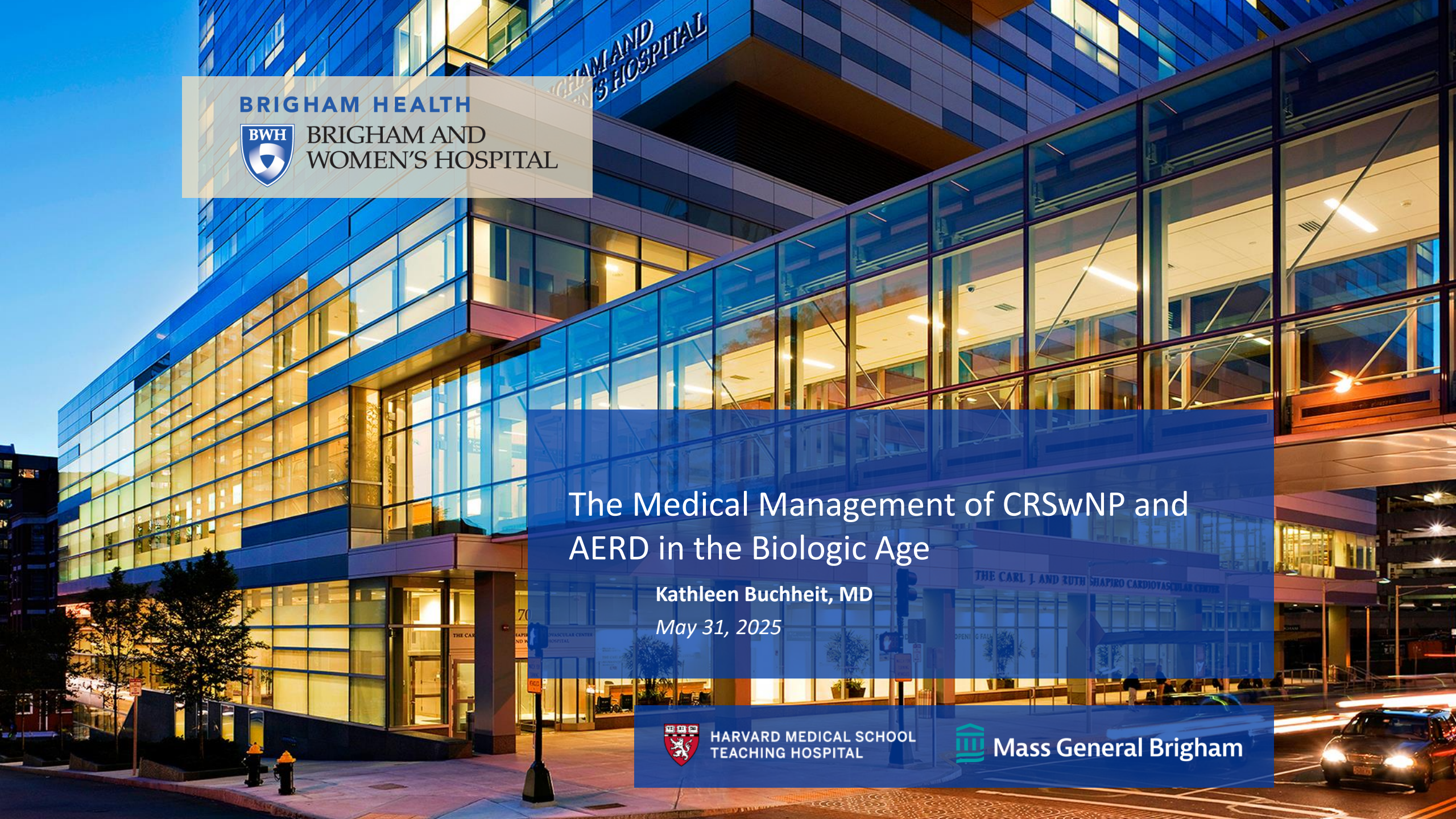
BRIGHAM HEALTH
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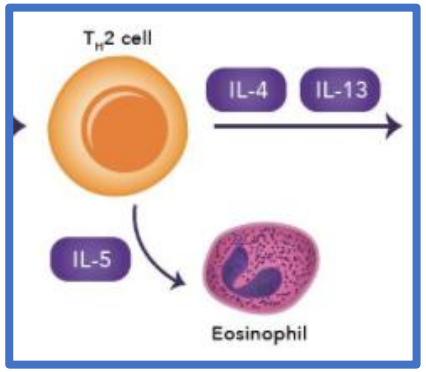
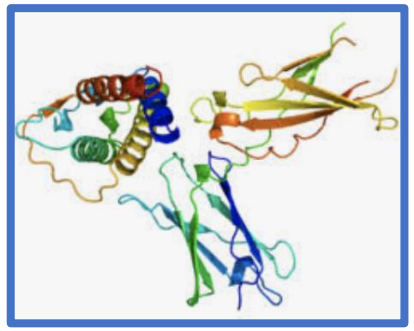
The Medical Management of CRSwNP and AERD in the Biologic Age
Kathleen Buchheit, MD
May 31, 2025
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL
Mass General Brigham

Objectives



Review the clinical presentation and pathophysiology of CRSwNP and AERD

Understand the current treatment guidelines for CRSwNP and AERD



Review updates in CRSwNP and AERD management in the biologic era

Evaluation and Diagnosis of Chronic Rhinosinusitis (CRS)

Symptoms[1,2]

≥2 of the following for **≥12 weeks:**

- Mucopurulent drainage (anterior and/or posterior)
- Nasal obstruction
- Facial pain/pressure/fullness
- Hyposmia/anosmia

+

Objective findings[1,2]

Endoscopic inflammation:

- **Nasal polyps**
- Purulent mucus
- Mucosal edema

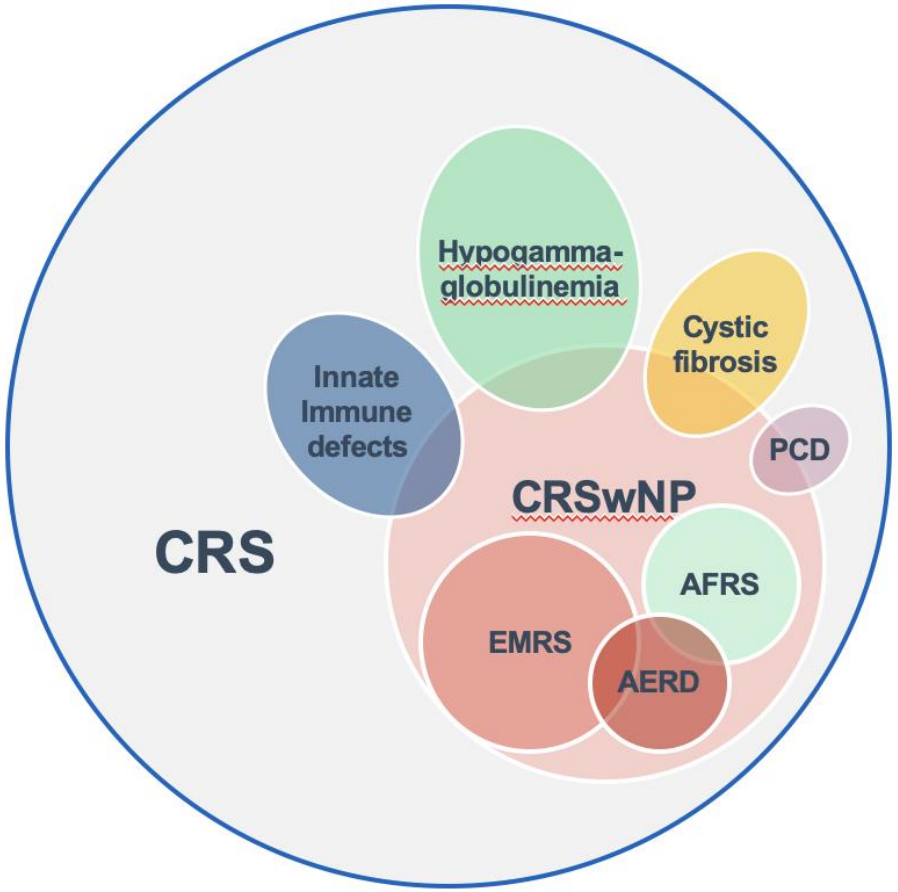
Radiographic findings:

- Inflammation of paranasal sinuses

1. Rosenfeld RM, et al. Otolaryngol Head Neck Surg 2015;152(Suppl 2):S1–S39; 2. Orlandi RR et al. Int Forum Allergy Rhinol. 2021 Mar;11(3):213-739.
;Left image: Rosenfeld RM, et al. Otolaryngol Head Neck Surg 2015;152(Suppl 2):S1–S39;, Right image: Laidlaw TM, et al. Ann Allergy Asthma Immunol 2020;124:326–332

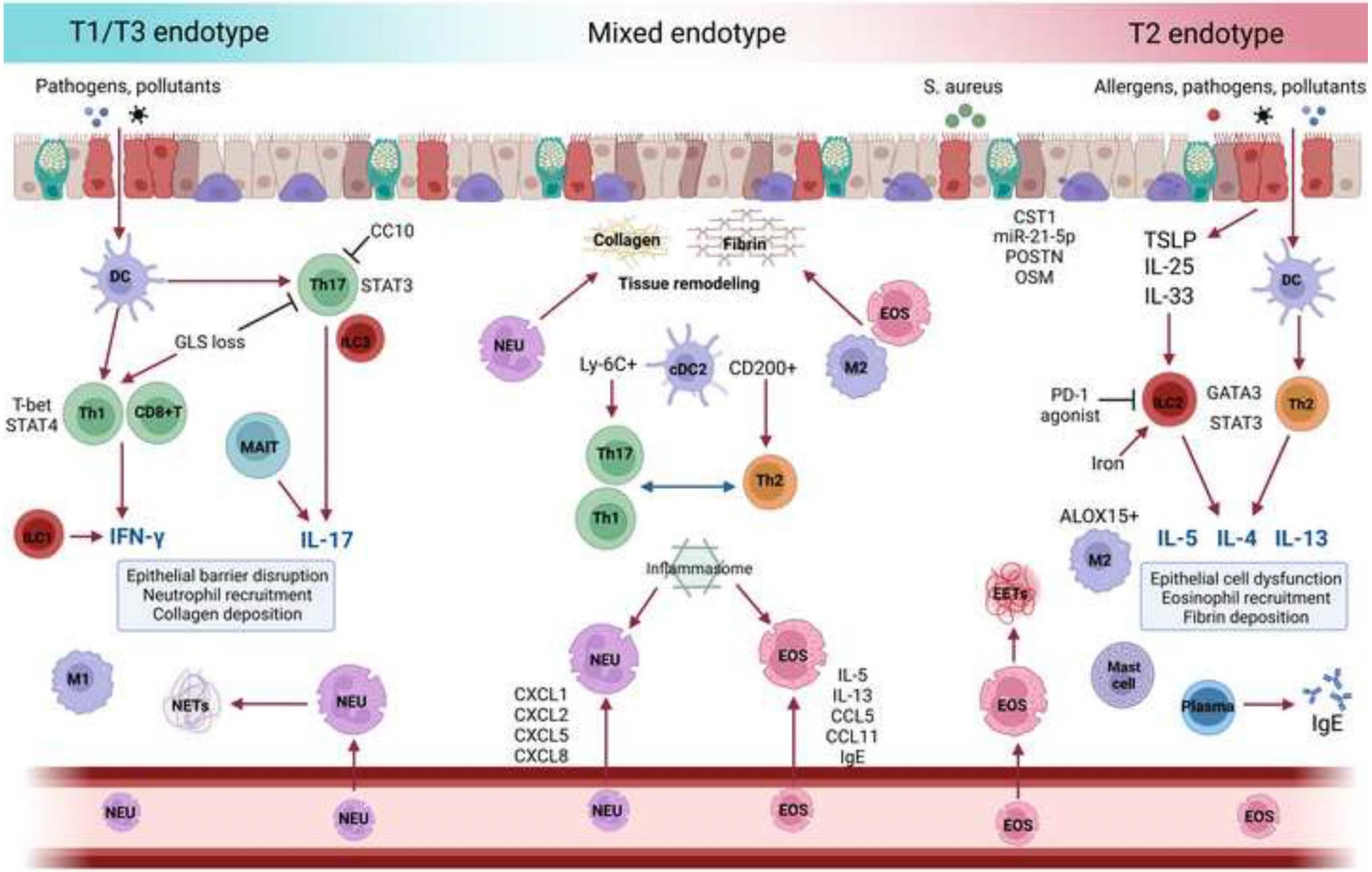
Chronic Rhinosinusitis with nasal polyps (CRSwNP)

- CRSwNP prevalence of 1.7–2.7% of the US population[1]
- Average age of diagnosis: ~39 years[2]
  - Age of diagnosis is younger in aspirin-exacerbated respiratory disease (AERD): ~34 years[3]
- Prevalence may be higher in women[2]
- Important phenotypes include: AERD, AFRS
- Impairment in quality of life
- Lost productivity, high healthcare utilization



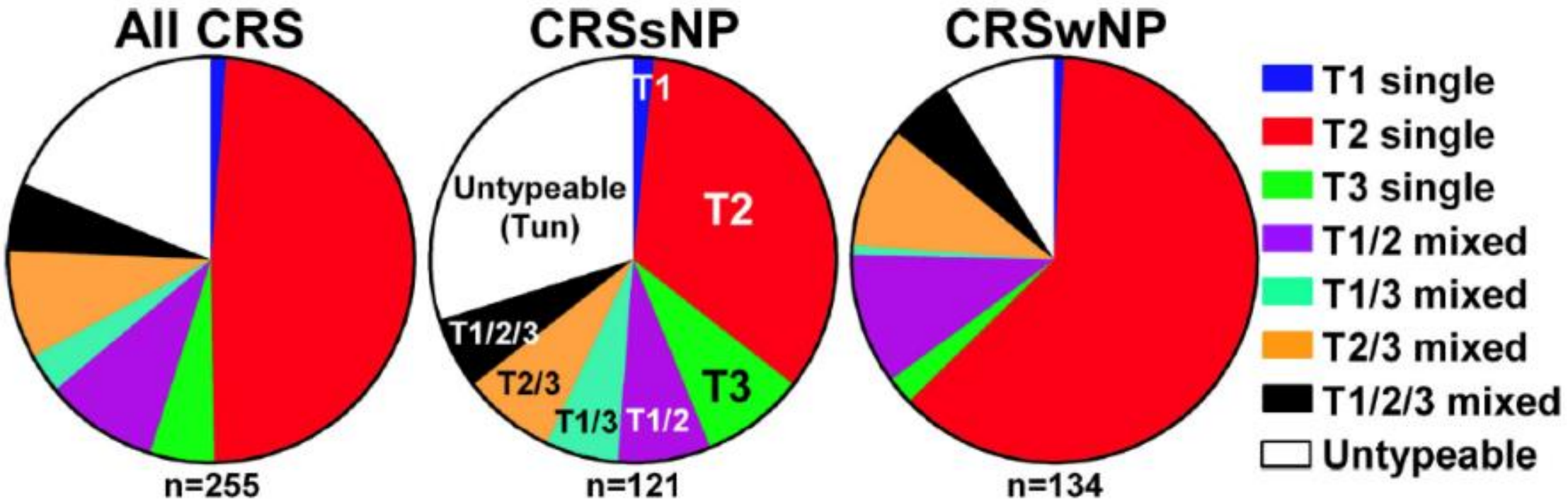
1. Blackwell DL, Lucas JW, Clarke TC. VitalHealth Stat 10 2014;(260):1-161;
2. 2. Shashy RG, et al. Arch Otolaryngol Head Neck Surg 2004;130:320–323;
3. Buchheit KM, et al. World J Otorhinolaryngol Head Neck Surg 2020;6:203–206;
Image: Cho SH, et al. J Aller Clin Immunol Pract 2020;8:1505–1511

