Section 2: Biomarkers to predict response to biologic therapies and macrolides
Summary of randomized controlled trials

Biomarkers		Study Design	N	Drug	Predictive ability to identify responders	Authors
Cut-offs	**Cut-off selection**					
Sputum eosinophils						
>3%	Inclusion criteria	RCT	61	mepolizumab	**No subgroup analyses by baseline sputum eosinophils** overall ↓ Exacerbations and ↑ AQLQ	Haldar P et al NEJM 2009;360: 973-84
>3%	Inclusion criteria	RCT	19	mepolizumab	**No subgroup analyses by baseline sputum eosinophils** ↓Exacerbations ↓ ACQ	Nair P et al. NEJM 2009; 360: 985-93
≥10%	Not specified	Post-hoc analysis of double-blind RCT	53	reslizumab	No change in ACQ and FEV1	Castro M et al. AJRCCM 2011; 184: 1125-32
Sputum neutrophil						
Non-eosinophilic sputum (Neutrophil >61% or Neutrophils <61% and sputum eosinophils <1.01%)	Median	RCT, randomization stratified by sputum neutrophils	28	Clarithromycin	Decreased airway IL-8, neutrophil numbers, neutrophil elastase and MMP-9 levels in those with non-eosinophilic sputum compared to eosinophilic sputum: Did not predict change in overall AQLQ	Simpson JL et al. AJRCCM 2008; 177:148-55
Mixed markers						
Sputum eos<3% or blood eos <300/uL	Median	Prespecified analysis of RCT	331 sputum; 89 blood	Azithromycin	**No greater effect size in the ↓RR (95% CI) of exacerbations in patients with non-eosinophilic phenotype** 'Eosinophilic' group: RR 0.52 (0.29-0.94) 'Non-eosinophilic' group: RR 0.66 (0.47-0.93)	Gibson PG et al. Lancet 2017; 390: 659-668

FeNO (ppb)						
≥19.5 ppb	Median value	Prespecified subgroups of double-blind RCT	394	omalizumab	**Greater effect size in the ↓RR (95% CI) of exacerbations with increased FeNO -**omalizumab vs. placebo ≥19.5 ppb: 0.50 vs. 1.07; 53% lower rate (95% CI 37%-70%, p=0.001) <19.5 ppb: 0.60 vs. 0.71; 9% lower rate (95% CI 32%-46%, p=0.45)	Hanania NA et al. AJRCCM 2013: 187:804-11
≥24 ppb	Post-hoc, based on ATS guidelines	Post-hoc analysis of double-blind RCT	394	omalizumab	**Greater effect size in the ↓RR (95% CI) of exacerbations with increased FeNo** = omalizumab vs. placebo ≥24 ppb: 0.55 vs. 1.01; 46% lower rate (95% CI 14%-66%, p=0.009) <24 ppb: 0.56 vs. 0.81; 31% lower rate (95% CI 10%-55%, p=0.087)	Hanania NA et al. AJRCCM 2013: 187:804-11
≥23.5 ppb	Median value	Prespecified subgroups of double-blind RCT	not reported	omalizumab	**No greater effect size in the ↓ OR (95% CI) of ≥1 exacerbation in the next 90 days** - mepolizumab vs. placebo ≥23.5: OR 0.36 (0.14-0.91) <23.5: OR 0.75 (0.28, 2.03), group difference p=0.283	Teach SJ et al. JACI 2015: 136: 1476-85
	Not specified	Prespecified subgroups of double-blind RCT		Mepolizumab	**No greater effect size in the ↓ RR (95% CI) of exacerbations with increasing FeNO** - mepolizumab vs. placebo	Pavord I et al Lancet 2012 ; 380 651-9
<50 ppb			411		RR 0.63 (0.47-0.84)	
≥50 ppb			195		RR 0.43 (0.30-0.63	
Serum eosinophils (cells/ul)						
≤200	Not specified	Prespecified analysis of RCT	109	Azithromycin	**Greater effect in ↓ RR of exacerbations with <u>lower</u> serum eosinophils**- azithromycin vs. placebo *↓ RR of severe exacerbations or LRTI* **If serum eo ≤200 /uL**: 0.44 (0.25-0.78)/patient vs. 1.03 (0.72-1.48), p=0.013, **All patients:** 0.75 (0.55-1.01)/patient vs. 0.81 (0.61-1.09), p=0.682 *↓ RR (95% CI) of severe exacerbations* **If serum eo ≤200 /uL**: 0.42 (0.17-1) vs 2.19 (95% CI 1.01 to 4.73) **All patients:** 0.75 (0.55-1.01)/patient vs. 0.81 (0.61-1.09), p=0.682	Brusselle GG et al Thorax 2013; 68: 322-9

≥300 <300	Median value	Prespecified analysis of RCT	420 187 233	Azithromycin	**No difference in exacerbation rate between those with high or low serum eosinophils - azithromycin vs. placebo** 0.95 vs 2.11; IRR 0.51 (95% CI 0.28-0.94, p=0.031) 1.14 vs 1.63; IRR 0.68 (95% CI 0.43-1.05, p=0.084)	Gibson PG et al (unpublished data)
≥260	Median value	Prespecified subgroups of double-blind RCT	797	omalizumab	**Greater effect in the ↓RR of exacerbations with <u>higher</u> blood eosinophil counts - omalizumab vs. placebo** ≥260 eo/uL: 0.70 vs. 1.03; 32% lower rate (95% CI 11-48, p=0.005) <260 eo/uL: 0.65 vs. 1.03; 9% lower rate (95% CI 24-34, p=0.54)	Hanania NA et al. AJRCCM 2013: 187:804-11
>300	Not specified	Prespecified subgroups of double-blind RCT	217	omalizumab	**Greater effect in ↓RR (95% CI) of exacerbations with <u>higher</u> blood eosinophils counts** = omalizumab vs. placebo ≥300 eo/uL: 0.25 vs 0.59/patient, RR 0.41 (0.20-0.82), p=0.0125 <300 eo/uL: 0.17 vs 0.16/patient, RR 1.07 (0.45-2.53), p=0.8807	Busse W et al. JACI 2013; 132:485-6
≥320 <320	Median	Prespecified subgroups of double-blind RCT	Not reported	omalizumab	**No greater effect size in the ↓ OR (95% CI) of ≥1 exacerbation in the next 90 days** - omalizumab vs. placebo ≥320 eo/uL: OR 0.31 (0.14-0.7) <320 eo/uL: OR 1.08 (0.27-4.3), group difference p=0.13	Teach SJ et al. JACI 2015: 136: 1476-85
	Not specified	Prespecified subgroups of double-blind RCT	161	Mepolizumab	**Greater effect in ↓RR (95% CI) of exacerbations with higher blood eosinophils counts**	Pavord I et al Lancet 2012 ; 380 651-9
≤150					RR 0.92 [0.58-1.45]	
150-≤300			161		RR 0.45 [0.25-0.80]	
>300-≤500			135		RR 0.69 [0.43-1.09]	
≥500			159		RR 0.27 [0.19-0.39]	

