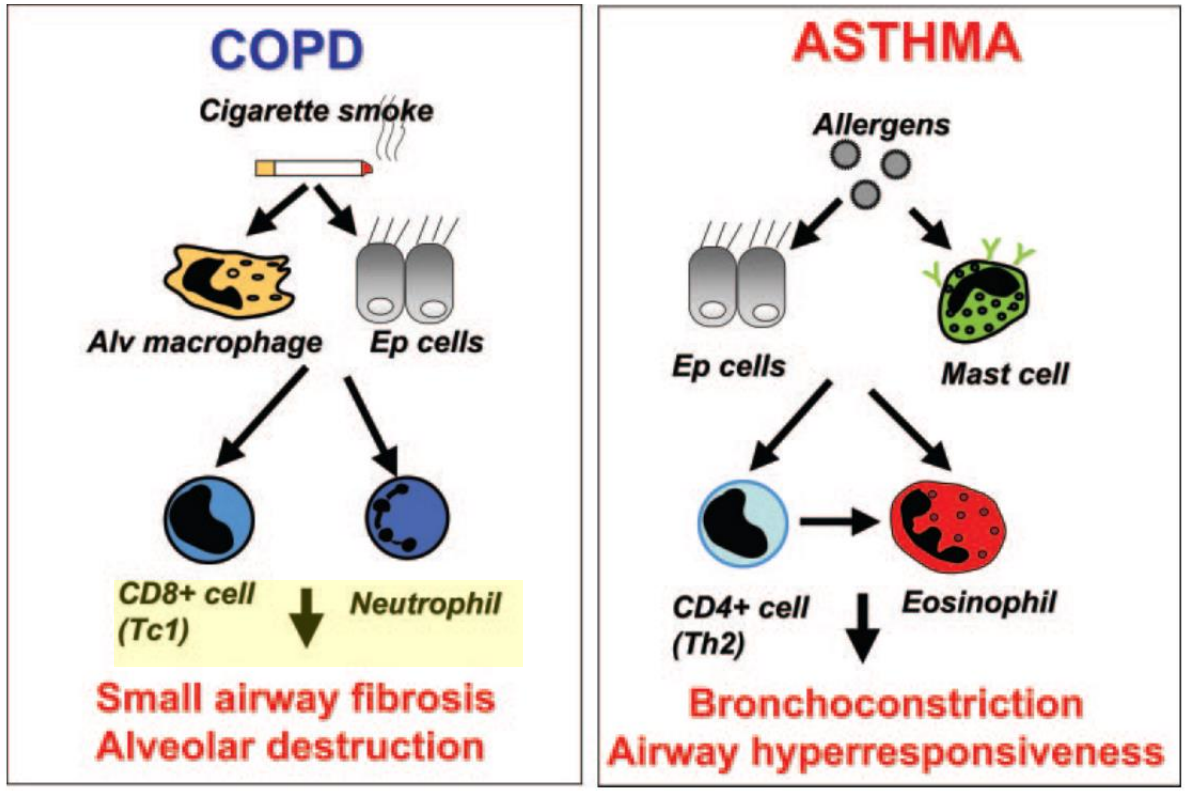
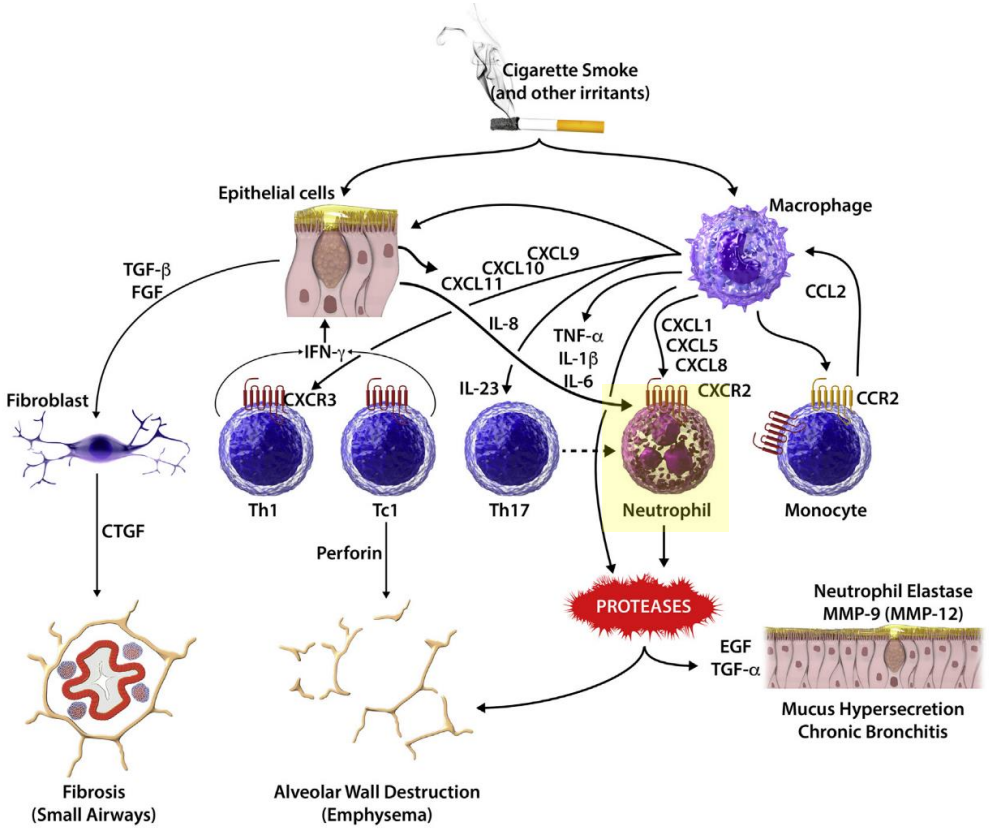
Biologics in COPD

가톨릭대학교
최준영

Index

Inflammatory mechanisms in COPD





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

Eosinophilic inflammation in COPD

ECLIPSE study

	Persistently ⩾2%	Intermittent	Persistently <2%	ANOVA p-value
Subjects n	554	728	201	
Age years	64±7	62±7	62±7	0.025
Male sex	68	64	56	0.007
Smoking history pack-years	47±26	47±26	48±30	0.810
Current smokers	30	36	42	0.004
Post-bronchodilator FEV_1 L	1.45±0.51	1.37±0.52	1.33±0.51	0.003
Post-bronchodilator FVC L	3.20±0.84	3.05±0.91	3.01±0.96	0.005
FEV_1 % predicted	51±15	49±16	48±15	0.009
Post-bronchodilator FEV_1/FVC %	46±12	45±11	45±11	0.445
BMI $kg \cdot m^{-2}$	27±5	27±6	26±6	0.190
Fat free mass index $kg \cdot m^{-2}$	53±12	52±13	50±13	0.009
6MWD m	395±116	385±115	377±127	0.142
Emphysema by CT (LAA%)	17±12	17±12	18±12	0.486
Oxygen saturation %	94.9±3.1	94.9±2.5	94.7±2.5	0.676
SGRQ total Score	44±18	47±18	49±19	0.002
FACIT fatigue score	37±10	36±10	36±10	0.106

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

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

Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Identification of Biologic Clusters and Their Biomarkers

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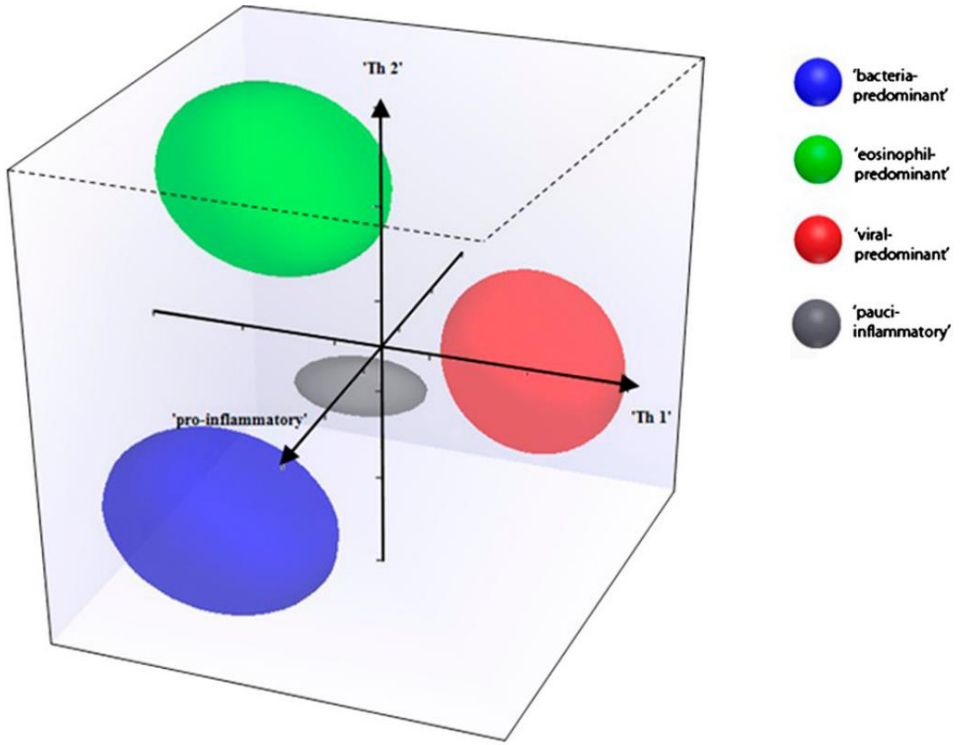


TABLE 2. BIOLOGIC CLUSTERS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATIONS, WITH CLINICAL EXACERBATION AND BASELINE CHARACTERISTICS

	Cluster 1: Bacteria-predominant	Cluster 2: Eosinophil-predominant	Cluster 3: Virus-predominant	Cluster 4: Pauciinflammatory	*P* Value
Exacerbation characteristics					
Number (%)	52 (35)	44 (30)	36 (24)	16 (11)	—
Sputum TNFRII (pg/ml)*	1,722 (1,402–2,117)	353 (287–433)	1,254 (969–1,623)	77 (41–147)	<0.0001
Sputum CXCL11 (pg/ml)*	3.1 (2.2–4.3)	10.9 (7.7–15.5)	799 (415–1,539)	17.3 (5.6–53.1)	<0.0001
Sputum CCL17 (pg/ml)*	5.5 (4.5–6.7)	34.8 (27.3–44.5)	23.5 (16.2–34.1)	4.7 (3.5–6.3)	<0.0001
Bacterial exacerbation, % (95% CI)	86 (73–92)	29 (18–45)	44 (28–61)	31 (12–58)	<0.0001
Viral exacerbation, % (95% CI)	22 (13–35)	10 (3–23)	57 (39–73)	30 (10–61)	<0.0001
Eosinophilic exacerbation, % (95% CI)	6 (1–16)	60 (45–74)	28 (16–44)	27 (10–52)	<0.0001
Δ FEV_1, ml†	−132 (−251 to −35)	−110 (−230 to −31)	−232 (−340 to −124)	−280 (−524 to −36)	0.32
Δ CRQ, units †	−0.9 (−1.2 to −0.6)	−0.9 (−1.3 to −0.5)	−0.9 (−1.4 to −0.4)	−1 (−1.9 to −0.1)	0.99
Δ VAS_{TOTAL}, mm†	79 (42–116)	80 (41–119)	120 (86–154)	73 (38–108)	0.39
Baseline characteristics					
Number, (%)	28 (37)	19 (25)	20 (27)	8 (11)	—
Male, n (%)	18 (64)	14 (74)	14 (70)	7 (88)	0.63
Age, yrs‡	69 (52–84)	68 (45–88)	70 (49–84)	69 (61–85)	0.62
Current smokers, n (%)	8 (29)	8 (42)	4 (20)	3 (38)	0.48
Pack-years smoked‡	44 (10–122)	50 (20–106)	47 (10–134)	72 (23–120)	0.11
Exacerbation rate in previous 12 mo	3.8 (0.5)	4.3 (0.5)	4 (0.7)	4.9 (1.2)	0.58
Exacerbation rate during study	3.8 (0.3)	3.6 (0.4)	3.2 (0.3)	3.1 (0.5)	0.64
Inhaled corticosteroid dose, μg§	1,507 (147)	1,567 (133)	1,470 (160)	1,150 (188)	0.55
Residual volume, %	134 (8)	150 (9)	120 (8)	146 (23)	0.11
TLCO % predicted	56 (5)	59 (5)	57 (6)	46 (7)	0.62
$FEV_{1\%}$ predicted, baseline	53 (3)	51 (5)	53 (5)	40 (7)	0.34
FEV_1/FVC ratio (%)	51 (2)	47 (2)	50 (3)	47 (5)	0.67
CRQ_{TOTAL}, units	4.14 (0.20)	3.90 (0.22)	4.10 (0.26)	3.66 (0.50)	0.74
VAS_{TOTAL}, mm	178 (15)	142 (18)	124 (18)	147 (37)	0.14
Total sputum cell count ($\times 10^6$ cells/g)*	8.3 (5.5–12.5)	2.3 (1.6–3.2)	2.5 (1.2–5.3)	3.5 (1.2–10.7)	0.002
Sputum neutrophil count, %	75 (5)	53 (4)	68 (4)	81 (6)	0.003
Sputum eosinophil count, %*	1 (0.6–1.6)	3.1 (1.4–6.6)	1 (0.5–1.9)	0.5 (0.2–1)	0.012
Bacterial colonization, % (95% CI)	63 (48–77)	27 (15–43)	11 (3–29)	38 (18–61)	0.001

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

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

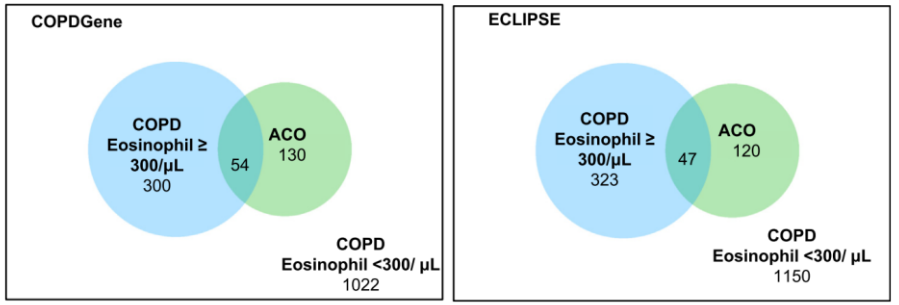
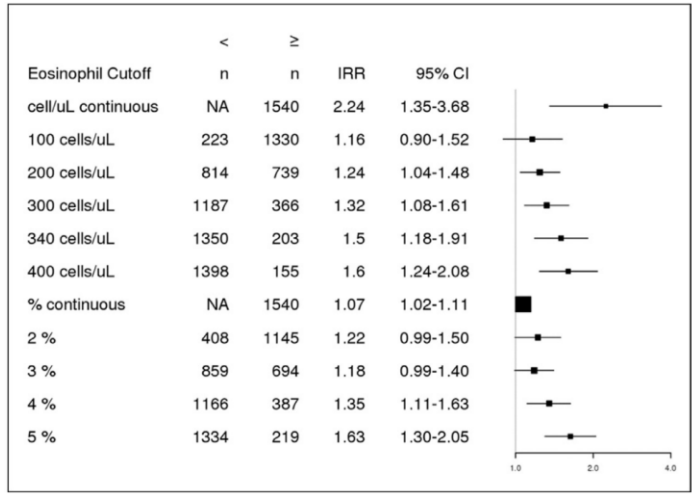


FIG 3. Venn diagrams of the number of subjects with ACO (defined by asthma diagnosis before the age of 40 years)[30] and patients with COPD with blood eosinophil counts of 300 cells/µL or greater in the COPDGene and ECLIPSE studies.

