Eosinophilic and Neutrophilic asthma

연세의대 변민광

Eosinophilic vs. Neutrophilic asthma

- Eosinophilic asthma is a distinct phenotype of asthma that is associated pathologically by thickening of the basement membrane zone and pharmacologically by corticosteroid responsiveness.

- Non-eosinophilic asthma, a sizeable subgroup of asthma that includes patients with severe disease, is not characterized by thickening of the basement membrane zone, and it appears to be relatively corticosteroid resistant.

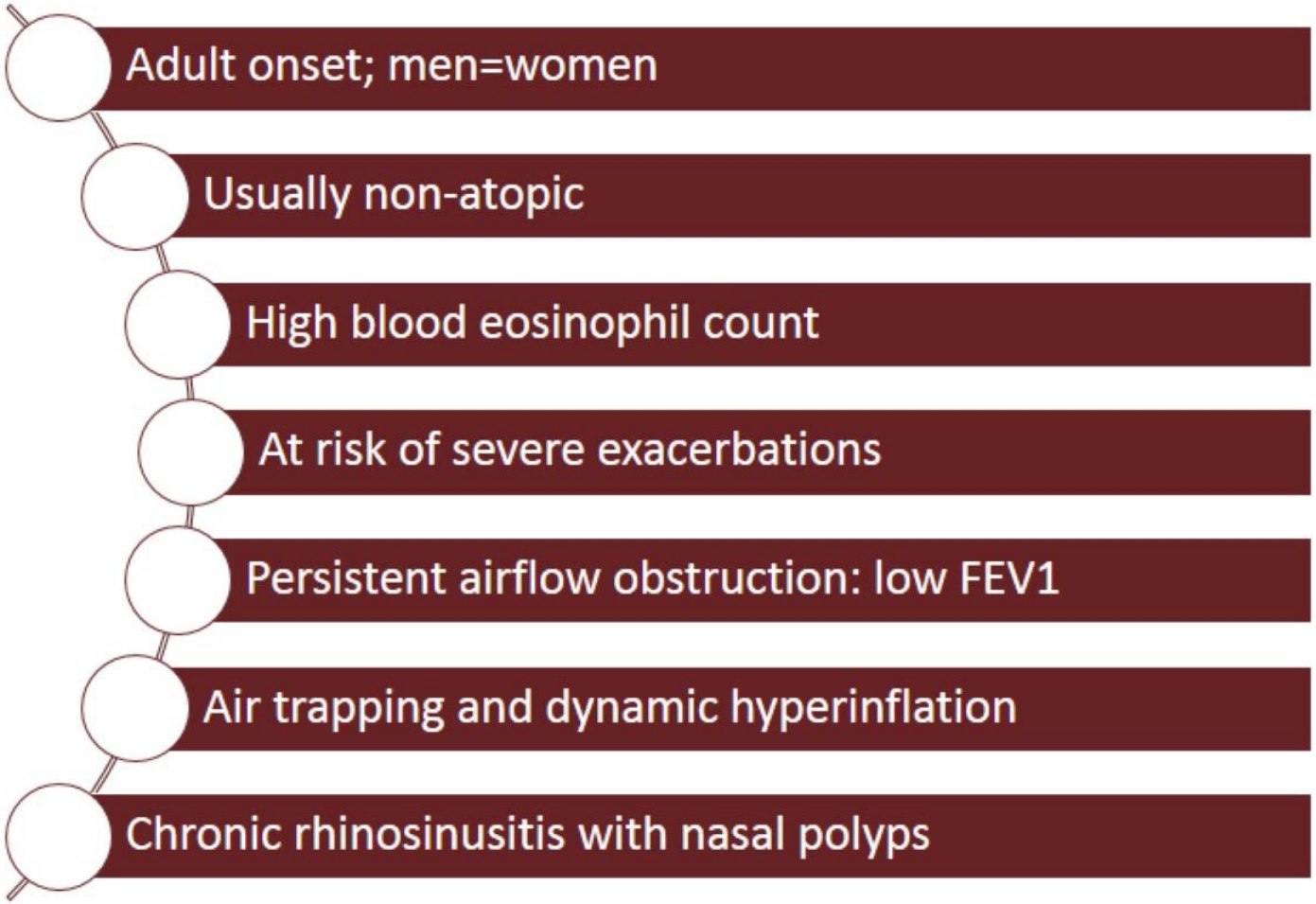
- Eosinophilic asthma vs.

- Neutrophilic asthma
  (Non-eosinophilic asthma)

Evidence for Eosinophils as an Important Effector Cell in Asthma

- Present in airways of patients who died from asthma episodes and in living asthmatics with chronic symptoms
- Presence of eosinophils in sputum an indicator of good therapeutic response to inhaled or oral corticosteroid therapy
- Use of sputum eosinophil count as a guide to treating asthma provides better asthma outcomes than using conventional method
- Persistence of sputum or airway eosinophilia in severe asthma patients is a marker of severity

Clinical Profile of Late-Onset Eosinophilic Asthma



De Groot JC, et al. *ERJ Open Res.* 2016:2;00100-02015.

U-BIOPRED: Clustering on Clinical Features

← *Severe eosinophilic asthma* →

	Phenotype 1	Phenotype 2	Phenotype 3	Phenotype 4
Clinical features	Moderate/ severe	Severe	Severe	Severe
	Well-controlled	Late-onset	Oral CS dependent	Female
	Medium-to-high dose ICS	Smoker/ex-smoker	Moderate/severe airflow obstruction	Mild-to-no airflow obstruction
	Mild-to-no airflow obstruction	Severe airflow obstruction		Frequent exacerbations
	↓	↓	↓	↓
Blood eosinophils, µL (*P* < .05)	199	301	220	200
Sputum eosinophils, % (*P* < .02)	0.8	**4.9**	**3.7**	**2.4**
FeNO (ppb) (NS)	24	29	34	26.5

Lefaudeux D, et al. *J Allergy Clin Immunol.* 2016 Oct 20. doi: 10.1016/j.jaci.2016.08.048. [Epub ahead of print].

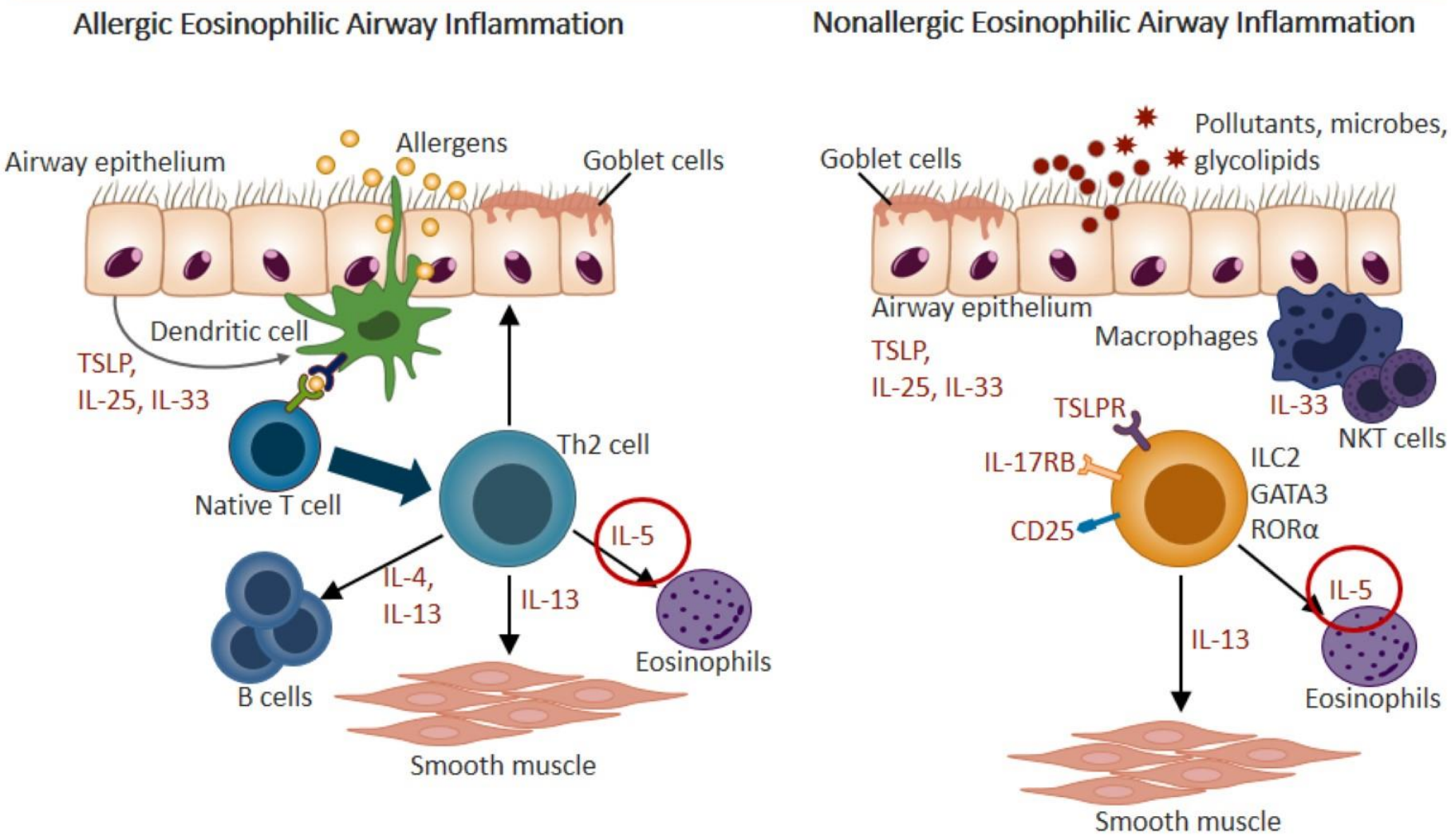
U-BIOPRED: Transcriptome-associated Clusters of Moderate-Severe Asthma

