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Clinical Remission in Asthma: What is it? Is it an achievable Goal of Therapy?

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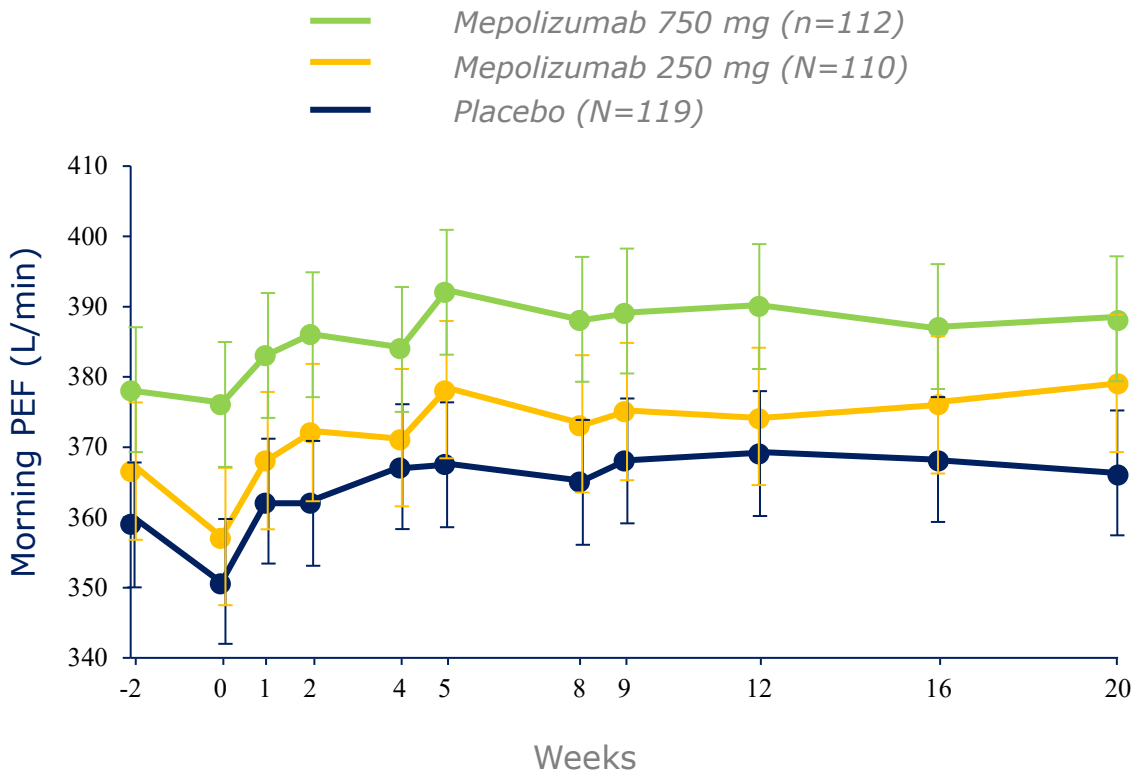
Disclosures

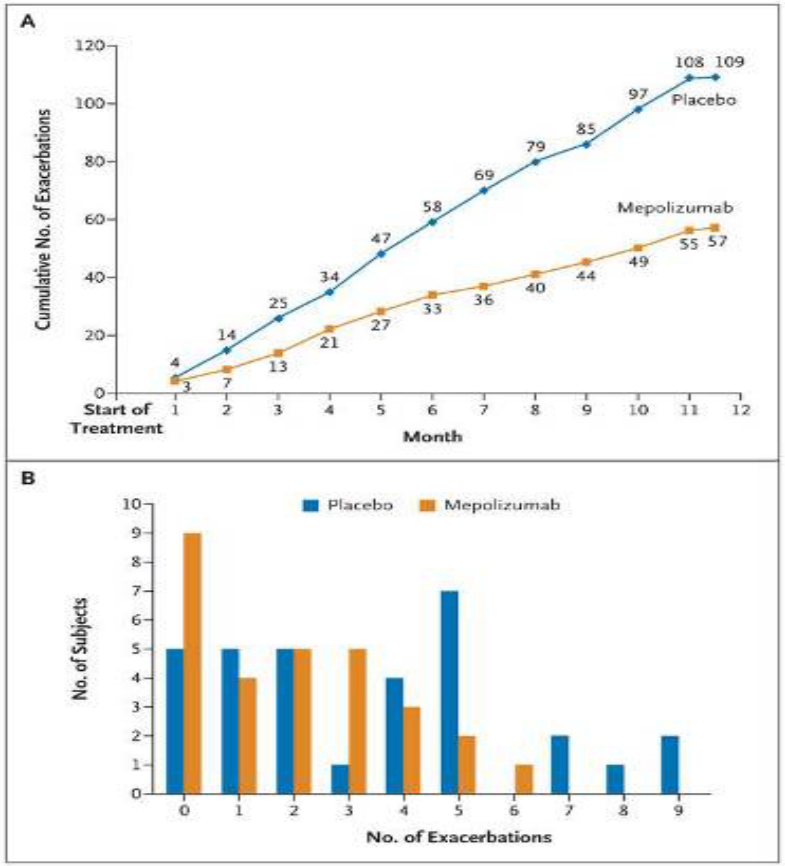
- **Speaker's Honoraria:** AstraZeneca, Aerocrine, Chiesi, Novartis, Sanofi, Regeneron and GSK.
- **Advisory Panels:** AstraZeneca, GSK, MSD, Novartis, Areteia, Aerocrine, Sanofi and Regeneron.

Outline

- The clinical development of biologics in severe asthma and an answer to the ‘in whom is this treatment effective’ question
- More ambitious goals of treatment are within target
- Remission as a goal for severe asthma therapy.

Mepolizumab (anti-IL-5): effect in 'asthma' and eosinophilic airways disease

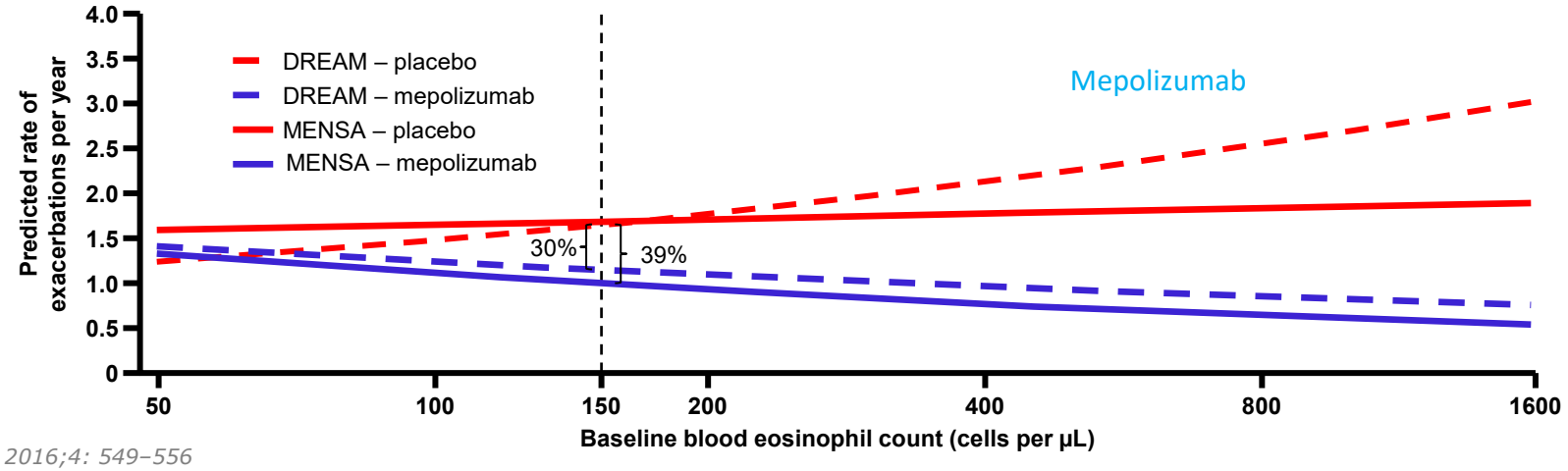




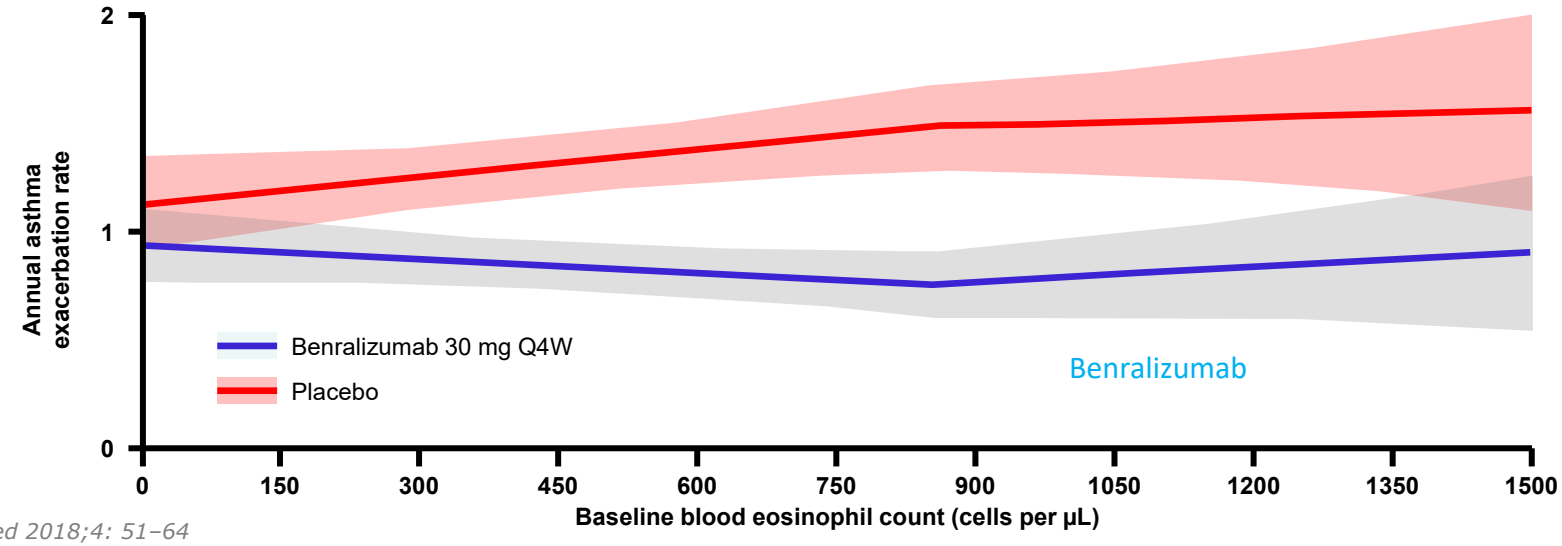
Flood-Page et al. AJRCCM 2007;176:1062-71

