determine whether the use of biomarkers such as eosinophil level to determine therapeutic response would be useful and acceptable.</p> <p>However, as noted above, blood measurement of eosinophils is more easily accessible in standard clinical laboratories than sputum eosinophil measurement.</p>
FEASIBILITY	<p>Is the intervention feasible to implement?</p> <ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know 	No research evidence available.	<p>Patients may find that some practicalities limit the use / make less feasible the use of the recommended intervention for example the use of sputum eosinophils as it requires a specialized center.</p> <p>It is feasible to implement baseline blood measurement in most settings.</p>

Should a measurement of a specific biomarker be used, in addition to total IgE level, to guide initiation of treatment with a monoclonal anti-IgE antibody in adults and children with severe asthma? (biomarkers being exhaled NO, peripheral or sputum eosinophils, and serum periostin)

GRADE Evidence Profile: OMALIZUMAB - PERIOSTIN

Certainty assessment							№ of patients		Effect		Certainty	Importance																																																		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	omalizumab	placebo	Relative (95% CI)	Absolute (95% CI)																																																				
Reduction in exacerbation rates per patient Follow up: 48 weeks (higher percentage, better reduction)																																																														
1 (534 participants) ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	Relative reduction in exacerbation rate of omalizumab compared to placebo were: Periostin (≥50 ng/ml): 30% (95% CI: -2 to 51); p-value= 0.07 Periostin (<50 ng/ml): 3% (95% CI: -43 to 32); p-value= 0.94 Number of patients: 534; test for subgroup differences: no available				⊕⊕○○ LOW																																																			
Change from baseline at week 48 in AQLQ Follow up: 48 weeks 7-point scale (7 = not impaired at all - 1 = severely impaired; higher values, better QoL)																																																														
1 (534 participants) ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	<p>Mean change from baseline to week 48 of omalizumab compared to placebo were: Periostin (≥50 ng/ml): Least square mean difference= 0.10 (95% CI: -0.19 to 0.40); p-value= 0.51 Periostin(<50 ng/ml): Least square mean difference= 0.50 (95% CI: 0.22 to 0.77); p-value= 0.0005 Number of patients: 534; test for subgroup differences: P=0.05 ^c</p> <table><thead><tr><th>Study or Subgroup</th><th>Mean Difference</th><th>SE</th><th>Weight</th><th>Mean Difference IV, Fixed, 95% CI</th></tr></thead><tbody><tr><td colspan="5">3.1.1 High periostin levels</td></tr><tr><td>Hanania 2013</td><td>0.1</td><td>0.148</td><td>100.0%</td><td>0.10 [-0.19, 0.39]</td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>100.0%</td><td>0.10 [-0.19, 0.39]</td></tr><tr><td colspan="5">Heterogeneity: Not applicable Test for overall effect: Z = 0.68 (P = 0.50)</td></tr><tr><td colspan="5">3.1.2 Low periostin levels</td></tr><tr><td>Hanania 2013</td><td>0.5</td><td>0.1428</td><td>100.0%</td><td>0.50 [0.22, 0.78]</td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>100.0%</td><td>0.50 [0.22, 0.78]</td></tr><tr><td colspan="5">Heterogeneity: Not applicable Test for overall effect: Z = 3.50 (P = 0.0005)</td></tr><tr><td colspan="5">Test for subgroup differences: Chi² = 3.78, df = 1 (P = 0.05), I² = 73.5%</td></tr></tbody></table> 				Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI	3.1.1 High periostin levels					Hanania 2013	0.1	0.148	100.0%	0.10 [-0.19, 0.39]	Subtotal (95% CI)			100.0%	0.10 [-0.19, 0.39]	Heterogeneity: Not applicable Test for overall effect: Z = 0.68 (P = 0.50)					3.1.2 Low periostin levels					Hanania 2013	0.5	0.1428	100.0%	0.50 [0.22, 0.78]	Subtotal (95% CI)			100.0%	0.50 [0.22, 0.78]	Heterogeneity: Not applicable Test for overall effect: Z = 3.50 (P = 0.0005)					Test for subgroup differences: Chi² = 3.78, df = 1 (P = 0.05), I² = 73.5%					⊕⊕○○ LOW	
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1 (534 participants) ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	<p>Mean change from baseline to week 48 of omalizumab compared to placebo were: Periostin (≥50 ng/ml): Least square mean difference= 0.42 (95% CI: -3.22 to 4.06); p-value= 0.82 Periostin (<50 ng/ml): Least square mean difference= 1.79 (95% CI: -1.15 to 4.73); p-value= 0.23 Number of patients: 534; test for subgroup differences: P=0.57 ^c</p> <table><thead><tr><th>Study or Subgroup</th><th>Mean Difference</th><th>SE</th><th>Weight</th><th>N, Fixed, 95% CI</th><th>Mean Difference IV, Fixed, 95% CI</th></tr></thead><tbody><tr><td colspan="6">3.2.1 High periostin levels</td></tr><tr><td>Hanania 2013</td><td>0.42</td><td>1.8572</td><td>100.0%</td><td>0.42 [-3.22, 4.06]</td><td></td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>100.0%</td><td>0.42 [-3.22, 4.06]</td><td></td></tr><tr><td colspan="6">Heterogeneity: Not applicable</td></tr><tr><td colspan="6">Test for overall effect: Z = 0.23 (P = 0.82)</td></tr><tr><td colspan="6">3.2.2 Low periostin levels</td></tr><tr><td>Hanania 2013</td><td>1.79</td><td>1.5</td><td>100.0%</td><td>1.79 [-1.15, 4.73]</td><td></td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>100.0%</td><td>1.79 [-1.15, 4.73]</td><td></td></tr><tr><td colspan="6">Heterogeneity: Not applicable</td></tr><tr><td colspan="6">Test for overall effect: Z = 1.19 (P = 0.23)</td></tr><tr><td colspan="6">Test for subgroup differences: Chi² = 0.33, df = 1 (P = 0.57), I² = 0%</td></tr></tbody></table> 				Study or Subgroup	Mean Difference	SE	Weight	N, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	3.2.1 High periostin levels						Hanania 2013	0.42	1.8572	100.0%	0.42 [-3.22, 4.06]		Subtotal (95% CI)			100.0%	0.42 [-3.22, 4.06]		Heterogeneity: Not applicable						Test for overall effect: Z = 0.23 (P = 0.82)						3.2.2 Low periostin levels						Hanania 2013	1.79	1.5	100.0%	1.79 [-1.15, 4.73]		Subtotal (95% CI)			100.0%	1.79 [-1.15, 4.73]		Heterogeneity: Not applicable						Test for overall effect: Z = 1.19 (P = 0.23)						Test for subgroup differences: Chi² = 0.33, df = 1 (P = 0.57), I² = 0%						⊕⊕○○ LOW																																									
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1 (534 participants) ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	<p>Percentage of patients with treatment-related adverse events of omalizumab compared to placebo were: Periostin (≥50 ng/ml): 82% versus 81%; RR= 1.01 (95% CI= 0.90 to 1.14) Periostin (<50 ng/ml): 84% versus 82%; RR= 1.03 (95% CI= 0.92 to 1.14) Number of patients: 534; test for subgroup differences: P=0.87</p> <table><thead><tr><th>Study or Subgroup</th><th>Experimental Events</th><th>Experimental Total</th><th>Control Events</th><th>Control Total</th><th>Weight</th><th>Risk Ratio M-H, Fixed, 95% CI</th><th>Risk Ratio M-H, Fixed, 95% CI</th></tr></thead><tbody><tr><td colspan="8">3.3.1 High periostin levels</td></tr><tr><td>Hanania 2013</td><td>105</td><td>128</td><td>103</td><td>127</td><td>100.0%</td><td>1.01 [0.90, 1.14]</td><td></td></tr><tr><td>Subtotal (95% CI)</td><td></td><td>128</td><td></td><td>127</td><td>100.0%</td><td>1.01 [0.90, 1.14]</td><td></td></tr><tr><td colspan="8">Total events: 105 103</td></tr><tr><td colspan="8">Heterogeneity: Not applicable</td></tr><tr><td colspan="8">Test for overall effect: Z = 0.19 (P = 0.85)</td></tr><tr><td colspan="8">3.3.2 Low periostin levels</td></tr><tr><td>Hanania 2013</td><td>119</td><td>142</td><td>112</td><td>137</td><td>100.0%</td><td>1.03 [0.92, 1.14]</td><td></td></tr><tr><td>Subtotal (95% CI)</td><td></td><td>142</td><td></td><td>137</td><td>100.0%</td><td>1.03 [0.92, 1.14]</td><td></td></tr><tr><td colspan="8">Total events: 119 112</td></tr><tr><td colspan="8">Heterogeneity: Not applicable</td></tr><tr><td colspan="8">Test for overall effect: Z = 0.45 (P = 0.65)</td></tr><tr><td colspan="8">Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%</td></tr></tbody></table> 				Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	3.3.1 High periostin levels								Hanania 2013	105	128	103	127	100.0%	1.01 [0.90, 1.14]		Subtotal (95% CI)		128		127	100.0%	1.01 [0.90, 1.14]		Total events: 105 103								Heterogeneity: Not applicable								Test for overall effect: Z = 0.19 (P = 0.85)								3.3.2 Low periostin levels								Hanania 2013	119	142	112	137	100.0%	1.03 [0.92, 1.14]		Subtotal (95% CI)		142		137	100.0%	1.03 [0.92, 1.14]		Total events: 119 112								Heterogeneity: Not applicable								Test for overall effect: Z = 0.45 (P = 0.65)								Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%								⊕⊕○○ LOW	
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Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	omalizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
1 (534 participants) ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	Time to first asthma exacerbation of omalizumab compared to placebo were: Periostin (≥50 ng/ml): HR= 0.72 (95% CI= 0.49 to 1.1) Periostin(<50 ng/ml): HR= 1.1 (95% CI= 0.77 to 1.6) Number of patients: 534; test for subgroup differences: P=0.11				⊕⊕○○ LOW	

CI: Confidence interval

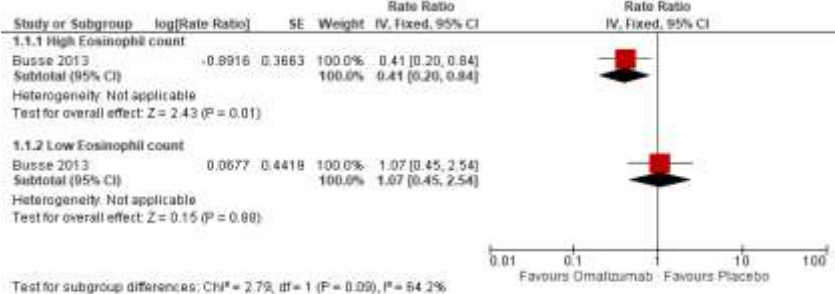


Explanations

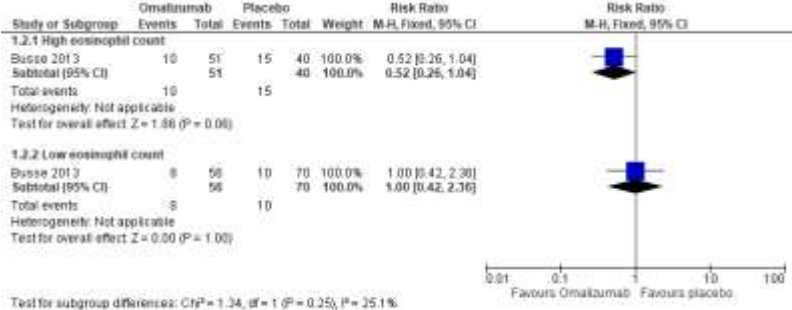
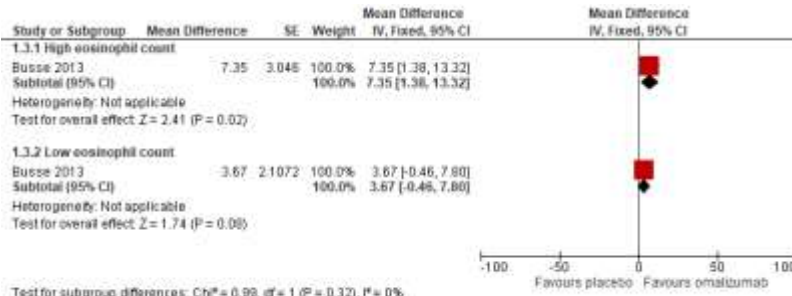
- a. Risk of bias due to a considerable number of patients was not evaluated at baseline for biomarker levels
- b. Optimal information size not reached for the main objective (and then for the subgroup analysis), reported by authors
- c. P values about Test for subgroup differences were estimated in RevMan and assuming that LSM is similar to Mean differences (just for descriptive purposes)

References

1. Hanania NA¹, Wenzel S, Rosén K, Hsieh HJ, Mosesova S, Choy DF, Lal P, Arron JR, Harris JM, Busse W. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med; 2013.

GRADE Evidence Profile: OMALIZUMAB - EOSINOPHIL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Omalizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Exacerbation rates per patient Follow up: 24 weeks (lower rates, better reduction)												
1 (217 participants) 1	randomised trials	serious ^a	not serious	not serious	serious ^b	none	<p>Exacerbation rate of omalizumab compared to placebo were: Eosinophil (≥300/uL): 0.25 vs 0.59, Rate ratio 0.41 (95%CI 0.20 to 0.82) Eosinophil (<300/uL): 0.17 vs 0.16, Rate ratio 1.07 (95%CI 0.45 to 2.53) Number of patients: 217; test for subgroup differences, p=0.09</p> 				 LOW	
Reduction in exacerbation rates per patient Follow up: 48 weeks (higher percentage, better reduction)												
1 (797 participants) 2	randomised trials	serious ^{a,c}	not serious	not serious	serious ^b	none	<p>Relative reduction in exacerbation rate of omalizumab compared to placebo were: Eosinophil (≥260/uL): 32% (95% CI: 11 to 48); p-value= 0.005 Eosinophil (<260/uL): 9% (95% CI: -24 to 34); p-value= 0.54 Number of patients: 797; test for subgroup differences: no available</p>				 LOW	
At least one exacerbation Follow up: 24 weeks (lower rates, better outcome)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Omalizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
1 (217 participants) ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	<p>Exacerbation rate of omalizumab compared to placebo were: Eosinophil (≥300/uL): Risk ratio 0.52 (95%CI 0.26 to 1.04) Eosinophil (<300/uL): Risk ratio 1.00 (95%CI 0.42 to 2.36) Number of patients: 217; test for subgroup differences, p=0.25</p>  <p>Test for subgroup differences: Chi² = 1.34, df = 1 (P = 0.25), I² = 25.1%</p>				⊕⊕○○ LOW	
Relative change from baseline to week 24 in % predicted FEV1 (higher change, better outcome) Follow up: 24 weeks												
1 (217 participants) ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	<p>Relative change in % predicted FEV1 when omalizumab is compared to placebo were: Eosinophil (≥300/uL): Least squares mean treatment (ANOVA): 7.35% (95% CI: 1.38 to 13.31) Eosinophil (<300/uL): Least squares mean treatment (ANOVA): 3.67% (95% CI: -0.46 to 7.81) Number of patients: 217; test for subgroup differences: P= 0.32^d</p>  <p>Test for subgroup differences: Chi² = 0.99, df = 1 (P = 0.32), I² = 0%</p>				⊕⊕○○ LOW	
Change from baseline in Asthma Quality of Life Questionnaire (AQLQ) Follow up: 48 weeks 7-point scale (7 = not impaired at all - 1 = severely impaired; higher values, better QoL)												