Sputum Analysis	TAC 1 (29%)*	TAC 2 (21%)	TAC 3 (50%)
"Mechanisms"	"T-2 associated"	"Inflammasome"	Mitochondrial Oxidative stress
Affymetrix Microarray	IL33R, TSLPR, CCR3, IL3RA	IFN & TNF superfamily, CASP4	Metabolic genes
Gene set variation analysis	**Th2/ILC2**	NLPR3/DAMP-associated	Th17; OXPHOS; ageing
Protein (Somalogic)	IL-16, Periostin, Serpin peptidase inhibitor 1, Adiponectin, PAPPA	TNFAIP6, MIF, Tyrosine kinase src	Cathepsin B, G
Blood eosinophils, /µL	**430**	250	200
Sputum eosinophils, %	**30.9**	0.6	1.0
FeNO, ppb	29.5	22.0	27.5
Clinical features	Severe asthma Highest nasal polyps Oral OCS dependent Severe airflow obstruction	Moderate-to-severe asthma Moderate airflow obstruction High blood CRP levels More eczema	Moderate-to-severe asthma Mild airflow obstruction Lowest oral prednisolone Less frequent exacerbations

*Severe eosinophilic asthma

Kuo CS, et al. *Eur Resp J.* 2017 Feb 8 [Epub ahead of print]

Mechanisms of Eosinophilic Asthma



Pelaia G, et al. *Nat Rev Drug Discov.* 2012;11:958-997.
De Groot JC, et al. *ERJ Open Res.* 2015;1:00024-2015.

Emerging Asthma Phenotypes

T-2 Type Asthma

- Childhood onset asthma
  - Allergic asthma
  - Asthma induced by exercise
- Late-onset eosinophilic asthma
- Aspirin-associated exacerbated respiratory disease
- Very late-onset asthma (women)

Non-T2-type Asthma

- Very late-onset asthma (women)
- Asthma associated with obesity
- Neutrophilic asthma related to smoking
- Smooth-muscle-mediated paucigranulocytic asthma

Wenzel SE, et al. *Nat Med.* 2012;18:716-725.

Current and Emerging Targeted Therapies in Severe Asthma

T2 High	T2 Low	
Eosinophilic	Neutrophilic	Paucigranuloctic
High eNO	Steroid resistant	Steroid resistant
High periostin	Macrolides	LAMA
Steroids	CXCR2 antagonists	LABA/LAMAs
Anti-IgE	Anti-TNF	LABA/LAMA/ICS
Anti IL-5	Anti IL-1	Bronchial thermoplasty
Anti IL-4/IL-13	Inflammasome inhibitors	
Anti IL-13	Anti IL-17/23	
Anti TSLP	P38 MAPK inhibitors	
Anti IL-33	PDE4 inhibitors	
CRTH2 antagonists		

Barnes PJ. *J Allergy Clin Immunol*. 2015;136:531-545.

Asthma Heterogeneity: Asthma Phenotypes

Severe allergic asthma

- **Associations**
  - Blood and sputum eosinophilia, High serum IgE, High FeNo
- **Targeted treatments**
  - Anti-IgE (children and adults), Anti-IL-4/IL-13, Anti-IL-4 receptor

Eosinophilic asthma

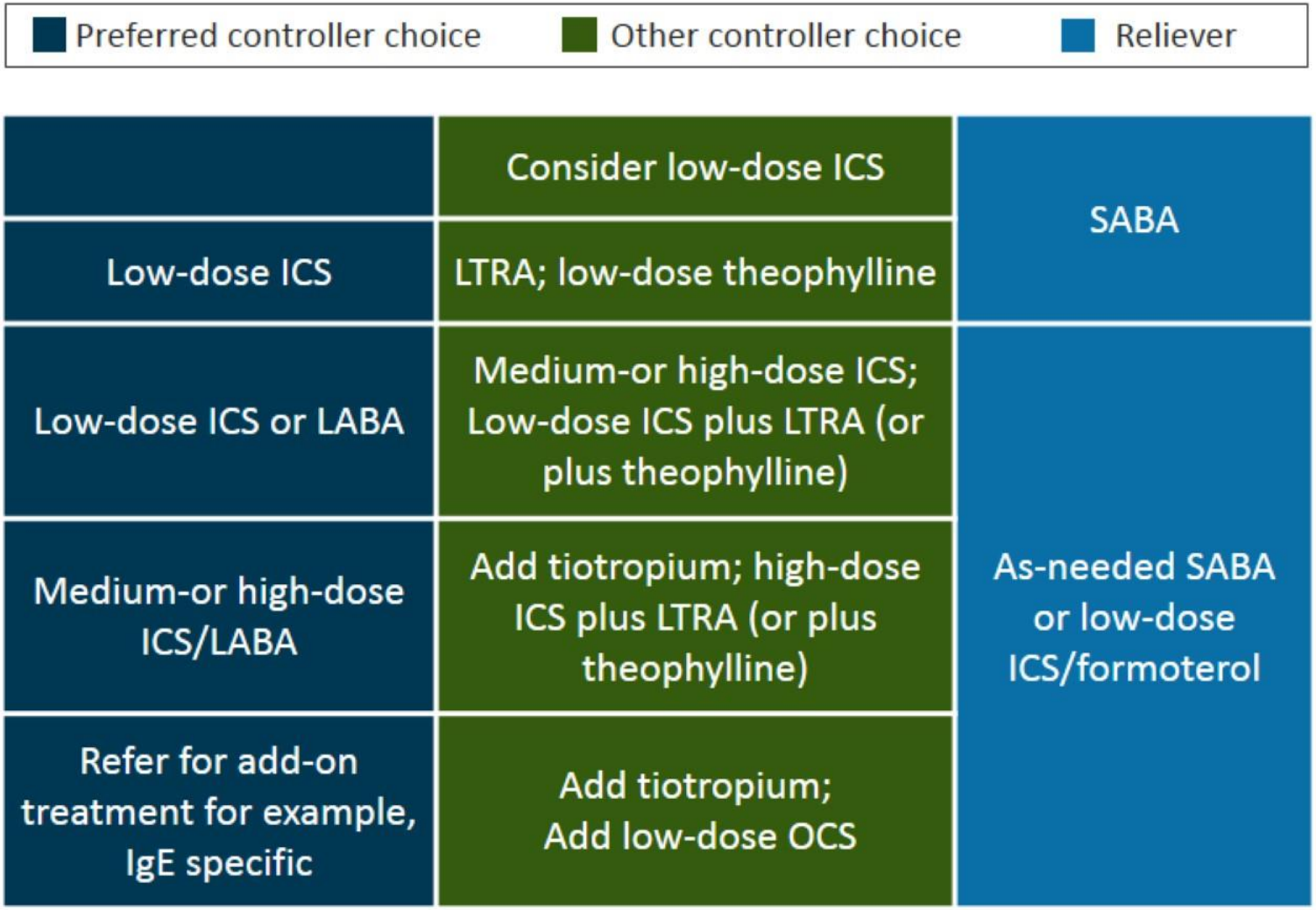
- **Associations**
  - Blood and sputum eosinophilia, recurrent exacerbations, high FeNo
- **Targeted treatments**
  - Anti-IL-5, anti-IL-4/IL-3, anti-IL-4 receptor

Neutrophilic asthma

- **Associations**
  - Corticosteroid insensitivity, bacterial infections
- **Targeted treatments**
  - Anti-IL-8, CXCR2 antagonists, Anti-LTB4 (children and adults), macrolides (children and adults)

Chung KF, et al. *Eur Respir J.* 2014;43:343-373.

