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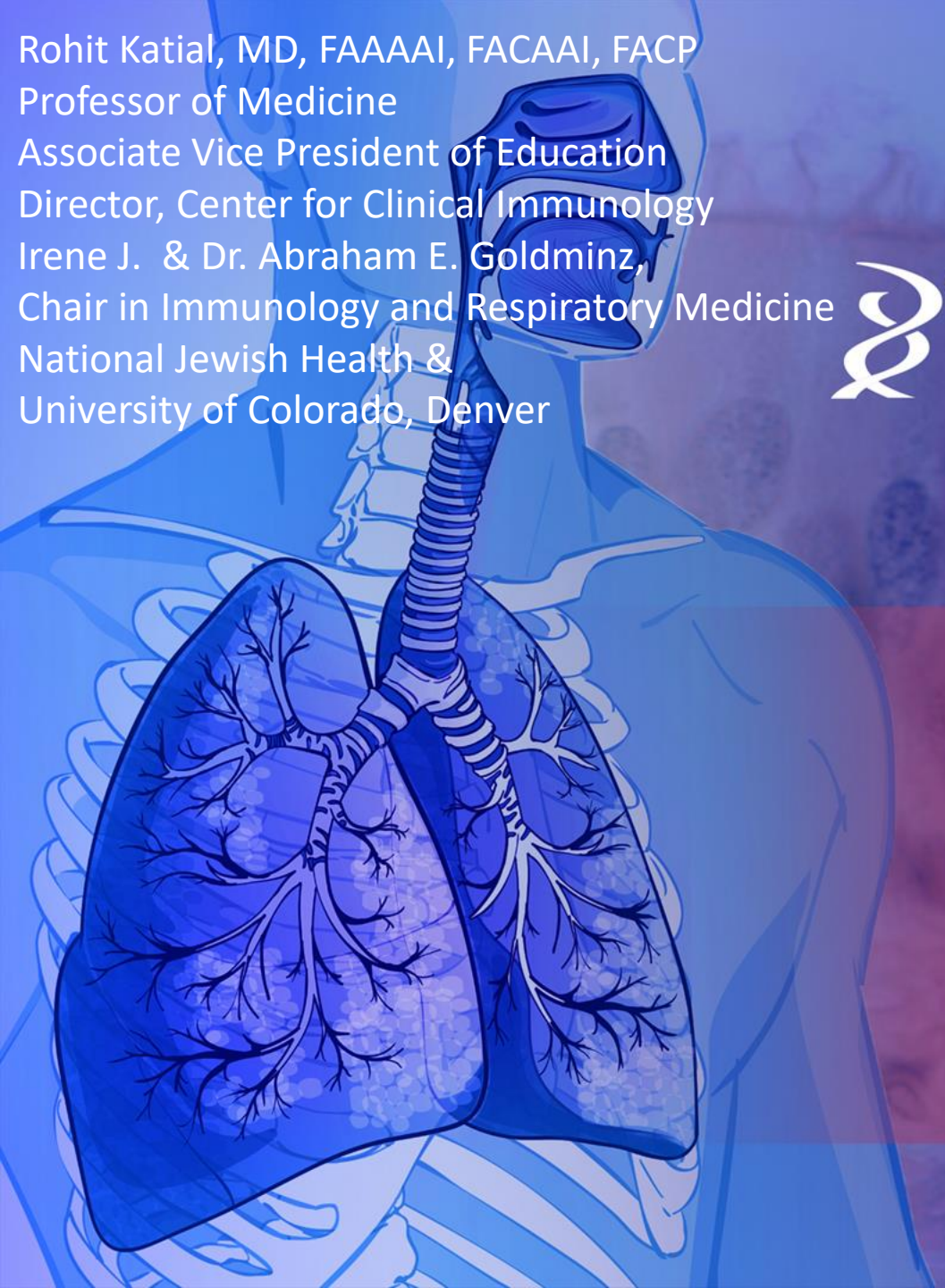

125 YEARS
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Breathing Science is Life.®

Severe Asthma and the Role of the Upper Airway

A Comprehensive Approach to Chronic Inflammatory Airway Diseases

Learning Objectives

- Describe the major comorbidities that coexist with asthma
- Assess the role of type 2 cytokines in the inflammatory pathways in severe asthma and upper airway disease
- Identify appropriate biomarkers to guide treatment selection for severe asthma and upper airway chronic inflammatory disease
- Incorporate an understanding of the impact of comorbid upper airway diseases to personalize treatment strategies for severe asthma

How should an accurate diagnosis of severe uncontrolled asthma be made?

Check adherence/ inhaler technique

Screen for comorbidities

Rule out other potential diagnoses

Check for triggers/irritants

Assess asthma control

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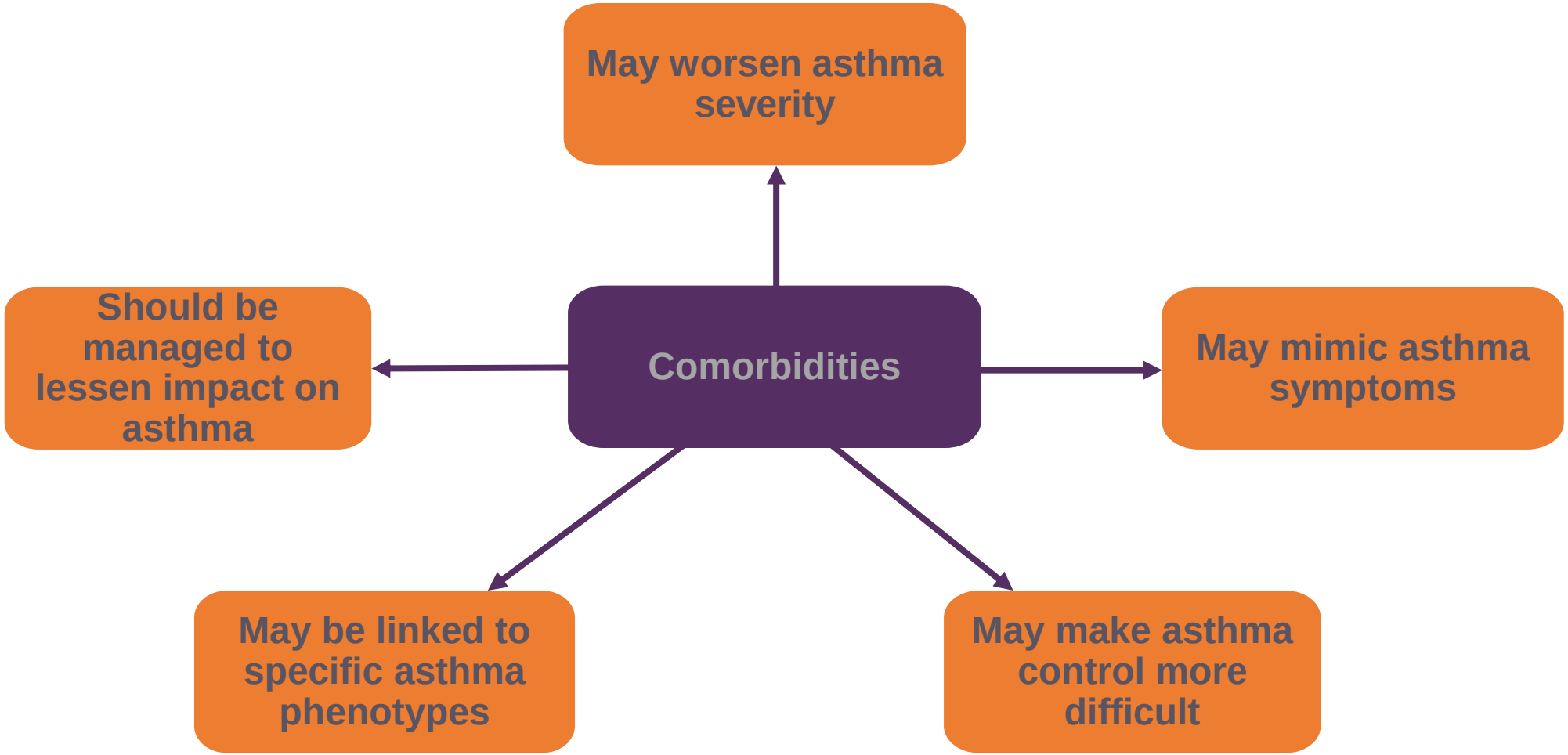
Comorbidities Have Significant Implications For Evaluation/ Assessment Of Asthma Control And Medication Needs



Boulet LP. *Eur Respir J.* 2009;33:897-906.

