Role of Biologics in COPD

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Review

trd
Tuberculosis & Respiratory Diseases

Biologics in Chronic Obstructive Pulmonary Disease: Current Status and Future Prospects

https://doi.org/10.4046/trd.2025.0180
ISSN: 1738-3536(Print)/
2005-6184(Online)
Tuberc Respir Dis 2026;89:121-132

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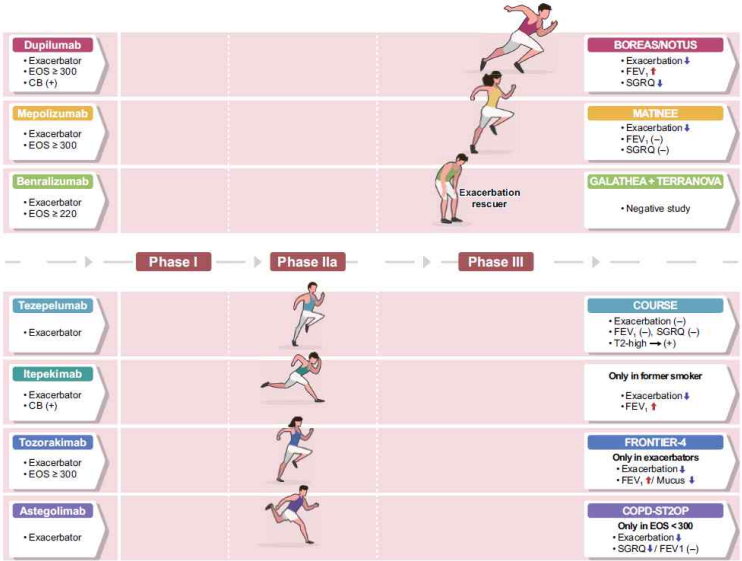
Table 1. Summary of key clinical trials of biologic therapies in COPD

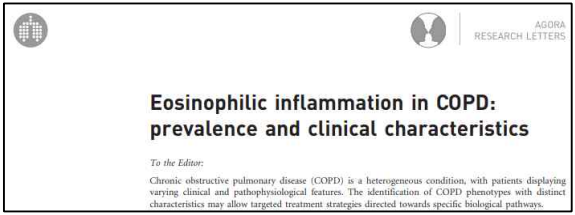
Target	Agent	Trial (phase)	Study population (key inclusion criteria)	Primary endpoint (exacerbation rate)	Key secondary outcomes& Subgroup findings	Reference
IL-4Rα	Dupilumab	BOREAS (Ph3)	BEC ≥300 cells/μL	Met (~30% vs. placebo)	Improved FEV_1 (mean difference, 83 mL) and SGRQ	17
		NOTUS (Ph3)	BEC ≥300 cells/μL	Met (~34% vs. placebo)	Confirmed efficacy in FEV_1 (mean difference, 82 mL) and SGRQ	18
IL-5	Mepolizumab	METREX (Ph3)	All comers (stratified by BEC)	Not met (overall)	Met in subgroup with BEC ≥150 cells/μL (~18%)	21
		METREO (Ph3)	BEC ≥150 cells/μL	Not met	Dose-response relationship observed with higher BEC	21
		MATINEE (Ph3)	BEC ≥300 cells/μL	Met (~21% vs. placebo)	No significant improvement in lung function or SGRQ	22
IL-5Rα	Benralizumab	GALATHEA & TERRANOVA (Ph3)	BEC ≥220 cells/μL	Not met	Failed to consistently reduce exacerbations	25
		RESOLUTE (Ph3)	BEC ≥300 cells/μL	Not met	Confirmed lack of prophylactic efficacy even in high eosinophil subgroup	27
IL-33	Itepekimab	Phase 2a	Mod-severe COPD (no BEC cutoff)	Not met (overall)	Met in former smokers (~42% exacerbations, 90 mL FEV_1)	39
ST2 (IL-33R)	Astegolimab	COPD-ST2OP (Ph2a)	Mod-severe COPD (no BEC cutoff)	Not met (overall)	Reduced exacerbations in low BEC (<300 cells/μL) subgroup (~37%)	42
		ALIENTO (Ph2b)	Mod-severe COPD	Met (~15.4% vs. placebo)	Trend towards benefit in non-eosinophilic subgroup, but not statistically significant	44,45
TSLP	Tezepelumab	COURSE (Ph2a)	Mod-severe COPD (no BEC cutoff)	Not met (overall)	Significant benefit in patients with BEC ≥150 cells/μL and FeNO ≥25 ppb	38

COPD: chronic obstructive pulmonary disease; IL: interleukin; Ph: phase; BEC: blood eosinophil count; FEV_1: forced expiratory volume in 1 second; SGRQ: St. George's Respiratory Questionnaire; Mod-severe: moderate-to-severe; ST2: suppression of tumorigenicity 2; TSLP: thymic stromal lymphopoietin; FeNO: fractional exhaled nitric oxide.


Dupilumab
• Exacerbator
• EOS ≥ 300
• CB (+)
BOREAS/NOTUS
• Exacerbation ↓
• FEV1 ↑
• SGRQ ↓
Mepolizumab
• Exacerbator
• EOS ≥ 300
MATINEE
• Exacerbation ↓
• FEV1 (–)
• SGRQ (–)
Benralizumab
• Exacerbator
• EOS ≥ 220
Exacerbation rescuer
GALATHEA + TERRANOVA
• Negative study
Phase I
Phase IIa
Phase III
Tezepelumab
• Exacerbator
COURSE
• Exacerbation (–)
• FEV1 (–), SGRQ (–)
• T2-high → (+)
Itepekimab
• Exacerbator
• CB (+)
Only in former smoker
• Exacerbation ↓
• FEV1 ↑
Tozorakimab
• Exacerbator
• EOS ≥ 300
FRONTIER-4
Only in exacerbators
• Exacerbation ↓
• FEV1 ↑/ Mucus ↓
Astegolimab
• Exacerbator
COPD-ST2OP
Only in EOS < 300
• Exacerbation ↓
• SGRQ ↓ / FEV1 (–)

Contents

Eosinophils as a Treatable Trait in COPD



AGORA
RESEARCH LETTERS

Eosinophilic inflammation in COPD: prevalence and clinical characteristics

To the Editor:

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition, with patients displaying varying clinical and pathophysiological features. The identification of COPD phenotypes with distinct characteristics may allow targeted treatment strategies directed towards specific biological pathways.

- ECLIPSE study
- Eosinophil - baseline, 1년, 2년, 3년에 반복 측정
- 추적 기간 동안 계속 ≥2%이면 persistently eosinophilic, 계속 <2%이면 persistently non-eosinophilic, 왔다 갔다 하면 intermittent로 분류

	Persistently ≥2%	Intermittent	Persistently <2%
Subjects n	554 37.4%	728 49.0%	201 13.6%

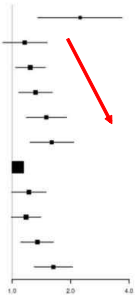
Eur Respir J. 2014 Dec;44(6):1697-700

Eosinophilia is common in COPD

C

COPDGene : 24%, 366/1553

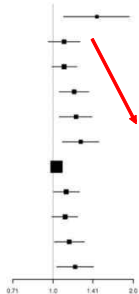
Eosinophil Cutoff	< n	≥ n	IRR	95% CI
cell/uL continuous	NA	1540	2.24	1.35-3.68
100 cells/uL	223	1330	1.16	0.90-1.52
200 cells/uL	814	739	1.24	1.04-1.48
300 cells/uL	1187	366	1.32	1.08-1.61
340 cells/uL	1350	203	1.5	1.18-1.91
400 cells/uL	1398	155	1.6	1.24-2.08
% continuous	NA	1540	1.07	1.02-1.11
2 %	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



C

ECLIPSE : 22%, 418/1895

Eosinophil Cutoff	< n	≥ n	IRR	95% CI
continuous cells/uL	NA	1895	1.46	1.09-1.93
100 cells/uL	368	1527	1.1	0.96-1.26
200 cells/uL	1032	863	1.1	0.99-1.23
300 cells/uL	1477	418	1.2	1.05-1.36
340 cells/uL	1584	311	1.22	1.06-1.40
400 cells/uL	1668	227	1.27	1.08-1.48
continuous %	NA	1895	1.03	1.01-1.06
2 %	720	1175	1.12	1.00-1.25
3 %	1178	717	1.11	0.99-1.24
4 %	1476	419	1.15	1.01-1.31
5 %	1660	235	1.21	1.03-1.42



- Blood eosinophils predict exacerbation risk in COPD

J Allergy Clin Immunol. 2018 June ; 141(6): 2037–2047

Eosinophilia independently predicts exacerbation risk

	COPDGene: Year Prior to Visit 2 (Cross sectional)			
	Exacerbation Frequency * (n=1553)		Frequent Exacerbations † (n=1281)	
Factors	**IRR * (95% CI)**	**p value**	**OR † (95% CI)**	**p value**
Age	**0.98 (0.97–1.00)**	**0.007**	**0.96 (0.94–0.99)**	**0.003**
Female	**1.43 (1.20–1.71)**	**<0.001**	**1.83(1.30–2.58)**	**<0.001**
Non White Race	**0.73 (0.57–0.92)**	**0.008**	**0.63(0.40–0.99)**	**0.05**
SGRQ total score #	**1.02 (1.02–1.03)**	**<0.001**	**1.04(1.03–1.05)**	**<0.001**
post-bronchodilator FEV_1 % predicted §	**0.98 (0.98–0.99)**	**<0.001**	**0.97(0.96–0.98)**	**<0.001**
GERD	**1.33 (1.11–1.59)**	**0.002**	**1.35(0.95–1.91)**	**0.09**
Current smoking	**0.71(0.57–0.89)**	**0.002**	**0.56(0.37–0.84)**	**0.006**
Previous Exacerbations	NA	NA	NA	NA
WBC	1.00 (0.96–1.04)	0.97	1.02(0.94–1.10)	0.66
Eosinophil ≥300	**1.32 (1.08–1.61)**	**0.006**	**1.58(1.07–2.30)**	**0.019**

	ECLIPSE			
	1 year		overall study period	
Factors associated with Exacerbation Rate	**IRR (95% CI)**	**p value**	**IRR (95% CI)**	**p value**
Age	**1.01 (1.00–1.02)**	**0.008**	**1.01 (1.00–1.02)**	**0.01**
Female	**1.23 (1.10–1.38)**	**<0.001**	**1.31 (1.15–1.49)**	**<0.001**
Non White race	0.82(0.56–1.18)	0.29	0.71(0.45–1.08)	0.12
SGRQ total score #	**1.01 (1.01–1.01)**	**<0.001**	**1.01 (1.01–1.01)**	**<0.001**
Post-bronchodilator FEV_1 % predicted †	**0.99 (0.98–0.99)**	**<0.001**	**0.98 (0.97–0.98)**	**<0.001**
GERD	**1.39 (1.24–1.56)**	**<0.001**	**1.36 (1.19–1.56)**	**<0.001**
Current smoking	1.10(0.98–1.24)	0.11	**1.21(1.06–1.39)**	**0.005**
previous exacerbations	**2.45 (2.18–2.74)**	**<0.001**	**2.87 (2.51–3.29)**	**<0.001**
WBC	**1.04 (1.01–1.06)**	**0.001**	**1.04 (1.02–1.07)**	**<0.001**
Eosinophil ≥300 at screening	**1.20 (1.05–1.36)**	**0.005**	**1.22 (1.06–1.42)**	**0.006**

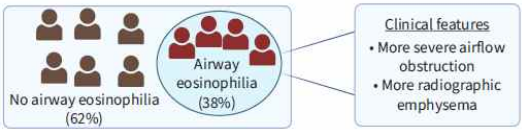
J Allergy Clin Immunol. 2018 June ; 141(6): 2037–2047

Airway eosinophilia reflects type 2 airway biology

EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
C. LEUNG ET AL.

