# Biologics in COPD: Current Status and Future Prospects

가톨릭대학교
최준영

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2. Biologics targeting neutrophilic inflammation
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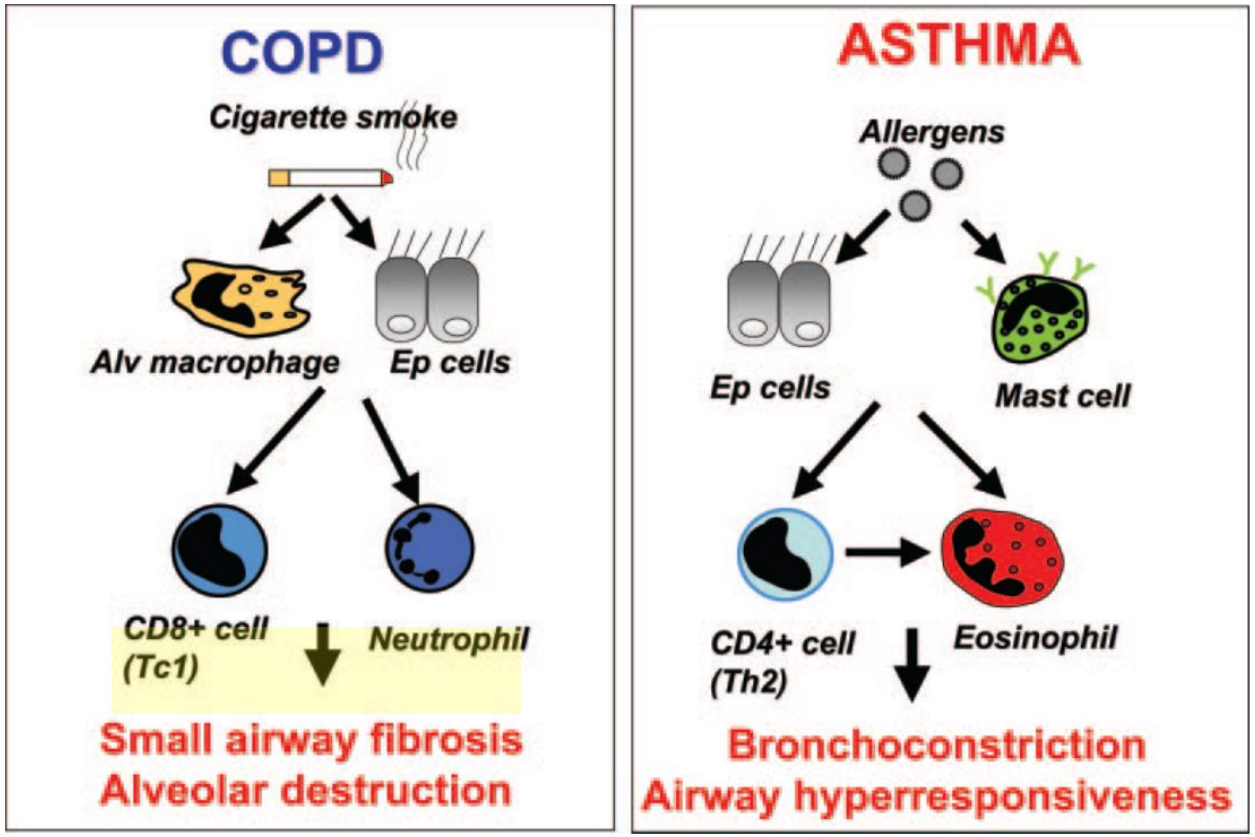
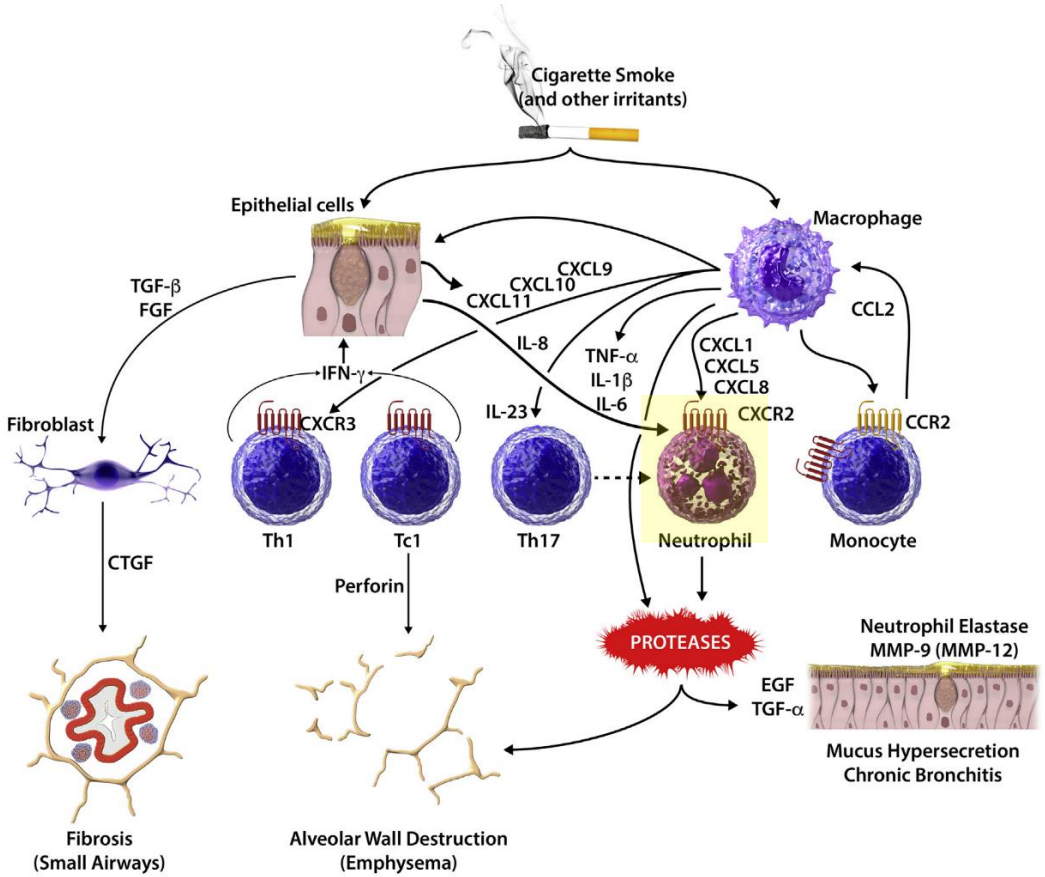
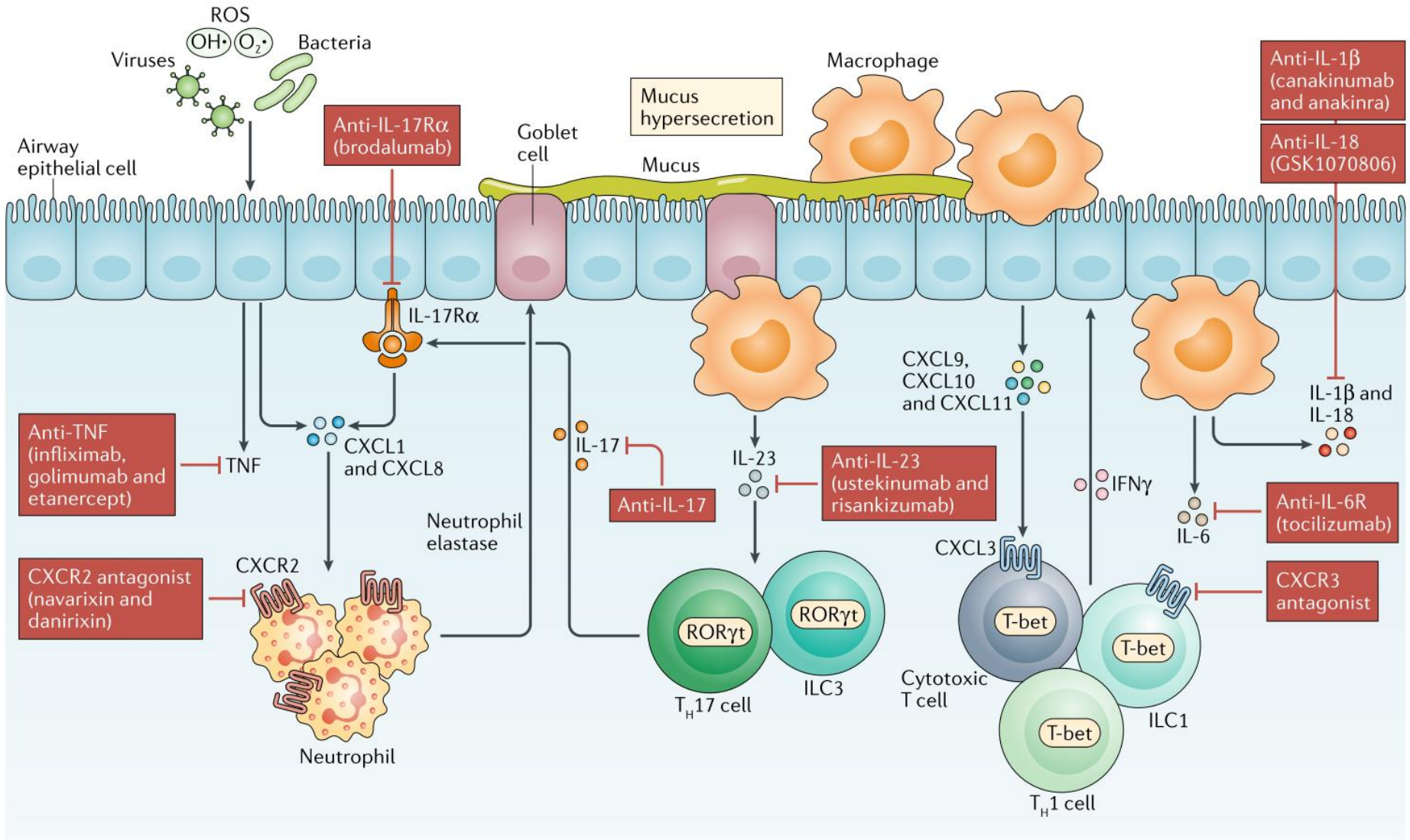
5. Conclusions

# Inflammatory mechanisms in COPD




Pharmacol Rev. 2004 Dec;56(4):515-48.




## Targeting non-type 2 immunity in airway disease

Nat Rev Immunol. 2018 Jul;18(7):454-466.

# Failure in biologics targeting neutrophilic inflammation in COPD

| Agent; Target | Study | Regimen | Primary outcome (if available) | Secondary outcome (if available) |
|---|---|---|---|---|
| Anti−IL-8; IL-8[47] | A multicenter, randomized, double-blind, placebo-controlled trial of anti−IL-8 in COPD<br>N = 109<br>NCT00035828 | 800 mg loading dose, 400 mg/mo for 3 mo, 5-mo follow-up | ↓ Severity of dyspnea as measured by transition dyspnea index | ↔ Health status, lung function, 6-min walk test, rescue use of albuterol |
| Etanercept[50]; TNF-α | A randomized double-blind double-dummy controlled multicenter trial of etanercept in COPD<br>N = 81<br>NCT00789997 | 50 mg, for 90 d | ↔ $FEV_1$ over 14 d from AECOPD onset | ↔ 90-d treatment failure, dyspnea, health status |
| Infliximab; TNF-α[54] | Exploratory single-center, double-blind, placebo-controlled, randomized, phase 2 trial in mild-moderate COPD<br>N = 22<br>NCT00244192 | 5 mg/kg, for 8 wk | ↔ Sputum inflammatory cells | ↔ $FEV_1$, SGRQ |
| Infliximab; TNF-α[49] | A multicenter, randomized, double-blind, placebo-controlled trial of infliximab in moderate-to-severe COPD<br>N = 157<br>NCT00056264 | 3 mg/kg or 5 mg/kg, 44 wk | ↔ CRQ | ↔ $FEV_1$, 6-min walk test, TDI<br>↑ Malignancy and pneumonia |
| MEDI 8968[57]; IL-1 | A multicenter, randomized, placebo-controlled phase II trial of anti−IL-1 antibody (MEDI8968) in COPD<br>N = 160<br>NCT01448850 | 300 mg every 4 wk, 52 wk | ↔ Moderate-to-severe AECOPD | ↔ SGRQ-C |
| CNTO 6785[62]; IL-17 | A multicenter randomized, placebo-controlled, double- blind, parallel-group phase 2 trial of anti−IL-17 antibody (CNTO 6785) in COPD<br>N = 186<br>NCT01966549 | 6 mg/kg every 2 wk for 4 wk, then every 4 wk for remaining 8 wk | ↔ pre-BD % predicted $FEV_1$ | ↔ Post-BD % predicted $FEV_1$<br>↔ SGRQ-C<br>↔ frequency of AECOPD<br>↔ weekly usage of rescue medication |

J Allergy Clin Immunol Pract. 2019 May-Jun;7(5):1405-1416.

# Eosinophilia is common in COPD

AGORA
RESEARCH LETTERS

ECLIPSE study

**Eosinophilic inflammation in COPD: prevalence and clinical characteristics**

| Persistently ≥ 2% | Intermittent | Persistently <2% |
|---|---|---|
| 554 (37.4%) | 728 (49%) | 201 (13.6%) |

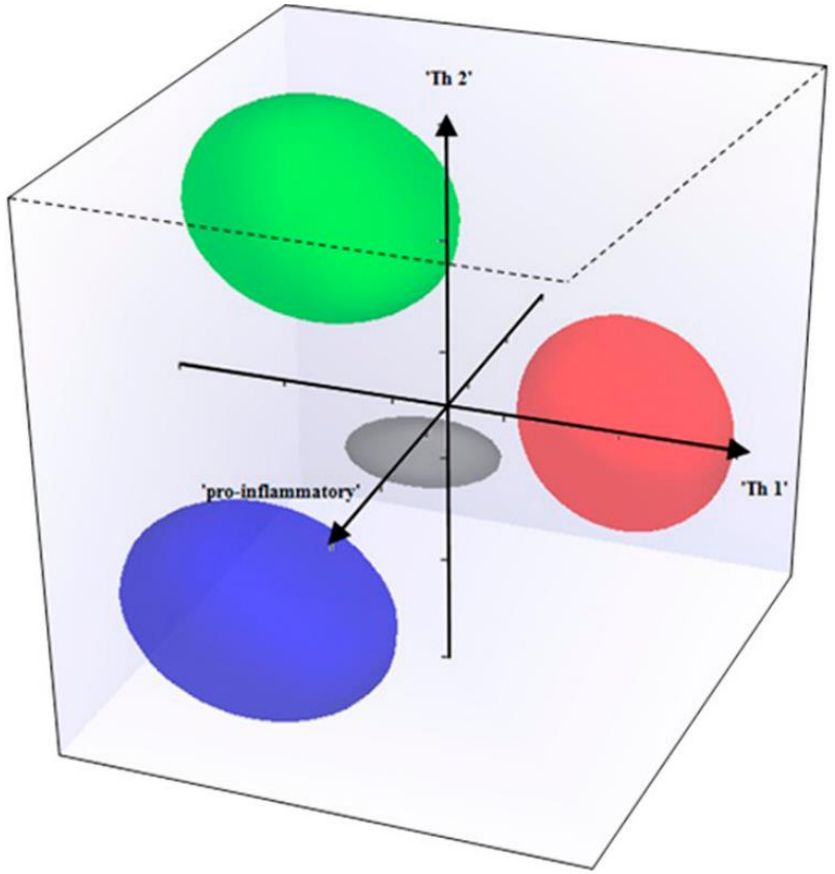
Eur Respir J. 2014 Dec;44(6):1697-700.

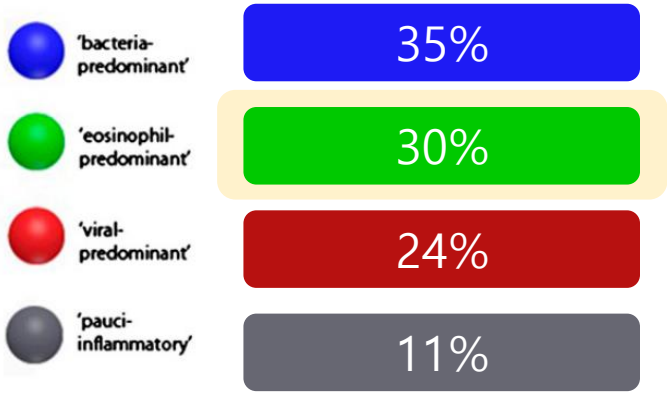
# Eosinophilia is common in COPD

**Acute Exacerbations of Chronic Obstructive Pulmonary Disease**

Identification of Biologic Clusters and Their Biomarkers

Mona Bafadhel[1,2], Susan McKenna[1], Sarah Terry[1], Vijay Mistry[1,2], Carlene Reid[1], Pranabashis Haldar[2], Margaret McCormick[3], Koirobi Haldar[2], Tatiana Kebadze[4], Annelyse Duvoix[5], Kerstin Lindblad[6], Hemu Patel[7], Paul Rugman[3], Paul Dodson[3], Martin Jenkins[3], Michael Saunders[3], Paul Newbold[3], Ruth H. Green[1], Per Venge[6], David A. Lomas[5], Michael R. Barer[2,7], Sebastian L. Johnston[4], Ian D. Pavord[1], and Christopher E. Brightling[1,2]




Am J Respir Crit Care Med. 2011 Sep 15;184(6):662-71

# Eosinophilia is associated with exacerbation↑

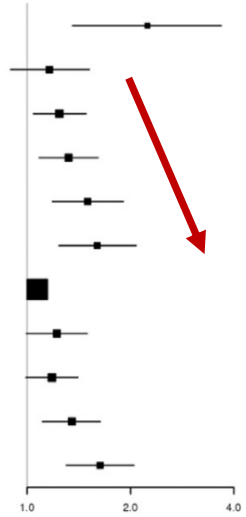
**Blood eosinophil count thresholds and exacerbations in patients with chronic obstructive pulmonary disease**

Jeong H. Yun, MD, MPH,[a,b,c] Andrew Lamb, MS,[a] Robert Chase, MS,[a] Dave Singh, MD,[d] Margaret M. Parker, PhD,[a,c] Aabida Saferali, PhD,[a,c] Jørgen Vestbo, DMSc,[d,e] Ruth Tal-Singer, PhD,[f] Peter J. Castaldi, MD,[a,c] Edwin K. Silverman, MD, PhD,[a,b,c] and Craig P. Hersh, MD, MPH,[a,b,c] for the COPDGene and ECLIPSE Investigators

*Boston, Mass, Manchester, United Kingdom, and King of Prussia, Pa*

| | COPDGene: Year before visit 2 (cross-sectional) | | | |
|---|---|---|---|---|
| | Exacerbation frequency* (n = 1,553) | | Frequent exacerbation† (n = 1,281) | |
| **Factors** | **IRR* (95% CI)** | ***P* value** | **OR† (95% CI)** | ***P* value** |
| Age | **0.98 (0.97-1.00)** | **.007** | **0.96 (0.94-0.99)** | **.003** |
| Female sex | **1.43 (1.20-1.71)** | **<.001** | **1.83 (1.30-2.58)** | **<.001** |
| Nonwhite race | **0.73 (0.57-0.92)** | **.008** | **0.63 (0.40-0.99)** | **.05** |
| SGRQ total score‡ | **1.02 (1.02-1.03)** | **<.001** | **1.04 (1.03-1.05)** | **<.001** |
| Postbronchodilator $FEV_1$ (% predicted)§ | **0.98 (0.98-0.99)** | **<.001** | **0.97 (0.96-0.98)** | **<.001** |
| GERD | **1.33 (1.11-1.59)** | **.002** | 1.35 (0.95-1.91) | .09 |
| Current smoking | **0.71 (0.57-0.89)** | **.002** | **0.56 (0.37-0.84)** | **.006** |
| Previous exacerbations | NA | NA | NA | NA |
| WBC count | 1.00 (0.96-1.04) | .97 | 1.02 (0.94-1.10) | .66 |
| Eosinophil count ≥300 cells/μL | **1.32 (1.08-1.61)** | **.006** | **1.58 (1.07-2.30)** | **.019** |

| Eosinophil Cutoff | < n | ≥ n | IRR | 95% CI |
|---|---|---|---|---|
| cell/uL continuous | NA | 1540 | 2.24 | 1.35-3.68 |
| 100 cells/uL | 223 | 1330 | 1.16 | 0.90-1.52 |
| 200 cells/uL | 814 | 739 | 1.24 | 1.04-1.48 |
| 300 cells/uL | 1187 | 366 | 1.32 | 1.08-1.61 |
| 340 cells/uL | 1350 | 203 | 1.5 | 1.18-1.91 |
| 400 cells/uL | 1398 | 155 | 1.6 | 1.24-2.08 |
| % continuous | NA | 1540 | 1.07 | 1.02-1.11 |
| 2 % | 408 | 1145 | 1.22 | 0.99-1.50 |
| 3 % | 859 | 694 | 1.18 | 0.99-1.40 |
| 4 % | 1166 | 387 | 1.35 | 1.11-1.63 |
| 5 % | 1334 | 219 | 1.63 | 1.30-2.05 |



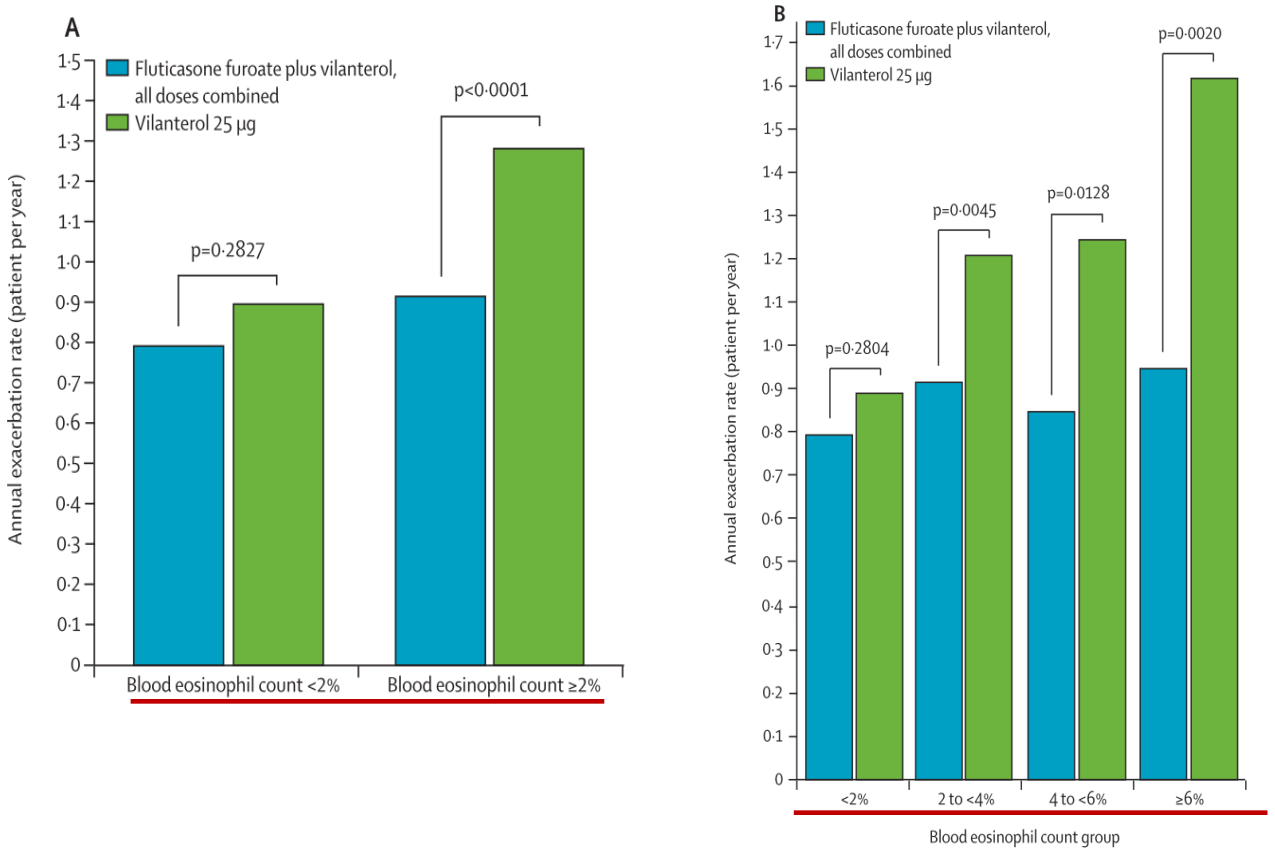

J Allergy Clin Immunol. 2018 Jun;141(6):2037-2047.e10.

# Eosinophil is a predictor of ICS response

**Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials**

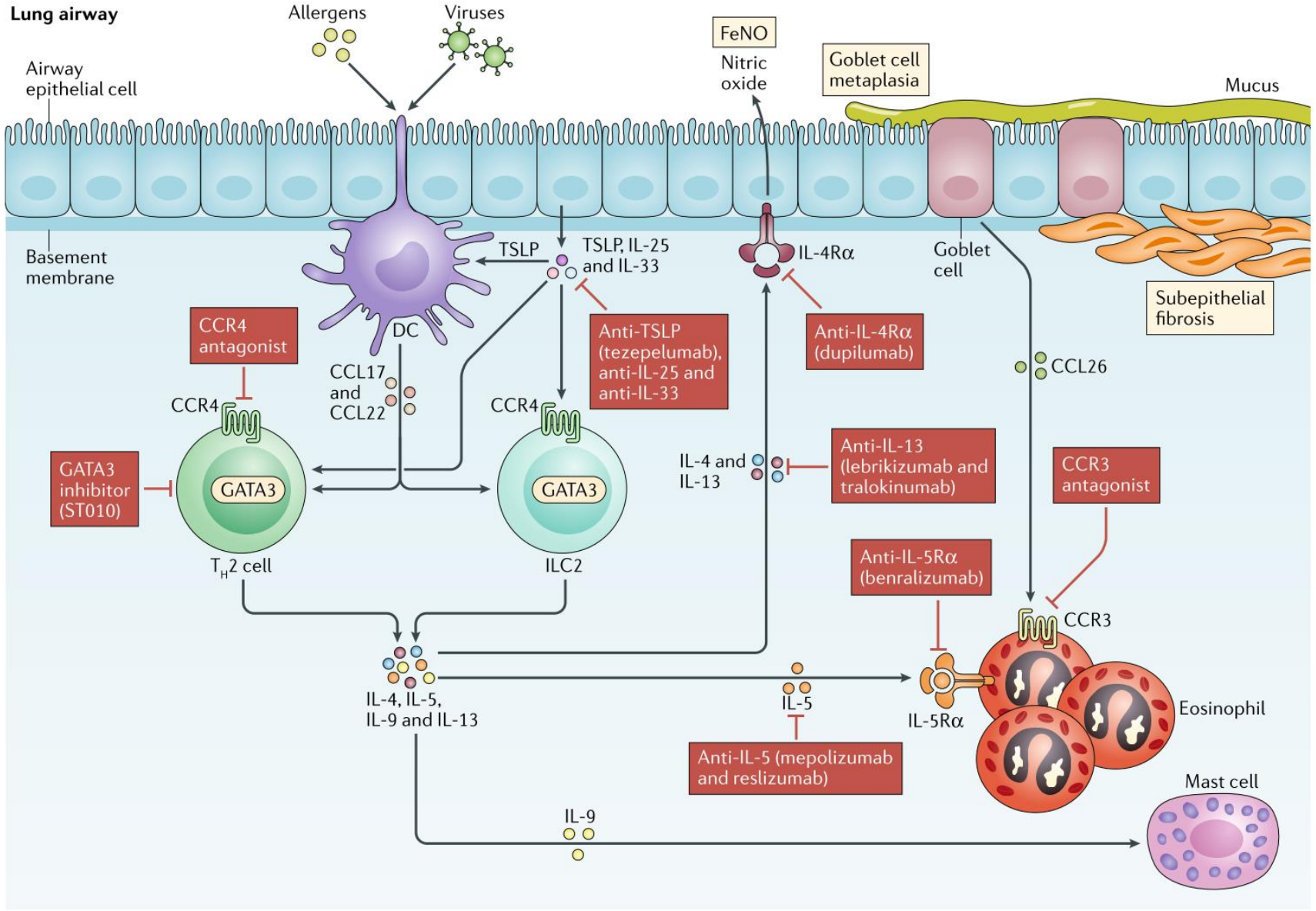
*Steven Pascoe, Nicholas Locantore, Mark T Dransfield, Neil C Barnes, Ian D Pavord*

**Annual Exacerbation rate**




Lancet Respir Med. 2015 Jun;3(6):435-42

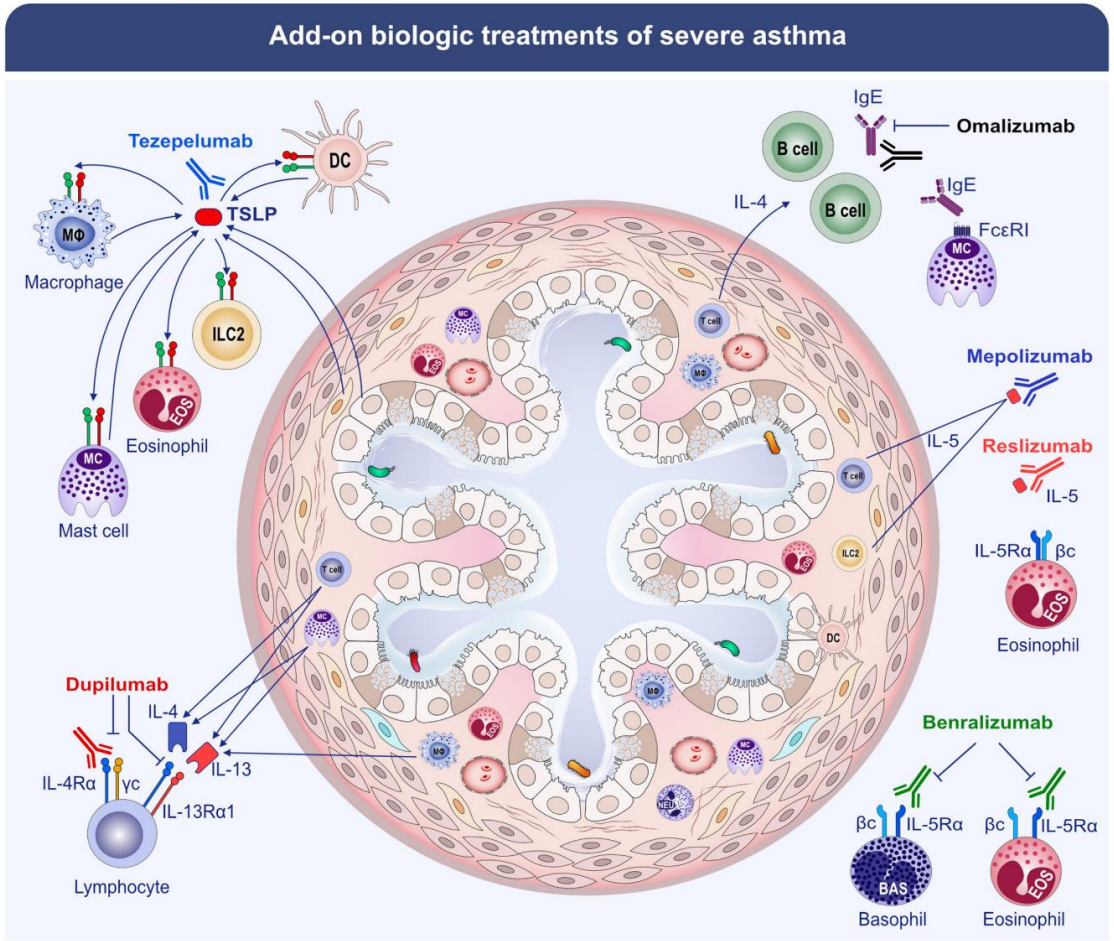
# Biologics targeting Th2 inflammation




**Targeting type 2 immunity in airway disease**

Nat Rev Immunol. 2018 Jul;18(7):454-466.

