The Role and Expectation of IL-4 and IL-13 Therapy in Airway Disease

Kenneth Chapman

Asthma & Airway Centre of The University Health Network

Professor of Medicine, University of Toronto

Toronto, Canada

Disclosures

Consultations

Amgen, AstraZeneca, Boehringer Ingelheim, CSL Behring, GlaxoSmithKline, Grifols, InhibRx, Kamada, *Merck Frosst, Novartis,* Regeneron, *Roche,* Sanofi, Takeda

Research Grants/Contracts

Amgen, AstraZeneca, Bellus, BMS, CSL Behring, Genentech, GlaxoSmithKline, Grifols, Kamada, Novartis, Regeneron, Roche, Sanofi, Takeda

Lectures

AstraZeneca, Boehringer-Ingelheim, Grifols, GlaxoSmithKline, Merck Frosst, Novartis, Regeneron, Sanofi

Outline of Biologic Therapy Presentation

- An illustrative case.
- Are we aiming for remission?
- The roles of IL-4 and IL-13.
- BOREAS – off label but interesting.
- Summary

Case 1

Mr. C
68-Year-Old Man With Late-Onset Asthma

Age: 68
Gender: Male

- Presented with asthma exacerbation to the ER 7 years ago
- Nasal polyp surgery 8 years ago and no history of asthma previously
- Nasal congestion, partial anosmia has returned
- Asthma episode appears to have occurred following ingestion of NSAID
- Former smoker (15 pack-years); quit >20 years ago.
- On disability leave from employment in an auto factory because of frequent asthma exacerbations in past 3 years

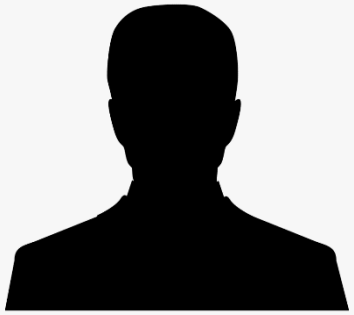
Mr. C
68-Year-Old Man With Late-Onset Asthma

Age: 68
Gender: Male

Medications at Referral

- Budesonide/formoterol 200 mcg; 2 inhalations BID
- Budesonide 200mcg; 2 inhalations BID
- Montelukast 10 mg; QD
- Nasal ciclesonide; 3 sprays each nostril QD

Mr. C
68-Year-Old Man With Late-Onset Asthma



Age: 68
Gender: Male

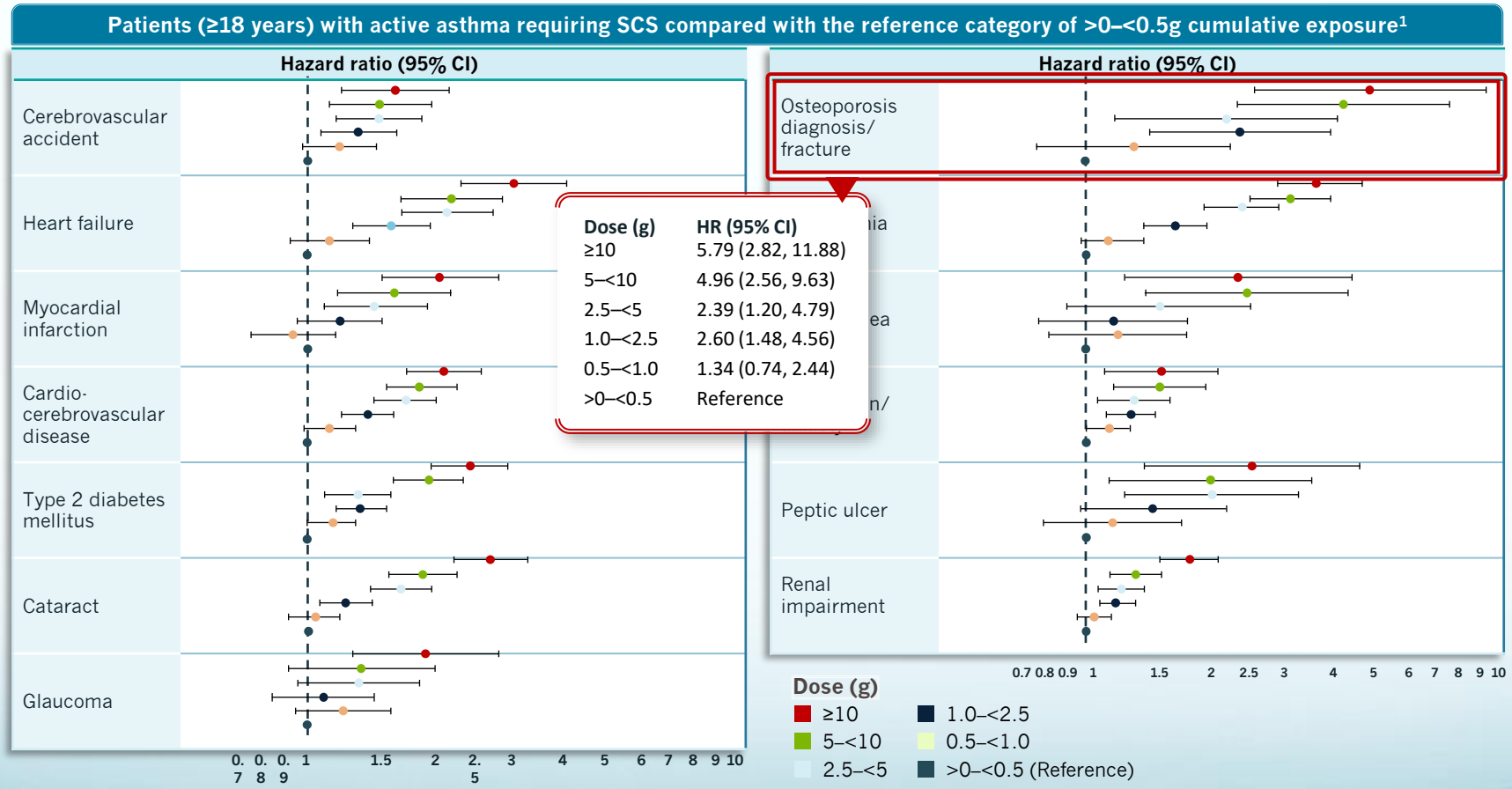
Clinical status:

- ACT 7/25
- ACQ6 3.1
- ER visits every 6 to 8 weeks
- Absent from work

Should we be concerned about short courses of prednisone?

We

Treatment of exacerbations with SCS increases the risk of comorbidity development in a dose-dependent manner



SCS = systemic corticosteroids

1. Price D, et al. J Allergy Asthma 2018;11:193–204

Low-Dose Cumulative OCS Exposure Is Associated With Significant Adverse Effects[1,a]

44% of adults with asthma reported OCS use in the past 12 months[2]

Cumulative OCS Exposure[a]	Osteoporosis Diagnosis and Fracture	Pneumonia	Type 2 Diabetes Mellitus	Cardio-/Cerebrovascular Disease
HR (95% CI) vs reference of >0 to <0.5 g cumulative OCS exposure				
0.5 to <1.0 g	1.34 (0.74-2.44)	1.17 (0.97-1.42)	1.16 (1.01-1.34)	1.14 (0.98-1.32)
1.0 to <2.5 g	2.60 (1.48-4.56)	1.70 (1.41-2.05)	1.37 (1.18-1.58)	1.42 (1.22-1.66)
2.5 to <5 g	2.39 (1.20-4.79)	2.52 (2.02-3.14)	1.34 (1.11-1.63)	1.79 (1.49-2.14)
5 to <10 g	4.96 (2.56-9.63)	3.36 (2.65-4.26)	2.03 (1.65-2.50)	1.96 (1.59-2.41)
≥10 g	5.79 (2.82-11.88)	3.98 (3.09-5.14)	2.59 (2.07-3.24)	2.23 (1.79-2.77)

Most adverse effects become significant above 0.5 to <1.0 g, equal to 4 lifetime "bursts"[1]

HR, hazard ratio.

[a]For cumulative systemic CS exposure, HR are presented per 1.0 g increase in cumulative SCS dose as a continuous variable.[1]

1. Price DB et al. *J Asthma Allergy*. 2018;11:193-204. 2. Price D et al. *NPJ Prim Care Respir Med*. 2014;24:14009.

Low-Dose Cumulative OCS Exposure Is Associated With Significant Adverse Effects[1,2]

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	HR (95% CI) vs reference of >0 to <0.5 g cumulative OCS exposure			
2 – 3	1.34 (0.74-2.44)	1.17 (0.97-1.42)	1.16 (1.01-1.34)	1.14 (0.98-1.32)
4 – 9	2.60 (1.48-4.56)	1.70 (1.41-2.05)	1.37 (1.18-1.58)	1.42 (1.22-1.66)
10 - 19	2.39 (1.20-4.79)	2.52 (2.02-3.14)	1.34 (1.11-1.63)	1.79 (1.49-2.14)
20 - 39	4.96 (2.56-9.63)	3.36 (2.65-4.26)	2.03 (1.65-2.50)	1.96 (1.59-2.41)
≥ 40	5.79 (2.82-11.88)	3.98 (3.09-5.14)	2.59 (2.07-3.24)	2.23 (1.79-2.77)

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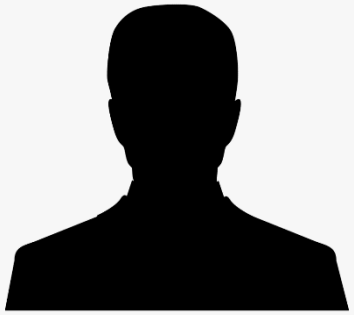
Mr. C
68-Year-Old Man With Late-Onset Asthma



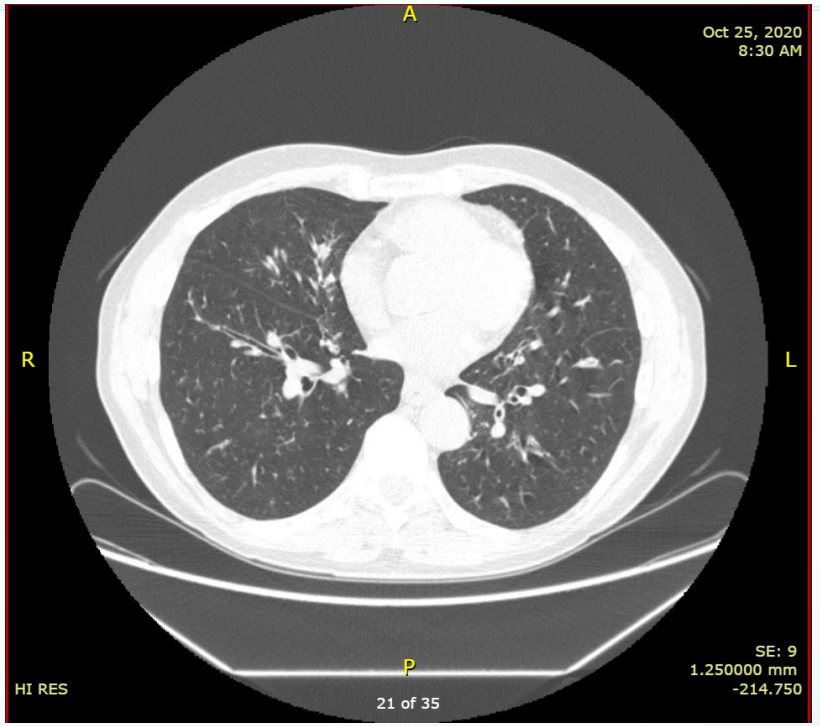
Age: 68
Gender: Male

Labwork:

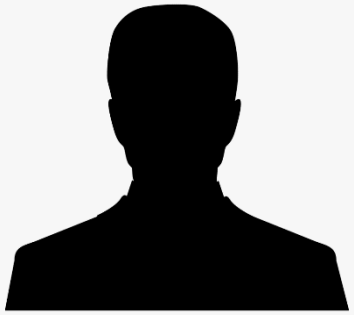
- Blood eosinophil count 500 to 700
- Serum IgE 465 iU/ml
- ANCA negative
- Aspergillus IgG negative
- Sputum eosinophils – not done
- FeNO – not done

Mr. C has Markedly Impaired Lung Function, Abnormal CT

Spirometry	**FEV_1=58% of predicted**
Asthma Control Test	**7 out of 25** *(poorly controlled)*
Thorax CT Scan	**mild cylindrical right upper lobe bronchiectasis with mucus plugging**
Adherence	**>80% controller therapy adherence** *(pharmacy records)*



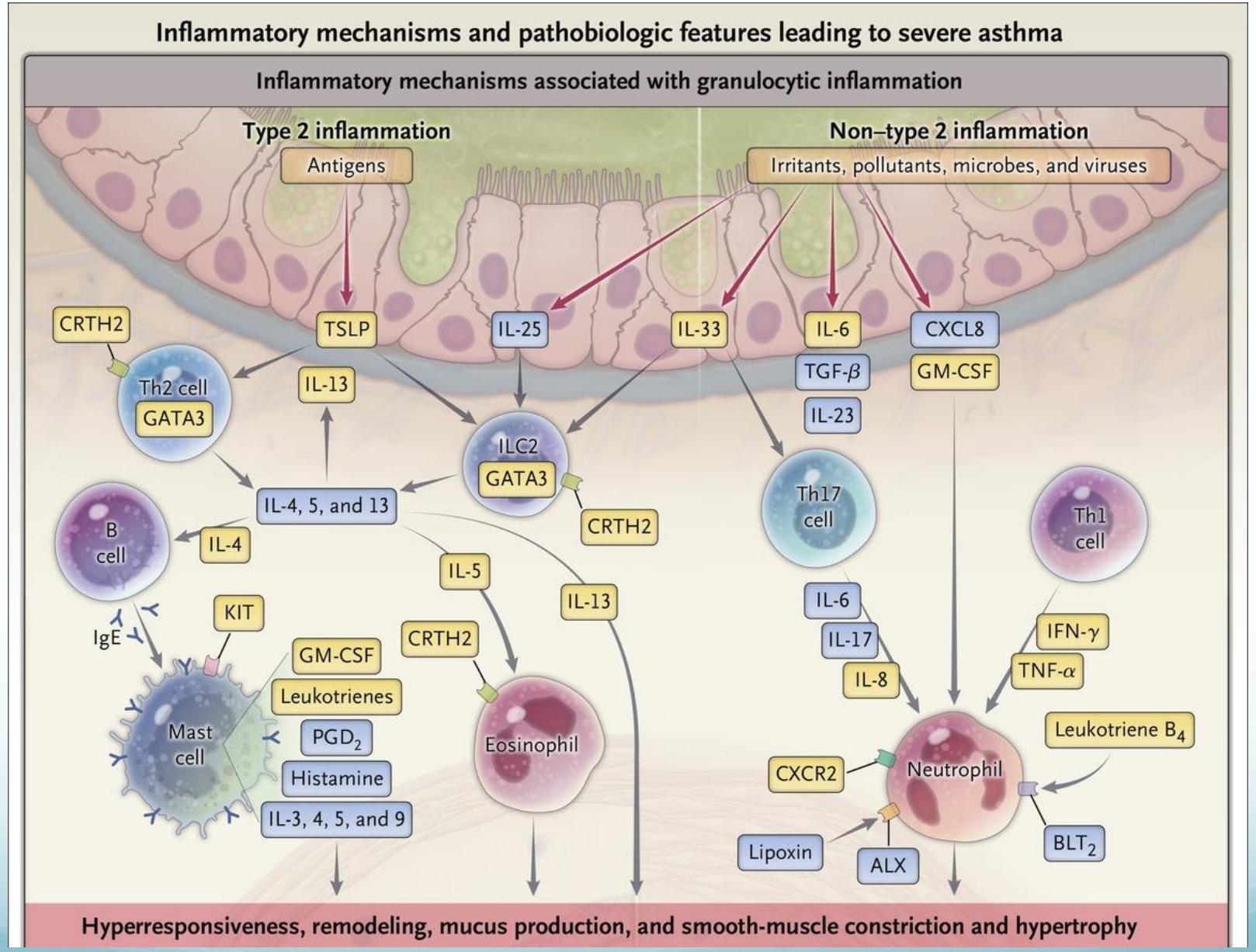
Mr. C
68-Year-Old Man With Late-Onset Asthma



Age: 68
Gender: Male

- A biologic therapy for severe asthma is started – benralizumab.