Haldar et al. NEJM 2009;360:973-84

Relationship between blood eosinophils and response to anti-IL-5

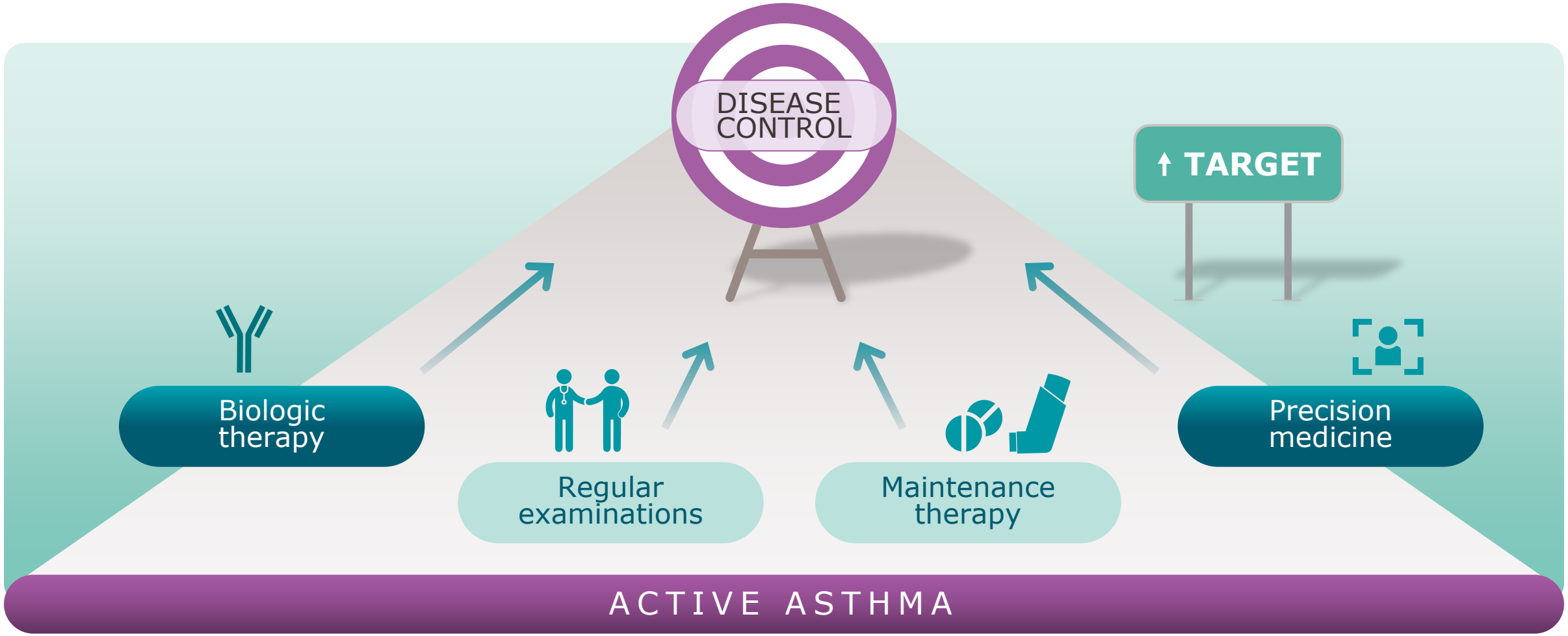


Ortega et al. Lancet Respir Med 2016;4: 549–556



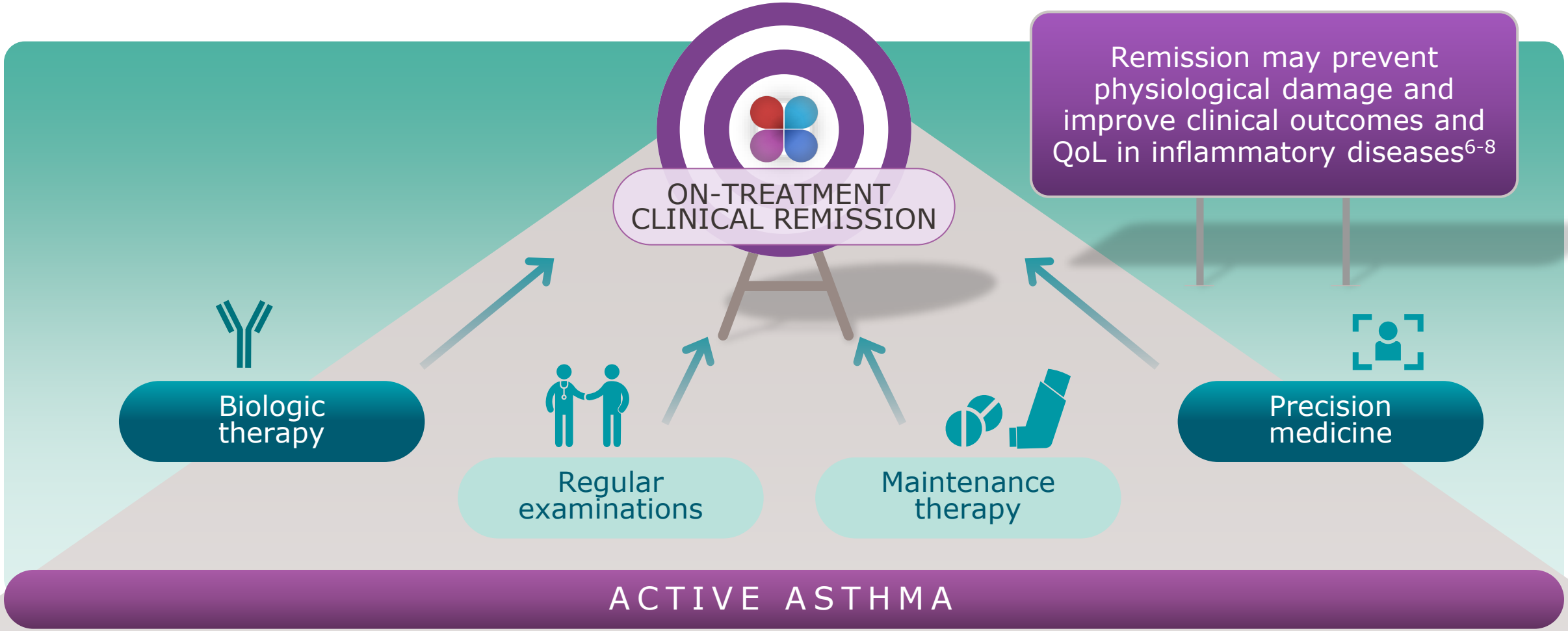
FitzGerald et al. Lancet Respir Med 2018;4: 51–64

On-Treatment Clinical Remission Is a New Target in Asthma, Beyond Disease Control[1-8]



1. Lommatzsch M, et al. *Lancet*. 2022;399(10335):1664-1668. 2. Crompton G. *Prim Care Respir J*. 2006;15(6):326-331. 3. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Updated May 2023. Accessed July 15, 2023. https://ginasthma.org/2023-gina-main-report/. 4. Canonica GW, et al. *Curr Opin Allergy Clin Immunol*. 2018;18(1):51-58. 5. Menzies-Gow A, et al. *J Allergy Clin Immunol.* 2020;145(3):757-765. 6. Ostor AJ, et al. *Adv Ther*. 2022;39(1):75-93. 7. Pawlak-Buś K, Leszczyński P. *Reumatologia.* 2022;60(2):125-132. 8. Ungaro RC, et al. *Gastroenterology.* 2020;159(1):139-147.

On-Treatment Clinical Remission Is a New Target in Asthma, Beyond Disease Control[1-8]



QoL, quality of life.

1. Lommatzsch M, et al. *Lancet*. 2022;399(10335):1664-1668. 2. Crompton G. *Prim Care Respir J*. 2006;15(6):326-331. 3. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Updated May 2023. Accessed July 15, 2023. https://ginasthma.org/2023-gina-main-report/. 4. Canonica GW, et al. *Curr Opin Allergy Clin Immunol*. 2018;18(1):51-58. 5. Menzies-Gow A, et al. *J Allergy Clin Immunol.* 2020;145(3):757-765. 6. Ostor AJ, et al. *Adv Ther*. 2022;39(1):75-93. 7. Pawlak-Buś K, Leszczyński P. *Reumatologia.* 2022;60(2):125-132. 8. Ungaro RC, et al. *Gastroenterology.* 2020;159(1):139-147.