# Biologics in Asthma : Revolutionary




| Biologics | Form | Target | Biological effects | Effects on airway remodeling |
|---|---|---|---|---|
| Omalizumab | Humanized IgG1-κ mAb | IgE | • ↓ circulating total IgE<br>• Downregulation of FcεRI receptors on basophils, mast cells, and DCs | • ↑ $FEV_1$<br>• ↓ RBM thickness<br>• ↓ airway wall thickness in CT<br>• ↓ fibronectin deposition<br>• Prevents IgE-mediated ECM deposition in vitro |
| Reslizumab | Humanized IgG4-κ mAb | IL-5 | Blockage of IL-5/IL-5R binding | • ↑ $FEV_1$ |
| Mepolizumab | Humanized IgG1-κ mAb | IL-5 | Blockage of IL-5/IL-5R binding | • ↑ $FEV_1$<br>• ↓ airway eosinophils and TGF-$\beta1^+$ eosinophils<br>• ↓ tenascin expression |
| Benralizumab | Humanized IgG1-κ mAb | IL-5 receptor (IL-5Rα) | ↓ eosinophils and basophils via antibody-dependent cell-mediated cytotoxicity (ADCC) | • ↑ $FEV_1$<br>• ↓ airway eosinophils<br>• ↓ ASM mass |
| Dupilumab | Human IgG4 mAb | IL-4 receptor α chain (IL-4Rα) | • Blockage of IL-4/IL-4Rα binding<br>• Blockage of IL-13/IL-4Rα binding | • ↑ $FEV_1$<br>• prevents eosinophil infiltration into lung tissue in a mouse model of asthma |
| Tezepelumab | Human IgG2-λ mAb | TSLP | Blockage of TSLP/TSLPR binding | • ↑ $FEV_1$<br>• ↓ airway eosinophils<br>• ↓ AHR to mannitol<br>• ↓ airway inflammation<br>• ↓ TGF-β1<br>• ↑ CT scan-determined lumen area |

Allergy. 2022 Dec;77(12):3538-3552.

# Mechanisms of eosinophilic inflammation may be different between asthma and COPD

Received: 2 April 2019 | Revised: 30 May 2019 | Accepted: 21 June 2019
DOI: 10.1111/all.14016

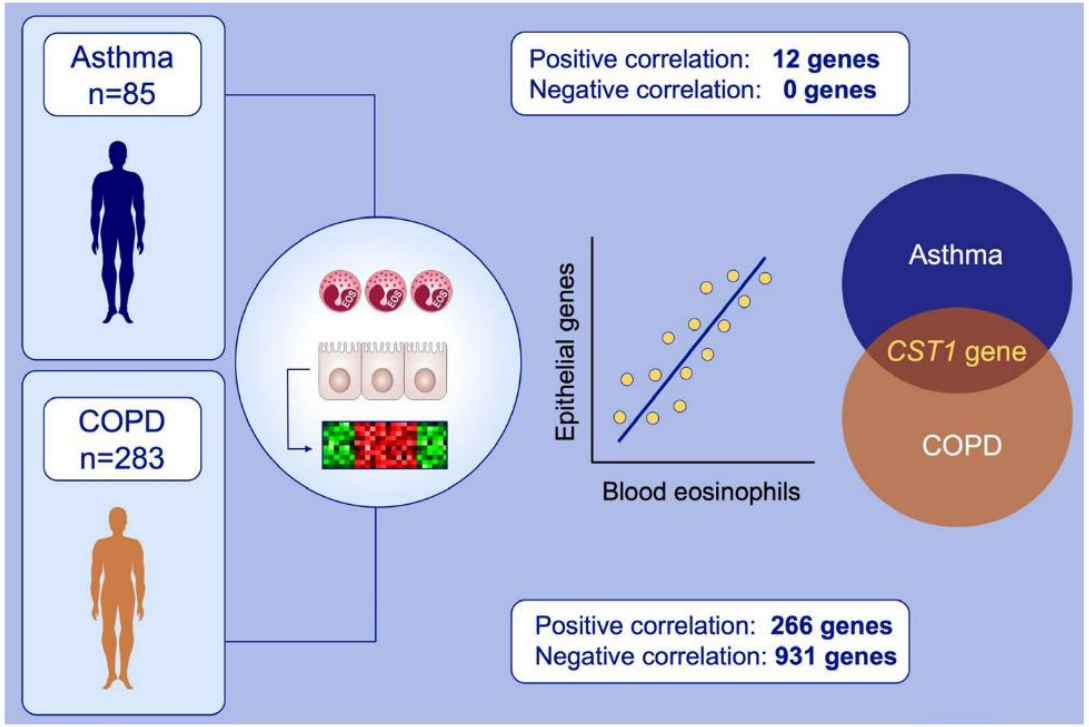
ORIGINAL ARTICLE
Asthma and Lower Airway Disease

Allergy WILEY

**Blood eosinophil count and airway epithelial transcriptome relationships in COPD versus asthma**

**Asthma Cohort (U-BIOPRED)**

**COPD Cohort (EvA)**




**Regression analysis: Blood eosinophil and gene expression**

Allergy. 2020 Feb;75(2):370-380.

# Mechanisms of eosinophilic inflammation may be different between asthma and COPD

| Gene symbol | Regression coefficient | Average gene expression (log2) | *P* value | *P* value FDR corrected |
|---|---|---|---|---|
| (a) | | | | |
| *CST1* | 3.78 | −1.03 | 2.8E-19 | 2.8E-15 |
| *CLCA1* | 3.73 | −2.35 | 1.8E-26 | 3.6E-22 |
| *FETUB* | 2.67 | −2.11 | 3.8E-14 | 2.6E-10 |
| *CPA4* | 2.39 | −0.78 | 7.1E-10 | 2.9E-06 |
| *KLK7* | 2.20 | −2.11 | 5.2E-07 | 1.3E-03 |
| *SPRR3* | 2.18 | 1.69 | 2.0E-06 | 4.0E-3 |
| *CAPN14* | 2.12 | −1.88 | 5.3E-10 | 2.7E-06 |
| *C5orf17* | 2.11 | −3.89 | 3.6E-06 | 6.7E-3 |
| *AC019349.5* | 2.03 | −0.60 | 7.3E-07 | 1.6E-03 |
| *CCL26* | 1.99 | −2.84 | 2.2E-09 | 7.2E-06 |
| (b) | | | | |
| *RP11-627G23.1* | −2.42 | 0.33 | 3.0E-04 | 0.08 |
| *RP11-532E4.2* | −1.88 | −0.38 | 2.0E-04 | 0.06 |
| *MUC5B* | −1.30 | 8.63 | 2.0E-04 | 0.06 |
| *C3* | −1.08 | 9.05 | 4.0E-04 | 0.08 |
| *TMEM45A* | −1.05 | 5.75 | 4.0E-04 | 0.09 |
| *PLK3* | −0.78 | 2.59 | 4.0E-04 | 0.08 |
| *INPP5J* | −0.75 | 1.48 | 4.0E-04 | 0.08 |
| *SPAG17* | −0.69 | 6.49 | 2.0E-04 | 0.06 |
| *SLC34A2* | −0.57 | 8.92 | 5.0E-04 | 0.09 |
| *PDE4DIP* | −0.37 | 6.53 | 4.0E-04 | 0.09 |

**Upregulated genes**

**Downregulated genes**

| Gene symbol | Regression coefficient | Average intensity | *P* value | *P* value FDR corrected |
|---|---|---|---|---|
| (a) | | | | |
| *CST1* | 5.20 | 5.37 | 4.0E-05 | 2.0E-03 |
| *SRGN* | 3.22 | 5.52 | 9.1E-05 | 3.0E-03 |
| *TPSAB1///TPSB2* | 3.12 | 6.14 | 4.8E-05 | 2.0E-03 |
| *CST4* | 3.12 | 5.32 | 3.7E-06 | 1.0E-03 |
| *S100A8* | 3.05 | 7.00 | 3.9E-04 | 7.0E-03 |
| *IGK///IGKC* | 2.99 | 5.81 | 2.7E-05 | 1.0E-03 |
| *PTPRC* | 2.97 | 5.47 | 1.2E-04 | 3.0E-03 |
| *ALOX5AP* | 2.65 | 6.22 | 1.5E-04 | 4.0E-03 |
| *LCP1* | 2.65 | 5.98 | 1.2E-04 | 3.0E-03 |
| *CXCR4* | 2.59 | 6.89 | 5.3E-04 | 8.0E-03 |
| (b) | | | | |
| *MSMB* | −2.90 | 10.72 | 1.4E-06 | 3.0 E-04 |
| *MUC5B* | −2.74 | 10.92 | 8.8E-08 | 1.0E-04 |
| *MKL2* | −2.50 | 5.48 | 6.3E-06 | 7.0E-04 |
| *SCGB3A1* | −2.44 | 11.5 | 1.1E-05 | 9.0E-04 |
| *THSD4* | −2.29 | 5.98 | 4.4E-06 | 6.0E-04 |
| *SULT1E1* | −2.21 | 5.44 | 1.9E-04 | 4.4E-03 |
| *ANKUB1* | −2.20 | 5.44 | 3.6E-04 | 6.6E-03 |
| *ADAM12* | −2.19 | 5.88 | 7.2E-06 | 7.0E-03 |
| *RIBC1* | −2.08 | 6.35 | 2.3E-05 | 1.3E-03 |
| *BMS1P6* | −2.06 | 5.93 | 1.2E-06 | 3.0E-04 |

**COPD Cohort (EvA)**

**Asthma Cohort (U-BIOPRED)**

Allergy. 2020 Feb;75(2):370-380.

# Biologics targeting Th2 inflammation

## 1) Anti-IL4R (Dupilumab)

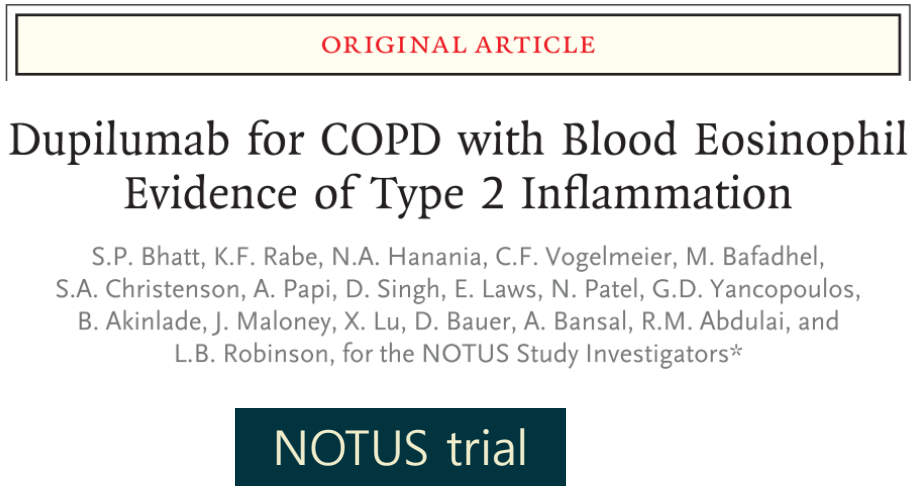
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 20, 2023 VOL. 389 NO. 3

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*

BOREAS trial



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dupilumab for COPD with Blood Eosinophil Evidence of Type 2 Inflammation

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

NOTUS trial

- Age: 40 to 85 years
- Treatment history:
  - On stable triple inhaler therapy ≥3 months
- Exacerbation history (past 12 months):
  - ≥2 moderate or ≥1 severe exacerbation
  - ≥1 moderate event treated with systemic corticosteroids
- Symptoms:
  - MRC dyspnea score ≥2
  - Chronic bronchitis symptoms
- Eosinophils: ≥300 cells/μL during screening

*N Engl J Med. 2024;390(24):2274-2283.; N Engl J Med. 2023;389(3):205-214.*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 20, 2023 VOL. 389 NO. 3

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BOREAS trial

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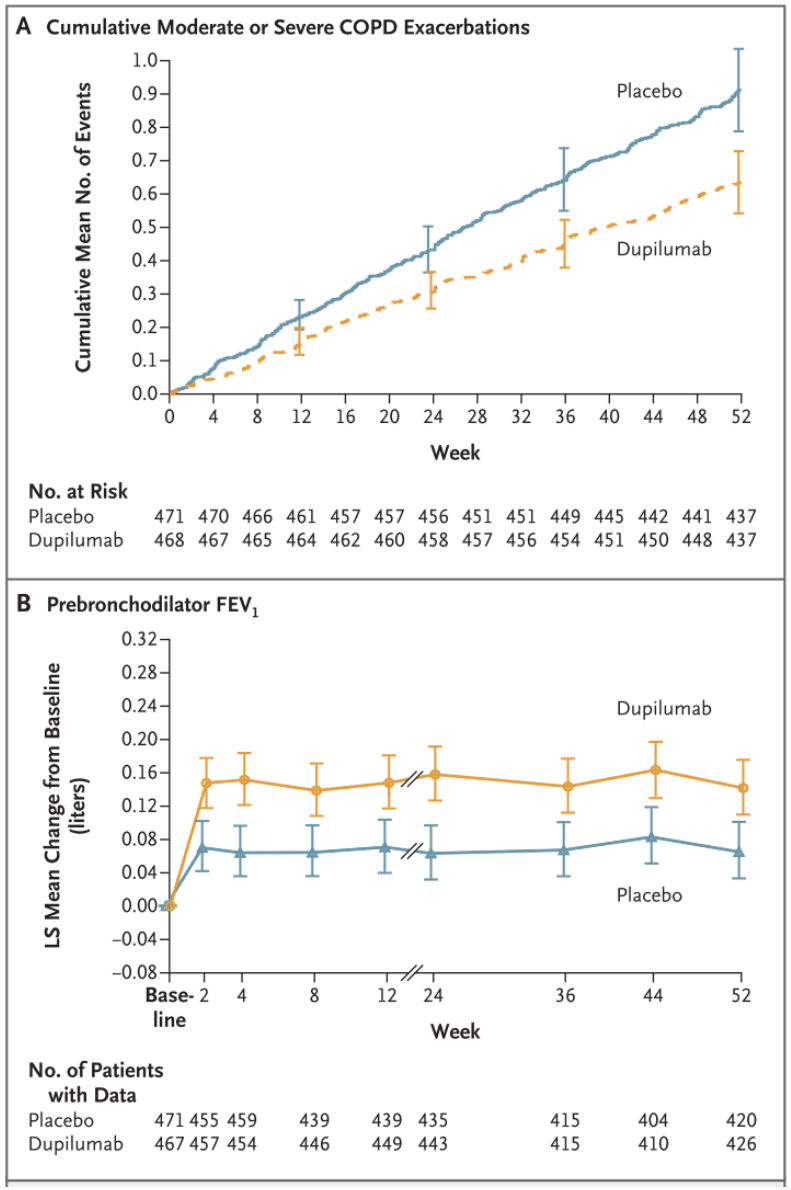
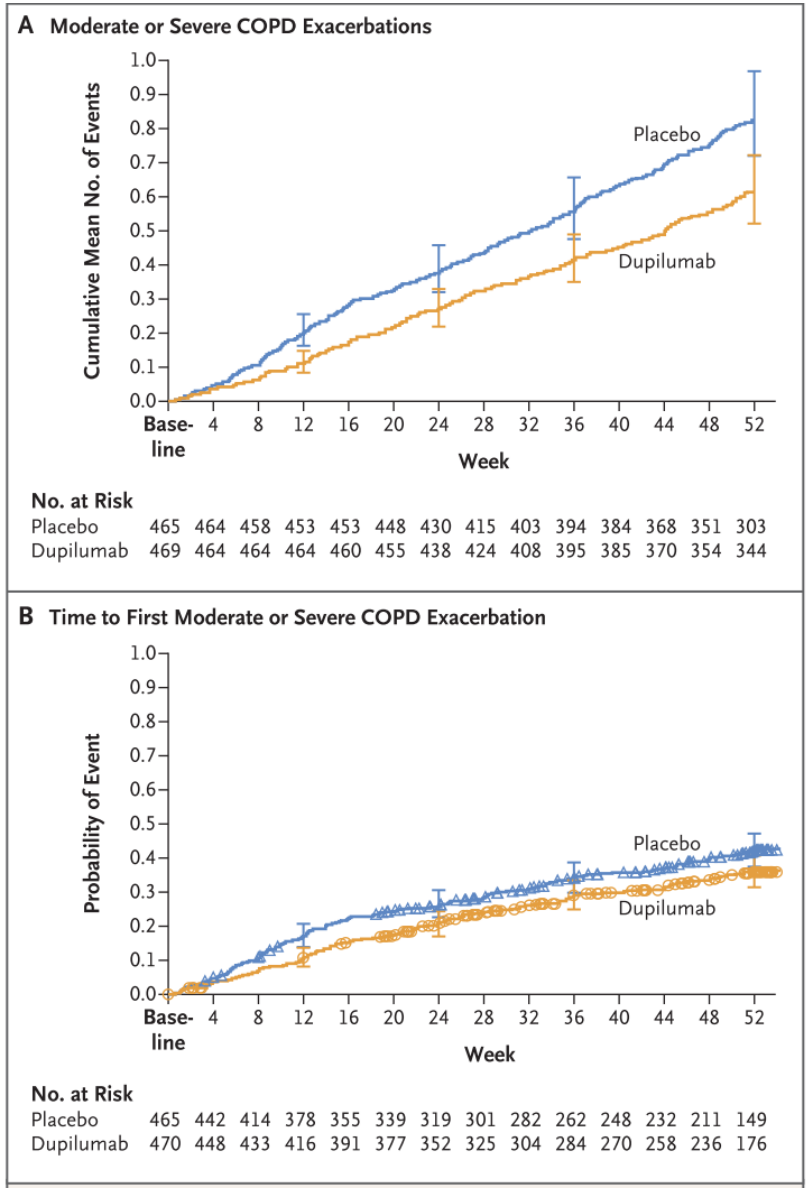



*N Engl J Med. 2024;390(24):2274-2283.; N Engl J Med. 2023;389(3):205-214.*

# Pooled analysis of NOCTUS and BOREAS

**Dupilumab for chronic obstructive pulmonary disease with type 2 inflammation: a pooled analysis of two phase 3, randomised, double-blind, placebo-controlled trials**

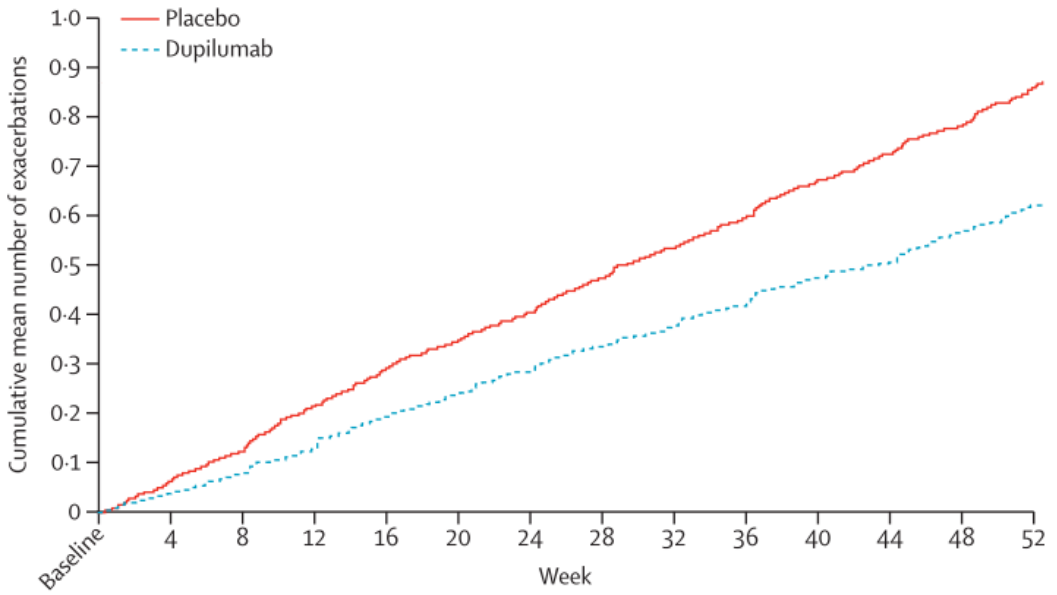
*Surya P Bhatt*, Klaus F Rabe*, Nicola A Hanania, Claus F Vogelmeier, Mona Bafadhel, Stephanie A Christenson, Alberto Papi, Dave Singh, Elizabeth Laws, Paula Dakin, Jennifer Maloney, Xin Lu, Deborah Bauer, Ashish Bansal, Raolat M Abdulai, Lacey B Robinson*

| | Placebo (n=936)* | Dupilumab (n=938)* | Difference *vs* placebo (95% CI)† | Nominal p value‡ |
|---|---|---|---|---|
| **Primary outcome** | | | | |
| Annualised rate of moderate or severe COPD exacerbation during the 52-week treatment period§ | 1·156 | 0·794 | 0·687 (0·595 to 0·793) | <0·0001 |

Lancet Respir Med. 2025;13(3):234-43.

# Pooled analysis of NOCTUS and BOREAS

A

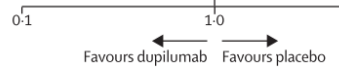



**Number at risk**

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 936 | 934 | 924 | 914 | 910 | 905 | 886 | 866 | 854 | 843 | 829 | 810 | 791 | 709 |
| Dupilumab | 937 | 931 | 929 | 928 | 922 | 915 | 896 | 881 | 864 | 849 | 835 | 820 | 802 | 777 |

B

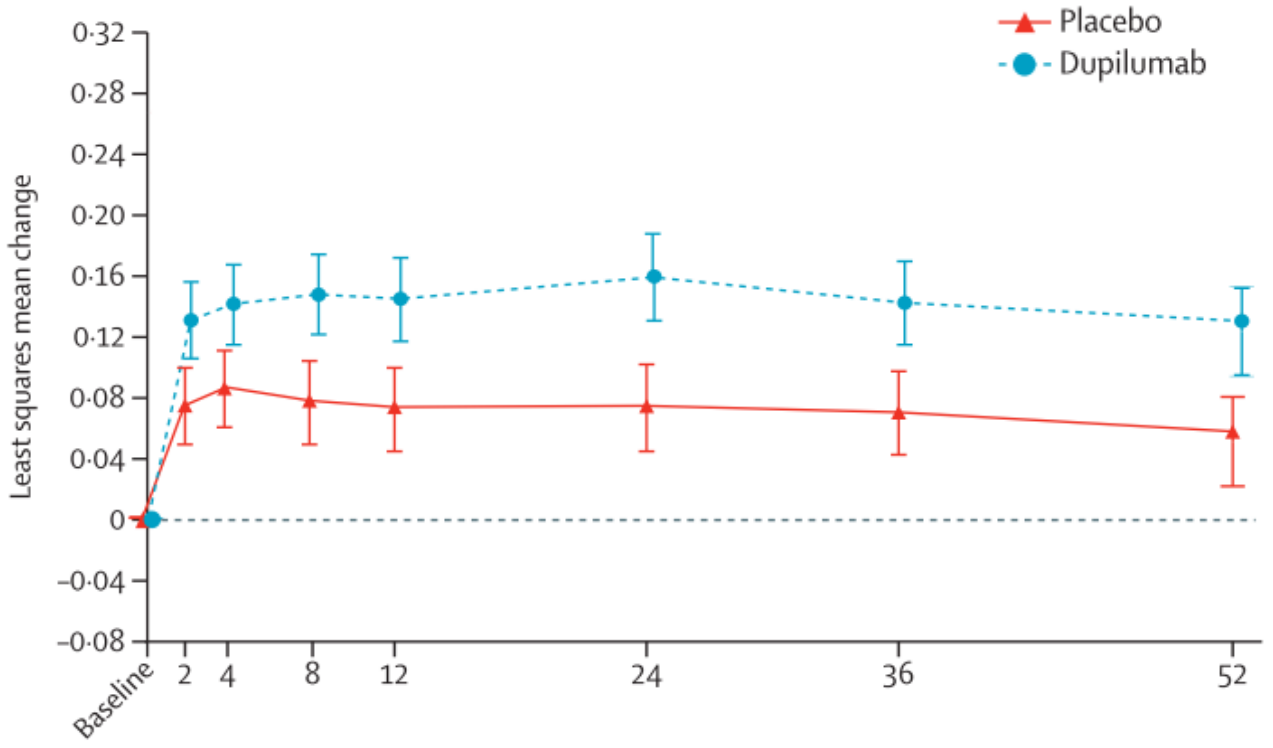
| | Placebo (n) | Dupilumab (n) | Incidence rate ratio (95% CI) | $p_{interaction}$ |
|---|---|---|---|---|
| **Age group** | | | | 0·50 |
| <65 years | 414 | 388 | 0·651 (0·525–0·808) | |
| ≥65 years | 522 | 550 | 0·716 (0·590–0·870) | |
| **Age group** | | | | 0·70 |
| 40–64 years | 414 | 388 | 0·651 (0·525–0·808) | |
| 65–74 years | 394 | 434 | 0·741 (0·594–0·925) | |
| 75–85 years | 128 | 116 | 0·681 (0·453–1·022) | |
| **Sex** | | | | 0·96 |
| Male | 634 | 618 | 0·687 (0·575–0·821) | |
| Female | 302 | 320 | 0·690 (0·538–0·883) | |
| **Smoking status at screening** | | | | 0·85 |
| Current | 282 | 276 | 0·683 (0·528–0·884) | |
| Former | 654 | 662 | 0·685 (0·576–0·815) | |
| **Number of moderate or severe COPD exacerbations in previous year before visit 1** | | | | 0·63 |
| ≤2 | 751 | 752 | 0·713 (0·599–0·849) | |
| 3 | 140 | 114 | 0·565 (0·401–0·795) | |
| ≥4 | 45 | 72 | 0·616 (0·417–0·911) | |
| **Number of severe COPD exacerbations in previous year before visit 1** | | | | 0·94 |
| 0 | 722 | 695 | 0·686 (0·579–0·812) | |
| 1 | 181 | 198 | 0·720 (0·532–0·976) | |
| ≥2 | 33 | 44 | 0·585 (0·313–1·094) | |
| **Number of severe COPD exacerbations in previous year before visit 1** | | | | 0·96 |
| 0 | 722 | 695 | 0·686 (0·579–0·812) | |
| ≥1 | 214 | 242 | 0·684 (0·520–0·901) | |
| **Baseline predicted post-bronchodilator $FEV_1$** | | | | 0·64 |
| <50% | 468 | 477 | 0·705 (0·584–0·852) | |
| ≥50% | 467 | 458 | 0·658 (0·526–0·823) | |
| **Comorbid ongoing history of emphysema** | | | | 0·66 |
| Yes | 301 | 289 | 0·658 (0·526–0·823) | |
| No | 635 | 649 | 0·703 (0·584–0·848) | |
| **Baseline BODE score** | | | | 0·87 |
| ≤4 | 602 | 561 | 0·678 (0·558–0·824) | |
| >4 | 329 | 367 | 0·673 (0·543–0·833) | |
| **Baseline fractional exhaled nitric oxide** | | | | 0·010 |
| <20 ppb | 494 | 495 | 0·824 (0·680–1·000) | |
| ≥20 ppb | 371 | 367 | 0·552 (0·434–0·701) | |
| **Baseline serum total IgE** | | | | 0·29 |
| <100 IU/mL | 416 | 390 | 0·761 (0·613–0·943) | |
| ≥100 IU/mL | 469 | 507 | 0·632 (0·517–0·773) | |
| **Baseline eosinophil count** | | | | 0·76 |
| <300 cells per µL | 374 | 364 | 0·655 (0·517–0·829) | |
| ≥300 cells per uL | 562 | 573 | 0·700 (0·583–0·840) | |
| **Race** | | | | NA |
| Black* | 14 | 12 | 0·491 (0·113–2·125) | |
| Not Black | 922 | 926 | 0·689 (0·596–0·796) | |




Lancet Respir Med. 2025;13(3):234-43.