Inflammatory, Immunologic, and Pathobiologic Features Leading to Severe Asthma.

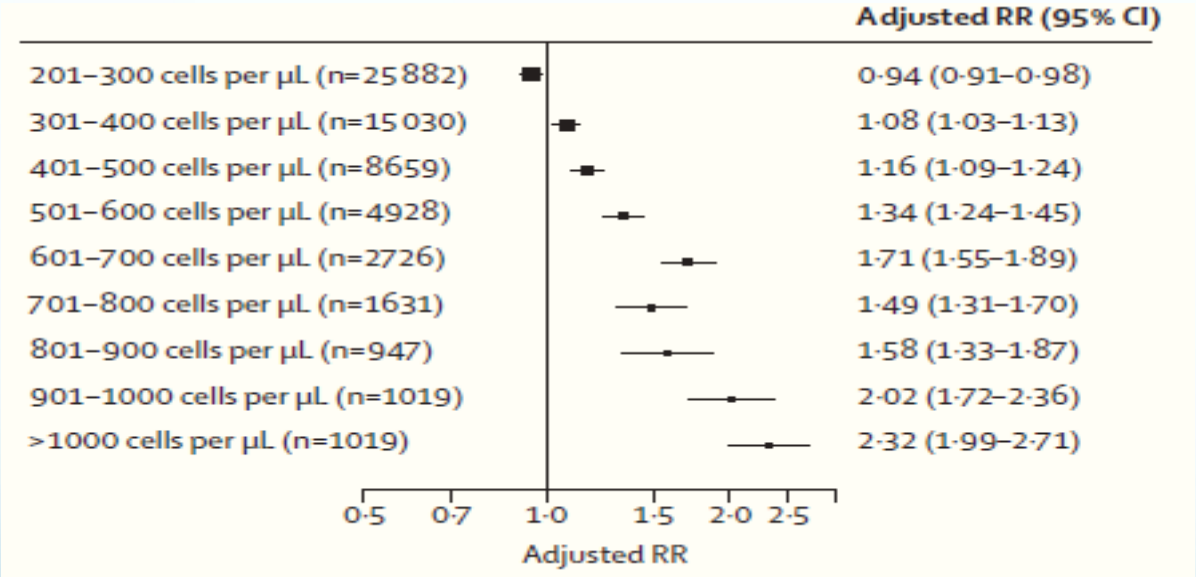


Israel E, Reddel HK. N Engl J Med 2017;377:965-976

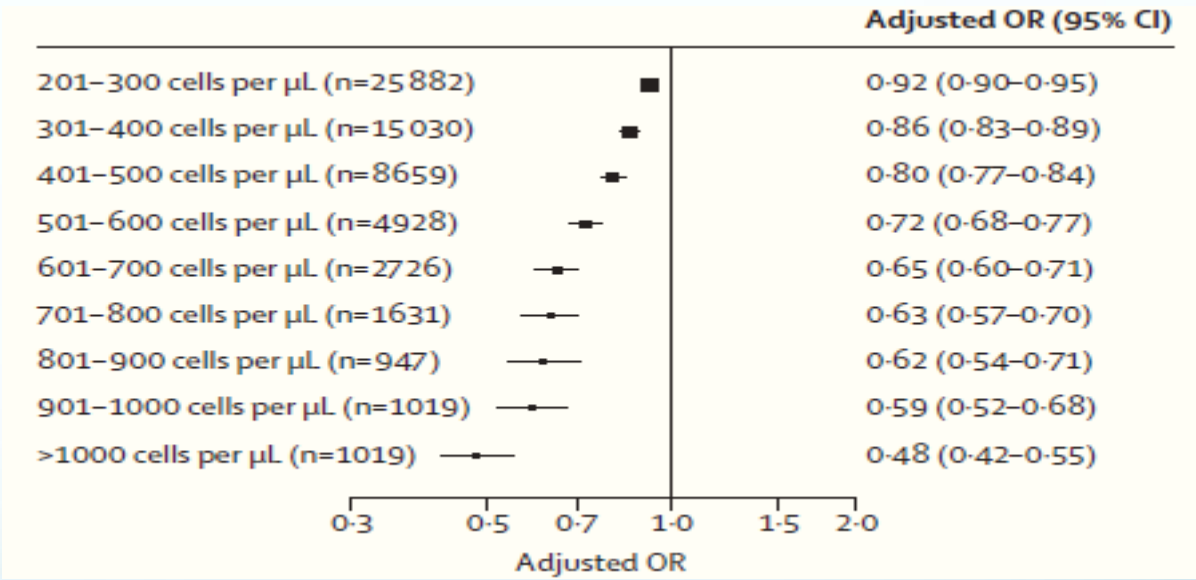
Should our therapy be driven by the blood eosinophil signal?

Blood Eosinophils in Asthma: Relationship to Exacerbations and Control

A



B



Adjusted rate ratios (RRs) for severe exacerbations

Adjusted odds ratios (ORs) for overall asthma control

1-DB Price et Al., October 2015 Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study, The Lancet Respiratory Medicine
2- Wardlaw AJ et al. Br Med Bull. 2000;56(4):985-1003.
3- Van Veen et al. J Allergy Clin Immunol. 2009;124(3): 615-616 4- Tran et Al., Ann Allergy Asthma Immunol. 2014 Jul; 113(1):19-24

Assess and treat severe asthma phenotypes *cont'd*

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities, non-pharmacologic strategies)

8 Consider *add-on biologic Type 2-targeted* treatments

- Consider add-on Type 2-targeted biologic therapy for patients with exacerbations or poor symptom control on high dose ICS-LABA, who have evidence of Type 2 inflammation*
- Consider **local payer eligibility criteria***, **comorbidities** and **predictors of response** when choosing between available therapies
- Also consider cost, dosing frequency, route (SC or IV), patient preference

Which biologic is appropriate to start first?

Eligibility | *Predictors of asthma response*

Anti-IgE *(omalizumab)*

*Is the patient eligible for **anti-IgE** for severe allergic asthma?**
- Sensitization on skin prick testing or specific IgE
- Total serum IgE and weight within dosage range
- Exacerbations in last year

What factors may predict good asthma response to anti-IgE?
- Blood eosinophils ≥260/µl ++
- FeNO ≥20 ppb +
- Allergen-driven symptoms +
- Childhood-onset asthma +

no / *no*

Anti-IL5 / Anti-IL5R *(benralizumab, mepolizumab, reslizumab)*

*Is the patient eligible for **anti-IL5 / anti-IL5R** for severe eosinophilic asthma?**
- Exacerbations in last year
- Blood eosinophils, e.g. ≥150/µl or ≥300/µl

What factors may predict good asthma response to anti-IL5/5R?
- Higher blood eosinophils +++
- More exacerbations in previous year +++
- Adult-onset of asthma ++
- Nasal polyposis ++

no / *no*

Anti-IL4R *(dupilumab)*

*Is the patient eligible for **anti-IL4R** for severe eosinophilic/Type 2 asthma?**
- Exacerbations in last year
- Blood eosinophils ≥150 and ≤1500/µl, or FeNO ≥25 ppb, or taking maintenance OCS

What factors may predict good asthma response to anti-IL4R?
- Higher blood eosinophils +++
- Higher FeNO +++

no / *no*

Anti-TSLP *(tezepelumab)*

*Is the patient eligible for **anti-TSLP** for severe asthma?**
- Exacerbations in last year

What factors may predict good asthma response to anti-TSLP?
- Higher blood eosinophils +++
- Higher FeNO +++

Eligible for none? Return to section **7**

Choose one if eligible*; trial for at least 4 months and assess response

*Good asthma response?**

unclear → Extend trial to 6-12 months*

yes → Good response to T2-targeted therapy

no → **STOP add-on**

Consider switching to a different Type 2-targeted therapy, if eligible*

no → Little/no response to T2-targeted therapy

No evidence of Type 2 airway inflammation

No evidence of Type 2 airway inflammation. Go to section **10**

* *Check local eligibility criteria for specific biologic therapies as these may vary from those listed*

Anti-IgE *(omalizumab)*

*Is the patient eligible for **anti-IgE** for severe allergic asthma?**

- Sensitization on skin prick testing or specific IgE
- Total serum IgE and weight within dosage range
- Exacerbations in last year

no ↑

What factors may predict good asthma response to anti-IgE?

- Blood eosinophils ≥260/µl ++
- FeNO ≥20 ppb +
- Allergen-driven symptoms +
- Childhood-onset asthma +

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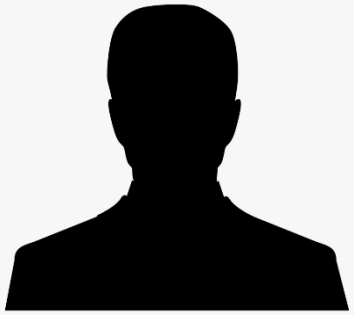
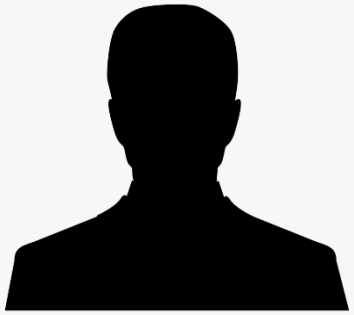


Age: 68
Gender: Male

- A follow-up is booked 4 months after the introduction of biologic therapy - benralizumab.

Mr. C
Evaluation on Biologic Therapy: 4 months



Age: 68
Gender: Male

Clinical status:

- ACT 8/25
- ACQ6 2.7
- No ER visits, no prednisone
- Still absent from work
- Spirometry unchanged.

Mr. C
Decision on Biologic Therapy: 4 months

Age: 68
Gender: Male

You would:

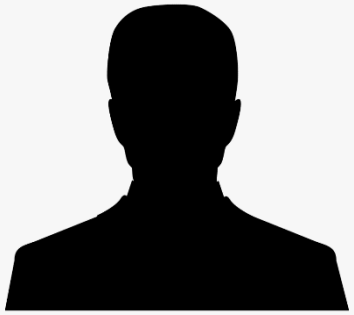
- Continue the current biologic therapy.
- Discontinue the current biologic therapy.
- Switch to an alternative biologic therapy of a different class.
- Phone a friend.

Mr. C
68-Year-Old Man With Late-Onset Asthma

Age: 68
Gender: Male

- After 12 months on biologic therapy - referred to the Asthma & Airway Centre because he continued to have exacerbations requiring prednisone every 6 to 8 weeks despite ICS/LABA and a biologic therapy.

Mr. C
68-Year-Old Man With Late-Onset Asthma



Age: 68
Gender: Male

Clinical status at referral:

- ACT 8/25
- ACQ6 3.2
- 4 bursts of prednisone in the previous 12 months.
- Inhaler technique adequate
- Adherence to inhaled therapy (per pharmacy records) >80%
- Negative skin prick tests to common aeroallergens

Mr. C
68-Year-Old Male With Late-Onset Asthma

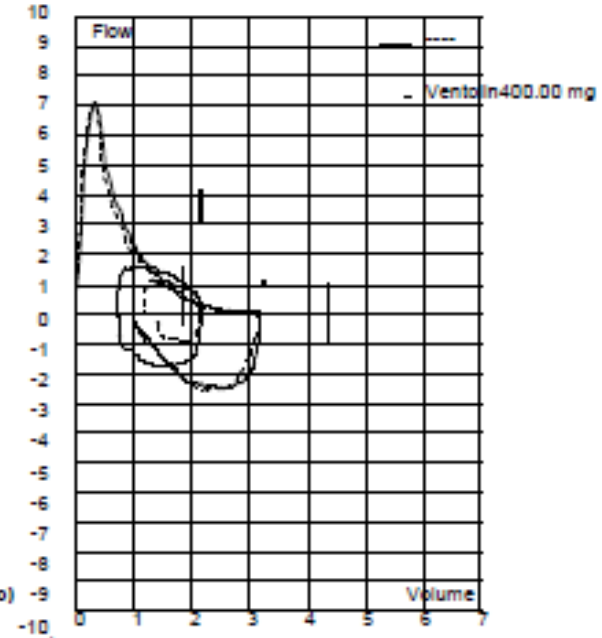
Spirometry	Lower Limit	Upper Limit	Predicted Value	Observed Pre	% Pred.	Observed Post	% Pred.	Percent Change
FVC(L)	3.4	5.3	4.3	** 3.17	** 73	** 3.16	** 73	-0.1
FEV1(L)	2.4		3.2	** 1.86	** 58	** 1.84	** 58	-0.9
FEV1/FVC(%)	66		76	** 59		** 58		-0.9
PEF(L/S)			8.0	7.1	89	7.1	89	-0.2
FEF50(L/S)	LLN: M-61%, F-65%		3.60	0.94	26	0.91	25	-2.5
FEF75(L/S)	LLN: M-55%, F-65%		1.03	0.19	19	0.21	20	6.0
MVV (L/min)	70% --- 130%		128	---	---			
Raw (cmH2O/L/s)	~66% --- ~177%		1.3	2.5	199			
Lung Volumes								
SVC(L)	3.4	5.4	4.4	** 3.1	** 71			
IC(L)	2.4	4.0	3.2	** 2.3	** 72			
ERV(L)				0.8				
FRC PL (L)	2.1	4.5	3.3	4.0	121			
RV(L)	1.7	3.2	2.4	3.1	127			
TLC(L)	5.5	8.2	6.9	6.3	91			
RV/TLC(%)	32	50	41	50	121			
Diffusion	Normal Hb: M; 14.6, F; 13.4							
DLCO (ml/min/mmHg)	~75% --- ~125%		20.7	22.2	107			
Va	5.4	8.1	6.7	** 4.4	** 66			

NOTE: Values are **BOLD outside of normal limits. (excluding FEF 50, 25, Raw & DLco)

Test Tech : S. Amar

Predicted set: Canadian-Gutierrez, C. CRJ-2004

Pre-Post Selected Flow-Volume Loops



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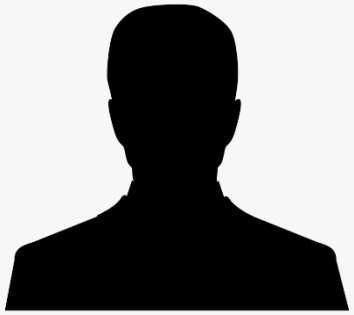
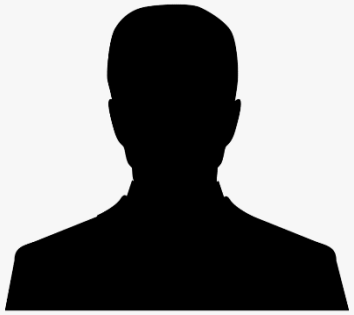


Age: 68
Gender: Male

- The patient is switched to dupilumab.