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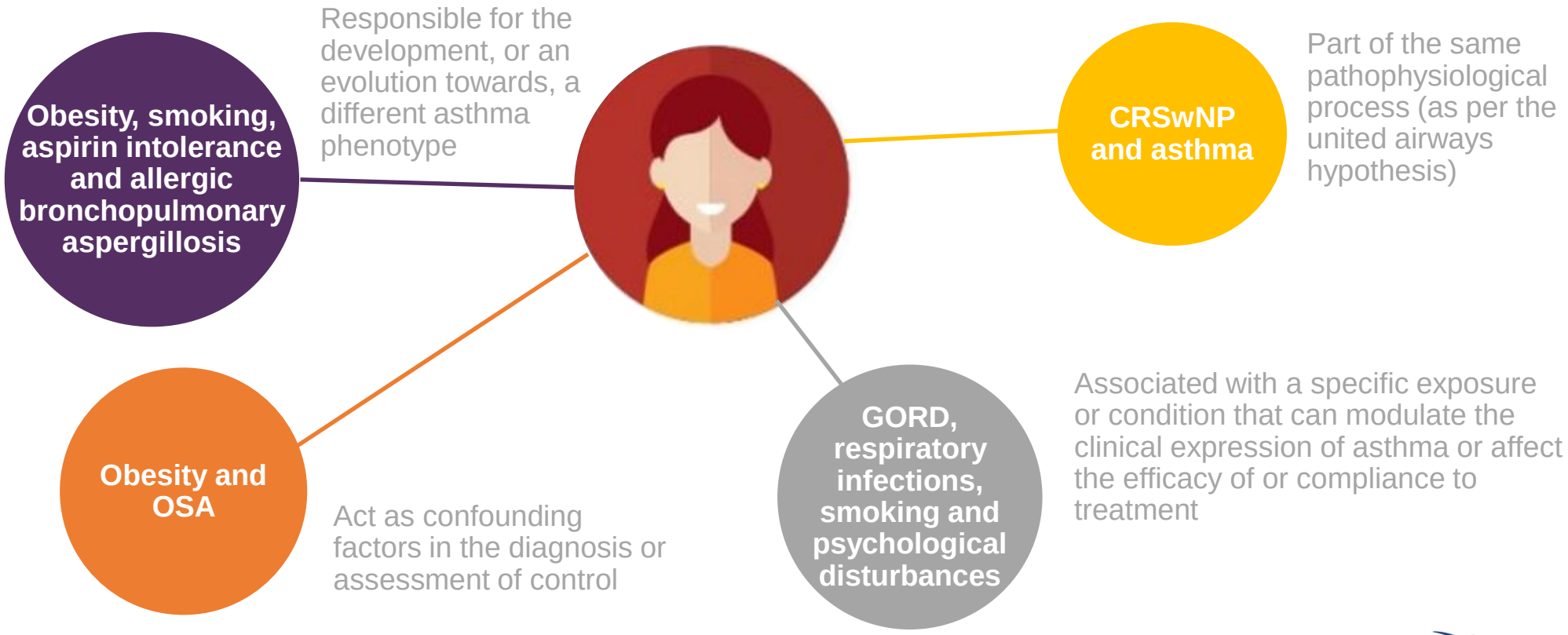
Why Are Comorbidities Important In The Management Of Severe Asthma?

Comorbidities Influence Disease Severity

Identification of comorbidities is an integral part of phenotyping and management of asthma, particularly in severe asthma



OSA, obstructive sleep apnoea; GORD, gastro-oesophageal reflux disease

Boulet LP. *Eur Respir J*. 2009;33:897-906.

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Eosinophilic Inflammation & Co-morbidities

- Eosinophilic inflammation characterizes the dysregulation of biological mechanisms involved in eosinophil recruitment and activation in disease

- Role of eos are well established in some atopic/respiratory disease, while others where eos role is less clear

Established Eos Diseases	Diseases where the role of eos is less clear, or may play a role in certain subgroups
SEA	COPD
ABPA?	BRx
HES	CRSwNP
EGPA	AD
	CSU
	BP
	EoE? EG? EGE?

- ABPA, allergic bronchopulmonary aspergillosis; AD, atopic dermatitis; BP, bullous pemphigoid; BRx, bronchiectasis; COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyps; CSU, chronic spontaneous urticaria; EG, eosinophilic gastritis; EGE, eosinophilic gastroenteritis; EGPA, eosinophilic granulomatosis with polyangiitis; EID, eosinophilic immune dysfunction; EoE, eosinophilic esophagitis; HES, hypereosinophilic syndrome; SEA, severe eosinophilic asthma

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Quality of Life Impact

Health state	Health utility score
Perfect health	1
US norms	0.81
COPD (mod)	0.73
Parkinson disease (1st year)	0.67
CAD requiring PCI	0.67
CRS	0.65
Asthma (mod)	0.64
ESRD with HD	0.64
HIV	0.52
Death	0

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; HD, hemodialysis; MOD, moderate; PCI, percutaneous coronary intervention.

Adapted from DeConde AS, Soler ZM. *Am J Rhinol Allergy*. 2016;30(2):134-139.

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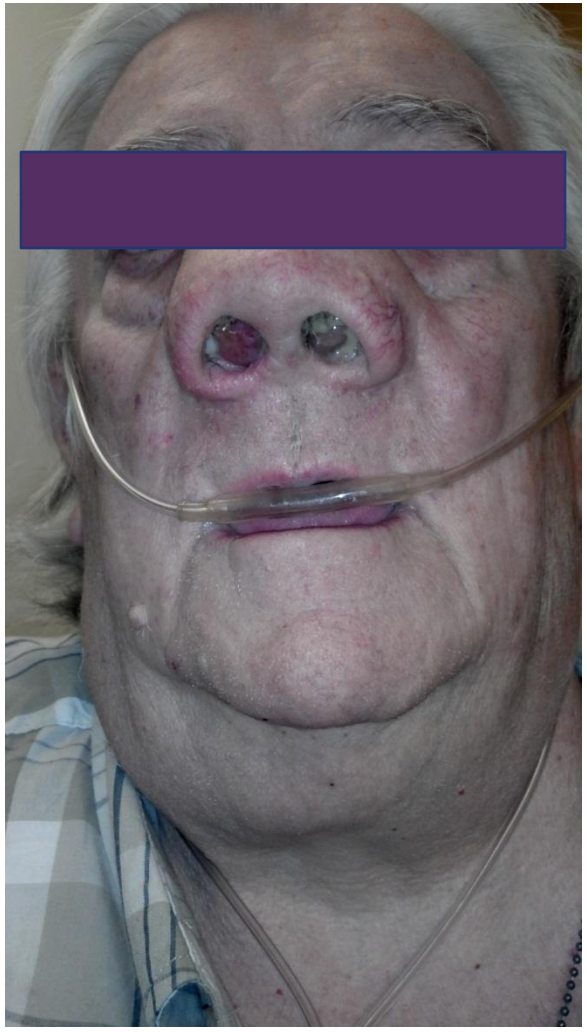

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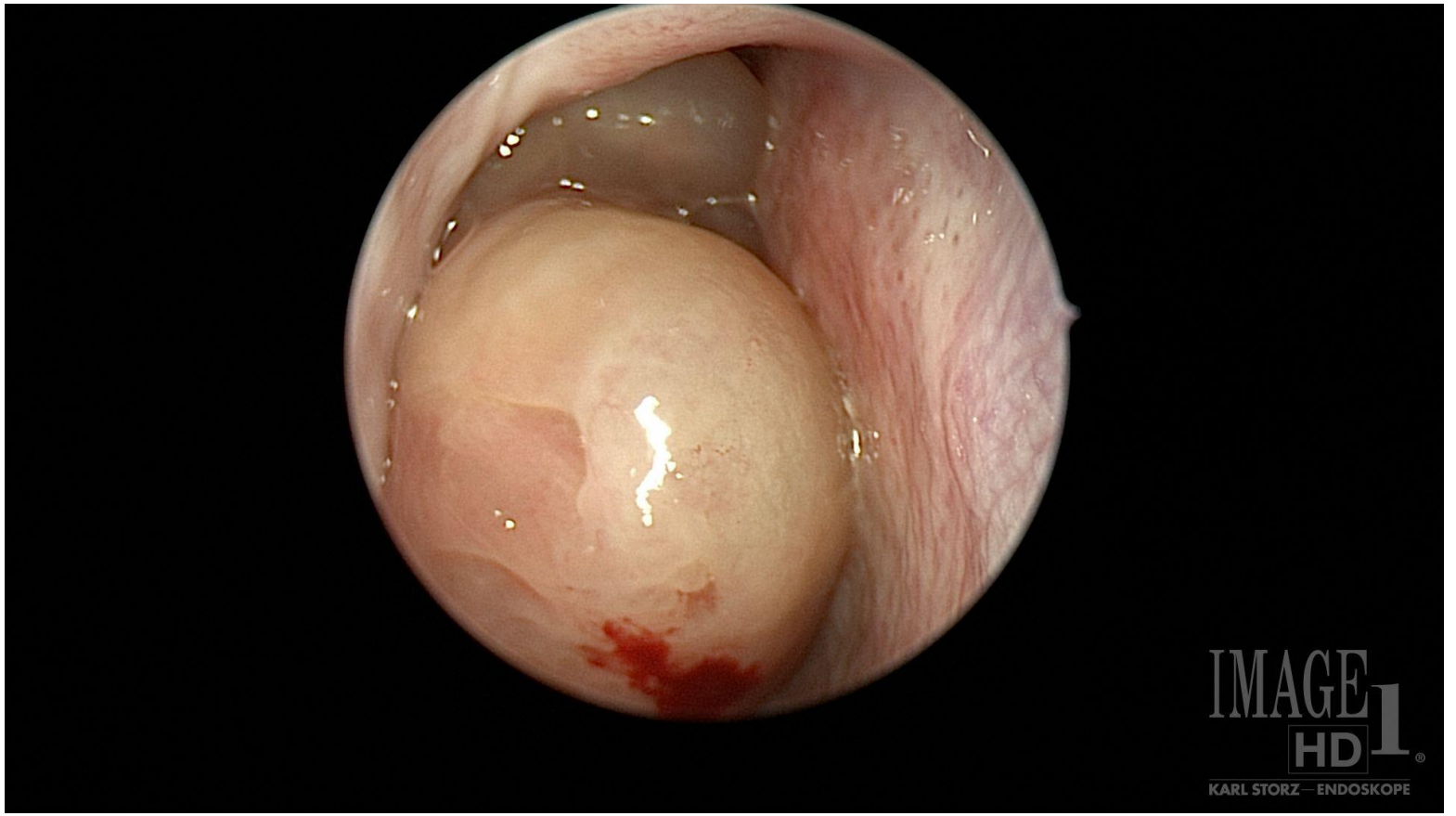