# Pooled analysis of NOCTUS and BOREAS

PostBD FEV1

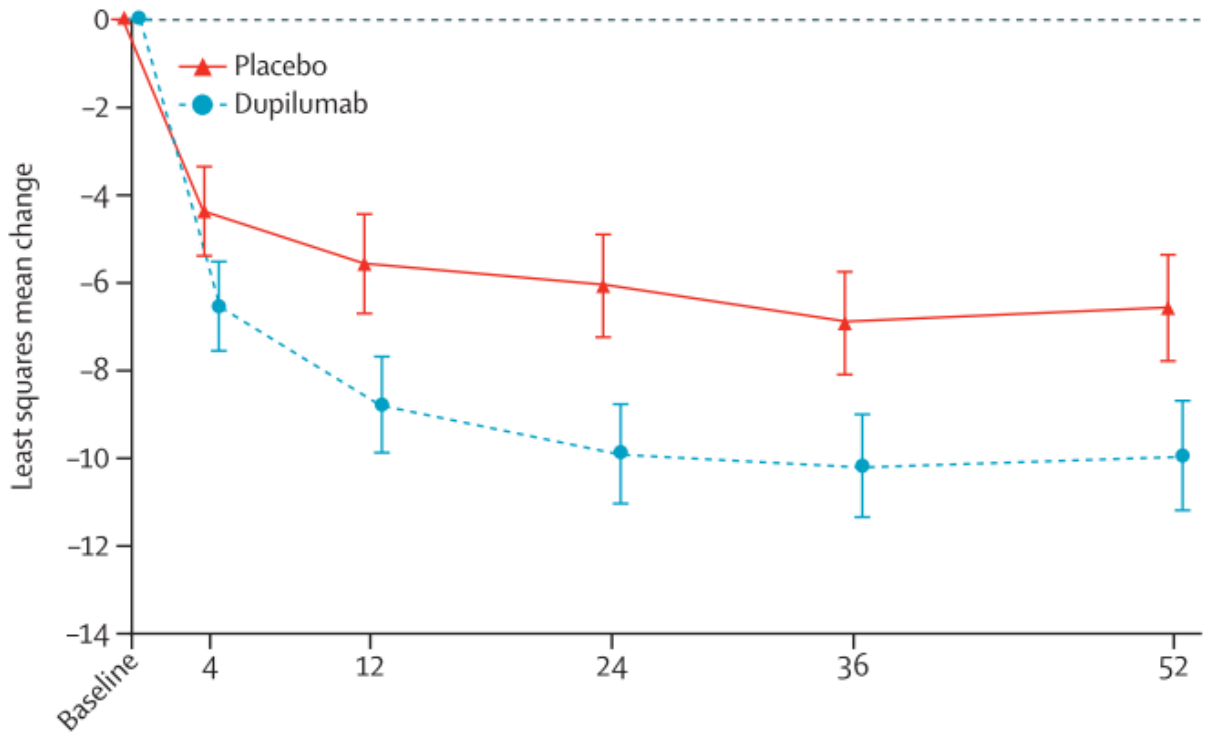



| Number of participants with observed change from baseline | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo | 830 | 798 | 808 | 780 | 767 | 750 | 748 | 738 |
| Dupilumab | 828 | 810 | 805 | 795 | 776 | 773 | 749 | 752 |

Lancet Respir Med. 2025;13(3):234-43.

# Pooled analysis of NOCTUS and BOREAS

SGRQ




| Number of participants with observed change from baseline | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 808 | 764 | 748 | 720 | 732 | 710 |
| Dupilumab | 813 | 770 | 763 | 765 | 729 | 732 |

Lancet Respir Med. 2025;13(3):234-43.

# Real-world evidence of dupilumab in COPD

Brief report

**Clinical effectiveness and safety of dupilumab in patients with chronic obstructive pulmonary disease: A 7-year population-based cohort study**

Check for updates

Chuan-Yen Sun, MD,[a,b,c] Yohannes Tesfaigzi, PhD,[d] Gin-Yi Lee, MD,[e] Yi-Hsuan Chen, ScM,[f] Scott T. Weiss, MD, MS,[g,h]* and Kevin Sheng-Kai Ma, DDS, FRSPH, FRSM[a]** *Philadelphia, Pa; Taipei, Taiwan; Boston, Mass; and Baltimore, Md*

- Population-based cohort study
- Multiple centers in the US
- April 2017-August 2024.

- **Dupilumab vs LABA therapy.**

| | After propensity score matching | | | | |
|---|---|---|---|---|---|
| Outcome | Dupilumab (n = 1,531) Events | LABA-containing therapy (n = 1,521) Events | HR | 95% CI | Adjusted log-rank *P* value* |
| General medical outcome | | | | | |
| All-cause mortality | 130 | 362 | 0.527 | (0.430-0.647) | <.001 |
| Emergency visit | 414 | 623 | 0.781 | (0.688-0.886) | <.001 |
| Hospitalization | 36 | 60 | 0.721 | (0.473-1.100) | .169 |
| COPD-related outcome | | | | | |
| AE | 652 | 999 | 0.585 | (0.530-0.646) | <.001 |

Sun et al. J Allergy Clin Immunol. 2025

# Biologics targeting Th2 inflammation

## 2) Anti-IL-5 (mepolizumab)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 26, 2017 VOL. 377 NO. 17

# Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease

I.D. Pavord, P. Chanez, G.J. Criner, H.A.M. Kerstjens, S. Korn, N. Lugogo, J.-B. Martinot, H. Sagara, F.C. Albers, E.S. Bradford, S.S. Harris, B. Mayer, D.B. Rubin, S.W. Yancey, and F.C. Sciurba

- Two phase 3, double-blind, RCT (METREX & METREO)
- Comparing mepolizumab with placebo
  - 100 mg in METREX
  - 100 or 300 mg in METREO
- COPD patients with
  - history of moderate-to-severe exacerbations
  - triple maintenance therapy.
  - METREX ; non-eosinophilic & eosinophilic COPD
  - METREO ; only eosinophilic COPD

Eosinophilic COPD :
blood eosinophil count
- ≥150 at screening or
- ≥300 during the previous year

- The primary endpoint : the annual rate of moderate-to-severe exacerbations.

N Engl J Med. 2017 Oct 26;377(17):1613-1629.

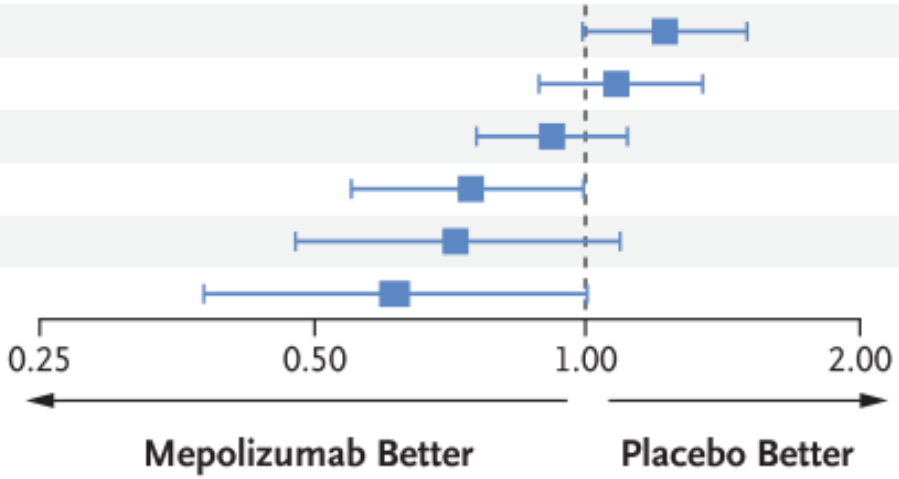
**Table 2. Primary and Secondary Efficacy End Points.***

| End Point | METREX Modified Intention-to-Treat Population with an Eosinophilic Phenotype | | METREX Overall Modified Intention-to-Treat Population | | METREO Modified Intention-to-Treat Population | | |
|---|---|---|---|---|---|---|---|
| | Mepolizumab, 100 mg (N=233) | Placebo (N=229) | Mepolizumab, 100 mg (N=417) | Placebo (N=419) | Mepolizumab, 100 mg (N=223) | Mepolizumab, 300 mg (N=225) | Placebo (N=226) |
| Primary end point: moderate or severe exacerbations | | | | | | | |
| Mean annual rate — events/yr† | 1.40 | 1.71 | 1.49 | 1.52 | 1.19 | 1.27 | 1.49 |
| Rate ratio vs. placebo (95% CI) | 0.82 (0.68 to 0.98) | — | 0.98 (0.85 to 1.12) | — | 0.80 (0.65 to 0.98) | 0.86 (0.70 to 1.05) | — |
| Adjusted P value | 0.04 | — | >0.99 | — | 0.07 | 0.14 | — |
| Secondary end points | | | | | | | |
| Time to first moderate or severe exacerbation | | | | | | | |
| Kaplan–Meier median time to first moderate or severe exacerbation — days | 192 | 141 | 194 | 176 | 267 | 258 | 166 |
| Estimated risk of a moderate or severe exacerbation by wk 52 — % (95% CI)‡ | 64.6 (58.3 to 70.8) | 75.2 (69.3 to 80.8) | 65.5 (60.7 to 70.1) | 71.2 (66.6 to 75.6) | 57.9 (51.5 to 64.5) | 58.8 (52.4 to 65.3) | 66.7 (60.2 to 73.1) |
| Hazard ratio vs. placebo (95% CI) | 0.75 (0.60 to 0.94) | — | 0.89 (0.75 to 1.05) | — | 0.82 (0.64 to 1.04) | 0.77 (0.60 to 0.97) | — |
| Adjusted P value | 0.04 | — | >0.99 | — | 0.14§ | 0.14§ | — |
| Exacerbations leading to emergency department visit or hospitalization | | | | | | | |
| Mean annual rate — events/yr† | 0.30 | 0.26 | 0.29 | 0.26 | 0.17 | 0.23 | 0.28 |
| Rate ratio vs. placebo (95% CI) | 1.16 (0.77 to 1.75) | — | 1.10 (0.81 to 1.49) | — | 0.59 (0.35 to 0.98) | 0.83 (0.51 to 1.34) | — |
| Adjusted P value | 0.60 | — | >0.99 | — | 0.14§ | 0.45§ | — |
| SGRQ total score at wk 52 | | | | | | | |
| Change from baseline | −2.8±1.1 | −3.0±1.1 | −3.2±0.8 | −4.0±0.8 | −5.0±1.0 | −3.3±1.0 | −3.1±1.0 |
| Difference vs. placebo (95% CI) | 0.2 (−2.8 to 3.2) | — | 0.7 (−1.5 to 2.9) | — | −1.8 (−4.5 to 0.8) | −0.1 (−2.8 to 2.6) | — |
| Adjusted P value | >0.99 | — | >0.99 | — | 0.45§ | 0.93§ | — |
| CAT score at wk 52 | | | | | | | |
| Change from baseline | −0.8±0.5 | 0.0±0.5 | −1.0±0.3 | −0.4±0.4 | −1.6±0.42 | −0.8±0.42 | −0.4±0.42 |
| Difference vs. placebo (95% CI) | −0.8 (−2.0 to 0.5) | — | −0.6 (−1.5 to 0.4) | — | −1.1 (−2.3 to 0.0) | −0.4 (−1.5 to 0.8) | — |
| Adjusted P value | >0.99 | — | >0.99 | — | 0.93§ | 0.93§ | — |

N Engl J Med. 2017 Oct 26;377(17):1613-1629.

# Pre-specified meta-analysis of METREX & METREO

| Blood Eosinophil Count | Mepolizumab Group | Placebo Group | Rate Ratio (95% CI) |
|---|---|---|---|
| *cells/mm³* | *no. of patients meeting criterion/total no. of patients* | | |
| <150 with no historical count ≥300 | 184/184 | 190/190 | 1.23 (0.99–1.51) |
| <150 regardless of historical count | 236/640 | 230/645 | 1.10 (0.91–1.34) |
| ≥150 to <300 | 237/456 | 235/455 | 0.92 (0.76–1.11) |
| ≥300 to <500 | 112/456 | 110/455 | 0.75 (0.55–1.00) |
| ≥500 | 53/456 | 67/455 | 0.72 (0.48–1.09) |
| <150 with historical count ≥300 | 53/456 | 42/455 | 0.64 (0.40–1.03) |




N Engl J Med. 2017 Oct 26;377(17):1613-1629.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Mepolizumab to Prevent Exacerbations of COPD with an Eosinophilic Phenotype

F.C. Sciurba,[1] G.J. Criner,[2] S.A. Christenson,[3] F.J. Martinez,[4] A. Papi,[5] N. Roche,[6] J. Bourbeau,[7] S. Korn,[8] M. Bafadhel,[9] M.L.K. Han,[10] S. Kolterer,[11] K. Miller,[12] D. Mouneimne,[13] J. Fletcher,[13] B. Mayer,[14] J. Min,[15] and I.D. Pavord,[16] for the MATINEE Study Investigators*

- Phase 3, double-blind, RCT
- COPD patients
  - with a history of exacerbations
  - BEC ≥300
  - On triple therapy
- 1:1 ratio, to receive mepolizumab or placebo every 4 weeks for 52 to 104 weeks.
- Primary end point : the annualized rate of moderate or severe exacerbations.

| End Point | Mepolizumab (N=403) | Placebo (N=401) |
|---|---|---|
| **Primary end point** | | |
| Annualized rate of moderate or severe exacerbations (95% CI) — events/yr | 0.80 (0.70–0.91) | 1.01 (0.89–1.15) |
| Rate ratio vs. placebo (95% CI) | 0.79 (0.66–0.94) | — |
| P value | 0.01 | — |

N Engl J Med. 2025;392(17):1710-20.

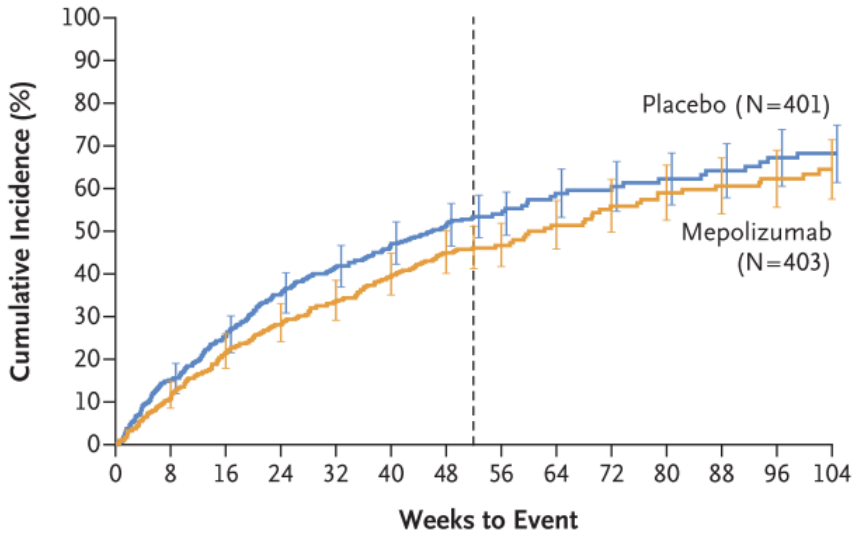
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Mepolizumab to Prevent Exacerbations of COPD with an Eosinophilic Phenotype

F.C. Sciurba,[1] G.J. Criner,[2] S.A. Christenson,[3] F.J. Martinez,[4] A. Papi,[5] N. Roche,[6] J. Bourbeau,[7] S. Korn,[8] M. Bafadhel,[9] M.L.K. Han,[10] S. Kolterer,[11] K. Miller,[12] D. Mouneimne,[13] J. Fletcher,[13] B. Mayer,[14] J. Min,[15] and I.D. Pavord,[16] for the MATINEE Study Investigators*

**B First Moderate or Severe Exacerbation**




**No. at Risk**

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 401 | 333 | 292 | 250 | 223 | 203 | 180 | 71 | 56 | 46 | 41 | 37 | 32 | 22 |
| Mepolizumab | 403 | 355 | 309 | 277 | 251 | 222 | 202 | 82 | 69 | 58 | 52 | 48 | 41 | 24 |

| | | |
|---|---|---|
| **Secondary end points** | | |
| Time to first moderate or severe exacerbation | | |
| Kaplan–Meier median time to first moderate or severe exacerbation (95% CI) — days | 419 (332–530) | 321 (262–396) |
| Estimated risk of a moderate or severe exacerbation up to wk 104 (95% CI) — % | 64.5 (57.5–71.4) | 68.3 (61.4–74.9) |
| Hazard ratio for the first moderate or severe exacerbation up to wk 104 vs. placebo (95% CI) | 0.77 (0.64–0.93) | — |
| P value | 0.009 | — |
| Response, defined as a decrease in the CAT score†‡ | | |
| No. of patients with a response (%) | 162 (41) | 180 (46) |
| No. of patients without a response (%) | 220 (56) | 206 (52) |
| Odds ratio of response vs. placebo (95% CI) | 0.81 (0.60–1.09) | — |
| Relative risk of response vs. placebo (95% CI)§ | 0.92 (0.81–1.05) | — |
| Response, defined as a decrease in the SGRQ total score¶ | | |
| No. of patients with a response (%) | 195 (50) | 179 (46) |
| No. of patients without a response (%) | 186 (48) | 206 (52) |
| Odds ratio of response vs. placebo (95% CI) | 1.17 (0.87–1.57) | — |
| Relative risk of response vs. placebo (95% CI)§ | 1.04 (0.91–1.20) | — |
| Response, defined as a decrease in the E-RS–COPD total score‖ | | |
| No. of patients with a response (%) | 123 (31) | 137 (34) |
| No. of patients without a response (%) | 271 (67) | 254 (64) |
| Odds ratio of response vs. placebo (95% CI) | 0.82 (0.60–1.12) | — |
| Relative risk of response vs. placebo (95% CI)§ | 0.87 (0.72–1.04) | — |
| Annualized rate of exacerbations resulting in emergency department visit, hospitalization, or both | | |
| Events/yr (95% CI) | 0.13 (0.10–0.18) | 0.20 (0.15–0.27) |
| Rate ratio vs. placebo (95% CI) | 0.65 (0.43–0.96) | — |

N Engl J Med. 2025;392(17):1710-20.

# Adverse events of mepolizumab

**Table 3. Adverse Events during or after the Treatment Period (Safety Population).***

| Adverse Events | Mepolizumab (N=403) | Placebo (N=401) |
|---|---|---|
| | *number of patients (percent)* | |
| Any event during the treatment period | 299 (74) | 307 (77) |
| Any event during or after the treatment period | | |
| Overall | 301 (75) | 308 (77) |
| Event leading to treatment discontinuation | 14 (3) | 18 (4) |
| Event leading to withdrawal from the trial | 15 (4) | 16 (4) |
| Any serious adverse event or death during the treatment period | 99 (25) | 112 (28) |
| Death during or after the treatment period | 11 (3) | 11 (3) |
| Adverse events of special interest | | |
| Systemic reaction during the treatment period† | 5 (1) | 5 (1) |
| Local site reaction during the treatment period† | 2 (<1) | 3 (1) |
| Cancer during the treatment period‡ | 8 (2) | 13 (3) |
| Independently adjudicated MACE during or after the treatment period§ | 11 (3) | 11 (3) |
| Death from a cardiovascular cause¶ | 6 (1) | 3 (1) |
| Nonfatal myocardial infarction | 2 (<1) | 6 (1) |
| Nonfatal stroke | 3 (1) | 3 (1) |
| Fatal or nonfatal myocardial infarction¶ | 2 (<1) | 6 (1) |
| Fatal or nonfatal stroke¶ | 3 (1) | 3 (1) |

N Engl J Med. 2025;392(17):1710-20.

NEJM Evidence

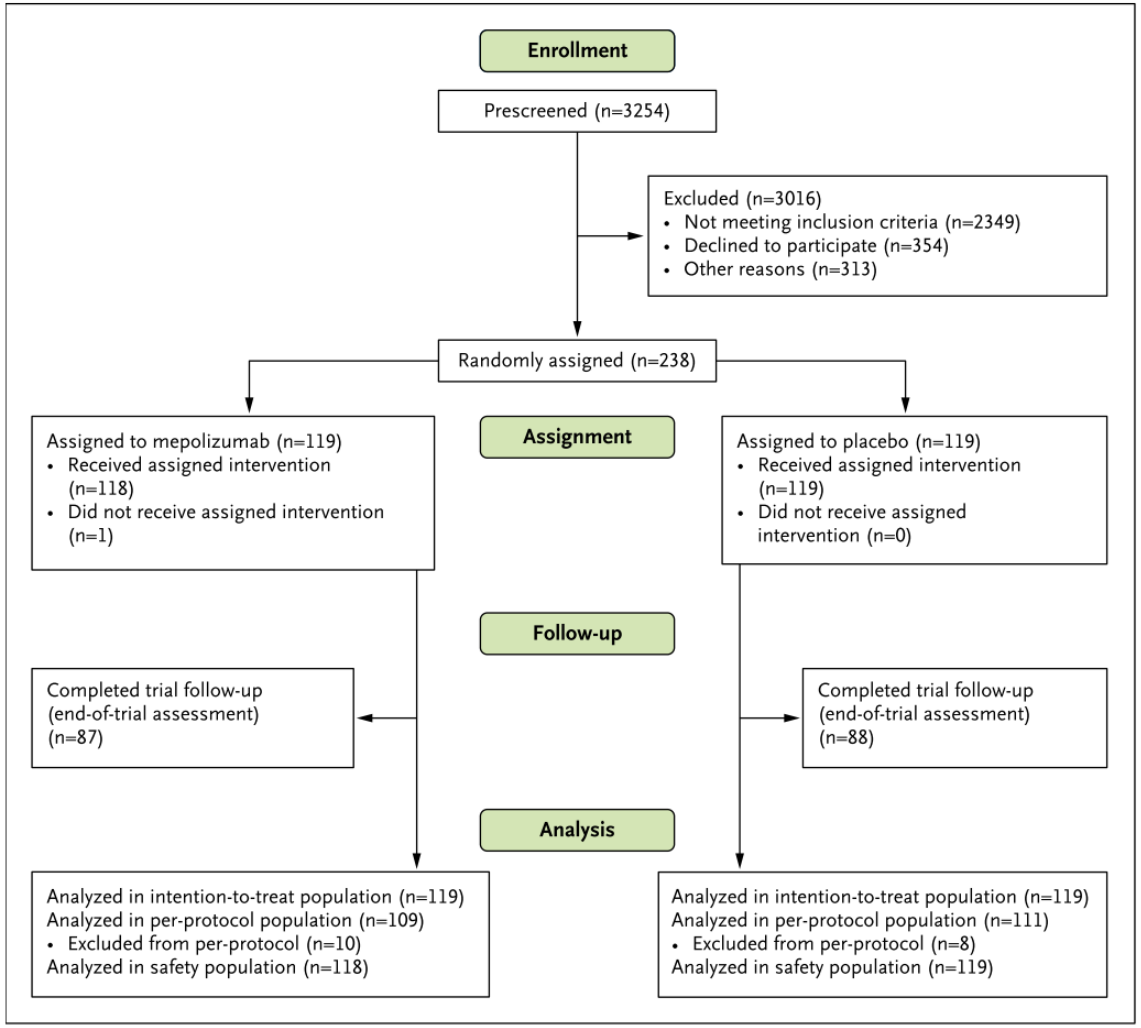
Published April 30, 2025
NEJM Evid 2025;4(6)
DOI: 10.1056/EVIDoa2500012

ORIGINAL ARTICLE

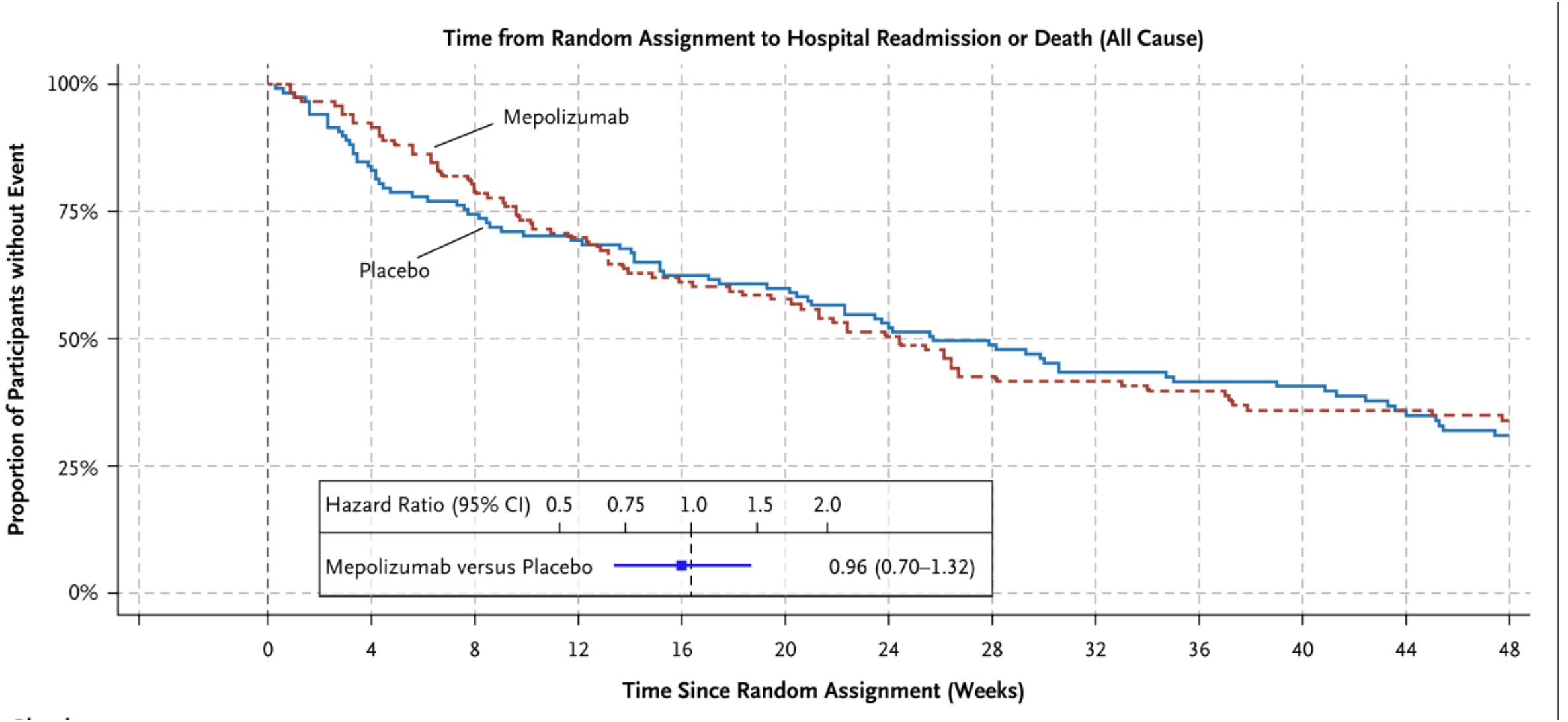
# Mepolizumab for COPD with Eosinophilic Phenotype following Hospitalization

Cara A. Flynn, M.B.Ch.B.,[1] Hamish J.C. McAuley, Ph.D.,[1] Omer Elneima, Ph.D.,[1] Hnin W.W. Aung, M.B.B.S.,[1] Wadah Ibrahim, Ph.D.,[1] Thomas J.C. Ward, Ph.D.,[1] Michelle Bourne, R.N.,[1] Tracey D. Thornton,[1] Vijay Mistry, B.Sc.,[1] Hannah R. Gilbert, M.Sc.,[2] Ghazala Waheed, M.Sc.,[2] Adam K.A. Wright, Ph.D.,[1] Rachel A. Evans, Ph.D.,[1] Michael C. Steiner, M.D.,[1] Cassandra L. Brookes, Ph.D.,[2] Christopher E. Brightling, F.Med.Sci.,[1] and Neil J. Greening, Ph.D.[1]

- Phase 2b, single-center, double-blind, RCT
- Conducted at Glenfield Hospital, Leicester, UK.
- BEC≥300
- Hospitalized for exacerbation




NEJM Evid. 2025;4(6):EVIDoa2500012.