Transcriptomic profiling of the airway epithelium in COPD links airway eosinophilia to type 2 inflammation and corticosteroid response

Clarus Leung, Hye Yun Park, Xuan Li, Graeme J. Koelwyn, Josie Tuong, Seyed Milad Vahedi, Fernando Sergio Leitao Filho, Julia S. Yang, Rachel L. Eddy, Stephen Milne, Min Hyung Ryu, Hiroto Takiguchi, Kentaro Akata, Seung Won Ra, Ji-Yong Moon, Hyun Kuk Kim, Yuji Cho, Kei Yamasaki, Stephan F. van Eeden, Tawimas Shaipanich, Stephen Lam, Janice M. Leung and Don D. Sin



Airway eosinophilia reflects selective type 2 biology

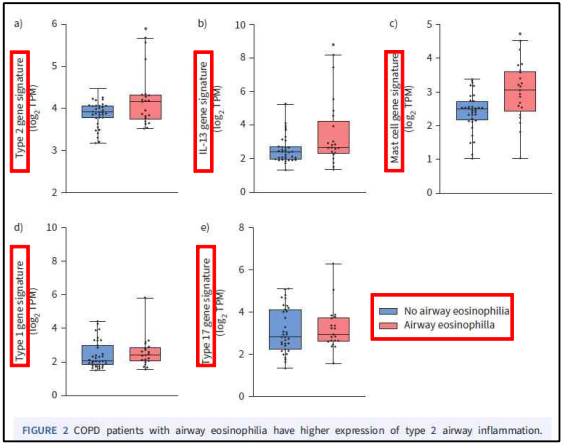


FIGURE 2 COPD patients with airway eosinophilia have higher expression of type 2 airway inflammation.

- Airway eosinophilia was linked to higher type 2, IL-13, and mast cell gene signatures — but not type 1 or type 17 signatures.

Blood eosinophils: a practical, but imperfect, marker of type 2 COPD

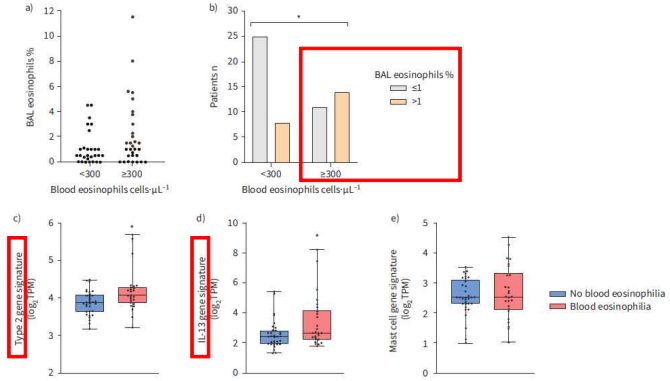


FIGURE 5 Relationship between eosinophil levels in the blood and in the airways and characterisation of type 2 airway inflammation in COPD

Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials

Mona Bafadhel, Stefan Peterson, Miguel A De Blas, Peter M Calverley, Stephen I Rennard, Kai Richter, Malin Fagerås

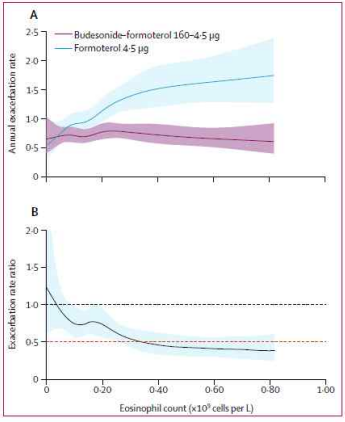


Figure 1: Exacerbation rate by eosinophil count

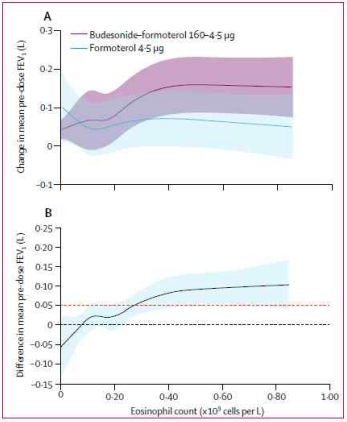


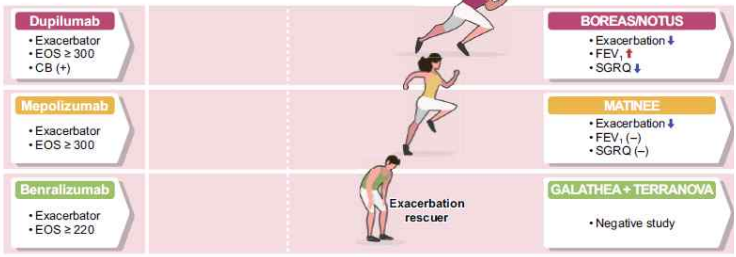
Figure 3: Mean pre-bronchodilator FEV_1 by eosinophil count*

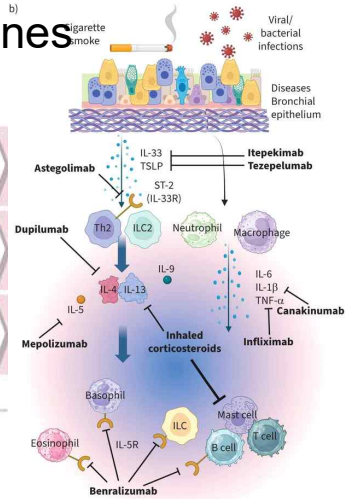
Lancet Respir Med. 2018 Feb;6(2):117-126.

Why Biologics Matter in COPD

- Eosinophilic COPD is not merely a biomarker-defined subgroup ; it represents a treatable biology.
- Eosinophilia in COPD suggests that:
  - A sizable subgroup of COPD patients has elevated blood or airway eosinophils
  - Eosinophilia is associated with increased exacerbation risk
  - Airway eosinophilia reflects type 2 epithelial biology
  - Higher eosinophils predict greater corticosteroid responsiveness
- Targeting type 2 inflammation may provide additional benefit beyond conventional inhaled therapy in selected COPD patients.

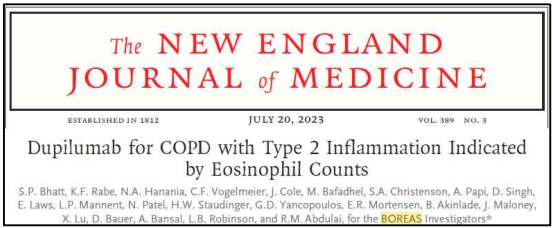
Biologics Targeting Type 2 cytokines





Eur Respir J. 2024 May 28;63(5):2400150.
Tuberc Respir Dis (Seoul). 2026 Apr;89(2):121-132

Anti-IL4R (Dupilumab)

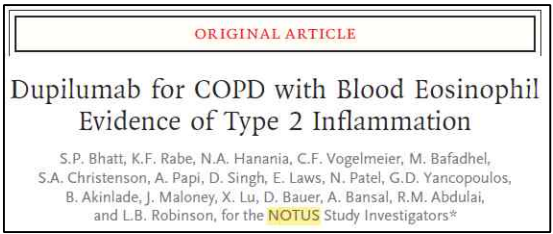


The NEW ENGLAND JOURNAL of MEDICINE

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*



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*

- dupilumab 300 mg every 2 weeks
- Eosinophils: ≥300 cells/μL during screening

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

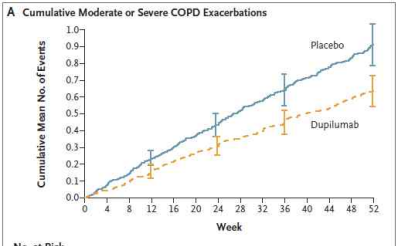


Table 2. End Points Corrected for Multiplicity (Intention-to-Treat Population).*

End Point	Placebo (N=471)	Dupilumab (N=468)	P Value
Primary end point			
Annualized rate of moderate or severe exacerbations of COPD			
Adjusted annualized rate of moderate or severe exacerbations — events per yr (95% CI)	1.10 (0.93 to 1.30)	0.78 (0.64 to 0.93)	
Rate ratio vs. placebo (95% CI)	—	0.70 (0.58 to 0.86)	<0.001

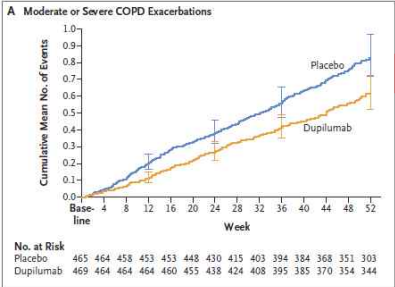


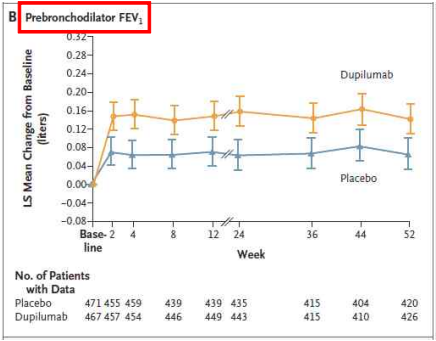
Table 2. Summary of End Points Included in the Hierarchical Testing Procedure.