Mr. C
Evaluation on Alternative Biologic Therapy: 6 months



Age: 68
Gender: Male

Clinical status:

- ACT 24/25
- ACQ6 0.4
- No ER visits, no prednisone
- Still absent from work
- Spirometry normal.

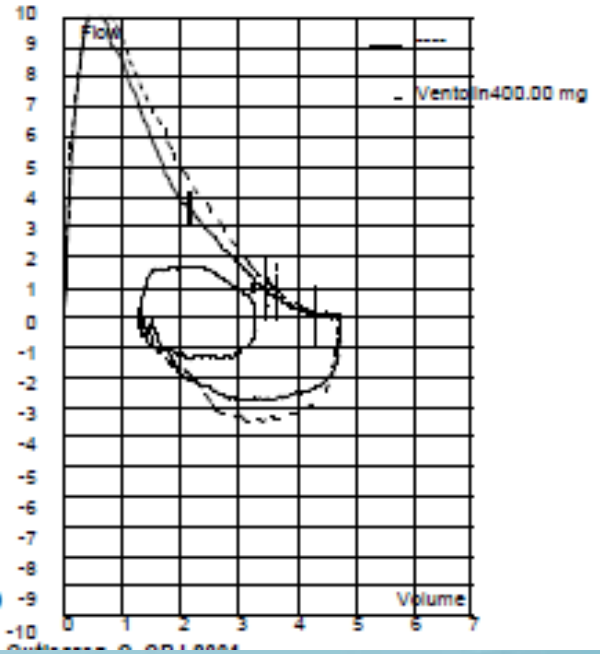
Mr. C
68-Year-Old Male With Late-Onset Asthma

Spirometry	Lower Limit	Upper Limit	Predicted Value	Observed Pre	% Pred.	Observed Post	% Pred.	Percent Change
FVC(L)	3.3	5.3	4.3	4.76	110	4.68	108	-1.6
FEV1(L)	2.3		3.2	3.43	108	3.65	115	6.2
FEV1/FVC(%)	66		75	72		78		8.0
PEF(L/S)			7.9	11.1	140	11.7	148	5.8
FEF50(L/S)	LLN: M-61%, F-65%		3.57	2.99	84	3.97	111	33.1
FEF75(L/S)	LLN: M-55%, F-65%		1.01	0.70	70	1.16	115	64.8
MVV (L/min)	70% --- 130%		127	---	---			
Raw (cmH2O/L/s)	~66% --- ~177%		1.5	1.7	118			
Lung Volumes								
SVC(L)	3.4	5.4	4.4	4.8	110			
IC(L)	2.4	4.1	3.3	3.0	92			
ERV(L)				1.8				
FRC PL (L)	2.1	4.5	3.3	3.3	99			
RV(L)	1.7	3.2	2.5	** 1.5	** 60			
TLC(L)	5.5	8.2	6.9	6.3	91			
RV/TLC(%)	32	50	41	** 23	** 57			
Diffusion	Normal Hb: M; 14.6, F; 13.4							
DLCO (ml/min/mmHg)	~75% --- ~125%		26.0	26.5	102			
Va	5.4	8.1	6.7	6.3	94			

NOTE: Values are **BOLD outside of normal limits. (excluding FEF 50, 25, Raw & DLco)

Test Tech : S. Amar

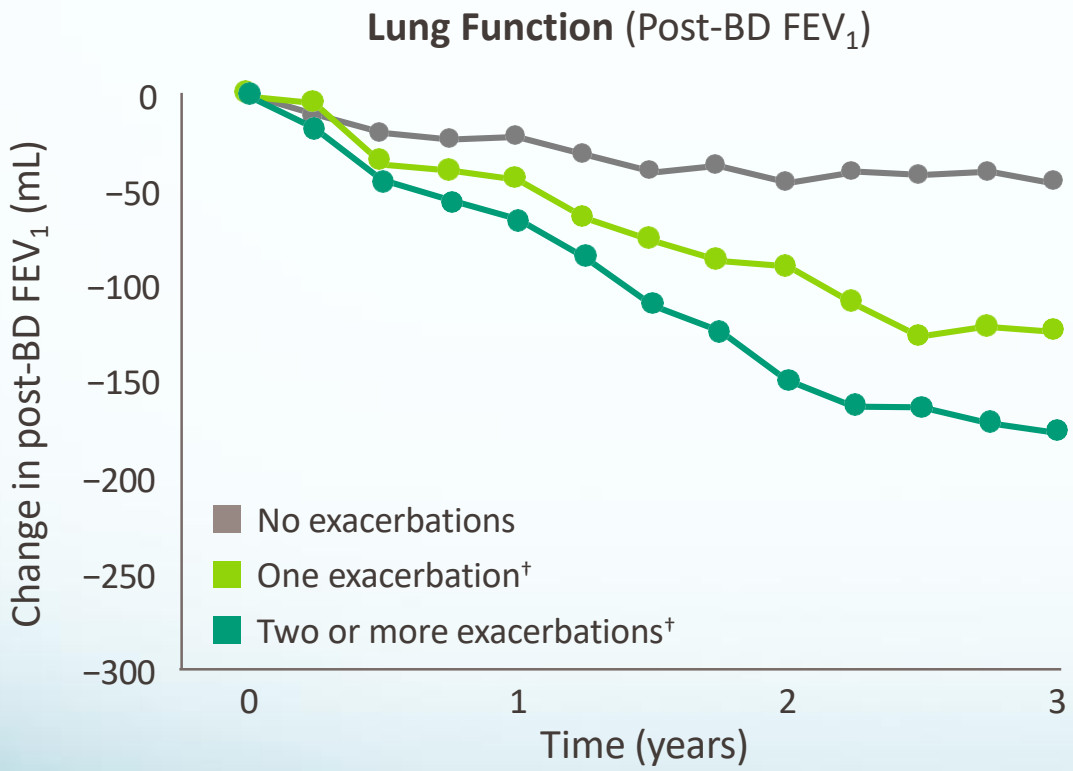
Pre-Post Selected Flow-Volume Loops



On dupilumab (6 months)

Frequent Exacerbations Lead to Increasing Airflow Limitation

Patients with well-controlled asthma at baseline followed for 3 years (N=128)*



Post-BD FEV_1 -13.6 mL/year

Post-BD FEV_1 -41.3 mL/year

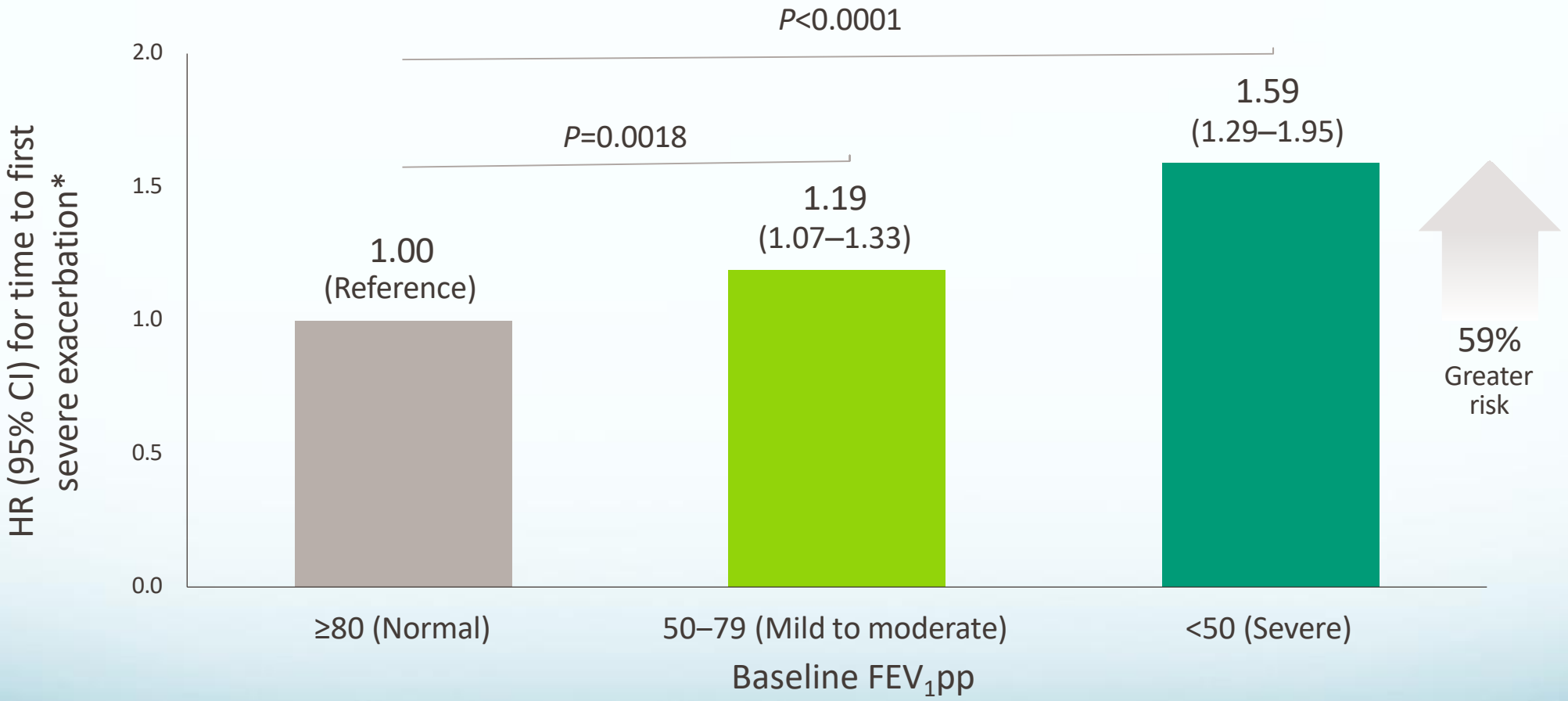
Post-BD FEV_1 -58.3 mL/year

Asthma exacerbations could have long-term adverse consequences on airway structure and function

Graph created from publication data.
*No exacerbations (n=100); exacerbations (n=28). †Severe exacerbation was defined as worsening asthma requiring at least 3 days of treatment with systemic corticosteroids, or a hospitalization due to asthma.
BD, bronchodilator; FEV_1, forced expiratory volume in 1 second.
Matsunaga K, et al. *J Allergy Clin Immunol Pract*. 2015;3(5):759-764.

Low FEV_1 Is a Predictor of Future Severe Exacerbations

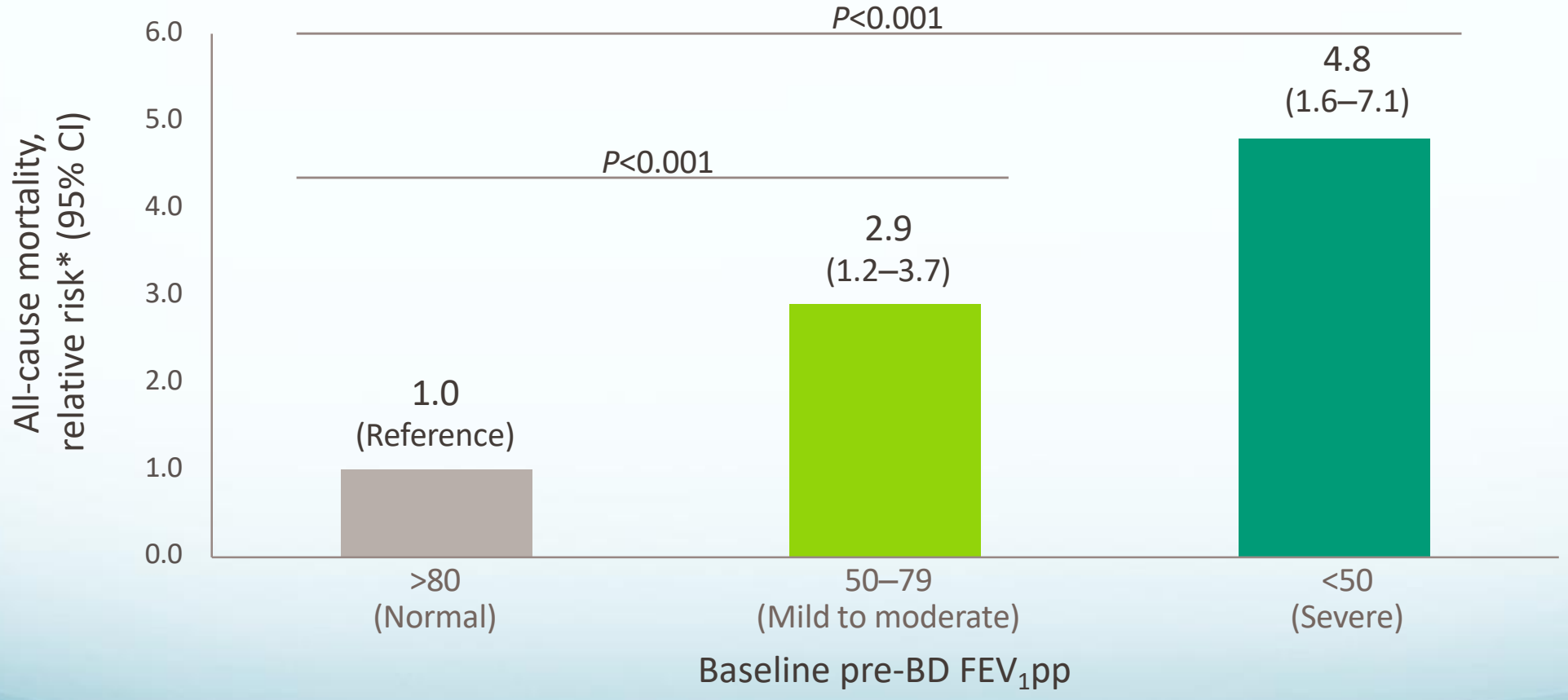
Adults with moderate-to-severe asthma over a 36-month follow-up period (n=1865)



Graph created from publication data.
*Cox proportional hazard model analysis adjusted for age at index date, smoking status, BMI, gender, rhinitis, chronic sinusitis, nasal polyps, atopic dermatitis, diabetes, anaphylaxis, ischemic heart disease, heart failure, food allergy, anxiety, depression, and psoriasis.
BMI, body mass index; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; HR, hazard ratio; pp, percent predicted.
Khan A, et al. *Ann Allergy Asthma Immunol*. 2018;121:S22-S62.