≥ 15L at screening or ≥300 in past year	inclusion criteria	RCT	135	Mepolizumab	**No subgroup analyses by baseline eosinophils** ↓ Exacerbations, ↓OCS, ↓ ACQ-5, ↓SGRQ in the whole group.	Bel EH et al. NEJM 2014; 371: 1189-97
≥500	Not specified	Prespecified subgroups of double-blind RCT	177	Mepolizumab	**Greater effect size in the ↓RR (95% CI) of exacerbations Iin subgroup with higher eosinophil counts vs. all patients** (IV vs. SC mepolizumab vs. placebo) **≥500 eo/uL (subgroup):** 0.59/patient/yr (IV) vs. 0.47/patient/yr (SC) vs. 2.26/patient/year: RR 0.26 (IV) vs. RR 0.21 (SC) **≥300 eo/uL (all patients)** : RR 0.47 (0.28-0.60) IV and 0.53 (0.36-0.65) SC	Ortega H et al. ERJ 2014; 44: 239-41
	Not specified	Secondary analysis of two RCT, with pre-specified subgroup analysis of various range of blood eosinophils		Mepolizumab	**Greater effect size in the ↓ RR (95% CI) in 'clinically significant' exacerbations with increasing baseline blood eosinophils**	Ortega H et al. Lancet Resp Med 2016; 4: 549-56
≥150			920		Exacerbation rate: 0·92/yr, RR 0·48 (0·39–0·58)	
≥300			610		Exacerbation rate: 0·89/year, RR 0·41 (0·33–0·51)	
≥400			461		Exacerbation rate: 0·81/year, RR 0·34 (0·27–0·44)	
≥500			354		Exacerbation rate:0·75/year, RR 0·30 (0·23–0·40)	
	Not specified	Post-hoc analysis of double-blind RCT		Reslizumab	**No impact of blood eosinophil counts on the ACQ, small effect on with elevated eosinophils FEV1**	Castro M et al. AJRCCM 2011; 184: 1125-32
<500			49		**Least-square Mean Difference (95% CI)0.19 (–0.02, 0.39)**	
≥500			55		**Least-square Mean Difference (95% CI)0.25 (0.01, 0.50)**	
	Identified by analysis of 2 dataset for correlation of sputum eosinophils	RCT	315	Reslizumab	**No greater effect size on ↑ FEV1 with increasing blood eosinophil counts**	Bjermer L et al. Chest 2016 150: 789-98
400-499						
500-599						

≥400	Identified by analysis of 2 dataset for correlation of sputum eosinophils	2 52-wk RCT with pre-specified subgroup analysis on ≥500 /uL and ≥700 /uL		Reslizumab	**No greater effect size in the ↓ RR (95% CI) in exacerbations with increasing baseline blood eosinophils** All patients : RR 0.46 (0.37,0.58)	Castro M et al Lancet Resp med 2015; 3: 355-66
≥500			567		RR 0.49 (0.36,0.65)	
≥700			344		RR 0.41 (0.28,0.60)	
≥400	Identified by analysis of 2 dataset for correlation of sputum eosinophils	Prespecified subgroups of double-blind RCT	96	Reslizumab	**Greater effect size in the ↑ from baseline FEV1 (primary outcome) -mean difference (MD) (95% CI) and in ↑ FVC↓ ACQ, ↓ SABA in the subgroup with higher compared to lower blood eosinophils** ≥400 eo/uL (subgroup): 0.27 (0.008 to 0.53) L	Corren J et al. Chest 2016; 150: 799-810
<400			392		<400 eo/uL (all patients): 0.33 (-0.7 to 0.14) L	
≥300	Not specified	Post-hoc analysis of double-blind RCT	81	Benralizumab	**No greater effect size in the ↓ RR (95% CI) in exacerbations with increasing baseline blood eosinophils** ≥300 eo/uL: RR 1.90 (1.24, 2.78) <300 eo/uL: RR 1.50 (0.49, 3.51)	Nowak RM et al. AJEM 2015; 33: 14-20
≥300	Not specified	Prespecified subgroups of double-blind RCT	165	Benralizumab	Significant decrease in exacerbation in benralizumab (20 and 100 mg) in patient with increased blood eosinophils -7 %(–55 to 26) 57% (33 to 72) 43% (18 to 60)	Castro M et al . Lancet Resp med 2014: 2: 879-90
300	Not specified	Prespecified subgroups of double-blind RCT	809	Benralizumab	0·70 (0·50–1·00; 0·0471) 0·83 (0·59–1·16; 0·2685)	Bleecker ER at al. Lancet 2016 ; 388: 2128-41

>=300			395		0·55 (0·42–0·71; <0·0001) 0·49 (0·37–0·64; <0·0001)	
overall group	Not specified	Prespecified subgroups of double-blind RCT		Benralizumab		Fitzgerald JM et al. Lancet 2016; 388: 2128-41
<300			728		0·64 (0·45–0·92) 0·60 (0·42–0·86)	
>=300			363		0·64 (0·49–0·85) 0·72 (0·54–0·95)	
	Not specified	Prespecified subgroups of double-blind RCT	33	Benralizumab	Median reduction in final OCS dose compared with baseline (range)50.0 (0.0–100), 37.5 (–16.7 to 100),57.5 (–50.0 to 100)	Nair P et al, NEJM 2017; 376: 2448-58
≥300			187		Greater ↓ OCS 0.0 (–150 to 100), 75.0 (–100 to 100), 75.0 (–50.0 to 100)	
	Not specified	Secondary analysis of two RCT, with pre-specified subgroup analysis of various range of blood eosinophils		Benralizumab	**Greater ↓ in exacerbations with increasing baseline blood eosinophils**	Goldman M Curr Med Res Opin 2017; 33: 1605-13
<150			122 88		SIROCCO: RR 0.76 [0.45 to1.27), p=0.29 CALIMA: RR 0.65 (0.39 to 1.09), p=0.11	
≥150			631 615		SIROCCO: RR 0.58 [0.46 to 0.74), p<0.001 CALIMA: RR 0.64 (0.50 to 0.81), p<0.001	
Serum IgE (IU/L)						
Range	No cutoff used for logistic regression	Post hoc logistic regression of double blind RCT	1070	omalizumab	No change in composite outcome (no exacerbations, improvement in FEV12, SABA use, symptoms, QoL) according to baseline IgE	Bousquet J et al. Chest 2004: 125: 1378-86

