Con: The Use of Biologics cannot Achieve Disease Remission in Severe Asthma

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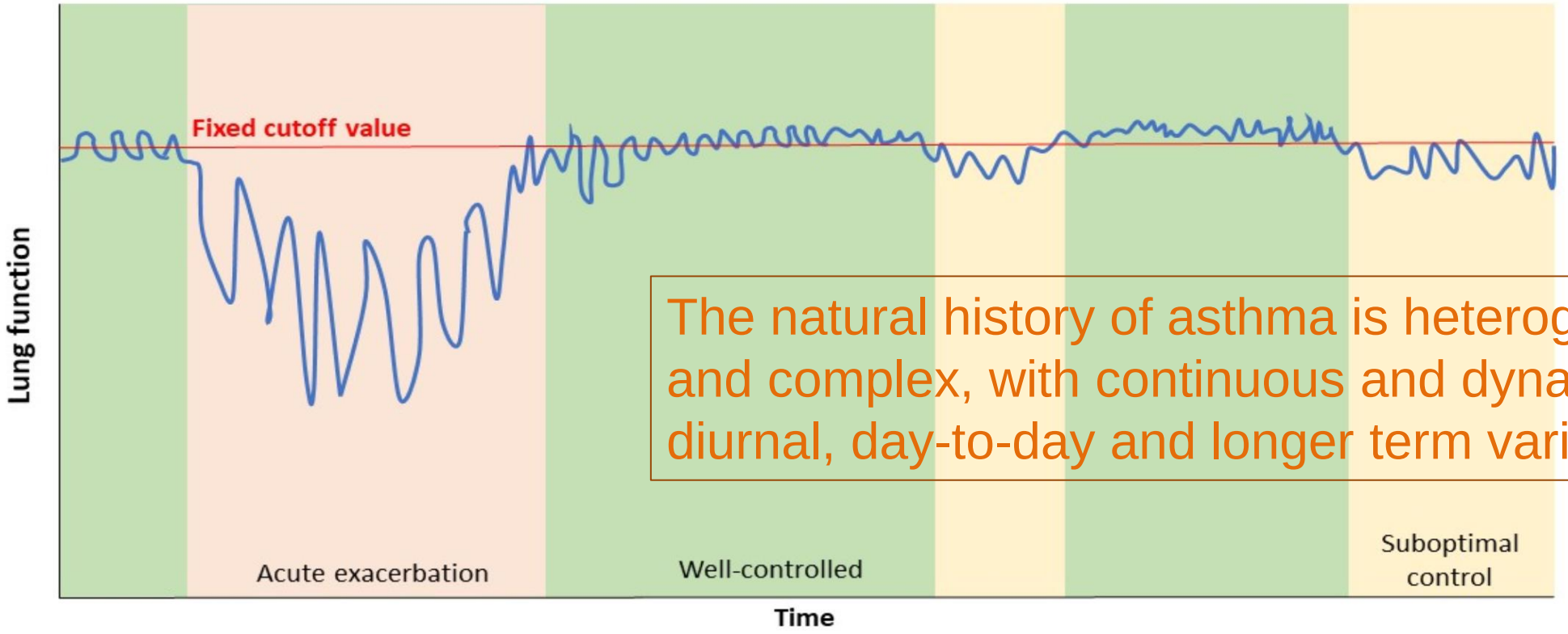
Variability of asthma with time

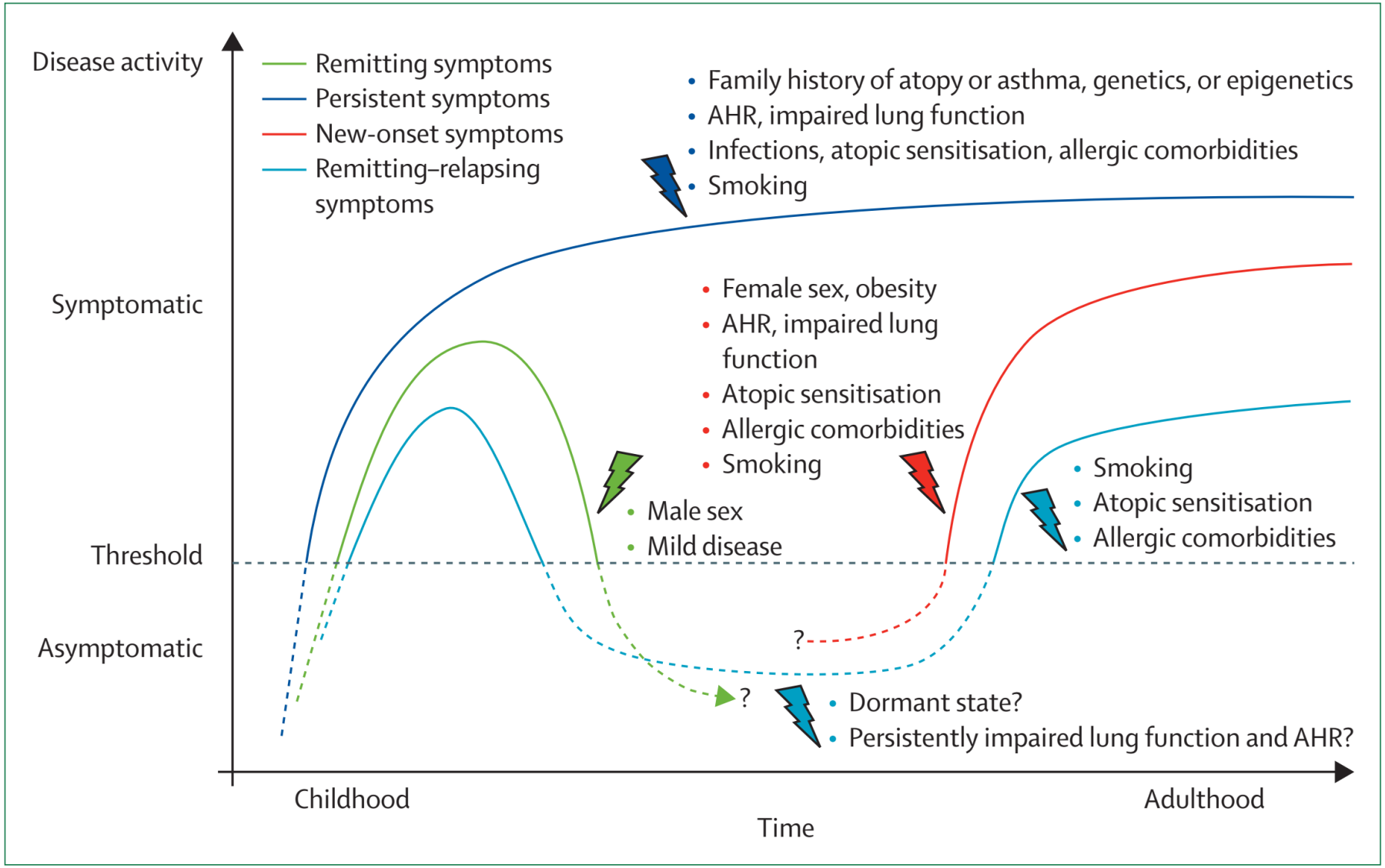


The natural history of asthma is heterogeneous and complex, with continuous and dynamic diurnal, day-to-day and longer term variability.

- **Well-controlled period:** characterized by better lung function and less diurnal variability. However, diurnal variation may straddle diagnostic cut offs in some patients.
- **Period of suboptimal control:** may be predictable in individual patients based on the triggers, such as cold weather or during pollen seasons.
- **Acute exacerbation:** characterized by marked deterioration in lung function and exaggerated diurnal variability.

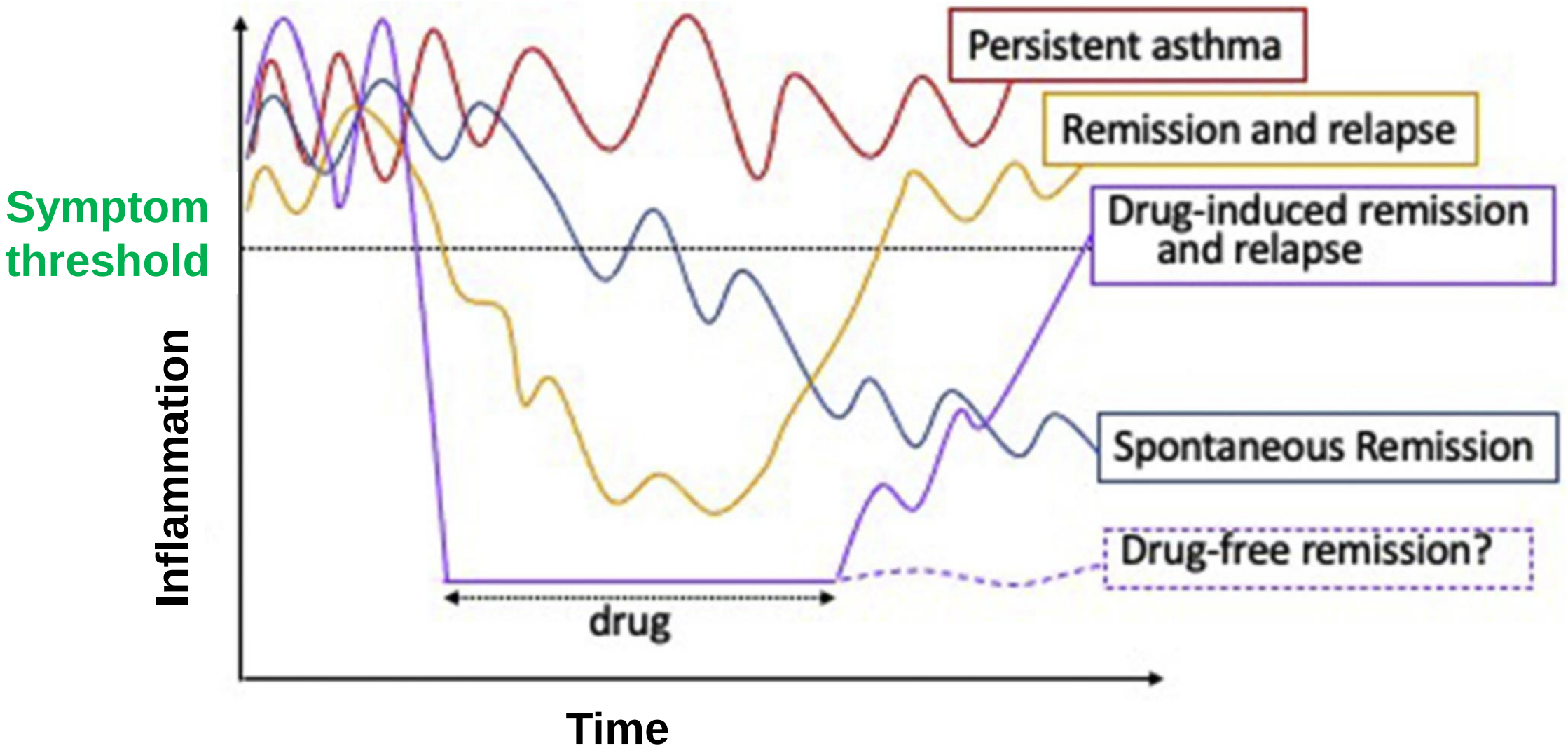
Wang R, et al. Thorax 2021;76:624-31.

Determinants of disease course across asthma transition



Fuchs O, et al. Lancet Respir Med 2017:5(3):224-234.

Theoretical trajectory of asthma remission over time



Cohn L. J Allergy Clin Immunol 2022;150(1):59-61.

Expert consensus framework for asthma remission as a treatment goal

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

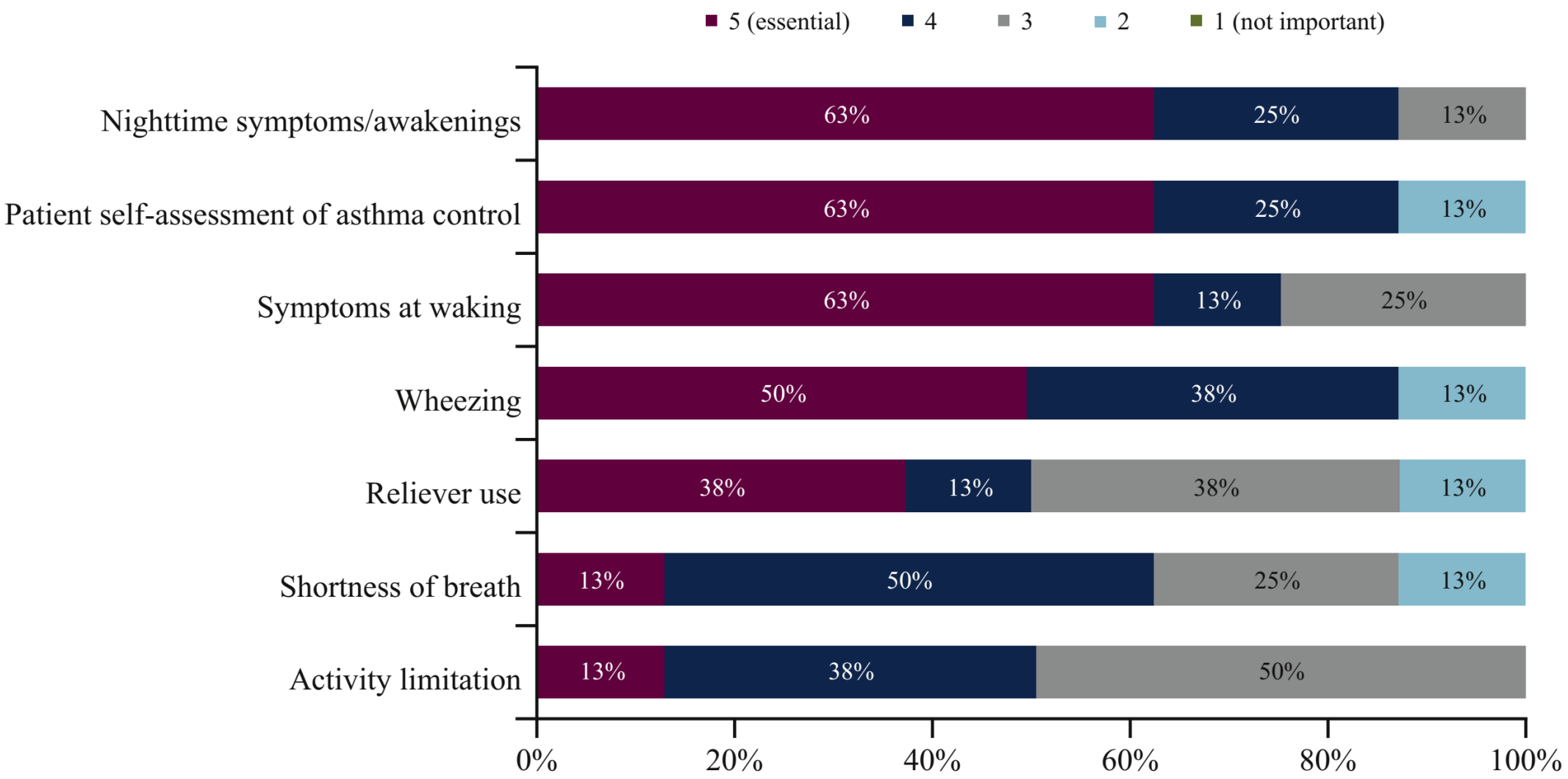
Complete Remission off Treatment

Same criteria maintained without asthma treatment for ≥12 months

*HCP: healthcare provider

Menzies-Gow A, et al. J Allergy Clin Immunol 2020;145:757-65.

Importance of asthma symptoms in the context of asthma remission



Menzies-Gow A, et al. J Allergy Clin Immunol 202;145:757-65.

Types and measures of asthma remission

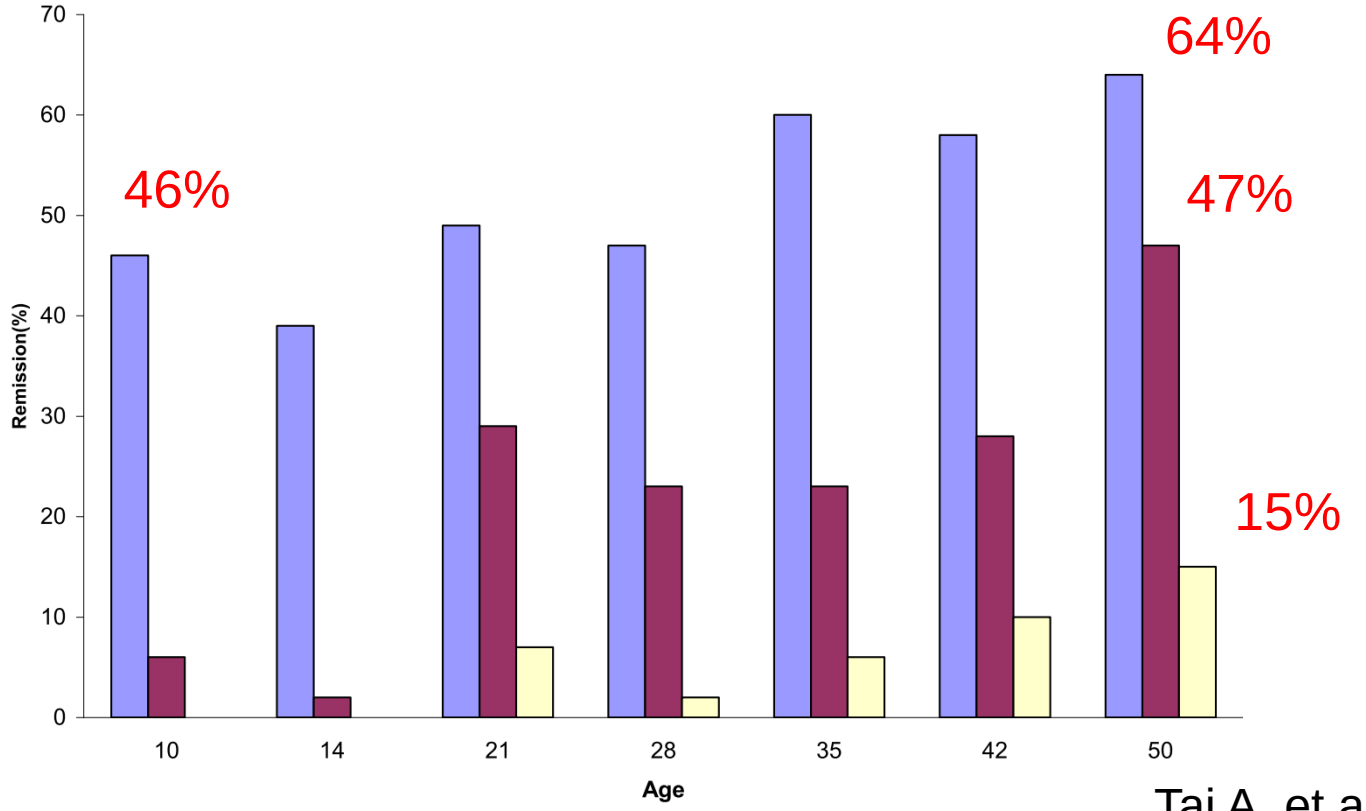
Type	Criteria	Assessments
Clinical remission	No symptoms	Sustained absence of significant asthma symptoms established using a validated instrument (*e.g.* ACQ score ⩽1 or ACT score ⩾20); the use of relievers is not permitted during the remission period
	No exacerbations	The use of systemic corticosteroids for exacerbation treatment is not permitted during the remission period; hospitalisation or emergency department visit or unscheduled doctor visit for asthma exacerbation management are also not permitted during the remission period
	Optimisation of lung function	Example: post-bronchodilator FEV_1 ⩾80% predicted
Complete remission	Clinical remission plus normalisation of underlying pathology	No evidence of current inflammation established using either blood eosinophil count (<300 cells·μL^{-1}), sputum eosinophil count (<3%) or F_{ENO} (<40 ppb) [97, 98]; other measures of underlying pathology may include a negative bronchial hyperresponsiveness test (*e.g.* histamine or methacholine provocation tests) or degree of subepithelial fibrosis (subepithelial thickness)

Thomas D, et al. Eur Respir J 2022;60(5):2102583.

