

## *Taking a Deep Breath:*

# *Addressing Unmet Needs in the Management of Moderate to Severe Asthma – A Community Approach*

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## **Disclosures**

**Dr. Chupp** reports the following financial relationships:

- **Ongoing clinical trials:** GSK, AZ, RAPT Therapeutics, NHLBI (PRECISE), Epiphany (NHLBI)
  - **Consultant:** Genentech, AZ, Sanofi-Regeneron, GSK, MERCK, RAPT Therapeutics
  - All relevant financial relationships have been mitigated
- During the course of this activity, faculty may be discussing investigational agents for asthma that are not yet FDA approved.

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## Learning Objectives

- Identify strategies to proactively manage uncontrolled asthma to reduce exacerbations and associated hospitalizations
- Assess evidence-based, multidisciplinary strategies to improve patient education to reduce inadequate home care of asthma and exacerbations
- Discuss the clinical evidence for recently approved and investigational agents for the potential treatment of moderate to severe asthma

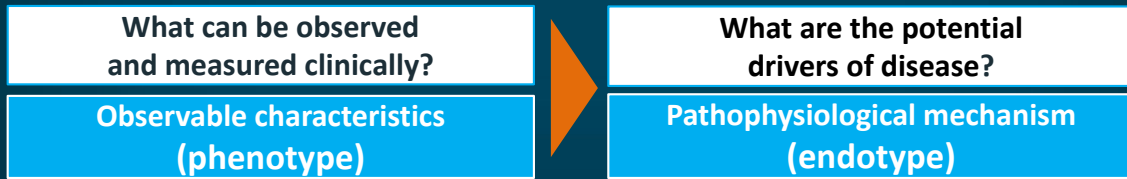
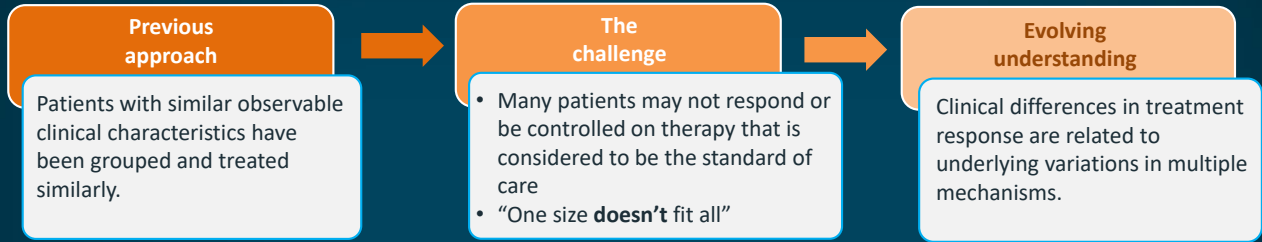
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## Asthma ECHO Pre-Read Slides

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# Our Understanding of Asthma Is Changing

## Focus shifting toward disease mechanisms



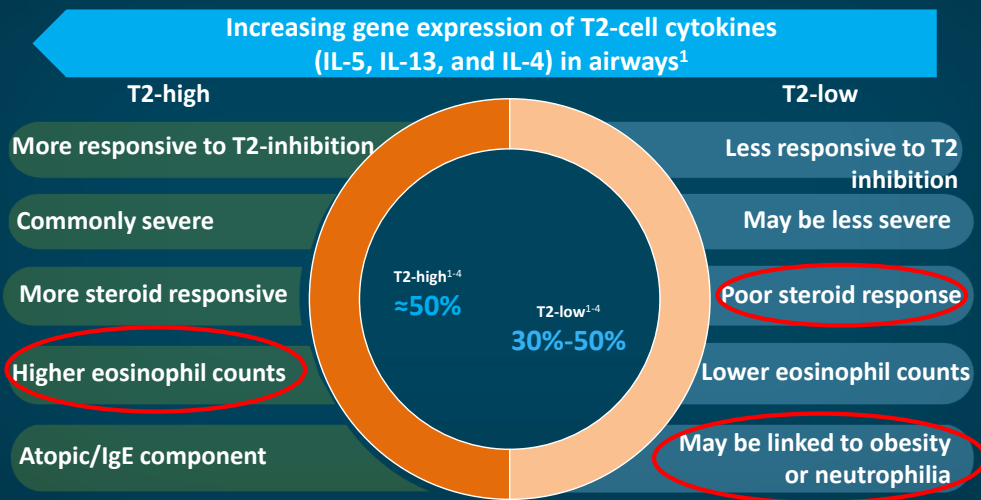
The heterogeneity in treatment response has inspired discussions of a precision approach to care that tailors treatment to the patient.