≥ 76	Lower quartile	Post-hoc analysis of pooled population from 7 RCT	4294	omalizumab	Decreased asthma exacerbation rate if IgE in each of the three highest quartiles compared to lowest quartile: -13.8% (p=0.227), -41.9% (<0.001), -45.4% (<0.001), -46.5% (<0.001) for IgE 0-75IU/ml, 76-147IU/ml, 148-273IU/ml, >=274IU/ml: Decreased ER visits, AQLQ with IgE quartiles and no difference in severe exacerbation rate FEV1, physician's overall assessment with IgE quartile	Bousquet J et al. Respir Med 2007; 101:1483-92
IgE ≥255	Median	Prespecified subgroups of double-blind RCT	513	omalizumab	**No greater effect size in the ↓ OR (95% CI) of ≥1 exacerbation in the next 90 days** - mepolizumab vs. placebo ≥255 IU/L: OR 1.11 (0.31-4.02), <255 IU/L: OR 0.34 (0.14-0.80), Group difference p=0.13	Teach SJ et al. JACI 2015: 136: 1476-85
				Mepolizumab	**No greater effect size on ↓ RR in 'clinically significant' exacerbations with increasing IgE**	
≤30	Not specified	Prespecified subgroups of double-blind RCT	70		**0.39[0.22-0.70]**	
>30-≤700			461		0.61[0.47-0.80]	
>700			83		0.38[0.21-0.68]	Pavord I et al Lancet 2012 ; 380 651-9

Section 3: Long acting muscarinic antagonists (LAMA) in severe asthma: tiotropium bromide inhalation therapy
Summary of evidence for efficacy and safety of tiotropium bromide in adults and adolescents aged 12 years of age and over

Study design	n	Inclusion criteria and baseline characteristics	Primary outcome	Results	Ref
SR-MA: Tiotropium vs placebo add-on therapy to ICS	5 trials including 2563 patients	Parallel or cross-over RCT completed up to April 2015 Asthma not controlled by ICS therapy (dose range 400-1000 BDP equivalent) Minimum duration 12 weeks (range 12-52 weeks) Baseline mean age 41-48 years; predicted FEV1 72-75%	Severe exacerbations ACQ Serious AE Secondary outcomes:	Severe exacerbations* lower with tiotropium vs placebo (53 vs 80 per 1000 subjects over 21 weeks; OR 0.65, 95% CI 0.46-0.93). I^2=0% (high quality evidence) No significant difference Non-significant decrease in tiotropium vs placebo (18 vs 29 per 1000 subjects) Mean trough FEV1 140 mL(100-170) higher in tiotropium group No difference in any AE at 24 weeks for tiotropium vs placebo (493 vs 506 per 1000 subjects)	Anderson DE et al. Cochrane Database Syst Rev 2015:CD011397.
SR-MA: Tiotropium vs placebo add-on therapy to ICS/LABA	3 trials including 1197 patients	Parallel or cross-over RCT completed up to January 2016 Asthma diagnosed before age 40 years not controlled by ICS+LABA therapy Smokers and COPD excluded Minimum duration 12 weeks (range 48-52 weeks) Baseline mean age 42.6-53.9 years; mean predicted FEV1 55%	Severe exacerbations ACQ Serious AE Secondary outcomes:	Severe exacerbations* lower with tiotropium vs placebo (271 vs 328 per 1000 subjects over 48 weeks) but imprecise results (OR 0.76 with 95% CI 0.57-1.02) (moderate quality evidence) No clinical significant difference Inconsistent protective effect with tiotropium vs placebo (low quality evidence) Mean trough FEV1 70 mL (95% CI 30-110) higher in tiotropium group Hospitalization: lower in tiotropium group but not significant (OR 0.68, 95% CI 0.34-1.38) Less AE for tiotropium vs placebo (753 vs 813 per 1000)	Kew KM et al. Cochrane Database Syst Rev 2016:CD011721

SR-MA: Tiotropium vs placebo add-on to ICS Tiotropium vs placebo add-on to ICS-salmeterol	13 trials including 4966 patients 10 trials 3 trials including 1169 patients	Parallel or cross-over RCT completed up to May 2015; adults and adolescents with asthma; treatment duration minimum 4 weeks Predominantly patients with mild-moderate asthma Predominantly patients with severe asthma	Peak and trough FEV1 Secondary outcomes: Peak and trough FEV1 Secondary outcomes:	Increased Peak (150 ml,) and trough (140 ml) FEV1 in tiotropium vs placebo, p<.00001 Decreased severe exacerbations in tiotropium group (10.5 vs 13.6 % NNTB 36); I^2 = 0% Increased Peak (120 ml,) and trough (80 ml) FEV1 in tiotropium vs placebo, p< .00001 Decreased severe exacerbations (18.2 vs 24%, RR 0.70, 95% CI 0.53-0.94) NNTB 17; I^2 = 0% Inconsistent effects on asthma control	Rashid Q et al. South Med J 2014;107:330-7
SR-MA: Tiotropium add-on to ICS or ICS/LABA in adolescents	3 trials including 1001 patients All parallel group trials	Parallel or cross-over RCT completed up to May 2015 Minimum treatment duration 4 weeks (range 4-48 weeks) Adolescents aged 12-17 years with moderate to severe symptomatic asthma (all at least medium dose ICS) Mean age 14 years, mean FEV1 76-83%	Peak and trough FEV1 Secondary outcomes:	Increased Peak (120 ml) and trough (100 ml) FEV1 in tiotropium vs placebo, p< .0001 Decreased severe exacerbations (17.6% vs 23.8%, OR 0.74 95% CI 0.56-0.98) NNT = 16 No advantage of 5 ug vs 2.5 ug dose No significant differences in rescue medication use, ACT7 responder rate, AEs, serious AEs	Rodrigo GJ et al. Ann Allergy Asthma Immunol 2015;115:211-6
SR-MA: Tiotropium vs placebo add-on to at least ICS therapy	7 trials including 3474 patients	Parallel group phase 2 and 3 RCTs	Adverse events Serious adverse events	No difference compared to placebo for all outcomes: Tiotropium 5ug (60.8%) vs placebo (62.5%); tiotropium 2.5 mug (57.1%) vs placebo (55.1%) Tiotropium 5ug (4.0%) vs placebo (4.9%); tiotropium 2.5 mug (2.0%) vs placebo (3.3%)	Dahl R et al. Respir Med 2016;118:102-11

			Dry mouth	Tiotropium 5ug (1.0%) vs placebo (0.5%); tiotropium 2.5 mug (0.4%) vs placebo (0.5%)	

Caption: ACQ: Asthma Control Questionnaire, FEV1: forced expiratory volume in one second; ICS: inhaled corticosteroids; LABA: long acting beta agonist; NNTB: number need to treat for benefit; RCT: randomized controlled trial; SR-MA: systematic review with meta-analysis