Remission of childhood-onset asthma

- 458 primary school children, from 7 to 50 years old, Melbourne Asthma Study
- **Asthma remission**: no wheeze symptoms in the past 3 years; no use of bronchodilators, oral corticosteroids, or ICS

Asthma remission percentages at each review

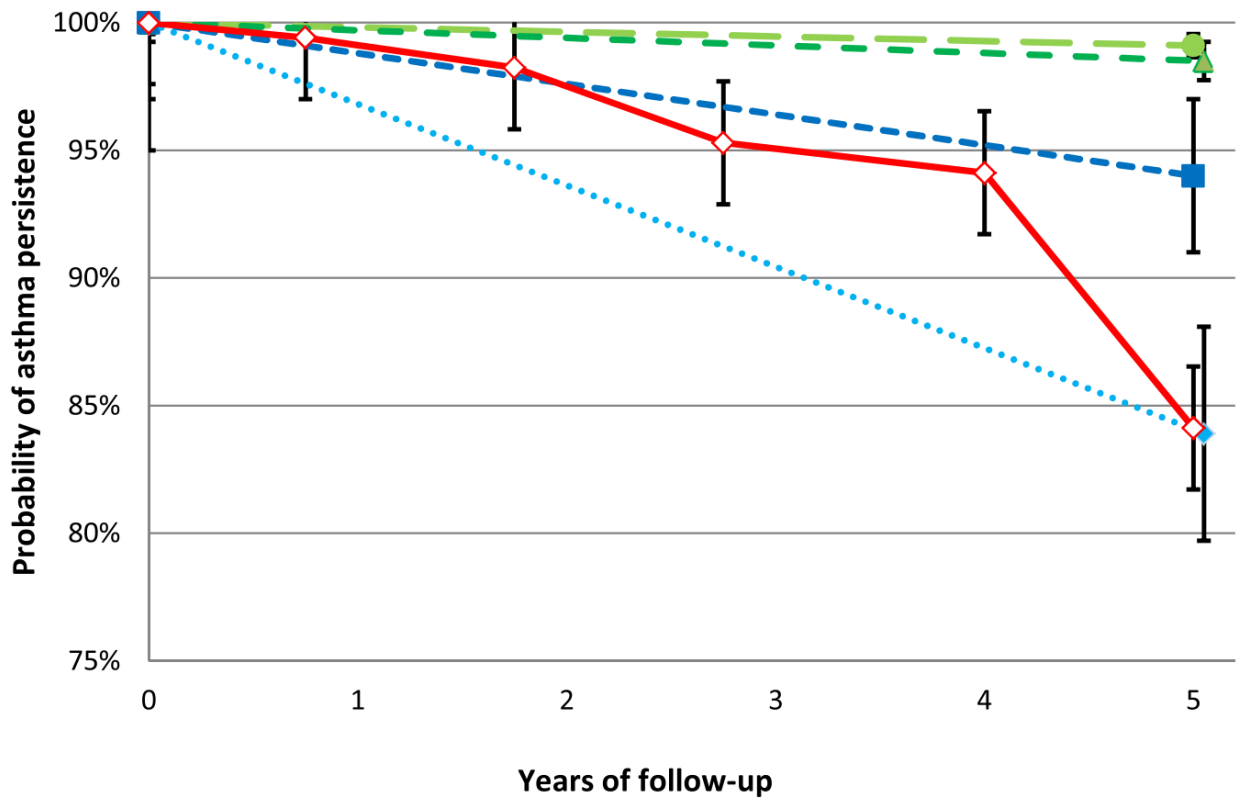


Tai A, et al. J Allergy Clin Immunol 2014;133(6):1572-8.

Remission of adult-onset asthma

- 170 adult patients with recently diagnosed (<1 year) asthma, 5-year follow-up
- **Asthma remission**: No asthma symptoms and medication use for ≥1 year

Probability of asthma persistence



Asthma remission: 16%

- NP + and severe BHR
- NP + and mild BHR
- NP - and severe BHR
- NP - and mild BHR
- Clinical observed remission

Westerhorf GA, et al. J Allergy Clin Immunol 2018;141;104-9.

Clinical characteristics of persistent asthma vs. remission

	Persistent asthma (n = 143)	Clinical remission (n = 27)	P-value
Age, year	50 ± 14	44 ± 15	0.039
ACQ-6 score	1.34 ± 0.92	0.89 ± 0.67	0.026
ICS dose, fluticasone equivalent	313 (250-500)	250 (0-250)	0.007
PC_{20} methacholine, mg/mL	2.7 (0.8-6.6)	5.8 (2.9-32)	0.003
Nasal polyps	25	0	0.004
FeNO, parts/billion	21 (13-45)	29 (12-44)	0.698
Blood eosinophils, 10^9/L	0.17 (0.1-0.28)	0.15 (0.08-0.26)	0.601

Westerhorf GA, et al. J Allergy Clin Immunol 2018;141;104-9.

Childhood-onset asthma remission by more strict criteria

- 406 children in asthma cohort from childhood to age 25 and 49
- Clinical remission: no symptoms without asthma medication use for ≥1 year
- Complete remission: clinical remission + negative BHR test, normal FEV1

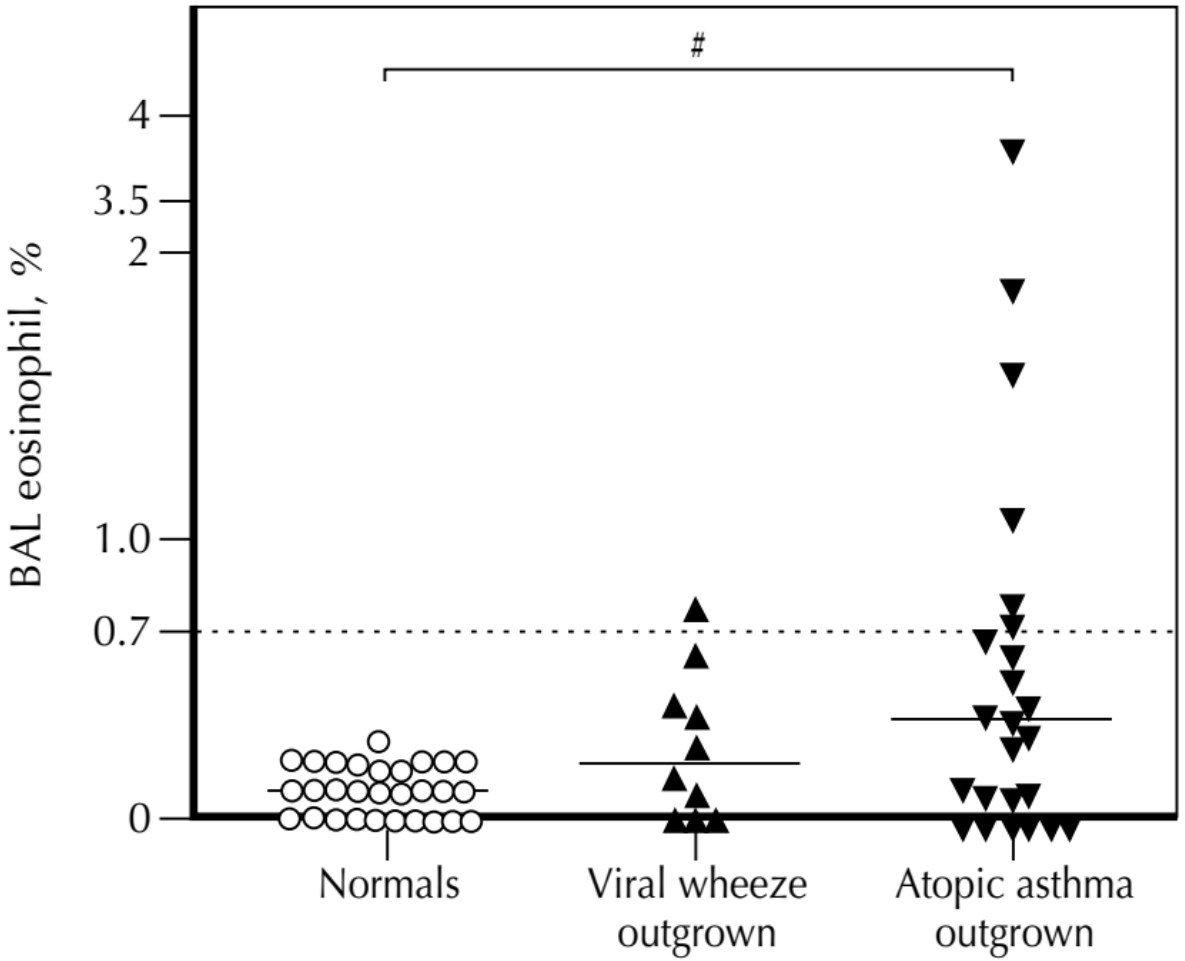
	Visit 1 (1972–76) 406 subjects	Visit 2 (1987-89) 209 subjects	Visit 3 (2013-14) 209 subjects
Excluded	187 No BHR 10 Incomplete childhood data	21 Lost to follow-up	65 No response 31 Untraceable 6 Not cooperative 5 Deceased
Included	209 subjects	188 subjects	102 subjects
Asthma outcome	-	154 PersA (81.9%) 20 ClinR (10.6%) 14 ComR (7.5%)	61 PersA (59.8%) 31 ClinR (30.4%) 10 ComR (9.8%)

- ✓ 75% of the subjects with complete remission at age 25
  - no relapse of asthma by age 49

Carpaij OA, et al. Eur Respir J 2017;49(6):1601974.

Clinical remission ≠ No airway inflammation

- Children with apparently outgrown asthma
- 35 healthy; 10 outgrown viral wheeze; 25 outgrown asthma



BAL fluid eosinophil

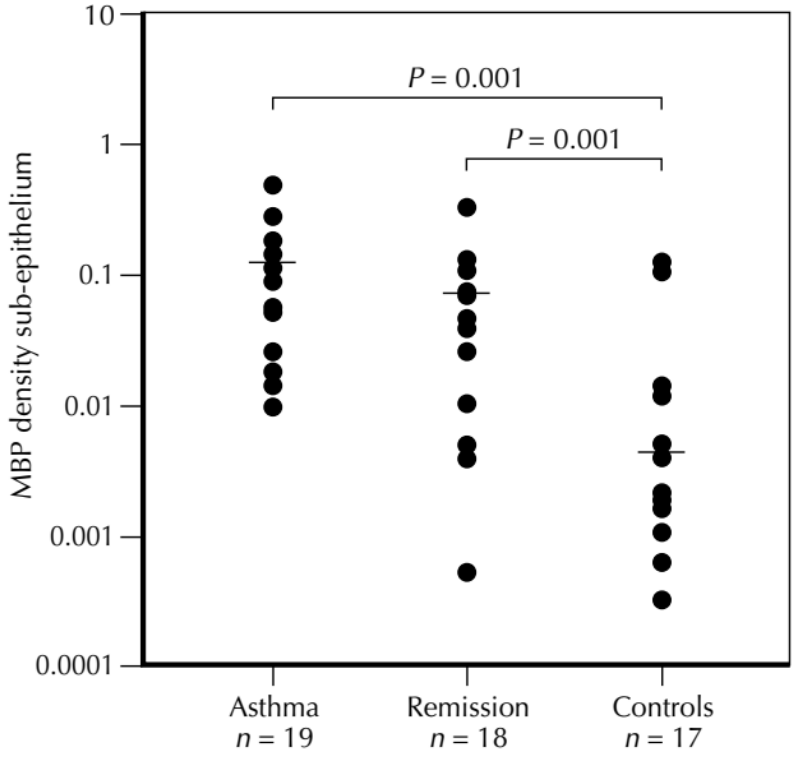
✓ No relationship between length of remission and degree of airways eosinophilia

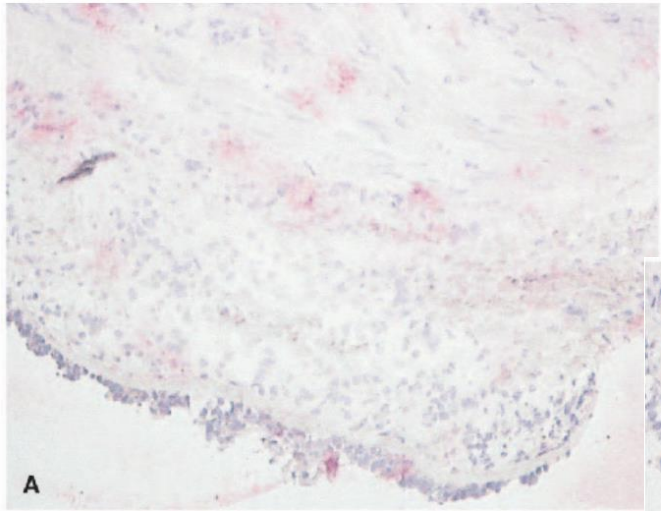
Warke TJ, et al. Eur Respir J 2002;1919:284-287.

Clinical remission ≠ No airway inflammation

- Bronchoscopic evaluation in 18 subjects with clinical remission of ashtma, 19 subjects with symptomatic asthma, and 17 healty subjects
- Bronchial mucosa samples with biopsies from subcarinae of the main bronchi

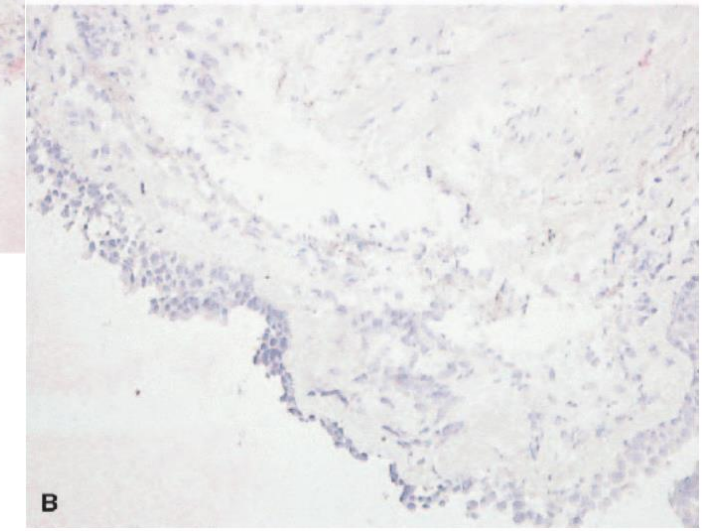
Eosinophil density via major basic protein staining





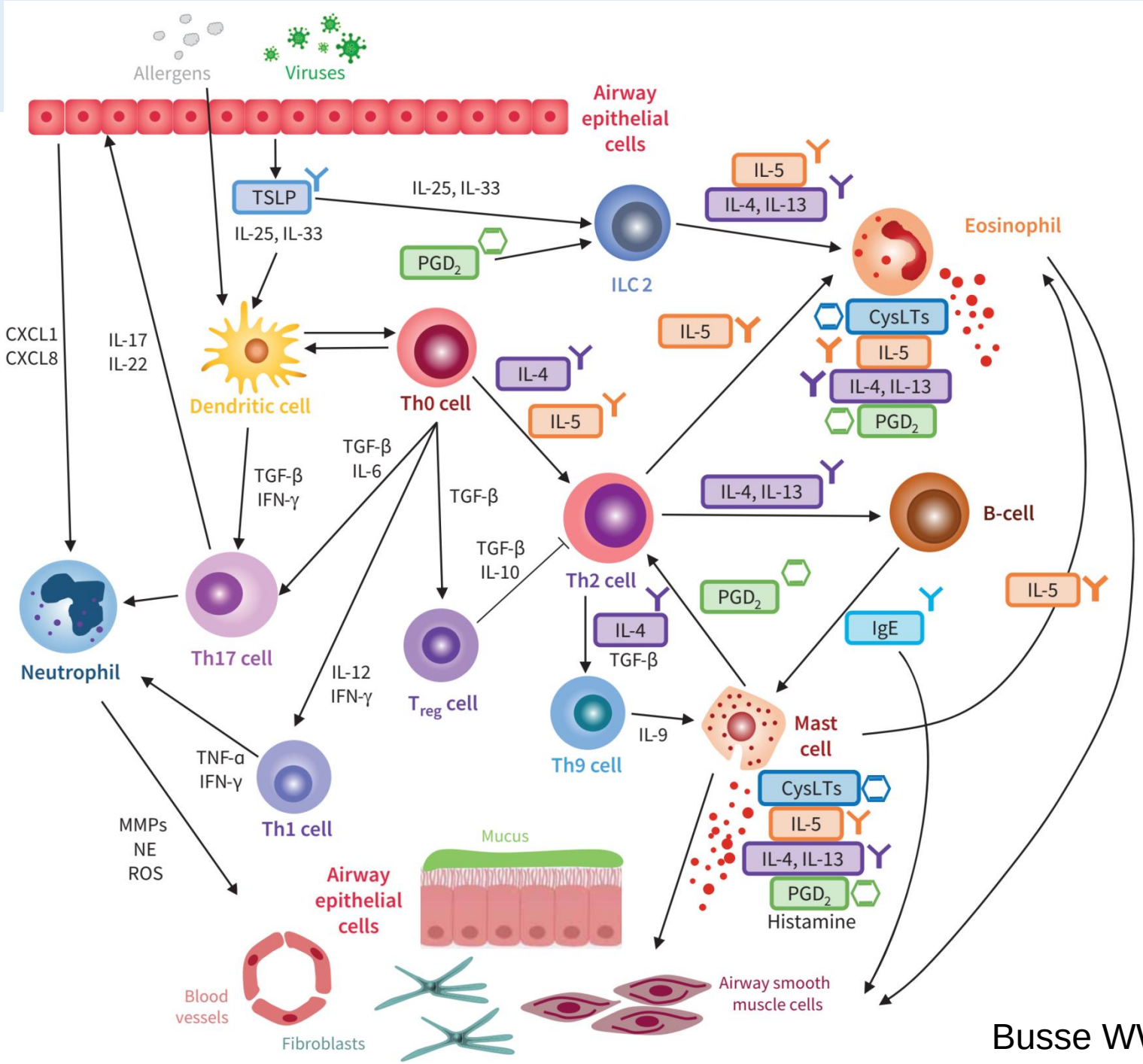
Clinical remission of asthma

Healthy control



Toom VD, et al. Am J Respir Crit Med 2001;164:2107-2113.

Asthma therapies with disease-modifying potential and targets



- Anti-TSLP mAbs
- Anti-IL-4R mAbs
- Anti-IL-5/-5R mAbs
- Anti-IgE mAbs
- PGD_2 antagonists
- CysLT receptor antagonists

Busse WW, et al Eur Respir Rev 2022;31(163):210183.

T2-directed biologics available for severe asthma

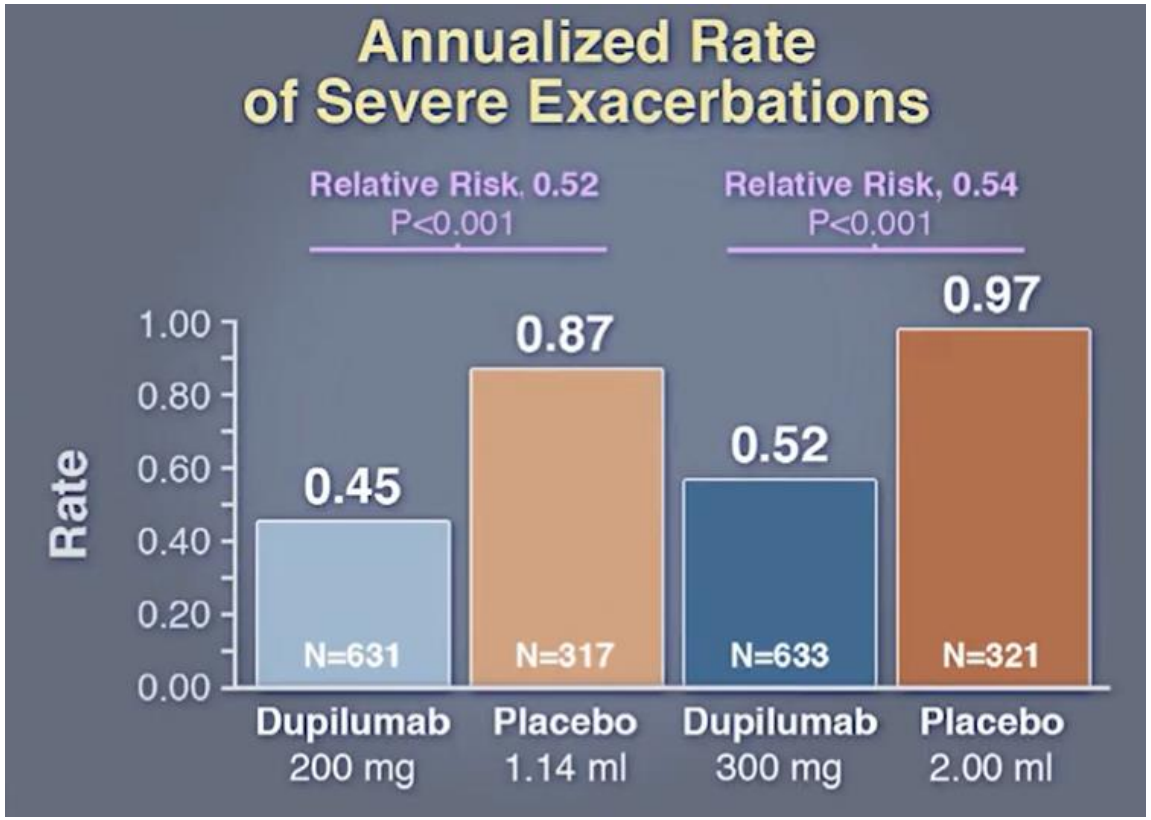
Agent	↓ Exacerbations	↑ Lung function	Symptoms	Special feature
Omalizumab (IgE)	25%	±	+/±	Aged >6 y; also approved for CIU
Mepolizumab (IL-5)	50%	+	+	Greatest experience of anti−IL-5s; also approved for EGPA
Reslizumab (IL-5)	50%	++	+	Weight-base dose (intravenously)
Benralizumab (IL-5R)	50%	++	++	Every 8 wk and IL-5R
Dupilumab (IL-4/IL-13)	50%	++	+++	Eosinophils, FENO; also approved for AD and CRSwNP

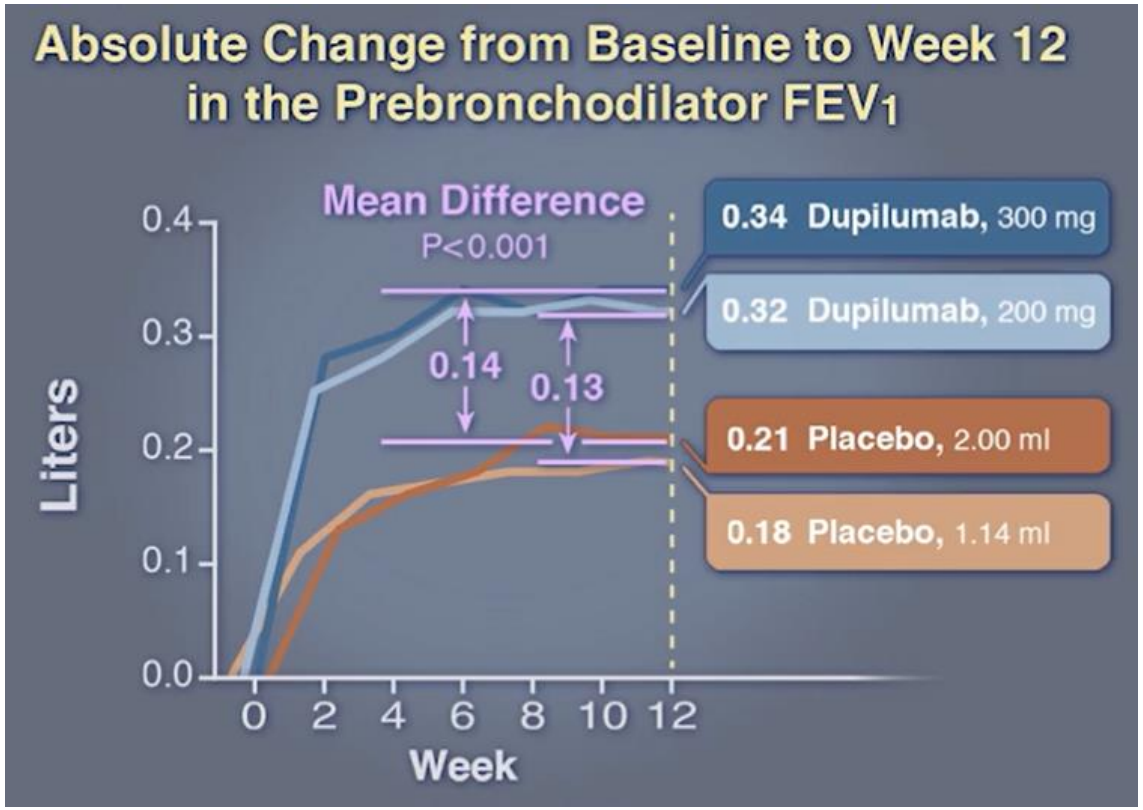
AD, Atopic dermatitis; *CIU*, chronic idiopathic urticaria; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *EGPA*, eosinophilic granulomatosis with polyangiitis; *FENO*, fractional exhaled nitric oxide.