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The “Unified Airway”

Two anatomic “compartments” with overlapping disease and etiologies

Shared stimuli (allergens, infectious agents, inhaled agents) and shared anatomic, signaling and immune crosstalk

- Allergic rhinitis
- Chronic rhinosinusitis with nasal polyposis
- Chronic rhinosinusitis without nasal polyposis
- Nonallergic rhinitis
- Mixed rhinitis
- Otitis media
- AERD/NSAID-ERD

- Asthma
  - Type 2
  - Non Type 2
- Asthma COPD Overlap Syndrome
- Eosinophilic COPD

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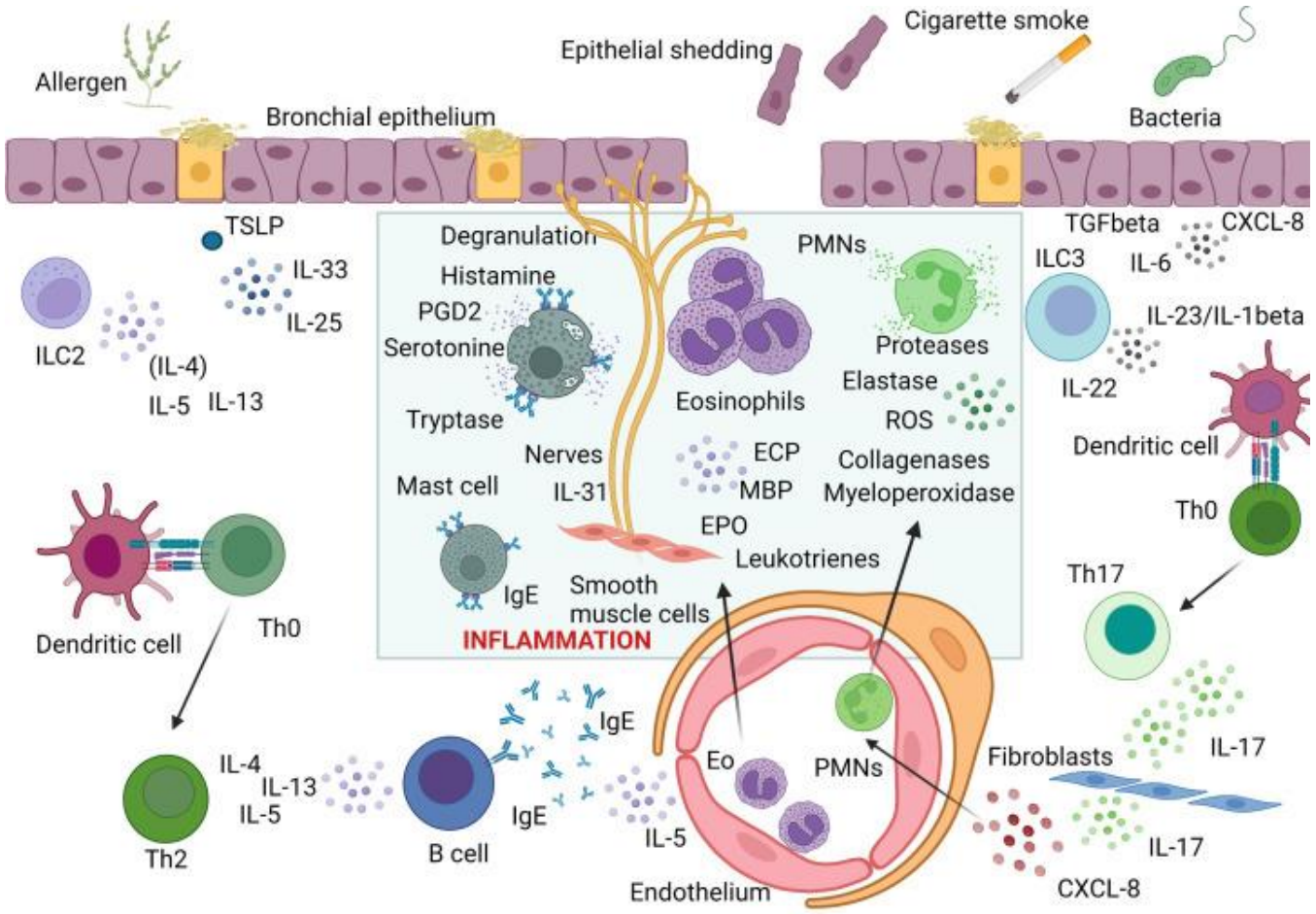
Severe Asthma: Multiple Pathways



Cellular and cytokine interactions involved in allergic (Type 2) and non-allergic (non-Type 2) asthma by Striz I, et al. in New insights into the pathophysiology and therapeutic targets of asthma and comorbid chronic rhinosinusitis with or without nasal polyposis. *Clin Sci (Lond)*. 2023;137(9): 727-753. doi:10.1042/CS20190281. Used under the Creative Commons Attribution License 4.0 (CC BY) <https://creativecommons.org/licenses/by/4.0/>

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Severe Asthma: Treatment Options and Escalation

- High dose ICS/LABA with adherence
- LAMA
- Ongoing evaluation and treatment of comorbidities
- Consider biologic therapy
  - Anti-IgE
  - Anti-IL5
  - Anti-IL5R
  - Anti-IL4/13
  - Anti-alarmin therapy (currently anti-TSLP)
- Ongoing role for systemic corticosteroids?
- What about comorbid diseases of the upper airway that may share common molecular features and contribute to severity of asthma?

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Personalized Approach: Initial Biologic Selection

- Phenotype/endotype with available biomarkers
- Co-morbidities (CRSwNP, EGPA, HES, atopic dermatitis, chronic urticaria, eosinophilic esophagitis)
- Shared-decision making with the patient
  - Set realistic expectations
  - Logistical considerations
    - In-office versus at-home administration
    - Frequency of dosing
    - Insurance coverage
    - Side effect profiles

Personalized Approach: Assessing Response to Therapy

- Continue for a minimum of 4-12 months, depending on the patient's situation
- Keep in mind the reason for starting the biologic
- Look for improvement in
  - Patient Reported Outcomes
  - Control (SNOT-22, ACT, ACQ, AIRQ)
  - Quality of life measures, impact on sleep
  - Exacerbation frequency
  - Chronic or recurrent OCS dose
  - Objective measures (Sinus CT scan, nasal endoscopy, lung function, exhaled nitric oxide)

Personalized Approach: When to Switch Biologics

- Non-responder (or partial responder)
- Initial responder who has stopped responding
- Adverse effects
- Suspected non-adherence
- Development of new co-morbidities

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Approved Biologics for CRSwNP

Drug	Target	Approval in US	Age (years)	Dosing and Frequency for CRSwNP		Route	Phase 3 Clinical Trial Results		
							Nasal Polyp Burden	Nasal Congestion	Reduced Need for Surgery
Dupilumab	IL-4Rα (blocks IL-4 and IL-13)	2017 A.D. 2018: Asthma **2019: CRSwNP (add on)** 2022: EoE	A.D.≥0.5; Asthma≥6; **CRSwNP≥18;** EoE≥12	300 mg	Q2W	s.q. prefilled auto-injector or syringe	✓	✓	✓
Omalizumab	IgE	2003 Asthma 2016 CSU **2020: CRSwNP (add on)**	Asthma≥6; CSU≥12; **CRSwNP≥18**	75-600 mg (based upon weight, IgE level)	Q2W Q4W	s.q. prefilled syringe	✓	✓	Not done
Mepolizumab	IL-5	2015 Asthma 2019 EGPA 2020 HES **2021: CRSwNP (add on)**	Asthma≥6; EGPA≥18; HES≥12 **CRSwNP≥18**	100 mg	Q4W	s.q. prefilled auto-injector or syringe	✓	✓	✓