*Severe exacerbations= asthma exacerbations requiring oral corticosteroids

Section 4: Macrolides
Summary of randomized controlled trials

Study Design	n	Inclusion criteria and baseline characteristics	Primary outcome	Results	Ref
Double blind RCT 48 weeks Azithromycin (AZ) 500mg 3x/week VS placebo	420	>=18yo Asthma symptomatic (ACQ6>=0.75) despite treatment with ICS or LABA (86% on high dose ICS)	Total number of exacerbations Severe exacerbations QoL	Placebo 1.86 exacerbations/person yr (1.54-2.18) AZ 1.07 exacerbations/person yr (0.85-1.29) Incidence rate ratio 0.59 (95% CI 0.47-0.74, p<0.0001) Placebo 1.07 exacerbations/person yr AZ 0.61 exacerbations/person yr Incidence rate ratio 0.59 [95% CI 0.42-0.83, p=0.002) Adjusted mean difference AZ versus placebo 0.36 (95% CI 0.21-0.52) p=0.001	Gibson PG et al. Lancet 2017; 390: 659-668
Double blind RCT 26 weeks Azithromycin (AZ) 250mg daily x 5 days then 3x/week VS Placebo	109	18-75yo Persistent asthma On high dose ICS (>=1000ug fluticasone or equivalent) + LABA for at least 6 months 2 severe exacerbations requiring oral steroids or LRTI requiring antibiotics within last year FeNO < LLN Mean age	Rate of primary endpoints (severe asthma exacerbation and/or LRTI requiring antibiotics)	No difference in rate of primary endpoints AZ 0.71 (95% CI 0.52 to 0.97) vs. Placebo 0.80 (95% CI 0.59 to 1.07) Adjusted rate ratio AZ vs. Placebo 0.89 (95% CI 0.58-1.37, p=0.6) No difference in exacerbations AZ 0.55 (95% CI 0.38-0.78) vs 0.52 (95% CI 0.36-0.75) Estimated ratio ratio AZ vs placebo 1.05 (95% CI 0.63 – 1.76, p=0.847)	Brusselle GG et al Thorax 2013; 68: 322-9
Double blind parallel RCT 12 weeks Troleandomycin (TAO) 250mg + prednisolone (Pn) or methylprednisolone (MPn) daily or alternate day VS Placebo	19	6-17yo Reversible obstruction Minimum dose of Prednisone >=20mg on alternate days Using SABA at least 4 times per day Theophylline High dose ICS (flunisolide 500-1000ug)	Reduction in oral steroid dose compared to baseline	TAO-MPn 80+/- 6% TAO-Pn 55+/-8% MPn 44+/- 14% Significant difference between TAO-Mpn and Mpn groups (p value not stated)	Kamada AK et al. JACI 1993;9 : 873-882.

Double blind RCT 8 weeks Clarithromycin 500mg bid VS Placebo	N=46	Adults with symptomatic refractory asthma (500-1000ug fluticasone equivalent)	IL-8 levels in sputum supernatant	Decreased in clarithromycin 6.6 (2.7-11.8)ng/ml to 3.9 (1.8-5.4) (p=0.0014) No change in placebo 6.3 (3.1-17.3)ng/ml to 6.4 (3.7-11.3) ng/ml placebo(p=0.931)	Simpson JL et al. AJRCCM 2008;177:148-155
Double blind RCT parallel group 1-2 years Troleandomycin (TAO) 250mg daily VS Placebo		Receiving minimum of 15mg prednisone per day Theophylline Inhaled SABA 4 times per day Not on ICS or inhaled cromolyn	Reduction in oral steroid dose	Both groups showed a decrease in oral steroid dosage Decreased in TAO from 17.6+/- 1.5 to 6.3+/-1.3 Decreased in Placebo 22.8+/- 1.9 to 17.6+/-1.5mg/day Did not report difference between groups	Nelson HS et al. Am Rev Respir Dis. 1993;147:398-404.

Section 5: Biologic Therapy: Anti-IgE Omalizumab

Summary of randomized controlled trials comparing omalizumab (sc) versus placebo in severe asthma

Study Design	N	Inclusion Criteria	Primary Outcome	Results	Ref
Efficacy					
RCT: OMA vs placebo 60 weeks	419 (54% with severe asthma)	6-20yo inner city children Persistent allergic asthma (long term controller therapy and hospitalization or urgent care in last 12m or not on long term therapy and persistent symptoms) Positive skin test to 1 perennial allergen Serum IgE 30-1300IU/ml Weight 20-150kg (55% severe)	Number of days with symptoms in last 2 weeks assessed q4 weeks	Mean change from baseline to end of therapy in symptom days Omalizumab : 1.96 +/-0.1 Placebo : 1.48 +/- 0.1 ($p < 0.001$) Secondary outcome : Percentage with Exacerbations Omalizumab : 30.3 % Placebo : 48.8% ($p<0.001$)	Busse W et al. B et al. NEJM 2011364:1005 -15
RCT: OMA vs. placebo 52 weeks	627 (64% severe asthma)	6-12yo; moderate to severe asthma uncontrolled on >= 200 mcg/day fluticasone or equivalent and history of exacerbations 20-150kg Positive skin test to at least 1 perennial allergen IgE 30-1300IU/ml Weight 20-150kg	Exacerbations at 24 weeks (worsening of asthma symptoms requiring doubling of baseline ICS or oral steroids)	Rate of exacerbations Omalizumab 0.45 Placebo 0. 45 ($p=0.007$) RR omalizumab:placebo (95% CI) =0.69 (0.53-0.9)	Lanier B et al. JACI: 2009;124 : 1210–6.
RCT: OMA vs placebo 24 weeks	271	>12 yo with inadequately controlled severe asthma on medium dose ICC plus second controller (GINA step 4) and ACT<or = 19 Positive skin test to at least 1 perennial allergen IgE 30-700 IU/ml Weight < = 150 kg	Change from baseline ACT score	Least squares mean changes from baseline Omalizumab 5.01 Placebo 4.36 Difference = 0.64 (95% CI -0.30 – 1.59, $p=0.178$) Secondary outcome: exacerbations requiring oral steroids RR 0.63 (95%CI 0.26-1.53, $p=0.0307$)	Bardelas J et al. J Asthma 2012;49(2):14 4-152