GINA-Based Treatment Steps



Holgate ST, et al. *Nature Rev Dis Prim*. 2015;1:15025. [Epub ahead of print]

Step 5: Management in Guidelines

The preferred option is referral for specialist investigation

Add-on therapy should be considered

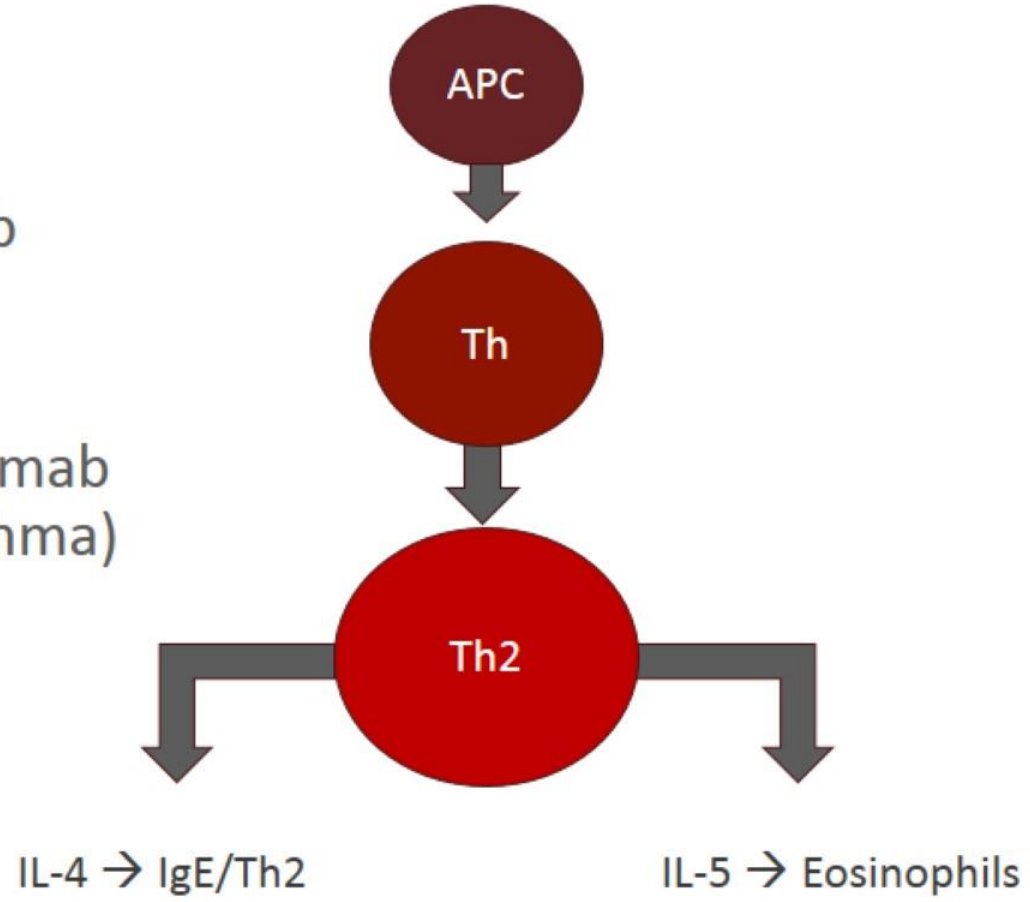
- Check inhaler technique and adherence before referring
- Add-on tiotropium for patients ≥ 12 years of age with history of exacerbations
- Add-on anti-IgE (omalizumab) for patients with severe allergic asthma
- Add-on anti-IL-5 (mepolizumab [SC] or reslizumab [IV]) for severe eosinophilic asthma in patients ≥ 12 years of age

GINA. 2017 global strategy for asthma management and prevention.

Targets for Biologic Treatments of Asthma

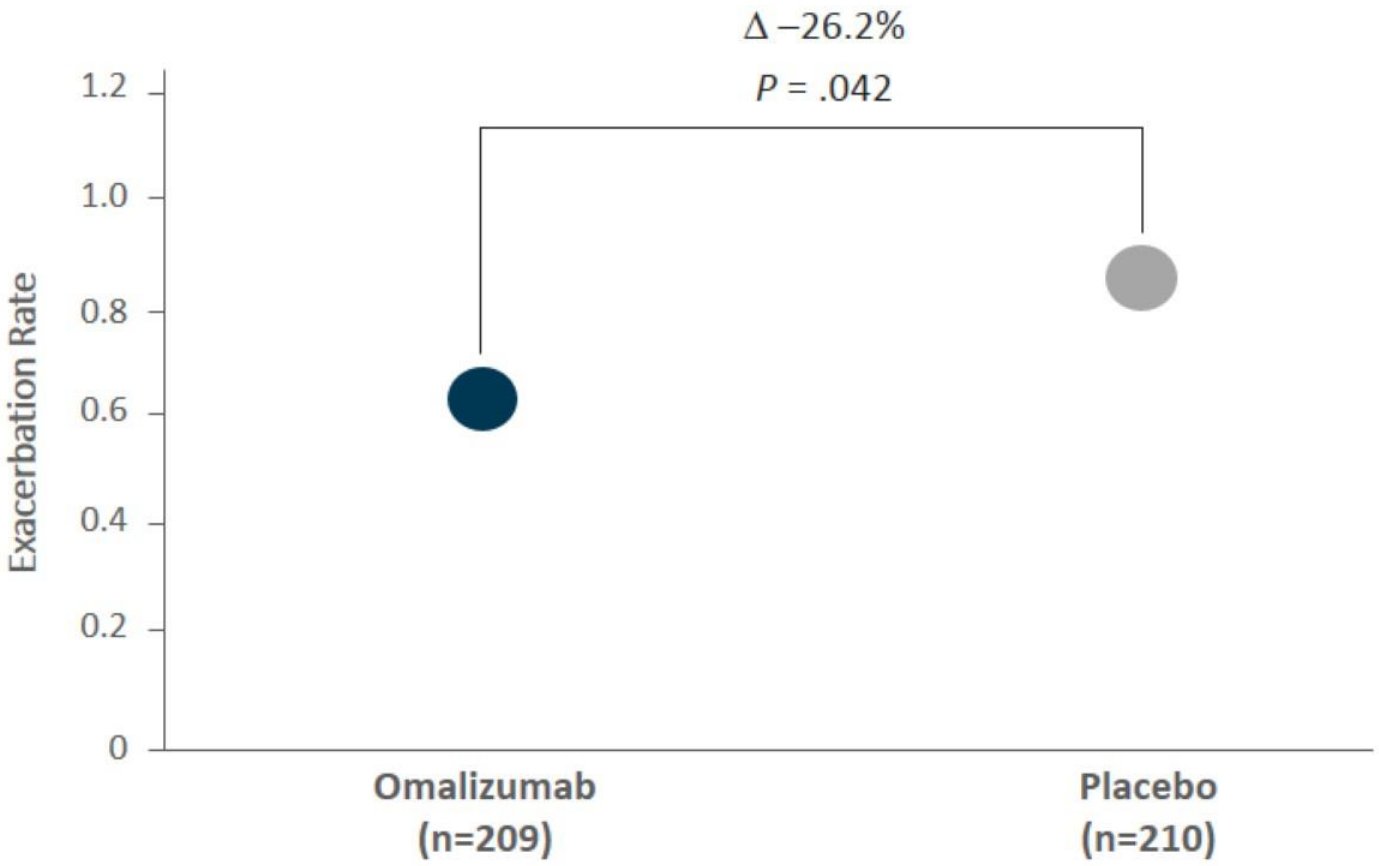
Approved biologics for personalized medicine

- Anti-IgE: SC Omalizumab (severe allergic asthma)
- Anti IL-5/IL-5: SC mepolizumab, IV reslizumab (severe eosinophilic asthma)