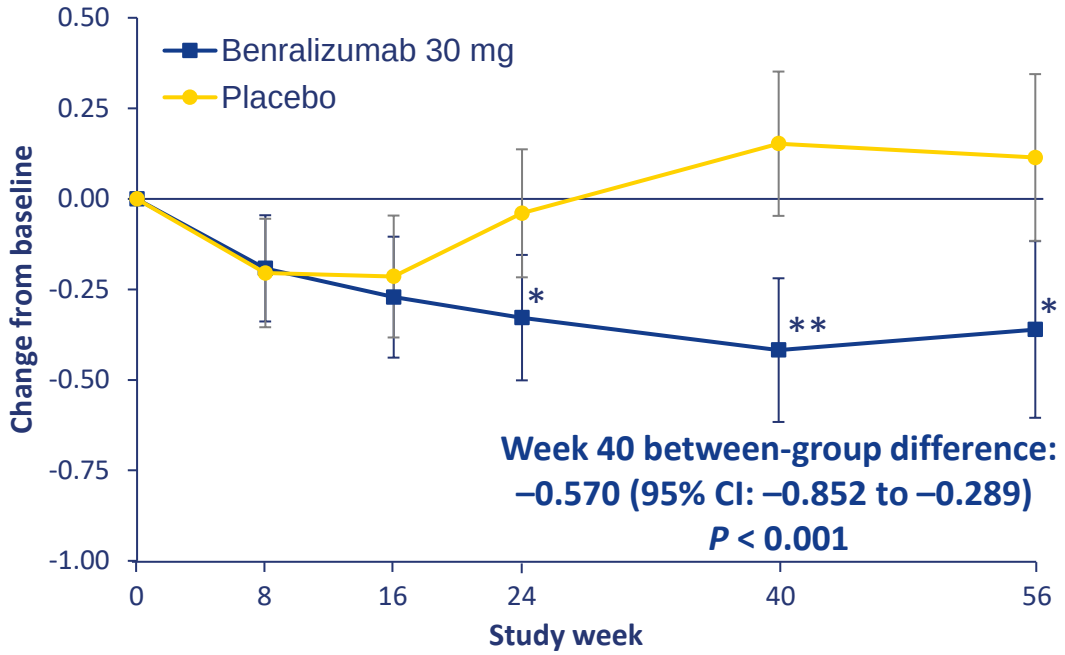
Phase III studies in NP: Results

* not significant
**Pooled SINUS-52 and -24
Darker shaded cells are primary endpoints

	Dupilumab SINUS-52[1,2,]		Dupilumab SINUS-24[3,4]		Omalizumab POLYP-1[5]		Omalizumab POLYP-2[6]		Mepolizumab SYNAPSE[7,8]
	DUPI (n=295)	PBO (n=153)	DUPI (n=143)	PBO (n=133)	OMA (n=72)	PBO (n=66)	OMA (n=62)	PBO (n=65)	
NPS	-1.71	0.10	-1.89	0.17	-1.08	0.06	-0.90	-0.31	-0.73 median change from BL (p<0.001)
	@week 24 P<0.0001		P<0.0001		P<0.0001		P=0.0140		
Lund-Mackay CT score	-5.21	-0.09	-8.18	-0.74	N/A		N/A		
	@week 24 P<0.0001		P<0.0001						
NCS (or OS for DUPI)	–1.25	-0.38	-1.34	-0.45	-0.89	-0.35	-0.70	-0.20	Nasal obstruction visual analogue score (median) P<0.001
	@week 24 p<0.0001		p<0.0001		P=0.0004		P=0.0017		
Loss/Sense of smell	-1.21	-0.23	-1.41	-0.29	-0.56	-0.23	-0.58	-0.13	
	@week 24 p<0.0001		P<0.0001		P=0.0161		0.0024		
Post Rhinorrhea Score	N/A		N/A		-0.72	-0.16	-0.55	0	
					P=0.0001		P=0.0001		
Ant Rhinorrhea Score	N/A		N/A		-0.77	-0.34	-0.7	-0.08	
					P=0.0023		p<0.0001		
SNOT-22	-27.77	-10.40	-30.43	-9.31	-24.7	-8.58	-21.59	-6.55	
	@week 24 p<0.0001		p<0.0001		P<0.0001		p<0.0001		
Rescue Tx (CS or NP Surgery)	**POOLED**** DUPI (n=438) 42 (10%) PBO (n=286) 97 (34%)				2 (2.8%)*	3 (4.5%)*	1 (1.6%)*	5 (7.7%)*	
	p<0.0001								
Surgery for NP					0*	1.5%*	0*	1.5%*	57% (p=0.003) reduction in time to first surgery
TNSS					-2.97	-1.06	-2.53	-0.44	
					P=0.0001		p<0.0001		
UPSIT	9.71	-0.81	11.26	0.70	4.44	0.63	4.31	0.44	
	@week 24 p<0.0001		p<0.0001		(p=0.0024)		P=0.0011		

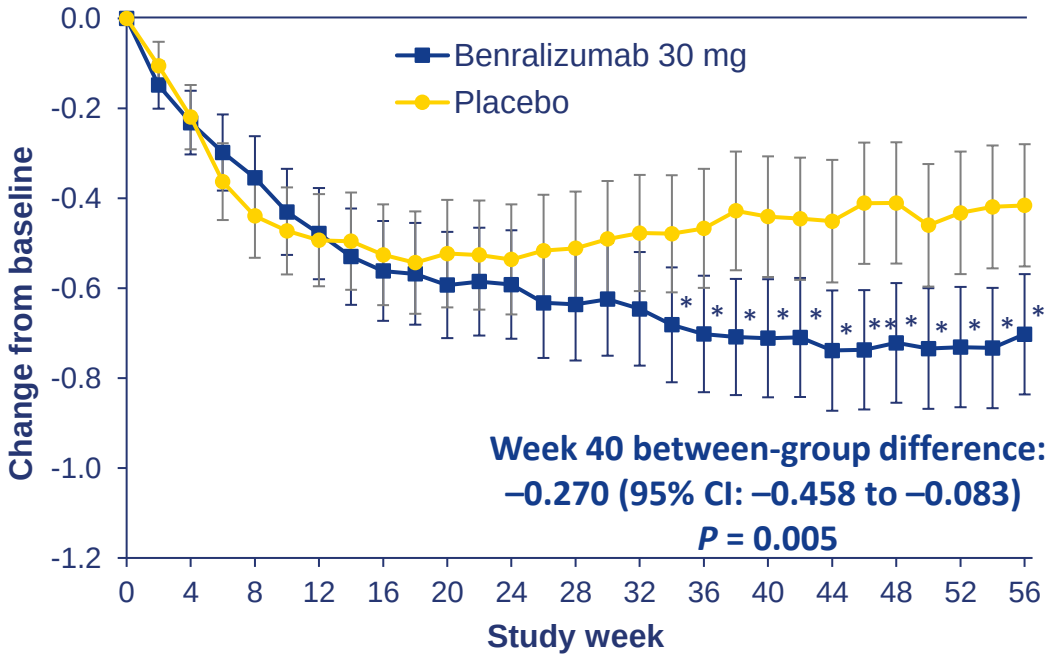
OSTRO: Co-Primary Endpoint Results

Nasal Polyp Score



Benralizumab	204	202	193	199	187	161
Placebo	198	193	194	190	187	171

Nasal Blockage Score



	207	200	200	196	192	191	186	179
	203	195	194	191	186	181	184	175

Data are least-squares means ± 95% confidence intervals (CIs) for the full analysis set.
Nasal Polyp Score range: 0-8. Nasal Blockage Score range: 0-3.
*P < .05; **P < .001 for the comparison of benralizumab and placebo.

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Published Randomized Controlled Trials of Biologic Therapies in CRSwNP

Biologic	Study name	Nasal Polyp Score (NPS)	Nasal Obstruction (Nasal Congestion Score or VAS)	SNOT-22	Smell Score	Time to OCS or surgery
Dupilumab[1]	SINUS-24 SINUS-52	Improved	Improved	Improved	Improved	Prolonged
Omalizumab[2]	POLYP 1 POLYP 2	Improved	Improved	Improved	Improved	Prolonged
Mepolizumab[3]	SYNAPSE	Improved	Improved	Improved	Improved	Prolonged
Benralizumab[4]	OSTRO	Improved	Improved	Not statistically different	Improved	Not statistically different

1. Bauchert et al. Lancet 2019; 394: 1638–50.
2. Gevaert et al. JACI 2020;146:595-605.
3. Bauchert et al. JACI 2022; 141(5): 1711-21.
4. Bauchert et al. JACI 2022; 149(4): 1309-17.

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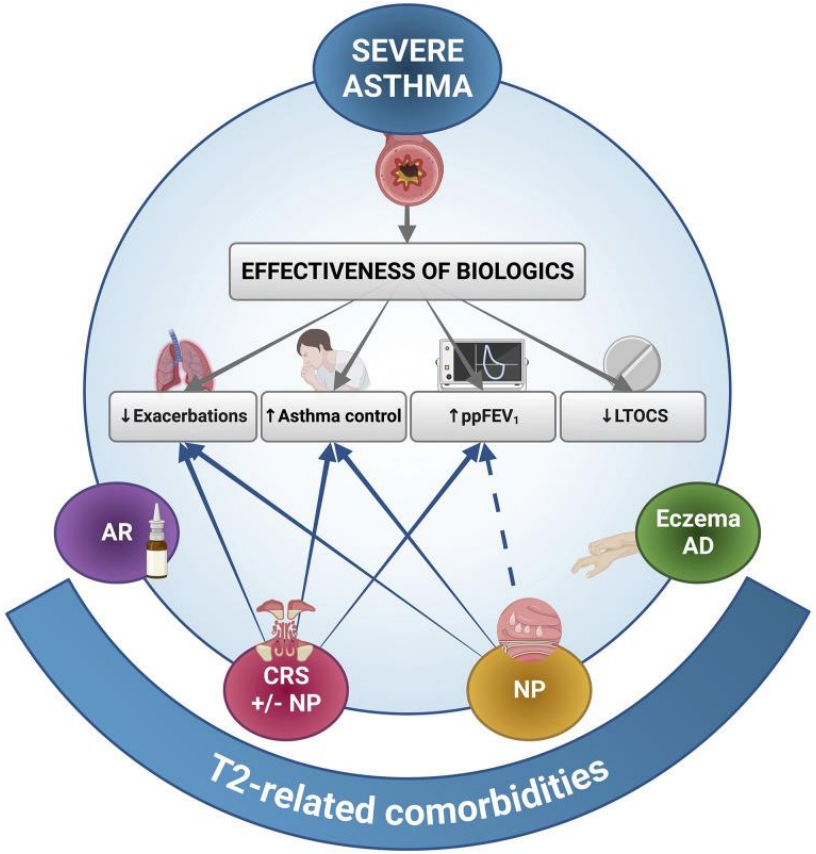
Comorbidities Can Impact Degree of Asthma Improvement with Biologics



- International Severe Asthma Registry (ISAR)
- 1765 patients started on biologics, most on anti-IL-5 therapy
- Compared to those without, those with co-morbid CRS with or without NPs:
  - 23% fewer exacerbations per year
  - 59% higher odds of better asthma control after starting biologics
  - Additional FEV1% predicted improvement of 3.2%
  - No difference in weaning OCS doses
- No effect of co-morbid AR or AD
- Corroborates findings of individual biologic agents in sub-analysis studies of RTCs & real-world trials

Wechsler ME, et al. Respir Crit Care Med. 2024;209(3):262-272.