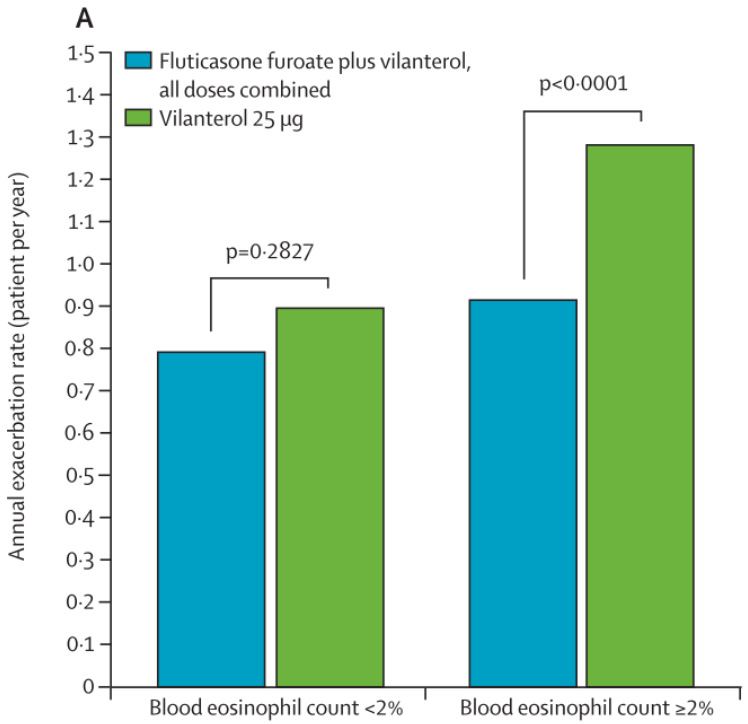
	COPDGene: Year before visit 2 (cross-sectional)				COPDGene: Longitudinal follow-up	
	Exacerbation frequency* (n = 1,553)		Frequent exacerbation† (n = 1,281)		Exacerbation rate* (n = 1,113)	
Factors	**IRR* (95% CI)**	***P* value**	**OR† (95% CI)**	***P* value**	**IRR* (95% CI)**	***P* value**
Age	**0.98 (0.97-1.00)**	**.007**	**0.96 (0.94-0.99)**	**.003**	0.99 (0.97-1.01)	.48
Female sex	**1.43 (1.20-1.71)**	**<.001**	**1.83 (1.30-2.58)**	**<.001**	0.87 (0.65-1.15)	.31
Nonwhite race	**0.73 (0.57-0.92)**	**.008**	**0.63 (0.40-0.99)**	**.05**	**1.73 (1.19-2.55)**	**.005**
SGRQ total score‡	**1.02 (1.02-1.03)**	**<.001**	**1.04 (1.03-1.05)**	**<.001**	**1.02 (1.01-1.03)**	**<.001**
Postbronchodilator FEV_1 (% predicted)§	**0.98 (0.98-0.99)**	**<.001**	**0.97 (0.96-0.98)**	**<.001**	**0.99 (0.98-1.00)**	**.003**
GERD	**1.33 (1.11-1.59)**	**.002**	1.35 (0.95-1.91)	.09	1.08 (0.81-1.45)	.57
Current smoking	**0.71 (0.57-0.89)**	**.002**	**0.56 (0.37-0.84)**	**.006**	**0.63 (0.45-0.90)**	**.01**
Previous exacerbations	NA	NA	NA	NA	**2.51 (1.87-3.37)**	**<.001**
WBC count	1.00 (0.96-1.04)	.97	1.02 (0.94-1.10)	.66	1.03 (0.96-1.10)	.44
Eosinophil count ≥300 cells/µL	**1.32 (1.08-1.61)**	**.006**	**1.58 (1.07-2.30)**	**.019**	1.33 (0.92-1.95)	.13

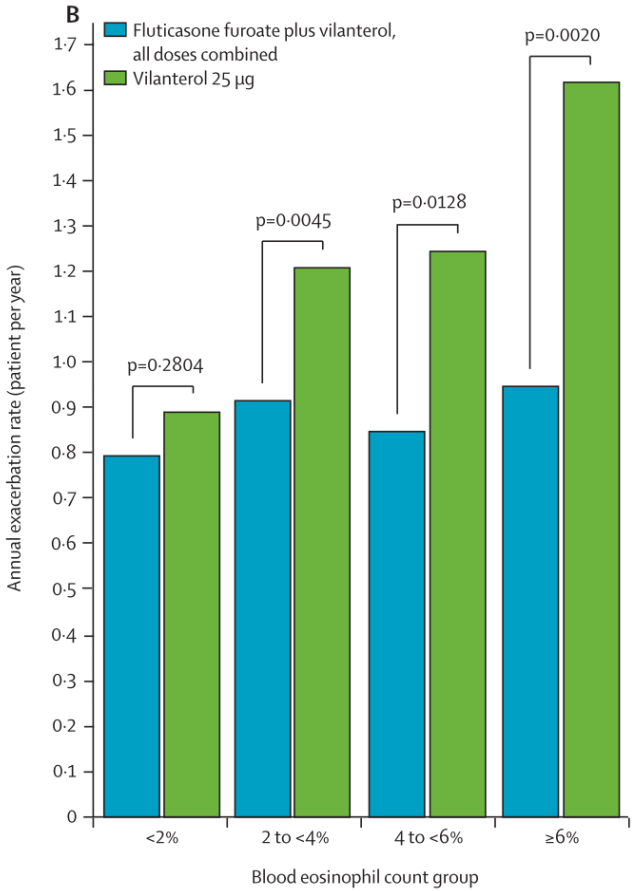


J Allergy Clin Immunol. 2018 Jun;141(6):2037-2047.e10.

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





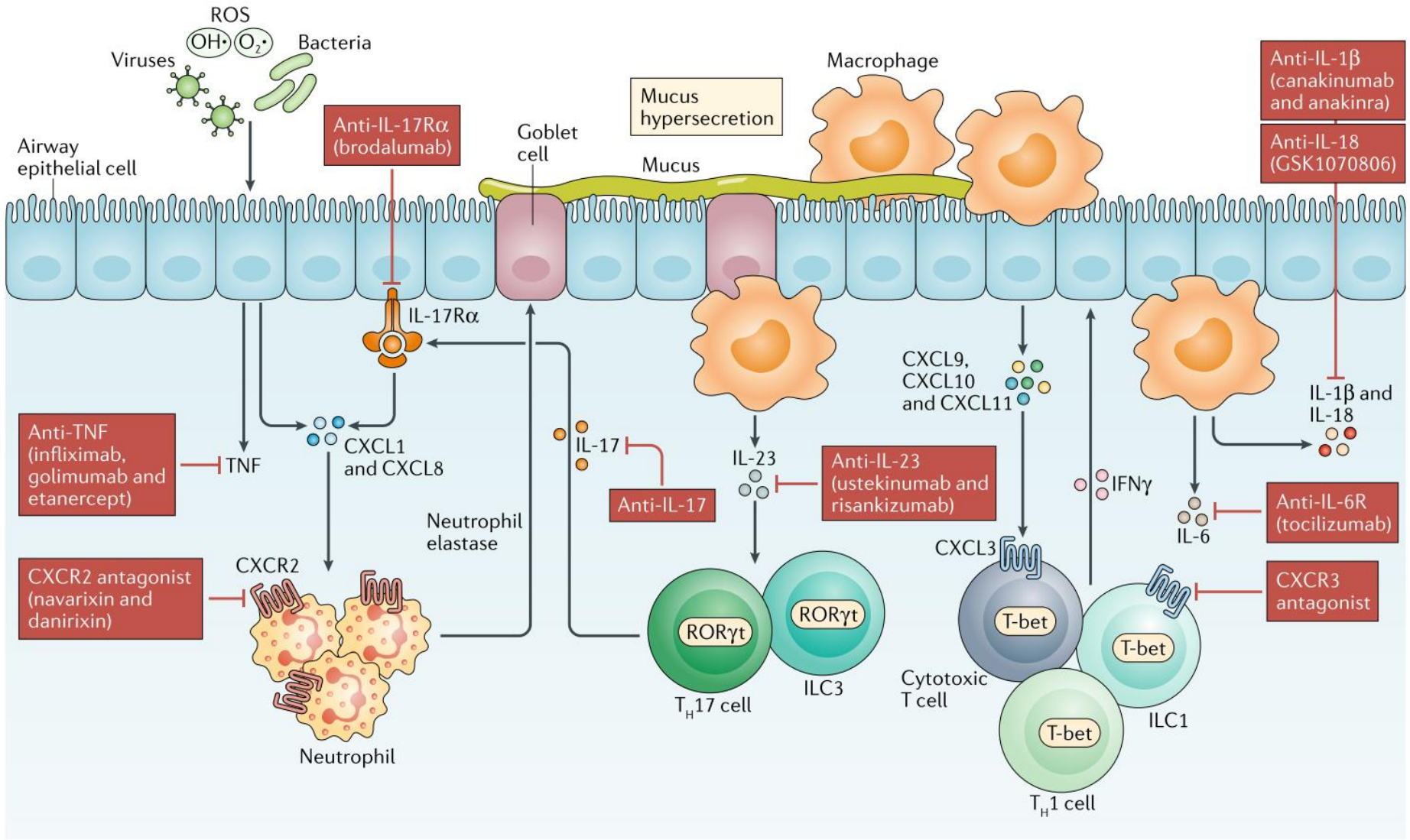
Lancet Respir Med. 2015 Jun;3(6):435-42

Table 1 Eosinophil thresholds and findings in recent COPD clinical trials

Trial	Intervention	Eosinophil thresholds	Clinical findings
ECLIPSE[8]	NA	Blood ≥2% of total leukocytes or ≥150 cells/μL; sputum ≥2% of total leukocytes	Some evidence of clinical benefit in patients with blood eosinophil counts persistently ≥2% vs <2% for blood and sputum counts
TRISTAN[49]	Salmeterol 50 μg BID vs fluticasone propionate 500 μg BID, vs salmeterol 50 μg + fluticasone propionate 500 μg BID, vs placebo	Blood ≥2% of total leukocytes	Greater reduction in moderate/severe exacerbation rates for patients who received ICS/LABA with ≥2% eosinophils vs <2%
ISOLDE[57]	Fluticasone propionate 500 μg BID vs placebo	Blood ≥2% of total leukocytes	Patients with ≥2% eosinophils had slower rates of FEV_1 decline
FLAME[56]	Indacaterol 110 μg + glycopyrronium 50 μg QD vs salmeterol 50 μg + fluticasone 500 μg BID	Blood ≥2% of total leukocytes	Effect of indacaterol–glycopyrronium vs fluticasone–salmeterol on COPD exacerbations independent of baseline eosinophil count
WISDOM[53]	Tiotropium 18 μg QD, salmeterol 50 μg BID + fluticasone propionate 500 μg BID for 6 weeks, then patients were randomized to continued triple therapy or gradual withdrawal of fluticasone propionate over 12 weeks	Blood ≥2%, ≥4%, ≥5%, and ≥6% of total leukocytes; ≥150, ≥300, and ≥400 cells/μL	Baseline blood eosinophil counts of ≥4% or 300 cells/μL correlated with the most deleterious effect of ICS withdrawal on moderate or severe exacerbation rates in patients with severe–very severe COPD
FORWARD[55]	Beclomethasone dipropionate (100 μg)–formoterol fumarate (6 μg) BID vs formoterol fumarate 12 μg BID	Blood <110, <182, <280, and ≥280 cells/μL	Pattern of increasing exacerbation frequency at the highest quartile (≥280 cells/μL) in patients treated with formoterol fumurate alone
NCT01227278[54]	Benralizumab 100 mg SC injection Q4W for first 3 doses, then Q8W for next five doses vs placebo	Blood <150, ≥150, <200, ≥200, <300, and ≥300 cells/μL	Numerical but nonsignificant improvements in acute exacerbations, quality of life, and FEV_1 noted in the ≥200 and ≥300 cells/μL groups
NCT01009463 and NCT01017952[90]	Fluticasone furoate/vilanterol 50/25, 100/25, or 200/25 μg (QD) or vilanterol 25 μg alone (QD)	Blood 2.4% of total leukocytes	Linear relationship between eosinophil concentrations and treatment outcomes. Cluster-analysis algorithm separated the clusters close to the median percentage of blood eosinophils (2.6%)

Int J Chron Obstruct Pulmon Dis. 2018 Jan 17;13:335-349.

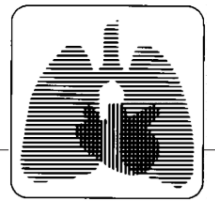
Biologics targeting neutrophilic inflammation



Targeting non-type 2 immunity in airway disease

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

Anti-IL-8 (ABX-IL8)

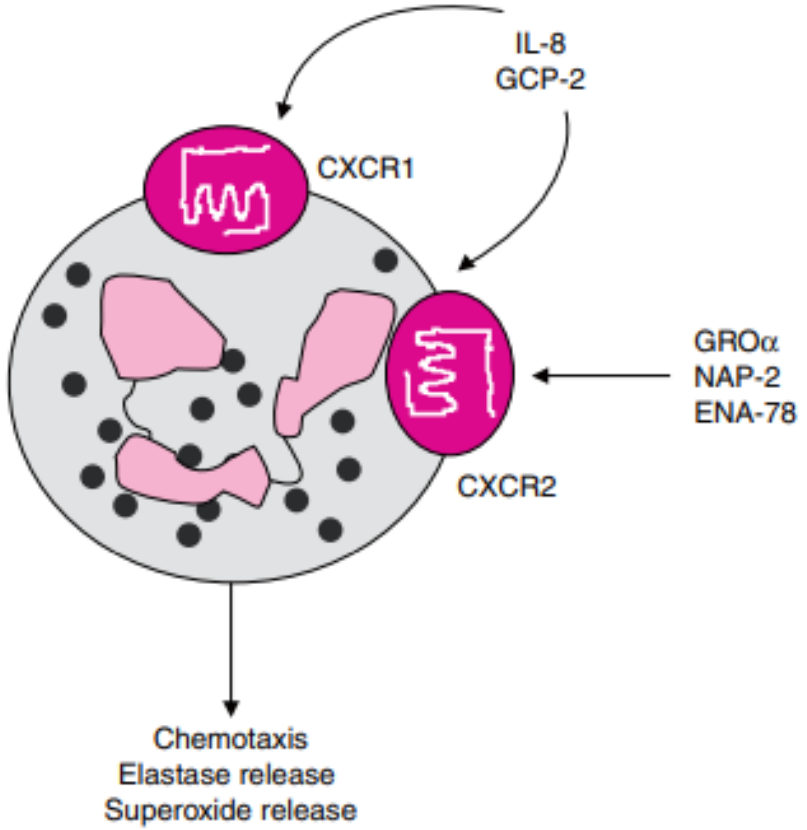


preliminary reports

Efficacy and Safety of a Monoclonal Antibody Recognizing Interleukin-8 in COPD*

A Pilot Study

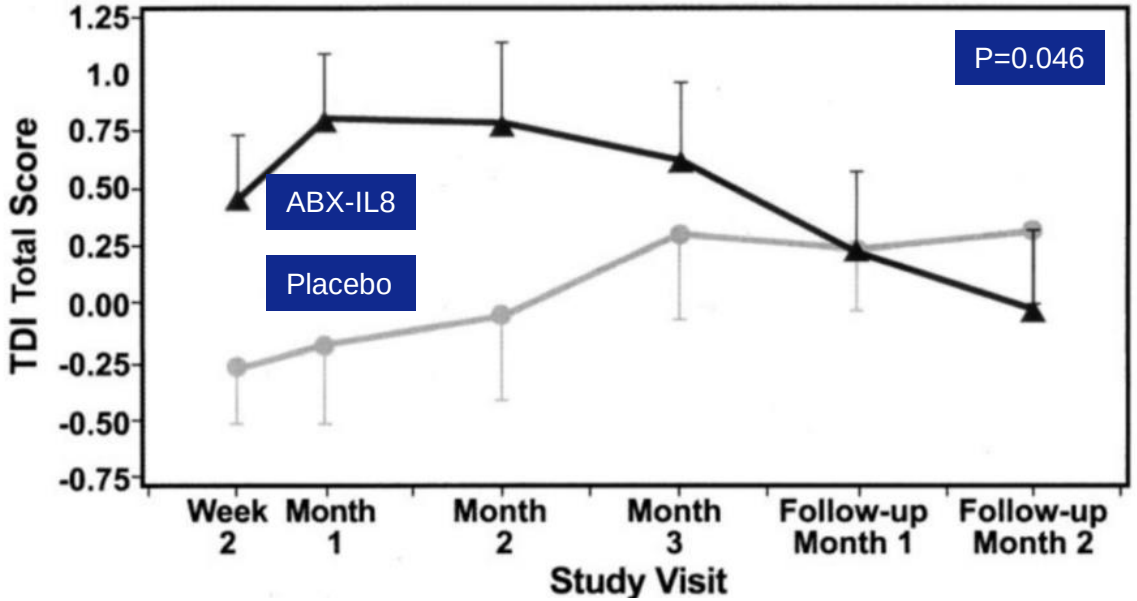
Donald A. Mahler, MD, FCCP; Saling Huang, PhD; Mohammad Tabrizi, PhD; and Gregory M. Bell, MD

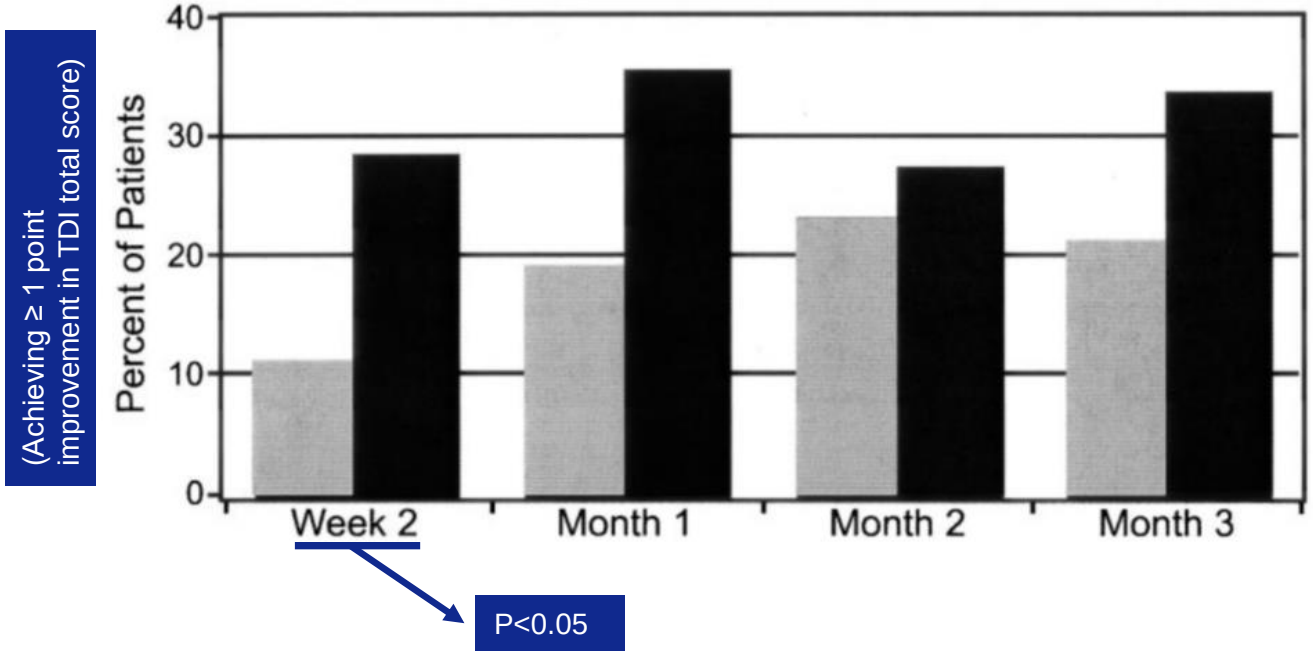


Inclusion criteria

- Age > 50 years
- Diagnosis of COPD and a history of CB
- >20PY smoking Hx.
- mMRC≥1
- FEV1 30-70% & FVC <70%

Chest. 2004 Sep;126(3):926-34



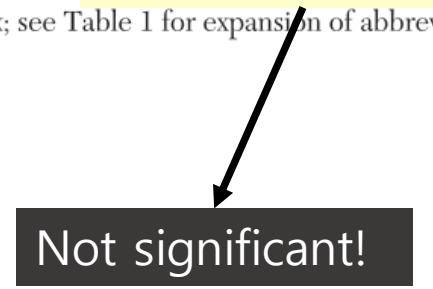


Chest. 2004 Sep;126(3):926-34

Table 3—*Results of the TDI Total Scores, Lung Function, Health Status, and the 6-min Walking Distance at the Different Visits**

	Baseline		Week 2		Month 1		Month 2		Month 3	
Variables	ABX-IL8	Placebo	ABX-IL8	Placebo	ABX-IL8	Placebo	ABX-IL8	Placebo	ABX-IL8	Placebo
BDI/ TDI	5.6 (0.25)	5.6 (0.35)	+0.5 (0.26)	−0.3 (0.25)	+0.8 (0.28)	−0.2 (0.34)	+0.8 (0.34)	0 (0.38)	+0.6 (0.32)	0.3 (0.36)
FEV_1, L	1.3 (0.06)	1.2 (0.06)	1.3 (0.06)	1.3 (0.07)	1.3 (0.07)	1.2 (0.06)	1.2 (0.06)	1.2 (0.06)	1.3 (0.06)	1.3 (0.06)
FVC, L	3.08 (0.13)	3.09 (0.12)	3.03 (0.12)	3.07 (0.12)	3.04 (0.12)	3.05 (0.12)	3.00 (0.11)	3.03 (0.13)	2.98 (0.12)	3.08 (0.12)
TLC, L	7.1 (0.25)	6.6 (0.23)	ND	ND	ND	ND	ND	ND	7.0 (0.23)	6.7 (0.22)
FRC, L	3.9 (0.19)	3.6 (0.17)	ND	ND	ND	ND	ND	ND	4.0 (0.18)	3.6 (0.16)
SGRQ	50.0 (2.0)	47.6 (2.6)	ND	ND	48.7 (1.9)	47.9 (2.8)	47.4 (2.3)	46.3 (2.9)	46.4 (2.0)	46.1 (2.7)
6MW, m	400.3 (13.3)	401.1 (13.4)	ND	ND	417.3 (14.1)	396.7 (15.7)	403.0 (12.3)	405.3 (16.1)	398.8 (12.9)	418.8 (18.5)

*All available data at each visit are included and presented as mean (SEM). TLC = total lung capacity; FRC = functional residual capacity; 6MW = 6-min walk; see Table 1 for expansion of abbreviation.