Reduced FEV_1 Is Associated With Increased Mortality

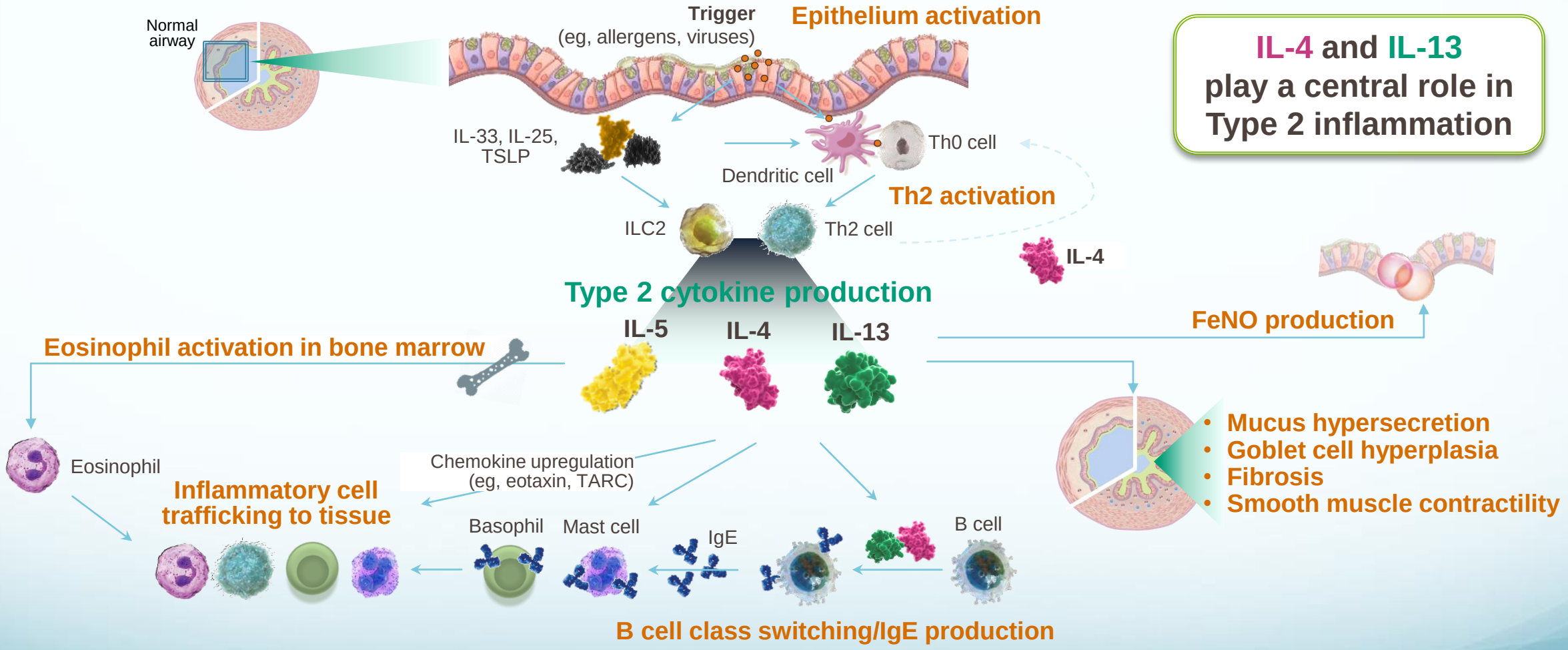
25-year follow-up in adult patients with asthma (n=1075)



Graph created from publication data.
*Relative risk of death from asthma during 25 years of follow-up.
BD, bronchodilator; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; pp, percent predicted.
Ali Z, et al. *Chest*. 2013;143:1649-1655.

What accounts for these improvements?

Type 2 Inflammation in the Airway Is Characterised by Type 2 Cytokine Activity[1-6]

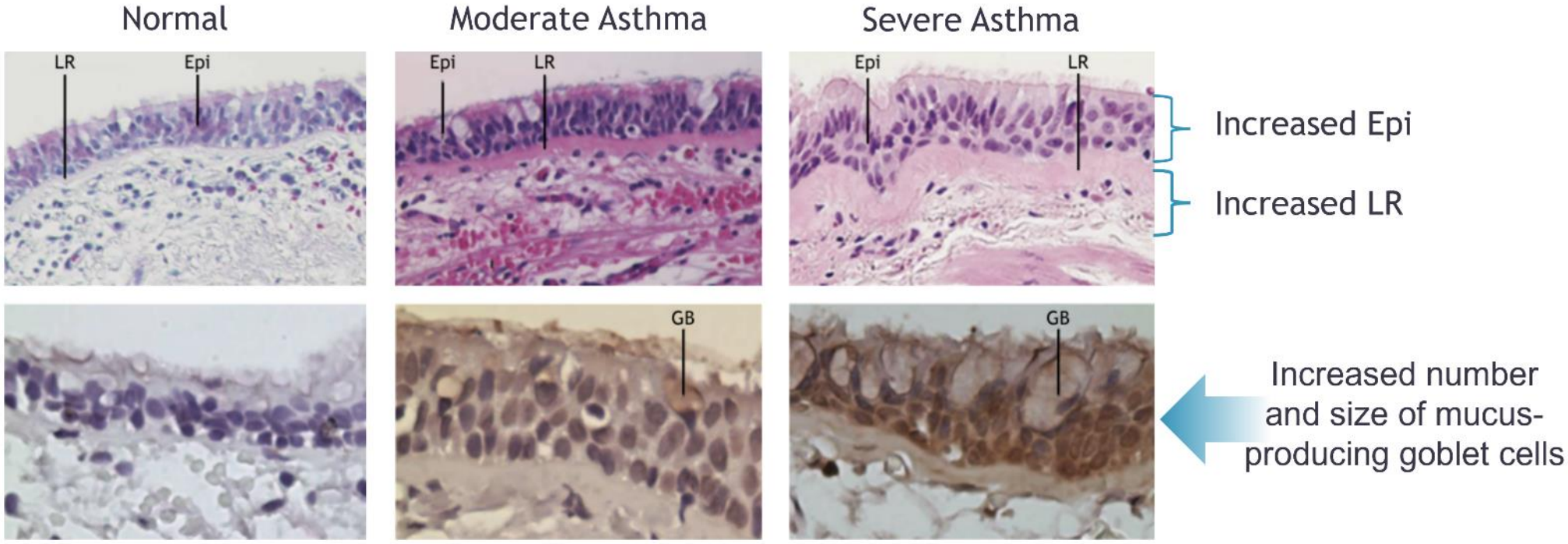


IL-4 and IL-13 play a central role in Type 2 inflammation

From: *N Engl J Med,* Israel E, Reddel HK, Severe and Difficult-to-Treat Asthma in Adults, 377, 965-976. Copyright © (2017) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.
IgE=immunoglobulin E; IL=interleukin; ILC2=Type 2 innate lymphoid cells; TARC=thymus and activation-regulated chemokine; Th0=naïve T-helper cell; Th2=Type 2 T-helper cells; TSLP=thymic stromal lymphopoietin.
1. Gandhi NA, et al. *Nat Rev Drug Discov*. 2016;15(1):35-50. 2. Fahy JV. *Nat Rev Immunol*. 2015;15(1):57-65. 3. Israel E, Reddel HK. *N Engl J Med*. 2017;377(10):965-976. 4. Drake LY, et al. *Allergy*. 2014;69(10):1300-1307. 5. Robinson D, et al. *Clin Exp Allergy*. 2017;47(2):161-175. 6. Menzies-Gow AN, et al. *Clin Exp Allergy*. 2007;37(7):1023-1032.

Airway Epithelial Remodeling Is Evident in Moderate-to-Severe Asthma[1]

Increased Airway Epithelium, Lamina Reticularis, and Goblet Cell Hyperplasia Evident in Moderate and Severe Asthma

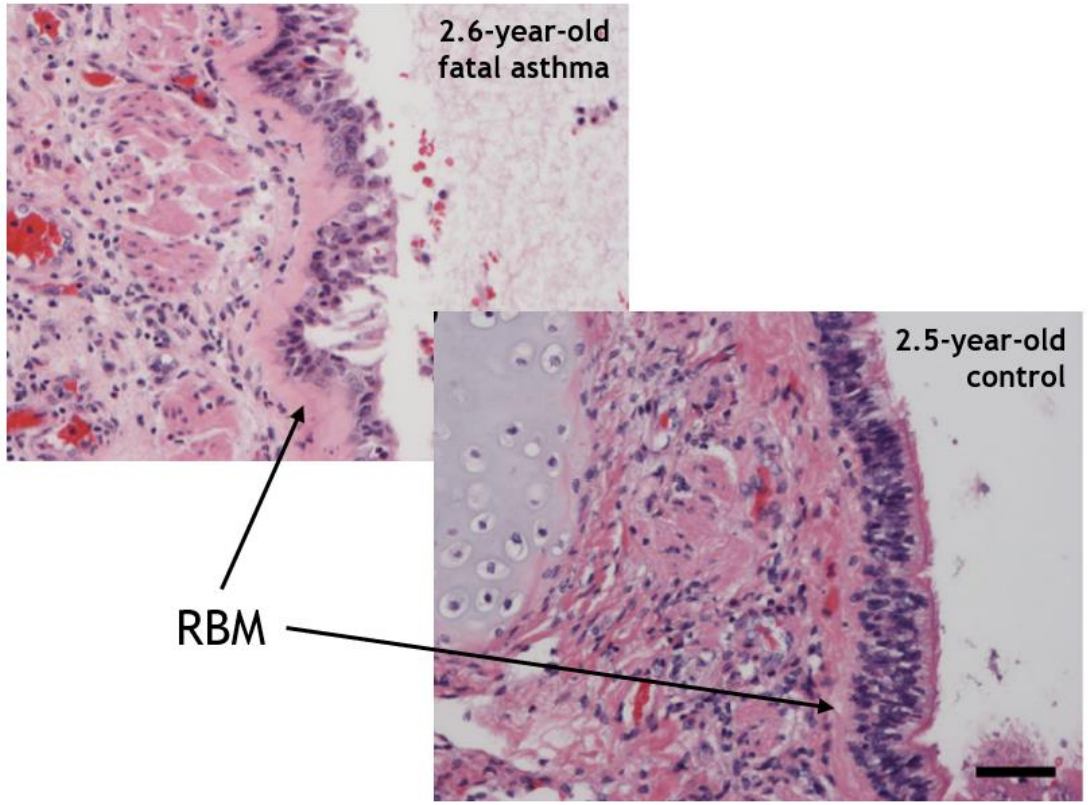


Ab, antibody; Epi, epithelium; GB, goblet cell; H&E, hematoxylin and eosin; LR, lamina reticularis.

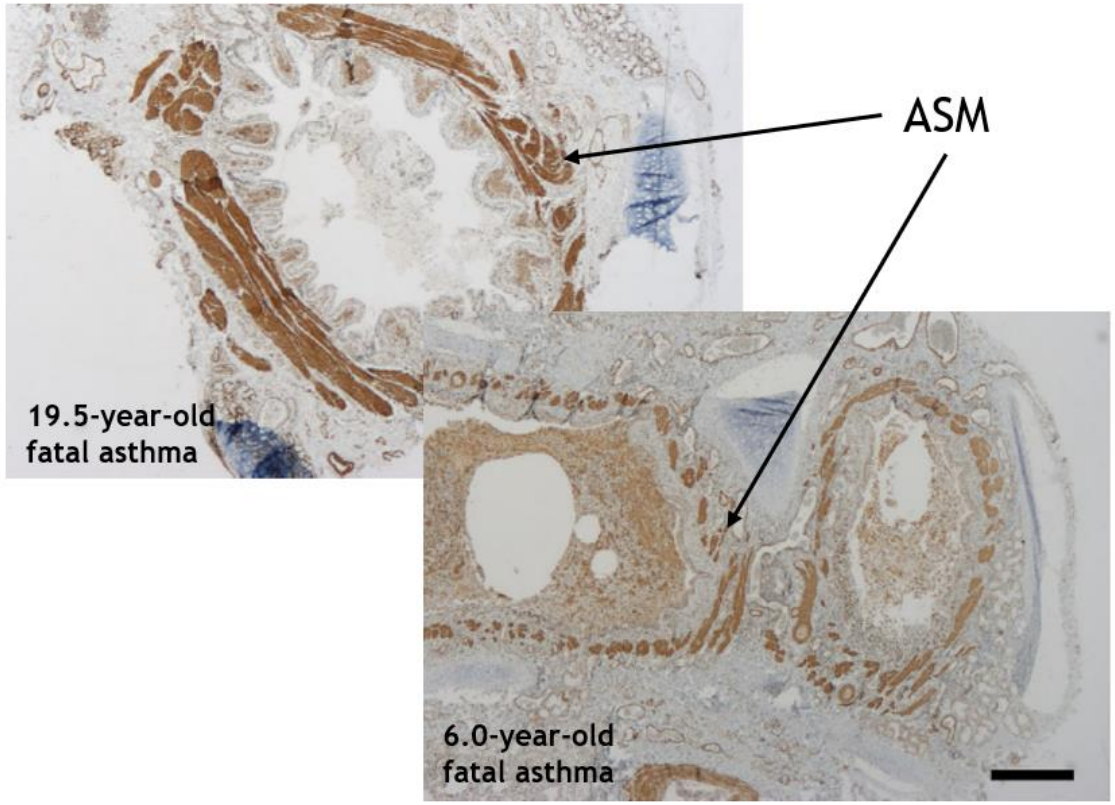
1. Shifren A et al. *J Allergy (Cairo).* 2012;2012:316049.