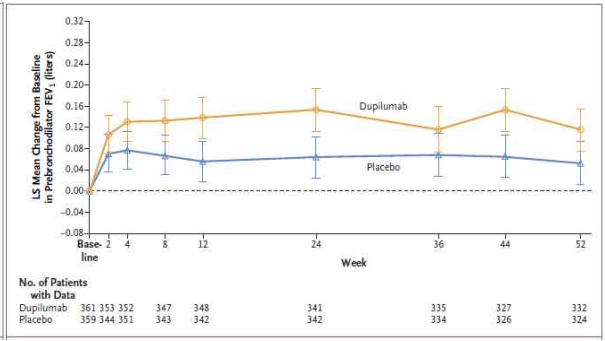
End Point*	Placebo (N=465)	Dupilumab (N=470)	P Value
Primary end point			
Annualized rate of moderate or severe exacerbations of COPD			
Adjusted annualized rate of moderate or severe exacerbations — no. of events/yr (95% CI)	1.30 (1.05 to 1.60)	0.86 (0.70 to 1.06)	
Rate ratio vs. placebo (95% CI)	—	0.66 (0.54 to 0.82)	<0.001

- Consistent efficacy in reducing AE
  - BOREAS: 30% reduction in AE
  - NOTUS: 34% reduction in AE

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

Dupilumab improved pre-bronchodilator FEV1, with early and sustained





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

Pooled analysis of BOREAS and NOTUS

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

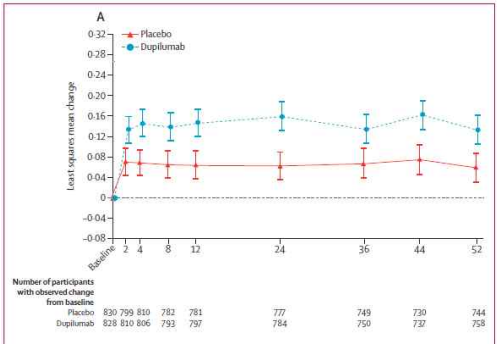
Surya P Bhatt, Klaus F Rabe*, Nicola A Hanania, Claus F Vogelmeier, Mona Bafadhel, Stephanie A Christenson, Alberto Papi, Dave Singh, Elizabeth Laws, Paula Dakin, Jennifer Maloney, Xin Lu, Deborah Bauer, Ashish Bansal, Raolat M Abdulai, Lacey B Robinson*

	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

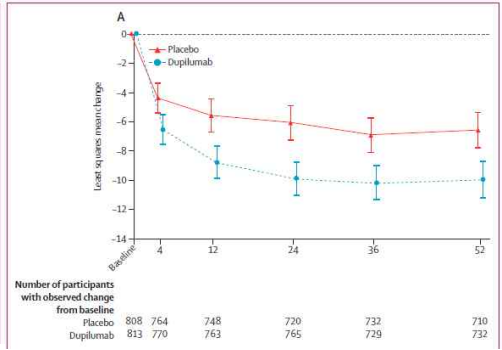
→ 31.3% reduction in mod/severe AE

Lancet Respir Med. 2025 Mar;13(3):234-243

Dupilumab improved FEV1 and health-related quality of life



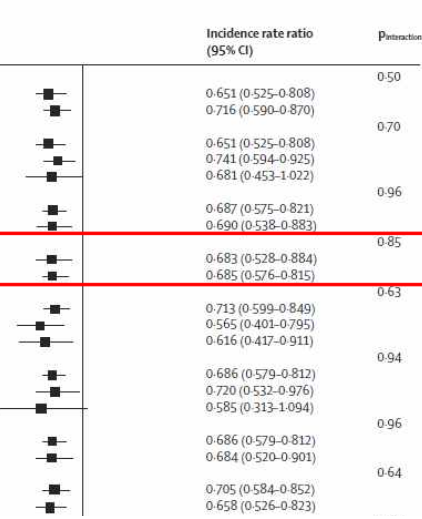
FEV1



SGRQ

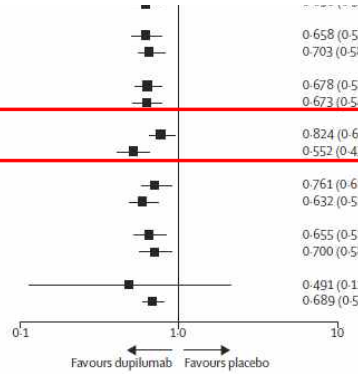
Lancet Respir Med. 2025 Mar;13(3):234-243

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)	

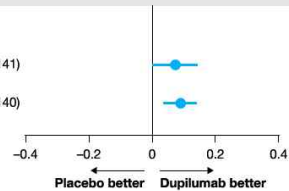


Original Research

Dupilumab reduces exacerbations and improves lung function in patients with chronic obstructive pulmonary disease and emphysema: Phase 3 randomized trial (BOREAS)

Surya P. Bhatt[a,*,1], Klaus F. Rabe[b,**,1], Nicola A. Hanania[c], Claus F. Vogelmeier[d], Mona Bafadhel[e], Stephanie A. Christenson[f], Alberto Papi[g], Dave Singh[h], Elizabeth Laws[i], Paula Dakin[j], Jennifer Maloney[j], Xin Lu[i], Deborah Bauer[i], Ashish Bansal[j], Lacey B. Robinson[k], Raolat M. Abdulai[k]

	Placebo, n	Dupilumab, n	LS mean difference[b] vs placebo (95% CI)	*P*-value for interaction[c]
Emphysema at baseline				
Emphysema	151	155	0.071 (0.002 to 0.141)	0.6438
No emphysema	320	312	0.088 (0.036 to 0.140)	



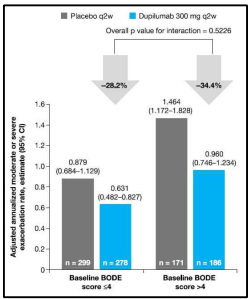
- Dupilumab benefit was consistent regardless of baseline emphysema.

Original Research

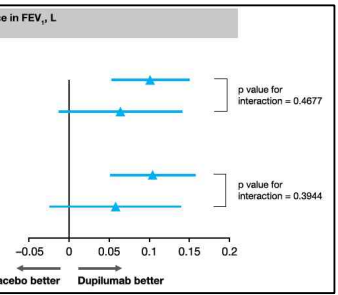
Dupilumab reduces acute exacerbations and improves lung function in patients with COPD with type 2 inflammation irrespective of body mass index, airflow obstruction, dyspnea, and exercise capacity index scores

Claus F. Vogelmeier [a,*], Klaus F. Rabe [b], Surya P. Bhatt [c], Nicola A. Hanania [d], Mona Bafadhel [e], Stephanie A. Christenson [f], Alberto Papi [g], Dave Singh [h], Elizabeth Laws [k], Jennifer Maloney [i], Paula Dakin [i], Xin Lu [i], Deborah Bauer [i], Ashish Bansal [i], Lacey B. Robinson [k], Raolat M. Abdulai [k]

- Question: Is dupilumab effective in patients with higher COPD burden, as reflected by BODE index?
- Finding: Dupilumab reduced exacerbations and improved FEV1 regardless of baseline BODE index.



Baseline BODE score	Placebo, n	Dupilumab, n	LS mean difference in FEV_1, L (95% CI)
Week 12			
≤4 points	299	277	0.101 (0.053, 0.150)
>4 points	169	185	0.064 (–0.013, 0.141)
Week 52			
≤4 points	299	277	0.104 (0.051, 0.157)
>4 points	169	185	0.058 (0.024, 0.139)



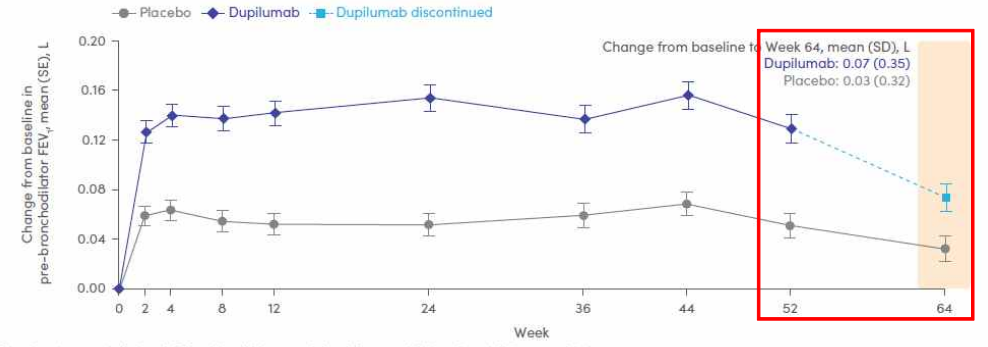
Respir Med. 2025 Jan:236:107846.

Continuation of Dupilumab Sustains Treatment-Associated Benefits in Patients with Chronic Obstructive Pulmonary Disease: Pooled Data from BOREAS and NOTUS

Yongchang Sun[1], Yuanlin Song[2], Surya P. Bhatt[3], Klaus F. Rabe[4,5], Jessica Bon[6], Mei Zhang[7], Mena Soliman[8], Danen M. Cunoosamy[8], Lydia Finney[10]

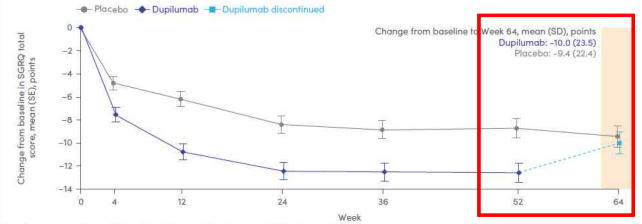
[1]Peking University Third Hospital, Beijing, China; [2]Zhongshan Hospital, Fudan University, Shanghai, China; [3]University of Alabama at Birmingham, Birmingham, AL, USA; [4]Christian-Albrechts University (member of the German Center for Lung Research [DZL]), Airway Research Center North (ARCN), Kiel, Germany; [5]LungenClinic Grosshansdorf (member of the German Center for Lung Research [DZL]), Airway Research Center North (ARCN), Grosshansdorf, Germany; [6]Wake Forest University School of Medicine, Winston-Salem, NC, USA; [7]Sanofi, Morristown, NJ, USA; [8]Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA; [9]Sanofi, Cambridge, MA, USA; [10]National Heart and Lung Institute, Imperial College, London, UK

Figure 1. Following 52 weeks of treatment, discontinuation of dupilumab during the 12-week follow up period resulted in an attenuation of treatment-associated improvement of pre-bronchodilator FEV_1



Data on the poster are presented for the pooled ITT population, which has an expanded sample size compared with the results reported in the congress abstract.

Figure 3. Greater reductions in SGRQ total score were observed for dupilumab vs placebo during the treatement period, with an attenuation in the treatment effect during the 12-week follow-up period



Data on the poster are presented for the pooled ITT population, which has an expanded sample size compared with the results reported in the congress abstract.