Chest. 2004 Sep;126(3):926-34

Pulmonary Pharmacology & Therapeutics 31 (2015) 36–41

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Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

The safety and tolerability of oral AZD5069, a selective CXCR2 antagonist, in patients with moderate-to-severe COPD

A.M. Kirsten [a, *], K. Förster [b], E. Radeczky [c], A. Linnhoff [d], B. Balint [e], H. Watz [a], H. Wray [f], L. Salkeld [f], M. Cullberg [f], B. Larsson [f]

Table 2
Number of patients who experienced at least one adverse event, described by system organ class and preferred term (with a frequency of >1% in any group).

	Number (%) of patients[a]		
	Placebo bid (n = 29)	AZD5069 50 mg bid (n = 30)	AZD5069 80 mg bid (n = 28)
System organ class			
Patients with any AE	9 (31)	10 (33)	6 (21)
Infections and infestations	5 (17)	5 (17)	3 (11)
Gastrointestinal disorders	1 (3)	3 (10)	1 (4)
General disorders and administration site conditions	2 (7)	1 (3)	1 (4)
Investigations	1 (3)	3 (10)	1 (4)
Metabolism and nutrition disorders	0	0	1 (4)
Musculoskeletal and connective tissue disorders	2 (7)	0	1 (4)
Nervous system disorders	1 (3)	0	1 (4)
Respiratory, thoracic and mediastinal disorders	2 (7)	4 (13)	1 (4)
Cardiac disorders	2 (7)	1 (3)	0
Preferred term			
COPD (*exacerbation*)	0	2 (7)	1 (4)
Neutrophil count decreased[b]	0	3 (10)	1 (4)
Diarrhea	1 (3)	2 (7)	0
Nasopharyngitis	2 (7)	4 (13)	0
Pyrexia	2 (7)	1 (3)	0

Pulm Pharmacol Ther. 2015 Apr;31:36-41

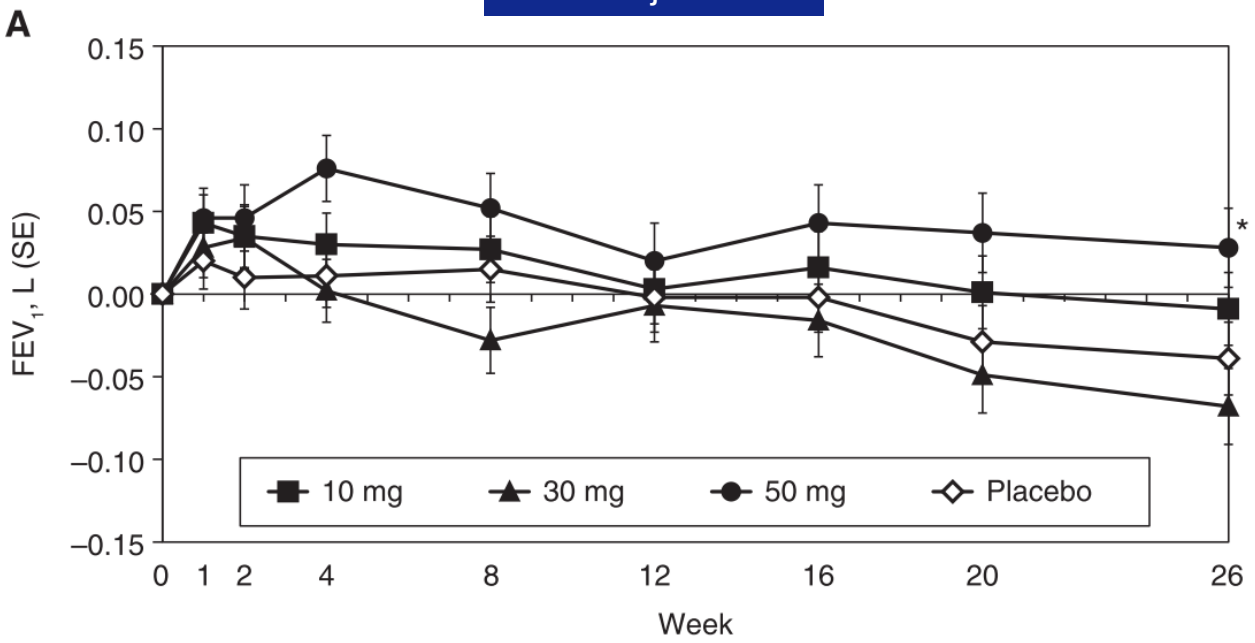
ORIGINAL ARTICLE

CXCR2 Antagonist MK-7123

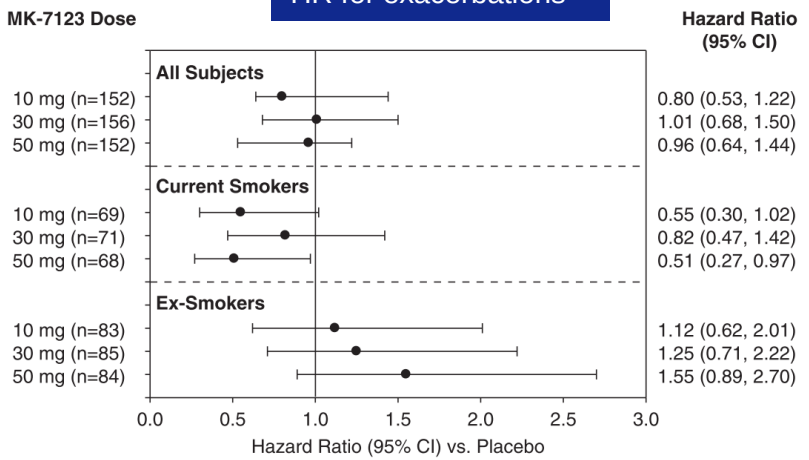
A Phase 2 Proof-of-Concept Trial for Chronic Obstructive Pulmonary Disease

Stephen I. Rennard[1], David C. Dale[2], James F. Donohue[3], Frank Kanniess[4], Helgo Magnussen[5], E. Rand Sutherland[6], Henrik Watz[5], Susan Lu[7], Paul Stryszak[7], Elizabeth Rosenberg[7], and Heribert Staudinger[7]

FEV1 trajectories



HR for exacerbations



Change in SGRQ total score

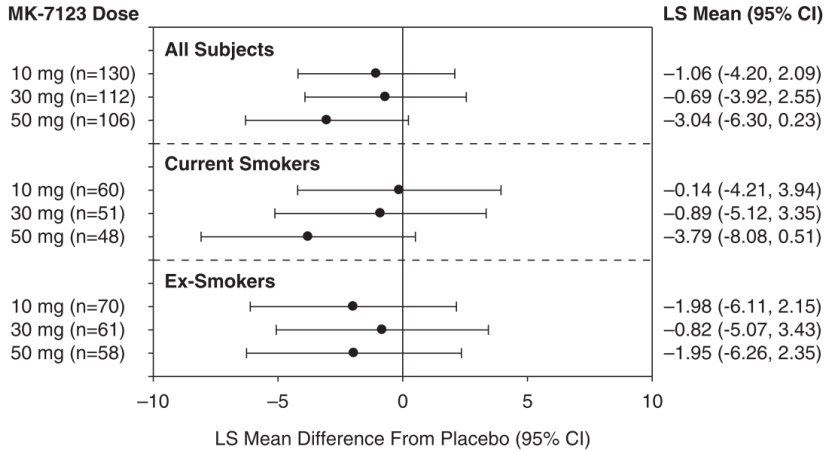


Figure 4. Change from baseline after 6 months of treatment with MK-7123 doses versus placebo in total score in St. George's Respiratory Questionnaire. CI = confidence interval; LS = least squares.

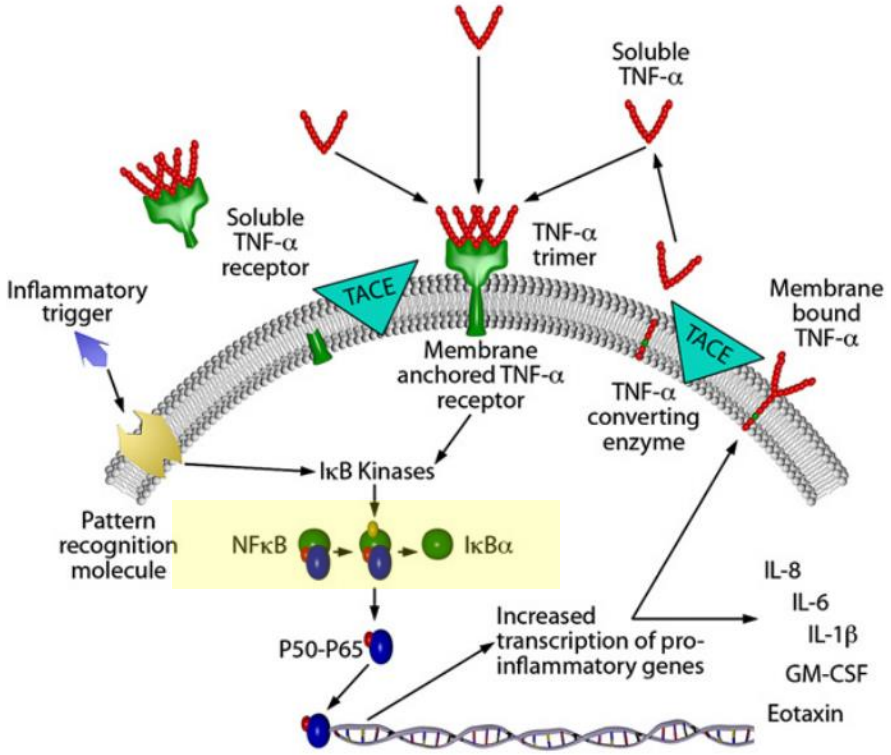
Am J Respir Crit Care Med. 2015 May 1;191(9):1001-11.

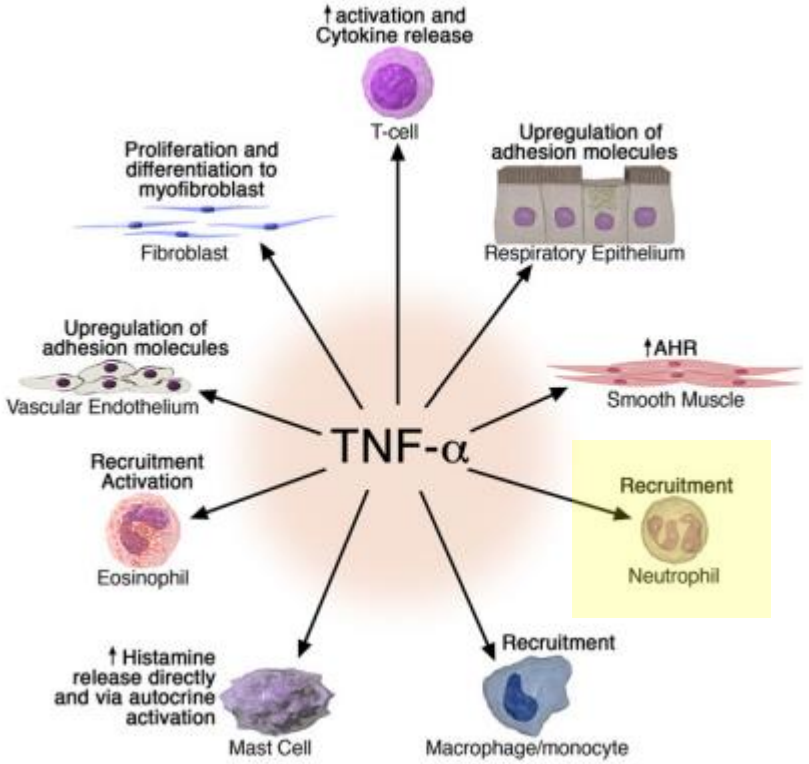
Side-effects

	MK-7123			
	10 mg	30 mg	50 mg	Placebo
At 6 mo	N = 152	N = 156	N = 152	N = 154
Treatment-emergent AEs	110 (72.4)	116 (74.4)	112 (73.7)	97 (63.0)
Treatment-related AEs*	24 (15.8)	45 (28.8)	55 (36.2)	22 (14.3)
Serious AEs	11 (7.2)	18 (11.5)	13 (8.6)	12 (7.8)
Serious treatment-related AEs	1 (0.7)	4 (2.6)	1 (0.7)	4 (2.6)
AEs leading to discontinuation	10 (6.6)	31 (19.9)	37 (24.3)	9 (5.8)
Death	1 (0.7)	2 (1.3)	1 (0.7)	1 (0.6)
AEs of special interest				
At 6 mo	N = 152	N = 156	N = 152	N = 154
Drop in ANC to $<1.5 \times 10^9$/L (mandatory discontinuation)	4 (2.6)	18 (11.5)	28 (18.4)	1 (0.6)
Infections				
Total	52 (34.2)	58 (37.2)	41 (27.0)	48 (31.8)
Respiratory infections	46 (30.3)	47 (30.1)	34 (22.4)	37 (24.0)
Pneumonia	3 (2.0)	4 (2.6)	1 (0.7)	3 (1.9)
Cardiac AEs	8 (5.3)	5 (3.2)	10 (6.6)	7 (4.5)
At ⩾12 mo	N = 75	N = 63	N = 55	N = 82
Infections				
Total	36 (48.0)	29 (46.0)	25 (45.5)	29 (35.4)
Respiratory infections	31 (41.3)	26 (41.3)	21 (38.2)	23 (28.0)
Pneumonia	1 (1.3)	1 (1.6)	3 (5.5)	4 (4.9)
Cardiac AEs	7 (9.3)	2 (3.2)	5 (9.1)	7 (8.5)

Am J Respir Crit Care Med. 2015 May 1;191(9):1001-11.

Anti-TNFα (Infliximab, Etanercept)





J Allergy Clin Immunol. 2008 Jan;121(1):5-10

First Study of Infliximab Treatment in Patients with Chronic Obstructive Pulmonary Disease

Hester van der Vaart, Gerard H. Koëter, Dirkje S. Postma, Henk F. Kauffman, and Nick H. T. ten Hacken

Departments of Pulmonology and Allergology, University Medical Center Groningen, Groningen, the Netherlands

- Single-center, double-blind RCT, phase II trial
- 22 current smokers with mild-to-moderate COPD.
  - 14 patients: three infusions of infliximab
  - 8 patients : placebo

TABLE 2. LUNG FUNCTION PARAMETERS

	Baseline	Day 2	Week 2	Week 6	Week 8
Placebo					
	7.4	5.1	6.2	4.4	5.9
eNO, ppb	4.7–17.8	3.4–11.1	3.3–17.1	2.7–9.1	2.6–11.6
	76.6	75.2	76.4	80.9	79.4
FEV_1, % pred	52.9–100.9	49.3–103.6	50.7–98.6	53.0–99.5	57.0–101.0
	76.1	77.2	76.9	77.8	80.8
TL_{CO}/VA, % pred	48.0–113.0	49.3–118.8	54.0–115.6	50.7–118.8	45.3–114.9
	114.1	109.4	107.0	110.6	101.1
REE, % pred	89.3–125.2	81.5–125.5	86.9–121.1	100.9–124.7	93.7–122.0
	20.4				10.3
PC_{20} AMP, mg/ml*	3.7–640	ND	ND	ND	0.3–84.6‡
Infliximab Treatment					
	7.7	9.4†	8.7	9.6‡	9.7‡
eNO, ppb	3.1–26.1	3.8–28.7	3.8–37.5	2.8–47.5	6.0–29.1
	77.9	79.2	77.7	79.6	76.8
FEV_1, % pred	53.6–96.4	49.3–93.0	55.5–100.6	42.6–96.0	46.4–93.1
	83.7	83.0	85.8	81.9	82.3
TL_{CO}/VA, % pred	57.6–108.6	54.2–107.8	56.9–120.1	53.5–107.9	51.4–102.9
	102.4	101.9	104.5	103.8	103.5
REE, % pred	83.3–116.0	88.6–129.5	95.7–121.3	91.3–124.0	90.4–136.6
	12.2				11.4
PC_{20} AMP, mg/ml*	1.13–640	ND	ND	ND	0.9–640‡

Definition of abbreviations: eNO = exhaled nitric oxide; ND = not done; REE = resting energy expenditure; TL_{CO}/VA = diffusion capacity for carbon monoxide corrected for the alveolar volume.
Values are presented as medians or geometric means (*) with ranges.
† The change from baseline is significantly different with infliximab compared with placebo, $p < 0.05$.
‡ PC_{20} AMP is measured at Week 9.