Mechanisms for T2 and non-T2 inflammation in CRSwNP



Wang M, et al. J Allergy Clin Immunol. 2025 *In Press*

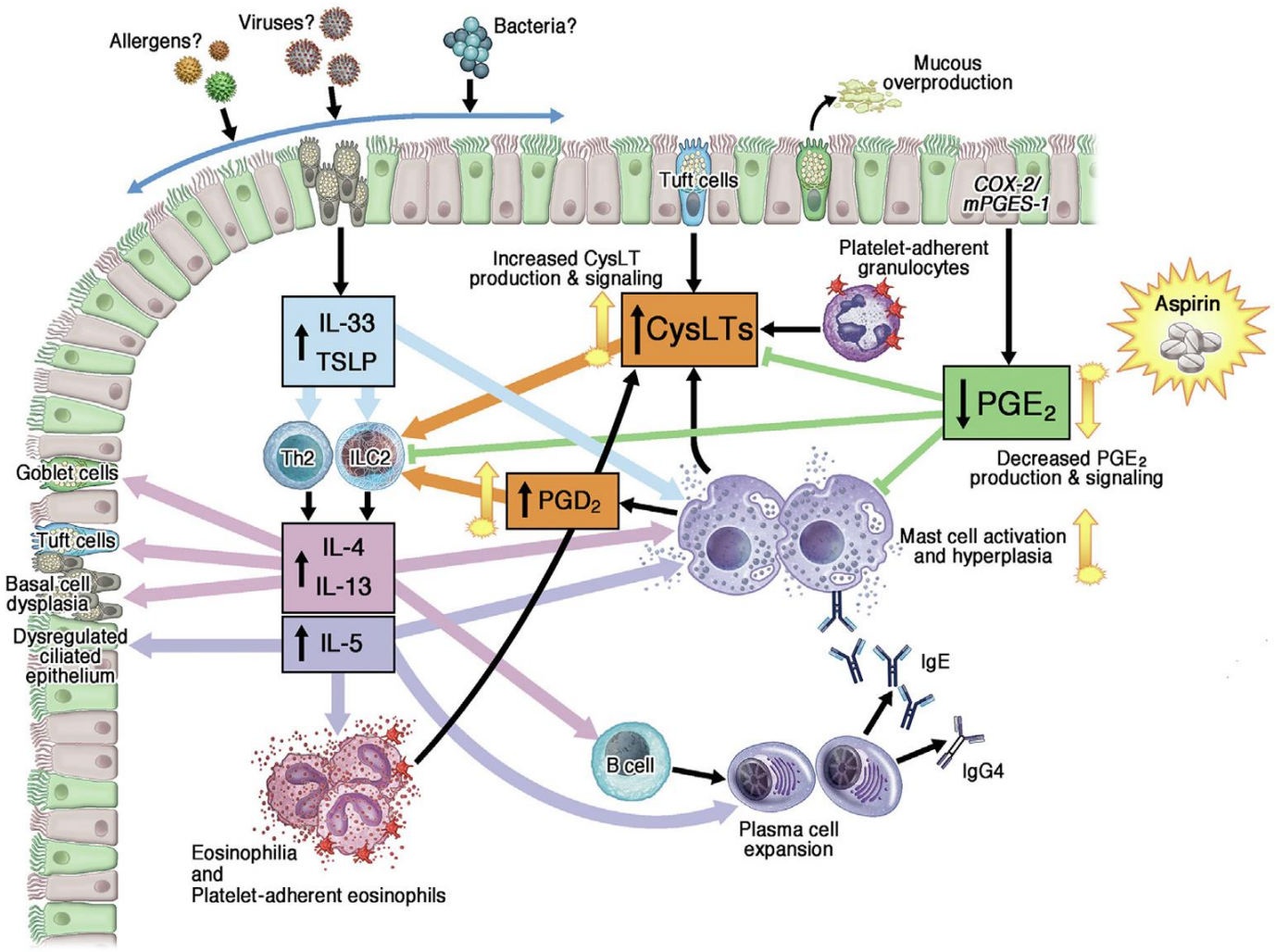
Patterns of Inflammatory Endotypes in Patients With CRS, CRSsNP, or CRSwNP in a US Cohort



Stevens WW, et al. J Allergy Clin Immunol Pract. 2019;7(8):2812-2820.

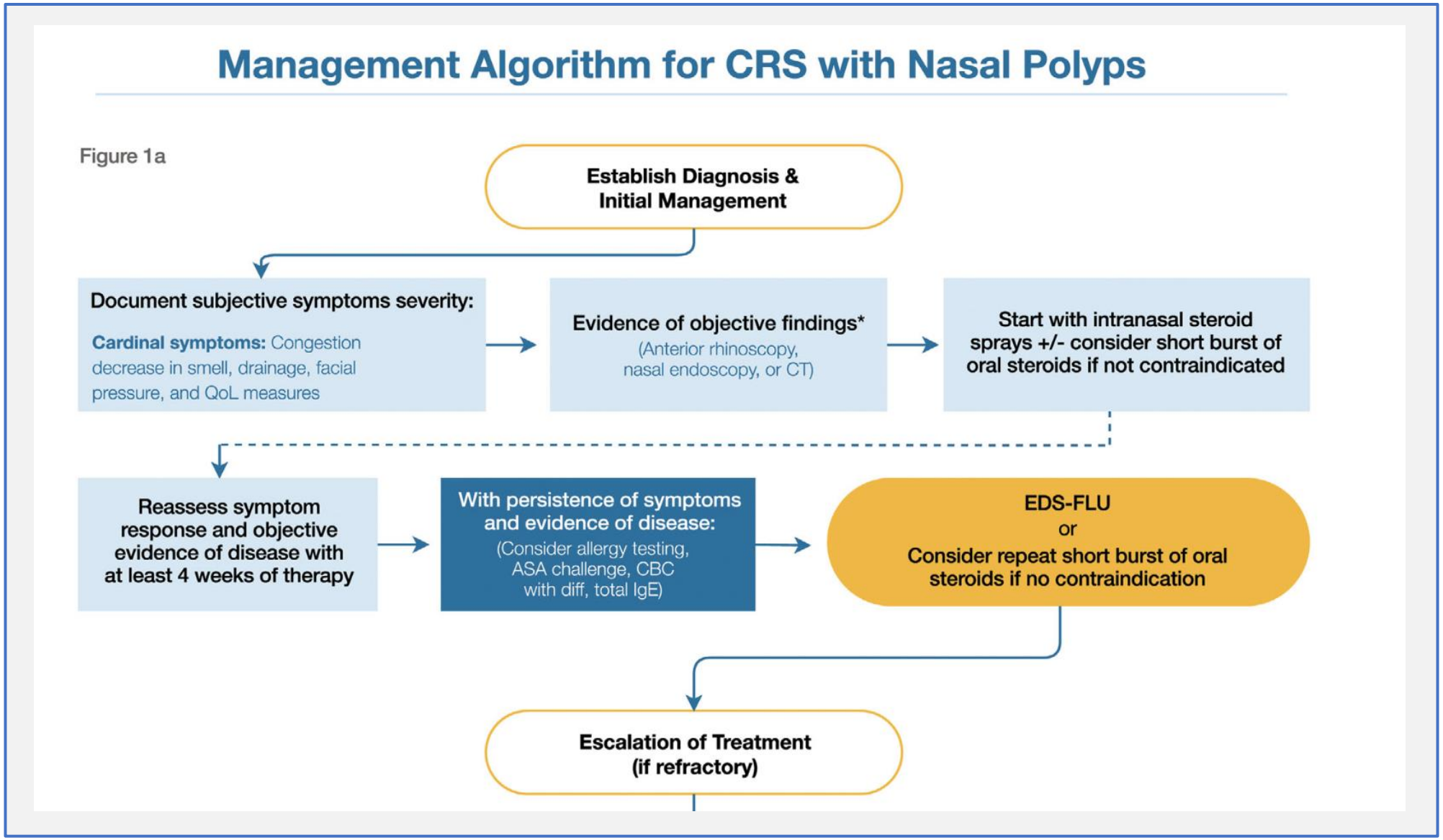
CRS = chronic rhinosinusitis; CRSsNP = CRS without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps; T1 = type 1; T2 = type 2; T3 = type 3.

Pathogenesis of chronic inflammation in AERD



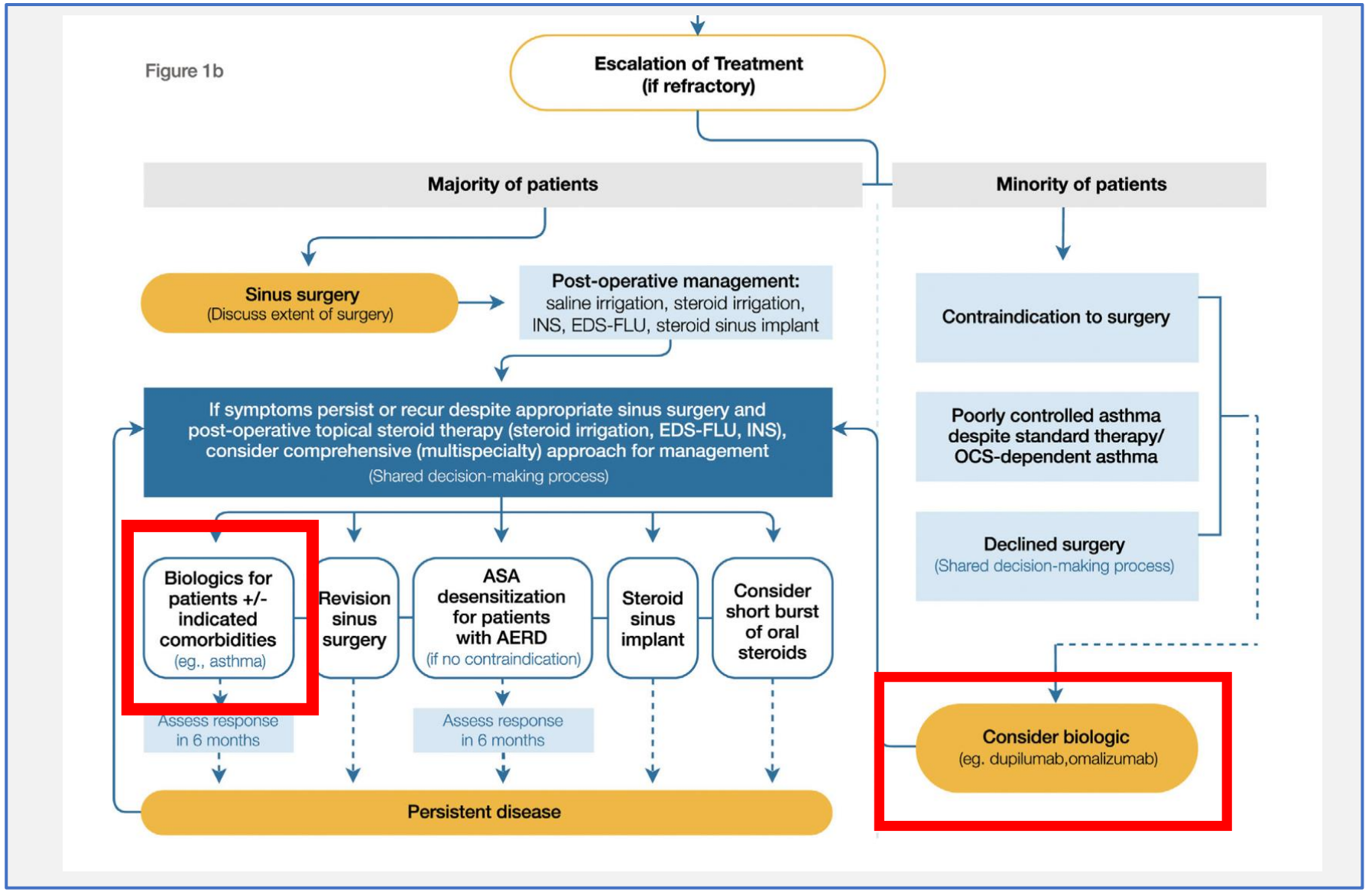
Laidlaw TM and Boyce JA. JACI 2023; Feb;151(2):301-309.

Management algorithm for CRSwNP: first line therapy



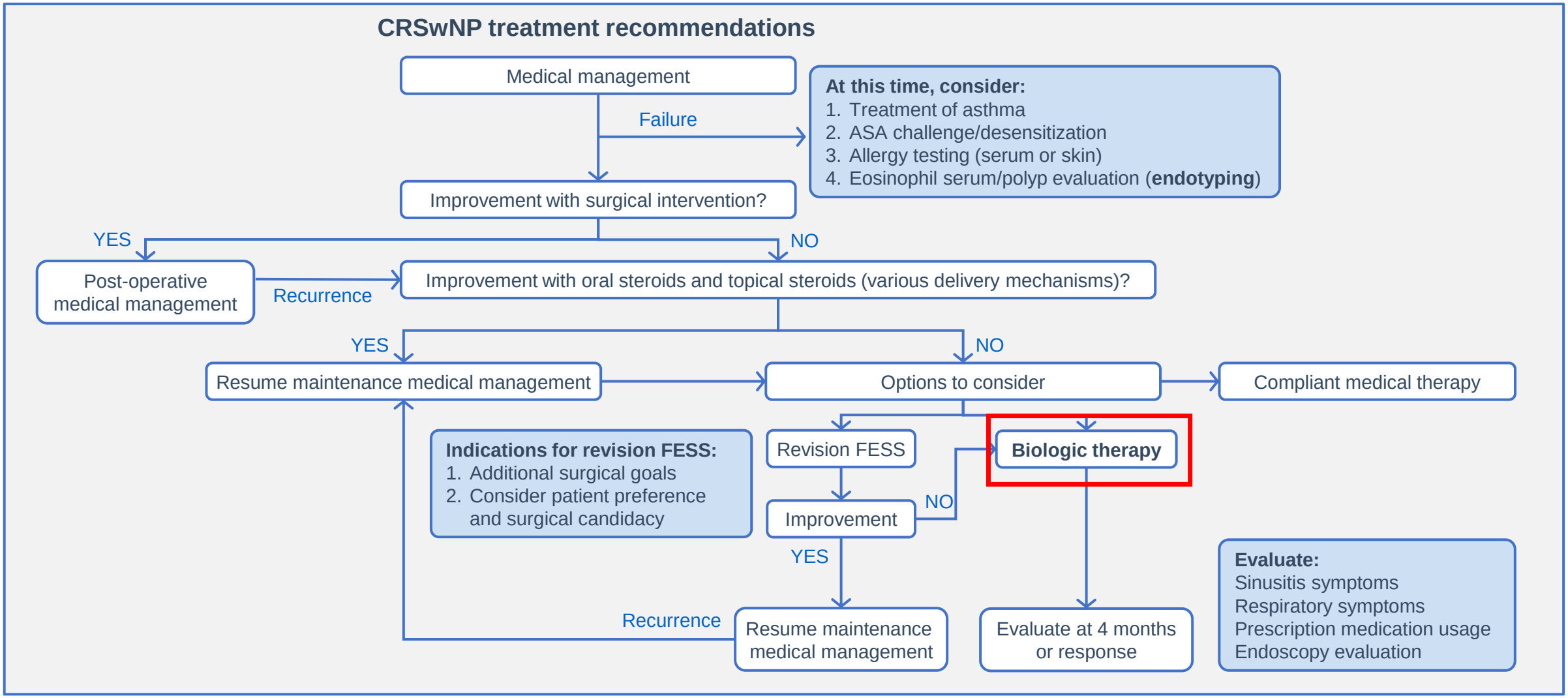
Han JK, et al. Int Forum Allergy Rhinol. 2022;11:1407-1416

Management algorithm for CRSwNP: refractory to first line therapy



Han JK, et al. Int Forum Allergy Rhinol. 2022;11:1407-1416

2020 National Institutes of Health: Workshop for Biologic Use in CRSwNP – surgery vs biologic??



ASA, acetylsalicylic acid; CRSwNP, chronic rhinosinusitis with nasal polyps; FESS, functional endoscopic sinus surgery

Adapted from: Roland LT, et al. Int Forum Allergy Rhinol 2020;10:1037–1042

EPOS/EUFOREA update on indication and evaluation of biologics in CRSwNP (2023)