RCT:OMA vs placebo ICS reduction phase 28 weeks	525	12-75 yo Severe persistent asthma 420-800 mcg BDP and still have symptoms Asthma diagnosis for > 1 year Positive skin prick test to common allergens	Number of exacerbations	Steroid stable phase Number of exacerbations Omalizumab: 0.28 Placebo: 0.54 p=0.006 Steroid reduction phase Number of exacerbations Omalizumab: 0.39 Placebo: 0.66 p=0.003	Busse W et al. JACI 2001; 108:184-90.
RCT: OMA vs placebo 48 weeks	848	12-75 yo with severe allergic asthma Not well controlled despite high-dose ICS (>500mcg fluticasone) and LABA =/- other controllers At least one exacerbation in last 12 months Positive allergy test to perennial aeroallergen sIgE 30-700 IU/mL body weight 30-150	Rate of asthma exacerbations	Omalizumab =0.66 Placebo = 0.88 per patient IRR = 0.75(0.61-0.92); p = 0.006	Hanania NA et al. Ann Intern Med 2011;154: 573-582.
RCT: Omalizumab vs placebo 32 weeks	246	12-75 yo Severe asthma required > = 1000 mcg fluticasone for symptom control Positive skin prick test to aeroallergen sIgE 30-700 IU/mL	Percentage reduction from baseline in fluticasone dose at 32 weeks	Percentage reduction in fluticasone dose Omalizumab: 57.2% Placebo: 43.3%, p=0.003 Mean number of exacerbations: Omalizumab: 0.15 Placebo: 0.23, NS	Holgate ST Clin Ep Allergy 2004;34:632-638.
RCT: Omalizumab vs placebo Steroid stable and steroid reduction phase 28 weeks	546	12-75 yo with moderate/severe (ICS dose of 500-1200 of beclomethasone or equivalent, but not on OCS) and still symptomatic IgE 30-700 Body weight < =150 kg	Number of exacerbations	Steroid stable phase: Omalizumab 0.28 (0.15-0.41) Placebo 0.66 (0.49-0.83); p<0.001 Steroid reduction phase: Omalizumab 0.36 (0.24-0.48) Placebo 0.75 (0.58-0.92); p<0.001	Soler M et al. Eur Respir J 2001;18:254-261.

RCT: Omalizumab vs placebo 28 weeks	419 (97% severe asthma)	12-75 yo severe persistent asthma positive skin prick test to at least 1 aeroallergen IgE 30-00 IU/mL High dose ICS and LABA At least 2 exacerbations requiring steroids or 1 severe exacerbation	Rate of clinically significant asthma exacerbations	Exacerbations: Omalizumab rate ratio: 0.68 Placebo rate: 0.738 P= 0.042, NNT 2.2	Humbert M et al. Allergy 2005;60:309-316
RCT: Omalizumab vs placebo Steroid stable and steroid reduction phase 28 weeks	334	6-12 yo moderate asthma (168-420 mcg/day beclomethasone diproprionate (BDP)) for at least 1 year At least 1 positive skin prink test sIgE 30-1300 IU/mL Body weight < 90kg FEV1 >=60% predicted	Percentage reduction in dose of beclomethasone from baseline Proportion of patients with a reduction in dose of becomethasone	Mean reduction in BDP dose Omalizumab: 100% Placebo: 66.7%, p=0.001 Proportion of patients with complete withdrawal of BDP: Omalizumab: 55% Placebo: 39%, p=0.004 Significant reduction in exacerbation with omalizumab in steroid reduction phase (18.2 vs 38.5%,p<0.001)	Milgrom H et al. Pediatrics 2001;108:36
Randomized open-label study Omalizumab vs best standard care 52 weeks	312	12-73 yo moderate to severe asthma (>=400 in adolescents and >=800 mcg/day beclomethasone equivalents At least one exacerbation in last 12 months At least 2 positive skin prick tests sIgE 30-700 IU/mL	Annualized number of asthma deterioration related events (oral steroids or antibiotics;3 or more missed days work/school; unscheduled physician visit; hospitalization or ED visit)	Omalizumab associated with a 49.6% reduction (95%CI 27.8-64.8) compared to best standard care. Annualized mean number of clinically significant exacerbations: Omalizumab: 1.12 Placebo:2.86 p< 0.001	Ayres JG Allergy 2004:59;791-708.
Randomized open-label study Omalizumab vs best standard care 52 weeks subgroup analysis of Ayers 2004		Post –hoc analysis of inadequately controlled severe persistent asthma on high dose ICS and LABA from Ayers study	Annual rate of asthma exacerbations	Omalizumab : 1.26 Placebo: 3.06, p<0.001	Niven R et al. Respiratory Medicine 2008;102:1371-1378.

RCT, 3 arms: OMA vs placebo vs ICS boost 90 days	478	6-17yo At least one exacerbation requiring oral steroids or hospitalization within 19 months Positive skin test to 1 perennial allergen IgE 30-1300IU/ml Weight 20-150kg (38% severe)	Fall season asthma exacerbation (requiring oral steroids or hospitalization)	At least one exacerbation during trial Omalizumab 11.3% Placebo 21% OR 0.48 (95% CI 0.25-0.92) In severe asthma group Omalizumab 15.1% Placebo 32.6% OR 0.37 (95% 0.17-0.81)	Teach SJ et al. JACI 2015 Dec;136:1476-85.
RCT: omalizumab vs placebo 28 weeks	405	12-75 yo with allergic asthma IgE 30-1300 IU/mL Positive skin prick test to at least one indoor allergen Concomitant moderate to severe allergic rhinitis ICS >= 400 ug/day and at least 2 unscheduled MD visits in last year Exclude pts on systemic steroids	1) Asthma exacerbations	Exacerbations: Omalizumab: 20.6% Placebo: 30.1%, p=0.02	Vignola AM et al. Allergy 2004;59:709-717
RCT: 24 week extension to Busse 2001 RCT omalizumab vs placebo	460	12-75 yo Severe persistent asthma 420-800 mcg BDP and still have symptoms Asthma diagnosis for > 1 year Positive skin prick test to common allergens	Number of asthma exacerbations	Exacerbations Omalizumab: 0.60 Placebo: 0.83, p=0.023	Lanier BQ et al. Ann Allergy Asthma Immunol 2003;91:154-159
RCT: omalizumab vs placebo Subanalysis of Lanier 2009 28 weeks fixed steroid dose 28 weeks adjustable steroid phase	235	6-12 yo Severe allergic asthma inadequately controlled on fluticasone > = 500 mcg/day + LABA Exacerbations in last 2 years	Rate of clinically significant exacerbations	Fixed steroid phase exacerbations Omalizumab: 0.42 Placebo : 0.63, p=0.047 Total 52 weeks Omalizumab: 0.73 Placebo: 1.44, p<0.001	Kulus M et al. Curr Med Res and Opin. 2010; 26: 1285-1293.
RCT (open label): Omalizumab vs placebo 20 weeks	202	12-75 yo Severe persistent asthma uncontrolled despite >= 500 mcg/day flucticasone and LABA sIgE 30-700 IU/mL positive skin prick test to at least one aeroallergen	Asthma related quality of life	Mean change from baseline AQLQ score Omalizumab: 1.2 Placebo: 0, p < 0.001 Asthma exacerbations: no significant difference	Rubin AS et al. J of Asthma 2013;49:288-293

RCT: omalizumab vs placebo	41	18-70 yo Severe nonatopic asthma uncontrolled despite > 1000 mcg beclomethasone and LABA +/- oral steroids At 2 exacerbations and 1 hospitalization or ED visit sIgE 30-700 IU/mL	Change in FcεRI receptor expression (basophils and pDC2)	Mean decrease in FcεRI from baseline greater in Omalizumab, $p<0.001$ No significant effect on exacerbation rates	Garcia G et al. Chest 2013; 144:411-419.

