

Can't Miss Articles

The treatable trait of CRSwNP

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Disclosures of Conflicts of Interest

None

Treatable Traits

Chronic Rhinosinusitis with Nasal Polyposis:

- [Dupilumab versus omalizumab in patients with chronic rhinosinusitis with nasal polyps and coexisting asthma \(EVEREST\): a multicentre, randomised, double-blind, head-to-head phase 4 trial – PubMed](#)
- [Tezepelumab in Adults with Severe Chronic Rhinosinusitis with Nasal Polyps - PubMed](#)

Mucus Plugging:

- [Tezepelumab and Mucus Plugs in Patients with Moderate-to-Severe Asthma](#)
- [Effect of dupilumab on exhaled nitric oxide, mucus plugs, and functional respiratory imaging in patients with type 2 asthma \(VESTIGE\): a randomised, double-blind, placebo-controlled, phase 4 trial - PubMed](#)

EVEREST: Study Design

- RDBCT comparing efficacy and safety of **dupilumab** versus **omalizumab** in patients with severe CRSwNP and coexisting mild, mod, or severe asthma.
- >18, CRSwNP with score of 5 or more despite surgery or oral steroids. Active symptoms. Weight and IgE in Xolair dosing range. Excluded viral illness, acute sinusitis, suspected or known CF or EGPA, recent surgery (6 mos), recent biologic (5 ½ lives)
- Dupixent 300 mg every 2 weeks, Omalizumab up to 600 mg every 2-4 weeks. Followed for 24 weeks.

EVEREST

Table 1

	Dupilumab group (n=181)	Omalizumab group (n=179)	Total (n=360)
Age, years	51 (13.3)	52 (12.9)	52 (13.1)
Sex			
Male	107 (59%)	91 (51%)	198 (55%)
Female	74 (41%)	88 (49%)	162 (45%)
Race			
American Indian or Alaska Native	0	2 (1%)	2/358 (1%)
Asian	1/179 (1%)	1 (1%)	2/358 (1%)
Black or African American	2/179 (1%)	1 (1%)	3/358 (1%)
White	171/179 (96%)	170 (95%)	341/358 (95%)
Multiple	0	1 (1%)	1/358 (<1%)
Not reported or unknown	5/179 (3%)	4 (2%)	9/358 (3%)
BMI (kg/m ²)	27.43 (5.03)	26.85 (3.98)	27.14 (4.54)
CRSwNP duration, years	13.3 (9.64)	13.2 (9.91)	13.3 (9.76)
Previous endoscopic sinus surgery			
No previous surgeries	36 (20%)	34 (19%)	70 (19%)
One previous surgery	59 (33%)	61 (34%)	120 (33%)
Two previous surgeries	35 (19%)	33 (18%)	68 (19%)
Three or more previous surgeries	51 (28%)	51 (29%)	102 (28%)
Age of onset of asthma, years	34.9 (16.48)	36.1 (16.35)	35.5 (16.40)
NSAID-ERD	74 (41%)	71 (40%)	145 (40%)
Ongoing allergic rhinitis	83 (46%)	81 (45%)	164 (46%)
Ongoing seasonal allergic rhinitis	73 (40%)	66 (37%)	139 (39%)
Ongoing perennial allergic rhinitis	60 (33%)	46 (26%)	106 (29%)
Nasal polyp score (scale 0-8)*	6.11 (1.17)	6.15 (1.28)	6.13 (1.22)
Smell test (UPSIT) score (scale 0-40)†	11.10 (5.45)	11.00 (6.13)	11.10 (5.79)
Loss of smell score (scale 0-3)*	2.86 (0.40)	2.83 (0.44)	2.84 (0.42)
Nasal congestion score (scale 0-3)*	2.47 (0.56)	2.44 (0.63)	2.46 (0.59)
Total symptom score (scale 0-9)*	7.38 (1.27)	7.30 (1.49)	7.34 (1.38)
SNOT-22 total score (scale 0-110)*	64.80 (19.06)	66.20 (20.56)	65.50 (19.81)

(Table 1 continues on next page)

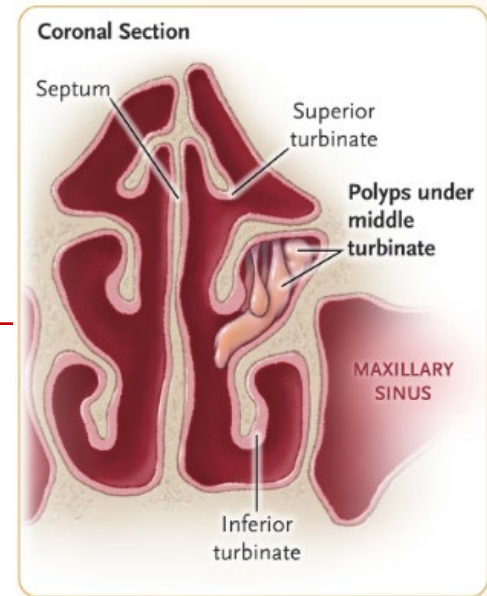
EVEREST

Table 1



	Dupilumab group (n=181)	Omalizumab group (n=179)	Total (n=360)
(Continued from previous page)			
Peak nasal inspiratory flow, L/min†	79.78 (50-16)	77.68 (59-44)	78.74 (54-89)
Rhinosinusitis disease severity (visual analogue scale, 0–10 cm)*	8.63 (1-50)	8.75 (1-41)	8.69 (1-45)
Pre-bronchodilator FEV ₁ , L	2.68 (0-92)	2.59 (0-82)	2.63 (0-87)
Pre-bronchodilator FEV ₁ , % predicted	77.4 (19-68)	77.9 (16-06)	77.6 (17-96)
ACQ-7 score (scale 0–6)*	2.82 (0-99)	2.69 (0-96)	2.76 (0-97)
Forced expiratory flow 25–75%, L/s	1.84 (1-11)	1.72 (0-91)	1.78 (1-02)
AQLQ (scale 1–7)*	4.13 (1-20)	4.23 (1-25)	4.18 (1-22)
Blood eosinophil count, cells per µL	562 (385)	550 (351)	556 (368)
Baseline serum total immunoglobulin E, IU/mL	212 (181)	220 (185)	216 (183)
FeNO (ppb)	54.30 (40-78)	54.60 (38-52)	54.40 (39-65)
Number of severe asthma exacerbations in the year before screening	0.6 (1-9)	0.9 (2-7)	0.7 (2-3)
Inhaled corticosteroid dose level‡			
Low	64 (35%)	63 (35%)	127 (35%)
Medium or high	117 (65%)	116 (65%)	233 (65%)
Systemic corticosteroid use in the previous 2 years	86 (48%)	90 (50%)	176 (49%)
Indication for previous systemic corticosteroid use			
CRSwNP	67/86 (78%)	77/90 (86%)	144/176 (82%)
Asthma	18/86 (21%)	15/90 (17%)	33/176 (19%)
Other	5/86 (6%)	5/90 (6%)	10/176 (6%)
<p>Data are n (%), n/N (%), or mean (SD). Additional demographic data are presented in appendix 1 (p 5). CRSwNP=chronic rhinosinusitis with nasal polyps. NSAID-ERD=non-steroidal anti-inflammatory drug-exacerbated respiratory disease. SNOT-22=22-item Sino-Nasal Outcome Test. UPSIT=University of Pennsylvania Smell Identification Test. ACQ-7=asthma control questionnaire 7-item version. AQLQ=asthma quality of life questionnaire with standardised activities. FeNO=fractional exhaled nitric oxide. ppb=parts per billion. *Higher scores indicate greater disease severity. †Higher scores indicate lower disease severity. ‡According to The Global initiative for Asthma 2020 guidelines.</p>			
Table 1: Baseline characteristics			

EVEREST: Polyp Size



Total Nasal Polyp Score

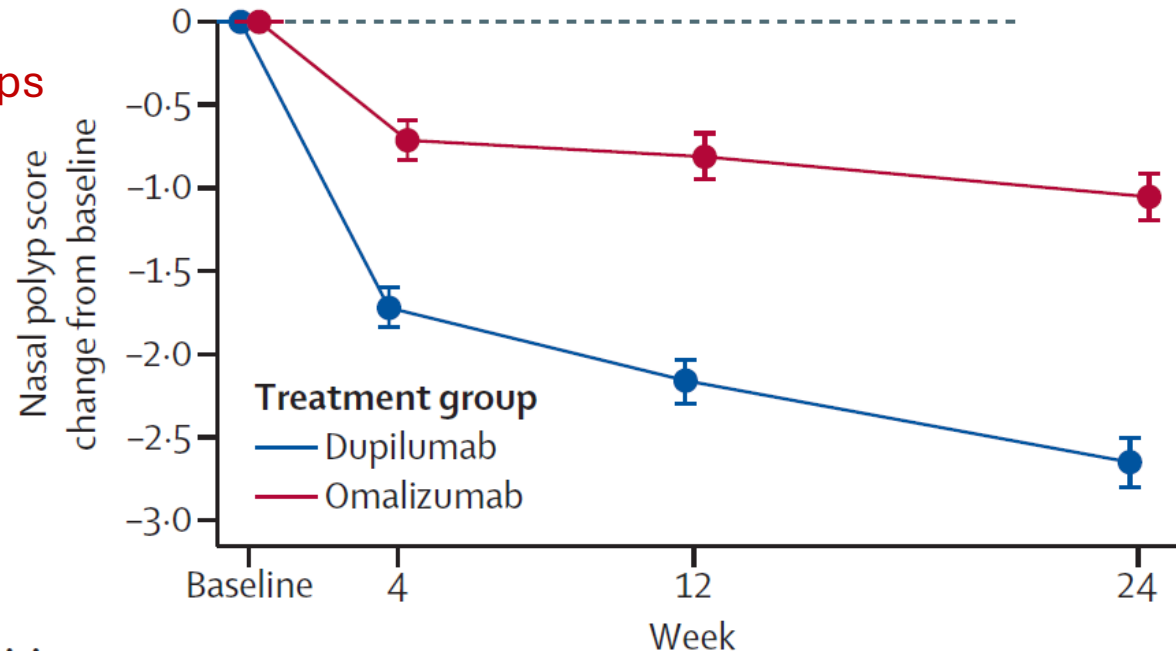
Measures occlusion of the nasal passages on endoscopy

0 = no polyp

8 = bilateral occlusive polyps

$\Delta 1$ = Minimal Clinically Important Difference

A Nasal polyp score



EVEREST: Smell

Upenn Smell Identification Test

measures sense of smell.

40-item, "scratch-and-sniff".