NEJM Evid. 2025;4(6):EVIDoa2500012.

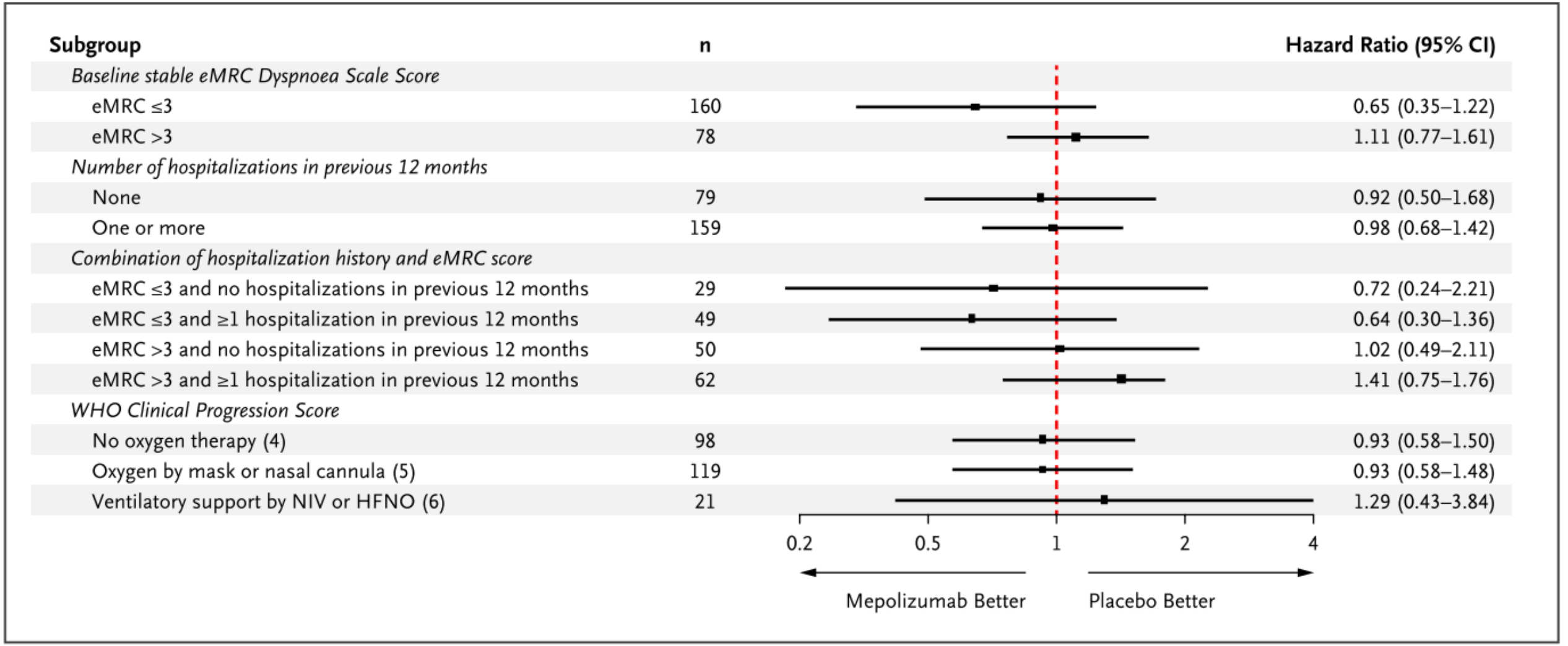
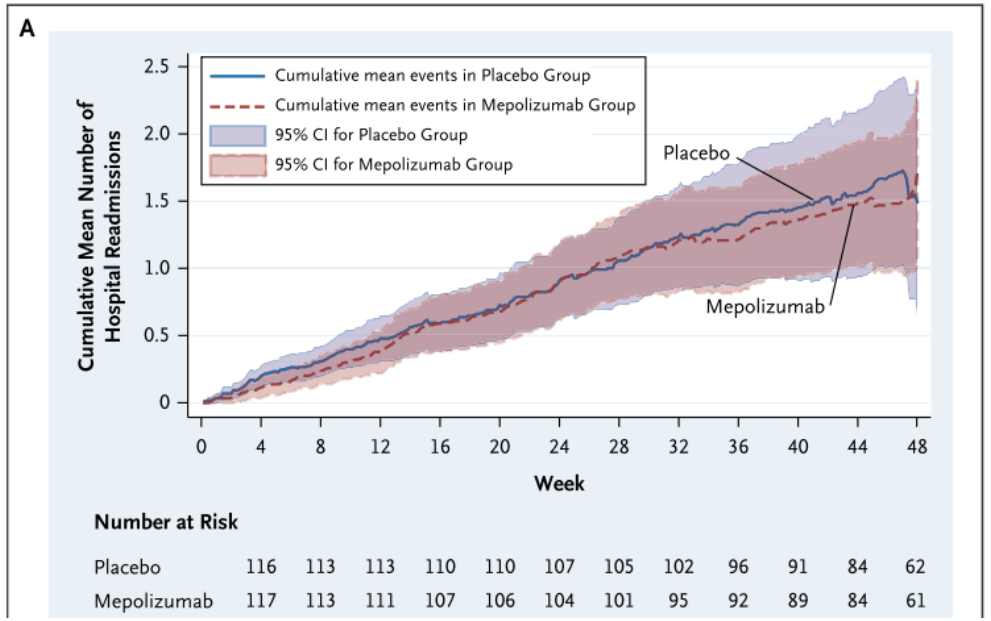
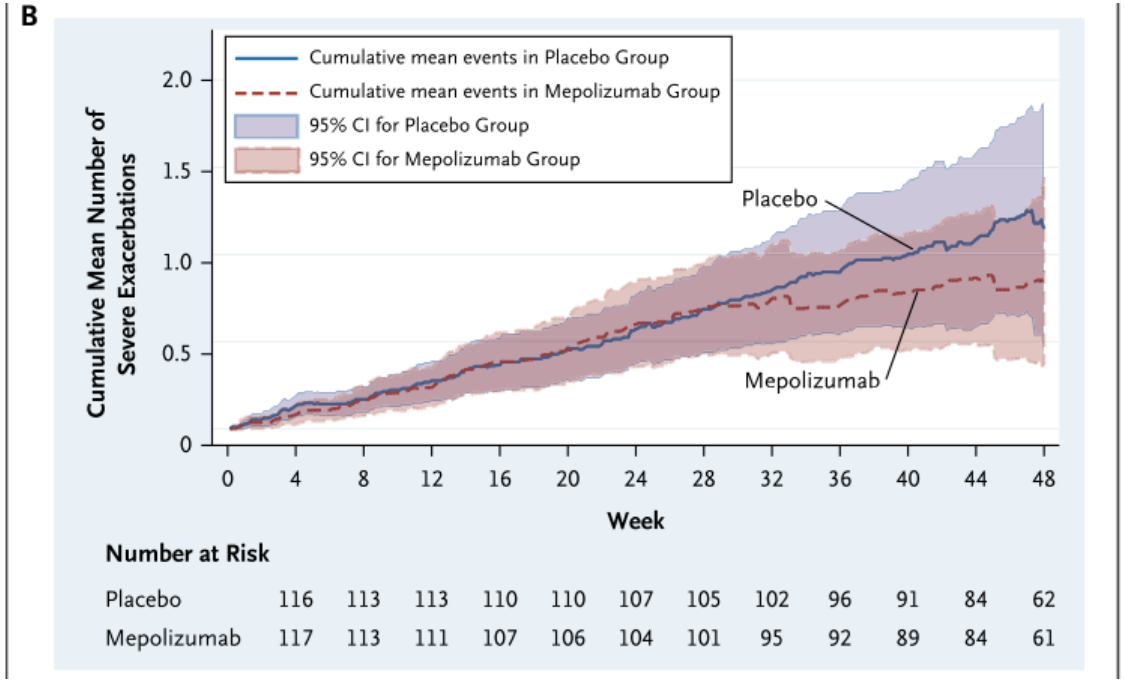
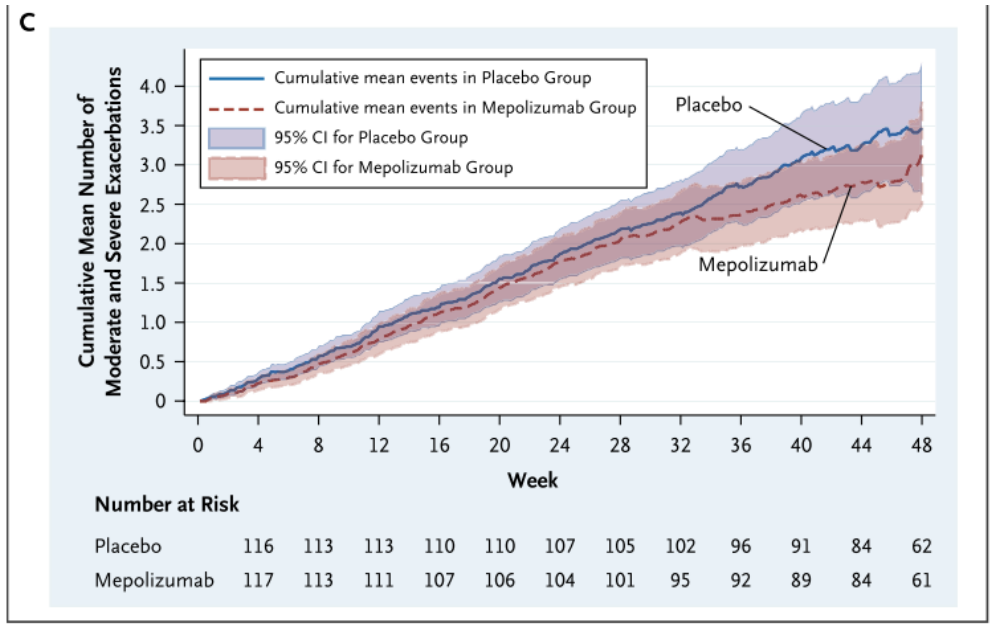



Figure 3. Forest Plot of the Prespecified Subgroup Analyses of the Primary Outcome (Time to Rehospitalization or Death).

NEJM Evid. 2025;4(6):EVIDoa2500012.




NEJM Evid. 2025;4(6):EVIDoa2500012.

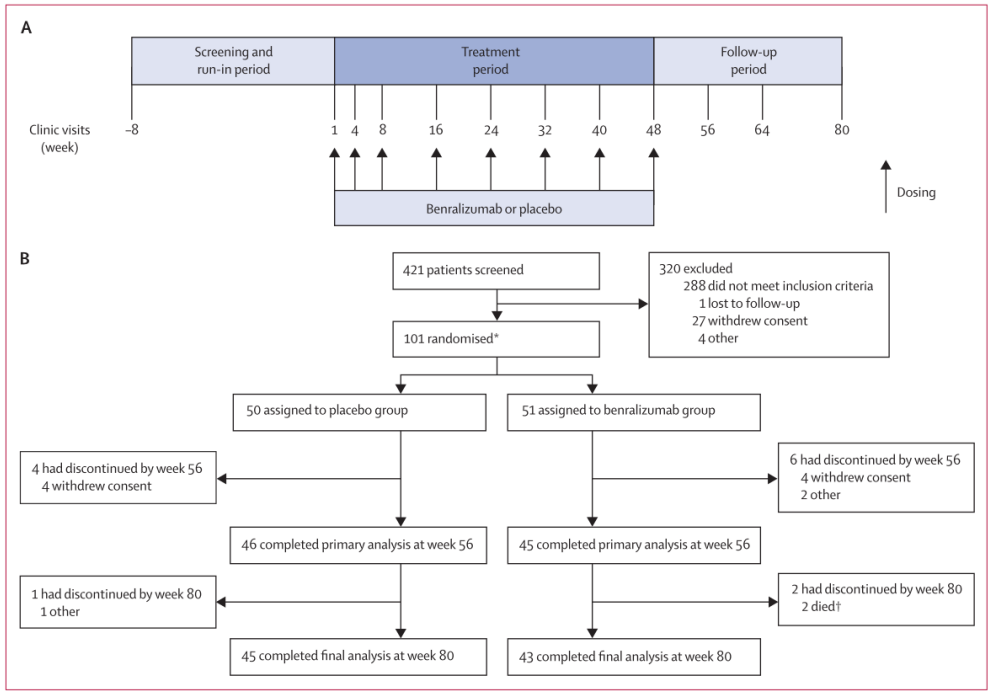
# Biologics targeting Th2 inflammation

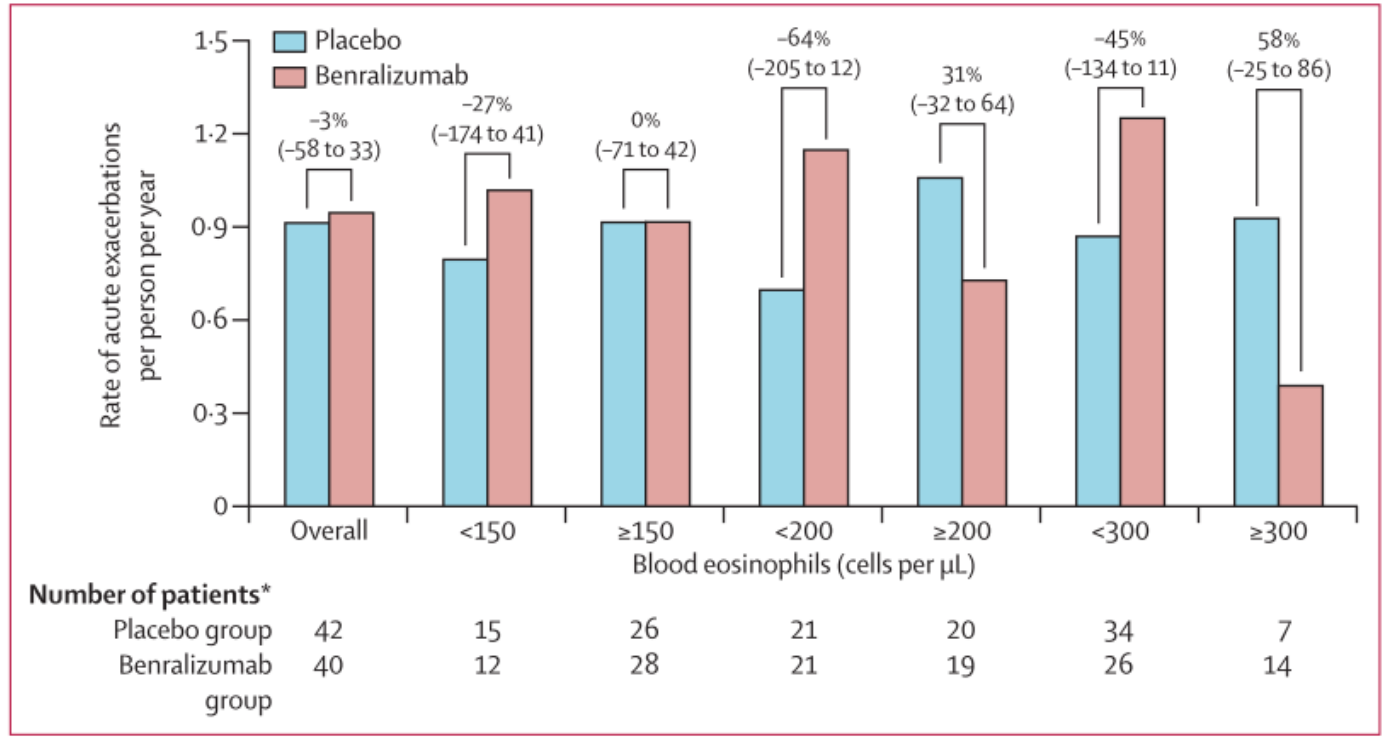
## 3) Anti-IL-5R (benralizumab)

# Benralizumab

## Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study

*Christopher E Brightling, Eugene R Bleecker, Reynold A Panettieri Jr, Mona Bafadhel, Dewei She, Christine K Ward, Xiao Xu, Claire Birrell, René van der Merwe*




Lancet Respir Med. 2014 Nov;2(11):891-901

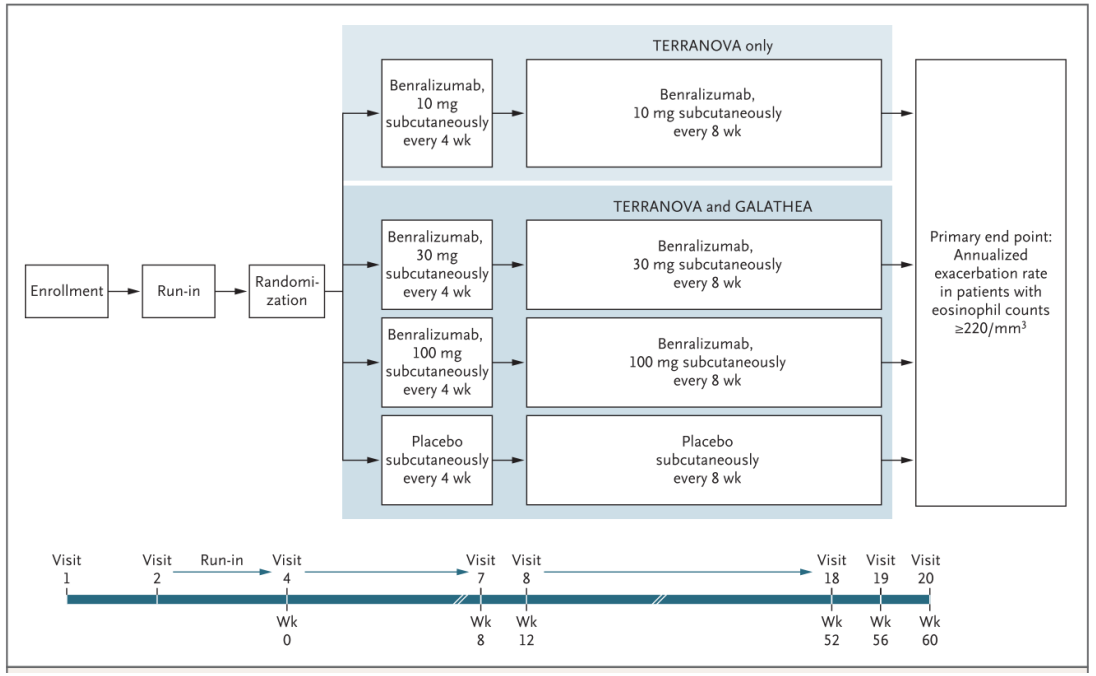
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Benralizumab for the Prevention of COPD Exacerbations

G.J. Criner, B.R. Celli, C.E. Brightling, A. Agusti, A. Papi, D. Singh, D.D. Sin, C.F. Vogelmeier, F.C. Sciurba, M. Bafadhel, V. Backer, M. Kato, A. Ramírez-Venegas, Y.-F. Wei, L. Bjermer, V.H. Shih, M. Jison, S. O'Quinn, N. Makulova, P. Newbold, M. Goldman, and U.J. Martin, for the GALATHEA and TERRANOVA Study Investigators*

- GALATHEA + TERRANOVA trials (Phase III trials)
- COPD patients
  - EOS ≥220
  - 40-85 years of age
  - moderate to very severe COPD
- Frequent exacerbators




N Engl J Med. 2019 Sep 12;381(11):1023-1034.

**Table 2. Analysis of Efficacy in Patients with Baseline Blood Eosinophil Counts of 220 per Cubic Millimeter or Greater.***

| End Point | GALATHEA | | | TERRANOVA | | | |
|---|---|---|---|---|---|---|---|
| | Benralizumab, 30 mg (N=382) | Benralizumab, 100 mg (N=379) | Placebo (N=359) | Benralizumab, 10 mg (N=377) | Benralizumab, 30 mg (N=394) | Benralizumab, 100 mg (N=386) | Placebo (N=388) |
| Exacerbations | | | | | | | |
| Estimated annual rate (95% CI) — exacerbations/yr | 1.19 (1.04–1.36) | 1.03 (0.90–1.19) | 1.24 (1.08–1.42) | 0.99 (0.87–1.13) | 1.21 (1.08–1.37) | 1.09 (0.96–1.23) | 1.17 (1.04–1.32) |
| Rate ratio, benralizumab vs. placebo (95% CI)† | 0.96 (0.80–1.15) | 0.83 (0.69–1.00) | — | 0.85 (0.71–1.01) | 1.04 (0.88–1.23) | 0.93 (0.78–1.10) | — |
| Unadjusted P value | 0.65 | 0.05 | — | 0.06 | 0.66 | 0.40 | — |
| Severe exacerbations | | | | | | | |
| Estimated annual rate (95% CI) — exacerbations/yr | 0.25 (0.19–0.33) | 0.12 (0.08–0.17) | 0.21 (0.15–0.28) | 0.18 (0.14–0.25) | 0.22 (0.17–0.28) | 0.17 (0.13–0.22) | 0.25 (0.19–0.32) |
| Rate ratio, benralizumab vs. placebo (95% CI)‡ | 1.20 (0.80–1.80) | 0.57 (0.36–0.91) | — | 0.75 (0.51–1.11) | 0.88 (0.61–1.27) | 0.68 (0.46–1.00) | — |
| Lung function | | | | | | | |
| No. of patients with data | 329 | 326 | 317 | 325 | 322 | 347 | 344 |
| Change from baseline to wk 56 in prebronchodilator $FEV_1$ — liters | 0.014±0.282 | 0.031±0.294 | 0.010±0.275 | 0.021±0.346 | 0.011±0.289 | 0.033±0.291 | 0.016±0.292 |
| Health-related quality of life | | | | | | | |
| No. of patients with data | 338 | 331 | 317 | 331 | 329 | 354 | 349 |
| Change from baseline to wk 56 in SGRQ total score§ | −5.025±14.677 | −6.723±15.723 | −3.913±15.039 | −7.733±14.996 | −8.674±17.910 | −7.257±15.989 | −6.863±16.344 |

N Engl J Med. 2019 Sep 12;381(11):1023-1034.

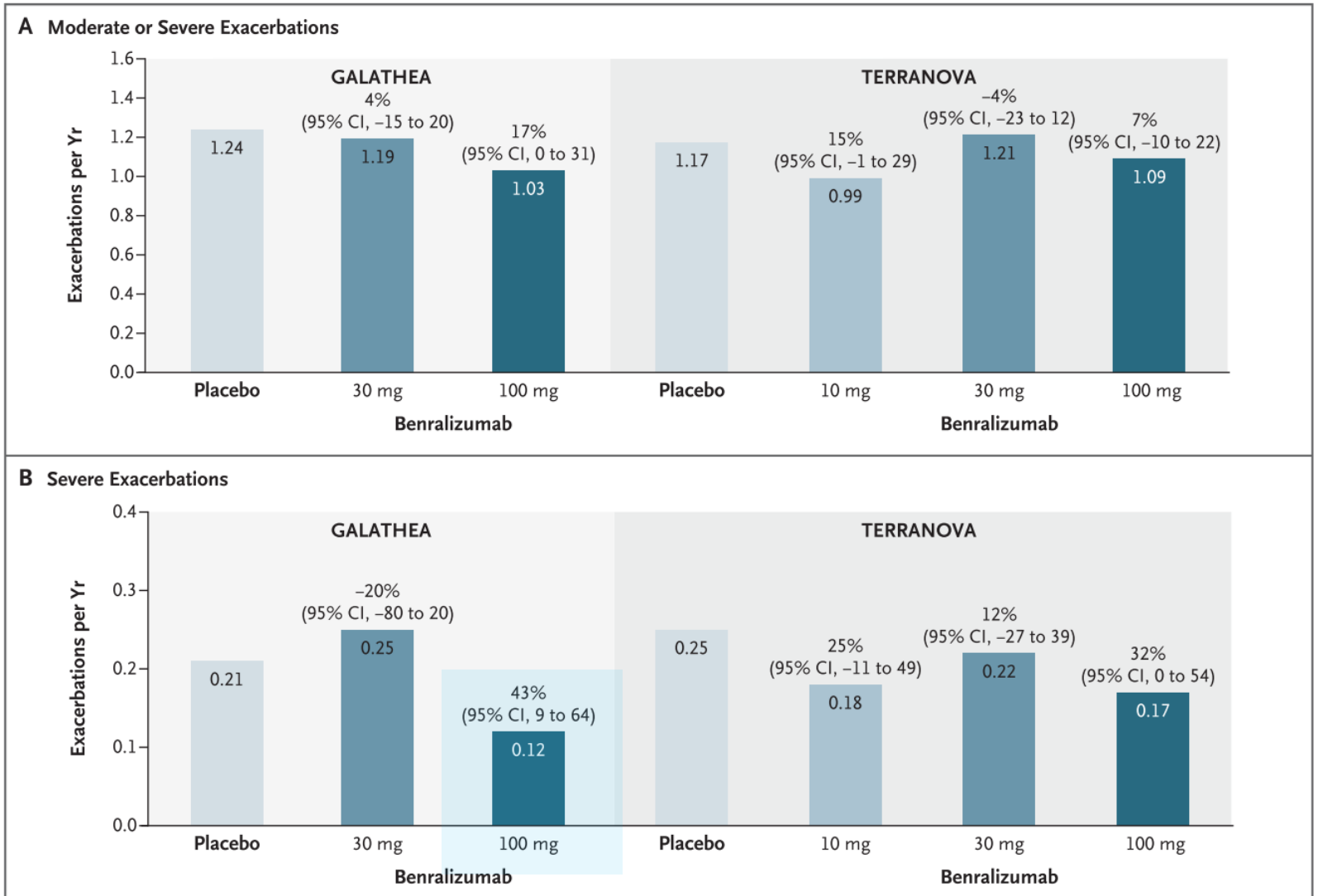



**Figure 2. Annualized Exacerbation Rates among Patients with Baseline Blood Eosinophil Counts of 220 per Cubic Millimeter or Greater.**

The percentages and corresponding 95% confidence intervals reflect the degree to which the rate is lower in the benralizumab group than in the placebo group (i.e., a positive percentage indicates a lower rate in the benralizumab group than in the placebo group) and are based on the annualized exacerbation rate ratios (benralizumab vs. placebo); for example, a rate ratio of 0.96 corresponds to a 4% lower annualized exacerbation rate in the 30-mg benralizumab group than in the placebo group.