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Comparisons

EVEREST (NCT04998604): phase 4 RCT, dupilumab vs omalizumab, N=422

- First head-to-head trial comparing 2 biologics in patients with CRSwNP and comorbid asthma
- Primary objective: evaluate efficacy of dupilumab compared to omalizumab in reducing polyp size and improving sense of smell

Meta-analyses:

- **Cai S, et al**: 7 RCTs involving 1913 patients, 4 biologics (benralizumab, dupilumab, mepolizumab, omalizumab)
  - Dupilumab better effects in decreasing NPS and nasal congestion severity
  - Benralizumab least effective in reducing nasal congestion severity and SNOT-22
  - No significant differences between effects of the other biologics
- **Oykhman P, et al**: 29 RCTs involving 3461 patients
  - Moderate to high certainty: dupilumab ranks among most beneficial for 7 of 7 outcomes, omalizumab 2 of 7, mepolizumab 1 of 7 and aspirin therapy after desensitization 1 of 7

De Prado Gomez L, et al. *Am J Rhinol Allergy*. 2022;36(6):788-795; Cai S, et al. *J Allergy Clin Immunol Pract*. 2022;10(7):1876-1886.e7; Oykhman P, et al. *J Allergy Clin Immunol*. 2022;149(4):1286-1295; https://clinicaltrials.gov/study/NCT04998604

HES is a heterogenous group of rare disorders characterized by eosinophilia and end-organ damage

HES is defined by:

Persistent **hypereosinophilia** (≥1500 cells/μL)

+

No evidence for **secondary/reactive eosinophilia** (eg parasitic infection or allergic reactions)

+

Signs of **organ involvement**[1,2]

There are **multiple variants** of HES, which vary in terms of aetiology and clinical features[3,4]

Incidence: 0.2–0.4 per 100,000 person-years[4]

Prevalence: 0.3–6.3 per 100,000 individuals[4]

Male-to-female ratio: 1.4[1,5]

Incidence and prevalence were estimated for the US population[4]

Limited other population-based data exist[4]

1. Gotlib J. *Am J Hematol* 2017;92:1243–59; 2. Cogan E, Roufosse F. *Expert Rev Hematol* 2012;5:275–90; 3. Valent P *et al. J Allergy Clin Immunol* 2012;130:607–12; 4. Crane MM *et al. J Allergy Clin Immunol* 2010;126:179–81; 5. Ogbogu PU *et al. JACI* 2009;124:1319

HES, hypereosinophilic syndrome

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HES Subtypes

Classification of HES by the International Eosinophil Society HES Working Group[1,2]

Familial

Rare subtype characterized by blood eosinophilia with unclear cause, repeated in successive generations[a]

~1%

Associated

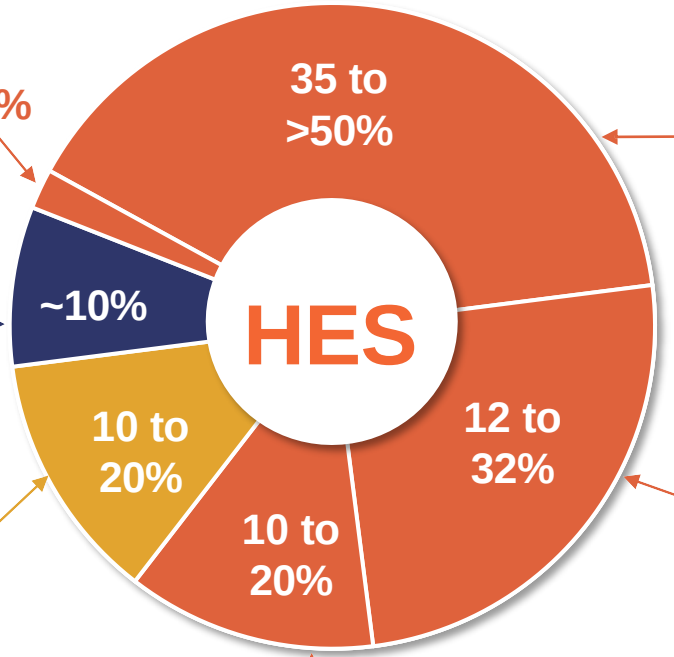
Associated with other causes of reactive HE, eg, allergic reactions, infectious disease, acute and chronic eosinophilic pneumonia, neoplasms

~10%

Myeloproliferative

Severe, commonly associated with *F/P* fusion kinase or CEL-NOS, with clonal eosinophilia

10 to 20%



Idiopathic

Symptomatic with organ involvement, but not meeting criteria for other subtypes

Overlap

Restricted to a single organ system, such as EGID, or eosinophilic disorders with a defined eosinophilic syndrome, such as EGPA

Lymphocytic

Due to overproduction of eosinophilopoietic cytokines by a clonal population of activated T lymphocytes

Etiology not fully known; treatment approach varies

Treatable target in most cases

Treatable secondary cause

[a]Most affected individuals are asymptomatic and therefore would qualify as HE and not HES.

CEL-NOS = chronic eosinophilic leukemia-not otherwise specified; EGID = eosinophilic gastrointestinal disorders; EGPA = eosinophilic granulomatosis with polyangiitis; F/P = FIP1-like-1 platelet-derived growth factor receptor alpha; HE = hypereosinophilia; HES = hypereosinophilic syndrome.

1. Klion A. Hematology Am Soc Hematol Educ Prog. 2018(1):326-331; 2. Kuang FL, Klion AD, J Allergy Clin Immunol Pract. 2017;5(6):1502-1509; 3. Williams KW, et al. J Allergy Clin Immunol Pract. 2016;4(5):941-947e1; 4. Klion A. Blood. 2015;126(9):1069-1077.; 5. Kahn JE, et al. Front Med. 2017;4:216; 6. Ogbogu PU, et al. J Allergy Clin Immunol. 2009;124(6):1319-1325e3; 7. Klion A et al. J Allergy Clin Immunol. 2006;117(6):1292-1302; 2. Valent P, et al. J Allergy Clin Immunol. 130(3):607-612.e9; 9. Klion A, et al. Annu Rev Pathol Mech Dis. 2020;15:179-209.

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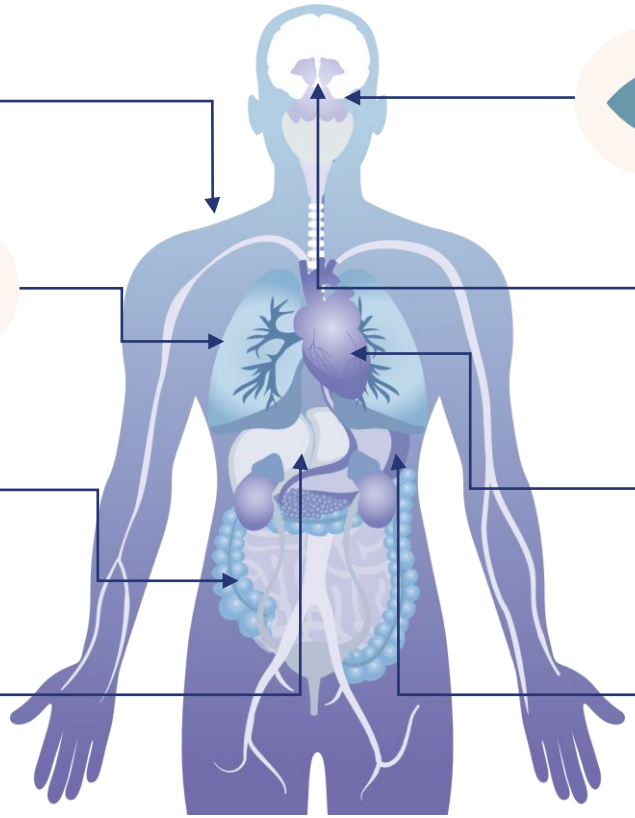
HES is a potentially fatal disease that can cause damage to multiple organs and systems

HES can manifest as tissue-specific or widespread organ damage, resulting in diverse symptoms[1]

HES-related worsening of clinical signs, or flares, can occur during treatment or upon withdrawal[2]

Proportion of patients with symptoms of HES



Dermatologic: 69%
(eczema, itching, rash)

Pulmonary: 44%
(cough, shortness of breath)

Gastrointestinal: 38%
(pain, vomiting)