Section 6: Biologic therapies in severe asthma: Anti-IL5

Summary of randomized controlled trials comparing mepolizumab to placebo in severe asthma

Study design	n	Inclusion criteria	Primary outcome	Results	Ref
Efficacy					
RCT: 750 IV vs placebo 50 weeks	61	Eighteen years and older, clinical diagnosis of asthma Refractory asthma, Sputum eosinophil>3% in the previous 2 years despite high dose ICS, ≥2 asthma exacerbations	Severe asthma exacerbations (n) per subjects during 50 weeks	2.0 (mepo) vs. 3.4 (placebo) mean exacerbations per subject; relative risk, 0.57; 95% CI, 0.32 to 0.92; P = 0.02.	Haldar P et al. NEJM. 2009;360:973-84
RCT: 750, 250, 75 mg vs placebo. 52 weeks	621	12-74 years old. Clinical diagnosis of asthma; ≥2 asthma exacerbations and evidence of eosinophilic inflammation sputum eosinophil count ≥ 3%, (FE_{NO}) ≥ 50 ppb peripheral blood eosinophil count ≥0·3×10^9 per L, or prompt deterioration of asthma control after a 25% or less reduction in regular maintenance inhaled or oral corticosteroids.	Rate of clinically significant asthma exacerbations	Rate of exacerbation in placebo: 2.4 Relative reduction in exacerbation rate per year compared to placebo : Mepo 75mg 1.24 ; 48% (95% CI 31–61%; p<0·0001), Mepo 250 mg : 1.46; 39% (19–54%; p=0·0005), Mepo : 750 mg : 1.15; 52% (36–64%; p<0·0001;	Pavord ID et al. Lancet. 2012;380:651-9.
RCT: 75 mg IV, 100 mg SC or placebo 32 weeks	576	12-82 years old; Clinical diagnosis of asthma; FEV_1 <80% of the predicted value (adults) FEV_1 <90% of predicted and FEV_1/FVC<0.8 (adolescents).. ≥2 asthma exacerbations and ≥150 blood eosinophils/ µL at screening or ≥300 eosinophils/ µL during the previous year.	Annualized frequency of clinically significant Asthma exacerbations	Rate of asthma exacerbation; Relative reduction in exacerbation rate Placebo group: 1.74 Mepo: 75mg IV: 0.93: 47% (28-6), 100 mg SC 0.83; 53%(36-65)	Bel EH et al. NEJM. 2014; 371 :1189-97
Corticosteroid-sparing effect					
RCT: 750 mg IV or placebo 18 week	20	Corticodepenent adults with asthma, persistent eosinophilic inflammation Sputum eos >3%)	Proportion of patients with exacerbation, mean reduction of prednisone dose (percentage of the maximum possible reduction (MPR))	Nb of asthma exacerbation, MPR Placebo: 12, 47.7±40.5% Mepo : 2, 83.8±33.4% (P=0.04).	Nair P et al. NEJM. 2009;360:985-93.
RCT: 100mg SC vs placebo 32 weeks	135	12 years and older; High dose ICS with additional controller; Maintenance treatment with	Percentage reduction in the daily OCS dose during weeks 20 to 24 vs. the dose	Reduction of 90 to 100% in the OCS dose (23% vs. 11%) a reduction of 70 to less than 90% (17% vs. 8%).	Bel EH

		systemic glucocorticoids for at least 6 months. blood eosinophils ≥300 cells/ μL during the 12-month period before screening or ≥150 cells/ μL during the optimization phase	determined during the optimization phase.	median percentage reduction from baseline in the daily oral glucocorticoid dose was 50% among patients in the mepolizumab group, as compared with no reduction among those in the placebo group (P=0.007). Relative reduction of 32% in the annualized rate of exacerbations (1.44 vs. 2.12, P=0.04)	NEJM. 2014;371:1189-97.

Caption: ACQ: Asthma Control Questionnaire, FE_{NO}: Fraction of exhaled nitric oxide; ICS: Inhaled corticosteroids; OCS: Oral corticosteroids; RCT: randomized controlled trial. PEF: Peak expiratory flow; ppb: parts per billion

Section 6: Biologic therapies in severe asthma: Anti-IL5
Summary of randomized controlled trials comparing reslizumab to placebo

Study design	n	Inclusion criteria	Primary outcome	Results	Ref
Efficacy					
RCT: 3 mg/kg IV vs placebo 15 weeks	106	18- 75 years old; high dose ICS; ACQ score ≥1.5 and sputum eosinophils ≥3%	Difference in ACQ score	Mean change from baseline to end of therapy in ACQ score Reslizumab : −0.7 Placebo : −0.3 (p = 0.054)	Castro M et al. AJRCCM. 2011;184(10): 1125-32.
Twin RCTs: 3 mg/kg IV vs placebo 52 weeks	953	12- 75 years old Asthma inadequately controlled by medium-to-high doses of ICS, ACQ 7≥1.5; blood eosinophils ≥ 400 /µL, ≥ 1 exacerbation in the previous year.	Annual frequency of clinical asthma exacerbations	Reslizumab associated with a significant reduction in the frequency of asthma exacerbations (study 1: rate ratio [RR] 0·50 [95% CI 0·37-0·67]; study 2: 0·41 [0·28-0·59]; both p<0·0001	Castro M et al. Lancet Respir Med.2015;3:355-66
RCT: 3 mg/kg IV vs placebo 16 weeks	492	18-65 years old; ACQ 7≥1.5 Uncontrolled asthma on a medium to high dose ICS, reversible airflow limitation ≥ 12% to short-acting β-agonist. No selection based on blood eosinophils.	Change in FEV_1 from baseline to week 16	No significant difference in change in FEV1 between reslizumab (255 ml) and placebo (187 ml) p= 0.17	Corren J et al. Chest. 2016;150 :799-810
RCT : 0.3 or 3.0 mg/kg reslizumab or placebo 16 weeks	315	12-75 years old; airway reversibility≥12% to short-acting β-agonist. ACQ 7≥1.5 Asthma inadequately controlled by at least a medium-dose ICS and with a blood eosinophil count ≥ 400 cells/µL.	Change in pre-BD FEV_1 from baseline over 16 weeks	Reslizumab significantly improved FEV_1 (difference vs placebo [reslizumab 0.3 and 3.0 mg/kg], 115 mL [95% CI, 16-215; p = 0.02] and 160 mL [95% CI, 60-259; p= 0.002]	Bjermer J et al. Chest 2016 150: 789-98

Caption: ACQ: Asthma Control Questionnaire, BD: bronchodilator; ICS: Inhaled corticosteroids; OCS: Oral corticosteroids; RCT: randomized controlled trial.