Certainty assessment							No of patients		Effect		Certainty	Importance																																																							
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Omalizumab	placebo	Relative (95% CI)	Absolute (95% CI)																																																									
1 (797 participants) ²	randomised trials	serious ^{a,c}	not serious	not serious	serious ^b	none	<p>Mean change from baseline to week 48 of omalizumab compared to placebo were: Eosinophil (≥260/uL): Least square mean difference= 0.14 (95% CI: -0.11 to 0.36); p-value= 0.29 Eosinophil (<260/uL): Least square mean difference= 0.26 (95% CI: 0.06 to 0.51); p-value= 0.01 Number of patients: 797; test for subgroup differences: P= 0.46^d</p> <table><thead><tr><th>Study or Subgroup</th><th>Mean Difference</th><th>SE</th><th>Weight</th><th>Mean Difference IV, Fixed, 95% CI</th></tr></thead><tbody><tr><td colspan="5">1.4.1 High eosinophil count</td></tr><tr><td>Hanania 2013</td><td>0.14</td><td>0.1276</td><td>100.0%</td><td>0.14 [-0.11, 0.39]</td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>100.0%</td><td>0.14 [-0.11, 0.39]</td></tr><tr><td colspan="5">Heterogeneity: Not applicable</td></tr><tr><td colspan="5">Test for overall effect: Z = 1.10 (P = 0.27)</td></tr><tr><td colspan="5">1.4.2 Low eosinophil count</td></tr><tr><td>Hanania 2013</td><td>0.26</td><td>0.102</td><td>100.0%</td><td>0.26 [0.06, 0.46]</td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>100.0%</td><td>0.26 [0.06, 0.46]</td></tr><tr><td colspan="5">Heterogeneity: Not applicable</td></tr><tr><td colspan="5">Test for overall effect: Z = 2.55 (P = 0.01)</td></tr></tbody></table> <p>Test for subgroup differences: Chi² = 0.54, df = 1 (P = 0.46), I² = 0%</p>				Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI	1.4.1 High eosinophil count					Hanania 2013	0.14	0.1276	100.0%	0.14 [-0.11, 0.39]	Subtotal (95% CI)			100.0%	0.14 [-0.11, 0.39]	Heterogeneity: Not applicable					Test for overall effect: Z = 1.10 (P = 0.27)					1.4.2 Low eosinophil count					Hanania 2013	0.26	0.102	100.0%	0.26 [0.06, 0.46]	Subtotal (95% CI)			100.0%	0.26 [0.06, 0.46]	Heterogeneity: Not applicable					Test for overall effect: Z = 2.55 (P = 0.01)					<p>⊕⊕○○</p> <p>LOW</p>	
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1 (797 participants) ²	randomised trials	serious ^{a,c}	not serious	not serious	serious	none	<p>Mean change from baseline to week 48 of omalizumab compared to placebo were: Eosinophil (≥260/uL): Least square mean difference= 1.3 (95% CI: -1.23 to 3.84); p-value= 0.31 Eosinophil (<260/uL): Least square mean difference= 1.72 (95% CI: -1.06 to 4.51); p-value= 0.02 Number of patients: 797; test for subgroup differences: P=0.83^d</p> <table><thead><tr><th>Study or Subgroup</th><th>Mean Difference</th><th>SE</th><th>Weight</th><th>Mean Difference IV, Fixed, 95% CI</th></tr></thead><tbody><tr><td colspan="5">1.5.1 High eosinophil count</td></tr><tr><td>Hanania 2013</td><td>1.3</td><td>1.2908</td><td>100.0%</td><td>1.30 [-1.23, 3.83]</td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>100.0%</td><td>1.30 [-1.23, 3.83]</td></tr><tr><td colspan="5">Heterogeneity: Not applicable</td></tr><tr><td colspan="5">Test for overall effect: Z = 1.01 (P = 0.31)</td></tr><tr><td colspan="5">1.5.2 Low eosinophil count</td></tr><tr><td>Hanania 2013</td><td>1.72</td><td>1.4184</td><td>100.0%</td><td>1.72 [-1.06, 4.50]</td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>100.0%</td><td>1.72 [-1.06, 4.50]</td></tr><tr><td colspan="5">Heterogeneity: Not applicable</td></tr><tr><td colspan="5">Test for overall effect: Z = 1.21 (P = 0.23)</td></tr></tbody></table> <p>Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.83), I² = 0%</p>				Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI	1.5.1 High eosinophil count					Hanania 2013	1.3	1.2908	100.0%	1.30 [-1.23, 3.83]	Subtotal (95% CI)			100.0%	1.30 [-1.23, 3.83]	Heterogeneity: Not applicable					Test for overall effect: Z = 1.01 (P = 0.31)					1.5.2 Low eosinophil count					Hanania 2013	1.72	1.4184	100.0%	1.72 [-1.06, 4.50]	Subtotal (95% CI)			100.0%	1.72 [-1.06, 4.50]	Heterogeneity: Not applicable					Test for overall effect: Z = 1.21 (P = 0.23)					<p>⊕⊕○○</p> <p>LOW</p>	
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1 (797 participants) ^{2a}	randomised trials	serious ^{a,c}	not serious	not serious	serious ^b	none	<p>Percentage of patients with treatment-related adverse events of omalizumab compared to placebo were: Eosinophil (≥260/uL): 80% versus 79.4%; RR= 1.01 (95% CI= 0.91 to 1.11) Eosinophil (<260/uL): 80.6% versus 81.7%; RR= 0.99 (95% CI= 0.90 to 1.09) Number of patients: 797; test for subgroup differences: P =0.77</p> <table><thead><tr><th>Study or Subgroup</th><th>Omalizumab Events</th><th>Omalizumab Total</th><th>Placebo Events</th><th>Placebo Total</th><th>Weight</th><th>Risk Ratio M-H, Fixed, 95% CI</th></tr></thead><tbody><tr><td colspan="7">1.6.1 High eosinophil count</td></tr><tr><td>Hanania 2013</td><td>172</td><td>215</td><td>158</td><td>199</td><td>100.0%</td><td>1.01 [0.91, 1.11]</td></tr><tr><td>Subtotal (95% CI)</td><td></td><td>215</td><td></td><td>199</td><td>100.0%</td><td>1.01 [0.91, 1.11]</td></tr><tr><td>Total events</td><td>172</td><td></td><td>158</td><td></td><td></td><td></td></tr><tr><td colspan="7">Heterogeneity: Not applicable</td></tr><tr><td colspan="7">Test for overall effect: Z = 0.15 (P = 0.88)</td></tr><tr><td colspan="7">1.6.2 Low eosinophil count</td></tr><tr><td>Hanania 2013</td><td>150</td><td>186</td><td>181</td><td>197</td><td>100.0%</td><td>0.99 [0.90, 1.09]</td></tr><tr><td>Subtotal (95% CI)</td><td></td><td>186</td><td></td><td>197</td><td>100.0%</td><td>0.99 [0.90, 1.09]</td></tr><tr><td>Total events</td><td>150</td><td></td><td>181</td><td></td><td></td><td></td></tr><tr><td colspan="7">Heterogeneity: Not applicable</td></tr><tr><td colspan="7">Test for overall effect: Z = 0.27 (P = 0.79)</td></tr><tr><td colspan="7">Test for subgroup differences: ChiP = 0.09, df= 1 (P = 0.77), I² = 0%</td></tr></tbody></table>				Study or Subgroup	Omalizumab Events	Omalizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI	1.6.1 High eosinophil count							Hanania 2013	172	215	158	199	100.0%	1.01 [0.91, 1.11]	Subtotal (95% CI)		215		199	100.0%	1.01 [0.91, 1.11]	Total events	172		158				Heterogeneity: Not applicable							Test for overall effect: Z = 0.15 (P = 0.88)							1.6.2 Low eosinophil count							Hanania 2013	150	186	181	197	100.0%	0.99 [0.90, 1.09]	Subtotal (95% CI)		186		197	100.0%	0.99 [0.90, 1.09]	Total events	150		181				Heterogeneity: Not applicable							Test for overall effect: Z = 0.27 (P = 0.79)							Test for subgroup differences: ChiP = 0.09, df= 1 (P = 0.77), I ² = 0%							⊕⊕○○ LOW	
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1 (797 participants) ²	randomised trials	serious ^{a,c}	not serious	not serious	serious ^b	none	<p>Time to first asthma exacerbation of omalizumab compared to placebo were: Eosinophil (≥260/uL): HR= 0.64 (95% CI= 0.48 to 0.86) Eosinophil (<260/uL): HR= 0.95 (95% CI= 0.68 to 1.3) Number of patients: 797; test for subgroup differences: P=0.08</p> <table><thead><tr><th>Study or Subgroup</th><th>log[Hazard Ratio]</th><th>SE</th><th>Weight</th><th>Hazard Ratio IV, Fixed, 95% CI</th></tr></thead><tbody><tr><td colspan="5">1.7.1 High eosinophil count</td></tr><tr><td>Hanania 2013</td><td>-0.4463</td><td>0.1468</td><td>100.0%</td><td>0.64 [0.48, 0.85]</td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>100.0%</td><td>0.64 [0.48, 0.85]</td></tr><tr><td colspan="5">Heterogeneity: Not applicable</td></tr><tr><td colspan="5">Test for overall effect: Z = 3.04 (P = 0.002)</td></tr><tr><td colspan="5">1.7.2 Low eosinophil count</td></tr><tr><td>Hanania 2013</td><td>-0.0513</td><td>0.1706</td><td>100.0%</td><td>0.95 [0.68, 1.33]</td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>100.0%</td><td>0.95 [0.68, 1.33]</td></tr><tr><td colspan="5">Heterogeneity: Not applicable</td></tr><tr><td colspan="5">Test for overall effect: Z = 0.30 (P = 0.76)</td></tr><tr><td colspan="5">Test for subgroup differences: ChiP = 3.08, df= 1 (P = 0.08), I² = 67.5%</td></tr></tbody></table>				Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	1.7.1 High eosinophil count					Hanania 2013	-0.4463	0.1468	100.0%	0.64 [0.48, 0.85]	Subtotal (95% CI)			100.0%	0.64 [0.48, 0.85]	Heterogeneity: Not applicable					Test for overall effect: Z = 3.04 (P = 0.002)					1.7.2 Low eosinophil count					Hanania 2013	-0.0513	0.1706	100.0%	0.95 [0.68, 1.33]	Subtotal (95% CI)			100.0%	0.95 [0.68, 1.33]	Heterogeneity: Not applicable					Test for overall effect: Z = 0.30 (P = 0.76)					Test for subgroup differences: ChiP = 3.08, df= 1 (P = 0.08), I ² = 67.5%					⊕⊕○○ LOW																																							
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CI: Confidence interval

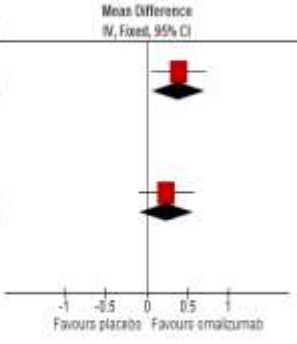
Explanations

- a. Risk of bias related to incomplete outcome data: eosinophil counts were not necessarily collected for all patients at baseline and may therefore have been missing at random depending on their availability in the original laboratory test records
- b. Optimal information size not reached for the main objective (and then for the subgroup analysis), reported by authors
- c. Potential risk of bias associated with selective reporting bias (subgroups analyses not stated in the protocol)
- d. P values about Test for subgroup differences were estimated in RevMan and assuming that LSM is similar to Mean differences (just for descriptive purposes)
- e. Only Hanania 2013 provided subgroup information for this outcome

References

1. Busse W, Spector S, Rosén K, Wang Y, Alpan O. High eosinophil count: a potential biomarker for assessing successful omalizumab treatment effects. *J Allergy Clin Immunol*; 2013.
2. Hanania NA¹, Wenzel S, Rosén K, Hsieh HJ, Mosesova S, Choy DF, Lal P, Arron JR, Harris JM, Busse W. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med*; 2013.

GRADE Evidence Profile: OMALIZUMAB – FeNO

Certainty assessment							№ of patients		Effect		Certainty	Importance																																																												
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	omalizumab	placebo	Relative (95% CI)	Absolute (95% CI)																																																														
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1 (394 participants) ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	Relative reduction in exacerbation rate of omalizumab compared to placebo were: FENO(≥19.5 ppb): 53% (95% CI: 37 to 70); p-value= 0.001 FENO(<19.5 ppb): 16% (95% CI: -32 to 46); p-value= 0.45 Number of patients: 394; test for subgroup differences: no available				⊕⊕○○ LOW																																																													
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1 (394 participants) ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	<div>Mean change from baseline to week 48 of omalizumab compared to placebo were: FENO (≥19.5 ppb): Least square mean difference= 0.39 (95% CI: 0.06 to 0.73); p-value= 0.02 FENO (<19.5 ppb): Least square mean difference= 0.24 (95% CI: -0.09 to 0.57); p-value= 0.16 Number of patients: 394; test for subgroup differences: P= 0.53 ^c</div> <table><thead><tr><th>Study or Subgroup</th><th>Mean Difference</th><th>SE</th><th>Weight</th><th>Mean Difference IV, Fixed, 95% CI</th><th>Mean Difference IV, Fixed, 95% CI</th></tr></thead><tbody><tr><td colspan="6">2.1.1 High FENO levels</td></tr><tr><td>Hanania 2013</td><td>0.39</td><td>0.1684</td><td>100.0%</td><td>0.39 [0.06, 0.72]</td><td></td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>100.0%</td><td>0.39 [0.06, 0.72]</td><td></td></tr><tr><td colspan="6">Heterogeneity: Not applicable Test for overall effect: Z = 2.32 (P = 0.02)</td></tr><tr><td colspan="6">2.1.2 Low FENO levels</td></tr><tr><td>Hanania 2013</td><td>0.24</td><td>0.1684</td><td>100.0%</td><td>0.24 [-0.09, 0.57]</td><td></td></tr><tr><td>Subtotal (95% CI)</td><td></td><td></td><td>100.0%</td><td>0.24 [-0.09, 0.57]</td><td></td></tr><tr><td colspan="6">Heterogeneity: Not applicable Test for overall effect: Z = 1.43 (P = 0.15)</td></tr><tr><td colspan="6">Test for subgroup differences: Chi²= 0.40, df= 1 (P = 0.53), I²= 0%</td></tr></tbody></table> <div></div>				Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	2.1.1 High FENO levels						Hanania 2013	0.39	0.1684	100.0%	0.39 [0.06, 0.72]		Subtotal (95% CI)			100.0%	0.39 [0.06, 0.72]		Heterogeneity: Not applicable Test for overall effect: Z = 2.32 (P = 0.02)						2.1.2 Low FENO levels						Hanania 2013	0.24	0.1684	100.0%	0.24 [-0.09, 0.57]		Subtotal (95% CI)			100.0%	0.24 [-0.09, 0.57]		Heterogeneity: Not applicable Test for overall effect: Z = 1.43 (P = 0.15)						Test for subgroup differences: Chi²= 0.40, df= 1 (P = 0.53), I²= 0%						⊕⊕○○ LOW	
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Heterogeneity: Not applicable Test for overall effect: Z = 1.43 (P = 0.15)																																																																								
Test for subgroup differences: Chi²= 0.40, df= 1 (P = 0.53), I²= 0%																																																																								

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	omalizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Change from baseline in % predicted FEV1 Follow up: 48 weeks (higher change, better outcome)												
1 (394 participants) ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	<p>Mean change from baseline to week 48 of omalizumab compared to placebo were: FENO (≥19.5 ppb): Least square mean difference= 3.26 (95% CI: -0.33 to 6.84); p-value= 0.08 FENO (<19.5 ppb): Least square mean difference= 1.97 (95% CI: -1.83 to 5.77); p-value= 0.31 Number of patients: 394; test for subgroup differences: P = 0.63 ^c</p> <p>Study or Subgroup Mean Difference SE Weight IV, Fixed, 95% CI</p> <p>2.2.1 High FENO levels</p> <p>Hanania 2013 3.26 1.8317 100.0% 3.26 [-0.33, 6.85]</p> <p>Subtotal (95% CI) 3.26 [-0.33, 6.85]</p> <p>Heterogeneity: Not applicable</p> <p>Test for overall effect: Z = 1.76 (P = 0.08)</p> <p>2.2.2 Low FENO levels</p> <p>Hanania 2013 1.97 1.9309 100.0% 1.97 [-1.83, 5.77]</p> <p>Subtotal (95% CI) 1.97 [-1.83, 5.77]</p> <p>Heterogeneity: Not applicable</p> <p>Test for overall effect: Z = 1.02 (P = 0.31)</p> <p>Test for subgroup differences: ChiP = 0.23, df = 1 (P = 0.63), I² = 0%</p>				⊕⊕○○ LOW	
Adverse events Follow up: 48 weeks (higher values, worst outcome)												
1 (394 participants) ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	<p>Percentage of patients with treatment-related adverse events of omalizumab compared to placebo were: FENO (≥19.5 ppb): 80.2% versus 73%; RR= 1.10 (95% CI= 0.94 to 1.28) FENO(<19.5 ppb): 83.5% versus 80%; RR= 1.04 (95% CI= 0.91 to 1.19) Number of patients: 394; test for subgroup differences: P=0.62</p> <p>Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI</p> <p>2.3.1 High FENO levels</p> <p>Hanania 2013 81 101 73 100 100.0% 1.10 [0.94, 1.28]</p> <p>Subtotal (95% CI) 81 101 73 100 100.0% 1.10 [0.94, 1.28]</p> <p>Total events: 81 73</p> <p>Heterogeneity: Not applicable</p> <p>Test for overall effect: Z = 1.36 (P = 0.17)</p> <p>2.3.2 Low FENO levels</p> <p>Hanania 2013 86 103 72 80 100.0% 1.04 [0.91, 1.19]</p> <p>Subtotal (95% CI) 86 103 72 80 100.0% 1.04 [0.91, 1.19]</p> <p>Total events: 86 72</p> <p>Heterogeneity: Not applicable</p> <p>Test for overall effect: Z = 0.82 (P = 0.42)</p> <p>Test for subgroup differences: ChiP = 0.24, df = 1 (P = 0.62), I² = 0%</p>				⊕⊕○○ LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	omalizumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Time to first asthma exacerbation Follow up: 48 weeks (lower values, better outcome)												
1 (394 participants) ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	Time to first asthma exacerbation of omalizumab compared to placebo were: FENO(≥19.5 ppb): HR= 0.38 (95% CI= 0.24 to 0.61) FENO(<19.5 ppb): HR= 1.0 (95% CI= 0.62 to 1.6) Number of patients: 394; test for subgroup differences: P=0.004				<div><div><div>⊕⊕○○</div><div>LOW</div></div></div>	
							<div><div><div><div><div>Study or Subgroup</div><div>log(Hazard Ratio)</div><div>SE</div><div>Weight</div><div>Hazard Ratio IV, Fixed, 95% CI</div></div><div><div>2.4.1 High FENO levels</div><div>Hamania 2013</div><div>Subtotal (95% CI)</div><div>Heterogeneity: Not applicable</div><div>Test for overall effect: Z = 4.13 (P = 0.0001)</div></div><div><div>2.4.2 Low FENO levels</div><div>Hamania 2013</div><div>Subtotal (95% CI)</div><div>Heterogeneity: Not applicable</div><div>Test for overall effect: Z = 0.00 (P = 1.00)</div></div></div><div><div>0.01</div><div>0.1</div><div>1</div><div>10</div><div>100</div></div><div><div>Favours omalizumab</div><div>Favours placebo</div></div></div></div>					

CI: Confidence interval

Explanations

- Risk of bias due to a considerable number of patients was not evaluated at baseline for biomarker levels
- Optimal information size not reached for the main objective (and then for the subgroup analysis), reported by authors
- P values about Test for subgroup differences were estimated in RevMan and assuming that LSM is similar to Mean differences (just for descriptive purposes)

References

- Hanania NA¹, Wenzel S, Rosén K, Hsieh HJ, Mosesova S, Choy DF, Lal P, Arron JR, Harris JM, Busse W. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med; 2013.