**Table 3. Safety of Benralizumab during the Trial Period (Safety Analysis Population).**

| Adverse Event* | GALATHEA | | | TERRANOVA | | | |
|---|---|---|---|---|---|---|---|
| | Benralizumab, 30 mg (N=554) | Benralizumab, 100 mg (N=552) | Placebo (N=550) | Benralizumab, 10 mg (N=561) | Benralizumab, 30 mg (N=563) | Benralizumab, 100 mg (N=562) | Placebo (N=568) |
| | *number of patients (percent)* | | | *number of patients (percent)* | | | |
| Any adverse event | 427 (77.1) | 445 (80.6) | 421 (76.5) | 395 (70.4) | 424 (75.3) | 397 (70.6) | 406 (71.5) |
| Adverse event leading to death | 15 (2.7) | 11 (2.0) | 13 (2.4) | 17 (3.0) | 21 (3.7) | 17 (3.0) | 19 (3.3) |
| Any severe adverse event | 151 (27.3) | 177 (32.1) | 176 (32.0) | 144 (25.7) | 177 (31.4) | 127 (22.6) | 158 (27.8) |
| Adverse event leading to discontinuation of trial agent | 30 (5.4) | 33 (6.0) | 26 (4.7) | 20 (3.6) | 33 (5.9) | 26 (4.6) | 16 (2.8) |
| COPD-related event | 98 (17.7) | 83 (15.0) | 105 (19.1) | 97 (17.3) | 113 (20.1) | 85 (15.1) | 93 (16.4) |
| Viral upper respiratory tract infection | 83 (15.0) | 95 (17.2) | 66 (12.0) | 62 (11.1) | 47 (8.3) | 60 (10.7) | 70 (12.3) |
| Bronchitis | 60 (10.8) | 86 (15.6) | 83 (15.1) | 66 (11.8) | 73 (13.0) | 64 (11.4) | 66 (11.6) |
| Upper respiratory tract infection | 69 (12.5) | 75 (13.6) | 66 (12.0) | 68 (12.1) | 71 (12.6) | 68 (12.1) | 67 (11.8) |
| Lower respiratory tract infection | 50 (9.0) | 32 (5.8) | 29 (5.3) | 26 (4.6) | 23 (4.1) | 15 (2.7) | 21 (3.7) |
| Pneumonia | 32 (5.8) | 29 (5.3) | 24 (4.4) | 28 (5.0) | 33 (5.9) | 22 (3.9) | 38 (6.7) |
| Urinary tract infection | 24 (4.3) | 23 (4.2) | 15 (2.7) | 25 (4.5) | 26 (4.6) | 28 (5.0) | 19 (3.3) |
| Death from any cause | 15 (2.7) | 12 (2.2) | 13 (2.4) | 17 (3.0) | 21 (3.7) | 17 (3.0) | 19 (3.3) |

N Engl J Med. 2019 Sep 12;381(11):1023-1034.

# Efficacy and Safety of Benralizumab in Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD) With a History of Frequent Exacerbations (RESOLUTE)

**ClinicalTrials.gov ID** NCT04053634

**Sponsor** AstraZeneca

**Information provided by** AstraZeneca (Responsible Party)

**Last Update Posted** 2025-04-14







## Study Overview

### Brief Summary

Phase 3 study to evaluate the efficacy and safety of a benralizumab in patients with moderate to very severe COPD with a history of frequent COPD exacerbations and elevated peripheral blood eosinophils (≥300/µL).

Eligible patients must have a history of ≥2 moderate and/or severe COPD exacerbations in the previous year despite receiving triple (ICS/LABA/LAMA) background therapy for at least 3 months and ICS-based dual inhaled treatment for the remainder of the year. Eligible patients must also have an elevated blood eosinophil count.

The treatment period will be of variable duration and will continue until the last patient has the opportunity to complete a minimum of 56 weeks, at which point all patients will complete the study. The primary endpoint will be analyzed at Week 56.

### Official Title

A Multicenter, Randomized, Double-blind, Chronic-dosing, Parallel-group, Placebo-controlled Phase 3 Study to Evaluate the Efficacy and Safety of Benralizumab 100 mg in Patients With Moderate to Very Severe **Chronic Obstructive Pulmonary Disease** (**COPD**) With a History of Frequent **COPD** Exacerbations and Elevated Peripheral Blood Eosinophils (RESOLUTE)

**Study Start (Actual)**
2019-08-26

**Primary Completion (Estimated)**
2025-08-08

**Study Completion (Estimated)**
2025-08-08

**Enrollment (Actual)**
689

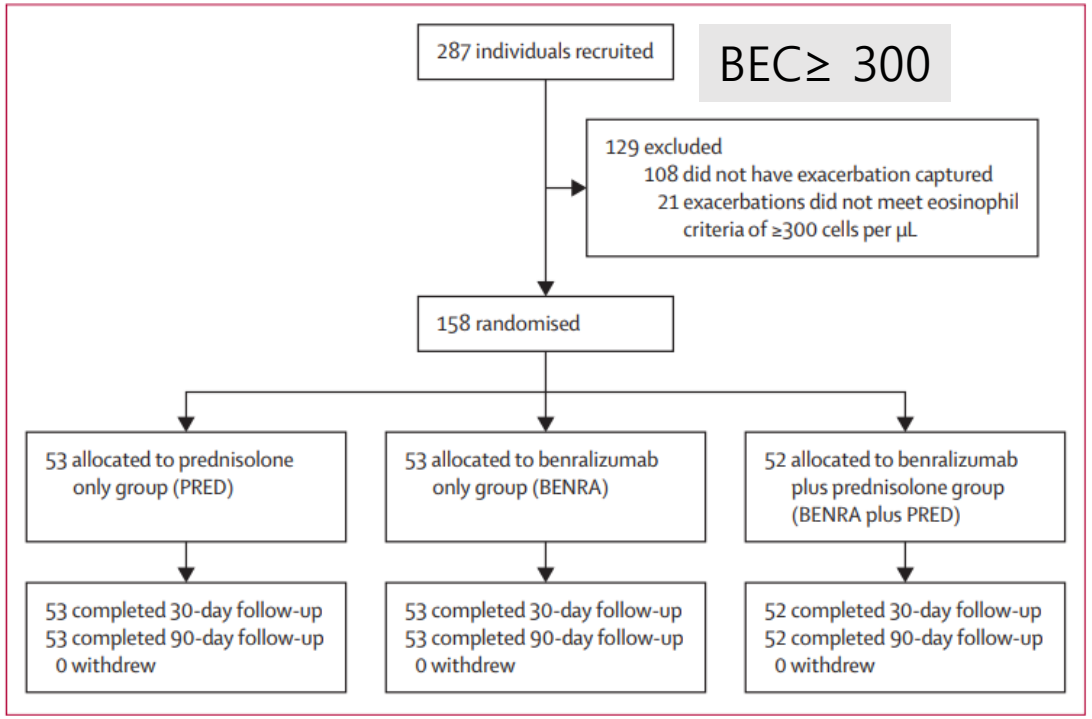
**Study Type**
Interventional

**Phase**
Phase 3

# Benralizumab as a exacerbation rescuer

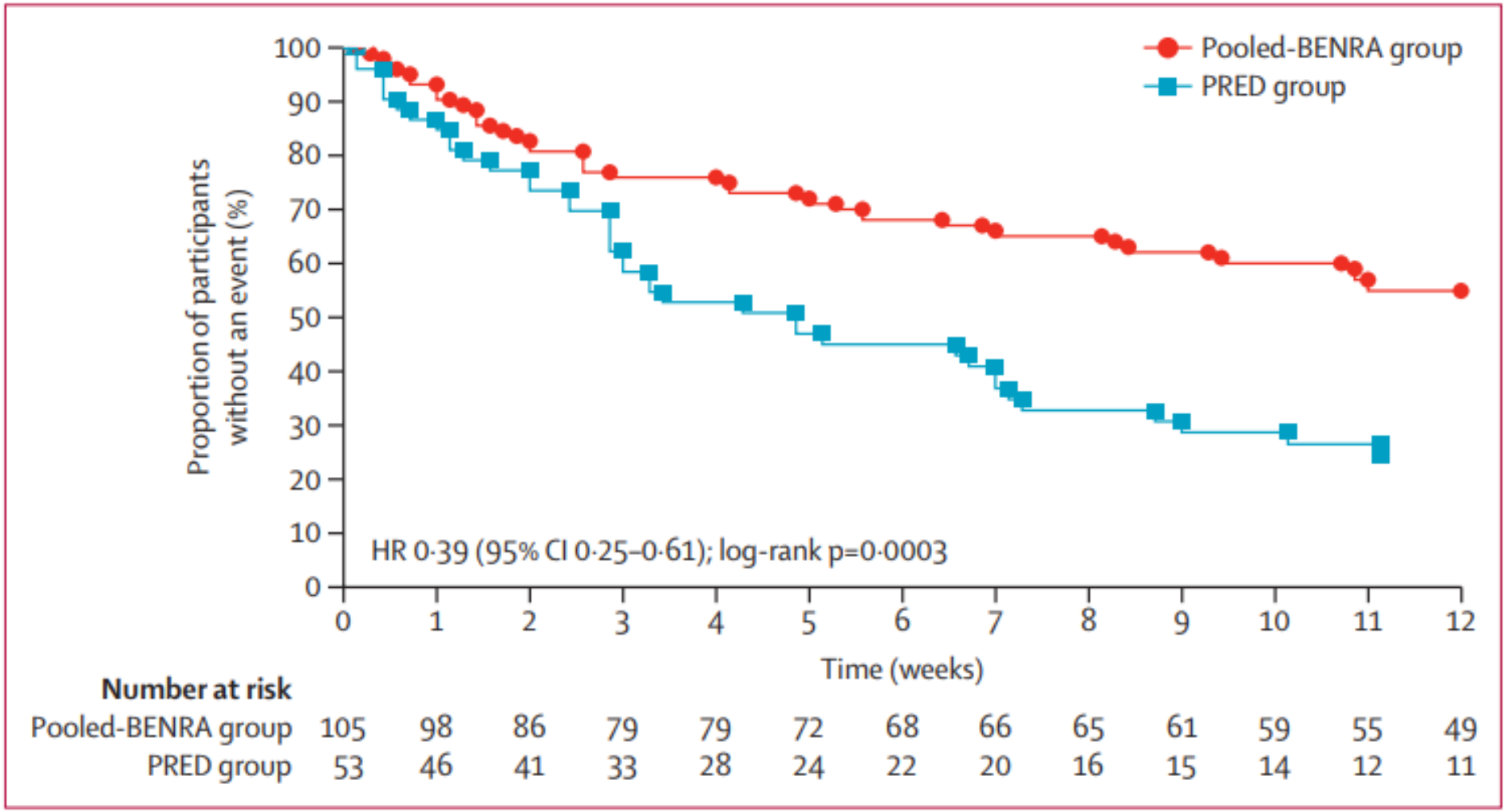
## Treating eosinophilic exacerbations of asthma and COPD with benralizumab (ABRA): a double-blind, double-dummy, active placebo-controlled randomised trial

*Sanjay Ramakrishnan, Richard E K Russell, Hafiz R Mahmood, Karolina Krassowska, James Melhorn, Christine Mwasuku, Ian D Pavord, Laura Bermejo-Sanchez, Imran Howell, Mahdi Mahdi, Stefan Peterson, Thomas Bengtsson, Mona Bafadhel*




| | PRED group (n=53) | Pooled-BENRA group (n=105) | p value |
|---|---|---|---|
| Number of patients with treatment failure at 90 days | 39 (74%) | 47 (45%) | .. |
| Odds ratio (95%CI) *vs* PRED group | .. | 0·26 (0·13 to 0·56) | 0·0005 |
| Change in total VAS symptoms from exacerbation to day 28 | | | |
| Mean change (95% CI) in mm | 103 (75 to 132) | 152 (131 to 173) | .. |
| Least-square mean difference *vs* PRED group | .. | 49 (14 to 84) | 0·0065 |

Ramakrishnan et al. *Lancet Respir Med. 2025*




Ramakrishnan et al. *Lancet Respir Med. 2025*

# Meta-analysis of biologics in eosinophilic COPD



SYSTEMATIC REVIEW

**Role of Monoclonal Antibodies in the Management of Eosinophilic Chronic Obstructive Pulmonary Disease**
A Meta-analysis of Randomized Controlled Trials

Mohamed M. G. Mohamed, Ghassan Kamel, and Edward Charbek

Division of Pulmonary, Critical Care, and Sleep Medicine, Saint Louis University School of Medicine, St. Louis, Missouri

ORCID IDs: 0000-0002-7514-7811 (M.M.G.M.); 0000-0001-6502-1505 (E.C.).

**Table 1.** Baseline characteristics of included studies

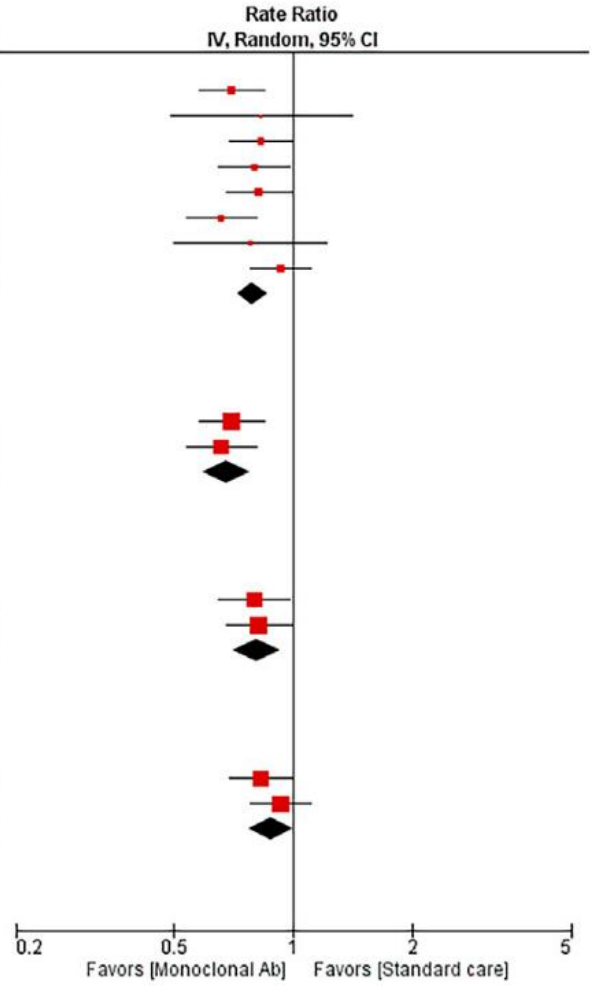
| Study, Year | Follow up Duration, wk | No. of Patients: MAb Arm | No. of Patients: SOC Arm | No. of Patients: Total | Subcutaneous MAb Regimen |
|---|---|---|---|---|---|
| Bhatt *et al.* (BOREAS), 2023 (18) | 52 | 468 | 471 | 939 | Dupilumab 300 mg q2w |
| Bhatt *et al.* (NOTUS), 2024 (19) | 52 | 470 | 465 | 935 | Dupilumab 300 mg q2w |
| Yousuf *et al.* (COPD-ST2OP), 2022 (15) | 60 | 42 | 39 | 81 | Astegolimab 490 mg q4w |
| Rabe *et al.*, 2021 (16) | 52 | 68 | 66 | 134 | Itepekimab 300 mg q2w |
| Criner *et al.* (GALATHEA), 2019 (17) | 56 | 379 | 359 | 738 | Benralizumab 100 mg, hybrid* |
| Criner *et al.* (TERRANOVA), 2019 (17) | 56 | 386 | 388 | 774 | Benralizumab 100 mg, hybrid* |
| Pavord *et al.* (METREO), 2017 (21) | 52 | 223 | 226 | 449 | Mepolizumab 100 mg q4w |
| Pavord *et al.* (METREX), 2017 (21) | 52 | 233 | 229 | 462 | Mepolizumab 100 mg q4w |
| Totals | — | 2,269 | 2,243 | 4,512 | — |

Ann Am Thorac Soc. 2025;22(5):768-75.

# Efficacy outcomes

**AE**

| Study or Subgroup | log[Rate Ratio] | SE | Monoclonal Ab Total | Standard of care Total | Weight | Rate Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.1.1 Annual exacerbation rate** | | | | | | |
| BOREAS 2023 | -0.3567 | 0.0959 | 468 | 471 | 15.9% | 0.70 [0.58, 0.84] |
| COPD-ST2OP 2022 | -0.1863 | 0.2689 | 23 | 17 | 2.5% | 0.83 [0.49, 1.41] |
| GALATHEA 2019 | -0.1863 | 0.0943 | 379 | 359 | 16.4% | 0.83 [0.69, 1.00] |
| METREO 2017 | -0.2231 | 0.1059 | 223 | 226 | 13.6% | 0.80 [0.65, 0.98] |
| METREX 2017 | -0.1985 | 0.0955 | 233 | 229 | 16.1% | 0.82 [0.68, 0.99] |
| NOTUS 2024 | -0.4155 | 0.1024 | 470 | 465 | 14.4% | 0.66 [0.54, 0.81] |
| Rabe et al 2021 | -0.2485 | 0.2269 | 68 | 66 | 3.5% | 0.78 [0.50, 1.22] |
| TERRANOVA 2019 | -0.0726 | 0.0897 | 386 | 388 | 17.7% | 0.93 [0.78, 1.11] |
| **Subtotal (95% CI)** | | | **2250** | **2221** | **100.0%** | **0.79 [0.73, 0.86]** |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.46$, df = 7 (P = 0.29); $I^2 = 17\%$ | | | | | | |
| Test for overall effect: Z = 5.44 (P < 0.00001) | | | | | | |
| **1.1.2 Dupilumab effect** | | | | | | |
| BOREAS 2023 | -0.3567 | 0.0959 | 468 | 471 | 53.3% | 0.70 [0.58, 0.84] |
| NOTUS 2024 | -0.4155 | 0.1024 | 470 | 465 | 46.7% | 0.66 [0.54, 0.81] |
| **Subtotal (95% CI)** | | | **938** | **936** | **100.0%** | **0.68 [0.59, 0.78]** |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.18$, df = 1 (P = 0.68); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 5.49 (P < 0.00001) | | | | | | |
| **1.1.3 Mepolizumab effect** | | | | | | |
| METREO 2017 | -0.2231 | 0.1059 | 223 | 226 | 44.8% | 0.80 [0.65, 0.98] |
| METREX 2017 | -0.1985 | 0.0955 | 233 | 229 | 55.2% | 0.82 [0.68, 0.99] |
| **Subtotal (95% CI)** | | | **456** | **455** | **100.0%** | **0.81 [0.71, 0.93]** |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.03$, df = 1 (P = 0.86); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 2.95 (P = 0.003) | | | | | | |
| **1.1.4 Benralizumab effect** | | | | | | |
| GALATHEA 2019 | -0.1863 | 0.0943 | 379 | 359 | 47.5% | 0.83 [0.69, 1.00] |
| TERRANOVA 2019 | -0.0726 | 0.0897 | 386 | 388 | 52.5% | 0.93 [0.78, 1.11] |
| **Subtotal (95% CI)** | | | **765** | **747** | **100.0%** | **0.88 [0.78, 1.00]** |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.76$, df = 1 (P = 0.38); $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 1.95 (P = 0.05) | | | | | | |



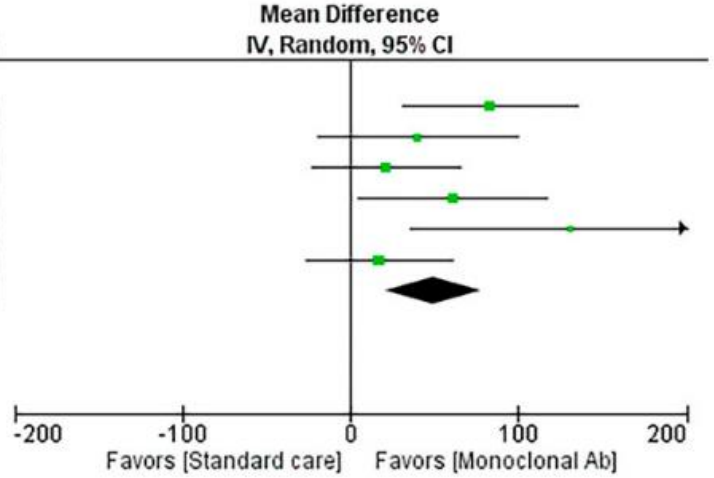

Ann Am Thorac Soc. 2025;22(5):768-75.

## FEV1

| Study or Subgroup | Monoclonal Ab Mean | SD | Total | Standard of care Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.2.1 Change in FEV1(ml)** | | | | | | | | |
| BOREAS 2023 | 153 | 407.3 | 468 | 70 | 408.6 | 471 | 17.9% | 83.00 [30.81, 135.19] |
| COPD-ST2OP 2022 | 0 | 9.6 | 42 | -40 | 191 | 39 | 15.0% | 40.00 [-20.01, 100.01] |
| GALATHEA 2019 | 31 | 294 | 326 | 10 | 275 | 317 | 21.5% | 21.00 [-22.99, 64.99] |
| NOTUS 2024 | 115 | 386.9971 | 362 | 54 | 385.3793 | 359 | 16.3% | 61.00 [4.62, 117.38] |
| Rabe et al 2021 | 111 | 300 | 68 | -20 | 260 | 66 | 7.6% | 131.00 [36.03, 225.97] |
| TERRANOVA 2019 | 33 | 291 | 347 | 16 | 292 | 344 | 21.8% | 17.00 [-26.47, 60.47] |
| **Subtotal (95% CI)** | | | **1613** | | | **1596** | **100.0%** | **48.89 [20.12, 77.66]** |

Heterogeneity: Tau² = 497.78; Chi² = 8.26, df = 5 (P = 0.14); I² = 39%

Test for overall effect: Z = 3.33 (P = 0.0009)

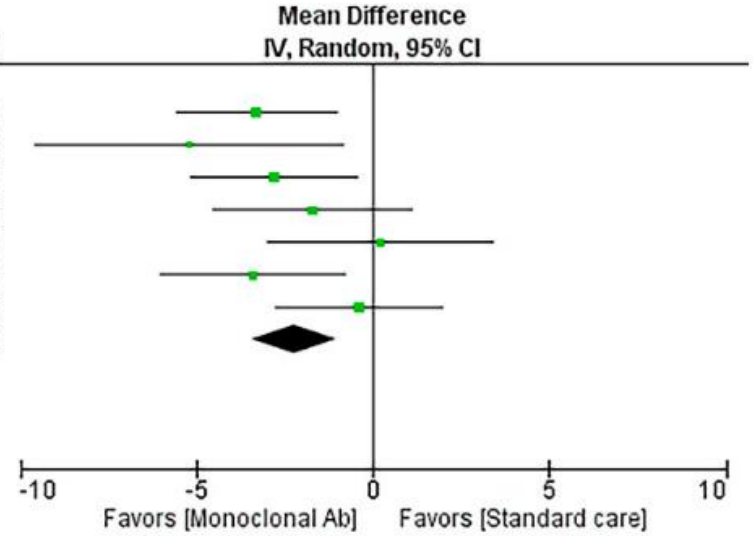



## SGRQ

| Study or Subgroup | Monoclonal Ab Mean | SD | Total | Standard of care Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.3.1 Change in SGRQ score** | | | | | | | | |
| BOREAS 2023 | -9.7 | 17.6144 | 468 | -6.4 | 17.6711 | 471 | 18.5% | -3.30 [-5.56, -1.04] |
| COPD-ST2OP 2022 | -4.26 | 9.4345 | 42 | 0.94 | 10.4577 | 39 | 6.7% | -5.20 [-9.55, -0.85] |
| GALATHEA 2019 | -6.7 | 15.7 | 331 | -3.9 | 15 | 317 | 17.4% | -2.80 [-5.16, -0.44] |
| METREO 2017 | -5 | 15.1354 | 223 | -3.3 | 15.1354 | 226 | 13.7% | -1.70 [-4.50, 1.10] |
| METREX 2017 | -2.8 | 17.5158 | 233 | -3 | 17.5158 | 229 | 11.2% | 0.20 [-2.99, 3.39] |
| NOTUS 2024 | -9.8 | 17.4149 | 362 | -6.4 | 18.3055 | 359 | 15.2% | -3.40 [-6.01, -0.79] |
| TERRANOVA 2019 | -7.26 | 16 | 354 | -6.86 | 16 | 349 | 17.4% | -0.40 [-2.77, 1.97] |
| **Subtotal (95% CI)** | | | **2013** | | | **1990** | **100.0%** | **-2.24 [-3.45, -1.03]** |

Heterogeneity: Tau² = 0.73; Chi² = 8.31, df = 6 (P = 0.22); I² = 28%

Test for overall effect: Z = 3.64 (P = 0.0003)

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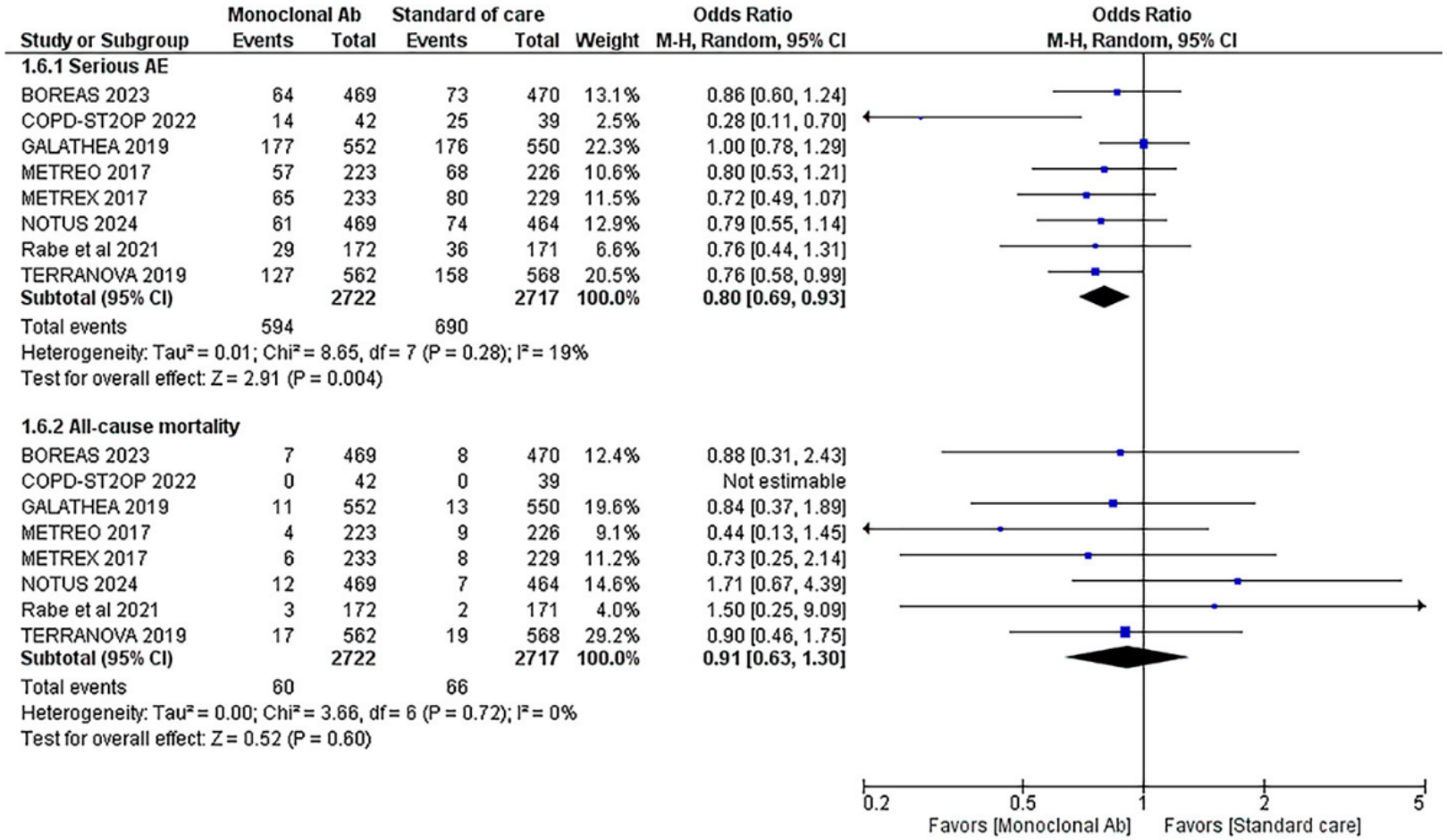
# Safety profiles