Muraro A, et al. *J Allergy Clin Immunol.* 2016;137:1347-1358. Lötvall J, et al. *J Allergy Clin Immunol.* 2011;127:355-360.

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# Examples of Asthma Phenotypes

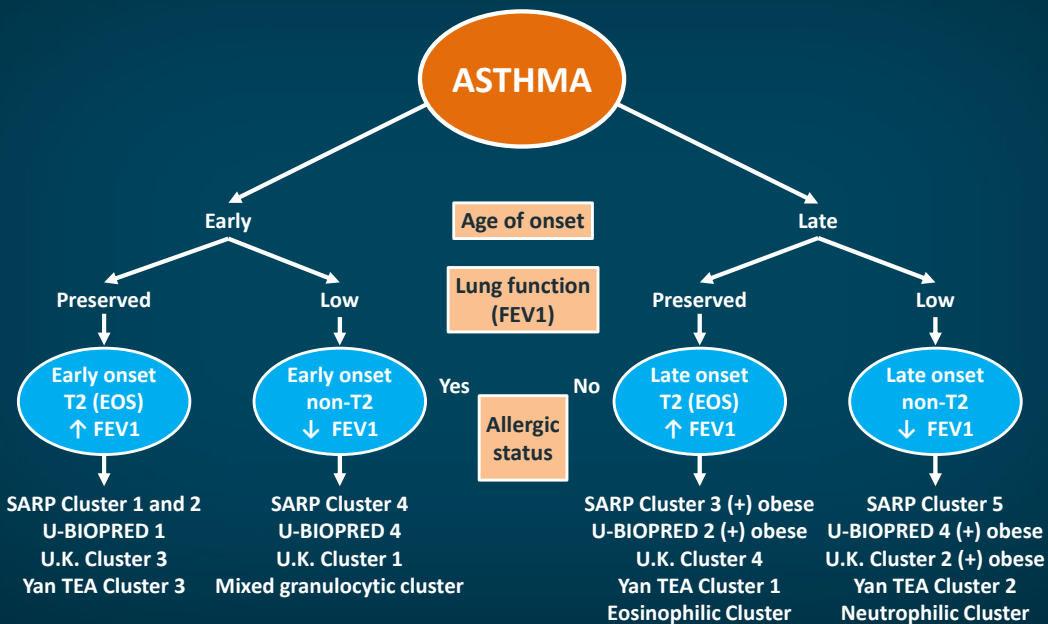
## T2-high and T2-low



1. Woodruff PG, et al. *Am J Respir Crit Care Med.* 2009;180:388-395. 2. Fahy JV. *Nat Rev Immunol.* 2015;15:57-65. 3. Wenzel SE. *Nat Med.* 2012;18:716-725. 4. Peters MC, et al. *J Allergy Clin Immunol.* 2014;133:388-394.

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# Current Clustering Paradigms to Dissect Heterogeneity of Asthma