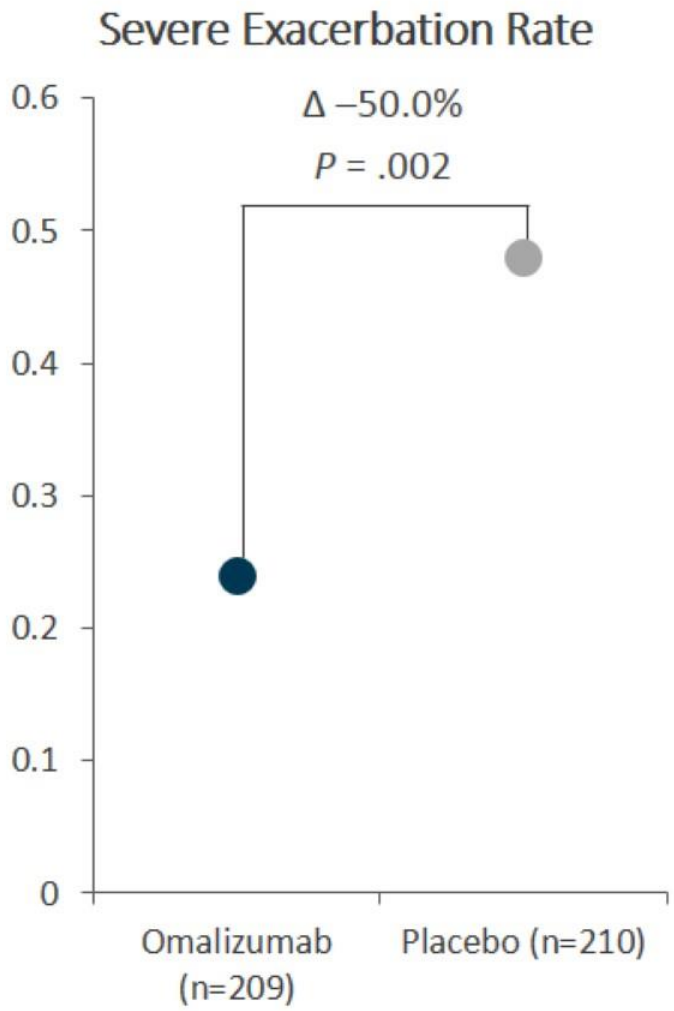
Barnes PJ. *J Allergy Clin Immunol*. 2015;136:531-545.

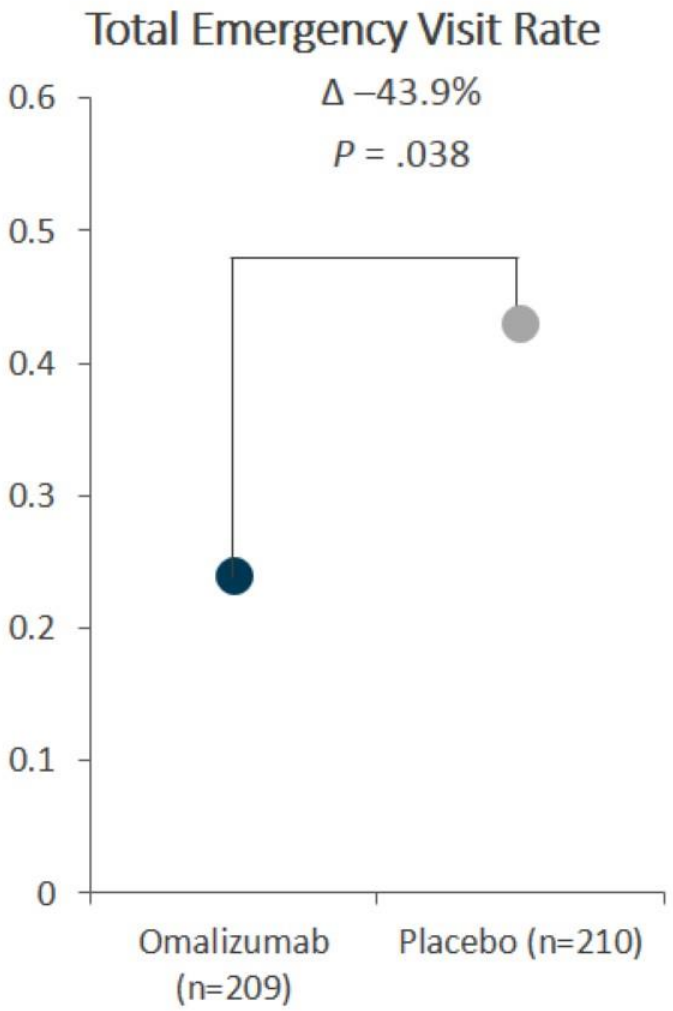
Omalizumab for Severe Asthma



Humbert M, et al. *Allergy.* 2005;60:309-316.

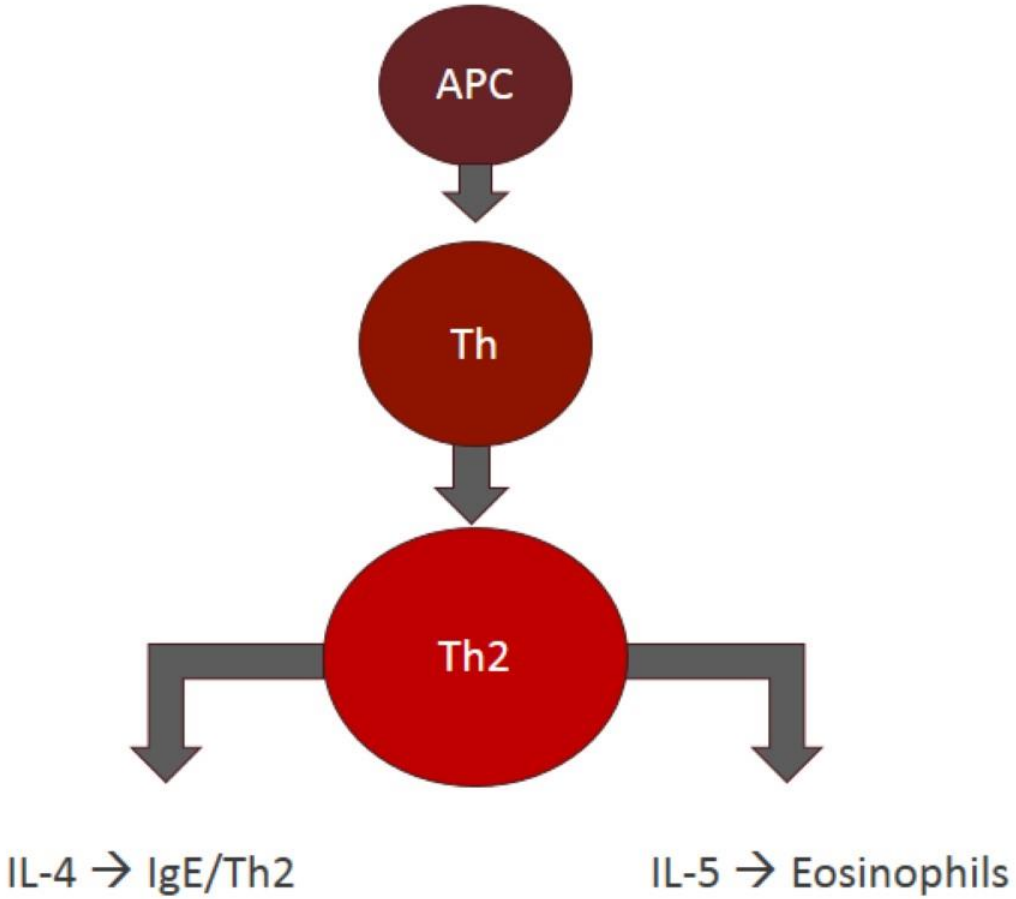
Omalizumab for Severe Asthma (cont)





Humbert M, et al. *Allergy.* 2005;60:309-316.

Targets for Biologic Treatments of Asthma



Barnes PJ. *J Allergy Clin Immunol*. 2015;136:531-545.