Menzies-Gow A, et al. J Allergy Clin Immunol 2021;9:1090-8.

Dupilumab in uncontrolled asthma

- 1,902 patients with moderate-to-severe asthma, refractory to maximized standard-of-care controller therapy, phase 3 LIBERTY ASTHMA QUEST study
- Dupilumab 200mg vs. 300mg vs. matched placebo, SC, q2wk, 52wk

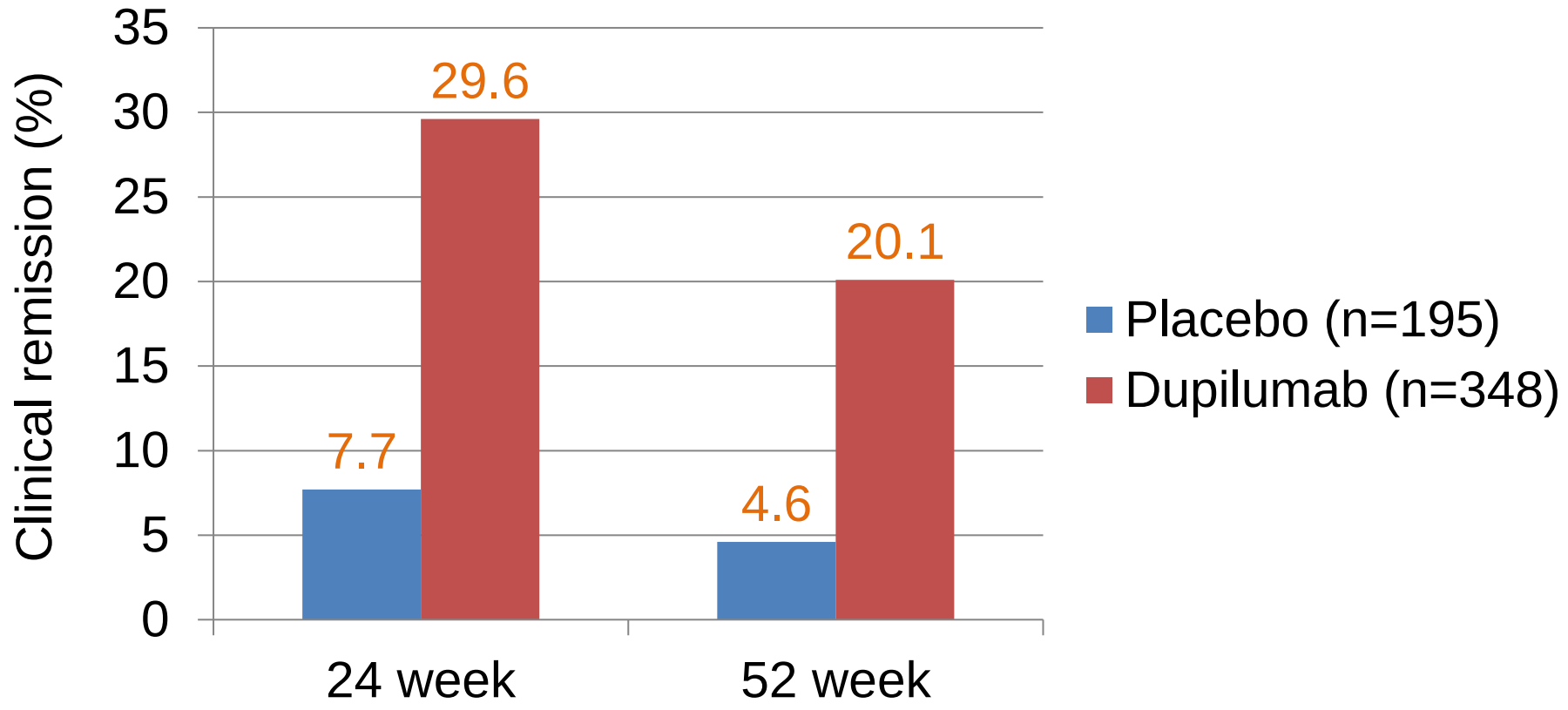




Castro MJ, et al. N Engl J Med 2018;378(26):2486-96.

On-treatment clinical remission with dupilumab

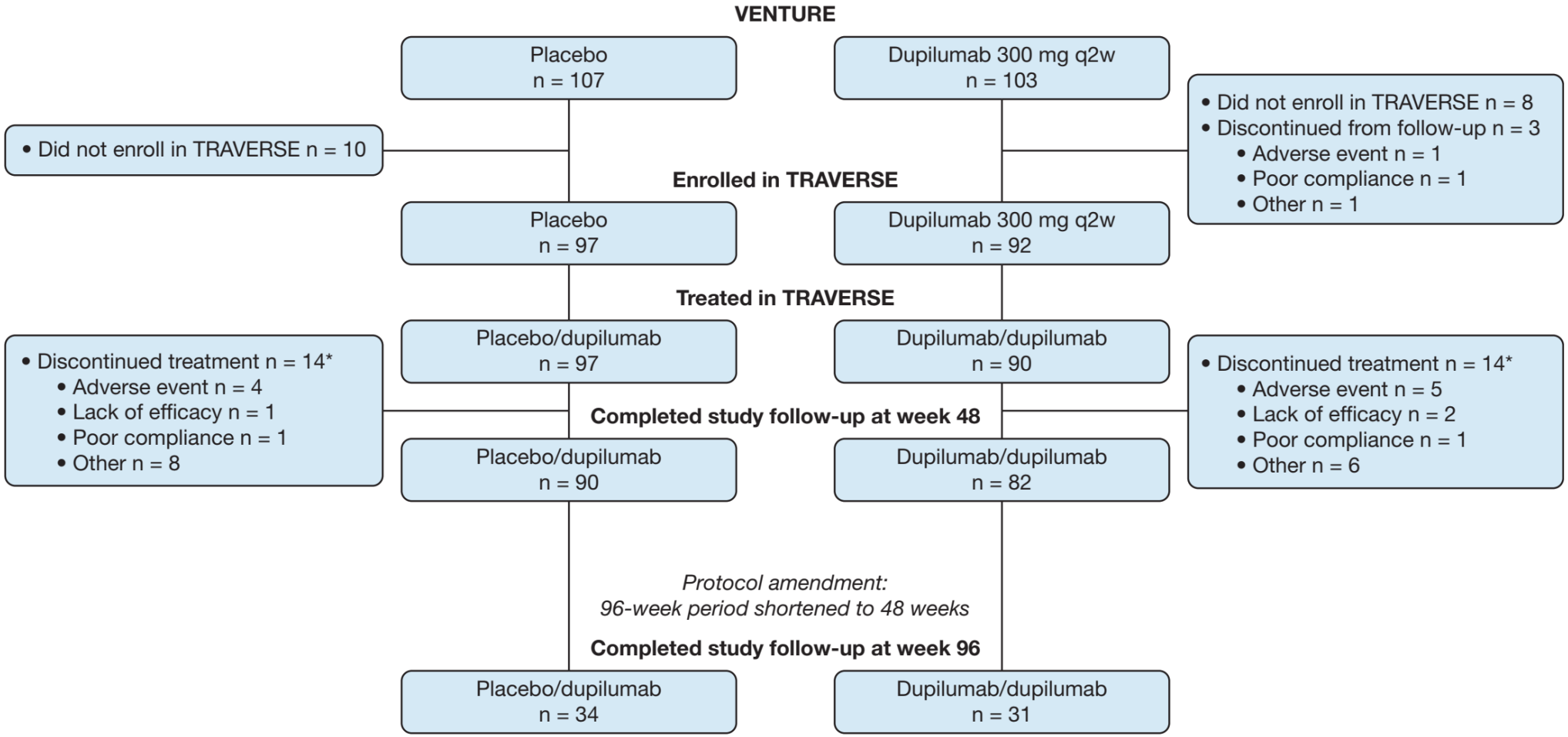
- Post-hoc analysis of LIBERTY ASTHMA QUEST
- Patients with baseline post-bronchodilator FEV1<80%, FeNO ≥25ppb, eosinophils ≥150/mL
- Clinical asthma remission (no exacerbations/ACQ-5 total score <1.5/post-bronchodilator FEV_1 ≥80%) at 24/52 week



Pavord I, et al. J Allergy Clin Immunol 2021;147(2):supplement.AB4 (Poster presention at AAAI 2021).

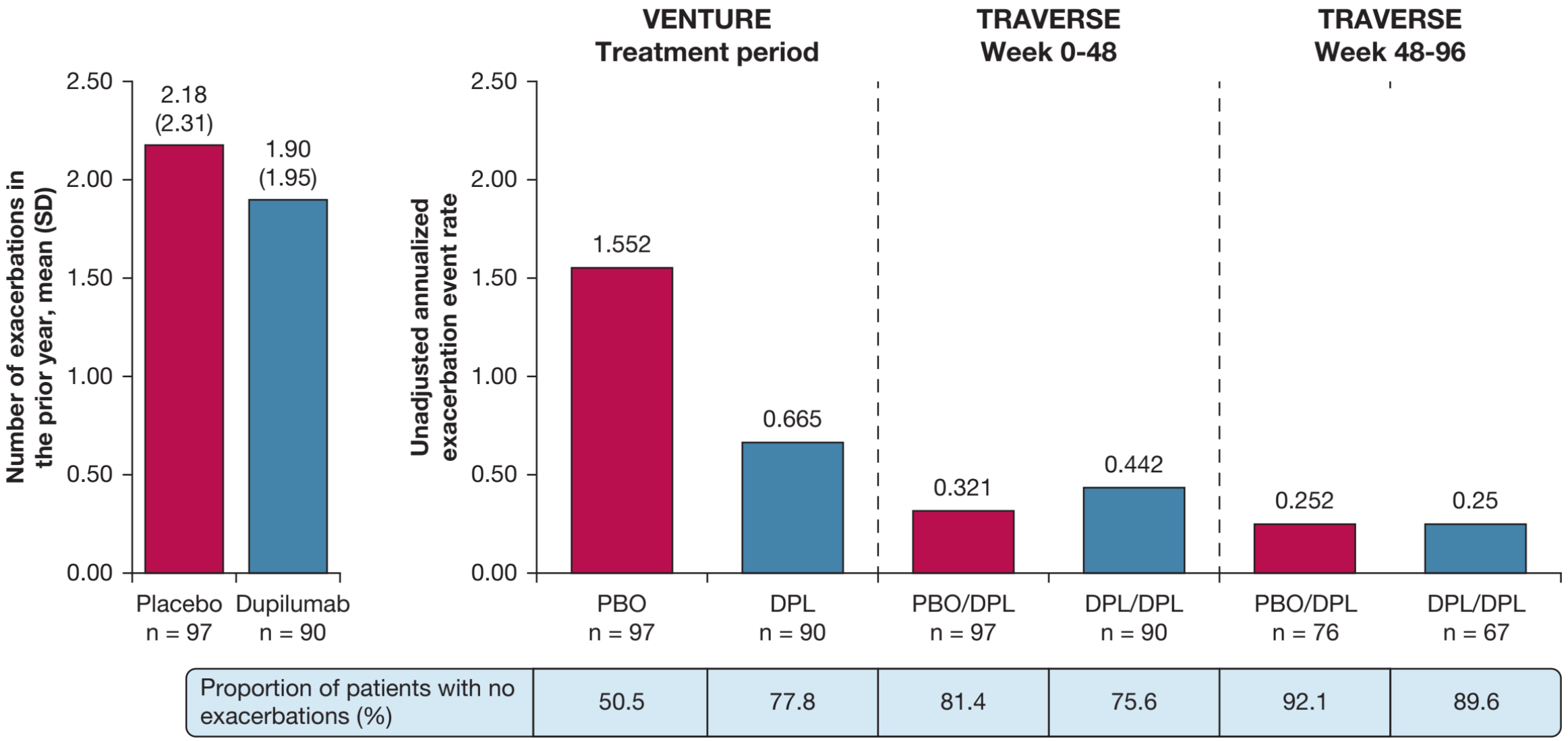
Extension study with dupilumab

- OCS-dependent severe asthma, dupilumab 300mg q2wk for 24 wks (VENTURE) → till 96 wks (TRAVERSE), LIBERTY ASTHMA TRAVERSE study



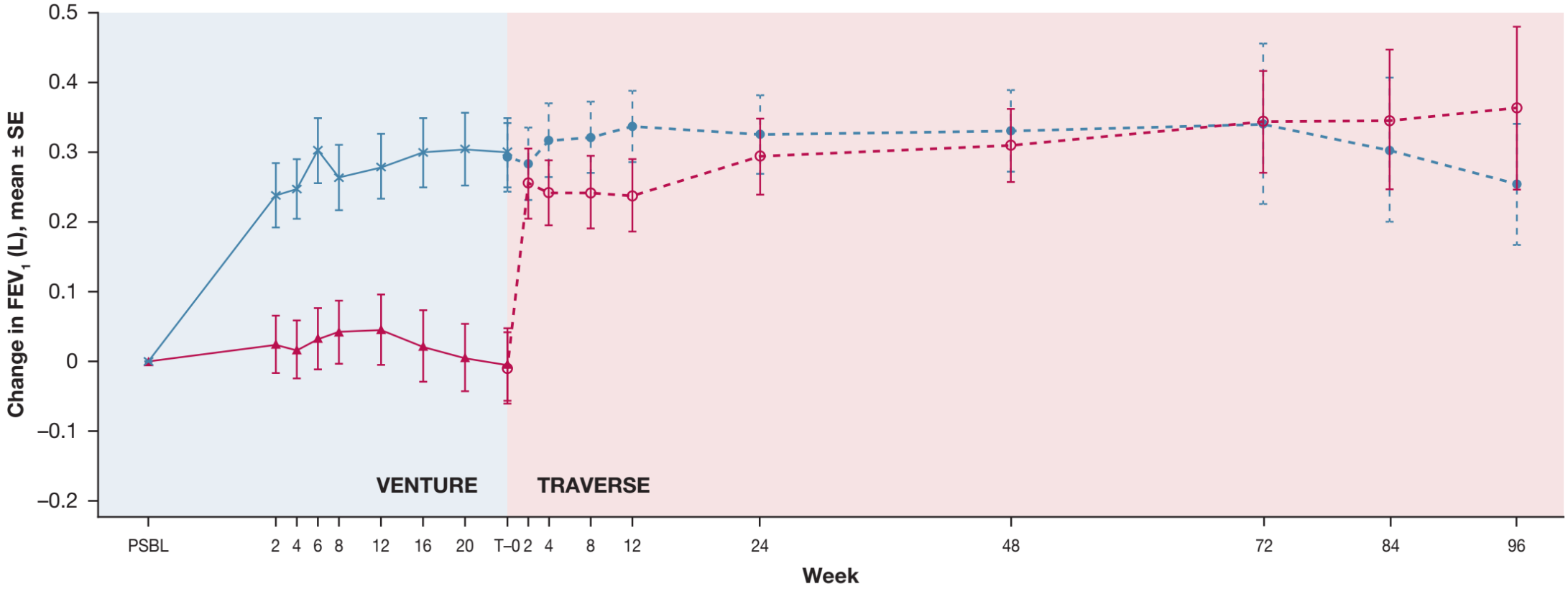
Sher LD, et al. CHEST 2022;162(1):46-55.

Extension study with dupilumab: Exacerbation



Sher LD, et al. CHEST 2022;162(1):46-55.

Extension study with dupilumab: Lung function



No. of patients																	
Placebo	97	96	95	96	97	96	96	97	96								
Dupilumab 300 mg q2w	90	88	86	90	90	88	88	89	87								
PBO/DPL									97	95	92	94	92	91	88	34	32	32
DPL/DPL									89	86	86	85	83	83	82	28	28	28

Sher LD, et al. CHEST 2022;162(1):46-55.

On-treatment clinical remission with dupilumab

- Patient from QUEST who were enrolled in TRAVERSE with baseline blood eosinophils ≥150 cells/μL or FeNO ≥20 ppb, and who had uncontrolled, non-OCS-dependent, moderate-to-severe asthma

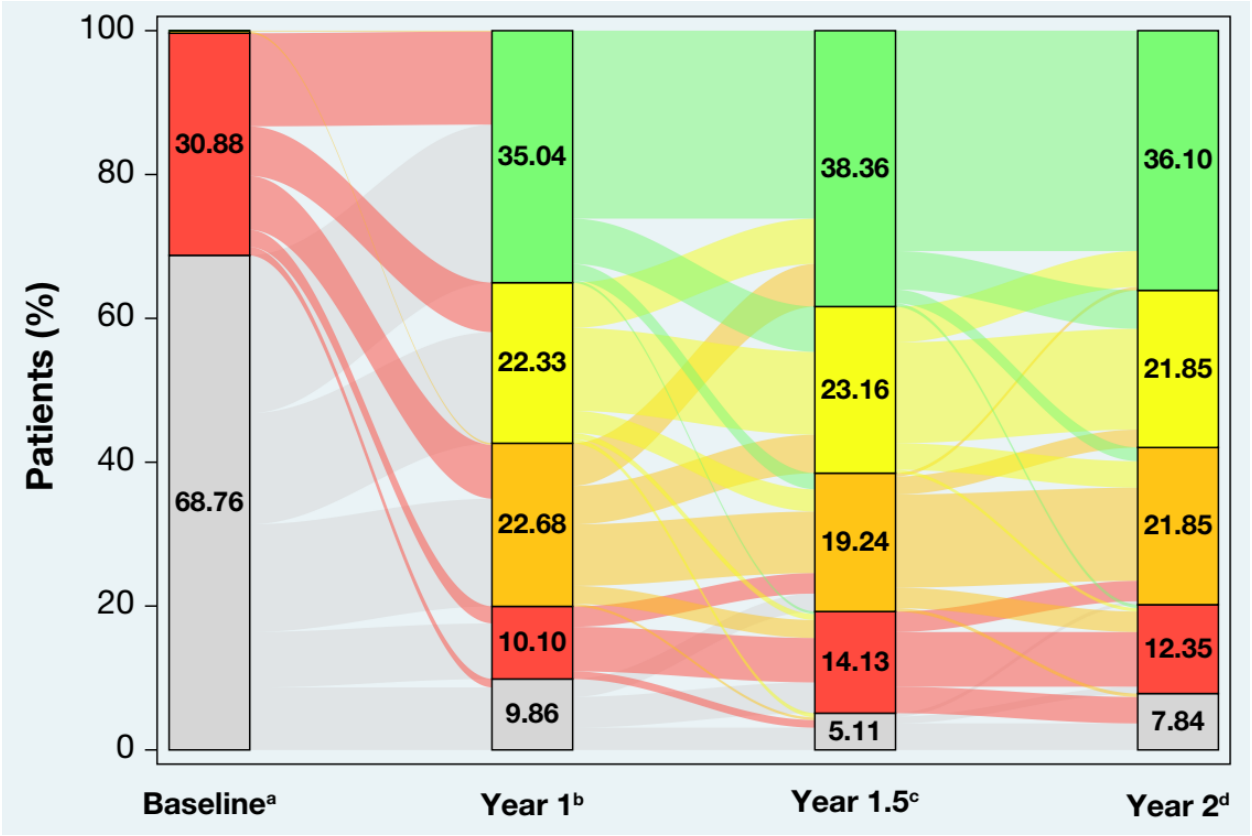
- Dupilumab/dupilumab vs. placebo/dupilumab group

- Clinical remission
  - ✓ No exacerbations
  - ✓ No OCS use
  - ✓ ACQ-5 total score <1.5
  - ✓ Improvement in pre-bronchodilator FEV1 ≥100mL (QUEST, TRAVERSE) or post-bronchodilator FEV_1 ≥80% (TRAVERSE)