Evidence to Decision Framework: OMALIZUMAB – PERIOSTIN

Should measurement of Periostin be used to select patients for initiation of a monoclonal anti-IgE strategy in adults and children with severe asthma?			
POPULATION:	Adults and children (≥12 years) with severe asthma	BACKGROUND:	Until relatively recently treatment options for patients with severe asthma who were refractory to standard treatments have been limited. Over the last two decades there have been major advances in treatment options for patients with severe disease. In the early 2000s omalizumab, a monoclonal antibody therapy that targets and neutralises IgE entered the market. Since that time a number of other monoclonal antibody therapies targeting the T2 pathway have emerged. The treatments have proven efficacy in reducing exacerbations and oral corticosteroid requirements, and improving patient reported outcomes. With multiple treatment options now available it has become increasingly important to ensure that the right targeted treatment is delivered to the right patient with severe asthma. This approach allows for the delivery of personalised or precision medicine. It is now critical to understand the population in which targeted therapies are likely to have the greatest effect. Serum periostin does not appear useful in predicting reponse to anti-IgE treatment.
INTERVENTION:	Omalizumab compared to placebo in patients with severe asthma who have serum periostin levels ≥50 ng/ml		
COMPARISON:	Omalizumab in patients with severe asthma who have serum periostin levels <50 ng/ml		
MAIN OUTCOMES:	Exacerbation rates, time to first exacerbations, asthma related quality of life, FEV ₁ , adverse effects		

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	<p>How substantial are the desirable anticipated effects?</p> <ul style="list-style-type: none"> ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know 	<p>Results from research evidence (studies)</p> <p>No differences were detected in terms of relative reduction of exacerbation rates at 48 weeks or FEV1 when omalizumab was compared to placebo in periostin high (50 ng/ml or more) or low (less than 50 ng/ml) patients. There were however improvements in baseline AQLQ scores with omalizumab compared to placebo in patients with low (less than 50 mg/ml) periostin levels at 48 weeks follow-up (MD 0.50 [0.22,0.78]), whereas there are no differences patients with high (50 ng/ml and more) periostin levels (MD 0.10 [-0.19,0.39]).</p>	Panel considerations
UNDESIRABLE EFFECTS	<p>How substantial are the undesirable anticipated effects?</p> <ul style="list-style-type: none"> ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know 		
CERTAINTY OF EVIDENCE	<p>What is the overall certainty of the evidence of effects?</p> <ul style="list-style-type: none"> ○ Very low ● Low ○ Moderate ○ High ○ No included studies 	<p>The risk of bias was high for completeness of data, due to a considerable number of patients that were not evaluated at baseline for biomarker levels.</p>	
VALUES	<p>Is there important uncertainty about or variability in how much people value the main outcomes?</p> <ul style="list-style-type: none"> ● Important uncertainty or variability 	<p>The test -Serum Periostin: In a study which aimed to evaluate the patient perception of tests used for the assessment of asthma and COPD venipuncture had a reasonable assessment profile, it was rated as more painful than comparator tests eg. Questionnaires but was acceptable in terms of comfort, difficulty and time taken to do the test¹.</p>	

	<ul style="list-style-type: none"> ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes 	The intervention did not lead to improvements in some outcomes that are valued by consumers in the biomarker high group, although there were larger quality of life improvements in the biomarker low group.	
BALANCE OF EFFECTS	<p>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</p> <ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know 	<p>There were no differences in terms of % predicted FEV1 mean change at 48 weeks of follow-up, when omalizumab is compared to placebo in high (50 ng/ml or more) or low (less than 50 ng/ml) periostin levels at baseline.</p> <p>There were no difference in time to first asthma exacerbation with omalizumab compared to placebo in those patients with high (50 ng/ml or more) or low (less than 50 ng/ml) periostin levels at the same follow-up. In addition, there are no statistically significant differences between these subgroups</p> <p>There were no differences in the adverse effects in patients treated with omalizumab versus placebo irrespective of high or low periostin.</p> <p>There was a significant mean change of baseline AQLQ scores with omalizumab compared to placebo in those patients with low (less than 50 ng/ml) periostin levels at 48 weeks follow-up, whereas there were no differences in the same outcome for those patients with high (50 ng/ml and more) periostin levels at the same follow-up</p>	
COST EFFECTIVENESS	<p>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</p> <ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies 	No research evidence identified.	There would be an additional cost of using Periostin.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	<p>What is the certainty of the evidence of resource requirements (costs)?</p> <ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate ○ High ● No included studies 	No research evidence identified.	There would be an additional cost of using Periostin.
EQUITY	<p>What would be the impact on health equity?</p> <ul style="list-style-type: none"> ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ● Increased ○ Varies ○ Don't know 	No research evidence identified.	Periostin is currently not available and is not applicable in children
ACCEPTABILITY	<p>Is the intervention acceptable to key stakeholders?</p> <ul style="list-style-type: none"> ● No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know 	No research evidence identified.	<p>Periostin is currently only available for research and is not applicable to children.</p> <p>There is no evidence that periostin levels are useful in predicting exacerbation and lung function response to treatment.</p>
FEASIBILITY	<p>Is the intervention feasible to implement?</p> <ul style="list-style-type: none"> ● No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know 	No research evidence identified.	At present periostin is only available in research setting and is not applicable to children.

Reference

- McDonald VM, Simpson JL, McElduff P, Gibson PG. Older peoples' perception of tests used in the assessment and management of COPD and asthma. *Clin Respir J* 2013; **20**(10): 12017.

Evidence to Decision Framework: OMALIZUMAB – EOSINOPHILS

Should measurement of blood eosinophils be used to select patients for initiation of a monoclonal anti-IgE strategy in adults and children with severe asthma?

<p>POPULATION: Adults and children (≥12 years) with severe asthma</p> <p>INTERVENTION: Measurement of blood eosinophil counts and treatment with Omalizumab in patients with severe asthma who have ≥260/μl</p> <p>COMPARISON: Measurement of blood eosinophil counts and treatment with Omalizumab in patients with severe asthma who have <260/μl</p> <p>MAIN OUTCOMES: Exacerbation rates, time to first exacerbations, asthma related quality of life, FEV₁, adverse effects</p>	<p>BACKGROUND: Until relatively recently treatment options for patients with severe asthma who were refractory to standard treatments have been limited. Over the last two decades there have been major advances in treatment options for patients with severe disease. In the early 2000s omalizumab, a monoclonal antibody therapy that targets and neutralises IgE entered the market. Since that time a number of other monoclonal antibody therapies targeting the T2 pathway have emerged. The treatments have proven efficacy in reducing exacerbations and oral corticosteroid requirements, and improving patient reported outcomes. With multiple treatment options now available it has become increasingly important to ensure that the right targeted treatment is delivered to the right patient with severe asthma. This approach allows for the delivery of personalised or precision medicine. It is now critical to understand the population in which targeted therapies are likely to have the greatest effect. An elevation of peripheral blood eosinophils can be used as a biomarker to predict response to anti-IgE treatment and enable this personalised approach.</p>
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Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	<p>How substantial are the desirable anticipated effects?</p> <ul style="list-style-type: none"> ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know 	<p>Results from research evidence (studies)</p> <p>Included in the evidence synthesis were two randomised controlled trials. Pooling of the studies was not possible. In one study¹ using there were improvements in exacerbations rates (HR 0.41 [0.20, 0.84]) and a small but significantly greater change in FEV1 predicted at 24 weeks (MD 7.35 [1.38, 13.32]) with omalizumab compared to placebo in patients with a high eosinophil count ($\geq 300/\mu\text{L}$), whereas there were no differences in patients with low eosinophils ($< 300/\mu\text{L}$).</p> <p>In another RCT² there was a significantly longer time to first asthma exacerbation with omalizumab compared to placebo in patients with high (260/uL or more) eosinophil count at 48 weeks follow-up (HR 0.64 [0.48, 0.85]), whereas there were no differences in patients with low (less than 260/uL) eosinophil count (HR 0.95 [0.68, 1.33]). However, there were no statistically significant differences between these subgroups.</p> <p>There were no differences in terms of percentage of treatment-related adverse events at 48 weeks of follow-up, when omalizumab is compared to placebo in patients with high or low blood eosinophils.</p> <p>Undergoing a test for peripheral blood eosinophils involves venepuncture which may be more painful than not having a blood test, as such there may be small undesirable effects of the test.</p>	Panel considerations
UNDESIRABLE EFFECTS	<p>How substantial are the undesirable anticipated effects?</p> <ul style="list-style-type: none"> ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know 		
CERTAINTY OF EVIDENCE	<p>What is the overall certainty of the evidence of effects?</p> <ul style="list-style-type: none"> ○ Very low ● Low ○ Moderate ○ High ○ No included studies 	<p>The risk of bias was high for completeness of data, due to a considerable number of patients that were not evaluated at baseline for blood eosinophils.</p>	
VALUES	<p>Is there important uncertainty about or variability in how much people value the main outcomes?</p> <ul style="list-style-type: none"> ○ Important uncertainty or variability 	<p>The test - peripheral blood eosinophils: In a study which aimed to evaluate the patient perception of tests used for the assessment of asthma and COPD, venipuncture had a reasonable assessment profile, it was rated as more painful than the comparator tests eg. Questionnaires, but was acceptable in terms of comfort, difficulty and time taken to do</p>	

	<ul style="list-style-type: none"> ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes 	<p>the test³.</p> <p>The intervention led to improvements in outcomes that are highly valued by the consumer, as rated by the representatives on the Taskforce. In a study in severe asthma evaluating which outcomes matter to patients, reduced exacerbations and improved quality of life were viewed amongst their highest priorities (Clark V et. al, TSANZ 2019).</p>	
BALANCE OF EFFECTS	<p>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</p> <ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know 	<p>People in the high and low eosinophil groups both experienced adverse effects, with no differences according to their subgroups. People in the eosinophil high group received the clinical benefit without any increase in side effects, whereas the low eosinophil group experienced the same side effects without the clinical benefit.</p>	
COST EFFECTIVENESS	<p>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</p> <ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ No included studies 	<p>No research evidence identified.</p>	<p>The intervention (measurement of eosinophils in the blood) is a low cost intervention that is already routinely used in practice in this population.</p>
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	<p>What is the certainty of the evidence of resource requirements (costs)?</p> <ul style="list-style-type: none"> ○ Very low ○ Low ● Moderate ○ High ○ No included studies 	<p>No research evidence identified.</p>	<p>While no studies evaluated the evidence of resource requirements the certainty is high as blood eosinophil counts are a low cost test already used in most areas of medicine, as the biomarker is included in the full blood count.</p>

EQUITY	<p>What would be the impact on health equity?</p> <ul style="list-style-type: none"> ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know 	No research evidence identified.	The measurement of peripheral blood eosinophil counts is low cost and readily accessible, so all patients are likely to have the biomarker measured.
ACCEPTABILITY	<p>Is the intervention acceptable to key stakeholders?</p> <ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know 	No research evidence identified.	The test is already available as a standard medical assessment at a low cost, so the use of this biomarker should not disadvantage any minority groups.
FEASIBILITY	<p>Is the intervention feasible to implement?</p> <ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know 	No research evidence identified.	There are likely to be few limitations since this test is already freely available, low cost, already used in practice and generally acceptable to patients ³ .

Reference

1. Busse W, Spector S, Rosen K, Wang Y, Alpan O. High eosinophil count: a potential biomarker for assessing successful omalizumab treatment effects. *The Journal of allergy and clinical immunology* 2013; **132**(2): 485-6.e11.
2. Hanania NA, Wenzel S, Rosen K, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *American journal of respiratory and critical care medicine* 2013; **187**(8): 804-11.
3. McDonald VM, Simpson JL, McElduff P, Gibson PG. Older peoples' perception of tests used in the assessment and management of COPD and asthma. *Clin Respir J* 2013; **20**(10): 12017.

Evidence to Decision Framework: OMALIZUMAB – FeNO

Should measurement of exhaled NO be used to select patients for initiation of a monoclonal anti-IgE strategy in adults and children with severe asthma?

POPULATION:	Adults and children (≥12 years) with severe asthma	BACKGROUND:	Until relatively recently treatment options for patients with severe asthma who were refractory to standard treatments have been limited. Over the last two decades there have been major advances in treatment options for patients with severe disease. In the early 2000s omalizumab, a monoclonal antibody therapy that targets and neutralises IgE entered the market. Since that time a number of other monoclonal antibody therapies targeting the T2 pathway have emerged. The treatments have proven efficacy in reducing exacerbations and oral corticosteroid requirements, and improving patient reported outcomes. With multiple treatment options now available it has become increasingly important to ensure that the right targeted treatment is delivered to the right patient with severe asthma. This approach allows for the delivery of personalised or precision medicine. It is now critical to understand the population in which targeted therapies are likely to have the greatest effect. An elevation of FeNO ≥19.5 ppb can be used as a biomarker to predict response to anti-IgE treatment and enable this personalised approach.
INTERVENTION:	Omalizumab compared to placebo in FeNO high (≥19.5 ppb) patients with severe asthma		
COMPARISON:	Omalizumab compared to placebo in FeNO high (<19.5 ppb) patients with severe asthma		
MAIN OUTCOMES:	Exacerbation rates, time to first exacerbations, asthma related quality of life, FEV ₁ , adverse effects		

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	<p>How substantial are the desirable anticipated effects?</p> <ul style="list-style-type: none"> ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know 	<p>Results from research evidence (studies)</p> <p>Only one RCT was included in this evidence synthesis</p> <p>There was a significant relative reduction of exacerbation rates with omalizumab compared to placebo in patients with high (19.5 ppb or more) FENO level at 48 weeks follow-up (53% [95% CI 37-70]); p=0.001, whereas there were no differences for those patients with low (less than 19.5 ppb) FENO levels (16% [95% CI: -32 to 46]); p= 0.45. The time to first asthma exacerbation with omalizumab compared to placebo was significantly longer in patients with high (19.5 ppb or more) FENO level at 48 weeks follow-up (HR 0.38 [0.24, 0.60]), whereas there were no differences in patients with low (less than 19.5 ppb) FENO (HR 1.00 [0.62, 1.61]). There were also larger changes of mean AQLQ with omalizumab compared to placebo in FeNO high patients (19.5 ppb or more) at 48 weeks of follow-up (MD 0.39 [0.06, 0.72]), whereas there were no differences in FeNO low patients (less than 19.5 ppb) (MD 0.24 [-0.09, 0.57]).</p> <p>Only one RCT was included in this evidence synthesis</p>	
UNDESIRABLE EFFECTS	<p>How substantial are the undesirable anticipated effects?</p> <ul style="list-style-type: none"> ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know 		<p>There are no differences in terms of percentage of treatment-related adverse events at 48 weeks of follow-up, when omalizumab is compared to placebo in high or low FENO levels at baseline.</p>

CERTAINTY OF EVIDENCE	<p>What is the overall certainty of the evidence of effects?</p> <ul style="list-style-type: none"> ○ Very low ● Low ○ Moderate ○ High ○ No included studies 	<p>The risk of bias was high for completeness of data, due to a considerable number of patients that were not evaluated at baseline for their FeNO level.</p>	<p>Each analysis only included single RCTs of patients with severe asthma eligible for anti-IgE treatment.</p>
VALUES	<p>Is there important uncertainty about or variability in how much people value the main outcomes?</p> <ul style="list-style-type: none"> ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes 	<p>The test - FeNO: In a study which aimed to evaluate the patient perception of tests used for the assessment of asthma and COPD, FeNO had a good assessment profile, with a favourable assessment overall compared to completing questionnaires and only being associated with some difficulty in test performance¹.</p> <p>The intervention lead to improvements in outcomes that are highly valued by the consumer, as rated by the representatives on this Taskforce. In a study in severe asthma evaluating which outcomes matter to patients, reduced exacerbations and improved quality of life were viewed amongst their highest priorities (Clark <i>V et al</i>, TSANZ 2019).</p>	
BALANCE OF EFFECTS	<p>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</p> <ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know 		<p>Their were no differences in the adverse effects in patients treated with omalizumab versus placebo irrespective of high or low FeNO. People in the FeNO high group received the clinical benefit without any increase in side effects, whereas the low FeNO group experienced the same side effects without the clinical benefit.</p>
COST EFFECTIVENESS	<p>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</p> <ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies 	<p>No research evidence identified.</p>	<p>There would be an additional cost of using FeNO to select patients for the treatment in non specialist centres. However, in specialist centres FeNO is commonly assessed. If the test is used to select patients most likely to respond, cost benefits are likely.</p>

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	<p>What is the certainty of the evidence of resource requirements (costs)?</p> <ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate ○ High ● No included studies 	No research evidence identified.	Cost of the test may limit widescale implementation.
EQUITY	<p>What would be the impact on health equity?</p> <ul style="list-style-type: none"> ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know 	No research evidence identified.	There is no evidence of an impact on health equity, however given the lack of widespread FeNO use, some groups may not have access to the test.
ACCEPTABILITY	<p>Is the intervention acceptable to key stakeholders?</p> <ul style="list-style-type: none"> ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know 	<p>Previous ERS/ATS Taskforce recommends against the use of FeNO to guide therapy of adults and children with severe asthma. This may impact acceptability².</p> <p>In terms of patient acceptability, a study which aimed to evaluate the patient perception of tests used for the assessment of asthma and COPD, found that FENO had a good assessment profile, with a favourable assessment overall compared to completing questionnaires, and only being associated with some difficulty in test performance¹.</p>	As treatment of omalizumab is initiated in specialist severe asthma clinics and FeNO is a common measure used in these clinics, it is likely that this is acceptable to severe asthma clinicians.

FEASIBILITY	<p>Is the intervention feasible to implement?</p> <ul style="list-style-type: none"> ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know 	No research evidence identified.	Cost of the test may limit widescale implementation.

References

1. McDonald VM, Simpson JL, McElduff P, Gibson PG. Older peoples' perception of tests used in the assessment and management of COPD and asthma. *Clin Respir J* 2013; **20**(10): 12017.
2. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *The European respiratory journal* 2014; (43): 343-73.

Should a long-acting inhaled muscarinic antagonist (LAMA) be used in adults and children with severe asthma?