Time for more ambitious composite outcome measures?

- Better reflect broad impact of treatment
- Helps to 'market' severe asthma as a treatable problem to payers
- Reflects an ambitious goal and a state that might be associated with disease modification
- Provides a rationale for earlier intervention

Clinical Remission on Treatment

For ≥12 months:

- Sustained absence of significant asthma symptoms based on validated instrument, **and**
- Optimization and stabilization of lung function, **and**
- Patient and HCP agreement regarding disease remission, **and**
- No use of systemic corticosteroid therapy for exacerbation treatment or long-term disease control

Clinical Remission off Treatment

Same criteria maintained without asthma treatment for ≥12 months

Complete Remission on Treatment

Clinical remission plus the following:

- Current, objective evidence of the resolution of previously documented asthma-related inflammation (eg, reduced blood or sputum eosinophil counts, FENO, and/or other relevant measures), **and**
- In appropriate research settings: Current negative bronchial hyperresponsiveness

Complete Remission off Treatment

Same criteria maintained without asthma treatment for ≥12 months

Menzies-Gow et al. JACI 2020

Compared with asthma control, remission represents a stricter multidimensional criteria requiring ≥12-month stability

	Asthma control[1,2a]	Remission[3,4]
1	**ppFEV$_1$≥80%**	**ppFEV$_1$≥80%** or **FEV$_1$ improvement ≥100mL** sustained for ≥12 months
2	**ACQ <1.5** or **ACT≥20**	**ACQ <1.5 (or 0.75)** or **ACT ≥20** sustained for ≥12 months
3	**<2 exacerbations requiring OCS** in the past 12 months **No hospitalization-requiring exacerbations** in the past 12 months	**No exacerbations** for ≥12 months
4	/	**No OCS treatment** for ≥12 months

[a]Source: GINA and ERS/ATS guidelines. Abbreviations: ppFEV$_1$: percent predicted forced expiratory volume in 1 second; ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; OCS: oral corticosteroids; FEV$_1$: forced expiratory volume in 1 second; GINA: Global Initiative for Asthma; ATS: American Thoracic Society; ERS: European Respiratory Society.

1. GINA 2025. 2. Chung KF, et al. Eur Respir J. 2014;43:343-373. 3. Principe S, et al. Eur Respir Rev. 2025 Apr 2;34(176):240181. 4. Shackleford A, et al. Lancet Respir Med. 2025 Jan;13(1):23-34.

What can be achieved with biologics?

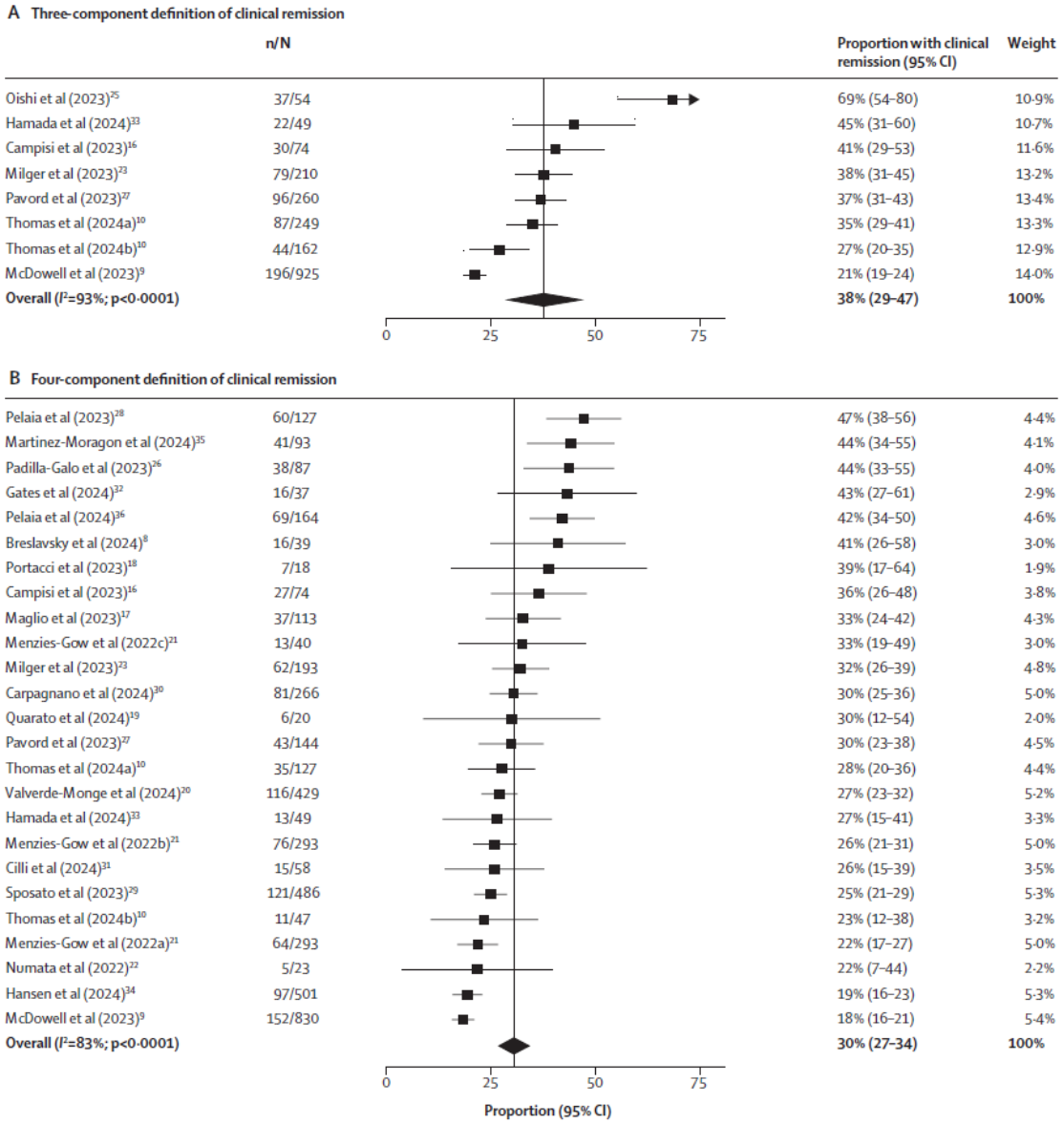
What can be achieved with biologics?

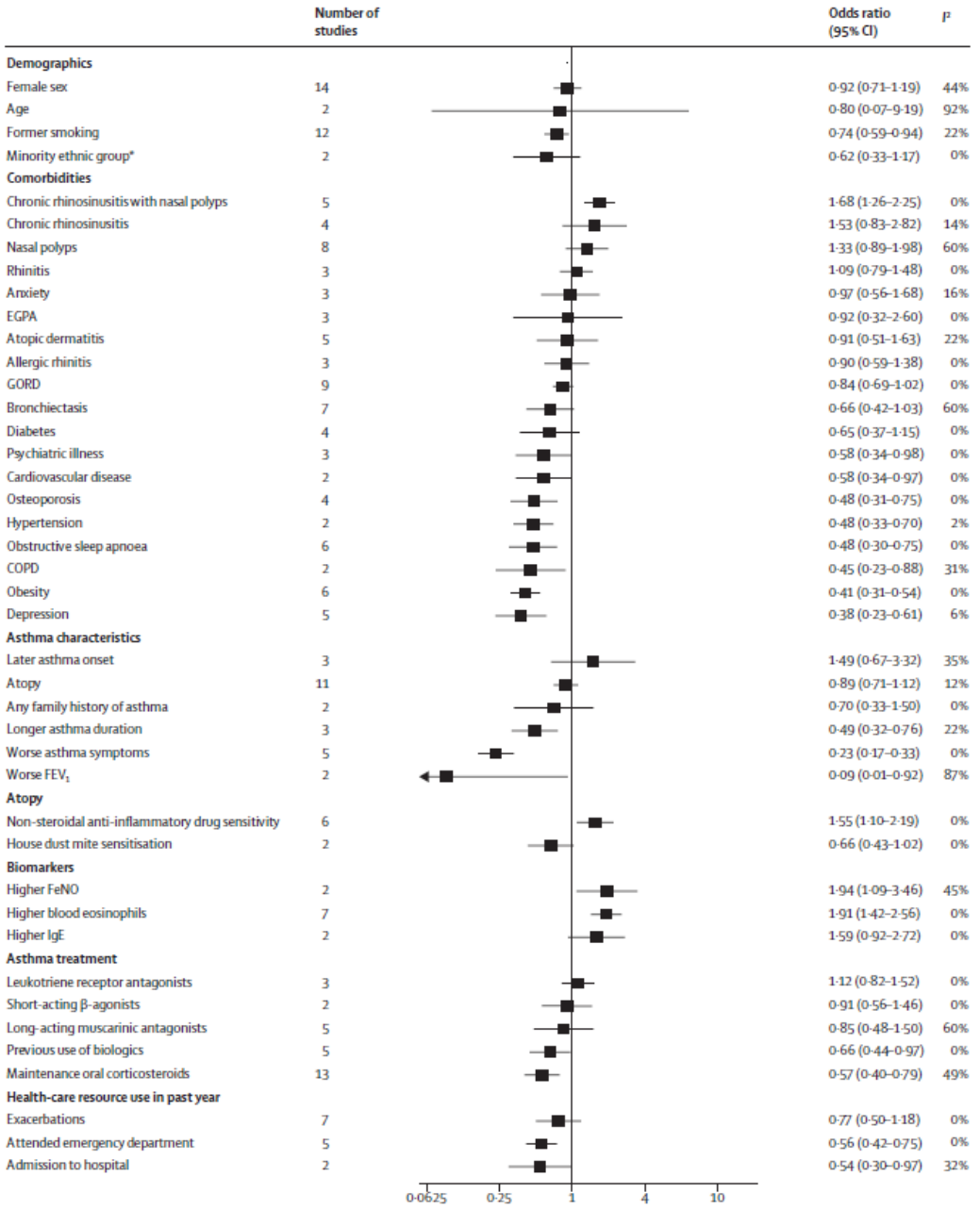
	Dupilumab	Dupilumab	Benralizumab	Benralizumab	Tezepelumab	Mepolizumab	Multiple Biologics	
	2021[1] QUEST Phase 3	2022[2] TRAVERSE OLE	2022[3] SIROCCO/CALIMA Phase 3	2022[4] ANDHI Phase 3b	2022[5] NAVIGATOR Phase 3	2022[6] REDES	2022[7] CHRONICLE	2022[8] Danish Registry
Absence of symptoms[a,b] and	ACQ-5 <1.5	ACQ-5 <1.5	ACQ-6 <1.5 or ≤0.75	ACQ-6 <1.5 or ≤0.75	ACQ-6 ≤0.75[a,b]	ACT ≥ 20	Majority≥ (50%) ACT ≥ 20	ACQ ≤ 1.5
Optimized/ stabilized lung function and	Post-BD FEV_1pp ≥80%	Post-BD FEV_1 ≥80% *OR* pre-BD FEV_1 ≥100 mL	Pre-BD FEV_1 increase ≥100 mL	Pre-BD FEV_1 increase ≥100 mL	Pre-BD FEV_1pp >80% *OR* Pre-BD FEV_1 >20% from baseline	Not included	Not included	Post-BD FEV_1pp ≥80%
No exacerbations; no OCS[c]	✓	✓	✓	✓	✓[d]	✓	✓	✓
Prevalence of clinical remission	31.7%	36.4%	14.5%	28.7%	12.7%	37%	35%	19%