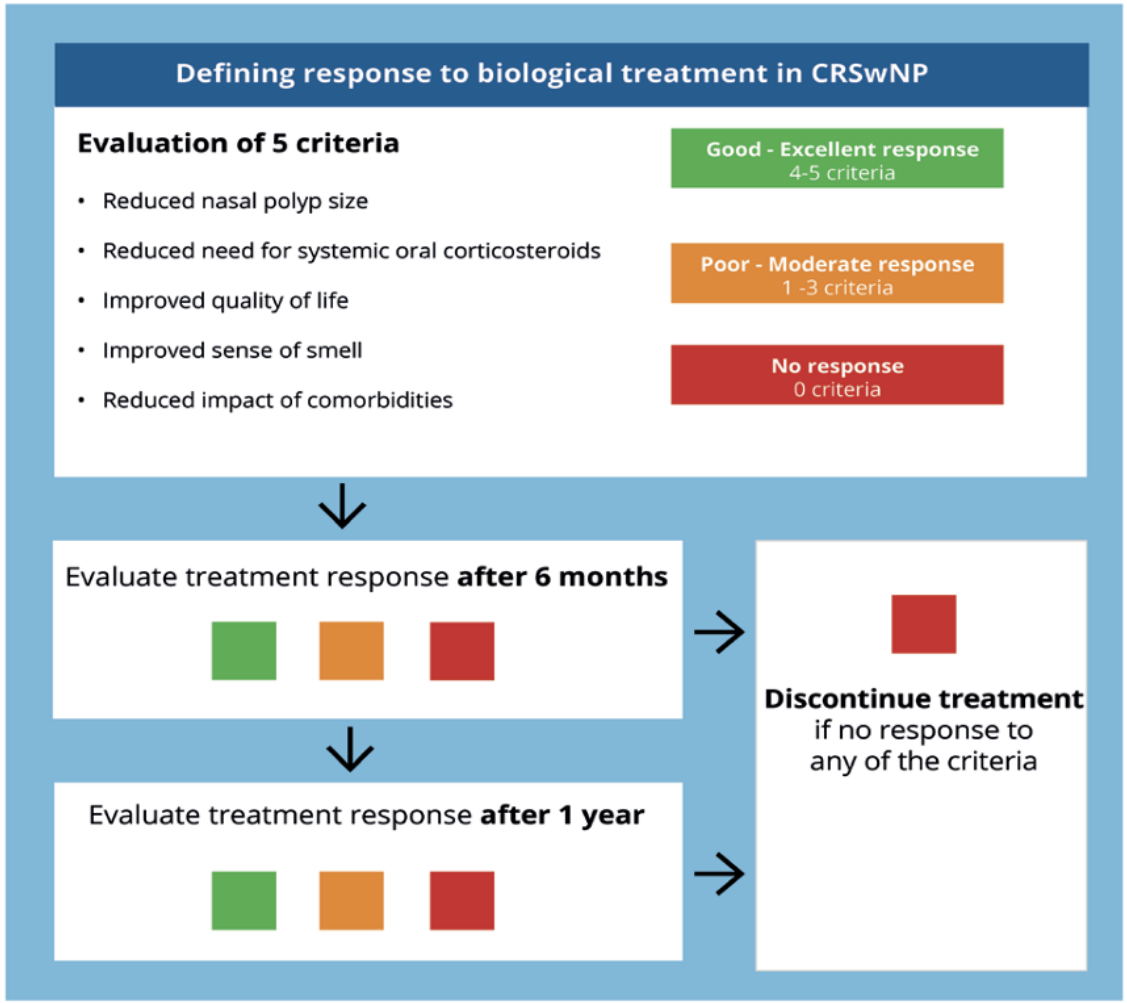
Indication for biological treatment in CRSwNP

Presence of bilateral polyps in patient who had ESS**

THREE criteria are required

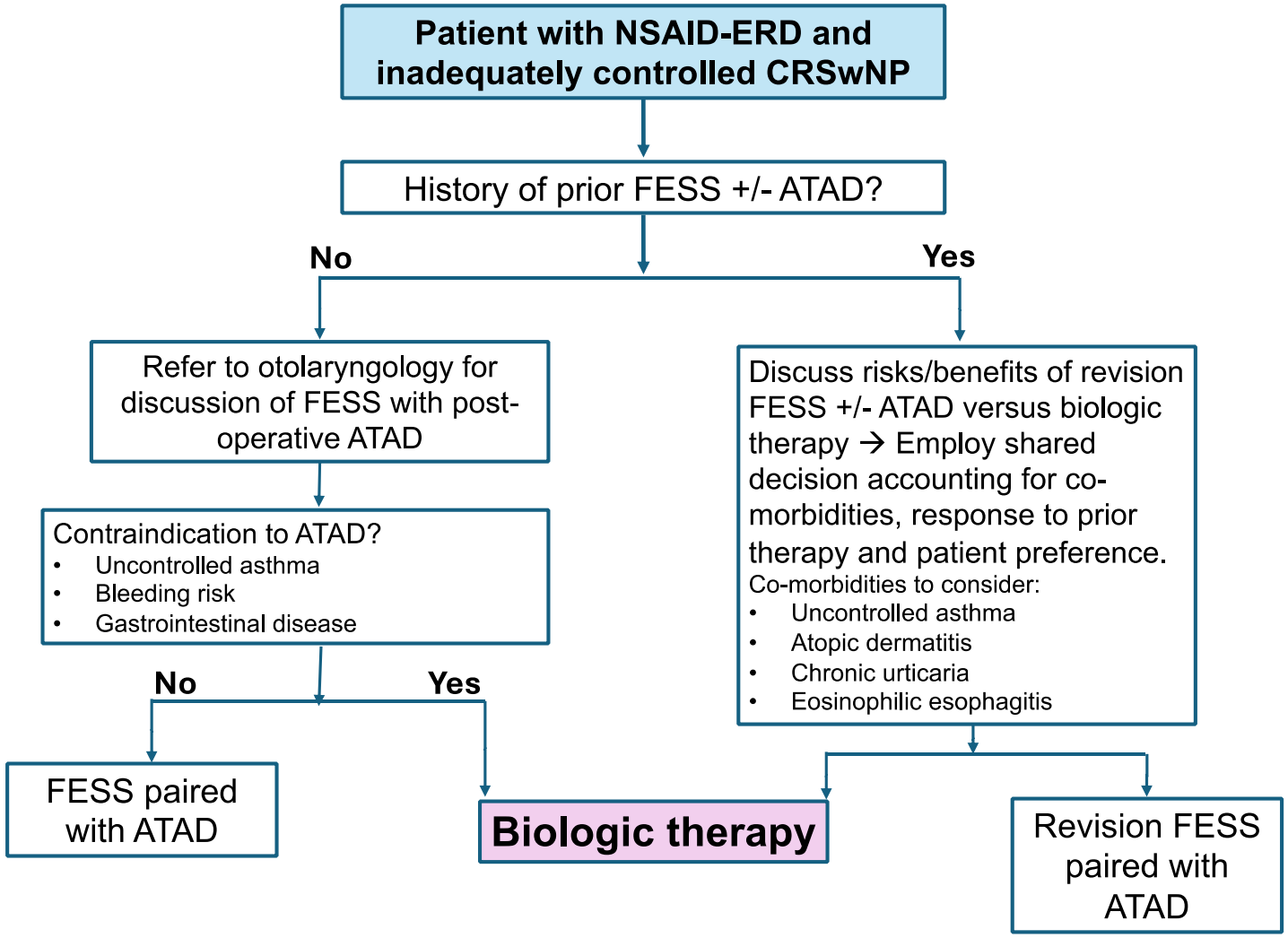
Criteria	Cut-off points
Evidence of type 2 inflammation	Tissue eos ≥10/hpf, **OR** blood eos **≥ 150** **OR** total IgE ≥100
Need for systemic corticosteroids or contraindication to systemic steroids	≥2 courses per Yr **OR** long term (> 3 months) low dose steroids
Significantly impaired quality of life	SNOT-22 ≥40
Significant loss of smell	Anosmic on smell test (score depending on test)
Diagnosis of comorbid asthma	In case of asthma: regular need for inhaled corticosteroids

* Exceptional circumstances excluded (e.g., not fit for surgery)



Fokkens WJ, et al. *Rhinology*. 2023;61(3):194-202.

Where does biologic therapy fit in treatment algorithm for patients with AERD?



Buchheit, K et al. JACI IP 2024.

Summary: CRSwNP presentation and treatment guidelines

- Most common presenting symptoms of CRSwNP include nasal congestion/blockage and hyposmia/anosmia
  - Consider diagnosis of AERD: ask all adult-onset asthmatic patients about nasal polyps, sense of smell, and COX-1 inhibitor tolerance
- 80 – 90% of patients in the US have a predominantly T2 inflammatory endotype marked by **eosinophilic inflammation, T2 cytokines (IL-4, IL-5, IL-13), high tissue IgE levels, mast cell activation**
- Current CRSwNP management guidelines suggest reserving biologic therapy for patients who fail surgical management
  - Exceptions for patients with co-morbidities and contra-indication to surgery

Next: biologic therapy updates

Biologic therapy for CRSwNP and AERD

- Biologic therapy for CRSwNP and AERD
  - Anti-IL-4Rα
  - Anti-IgE
  - Anti-IL-5/IL-5Rα
  - Anti-TSLP

- Choosing between specific biologic agents
- Biologic therapy versus aspirin therapy after desensitization in AERD

Biologics: What we have and what might be coming

Efficacy and safety of dupilumab in patient
chronic rhinosinusitis with nasal polyps (LI
SINUS-24 and LIBERTY NP SINUS-52): resu
two multicentre, randomised, double-blin
placebo-controlled, parallel-group phase 3

Claus Bachert, Joseph K Han, Martin
Tanya M Laidlaw, Anders U Cervin, J
Wytske J Fokkens, Shigeharu Fujieda
Gianluca Pirozzi, Naimish Patel, Neil
Leda P Mannent

Clinical Communications

Dupilumab improves nasal polyp burden and asthma control in patients with CRSwNP and AERD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma

Andrew Menzies-Gow, M.D., Jonathan Corren, M.D., Arnaud Bourdin, M.D.,

Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials

Philippe Gevaert, MD, PhD,[a] Theodore A. Omachi, MD,[b] Jonathan Corren, MD,[c] Joaquim Mullol,
Joseph Han, MD,[e] Stella E. Lee, MD,[f] Derrick Kaufman, PhD,[b] Monica Ligueros-Saylan, MD,[g] Mor
Rui Zhu, PhD,[b] Ryan Owen, PhD,[b] Kit Wong, PhD,[b] Lutaf Islam, DVM, MSc,[h] and Claus Bachert, MD, PhD[a,i]
*Belgium; South San Francisco and Los Angeles, Calif; Catalonia, Spain; Norfolk, Va; Pittsburgh, Pa; East Hanover, NJ; Welwyn Ga
United Kingdom; and Stockholm, Sweden*

Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial

J Mark FitzGerald, Eugene R Bleecker, Parameswaran Nair, Stephanie Korn, Ken Ohta, Marek Lommatzsch, Gary T Ferguson, William W Busse, Peter Barker, Stephanie Sproule, Geoffrey Gilmartin, Viktoria Werkström, Magnus Aurivillius, Mitchell Goldman, on behalf of the CALIMA study investigators*

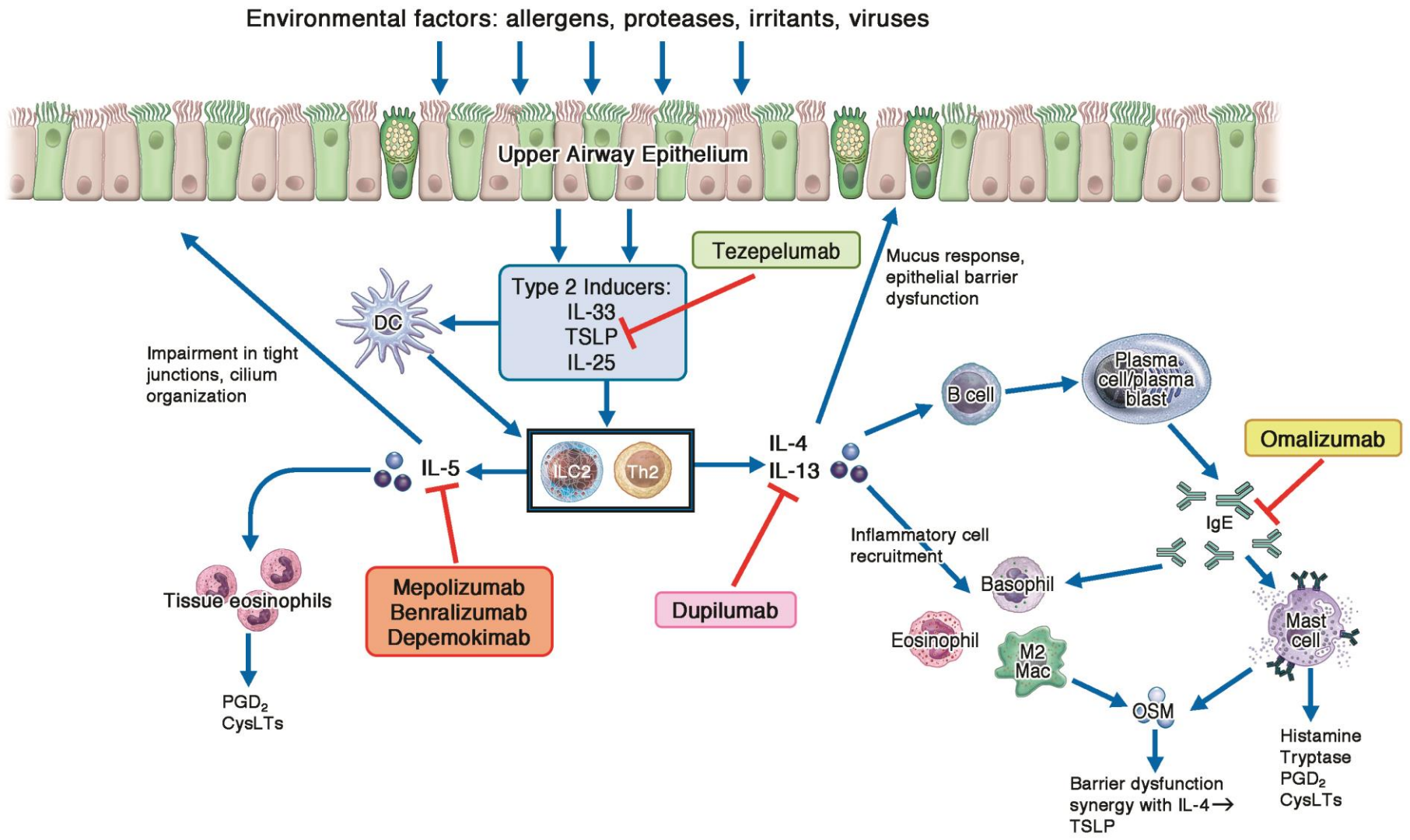
Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma

Philippe Gevaert, MD, PhD,[a*] Lien Calus, MD,[a*] Thibaut Van Zele, MD, PhD,[a] Katrien Blomme, MSc,[a] Natalie De Ruyck, MSc,[a] Wouter Bauters, MD, PhD,[b] Peter Hellings, MD, PhD,[c] Guy Brusselle, MD, PhD,[d] Dirk De Bacquer, MD, PhD,[e] Paul van Cauwenberge, MD, PhD,[a] and Claus Bachert, MD, PhD[a] *Ghent and Leuven, Belgium*

Biologics: What we have and what might be coming

Target	Drug	CRSwNP phase
Interleukin 4 Receptor alpha	Dupilumab	Approved 2019
Immunoglobulin E	Omalizumab	Approved 2020
Interleukin 5	Mepolizumab	Approved 2021
Interleukin 5 Receptor alpha	Benralizumab	Phase 3 completed
Thymic stromal lymphopoietin	Tezepelumab	Phase 3 completed
Interleukin 5	Depemokimab	Phase 3 completed
Interleukin 13	Lebrikizumab	Phase 3
Interleukin 4 Receptor alpha	CM310/stapokibart	Phase 3
Interleukin 33	Itepekimab	Phase 3

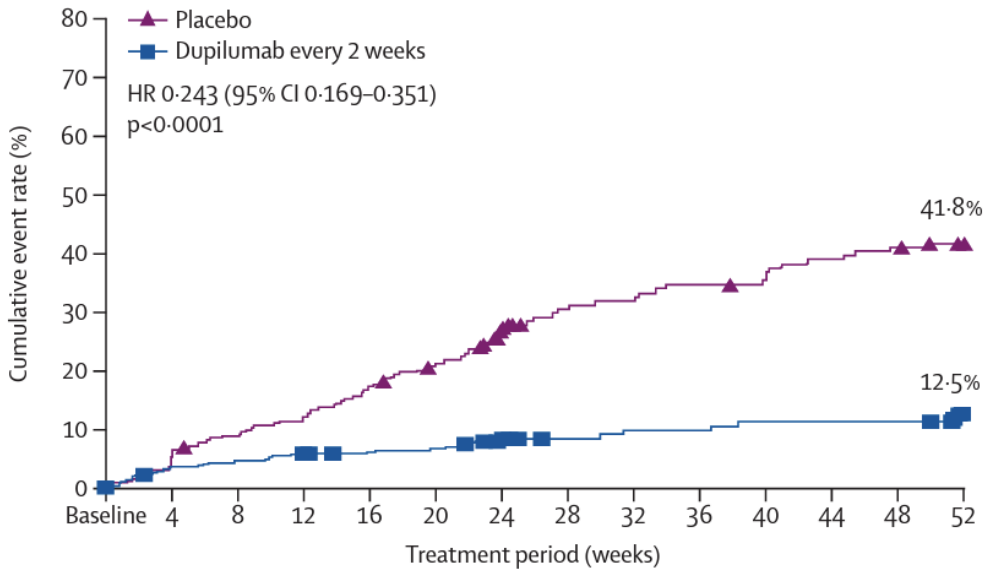
Targets of approved and investigational biologic medications for treatment of CRSwNP



Kratchmarov R et al. JACI, *In Press*.