GRADE Evidence Profile: LAMA (tiotropium)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LAMA (tiotropium)	placebo	Relative (95% CI)	Absolute (95% CI)		

Peak FEV1 response - Children 2.5 ug

1 ¹	randomised trials	serious ^a	not serious	not serious	not serious	none	135	130	MD 35 higher (27.99 lower to 97.99 higher)	⊕⊕⊕○ MODERATE	CRITICAL
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Peak FEV1 response - Adolescents 2.5 ug

1 ²	randomised trials	not serious	not serious	not serious	serious ^b	none	127	135	MD 111 higher (2.01 higher to 219.99 higher)	⊕⊕⊕○ MODERATE	CRITICAL
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Peak FEV1 response - Children 5 ug

1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	128	130	MD 139 higher (74.32 higher to 203.68 higher)	⊕⊕⊕○ MODERATE	CRITICAL
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Peak FEV1 response - Adolescents 5 ug

1 ²	randomised trials	not serious	not serious	not serious	serious ^b	none	130	135	MD 90 higher (18.99 lower to 198.99 higher)	⊕⊕⊕○ MODERATE	CRITICAL
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Peak FEV1 response - Adults 5 ug

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LAMA (tiotropium)	placebo	Relative (95% CI)	Absolute (95% CI)		
2 ^{3,4}	randomised trials	not serious	not serious	not serious	serious ^b	none	456	456	MD 120.74 higher (54.12 higher to 187.36 higher)		⊕⊕⊕○ MODERATE	CRITICAL

Change in ACQ-7 scores - Children 2.5 ug

1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	136	130	MD 0.02 higher (0.14 lower to 0.18 higher)		⊕⊕⊕⊕ HIGH	CRITICAL
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Change in ACQ-7 scores - Adolescents 2.5 ug

1 ²	randomised trials	not serious	not serious	not serious	not serious	none	127	135	MD 0.06 higher (0.1 lower to 0.22 higher)		⊕⊕⊕⊕ HIGH	CRITICAL
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Change in ACQ-7 scores - Children 5 ug

1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	126	130	MD 0.08 lower (0.24 lower to 0.08 higher)		⊕⊕⊕⊕ HIGH	CRITICAL
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Change in ACQ-7 scores - Adolescents 5 ug

1 ²	randomised trials	not serious	not serious	not serious	not serious	none	130	135	MD 0.04 higher (0.12 lower to 0.19 higher)		⊕⊕⊕⊕ HIGH	CRITICAL
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Change in ACQ-7 scores - Adults 5 ug

2 ^{3,4}	randomised trials	not serious	not serious	not serious	not serious	none	456	456	MD 0.17 lower (0.25 lower to 0.09 lower)		⊕⊕⊕⊕ HIGH	CRITICAL
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Asthma worsening (at least 1) - Children 2.5 ug

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LAMA (tiotropium)	placebo	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^c	none	29/135 (21.5%)	23/65 (35.4%)	RR 0.61 (0.38 to 0.96)	138 fewer per 1.000 (from 219 fewer to 14 fewer)	⊕⊕⊕○ MODERATE	CRITICAL

Asthma worsening (at least 1) - Adolescents 2.5 ug

1 ²	randomised trials	not serious	not serious	not serious	serious ^c	none	18/127 (14.2%)	12/67 (17.9%)	RR 0.79 (0.41 to 1.54)	38 fewer per 1.000 (from 106 fewer to 97 more)	⊕⊕⊕○ MODERATE	CRITICAL
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Asthma worsening (at least 1) - Children 5 ug

1 ¹	randomised trials	not serious	not serious	not serious	serious ^c	none	35/128 (27.3%)	23/65 (35.4%)	RR 0.77 (0.50 to 1.19)	81 fewer per 1.000 (from 177 fewer to 67 more)	⊕⊕⊕○ MODERATE	CRITICAL
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Asthma worsening (at least 1) - Adolescents 5 ug

1 ²	randomised trials	not serious	not serious	not serious	serious ^c	none	15/130 (11.5%)	12/67 (17.9%)	RR 0.64 (0.32 to 1.30)	64 fewer per 1.000 (from 122 fewer to 54 more)	⊕⊕⊕○ MODERATE	CRITICAL
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Asthma worsening (at least 1) - Adults 5 ug

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LAMA (tiotropium)	placebo	Relative (95% CI)	Absolute (95% CI)		
1 ⁴	randomised trials	not serious	not serious	not serious	not serious	none	226/453 (49.9%)	287/454 (63.2%)	RR 0.79 (0.70 to 0.89)	133 fewer per 1.000 (from 190 fewer to 70 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

Peak FEV1 % predicted - Children 2.5 ug

1 ¹	randomised trials	serious ^a	not serious	not serious	not serious	none	135	130	MD 3.6 higher (0.5 higher to 6.7 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
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Peak FEV1 % predicted - Children 5 ug

1 ¹	randomised trials	serious ^a	not serious	not serious	not serious	none	128	130	MD 6.3 higher (3.3 higher to 9.3 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
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Peak FEV1 % predicted - Children 5 ug

1 ¹	randomised trials	serious ^a	not serious	not serious	very serious ^c	none	Narrative report + figure: " Post hoc analyses of adjusted mean trough FEV1/FVC responses demonstrated statistically significant improvements at all-time points versus placebo with both tiotropium doses, with the exception of tiotropium 2.5 mg at week 8"			⊕⊕○○ LOW	IMPORTANT
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Peak FEV1 % predicted - Children 5 ug

1 ¹	randomised trials	serious ^a	not serious	not serious	very serious ^c	none	Narrative report + figure: " Post hoc analyses of adjusted mean trough FEV1/FVC responses demonstrated statistically significant improvements at all-time points versus placebo with both tiotropium doses, with the exception of tiotropium 2.5 mg at week 8"			⊕⊕○○ LOW	IMPORTANT
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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LAMA (tiotropium)	placebo	Relative (95% CI)	Absolute (95% CI)		

AQLQ scores - Adults 5 ug

2 ^{3,4}	randomised trials	not serious	not serious	not serious	not serious	none	456	456	MD 0.1 higher (0.04 lower to 0.23 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
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Time to first exacerbation - Adults 5 ug

1 ⁴	randomised trials	not serious	not serious	not serious	serious ^d	none	-/456	-/456	HR 0.79 (0.62 to 1.01)	⊕⊕⊕○ MODERATE	CRITICAL
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Hospitalizations for asthma - Adults 5 ug

1 ⁴	randomised trials	not serious	not serious	not serious	serious ^c	none	16/453 (3.5%)	20/454 (4.4%)	RR 0.80 (0.42 to 1.53)	9 fewer per 1.000 (from 26 fewer to 23 more)	⊕⊕⊕○ MODERATE	IMPORTANT
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Any adverse event - Children 2.5 ug

1 ¹	randomised trials	not serious	not serious	not serious	serious ^c	none	59/136 (43.4%)	33/67 (49.3%)	RR 0.88 (0.65 to 1.20)	59 fewer per 1.000 (from 172 fewer to 99 more)	⊕⊕⊕○ MODERATE	CRITICAL
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Any adverse event - Adolescents 2.5 ug

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LAMA (tiotropium)	placebo	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	not serious	not serious	not serious	serious ^c	none	42/127 (33.1%)	24/68 (35.3%)	RR 0.94 (0.62 to 1.41)	21 fewer per 1.000 (from 134 fewer to 145 more)	⊕⊕⊕○ MODERATE	CRITICAL

Any adverse event - Children 5 ug

1 ¹	randomised trials	not serious	not serious	not serious	serious ^c	none	56/130 (43.1%)	33/67 (49.3%)	RR 0.87 (0.64 to 1.20)	64 fewer per 1.000 (from 177 fewer to 99 more)	⊕⊕⊕○ MODERATE	CRITICAL
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Any adverse event - Adolescents 5 ug

1 ²	randomised trials	not serious	not serious	not serious	serious ^c	none	43/130 (33.1%)	24/68 (35.3%)	RR 0.94 (0.63 to 1.40)	21 fewer per 1.000 (from 131 fewer to 141 more)	⊕⊕⊕○ MODERATE	CRITICAL
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Any adverse event - Adults 5 ug

2 ^{3,4}	randomised trials	not serious	not serious	not serious	not serious	none	335/456 (73.5%)	366/456 (80.3%)	RR 0.92 (0.86 to 0.98)	64 fewer per 1.000 (from 112 fewer to 16 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
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Serious adverse events - Children 2.5 ug

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LAMA (tiotropium)	placebo	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	very serious _c	none	2/136 (1.5%)	1/67 (1.5%)	RR 0.99 (0.09 to 10.67)	0 fewer per 1.000 (from 14 fewer to 144 more)	⊕⊕○○ LOW	IMPORTANT

Serious adverse events - Adolescents 2.5 ug

1 ²	randomised trials	not serious	not serious	not serious	very serious _c	none	0/127 (0.0%)	0/68 (0.0%)	not estimable		⊕⊕○○ LOW	IMPORTANT
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Serious adverse events - Children 5 ug

1 ¹	randomised trials	not serious	not serious	not serious	very serious _c	none	4/130 (3.1%)	1/67 (1.5%)	RR 2.06 (0.24 to 18.08)	16 more per 1.000 (from 11 fewer to 255 more)	⊕⊕○○ LOW	IMPORTANT
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Serious adverse events - Adolescents 5 ug

1 ²	randomised trials	not serious	not serious	not serious	very serious _c	none	3/130 (2.3%)	0/68 (0.0%)	RR 3.69 (0.19 to 70.36)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	⊕⊕○○ LOW	IMPORTANT
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Serious adverse events - Adults 5 ug

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LAMA (tiotropium)	placebo	Relative (95% CI)	Absolute (95% CI)		
2 ^{3,4}	randomised trials	not serious	not serious	not serious	serious ^c	none	37/456 (8.1%)	40/456 (8.8%)	RR 0.93 (0.61 to 1.43)	6 fewer per 1.000 (from 34 fewer to 38 more)	⊕⊕⊕○ MODERATE	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **RR:** Risk ratio; **HR:** Hazard Ratio

Explanations

- a. Selective reporting bias: Some outcomes were assessed post-hoc including peak FEV1 (0-3h)
- b. Although we cannot exclude futility because all estimates do not reach MID, upper 95%CI boundary is next to clinically important effect. Minimal important differences for FEV1 change= 230 millilitres
- c. Small number of events, large 95%CI
- d. Large 95CI% which includes no effect or a relevant benefit

References

1. Szeffler SJ, Murphy K, Harper T 3rd, Boner A, Laki I, Engel M, El Azzi G, Moroni-Zentgraf P, Finnigan H, Hamelmann E.. A phase III randomized controlled trial of tiotropium add-on therapy in children with severe symptomatic asthma. J Allergy Clin Immunol.; 2017.
2. Hamelmann E, Bernstein JA, Vandewalker M, Moroni-Zentgraf P, Verri D, Unseld A, Engel M, Boner AL. A randomised controlled trial of tiotropium in adolescents with severe symptomatic asthma. Eur Respir J; 2017
3. Kerstjens HA, Moroni-Zentgraf P, Tashkin DP, Dahl R, Paggiaro P, Vandewalker M, Schmidt H, Engel M, Bateman ED.. Tiotropium improves lung function, exacerbation rate, and asthma control, independent of baseline characteristics including age, degree of airway obstruction, and allergic statu. Respir Med; 2016.
4. Kerstjens HA, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, Sigmund R, Seibold W, Moroni-Zentgraf P, Bateman ED.. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med; 2012.

Evidence to Decision Framework: LAMA (tiotropium)

Should tiotropium vs. no tiotropium be used for children, adolescents, and adults with severe asthma uncontrolled despite GINA step 4-5 or NAEPP step 5 therapies?		
POPULATION:	Patients with severe asthma not controlled or experiencing exacerbations despite treatment with high-dose inhaled glucocorticoids in combination with a long-acting beta2-adrenergic receptor agonist and a third controller such as a leukotriene modifier if the patient is treated with medium-dose inhaled glucocorticoids.	BACKGROUND: Several randomized clinical trials have demonstrated that the addition of a long-acting muscarinic antagonist as a second long-acting bronchodilator, initially in COPD, but more recently in mild to severe asthma cohorts, results in improvement in lung function and the prevention of exacerbations. Long-acting muscarinic antagonists such as tiotropium are the most frequently used long-acting bronchodilator for COPD and are a cost-effective and safe adjunct therapy for the management of asthma refractory to a combination of therapies which accounts for a substantial proportion of the burden related to asthma morbidity.
INTERVENTION:	Muscarinic antagonist therapy with tiotropium via soft-mist inhaler (5ug or 10ug) once daily. Tiotropium 2.5ug or 5ug once daily was also evaluated in children and adolescents.	
COMPARISON:	Placebo	
MAIN OUTCOMES:	FEV1, PEFr, severe exacerbations, asthma symptoms, ACQ-7, ACQ-6, AQLQ	

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	How substantial are the desirable anticipated effects? <ul style="list-style-type: none"> ○ Trivial ○ Small ○ Moderate <input checked="" type="radio"/> Large ○ Varies ○ Don't know 	<p>Results from research evidence (studies)</p> <p>There were three randomised placebo-controlled trials in adults greater than 18 years of age, one crossover and two parallel design, and two in either children or adolescents which impacted the dose of tiotropium (adults were randomized to 5 to 10ug while children and adolescents were randomized to 2.5-5ug once daily). All of these trials included individuals with severe asthma uncontrolled on GINA step 4-5 or NAEPP step 5 therapies. Each trial consistently demonstrated substantial and significant improvements in lung function measures and symptom control with the addition of tiotropium and a subgroup of sufficient duration demonstrated beneficial effects on time to exacerbation.</p>	
UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects? <ul style="list-style-type: none"> ○ Large ○ Moderate ○ Small <input checked="" type="radio"/> Trivial ○ Varies ○ Don't know 	<p>Adverse events were less frequent in the tiotropium arm compared to placebo in these four trials, while severe adverse events were equally infrequent across treatment arms.</p>	
CERTAINTY OF EVIDENCE	What is the overall certainty of the evidence of effects? <ul style="list-style-type: none"> ○ Very low ○ Low <input checked="" type="radio"/> Moderate ○ High ○ No included studies 	<p>The five included studies were randomised, double-blind, placebo-controlled studies. All of the important primary and secondary outcomes were assessed as high quality according to GRADE Overall risk of bias was low and methodological procedures for random sequence generation, allocation concealment, and blinding were robust. However, one 12-week study of children (Szefer 2017 [PMID:28189771]) may be subject to selective reporting bias as outcomes related to FEF-25-75%, peak and trough FEV1 responses at week 12, and time to exacerbation were assessed post-hoc but presented as main findings. Industry bias is also unclear in four of the five included.</p>	
VALUES	Is there important uncertainty about or variability in how much people value the main outcomes? <ul style="list-style-type: none"> ○ Important uncertainty or variability 	<p>There is value placed on the measurement of lung function and the management and prevention of asthma exacerbations. Lung function measures derived from spirometry are a fundamental measure of lung health, are highly correlated with asthma severity and exacerbation risk, and one of the central components determining asthma severity and</p>	

	<input checked="" type="radio"/> Possibly important uncertainty or variability <input type="radio"/> Probably no important uncertainty or variability <input type="radio"/> No important uncertainty or variability <input type="radio"/> No known undesirable outcomes	<p>NAEPP guideline-based maintenance treatment (Denlinger Am J Respir Crit Care Med. 2017;195(3):302-13. PMID:27556234). Asthma exacerbations account for much of the cost related to asthma (Weiss J Allergy Clin Immunol 2001 PMID:11149982). Exacerbations defined by the need for an intervention such as treatment with systemic glucocorticoids, an emergency room visit, or hospitalization is validated as one the central components for determining asthma severity and GINA/NAEPP guideline-based maintenance therapy (Fuhlbrigge J Allergy Clin Immunol 2012 PMID: 22386508).</p>	
BALANCE OF EFFECTS	<p>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</p> <input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input checked="" type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know	<p>Long-acting muscarinic antagonist treatment was associated with substantial and significant improvements in peak lung function, symptom control, and a lower frequency of asthma worsening. There was a lower frequency of adverse events associated with tiotropium treatment while the frequency of severe adverse events was also low and nearly equal to placebo.</p>	
COST EFFECTIVENESS	<p>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</p> <input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input checked="" type="radio"/> No included studies	<p>No cost-effectiveness analyses were identified.</p>	<p>Long-acting muscarinic antagonist therapy was associated with beneficial effects on asthma control, severe exacerbations, and lung function in those severe asthma treated with GINA step 4-5 or NAEPP step 5 therapies. Whether these costs savings outweigh the cost of medication is unclear, but the addition of this inhaled therapy can be done at a lower cost compared to biologic therapies.</p>

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	<p>What is the certainty of the evidence of resource requirements (costs)?</p> <ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate ○ High ● No included studies 	No included studies.	
EQUITY	<p>What would be the impact on health equity?</p> <ul style="list-style-type: none"> ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies X Don't know 	<p>Kerstjens and colleagues evaluated subgroups based on age, sex, ethnic and racial groups, and BMI/obesity and found equally beneficial effects on peak FEV1 improvement across sexes and individuals ages 18 or higher and less than 18 years (Kerstjens Respir Med 2016 [PMID:27492532]). This analysis was unable to determine whether there were equally beneficial effects racial groups such as African Americans (N=41), or Asians (N=93) who were the minority of subjects compared to Whites (N=714). In addition, effects were unable to be determined for Hispanic ethnicity (N=25) compared to non-Hispanics (N=826). An anticipated impact could relate to the access and lower cost of tiotropium when compared to biologic drugs which could impact health equity as it relates to socioeconomic status and the treatment of severe asthma.</p>	
ACCEPTABILITY	<p>Is the intervention acceptable to key stakeholders?</p> <ul style="list-style-type: none"> ○ No ○ Probably no X Probably yes ○ Yes ○ Varies ○ Don't know 	<p>Long-acting muscarinic antagonist therapy improves FEV1 and prevents asthma worsening and exacerbations which may be important in this important subgroup of asthma who experience a substantial proportion of the burden related to asthma morbidity. An introduction of this feasible and cost-effective add-on therapy which effectively impacts these important outcomes is assumed to be highly acceptable to patients and healthcare providers.</p>	
FEASIBILITY	<p>Is the intervention feasible to implement?</p> <ul style="list-style-type: none"> ○ No ○ Probably no X Probably yes ○ Yes ○ Varies ○ Don't know 	<p>An inhaled therapy delivered once daily is a feasible intervention to implement in terms of convenience and ease of use. Feasibility could be limited by cost in individuals who are already treated with multiple inhaled therapies. Access to providers with sufficient expertise to add-on therapy above GINA step 4-5 or NAEPP step 5 therapies in these subgroups. In these settings, implementation of a once-daily inhaled device which could be used at home is substantially more feasible compared to more costly biologic therapies which are regularly administered in a clinic setting.</p>	

Should a macrolide (i.e., azithromycin, clarithromycin) be used in adults and children with severe asthma?