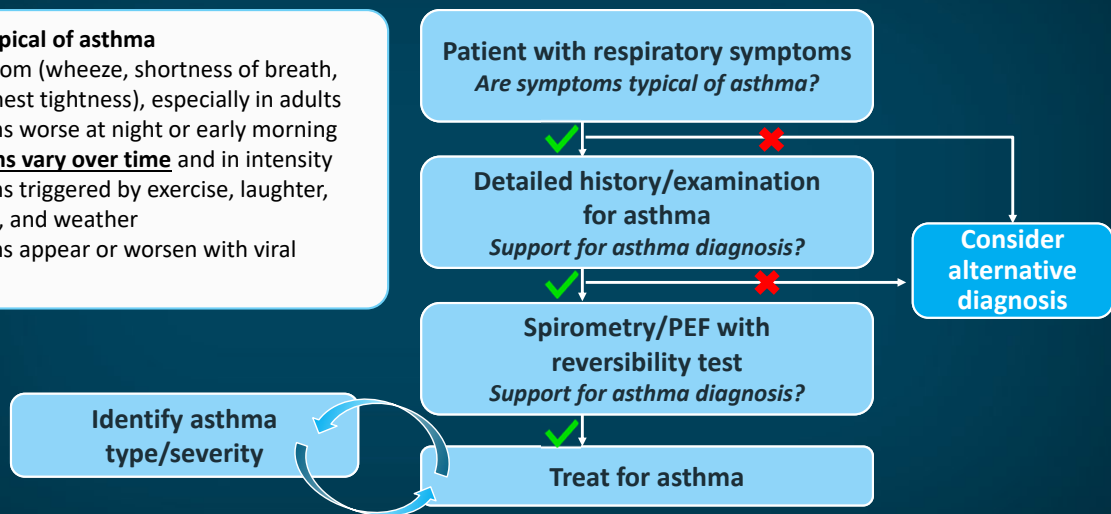


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# Diagnosis of Asthma Is Based on Characteristic Pattern of Respiratory Symptoms

## Features typical of asthma

- ≥1 symptom (wheeze, shortness of breath, cough, chest tightness), especially in adults
- Symptoms worse at night or early morning
- **Symptoms vary over time** and in intensity
- Symptoms triggered by exercise, laughter, allergens, and weather
- Symptoms appear or worsen with viral infection

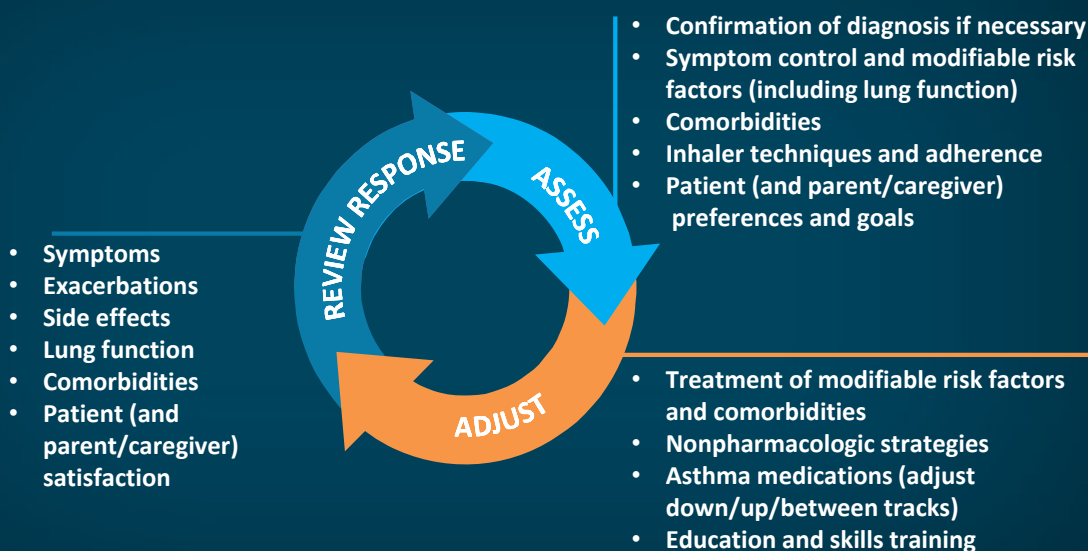


PEF = peak expiratory flow.

Adapted from Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention 2022 (<https://ginasthma.org/gina-reports/>). URLs accessed 7/18/23.

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## GINA 2023: Personalized Asthma Care



Adapted from GINA. Global strategy for asthma management and prevention 2023 (<https://ginasthma.org/wp-content/uploads/2023/05/GINA-2023-Full-Report-2023-WMS.pdf>). Accessed 7/18/23.

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## Targeted Therapies for Severe Asthma

Biologic	Target	Key trials	Administration			Approved or studied in other diseases
			Age*	Route	Frequency	
Omalizumab	IgE	Study 008/009/ALTO	≥6 years	SC	Q2W/Q4W	CRSwNP CSU Food allergy
Mepolizumab	IL-5	MENSA/SIRIUS	≥6 years	SC	Q4W	CRSwNP EGPA HES COPD
Reslizumab	IL-5	BREATH trials	≥18 years	IV	Q4W	Sinusitis Eosinophilic esophagitis
Benralizumab	IL-5R	SIROCCO/CALIMA/ ZONDA	≥12 years	SC	Q4W/Q8W	COPD
Dupilumab	IL-4R <sup>†</sup>	LIBERTY QUEST LIBERTY VENTURE SOLO1/SOLO2 CHRONOS	≥6 years	SC	Q2W	Atopic dermatitis CRSwNP Eosinophilic esophagitis Prurigo nodularis COPD
Tezepelumab	TSLP	PATHWAY, NAVIGATOR SOURCE	≥12 years	SC	Q4W	Atopic dermatitis

\*FDA-approved ages for asthma indication; <sup>†</sup>Inhibits IL-4 and IL-13 signaling pathways.