Table. Serum dupilumab concentrations decreased while FeNO increased following discontinuation of dupilumab treatment after Week 52 during the BOREAS and NOTUS trials

	Placebo N = 934	Dupilumab N = 938
Change from baseline in FeNO, mean (SD), ppb		
Week 12	−2.2 (19.4)	−8.9 (23.7)
Week 24	−1.7 (20.9)	−9.8 (23.0)
Week 52	−2.0 (21.7)	−9.7 (24.2)
Week 64	−1.3 (23.9)	−1.2 (20.4)
Absolute serum dupilumab concentration, median (min:max), ng/mL		
Week 12	–	45,000 (39:237,000)
Week 24	–	50,800 (39:235,000)
Week 52	–	49,050 (39:234,000)
Week 64	–	39 (39:121,000)

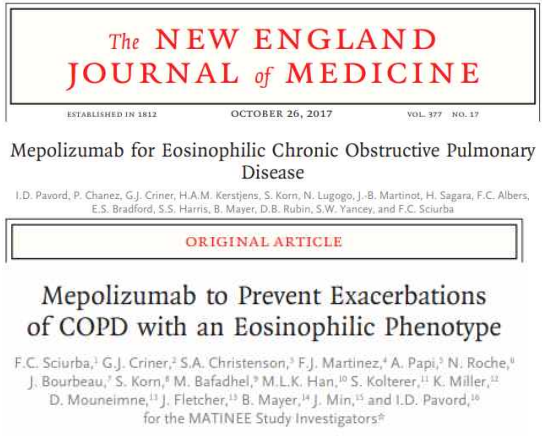
Dupilumab concentration data and FeNO levels are reported for the pharmacokinetic and safety populations, respectively. Treatment was discontinued after Week 52.

Dupilumab benefits attenuate after treatment discontinuation

- After 52 weeks of dupilumab treatment, discontinuation led to attenuation of improvements in FEV_1 and SGRQ.
- FeNO increased again after discontinuation, while serum dupilumab concentrations decreased markedly.
- These findings suggest that continued treatment may be needed to sustain clinical and type 2 inflammatory benefits.

Mepolizumab (anti-IL-5)

- METREX
- METREO
- MATINEE



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

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*

N Engl J Med. 2017 Oct 26;377(17):1613-1629
N Engl J Med. 2025 May 1;392(17):1710-1720

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

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

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§	—

Greater blood eosinophil counts were associated with greater exacerbation reduction with mepolizumab.

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)

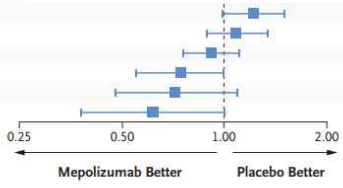
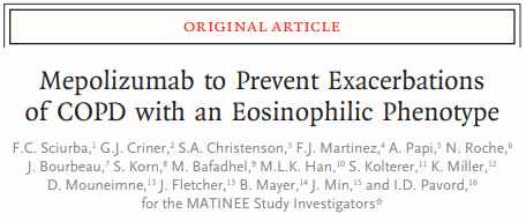


Figure 5. Moderate or Severe Exacerbations According to Blood Eosinophil Count Category at Screening.

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



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.

Table 2. Primary and Secondary Efficacy End Points.*

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	—

- No improvement in secondary endpoints

N Engl J Med. 2025 May 1;392(17):1710-1720

NEJM Evidence

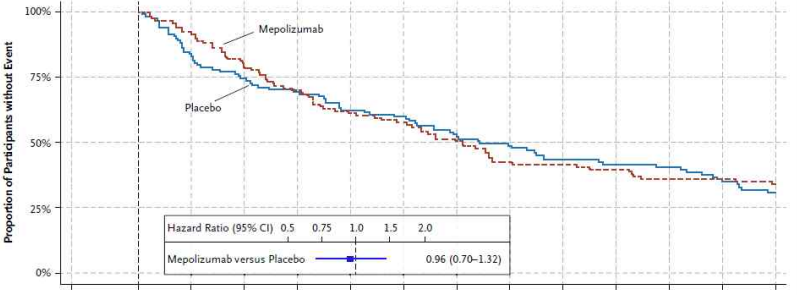
Published April 30, 2025
NEJM Evid 2025;4(6)
DOI: 10.1056/EVIDoa2500012

ORIGINAL ARTICLE

Mepolizumab for COPD with Eosinophilic Phenotype following Hospitalization

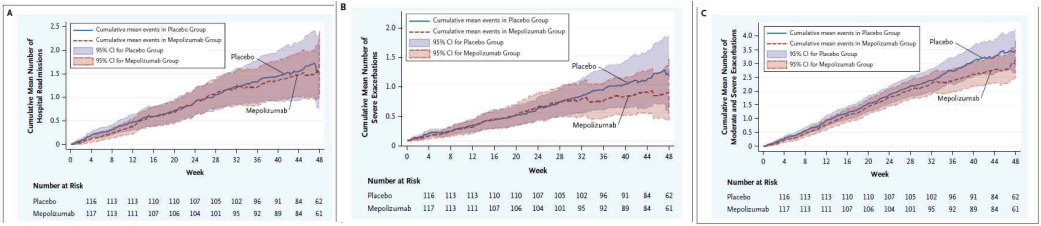
Cara A. Flynn, M.B.Ch.B.,[1] Hamish J.C. McAuley, Ph.D.,[1] Omer Elneima, Ph.D.,[1] Hnin W.W. Aung, M.B.B.S.,[1] Wadah Ibrahim, Ph.D.,[1] Thomas J.C. Ward, Ph.D.,[1] Michelle Bourne, R.N.,[1] Tracey D. Thornton,[1] Vijay Mistry, B.Sc.,[1] Hannah R. Gilbert, M.Sc.,[2] Ghazala Waheed, M.Sc.,[2] Adam K.A. 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]

- Question: Can mepolizumab started around discharge reduce readmission or death after AECOPD hospitalization?
- Design: Phase 2b, single-center, randomized, double-blind, placebo-controlled trial
- Population: COPD patients hospitalized for AECOPD
- Eligibility: Historical blood eosinophil count ≥300/μL within the previous 12 months
- Treatment: Mepolizumab 100 mg vs placebo every 4 weeks
- Timing: Before discharge or within 7 days after discharge
- Duration: Up to 48 weeks

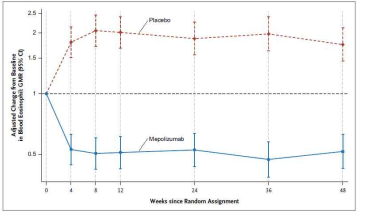


Placebo													
No. at risk now	119	99	87	81	73	70	62	56	48	45	43	37	31
Censored now	0	1	2	2	2	2	2	3	5	6	7	8	9
Event by now	0	19	30	36	44	47	55	60	66	68	69	74	79
Mepolizumab													
No. at risk now	119	108	93	81	69	65	57	48	46	43	37	36	29
Censored now	0	2	3	3	5	5	5	5	6	7	9	10	15
Event by now	0	9	23	35	45	49	57	66	67	69	73	73	75

Eosinophils were reduced, but clinical outcomes were not improved.



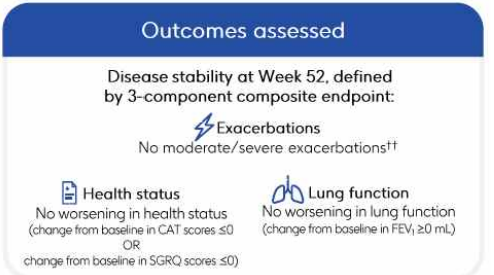
- Readmission/Severe exacerbation/Moderate-to-severe exacerbation
- Eosinophil count는 감소



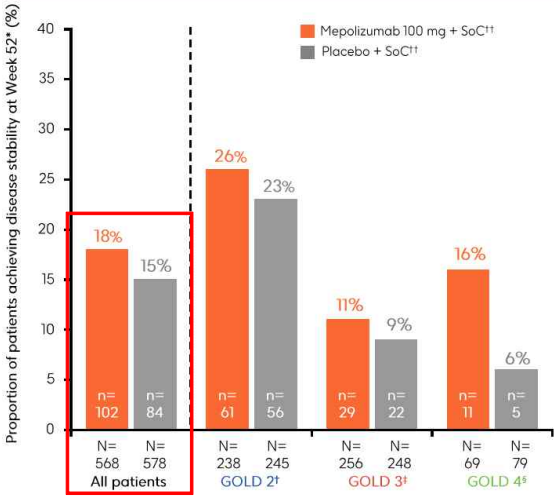
Disease Stability Is Achievable in a Wide Spectrum of Patients with Chronic Obstructive Pulmonary Disease Receiving Mepolizumab: Pooled Results from Phase III Randomized Controlled Trials

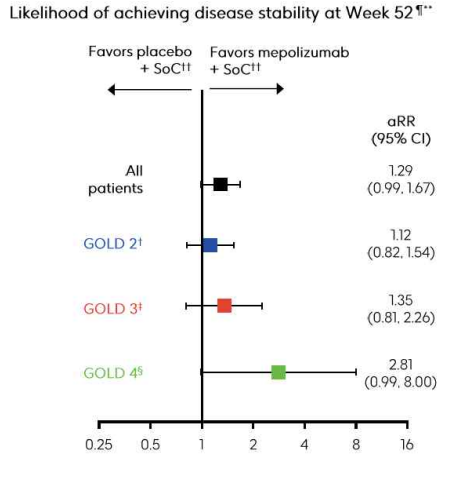
Dave Singh[1,2], Claus F Vogelmeier[3], Fernando J Martinez[4], Nicolas Roche[5], Henrik Watz[6], Arunangshu Biswas[7], Rianne Stacey[8], Stefanie Kolterer[9], MeiLan K Han[10]

[1]Division of Immunology, Immunity to Infection and Respiratory Medicine, School of Biological Sciences, The University of Manchester, Manchester, UK; [2]Medicines Evaluation Unit, Manchester University NHS Foundation Trust, Manchester, UK; [3]Department of Medicine, Pulmonary and Critical Care Medicine, University Medical Centre Giessen and Marburg, Philipps-University Marburg, German Center for Lung Research (DZL), Marburg, Germany; [4]University of Massachusetts Chan, Worcester, MA, USA; [5]Service de Pneumologie, APHP Centre – Université Paris Cité, Hôpital et Institut Cochin, Paris, France; [6]Velocity Clinical Research Germany GmbH, Ahrensburg, Germany; [7]Biostatistics, GSK, Bengaluru, Karnataka, India; [8]Global Medical Affairs, General Medicines, GSK, London, UK; [9]Specialty Care, GSK, London, UK; [10]Pulmonary and Critical Care, University of Michigan Health System, Ann Arbor, MI, USA