Postmortem Lung Autopsies Demonstrate Thickening of RBM and Increased ASM in Fatal Asthma[1]

Bronchial Thickness of RBM Is Increased in a Fatal Asthma Case Compared to Control[a]



In Large Airways, ASM Is Increased in Fatal Asthma Cases[a]

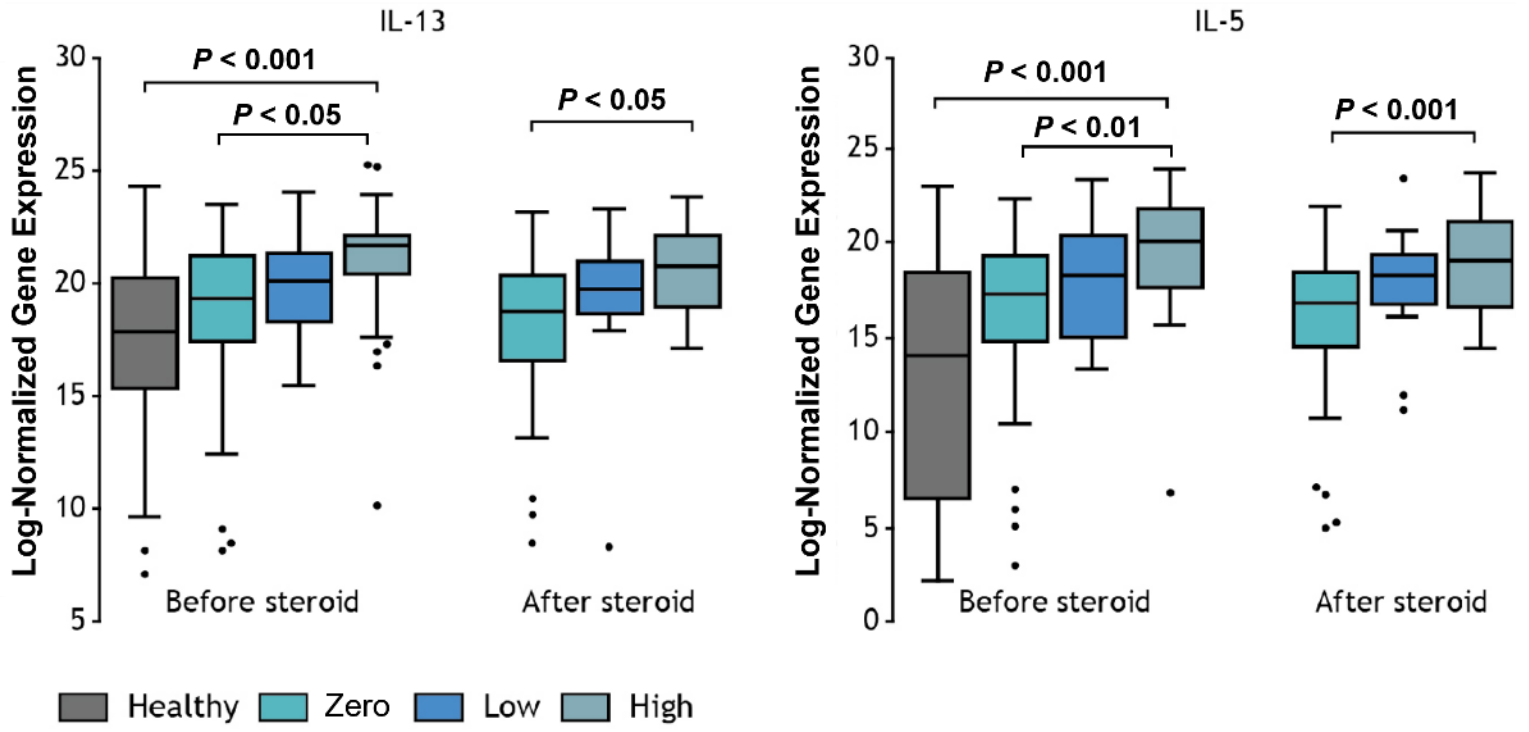


[a]Reprinted from Malmstrom K et al. Respir Res. 2017;18(1):94. https://creativecommons.org/publicdomain/zero/1.0/
ASM, airway smooth muscle; RBM, reticular basement membrane.

1. Malmstrom K et al. *Respir Res.* 2017;18(1):94.

Degree of Mucus Plugging Associated With Increased Type 2 Cytokine Expression and Reduced Lung function[1]

High Mucus Plug Scores Associated With Elevated Type 2 Cytokine Expression in Sputum



Increased mucus plugging is also associated with:

- Reduced lung function (FEV_1, FVC, FEV_1/FVC)
- Sputum and blood eosinophilia
- Elevated FeNO (high mucus scores only)

FVC, forced vital capacity.
Reprinted with permission from J Clin Invest. 2018;128(3):997-1009.
1. Dunican EM et al. *J Clin Invest*. 2018;128(3):997-1009.

Is Mr. C enjoying a remission on treatment?

Rostrum

An expert consensus framework for asthma remission as a treatment goal

Andrew Menzies-Gow, PhD,[a] Mona Bafadhel, PhD,[b] William W. Busse, MD,[c] Thomas B. Casale, MD,[d] Janwillem W. H. Kocks, MD, PhD,[e,f,g] Ian D. Pavord, MD,[b] Stanley J. Szefler, MD,[h] Prescott G. Woodruff, MD,[i] Alexander de Giorgio-Miller, PhD,[j] Frank Trudo, MD,[k] Malin Fageras, PhD,[l] and Christopher S. Ambrose, MD[m]

London, Oxford, and Cambridge, United Kingdom; Madison, Wis; Tampa, Fla; Groningen, The Netherlands; Singapore; Aurora, Colo; San Francisco, Calif; Wilmington, Del; Gothenburg, Sweden; and Gaithersburg, Md

Menzies-Gow JACI 2020

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

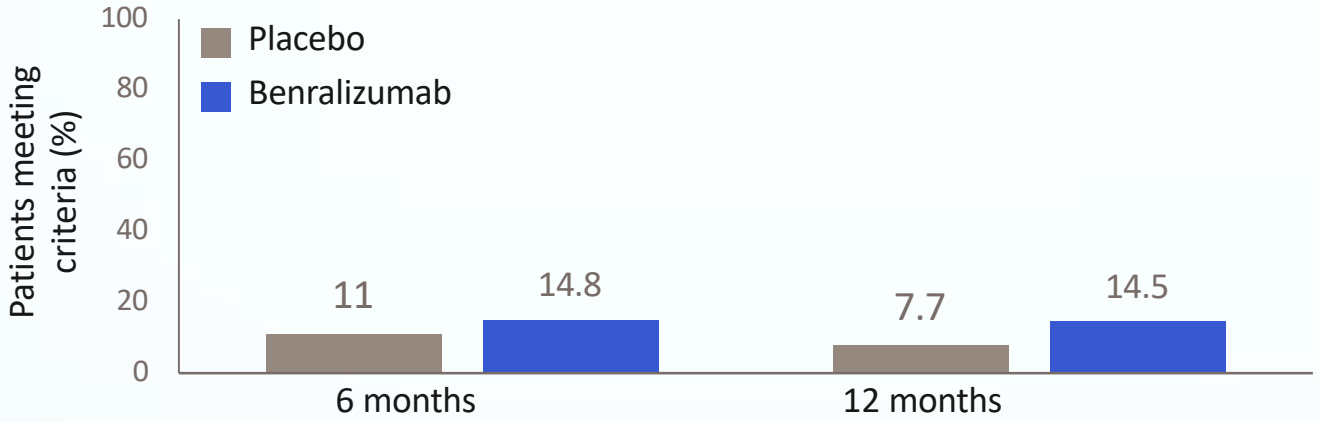
Same criteria maintained without asthma treatment for ≥12 months

Menzies-Gow JACI 2020

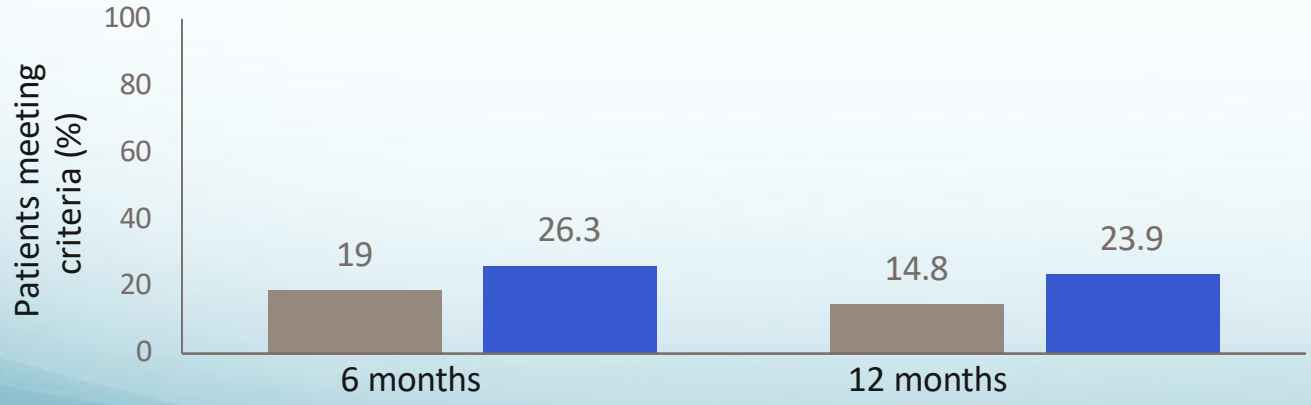
How many on biologics achieve remission?

Benralizumab Showed Benefits in Achieving On-Treatment Clinical Remission

SIROCCO/CALIMA* (Benralizumab)



SIROCCO/CALIMA* (Benralizumab)



On-treatment clinical remission at 12 months

No OCS and zero exacerbations†

ACQ-6 ≤0.75

Pre-BD FEV_1 increase ≥100 mL

No OCS and zero exacerbations†

ACQ-6 <1.5

Pre-BD FEV_1 increase ≥100 mL

Graph created from publication data.

*Post hoc analysis of the phase 3 SIROCCO and CALIMA trials including patients not receiving OCS at baseline. †An exacerbation was defined as a worsening of asthma resulting in use of systemic corticosteroids, temporary increase in OCS dose for ≥3 days, a dose of injected corticosteroids, or an emergency department visit or inpatient hospital admission.

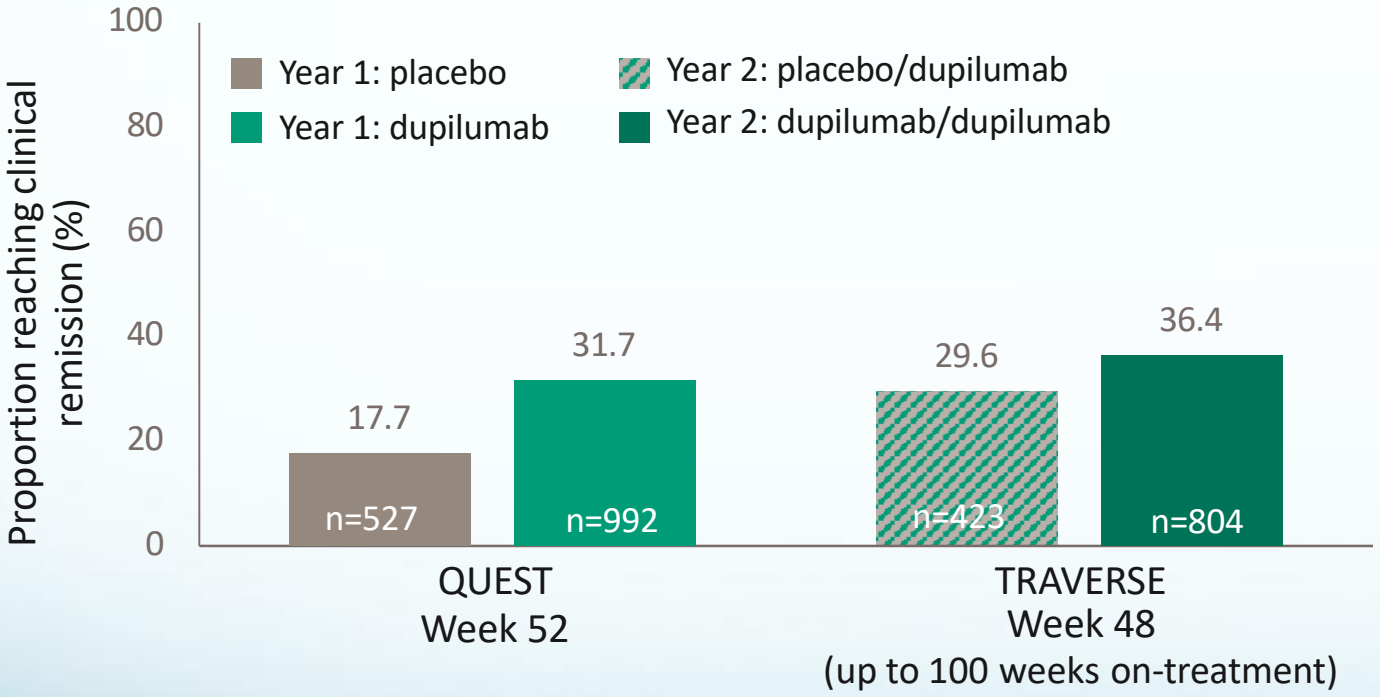
ACQ-6, 6-Item Asthma Control Questionnaire; pre-BD, pre-bronchodilator; FEV_1, forced expiratory volume in 1 second; OCS, oral corticosteroid.

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

Dupilumab Treatment Led to On-Treatment Clinical Remission Over 2 Years*

QUEST and TRAVERSE† (Dupilumab)

On-treatment clinical remission remission over 2 years



No OCS and zero exacerbations

ACQ-5 <1.5

Post-BD FEV_1pp ≥80% or pre-BD FEV_1 increase ≥100 mL

Graph created from publication data.

*Clinical remission was defined as patients having no exacerbations and no OCS use, ACQ-5 <1.5, and either percent predicted post-BD FEV_1 ≥80% or improvement over PSBL in pre-BD FEV_1 ≥100 mL.