CRSwNP = chronic rhinosinusitis with nasal polyps; CSU = chronic spontaneous urticaria; COPD = chronic obstructive pulmonary disease; DP2 = prostaglandin D2; EGPA = eosinophilic granulomatosis with polyangiitis; HES = hypereosinophilic syndrome; IV = intravenous; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; R = receptor; SC = subcutaneous; TSLP = thymic stromal lymphopoietin.

Prescribing information (PI) for each agent. Brusselle GG, et al. *N Engl J Med.* 2022;386(2):157-171.

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## Open-Label Trial of Omalizumab: Prospero

### Lung function 12 months after initiation of omalizumab

Adjusted mean change: FEV <sub>1</sub> , L	n	Baseline, mean (SD)*	End of study, LS mean (SE)†	Adjusted P value (low vs high)‡
Eosinophils low (<300 cells/μL)	362	2.28 (0.82)	-0.01 (0.02)‡	.011
Eosinophils high (≥300 cells/μL)	188	2.19 (0.78)	0.08 (0.03)‡	
FeNO low (<25 ppb)	310	2.25 (0.78)	-0.02 (0.02)‡	.002
FeNO high (≥25 ppb)	253	2.28 (0.83)	0.08 (0.02)‡	

FeNO = fractional exhaled nitric oxide; FEV<sub>1</sub> = forced expiratory volume in 1 second; LS = least-squares; ppb = parts per billion; SD = standard deviation; SE = standard error.

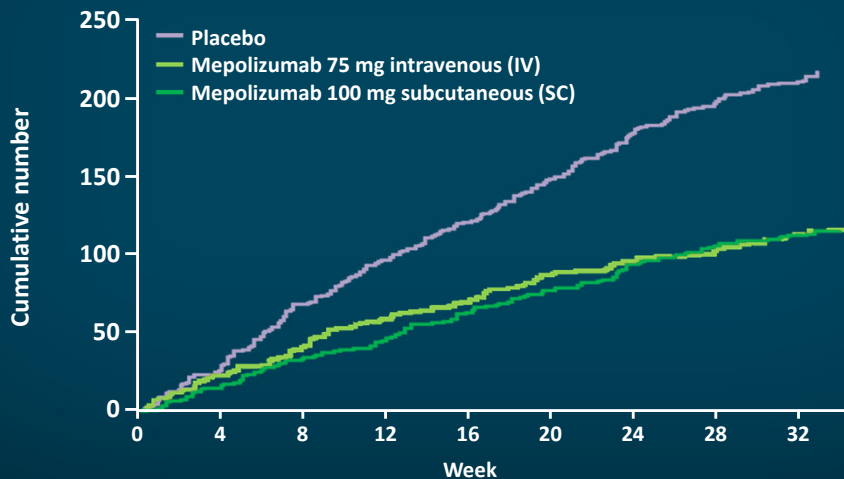
\*n reflects the number of patients with biomarker measurement and variable measured. †LS means and P values come from baseline adjustments. ‡LS mean change from baseline.

Casale TB, et al. *J Allergy Clin Immunol Pract.* 2019;7(1):156-164.

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## Phase 3 Trial of Mepolizumab: Exacerbation Rate Reduction