Evidene Profile: MACROLIDES

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide	Placebo	Relative (95% CI)	Absolute (95% CI)		
Number of exacerbations requiring hospitalisation (follow up: mean 26 weeks)												
1 ¹	randomised trials	not serious	not serious	not serious	very serious ^{a,b}	none	2/55 (3.6%)	2/54 (3.7%)	RR 0.98 (0.14 to 6.72)	1 fewer per 1,000 (from 32 fewer to 212 more)	⊕⊕○○ LOW	CRITICAL
Number of 'severe' exacerbations - requiring at least oral corticosteroids (follow up: range 24 weeks to 48 weeks)												
3 ¹⁻³	randomised trials	not serious	serious ^c	not serious	serious ^a	none	72/285 (25.3%)	97/280 (34.6%)	RR 0.77 (0.44 to 1.34)	80 fewer per 1,000 (from 118 more to 194 fewer)	⊕⊕○○ LOW	CRITICAL
Incidence rate (moderate and severe combined) asthma exacerbations (follow up: mean 48 weeks)												
1 ²	randomised trials	not serious	not serious	not serious		none	213	207	Rate ratio 0.59 (0.47 to 0.74)	Incidence rate (events/patient/year): macrolides 1.07; placebo 1.86	-	CRITICAL
Number of patients with at least one moderate or severe asthma exacerbation (follow up: mean 48 weeks)												
1 ²	randomised trials	not serious	not serious	not serious	not serious	none	94/213 (44.1%)	127/207 (61.4%)	RR 0.72 (0.60 to 0.87)	172 fewer per 1,000 (from 80 fewer to 245 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Time to asthma exacerbation (moderate or severe) (follow up: mean 48 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide	Placebo	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	not serious	not serious	not serious	not serious	none	94	127	HR 0.65 (0.50 to 0.85)	-	⊕⊕⊕⊕ HIGH	CRITICAL
Note: HR is 0.65 (95%CI up to 0.85) and the median difference (point estimate) almost 200 days which suggests that the HR reduction is substantial.												
Number of lower respiratory tract infections requiring antibiotics (follow up: range 26 weeks to 48 weeks)												
2 ^{1,2}	randomised trials	not serious	not serious	not serious	not serious	none	56/268 (20.9%)	93/261 (35.6%)	RR 0.60 (0.45 to 0.79)	143 fewer per 1,000 (from 75 fewer to 196 fewer)	⊕⊕⊕⊕ HIGH	
Note: Although exacerbations were designated to be of critical importance by the panel, it is not known how lower respiratory tract infections were considered therefore importance is left blank awaiting outcome of further discussion with the panel.												
Change in Asthma Control Questionnaire (ACQ) score from baseline (follow up: range 16 weeks to 48 weeks; Scale from: 0 to 7; MID 0.5)												
3 ^{1,4,5}	randomised trials	not serious	not serious	not serious	not serious	none	140	136	-	MD 0.11 lower (0.34 lower to 0.12 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Post treatment ACQ score (follow up: range 8 weeks to 48 weeks; Scale from: 0 to 7; MID 0.5)												
2 ^{2,6}	randomised trials	not serious	not serious	not serious	not serious	none	236	229	-	MD 0.07 lower (0.24 lower to 0.11 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Change in symptom score from baseline (follow up: mean 48 weeks; Scale from: 0 to 4)												
1 ⁴	randomised trials	not serious	not serious	not serious	very serious ^{a,b}	none	38	37	-	MD 0.17 higher (0.28 lower to 0.63 higher)	⊕⊕○○ LOW	CRITICAL
Post treatment total symptom score (follow up: mean 8 weeks; Scale from: 0 to 14)												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide	Placebo	Relative (95% CI)	Absolute (95% CI)		
1 ⁶	randomised trials	not serious	not serious	not serious	very serious ^{a,b}	none	23	22	-	MD 0.3 lower (2.08 lower to 1.48 higher)	⊕⊕○○ LOW	CRITICAL
Mean end of treatment breathlessness score (Visual Analogue Score) (follow up: mean 48 weeks; Scale from: 0 to 10 cm; MID 1.9 cm)												
1 ²	randomised trials	not serious	not serious	not serious	serious ^a	none	212	207	-	MD 0.49 lower (1.18 lower to 0.2 higher)	⊕⊕⊕○ MODERATE	CRITICAL
Mean end of treatment wheeze score (Visual Analogue Score) (follow up: mean 48 weeks; Scale from: 0 to 10 cm)												
1 ²	randomised trials	not serious	not serious	not serious	serious ^a	none	212	207	-	MD 0.11 lower (1.15 lower to 0.94 higher)	⊕⊕⊕○ MODERATE	CRITICAL
Mean end of treatment sputum production score (Visual Analogue Score) (follow up: mean 48 weeks; Scale from: 0 to 10 cm)												
1 ²	randomised trials	not serious	not serious	not serious	serious ^f	none	212	207	-	MD 0.62 lower (1.23 lower to 0.002 lower)	⊕⊕⊕○ MODERATE	CRITICAL
Mean end of treatment cough score (Visual Analogue Score) (follow up: mean 48 weeks; Scale from: 0 to 10 cm, MID 1.7 cm)												
1 ²	randomised trials	not serious	not serious	not serious	serious ^e	none	212	207	-	MD 0.73 lower (1.42 lower to 0.04 lower)	⊕⊕⊕○ MODERATE	CRITICAL
Number of patients with at least 1 adverse effect (follow up: mean 26 weeks)												
1 ¹	randomised trials	not serious	not serious	not serious	very serious ^{a,b}	none	37/55 (67.3%)	39/54 (72.2%)	RR 0.93 (0.73 to 1.19)	51 fewer per 1,000 (from 137 more to 195 fewer)	⊕⊕○○ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide	Placebo	Relative (95% CI)	Absolute (95% CI)		
Number of serious adverse events (including mortality) (follow up: range 16 weeks to 48 weeks)												
4 ^{1,2,4,5}	randomised trials	not serious	not serious	not serious	very serious ^{a,b}	none	32/353 (9.1%)	39/343 (11.4%)	RR 0.81 (0.52 to 1.24)	22 fewer per 1,000 (from 27 more to 55 fewer)	⊕⊕○○ LOW	CRITICAL
Number of withdrawals due to adverse events (follow up: range 16 weeks to 48 weeks)												
4 ¹⁻⁴	randomised trials	not serious	not serious	not serious	very serious ^{a,b}	none	17/323 (5.3%)	13/317 (4.1%)	RR 1.28 (0.64 to 2.59)	11 more per 1,000 (from 15 fewer to 65 more)	⊕⊕○○ LOW	CRITICAL
Note: Note that although serious adverse events were lower in the treatment group, there were more withdrawals due to adverse events, suggesting these results should be considered with low confidence.												
Change in Asthma Quality of Life Questionnaire (AQLQ) from baseline (follow up: range 16 weeks to 48 weeks; Scale from: 1 to 7, MID 0.5)												
3 ^{1,4,5}	randomised trials	not serious	not serious	not serious	not serious	none	140	136	-	MD 0.16 higher (0.06 lower to 0.37 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Mean end of treatment AQLQ score (follow up: mean 48 weeks; Scale from: 1 to 7, MID 0.5)												
1 ²	randomised trials	not serious	not serious	not serious	serious ^e	none	209	204	-	MD 0.36 higher (0.21 higher to 0.52 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
Mean end of treatment nasal symptom score (Visual Analogue Score) (follow up: mean 48 weeks; Scale from: 0 to 10 cm; MID 2.3 cm)												
1 ²	randomised trials	not serious	not serious	not serious	serious ^e	none	212	207	-	MD 0.51 lower (1.04 lower to 0.02 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
Change in post-bronchodilator FEV1 (% predicted) from baseline (follow up: mean 26 weeks; MID 10.38 %)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide	Placebo	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	55	54	-	MD 1.95 higher (2.42 lower to 6.32 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
Change in pre-bronchodilator FEV1 (% predicted) from baseline (follow up: range 16 weeks to 26 weeks; MID 10.38 %)												
2 ^{1,5}	randomised trials	not serious	not serious	not serious	serious ^b	none	102	99	-	MD 0.37 higher (2.17 lower to 2.91 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
Change in pre-bronchodilator FEV1 (L) (follow up: mean 16 weeks; MID 0.23 L)												
1 ⁵	randomised trials	not serious	not serious	not serious	serious ^b	none	47	45	-	MD 0 (0.2 lower to 0.2 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
Mean end of treatment pre-bronchodilator FEV1 (% predicted) (follow up: mean 8 weeks; MID 10.38 %)												
1 ⁶	randomised trials	not serious	not serious	not serious	very serious ^{a, b}	none	23	22	-	MD 5.6 higher (5.62 lower to 16.82 higher)	⊕⊕○○ LOW	IMPORTANT
Mean end of treatment pre-bronchodilator FEV1 (L) (follow up: mean 48 weeks; MID 0.23 L)												
1 ²	randomised trials	not serious	not serious	not serious	serious ^e	none	210	205	-	MD 0.12 lower (0.27 lower to 0.03 higher)	⊕⊕⊕○ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio; **MD:** Mean difference

Explanations

a. The ends of the 95% CI include both appreciable benefit and appreciable harm and would lead to opposite clinical decisions.

- b. Limited number of patients or events, does not meet OIS
- c. There is variation in point estimates for included studies with an I2 of 70% which may indicate moderate inconsistency
- d. One study reports 'number of patients with at least one primary endpoint' which is a composite of severe asthma exacerbations and lower respiratory tract infections requiring antibiotics. This study contributes 42% of events. Inclusion of lower respiratory tract infections means this data cannot be considered completely representative of exacerbations alone.
- e. The lower end of the 95% CI crosses the minimally important difference (MID) for this outcome.
- f. MID not established for this measure however lower end of confidence interval (score 0.002 lower) unlikely to be clinically meaningful.

Bibliography:

1. Brusselle GG, Vanderstichele C, Jordens P, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. *Thorax* 2013; **68**(4): 322-9.
2. Gibson PG, Yang IA, Upham JW, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. *Lancet* 2017; **390**(10095): 659-68.
3. Strunk RC, Bacharier LB, Phillips BR, et al. Azithromycin or montelukast as inhaled corticosteroid-sparing agents in moderate-to-severe childhood asthma study. *J Allergy Clin Immunol* 2008; **122**(6): 1138-44 e4.
4. Hahn DL, Grasmick M, Hetzel S, Yale S. Azithromycin for bronchial asthma in adults: an effectiveness trial. *J Am Board Fam Med* 2012; **25**(4): 442-59.
5. Sutherland ER, King TS, Icitovic N, et al. A trial of clarithromycin for the treatment of suboptimally controlled asthma. *J Allergy Clin Immunol* 2010; **126**(4): 747-53.
6. Simpson JL, Powell H, Boyle MJ, Scott RJ, Gibson PG. Clarithromycin targets neutrophilic airway inflammation in refractory asthma. *Am J Respir Crit Care Med* 2008; **177**(2): 148-55.

Should a macrolide (i.e., azithromycin, clarithromycin) be used in adults and children with severe asthma?		
POPULATION:	Adults and children with severe asthma	BACKGROUND: By definition, patients with severe asthma have disease that is either unresponsive to traditional therapies with inhaled corticosteroids and bronchodilators or require these therapies to maintain adequate control. To address this unmet need for improved therapies, in particular in patients not responding to step 5 biologicals or having no access to those treatments, and in view of the possible immunomodulatory effect of macrolides, these medications are being used long-term for the management of the disease. This systematic review and meta-analysis synthesizes the data from randomized controlled trials and meta-analyses investigating the use of macrolides and provides treatment recommendations based on the results.
INTERVENTION:	Macrolide	
COMPARISON:	No macrolide	
MAIN OUTCOMES:	Rate of exacerbations	
	Time to first asthma exacerbation	
	Asthma exacerbations requiring ER visits or hospitalization	
	Lung function	
	Asthma control	
	Maintenance corticosteroid dose reduction	
	Adverse events	
	Serious adverse events	
	Quality of life	

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	<p>How substantial are the desirable anticipated effects?</p> <ul style="list-style-type: none"> ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know 	<p>We identified a total of 6 clinical trials assessing the effectiveness of macrolide treatment to placebo. Four assessed azithromycin (Bruselle 2013, Gibson 2017, Strunk 2008, Hahn 2012) and two assessed clarithromycin (Sutherland 2010, Simpson 2008).</p> <p>In the largest study to date (Gibson), azithromycin 500mg (three times/week during 48 weeks) reduced asthma moderate to severe exacerbations (1.07 per patient-year [95% CI 0.85-1.29]) compared with placebo (1.86 per patient-year [1.54-2.18]; incidence rate ratio [IRR] 0.59 [95% CI 0.47-0.74]) and time to moderate to severe exacerbation; hazard ratio [HR] 0.65 [95% CI 0.50-0.85]. The proportion of patients experiencing at least one asthma exacerbation was reduced by azithromycin treatment (127 [61%] patients in the placebo group vs 94 [44%] patients in the azithromycin group; rate ratio [RR] 0.72 [95% CI 0.60-0.87]). Azithromycin significantly improved asthma-related quality of life questionnaire (AQLQ) at the end of treatment (adjusted mean difference, 0.36 [95% CI 0.21-0.52]).</p> <p>Macrolides were not associated to a reduction of severe exacerbations (Bruselle 2013, Gibson 2017, Strunk 2008), improvements in asthma control questionnaire (ACQ) (Bruselle 2013, Gibson 2017, Strunk 2008, Hahn 2012, Sutherland 2010, Simpson 2008) or lung function (FEV1) (Bruselle 2013, Gibson 2017, Sutherland 2010, Simpson 2008).</p> <p>In the AZISAST trial, in a predefined subgroup with non-eosinophilic severe asthma (blood eosinophilia $\leq 200/\mu\text{l}$), azithromycin was associated with a significantly lower combined primary endpoint rate* (PEP) than placebo in subjects: 0.44 PEPs (95% CI 0.25 to 0.78) versus 1.03 PEPs (95% CI 0.72 to 1.48) ($p=0.013$). Azithromycin significantly improved the AQLQ score but there were no significant between-group differences in the ACQ score or lung function</p> <p>In the small study by Sutherland et al. clarithromycin improved airway hyperresponsiveness, increasing the methacholine PC(20) by 1.2 ± 0.5 doubling doses ($P = .02$) in the study population but had no effect on other outcomes..</p> <p>* PEP is a rate of "primary endpoints" which is a combined measure of effect of severe asthma exacerbations and LRTI requiring antibiotics</p>	<ul style="list-style-type: none"> ● Rate ratios are difficult to judge (as any relative measure of effect). However, the absolute difference in this study is -0.46 (-0.79 to -0.14) exacerbations per patient-year (Table 2 - primary outcomes). The panel can better consider if less 0.14 exacerbations per patient-year is something meaningful ● One approach would be also the NNT (at one year) as 1/absolute difference which seems to be 2 (1 to 7). The absolute difference estimate is adjusted in the trial so this NNT seems reliable. The panel can also judge whether treating 7 patients with azithromycin to avoid one (moderate or severe) exacerbation a year is acceptable. ● The panel have to consider that patients with exacerbations (as defined) will need increased doses of steroids, B-agonists, ED visits or hospitalisations

UNDESIRABLE EFFECTS	<p>How substantial are the undesirable anticipated effects?</p> <ul style="list-style-type: none"> ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know 	<p>There were no differences between macrolides and placebo in the number of patients with serious adverse events or treatment withdrawal due to toxicity (Bruselle 2013, Gibson 2017, Strunk 2008, Hahn 2012, Sutherland 2010).</p> <p>The main concern is resistance which has been shown to develop in long-term use of macrolides. In the Azistast study azithromycin was associated with increased oropharyngeal carriage of macrolide-resistant streptococci (87% of the subjects in the azithromycin group and 35% of the subjects in the placebo group were colonised with erythromycin-resistant oropharyngeal streptococci $p<0.001$).</p> <p>There are more data in the literature about macrolide resistance from studies in other diseases where the medication is used long-term, such as non-CF bronchiectasis, where Valery et al. showed increased resistance to streptococcus pneumoniae and staph aureus rising from 12% to 27% after long term use compared to placebo ($p=0.015$ and 0.046 respectively). Similar data were found in other studies. (Wong LANCET 2012, Altenburg JAMA 2013).</p> <p>Diarrhoea is the most common adverse event. In the AZISAST study 72 [34%] azithromycin-treated patients experienced diarrhea vs 39 [19%] of those on placebo $p=0.001$.</p>	<ul style="list-style-type: none"> ● This is the most important consideration. However studies in non CF bronchiectasis showed that these bacteria were susceptible to other antibiotics.
CERTAINTY OF EVIDENCE	<p>What is the overall certainty of the evidence of effects?</p> <ul style="list-style-type: none"> ● Very low ● Low ○ Moderate ○ High ○ No included studies 	<p>As shown in the table by Sarah Diver, the certainty of the evidence is low.</p>	<p>Our certainty assessment relies on study design (randomized controlled trials), risk of bias, inconsistency, indirectness, and imprecision.</p> <p>Further the certainty is based on the quality of evidence that is lowest among critical outcomes.</p>
VALUES	<p>Is there important uncertainty about or variability in how much people value the main outcomes?</p> <ul style="list-style-type: none"> ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes 	<p>No evidence identified.</p>	<p>There is no important uncertainty about how patients and clinicians assess asthma exacerbations. There is more variability concerning QoL which however is a patient related outcome. Regarding the interpretation of lung function which is more objective there doesn't seem to be any effect of macrolide treatment on lung function.</p>

BALANCE OF EFFECTS	<p>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</p> <ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know 	Diarrhea does not seem to be a major concern, however the problem of resistance needs to be evaluated long-term in actual clinical studies (not only laboratory testing).	<p>The group placed a higher value on the potential benefit of reduction in exacerbations which can be life-threatening and the potential positive impact in quality of life. Potential adverse events were considered to have a lower value.</p> <p>Regarding resistance in particular, which is a concern, the studies show that the bacteria are susceptible to other commonly used antibiotics</p>
COST EFFECTIVENESS	<p>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</p> <ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ No included studies 	If, as the statistician points out, 7 patients need to be treated to avoid 1 exacerbation then probably the cost-effectiveness favors the intervention as the cost of the intervention is low while direct/indirect costs of exacerbations are high	<p>No cost-effectiveness studies have been identified however the impact of asthma exacerbations on health care costs among patients with moderate and severe persistent asthma are estimated to be 9,223 USD compared to 5,011 USD in those asthmatic patients without exacerbations (Ivanova 2012).</p> <p>The estimated total healthcare cost of patients with exacerbations is 4,212 USD per year.</p> <p>Considering that macrolides are low-cost interventions, the panel considers that the intervention will be cost-saving.</p>
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	<p>What is the certainty of the evidence of resource requirements (costs)?</p> <ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate ○ High ● No included studies 	No specific studies were identified, however due to the relatively low cost of macrolides resource requirements are expected to be low.	
EQUITY	<p>What would be the impact on health equity?</p> <ul style="list-style-type: none"> ○ Reduced 	No evidence identified.	In the US, racial and ethnic minorities, and individuals of lower socioeconomic status have been documented to have less access to specialty clinics and are less likely to use expensive controller therapy for asthma.