TABLE 3. SPUTUM INFLAMMATORY PARAMETERS

	Baseline	Day 2	Week 2	Week 6	Week 8
Placebo					
	7.7	5.8	8.0	7.1	7.1
Sputum weight, g	1.6–13.5	2.1–14.5	1.2–12.1	2.8–12.7	1.0–10.4
	2.2	2.5	4.3	3.8	1.9
Total cells, 10^6/ml	1.1–14.8	0.6–12.5	1.9–5.7	0.6–5.3	0.6–12.0
	26.7	35.7	27.0	26.8	37.8
Macrophages, %	21.0–41.2	19.0–62.2	13.3–35.2	9.8–45.5	13.5–47.3
	68.3	61.4	66.7	68.7	57.3
Neutrophils, %	56.8–77.3	36.5–74.3	49.0–73.8	50.5–84.2	49.7–82.0
	0.7	0.8	1.0	1.2	1.0
Eosinophils, %	0.3–1.8	0.0–1.7	0.5–1.80	0.3–2.5	0.5–2.0
	0.3	0.7	0.7	0.7	0.5
Lymphocytes, %	0.2–2.0	0.0–0.8	0.0–5.2	0.0–1.5	0.0–1.8
	2,470	2,317	2,071	1,756	1,811
IL-8, ng/ml	1,117–20,749	1,485–14,286	1,224–28,409	697–29,015	932–27,737
	146	106	103	87.4	80.4
IL-6, ng/ml	16.3–200	12.4–260	20.1–584	10.7–428	9.6–596
Infliximab Treatment					
	6.0	7.5	6.2	7.7	8.0
Sputum weight, g	1.3–17.0	1.9–16.3	3.7–14.0	2.3–12.6	1.6–14.8
	3.8	3.5	4.6	5.2	5.2
Total cells, 10^6/ml	0.2–24.5	0.4–11.5	0.5–23.2	0.7–29.2	1.1–48.9
	26.3	36.0	26.8	27.1	27.0
Macrophages, %	16.3–48.7	10.5–56.5	6.5–55.5	10.2–42.2	4.8–52.3
	66.5	49.7	62.9	62.0	65.7
Neutrophils, %	48.7–80.2	31.3–81.3	24.3–90.3	47.5–85.0	18.3–92.0
	1.3	1.5	1.8	1.4	1.5
Eosinophils, %	0.3–16.0	0.3–18.5	0.2–23.7	0.0–18.7	0.0–18.7
	0.5	0.5	0.5	0.7	0.8
Lymphocytes, %	0.2–4.8	0.0–1.3	0.0–2.3	0.0–4.5	0.3–3.0
	7,199	4,102	5,334	4,613	3,624
IL-8, ng/ml	954–16,526	1,197–13,430	1,040–20,490	439–32,280	1,264–32,412
	223	130	179	164	123
IL-6, ng/ml	18.2–1,181	12.5–369	3.8–1,595	7.7–1,926	9.8–1,181

Definition of abbreviation: IL = interleukin.
Values are presented as medians with ranges. There were no significant differences between the two groups.

TABLE 4. ADVERSE EVENTS

	Infliximab, No. Patients ($n = 14$)	Placebo, No. Patients ($n = 8$)
Coughing	8*	0
Sputum production	5	1
Dyspnea	4	2
Irritated bowel	3	1
Nose cold	3	0
Respiratory tract infection	3	3
Dizziness	3	0
Diarrhea	2	2
Chest pain	2	1
Myalgia	2	0

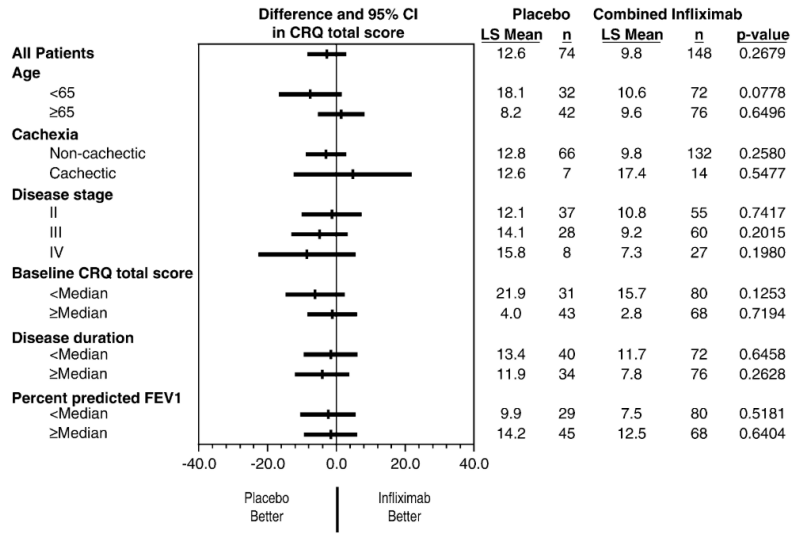
At each visit, the following question was asked to evaluate adverse events: "Did you have any complaints (especially fever, or extra or new symptoms) since the last visit?"
*$p < 0.05$ compared with placebo.

Am J Respir Crit Care Med. 2005 Aug 15;172(4):465-9

The Safety and Efficacy of Infliximab in Moderate to Severe Chronic Obstructive Pulmonary Disease

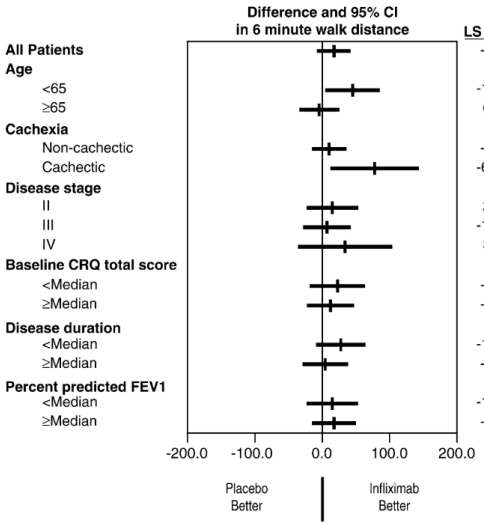
Stephen I. Rennard[1], Charles Fogarty[2], Steven Kelsen[3], William Long[4], Joe Ramsdell[5], James Allison[6], Donald Mahler[7], Constantine Saadeh[8], Thomas Siler[9], Phillip Snell[10], Phillip Korenblat[11], William Smith[12], Mitchell Kaye[13], Michael Mandel[14], Charles Andrews[15], Rachakonda Prabhu[16], James F. Donohue[17], Rosemary Watt[18], Kim Hung Lo[18], Rozsa Schlenker-Herceg[18], Elliot S. Barnathan[18], and John Murray[19], on behalf of the COPD Investigators

- Multicenter, double-blind RCT
- 234 patients with moderate to severe COPD
  - infliximab (3 mg/kg [n = 78] or 5 mg/kg [n = 79])
  - placebo (n // 77)
- Weeks 0, 2, 6, 12, 18, and 24
- Efficacy, health status, and safety were assessed through Week 44



	Placebo LS Mean	Placebo n	Combined Infliximab LS Mean	Combined Infliximab n	p-value
All Patients	12.6	74	9.8	148	0.2679
Age					
<65	18.1	32	10.6	72	0.0778
≥65	8.2	42	9.6	76	0.6496
Cachexia					
Non-cachectic	12.8	66	9.8	132	0.2580
Cachectic	12.6	7	17.4	14	0.5477
Disease stage					
II	12.1	37	10.8	55	0.7417
III	14.1	28	9.2	60	0.2015
IV	15.8	8	7.3	27	0.1980
Baseline CRQ total score					
<Median	21.9	31	15.7	80	0.1253
≥Median	4.0	43	2.8	68	0.7194
Disease duration					
<Median	13.4	40	11.7	72	0.6458
≥Median	11.9	34	7.8	76	0.2628
Percent predicted FEV1					
<Median	9.9	29	7.5	80	0.5181
≥Median	14.2	45	12.5	68	0.6404

Figure 2. Change from baseline to Week 24 in Chronic Respiratory Questionnaire (CRQ) total score (patients with available data; patients with GOLD stage I disease not included). Each *horizontal bar* represents the difference and 95% confidence interval in the least square (LS) means of change from baseline to Week 24 between the combined infliximab and placebo groups.



	Placebo LS Mean	Placebo n	Combined Infliximab LS Mean	Combined Infliximab n	p-value
All Patients	-7.4	69	10.0	134	0.1137
Age					
<65	-19.5	31	25.6	66	0.0190
≥65	6.5	38	2.2	68	0.7448
Cachexia					
Non-cachectic	-3.1	61	7.2	120	0.3607
Cachectic	-61.1	7	16.7	13	0.0180
Disease stage					
II	2.4	35	17.6	52	0.3937
III	-13.5	25	-6.5	53	0.6692
IV	3.0	8	37.0	23	0.2802
Baseline CRQ total score					
<Median	-6.1	27	16.5	69	0.2370
≥Median	-9.7	39	2.4	58	0.4473
Disease duration					
<Median	-14.8	38	12.8	62	0.1044
≥Median	-0.4	31	4.2	72	0.7678
Percent predicted FEV1					
<Median	-18.3	25	-3.5	68	0.4037
≥Median	-3.0	44	14.6	66	0.2358

Figure 3. Subgroup analysis for 6-min-walk distance at Week 24 (patients with available data). Each *horizontal bar* represents the difference (in meters) and 95% confidence interval (CI) in the least square (LS) means of change from baseline to Week 24 between the combined infliximab and placebo groups. Median values: age (66 yr), % predicted FEV_1 (43.0), disease duration (5.1 yr). Cachexia defined as fat-free mass less than 67% or less than 63% of ideal weight in males and females, respectively.

Am J Respir Crit Care Med. 2007 May 1;175(9):926-34.

TABLE 2. SUMMARY OF SAFETY ANALYSES FOR TREATED SUBJECTS THROUGH WEEK 44

Variable	Placebo (*n = 77*) n (%)	Infliximab, 3 mg/kg (*n = 77*) n (%)	Infliximab, 5 mg/kg (*n = 80*) n (%)
Extent of infliximab exposure over 24-wk period			
Mean no. of infliximab infusions	NA	4.9	5
AEs	68 (88.3)	68 (88.3)	74 (92.5)
All serious AEs	16 (20.8)	15 (19.5)	20 (25.0)
Related serious AEs	1 (1.3)	3 (3.9)	6 (7.5)
AEs leading to discontinuation of study agent	7 (9.1)	21 (27.3)	16 (20.0)
No. of subjects with most frequent AEs*			
COPD exacerbation	32 (41.6)	28 (36.4)	31 (38.8)
Serious COPD exacerbation	7 (9.1)	4 (5.2)	7 (8.8)
Upper respiratory tract infection	17 (22.1)	12 (15.6)	11 (13.8)
Sinusitis	6 (7.8)	9 (11.7)	13 (16.3)
Pain	7 (9.1)	12 (15.6)	7 (8.8)
Back pain	3 (3.9)	9 (11.7)	6 (7.5)
Headache	6 (7.8)	9 (11.7)	4 (5.0)
Pneumonia†	1 (1.3)	4 (5.2)	6 (7.5)
Diarrhea	8 (10.4)	5 (6.5)	3 (3.8)
Rhinitis	6 (7.8)	2 (2.6)	2 (2.5)
Infections			
Infections requiring oral or parenteral antimicrobial treatment	40 (51.9)	38 (49.4)	42 (52.5)
Serious infections	9 (11.7)	8 (10.4)	9 (11.3)
Infusion reactions	3 (3.9)	12 (15.6)	4 (5.0)
Delayed hypersensitivity reactions‡	0	2 (2.6%)	4 (5.0%)
Development of antibodies against dsDNA§	3/71 (4.2)	27/66 (40.9)	28/70 (40.0)

Definition of abbreviations: AE = adverse event; COPD = chronic obstructive pulmonary disease; dsDNA = double-stranded DNA; NA = not applicable.

* More than 5 subjects in any treatment group.

† Data represent combined cases of pneumonia and lobar pneumonia.

‡ AEs of serum sickness occurring at any time more than 1 hour after the end of an infusion, or a symptom complex characterized by arthralgia and/or myalgia with fever and/or rash occurring 1–14 days after the day of infusion.

§ Number of subjects/total number (%)

TABLE 3. MALIGNANCIES REPORTED THROUGH WEEK 44

Subject (*Age [yr]/Sex*)	Study Agent*	No. of Infliximab Infusions Received	Smoking Status (*Pack-years*)†	Duration of COPD Diagnosis (*yr*)	Malignancy
Malignancies reported Weeks 0–24 during study drug administration					
77/Male	Placebo	0	Current smoker (90)	2.2	Adenocarcinoma prostate
67/Male	3 mg/kg	2	Ex-smoker 1 yr (70)	4.9	Laryngeal carcinoma
67/Male	3 mg/kg	3	Current smoker (81)	2.5	Pulmonary carcinoma
72/Female	3 mg/kg	1	Ex-smoker > 1 yr (50)	10.3	Renal cell carcinoma
65/Male	3 mg/kg	5	Ex-smoker > 1 yr (82)	4.8	Bronchioalveolar carcinoma
77/Male	5 mg/kg	2	Current smoker (59)	8.1	Squamous cell carcinoma of larynx and epiglottis
Malignancies reported after Weeks 24–44 during safety follow-up					
56/Female	3 mg/kg	6	Current smoker (45)	0.2	Hodgkin's lymphoma (mixed cellularity)
74/Female	5 mg/kg	5	Current smoker (40)	0.3	Pulmonary carcinoma
59/Male	5 mg/kg	6	Current smoker (61.5)	0.8	Squamous cell carcinoma lung
59/Female	5 mg/kg	6	Ex-smoker > 1 yr (52.5)	11	Breast cancer

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

* Placebo or dosage of infliximab.

† One pack-year equals 20 cigarettes smoked per day for 1 year or equivalent.

ORIGINAL ARTICLE

TNFα antagonists for acute exacerbations of COPD: a randomised double-blind controlled trial

Shawn D Aaron,[1] Katherine L Vandemheen,[1] François Maltais,[2] Stephen K Field,[3] Don D Sin,[4] Jean Bourbeau,[5] Darcy D Marciniuk,[6] J Mark FitzGerald,[4] Parameswaran Nair,[7] Ranjeeta Mallick[1]

- Multicenter, double-blind RCT
- 81 patients with AE COPD
- randomly assigned them to treat with
  - 40 mg oral prednisone or
  - 50 mg etanercept
- Both groups received levofloxacin + inhaled bronchodilators.
- The primary endpoint : change in FEV_1
- Secondary endpoints : 90-day treatment failure rates / dyspnea / QOL

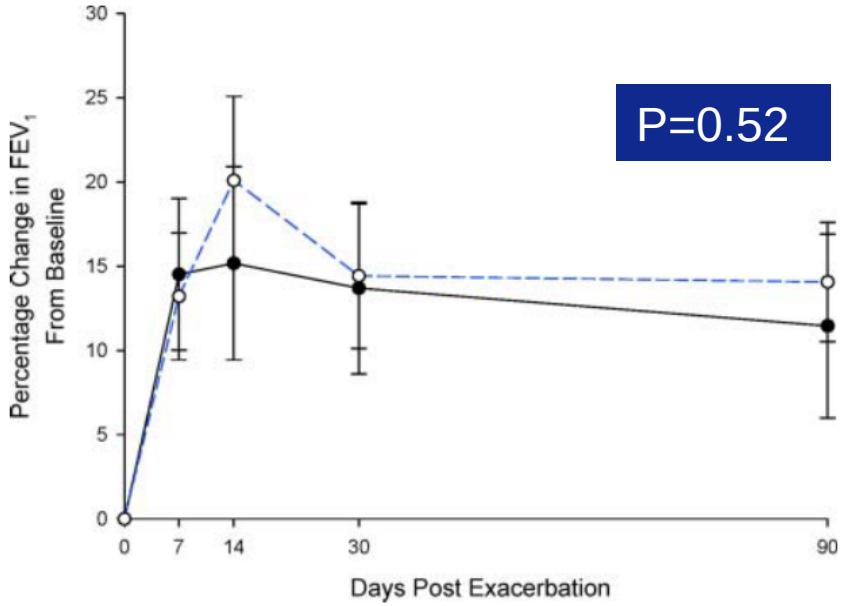


Figure 2 Changes in forced expiratory volume in 1 s (FEV_1) from baseline in the two treatment groups. Black solid line represents etanercept group, blue dashed line represents prednisone group.

Thorax. 2013 Feb;68(2):142-8.

Table 2 Ninety-day treatment failure outcome according to treatment assignment

Outcome	Etanercept (N=40)	Prednisone (N=38)	p Value
Death	1	0	
Mechanical ventilation	0	2	
Admission or readmission for COPD	2	1	
Intensification of therapy with open-label steroids	13	9	
Total	16 (40%)	12 (32%)	0.44

COPD, chronic obstructive pulmonary disease.

Table 3 Changes in dyspnoea and quality of life according to treatment assignment

Outcomes at 14 days	Etanercept (n=39)	Prednisone (n=37)	p Value
Transitional dyspnoea index score (95% CI)	2.92 (1.49 to 4.35)	4.65 (3.45 to 5.85)	0.07
Change in dyspnoea domain of the CRQ (95% CI)	1.08 (0.69 to 1.46)	1.50 (1.04 to 1.96)	0.16
Change in emotional domain of the CRQ (95% CI)	0.74 (0.40 to 1.08)	1.05 (0.64 to 1.45)	0.24
Change in fatigue domain of the CRQ (95% CI)	1.05 (0.59 to 1.50)	1.41 (0.95 to 1.88)	0.16
Change in mastery domain of the CRQ (95% CI)	0.69 (0.34 to 1.03)	1.45 (0.94 to 1.97)	0.015

CRQ, Chronic Respiratory Questionnaire.