[a]Sustained absence of significant asthma symptoms based on validated instrument; [b]There should be agreement between the HCP and patient regarding symptom improvement and remission; [c]No OCS use for exacerbations *OR* long-term disease control; [d]In this analysis, exacerbations and OCS use were individually evaluated· ACQ:Asthma Control Questionnaire; ACT, Asthma Control Test; BD, bronchodilator; FEV_1, forced expiratory volume in 1 second; HCP, healthcare provider; OCS, oral corticosteroid; OLE, open-label extension; pp, percent predicted

1. Pavord ID, et al. Poster presented at ACAAI, November 4–8, 2021, New Orleans, LA, USA; 2. Pavord ID, et al. Poster presented at ASCIA, August 30–September 2, 2022, Melbourne, Australia; 3. Menzies-Gow A, et al. Adv Ther 2022;39:2065–2084; 4. Harrison T, et al. Presented at ATS International Conference, May 13–18, 2022, San Francisco, CA, USA. Poster 625; 5. Castro M, et al. Poster presented at ERS, September 4–6, 2022, Barcelona, Spain; 6. Ribas DC et al. Drugs 2021;81(15):1763-1774. 7. Chipps, B et al. JACI 2022;149:Suppl AB147 8. Hansen S et al ERJ 2022;60:3553

Remission on biologics in severe asthma: a meta-analysis

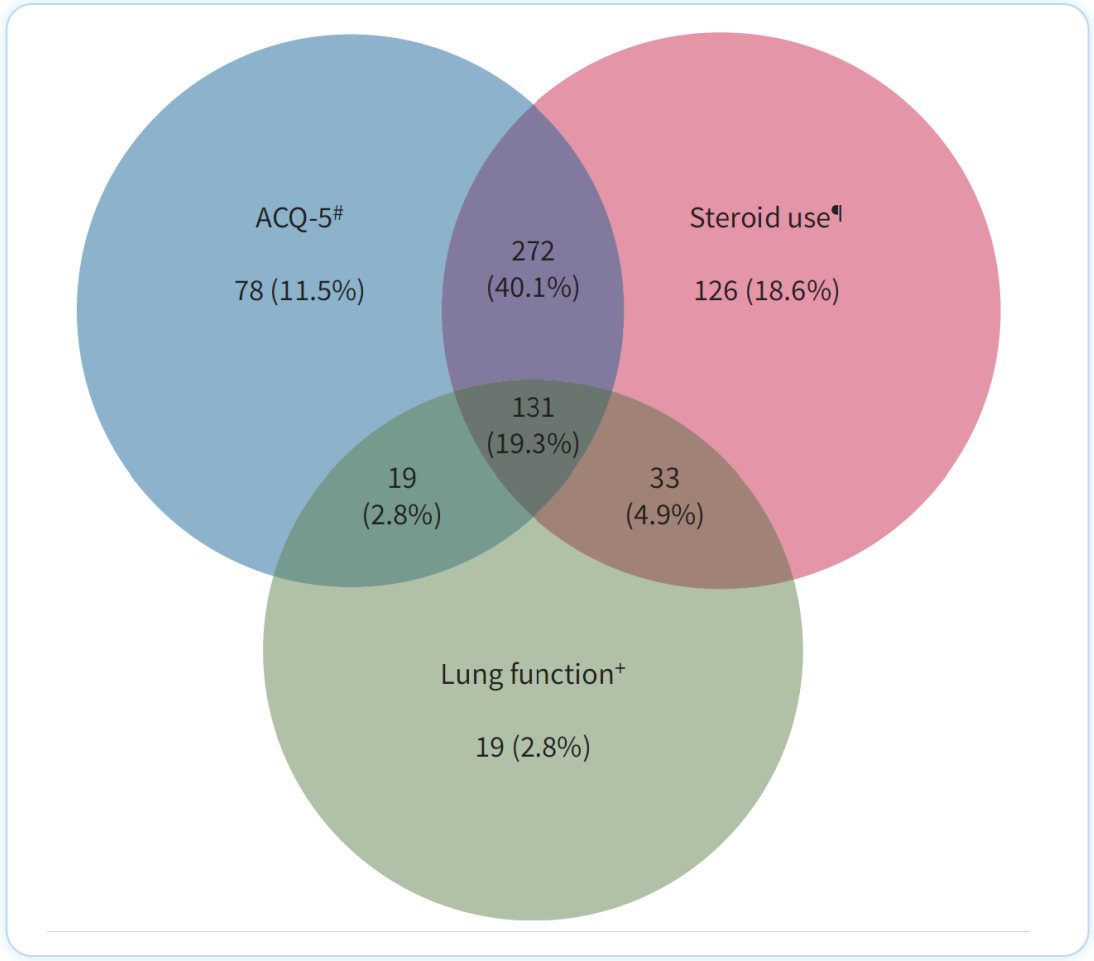


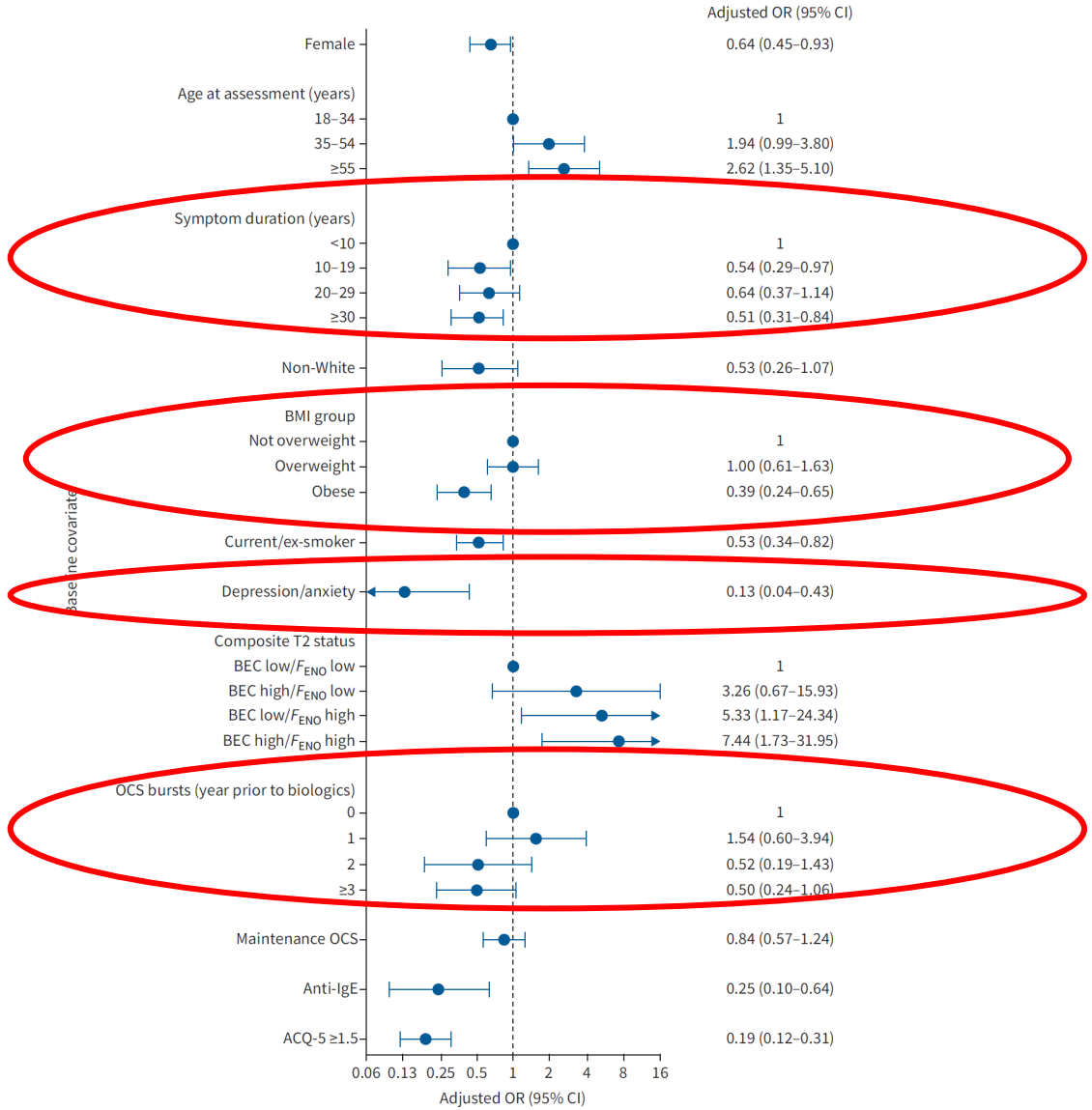


Shackleford et al. Lancet Resp Med 2025;13:23-34

How can we achieve remission more often?