†Post hoc analysis of the phase 3 QUEST and TRAVERSE OLE studies.

ACQ-5, 5-Item Asthma Control Questionnaire; FEV_1, forced expiratory volume in 1 second; OCS, oral corticosteroids; OLE, open label extension; post-BD, post-bronchodilator; PSBL, parent study baseline.

Pavord ID, et al. Poster presented at the Australasian Society of Clinical Immunology and Allergy Annual Conference (hybrid); August 30–September 2, 2022; Melbourne, Australia.

Is the anti-IL13 effect important?

Dupilumab Reduces Sputum Eosinophils, Mucus Plugging and Improves Ventilation in Patients With Moderate-to-Severe Asthma

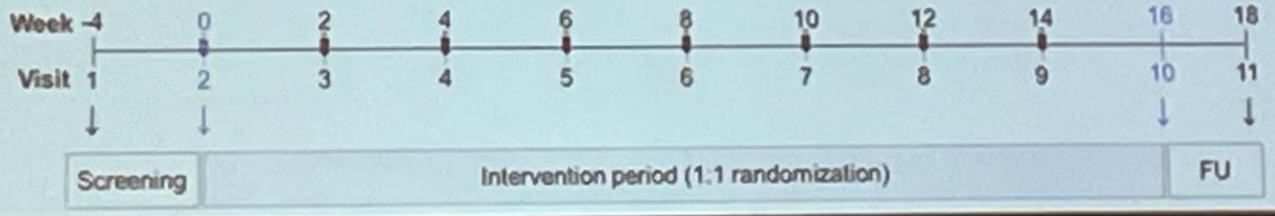
Study design
Single-center, randomized, double-blind, placebo-controlled trial

Eligible Patients
Adults with uncontrolled moderate-to-severe asthma, airway hyperresponsiveness, and T2 immu
- ACQ-5 > 1.0, medium or high dose ICS with or without additional oral corticosteroids
- Airway hyperresponsiveness: methacholine PC_{20} ≤4 mg/mL OR ≥15% decrease in FEV_1 during saline inhalation for sputum induc improvement in FEV_1 after bronchodilator
- Type 2 inflammation: FeNO >25ppb OR sputum eosinophils ≥3% OR blood eosinophils ≥0.3x10^9cells/L

Study Duration
22-weeks, consisting of a screening period of 4-weeks, a randomized treatment period of 16-we post-treatment follow-up period of 2-weeks

Intervention
Patients were randomly assigned at a 1:1 ratio to receive dupilumab (600mg loading dose follow sub-cutaneous injections) or matching placebo every 2-weeks for a total of 16-weeks

Outcomes
Change from baseline (week 0) to end-of-treatment (week 16)

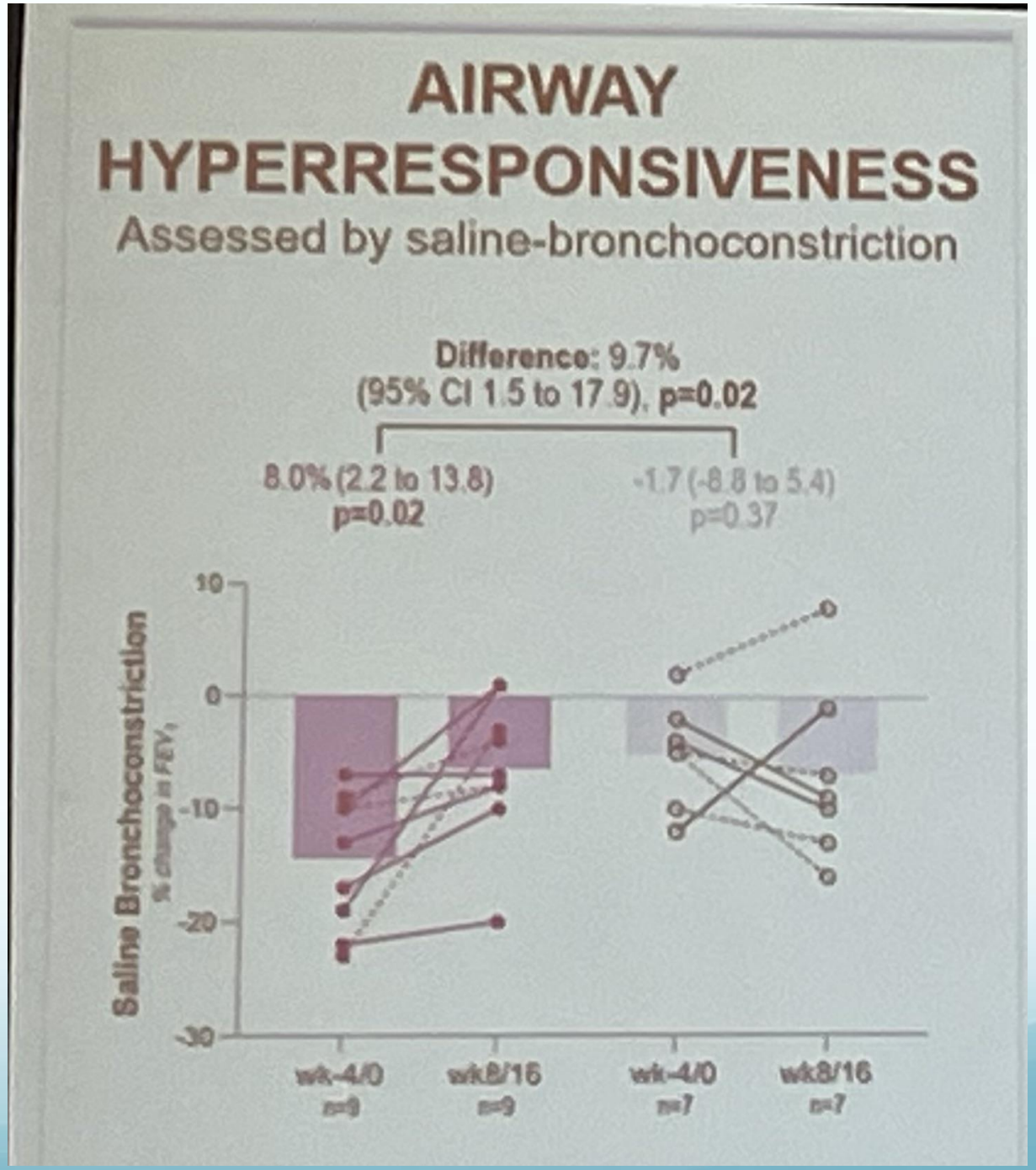


Baseline Demographics

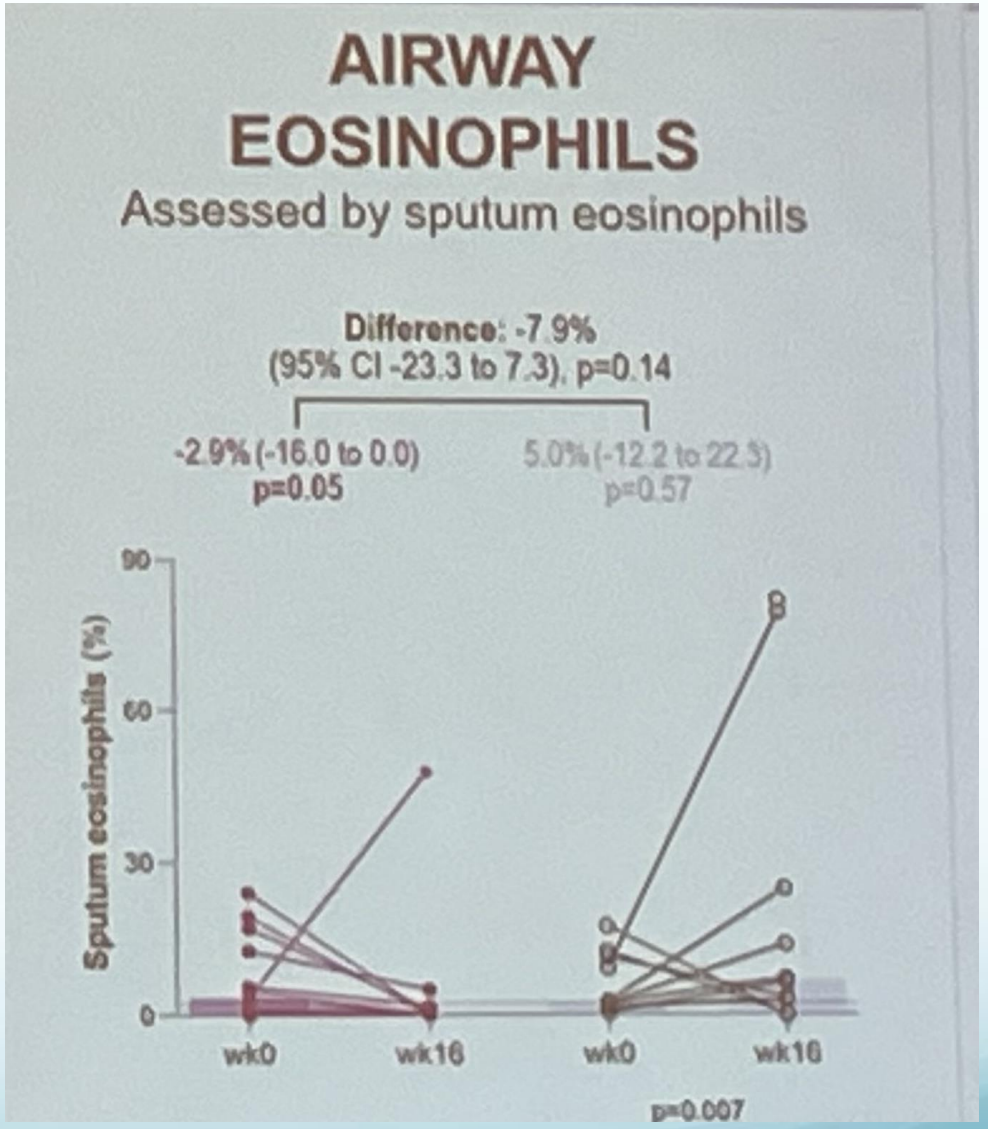
	Dupilumab (n=13)	Placebo (n=11)
Age years	48 (16)	60 (8)
Female sex	8 (62%)	4 (36%)
BMI kg/m²	29 (5)	31 (4)
ACQ-5 score	2.0 (1.1)	3.0 (1.2)
AQLQ score	5.0 (1.2)	3.8 (1.2)
Spirometry		
FEV_1 pre-BD $\%_{pred}$	55 (21)	62 (20)
FEV_1 post-BD $\%_{pred}$	68 (22)	77 (21)
BD reversibility of FEV_1 (%)	19 (12 – 32)	22 (12 – 40)
FEV_1/FVC post-BD %	63 (45 – 74)	66 (62 – 68)
Inflammatory Biomarkers		
FeNO ppb	39 (24 – 55)	56 (32 – 86)
Sputum eosinophils %	3.5 (0.5 – 14.8)	2.5 (1.5 – 11.8)
Blood eosinophils $x10^9$cells/L	0.6 (0.2 – 0.9)	0.5 (0.3 – 0.8)
Asthma Medications		
ICS dose µg/day	1000 (500 – 1000)	1000 (750 – 1500)
OCS dependent	3 (23%)	3 (27%)

Data are mean (SD), median (IQR), or n (%).

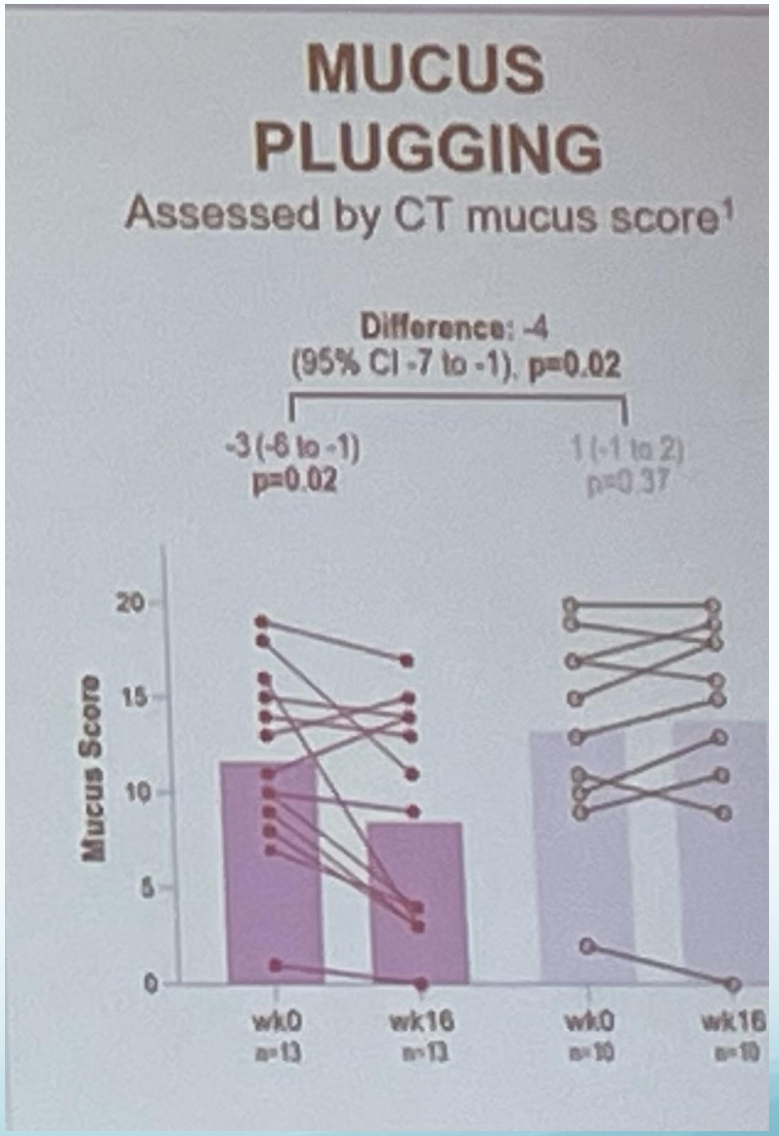
Outcomes


AIRWAY HYPERRESPONSIVENESS
Assessed by saline-bronchoconstriction
Difference: 9.7%
(95% CI 1.5 to 17.9), p=0.02
8.0% (2.2 to 13.8)
p=0.02
-1.7 (-8.8 to 5.4)
p=0.37
Saline Bronchoconstriction
10
0
-10
-20
-30
wk-4/0
n=9
wk8/16
n=9
wk-4/0
n=7
wk8/16
n=7