Thorax. 2013 Feb;68(2):142-8.

Anti-IL-1

Calverley *et al. Respiratory Research* (2017) 18:153
DOI 10.1186/s12931-017-0633-7

Respiratory Research

RESEARCH Open Access

A randomised, placebo-controlled trial of anti–interleukin-1 receptor 1 monoclonal antibody MEDI8968 in chronic obstructive pulmonary disease

Peter M. A. Calverley[1,7*], Sanjay Sethi[2], Michelle Dawson[3], Christine K. Ward[4,5], Donna K. Finch[3], Mark Penney[3,6], Paul Newbold[4] and René van der Merwe[3]

- Phase II, multicenter double-blind RCT, 52wks trial
- Aged 45–75 years
- ≥2 exacerbations in the past year
- randomised 1:1 to receive placebo or MEDI8968 300 mg
- Primary endpoint : moderate/severe AE

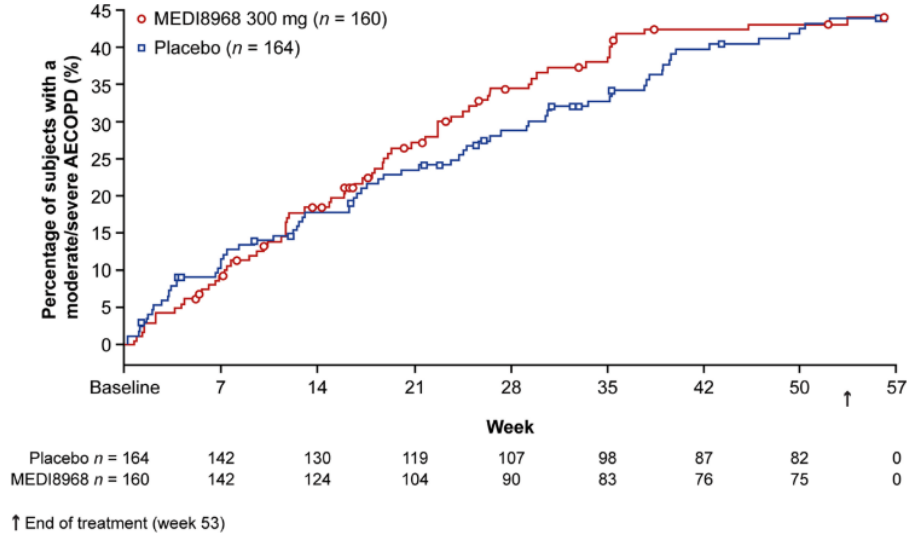


Fig. 2 Kaplan-Meier plot of time to first moderate or severe AECOPD (mITT population). Kaplan-Meier method used to estimate the percentage of subjects with a moderate/severe AECOPD*AECOPD* acute exacerbations of chronic obstructive pulmonary disease, *mITT* modified intention-to-treat

Respir Res. 2017 Aug 9;18(1):153.

Anti-IL-17A (CNTO 6785)

COPD: JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE
2017, VOL. 14, NO. 5, 476–483
https://doi.org/10.1080/15412555.2017.1335697

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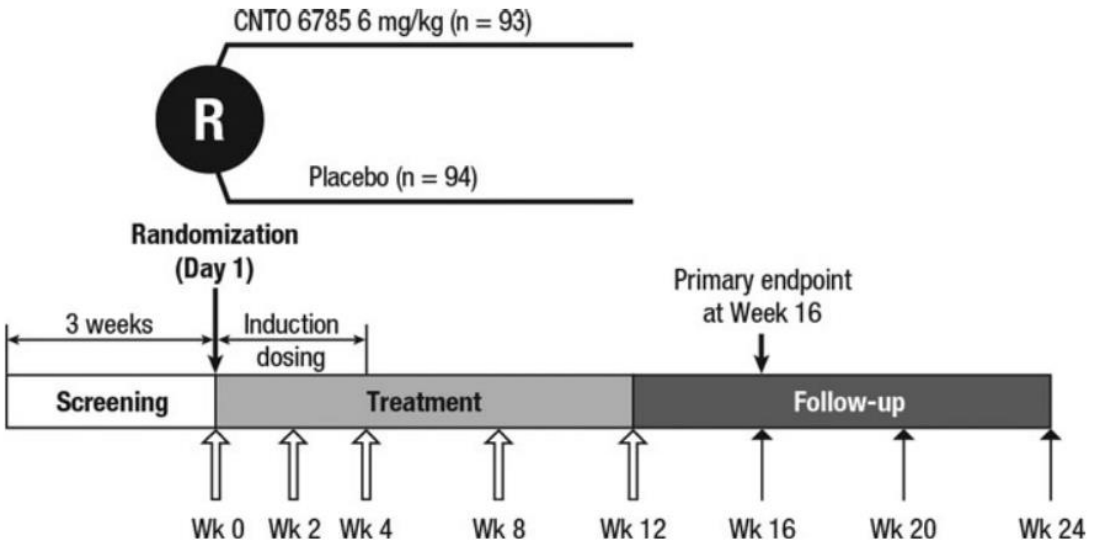
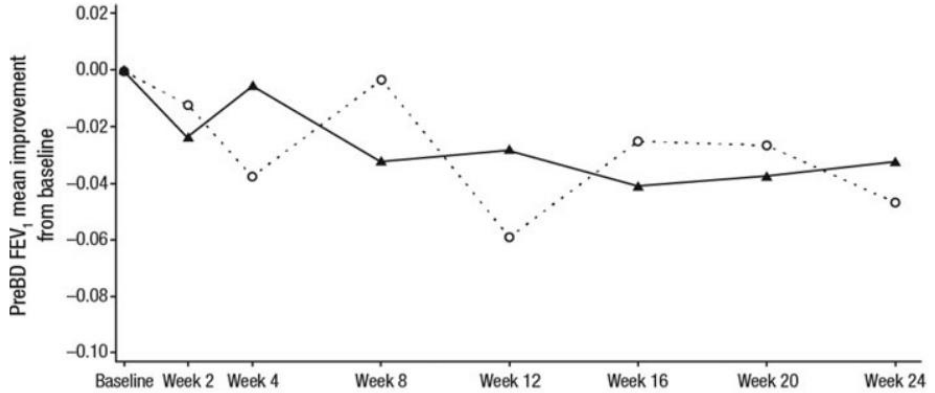
ORIGINAL RESEARCH

OPEN ACCESS Check for updates

A Randomized, Placebo-Controlled Phase 2 Trial of CNTO 6785 in Chronic Obstructive Pulmonary Disease

Andreas Eich[a], Veronika Urban[b], Marek Jutel[c], Jiri Vlcek[d], Jae Jeong Shim[e], Vasiliy I. Trofimov[f], Chong-Kin Liam[g], Ping-Hung Kuo[h], Yanyan Hou[i], Jun Xiao[i], Patrick Branigan[j], and Christopher D. O'Brien[j]





	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
PLACEBO	0	−0.012	−0.037	−0.003	−0.059	−0.025	−0.027	−0.047
CNTO 6785	0	−0.024	−0.005	−0.032	−0.028	−0.041	−0.037	−0.032
P value		0.653	0.270	0.260	0.274	0.574	0.736	0.635

No significant effect on 2ndary outcomes :
PostBD FEV1, SGRQ, rescue medicine…

COPD. 2017 Oct;14(5):476-483.

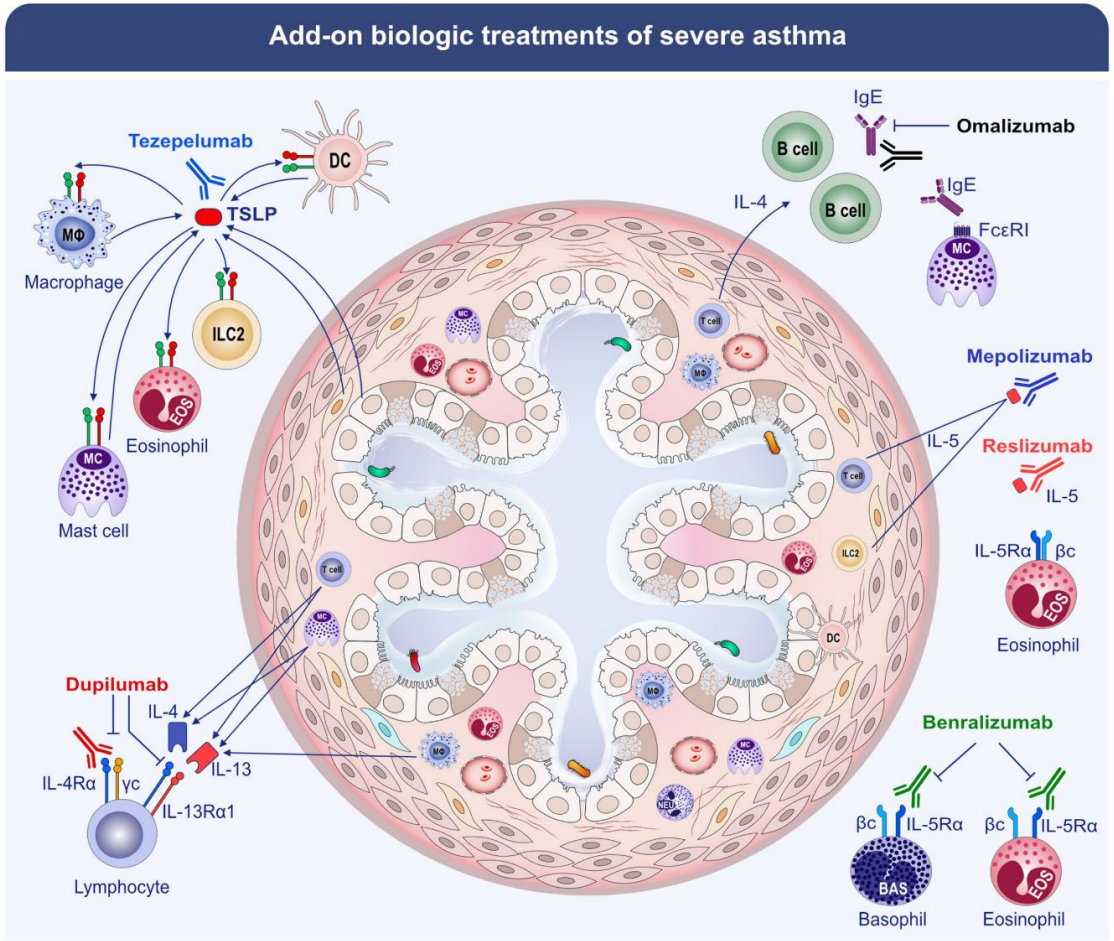
TABLE I. Completed phase 2 and 3 trials of biologics in COPD targeting neutrophilic pathways

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 N = 109 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 N = 81 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 N = 22 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 N = 157 NCT00056264	3 mg/kg or 5 mg/kg, 44 wk	↔ CRQ	↔ FEV_1, 6-min walk test, TDI ↑ Malignancy and pneumonia
MEDI 8968[57]; IL-1	A multicenter, randomized, placebo-controlled phase II trial of anti−IL-1 antibody (MEDI8968) in COPD N = 160 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 N = 186 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 ↔ SGRQ-C ↔ frequency of AECOPD ↔ weekly usage of rescue medication

AECOPD, Acute exacerbation of COPD; *CRQ*, Chronic Respiratory Disease Questionnaire; *SGRQ*, St George's Respiratory Questionnaire; *SGRQ-C*, St George's Respiratory Questionnaire-COPD; *TDI*, transitional dyspnea index.

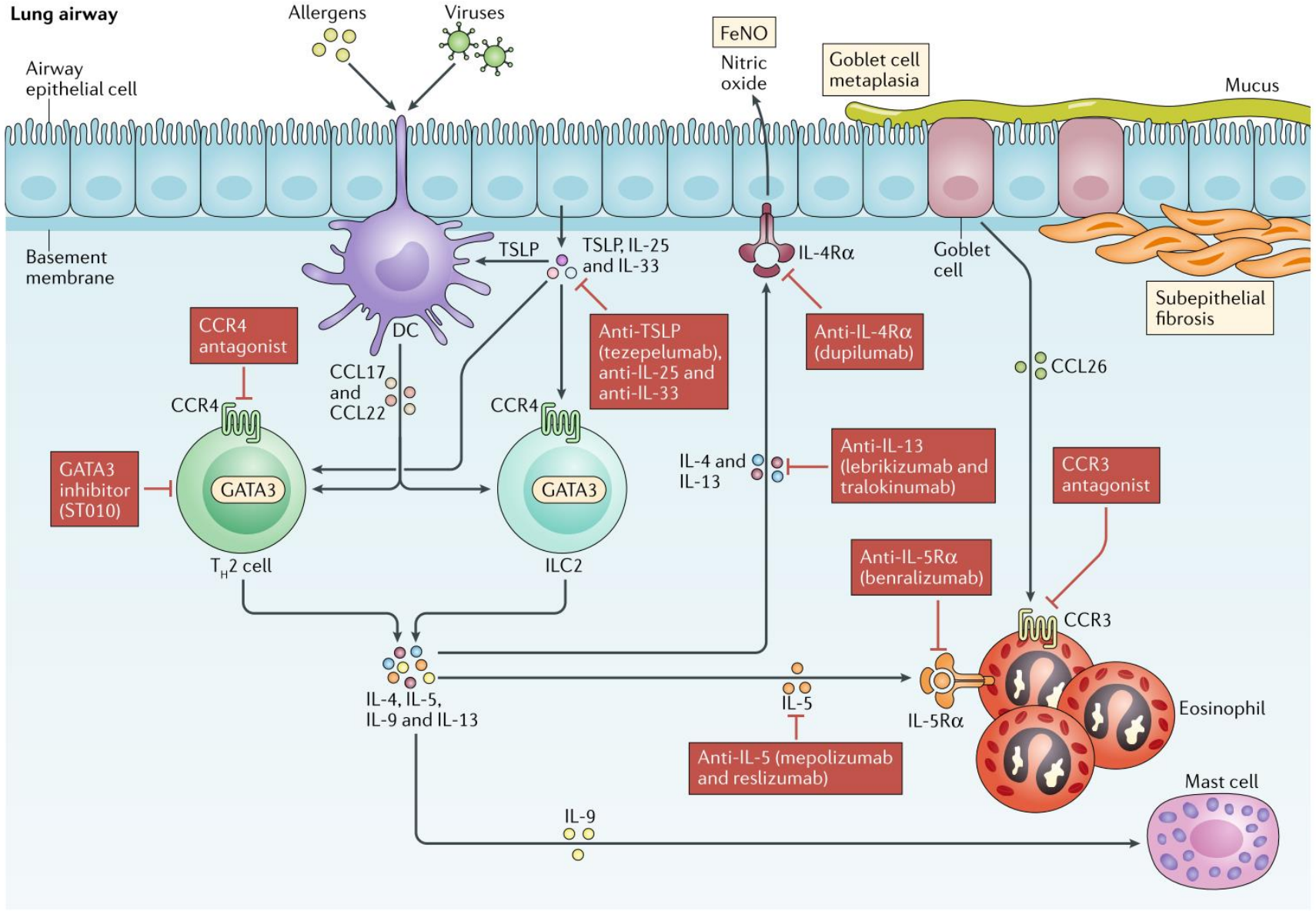
Biologics targeting Th2 inflammation

Biologics in Asthma : Revolutionary



Biologics	Form	Target	Biological effects	Effects on airway remodeling
Omalizumab	Humanized IgG1-κ mAb	IgE	• ↓ circulating total IgE • Downregulation of FcεRI receptors on basophils, mast cells, and DCs	• ↑ FEV_1 • ↓ RBM thickness • ↓ airway wall thickness in CT • ↓ fibronectin deposition • 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 • ↓ airway eosinophils and TGF-$\beta1^+$ eosinophils • ↓ tenascin expression
Benralizumab	Humanized IgG1-κ mAb	IL-5 receptor (IL-5Rα)	↓ eosinophils and basophils via antibody-dependent cell-mediated cytotoxicity (ADCC)	• ↑ FEV_1 • ↓ airway eosinophils • ↓ ASM mass
Dupilumab	Human IgG4 mAb	IL-4 receptor α chain (IL-4Rα)	• Blockage of IL-4/IL-4Rα binding • Blockage of IL-13/IL-4Rα binding	• ↑ FEV_1 • 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 • ↓ airway eosinophils • ↓ AHR to mannitol • ↓ airway inflammation • ↓ TGF-β1 • ↑ CT scan-determined lumen area

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



Targeting type 2 immunity in airway disease

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

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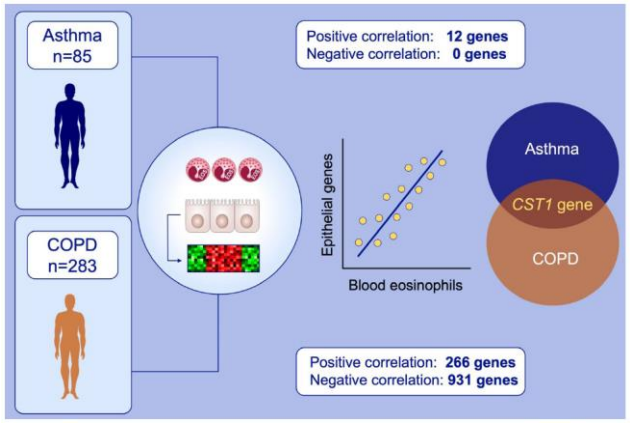
DOI: 10.1111/all.14016

ORIGINAL ARTICLE
Asthma and Lower Airway Disease

Allergy EAACI WILEY

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



Regression analysis: Blood eosinophil and gene expression

Upregulated genes

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

COPD Cohort (EvA)

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

Asthma Cohort (U-BIOPRED)