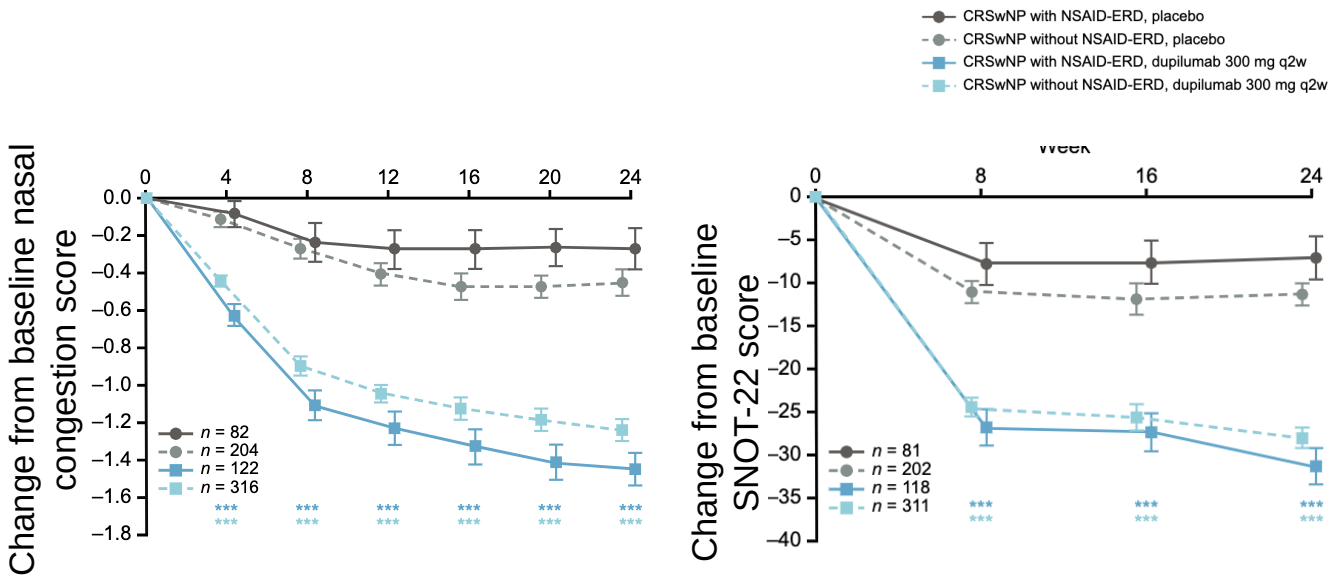
Biologic therapy (anti-IL4Rα) reduces need for surgery and improves sinonasal symptoms in CRSwNP/AERD

Time to first sinus surgery or systemic corticosteroid use for CRSwNP in anti-IL-4Rα therapy compared to placebo



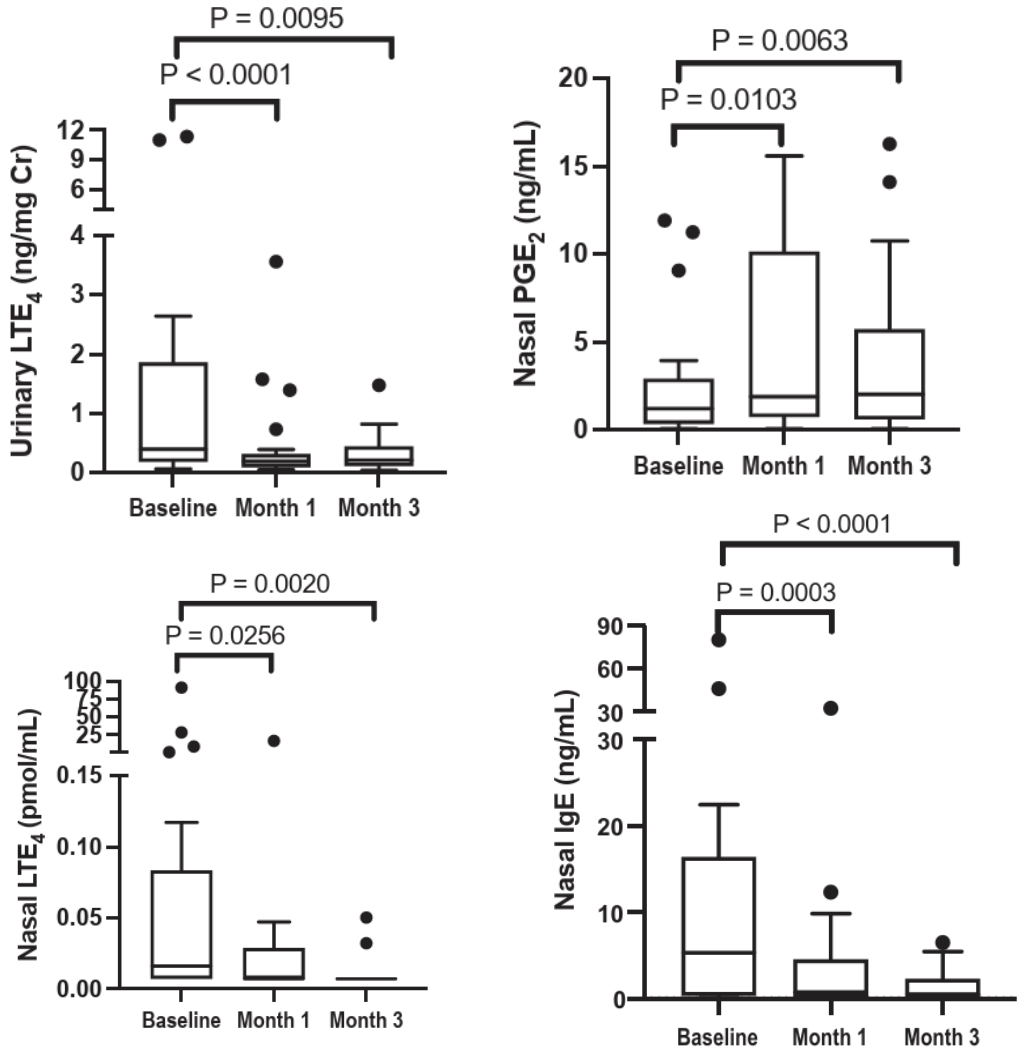
Bachert C et al. Lancet. 2019 Nov 2;394(10209):1638-1650.

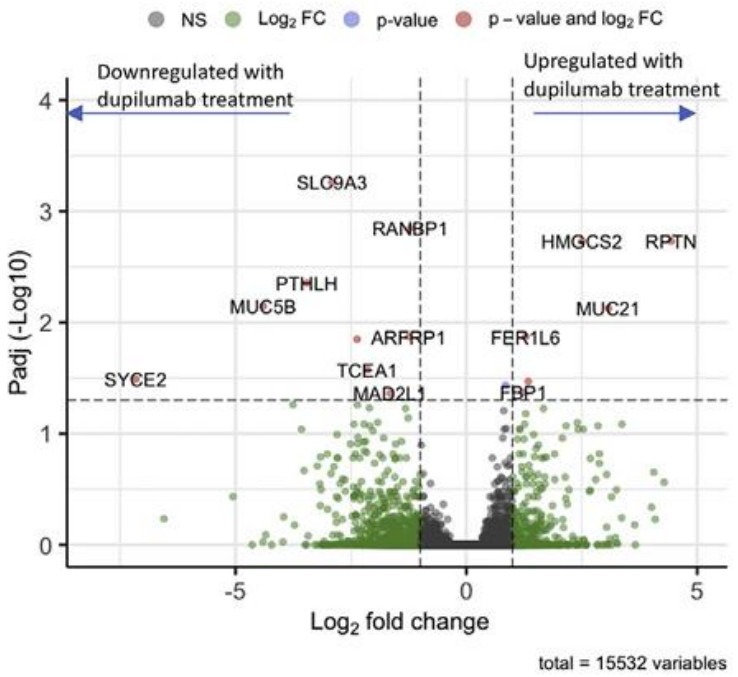
Improvement in sinonasal symptoms in patients with AERD and aspirin-tolerant CRSwNP

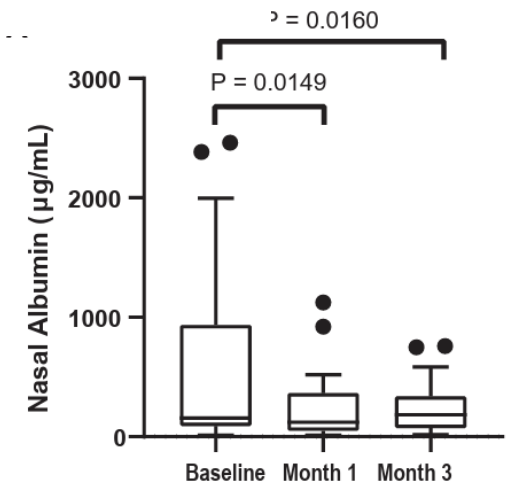


Mullol J et al. Allergy. 2022 Apr;77(4):1231-1244.

Dupilumab has impacts on eicosanoids, IgE, and nasal epithelium in AERD

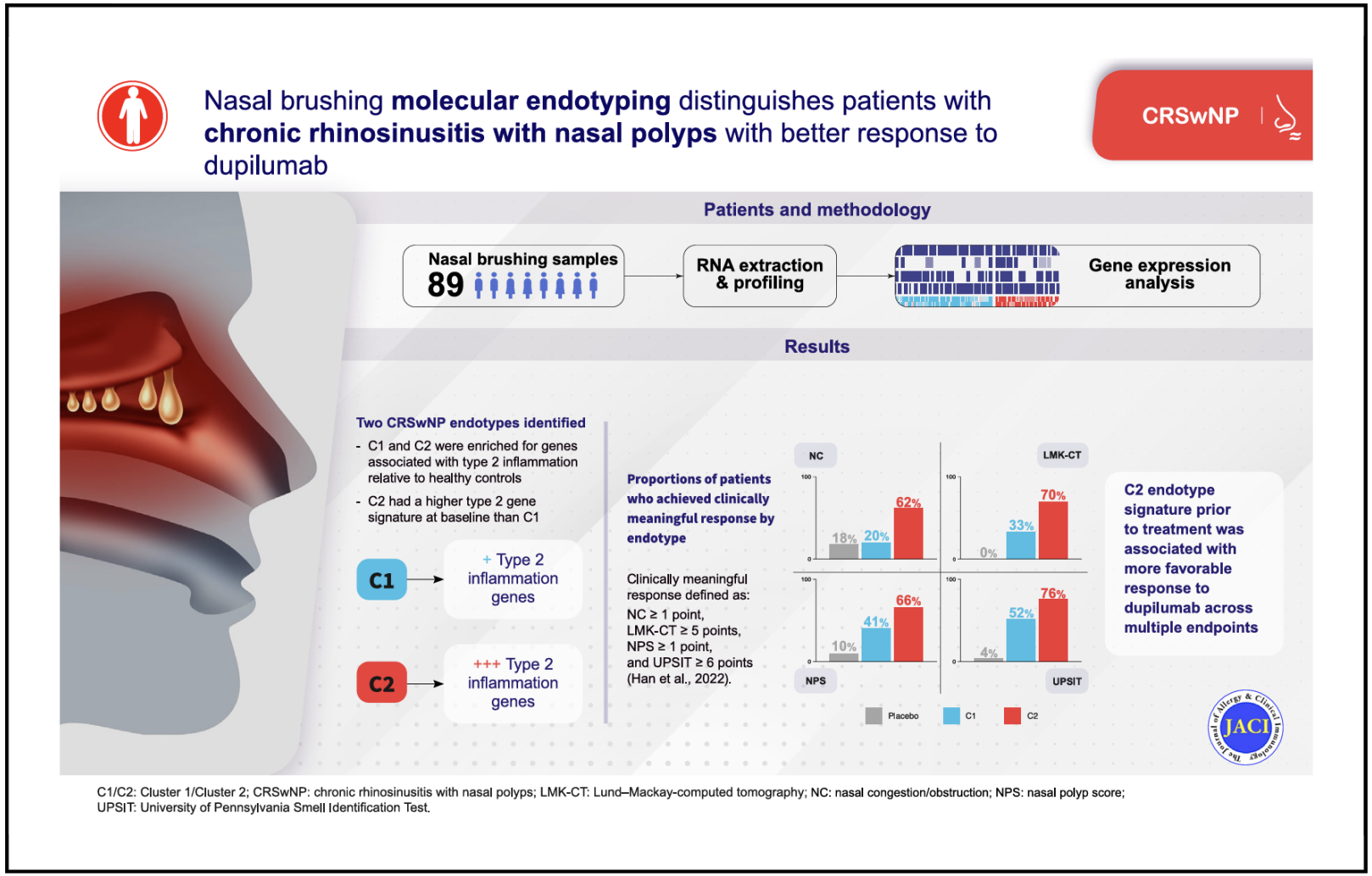






Buchheit KM et al. J Allergy Clin Immunol. 2022 Aug;150(2):415-424

Molecular endotying of nasal brushings shows T2 cluster with better response to dupilumab for CRSwNP



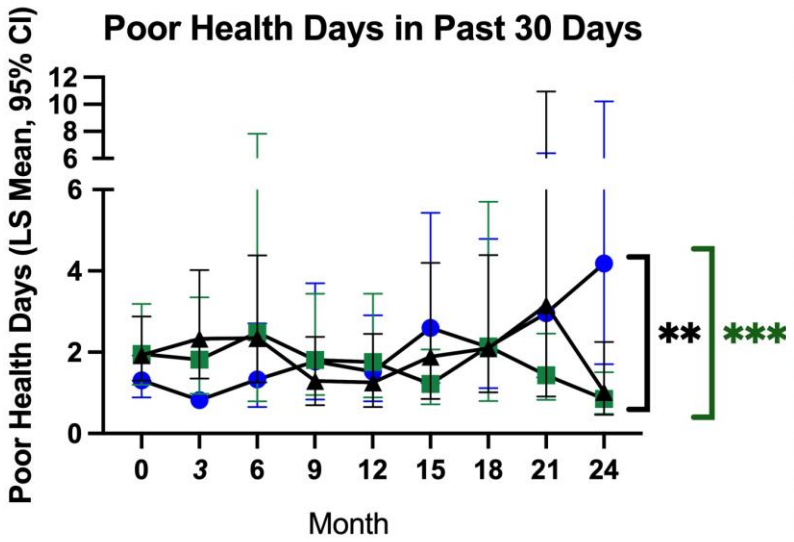
C1/C2: Cluster 1/Cluster 2; CRSwNP: chronic rhinosinusitis with nasal polyps; LMK-CT: Lund–Mackay-computed tomography; NC: nasal congestion/obstruction; NPS: nasal polyp score; UPSIT: University of Pennsylvania Smell Identification Test.