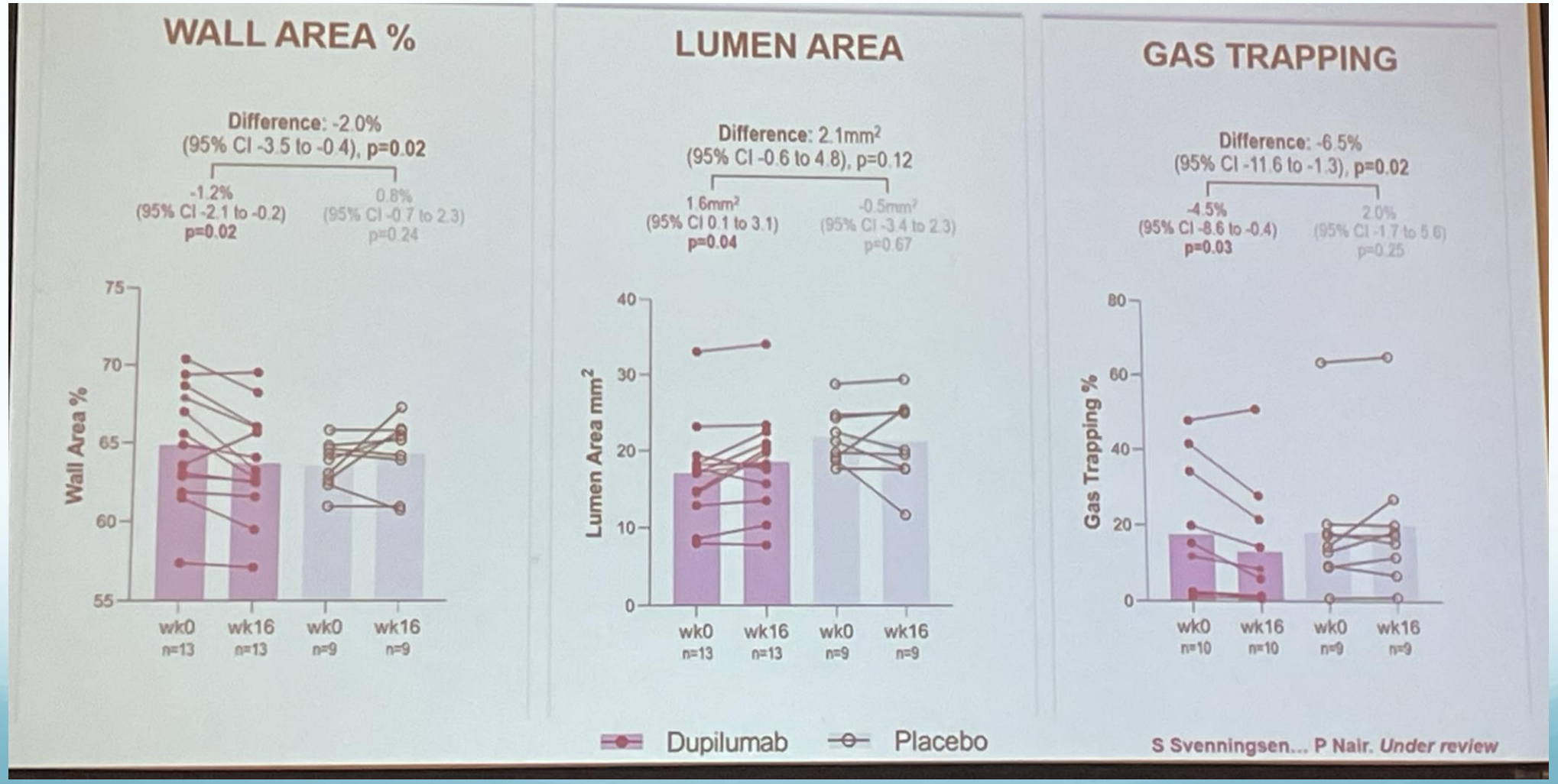
Outcomes


AIRWAY EOSINOPHILS
Assessed by sputum eosinophils
Difference: -7.9%
(95% CI -23.3 to 7.3), p=0.14
-2.9% (-16.0 to 0.0)
p=0.05
5.0% (-12.2 to 22.5)
p=0.57
Sputum eosinophils (%)
90
60
30
0
wk0
wk16
wk0
wk16
p=0.007

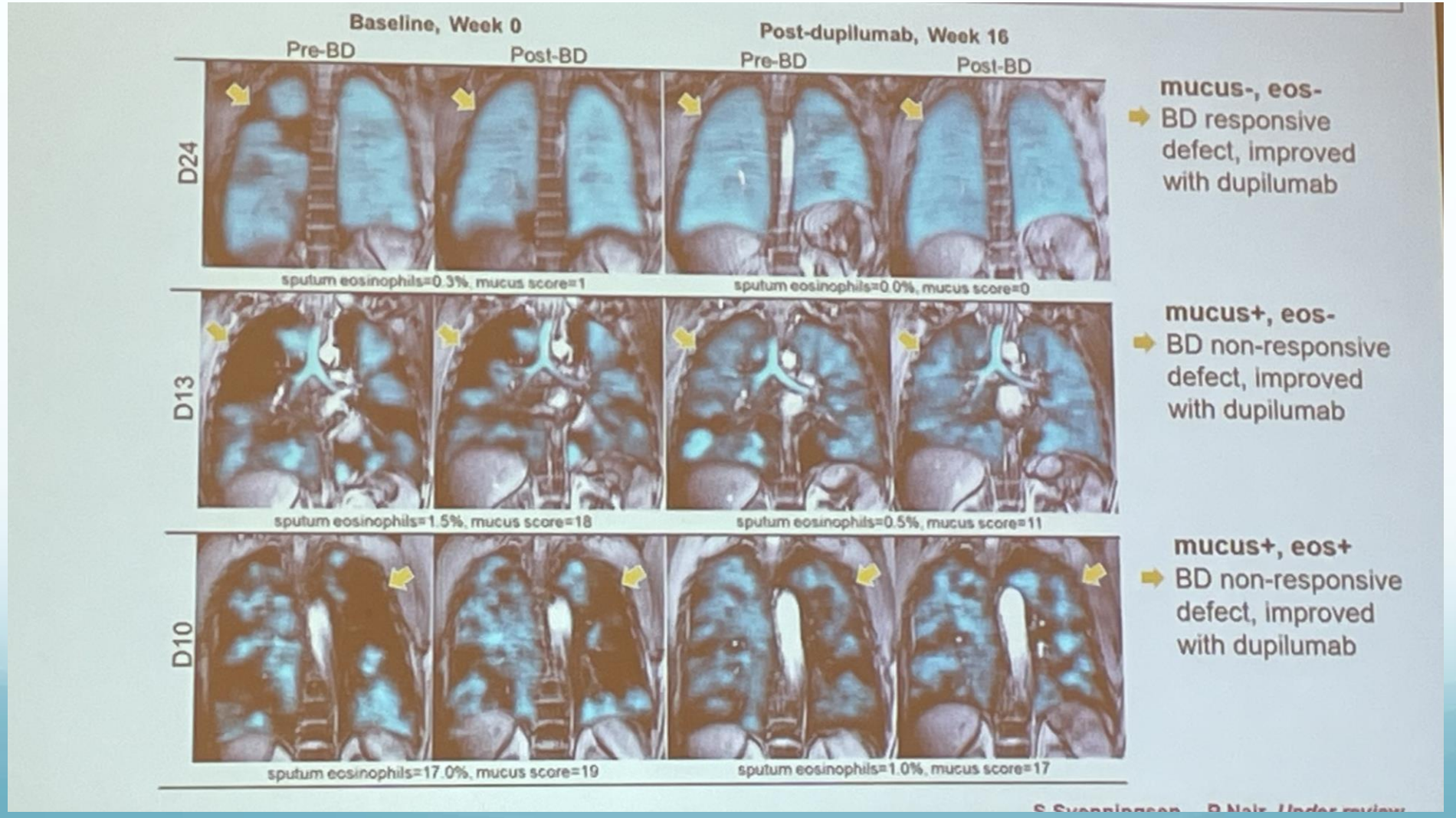
Outcomes


MUCUS PLUGGING
Assessed by CT mucus score[1]
Difference: -4
(95% CI -7 to -1), p=0.02
-3 (-6 to -1)
p=0.02
1 (-1 to 2)
p=0.37
Mucus Score
20
15
10
5
0
wk0
n=13
wk16
n=13
wk0
n=10
wk16
n=10

Exploratory CT Outcomes



Dupilumab Effects on Ventilation



And then there's COPD…

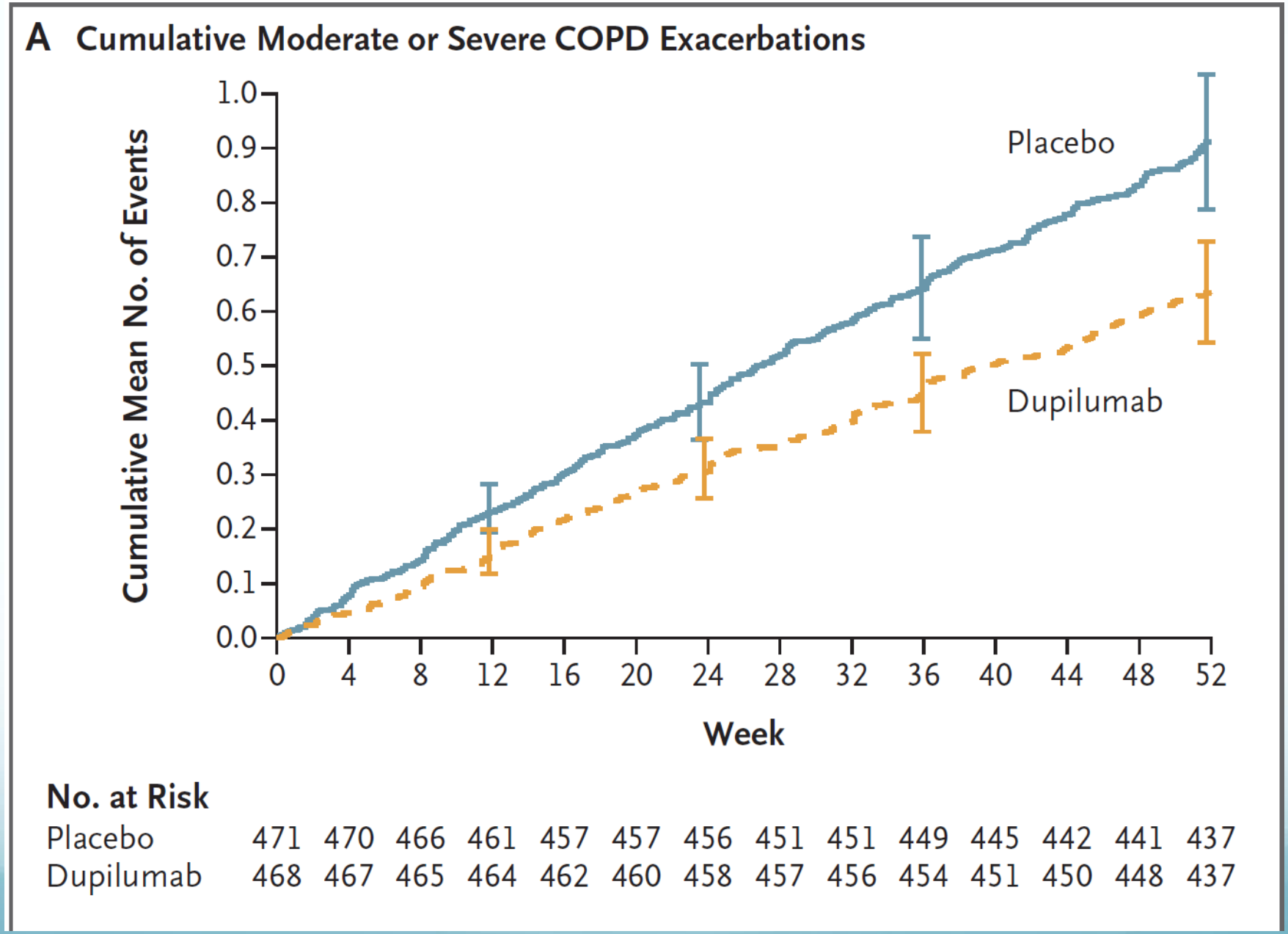
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

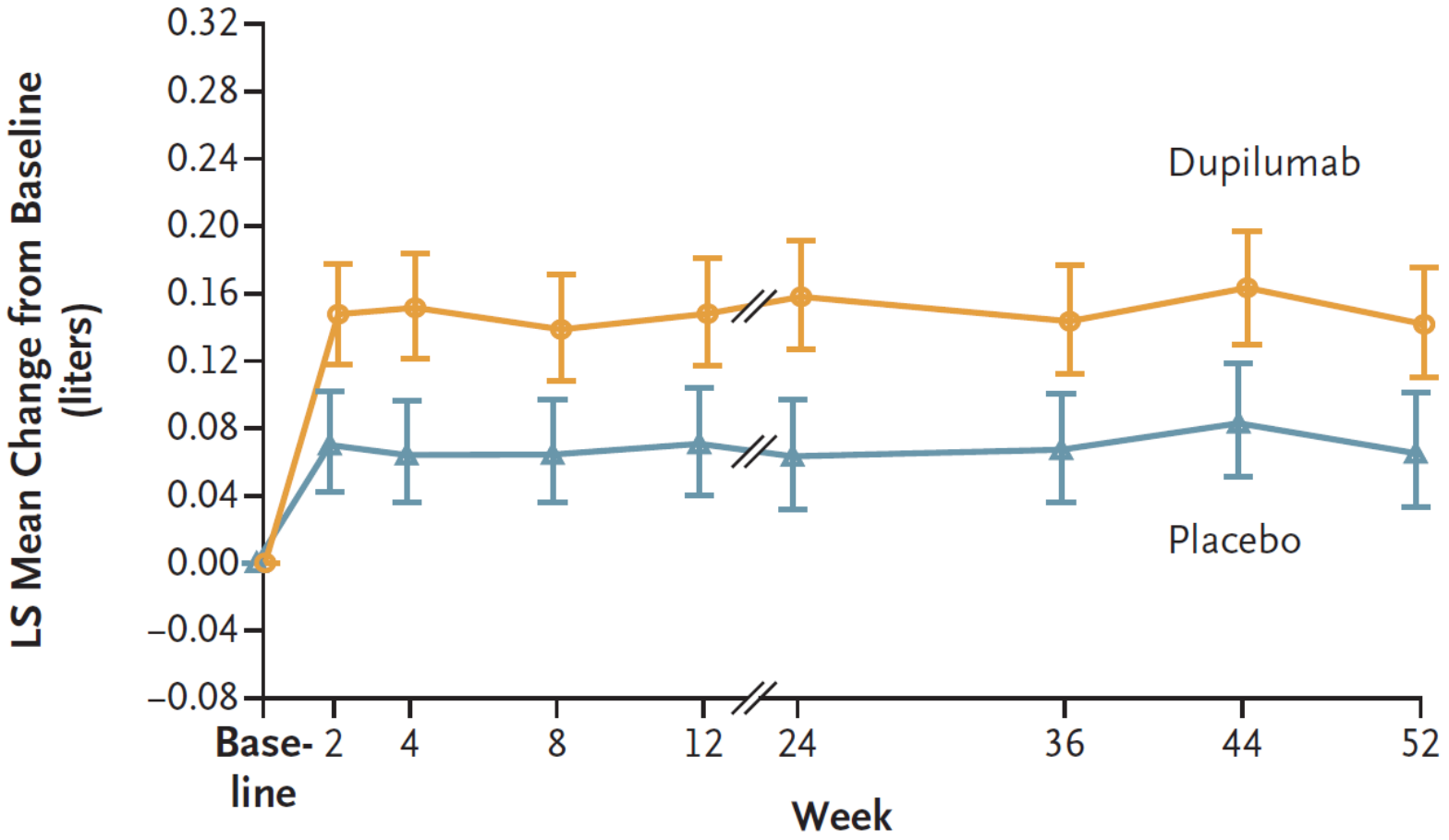
Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts

S.P. Bhatt, K.F. Rabe, N.A. Hanania, C.F. Vogelmeier, J. Cole, M. Bafadhel, S.A. Christenson, A. Papi, D. Singh, E. Laws, L.P. Mannent, N. Patel, H.W. Staudinger, G.D. Yancopoulos, E.R. Mortensen, B. Akinlade, J. Maloney, X. Lu, D. Bauer, A. Bansal, L.B. Robinson, and R.M. Abdulai, for the BOREAS Investigators*

ABSTRACT

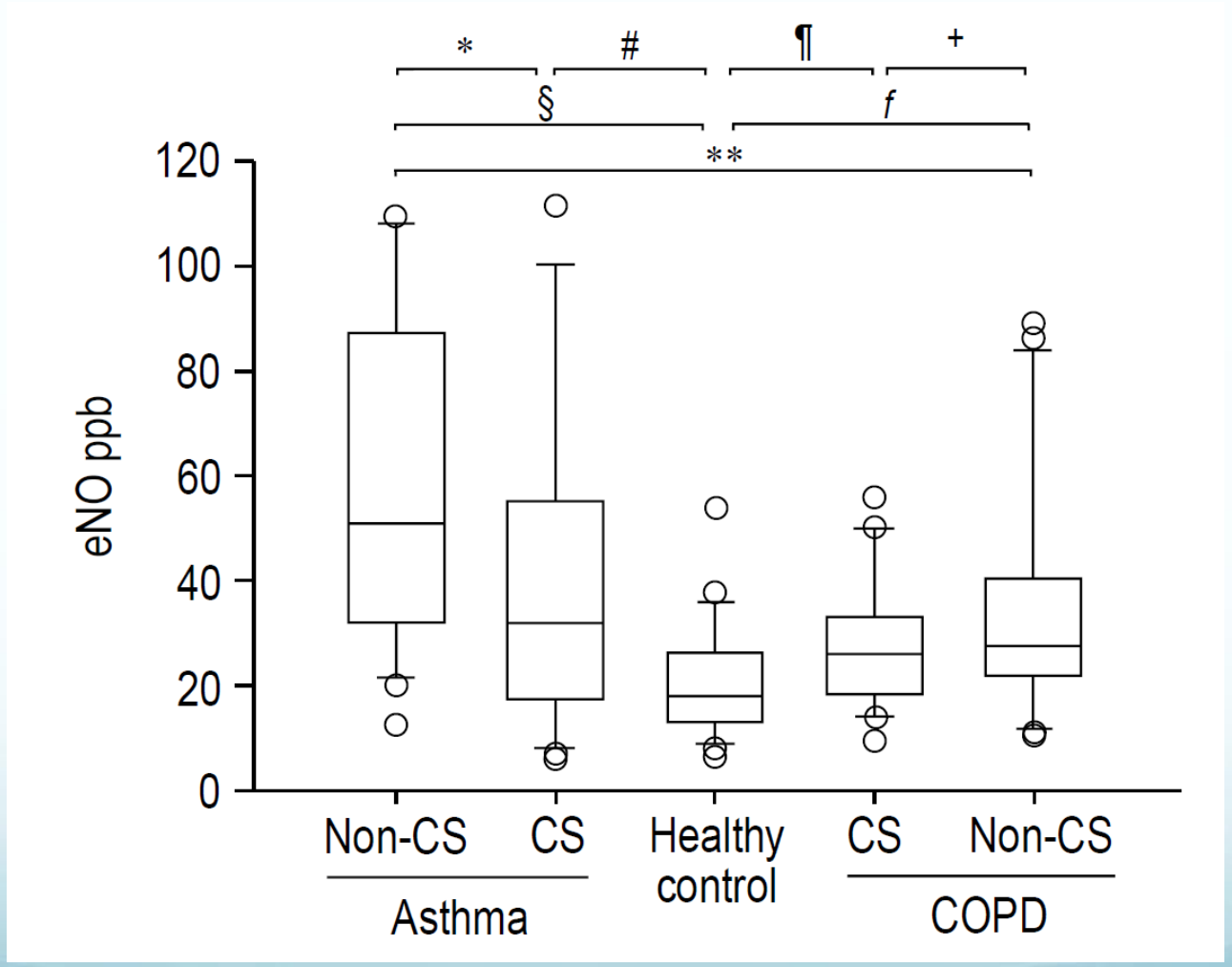

A Cumulative Moderate or Severe COPD Exacerbations
Cumulative Mean No. of Events
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Placebo
Dupilumab
0 4 8 12 16 20 24 28 32 36 40 44 48 52
Week
No. at Risk
Placebo 471 470 466 461 457 457 456 451 451 449 445 442 441 437
Dupilumab 468 467 465 464 462 460 458 457 456 454 451 450 448 437

B Prebronchodilator FEV_1



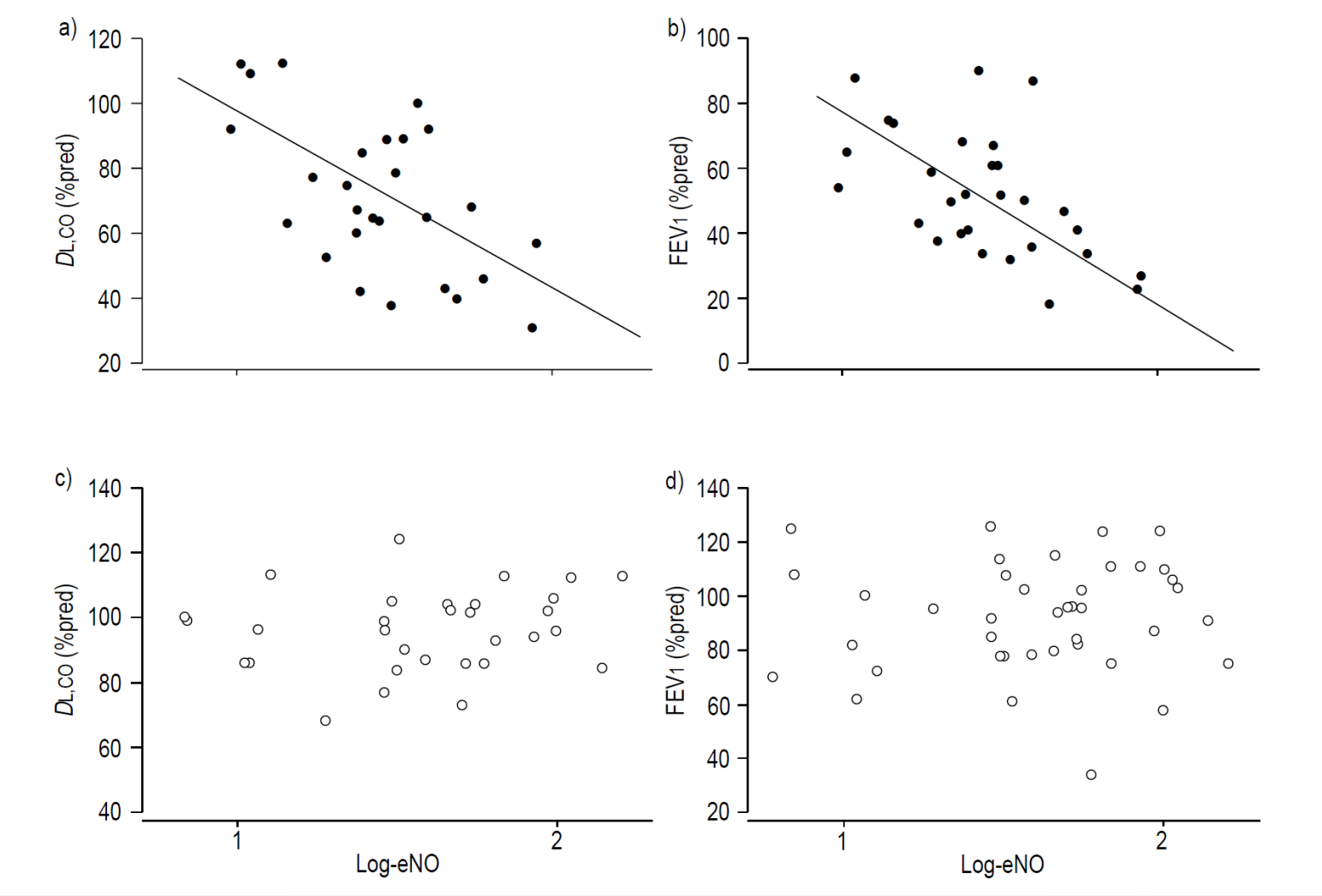
No. of Patients with Data								
Placebo	471	455	459	439	439	435	415	404	420
Dupilumab	467	457	454	446	449	443	415	410	426

Exhaled Nitric Oxide is Elevated in COPD



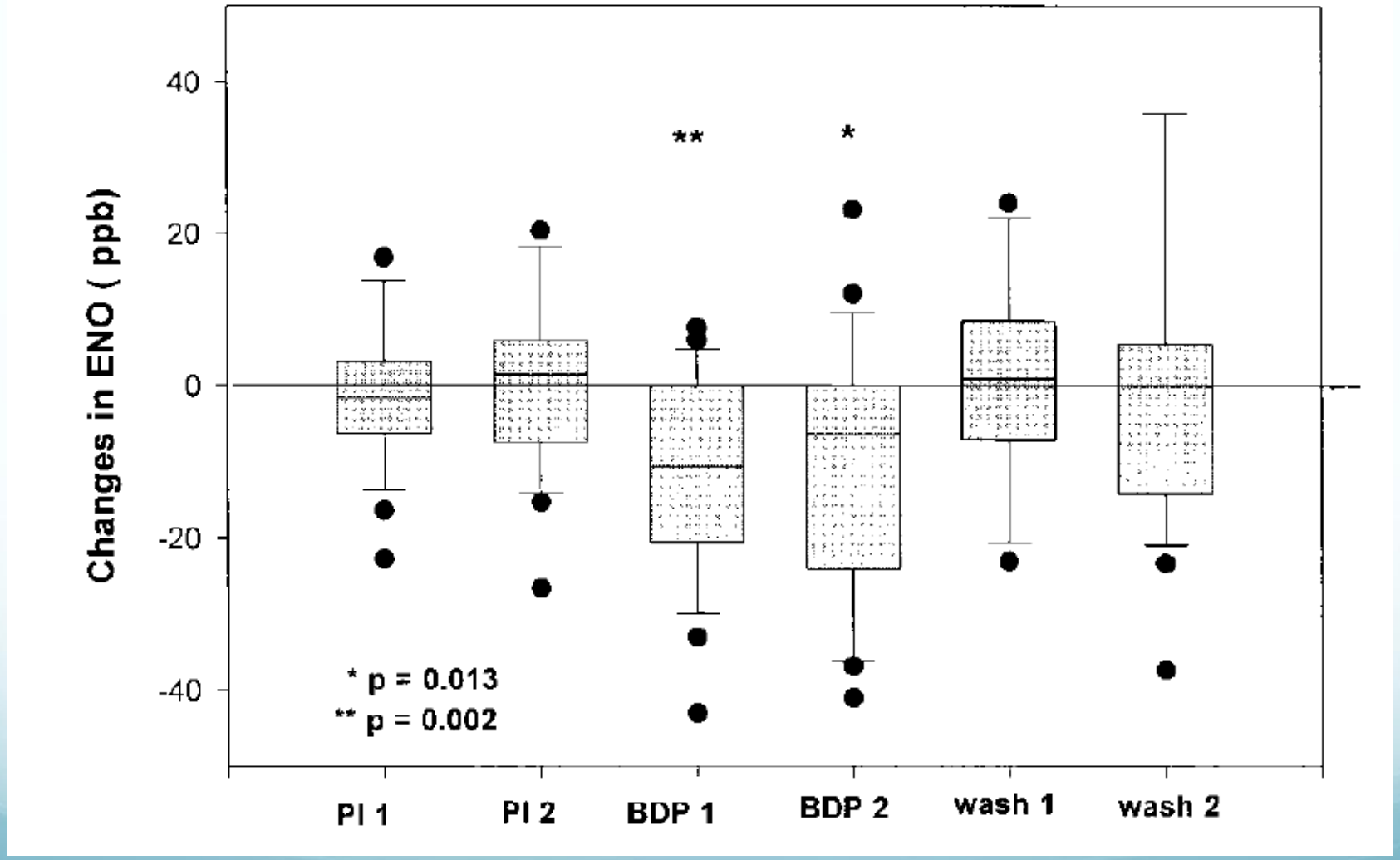
Ansarin ERJ 2001

Exhaled Nitric Oxide is Elevated in COPD – Association with Lung Function Abnormalities



Ansarin ERJ 2001

Nitric Oxide is Reduced by ICS in COPD



Ferreira AJRCCM 2001

Summary:

- Eosinophils are non-specific Type 2 biomarkers.
- If we aim for “remission” on or off therapy, we should decide what that looks like for each patient. That might include making lung function normal or addressing a co-morbidity. Only about one third of biologic treated patients seem to achieve optimal or complete response.
- Responder analyses should be reported as part of biologic clinical trials.
- The airway effects of dupilumab (an anti-IL13 effect) seem to be unique.
- Four months of biologic therapy may not be sufficient to gauge results.