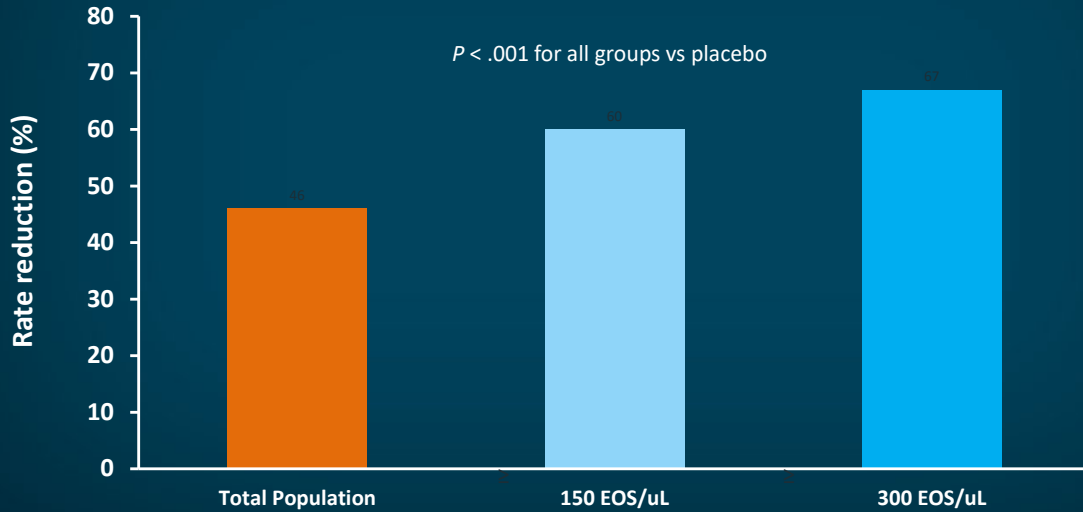
### Reduction in exacerbations vs placebo in phase 3 MENSEA trial (patients with severe eosinophilic asthma)



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## Dupilumab QUEST Study Primary endpoint

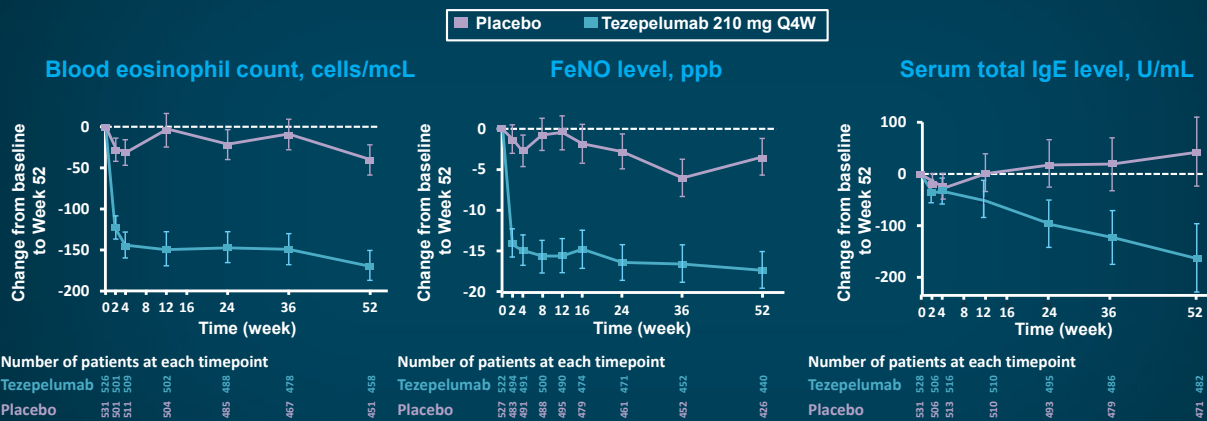
% reduction in annualized rate of severe exacerbation events



Castro M, et al. *N Engl J Med.* 2018;378:2486-2496.

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## Tezepelumab: Phase 3 NAVIGATOR Showed Reduction in Blood Eosinophil Counts, FeNO, and IgE Over 52 Weeks



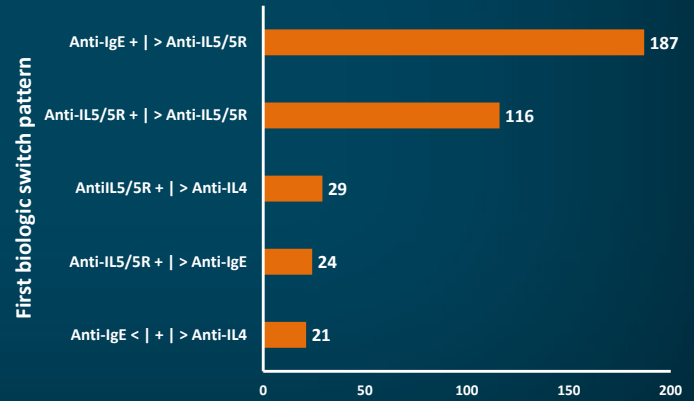
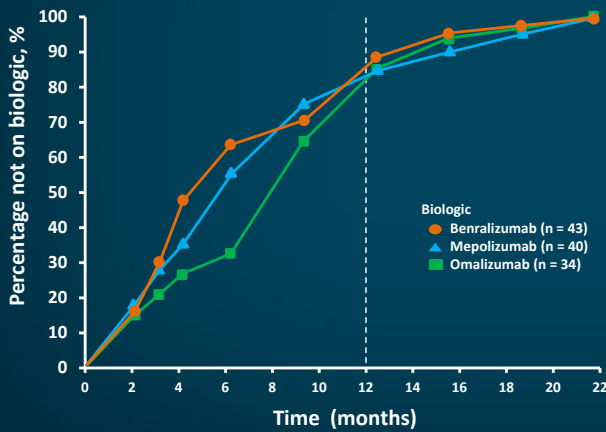
Data are LS means and 95% CIs.