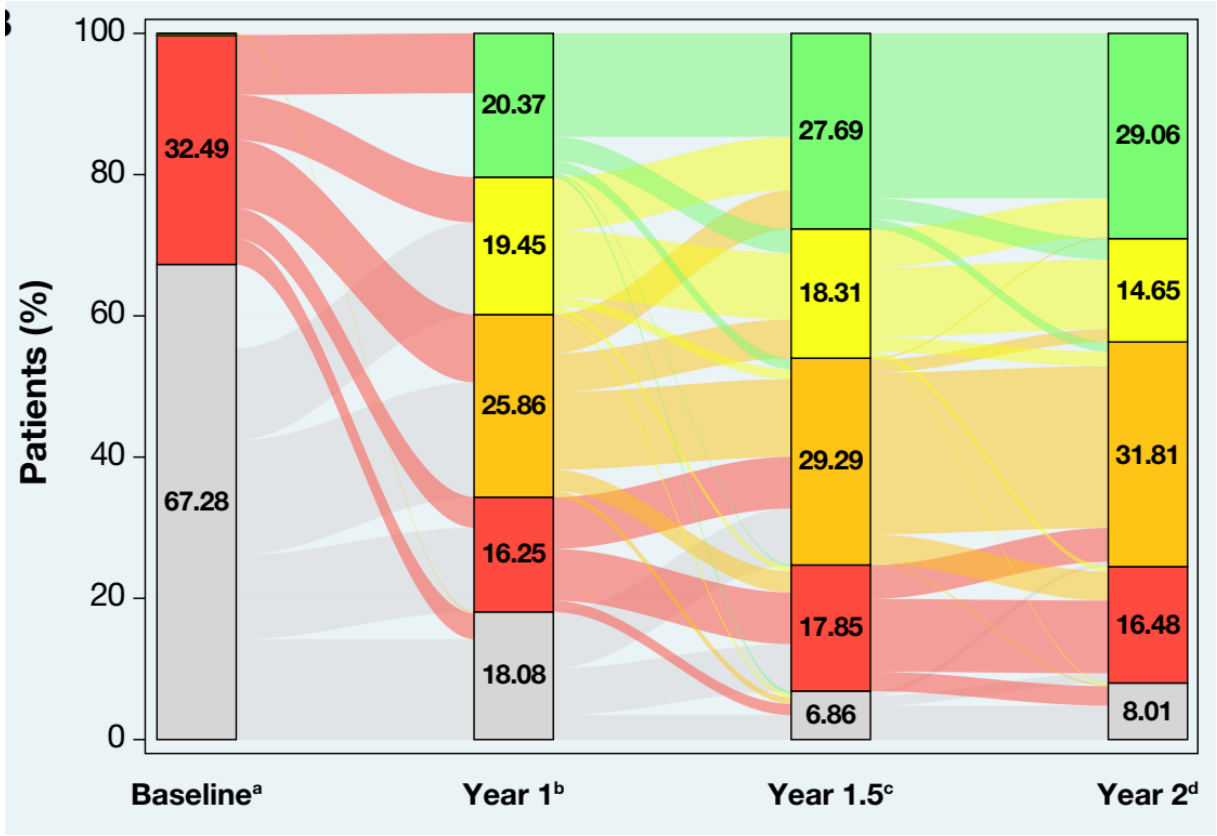
Pavord I, et al. Poster presentation at ATS 2023.

On-treatment clinical remission with dupilumab

Dupilumab/dupilumab group



Placebo/dupilumab group



Patients who met all 4 criteria

Patients who met any 3 criteria

Patients who met any 2 criteria

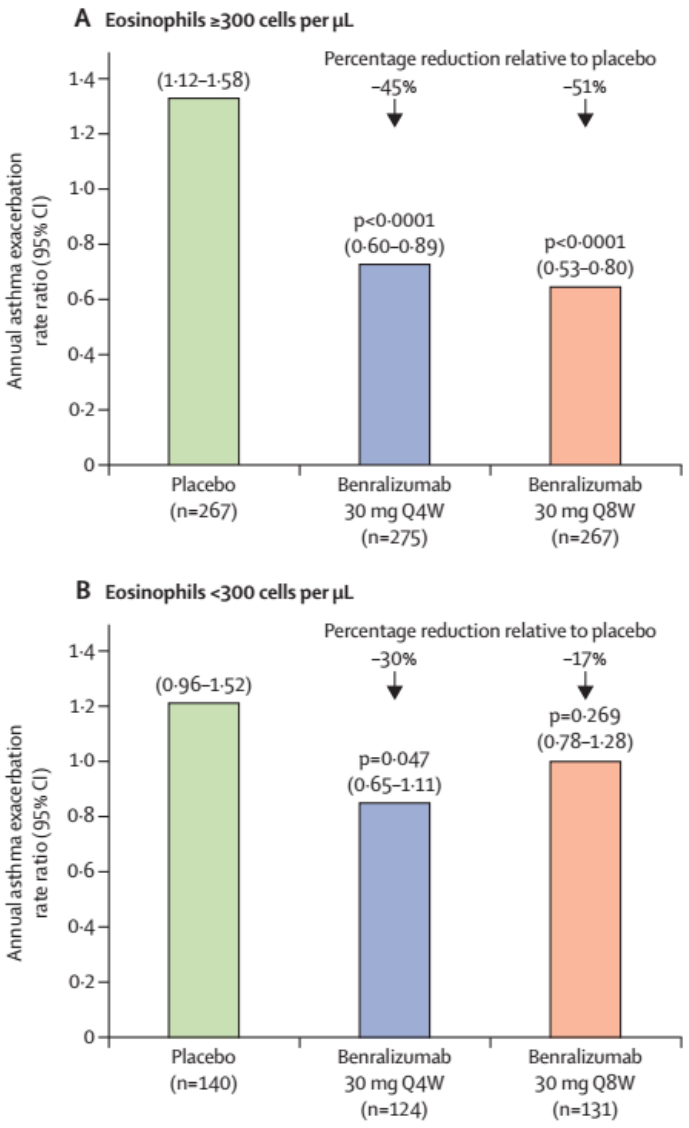
Patients who met any 1 criteria

Patients who did not meet any criteria

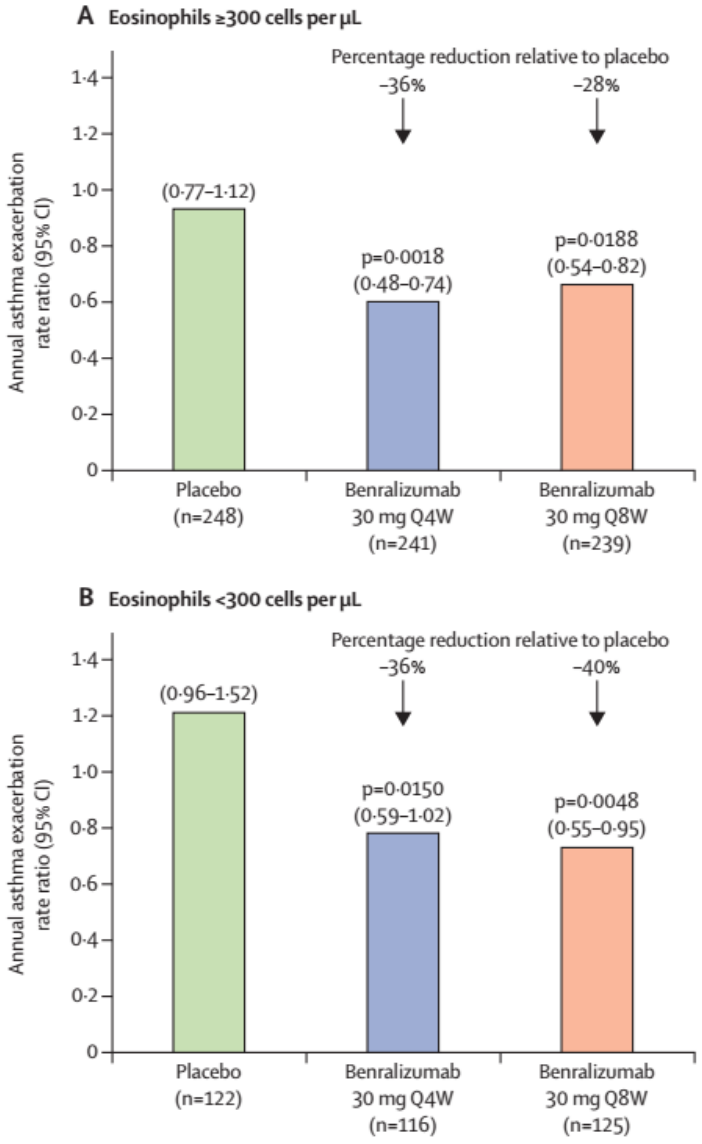
Pavord I, et al. Poster presentation at ATS 2023.

Efficacy of benralizumab for severe asthma

SIROCCO



CALIMA



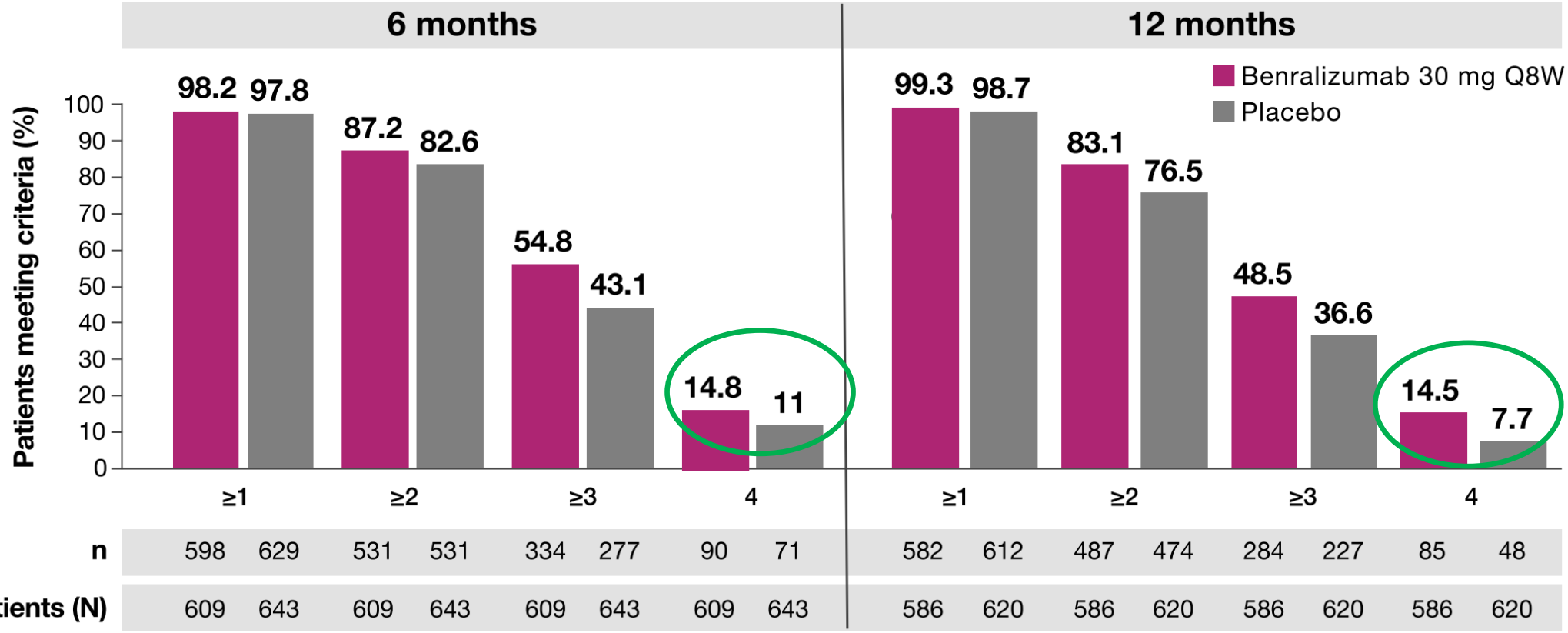
- Asthma patients, for at least 1 year, at least 2 exacerbations, high-dose ICS/LABA in the previous year
- Benralizumab 40 mg q4wk vs. q8wk vs. placebo, add-on therapy
- 48 wks in SIROCCO study
- 56 wks in CALIMA study

Bleecker ER, et al. Lancet 2016;388:2115-27.
FitzGerald JM, et al. Lancet 2016;388;2128-41.

Clinial remission in post-hoc analysis: benralizumab

- Post-hoc analysis included patients randomized to the approved benralizumab dose and not receiving OCS at baseline (SIROCCO/CALIMA) or OCS ≤12.5 mg/day (ZONDA)
- **Clinical remission**: No exacerbations, No OCS use, ACQ-6 score ≤0.75, and pre-bronchodilator FEV_1 increase ≥100 mL after 6 or 12 months

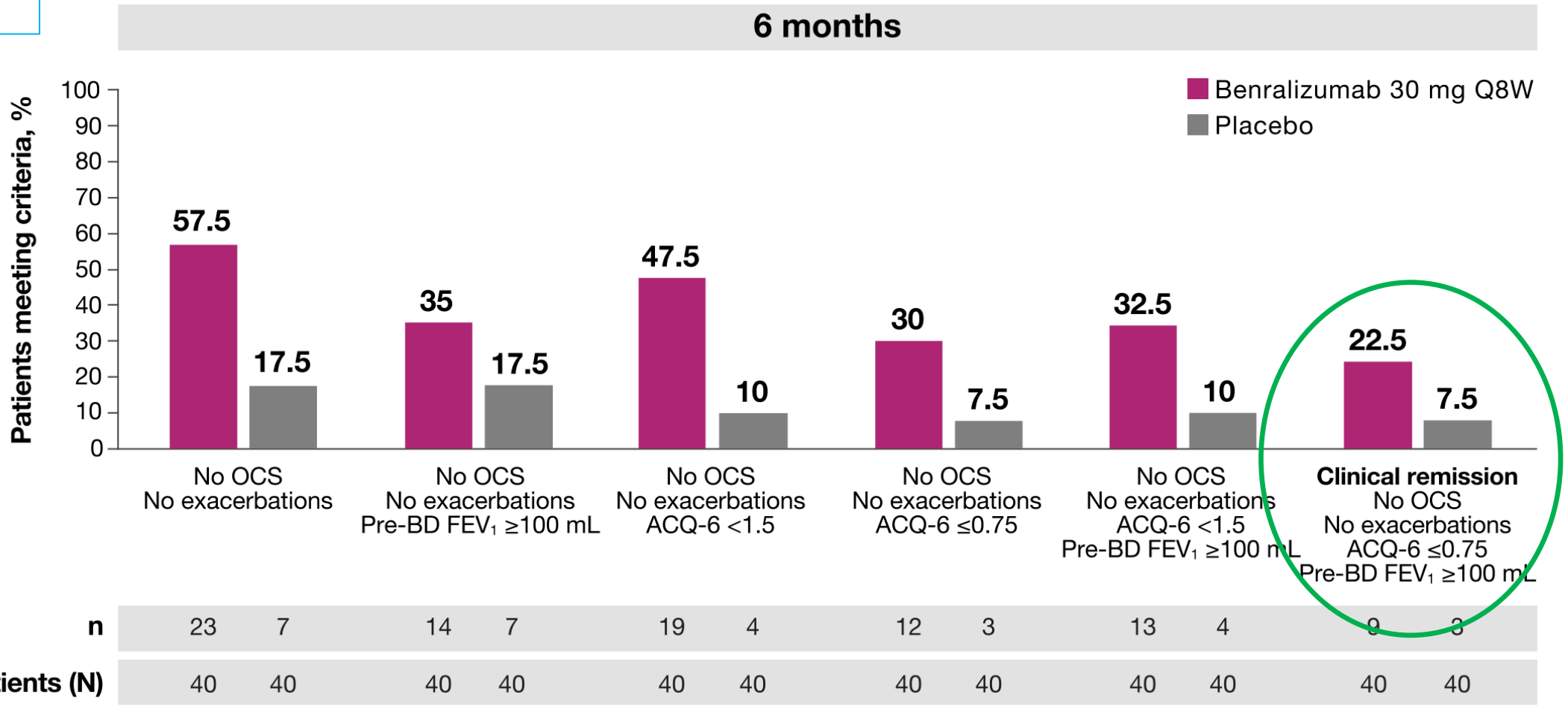
SIROCCO/ CALIMA



Menzies-Gow A, et al. Adv Ther 2022;39(5):2065-2084.

Clinial remission in post-hoc analysis: benralizumab

ZONDA



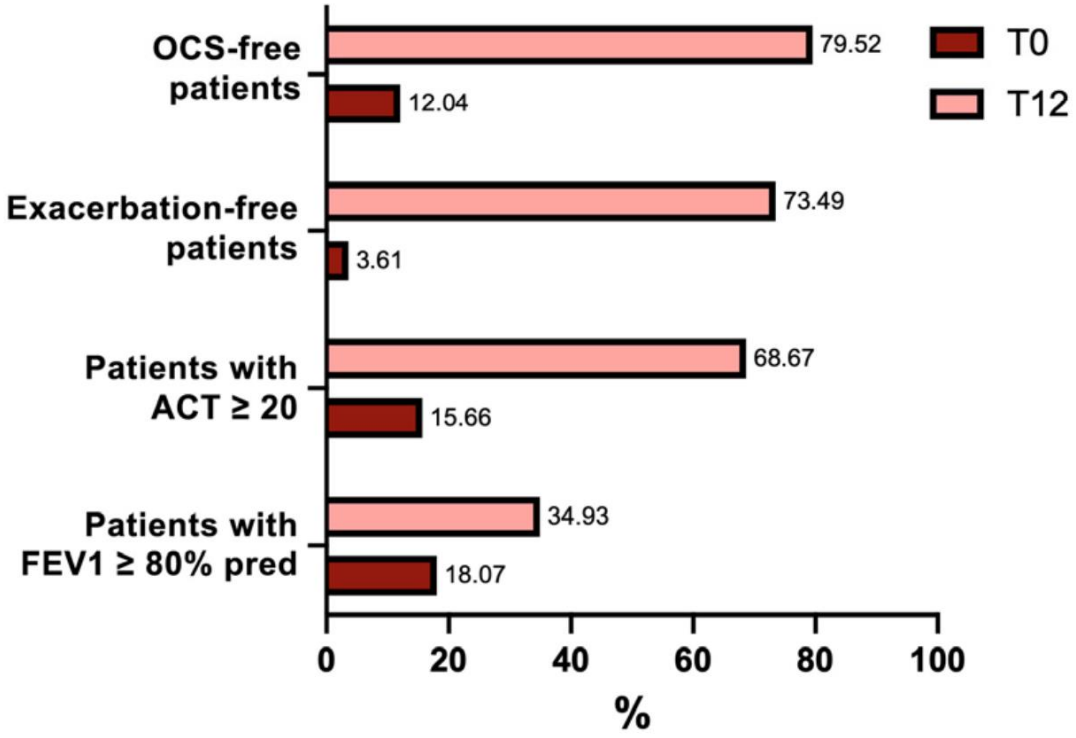
n	23	7	14	7	19	4	12	3	13	4	9	3
Total patients (N)	40	40	40	40	40	40	40	40	40	40	40	40

Menzies-Gow A, et al. Adv Ther 2022;39(5):2065-2084.

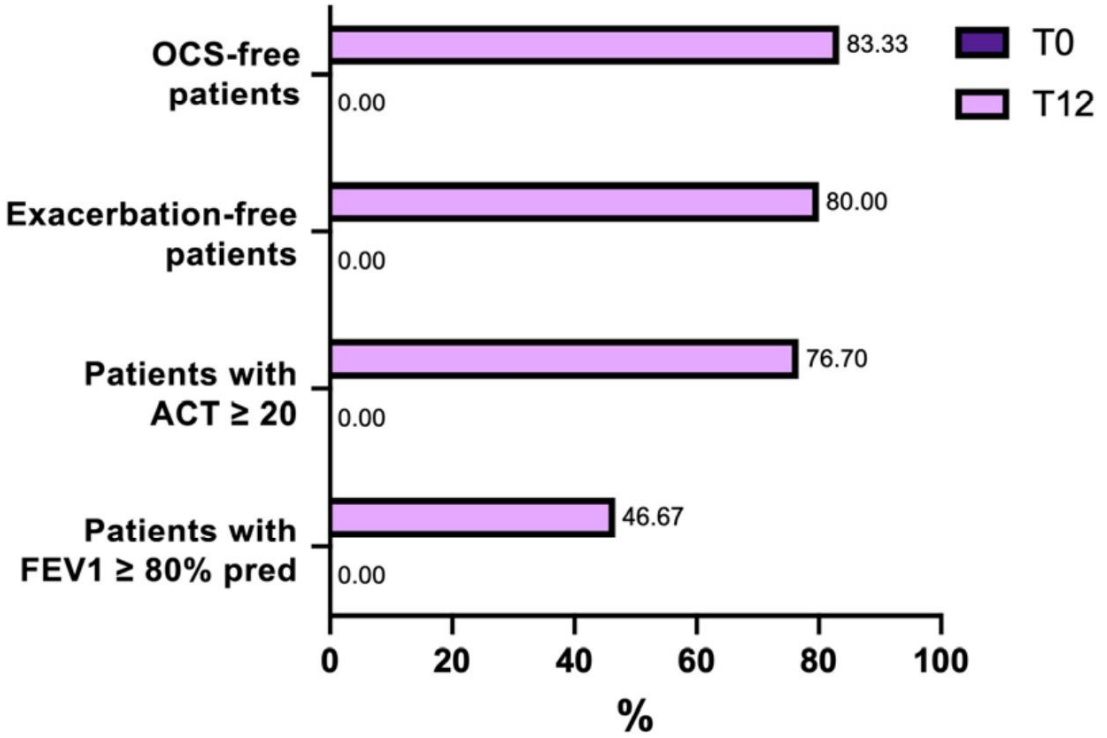
Real world evidence for clinical remission

- 113 severe asthma patients treated for 12 months with mepolizumab (n=83) or benralizumab (n=40), multicenter restrospective study, 12 months
- Clinical remission: 30.1% in mepolizumab group; 40% in benralizumab group

Mepolizumab-treated



Benralizumab-treated



Maglio A, et al. Int J Mol Sci 2023;24(3):2455.