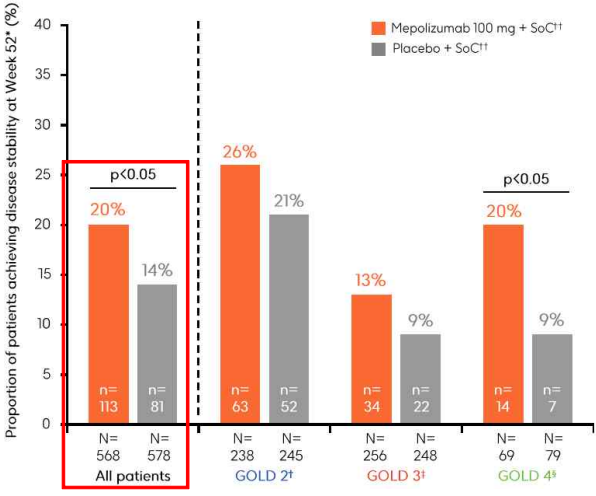


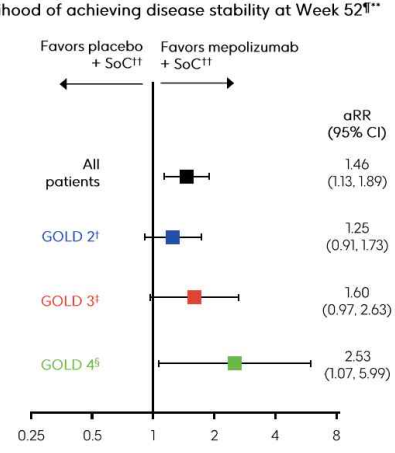
Disease stability at Week 52 (CAT-defined)



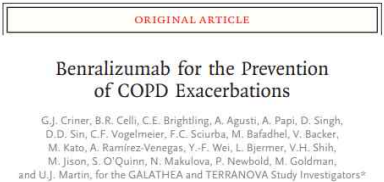


Disease stability at Week 52 (SGRQ-defined)





Benralizumab (anti-IL-5Rα)



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 : Negative study
- COPD patients
  - EOS ≥220
  - 40-85 years of age
  - moderate to very severe COPD
- Frequent exacerbator
- Primary endpoint not met

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

RESOLUTE

- phase 3, randomized, double-blind, placebo-controlled trial

- Moderate to very severe COPD
- Frequent exacerbators
- Blood eosinophils ≥300 cells/μL
- On background triple therapy: ICS/LABA/LAMA
- Current or former smokers

- Benralizumab 100 mg vs placebo
- Every 4 weeks for first 3 doses, then every 8 weeks

Update on the RESOLUTE Phase III trial for Fasenra in chronic obstructive pulmonary disease

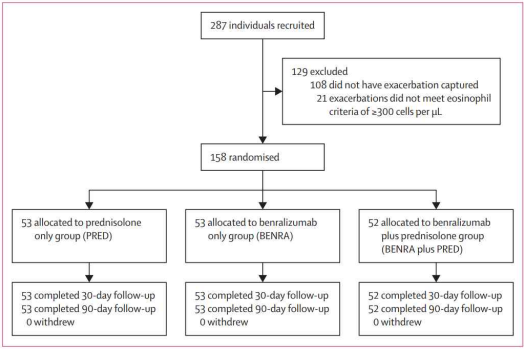
PUBLISHED
17 September 2025

- The RESOLUTE Phase III trial of AstraZeneca's *Fasenra* (benralizumab), despite showing numerical improvement, did not achieve statistical significance in the primary endpoint in patients with chronic obstructive pulmonary disease (COPD).

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

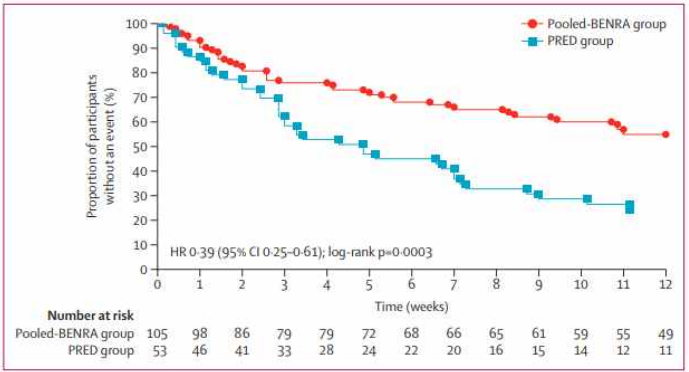
Sanjay Ramakrishnan, Richard E K Russell, Hafiz R Mahmood, Karolina Krassowska, James Melhorn, Christine Mwasuku, Ian D Pavord, Laura Berrmejo-Sanchez, Imran Hewell, Mahdi Mahdi, Stefan Peterson, Thomas Bengtsson, Mona Bafadhel



- 치료실패
  - 사망
  - 입원
  - 재치료 필요
    : systemic glucocorticoid 또는 antibiotics 추가 사용

Lancet Respir Med. 2025 Jan;13(1):59-68.

	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

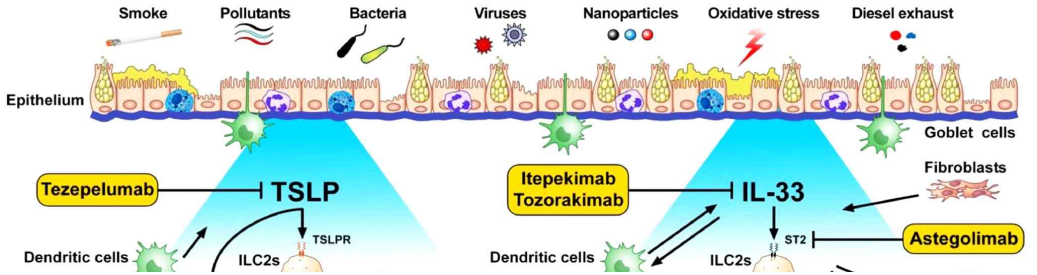


Lancet Respir Med. 2025 Jan;13(1):59-68.

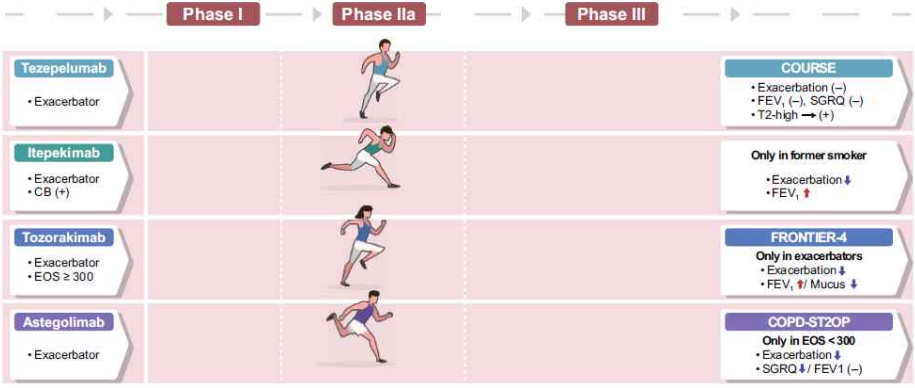
- Biologics Targeting Alarmins

Alarm(+)in / Alararm signal

- *Alarmins* are innate immune cytokines released by airway epithelial cells in response to various external stimuli, such as smoking, pollutants, viruses, and bacteria.



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


Phase I
Phase IIa
Phase III
Tezepelumab
• Exacerbator
COURSE
• Exacerbation (–)
• FEV1 (–), SGRQ (–)
• T2-high → (+)
Itepekimab
• Exacerbator
• CB (+)
Only in former smoker
• Exacerbation ↓
• FEV1 ↑
Tozorakimab
• Exacerbator
• EOS ≥ 300
FRONTIER-4
Only in exacerbators
• Exacerbation ↓
• FEV1 ↑/ Mucus ↓
Astegolimab
• Exacerbator
COPD-ST2OP
Only in EOS < 300
• Exacerbation ↓
• SGRQ ↓/ FEV1 (–)

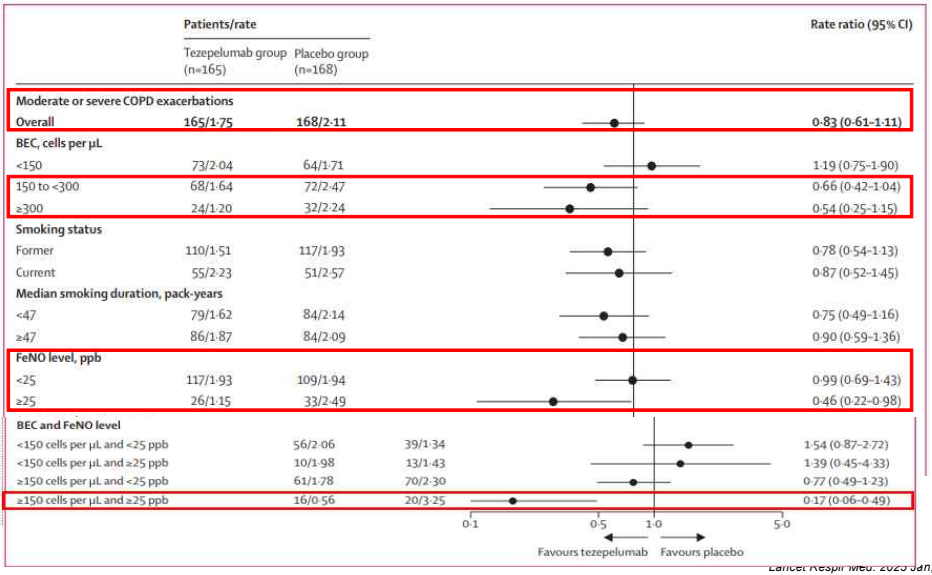
Tezepelumab (anti-TSLP)

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 annualized rate of moderate or severe COPD exacerbations
- A prespecified subgroup analysis assessed the primary endpoint in patients grouped by baseline BECs

Lancet Respir Med. 2025 Jan;13(1):47-58


Patients/rate
Tezepelumab group (n=165)
Placebo group (n=168)
Rate ratio (95% CI)
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)
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)
0·1
0·5
1·0
5·0
Favours tezepelumab
Favours placebo

Change from baseline to week 52 in pre-bronchodilator FEV_1 and SGRQ total score

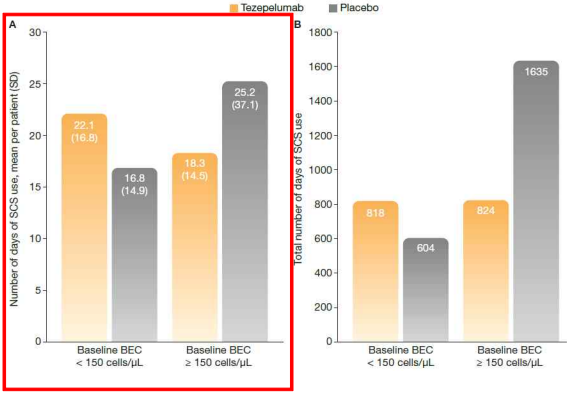
	Tezepelumab group (n=165)		Placebo group (n=168)		LS mean difference (95% CI)
	n	LS mean (SE)	n	LS mean (SE)	
Pre-bronchodilator FEV_1, L					
Overall	163	0·026 (0·015)	166	−0·029 (0·015)	0·055 (0·014 to 0·096)
Baseline BEC, cells per µL					
<150	73	−0·002 (0·022)	63	−0·053 (0·023)	0·051 (−0·012 to 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, and SGRQ total score in the overall population (secondary endpoint) and in prespecified patient subgroups by baseline BEC and FeNO level (full analysis set)**