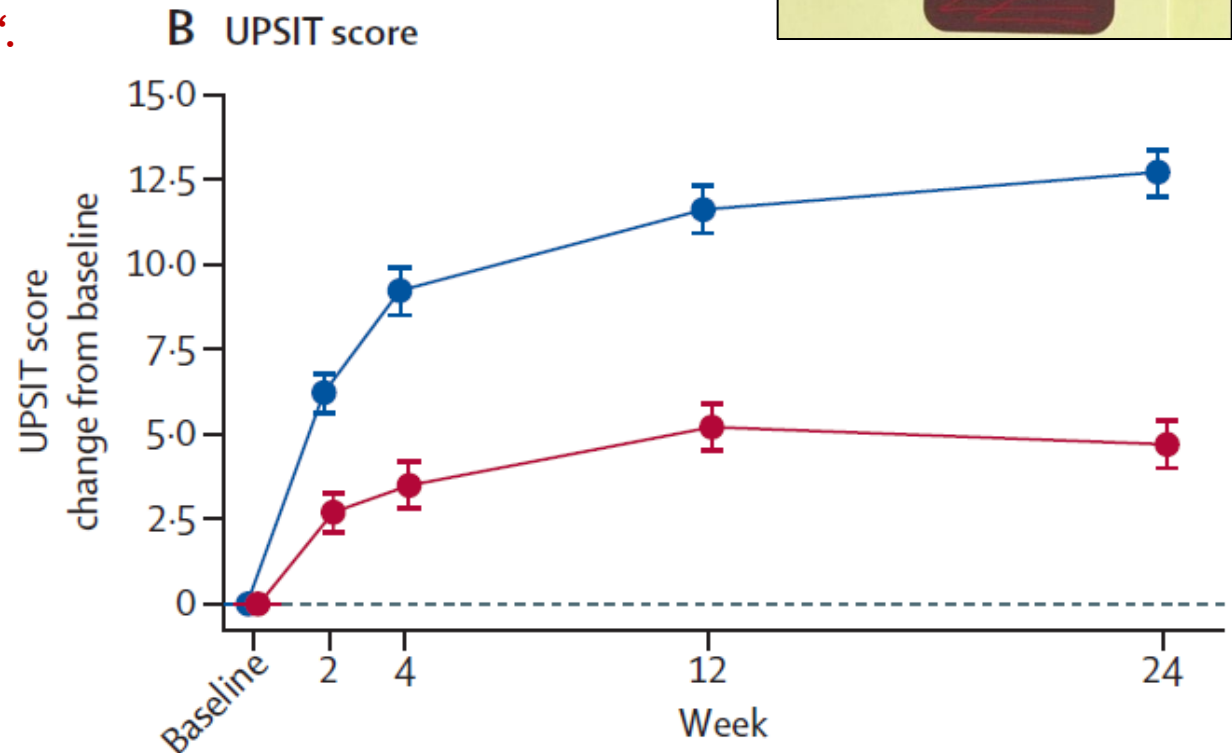
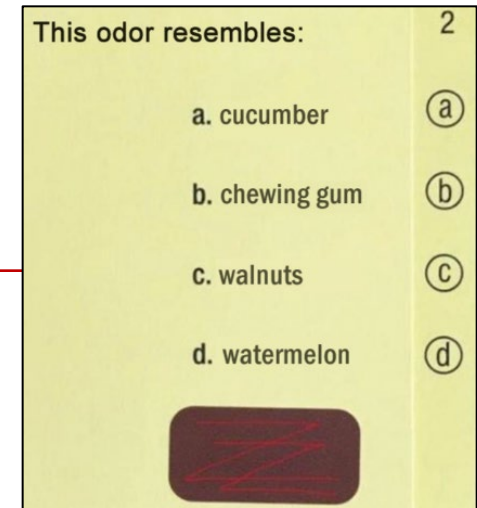
<18 = anosmia

>34 = normosmia

40 = perfect

$\Delta 4$ = Minimal Clinically Important Difference

Avg patient in omalizumab group was still anosmic.



EVEREST: Disease Burden

Sinonasal outcome test

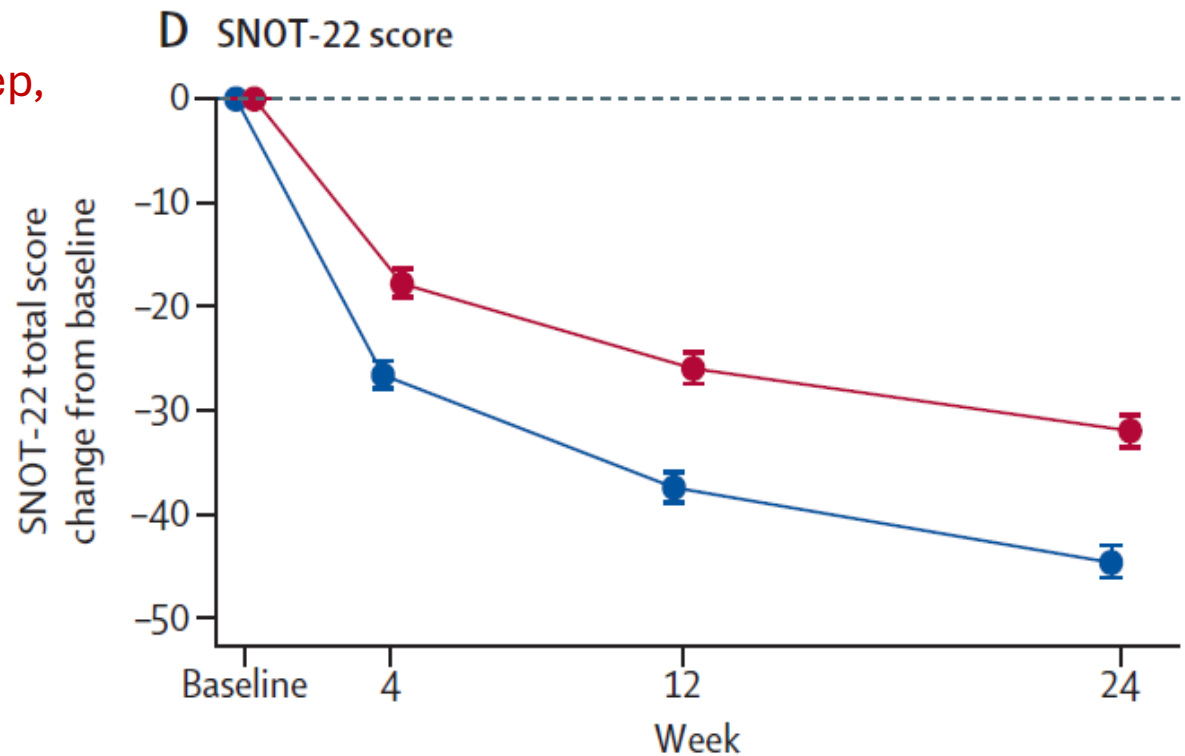
Questionnaire to measure disease burden (nasal sx, sleep, well being)

0 = excellent

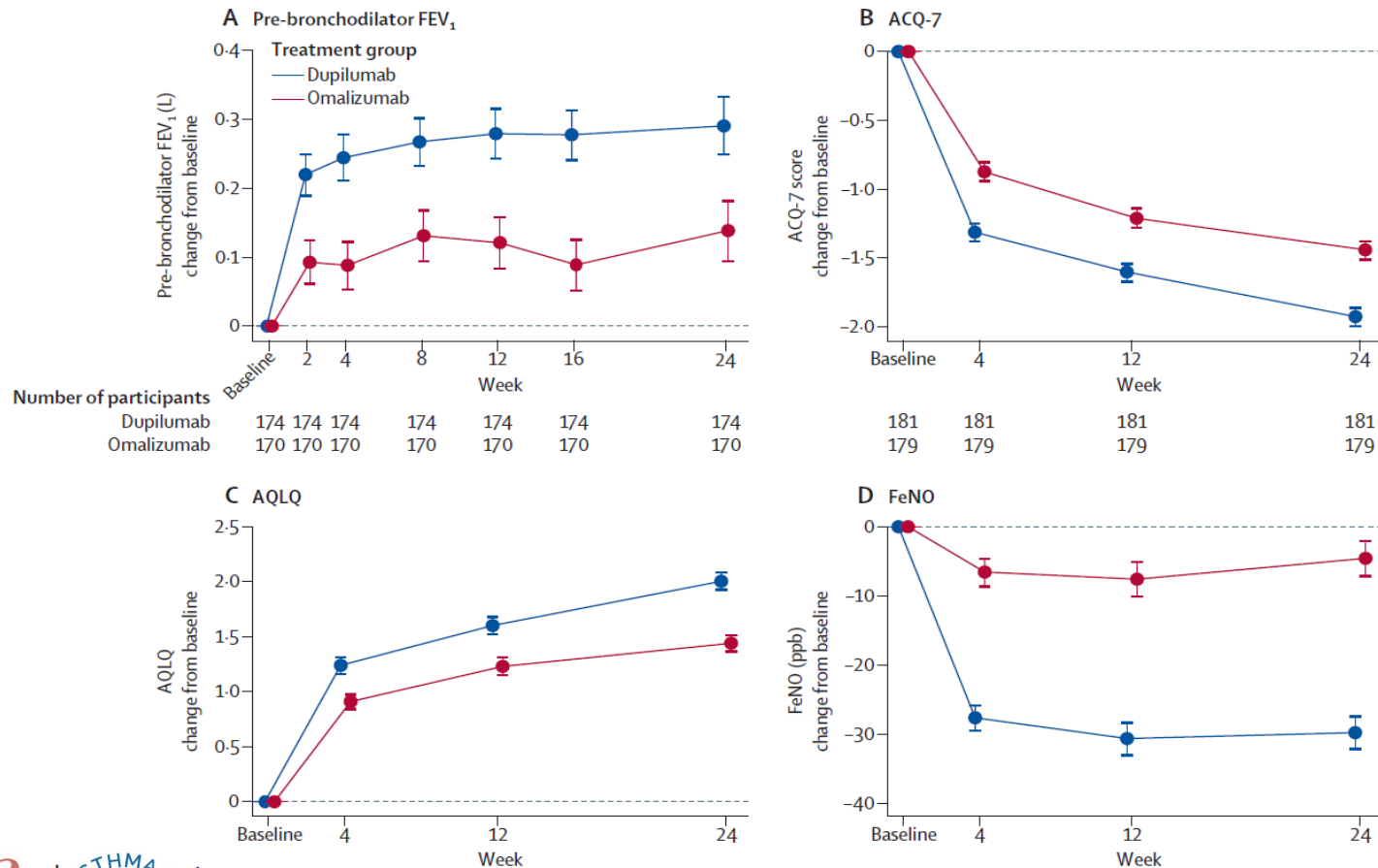
50 = severe impact

110 = worst

Δ 9 points is the Minimal Clinically Important Difference



EVEREST: Asthma Outcomes



EVEREST: Take Home

- Dupilumab was significantly better than Omalizumab in every primary and secondary outcome.
- In nearly all outcomes, the difference was $>$ the minimal clinically important difference.
- Dupilumab was superior across age, sex, bodyweight, age of onset of asthma, smoking history.