Real world evidence for clinical remission

➢ Among 113 patients; OCS-dependent 75.5%, CRS with NP 42.5%

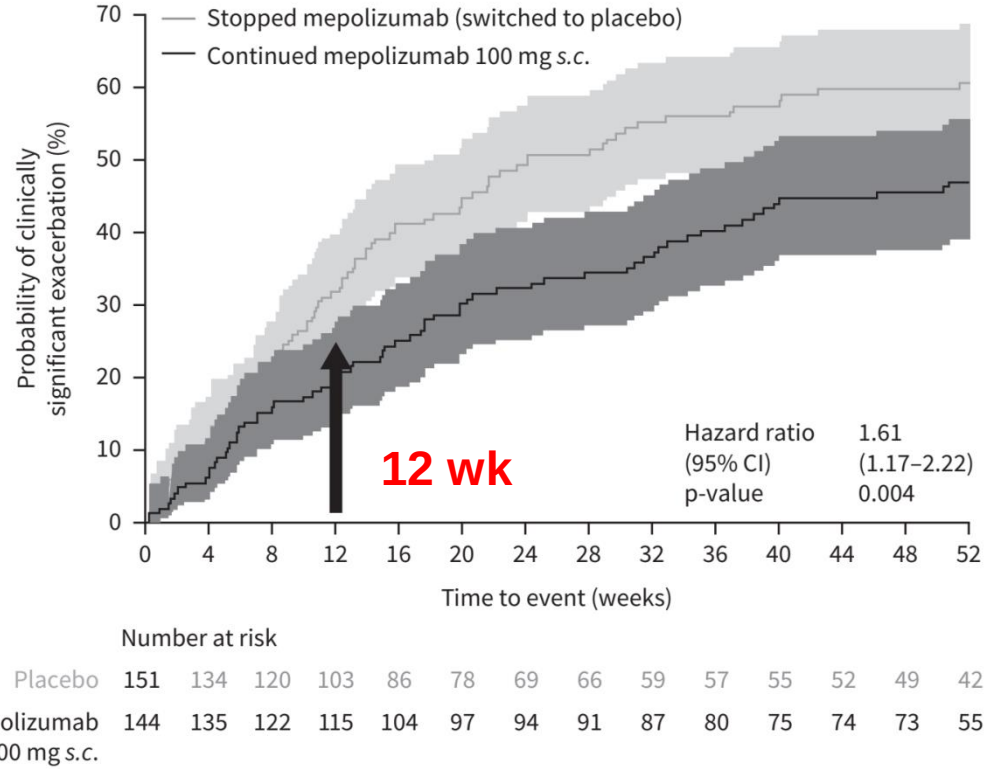
	Mepolizumab (n=83)	Benralizumab (n=30)
ACT ≥ 20, n (%)	13 (15.7)	0 (0)
Blood eosinophils, cells/μℓ	584.3 ± 333.6	867.7 ± 537.9
Exacerbation history, previous year, n/year	4.3 ± 2.6	6.7± 2.2
OCS user, n (%)	53 (63.8)	30 (100)
FEV_1, %	63.6 ± 17.1	54.6 ± 14.7
FEV_1/FVC, %	66.5 ± 12.9	59.2 ± 9.7

Maglio A, et al. Int J Mol Sci 2023;24(3):2455.

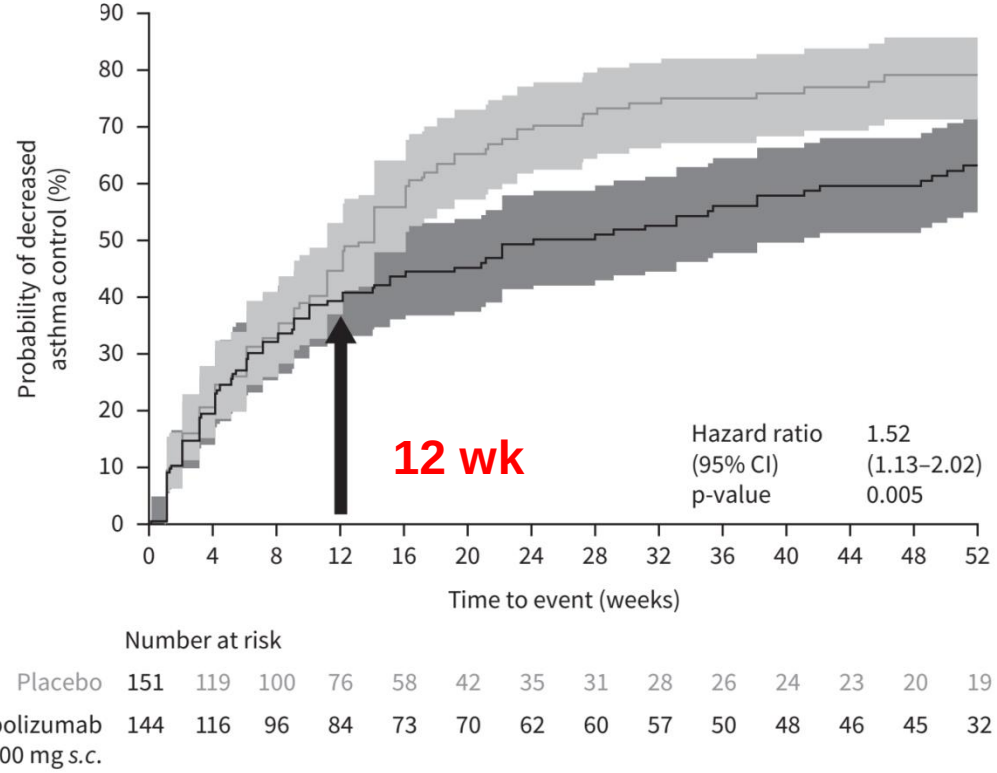
On- and off-treatment clinical remission with mepolizumab

- Severe eosinophilic asthma patients who received continous mepolizumab for ≥3 weeks from COLUMBA/COSMEX trial, COMET study
- Stop (switch to placebo) vs. continuous mepolizumab 100mcg SC q4wk, 52wks

Clinically significant exacerbation



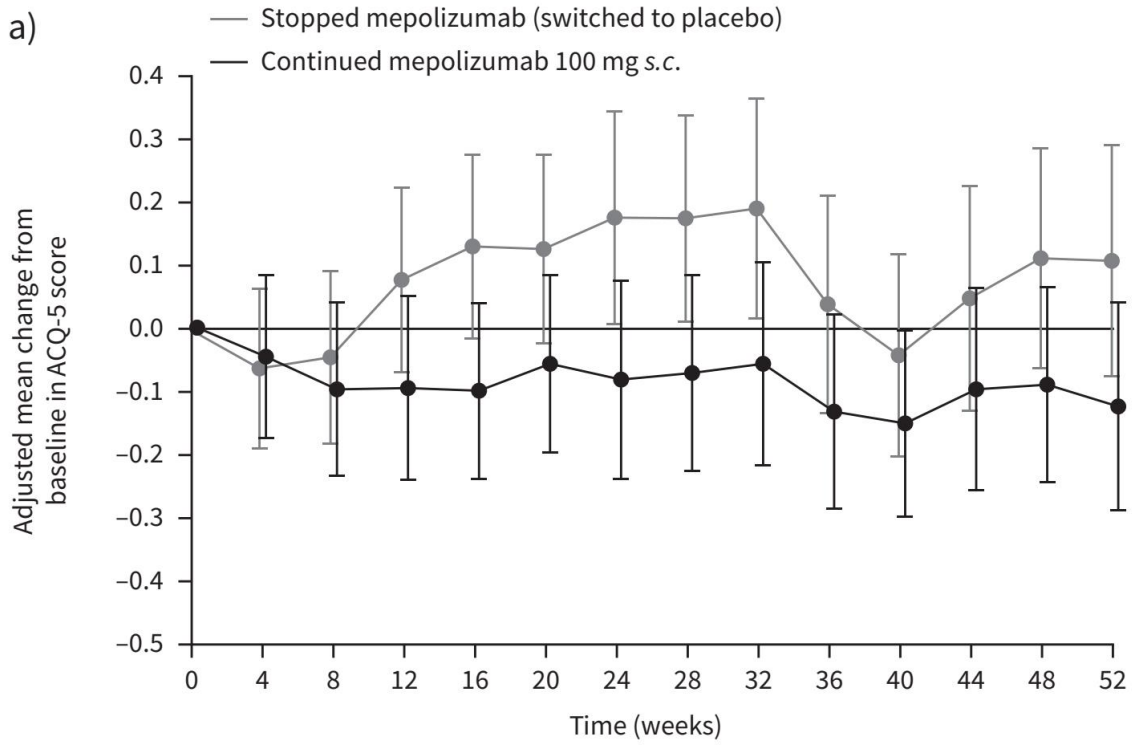
Decreased asthma control



Moore WC, et al. Eur Respir J 2022;59(1):2100396.

Clinical outcomes after stopping mepolizumab

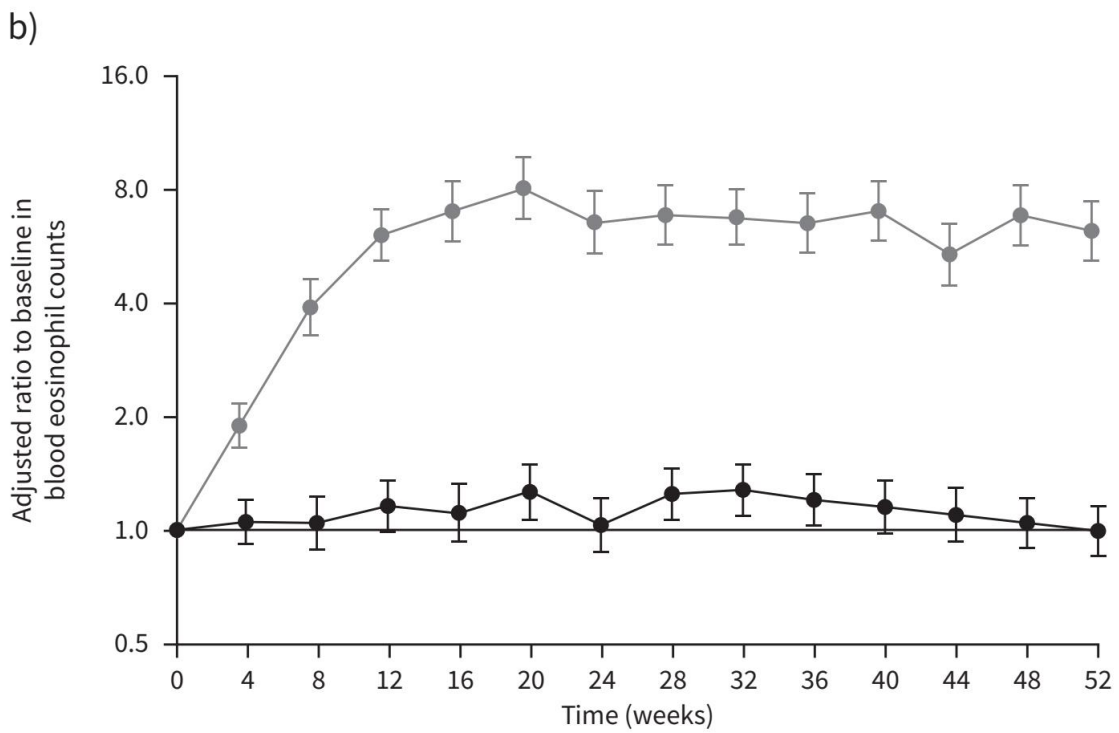
ACQ-5 score



Number of patients at each time point

Placebo	151	145	132	125	106	91	84	81	76	69	68	66	61	56
Mepolizumab 100 mg *s.c.*	144	143	134	130	124	117	110	107	105	98	95	96	93	74

Blood eosinophil counts



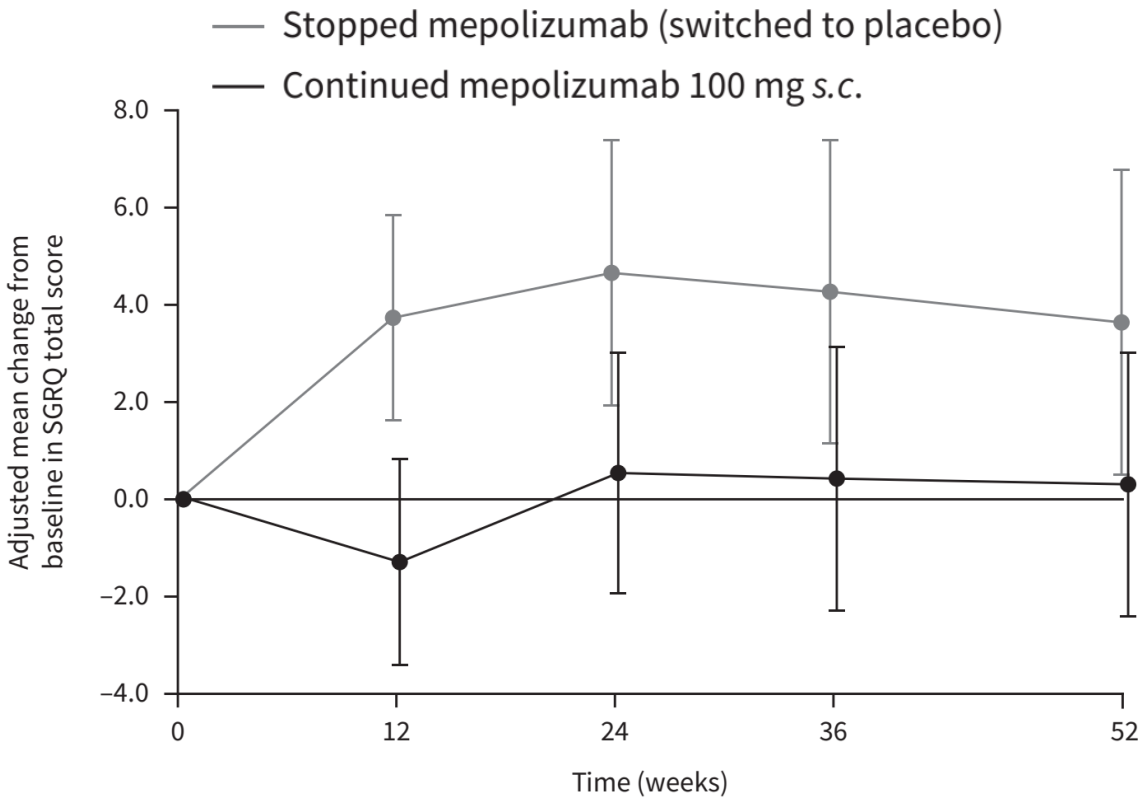
Number of patients at each time point

Placebo	150	145	136	121	103	84	79	77	75	65	68	66	60	60
Mepolizumab 100 mg *s.c.*	141	137	133	120	114	102	106	101	99	99	93	92	86	92

Moore WC, et al. Eur Respir J 2022;59(1):2100396.

Clinical outcomes after stopping mepolizumab

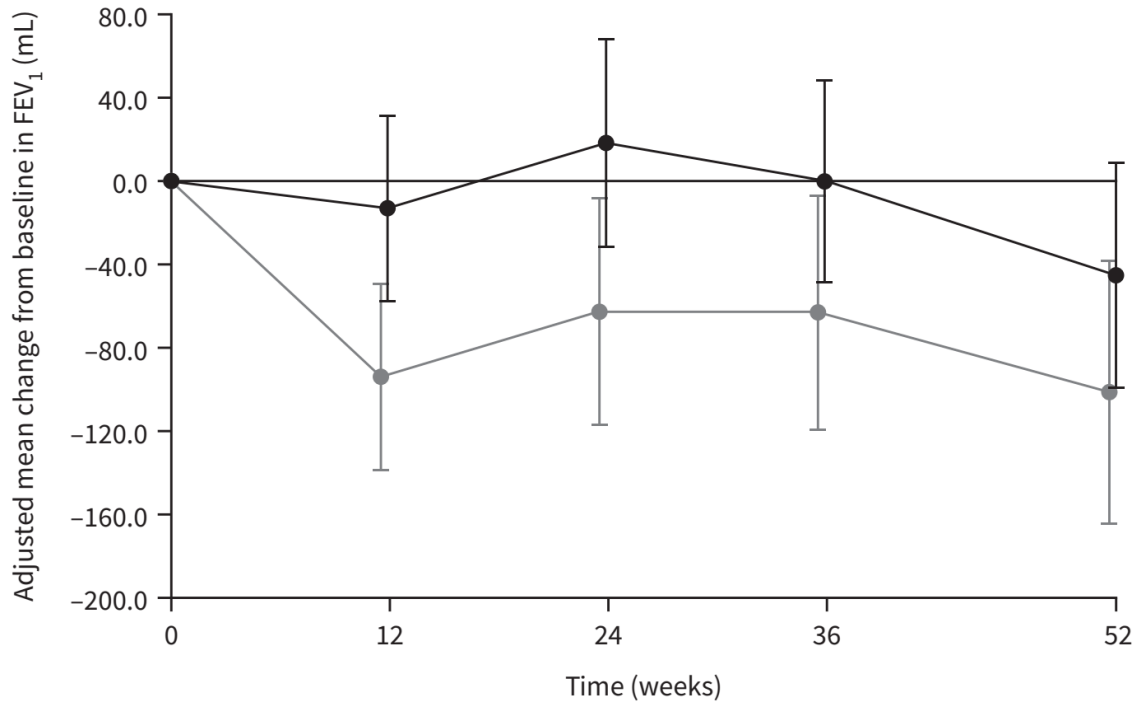
SGRQ total score



Number of patients at each time point

Placebo	151	137	92	74	65
Mepolizumab 100 mg *s.c.*	144	141	117	106	94

FEV_1 (mL)



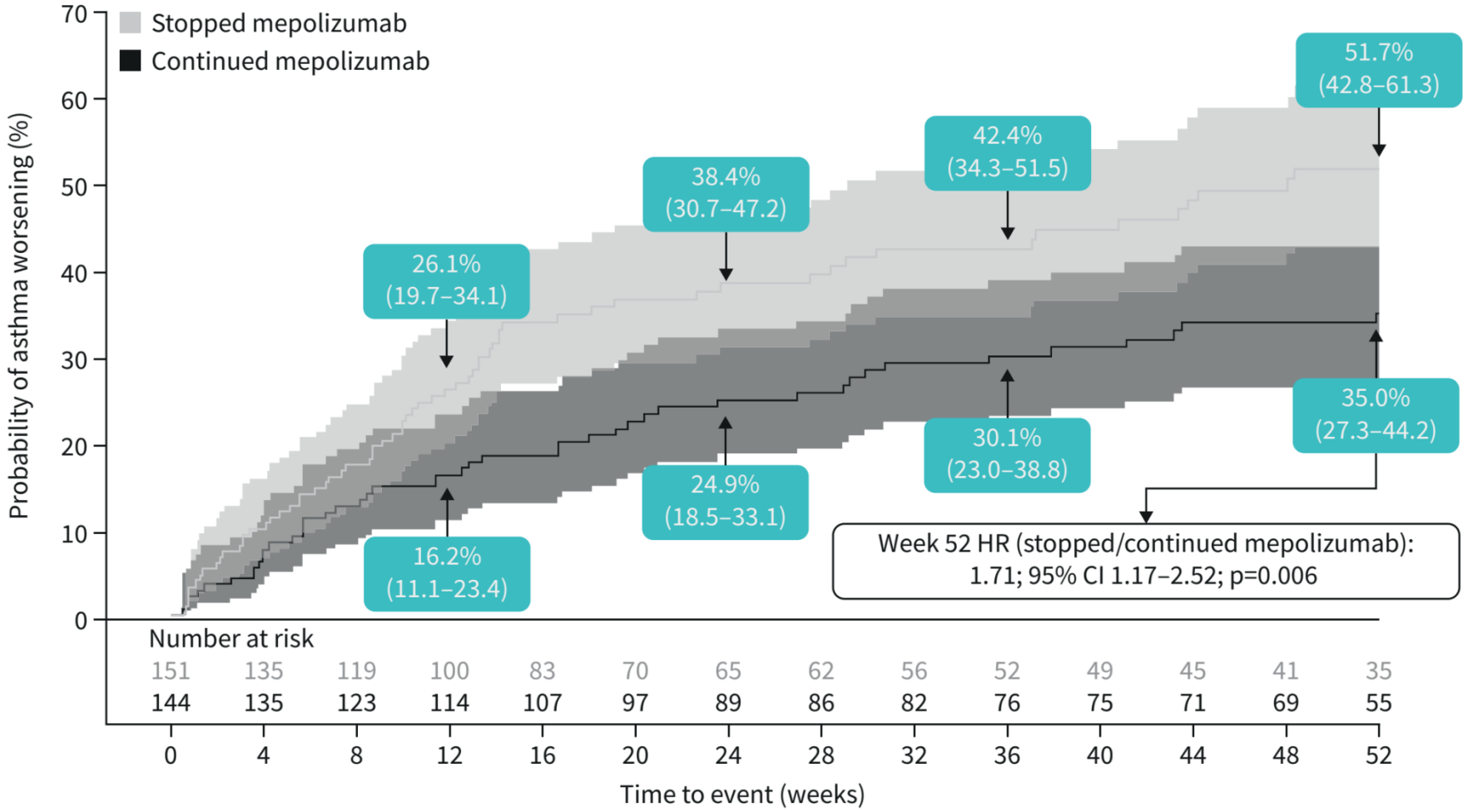
Number of patients at each time point

Placebo	150	137	93	75	65
Mepolizumab 100 mg *s.c.*	144	139	116	106	94

Moore WC, et al. Eur Respir J 2022;59(1):2100396.