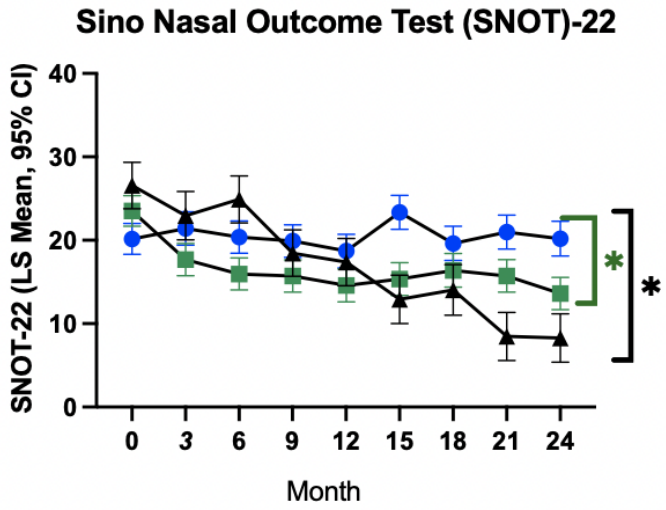
C1 (blue): Enriched for genes associated with T cell activation and IL-12

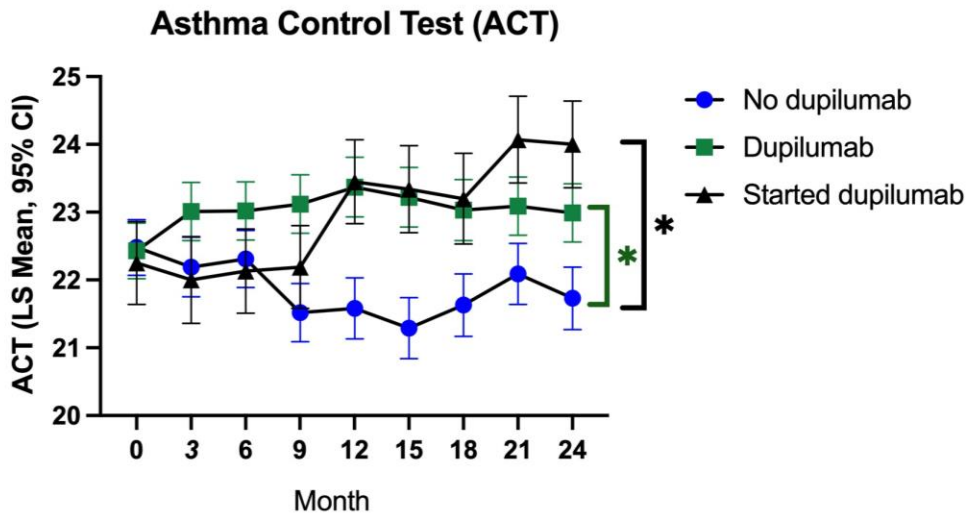
C2 (red): Enriched for genes associated with T2 inflammation

Gayvert K. J Allergy Clin Immunol. 2024 Sep;154(3):619-630.

IL-4Rα Inhibition leads to long-term improvement in quality of life in patients with AERD



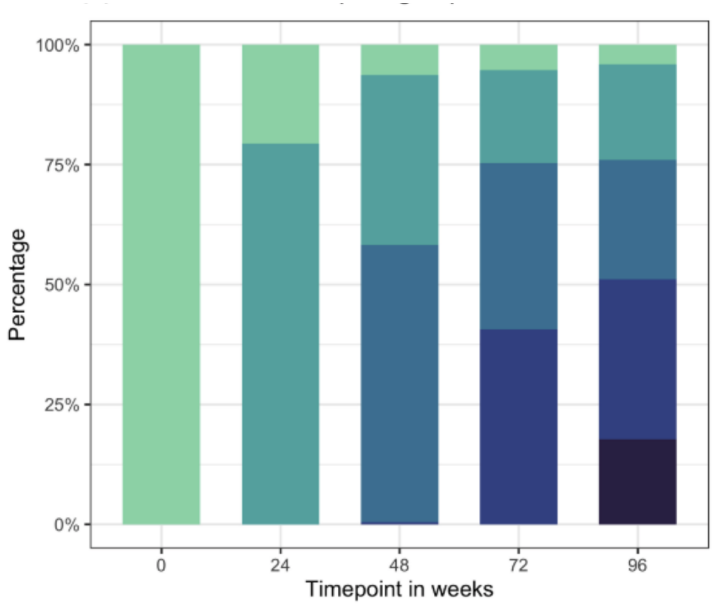




Mullur and Buchheit, Am J Rhinol Allergy. 2025 Mar;39(2):90-97.

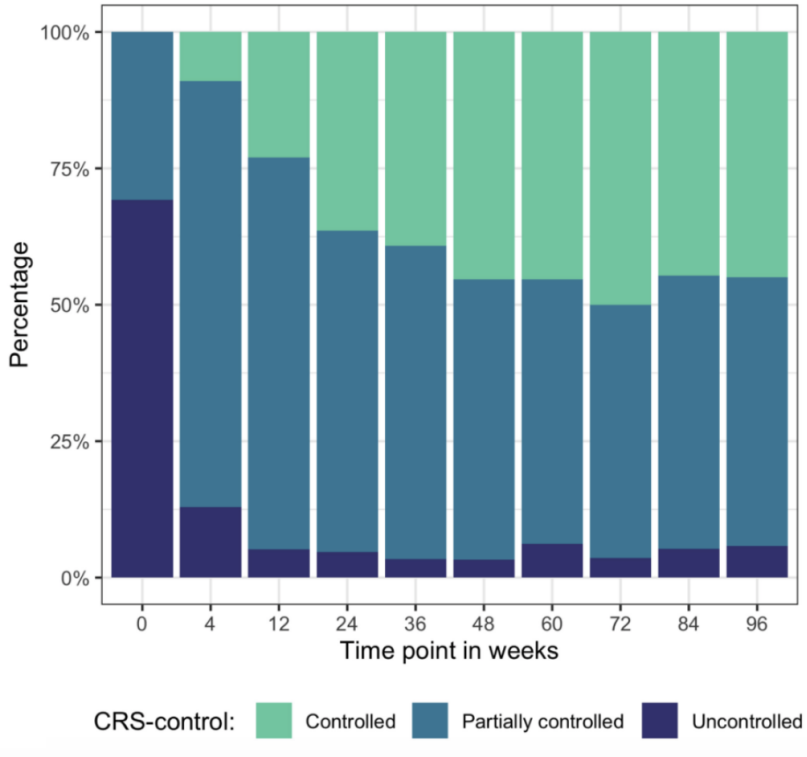
Efficacy of tapered dupilumab dose for CRSwNP*

Advancement of tapering dupilumab

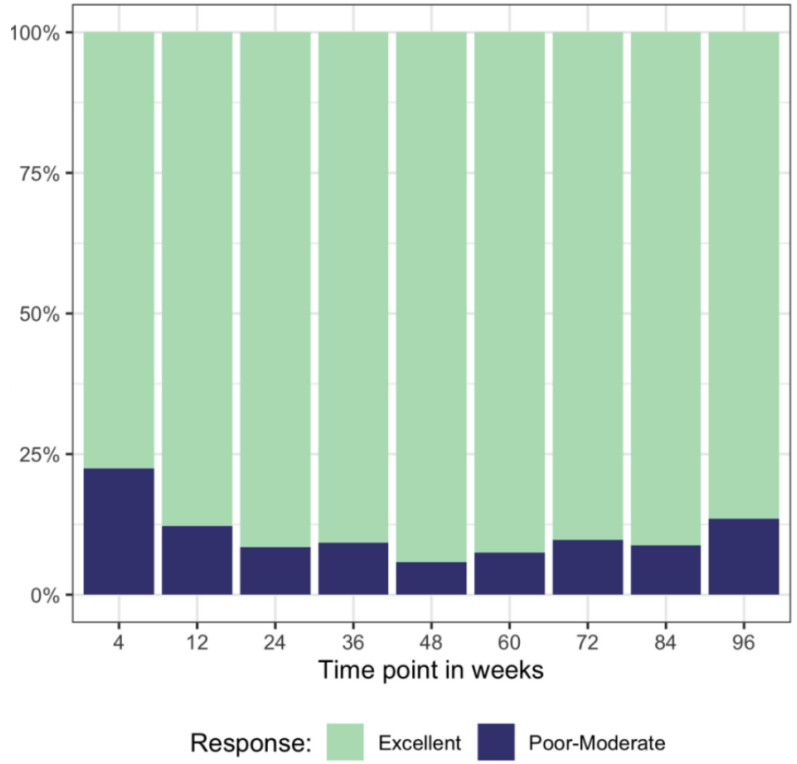


Dosing frequency: 2 4 6 8 12

EPOS 2020 current CRS-control



EUFOREA-2023 response evaluation

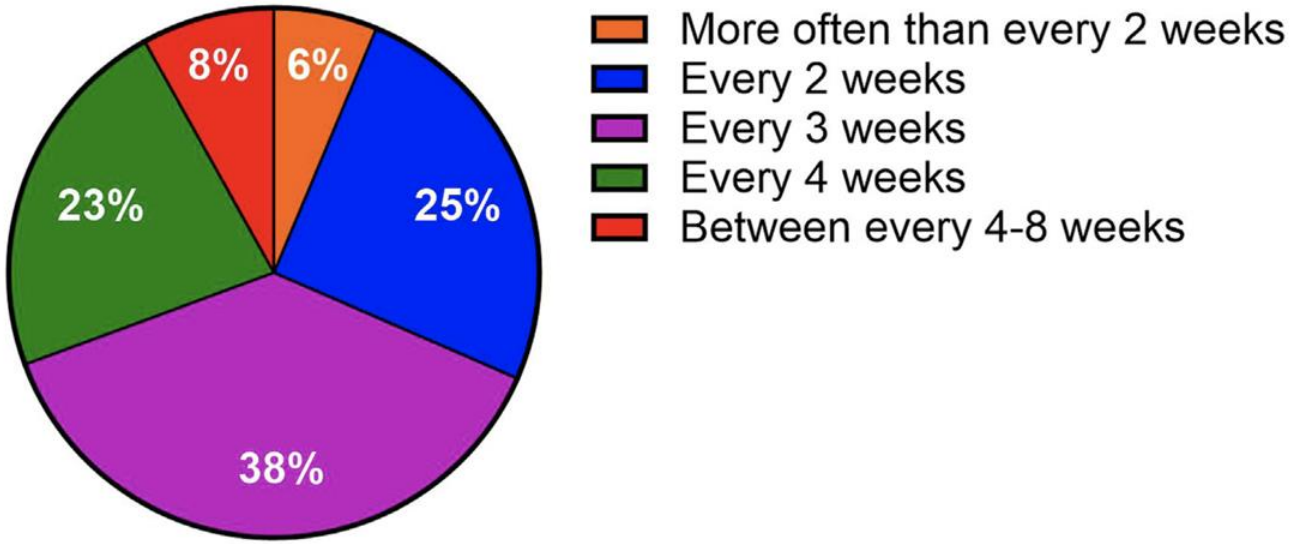


*40.6% of patients had NSAID-ERD

van der Lans RJL et al. Allergy. 2023 Oct;78(10):2684-2697.

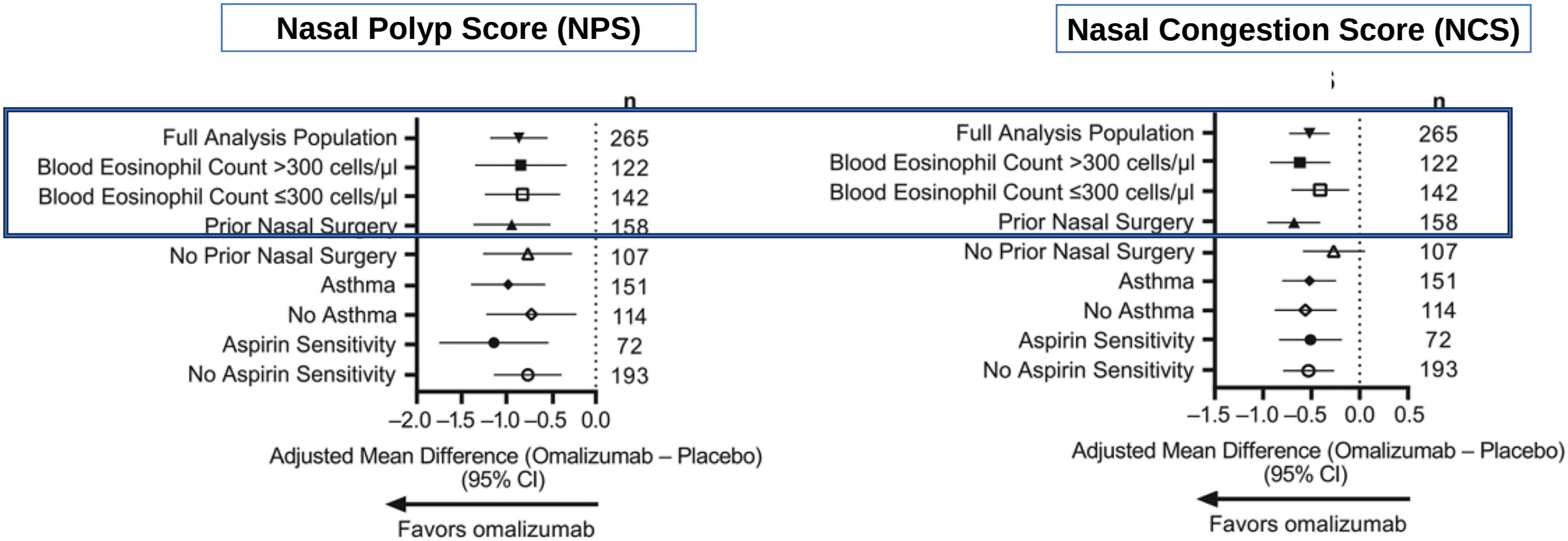
Dupilumab dosing frequency in AERD

Survey Study of BWH AERD Registry: Dosing intervals reported by 111 patients with NSAID-ERD who attempted dosing intervals other than q2 weeks



Brown A et al JACI IP. Allergy Clin Immunol Pract. 2024 Jun;12(6):1647-1648.

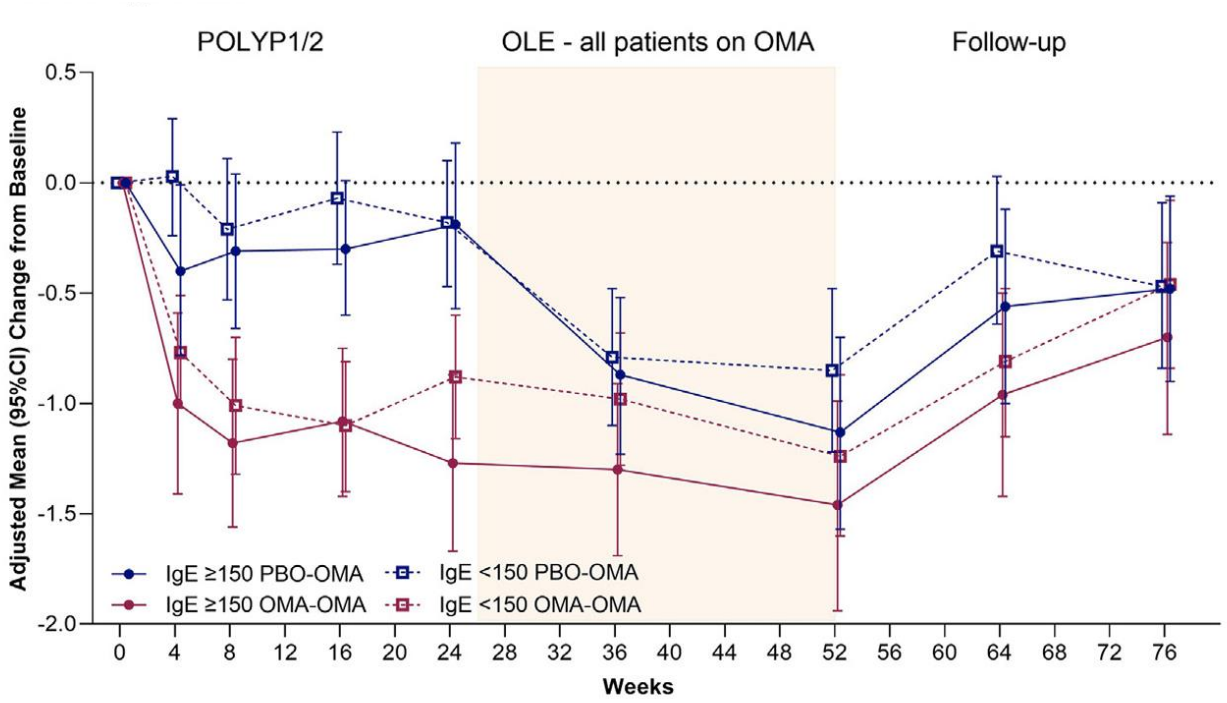
Post hoc analyses from phase 3 studies of omalizumab for CRSwNP: eosinophil levels