Clinical remission on biologics in severe asthma in UK

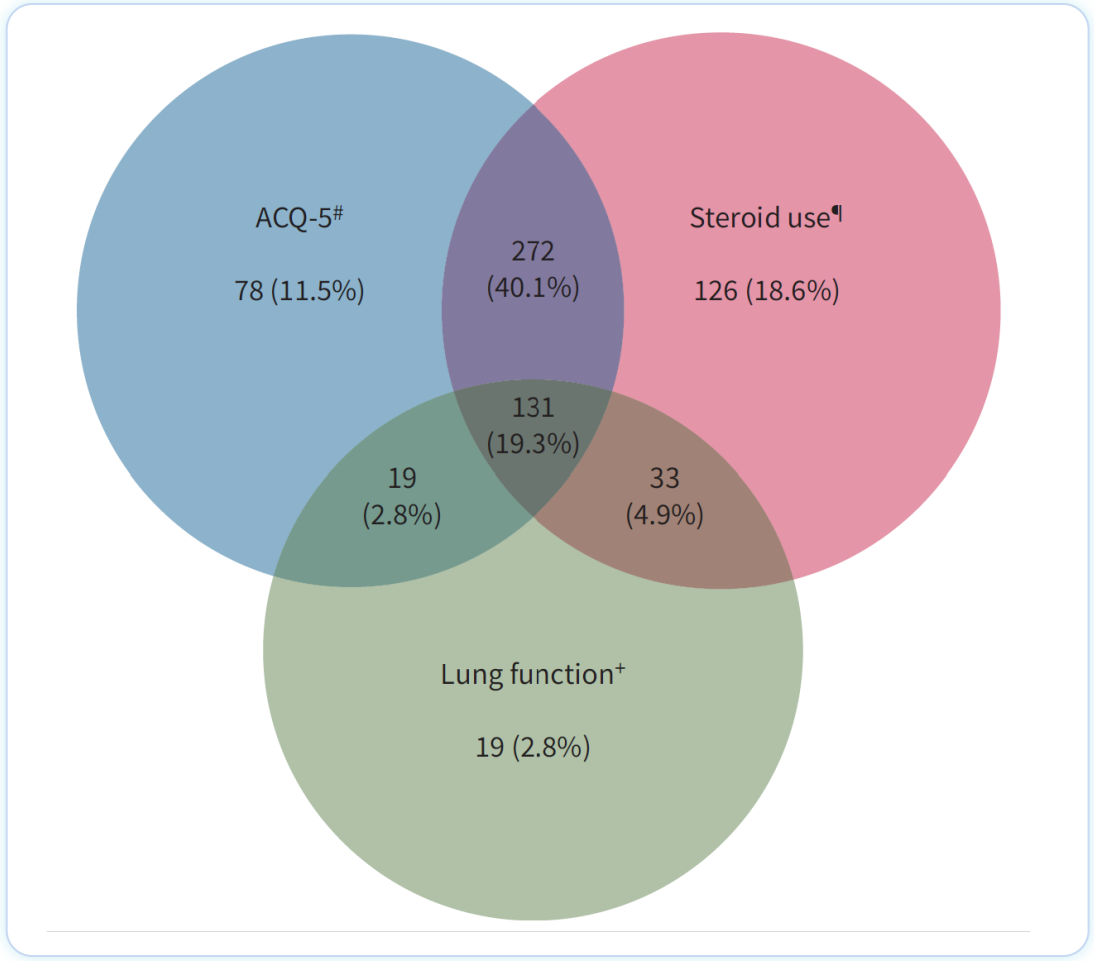


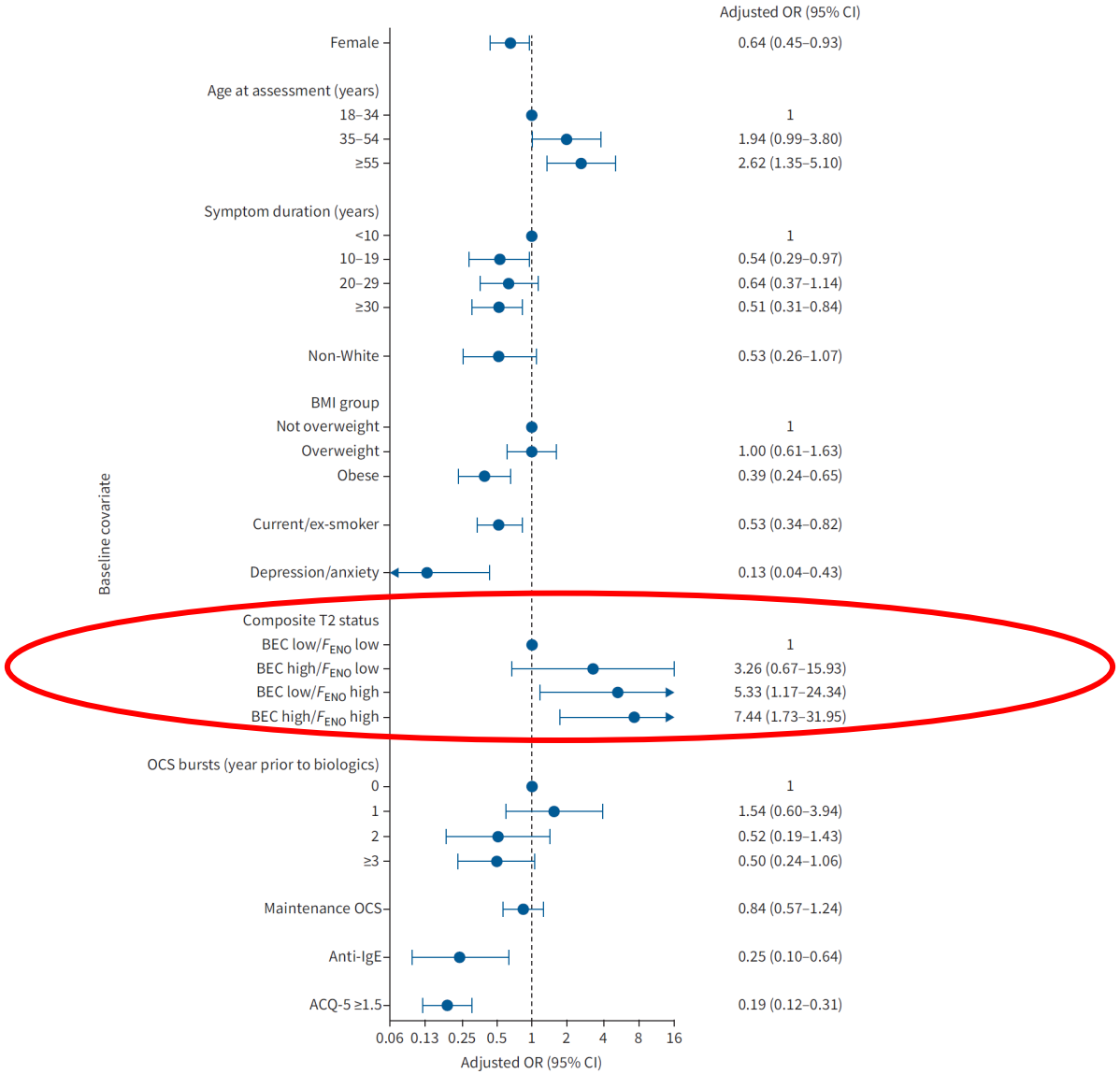


#: ACQ-5 ⩾1.5; ¶: at least one exacerbation and/or maintenance oral corticosteroids >5 mg;
+: forced expiratory volume in 1 s below lower limit of normal and >100 mL less than baseline.

McDowell et al. Clinical remission in severe asthma with biologic therapy: an analysis from the UK Severe Asthma Registry. Eur Respir J. 2023 Dec 14;62(6):2300819.ERJ 2023.