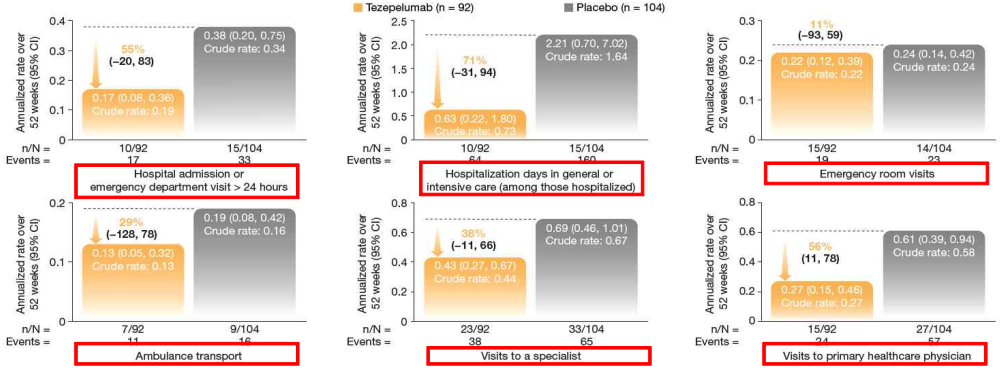
Lancet Respir Med. 2025 Jan;13(1):47-58

COURSE post hoc : Number of days of SCS use and total number of days of SCS use



- In patients with a baseline BEC ≥ 150 cells/µL, tezepelumab recipients experienced numerically lower mean numbers of days per patient (A) and total number of days (B) of SCS treatment associated with COPD exacerbations than placebo recipients.

COURSE post hoc : Among patients with a baseline BEC ≥ 150 cells/µL, tezepelumab recipients had numerically lower annualized rates of COPD-related HCRU over 52 weeks than placebo recipients.



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

- Moderate-to-severe COPD, Current or former smokers
- On triple or double inhaled maintenance therapy
- Itepekimab 300 mg SC every 2 weeks vs placebo
- Main result - Overall population
  - : Annualized moderate-to-severe exacerbation rate
  - : Placebo: 1.61, Itepekimab: 1.30, RR 0.81, p=0.13
  - : primary endpoint not met
- Key subgroup finding
  - Former smokers showed benefit
  - Exacerbation reduction: RR 0.58, p=0.0061
  - Pre-BD FEV1 improvement: +90 mL, p=0.0076
  - Current smokers: no benefit
  - Exacerbation RR 1.09, p=0.65

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

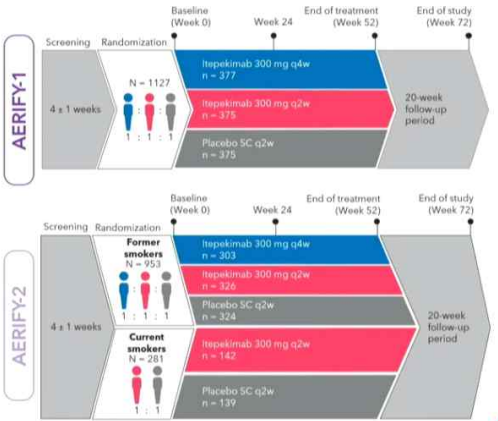
To investigate the **efficacy and safety** of **itepekimab** in **former smokers** with **COPD** in two phase 3 pivotal trials

Methods: trial design

Randomized, double-blind, placebo-controlled, international, phase 3 trials testing efficacy and safety of 2 dosing regimens of itepekimab

Inclusion criteria:

- Physician-diagnosed COPD for ≥1 year
- 40 to 85 years
- Moderate-to-severe airflow limitation (post-bronchodilator ppFEV$_1$ 30% to 80%)
- ≥2 moderate or ≥1 severe exacerbations in the previous year
- On stable inhaled triple or dual therapy
- **Former smokers** (smoking cessation ≥6 months before screening)
  - Current smokers (secondary population, AERIFY-2 only)



Approximately 35% of patients in both studies had a screening eosinophil count ≥300 cells/μL

Methods: endpoints

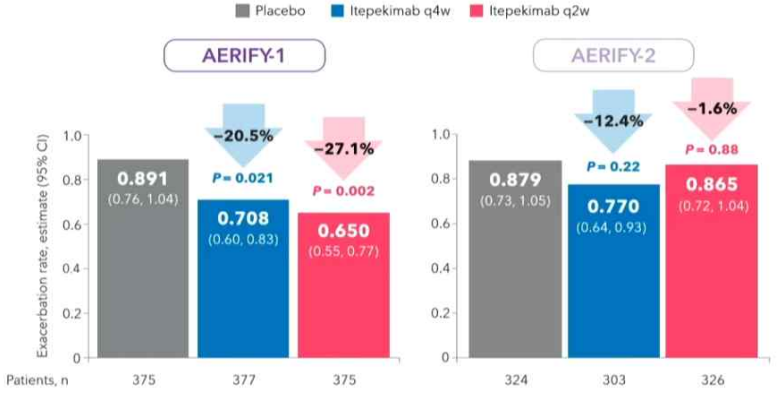
Primary endpoint:

- Annualized rate of moderate or severe exacerbations in former smokers

Secondary and other endpoints:

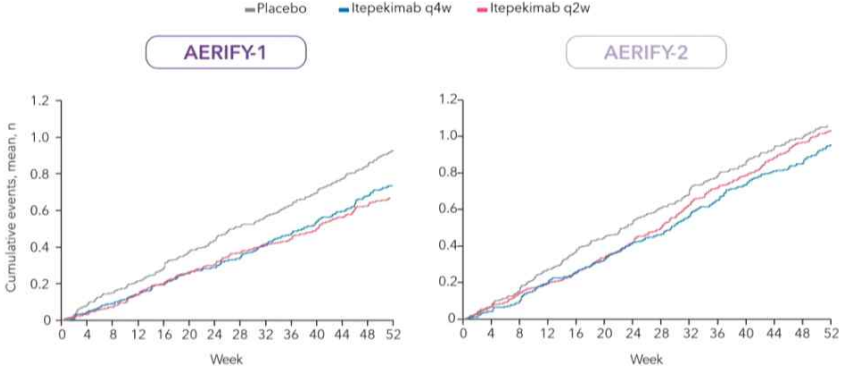
- Severe exacerbation rate in former smokers (prespecified pooled AERIFY-1 and AERIFY-2 analysis first, then individual studies)
- Change from baseline to Week 24 in pre-bronchodilator FEV_1 in former smokers (key secondary endpoint)
- Adverse events

Primary endpoint: annualized moderate or severe exacerbation rates (former smokers)

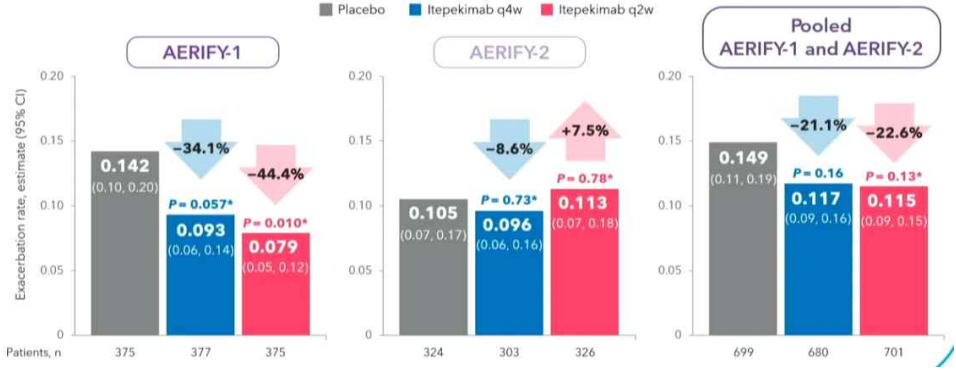


Annualized moderate or severe exacerbation rate was reduced by 7.1% ($P = 0.66$) in **current smokers**

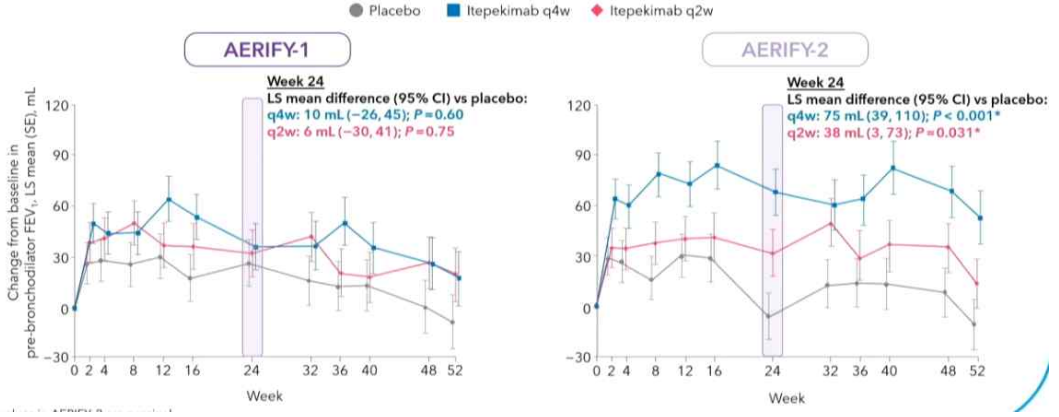
Cumulative mean number of moderate or severe exacerbations (former smokers)



Annualized severe exacerbation rates (former smokers)



Secondary endpoint: change in pre-bronchodilator FEV_1 (former smokers)



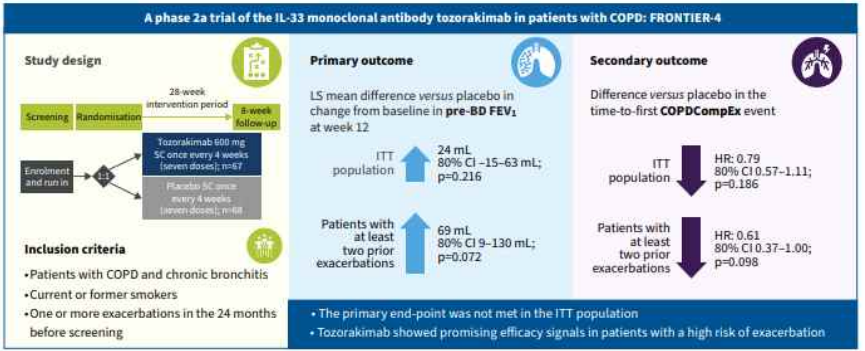
Conclusions

- In former smokers with COPD, itepekimab vs placebo **significantly reduced moderate or severe exacerbation rates** in **AERIFY-1,** but not AERIFY-2
- Itepekimab showed clinically meaningful **reductions in severe exacerbation** rates in **AERIFY-1,** but not in the AERIFY-2 or pooled populations
- Itepekimab had an acceptable safety profile in both trials

Tozorakimab (Anti-IL-33)

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

Dave Singh, Patricia Guller, Fred Reid, Sarah Doffman, Ulla Seppälä, Ioannis Psallidas, Rachel Moate, Rebecca Smith, Joanna Kiraga, Eulalia Jimenez, Dennis Brooks, Aoife Kelly, Lars H. Nordenmark, Muhammad Waqas Sadiq, Luis Mateos Caballero, Chris Kell, Maria G. Belvisi and Hitesh Pandya



Eur Respir J. 2025 Jul 14;66(1):2402231.