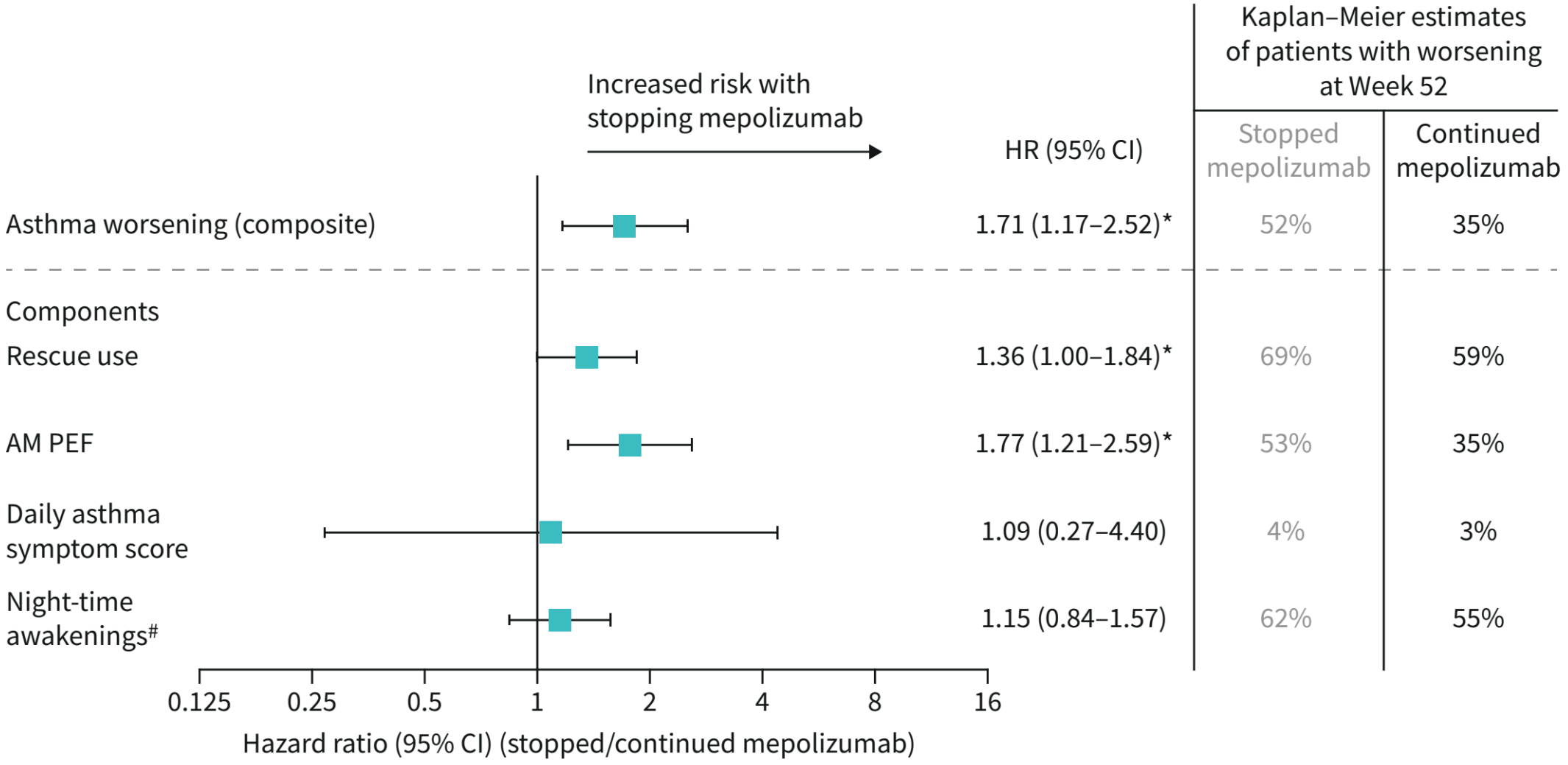
Cumulative incidence of asthma worsening

- Asthma worsening as composite endpoint (rescue medication use, symptoms, awakening at night, and morning peak expiratory flow)



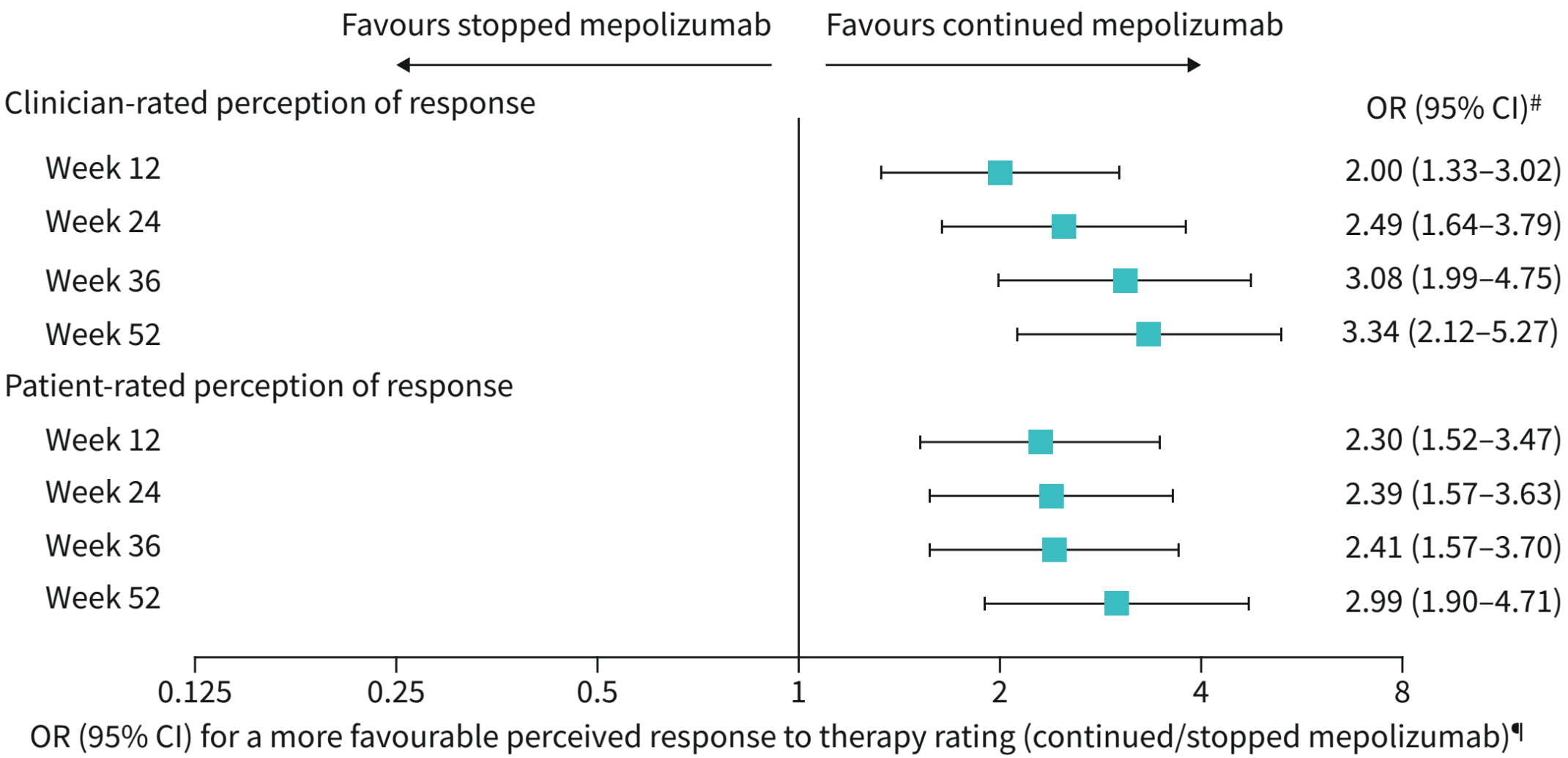
Liu MC, et al. ERJ Open Res 2022;8(1):00419-2021.

Risk of asthma worsening over 52 weeks



Liu MC, et al. ERJ Open Res 2022;8(1):00419-2021.

Overall perception of response to therapy

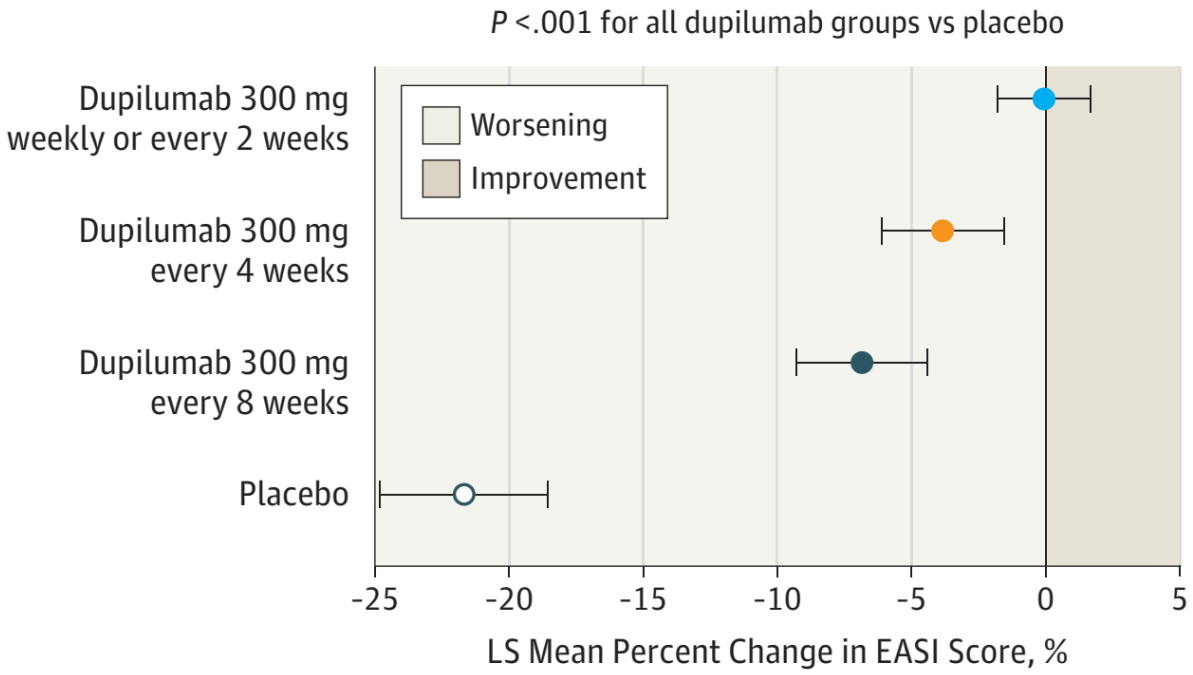


Liu MC, et al. ERJ Open Res 2022;8(1):00419-2021.

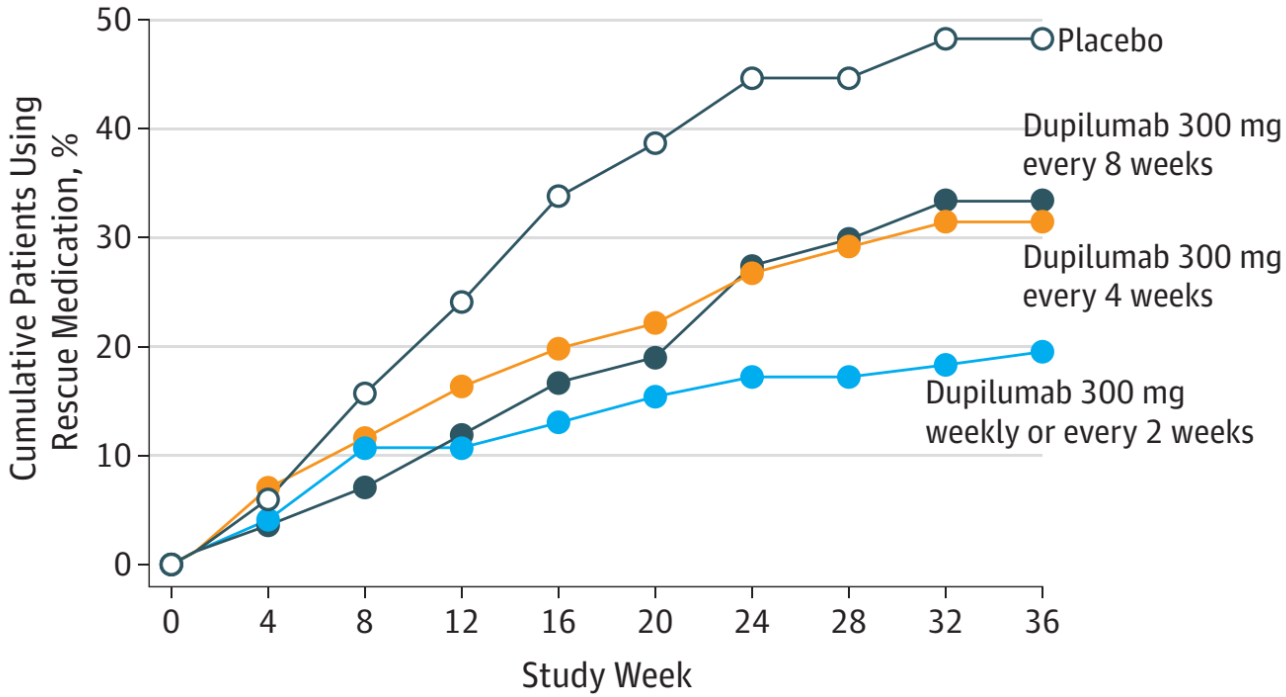
Tapering after initial successful treatment of atopic dermatitis

- 422 patients with moderate-to-severe atopic dermatitis who received dupilumab treatment and achieved improvement, SOLO-CONTINUE study
- Continuing once weekly or q2wk vs. q4wk vs. q8wk

Eczema area and severity index



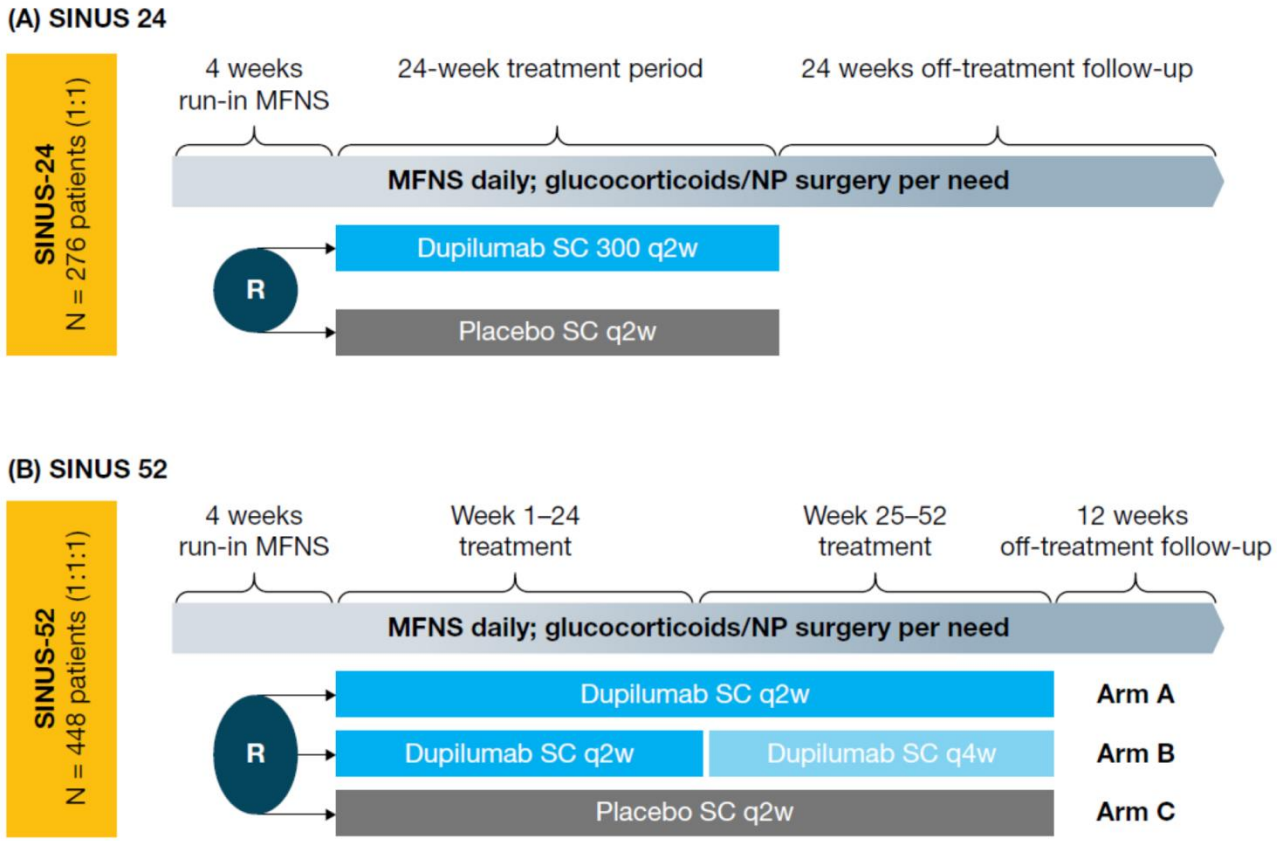
Rescue medication use



Worm M, et al. JAMA Dermatol 2020;156(2):131-143.

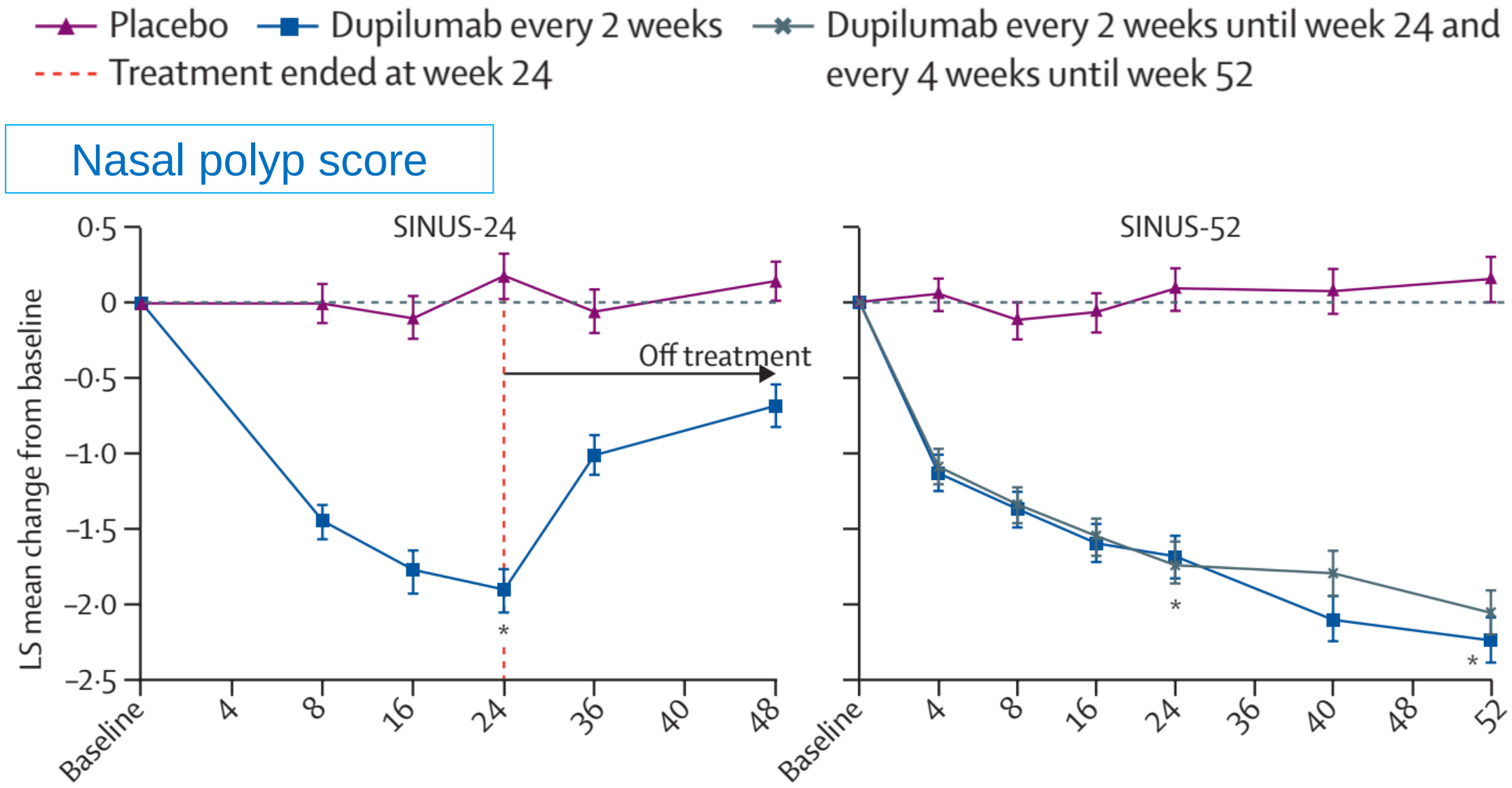
Dupilumab in severe chronic sinusitis with nasal polyp

- Patients with bilateral CRSwNP and symptoms despite intranasal corticosteroid use, receiving systemic corticosteroids in the preceding 2 years, or having had sinonasal surgery (SINUS-24, SINUS-52)
- Comorbid asthma: 57~63% in baseline



Bachert C, et al. Lancet 2019;394:1638-50.