Clinical remission on biologics in severe asthma in UK





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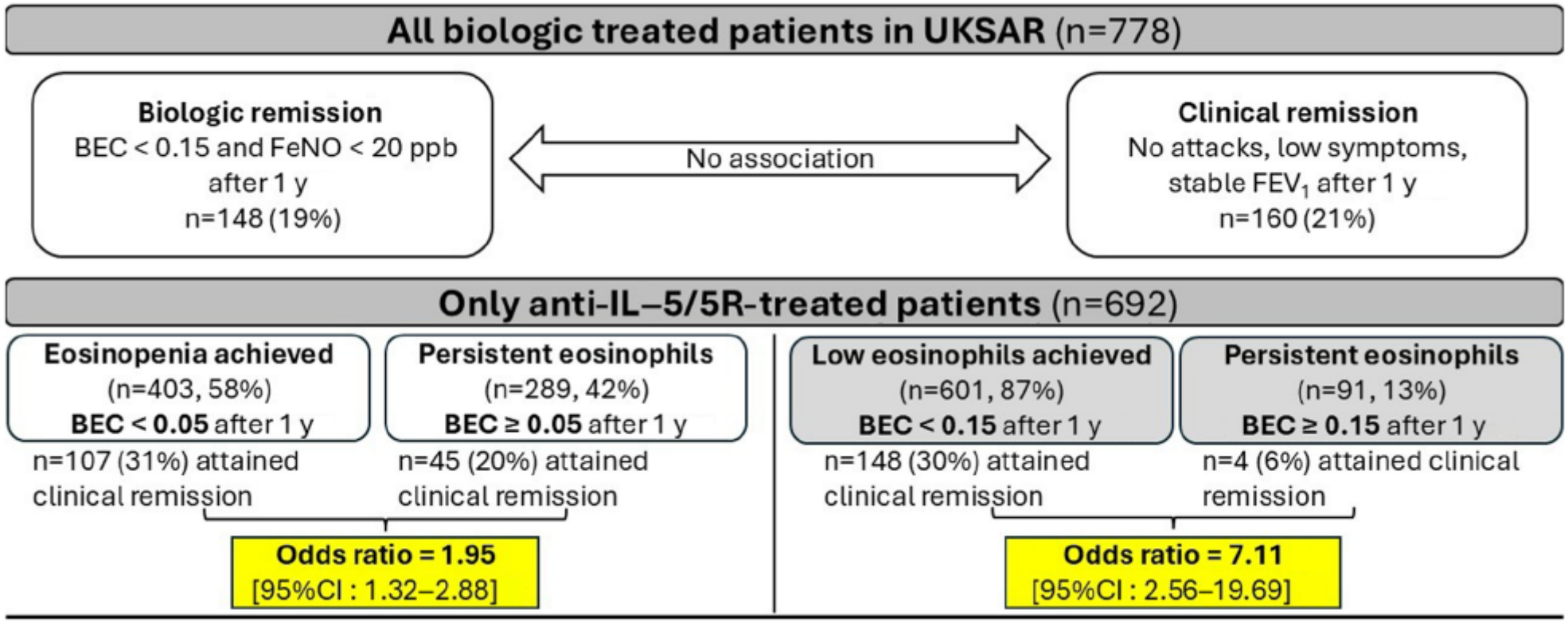
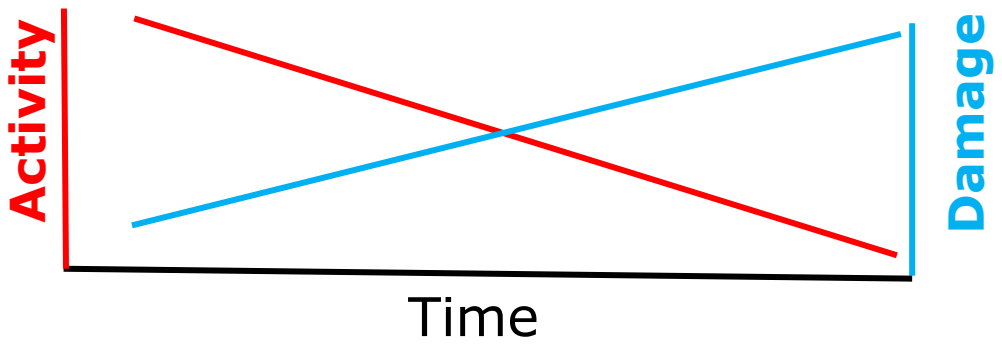
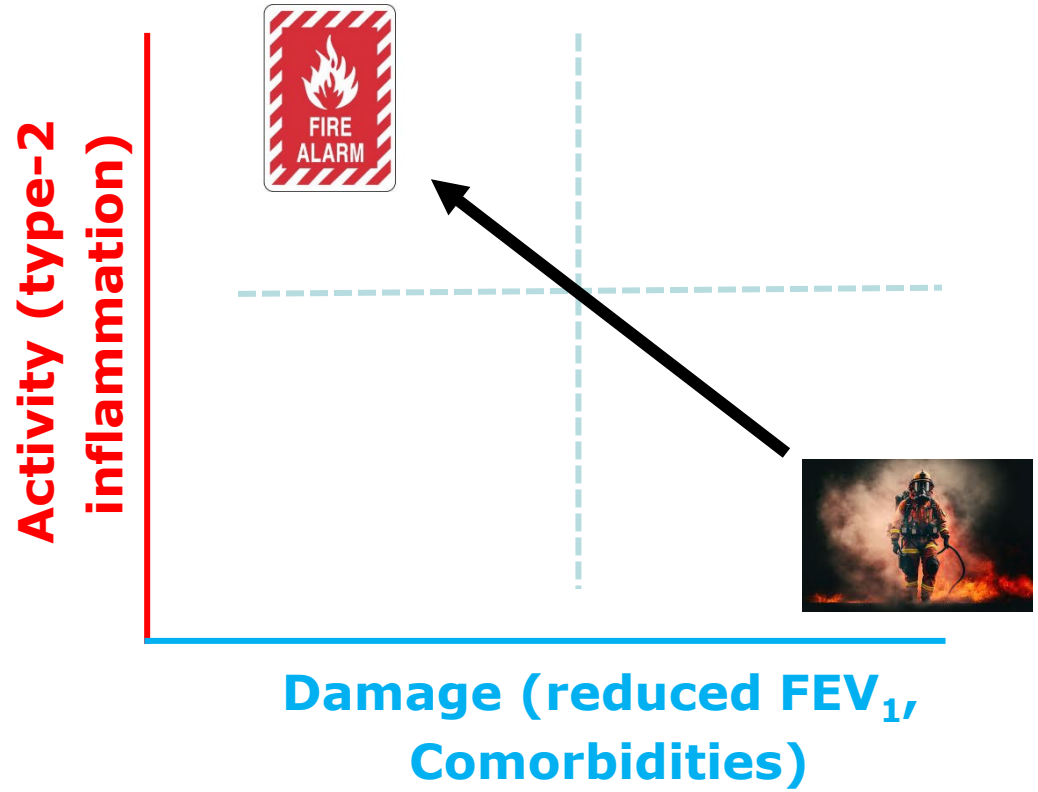
How low should you go? Biological vs clinical remission in asthma



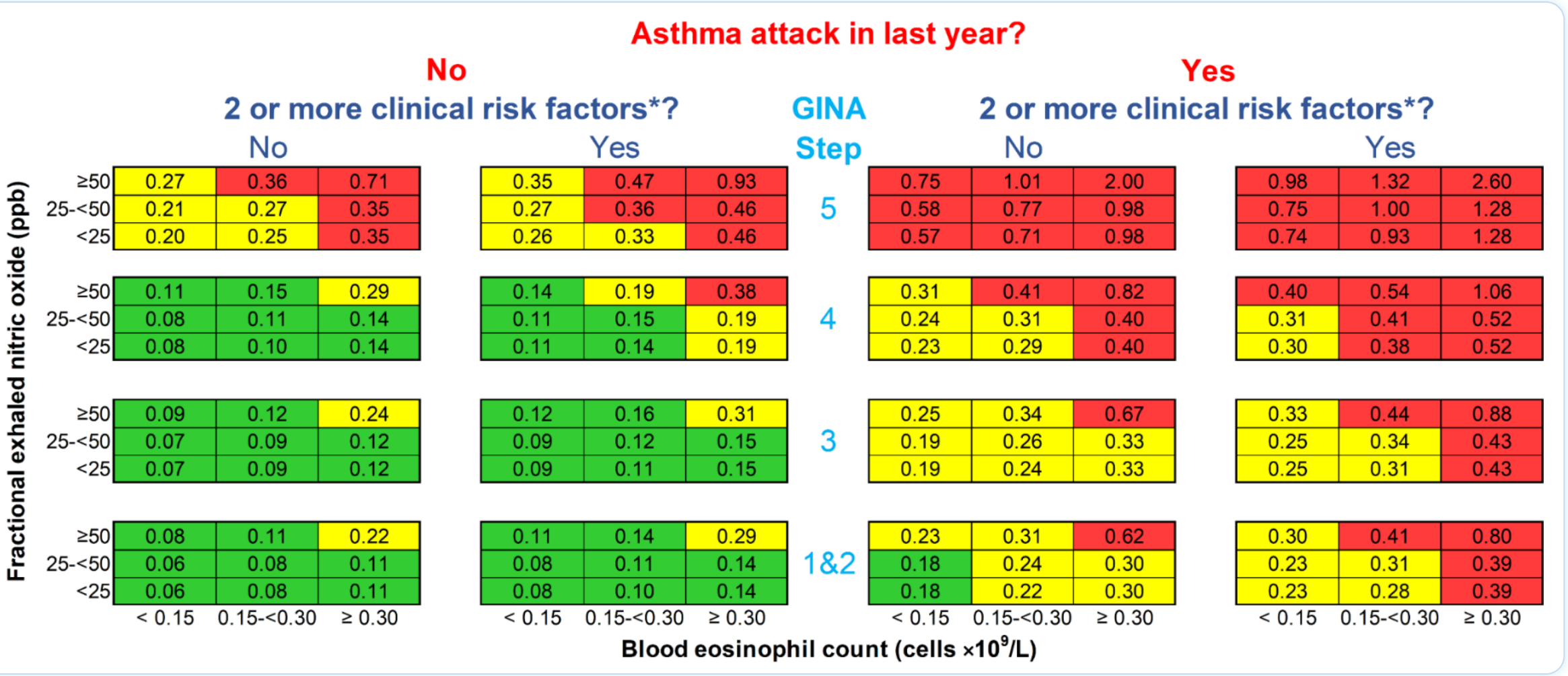
McDowell et al. J Allergy Clin Immunol Pract 2025;13:3765-73; St Pierre & Couillard. J Allergy Clin Immunol Pract 2025;13:3274-6