Hepatic: 30%
(hepatitis, cholangitis)

Ocular: 23%
(visual disturbances)

Neurological: 21%
(dizziness, fatigue)

Cardiac: 20%*
(heart failure, myocarditis)

Splenic: 10%
(eg splenomegaly)

1. Cogan E, Roufosse F. *Expert Rev Hematol* 2012;5:275–89; 2. Roufosse F *et al.* UpToDate 2018

*Includes cardiac and vascular involvement
HES, hypereosinophilic syndrome

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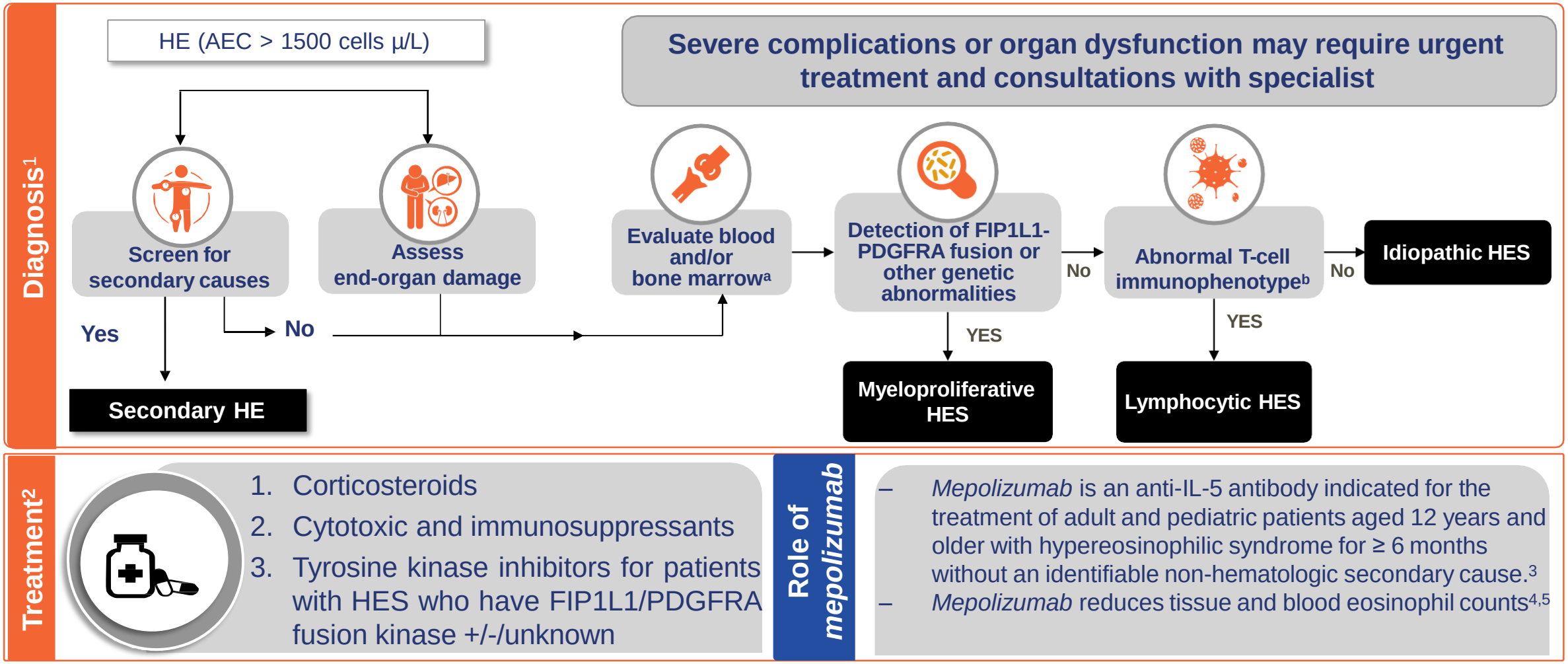
HES Diagnosis and Treatment



[a]serum B12, tryptase, IgE, FIP1L1-PDGFRA, and T cell receptor arrangement, etc; [b]T cell receptor rearrangement, etc.

AEC = absolute eosinophil count; FGFR1 = fibroblast growth factor receptor 1; FIP1L1/PDGFRA = FIP1-like-1 platelet-derived growth factor receptor alpha; HES = hypereosinophilic syndrome; NOS = not otherwise specified; OCS = oral corticosteroids.

1. Shomali W, et al. Am J Hematol. 2019;94:1149-1167; 2. Ogbogu PU, et al. J Allergy Clin Immunol. 2009;124:1319-1325; 3. Prescribing Information for Nucala;
4. Ortega HG, et al. N Engl J Med 2014;371:1198-1207; 5. Flood-Page PT, et al. Am J Respir Crit Care Med. 2003;167:199-204.

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SUMMARY: Mepolizumab in HES

- On **September 25, 2020**, the US Food and Drug Administration approved mepolizumab for the treatment of adults and children aged 12 years and older with HES for ≥6 months without an identifiable non-hematologic secondary cause of the disease.[1]

- Approval based on results of a randomized, multicenter, double-blind, placebo-controlled, Phase III trial in patients with HES[1,2]

- Results showed:[2]
  - **50% relative reduction in HES flares with mepo vs placebo** (15/54 [28%] *vs* 30/54 [56%]; p=0.002
  - **66% lower risk of experiencing a first flare** during the treatment period with mepo vs placebo (HR: 0.34; 95% CI: 0.18, 0.67; p=0.002)
  - **fewer flares** or study withdrawals with mepo vs placebo during **study weeks 20-32** (17% vs 35%, respectively, p=0.02).

1. US Food and Drug Admininstration website. 2. Roufosse et al. *J Allergy Clin Immunol*. 2020. Accessed, April , 2024.

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SUMMARY: Benralizumab in HES

- *Phase II study:* evaluated the efficacy and safety of benralizumab 30 mg administered subcutaneously (SC) every 4 weeks (Q4W) for 3 doses in addition to stable background therapy in 20 adult patients who had a symptomatic HES without the platelet-derived growth factor receptor-α (PDGFRA) mutation.[1]
  - 90% of patients in the benralizumab group versus 30% of patients in the placebo group experienced a reduction in their absolute eosinophil count (AEC) of at least 50% (primary endpoint).

- **NATRON**, a Phase III randomized, double blind, placebo-controlled, 24-week study evaluating the efficacy and safety of benralizumab SC Q4W in approximately 120 patients with HES, is currently **ongoing with an estimated completion date of July 2022**.[2]

1. Kuang FL N *Engl J Med*. 2019;380:1336–1346. 2. Clinicaltrials.gov website. NCT04191304.

EGPA is a complex, multisystem disease

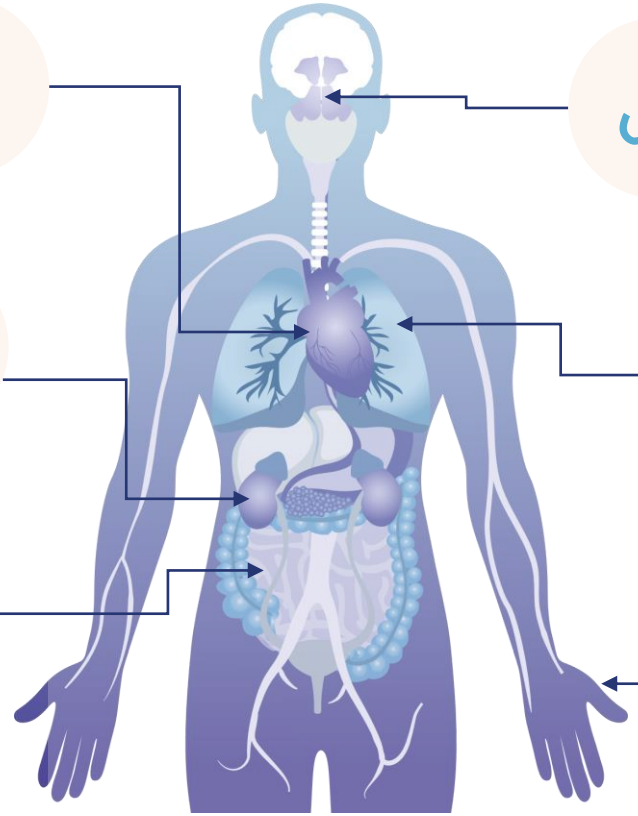
EGPA predominantly affects the airways, peripheral nerves, heart, kidney and GI tract[1]

Proportion of patients with clinical signs of EGPA[2]

Cardiac symptoms: ~25%

Renal involvement: ~25%
Most commonly glomerulonephritis

GI involvement: ~30%
Most commonly gastroenteritis, pain, diarrhoea and GI bleeding[3]



Chronic rhinitis: ~75%

Asthma: >95%

Neuropathy: 85%
CNS vasculitis accounts for 10–39% of neurological involvement[3]

1. Comarmond C *et al. Arthritis Rheum* 2013;65:270–81; 2. Chakraborty RK *et al.* Churg Strauss Syndrome (Allergic Granulomatosis); StatPearls Publishing 2019; 3. Gioffredi A *et al. Front Immunol* 2014;5:549

CNS, central nervous system; EGPA, eosinophilic granulomatosis with polyangiitis; GI, gastrointestinal; OCS, oral corticosteroids

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Diagnosis of EGPA is a complex clinical challenge

Delayed or missed diagnoses are frequent (mean time from onset to diagnosis is ~50 months)[1]