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

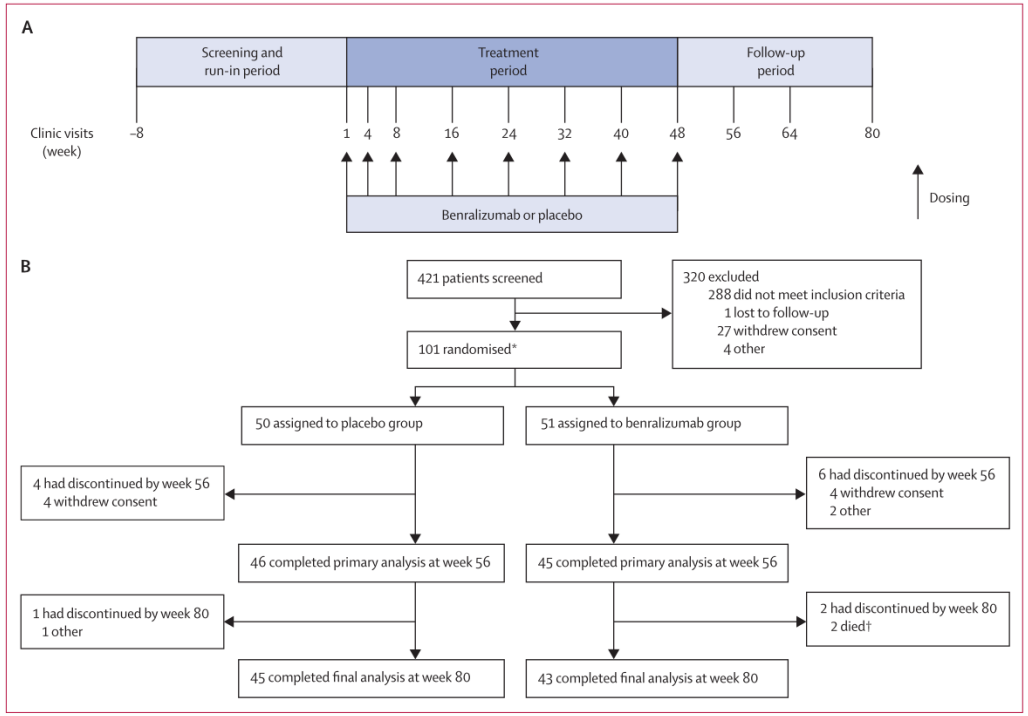
Anti-IL-5 and Anti-IL-5R

Benralizumab

Articles

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

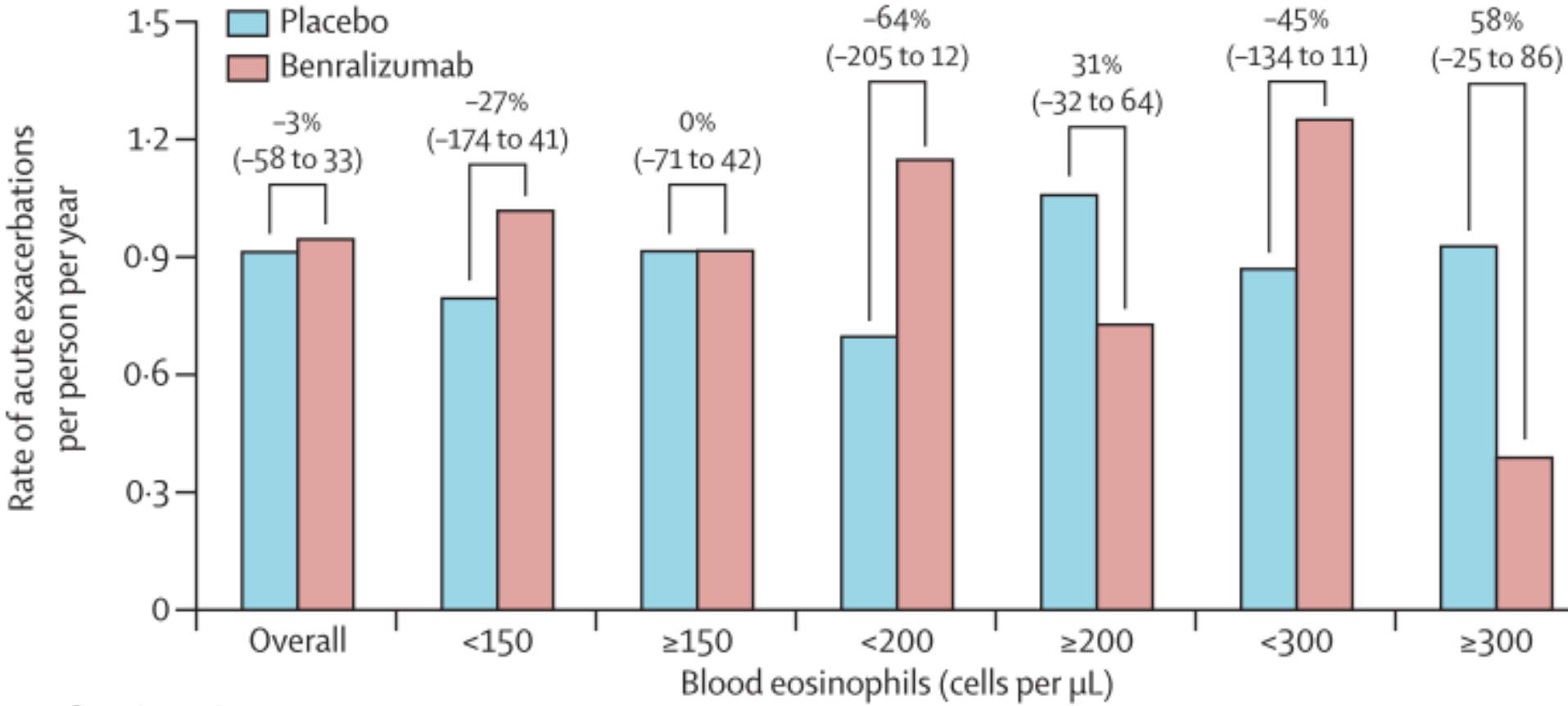
Christopher E Brightling, Eugene R Bleecker, Reynold A Panettieri Jr, Mona Bafadhel, Dewei She, Christine K Ward, Xiao Xu, Claire Birrell, René van der Merwe



- Double-blind RCT, phase 2a study (2010-2013)
- 26 sites in the UK, Poland, Germany, Canada, the USA, Denmark, and Spain.
- Aged 40–85
- Moderate-to-severe COPD,
- ≥ 1 acute exacerbation of COPD
- Sputum eosinophil count ≥ 3.0%
- Primary endpoint : exacerbation rate at week 56
- Secondary and exploratory endpoints : SGRQ-C, CRQSAS, FEV1 and safety

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

Rate of moderate-to-severe exacerbation at week 56

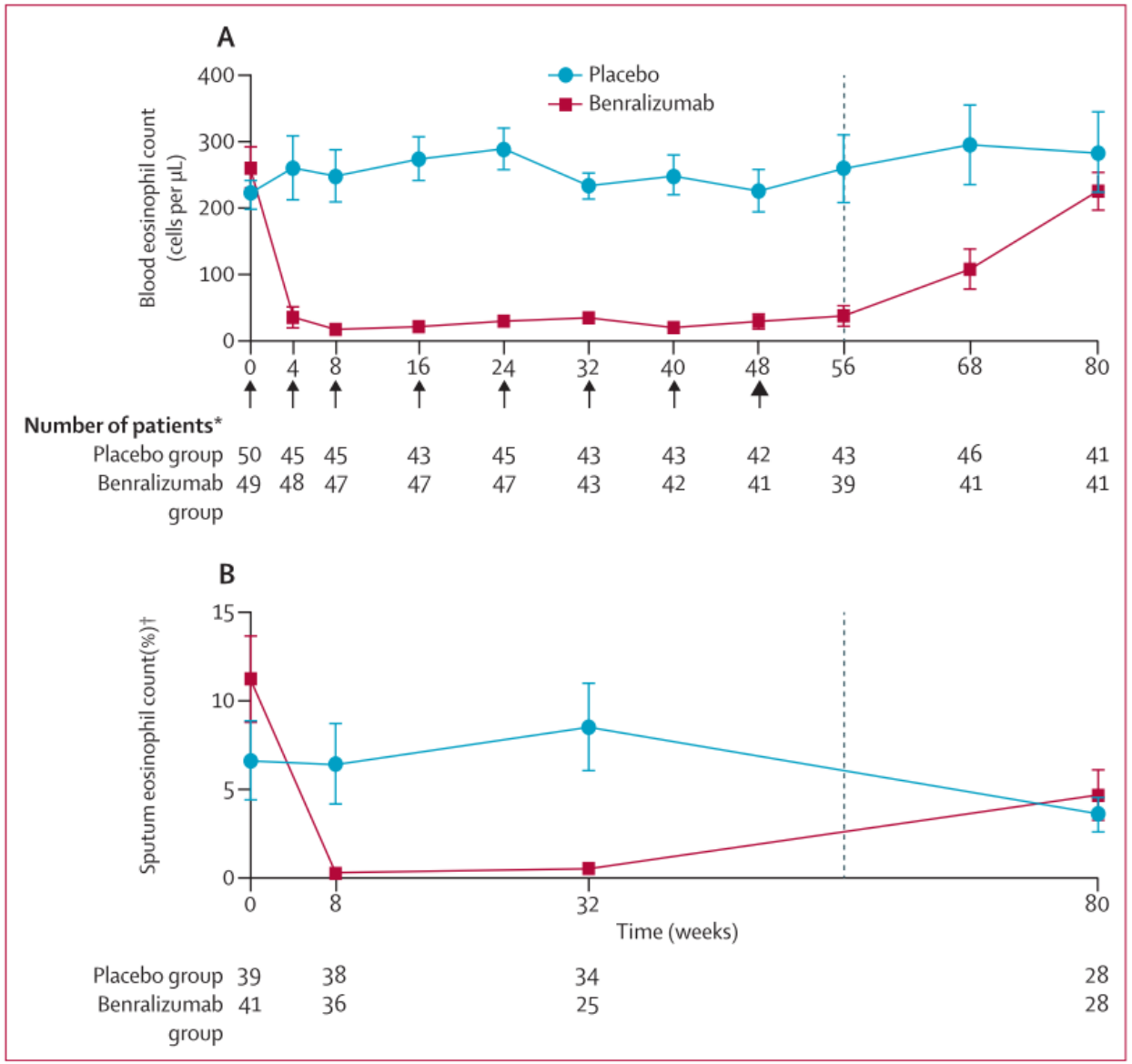


Number of patients*

Placebo group	42	15	26	21	20	34	7
Benralizumab group	40	12	28	21	19	26	14

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

Eosinophil count (Blood/sputum)



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

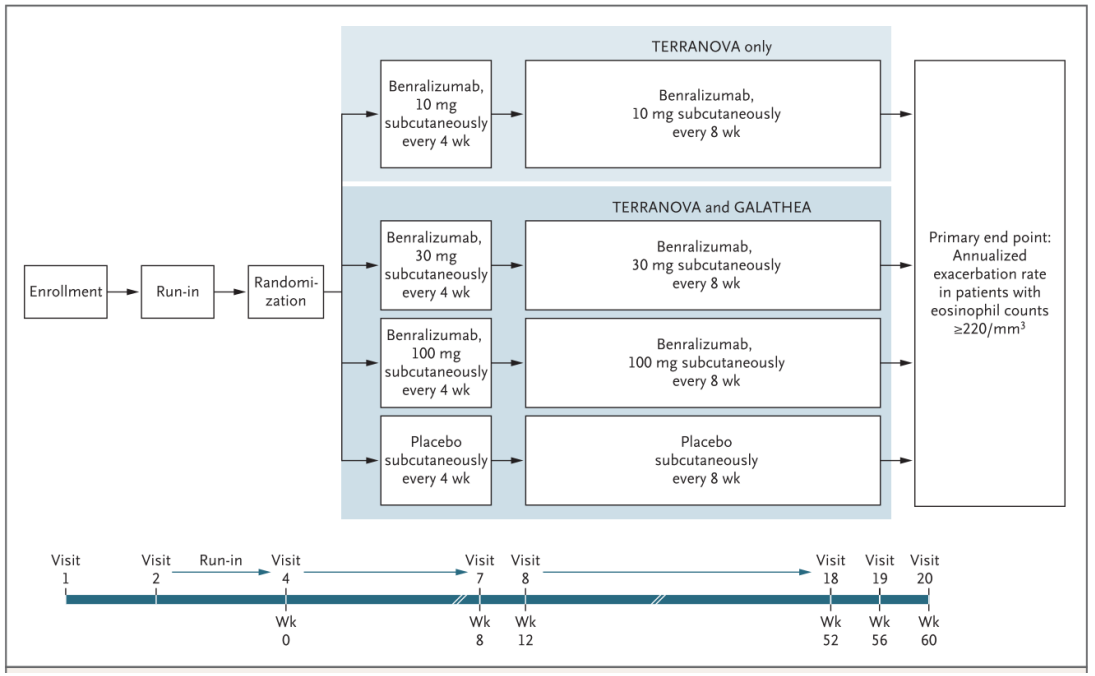
The NEW ENGLAND JOURNAL of MEDICINE

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
  - 2:1 on the basis of eosinophil count [≥220 vs <220]
  - 40-85 years of age
  - moderate to very severe COPD
- Frequent exacerbators



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

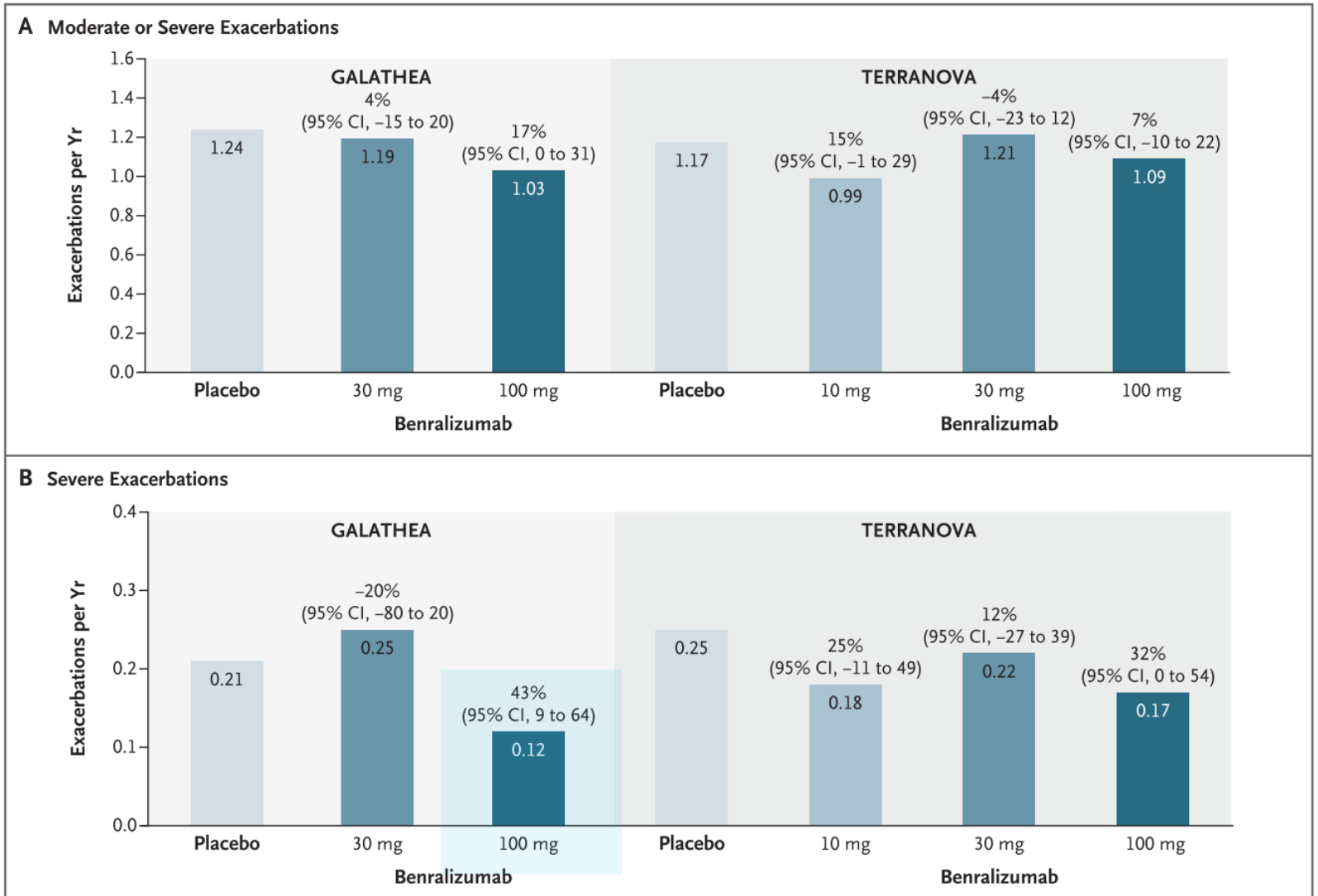


Figure 2. Annualized Exacerbation Rates among Patients with Baseline Blood Eosinophil Counts of 220 per Cubic Millimeter or Greater.

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 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.

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.

Benralizumab summary

- Primary outcome
  - ↔ Moderate-to-severe AE COPD
- Secondary outcome
  - ↔ FEV1 in the intervention group (↑ in phase IIa trial)
  - ↔ health status
  - ↓ Blood and sputum eosinophils

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

Study Design

Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	642 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Triple (Participant, Care Provider, Investigator)
Primary Purpose:	Treatment
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)
Actual Study Start Date :	August 26, 2019
Estimated Primary Completion Date :	June 27, 2025
Estimated Study Completion Date :	June 27, 2025

Study Description

Go to

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.