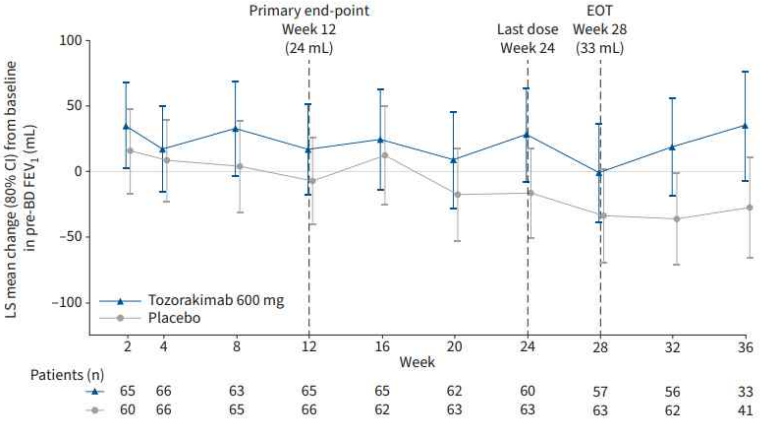


FIGURE 2 Change in pre-bronchodilator (BD) forced expiratory volume in 1 s (FEV_1) in the intent-to-treat population. CI: confidence interval; EOT: end of treatment; LS: least-squares.

FRONTIER-4 post hoc: Tozorakimab reduces quantitative mucus plugging metrics in patients with moderate-to-severe COPD

Figure 3. Changes from baseline to week 28 in mucus plug metrics

	CT sub-study population						
	Baseline mean (SD)		Change from baseline to week 28[a] Mean (SD)			Relative change from baseline[a] (%) Percentage change[b]	
	Tozorakimab 600 mg Q4W (n = 18)	Placebo (n = 20)	Tozorakimab 600 mg Q4W (n = 18)	Placebo (n = 20)	Tozorakimab 600 mg Q4W minus placebo, (difference in estimated means [80% CI])	Tozorakimab 600 mg Q4W (n = 18)	Placebo (n = 20)
Mucus plug volume, µL	247 (400)	134 (176)	−23 (376)	59 (356)	−88 (−235, 58)	↓9.3%	↑44.0%
Mucus plug mass, mg	200 (347)	86 (128)	−45 (305)	50 (282)	−89 (−203, 21)	↓22.5%	↑58.1%
Mucus-obstructed area,[c] mm²	26.0 (45.1)	15.0 (21.3)	−4.1 (30.6)	0.9 (19.6)	−4.9 (−14.6, 5.0)	↓15.7%	↑6.1%
Mucus-obstructed area fraction[d]	0.10 (0.19)	0.04 (0.06)	−0.04 (0.16)	0.00 (0.06)	−0.05 (−0.09, 0.00)	↓42.2%	0%
Segmental mucus score[e]	2.9 (3.7)	2.0 (2.2)	−0.3 (2.8)	0.4 (3.0)	−0.7 (−1.8, 0.4)	↓10.3%	↑20.0%

Tozorakimab met primary endpoint in both OBERON and TITANIA Phase III trials in patients with COPD

PUBLISHED
27 March 2026

This announcement contains inside information

First-ever IL-33-targeting biologic to demonstrate statistically significant and highly clinically meaningful reductions in COPD exacerbations in two replicate Phase III clinical trials

First-ever IL-33-targeting biologic to demonstrate statistically significant and highly clinically meaningful reductions in COPD exacerbations in two replicate Phase III clinical trials

Positive high-level results from the Phase III OBERON and TITANIA trials in patients with chronic obstructive pulmonary disease (COPD) showed that tozorakimab reduced the annualised rate of moderate-to-severe COPD exacerbations compared with placebo, in the primary population of former smokers, and in the overall population, which included former and current smokers, and patients across all blood eosinophil* counts and all stages of lung function severity. Tozorakimab was generally well tolerated with a favourable safety profile.

Tozorakimab met primary endpoint in Phase III MIRANDA trial in patients with COPD

PUBLISHED
20 April 2026

Third positive pivotal Phase III clinical trial of AstraZeneca's IL-33-targeting biologic further demonstrates its benefits in COPD

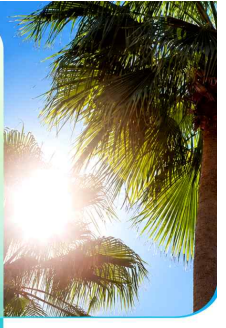
Positive high-level results from the pivotal Phase III MIRANDA trial showed potential first-in-class tozorakimab demonstrated a statistically significant and clinically meaningful reduction in the annualised rate of moderate-to-severe COPD exacerbations in the primary population of former smokers and in the overall population, which included former and current smokers, and patients across all blood eosinophil* counts and all stages of lung function severity.

Astegolimab (anti-ST2)

Astegolimab decreases exacerbation risk in patients with COPD with frequent exacerbations, irrespective of blood eosinophil count: Pooled analysis of the pivotal randomized trials ALIENTO and ARNASA

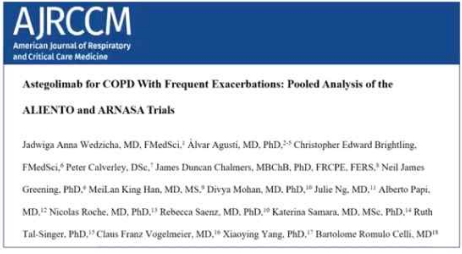
Jadwiga A. Wedzicha,[1] Álvar Agustí,[2,5] Christopher E. Brightling,[3] Peter Calverley,[7] James D. Chalmers,[8] Neil Greening,[6] Meilan K. Han,[9] Divya Mohan,[10] Julie Ng,[10] Alberto Papi,[11] Nicolas Roche,[12] Rebecca Saenz,[10] Katerina Samara,[13] Ruth Tal-Singer,[14] Claus F. Vogelmeier,[15] Xiaoying Yang,[10] Bartolome Celli[16]

[1]National Heart and Lung Institute, Imperial College London, London, UK; [2]University of Barcelona, Barcelona, Spain; [3]Respiratory Institute, Hospital Clínic Barcelona, Barcelona, Spain; [4]CIBERES, Madrid, Spain; [5]ISGlobal, Barcelona, Spain; [6]GSK, Spain; [7]Department of Respiratory Sciences, Institute for Life Sciences, University of Leicester, Leicester, UK; [8]Trinity College and Adelaide School, University of Liverpool, Liverpool, UK; [9]Realistic Department, GSK, Collegeville, PA, USA; [10]University of Michigan, Ann Arbor, MI, USA; [11]GSK, Singapore; [12]South San Francisco; CA, USA; [13]Pulmonary and Critical Care Medicine, University of Athens, Athens, Greece; [14]Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Hofstra/Northwell, Rockville Centre, NY, USA; [15]Medical University of Marburg, Marburg, Germany; [16]Brigham and Women's Pulmonary, Critical Care and Sleep Medicine, Philips University of Marburg (UMR), German Center for Lung Reuanch (DZL), Heidelberg, Germany; [17]Mass General Brigham Hospital, Harvard University Medical School, Boston, MA, USA



ATS 2026 Orlando May 15-20

Simultaneously published in *AJRCCM*



AJRCCM

American Journal of Respiratory and Critical Care Medicine

Astegolimab for COPD With Frequent Exacerbations: Pooled Analysis of the ALIENTO and ARNASA Trials

Jadwiga Anna Wedzicha, MD, FMedSci,[1] Àlvar Agustí, MD, PhD,[2-5] Christopher Edward Brightling, FMedSci,[6] Peter Calverley, DSc,[7] James Duncan Chalmers, MBChB, PhD, FRCPE, FERS,[8] Neil James Greening, PhD,[9] MeiLan King Han, MD, MS,[9] Divya Mohan, MD, PhD,[10] Julie Ng, MD,[11] Alberto Papi, MD,[12] Nicolas Roche, MD, PhD,[13] Rebecca Saenz, MD, PhD,[10] Katerina Samara, MD, MSc, PhD,[14] Ruth Tal-Singer, PhD,[15] Claus Franz Vogelmeier, MD,[16] Xiaoying Yang, PhD,[17] Bartolome Romulo Celli, MD[18]

Safety and efficacy of astegolimab for COPD with frequent exacerbations regardless of baseline blood eosinophil counts (ALIENTO and ARNASA): randomised, double-blind, placebo-controlled, phase 2b and 3 trials

Alberto Papi, Neil J Greening*, Surya P Bhatt, Nicolas Roche, Bartolome Celli, Jadwiga A Wedzicha, Àlvar Agustí, Ruth Tal-Singer, MeiLan K Han, Wim Janssens, Nicola A Hanania, Parameswaran Nair, Peter Bremner, Konstantinos Porpodis, Yoko Shibata, Stephanie Korn, Ting Yang, Oliver Gordon, Rebecca Saenz, Julie Ng, Dorothy S Cheung, Jacob Devine, Michele A Grimbaldeston, Wenhui Zhang, Xiaoying Yang, Divya Mohan, Claus F Vogelmeier†, Christopher E Brightling†, on behalf of the ALIENTO and ARNASA investigators‡*

Summary

Background Interleukin-33 and its receptor, ST2, are implicated in neutrophilic and eosinophilic inflammation during chronic obstructive pulmonary disease (COPD) exacerbations. We aimed to assess the efficacy and safety of astegolimab, an anti-ST2 human IgG2 monoclonal antibody, which were evaluated in two COPD pivotal trials.