EVEREST: Take Home

- Dupilumab was superior in patients of any severity/endotype: ICS level, NSAID-ERD, prior sinus surgery, asthma exacerbations in the year before the study, use of systemic OCS in the 2 years before the study.
- Dupilumab was superior in UPSIT but not total nasal polyp scores for patients with eos < 150 (9 patients) or eos <300 (70 patients).
- Dupilumab was superior irrespective of IgE level.
- There was no difference in adverse outcomes

WAYPOINT : Study Design

- RDBPCT of Tezspire for patients with CRSwNP.
- >18, CRSwNP with score of 5 or more. Active symptoms. SNOT22 \geq 30. Prior surgery at any time and OCS in the past year.
- Excluded confounding conditions, very recent surgery (w/in 6 mos), recent biologic (5 ½ lives).
- No requirement for asthma, but ~65% of patients had co-morbid asthma.
- Tezspire 210 mg monthly or control. Followed for 52 weeks.

WAYPOINT Table 1

Lower than other study →
 Lower than other study →
 Lower than other study →

Similar to other study →

Similar to other study →

Similar to other study →

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Tezepelumab (N=203)	Placebo (N=205)	Overall (N=408)
Age — yr	50.1±13.6	49.4±13.7	49.7±13.6
Male sex — no. (%)	126 (62.1)	140 (68.3)	266 (65.2)
Time since diagnosis of CRS with nasal polyps — yr	12.71±10.43	12.80±10.34	12.75±10.37
Previous nasal-polyp surgery — no. (%)	144 (70.9)	147 (71.7)	291 (71.3)
Time since last nasal-polyp surgery — yr†	7.71±6.54	7.68±6.24	7.70±6.38
Previous systemic glucocorticoid treatment for CRS with nasal polyps — no. (%)	130 (64.0)	137 (66.8)	267 (65.4)
Coexisting asthma — no. (%)‡	122 (60.1)	126 (61.5)	248 (60.8)
Coexisting NSAID-exacerbated respiratory disease — no. (%)	34 (16.7)	37 (18.0)	71 (17.4)
Blood eosinophil count			
Mean — cells/μl	357±229	359±248	358±238
Distribution — no. (%)§			
<150 cells/μl	26 (12.8)	25 (12.2)	51 (12.5)
150 to <300 cells/μl	63 (31.0)	72 (35.1)	135 (33.1)
≥300 cells/μl	112 (55.2)	106 (51.7)	218 (53.4)
Total serum IgE level — IU/ml	171.2±259.3	181.2±308.5	176.2±284.7
Endoscopic nasal-polyp score¶	6.1±1.2	6.1±1.3	6.1±1.2
Nasal-congestion score	2.59±0.47	2.55±0.54	2.57±0.51
Loss-of-smell score	2.9±0.4	2.8±0.4	2.9±0.4
SNOT-22 total score**	68.2±18.4	69.2±18.4	68.7±18.4
Lund-Mackay score††	18.9±3.7	18.5±3.9	18.7±3.8
NPSD total symptom score‡‡	16.3±4.1	16.4±4.5	16.3±4.3
Prebronchodilator FEV ₁ — liters§§	2.87±0.93	2.92±0.85	2.89±0.89
Prebronchodilator FEV ₁ — % of predicted normal value§§	87.2±16.7	84.4±16.1	85.8±16.4
UPSIT score¶¶	13.1±7.3	11.9±5.9	12.5±6.6
ACQ-6 score§§	1.85±1.23	1.80±1.10	1.82±1.16

WAYPOINT: Polyp Size

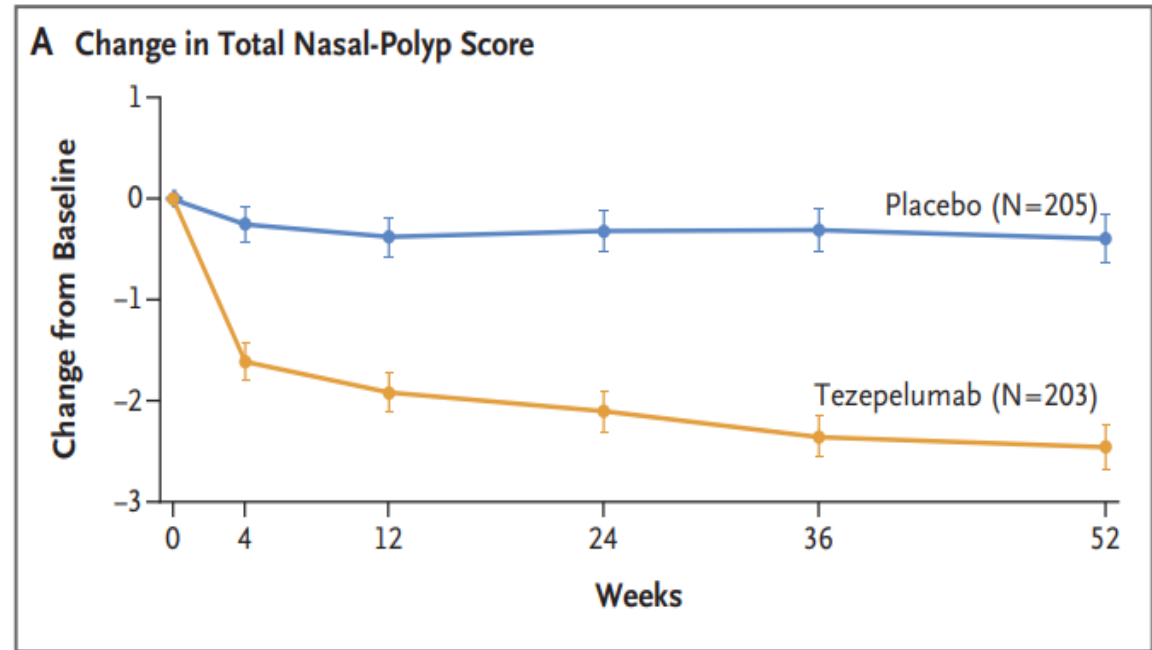
Total Nasal Polyp Score

Measures occlusion of the nasal passages (endoscopy)

0 = no polyp

8 = bilateral occlusive polyps

$\Delta 1$ = Minimal Clinically Important Difference



Very similar to Dupixent

WAYPOINT: Congestion Score

Nasal Congestion Score

Symptom score over 2 wks.

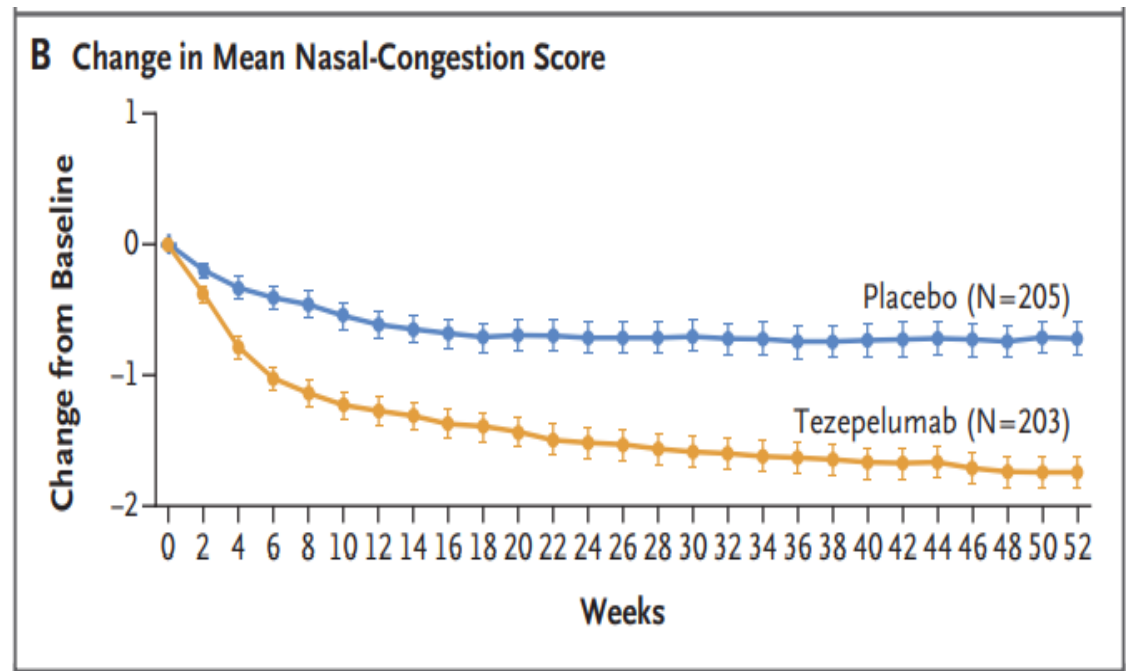
Scale: 0 to 3

0 = no symptoms

3 = severe symptoms

(interfere with activities or sleep)

$\Delta 1$ = Minimal Clinically Important Difference



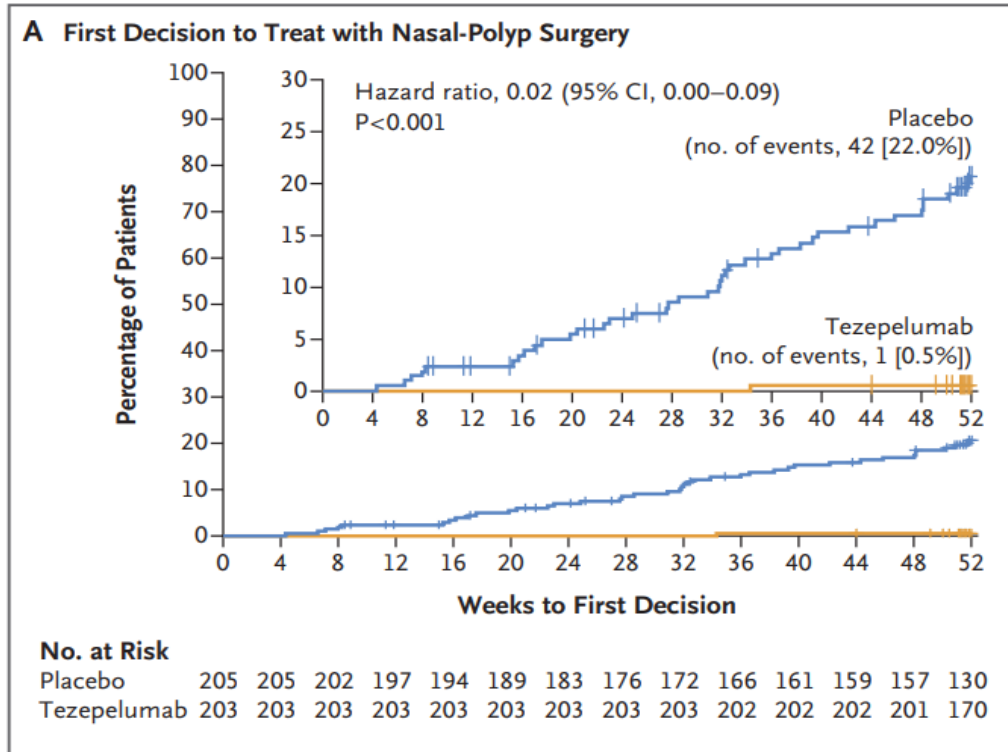
Very similar to Dupixent

WAYPOINT: Time to Surgery

Time to elective surgery in the scope of usual clinical care.