Condition or disease	Intervention/treatment	Phase
Chronic Obstructive Pulmonary Disease	Biological: Benralizumab Biological: Placebo	Phase 3

Mepolizumab

AGORA
RESEARCH LETTER

CrossMark

A pilot randomised clinical trial of mepolizumab in COPD with eosinophilic bronchitis

"Proof-of-concept" pilot study

Variables	Mepolizumab (n=8)			Placebo (n=10)		
	Baseline	3 months	6 months	Baseline	3 months	6 months
Sputum eosinophils %	11.00 (3.00–23.30)	0.75 (0.30–23.30)	0.50* (0.02–1.30)	7.35 (3.70–37.70)	3.15 (0.30–34.00)	2.20* (0.30–34.00)
Blood eosinophils cells·mm^{-3}	0.69±0.50	0.04±0.05*	0.03±0.05*	0.33±0.29	0.23±0.13*	0.26±0.12*
FEV_1 L pre-BD	1.35±0.49	1.47±0.57	1.43±0.55	0.99±0.28	1.22±0.61	1.18±0.59
FEV_1 % pre-BD#	55.00* (29–69)	58.05 (28–72)	54.50 (29–77)	29.50* (27–47)	36.35 (22–61)	34.50 (22–66)
FEV_1 L post-BD	1.53±0.57	1.61±0.62	1.58±0.60	1.24±0.52	1.35±0.70	1.33±0.71
FEV_1 % post-BD	58.50* (29–69)	65.50 (29–78)	63.50 (30–80)	35.00* (25–67)	43.50 (23–69)	43.50 (20–71)
SVC L pre-BD	2.69±0.68	2.79±0.78	2.66±0.75	2.85±0.46	3.09±0.71	2.98±0.67
SVC L post-BD	2.79±0.74	2.91±0.85	2.84±0.78	3.09±0.76	3.45±0.87	3.30±0.83
SVC % post-BD	82.50 (56–92)	88.00 (56–97)	84.50 (54–95)	75.00 (53–99)	83.00 (53–109)	78.50 (49–102)
FVC % post-BD	71.50 (46–81)	82.50 (43–90)	75.50 (46–87)	54.50 (31–87)	64.50 (31–94)	66.50 (31–84)
FEV_1/SVC %#	55.11* (35.88–63.77)	55.59 (38.58–64.86)	56.26 (36.02–66.98)	37.21* (29.41–51.02)	38.75 (13.86–53.72)	37.45 (13.86–64.15)
FEV_1/FVC %#	62.45* (43.38–74.00)	62.94 (39.52–66.93)	64.00 (36.80–72.20)	46.45* (40.90–61.50)	48.29 (38.39–62.53)	46.52 (36.00–72.00)
D_{LCO} mL·min^{-1}·mmHg^{-1}	14.92±4.67	15.07±5.27	15.72±4.86	14.39±4.54	14.22±4.54	13.97±4.86
RV# L	2.36±0.56*	2.32±0.52	2.29±0.56#	3.39±0.77*	3.06±0.96	3.38±0.75
TLC# L	5.20±0.85*	5.29±0.89	5.41±1.09#	6.60±1.01*	6.62±1.05	6.77±0.80
RV/TLC	0.46 (0.29–0.64)	0.45 (0.29–0.60)	0.43 (0.24–0.56)	0.51 (0.37–0.64)	0.42 (0.25–0.62)	0.47 (0.37–0.64)
CAT score	16* (12–24)	13 (6–23)	14 (3–29)	25* (15–29)	22 (0–27)	23 (4–39)
CRQ total score	93.75±18.75	100.25±20.41	103.25±22.65	82.7±21.16	93.33±18.47	102.11±15.55
Sputum hyaluron ng·mL^{-1}	466 (164–1050)		289.5 (32–979)	517 (162–847)		368 (56–596)
Sputum versican ng·mL^{-1}	3.74 (3.18–5.54)		3.24 (2.19–4.68)	3.55 (3.37–4.53)		3.34 (2.88–5.45)
RA_{950} %	6 (12)		5 (11)	6 (4)		5 (5)
PRM gas trapping %	25 (13)		30 (17)	40 (11)		40 (11)

↓ Sputum eosinophil

↔ Lung function, QOL, gas trapping

Eur Respir J. 2017 Mar 15;49(3):1602486.

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.

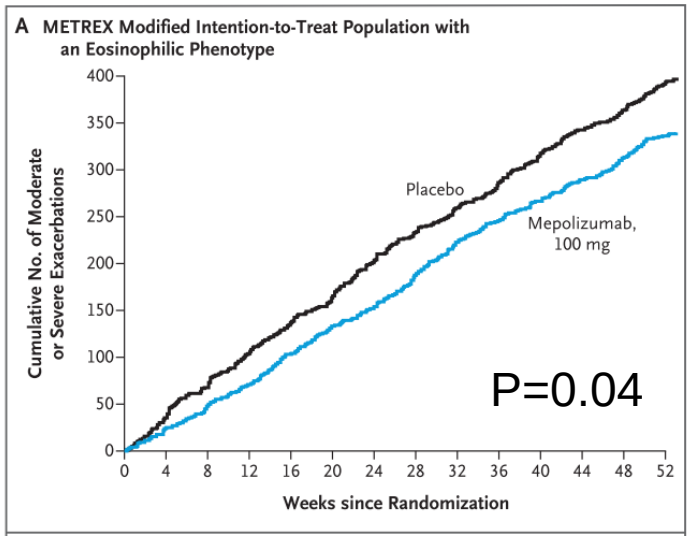
N Engl J Med. 2017 Oct 26;377(17):1613-1629.

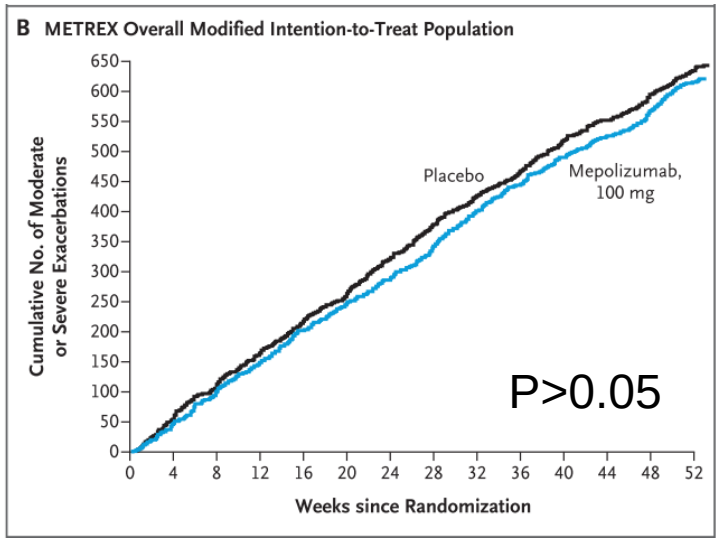
Table 2. Primary and Secondary Efficacy End Points.*

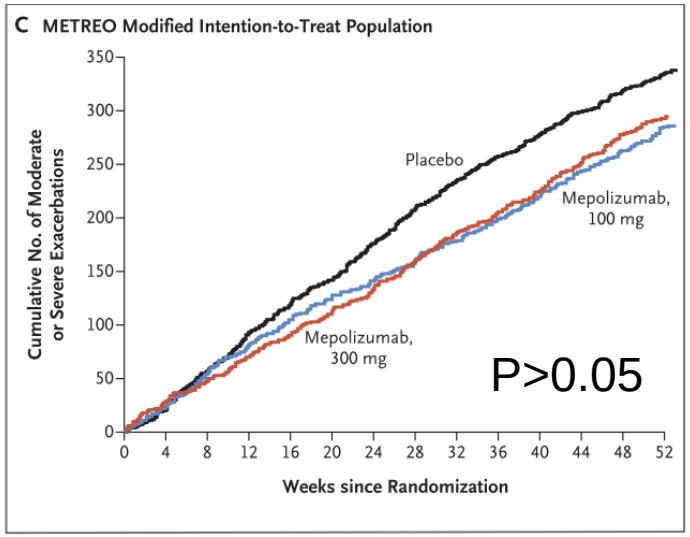
End Point	METREX Modified Intention-to-Treat Population with an Eosinophilic Phenotype		METREX Overall Modified Intention-to-Treat Population		METREO Modified Intention-to-Treat Population		
	Mepolizumab, 100 mg (N=233)	Placebo (N=229)	Mepolizumab, 100 mg (N=417)	Placebo (N=419)	Mepolizumab, 100 mg (N=223)	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.

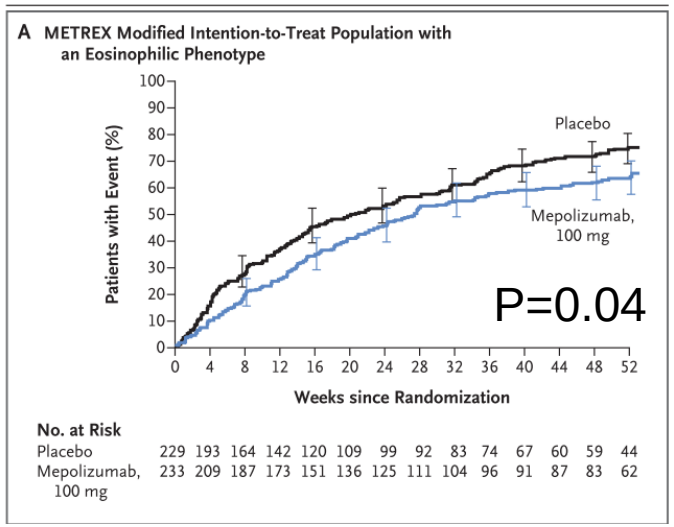
Cumulative Incidence of Moderate-to-Severe Exacerbations

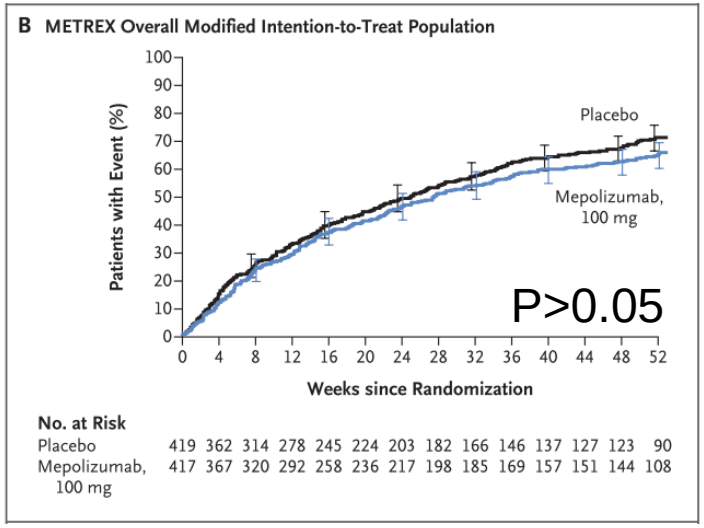


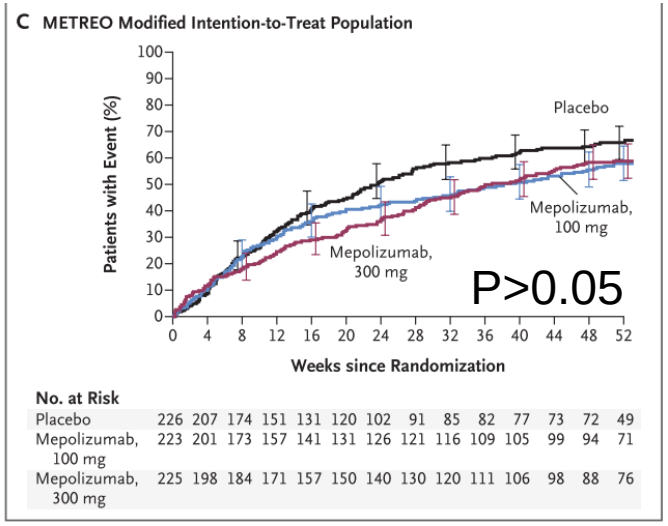




Time-to-first exacerbation

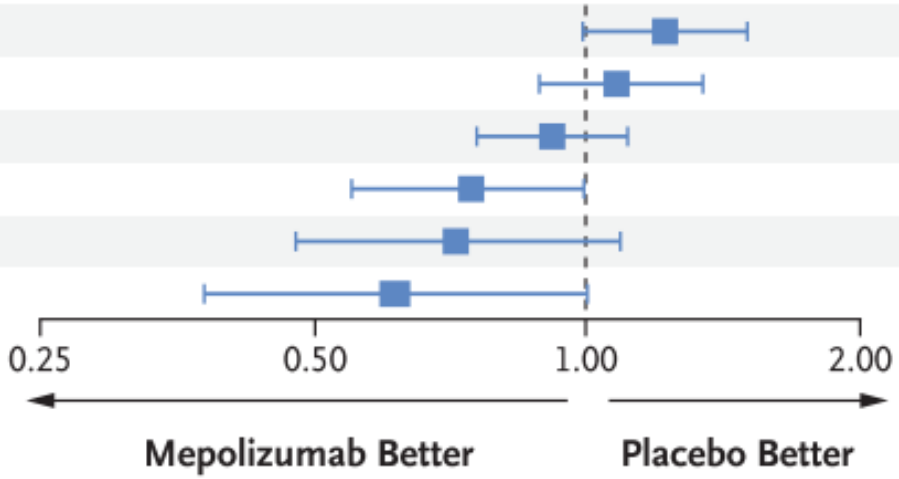






Pre-specified meta-analysis of METREX & METREO

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.

Adverse events

Event	METREX Safety Population with an Eosinophilic Phenotype*		METREX Overall Safety Population†		METREO Safety 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)
	number of patients (percent)						
Adverse events§							
Any event	190 (82)	189 (83)	332 (80)	342 (82)	191 (86)	196 (87)	185 (82)
Event leading to treatment discontinuation¶	16 (7)	20 (9)	31 (7)	35 (8)	9 (4)	25 (11)	27 (12)
Event leading to withdrawal from trial	7 (3)	10 (4)	18 (4)	21 (5)	7 (3)	13 (6)	18 (8)
Any serious adverse event§	65 (28)	80 (35)	115 (28)	131 (31)	57 (26)	60 (27)	68 (30)
Any death	6 (3)	8 (3)	16 (4)	17 (4)	4 (2)	8 (4)	9 (4)
Systemic or local site reaction during treatment period‖							
Systemic reaction	3 (1)	4 (2)	7 (2)	9 (2)	3 (1)	5 (2)	4 (2)
Injection-site reaction	7 (3)	7 (3)	12 (3)	12 (3)	6 (3)	11 (5)	10 (4)

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

International Journal of Chronic Obstructive Pulmonary Disease Dovepress
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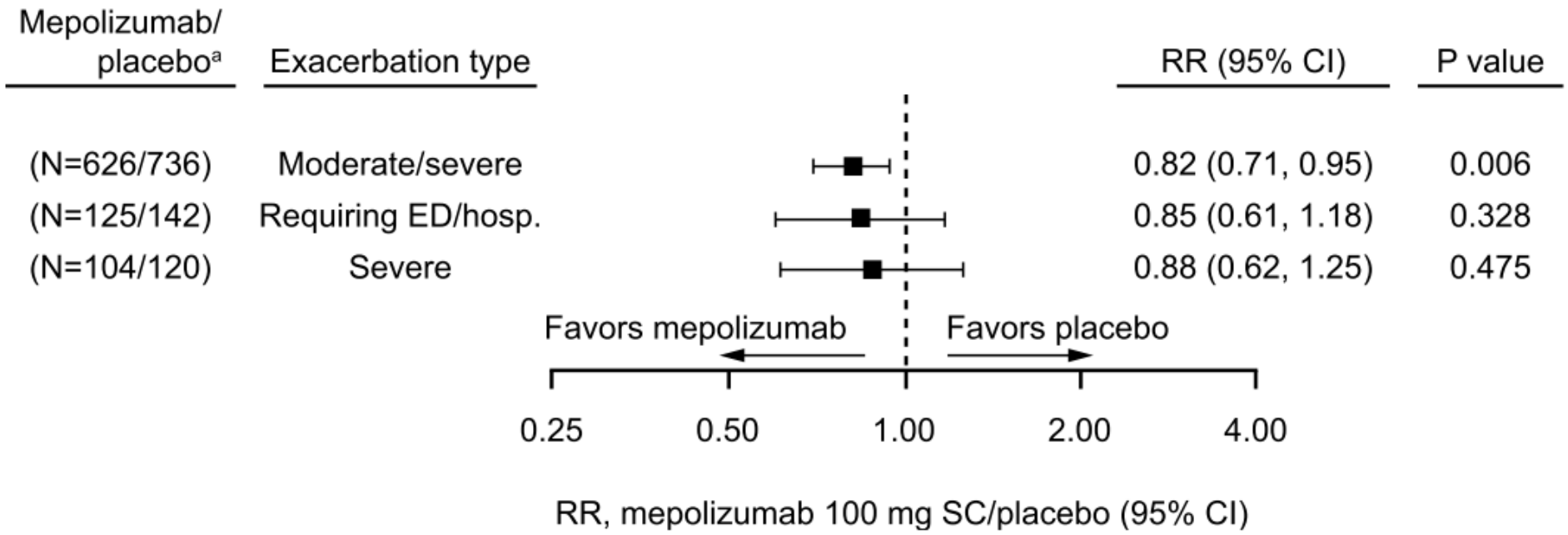
ORIGINAL RESEARCH

Mepolizumab for Eosinophil-Associated COPD: Analysis of METREX and METREO

- METREX+METREO
- Primary endpoint : annual rate of moderate/severe exacerbations
- Patients with blood eosinophil counts ≥150 cells/μL at screening or ≥300 cells/μL in the prior year.
- Secondary/other endpoints
  - time to first moderate/severe exacerbation,
  - exacerbations leading to emergency department visit/hospitalization
  - health-related quality of life (HRQoL).
- Relationship between blood eosinophil counts and exacerbation rates

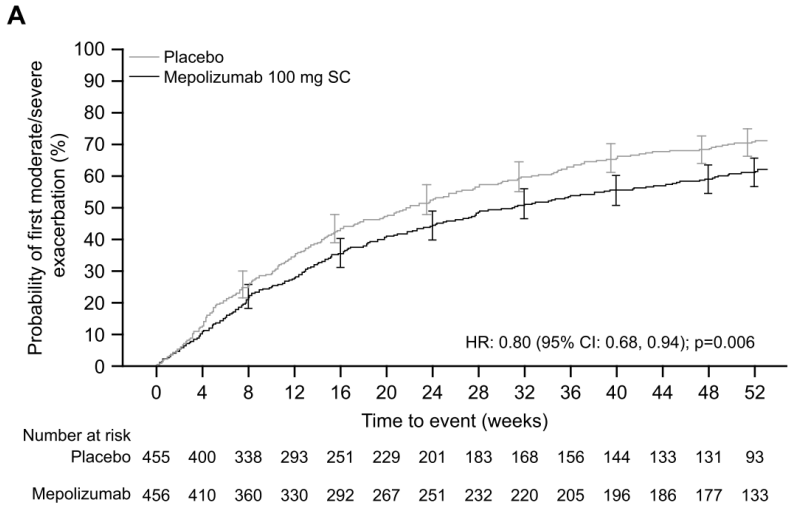
IJCOPD 2021 Jun 16;16:1755-1770.