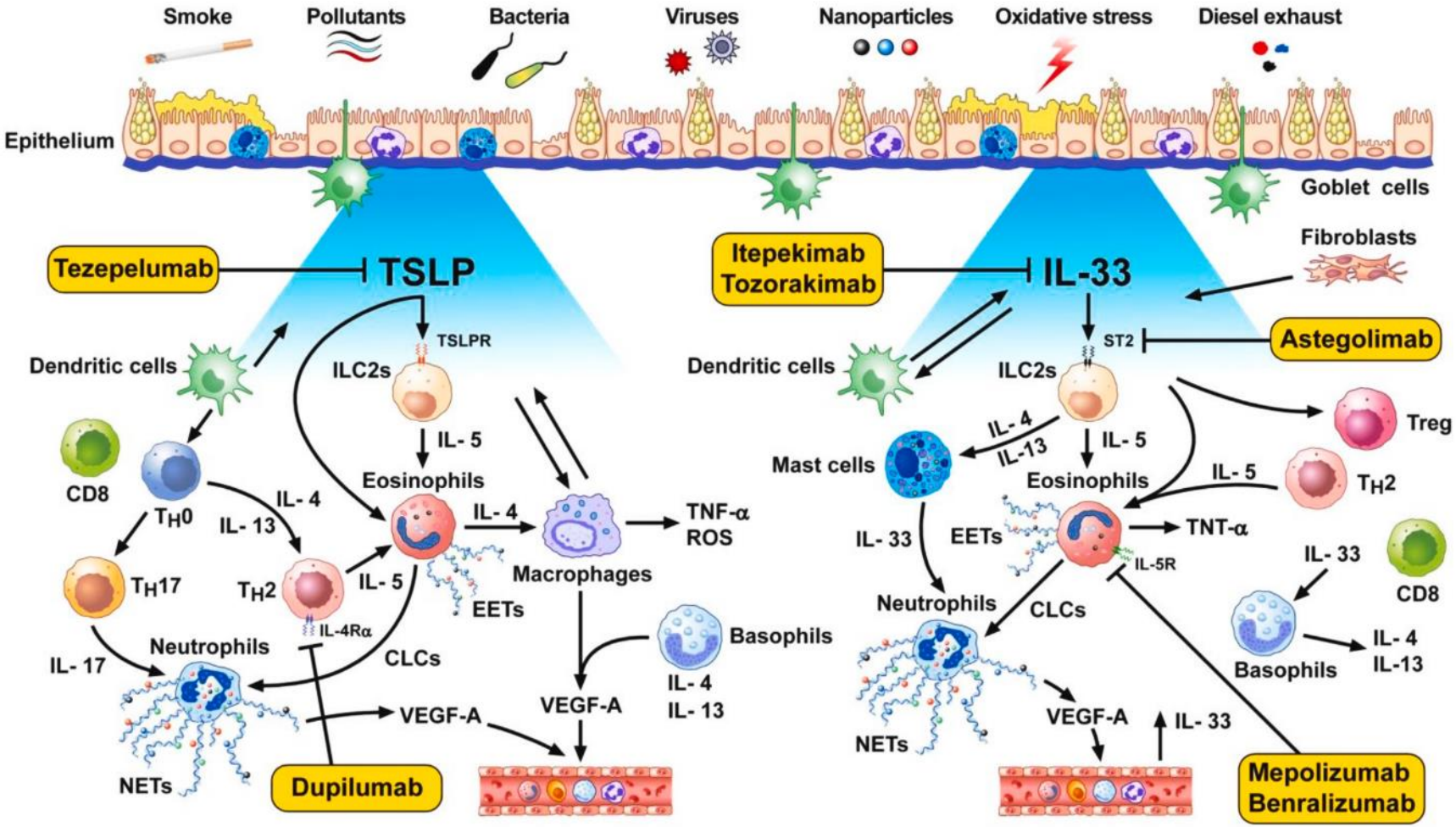
| Study or Subgroup | Monoclonal Ab Events | Total | Standard of care Events | Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.6.1 Serious AE** | | | | | | |
| BOREAS 2023 | 64 | 469 | 73 | 470 | 13.1% | 0.86 [0.60, 1.24] |
| COPD-ST2OP 2022 | 14 | 42 | 25 | 39 | 2.5% | 0.28 [0.11, 0.70] |
| GALATHEA 2019 | 177 | 552 | 176 | 550 | 22.3% | 1.00 [0.78, 1.29] |
| METREO 2017 | 57 | 223 | 68 | 226 | 10.6% | 0.80 [0.53, 1.21] |
| METREX 2017 | 65 | 233 | 80 | 229 | 11.5% | 0.72 [0.49, 1.07] |
| NOTUS 2024 | 61 | 469 | 74 | 464 | 12.9% | 0.79 [0.55, 1.14] |
| Rabe et al 2021 | 29 | 172 | 36 | 171 | 6.6% | 0.76 [0.44, 1.31] |
| TERRANOVA 2019 | 127 | 562 | 158 | 568 | 20.5% | 0.76 [0.58, 0.99] |
| **Subtotal (95% CI)** | | **2722** | | **2717** | **100.0%** | **0.80 [0.69, 0.93]** |
| Total events | 594 | | 690 | | | |
| Heterogeneity: Tau² = 0.01; Chi² = 8.65, df = 7 (P = 0.28); I² = 19% | | | | | | |
| Test for overall effect: Z = 2.91 (P = 0.004) | | | | | | |
| **1.6.2 All-cause mortality** | | | | | | |
| BOREAS 2023 | 7 | 469 | 8 | 470 | 12.4% | 0.88 [0.31, 2.43] |
| COPD-ST2OP 2022 | 0 | 42 | 0 | 39 | | Not estimable |
| GALATHEA 2019 | 11 | 552 | 13 | 550 | 19.6% | 0.84 [0.37, 1.89] |
| METREO 2017 | 4 | 223 | 9 | 226 | 9.1% | 0.44 [0.13, 1.45] |
| METREX 2017 | 6 | 233 | 8 | 229 | 11.2% | 0.73 [0.25, 2.14] |
| NOTUS 2024 | 12 | 469 | 7 | 464 | 14.6% | 1.71 [0.67, 4.39] |
| Rabe et al 2021 | 3 | 172 | 2 | 171 | 4.0% | 1.50 [0.25, 9.09] |
| TERRANOVA 2019 | 17 | 562 | 19 | 568 | 29.2% | 0.90 [0.46, 1.75] |
| **Subtotal (95% CI)** | | **2722** | | **2717** | **100.0%** | **0.91 [0.63, 1.30]** |
| Total events | 60 | | 66 | | | |
| Heterogeneity: Tau² = 0.00; Chi² = 3.66, df = 6 (P = 0.72); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.52 (P = 0.60) | | | | | | |



Ann Am Thorac Soc. 2025;22(5):768-75.

# Targeting alarmins

# Role of type 2 inflammatory pathways and epithelial-derived alarmins in COPD




Eur J Intern Med. 2024;125:28-31.

# Targeting alarmins

1) Anti-TSLP (Tezepelumab)

# Tezepelumab (anti-TSLP)

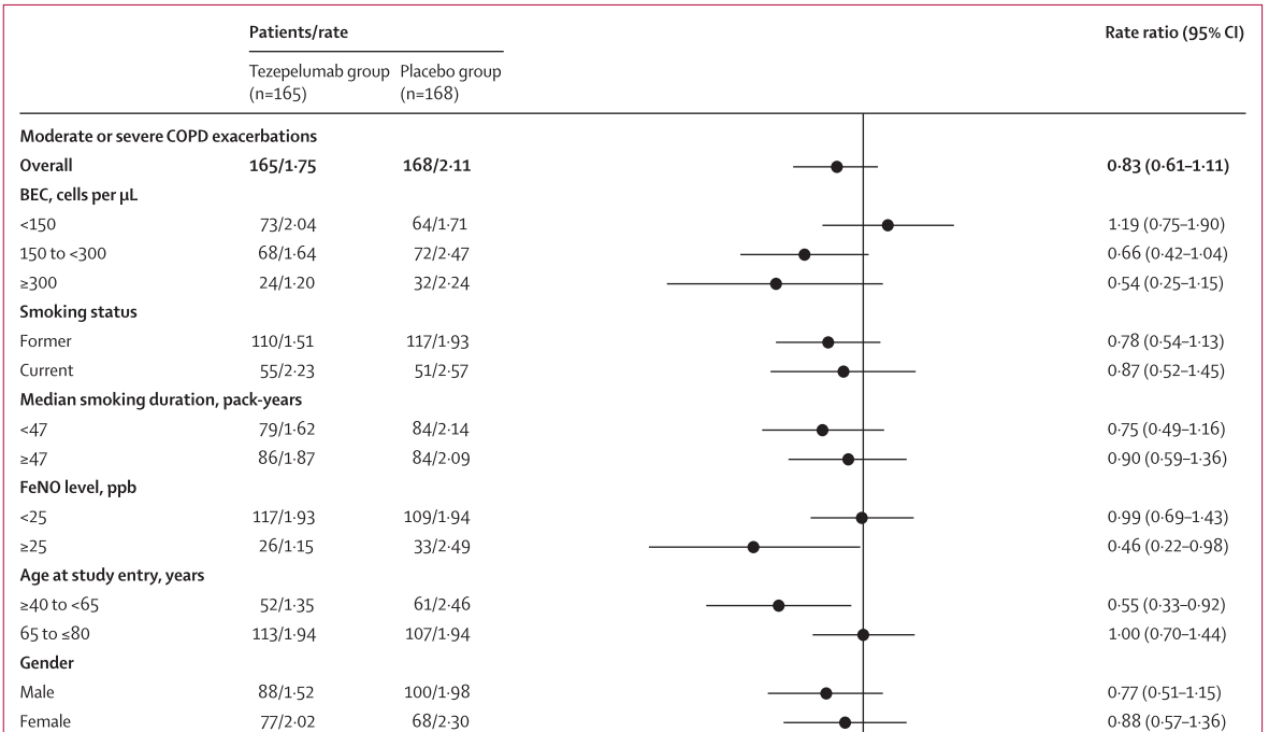
**Efficacy and safety of tezepelumab versus placebo in adults with moderate to very severe chronic obstructive pulmonary disease (COURSE): a randomised, placebo-controlled, phase 2a trial**

*Dave Singh, Christopher E Brightling, Klaus F Rabe, MeiLan K Han, Stephanie A Christenson, M Bradley Drummond, Alberto Papi, Ian D Pavord, Nestor A Molfino, Gun Almqvist, Ales Kotalik, Åsa Hellqvist, Monika Gołąbek, Navreet S Sindhwani, Sandhia S Ponnarambil, on behalf of the COURSE study investigators**

- Double-blind, RCT, phase 2a trial across 90 sites in ten countries in Asia, Europe, and North America.
- Eligible participants
  - aged 40–80 years,
  - moderate to very severe airflow limitation,
  - receiving triple therapy
  - at least two moderate to severe COPD exacerbations in the 12 months before enrollment.
- tezepelumab 420 mg or placebo every 4 weeks for up to 52 weeks.
- The primary endpoint
  - the annualised rate of moderate or severe COPD exacerbations
  - A prespecified subgroup analysis assessed the primary endpoint in patients grouped by baseline BECs.

Singh et al. Lancet Respir Med. 2025;13(1):47-58.

# The annualised rate of moderate or severe COPD exacerbations



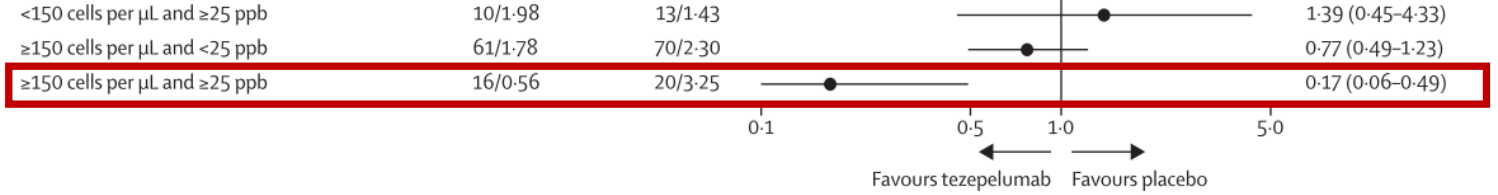
| | Patients/rate | | Rate ratio (95% CI) |
|---|---|---|---|
| | Tezepelumab group (n=165) | Placebo group (n=168) | |
| **Moderate or severe COPD exacerbations** | | | |
| **Overall** | **165/1·75** | **168/2·11** | **0·83 (0·61–1·11)** |
| **BEC, cells per μL** | | | |
| <150 | 73/2·04 | 64/1·71 | 1·19 (0·75–1·90) |
| 150 to <300 | 68/1·64 | 72/2·47 | 0·66 (0·42–1·04) |
| ≥300 | 24/1·20 | 32/2·24 | 0·54 (0·25–1·15) |
| **Smoking status** | | | |
| Former | 110/1·51 | 117/1·93 | 0·78 (0·54–1·13) |
| Current | 55/2·23 | 51/2·57 | 0·87 (0·52–1·45) |
| **Median smoking duration, pack-years** | | | |
| <47 | 79/1·62 | 84/2·14 | 0·75 (0·49–1·16) |
| ≥47 | 86/1·87 | 84/2·09 | 0·90 (0·59–1·36) |
| **FeNO level, ppb** | | | |
| <25 | 117/1·93 | 109/1·94 | 0·99 (0·69–1·43) |
| ≥25 | 26/1·15 | 33/2·49 | 0·46 (0·22–0·98) |
| **Age at study entry, years** | | | |
| ≥40 to <65 | 52/1·35 | 61/2·46 | 0·55 (0·33–0·92) |
| 65 to ≤80 | 113/1·94 | 107/1·94 | 1·00 (0·70–1·44) |
| **Gender** | | | |
| Male | 88/1·52 | 100/1·98 | 0·77 (0·51–1·15) |
| Female | 77/2·02 | 68/2·30 | 0·88 (0·57–1·36) |
| **BMI, kg/m²** | | | |
| <25 | 59/1·57 | 71/1·91 | 0·82 (0·51–1·33) |
| 25 to <30 | 64/1·61 | 41/1·75 | 0·92 (0·53–1·58) |
| ≥30 | 42/2·30 | 56/2·61 | 0·88 (0·51–1·51) |
| **Chronic bronchitis** | | | |
| Yes | 85/1·91 | 100/1·94 | 0·98 (0·66–1·47) |
| No | 80/1·58 | 68/2·39 | 0·66 (0·42–1·04) |
| **Emphysema** | | | |
| Yes | 91/2·07 | 101/2·41 | 0·86 (0·59–1·26) |
| No | 74/1·39 | 67/1·65 | 0·84 (0·52–1·35) |
| **Previous severe exacerbation at randomisation** | | | |
| Yes | 30/2·61 | 35/2·92 | 0·89 (0·47–1·71) |
| No | 135/1·57 | 133/1·90 | 0·82 (0·59–1·15) |
| **Number of previous exacerbations at randomisation** | | | |
| Two | 96/1·26 | 96/1·31 | 0·96 (0·64–1·45) |
| At least three | 69/2·33 | 72/3·33 | 0·70 (0·46–1·07) |
| **Severe COPD exacerbations** | | | |
| **Overall** | **165/0·13** | **168/0·25** | **0·52 (0·24–1·11)** |



Singh et al. Lancet Respir Med. 2025;13(1):47-58.

# Post-hoc analysis of the annualised exacerbation rates in patients grouped by baseline BEC and other variables

| | Patients/rate | | Rate ratio (95% CI) |
|---|---|---|---|
| | Tezepelumab group (n=165) | Placebo group (n=168) | |
| **Moderate or severe COPD exacerbations** | | | |
| **Overall** | **165/1·75** | **168/2·11** | **0·83 (0·61–1·11)** |
| **BEC and age** | | | |
| <150 cells per µL and 40 to <65 years | 22/1·80 | 20/2·29 | 0·79 (0·35–1·78) |
| <150 cells per µL and 65 to ≤80 years | 51/2·17 | 44/1·47 | 1·47 (0·84–2·56) |
| ≥150 cells per µL and 40 to <65 years | 30/0·99 | 41/2·58 | 0·38 (0·19–0·76) |
| ≥150 cells per µL and 65 to ≤80 years | 62/1·78 | 63/2·31 | 0·77 (0·48–1·24) |
| **BEC and previous exacerbations** | | | |
| <150 cells per µL and two exacerbations | 46/1·50 | 38/0·93 | 1·62 (0·87–3·02) |
| <150 cells per µL and three or more exacerbations | 27/2·71 | 26/3·26 | 0·83 (0·41–1·67) |
| ≥150 cells per µL and two exacerbations | 50/1·03 | 58/1·58 | 0·65 (0·38–1·13) |
| ≥150 cells per µL and three or more exacerbations | 42/2·09 | 46/3·36 | 0·62 (0·36–1·07) |
| **BEC and smoking status** | | | |
| <150 cells per µL and current smoker | 23/3·03 | 22/2·18 | 1·39 (0·63–3·07) |
| <150 cells per µL and former smoker | 50/1·62 | 42/1·50 | 1·08 (0·61–1·91) |
| ≥150 cells per µL and current smoker | 32/1·72 | 29/2·84 | 0·61 (0·31–1·18) |
| ≥150 cells per µL and former smoker | 60/1·40 | 75/2·23 | 0·63 (0·39–1·01) |
| **BEC and FeNO level** | | | |
| <150 cells per µL and <25 ppb | 56/2·06 | 39/1·34 | 1·54 (0·87–2·72) |
| <150 cells per µL and ≥25 ppb | 10/1·98 | 13/1·43 | 1·39 (0·45–4·33) |
| ≥150 cells per µL and <25 ppb | 61/1·78 | 70/2·30 | 0·77 (0·49–1·23) |
| ≥150 cells per µL and ≥25 ppb | 16/0·56 | 20/3·25 | 0·17 (0·06–0·49) |




Singh et al. Lancet Respir Med. 2025;13(1):47-58.

# Change from baseline to week 52 in pre-bronchodilator FEV1 and SGRQ total score

| | Tezepelumab group (n=165) | | Placebo group (n=168) | | LS mean difference (95% CI) |
|---|---|---|---|---|---|
| | n | LS mean (SE) | n | LS mean (SE) | |
| **Pre-bronchodilator $FEV_1$, L** | | | | | |
| Overall | 163 | 0·026 (0·015) | 166 | −0·029 (0·015) | 0·055 (0·014 to 0·096) |
| Baseline BEC, cells per µL | | | | | |
| <150 | 73 | −0·002 (0·022) | 63 | −0·053 (0·023) | 0·051 (−0·012 to 0·114) |
| 150 to <300 | 66 | 0·010 (0·023) | 72 | −0·025 (0·022) | 0·034 (−0·028 to 0·097) |
| ≥300 | 24 | 0·160 (0·038) | 31 | 0·013 (0·035) | 0·146 (0·044 to 0·248) |
| Baseline FeNO level, ppb | | | | | |
| <25 | 117 | 0·009 (0·018) | 107 | −0·022 (0·019) | 0·031 (−0·020 to 0·082) |
| ≥25 | 25 | 0·118 (0·038) | 33 | 0·000 (0·035) | 0·118 (0·016 to 0·220) |
| **SGRQ total score** | | | | | |
| Overall | 157 | −4·80 (1·18) | 156 | −1·86 (1·19) | −2·93 (−6·23 to 0·36) |
| Baseline BEC, cells per µL | | | | | |
| <150 | 69 | −1·91 (1·75) | 60 | −0·30 (1·89) | −1·62 (−6·69 to 3·45) |
| 150 to <300 | 66 | −6·05 (1·81) | 69 | −3·64 (1·75) | −2·41 (−7·36 to 2·55) |
| ≥300 | 22 | −10·22 (3·14) | 27 | −0·68 (3·01) | −9·53 (−18·11 to −0·96) |
| Baseline FeNO level, ppb | | | | | |
| <25 | 112 | −4·46 (1·43) | 102 | −2·28 (1·49) | −2·18 (−6·24 to 1·88) |
| ≥25 | 24 | −7·23 (3·08) | 29 | −1·90 (2·87) | −5·33 (−13·56 to 2·91) |

BEC=blood eosinophil count. FeNO=fractional exhaled nitric oxide. LS=least-squares. ppb=parts per billion. SGRQ=St George's Respiratory Questionnaire.

***Table 2:*** **Change from baseline to week 52 in pre-bronchodilator $FEV_1$ and SGRQ total score in the overall population (secondary endpoint) and in prespecified patient subgroups by baseline BEC and FeNO level (full analysis set)**

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# Safety profiles

| | Tezepelumab group (n=165) | Placebo group (n=168) |
|---|---|---|
| Any adverse event | 133 (81%) | 126 (75%) |
| Mild | 32 (19%) | 30 (18%) |
| Moderate | 56 (34%) | 62 (37%) |
| Severe | 45 (27%) | 34 (20%) |
| Any adverse event resulting in death | 2 (1%) | 3* (2%) |
| Any serious adverse event | 49 (30%) | 50 (30%) |
| Any adverse event leading to treatment discontinuation | 4 (2%) | 6 (4%) |
| Most frequent adverse events† | | |
| COVID-19 | 24 (15%) | 14 (8%) |
| COPD | 20 (12%) | 28 (17%) |
| Most frequent serious adverse events‡ | | |
| COPD | 16 (10%) | 23 (14%) |

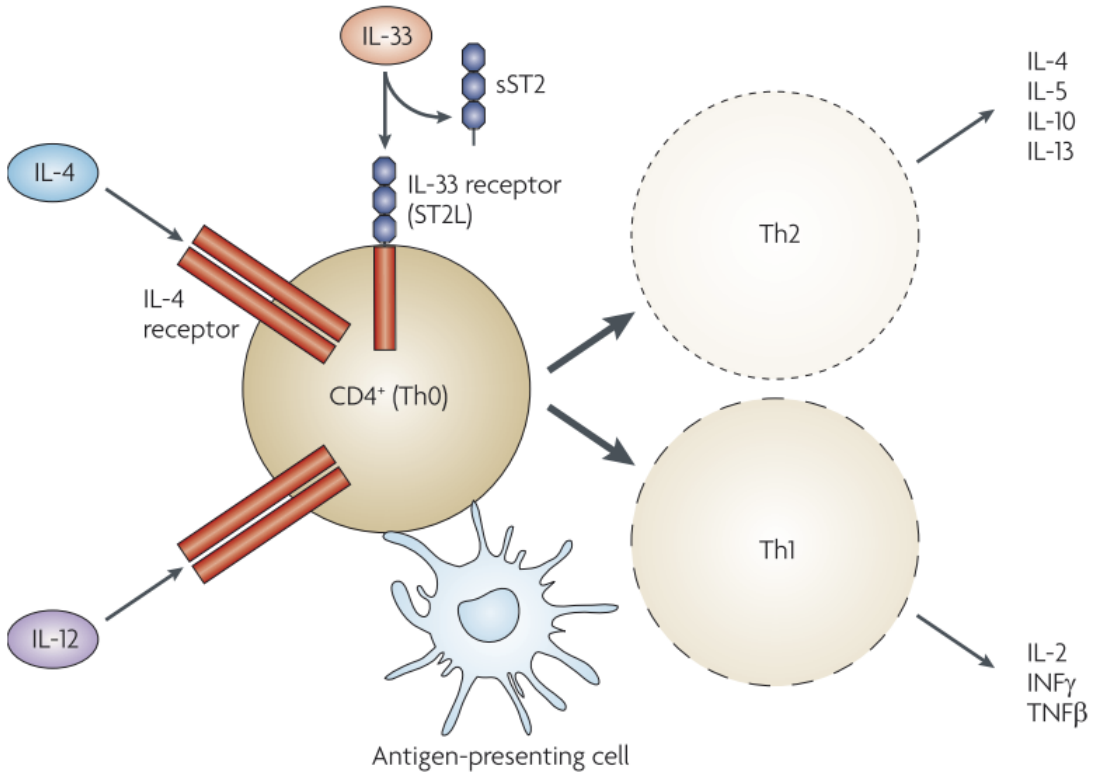
Data are n (%). COPD=chronic obstructive pulmonary disease. *One patient had an adverse event that started during treatment but whose death occurred after discontinuation of treatment and study withdrawal. †Adverse events that occurred in at least 10% of patients in any treatment group, irrespective of causality. ‡Serious adverse events that occurred in at least 5% of patients in any treatment group, irrespective of causality.

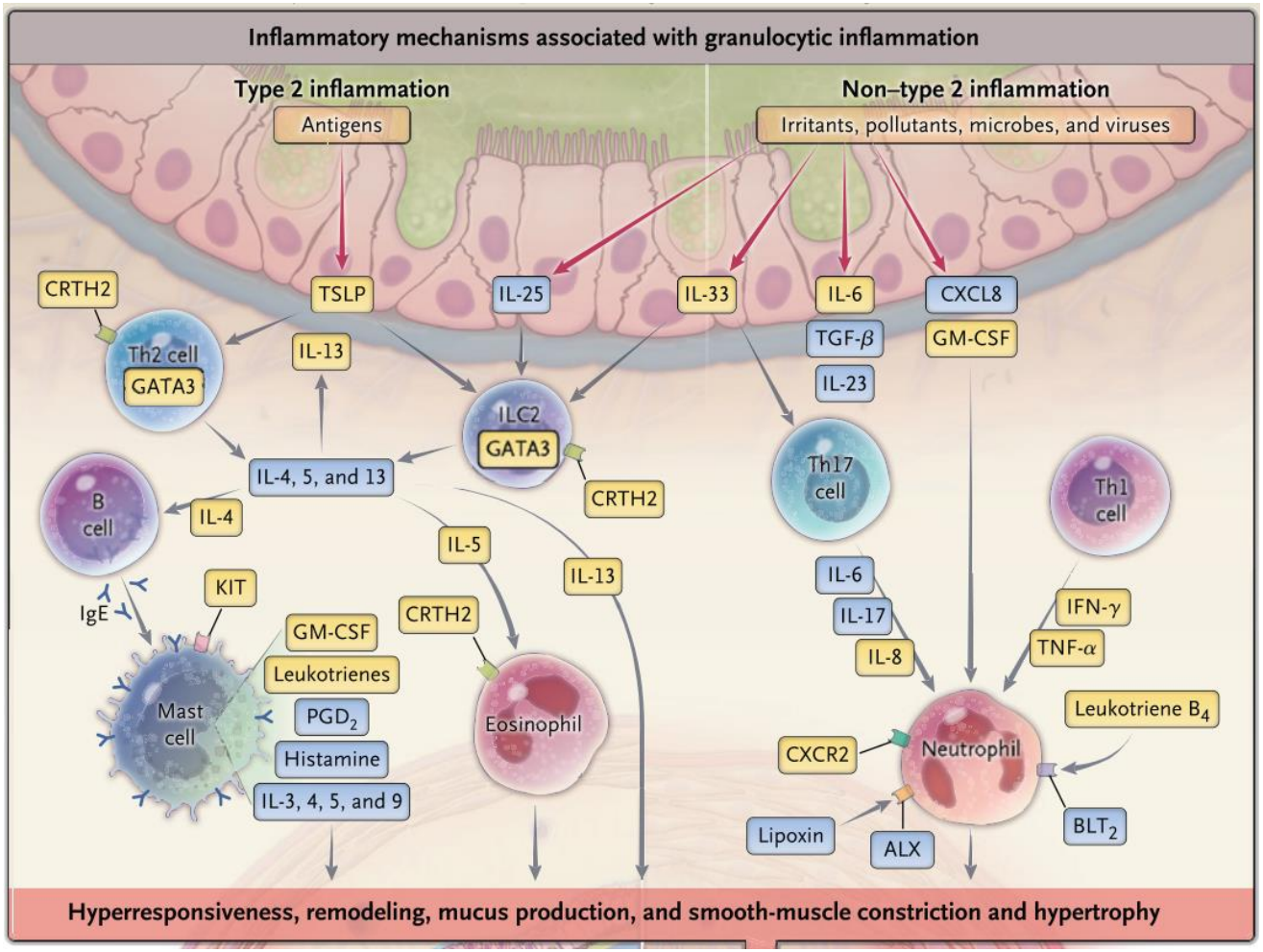
***Table 3:*** **Summary of on-treatment adverse events (safety analysis set)**

Singh et al. Lancet Respir Med. 2025;13(1):47-58.