Lancet 2026; 407: 2027–39

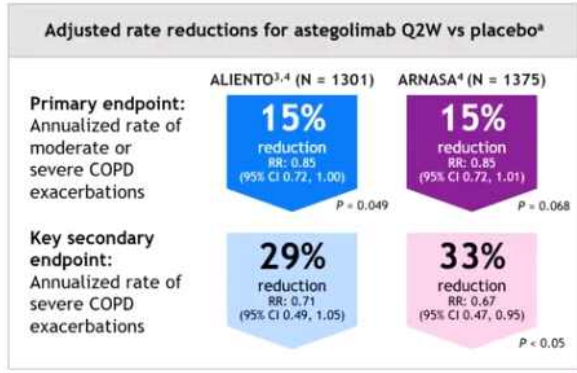
Published Online May 18, 2026

Am J Respir Crit Care Med. 2026 May 18:aamag226

Lancet. 2026 May 23;407(10543):2027-2039

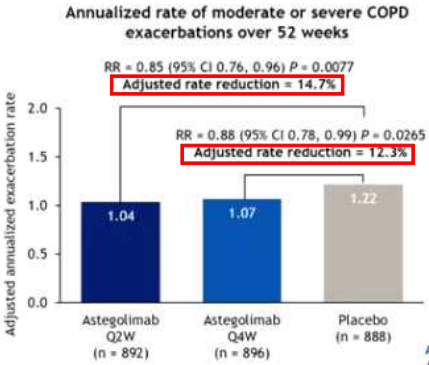
ALIENTO and ARNASA: impact of astegolimab on exacerbation rates

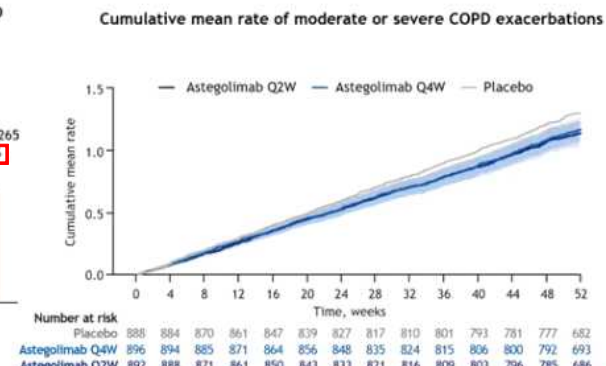
- Astegolimab is a human anti-ST2 IgG2 monoclonal antibody that blocks IL-33 activity and subsequent inflammatory responses[1,2]
- The efficacy and safety of astegolimab in patients with COPD with frequent exacerbations were evaluated in two randomized, double-blind, placebo-controlled trials:
  - Phase IIb **ALIENTO** (NCT05037929)
  - Phase III **ARNASA** (NCT05595642)



Am J Respir Crit Care Med. 2026 May 18:aamag226
Lancet. 2026 May 23;407(10543):2027-2039

Astegolimab Q2W and Q4W significantly reduced the adjusted annualized rate of moderate or severe exacerbations vs placebo





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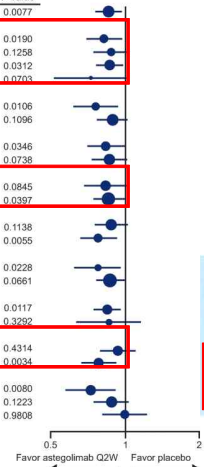
Astegolimab Q2W reduced exacerbation frequency across key prespecified subgroups, including current/former smokers and baseline blood eosinophil count

Baseline characteristic	Astegolimab Q2W *N*	Placebo *N*	RR	CI	*P*-value
All patients	892	888	0.85	(0.76–0.96)	0.0077
Baseline eosinophil level					
<150 cells/μL	459	427	0.82	(0.70–0.97)	0.0190
≥150 cells/μL	429	461	0.88	(0.74–1.04)	0.1258
<300 cells/μL	765	787	0.87	(0.77–0.99)	0.0312
≥300 cells/μL	123	101	0.73	(0.52–1.03)	0.0703
Age category					
40–64 years	325	301	0.76	(0.62–0.94)	0.0106
≥65 years	567	587	0.89	(0.77–1.03)	0.1096
Sex					
Female	354	352	0.83	(0.70–0.99)	0.0346
Male	538	536	0.86	(0.74–1.01)	0.0738
Smoking status					
Current smoker	302	303	0.84	(0.68–1.02)	0.0845
Former smoker	590	585	0.86	(0.75–0.99)	0.0397
Number of COPD exacerbations*					
2	612	649	0.88	(0.75–1.03)	0.1138
>2	279	237	0.79	(0.66–0.93)	0.0055
Hospitalization for COPD†					
Yes	221	197	0.78	(0.63–0.97)	0.0228
No	671	691	0.88	(0.77–1.01)	0.0661
Baseline COPD triple therapy					
Yes	695	672	0.85	(0.75–0.96)	0.0117
No	196	215	0.86	(0.64–1.16)	0.3292
Baseline chronic bronchitis					
Yes	420	427	0.94	(0.79–1.11)	0.4314
No	472	461	0.78	(0.66–0.92)	0.0034
Baseline GOLD Stage					
Moderate	333	303	0.73	(0.57–0.92)	0.0080
Severe	392	408	0.88	(0.75–1.04)	0.1223
Very severe	155	162	1.00	(0.81–1.23)	0.9808



Subgroups which suggested an enhanced treatment benefit of astegolimab Q2W vs placebo in both individual trials and the pooled analysis were:

- Moderate airflow obstruction → **27% reduction**
- History of >2 exacerbations → **21% reduction**
- No chronic bronchitis → **22% reduction**

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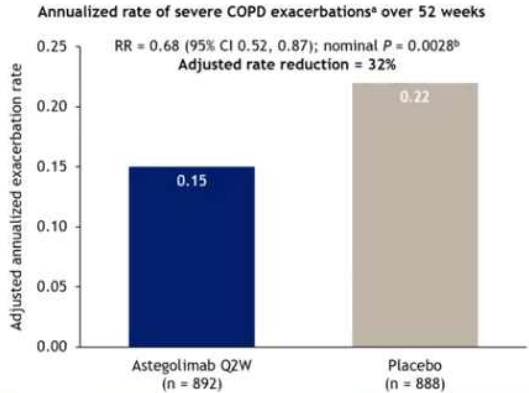
Nominally significant reduction in the annualized rate of severe COPD exacerbations was observed with astegolimab Q2W vs placebo



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Conclusions

In this pooled analysis of ALIENTO and ARNASA, treatment with astegolimab Q2W resulted in:

- Significant reduction in the annualized rate of moderate and severe exacerbations by 14.7% (and by 12.3% in the Q4W arm)
  - Reduced exacerbation frequency across key prespecified subgroups, including current/former smokers and baseline blood eosinophil count
  - Suggested enhanced treatment benefit in participants with history of >2 exacerbations, no chronic bronchitis, and moderate airflow obstruction
- Nominally significant 32% reduction in severe COPD exacerbation rate, and nominally significant increase in the proportion of participants with clinically meaningful improvement in SGRQ-C
- Astegolimab was well tolerated

The results of this pooled analysis further suggest a favorable benefit-risk profile for astegolimab 476 mg Q2W in patients with COPD and frequent exacerbations

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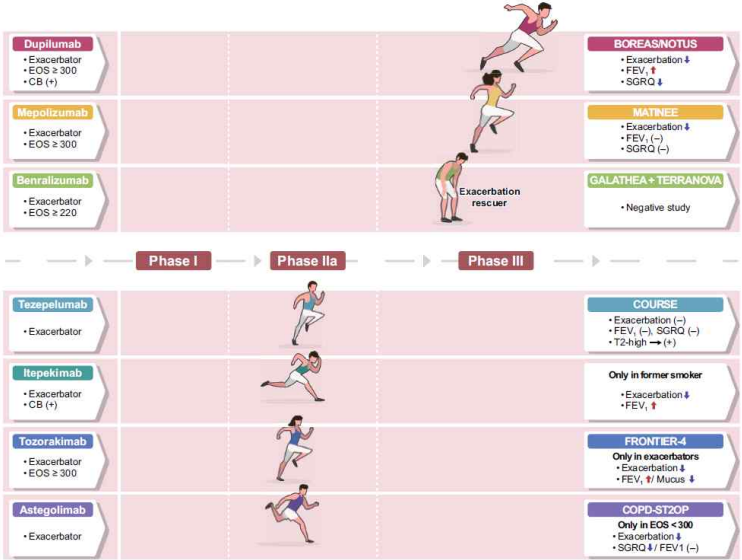
Dupilumab
• Exacerbator
• EOS ≥ 300
• CB (+)
BOREAS/NOTUS
• Exacerbation ↓
• FEV1 ↑
• SGRQ ↓
Mepolizumab
• Exacerbator
• EOS ≥ 300
MATINEE
• Exacerbation ↓
• FEV1 (–)
• SGRQ (–)
Benralizumab
• Exacerbator
• EOS ≥ 220
Exacerbation rescuer
GALATHEA + TERRANOVA
• Negative study
Phase I
Phase IIa
Phase III
Tezepelumab
• Exacerbator
COURSE
• Exacerbation (–)
• FEV1 (–), SGRQ (–)
• T2-high → (+)
Itepekimab
• Exacerbator
• CB (+)
Only in former smoker
• Exacerbation ↓
• FEV1 ↑
Tozorakimab
• Exacerbator
• EOS ≥ 300
FRONTIER-4
Only in exacerbators
• Exacerbation ↓
• FEV1 ↑/ Mucus ↓
Astegolimab
• Exacerbator
COPD-ST2OP
Only in EOS < 300
• Exacerbation ↓
• SGRQ ↓/ FEV1 (–)

Biologics in COPD: Type 2 and Alarmin Pathways

Where we stand in 2025–2026

TYPE 2–TARGETED BIOLOGICS

Phase I → Phase IIa → Phase III

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

BOREAS / NOTUS
- Exacerbation ↓
- FEV_1 ↑
- SGRQ ↓

Established in eosinophilic COPD

Mepolizumab
- Exacerbator
- EOS ≥ 300

MATINEE
- Exacerbation ↓
- FEV_1 (–)
- SGRQ (–)

Benefit mainly in eosinophilic COPD

Benralizumab
- Exacerbator
- EOS ≥ 220

Exacerbation rescuer?

GALATHEA / TERRANOVA / RESOLUTE
- Negative studies

ALARMINS / EPITHELIAL PATHWAY

Phase I → Phase IIa → Phase III

Tezepelumab
- Exacerbator
- T2-high signal

COURSE / EMBARK
- Overall negative
- FEV_1 (–), SGRQ (–)
- BEC/FeNO-high signal (+)

Phase III ongoing

Itepekimab
- Exacerbator
- CB (+)

?

Phase IIa / AERIFY-1 / AERIFY-2
- Former smoker signal (+)
- Phase III mixed
- Exacerbation ↓ / FEV_1 ↑ *in selected patients*

Tozorakimab
- Exacerbator
- Mucus / epithelial injury

OBERON / TITANIA / MIRANDA
- Phase III positive
- Exacerbation ↓
- Mucus ↓

Across BEC & smoking status

Astegolimab
- Exacerbator
- Broad COPD population

ALIENTO / ARNASA
- Individual trials mixed
- Pooled analysis positive
- Modest exacerbation ↓

Well tolerated

- 감사합니다.