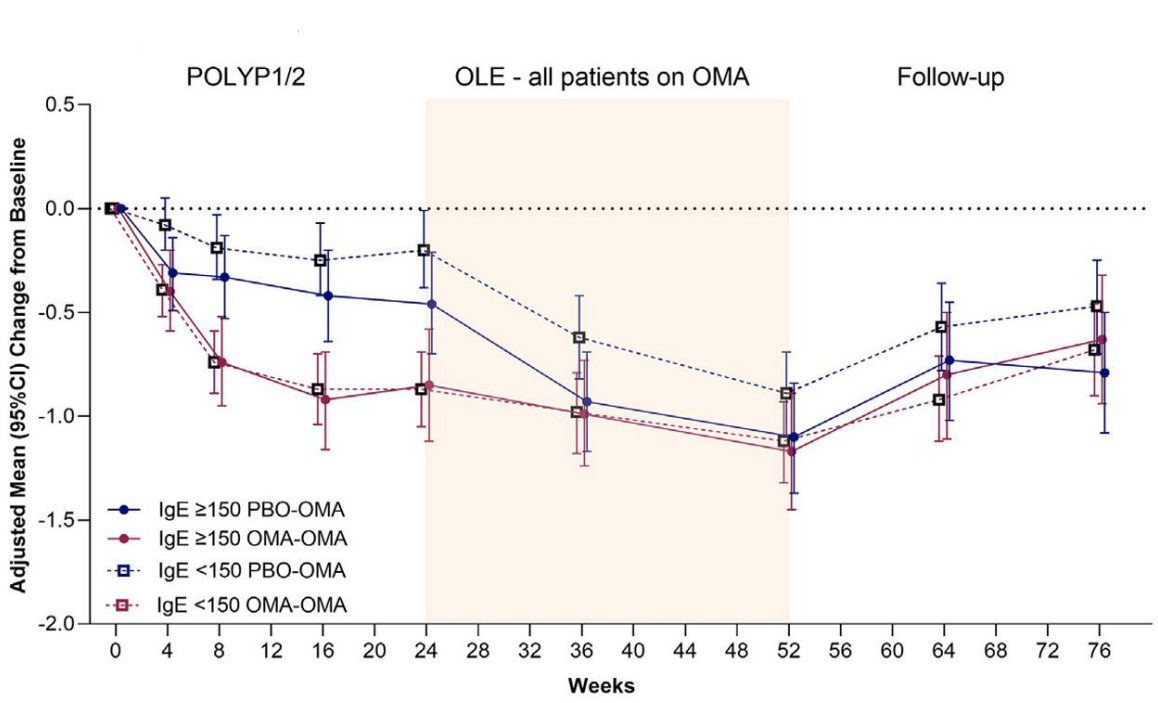
Damask C et al. Am J Rhinol Allergy. 2022 Jan;36(1):135-141.

Post hoc exploratory analysis from phase 3 studies of omalizumab for CRSwNP shows no difference in outcomes IgE < or ≥ 150 IU/mL

Nasal Polyp Score (NPS)



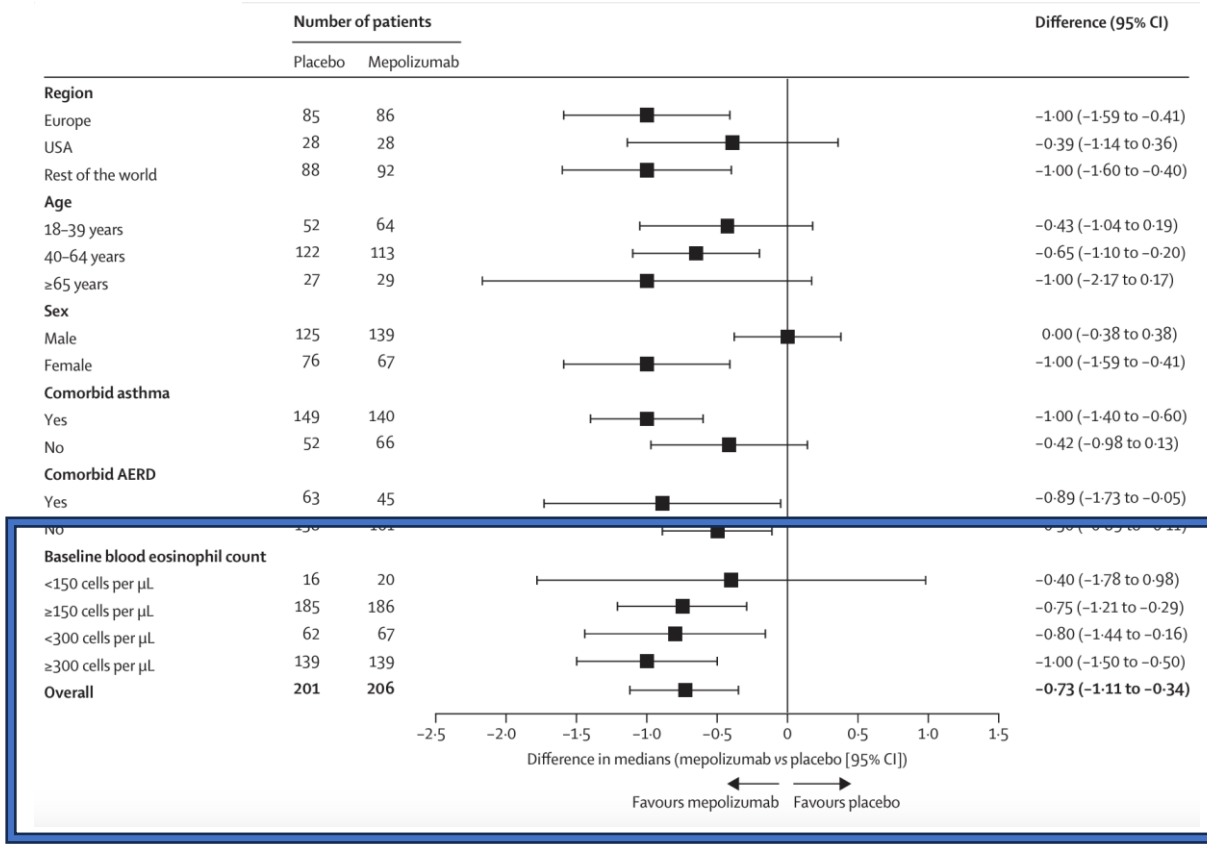
Nasal Congestion Score (NCS)



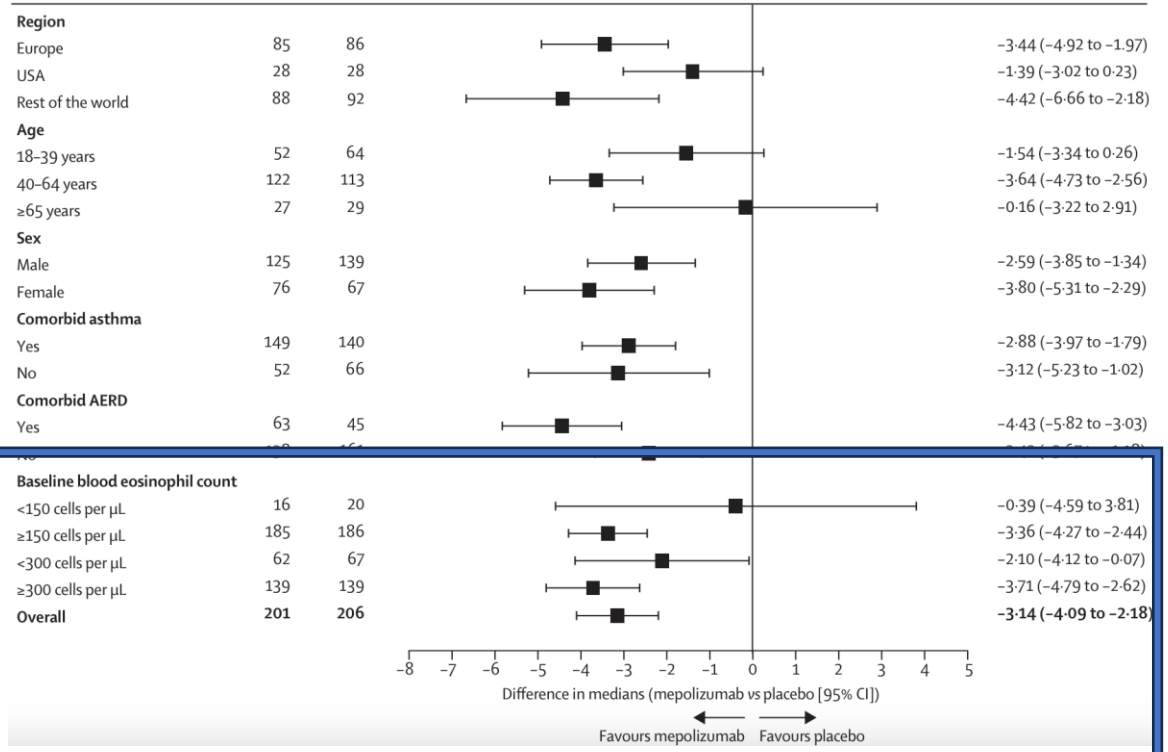
Gevaert P et al. Ann Allergy Asthma Immunol. 2024 Mar;132(3):355-362.

Prespecified subgroup analyses from phase 3 study of mepolizumab for CRSwNP: eosinophil levels

Nasal Polyp Score (NPS)

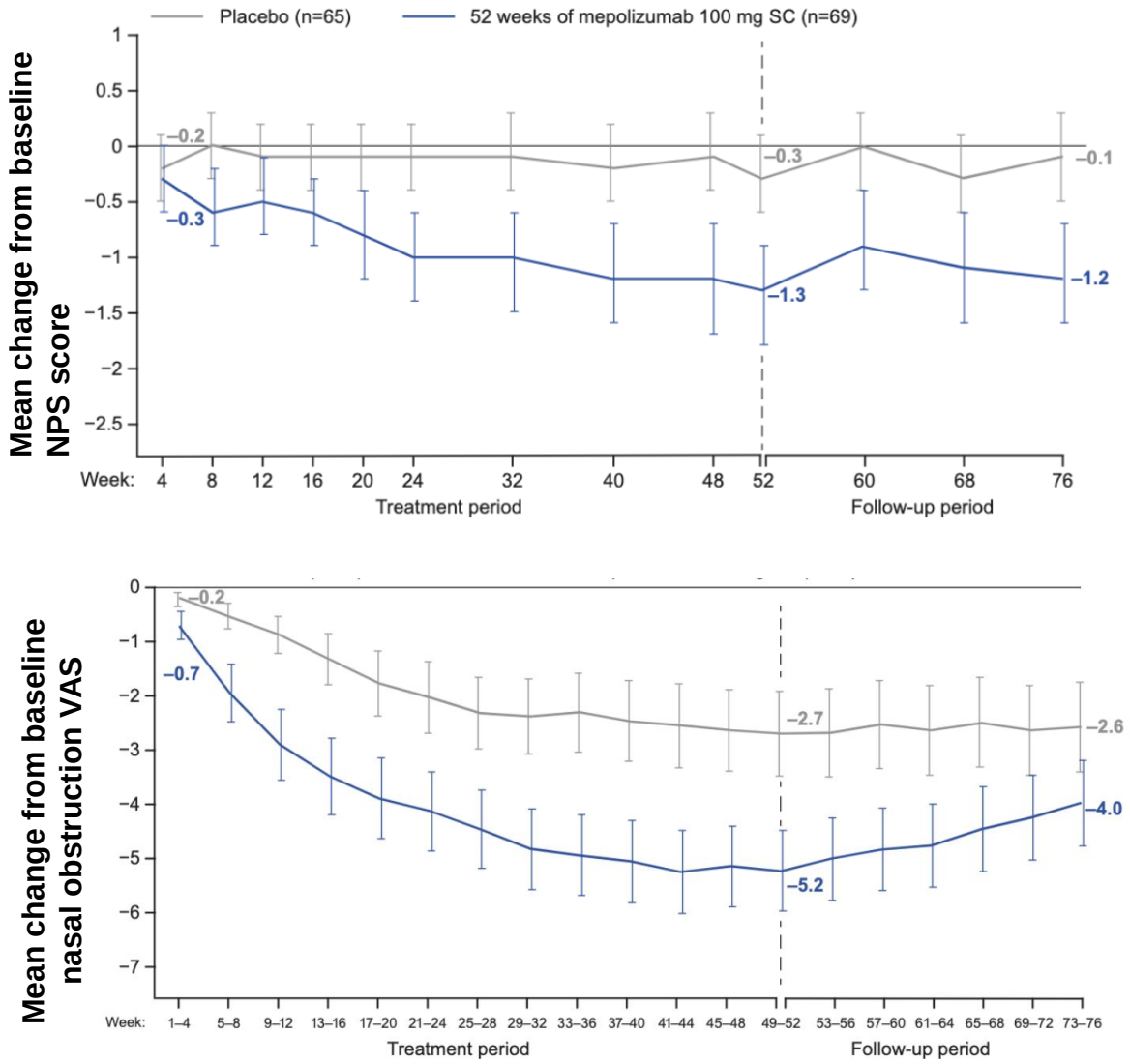


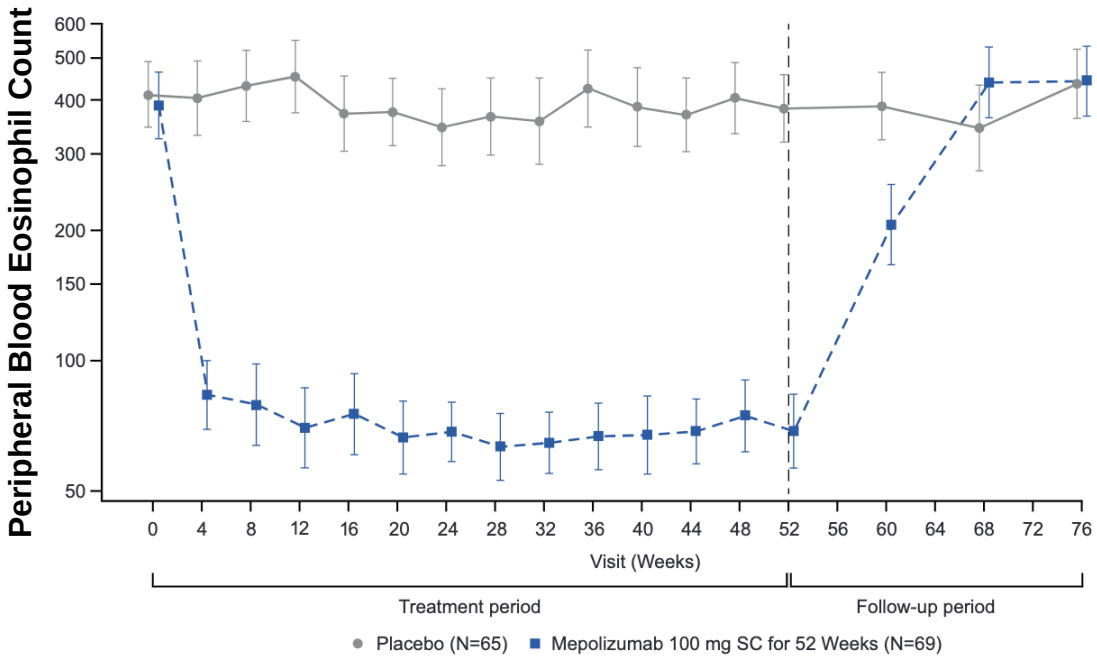
Nasal obstruction VAS score



Han J et al Lancet Respir Med 2021.