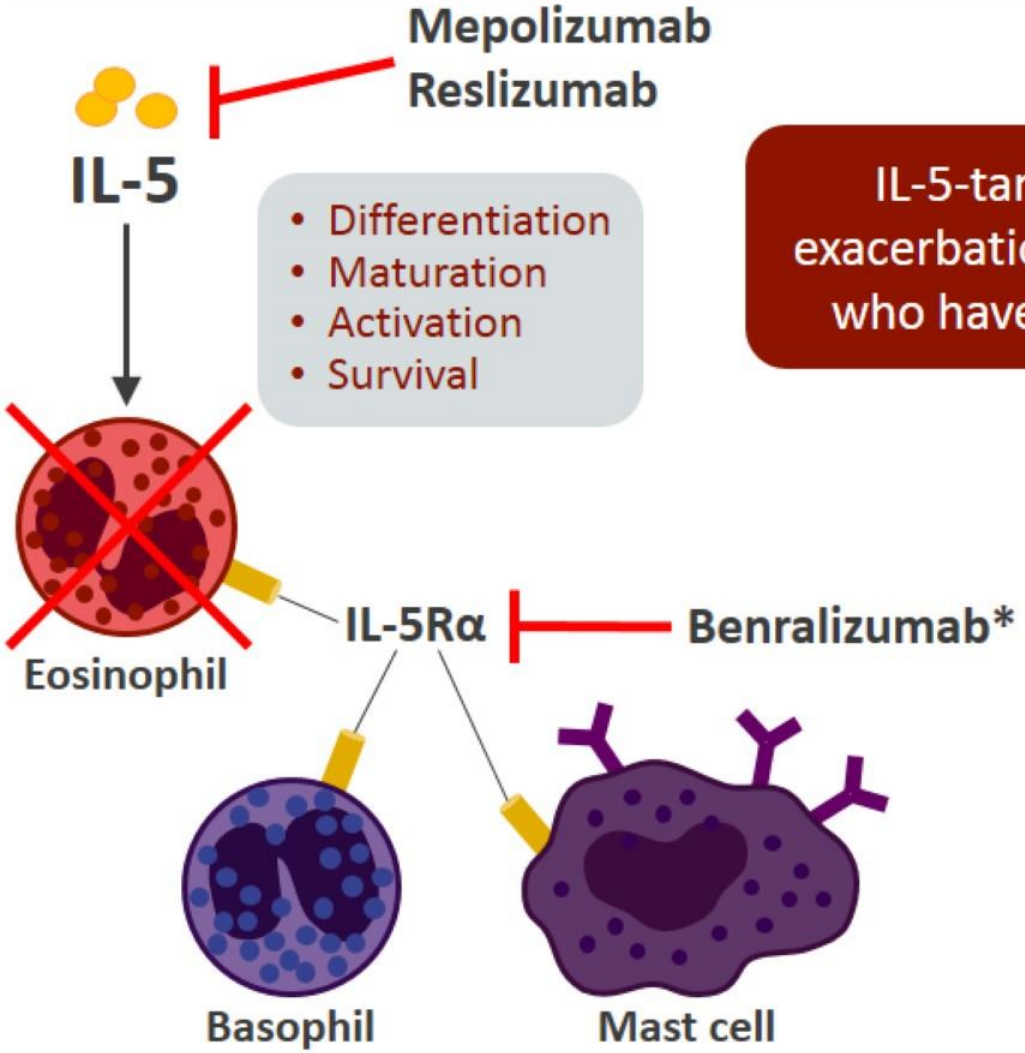
Anticytokines Against IL-5

3 anticytokines against IL-5 are currently being developed, and 2 are licensed in some countries:

Reslizumab[a]	Mepolizumab[b]	Benralizumab[c]
Ligand blockade	Ligand blockade	Receptor blockade
Anti-IL-5 mAb	Anti-IL-5 mAb	Anti-IL-5Rα mAb
Humanized IgG	Humanized IgG	Humanized IgG

a. Castro M, et al. *Lancet Respir Med*. 2015;3:355-366.
b. Abonia JP, et al. *Expert Rev Clin Immunol*. 2011;7:411-417.
c. Ghazi A, et al. *Expert Opin Biol Ther*. 2012;12:113-118.

Anti-IL-5 Therapy in Eosinophilic Asthma

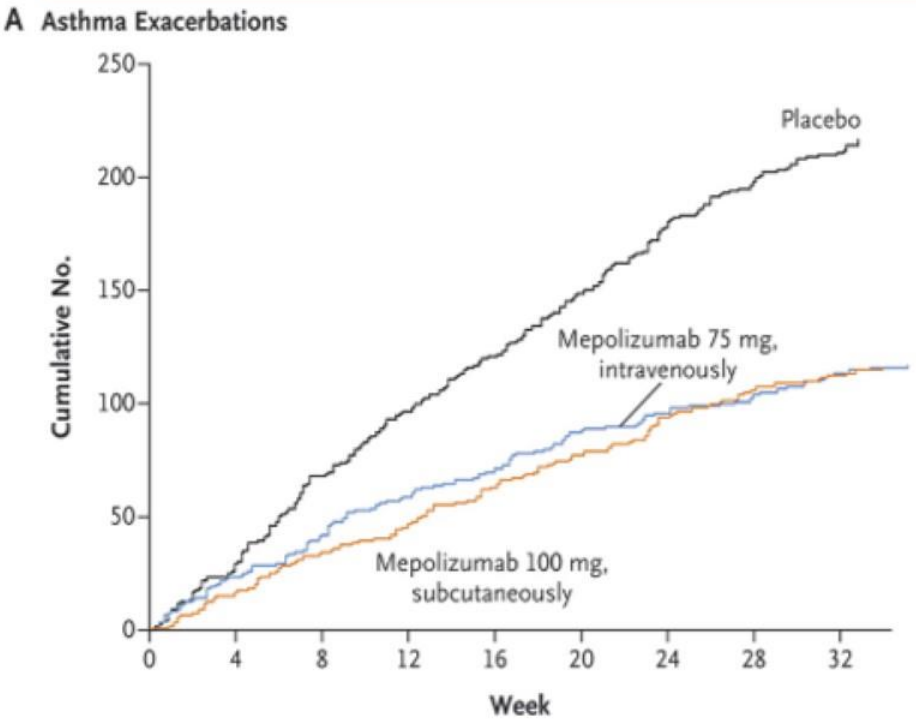


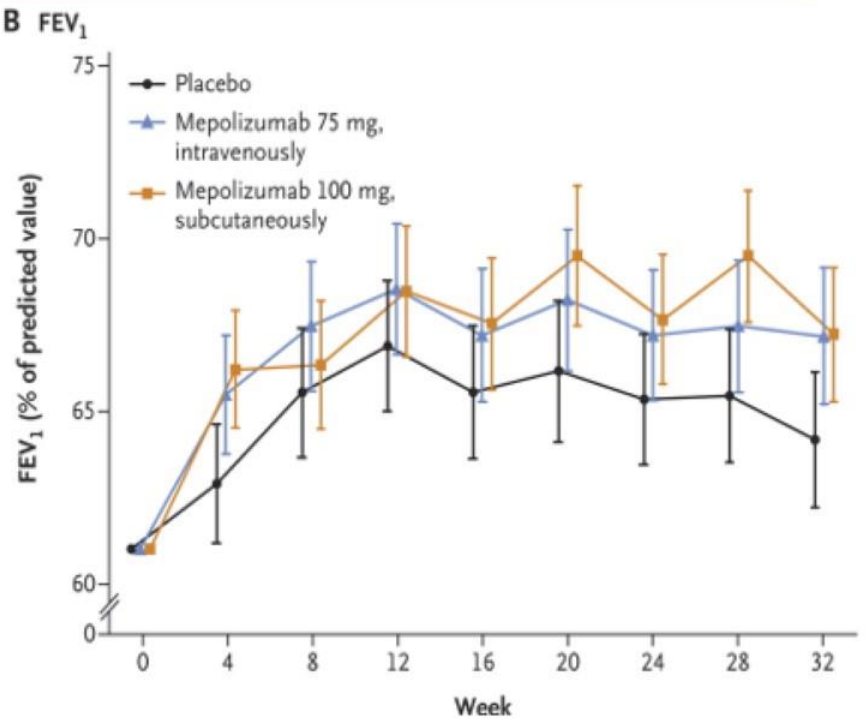
IL-5-targeted agents decrease asthma exacerbations in patients with severe asthma who have high blood eosinophil levels.[a,b]

*Benralizumab is not approved for use by the FDA

a. Ortega H, et al. *N Engl J Med*. 2014;371:1198-1207; b. Castro M, et al. *Lancet Respir Med*. 2015;3:355-366.