Nasal Polyp Score ≥ 5

Nasal Congestion Score = 3

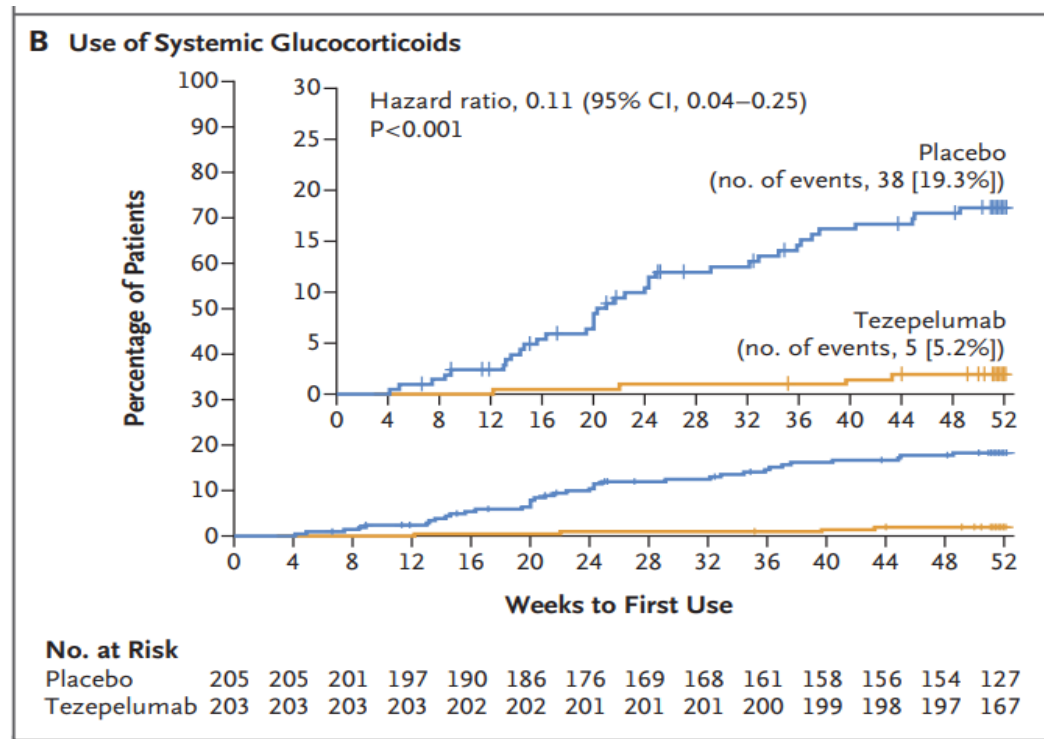


WAYPOINT: Time to Steroids

Time to elective use of oral corticosteroids in the scope of usual clinical care.

Nasal Polyp Score ≥ 5

Nasal Congestion Score = 3



WAYPOINT: Take Home

- Tezspire reduced polyp size, nasal congestion and all other scores (loss-of-smell score, SNOT-22 total score, and total symptom score).
- Improvements were greater than the minimal clinically important difference.
- Tezspire led to > 85% reductions in surgery and oral steroids.
- Improvements were seen in all prespecified subgroups that were assessed, including in patients with a blood eos < 150.

WAYPOINT: Take Home

- Among patients with coexisting asthma, there was no apparent difference between the tezepelumab and placebo groups in the change from baseline in prebronchodilator FEV1 at week 52.
- The mean percent predicted prebronchodilator FEV1 was 87.3% in the tezepelumab group and 84.4% in the placebo group, which potentially limited improvement in prebronchodilator FEV1.

Can't Miss Articles Mucus Plugs

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Disclosures of Conflicts of Interest

I have received research funding from Sanofi and Regeneron,
the makers of dupilumab

Severe Asthma Pathology – Mucus Obstruction

DEATH IN ASTHMATICS

BY

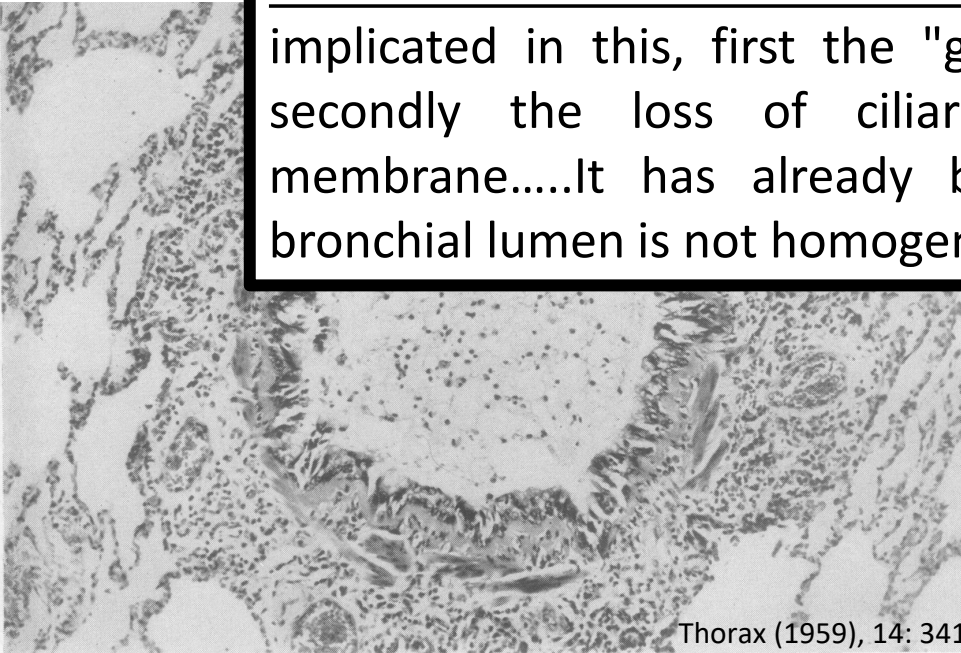
THE PATHOLOGY OF ASTHMA, WITH SPECIAL
REFERENCE TO CHANGES IN THE BRONCHIAL

“Pathologically the outstanding feature of the asthmatic lung lies in the failure of clearance of the bronchial secretions. Two factors are implicated in this, first the "glairy" quality of the mucus itself, and secondly the loss of ciliary action in the bronchial mucous membrane.....It has already been noted that the exudate in the bronchial lumen is not homogeneous and only partly mucoid in nature.”

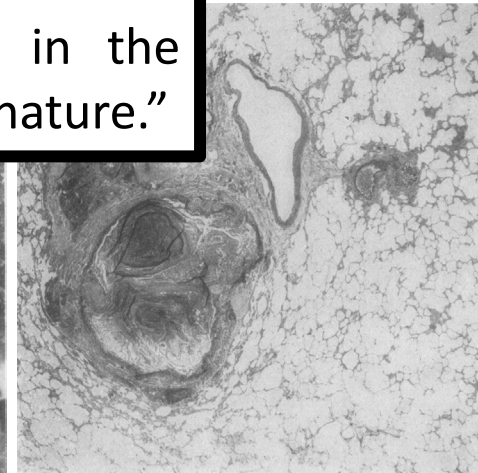
From the Departments

B.

, Oxford



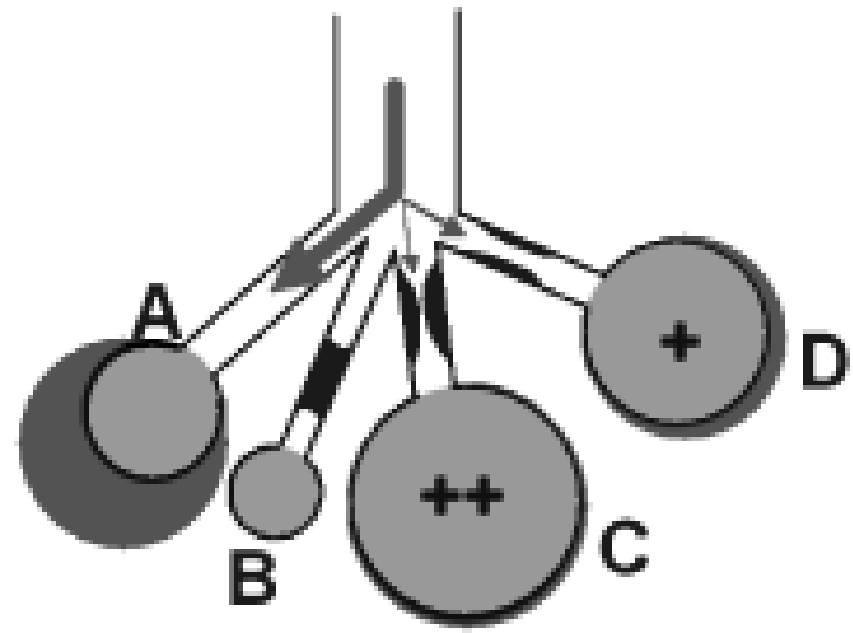
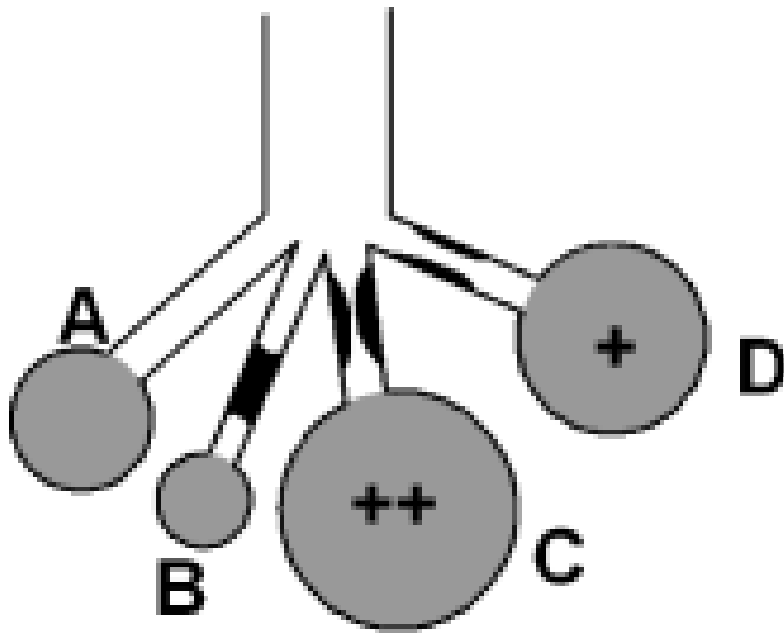
Thorax (1959), 14: 341