Differential diagnosis includes other vasculitides, eosinophilic disorders, drug reactions and infections[2]

There are **no commonly accepted diagnostic criteria** for EGPA[2]

The ACR criteria (1990) were created to enable the **classification** of vasculitides; the presence of **four of the six features below** identify EGPA with a sensitivity of 85% and a specificity of 99.7%[3,4]

Eosinophilia (>10% total white blood cells)	**Asthma**	**Extravascular eosinophilic infiltration**	**Neuropathy**	**Paranasal sinus abnormalities**	**Non-fixed pulmonary infiltrates**

- ANCA positivity is observed in ~40% of patients and is also suggestive of EGPA[5]
- While ACR criteria were developed before ANCA testing became widespread,[2] the **European Respiratory Society recommends biochemical** and **immunohistochemical ANCA testing** in patients with suspected EGPA[6]

1. Moosig F *et al. Ann Rheum Dis* 2013;72:1011–17; 2. Furuta S *et al. Allergol Int* 2019;68:430–6;
3. Masi A *et al. Arthritis Rheum* 1990;33:1094–100; 4. Jenette J *et al. Arthritis Rheum* 1994;37:187–92;
5. Pagnoux C *et al. Discov Med* 2010;9:243–52; 6. Groh M *et al. Eur J Int Med* 2015;26:545–53

ACR, American College of Rheumatology; ANCA, antineutrophil cytoplasmic antibody; EGPA, eosinophilic granulomatosis with polyangiitis

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Results

- Co-primary Endpoints
    - Subjects receiving 300 mg of mepolizumab achieved a significantly greater accrued time in remission compared with placebo.
    - A significantly higher proportion of subjects receiving 300 mg of mepolizumab achieved remission at both Week 36 and Week 48 compared with placebo.

- Secondary Endpoints
    - Significantly more subjects receiving 300 mg of mepolizumab achieved remission within the first 24 weeks and remained in remission for the remainder of the 52-week study treatment period compared with placebo (19% for 300 mg of mepolizumab versus 1% for placebo; OR 19.7; 95% CI: 2.3, 167.9).
    - Additionally, a statistically significant benefit for the co-primary endpoints and additional endpoint was demonstrated using remission defined as BVAS = 0 plus prednisolone/prednisone ≤7.5 mg/day.

OR = odds ratio; CI = confidence interval.

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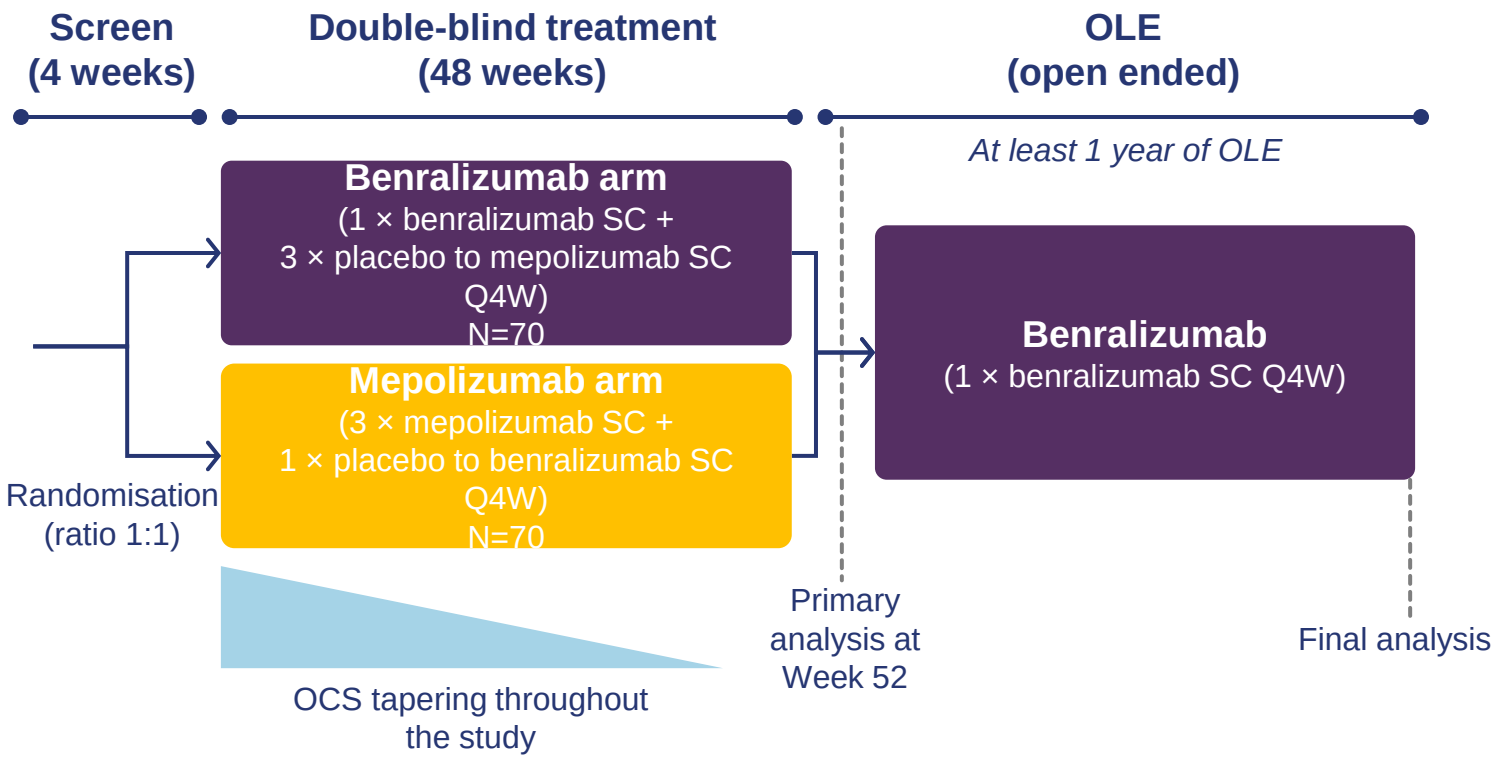
MANDARA study design

MANDARA (NCT03010436): non-inferiority study of benralizumab versus mepolizumab



Primary endpoint

Proportion of patients with relapsing or refractory EGPA achieving remission at both Weeks 36 and 48*

Key inclusion criteria

- Males/females aged ≥18 years
- EGPA diagnosis: history or presence of asthma and eosinophilia† and ≥2 other predefined criteria‡
- History of relapsing OR refractory disease
- Stable dose of oral prednisolone or prednisone ≥7.5 mg/day (but not >50 mg/day) for ≥4 weeks prior to randomisation

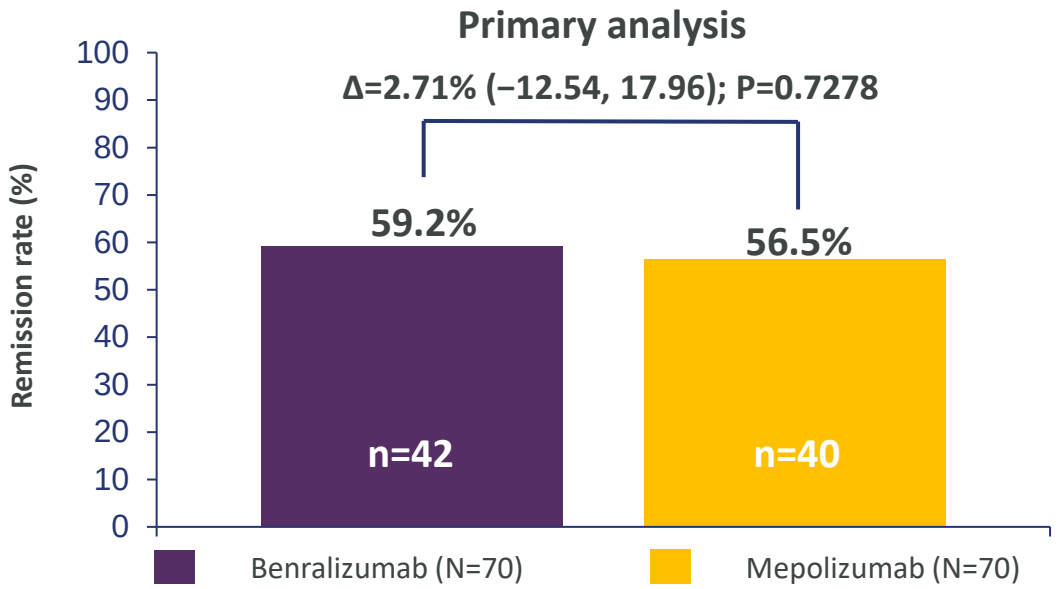
*Remission defined as a BVAS of 0 and OCS dose ≤4 mg/day; †>1.0x10^9/L and/or >10% of leucocytes; ‡biopsy with eosinophilic vasculitis or perivascular/granulomatous inflammation; mono-or polyneuropathy,
non-fixed pulmonary infiltrates, sinonasal abnormality; cardiomyopathy; glomerulonephritis; alveolar haemorrhage; palpable purpura; anti-neutrophil cytoplasmic antibody (ANCA) positivity (Myeloperoxidase
or proteinase 3)