	<ul style="list-style-type: none"> ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know 		Macrolides might be an easy and feasible strategy.
ACCEPTABILITY	<p>Is the intervention acceptable to key stakeholders?</p> <ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know 	No evidence identified.	<p>Most patients with severe asthma welcome any possibility of improvement through treatment although they are concerned about medication use</p> <p>Health insurance companies and clinic administrations should find macrolides acceptable due to their relatively low cost however there is concern about the resistance.</p>
FEASIBILITY	<p>Is the intervention feasible to implement?</p> <ul style="list-style-type: none"> ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know 	Probably yes.	Macrolides are relatively cheap and are available world-wide. .

Should an anti-interleukin 4/13 strategy be used for adults and children with severe asthma?

Evidence Profile: 300 mg of dupilumab every 2 weeks compared to placebo for patients with severe asthma according to blood eosinophils

Bibliography: Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, Busse WW, Ford L, Sher L, FitzGerald JM, Katelaris C, Tohda Y, Zhang B, Staudinger H, Pirozzi G, Amin N, Ruddy M, Akinlade B, Khan A, Chao J, Martincova R, Graham NMH, Hamilton JD, Swanson BN, Stahl N, Yancopoulos GD, Teper A. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. *N Engl J Med.* 2018;378(26):2486-2496. doi: 10.1056/NEJMoa1804092. Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, Pirozzi G, Sutherland ER, Evans RR, Joish VN, Eckert L, Graham NM, Stahl N, Yancopoulos GD, Louis-Tisserand M, Teper A. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet.* 2016;388(10039):31-44. doi: 10.1016/S0140-6736(16)30307-5.

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	300 mg of dupilumab every 2 weeks	placebo	Relative (95% CI)	Absolute (95% CI)		

EXACERBATION - annualised severe exacerbation event rate at week 24 (according to blood eosinophil 300 cells/mm³ or more)

2 ^{1,2}	randomised trials	serious ^a	not serious	not serious	not serious	none	-/109	-/112	Rate ratio 0.25 (0.14 to 0.46)	Low	⊕⊕⊕○ MODERATE	
										84 less severe exacerbations per 100 patients per year (from 49 to 139)		
										High		
										124 less severe exacerbations per 100 patients per year (from 94 to 155)		

EXACERBATION - annualised severe exacerbation event rate at week 24 (according to blood eosinophil <300 cells/mm³)

2 ^{1,2}	randomised trials	serious ^a	not serious	not serious	not serious	none	0/156	0/148	Rate ratio 0.49 (0.31 to 0.76)	Low	⊕⊕⊕○ MODERATE	
										47 less severe exacerbations per 100 patients per year (from 32 to 65)		
										High		

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	300 mg of dupilumab every 2 weeks	placebo	Relative (95% CI)	Absolute (95% CI)		
										66 less severe exacerbations per 100 patients per year (from 54 to 76)		

LUNG FUNCTION - change in FEV1 from baseline at week 24 (according to blood eosinophil 300 cells/mm3 or more) (assessed with: Liters)

2 ^{1,2}	randomised trials	serious ^a	not serious	not serious	serious ^b	none	103	91	-	least square MD 0.21 Liters more (0.06 more to 0.35 more)	⊕⊕○○ LOW	
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LUNG FUNCTION - change in FEV1 from baseline at week 24 (according to blood eosinophil <300 cells/mm3) (assessed with: Liters)

2 ^{1,2}	randomised trials	serious ^a	not serious	not serious	not serious	none	137	138	-	least square MD 0.14 Liters more (0.05 more to 0.22 more)	⊕⊕⊕○ MODERATE	
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LUNG FUNCTION - change in FEV1 from baseline at week 24 (according to blood eosinophil 300 cells/mm3 or more) (assessed with: % of change; Scale from: 0 to 100)

1 ¹	randomised trials	serious ^c	not serious	not serious	serious ^d	none	58	52	-	least square MD 12.09 percentage points more (3.2 more to 20.97 more)	⊕⊕○○ LOW	
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LUNG FUNCTION - change in FEV1 from baseline at week 24 (according to blood eosinophil <300 cells/mm3) (assessed with: % of change; Scale from: 0 to 100)

1 ¹	randomised trials	serious ^c	not serious	not serious	serious ^d	none	85	73	-	least square MD 7.9 percentage points more (1.98 more to 13.81 more)	⊕⊕○○ LOW	
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ASTHMA CONTROL - at week 24 according to blood eosinophil 300 cells/mm3 or more (assessed with: ACQ-5; Scale from: 0 to 6)^e

1 ¹	randomised trials	serious ^c	not serious ^f	not serious	serious ^b	none	58	52	-	least square MD 0.55 ACQ-5 units lower (0.9 lower to 0.2 lower)	⊕⊕○○ LOW	
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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	300 mg of dupilumab every 2 weeks	placebo	Relative (95% CI)	Absolute (95% CI)		

ASTHMA CONTROL - at week 24 according to blood eosinophil <300 cells/mm3 (assessed with: ACQ-5; Scale from: 0 to 6)^a

1 ¹	randomised trials	serious ^c	not serious ^f	not serious	not serious	none	87	75	-	least square MD 0.17 ACQ-5 units lower (0.44 lower to 0.1 higher)	⊕⊕⊕○ MODERATE	
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QUALITY OF LIFE - at week 24 according to blood eosinophil 300 cells/mm3 or more (assessed with: AQLQ ; Scale from: 0 to 7)^a

1 ¹	randomised trials	serious ^c	not serious ^f	not serious	serious ^b	none	56	53	-	least square MD 0.78 AQLQ units higher (0.42 higher to 1.15 higher)	⊕⊕○○ LOW	
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QUALITY OF LIFE - at week 24 according to blood eosinophil <300 cells/mm3 (assessed with: AQLQ; Scale from: 0 to 7)^a

1 ¹	randomised trials	serious ^c	not serious ^f	not serious	not serious	none	85	74	-	least square MD 0.06 AQLQ units higher (0.24 lower to 0.36 higher)	⊕⊕⊕○ MODERATE	
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Reduction in the glucocorticoid dose at week 24 (according to blood eosinophil 300 cells/mm3 or more) (assessed with: % reduction; Scale from: 0 to 100)

1 ²	randomised trials	serious ^h	not serious ^f	not serious	serious ⁱ	none	48	41	-	least square MD 36.38 percentage points lower (54.7 lower to 18.9 lower)	⊕⊕○○ LOW	
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Reduction in the glucocorticoid dose at week 24 (according to blood eosinophil <300 cells/mm3) (Scale from: 0 to 100)

1 ²	randomised trials	serious ^h	not serious ^f	not serious	serious ⁱ	none	55	66	-	least square MD 21.3 percentage points lower (38.8 lower to 3.9 lower)	⊕⊕○○ LOW	
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CI: Confidence interval

Explanations

- a. Relevant and differential attrition bias in NCT01854047 (Wenzel 2016) for placebo and dupilumab groups (more than 20% and around 10% respectively); Randomization was not stratified by blood eosinophil count and current 300 cells/mm³ was not included as a co-variate in the analysis (Rabe 2018)
- b. the lower CI boundary crosses the threshold for minimal important difference
- c. Relevant and differential attrition bias in NCT01854047 (Wenzel 2016) for placebo and dupilumab groups (more than 20% and around 10% respectively)
- d. Minimal important differences not known for % reduction in the FEV₁, however the 95CI is wide and does not exclude important benefit or no effect.
- e. minimal important difference for ACQ-5 is 0.5; lower values indicate better asthma control.
- f. not applicable (findings from 1 trial)
- g. minimal important difference for AQLQ is 0.5; higher scores indicates better QoL.
- h. Subgroup analysis, randomization was not stratified by blood eosinophil count and current 300 cells/mm³ was not included as a co-variate in the analysis.
- i. Minimal important differences not known for % reduction in the glucocorticoid doses, however the 95CI is wide and does not exclude important benefit or no effect.

References

1. Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, Pirozzi G, Sutherland ER, Evans RR, Joish VN, Eckert L, Graham NM, Stahl N, Yancopoulos GD, Louis-Tisserand M, Teper A.. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet*; 2016.
2. Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, Zhu H, Hamilton JD, Swanson BN, Khan A, Chao J, Staudinger H, Pirozzi G, Antoni C, Amin N, Ruddy M, Akinlade B, Graham NMH, Stahl N, Yancopoulos GD, Teper A.. Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma. *N Eng J Med*; 2018.

Evidence Profile: 300 mg of dupilumab every 2 weeks compared to placebo for patients with uncontrolled asthma

Bibliography: Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, Busse WW, Ford L, Sher L, FitzGerald JM, Katelaris C, Tohda Y, Zhang B, Staudinger H, Pirozzi G, Amin N, Ruddy M, Akinlade B, Khan A, Chao J, Martinova R, Graham NMH, Hamilton JD, Swanson BN, Stahl N, Yancopoulos GD, Teper A. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. *N Engl J Med.* 2018;378(26):2486-2496. doi: 10.1056/NEJMoa1804092. Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, Pirozzi G, Sutherland ER, Evans RR, Joish VN, Eckert L, Graham NM, Stahl N, Yancopoulos GD, Louis-Tisserand M, Teper A. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet.* 2016;388(10039):31-44. doi: 10.1016/S0140-6736(16)30307-5.

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	300 mg of dupilumab every 2 weeks	placebo	Relative (95% CI)	Absolute (95% CI)		

EXACERBATION - annualised severe exacerbation event rate (dupilumab during 24 weeks)

1	randomised trials	serious ^a	not serious ^b	not serious	not serious	none	NCT01854047 (Wenzel 2016) reported a risk reduction in event rates of 70.5% (45.4 to 84.1) in favour of 24 weeks of treatment (exacerbation rate for dupilumab 0.265 (0.157 to 0.445) versus exacerbation rate for placebo 0.897 (0.619 to 1.300)).			⊕⊕⊕○ MODERATE	
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EXACERBATION - annualised severe exacerbation event rate (dupilumab during 52 weeks)

1	randomised trials	serious ^c	not serious ^b	not serious	not serious	none	NCT02414854 (Castro 2018) reported a risk reduction in event rates of 46% (32 to 57) in favour of 52 weeks of treatment (exacerbation rate for dupilumab 0.456 (0.389 to 0.534) versus exacerbation rate for placebo 0.970 (0.810 to 1.160)).			⊕⊕⊕○ MODERATE	
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ASTHMA CONTROL (assessed with: ACQ-5 (dupilumab during 24 weeks); Scale from: 0 to 6)^d

2	randomised trials	serious ^{a,c}	not serious	not serious	not serious	none	790	479	-	least square MD 0.22 ACQ-5 units lower (0.34 lower to 0.11 lower)	⊕⊕⊕○ MODERATE	
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ASTHMA CONTROL (assessed with: ACQ-5 (dupilumab during 52 weeks); Scale from: 0 to 6)^d

1	randomised trials	serious ^c	not serious ^b	not serious	not serious	none	633	321	-	least square MD 0.22 ACQ-5 units lower (0.36 lower to 0.08 lower) ^e	⊕⊕⊕○ MODERATE	
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QUALITY OF LIFE (assessed with: AQLQ (dupilumab during 24 weeks); Scale from: 0 to 7)^f

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	300 mg of dupilumab every 2 weeks	placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious ^{a,c}	not serious	not serious	not serious	none	790	479	-	least square MD 0.23 AQLQ units higher (0.03 higher to 0.43 higher)	⊕⊕⊕○ MODERATE	

QUALITY OF LIFE (assessed with: AQLQ (dupilumab during 52 weeks); Scale from: 0 to 7)^f

1	randomised trials	serious ^c	not serious ^b	not serious	not serious	none	633	321	-	least square MD 0.26 AQLQ units higher (0.12 higher to 0.4 higher) ^e	⊕⊕⊕○ MODERATE	
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SIDE EFFECTS (assessed with: any side effect (dupilumab during 24 weeks))

1	randomised trials	serious ^a	not serious ^b	not serious	not serious	none	121/156 (77.6%)	118/158 (74.7%)	RR 1.04 (0.92 to 1.18)	3 more per 100 (from 6 fewer to 13 more)	⊕⊕⊕○ MODERATE	
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SIDE EFFECTS (assessed with: any side effect (dupilumab during 52 weeks))

1	randomised trials	serious ^c	not serious ^b	not serious	not serious	none	515/632 (81.5%)	270/321 (84.1%)	RR 0.97 (0.91 to 1.03)	3 fewer per 100 (from 8 fewer to 3 more)	⊕⊕⊕○ MODERATE	
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SIDE EFFECTS (assessed with: any serious side effect (dupilumab during 24 weeks))

1	randomised trials	serious ^a	not serious ^b	not serious	serious ^g	none	13/156 (8.3%)	9/158 (5.7%)	RR 1.46 (0.64 to 3.32)	3 more per 100 (from 2 fewer to 13 more)	⊕⊕○○ LOW	
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SIDE EFFECTS (assessed with: any serious side effect (dupilumab during 52 weeks))

1	randomised trials	serious ^c	not serious ^b	not serious	serious ^h	none	55/632 (8.7%)	27/321 (8.4%)	RR 1.03 (0.67 to 1.61)	0 fewer per 100 (from 3 fewer to 5 more)	⊕⊕○○ LOW	
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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	300 mg of dupilumab every 2 weeks	placebo	Relative (95% CI)	Absolute (95% CI)		

SIDE EFFECTS (assessed with: injection site reactions (dupilumab during 24 weeks))

1	randomised trials	serious ^a	not serious ^b	not serious	serious ^g	none	41/156 (26.3%)	21/158 (13.3%)	RR 1.98 (1.23 to 3.19)	13 more per 100 (from 3 more to 29 more)	⊕⊕○○ LOW	
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SIDE EFFECTS (assessed with: injection site reactions (dupilumab during 52 weeks))

1	randomised trials	serious ^c	not serious ^b	not serious	serious ^h	none	116/632 (18.4%)	33/321 (10.3%)	RR 1.79 (1.24 to 2.57)	8 more per 100 (from 2 more to 16 more)	⊕⊕○○ LOW	
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CI: Confidence interval; **RR:** Risk ratio

Explanations

- a. potential attrition bias in NCT01854047 (Wenzel 2016): trial report described an intention to treat analysis but results reported in tables does not fit with the intention to treat population
- b. not applicable (findings from 1 trial)
- c. potential attrition bias in NCT02414854 (Castro 2018): 75% participants completed the study. Reasons for discontinuation were not declared for 46% of patients that did not completed the 52 weeks intervention period.
- d. minimal important difference for ACQ-5 is 0.5; lower values indicate better asthma control.
- e. Castro 2018 reported effect estimates with standard errors. The effect estimated in the SoF table has been recalculated with the RevMan 5.3 statistical package
- f. minimal important difference for AQLQ is 0.5; higher scores indicates better QoL.
- g. low event rate, resulting in imprecise effect estimate
- h. imprecision of results resulting from the results from Castro 2018 (planned treatment duration of 52 weeks)

Evidence Profile: 300 mg of dupilumab every 2 weeks compared to placebo for glucocorticoid dependent severe asthma

Bibliography: Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, Zhu H, Hamilton JD, Swanson BN, Khan A, Chao J, Staudinger H, Pirozzi G, Antoni C, Amin N, Ruddy M, Akinlade B, Graham NMH, Stahl N, Yancopoulos GD, Teper A. Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma. N Engl J Med. 2018;378(26):2475-2485. doi: 10.1056/NEJMoa1804093.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	300 mg of dupilumab every 2 weeks	placebo	Relative (95% CI)	Absolute (95% CI)		

EXACERBATION - annualised severe exacerbation event rate (dupilumab during 24 weeks)

1	randomised trials	not serious	not serious ^a	not serious	not serious	none	NCT02528214 (Rabe 2018) reported a risk reduction in event rates of 59.3% (37 to 73.7) favouring 24 weeks of treatment (exacerbation rate for dupilumab 0.649 (0.442 to 0.955) versus exacerbation rate for placebo 1.597 (1.248 to 2.043).				⊕⊕⊕⊕ HIGH	
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ASTHMA CONTROL (assessed with: ACQ-5 (dupilumab during 24 weeks))^b

1	randomised trials	not serious	not serious ^a	not serious	serious ^b	none	NCT02528214 (Rabe 2018) reported a least square MD of -0.47 (-0.76 to -0.18) favouring 24 weeks of treatment with dupilumab				⊕⊕⊕○ MODERATE	
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LUNG FUNCTION (change in FEV1 from baseline to end of treatment) (assessed with: liters)

1	randomised trials	not serious	not serious ^a	not serious	serious ^c	none	NCT02528214 (Rabe 2018) reported a least square MD of 0.22 (0.09 to 0.34) L favouring 24 weeks of treatment with dupilumab (dupilumab 0.22 (0.05) versus placebo 0.01 (0.05)).				⊕⊕⊕○ MODERATE	
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SYSTEMIC STEROIDS USE (patients with ≥50% reduction in oral glucocorticoid dose at 24 w)

1	randomised trials	not serious	not serious ^a	not serious	not serious	none	82/103 (79.6%)	57/107 (53.3%)	RR 1.49 (1.22 to 1.83)	26 more per 100 (from 12 more to 44 more)	⊕⊕⊕⊕ HIGH	
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SYSTEMIC STEROIDS USE (patients with oral glucocorticoid reduced to <5 mg/day at 24 w)

1	randomised trials	not serious	not serious ^a	not serious	not serious	none	74/103 (71.8%)	40/107 (37.4%)	RR 1.92 (1.46 to 2.53)	344 more per 1.000 (from 172 more to 572 more)	⊕⊕⊕⊕ HIGH	
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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	300 mg of dupilumab every 2 weeks	placebo	Relative (95% CI)	Absolute (95% CI)		

SYSTEMIC STEROIDS USE (patients with maximum possible reduction of oral glucocorticoid dose at 24 w)

1	randomised trials	not serious	not serious ^a	not serious	not serious	none	54/103 (52.4%)	32/107 (29.9%)	RR 1.75 (1.24 to 2.47)	224 more per 1.000 (from 72 more to 440 more)	⊕⊕⊕⊕ HIGH	
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SYSTEMIC STEROIDS USE (patients no longer requiring oral glucocorticoid at 24 w)

1	randomised trials	not serious	not serious ^a	not serious	not serious	none	54/103 (52.4%)	31/107 (29.0%)	RR 1.81 (1.28 to 2.57)	235 more per 1.000 (from 81 more to 455 more)	⊕⊕⊕⊕ HIGH	
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SIDE EFFECTS (assessed with: any side effect (dupilumab during 24 weeks))

1	randomised trials	not serious	not serious ^a	not serious	serious ^d	none	64/103 (62.1%)	69/107 (64.5%)	RR 0.96 (0.78 to 1.18)	3 fewer per 100 (from 14 fewer to 12 more)	⊕⊕⊕○ MODERATE	
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SIDE EFFECTS (assessed with: any serious side effect (dupilumab during 24 weeks))

1	randomised trials	not serious	not serious ^a	not serious	serious ^d	none	9/103 (8.7%)	6/107 (5.6%)	RR 1.56 (0.58 to 4.22)	3 more per 100 (from 2 fewer to 18 more)	⊕⊕⊕○ MODERATE	
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SIDE EFFECTS (assessed with: injection site reactions (dupilumab during 24 weeks))

1	randomised trials	not serious	not serious ^a	not serious	serious ^d	none	9/103 (8.7%)	4/107 (3.7%)	RR 2.34 (0.74 to 7.35)	5 more per 100 (from 1 fewer to 24 more)	⊕⊕⊕○ MODERATE	
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CI: Confidence interval; **RR:** Risk ratio

Explanations

a. not applicable (findings from 1 trial)

b. minimal important difference for ACQ-5 is 0.5; lower values indicate better asthma control.