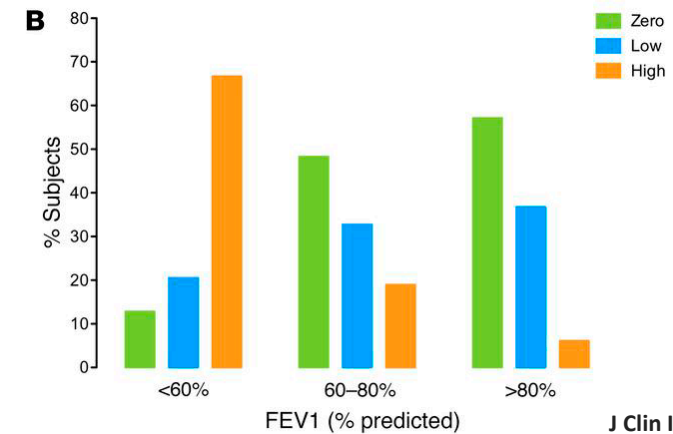
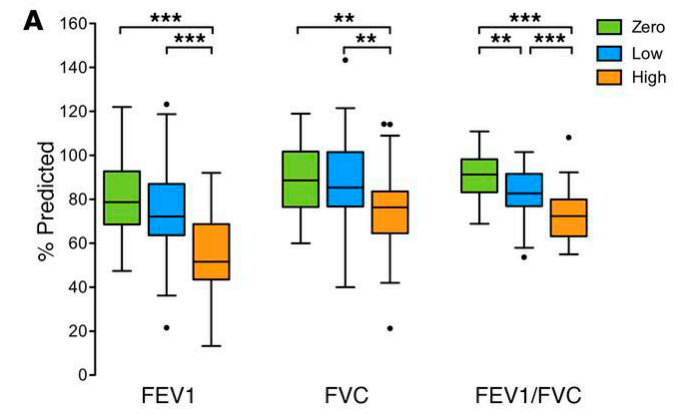
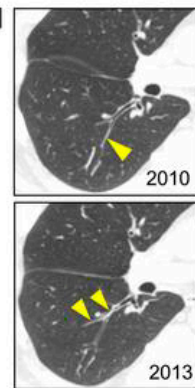
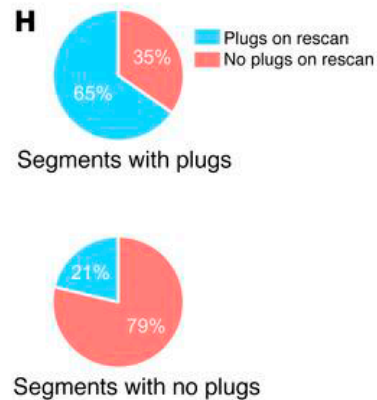
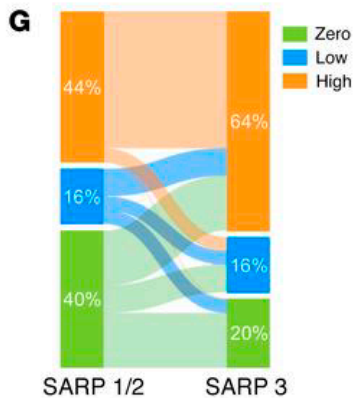
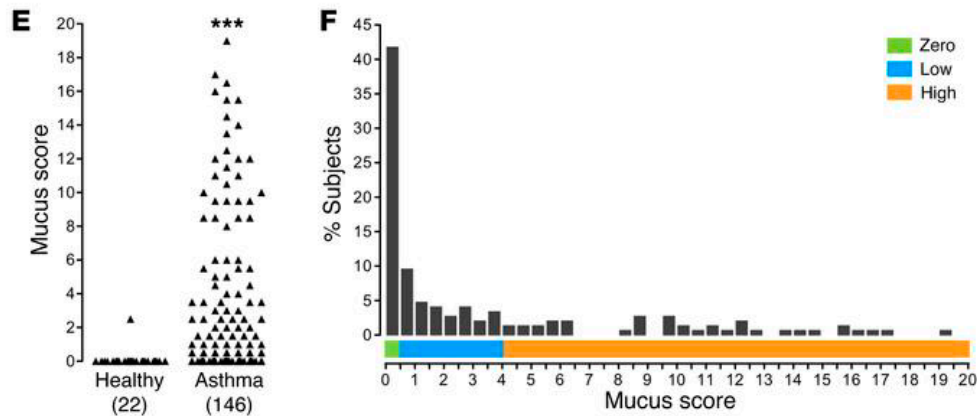
J. Clin. Path. (1960), 13, 27

Mucus Plugging – Physiologic Implications

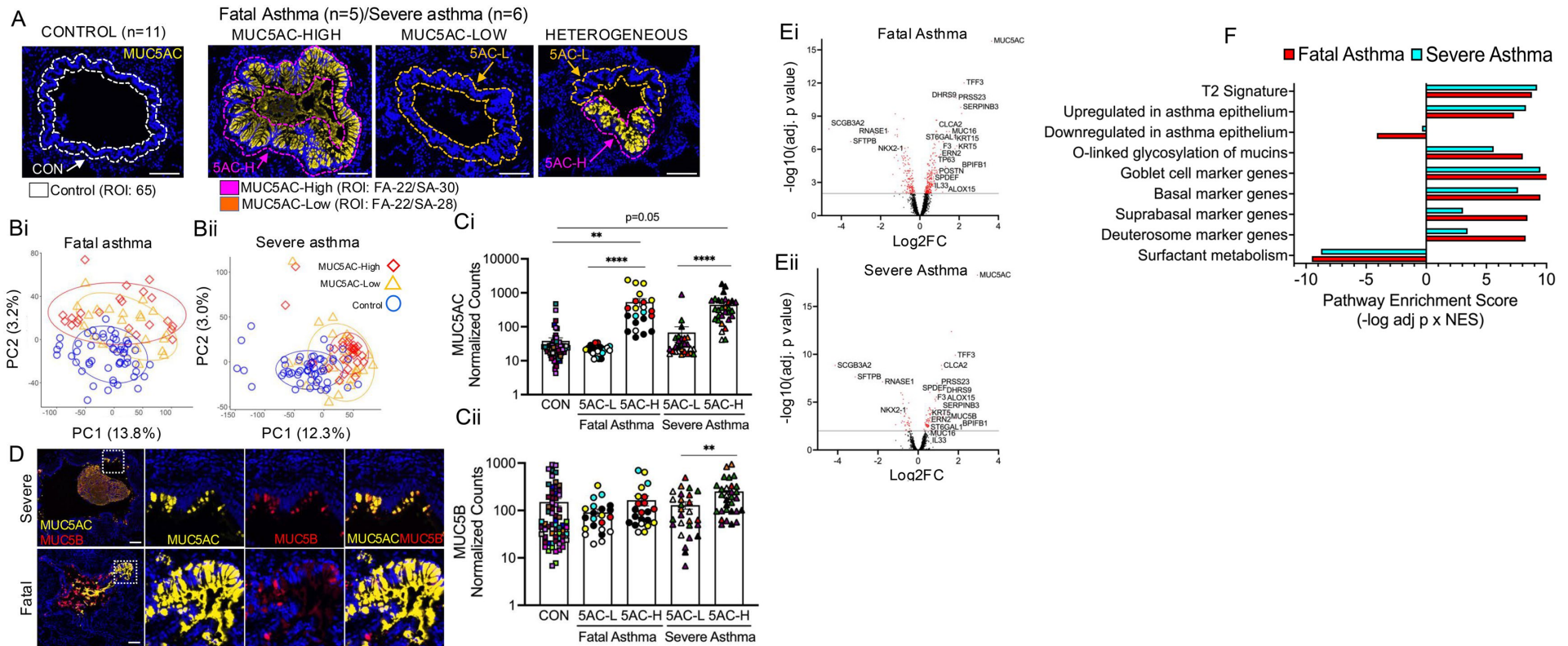
- Mucus Plugging => Heterogeneity:



Mucus Plugging – Physiologic Implications



Mucus Plugging – Molecular Implications



Intro Summary

- Mucus plugging has long been recognized as a significant contributor to severe and fatal asthma
- Mucus plugs may cause significant airway obstruction and complicate management due to heterogeneity of ventilation
- Asthmatics with a “high mucus plug” phenotype have worse lung function
- Changes to mucus composition can affect mucociliary transport/inflammation