We need to move the focus from damage to activity





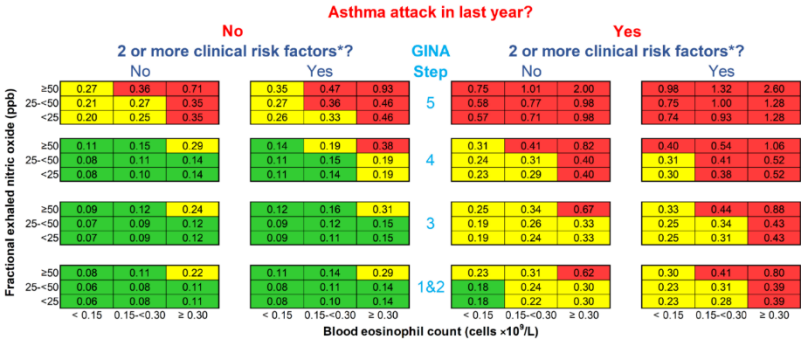
The Oxford Risk of Asthma attaCk scaLE (ORACLE)



Couillard et al. Thorax 2022

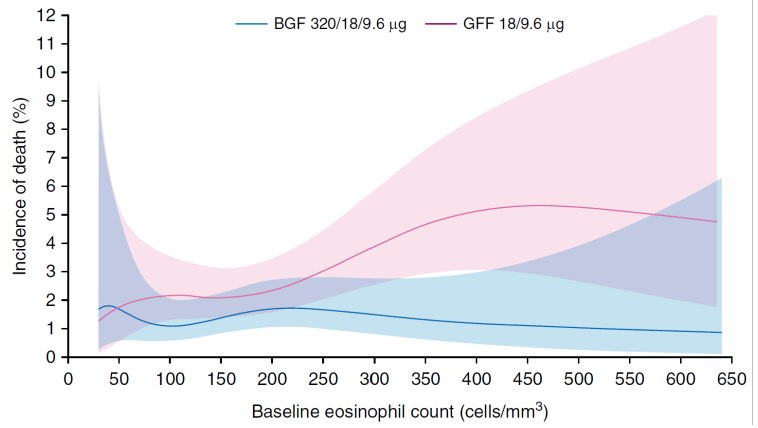
Type-2 airway inflammation kills and maims people