- c. minimal important difference for FEV1 is 0.23.
- d. low event rate, resulting in imprecise effect estimate

Evidence Profile: 200 mg of dupilumab every 2 weeks compared to placebo for patients with severe asthma according to blood eosinophils

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	200 mg of dupilumab every 2 weeks	placebo	Relative (95% CI)	Absolute (95% CI)		

EXACERBATION - annualised severe exacerbation event rate at week 24 (according to blood eosinophil 300 cells/mm3 or more)

1 ¹	randomised trials	not serious	not serious ^a	not serious	not serious	none	0/65	0/68	Rate ratio 0.29 (0.11 to 0.76)	74 less severe exacerbations per 100 patients per year (from 44 to 122)	⊕⊕⊕⊕ HIGH	
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EXACERBATION - annualised severe exacerbation event rate at week 24 (according to blood eosinophil <300 cells/mm3)

1 ¹	randomised trials	not serious	not serious ^a	not serious	not serious	none	0/85	0/90	Rate ratio 0.32 (0.14 to 0.74)	53 less severe exacerbations per 100 patients per year (from 37 to 71)	⊕⊕⊕⊕ HIGH	
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LUNG FUNCTION - change in FEV1 from baseline at week 24 (according to blood eosinophil 300 cells/mm3 or more) (assessed with: Liters)

1 ¹	randomised trials	serious ^b	not serious ^a	not serious	serious ^c	none	59	52	-	least square 0.16 Liters more (0.02 more to 0.31 more)	⊕⊕○○ LOW	
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LUNG FUNCTION - change in FEV1 from baseline at week 24 (according to blood eosinophil <300 cells/mm3) (assessed with: Liters)

1 ¹	randomised trials	serious ^b	not serious ^a	not serious	serious ^c	none	76	73	-	least square 0.14 Liters more (0.03 more to 0.25 more)	⊕⊕○○ LOW	
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LUNG FUNCTION - change in FEV1 from baseline at week 24 (according to blood eosinophil 300 cells/mm3 or more) (assessed with: % of change; Scale from: 0 to 100)

1 ¹	randomised trials	serious ^b	not serious ^a	not serious	serious ^d	none	59	52	-	least square 10.07 percentage points more (1.23 more to 18.9 more)	⊕⊕○○ LOW	
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LUNG FUNCTION - change in FEV1 from baseline at week 24 (according to blood eosinophil <300 cells/mm3) (assessed with: % of change; Scale from: 0 to 100)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	200 mg of dupilumab every 2 weeks	placebo	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	serious ^b	not serious ^a	not serious	serious ^d	none	76	73	-	least square 8.75 percentage points more (2.7 more to 14.81 more)	⊕⊕○○ LOW	

ASTHMA CONTROL - at week 24 according to blood eosinophil 300 cells/mm3 or more (assessed with: ACQ-5; Scale from: 0 to 6)^e

1 ¹	randomised trials	serious ^b	not serious ^a	not serious	serious ^c	none	59	52	-	least square MD 0.42 ACQ-5 units lower (0.76 lower to 0.07 lower)	⊕⊕○○ LOW	
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ASTHMA CONTROL - at week 24 according to blood eosinophil <300 cells/mm3 (assessed with: ACQ-5; Scale from: 0 to 6)^e

1 ¹	randomised trials	serious ^b	not serious ^a	not serious	serious ^c	none	75	75	-	least square MD 0.33 ACQ-5 units lower (0.61 lower to 0.05 lower)	⊕⊕○○ LOW	
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QUALITY OF LIFE - at week 24 according to blood eosinophil 300 cells/mm3 or more (assessed with: AQLQ ; Scale from: 0 to 7)^f

1 ¹	randomised trials	serious ^b	not serious ^a	not serious	serious ^c	none	58	53	-	least square MD 0.67 AQLQ units higher (0.31 higher to 1.03 higher)	⊕⊕○○ LOW	
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QUALITY OF LIFE - at week 24 according to blood eosinophil <300 cells/mm3 (assessed with: AQLQ; Scale from: 0 to 7)^f

1 ¹	randomised trials	serious ^b	not serious ^a	not serious	not serious	none	74	74	-	least square MD 0.05 AQLQ units higher (0.26 lower to 0.36 higher)	⊕⊕⊕○ MODERATE	
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CI: Confidence interval

Explanations

a. not applicable (findings from 1 trial)

b. Relevant and differential attrition bias in NCT01854047 (Wenzel 2016) for placebo and dupilumab groups (more than 20% and around 10% respectively)

- c. the lower CI boundary crosses the threshold for minimal important difference
- d. Minimal important differences not known for FEV1 % of change, however the 95CI is wide and does not exclude important benefit or no effect.
- e. minimal important difference for ACQ-5 is 0.5; lower values indicate better asthma control.
- f. minimal important difference for AQLQ is 0.5; higher scores indicates better QoL.

References

1. Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, Pirozzi G, Sutherland ER, Evans RR, Joish VN, Eckert L, Graham NM, Stahl N, Yancopoulos GD, Louis-Tisserand M, Teper A.. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β 2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet*; 2016.

Evidence to Decision Framework:DUPIUMAB

Should an anti-interleukin 4/13 strategy be used for adults and children with severe asthma?		
POPULATION:	Adults and children with severe asthma	BACKGROUND: Approximately half of patients with asthma exhibit elevated markers of type 2 inflammation. Two of the cytokines that orchestrate this type of inflammation are interleukins (IL) 4 and 13, each of which independently elicits pathobiologic changes in airway structural and immune cells characteristic of asthma. IL4 is required for the skewing of T helper cells into Th2 cells, and for the switching of B cell antibody production into the IgE isotype crucial for allergic inflammation. IL13 is a prime inducer of airway hyperresponsiveness and is implicated in airway remodeling. Both cytokines engage and signal through the interleukin 4 receptor subunit alpha. A monoclonal antibody that targets the interleukin 4 receptor subunit alpha, dupilumab, has been found to be efficacious in randomized controlled trials to improve asthma-related outcomes. This systematic review and meta-analysis synthesizes the data from three randomized controlled trials that have investigated the anti-IL4/13 strategy and provides treatment recommendations based on the results.
INTERVENTION:	Anti-interleukin 4/13 strategy (dupilumab, a monoclonal antibody directed against the interleukin 4 receptor subunit alpha)	
COMPARISON:	No anti-interleukin 4/13	
MAIN OUTCOMES:	Rate of exacerbations	
	Time to first asthma exacerbation	
	Asthma exacerbations requiring ER visits or hospitalization	
	Lung function	
	Asthma control	
	Maintenance corticosteroid dose reduction	
	Adverse events	
	Serious adverse events	
	Quality of life	

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	<p>How substantial are the desirable anticipated effects?</p> <ul style="list-style-type: none"> ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know 	<p>Asthma exacerbations are a critically important outcome for the patients with asthma who experience these and the clinicians who care for them.</p> <p>Relative to participants assigned to placebo, those assigned to dupilumab experienced substantial (46-70.5%) reduction in their rates of asthma exacerbations (PMID: 29782224, PMID: 29782217, PMID: 27130691) (insert evidence tables for the two doses and time intervals).</p> <p>One RCT evaluated the effects of dupilumab therapy in oral corticosteroid (OCS) dependent asthma (Rabe 2018. PMID: 29782224). Dupilumab therapy was associated with greater number of participants that experienced $\geq 50\%$ reduction in OCS dose (RR 1.49; 95% CI 1.22-1.83), were able to reduce OCS dose to $< 5\text{mg/d}$ (RR 1.92; 95% CI 1.46-2.53) and were able to discontinue maintenance OCS (RR 1.81; 95% CI 1.28-2.57).</p> <p>Asthma symptom scores are another critically important outcome in asthma studies. Although the evidence favors dupilumab relative to placebo on these outcomes, their relative change was not as large compared to the improvement observed with asthma exacerbations. Relative to participants assigned to placebo, those assigned to dupilumab experienced a 0.22-0.47 point decrease (i.e. improvement) in Asthma Control Questionnaire (ACQ) (insert evidence table). Although statistically significant, these decreases in ACQ-5 scores did not surpass the 0.5-point MCID for the ACQ symptom score for trials in asthma.</p> <p>Similarly, although the improvements in lung function (FEV1) were statistically significant (see evidence tables), they were small and did not cross the MCID threshold of 0.23 L.</p> <p>Efficacy is similar between doses. The effect size for all above outcomes was larger in subgroup of patients with higher blood eosinophil count.</p> <p>Meta-analytical results on other outcomes appear in the online supplement.</p>	<p>Although a defined threshold for clinically meaningful reductions in asthma exacerbations has not been universally agreed upon, the effect sizes in reductions in asthma exacerbations for this drug would be considered clinically substantial by most practitioners.</p> <p>The decision to consider changes in lung function [forced expiratory volume in the first second (FEV1)] as 'important' outcomes as opposed to 'critical' outcomes is due to their place relative to other critical outcomes. We understand that most clinicians would prescribe dupilumab due to its efficacy in reducing asthma exacerbations despite only modest improvements in lung function. Results from our meta-analysis on the modest effect on lung function relative to the effect on asthma exacerbations led us to downgrade the importance of lung function to an important outcome, as suggested by the methodological approach endorsed by Guyatt et al (PMID: 21194891)</p> <p>Taken together, the reduction in asthma exacerbations is substantial enough for this committee to judge the desirable effects of an anti-IL4/13 strategy as large, regardless of relatively smaller effects on symptom scores and lung function.</p> <p>Dupilumab is currently FDA approved in patients ≥ 12 years of age with moderate to severe eosinophilic asthma or those with systemic corticosteroid dependent asthma.</p>

			<p>Dupilumab is available in two doses for indication of asthma: 200 mg every 2 weeks after a loading dose of 400 mg; 300 mg every 2 weeks after a loading dose of 600 mg. This panel agrees with FDA recommendation to consider the higher dose for patients with OCS dependent asthma or comorbid atopic dermatitis.</p> <p>FDA notes that “the adolescent subgroup demonstrated a statistically significant improvement in lung function for both dose groups; however, the exacerbation benefit was not clearly demonstrated for either dose group. This review recommends approval in this age group, as there are no age-related differences in the pharmacokinetic and pharmacodynamic parameters, and no safety concerns for dupilumab in adolescent patients.”</p>
<p>UNDESIRABLE EFFECTS</p>	<p>How substantial are the undesirable anticipated effects?</p> <ul style="list-style-type: none"> ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know 	<p>In the RCTs analysed, the relative risk of a study participant developing an adverse event was 0.96-1.08 for those participants assigned to dupilumab compared to placebo. Similarly, the relative risk of participant developing a serious adverse event when assigned to dupilumab vs. placebo was 0.93-1.56. (insert evidence tables).</p> <p>Relative risk for injection site reactions varied from 1.47 (95% CI 0.88-2.47; 200 mg dose at 24 weeks) to 2.34 (95% CI 0.74-7.35; 300 mg dose at 24 weeks)</p>	<p>Dupilumab has been well tolerated, receiving its first FDA approval for atopic dermatitis in 2017 followed by its approval for asthma in 2018.</p> <p>Treatment related eosinophilia that met criteria for adverse event was observed in 4.1% of participants assigned to dupilumab vs. 0.6% in those assigned to placebo (PMID: 29782217). Associated symptoms of eosinophilia were noted in 0.2% of the total trial population in this study. Similarly, in another study of patients with corticosteroid-dependent asthma (PMID: 29782224), treatment related eosinophilia AE was observed in 13% of participants as compared to 1% of participants assigned to placebo. Long term follow-up for this and other side effects is unavailable. Monitoring for eosinophilia is not mandated in the package insert.</p>

			<p>Injection site reactions were the most common side effects and were dose-related.</p> <p>The ocular side effects seen in studies of dupilumab in atopic dermatitis were not observed in asthma trials.</p>
CERTAINTY OF EVIDENCE	<p>What is the overall certainty of the evidence of effects?</p> <ul style="list-style-type: none"> ○ Very low ○ Low ● Moderate ○ High ○ No included studies 	<p>Overall population (patients with moderate and severe persistent asthma): low quality of evidence;</p> <p>Population that meets criteria for the diagnosis of severe asthma defined by the ERS/ATS Guidelines: low quality of evidence</p>	<p>Our certainty assessment relies on study design (randomized controlled trials), risk of bias (not serious), inconsistency (not serious), indirectness (not serious), and imprecision (not serious).</p> <p>Further the certainty is based on the quality of evidence that is lowest among critical outcomes.</p>
VALUES	<p>Is there important uncertainty about or variability in how much people value the main outcomes?</p> <ul style="list-style-type: none"> ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes 	<p>No evidence identified</p>	<p>There is no important uncertainty about how patients and the clinicians who care for them assess asthma exacerbations. On the other hand, asthma exacerbations are not the only critical outcome for patients and clinicians, who also consider the effect of interventions on other outcomes, such as changes in lung function, change in maintenance dose of systemic corticosteroids, asthma symptoms, and quality of life. Although the effect size of anti-IL4/13 strategy drug is not uniform across these other outcomes, these drugs tended to improve to varying degrees all asthma related outcomes. Further, patients and clinicians rarely decide to prescribe these drugs based on only one of these outcomes in isolation.</p>

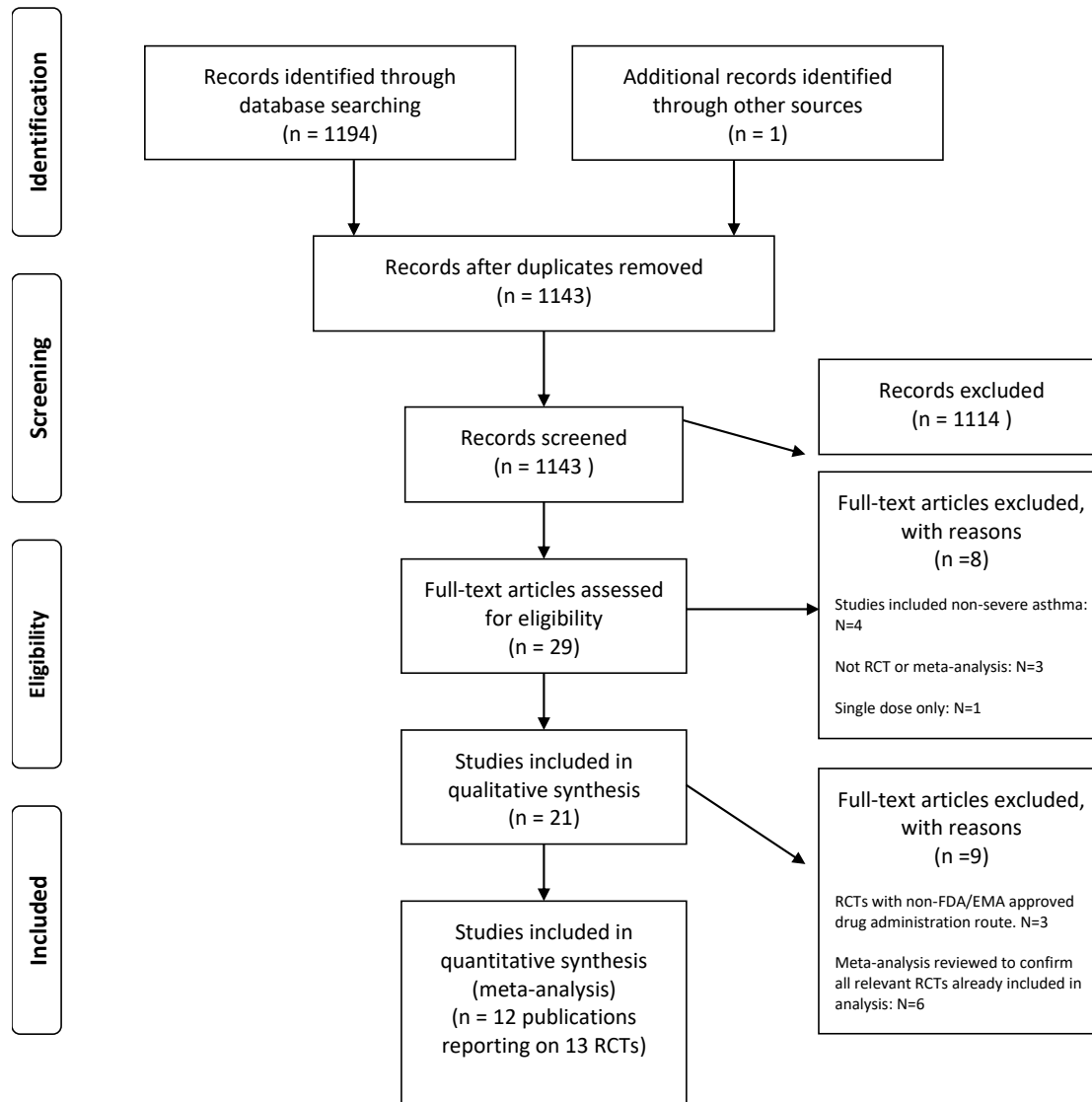
			Further, many pharmacy formularies for physician groups and hospitals restrict these drugs to patients with severe asthma and a recent history of asthma exacerbations. The decision whether or not to prescribe these drugs is likely to be important in this population.
BALANCE OF EFFECTS	<p>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</p> <ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know 	Dupilumab therapy was associated with large desirable and small undesirable effects.	Dupilumab was well tolerated in the clinical trials. Frequency of both serious and non-serious side effects were similar in placebo and intervention groups. Thus, considering the substantial benefit in terms of reducing asthma exacerbations, the balance favors using an anti-IL4/13 strategy.
AYBCOST EFFECTIVENESS	<p>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</p> <ul style="list-style-type: none"> ● Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies 	The December 2018 report by the Institute for Clinical and Economic Review (ICER) states that dupilumab costs >\$400,000 per quality-adjusted life years (QALY) gained when compared to standard of care (ICER 2018). These figures far exceed the accepted threshold for a cost-effective intervention of \$150,000 per QALY gained.	Therefore, the alternative is favored over an anti-IL4/13 strategy from a cost-effectiveness standpoint.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	<p>What is the certainty of the evidence of resource requirements (costs)?</p> <ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate ● High ○ No included studies 	The manufacturers' listed annual net price for dupilumab is \$36,000 (ICER 2018). The certainty of these costs is therefore high.	