Mepolizumab for Severe Eosinophilic Asthma (MENSA)





576 Patients

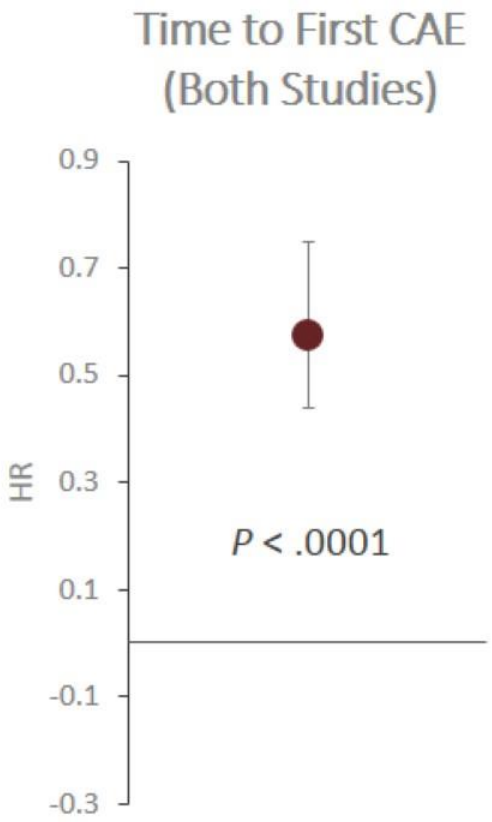
- Placebo n=191
- 75 mg mepolizumab IV, n=191
- 100 mg mepolizumab SC, n=194

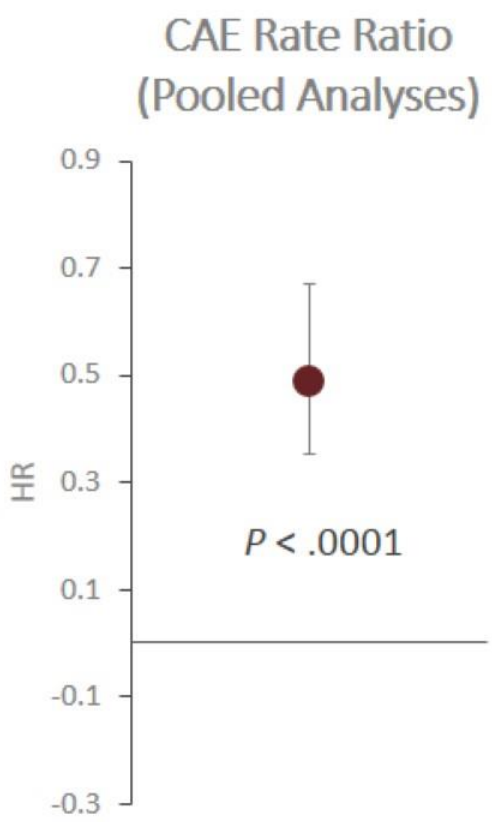
≥2 Exacerbations

- ≥880 mg fluticasone
- ≥150 EOS/ml at screening, or
- ≥300 EOS/ml in past year

Reslizumab for Inadequately Controlled Asthma

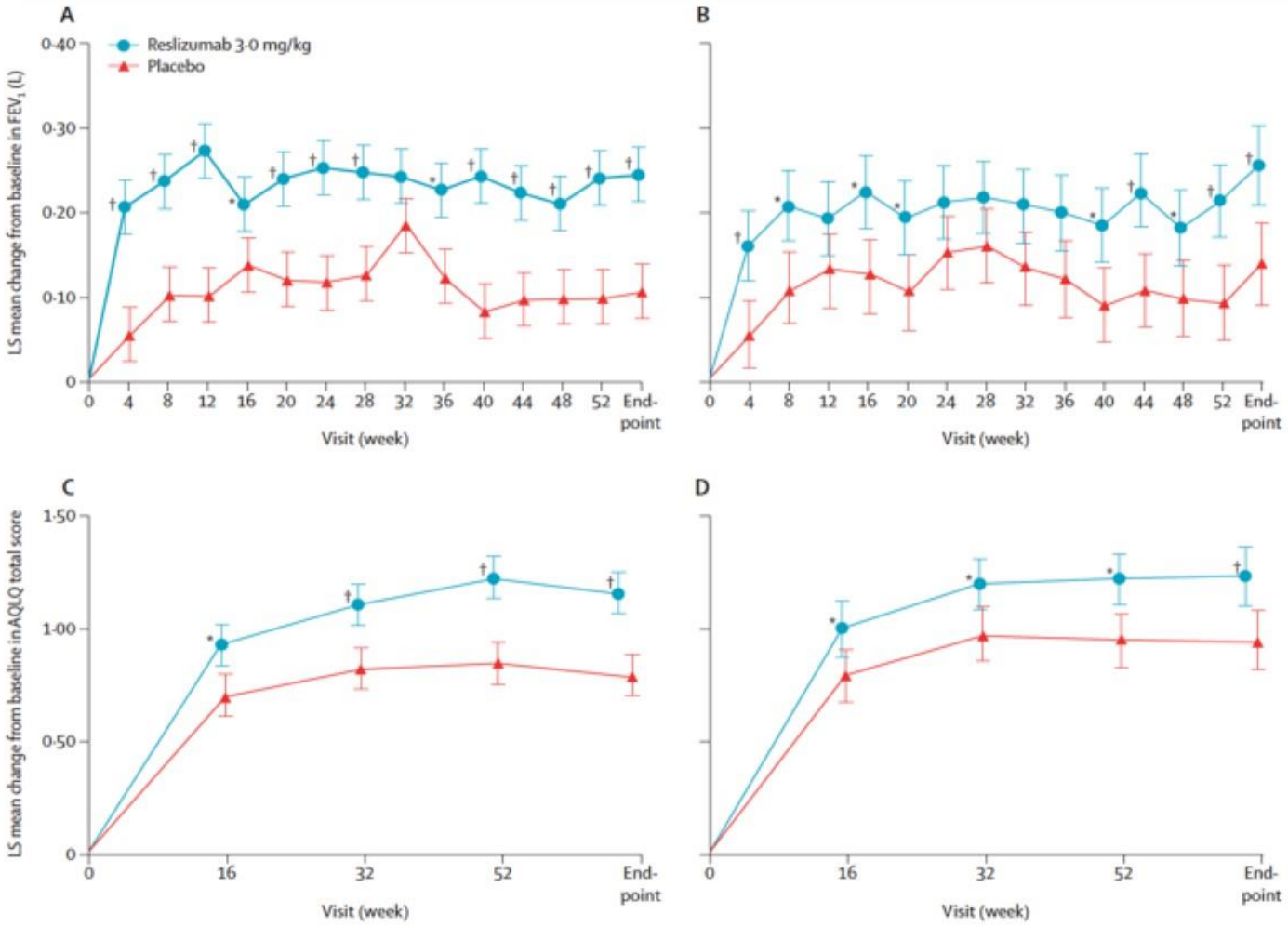
2 multicenter, parallel, phase 3 trials
> 400 eosinophils/mL
Medium-high dose ICS/LABAs
≥ 1 exacerbation in previous year
Reslizumab 3 mg/kg IV every 4 weeks





Castro M, et al. *Lancet Respir Med*. 2015;3:355-366.

Reslizumab for Inadequately Controlled Asthma (cont)