# Targeting alarmins

## 2) Anti-IL33 (Itepekimab and Tozorakimab)




Nat Rev Drug Discov. 2008 Oct;7(10):827-40., N Engl J Med. 2017 Sep 7;377(10):965-976

# Itepekimab (Anti-IL-33)

## Safety and efficacy of itepekimab in patients with moderate-to-severe COPD: a genetic association study and randomised, double-blind, phase 2a trial

*Klaus F Rabe, Bartolome R Celli, Michael E Wechsler, Raolat M Abdulai, Xiaodong Luo, Maarten M Boomsma, Heribert Staudinger, Julie E Horowitz, Aris Baras, Manuel A Ferreira, Marcella K Ruddy, Michael C Nivens, Nikhil Amin, David M Weinreich, George D Yancopoulos, Helene Goulaouic*

Lancet Respir Med. 2021 Nov;9(11):1288-1298

| | mITT population | | Baseline blood eosinophils ≥250 per mm³ | | Baseline blood eosinophils <250 per mm³ | | Former smokers | | Current smokers | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo group (n=171) | Itepekimab group (n=172) | Placebo group (n=66) | Itepekimab group (n=68) | Placebo group (n=105) | Itepekimab group (n=104) | Placebo group (n=89) | Itepekimab group (n=98) | Placebo group (n=82) | Itepekimab group (n=74) |
| **Moderate-to-severe acute exacerbations of COPD** | | | | | | | | | | |
| Adjusted annualised rate to week 52 (95% CI) | 1·61 (1·32 to 1·97) | 1·30 (1·05 to 1·61) | 1·71 (1·24 to 2·35) | 1·34 (0·95 to 1·89) | 1·51 (1·17 to 1·94) | 1·26 (0·96 to 1·64) | 1·55 (1·17 to 2·05) | 0·89 (0·66 to 1·21) | 1·70 (1·28 to 2·26) | 1·86 (1·37 to 2·52) |
| RR *vs* placebo (95% CI), p value | .. | 0·81 (0·61 to 1·07), 0·13 | .. | 0·78 (0·50 to 1·22), 0·28 | .. | 0·84 (0·59 to 1·19), 0·32 | .. | 0·58 (0·39 to 0·85), 0·0061 | .. | 1·09 (0·74 to 1·61), 0·65 |
| HR for time to first event *vs* placebo (95% CI), p value | .. | 0·83 (0·61 to 1·12), 0·22 | .. | 0·88 (0·54 to 1·45), 0·62 | .. | 0·76 (0·52 to 1·12), 0·16 | .. | 0·57 (0·37 to 0·88), 0·011 | .. | 1·15 (0·75 to 1·77), 0·51 |
| **Severe acute exacerbations of COPD** | | | | | | | | | | |
| Adjusted annualised rate to week 52 (95% CI) | 0·33 (0·21 to 0·52) | 0·19 (0·11 to 0·32) | 0·46 (0·26 to 0·83) | 0·16 (0·07 to 0·37) | 0·13 (0·05 to 0·31) | 0·10 (0·04 to 0·26) | 0·36 (0·19 to 0·67) | 0·08 (0·03 to 0·20) | 0·20 (0·09 to 0·43) | 0·29 (0·14 to 0·60) |
| RR *vs* placebo (95% CI), p value | .. | 0·57 (0·28 to 1·15), 0·11 | .. | 0·34 (0·13 to 0·89), 0·028 | .. | 0·76 (0·27 to 2·14), 0·60 | .. | 0·23 (0·08 to 0·65), 0·0054 | .. | 1·45 (0·53 to 3·99), 0·47 |
| **Prebronchodilator $FEV_1$, L** | | | | | | | | | | |
| Least squares mean change from baseline (SE) at weeks 16–24 | 0·00 (0·02) | 0·06 (0·02) | 0·01 (0·03) | 0·12 (0·03) | −0·01 (0·02) | 0·01 (0·02) | −0·02 (0·02) | 0·07 (0·02) | 0·02 (0·03) | 0·05 (0·03) |
| Least squares mean difference *vs* placebo (95% CI) at weeks 16–24 | .. | 0·06 (0·01 to 0·10), 0·024 | .. | 0·12 (0·02 to 0·21), 0·016 | .. | 0·02 (−0·03 to 0·07), 0·46 | .. | 0·09 (0·02 to 0·15), 0·0076 | .. | 0·02 (−0·05 to 0·09), 0·54 |

Eosinophil counts are based on values at the baseline visit. The p value for interaction for baseline blood eosinophils is 0·88 for moderate-to-severe acute exacerbations and 0·055 for prebronchodilator $FEV_1$, and for smoking status, it is 0·023 for moderate-to-severe acute exacerbations and 0·17 for prebronchodilator $FEV_1$. COPD=chronic obstructive pulmonary disease. HR=hazard ratio. mITT=modified intention-to-treat. RR=relative risk.

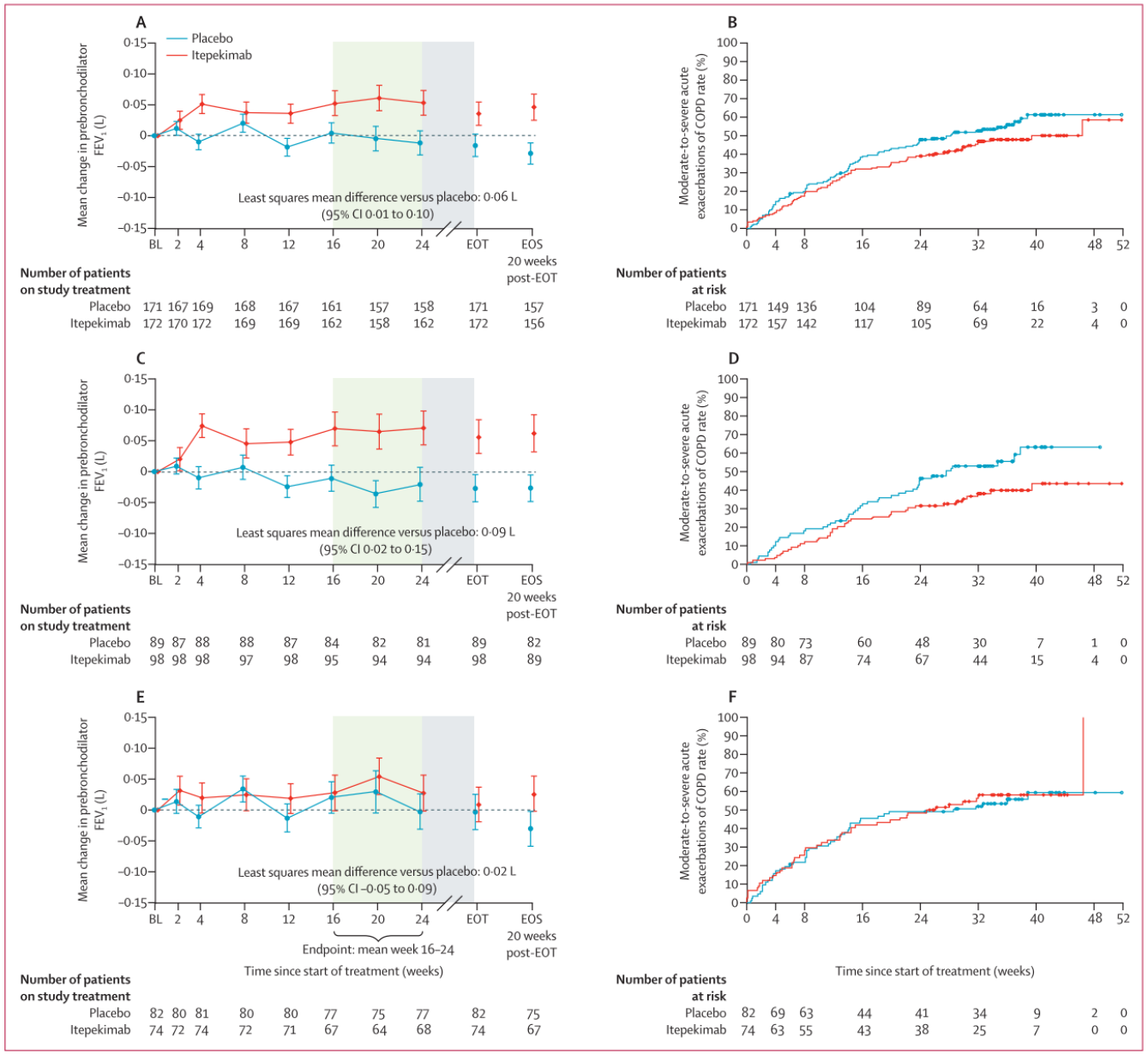
***Table 2:*** **Efficacy outcomes in the mITT population and relevant mITT subgroups**

Lancet Respir Med. 2021 Nov;9(11):1288-1298

Overall

Former smoker

Current smoker




Lancet Respir Med. 2021 Nov;9(11):1288-1298

# Phase 3 study protocol of Itepekimab

ERJ OPEN RESEARCH
STUDY PROTOCOL
K.F. RABE ET AL.

## AERIFY-1/2: two phase 3, randomised, controlled trials of itepekimab in former smokers with moderate-to-severe COPD

Klaus F. Rabe[1,2,3], Fernando J. Martinez[4], Surya P. Bhatt[5], Tomotaka Kawayama[6], Borja G. Cosio[7], Robert M. Mroz[8], Maarten M. Boomsma[9], Helene Goulaouic[10], Michael C. Nivens[11], Michel Djandji[12], Xavier Soler[11], Ying Liu[13], Matthew P. Kosloski[11], Christine R. Xu[13], Nikhil Amin[11], Heribert Staudinger[13], David J. Lederer[11] and Raolat M. Abdulai[14]

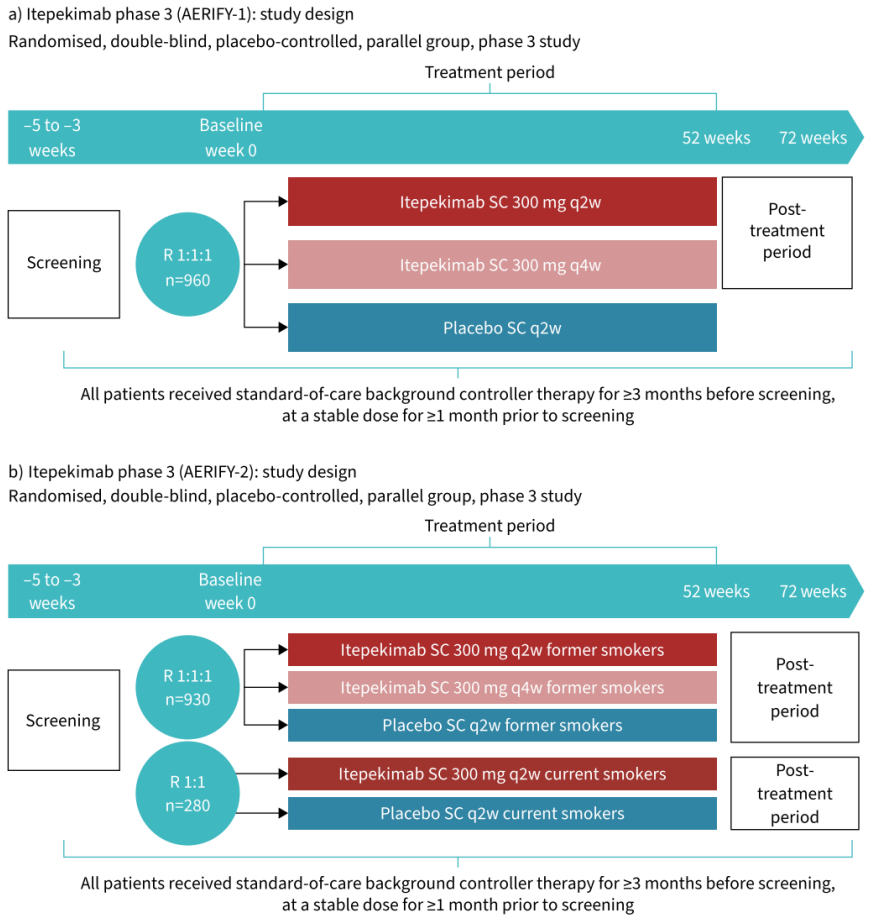



FIGURE 2 Itepekimab phase 3 study design: a) AERIFY-1; b) AERIFY-2. R: randomisation; SC: subcutaneous; q2w: every 2 weeks; q4w: every 4 weeks.

Rabe et al. ERJ Open Res. 2024

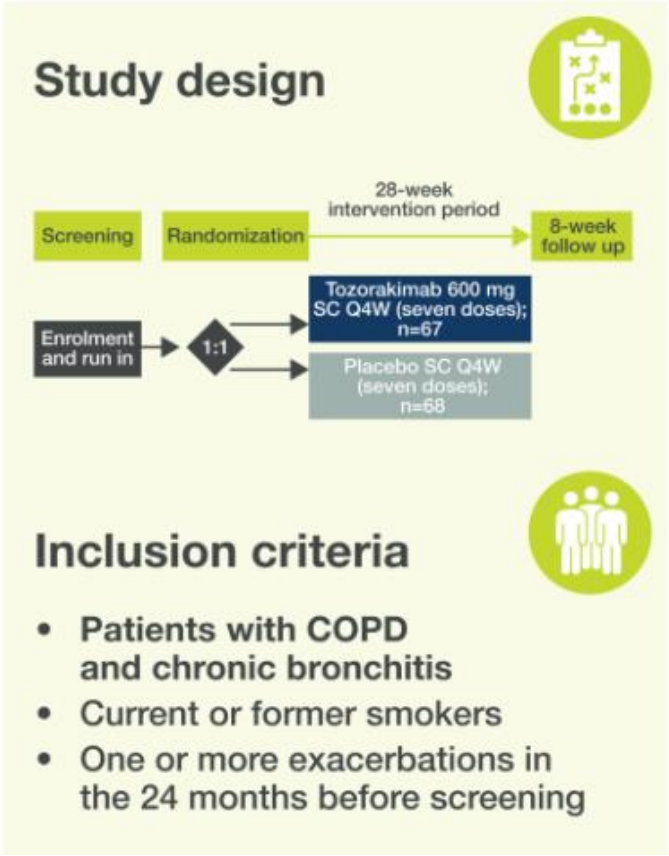
# Tozorakimab (Anti-IL-33)

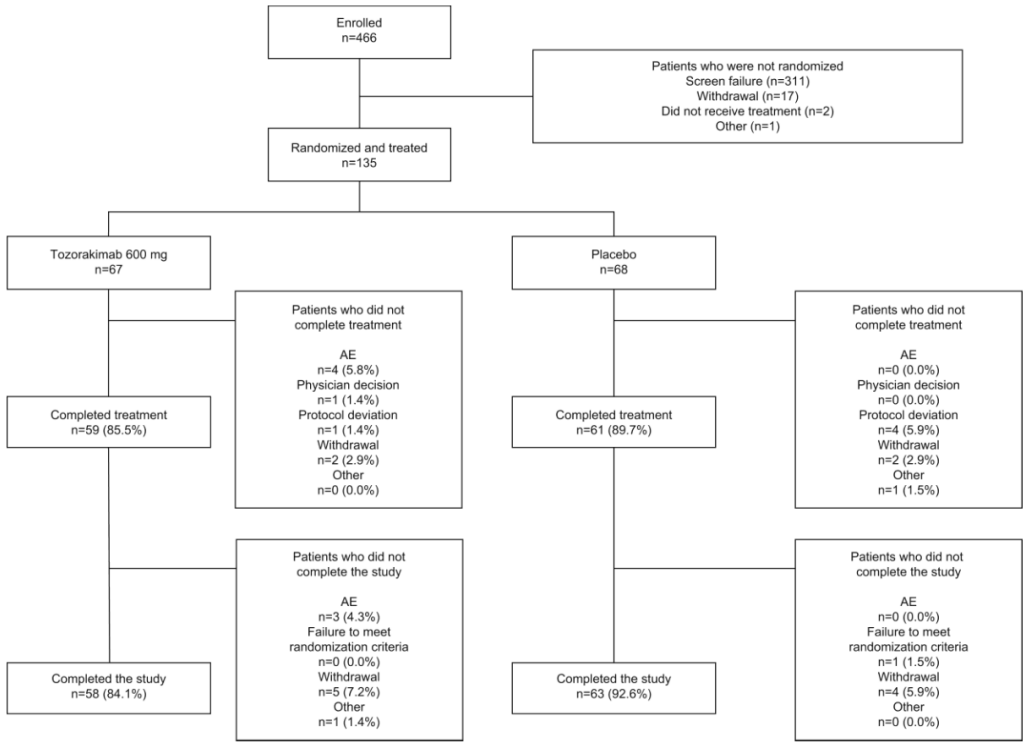
EUROPEAN RESPIRATORY *journal*
FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original Research Article

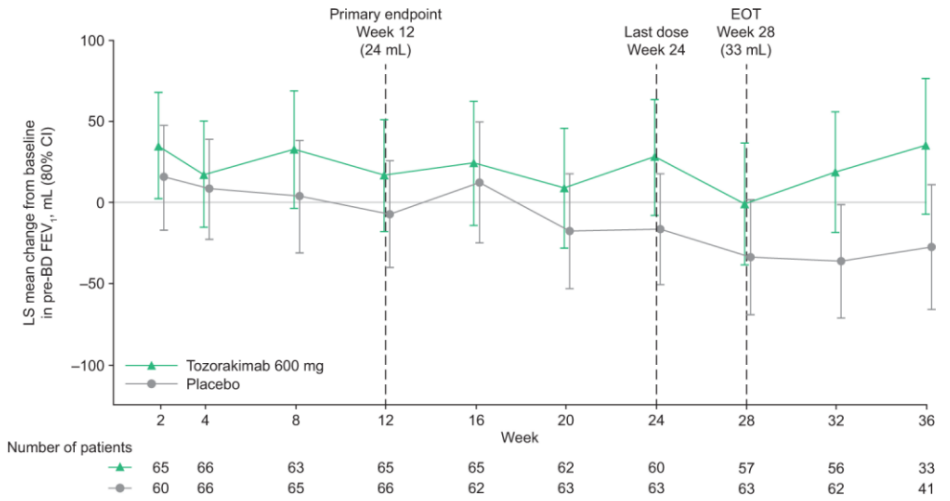
**A phase 2a trial of the IL-33 mAb tozorakimab in patients with COPD: FRONTIER-4**



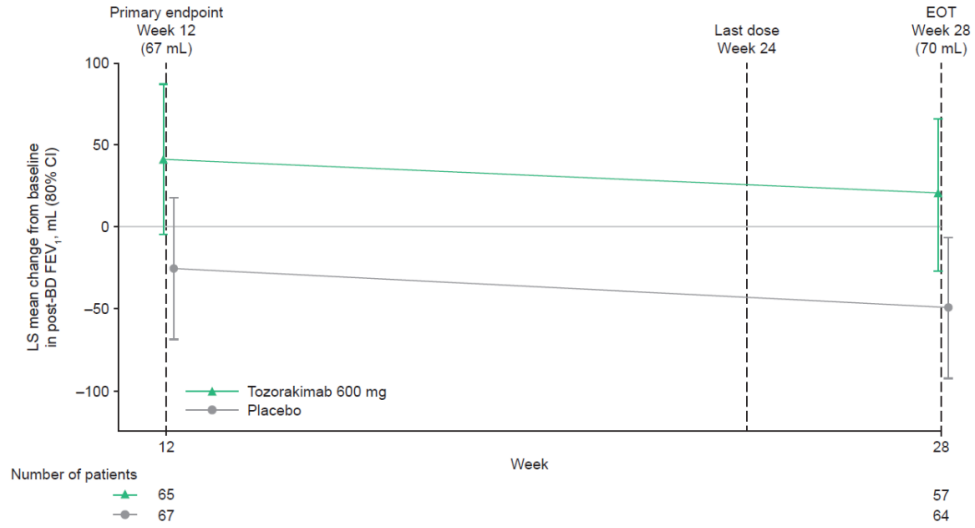




Eur Respir J. 2025.

## Pre-BD FEV1




## Post-BD FEV1




| Subgroup | Treatment | Pre-BD $FEV_1$ | | Post-BD $FEV_1$ | |
|---|---|---|---|---|---|
| | | Change from baseline to week 12, mean (SE), mL | Difference vs placebo Mean (80% CI), mL | Change from baseline to week 12, mean (SE), mL | Difference vs placebo Mean (80% CI), mL |
| ITT population | Tozorakimab 600 mg (n=67) | 19 (26) | 24 (−15, 63) *p*=0.216 | 41 (36) | 67 (17, 116) *p*=0.044 |
| | Placebo (n=68) | −5 (25) | N/A | −25 (34) | N/A |
| ≤1 exacerbation in last 12 months | Tozorakimab 600mg (n=41) | −14 (31) | −8 (−59, 43) *p*=0.418 | 1 (40) | 31 (−34, 96) *p*=0.269 |
| | Placebo (n=35) | −5 (32) | - | −31 (42) | - |
| ≥2 exacerbations in last 12 months | Tozorakimab 600mg (n=26) | 61 (38) | 69 (9, 130) *p*=0.072 | 103 (50) | 124 (47, 201) *p*=0.020 |
| | Placebo (n=33) | −8 (34) | - | −21 (44) | - |
| Baseline BEC <150 cells/µL | Tozorakimab 600 mg (n=37) | −12 (32) | −25 (−77, 28) *p*=0.275 | 5 (42) | -3 (−71, 64) *p*=0.474 |
| | Placebo (n=36) | 12 (31) | N/A | 8 (41) | N/A |
| Baseline BEC ≥150 cells/µL | Tozorakimab 600 mg (n=30) | 57 (35) | 82 (26, 138) *p*=0.031 | 97 (46) | 155 (84, 227) *p*=0.003 |
| | Placebo (n=32) | −25 (35) | N/A | −59 (45) | N/A |
| Current smokers | Tozorakimab 600 mg (n=24) | 42 (40) | 25 (−36, 86) *p*=0.300 | 21 (53) | 57 (−22,135) *p*=0.177 |
| | Placebo (n=32) | 17 (33) | N/A | −36 (43) | N/A |
| Former smokers | Tozorakimab 600 mg (n=43) | 5 (31) | 32 (−19, 83) *p*=0.208 | 49 (41) | 66 (1,131) *p*=0.098 |
| | Placebo (n=36) | −27 (33) | N/A | −17 (43) | N/A |

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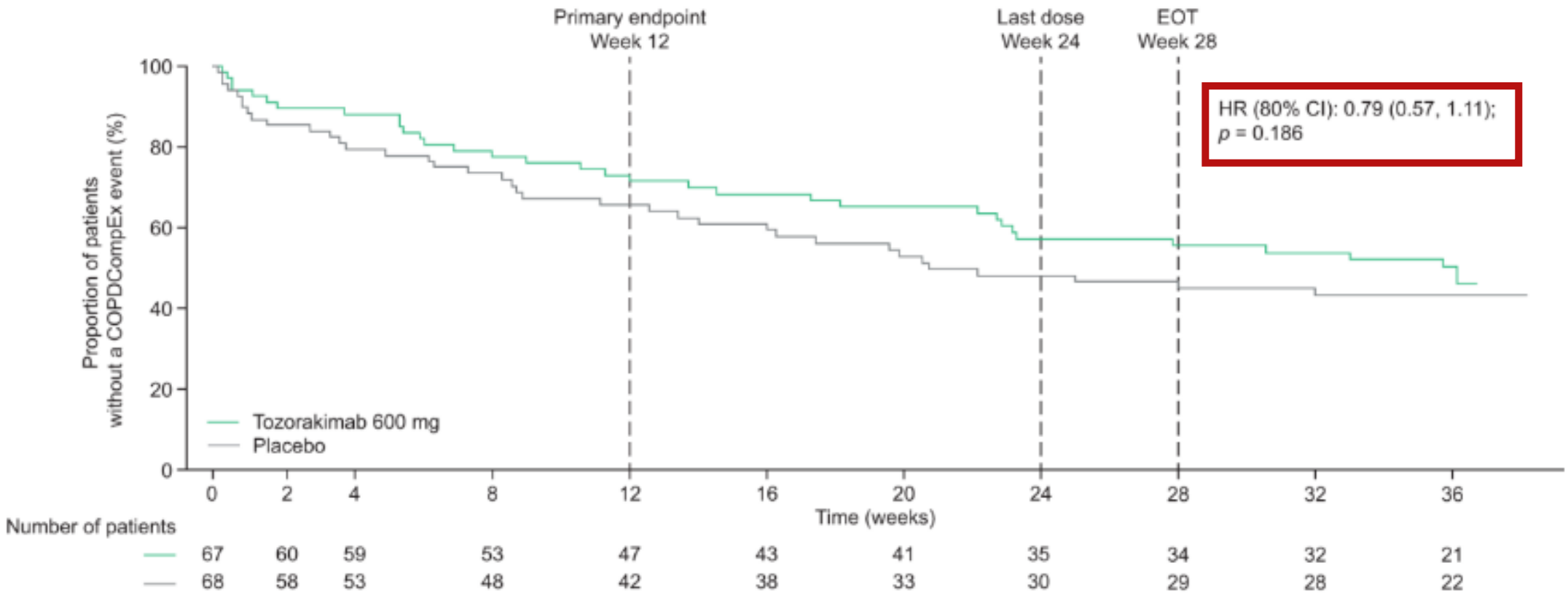
# Time to first exacerbation

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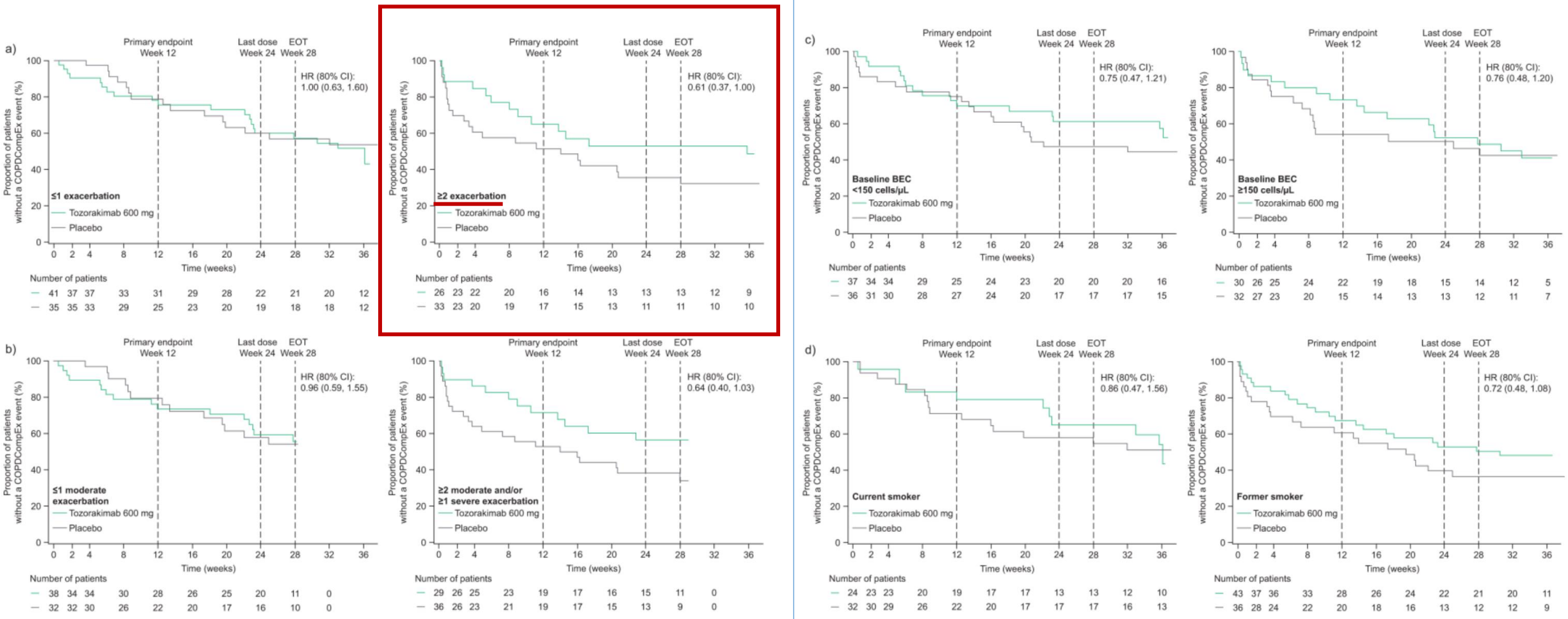
# Time to first exacerbation –Subgroup analysis