Sustained efficacy of mepolizumab for CRSwNP in 24-week post-treatment follow-up





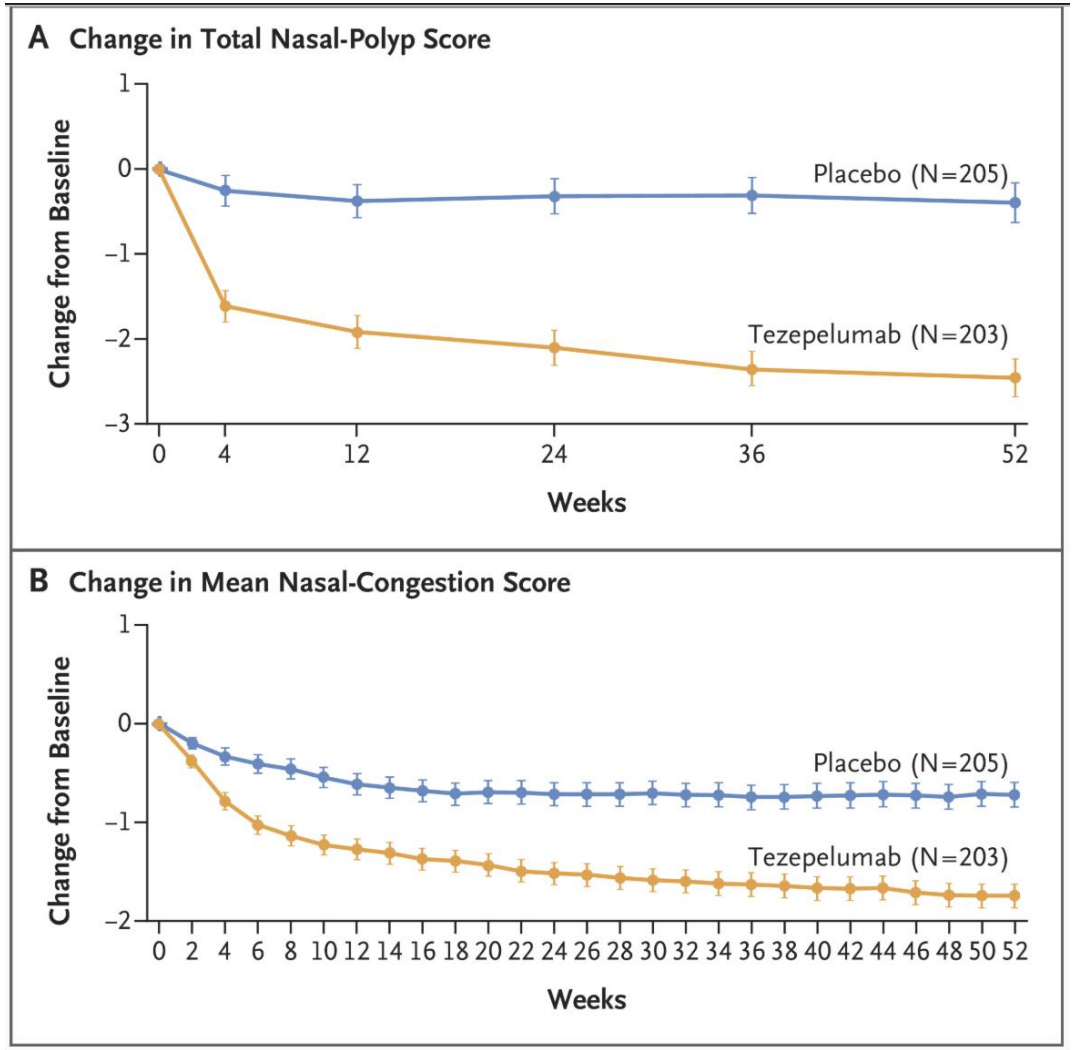
Desrosiers M et al. Int Forum Allergy Rhinol. 2024 Jan;14(1):18-31.

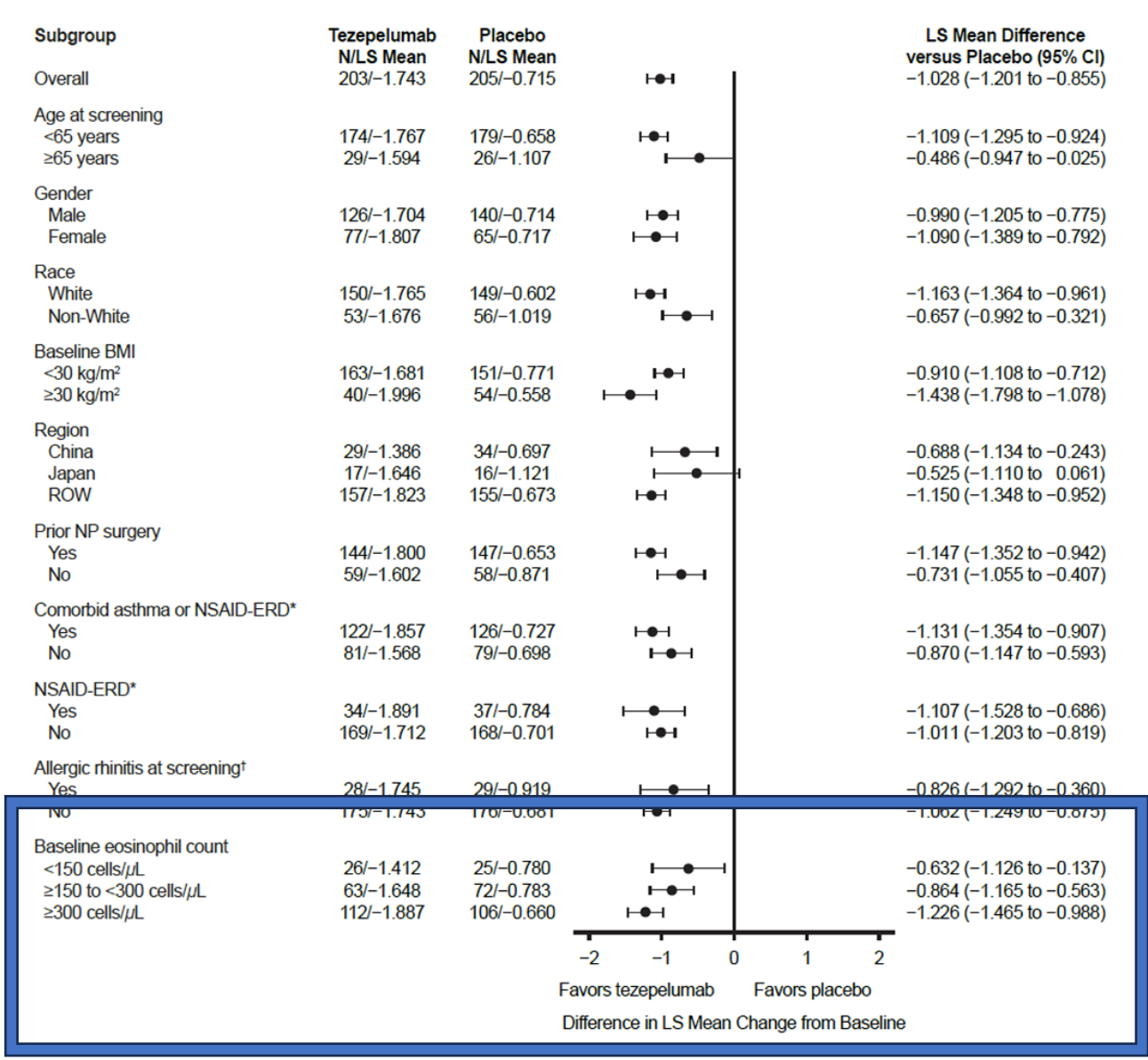
Depemokimab (ultra long-acting anti-IL-5) for CRSwNP

	ANCHOR-1			ANCHOR-2			Integrated		
	Placebo (n=128)	Depemokimab 100 mg subcutaneously (n=143)	Treatment difference, 95% CI; p value	Placebo (n=128)	Depemokimab 100 mg subcutaneously (n=129)	Treatment difference, 95% CI; p value	Placebo (n=256)	Depemokimab 100 mg subcutaneously (n=272)	Treatment difference, 95% CI; p value
Coprimary endpoint: change from baseline in total endoscopic nasal polyps score (0–8) at week 52									
Number of participants with available data	120	128	..	115	120	..	235	248	..
Least squares mean, SE	0·2 (0·15)	−0·6 (0·14)	−0·7 (−1·1 to −0·3); p<0·001	0·1 (0·15)	−0·5 (0·14)	−0·6 (−1·0 to −0·2); p=0·004	0·1 (0·10)	−0·5 (0·10)	−0·7 (−0·9 to −0·4); p<0·001*
Coprimary endpoint: change from baseline in mean nasal obstruction verbal response scale score (0–3) over weeks 49–52									
Number of participants with available data	116	125	..	111	119	..	227	244	..
Least squares mean, SE	−0·53 (0·083)	−0·76 (0·079)	−0·23 (−0·46 to 0·00); p=0·047	−0·53 (0·078)	−0·77 (0·076)	−0·25 (−0·46 to −0·03); p=0·025	−0·53 (0·057)	−0·77 (0·055)	−0·24 (−0·39 to −0·08); p=0·003*

Gevaert P et al. Lancet 2025 Mar 15;405(10482):911-926.

Efficacy of tezepelumab in CRSwNP

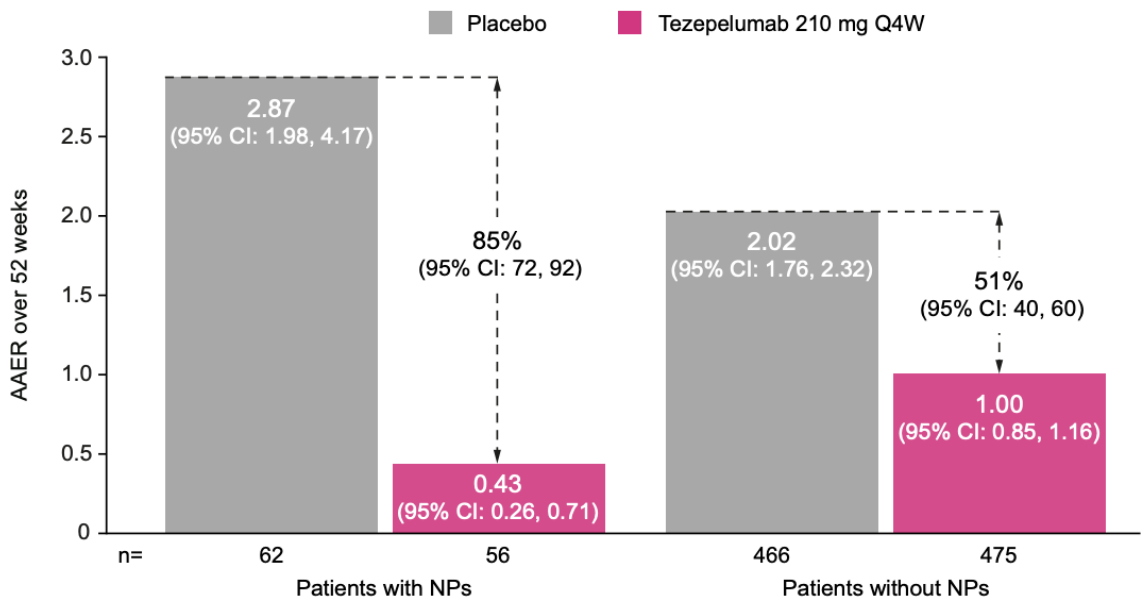




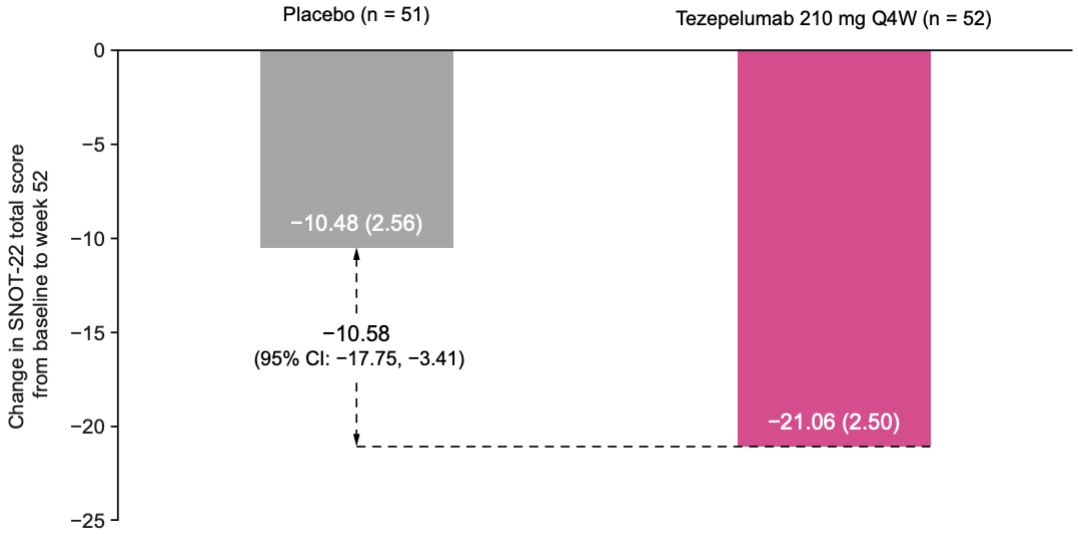
Lipworth BJ et al. N Engl J Med. 2025.

Anti-thymic stromal lymphopoietin (TSLP) for patients with CRSwNP

AAER over 52 weeks in patients with or without CRSwNP NAVIGATOR study



Change from baseline in SNOT-22 total score over 52 weeks in patients with NP

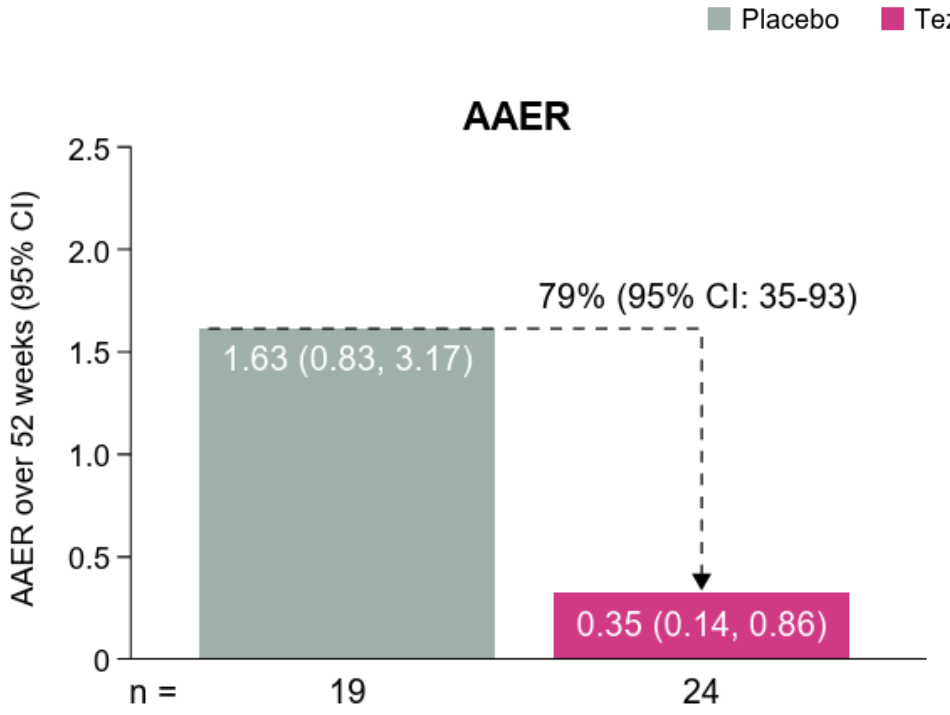


AAER=annualized asthma exacerbation rate

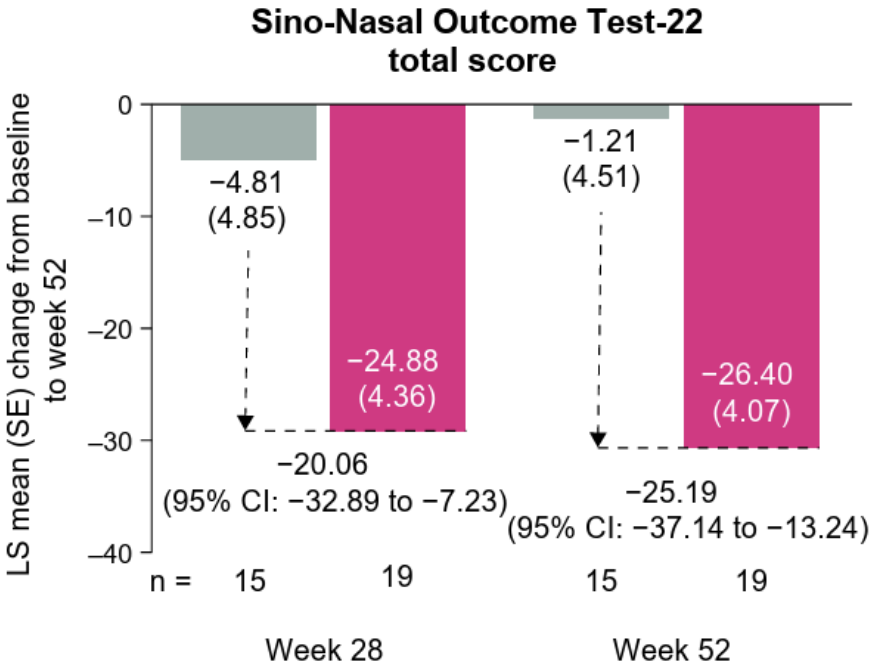
Laidlaw TM et al. *J Asthma Allergy.* 2023;16:915-932.