Section 6: Biologic therapies in severe asthma: Anti-IL5
Summary of randomized controlled trials comparing Benralizumab to placebo

Study Design	n	Inclusion criteria	Primary outcome	Results	Ref
Efficacy					
RDBPCT (Phase 1) *Cohort 1:* single dose IV 1 mg/kg vs placebo; *Cohort 2:* 100 mg sc vs 200 mg sc vs placebo monthly x 3, 56 days	*Cohort 1:* 13 *Cohort 2:* 14	18 – 65 years, sputum eos ≥ 2.5%, post BD FEV_1 ≥ 65% pred, and pre-BD FEV_1/FVC < "age – adjusted norms", asthma medication unchanged 4 weeks pre-randomization to first follow-up mucosal biopsy.	Eosinophil counts in airway/submucosal biopsies. *Secondary outcomes: sputum, bone marrow and peripheral blood eosinophil counts.*	Median change in airway mucosal eosinophil counts *Cohort 1:* benralizumab: - 61.9%; Placebo: +19.1%, p=0.28. *Cohort 2:* benralizumab (Combined 100 mg + 200 mg): -95.8%, Placebo: -46.7%, p=0.06; *Post hoc Pooled Cohorts at 28 days*: benralizumab: -83.1% [IQR – 95.8 - - 57.6%). Placebo: +4.7% [IQR -64.1 - + 84.3%], p=0.02	Laviolette M et al. JACI 2013;132 :1086-96.
RDBPCT (Phase 2b, dose ranging) *Eosinophilic Individuals:* Randomized 1:1:1:1 to 2 mg, 20 mg, 100 mg benralizumab sc vs placebo; *Non-eosinophilic individuals:* Randomized 1:1 to 100 mg benralizumab sc vs placebo Dosing was every 4 weeks for 3 doses, then every 8 weeks x 4 doses.	*Eosinophilic Individuals:* 324 *Non-eosinophilic individuals:* 285	18-75 years, never smokers, uncontrolled on medium-dose or high-dose ICS and LABAs, 2-6 exacerbations in prior year, am pre-BD FEV_1 ≥ 40%pr and < 90% pr, ACQ-6 score ≥ 1.5. ICS and LABA dose unchanged from screening to week 52. Stratified patients by eosinophilic status based on positive prediction index (ELEN) or FE_{NO} > 50 ppb.	Annual asthma exacerbation rate in eosinophilic individuals (total # exacerbations in each group up to week 52/total duration of person-year follow-up in each group). *Secondary outcomes: change from baseline in FEV_1, mean ACQ s-6 score, overall symptom score, and mean AQLQ score at week 52.* *Pre-specified subgroup analysis based on blood eos cutoff of 300 cells/uL.*	*Using a pre-specified statistical significance level of p<0.169*, benralizumab 100 mg was associated with reduced asthma exacerbations in eosinophilic asthma. Annual exacerbation rate: benralizumab 100 mg: 0.38 (SD 0.58), Placebo:0.57 (SD0.75); Rate reduction compared with placebo: 41% (80% CI: 11-60), p=0.096 *Exacerbation rate reduction was significantly reduced in eosinophilic individuals by both 20 mg and 100 mg doses, compared to placebo:* *benralizumab 20 mg: 0.30 vs 0.68, 57% reduction, 80% CI 33 – 72, p=0.015;* *benralizumab 100 mg: 0.38 vs 0.68, 43% reduction, 80% CI 18 – 60, p=0.049.*	Castro M et al. Lancet Respir Med. 2014;2: 879-90
RDBPCT (Phase 2) Single dose of IV benralizumab in the ED prior to discharge. Randomized 2:1 based on baseline	110	18 – 60 years, asthma diagnosis for ≥ 2 years, ≤ 20 pack-year smoking history, emergency department (ED) visit for asthma exacerbation, symptoms prior to ED for ≥ 2 hours, incomplete response to ≥ 2 treatments with inhaled	Proportion of subjects with ≥ 1 exacerbation at 12 weeks. *Secondary outcomes: proportion with exacerbations at weeks 4 and 24, eos counts, lung*	No significant difference between benralizumab and placebo in proportion of subjects with ≥ 1 exacerbation at 12 weeks (38.9% vs 33.3 %, p=0.67). *Exacerbation rates decreased by 49% in benralizumab vs placebo (1.82 vs 3.59, p=0.01) and hospitalizations by 60% (0.65 vs 1.62, p-0.020.*	Nowak RM et al. AJEM 2015; 33: 14-20

blood eos level ≤ 450 cells/uL or > 450 cells/uL, to 0.3 mg/kg or 1.0 mg/kg benralizumab, or placebo		bronchodilators (FEV_1 or PEF ≤ 70% pred post treatment), ≥ 1 urgent care visit for asthma in previous 12 months	*function, asthma symptoms, QoL, HCU, and safety.*		
RDBPCT (Phase 2a) 4 groups: Benralizumab 2, 20, or 100 mg or placebo 7 doses over 40 weeks Stratified by eosinophil count ≥ 300 cells/uL or <300 cells/uL.	106	20-75 years, asthma treated with medium to high-dose ICS/LABA combination for at least 1 year, 2-6 exacerbations needing systemic steroids in past year, morning pre-bronchodilator FEV_1 ≥ 40% buy<90%pr, ACQ-6 score ≥ 1.5 on at least 2 occasions in screening, post-bronchodilator reversibility ≥12% and ≥200mL, or a positive methacholine challenge (PC_{20} ≤8mg/mL, <10 pack year smoking history	Asthma exacerbation rate at 52 weeks	Asthma exacerbation rate decreased by 33,45 or 36% vs placebo when treated with 2, 20 or 200 mg benralizumab respectively ***No statistical tests completed ***	Park HS et al. Int Arch Allergy Immunol. 2016;169 :135-45.
RDBPCT, parallel group (Phase 3) Benralizumab 30 mg sc vs placebo. Dosing was every 4 weeks, or every 8 weeks (after 1st 3 doses every 4 weeks) Stratified 2:1 by blood eosinophil count ≥ 300 cells/uL or <300 cells/uL.	1205	12-75 years, physician-diagnosed asthma for >1year, ≥ 2 exacerbations while on <u>high-dose</u> ICS/LABA in previous year, pre-BD FEV1 <80% predicted (<90%pred for patients 12-17 years old), ACQ-6 score ≥ 1.5, post-BD reversibility in FEV1 of 12% or greater and ≥ 200 mL within 12 months pre-enrolment	Annual exacerbation rate ratio vs placebo for patients (all on high-dose ICS/LABA) with baseline blood eos ≥ 300 cells/uL *Secondary outcomes: pre-BD FEV_1, symptom score, time to 1st exacerbation, annual rate of exacerbations associated with ED or urgent care visit or hospitalization, post-BD FEV_1, ACQ-6, and AQLQ(S)+12 score.*	Statistically significant reduction in exacerbation rate at 48 weeks vs placebo in individuals with blood eos ≥ 300 cells/uL. Q4Week: rate ratio 0.55, 95% CI 0.42-0.71; p<0.0001) Q8Week: rate ratio 0.49, p5% CI 0.37-0.64, p<0.0001). *Both treatment regimens improved pre-BD FEV1 and prolonged the time to first exacerbation.* *Q8Weeks improved symptoms at week 48, ACQ-6 and AQLQ, and reduced exacerbations leading to ED visits or hospitalizations.*	Bleecker ER et al. Lancet. 2016;388(10056):2115-27
RDBPCT, parallel group (Phase 3)	1306	12-75 years, physician-diagnosed asthma for >1year, ≥ 2 exacerbations while on <u>medium- to high-dose</u>	Annual exacerbation rate ratio vs placebo for patients on high-dose ICS	Statistically significant reduction in exacerbation rate at 56 weeks vs placebo in individuals with blood eos ≥ 300 cells/uL.	FitzGerald JM et al. Lancet.