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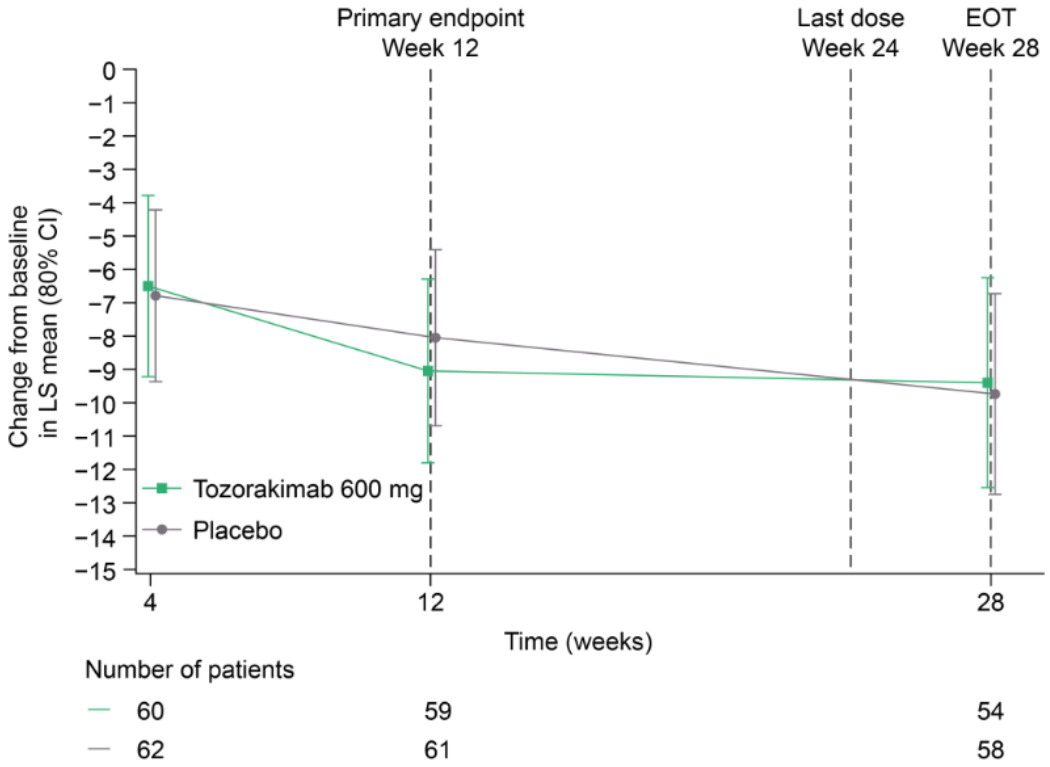
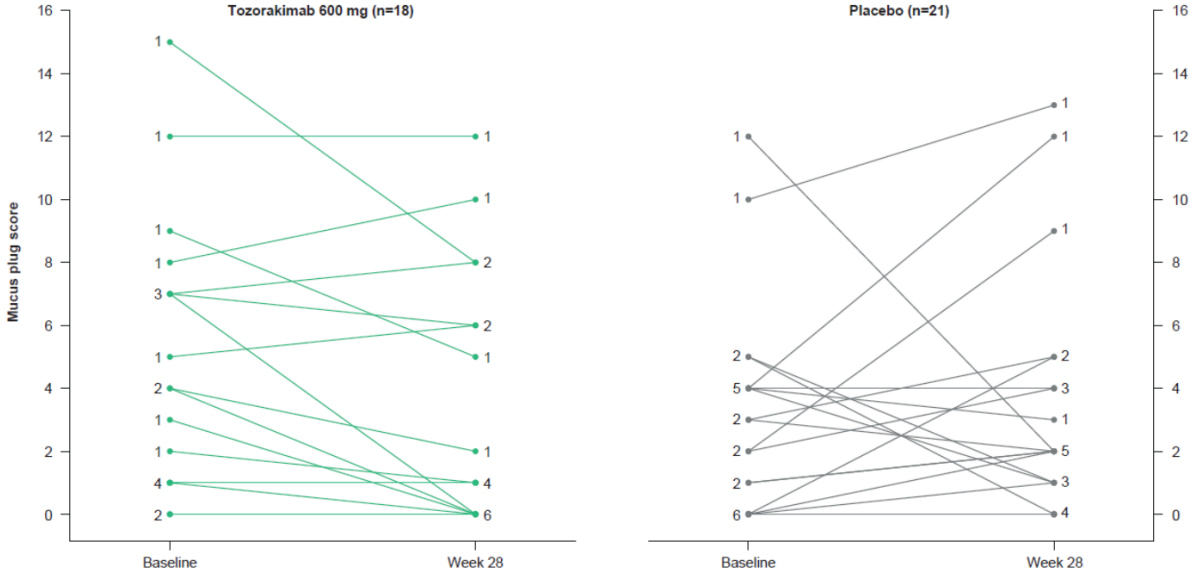
## SGRQ

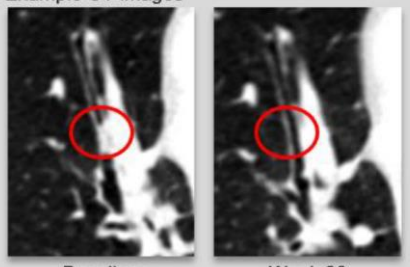



## Mucus plug




| Baseline mucus score category | Tozorakimab, n | Placebo, n |
|---|---|---|
| Zero | 2 | 6 |
| Low (1–3) | 6 | 6 |
| High (≥4) | 10 | 9 |

The change in mucus plugging in RB3 airway in a patient treated with tozorakimab
Example CT images

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# Targeting alarmins

## 3) Anti-ST2 (Astegolimab)

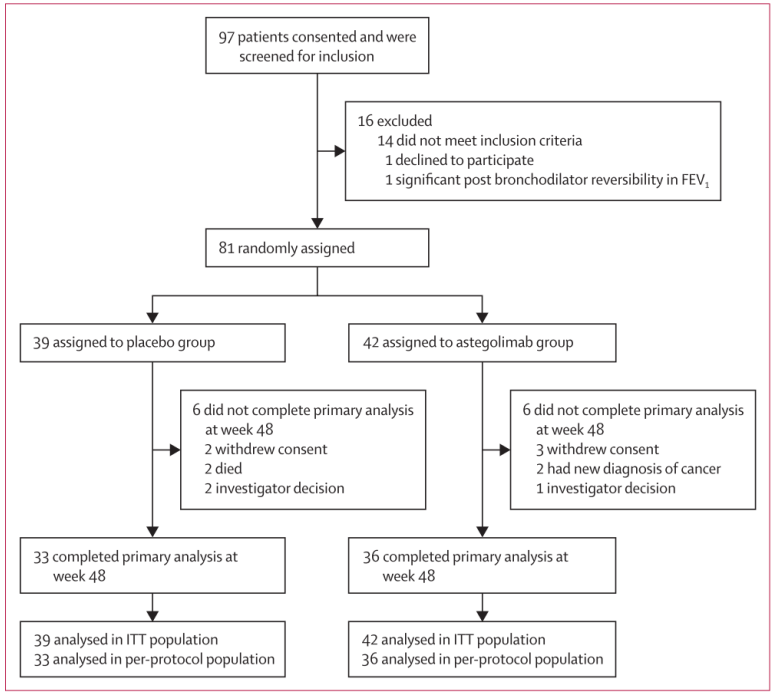
# Astegolimab, an anti-ST2, in chronic obstructive pulmonary disease (COPD-ST2OP): a phase 2a, placebo-controlled trial

*Ahmed J Yousuf, Seid Mohammed, Liesl Carr, Mohammadali Yavari Ramsheh, Claudia Micieli, Vijay Mistry, Kairobi Haldar, Adam Wright, Petr Novotny, Sarah Parker, Sarah Glover, Joanne Finch, Niamh Quann, Cassandra L Brookes, Rachel Hobson, Wadah Ibrahim, Richard J Russell, Catherine John, Michele A Grimbaldeston, David F Choy, Dorothy Cheung, Michael Steiner, Neil J Greening*, Christopher E Brightling**

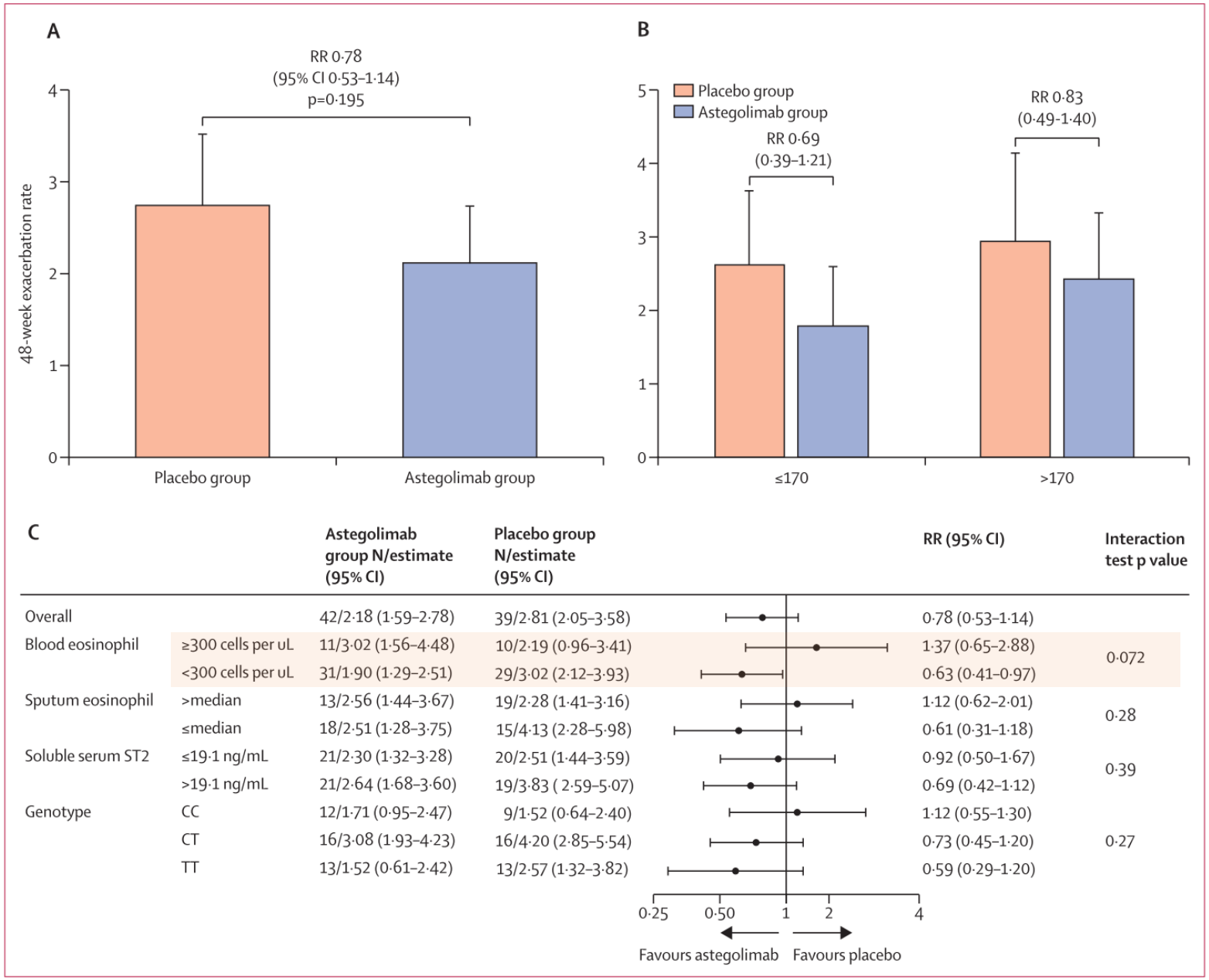
- Single-center, phase 2a RCT
- Aged ≥ 40
- Moderate-to-very severe COPD
- ≥ two acute exacerbations of COPD
- ≥ 10PY of smoking Hx.
- mMRC ≥ 2

- Randomly assigned (1:1) to receive astegolimab or placebo s.c.

- The primary endpoint : exacerbation rate assessed for 48 weeks
- Prespecified subgroup analysis by baseline blood eosinophil count
- Secondary endpoints : SGRQ-C, FEV1, blood and sputum cell counts
- Safety was assessed




Lancet Respir Med. 2022 May;10(5):469-477.

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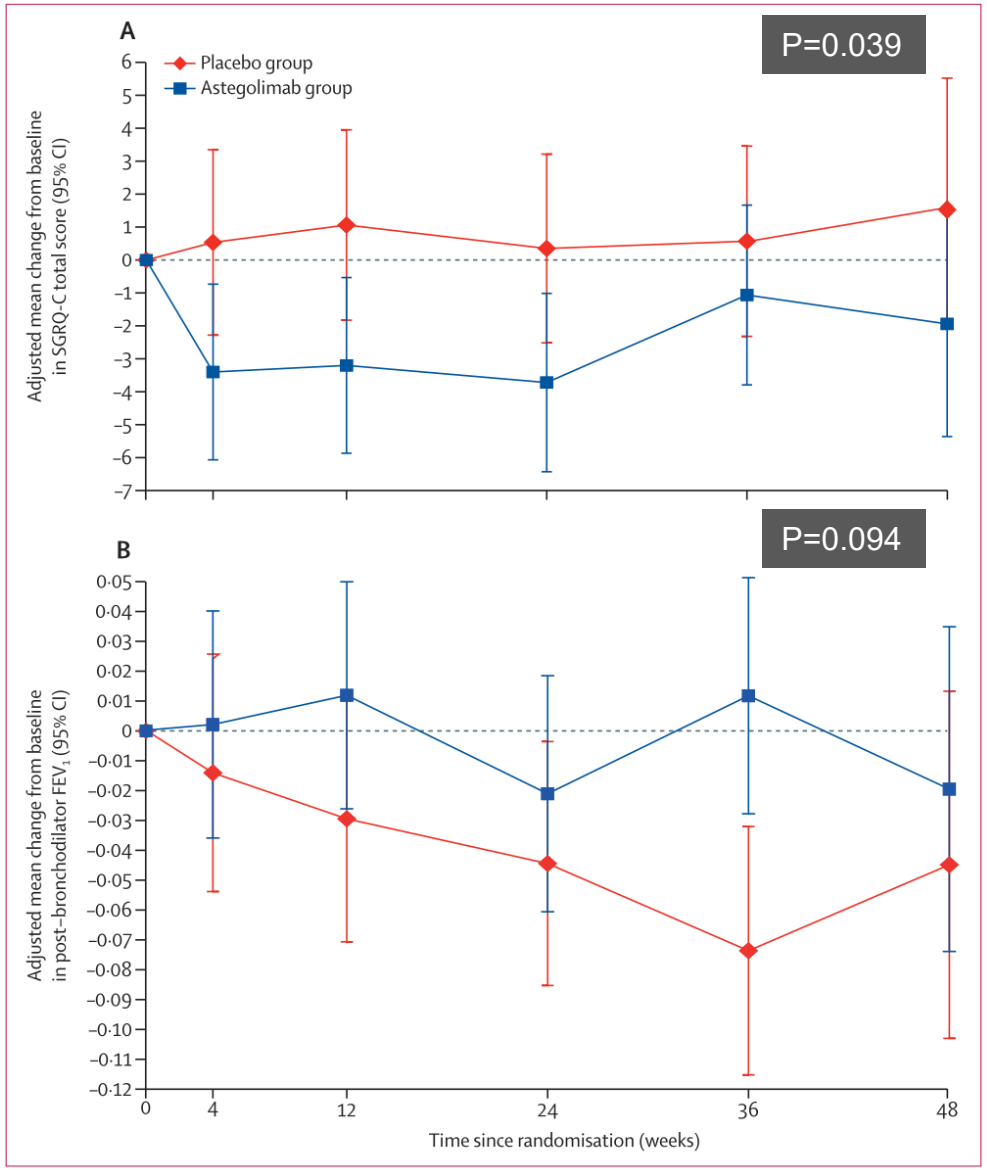
| | | Astegolimab group N/estimate (95% CI) | Placebo group N/estimate (95% CI) | RR (95% CI) | Interaction test p value |
|---|---|---|---|---|---|
| Overall | | 42/2·18 (1·59–2·78) | 39/2·81 (2·05–3·58) | 0·78 (0·53–1·14) | |
| Blood eosinophil | ≥300 cells per uL | 11/3·02 (1·56–4·48) | 10/2·19 (0·96–3·41) | 1·37 (0·65–2·88) | 0·072 |
| | <300 cells per uL | 31/1·90 (1·29–2·51) | 29/3·02 (2·12–3·93) | 0·63 (0·41–0·97) | |
| Sputum eosinophil | >median | 13/2·56 (1·44–3·67) | 19/2·28 (1·41–3·16) | 1·12 (0·62–2·01) | 0·28 |
| | ≤median | 18/2·51 (1·28–3·75) | 15/4·13 (2·28–5·98) | 0·61 (0·31–1·18) | |
| Soluble serum ST2 | ≤19·1 ng/mL | 21/2·30 (1·32–3·28) | 20/2·51 (1·44–3·59) | 0·92 (0·50–1·67) | 0·39 |
| | >19·1 ng/mL | 21/2·64 (1·68–3·60) | 19/3·83 ( 2·59–5·07) | 0·69 (0·42–1·12) | |
| Genotype | CC | 12/1·71 (0·95–2·47) | 9/1·52 (0·64–2·40) | 1·12 (0·55–1·30) | |
| | CT | 16/3·08 (1·93–4·23) | 16/4·20 (2·85–5·54) | 0·73 (0·45–1·20) | 0·27 |
| | TT | 13/1·52 (0·61–2·42) | 13/2·57 (1·32–3·82) | 0·59 (0·29–1·20) | |



Lancet Respir Med. 2022 May;10(5):469-477.

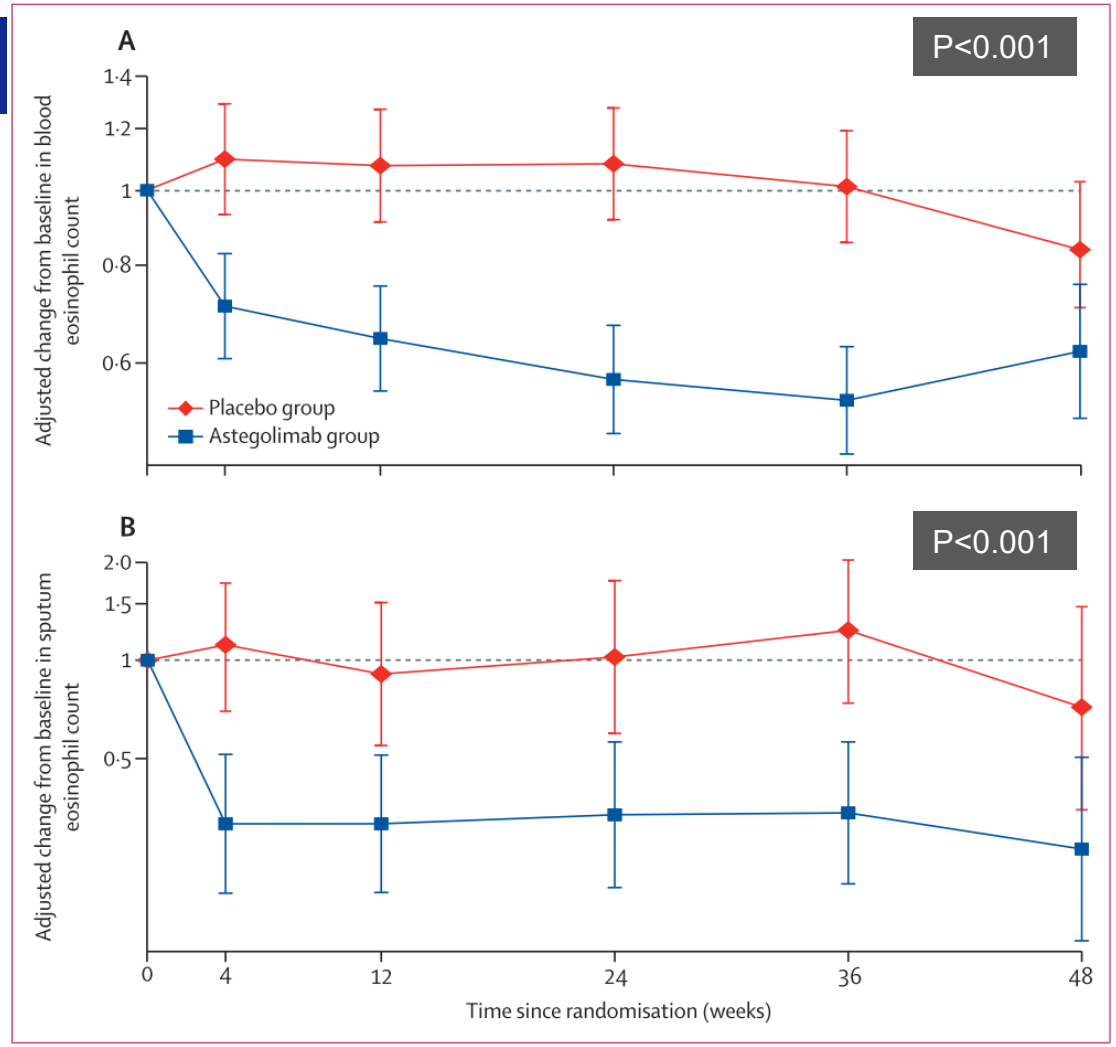
SGRQ-C

FEV$_1$




Blood eosinophil

Sputum eosinophil




Lancet Respir Med. 2022 May;10(5):469-477.

Recruiting

# A Study to Evaluate Astegolimab in Participants With Chronic Obstructive Pulmonary Disease (ARNASA)

**ClinicalTrials.gov ID** NCT05595642

**Sponsor** Hoffmann-La Roche

**Information provided by** Hoffmann-La Roche (Responsible Party)

**Last Update Posted** 2025-06-04

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**Study Details** | Researcher View | No Results Posted | Record History

On this page



## Study Overview

**Brief Summary**

This study will evaluate the efficacy and safety of astegolimab compared with placebo in participants with chronic obstructive pulmonary disease (COPD) who are former or current smokers and have a history of frequent exacerbations.

**Official Title**

A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Astegolimab in Patients With Chronic Obstructive Pulmonary Disease

**Conditions**

Chronic Obstructive Pulmonary Disease (COPD)

**Intervention / Treatment**

- Drug: Astegolimab
- Drug: Placebo

**Other Study ID Numbers**

- GB44332

**Study Start (Actual)**

2022-12-29

**Primary Completion (Estimated)**

2025-06-30

**Study Completion (Estimated)**

2027-03-11

**Enrollment (Estimated)**

1290

**Study Type**

Interventional

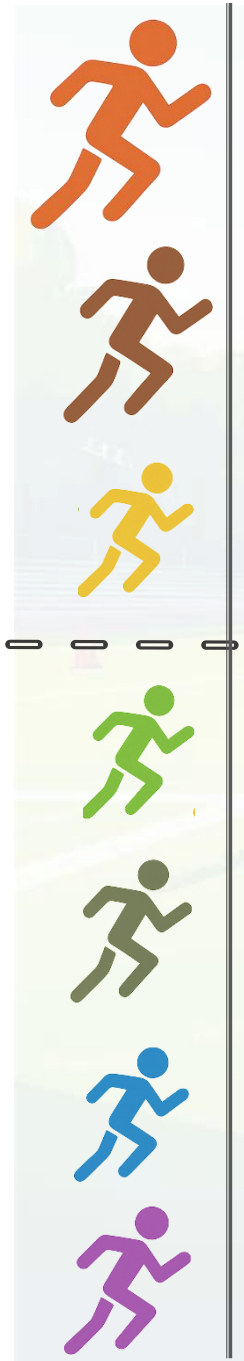
**Phase**

Phase 3

**Dupilumab**
- Exacerbator
- EOS≥ 300
- CB (+)

**Mepolizumab**
- Exacerbator
- EOS≥ 300

**Benralizumab**
- Exacerbator
- EOS≥ 220



Phase I — Phase IIa — Phase III

**Tezepelumab**
- Exacerbator

**Itepekimab**
- Exacerbator
- CB (+)

**Tozorakimab**
- Exacerbator
- EOS≥ 300

**Astegolimab**
- Exacerbator

Exacerbation rescuer

BOREAS/NOCTUS
- Exacerbation ↓
- FEV1↑
- SGRQ↓

MATINEE
- Exacerbation ↓
- FEV1 (-)
- SGRQ (-)

GALATHEA+TERRANOVA
- Negative study

COURSE
- Exacerbation (-)
- FEV1 (-), SGRQ (-)
- T2-high → (+)

❖ Only in former smoker
- Exacerbation ↓
- FEV1 ↑

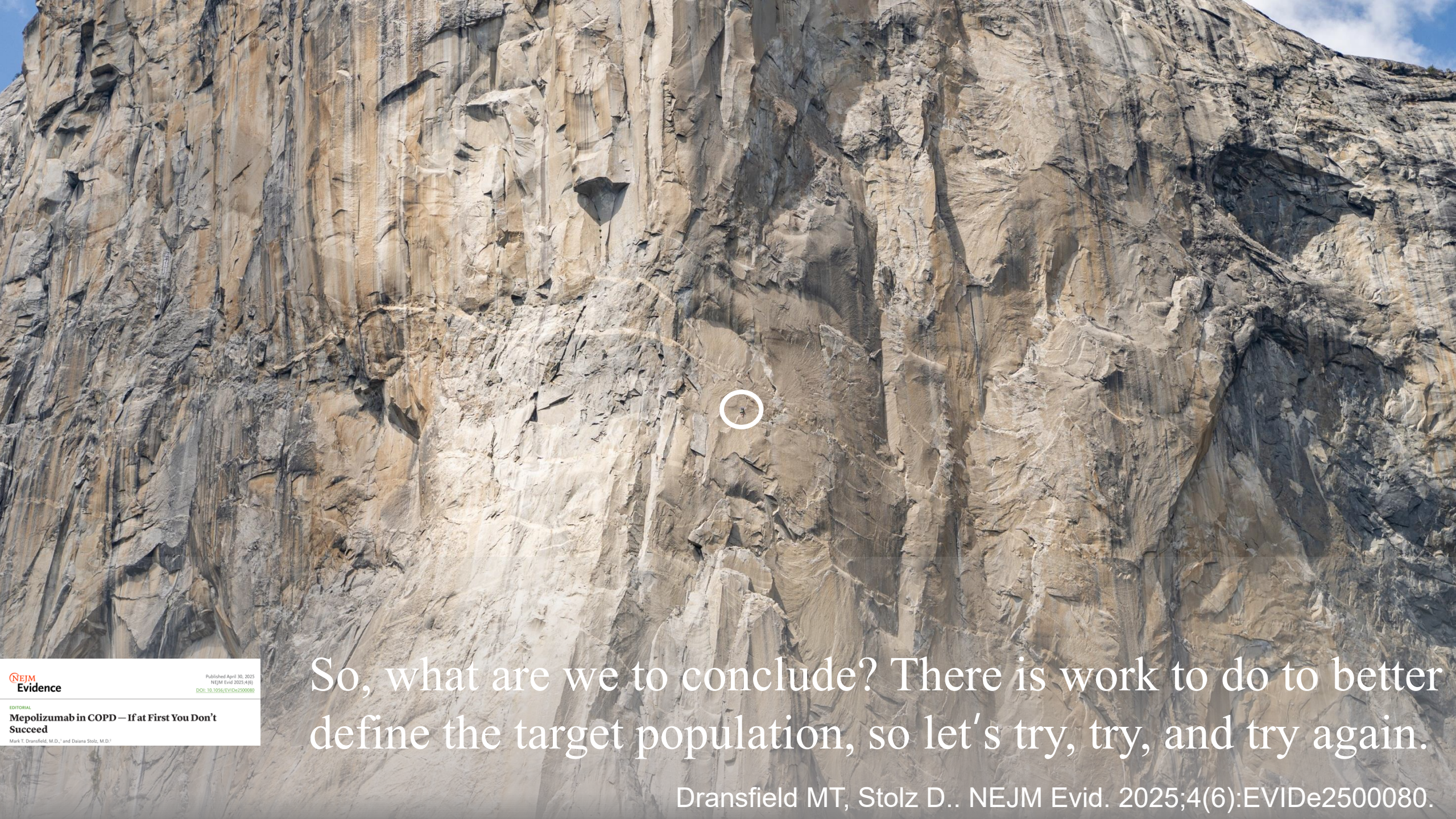
FRONTIER-4
❖ Only in exacerbators
- Exacerbation ↓
- FEV1 ↑ / Mucus ↓

COPD-ST2OP
❖ Only in EOS <300
- Exacerbation ↓
- SGRQ ↓ / FEV1 (-)

# Take home messages

- Failure of biologics targeting neutrophilic inflammations
  - Anti-IL-8/ Anti-CXCR2/ Anti-TNF-α/ Anti-IL-1/ Anti-17A

- Dupilumab : Significant effect in AE, FEV1 and SGRQ
- Mepolizumab : Significant effect in AE (controversial)
- Benralizumab : ↔ AE. Shown potential as an AE rescuer
- Tezepelumab, Itepekimab, Tozorakimab, Astegolimab
  : Further studies needed



NEJM Evidence

Published April 30, 2025
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DOI: 10.1056/EVIDe2500080

EDITORIAL

**Mepolizumab in COPD — If at First You Don't Succeed**

Mark T. Dransfield, M.D.,[1] and Daiana Stolz, M.D.[2]

So, what are we to conclude? There is work to do to better define the target population, so let′s try, try, and try again.

Dransfield MT, Stolz D.. NEJM Evid. 2025;4(6):EVIDe2500080.