Change in CRSwNP according to maintenance of dupilumab



Bachert C, et al. Lancet 2019;394:1638-50.

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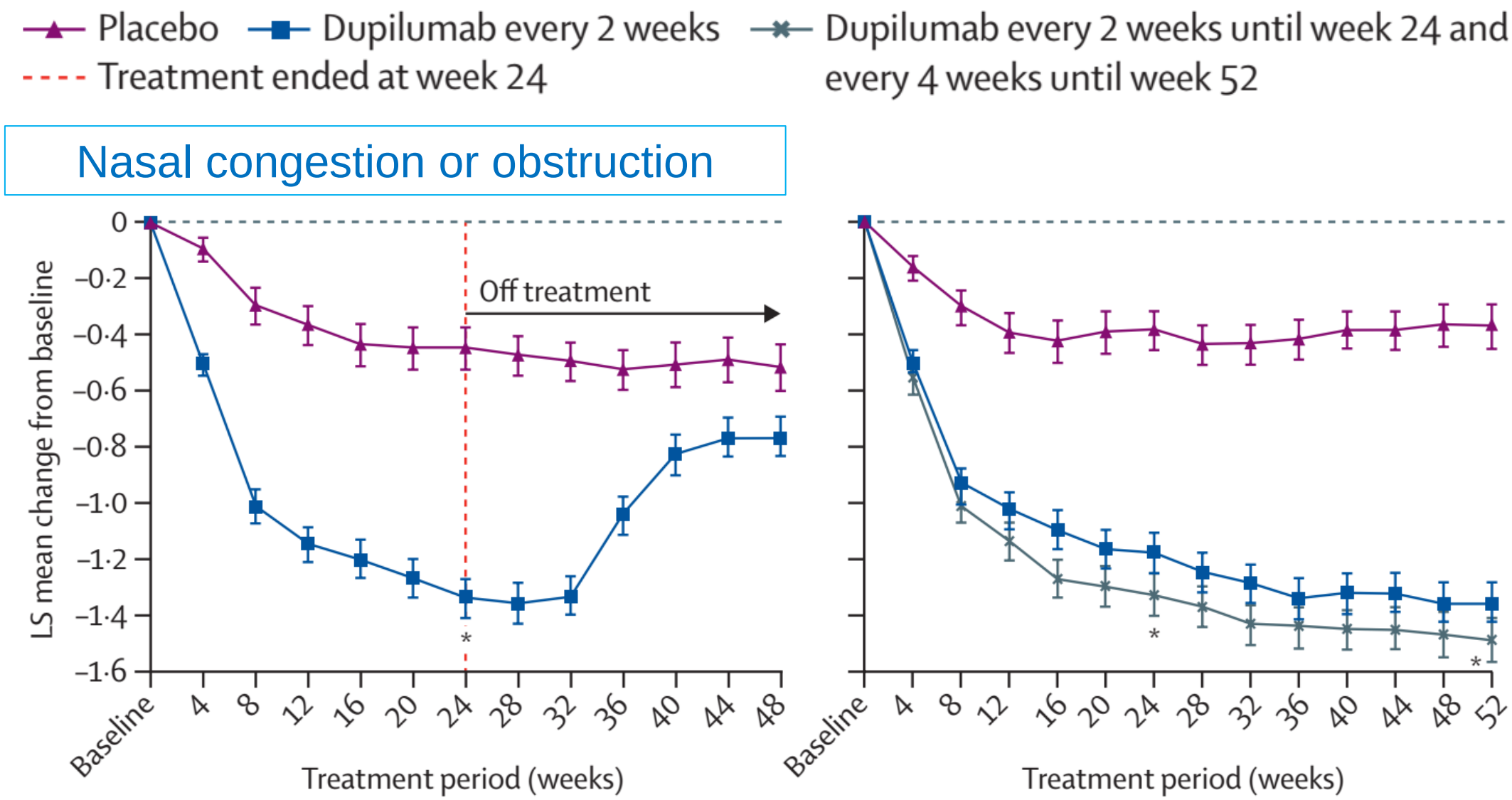
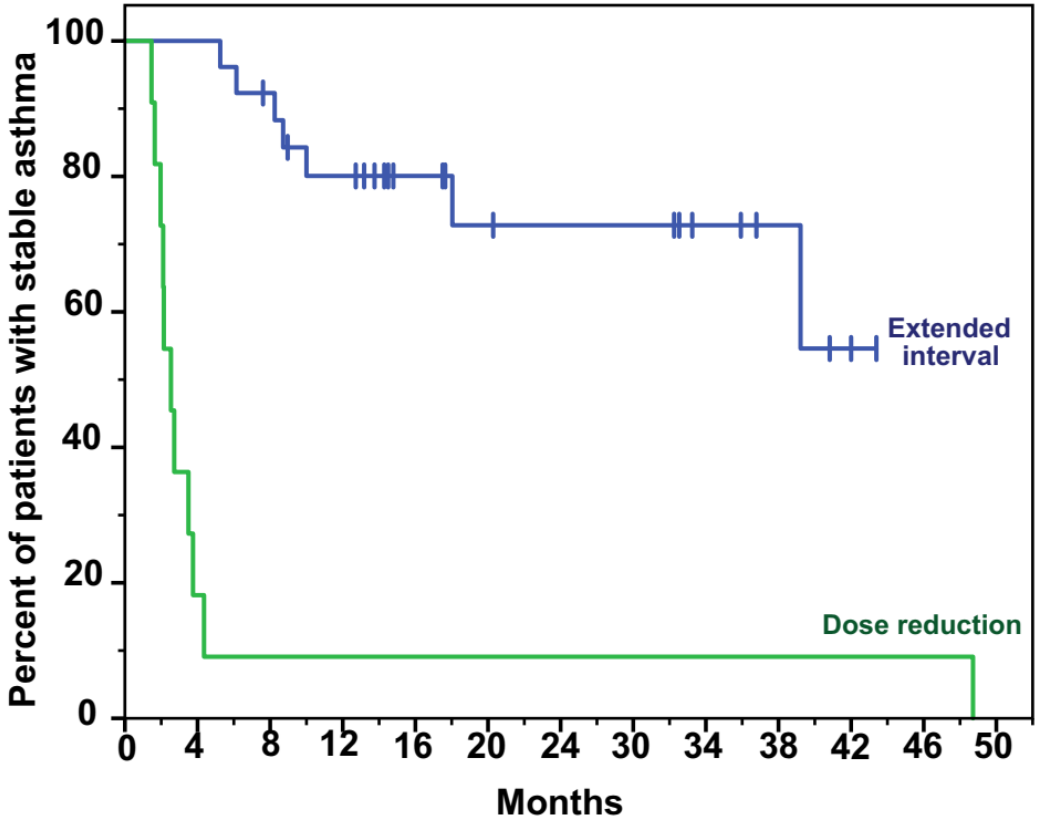


Bachert C, et al. Lancet 2019;394:1638-50.

Omalizumab tapering: Interval vs. Dose

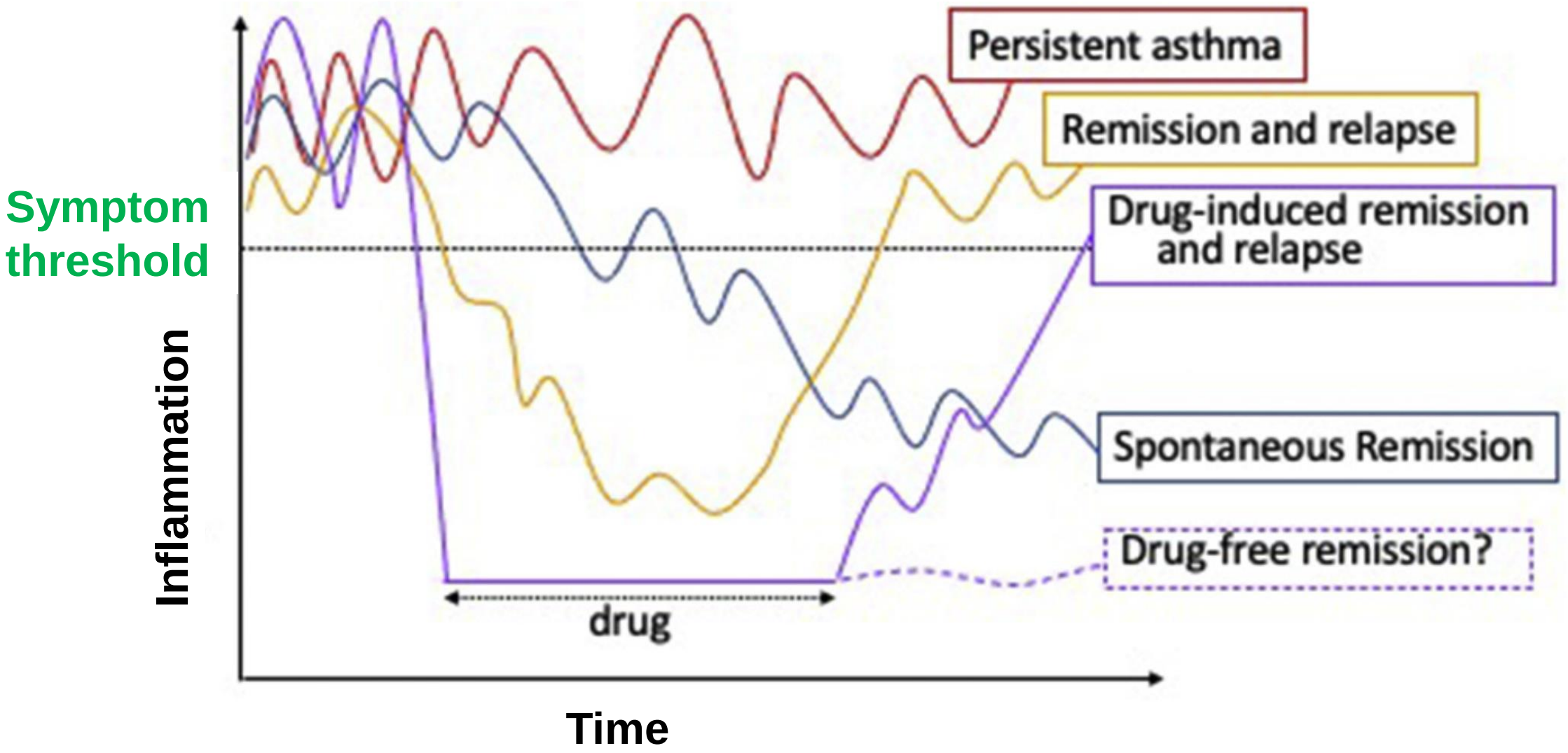
- 37 severe allergic asthma with symptoms during day and night, FEV_1 <80%, at least one sensitization to a perennial allergen and unstable disease though receiving maximum doses of ICS, retrospective study
- Stable condition for ≥4 months with omalizumab → tapering



- ✓ Extended interval group
  - 73% remained in control
- ✓ Dose reduction group
  - 100% loss of asthma control

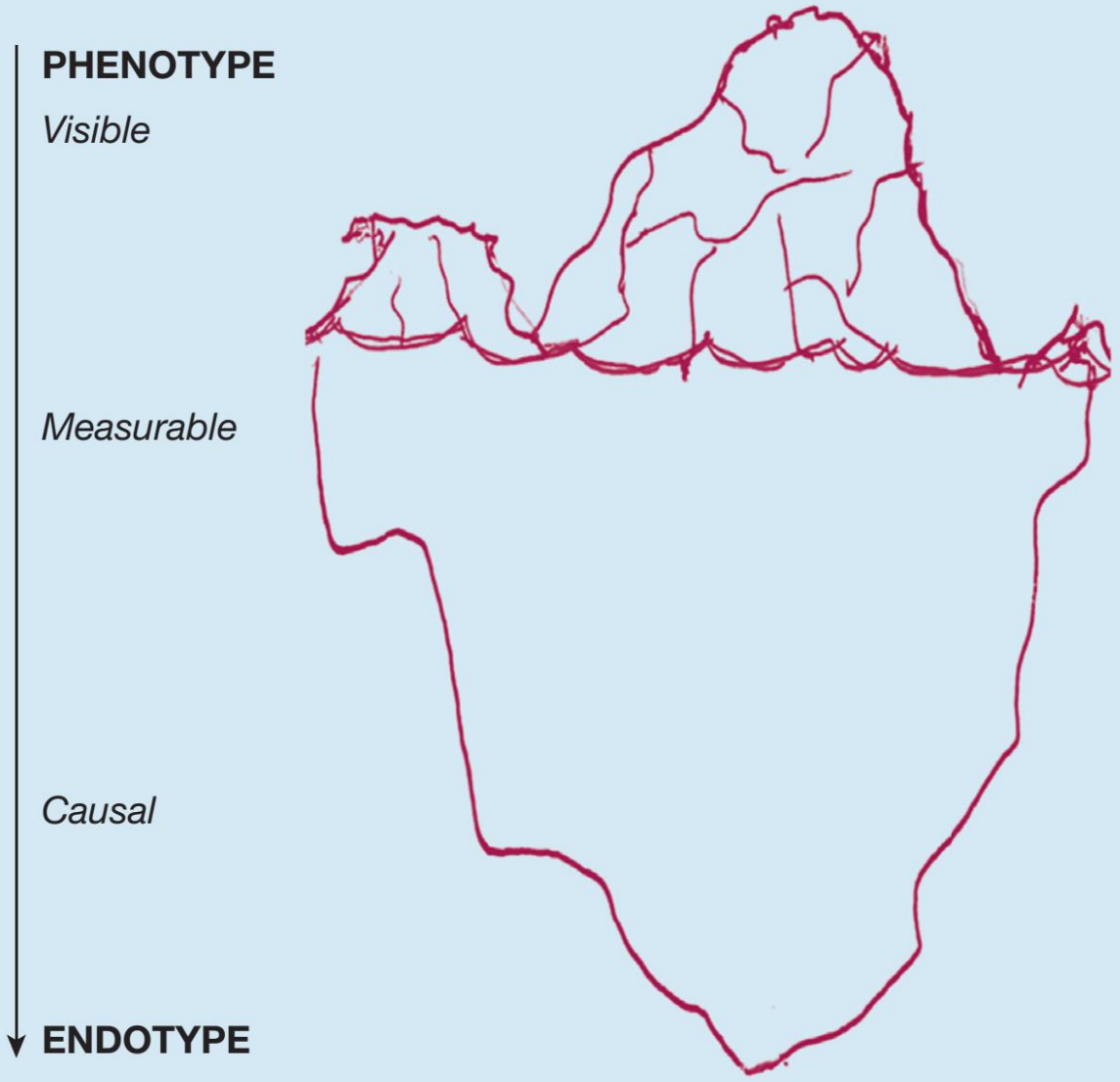
Bolke G, et al. Allergo J Int 2019;28:1-4.

Theoretical trajectory of asthma remission over time



Cohn L. J Allergy Clin Immunol 2022;150(1):59-61.

Predicting on-biologic remission in asthma



Predictive clinical characteristics

… suggesting an earlier start is better

- Younger age at initiation of biologic therapy
- Shorter disease duration
- Greater FEV_1 at baseline
- No maintenance OCS
- Lower maintenance OCS dose

Predictive type 2 inflammatory biomarkers

… suggesting 'hotter' disease is more responsive

- Blood eosinophil count > 500 cells/μL
  (for anti-IL-5 and anti-IL-5R, IL-4Rᵃ, anti-TSLP)
- F_{ENO} > 40 ppb
  (for anti-IL-4Rᵃ, anti-TSLP, anti-IgE)

Predictive molecular drivers of disease

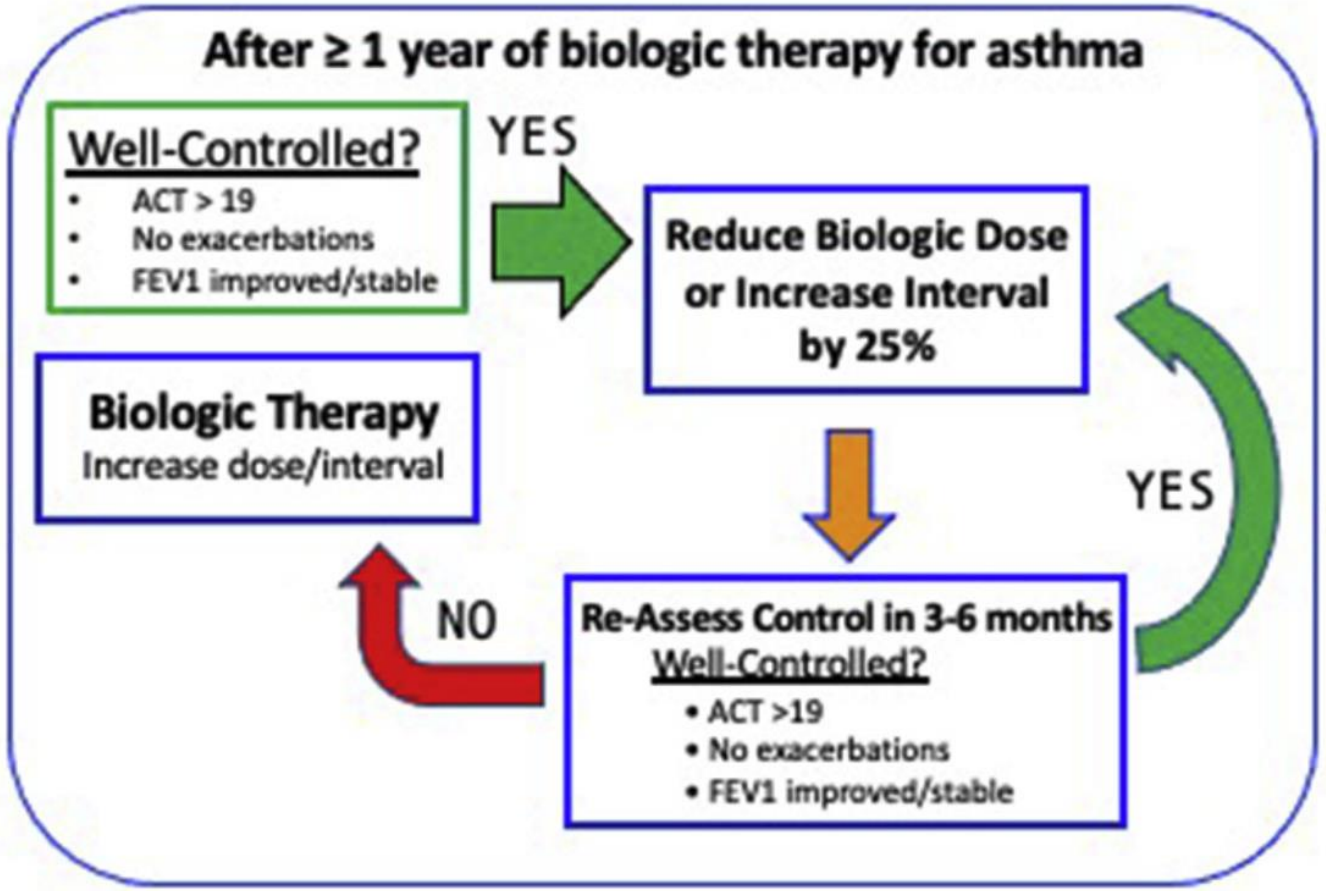
… suggesting treatment should be aligned to targetable drivers of disease active in the specific patient

- Sputum IL-5, sputum EPX (for anti-IL-5)
- ? (for anti-IL-4R, anti-TSLP, anti-IgE)

… Genetic/epigenetic signatures?

Couillard S, et al Chest 2023;163(6):1341-1343.

Proposed approach to reduce asthma biologics



Why reducing biologics may be effective in asthma:

1. Target of biologic may be lower after therapy >1 year
2. Disease may be modified directly due to therapy
3. Disease may be modified indirectly due to therapy affecting co-morbid condition.
4. Disease may be modified unrelated to therapy

Reasons to reduce biologic therapies:

1. Reduce cost and injections
2. Drug dose may be higher than patient requires
3. Minimize development of anti-drug antibodies

Cohn L. J Allergy Clin Immunol 2022;150(1):59-61.

Summary

- Asthma remission in natural course

  Not common, especially in adult-onset asthma
  Persisent risk of relapse

- On-treatment asthma remission

  Promising, but in limited/selected population

- Off-treatment asthma remission

  지못미.....