Menzies-Gow A, et al. *N Engl J Med.* 2021;384:1800-1809.

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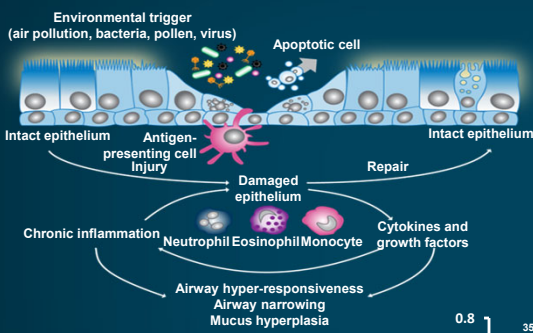
# Real-World Biologic Use and Switch Patterns: Data From the International Severe Asthma Registry and the US CHRONICLE Study

## Time to biologic cessation and pattern of biologic switching

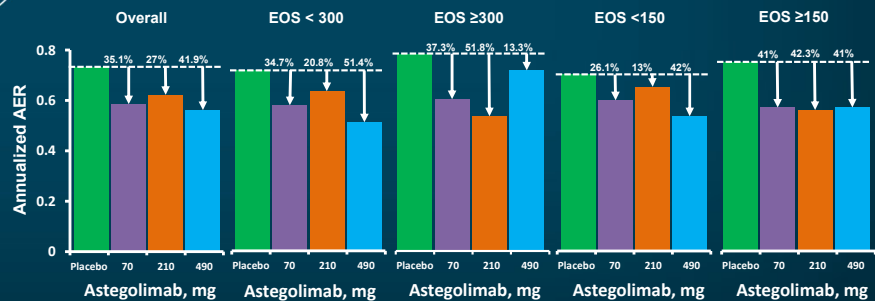


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## Other Emerging Therapies: Blocking IL-33 AsteGolimab (Anti-ST2)<sup>1</sup>



Annualized AERs in the overall population and patients stratified by baseline eosinophil levels (cells/mcL)  
Unadjusted rates by treatment groups  
Arrows indicate unadjusted percentage rate reductions



Kelsen SG, et al. *J Allergy Clin Immunol.* 2021;148:790-798.

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## Other Emerging Therapies: Blocking IL-33 Itepekimab

### Phase 2 results

Endpoint	Placebo (n = 74)	Itepekimab (n = 73)	Itepekimab + dupilumab (n = 74)	Dupilumab (n = 74)
Primary endpoint: Event indicating loss of asthma control during 12-week intervention period, n (%)	30 (41)	16 (22)	20 (27)	14 (19)
Odds ratio vs placebo (95% CI)	—	0.42 (0.20-0.88)	0.52 (0.26-1.06)	0.33 (0.15-0.70)
<i>P</i> vs placebo	—	0.02	0.07	N/A
Patients with baseline eosinophils <300 cells/mm <sup>3</sup> , n	33	37	42	43
Primary endpoint event, n (%)	11 (33)	7 (19)	13 (31)	10 (23)
Odds ratio vs placebo (95% CI)	—	0.46 (0.15-1.41)	0.92 (0.33-2.56)	0.62 (0.22-1.77)
Patients with baseline eosinophils ≥300 cells/mm <sup>3</sup> , n	41	36	32	31
Primary endpoint event, n (%)	19 (46)	9 (25)	7 (22)	4 (13)
Odds ratio vs placebo (95% CI)	—	0.39 (0.14-1.05)	0.30 (0.10-0.87)	0.17 (0.05-0.58)

Wechsler ME et al. *N Engl J Med.* 2021;385:1656-1668.