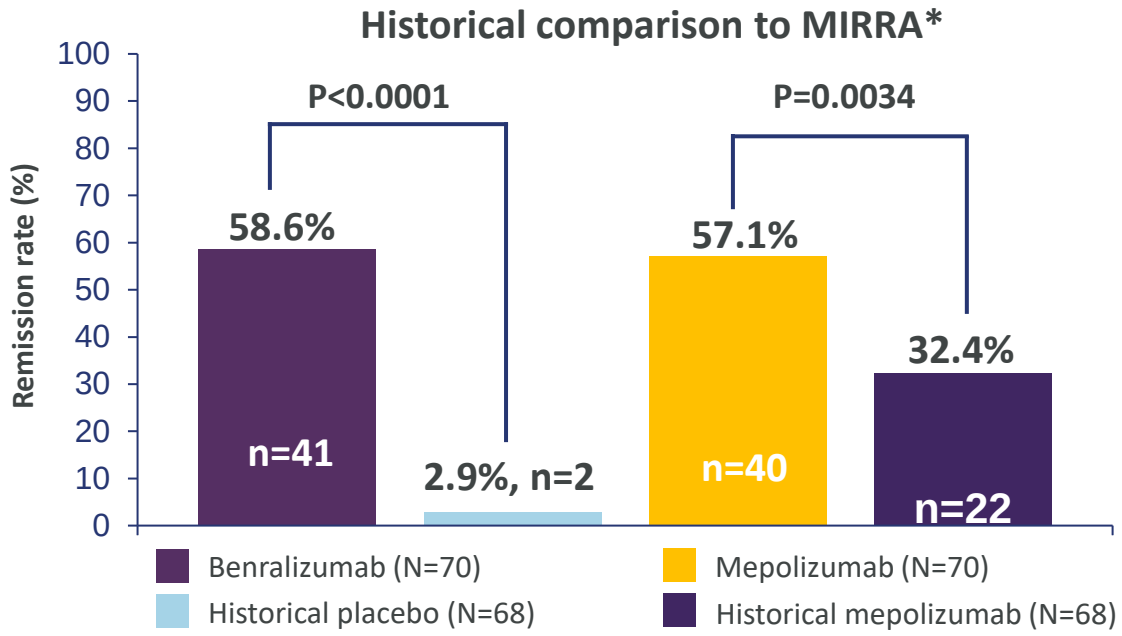
Wechsler ME, et al. NEJM 2024:390;911-21.

Primary outcome measures demonstrated non-inferiority versus mepolizumab

Remission (BVAS=0 and OCS ≤4mg/day) at Weeks 36 and 48

The remission rates were not significantly different between benralizumab and mepolizumab groups





- Non-inferiority demonstrated: lower 95% CI is well above NI margin of −25%
- Indirect treatment comparison demonstrated a highly significant improvement in remission for benralizumab vs historical placebo
  - ***Mepolizumab remission rate in MANDARA is higher than in MIRRA***

*Historical comparison for validation
Primary analysis results (%, Δ, 95% CI, p-value) are model adjusted rates from logistic regression, adjusting for baseline OCS, BVAS and region. Historic comparison to MIRRA are unadjusted for baseline covariates

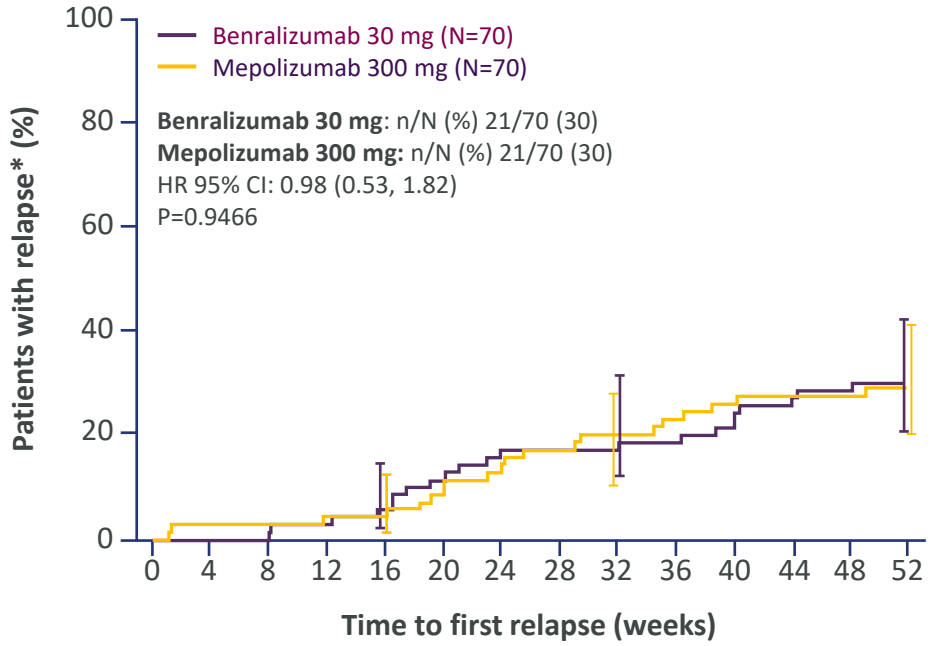
Wechsler ME, et al. NEJM 2024:390;911-21.

Secondary endpoint

Time to relapse was similar between treatment groups

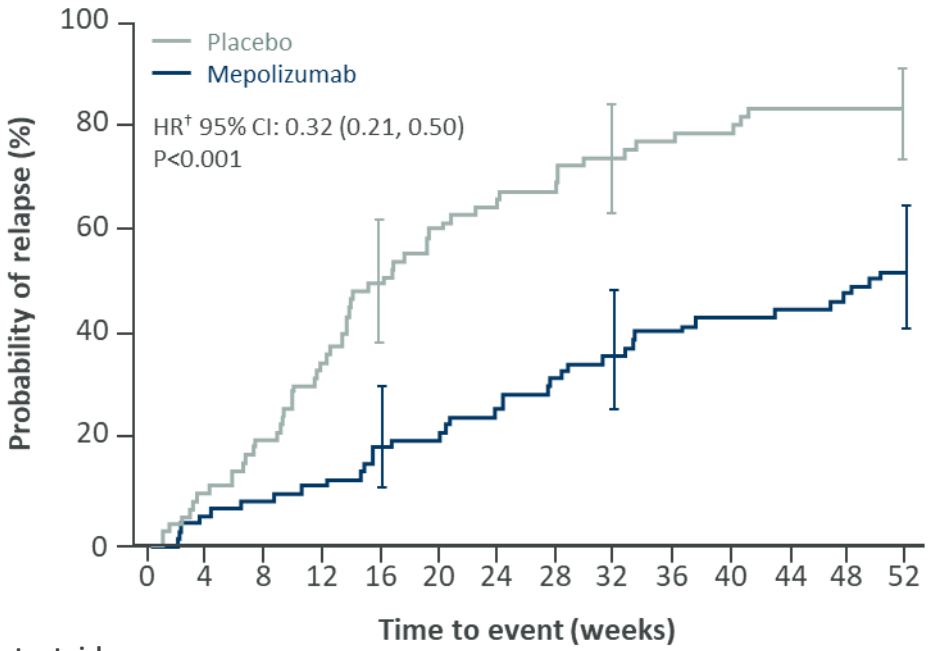
Three patients receiving mepolizumab in MANDARA had major relapse versus 0 patients receiving benralizumab

MANDARA: time to first relapse



No. of patients at risk:														
Benralizumab 30 mg (N=70)	70	70	70	68	66	62	58	58	58	57	55	51	50	41
Mepolizumab 300 mg (N=70)	70	68	68	66	66	63	60	57	54	52	50	49	49	38

MIRRA: time to first relapse[1]



No. of patients at risk:				
Placebo	68	33	16	9
Mepolizumab	68	55	43	25

Relapse was defined as any organ or life-threatening EGPA event; OR BVAS ≥6 (involving at least two organ systems in addition to any general symptoms where present [myalgia, arthralgia/arthritis, fever >38°C or weight loss >2 kg]); OR an asthma relapse requiring hospitalisation; OR sinonasal relapse requiring hospitalisation

*Error bars represent 95% CI; †A hazard ratio <1 favours mepolizumab

1. . Wechsler ME, et al. N Engl J Med 2017;376:1921–1932; Wechsler ME, et al. NEJM 2024:390;911-21.

MANDARA SUMMARY

- The MANDARA study demonstrated non-inferiority of benralizumab vs mepolizumab over 52 weeks in patients with relapsing/refractory EGPA receiving SoC
- More benralizumab-treated patients were fully tapered off OGCs
- Blood eosinophil depletion was greater with benralizumab than mepolizumab at all timepoints
- Benralizumab was well tolerated, and the safety profile was similar to known safety profiles from studies in asthma
  - No clinically meaningful differences in safety profiles of benralizumab and mepolizumab were seen
- This study provides evidence for the efficacy and utility of benralizumab in this population, confirming that eosinophil-targeting treatments are beneficial for patients with EGPA

Veeva ID: Z4-59194; Date of preparation: October 2023

Conclusion

- CRSwNP has significant burden on QOL, high direct and indirect costs
- Patient education: chronic inflammatory condition without curative treatment
- Goals of treatment to control inflammation and improve QOL
- Treatment options include nasal saline irrigation, topical and systemic corticosteroids, surgical intervention, and biologic therapies
- Biologics, such as dupilumab, omalizumab, and mepolizumab, have been shown to reduce nasal polyp size and improve nasal symptoms in the treatment of CRSwNP