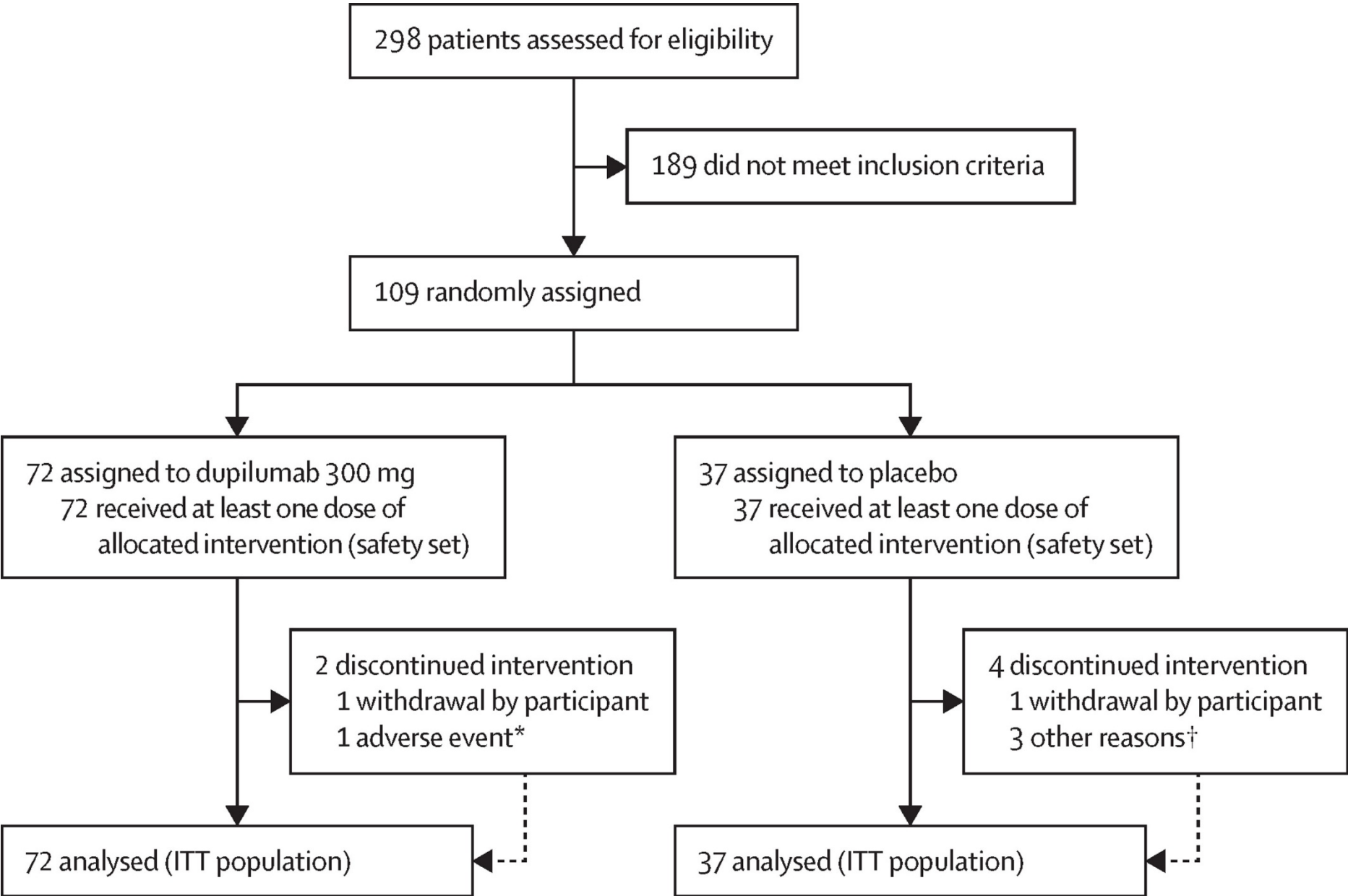
VESTIGE Trial

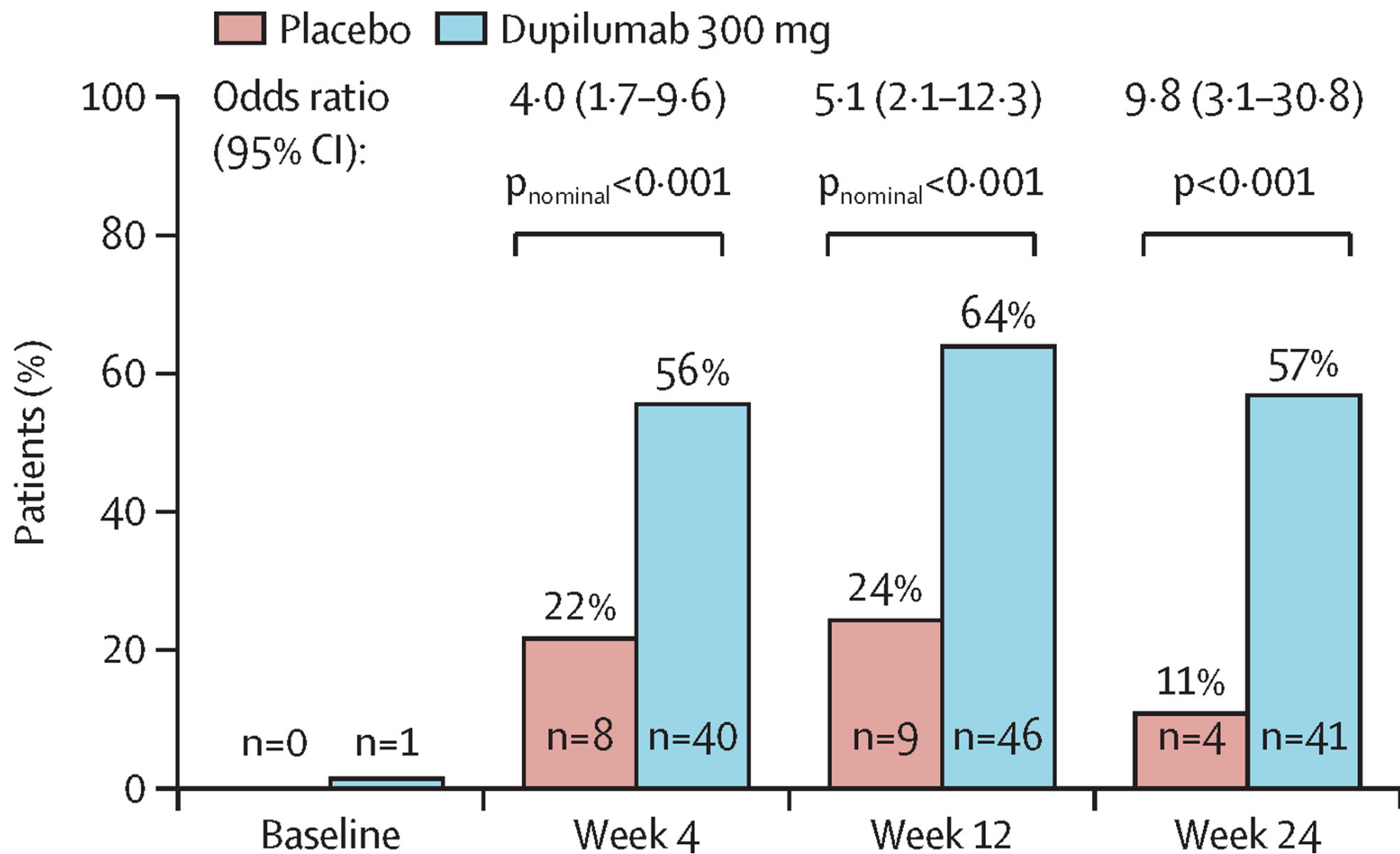


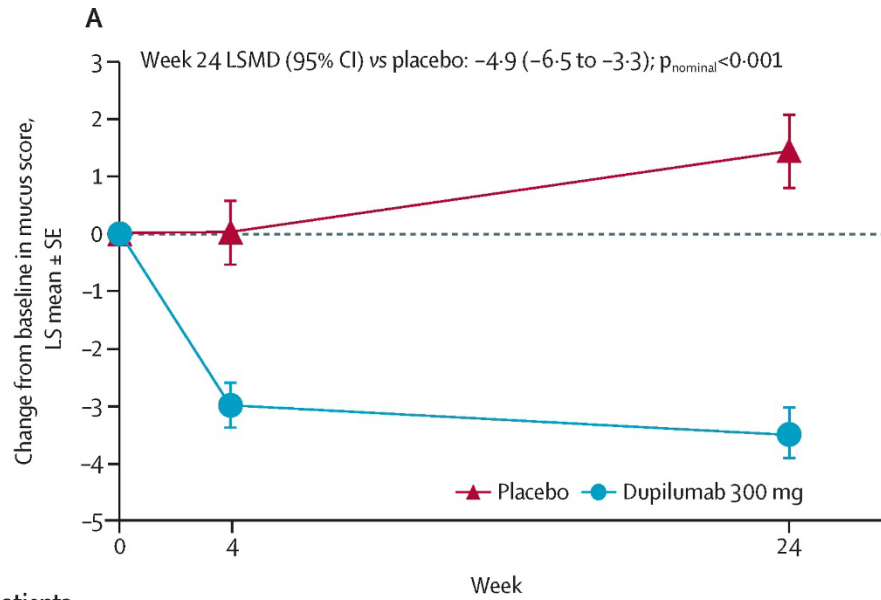
Effect of dupilumab on exhaled nitric oxide, mucus plugs, and functional respiratory imaging in patients with type 2 asthma (VESTIGE): a randomised, double-blind, placebo-controlled, phase 4 trial

Mario Castro, Alberto Papi, Celeste Porsbjerg, Njira L Lugogo, Christopher E Brightling, Francisco-Javier González-Barcala, Arnaud Bourdin, Mykola Ostrovskyy, Maria Staevska, Pai-Chien Chou, Liliana Duca, Ana Margarida Pereira, Charles Fogarty, Rufai Nadama, Mei Zhang, Amelie Rodrigues, Xavier Soler, Harry J Sacks, Yamo Deniz, Paul J Rowe, Lucía de Prado Gómez, Juby A Jacob-Nara

- Randomized, double-blind, placebo-controlled, phase 4 trial done at 72 research sites or academic centers in 14 countries.
- Adult patients (aged 18–70 years) with uncontrolled, moderate-to-severe type 2 asthma (blood eosinophil count ≥ 300 cells/ μL and fractional exhaled nitric oxide [FeNO] ≥ 25) being treated with medium-dose to high-dose ICS combined with other controller medications.
- Patients were randomly assigned (2:1) to receive add-on dupilumab 300 mg subcutaneously once every 2 weeks or volume-matched placebo up to week 24.
- The primary endpoints were the proportion of patients with a FeNO concentration below 25 ppb at week 24, and the percentage change from baseline to week 24 in airway volumes