Benralizumab 30 mg sc vs placebo. Dosing was every 4 weeks, or every 8 weeks (after 1st 3 doses every 4 weeks) Stratified 2:1 by blood eosinophil count ≥ 300 cells/uL or <300 cells/uL.		ICS/LABA in previous year, pre-BD FEV1 <80% predicted (<90%pred for patients 12-17 years old), ACQ-6 score ≥ 1.5, post-BD reversibility in FEV1 of 12% or greater and ≥ 200 mL within 12 months pre-enrolment	plus LABA with baseline blood eos ≥ 300 cells/uL *Secondary outcomes: pre-BD FEV_1 and total asthma symptom score for patients receiving high-dose ICS plus LABA with baseline blood eos ≥ 300 cells/uL time to first exacerbation, annual rate of exacerbations associated with ED or urgent care visit or hospitalization, post-BD FEV_1, ACQ-6, and AQLQ(S)+12 score.*	Q4week: rate ratio 0.64 [95% CI 0.49-0.85], p=-.0018 Q8week: rate ratio 0.72 [0.54-0.95],p=0.0188 *Both treatment regimens improved pre-BD FEV_1, time to 1st exacerbation, ACQ-6.* *Q8 week regimen improved AQLQ+12.* *No difference in rate of exacerbations required and ED visit or hospitalization or time to fir first exacerbation requiring ED visit or admission.* *Also improved annual exacerbation rates and blood eosinophils in patients with blood eosinophils < 300 cells/uL.*	2016;388 :2128-41
RDBPCT, parallel-group (Phase 3) Benralizumab 30 mg sc vs placebo. Dosing was every 4 weeks, or every 8 weeks (after 1st 3 doses every 4 weeks) Randomized 1:1:1 Stratified by blood eosinophil count (≥ 150 to <300 cells/uL vs. ≥ 300 cells/uL)	220	18-75 years, physician-diagnosed asthma requiring <u>medium- to high-dose ICS/LABA</u> for ≥ 12 months prior, or high-dose ICS/LABA for ≥ 6 months prior, AND <u>oral glucocorticoid for ≥ 6 months continuous prior</u> (7.5-40 mg/day prednisone/prednisolone, stable dose for 2 weeks prior), morning pre-BD FEV1 <80% predicted; asthma as evidence by either post-BD reversibility in FEV1 of 12% or greater and ≥ 200 mL at visits 1,2 or 3 or within 24 months pre-enrolment OR PC_{20} methacholine ≤ 8 mg/mL OR airflow variability in FEV1 ≥ 20% between consecutive visits.	% change in the oral glucocorticoid dose from baseline to week 28. *Secondary outcomes: annual asthma exacerbation rates, lung function, symptoms and safety.*	Statistically significant reduction in median final oral glucocorticoid does from baseline (75% vs. 25% in placebo group; P<0.001 for both dosing comparisons). Q4 week: OR 4.09 [95% CI 2.22-7.57] Q8 week: OR 4.12 [95% CI 2.22-7.63] *Both dosing regimens reduced annual asthma exacerbation rates, the odds of having at least one exacerbation, and prolonged the time to first exacerbation.* *The 8 week dosing regimen reduced ED visits.* *At 28 weeks, lung function (FEV_1) was not different in either treatment group compared to placebo. There were variable effects on symptoms.*	Nair P et al, NEJM 2017; 376: 2448-58

Caption: ACQ: Asthma Control Questionnaire, AQLQ: Asthma Quality of Life Questionnaire; BD: bronchodilator; FE_{NO}: Fraction of exhaled nitric oxide; FEV_1: forced expiratory volume in 1 second; ICS: Inhaled corticosteroids,; LABA: long-acting $beta_2$-agonist; OCS: Oral corticosteroids; PC_{20}: provocative concentration of methacholine causing a 20% decrease in FEV_1; Q: every; RCT: randomized controlled trial. PEF: Peak expiratory flow; ppb: parts per billion

Section 7: Bronchial thermoplasty

Summary of randomized controlled trials comparing bronchial thermoplasty to control in moderate and severe asthma.

Study design	n	Inclusion criteria	Primary outcome	Results	Ref
RCT: BT vs control 52 weeks	112	18-65 years old. Clinical diagnosis of moderate or severe persistent asthma. ICS and LABA. Loss of asthma control with LABA withdrawal.	Frequency mild exacerbations during 3 scheduled 2 week period LABA abstinence at 3, 6, 12 months	Reduction mild exacerbation rate BT vs control: - 0.16 ± 0.37 vs 0.04 ± 0.29 (P= 0.005)	Cox G et al. NEJM 2007;356 : 1327-37.
RCT: BT vs sham procedure 52 weeks	288	18-65 years old. Clinical diagnosis severe persistent asthma. ICS > 1000 mcg/d beclomethasone or equivalent and a LABA; AQLQ < 6.25; pre-b-d FEV_1 ≥60% predicted; > 2 days asthma symptoms 14 week baseline period.	Difference in integrated AQLQ from baseline to average of 6, 9 and 12 months	Improvement in integrated AQLQ superior in BT vs sham using posterion probability of superiority (PPS): 1.35 ± 1.1 vs 1.16 ± 1.23 (PPS 96%)	Castro M et al. AJRCCM 2010; 181 : 116-24.
RCT: BT vs control 52 weeks	32	18-65 years old. Clinical diagnosis severe persistent asthma. ICS > 750 mcg/d fluticasone or equivalent and a LABA with or without oral prednisone (≤30 mg/d); pre-b-d FEV_1 ≥ 50%; uncontrolled asthma symptoms	Reduction in SABA use from baseline BT vs control weeks 6-22 post BT	Reduction in puffs of SABA superior in BT vs control: - 26.6 ± 40.1 vs - 1.5 ± 11.7 (P < 0.05 at week 22)	Pavord ID et al. AJRCCM Med 2007; 176 : 1185-91

Caption: AQLQ: Asthma quality of life questionnaire; BT: bronchial thermoplasty; ICS: Inhaled corticosteroids; LABA: Long-acting-beta-2-agonist; RCT: randomized clinical trial; SABA: short-acting-beta-2-agonist