EQUITY	<p>What would be the impact on health equity?</p> <ul style="list-style-type: none"> ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know 	No evidence identified.	<p>In the US, racial and ethnic minorities, and individuals of lower socioeconomic status have been documented to have less access to specialty clinics and are less likely to use controller therapy for asthma. Since dupilumab is mainly prescribed by specialists it is likely that racial and ethnic minorities will be less likely to be prescribed one of these drugs. Other groups may thus experience greater reductions in asthma exacerbations due to access to these drugs, which will thus reduce health equity. Similarly, patients with severe asthma who live in regions with fewer specialists will be less likely to receive these drugs, thus reducing equity between areas with high and low access to specialty care.</p> <p>On the other hand, the manufacturers of these drugs have programs in place to reduce patients' out of pocket costs for these drugs, which may partly mitigate the decrease in equity posed by differences in access by socioeconomic status and race/ethnicity.</p>
ACCEPTABILITY	<p>Is the intervention acceptable to key stakeholders?</p> <ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know 	No evidence identified.	<p>Most patients with severe asthma welcome the possibility of relief from asthma through dupilumab, as long as the potential benefit is not offset by adverse effects, costs or other inconveniences (travel or prolonged waiting times in clinic, etc.).</p> <p>Health insurance companies and clinic administrations find anti-IL4/13 strategy drugs less acceptable due to their high cost.</p>
FEASIBILITY	<p>Is the intervention feasible to implement?</p> <ul style="list-style-type: none"> ○ No 	No evidence identified.	<p>The feasibility to implement is dependent on many variables including access to asthma specialists, clinical</p>

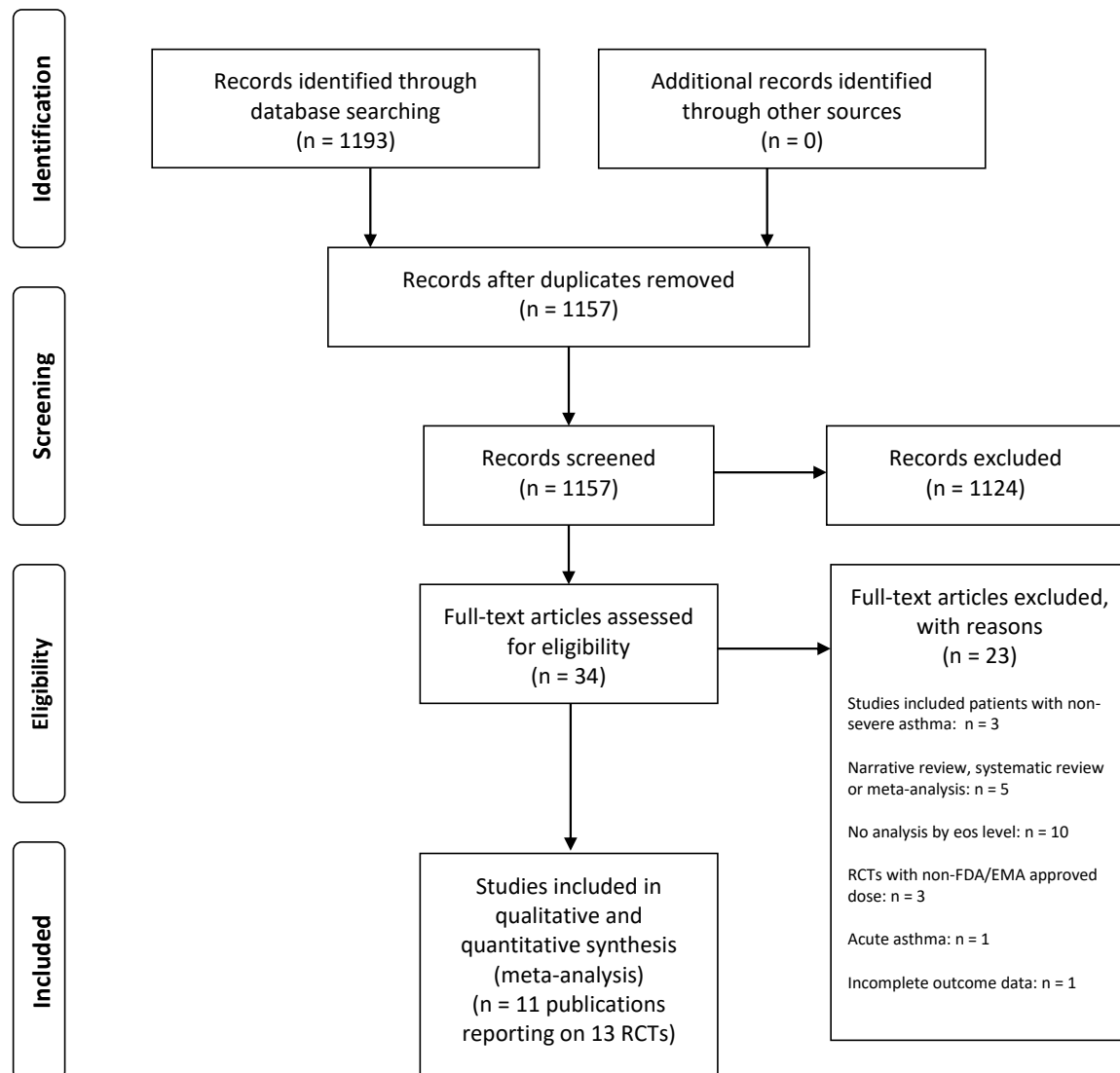
	<ul style="list-style-type: none"> ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know 		<p>resources to train patients to self-administer this drug, clinical set up that allows close follow-up of patients on therapy, as well as a laboratory that can measure blood eosinophils in these patients. Patients without access to these resources are unlikely to receive this therapy.</p>
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PRISMA FLOW CHARTS

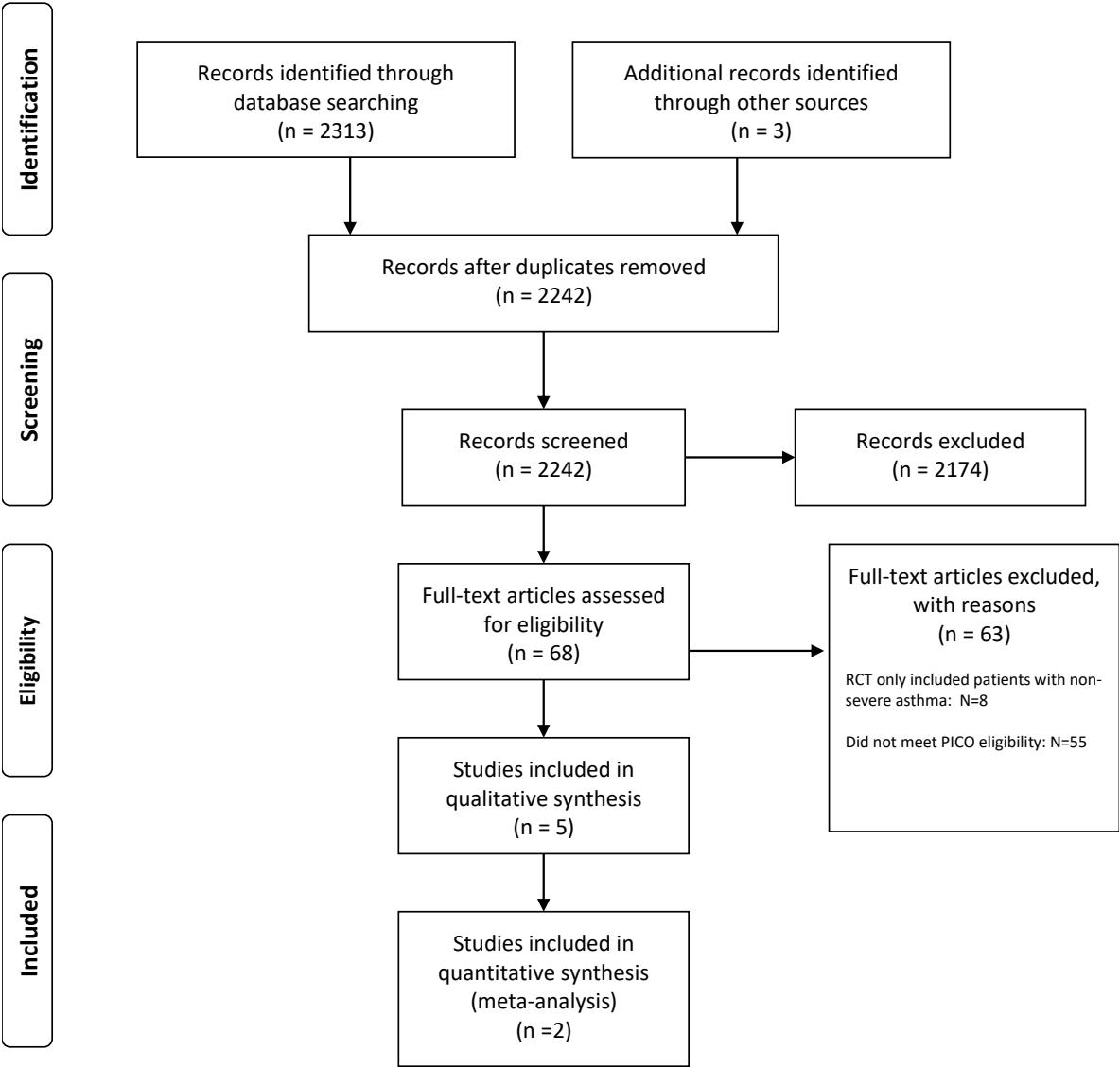
Should a monoclonal anti-IL5 antibody be used in adults and children with severe asthma?



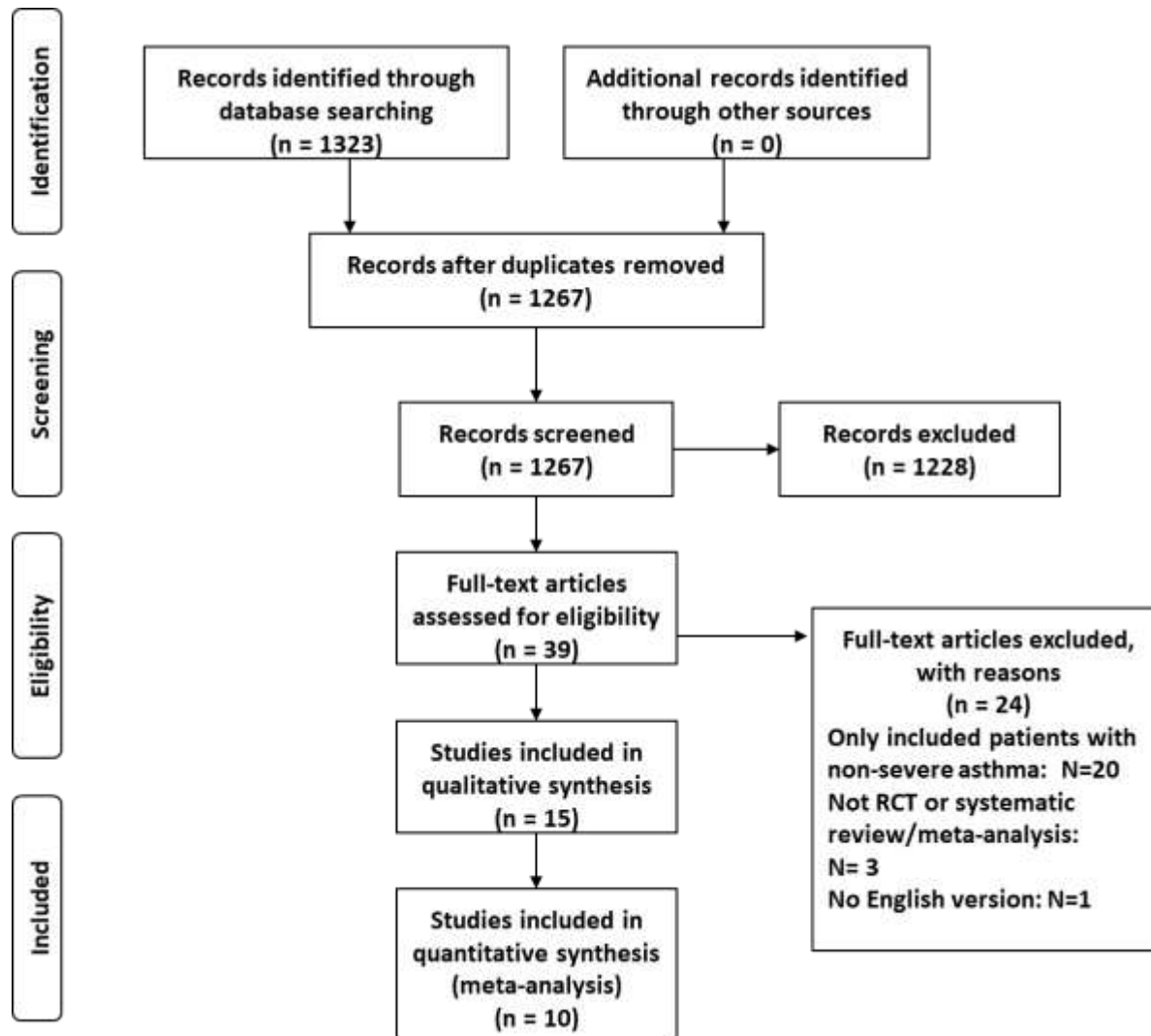
Should a measurement of a specific biomarker be used to guide initiation of treatment with a monoclonal anti-IL5 or IL5R α antibody in adults and children with severe asthma? (biomarkers being exhaled NO, peripheral or sputum eosinophils, and serum periostin)



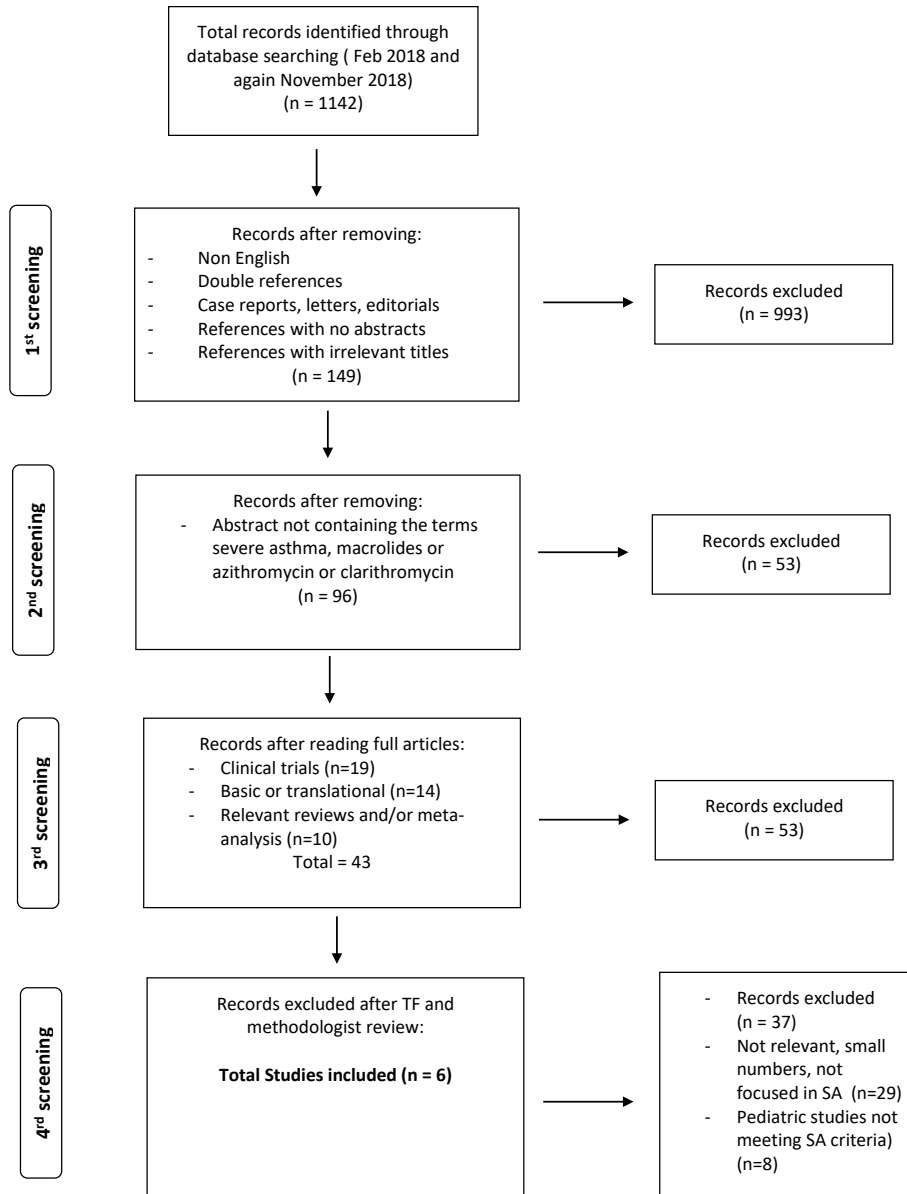
Should a measurement of a specific biomarker be used, in addition to total IgE level, to guide initiation of treatment with a monoclonal anti-IgE antibody in adults and children with severe asthma? (biomarkers being exhaled NO, peripheral or sputum eosinophils, and serum periostin)



Should a long-acting inhaled muscarinic antagonist (LAMA) be used in adults and children with severe asthma?



Should a macrolide (i.e., azithromycin, clarithromycin) be used in adults and children with severe asthma?



Should an anti-interleukin 4/13 strategy be used for adults and children with severe asthma?