Anti-TSLP for patients with AERD

AAER over 52 weeks in patients with or without AERD NAVIGATOR study



Change from baseline in SNOT-22 total score over 52 weeks in patients with AERD



AAER=annualized asthma exacerbation rate

Laidlaw TM et al. *JACI IP In Press*.

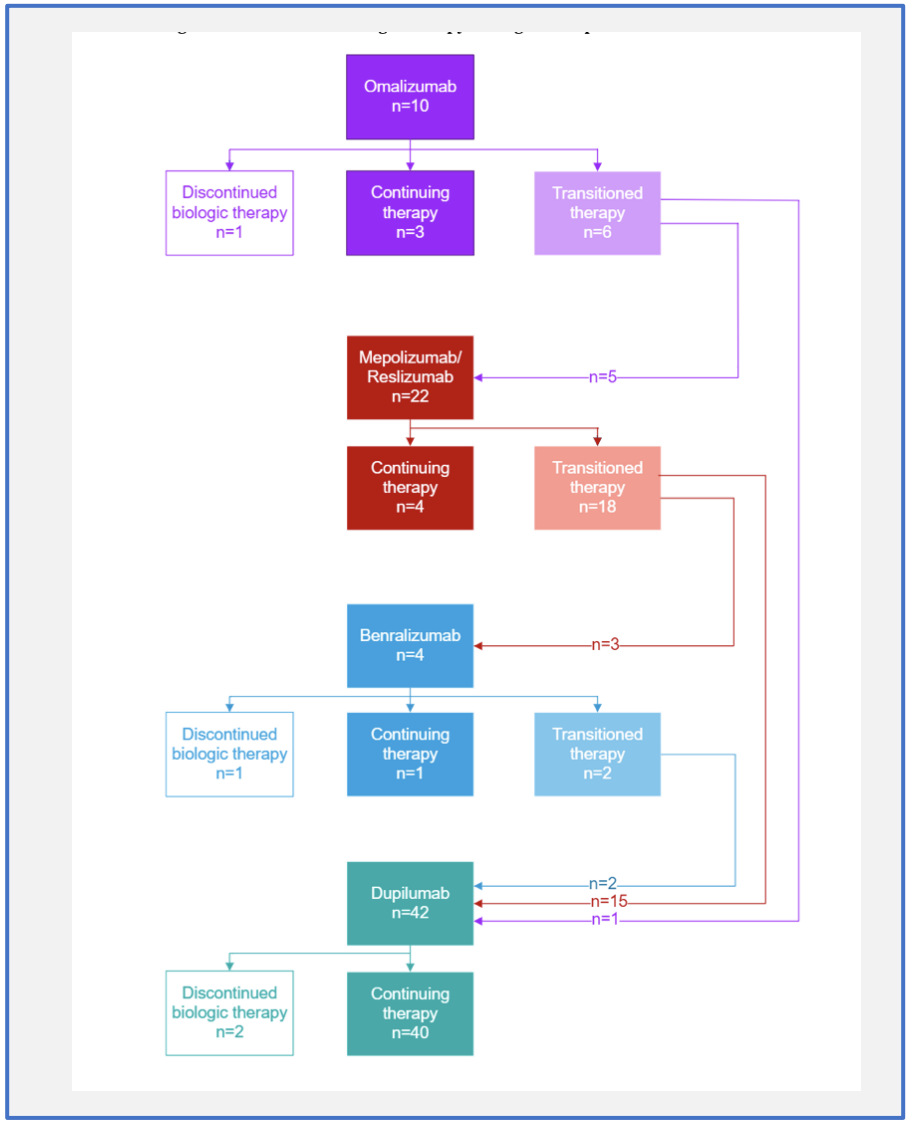
Meta-analysis of 29 RCTs: Efficacy of biologics for CRSwNP*

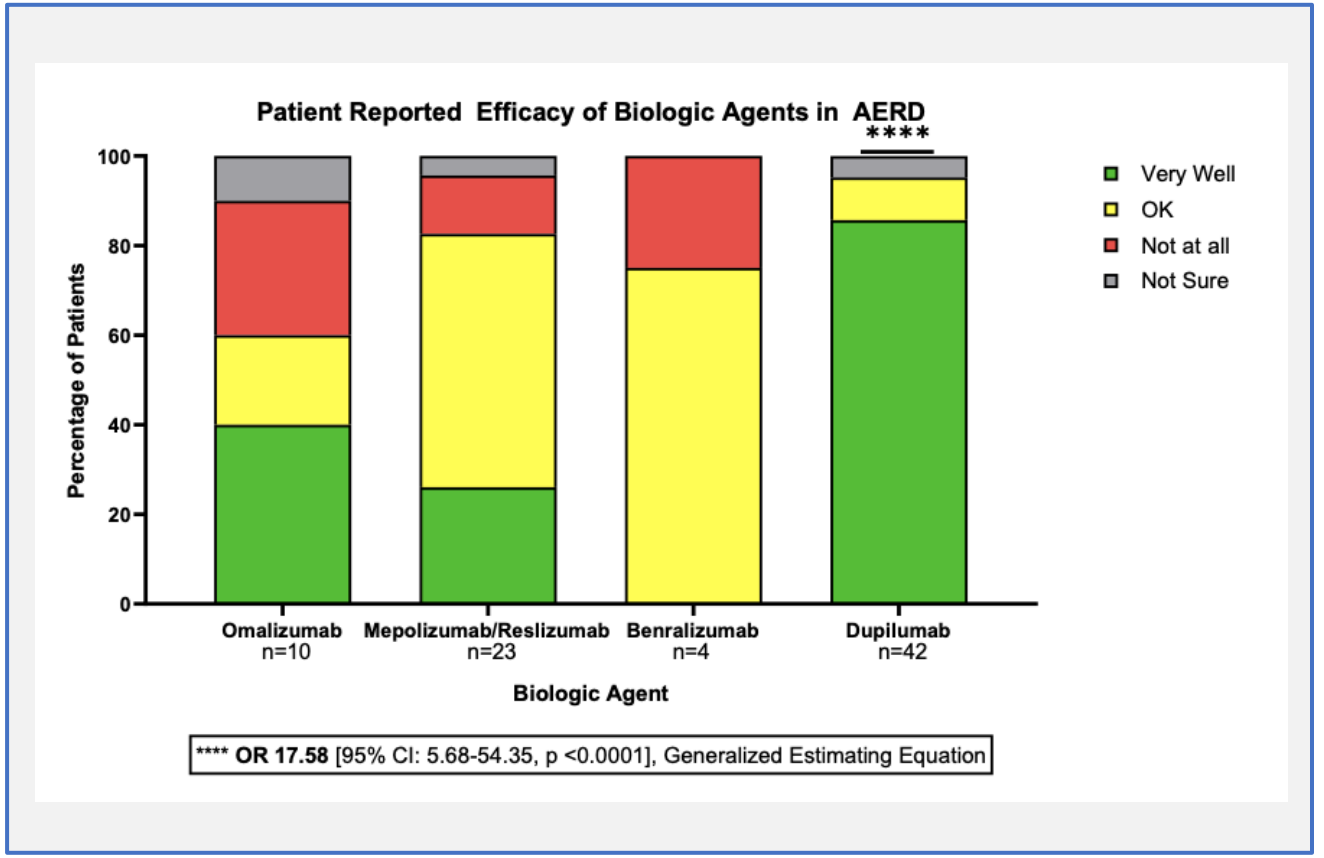
	Patient-important outcomes						Surrogate outcomes	
	HRQoL SNOT-22 (0-110)‡	Symptoms VAS (0-10 cm)	Smell UPSIT (0-40) †	Rescue OCS	Rescue polyp surgery	Adverse events	Nasal polyp size (0-8)	CT score LMK (0-24)
Standard care*	50.11	6.84	14.04	31.96%	21.05%	73.78%	5.94	18.35
Dupilumab	**-19.91** (-22.50, -17.32)	**-3.25** (-4.31, -2.18)	**10.96** (9.75, 12.17)	**-21.73** (-24.61, -18.22) RR 0.32 (0.23, 0.43)	**-16.35** (-18.13, -13.48) RR 0.22 (0.14, 0.36)	**0.13** (-8.12, 9.88) RR 1.00 (0.88, 1.13)	**-2.04** (-2.73, -1.35)	**-7.51** (-10.13, -4.89)
Omalizumab	**-16.09** (-19.88, -12.30)	**-2.09** (-3.15, -1.03)	**3.75** (2.14, 5.35)	**-12.46** (-23.65, 12.78) RR 0.61 (0.26, 1.40)	**-7.40** (-11.04, -2.43) RR 0.65 (0.48, 0.88)	**-2.60** (-15.58, 13.28) RR 0.96 (0.79, 1.18)	**-1.09** (-1.70, -0.49)	**-2.66** (-5.70, 0.37)
Mepolizumab	**-12.89** (-16.58, -9.19)	**-1.82** (-3.13, -0.50)	**6.13** (4.07, 8.19)	**-10.23** (-15.98, -2.88) RR 0.68 (0.50, 0.91)	**-12.33** (-15.56, -7.22) RR 0.41 (0.26, 0.66)	**-3.07** (-13.44, 9.07) RR 0.96 (0.82, 1.12)	**-1.06** (-1.79, -0.34)	
Benralizumab	**-7.68** (-12.09, -3.27)	**-1.15** (-2.47, 0.17)	**2.95** (1.02, 4.88)	**-9.91** (-16.30, -0.96) RR 0.69 (0.49, 0.97)	**-2.53** (-9.05, 7.16) RR 0.88 (0.57, 1.34)	**-1.48** (-13.28, 12.54) RR 0.98 (0.82, 1.17)	**-0.64** (-1.39, 0.12)	**-1.00** (-3.83, 1.83)
Reslizumab					**-18.82** (-20.93, 20.56) RR 0.11 (0.01, 1.98)	**-2.55** (-19.49, 19.18) RR 0.97 (0.74, 1.26)		
AK001						**2.54** (-27.11, 51.03) RR 1.03 (0.63, 1.69)	**-0.20** (-1.61, 1.21)	
Etokimab	**-1.30** (-8.99 to 6.40)					**188.14** (-59.76, 4879.1) RR 3.55 (0.19, 67.13)	**-0.33** (-1.58, 0.92)	
ASA Desensitization	**-10.61** (-14.51, -6.71)	**-2.74** (-3.92, -1.57)	**2.72** (-1.17, 6.61)		**-16.00** (-19.79, 0.21) RR 0.24 (0.06, 1.01)	**209.21** (8.30, 901.87) RR 3.84 (1.11, 13.22)	**-0.95** (-2.44, 0.55)	**-0.31** (-3.50, 2.88)

Classification of intervention (colour)[24]				Certainty (shading)[24, 29]
Among most beneficial	Among intermediate beneficial	Among least beneficial/not clearly different from placebo	No data (blank)	High/moderate (solid)
Among most harmful	Among intermediate harmful			Low/very low (shaded)

*Does not include tezepelumab or depemokimab studies

AERD: Patient reported outcomes – biologic efficacy





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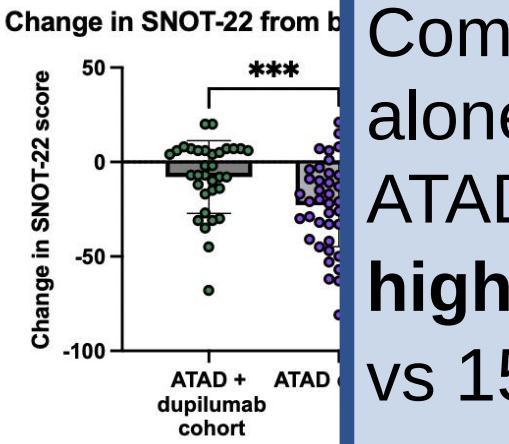
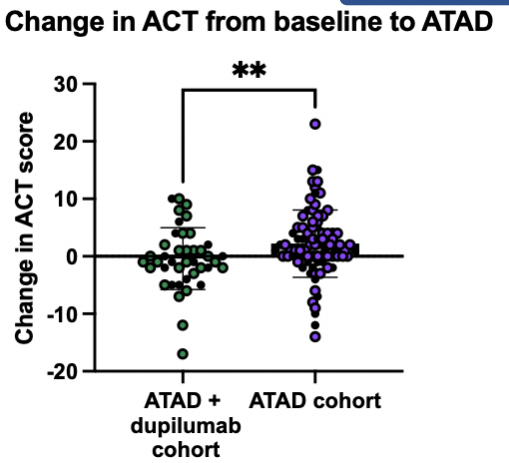
Possible role for IgE in predicting response to aspirin therapy after desensitization (ATAD) in patients with AERD

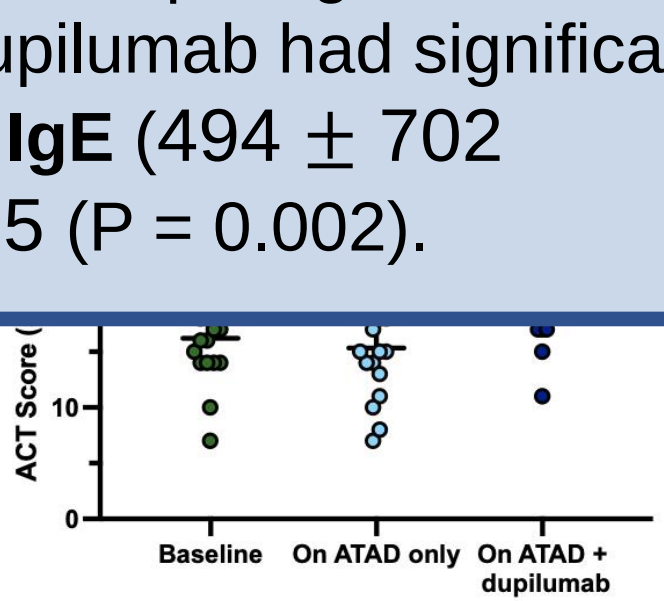
SNOT-22 and ACT scores obtained prior to initiation of any biologic

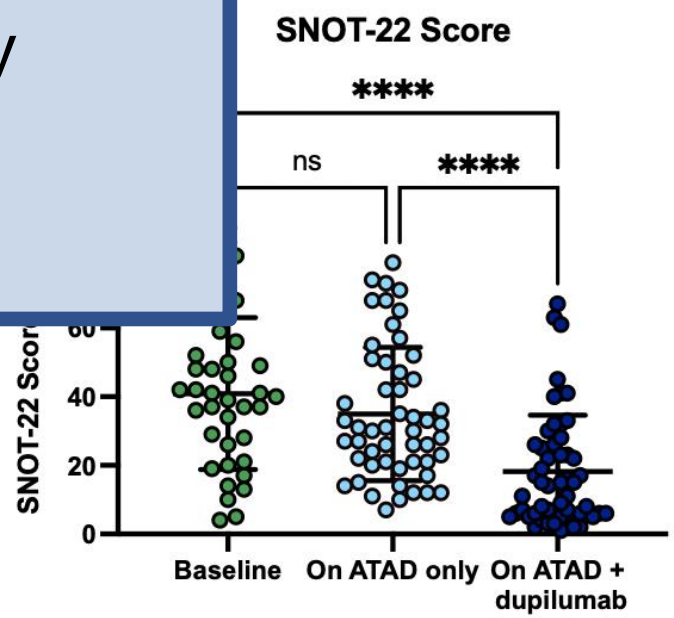




Changes in SNOT-22 and ACT scores at baseline, on ATAD, and on ATAD + dupilumab in patients AD + dupilumab

Compared to patients who did well on ATAD alone, patients requiring co-treatment with ATAD and dupilumab had significantly **higher total IgE** (494 ± 702 vs 155 ± 355 (P = 0.002).





Achanta and Buchheit, 2025 Unpublished data.

Conclusions: Biologic therapy for CRSwNP and AERD

- Biologic agents lead to substantial improvement CRSwNP and AERD quality of life and reduction in inflammatory disease burden.
- Systematic reviews and indirect treatment comparisons, while limited, suggest dupilumab is most efficacious for CRSwNP of current US FDA approved agents.
  - Head-to-head studies will further address this question.
- Future studies focused on biomarker-based endotyping and responder analyses will allow for optimization of personalized treatment for CRSwNP.