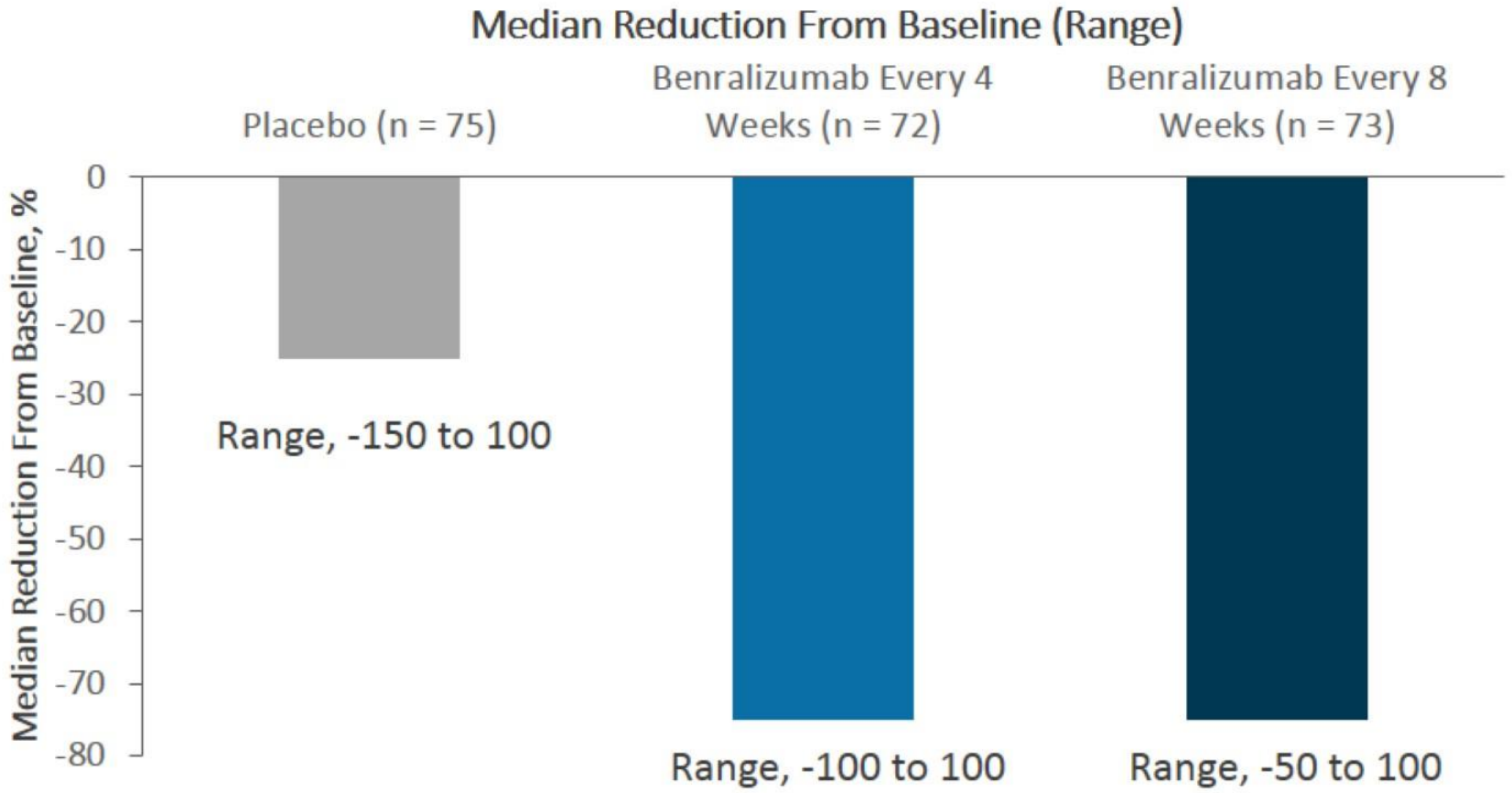
2 multicenter, parallel, phase 3 trials

>400 EOS/ml
Medium-high dose ICS/LABAs
≥1 exacerbation in previous year

Reslizumab 3mg/kg IV every 4 weeks

Reprinted from The Lancet Respiratory Medicine, 3 /5, Mario Castro,James Zangrilli,Michael E Wechsler,Eric D Bateman,Guy G Brusselle,Philip Bardin,Kevin Murphy,Jorge F Maspero,Christopher O'Brien,Stephanie Korn, Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials, 355-366., Copyright (2015), with permission from Elsevier.

Change From Baseline in the Oral Glucocorticoid Dose and Asthma Exacerbations: ZONDA Trial



- 28-week, randomized, controlled trial
- 369 patients enrolled
- 220 patients underwent randomization to benralizumab or placebo

Nair P, et al. *N Engl J Med*. 2017;376:2448-2458.

Anticytokines Against IL-5

3 anticytokines against IL-5 are currently being developed, and 2 are licensed in some countries:

Reslizumab[a]	Mepolizumab[b]	Benralizumab[c]
3 mg/kg BW every 4 weeks	100 mg every 4 weeks	30 mg every 8 weeks
IV	SC	SC
≥ 400 EOS/mL	≥ 150 EOS/mL	≥ 300 EOS/mL

a. Castro M, et al. *Lancet Respir Med.* 2015; 3:355-366.
b. Abonia JP, et al. *Expert Rev Clin Immunol.* 2011;7:411-417.
c. Ghazi A, et al. *Expert Opin Biol Ther.* 2012;12:113-118.

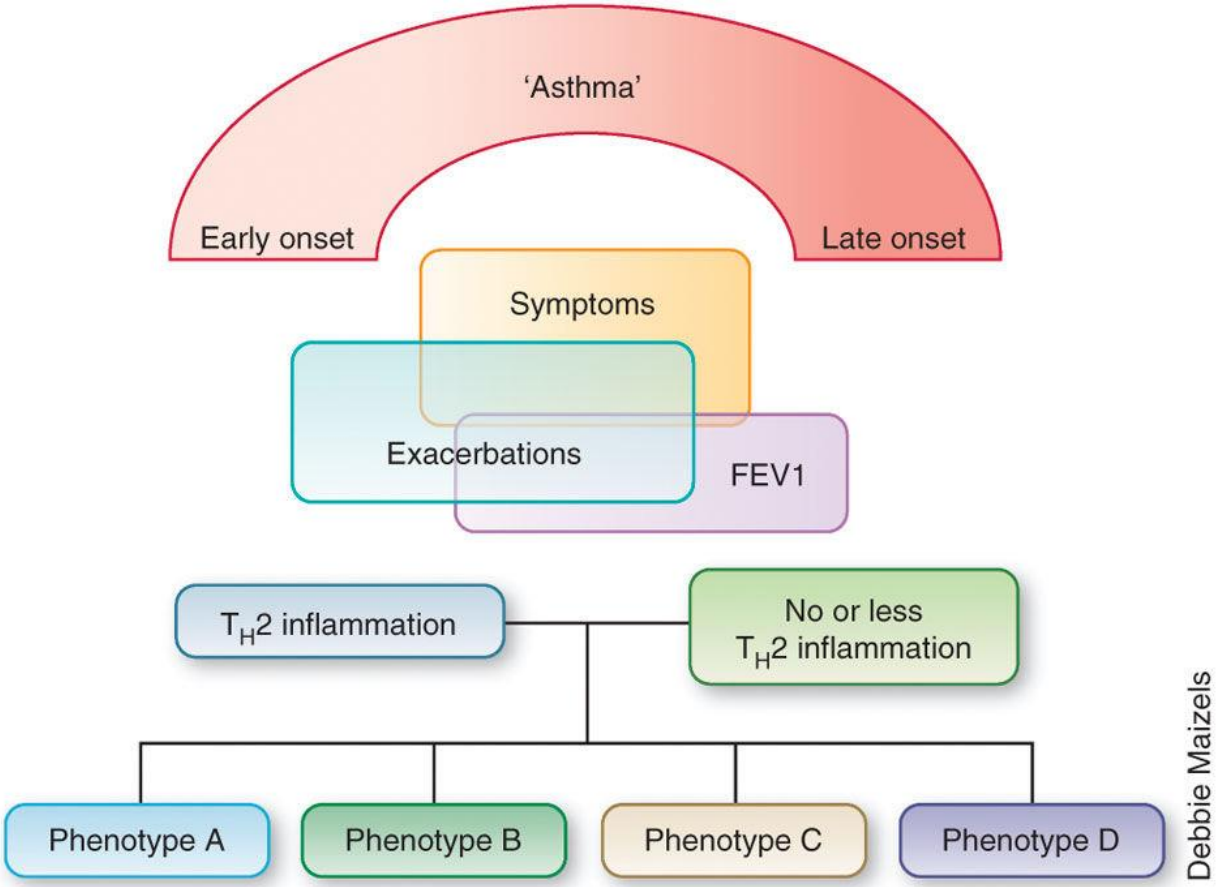
Conclusions

- We currently have a better definition and understanding of the diverse severe asthma phenotypes, including type 2 asthma
- Efficacious targeted therapies for personalized medicine are now available
  - IgE for severe asthma
  - IL-5 for severe eosinophilic asthma

- Eosinophilic asthma vs.

- Neutrophilic asthma
  (Non-eosinophilic asthma)

Umbrella term ‘asthma’



Wenzel SE. Nat Med 2012;18(5):716-25.