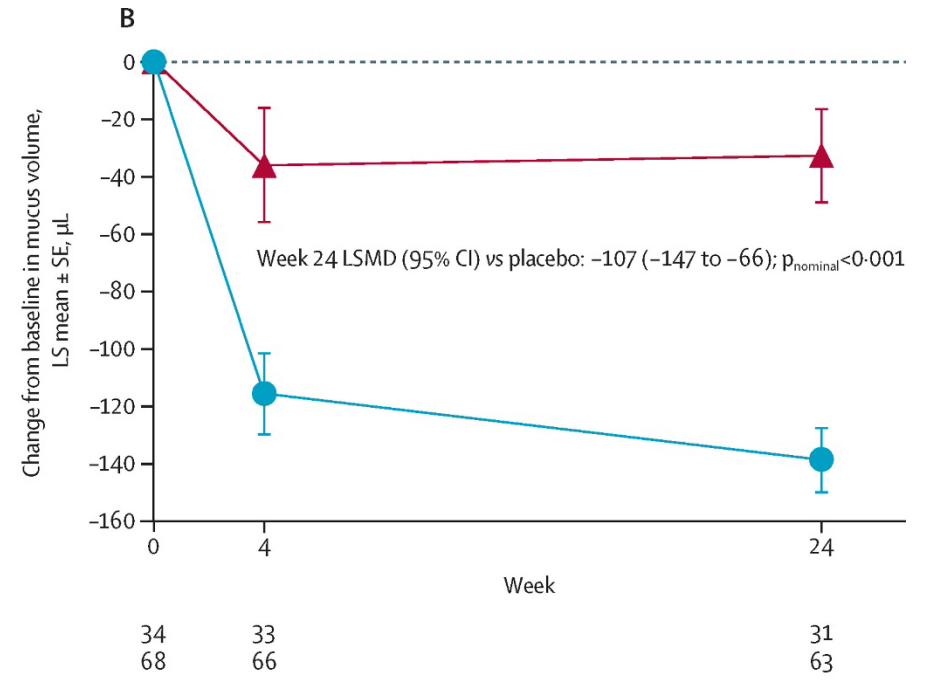




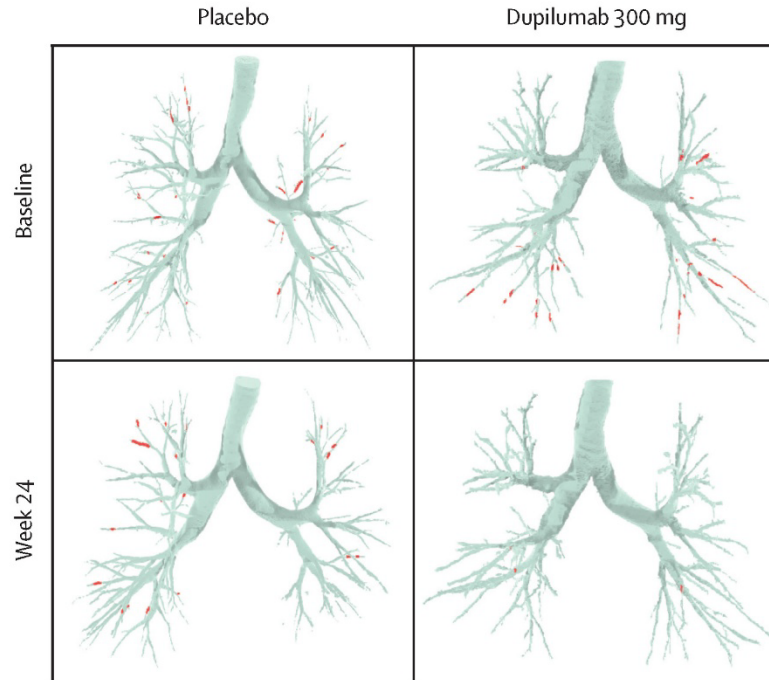


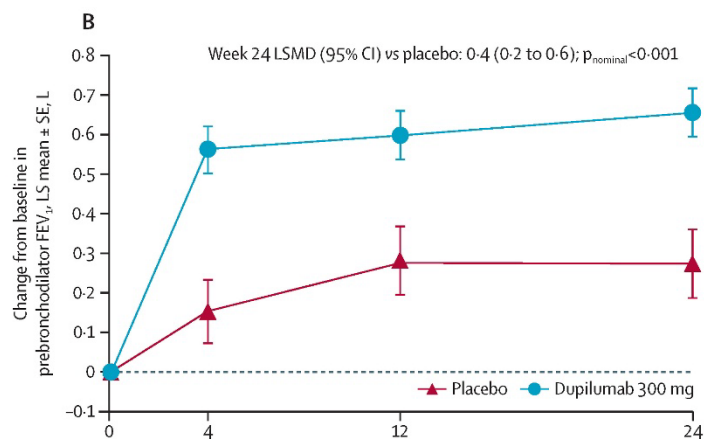
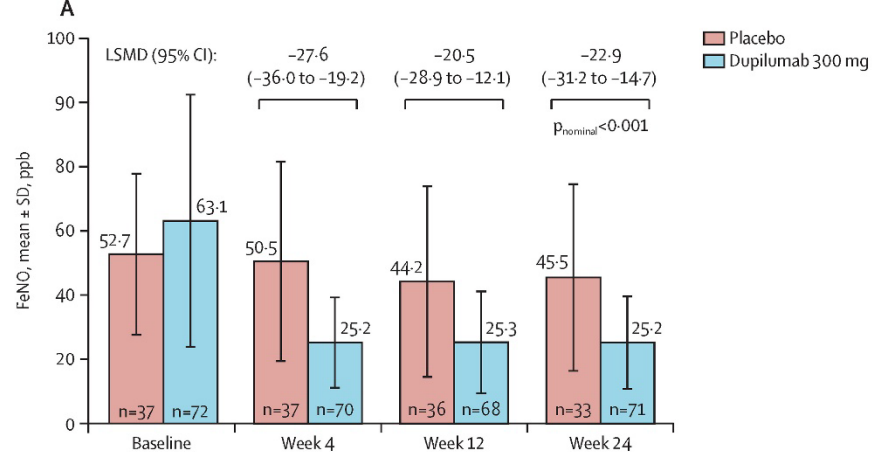
Number of patients

Placebo	33	33	31
Dupilumab 300 mg	68	66	63



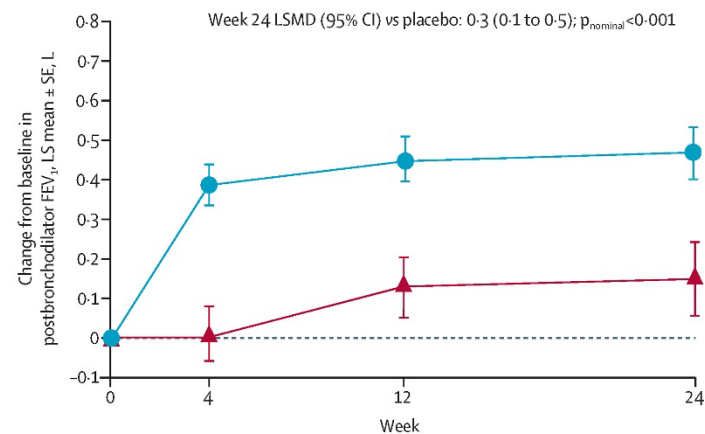
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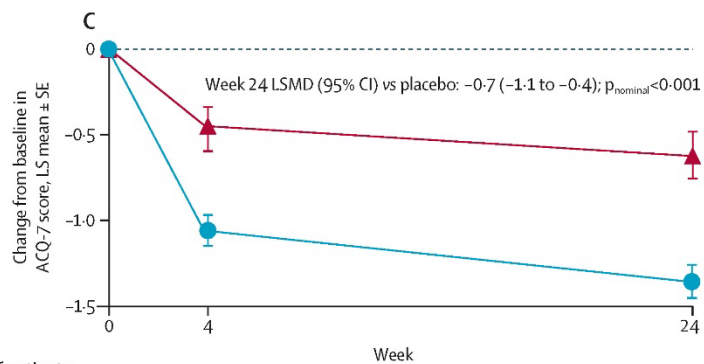
Number of patients

	Baseline	Week 4	Week 12	Week 24
Placebo	37	37	36	33
Dupilumab 300 mg	72	70	69	70



Number of patients

	Baseline	Week 4	Week 12	Week 24
Placebo	37	37	36	33
Dupilumab 300 mg	72	70	69	70



Number of patients

	Baseline	Week 4	Week 24
Placebo	36	36	32
Dupilumab 300 mg	70	69	66

ORIGINAL ARTICLE

Tezepelumab and Mucus Plugs in Patients with Moderate-to-Severe Asthma

Lars H. Nordenmark, Ph.D.,¹ Åsa Hellqvist, M.Sc.,² Claire Emson, Ph.D.,³ Sarah Diver, M.D.,⁴ Celeste Porsbjerg, M.D., Ph.D.,⁵ Janet M. Griffiths, Ph.D.,³ John D. Newell Jr, M.D.,^{6,7} Samuel Peterson, M.Sc.,⁷ Beata Pawlikowska, B.Sc.,⁸ Jane R. Parnes, M.D.,⁹ Ayman Megally, M.D.,¹⁰ Gene Colice, M.D.,¹⁰ and Christopher E. Brightling, F.Med.Sci.⁴