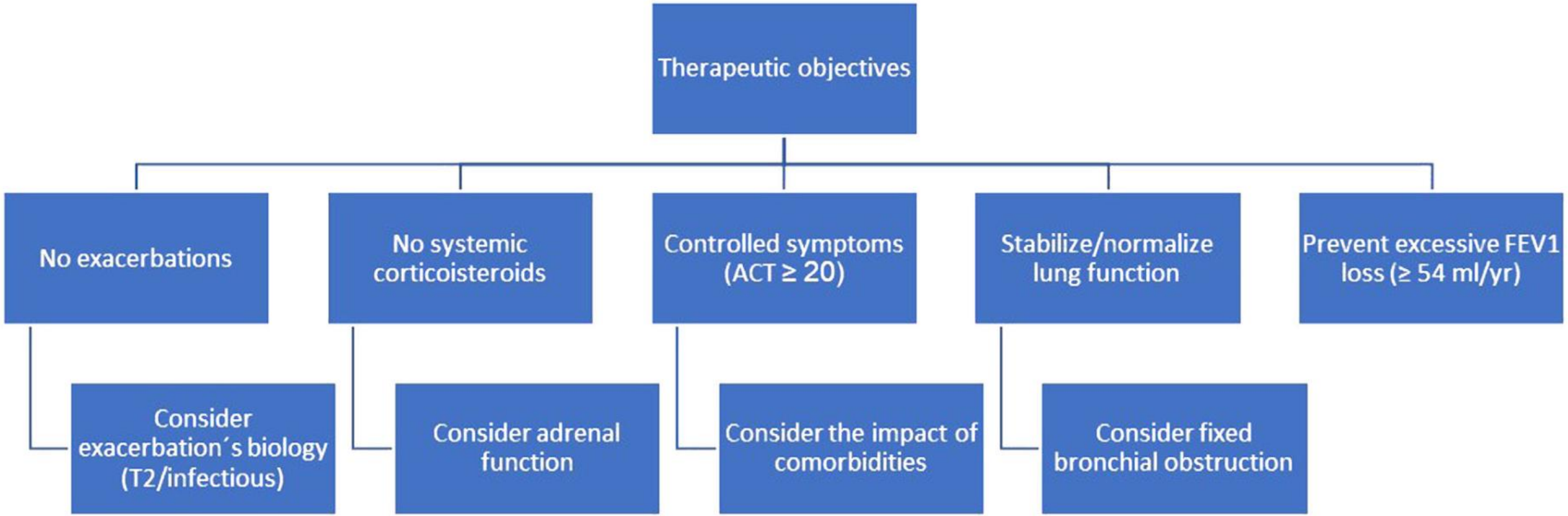
Thank You for Your Attention

Major obstacles in the clinical assessment of complete remission

- Measurement of BHR
  - ✓ Laborious and may be contraindicated in patients with bronchial obstruction
- Direct assessment of airway inflammation with bronchoscopy or induced sputum
  - ✓ Complex; limited accuracy; not practical
- Fixed airflow obstruction
  - ✓ Not amenable to improvement with treatment
- Symptoms may be greatly impacted by the co-morbidities that accompany asthma.

Perez-Llano L, et al. Arch Bronchoneumol 2023 Mar 21;S0300-2896(23)00108-4.

Therapeutic objectives for modifying natural history



Perez-Llano L, et al. Arch Bronchoneumol 2023 Mar 21;S0300-2896(23)00108-4.

Benefit of early intervention

- 181 adult asthma patients, 13-44 years (median 24 years)
- Retested 25 year later
  - ✓ 21% no BHR; 25% FEV_1>90%, 40% no pulmonary symptoms

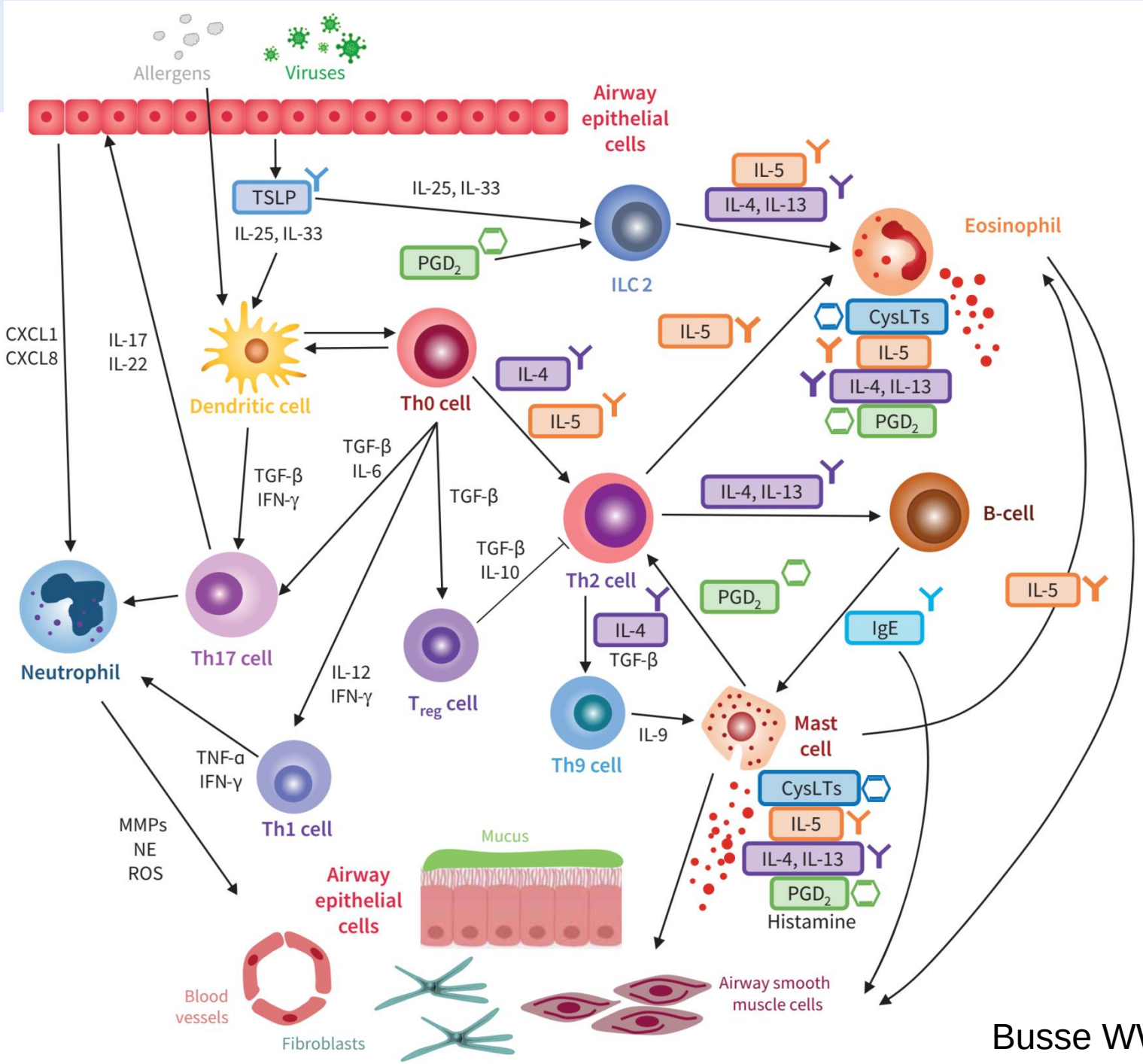
FOUR LOGISTIC REGRESSION ANALYSES. DEPENDENT VARIABLES: ABSENCE OF BHR (PC_{20} HISTAMINE > 16 mg/ml), FEV_1% PREDICTED > 90%, ABSENCE OF REPORTED ASTHMA SYMPTOMS, AND ABSENCE OF ASTHMA*

	No BHR 38 versus 135		FEV_1% pred > 90% 45 versus 128		No Asthma Symptoms 71 versus 102		No asthma 20 versus 153	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Age/10 yr at Visit 1	0.48	(0.27–0.84)§	0.26	(0.13–0.51)¶	0.70	(0.46–1.06)	0.36	(0.15–0.83)§
Sex, male	1.80	(0.71–4.59)	0.42	(0.16–1.08)	1.73	(0.88–3.39)	1.23	(0.37–4.06)
Current smoking at Visit 2	1.65	(0.66–4.14)	0.81	(0.31–2.13)	0.83	(0.40–1.73)	0.82	(0.25–2.61)
$FEV_1/height^2$ at Visit 1, dl/m^2	1.37	(1.08–1.74)‖	1.72	(1.31–2.25)¶	1.11	(0.94–1.31)	1.42	(1.05–1.91)§
ΔFEV_1% pred at Visit 1, %†	1.01	(0.96–1.05)	1.02	(0.98–1.06)	1.00	(0.97–1.03)	0.98	(0.93–1.04)
Ln (slope BHR) at Visit 1	0.95	(0.61–1.47)	0.93	(0.59–1.47)	0.94	(0.67–1.30)	1.06	(0.60–1.85)
Untreated period, yr‡	0.93	(0.88–0.99)§	1.00	(0.94–1.07)	1.00	(0.97–1.04)	0.98	(0.90–1.06)
Log (IgE) at Visit 2, IU/L	0.33	(0.14–0.78)§	0.46	(0.20–1.06)	1.47	(0.83–2.61)	0.38	(0.13–1.11)

- ✓ Factors associated with remission: mild asthma, better lung function, better asthma control, younger age, early-onset asthma, shorter duration of asthma, milder BHR, fewer comorbidities and smoking cessation or never smoking

Panhuysen CI, et al. Am J Respir Crit Care Med 1997;155(4):1267-72.

Asthma therapies with disease-modifying potential and targets

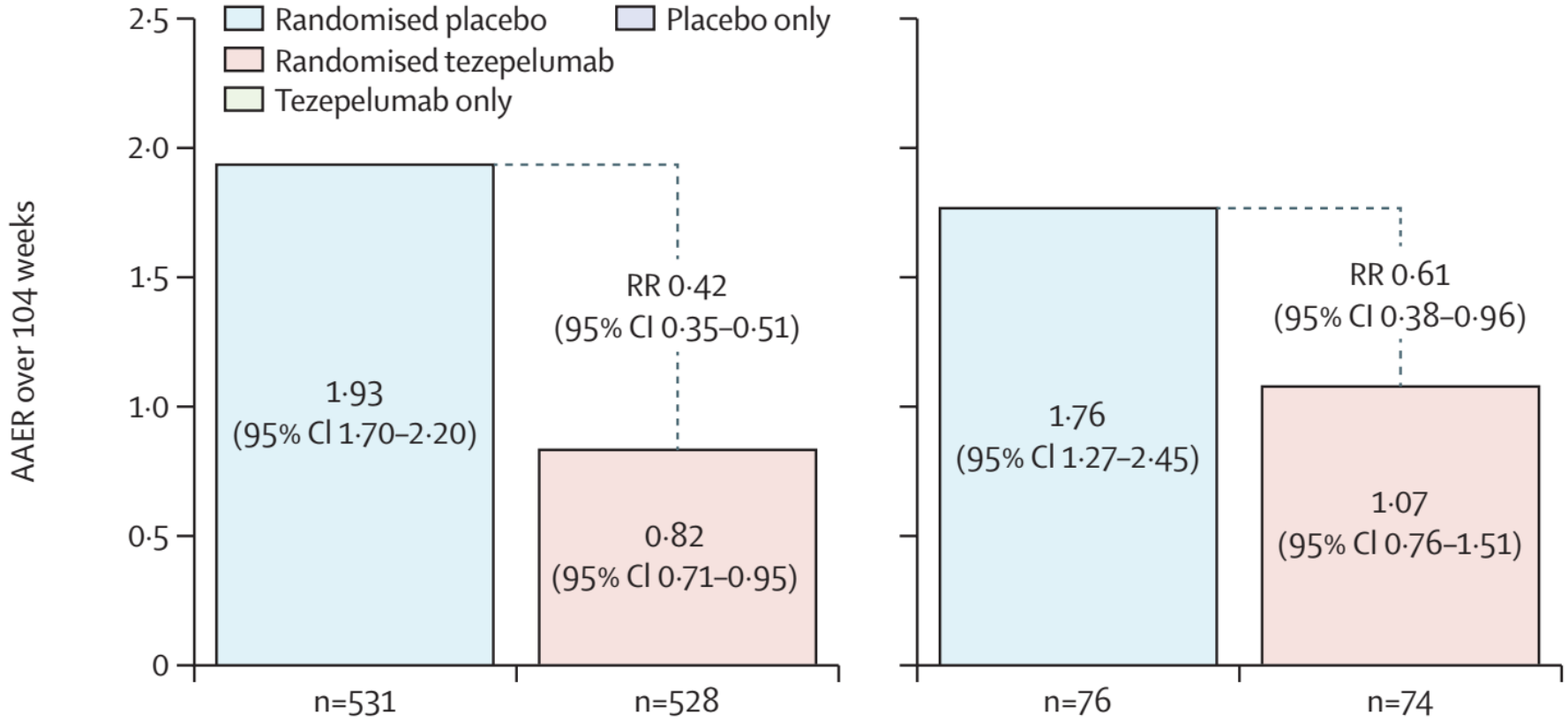


- Anti-TSLP mAbs
- Anti-IL-4R mAbs
- Anti-IL-5/-5R mAbs
- Anti-IgE mAbs
- PGD_2 antagonists
- CysLT receptor antagonists

Busse WW, et al Eur Respir Rev 2022;31(163):210183.

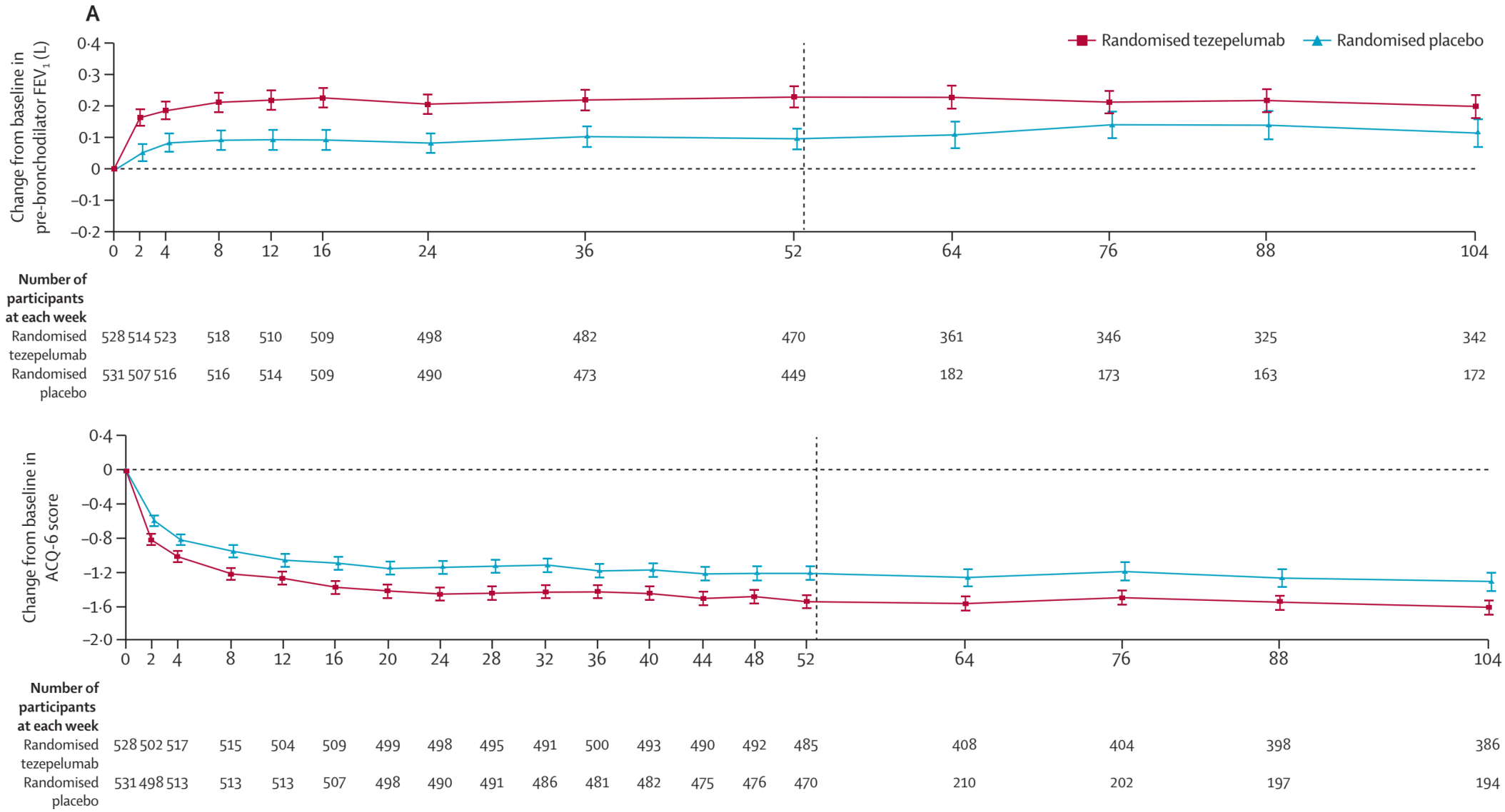
Long-term efficacy of tezepelumab in severe uncontrolled asthma

- Severe uncontrolled asthma patients, 12-80 years, medium-to-high does ICS with ≥1 additional asthma controller with or without OCS, DESTINATION
- Recruited from NAVIGATOR(52-wk)/SOURCE(48-wk), till 104 weeks



Mezies-Gow A, et al. Lancet Respir Med 2023;11:425-38.

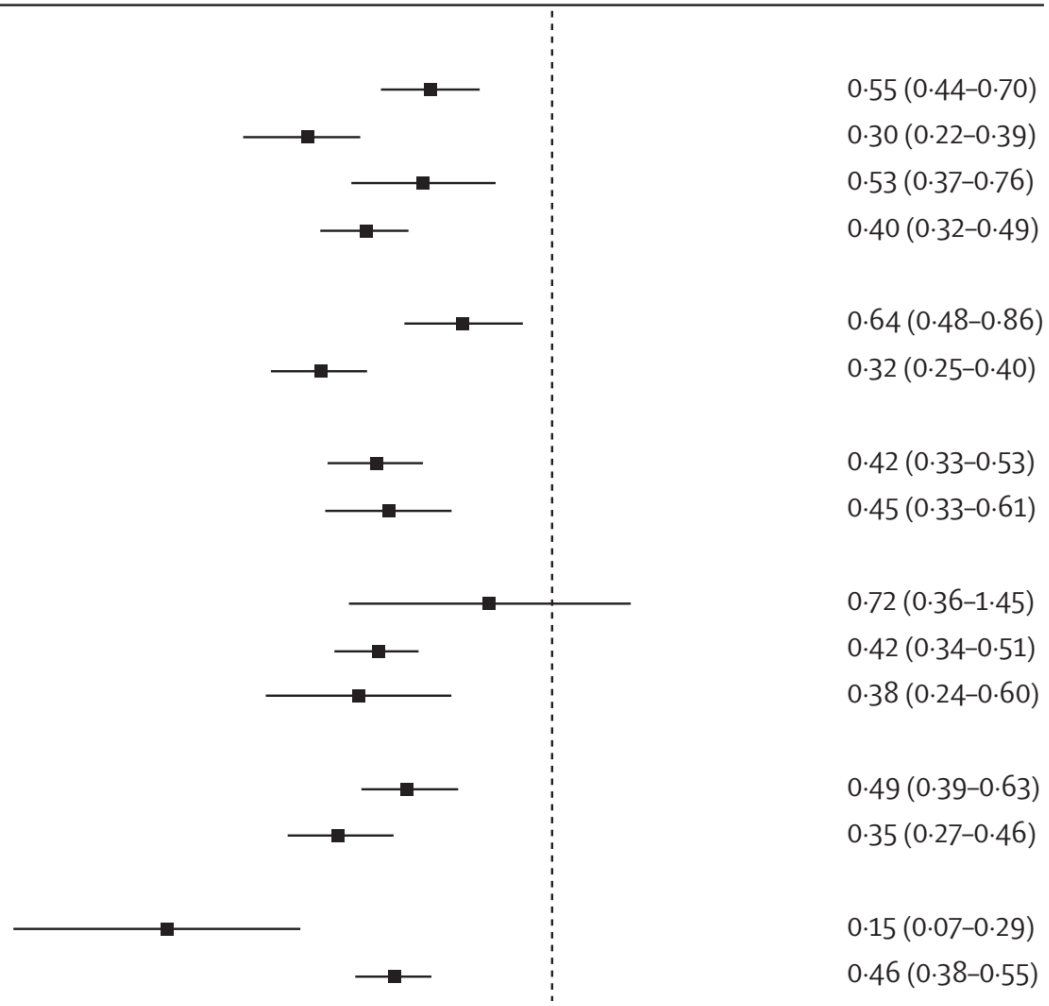
Long-term efficacy of tezepelumab: FEV_1 and ACQ-6



Mezies-Gow A, et al. Lancet Respir Med 2023;11:425-38.

Long-term efficacy of tezepelumab: sub-group analysis

	Randomised tezepelumab n/estimate	Randomised placebo n/estimate	Rate ratio (95% CI)
Baseline blood eosinophil count			
<300 cells per µL	309/0·88	309/1·60	0·55 (0·44–0·70)
≥300 cells per µL	219/0·73	222/2·46	0·30 (0·22–0·39)
<150 cells per µL	138/0·82	138/1·55	0·53 (0·37–0·76)
≥150 cells per µL	390/0·82	393/2·08	0·40 (0·32–0·49)
Baseline FeNO level			
<25 ppb	213/0·90	220/1·40	0·64 (0·48–0·86)
≥25 ppb	309/0·75	307/2·37	0·32 (0·25–0·40)
Allergy status			
FEIA positive for any perennial aeroallergen	339/0·77	341/1·84	0·42 (0·33–0·53)
FEIA negative for all perennial aeroallergens	184/0·94	177/2·09	0·45 (0·33–0·61)
Age at study entry			
Adolescent (≥12 to <18 years)	41/0·56	41/0·78	0·72 (0·36–1·45)
Adult (≥18 to <65 years)	391/0·88	416/2·11	0·42 (0·34–0·51)
Older adult (≥65 years)	96/0·65	74/1·73	0·38 (0·24–0·60)
Number of asthma exacerbations in the year before study entry			
≤2	310/0·61	325/1·23	0·49 (0·39–0·63)
>2	218/1·10	206/1·11	0·35 (0·27–0·46)
Nasal polyps in the 2 years before randomisation			
Yes	42/0·39	41/2·65	0·15 (0·07–0·29)
No	486/0·86	490/1·88	0·46 (0·38–0·55)



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