Asthma attack risk



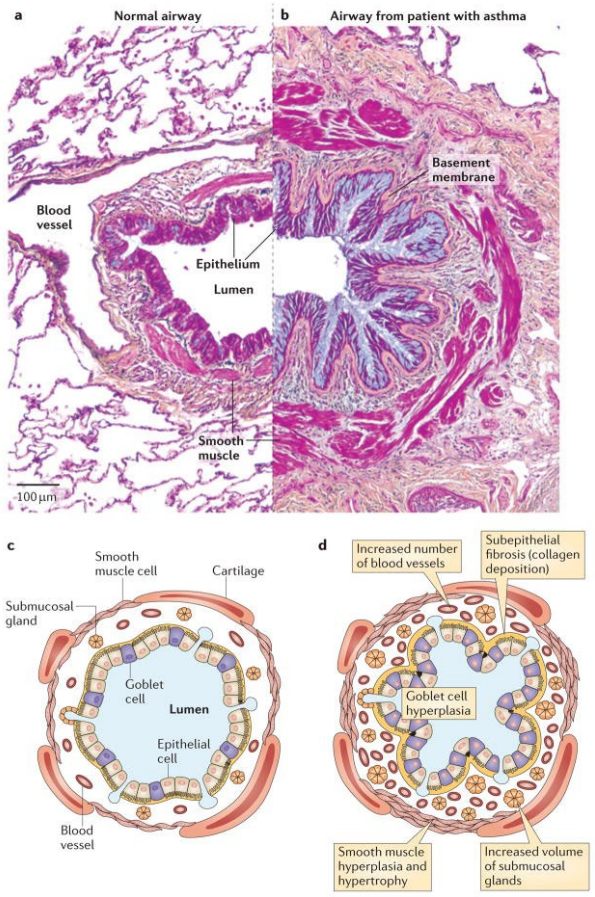
Couillard et al. Thorax 2022

Risk of death



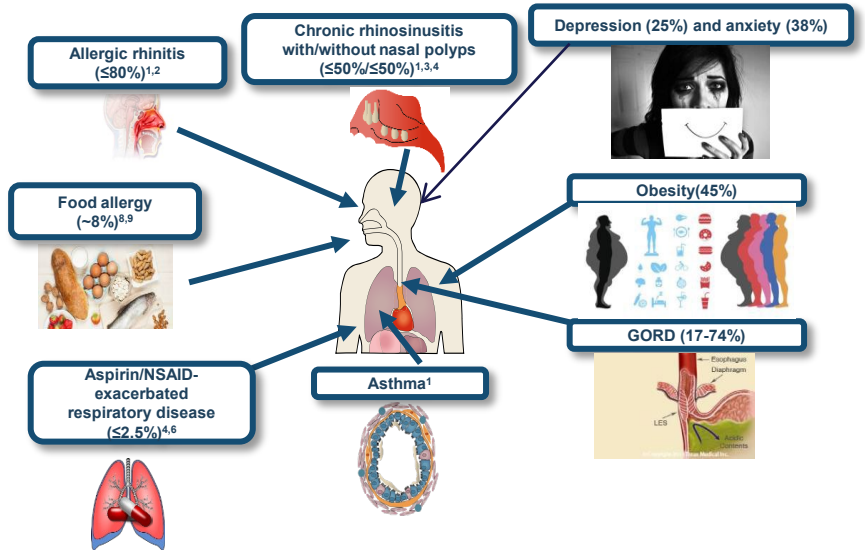
Martinez et al. AJRCCM 2021

Airway remodelling



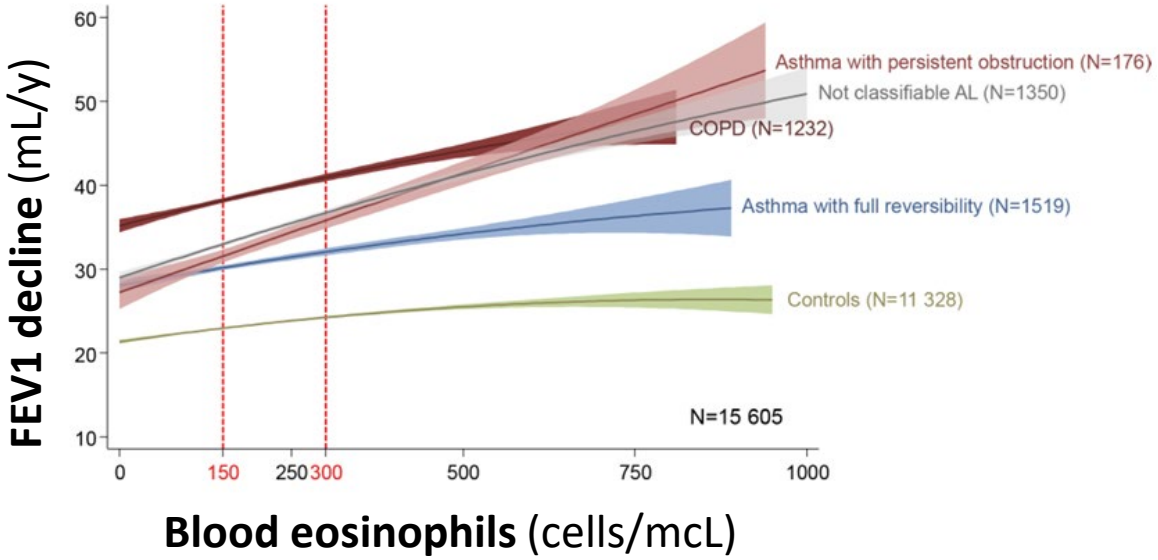
Fahy. Nature Rev Immunol 2015

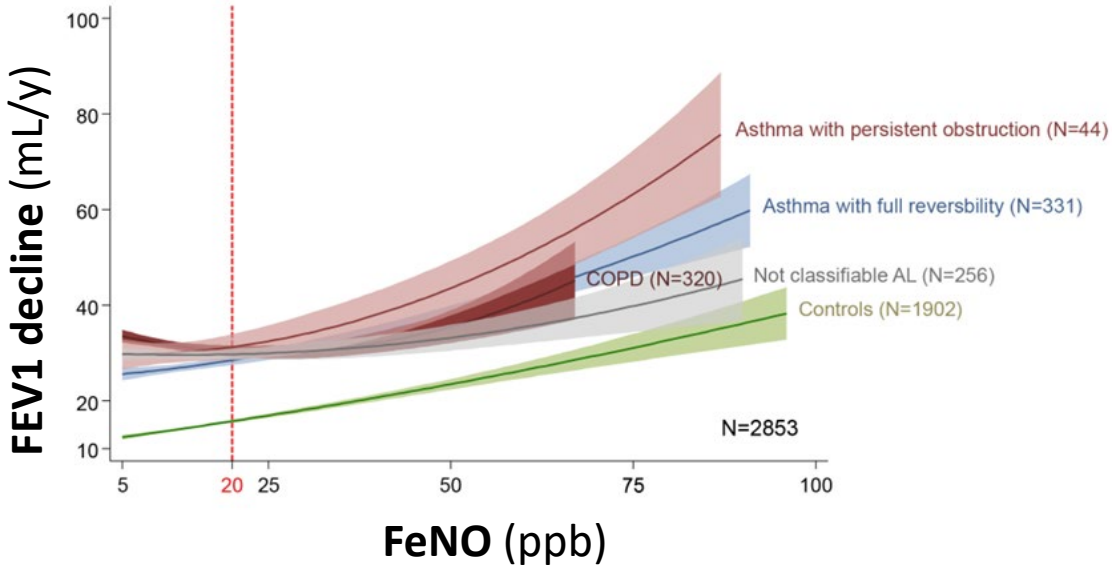
People remodelling

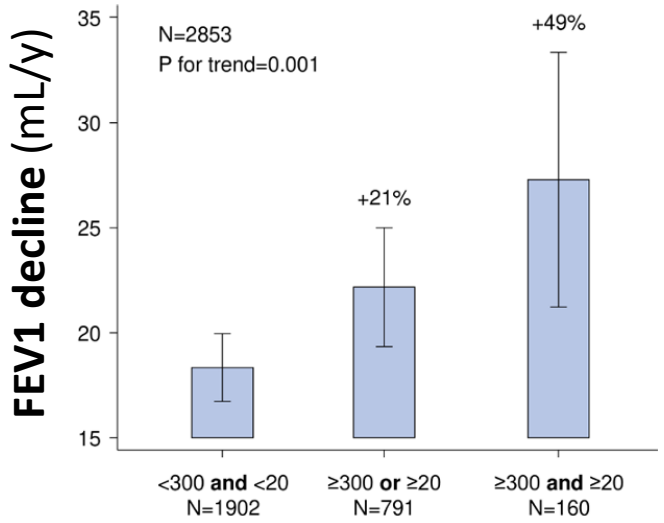


Couillard et al. JACI in practice 2022

Two biomarkers are associated with FEV1 decline

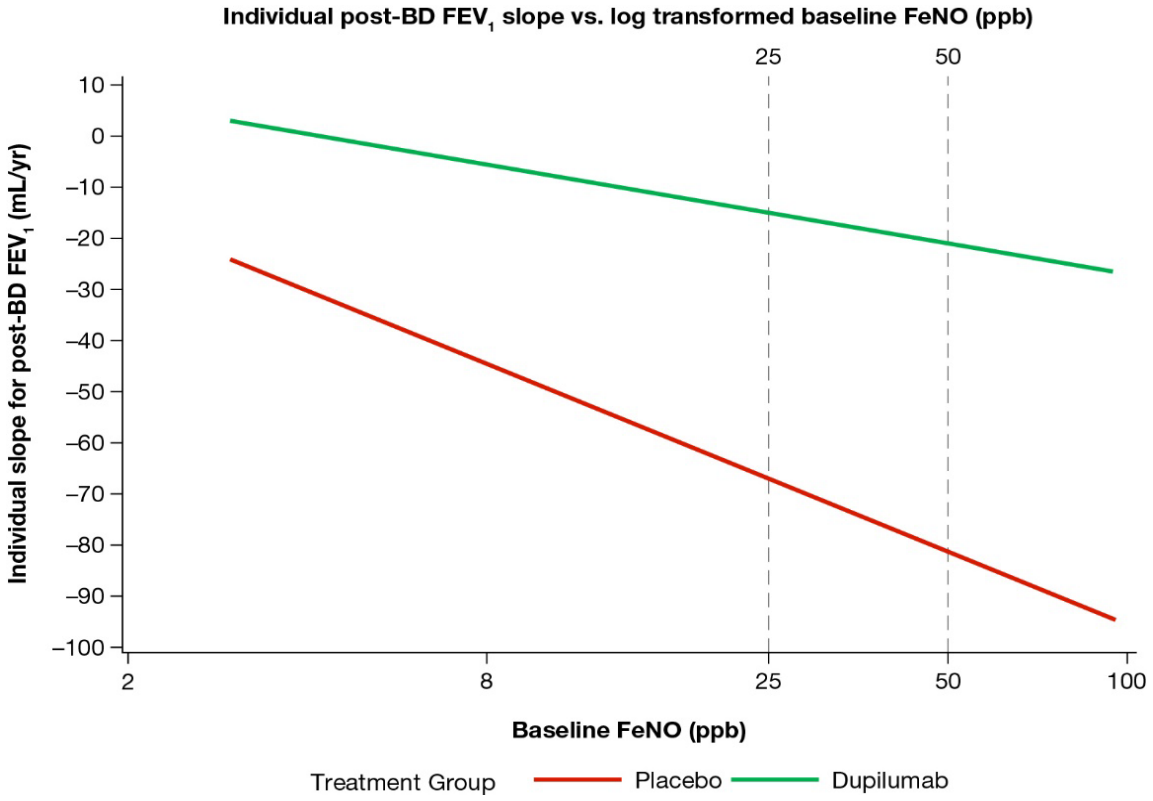






Colak et al Thorax 2024

Relationship between FeNO and decline in FEV_1: a post-hoc analysis of the QUEST study



Treatment	Subgroup	Post-BD FEV_1 change (mL/year)* Blood eosinophils (cells/µL) <150	≥150	≥300
Placebo	FeNO <25	**−49** (SE=26) (N=104)	**−56** (SE=19) (N=187)	**−71** (SE=27) (N=90)
Dupilumab	FeNO <25	**−12** (SE=17) (N=253)	**−17** (SE=14) (N=363)	**−35** (SE=20) (N=173)
Placebo	FeNO ≥25	**−116** (SE=37) (N=53)	**−47** (SE=20) (N=253)	**−59** (SE=24) (N=181)
Dupilumab	FeNO ≥25	**4** (SE=29) (N=99)	**−23** (SE=15) (N=475)	**−30** (SE=18) (N=334)
Placebo	FeNO ≥50	**−102** (SE=70) (N=20)	**−122** (SE=36) (N=109)	**−149** (SE=41) (N=85)
Dupilumab	FeNO ≥50	**43** (SE=61) (N=27)	**−41** (SE=27) (N=199)	**−50** (SE=32) (N=152)

BD=bronchodilator. FeNO=fractional exhaled nitric oxide. FEV_1= forced expiratory volume in 1 second. mL/year=milliliter per year. n=sample size. *Estimated from a mixed-effects model with repeated post-BD FEV_1 as outcome, and treatment, age, sex, height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, time since randomization and treatment-by-time interaction and baseline post-BD FEV_1 as covariates. Intercept and time since randomization are random effects.

Pavord et al. ATS 2022

Early intervention with biologics studies in asthma

Intervention/ study name	Phase	Exacerbation(s) in past year	ICS/LABA dose	ACQ	FEV_1 (% predicted)	Biomarker requirement	Primary endpoint	Trial identifier
Depemokimab (ultra-long-acting anti-IL-5; MODIFY)	IIIb/IV	≥1 in past 1 year with ≥2 in past 3 years	Low-med	NA	NA	BEC ≥300 cells/µL + FeNO ≥35 ppb or comorbid current CRSwNP OR BEC ≥500 cells/µL	Annualised asthma exacerbations over 2–3 years	EU CT 2025-524463-20
Dupilumab (anti-IL-4; AIM4)	IV	≥1	Med	≥1.5	Pre-BD FEV_1 50–80%	BEC ≥300 cells/µL	Annualised asthma exacerbations over 1 year	NCT06572228
Dupilumab (anti-IL-4; ATLAS)	IV	≥1	Med-high	≥1.5	Pre-BD FEV_1 ≤80%	FeNO ≥35 ppb	Post-BD FEV_1 slope over 1 year	NCT05097287
Dupilumab (anti-IL-4; HOTHOT)	III	≥1 in past 2 years *≥1 in past 1 year	Med-high ICS and optional other controller *High ICS	*≥1.5	≥12% reversibility *Post-BD ≤80%	BEC ≥300 cells/µL and FeNO ≥35 ppb	Win ratio for clinical remission, assessed at 1 year	NCT07309614
Tezepelumab (anti-TSLP; ARRIVAL)	III	≥1	High	≥1.5–<3	>12% reversibility	NA	Proportion stepping down from BUD/FOR	NCT06473779
CM326 (anti-TSLP)	III	≥1 in past year	Med-high and other controller	≥1.5	Pre-BD FEV_1 ≤80%	NA	Annualised asthma exacerbations over 1 year	NCT07372287
Lunsekimig (anti-IL-13/TSLP; AIRLYMPUS)	II	≥1	Low-med	NA	Pre-BD FEV_1 ≥40%	NA	Annualised asthma exacerbations over 1 year	NCT06676319

Presence of ≥1 of these characteristics required for study inclusion.

ACQ, Asthma Control Questionnaire; TSLP, thymic stromal lymphopoietin; BD, bronchodilator; BEC, blood eosinophil count; BUD, budesonide; CRSwNP, chronic rhinosinusitis with nasal polyps; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FOR, formoterol; ICS, inhaled corticosteroid; IL-5, interleukin-5; LABA, long-acting β_2-agonist; NA, not available; ppb, parts per billion

Conclusion

- For biologics we have an answer to the ‘in whom is this treatment effective’ question
- More ambitious goals of treatment are within target
- The main reason we do not achieve remission is that we are treating after rather than before damage occurs.
- There is a strong rational for earlier targeted intervention. The focus should be on severe type-2 airway inflammation rather than severe asthma (severe asthma = too late asthma)

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Laura Bermejo
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Our patients