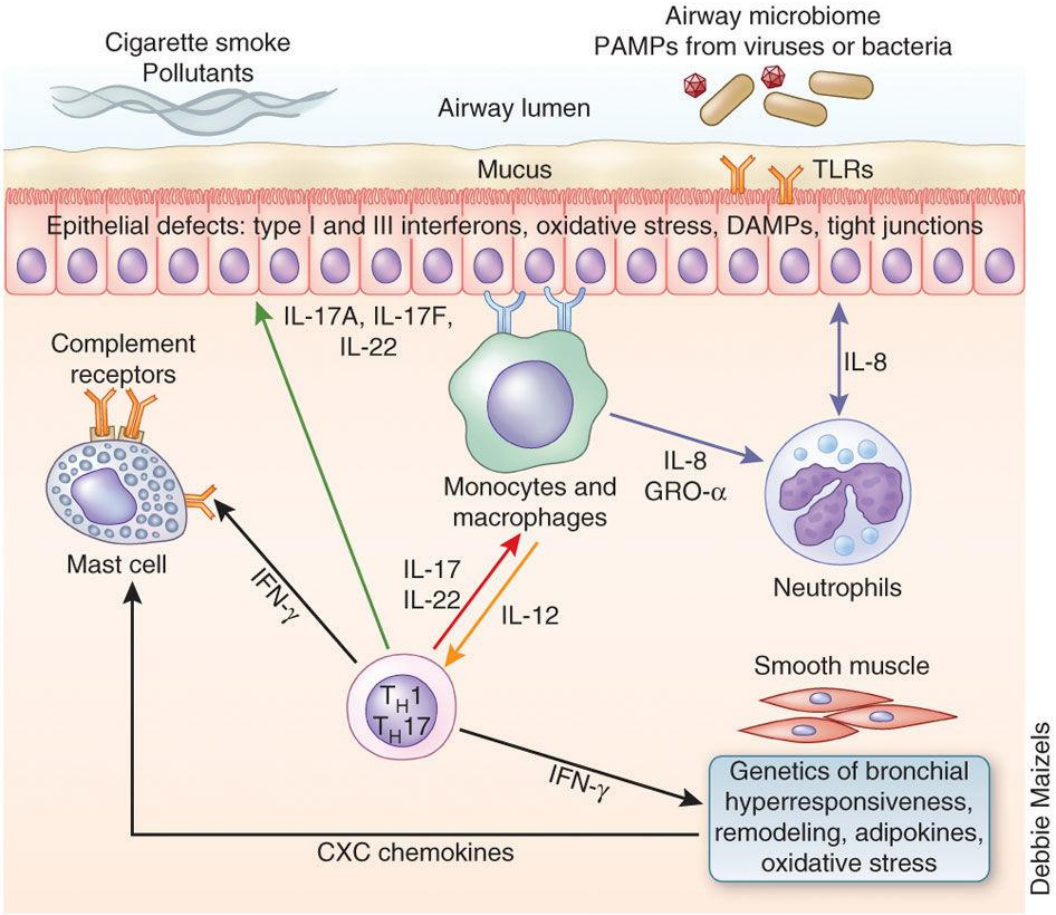
Asthma phenotype

Table 1 Asthma phenotypes in relation to characteristics

	Natural history	Clinical and physiological features	Pathobiology and biomarkers	Genetics	Response to therapy
Early-onset allergic	Early onset; mild to severe	Allergic symptoms and other diseases	Specific IgE; T_H2 cytokines; thick SBM	17q12; T_H2-related genes	Corticosteroid-responsive; T_H2-targeted
Late-onset eosinophilic	Adult onset; often severe	Sinusitis; less allergic	Corticosteroid-refractory eosinophilia; IL-5		Responsive to antibody to IL-5 and cysteinyl leukotriene modifiers; corticosteroid-refractory
Exercise-induced		Mild; intermittent with exercise	Mast-cell activation; T_H2 cytokines; cysteinyl leukotrienes		Responsive to cysteinyl leukotriene modifiers, beta agonists and antibody to IL-9
Obesity-related	Adult onset	Women are primarily affected; very symptomatic; airway hyperresponsiveness less clear	Lack of T_H2 biomarkers; oxidative stress		Responsive to weight loss, antioxidants and possibly to hormonal therapy
Neutrophilic		Low FEV1; more air trapping	Sputum neutrophilia; T_H17 pathways; IL-8		Possibly responsive to macrolide antibiotics

Wenzel SE. Nat Med 2012;18(5):716-25.

Development of non-T_H2 asthma



Wenzel SE. Nat Med 2012;18(5):716-25.

Non-T_H2 asthma

- Non-TH2 asthma may affect 50% or more of corticosteroid-naïve individuals
- less airway obstruction and hyperreactivity than people with T_H2-high asthma
- mild to moderate adult-onset asthma
- no history of childhood allergic features
- poorly respond to corticosteroid therapy

Neutrophilic asthma

- Neutrophilia has been inconsistently associated with asthma and severe asthma
- Neutrophilia is generally seen in corticosteroid-treated patients
- lung neutrophilia associated with lower lung function, more airway trapping, airway wall thickening
- sputum neutrophilia was greatest in a cluster of individuals who had generally adult-onset and severely obstructed (and incompletely reversible) asthma
- Neutrophilia can also co-exist with eosinophilia

Treatment responses

- Corticosteroids are less effective
- Neutrophilic asthma may be more responsive to treatment with macrolide antibiotics (Clarithrymycin)
- Azithromycin did not reduce the rate of severe exacerbations and LRTI in patients with severe asthma.
- Anti–TNF-α (golimumab) in severe asthma treated with high doses of corticosteroids was not efficient
- Anti-IL-17R (brodalumab) in human neutrophilic asthma phenotypes was not determined

Efficacy and safety of a CXCR2 antagonist, AZD5069, in patients with uncontrolled persistent asthma: a randomised, double-blind, placebo-controlled trial

Paul M O'Byrne, Hristo Metev, Margareta Puu, Kai Richter, Christina Keen, Mohib Uddin, Bengt Larsson, Marie Cullberg, Parameswaran Nair

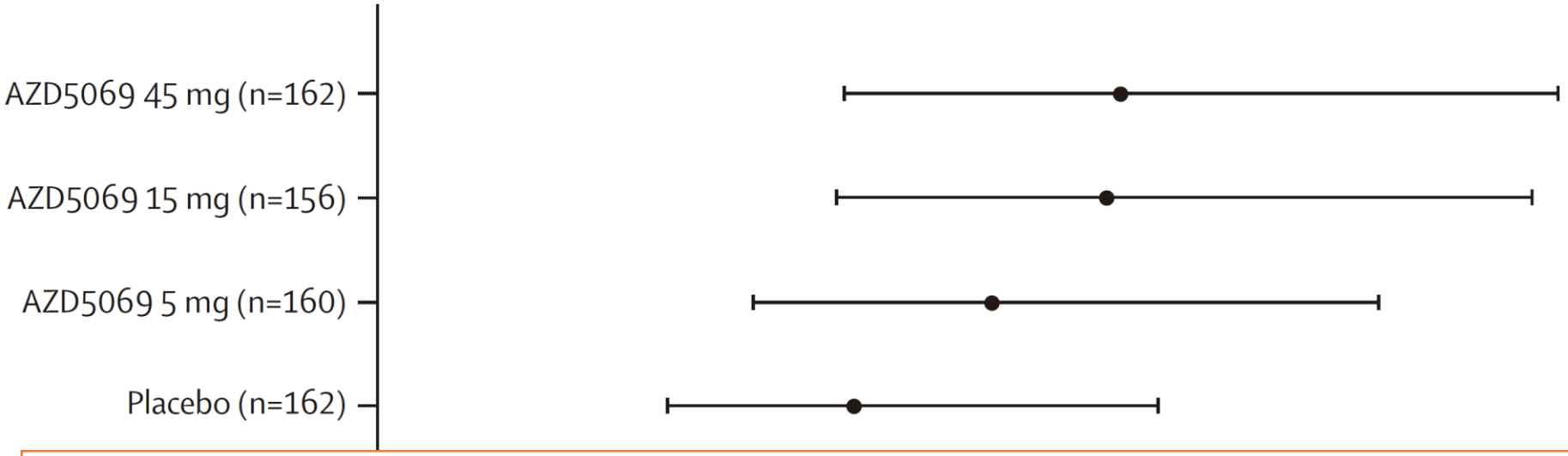
O'Byrne PM. Lancet Respir Med 2016;4:797–806

Study design

- Neutrophilic asthma
  - Eosinophil counts in blood lower than 0·5 × 10^9/L,
  - IgE concentrations in serum lower than 750 kIU/L
  - Neutrophil counts in blood greater than 2·7 × 10^9/L

- AZD5069 is a CXCR2 chemokine receptor antagonist that blocks the effects of interleukin 8
  - randomly assigned to receive 5, 15, or 45 mg oral AZD5069 twice daily or placebo as add-on therapy to standard Tx

- Primary endpoint was the number of severe asthma exacerbations in 6 months



Conclusion:
Selective CXCR2 antagonist did not reduce the frequency of severe exacerbations in patients with uncontrolled severe asthma.

	Number of patients	Number of events	Total follow-up time (years)	Severe exacerbation rate (90% CI)	Relative risk (90% CI)	p value*
AZD5069 45 mg (*n*=162)	161	35	71·8	0·31 (0·20–0·50)	1·56 (0·98–2·49)	0·12
AZD5069 15 mg (*n*=156)	153	33	69·0	0·31 (0·19–0·49)	1·53 (0·95–2·46)	0·14
AZD5069 5 mg (*n*=160)	156	28	69·9	0·26 (0·16–0·42)	1·29 (0·79–2·11)	0·40
Placebo (*n*=162)	159	25	71·7	0·20 (0·12–0·33)	..	..

Thank you for your attention!