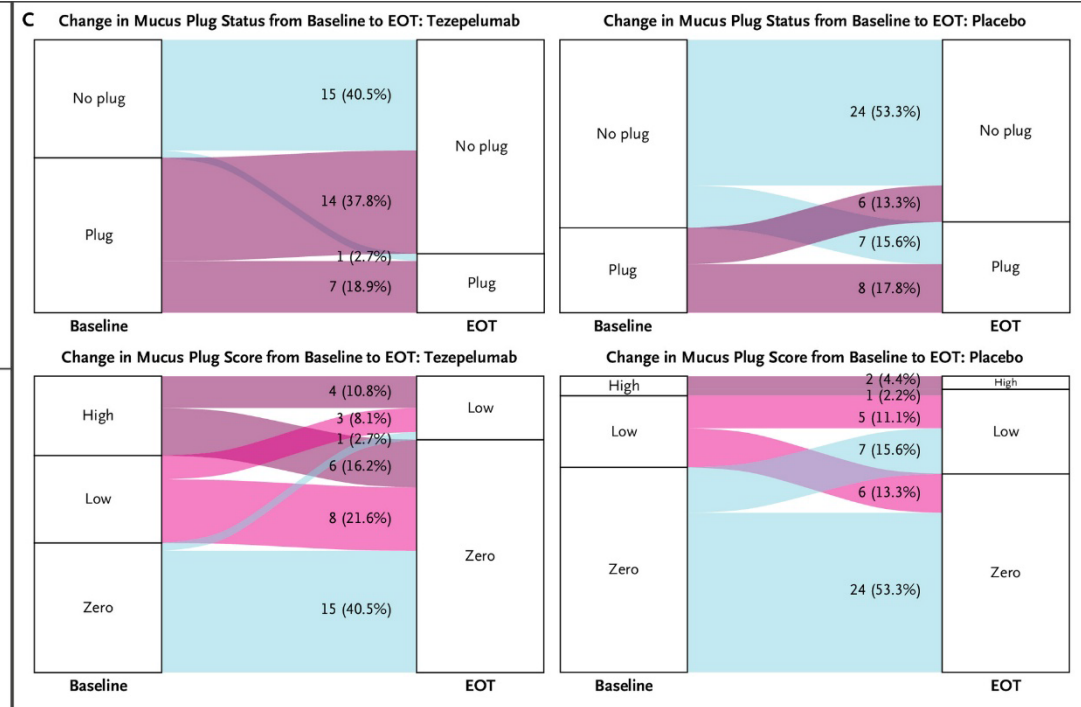
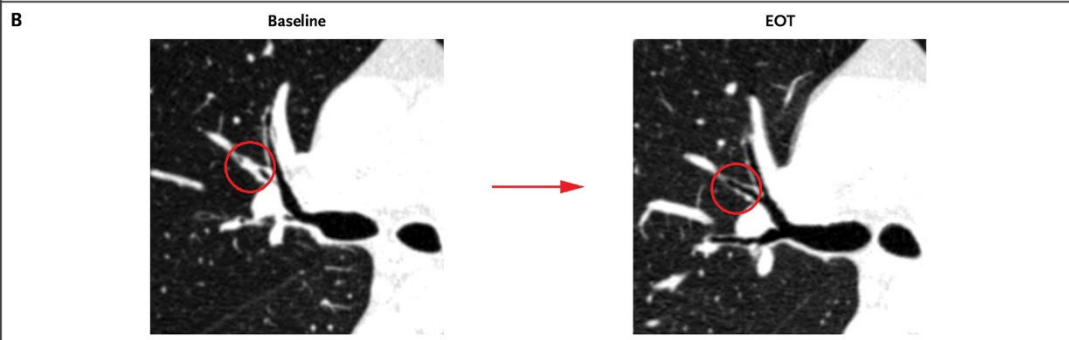
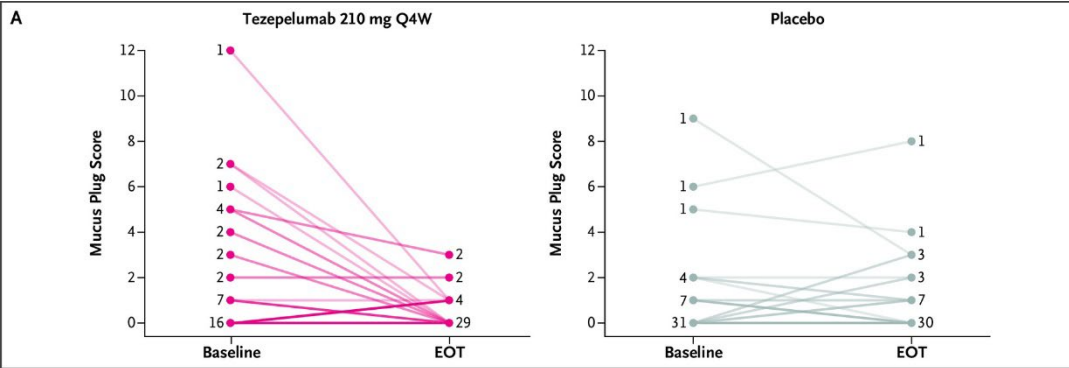
-
- Randomized, double-blind, placebo-controlled phase 2 trial at 27 centers.
 - Patients (aged 18 to 75 years old) were randomly assigned 1:1 to 210mg tezepelumab or placebo every 4 weeks subcutaneously for at least 28 weeks.
 - Moderate to high dose ICS, BD reversibility on PFTs, excluded if recent exacerbation.
 - 30% had blood eosinophils less than 300 cells/ul, 40% had eosinophils >300 cells/ul
 - An expert radiologist, blinded to treatment groups and time points, objectively scored 18 lung segments for the presence of mucus plugs in CT scans obtained before and after treatment.
 - Bronchoscopies performed at baseline and end of treatment (EOT)

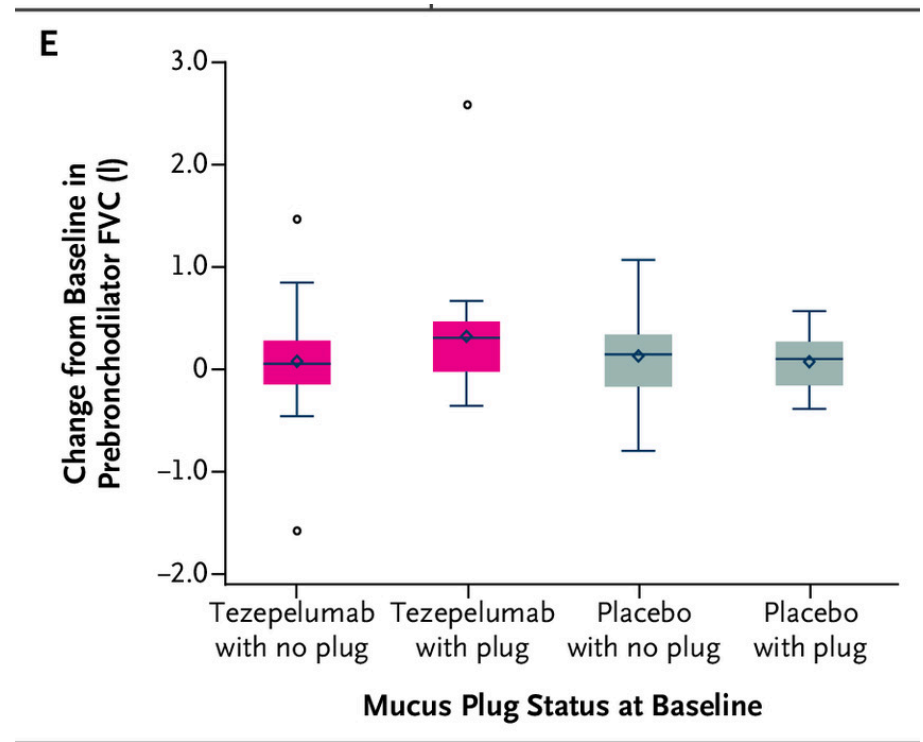
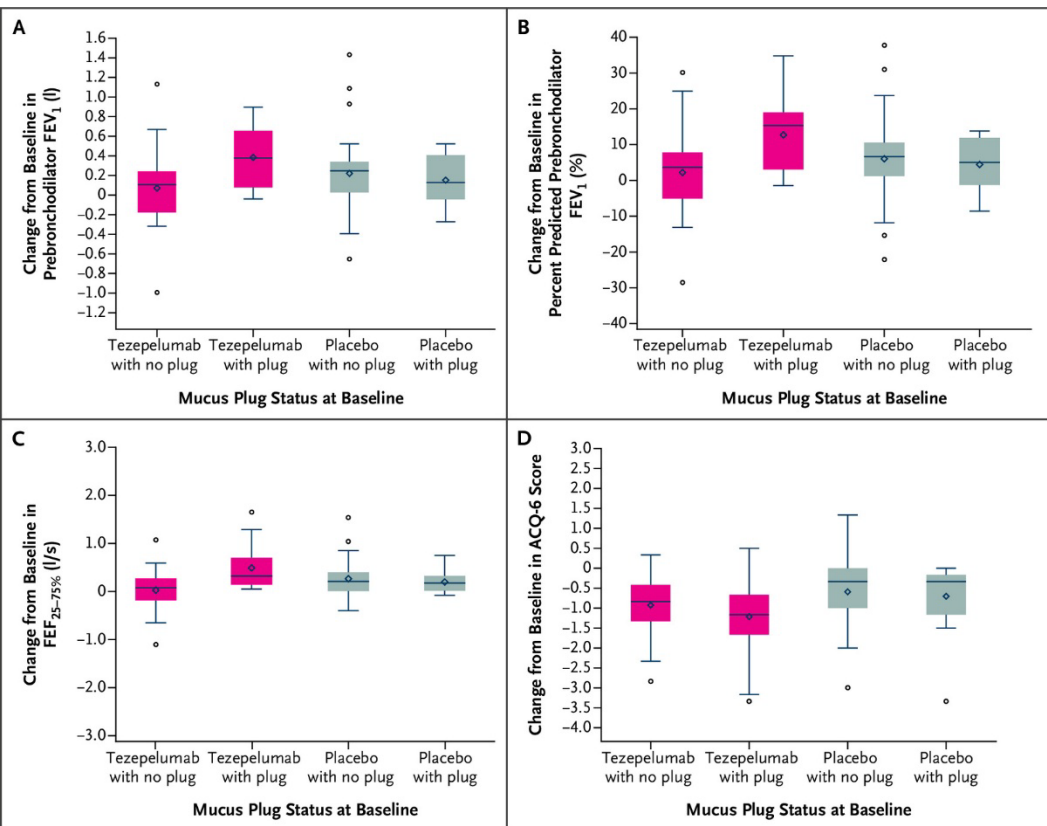
Baseline Mucus Plug Scores

Table 2. Baseline Mucus Plug Scores in Patients Grouped According to Baseline BEC and FeNO Level (Modified FAS).*

Baseline Mucus Plug Score	BEC <300 Cells/ μ l and FeNO <25 ppb (n=34)	BEC \geq 300 Cells/ μ l and FeNO <25 ppb (n=16)	BEC <300 Cells/ μ l and FeNO \geq 25 ppb (n=24)	BEC \geq 300 Cells/ μ l and FeNO \geq 25 ppb (n=13)
Baseline mucus plug score — mean (min, max)	0.53 (0, 5)	1.38 (0, 6)	1.29 (0, 9)	3.46 (0, 12)
Baseline mucus plug score — n (%)				
No mucus plugs (score of 0)	24 (70.6)	8 (50.0)	13 (54.2)	5 (38.5)
Low (score of 1–3)	8 (23.5)	6 (37.5)	8 (33.3)	2 (15.4)
High (score of >3)	2 (5.9)	2 (12.5)	3 (12.5)	6 (46.2)
With mucus plugs (score of \geq 1)	10 (29.4)	8 (50.0)	11 (45.8)	8 (61.5)

* BEC denotes blood eosinophil count; FAS, full analysis set; FeNO, fractional exhaled nitric oxide; max, maximum; and min, minimum.





Take Home

- Both dupilumab and tezepulimab are effective agents to reduce mucus plugging in asthmatics
- Mucus plugs correlate positively with levels of type 2 inflammatory biomarkers and negatively with lung function measures
- Dupilumab reduced airway inflammation and mucus plugging, and improved airway volume and flow, corresponding to improved lung function and asthma control.
- Tezepelumab reduced mucus plug scores, which correlated with improvements in lung function and reductions in blood eosinophil count and levels of eosinophil-derived neurotoxin.
- These studies highlight the potential of mucus plug scores to assess disease severity and evaluate therapeutic responses in moderate-to-severe type 2 asthma.

The Team