Reduction in annual rate of exacerbations

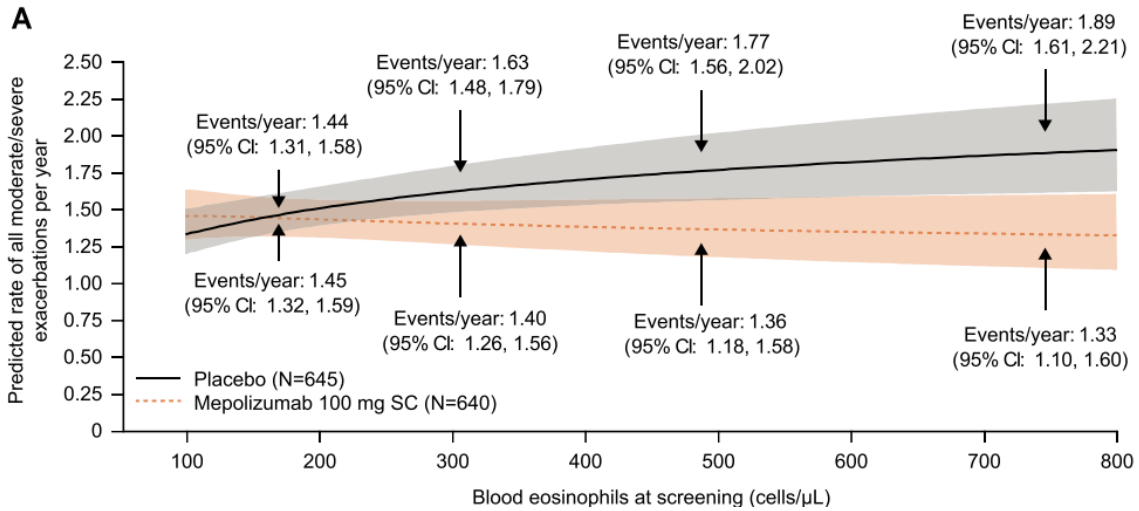


IJCOPD 2021 Jun 16;16:1755-1770.

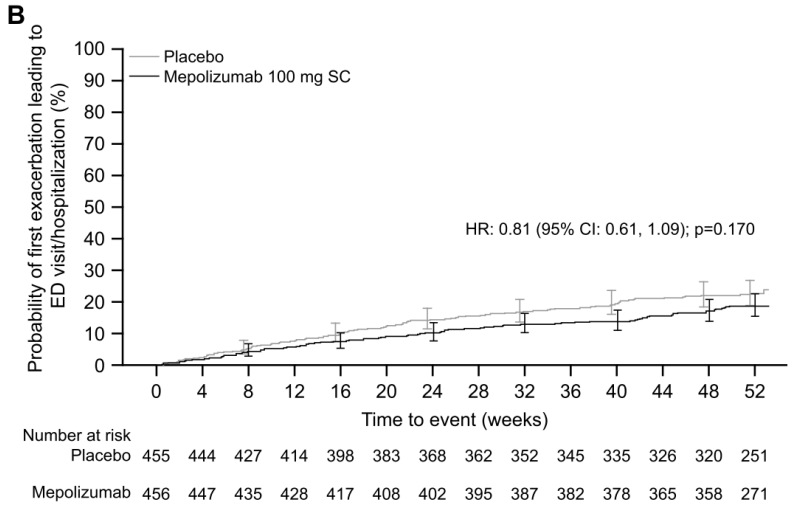
Time-to-first exacerbation



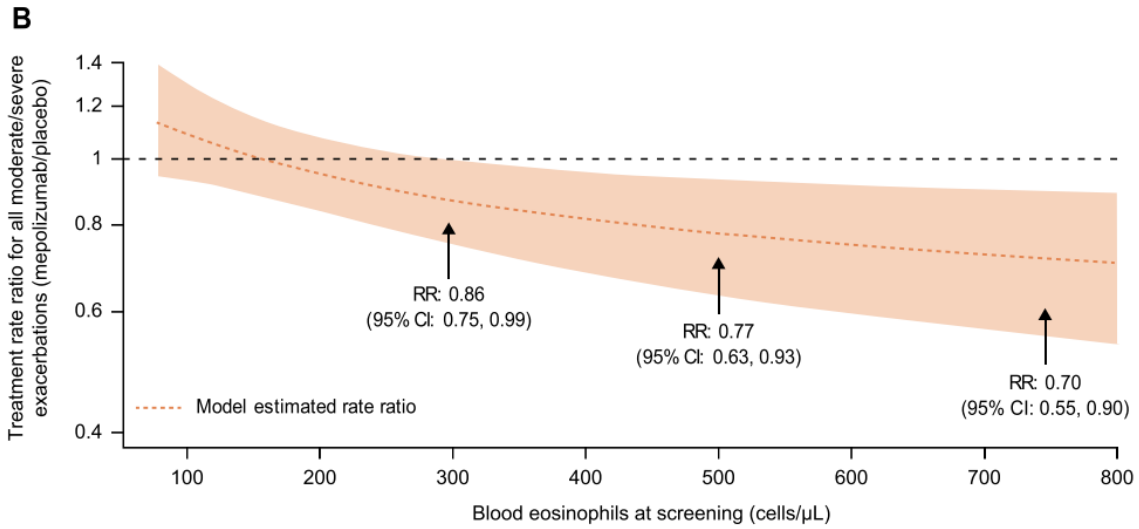
Predicted annual rate of exacerbation by blood eosinophil count



Time-to-first exacerbation leading ED visit/hospitalization



Predicted treatment RR of exacerbation by blood eosinophil count



IJCOPD 2021 Jun 16;16:1755-1770.

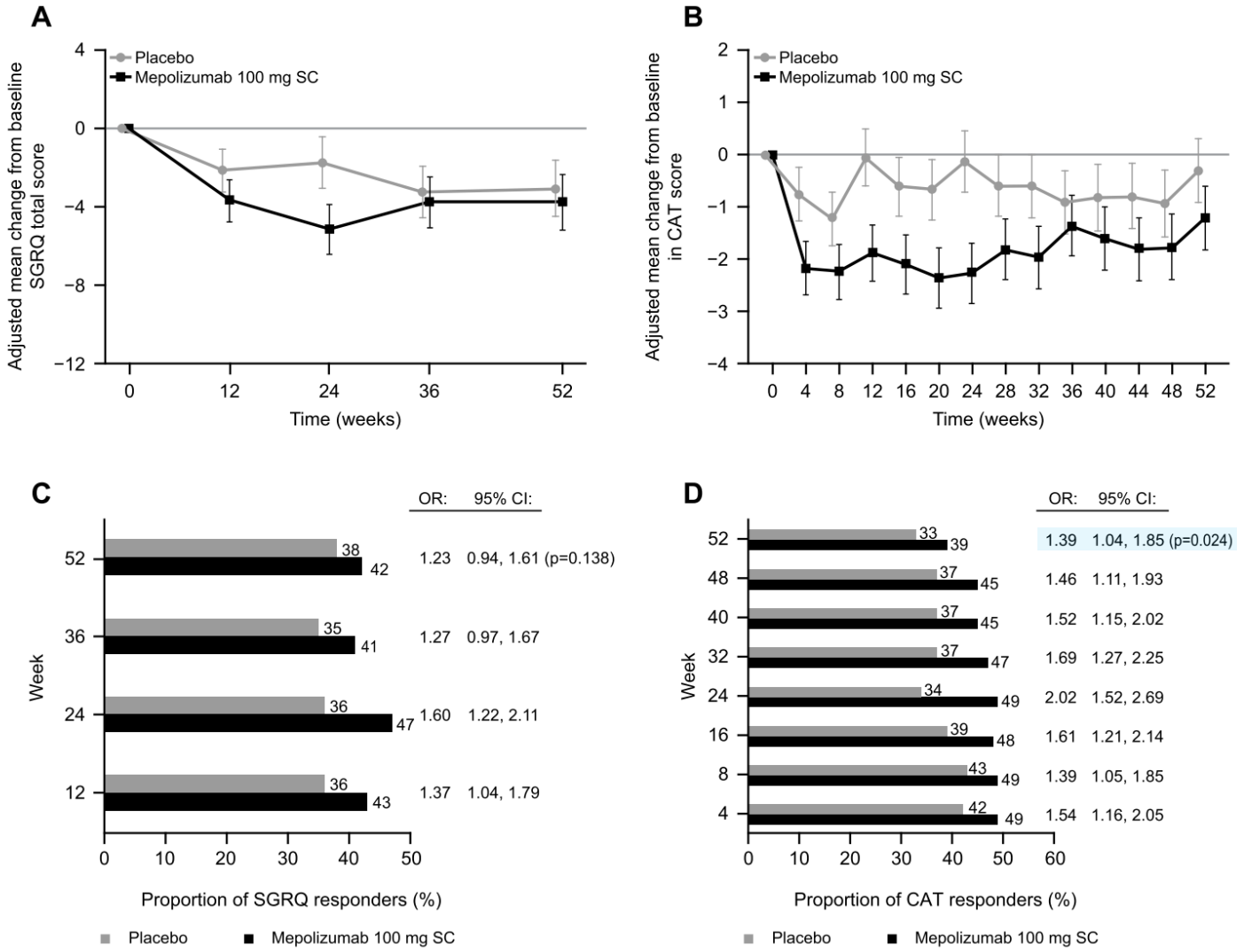


Figure 3 Change from baseline for (**A**) SGRQ total score and (**B**) CAT score, and (**C**) proportion of SGRQ responders[a] and (**D**) CAT responders[b]. In panels A and B, the vertical bars represent 95% CIs. [a]SGRQ responders are defined as patients achieving ≥4-point reduction in total score; [b]CAT responders are defined as patients achieving a ≥2-point decrease from baseline.

Abbreviations: CAT, COPD Assessment Test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio; SC, subcutaneous; SGRQ, St George's Respiratory Questionnaire.

IJCOPD 2021 Jun 16;16:1755-1770.

Mepolizumab as Add-on Treatment IN Participants With COPD Characterized by Frequent Exacerbations and Eosinophil Level (MATINEE)

ClinicalTrials.gov Identifier: NCT04133909

Recruitment Status : Recruiting
First Posted : October 21, 2019
Last Update Posted : January 23, 2023

See Contacts and Locations

Study Design

Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	800 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Double (Participant, Investigator)
Primary Purpose:	Treatment
Official Title:	A Multi-center, Randomized, Double-blind, Parallel-group, Placebo-controlled Study of Mepolizumab 100 mg SC as add-on Treatment in Participants With COPD Experiencing Frequent Exacerbations and Characterized by Eosinophil Levels (Study 208657)
Actual Study Start Date :	October 30, 2019
Estimated Primary Completion Date :	May 31, 2024
Estimated Study Completion Date :	May 31, 2024

Study Description

Go to

Brief Summary:

This is a multi-center, randomized, placebo-controlled, double-blind, parallel group study designed to confirm the benefits of mepolizumab treatment on moderate or severe exacerbations in chronic obstructive pulmonary disease (COPD) participants given as an add on to their optimized maintenance COPD therapy. The maximum duration of participant participation is approximately 109 weeks, consisting of 2 screening visits (up to 3 weeks), a run-in period (up to 2 weeks), and an intervention period of at least 52 weeks and up to 104 weeks. 800 participants will be randomized in a 1:1 ratio to receive mepolizumab 100 milligrams (mg) or placebo every 4 weeks for at least 13 doses (52 weeks treatment period) up to a maximum of 26 doses (104 weeks treatment period). The number of randomized participants may increase up to approximately 1400.

Condition or disease	Intervention/treatment	Phase
Pulmonary Disease, Chronic Obstructive	Drug: Placebo Biological: Mepolizumab	Phase 3

Mepolizumab summary

- Primary outcome
  - ↓ Moderate-to-severe AE COPD (eosinophilic COPD in METREX)
  - ↔ Moderate-to-severe AE COPD (overall METREX, METREO)
- Secondary outcome
  - ↑ Time-to-first exacerbation (METREX+METREO)
  - ↔ FEV1
  - ↔ SGRQ
  - ↓ CAT (METREX+METREO)

- Eosinophil count : potential biomarker for good responder

Lancet Respir Med. 2014 Nov;2(11):891-901, N Engl J Med. 2019 Sep 12;381(11):1023-1034.

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 02 November 2021
doi: 10.3389/fphar.2021.754268

Monoclonal Antibodies Targeting IL-5 or IL-5Rα in Eosinophilic Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis

*Chuchu Zhang [1,2], Yalei Wang [1,2], Meng Zhang [1,2], Xiaojie Su [1,2], Ting Lei [1,2], Haichuan Yu [1,2] and Jian Liu [1]**

Journal of Microbiology, Immunology and Infection (2022) 55, 26–35

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Original Article

Efficacy and safety of anti-interleukin-5 therapy in patients with chronic obstructive pulmonary disease: A meta-analysis of randomized, controlled trials

Shao-Huan Lan [a,1], Chih-Cheng Lai [b,1], Shen-Peng Chang [c], Chun-Chun Hsu [d,e,f], Cheng-Hsin Chen [g], Ya-Hui Wang [h], Yueh Lan Huang [g,**], Cheng-Yi Wang [g,*], You-Shuei Lin [i,***]

Heliyon 8 (2022) e09736

Contents lists available at ScienceDirect

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journal homepage: www.cell.com/heliyon

Research article

A systematic review and integrated analysis of biologics that target Type 2 inflammation to treat COPD with increased peripheral blood eosinophils

Hiroshi Ohnishi [a,*], Masamitsu Eitoku [b], Akihito Yokoyama [a]

[a] Department of Respiratory Medicine and Allergology, Oko-cho, Kohasu, Nankoku, Kochi, 780-8505, Japan
[b] Department of Environmental Medicine, Kochi Medical School, Kochi University, Oko-cho, Kohasu, Nankoku, Kochi, 780-8505, Japan

Front Pharmacol. 2021 Nov 2;12:754268.
Heliyon. 2022 Jun 16;8(6):e09736.
J Microbiol Immunol Infect. 2022 Feb;55(1):26-35.

Heliyon 8 (2022) e09736

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Research article

A systematic review and integrated analysis of biologics that target Type 2 inflammation to treat COPD with increased peripheral blood eosinophils

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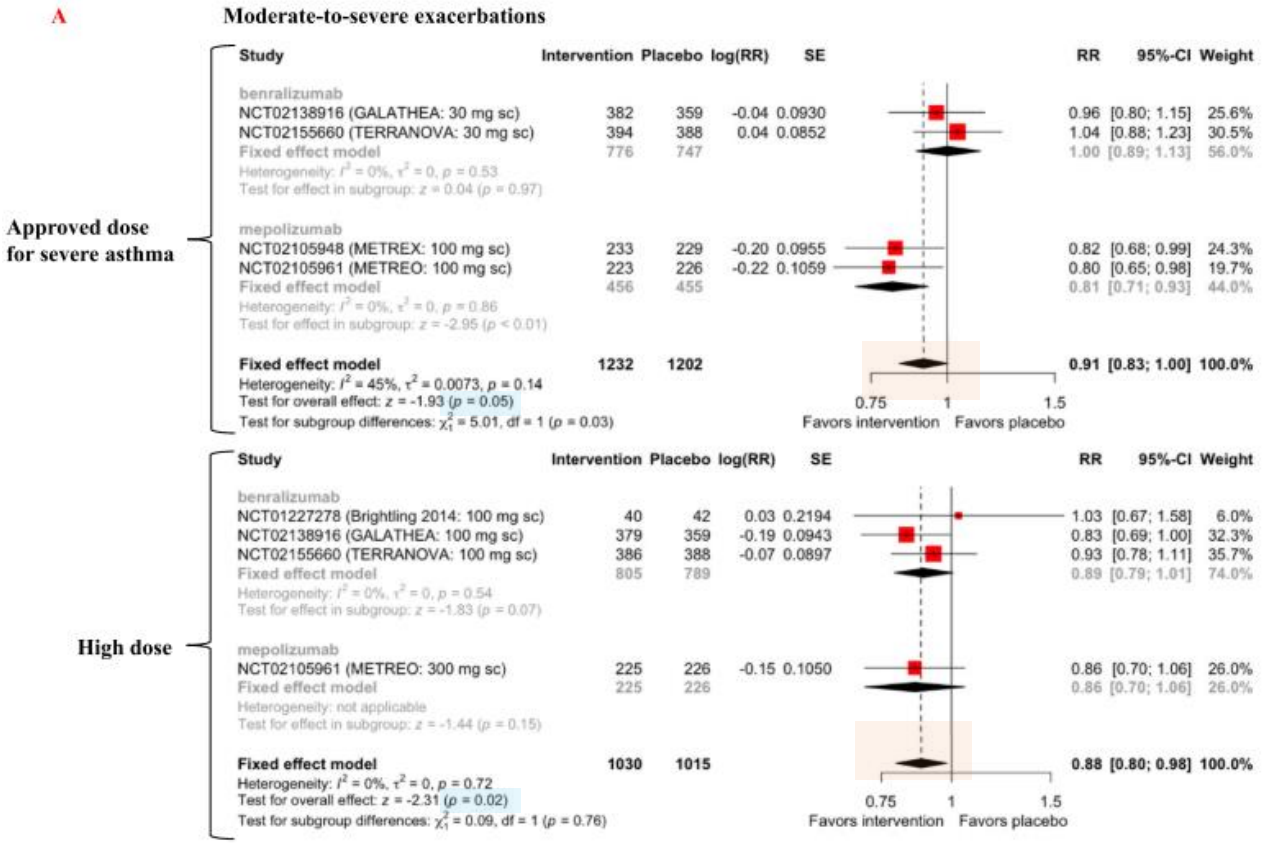
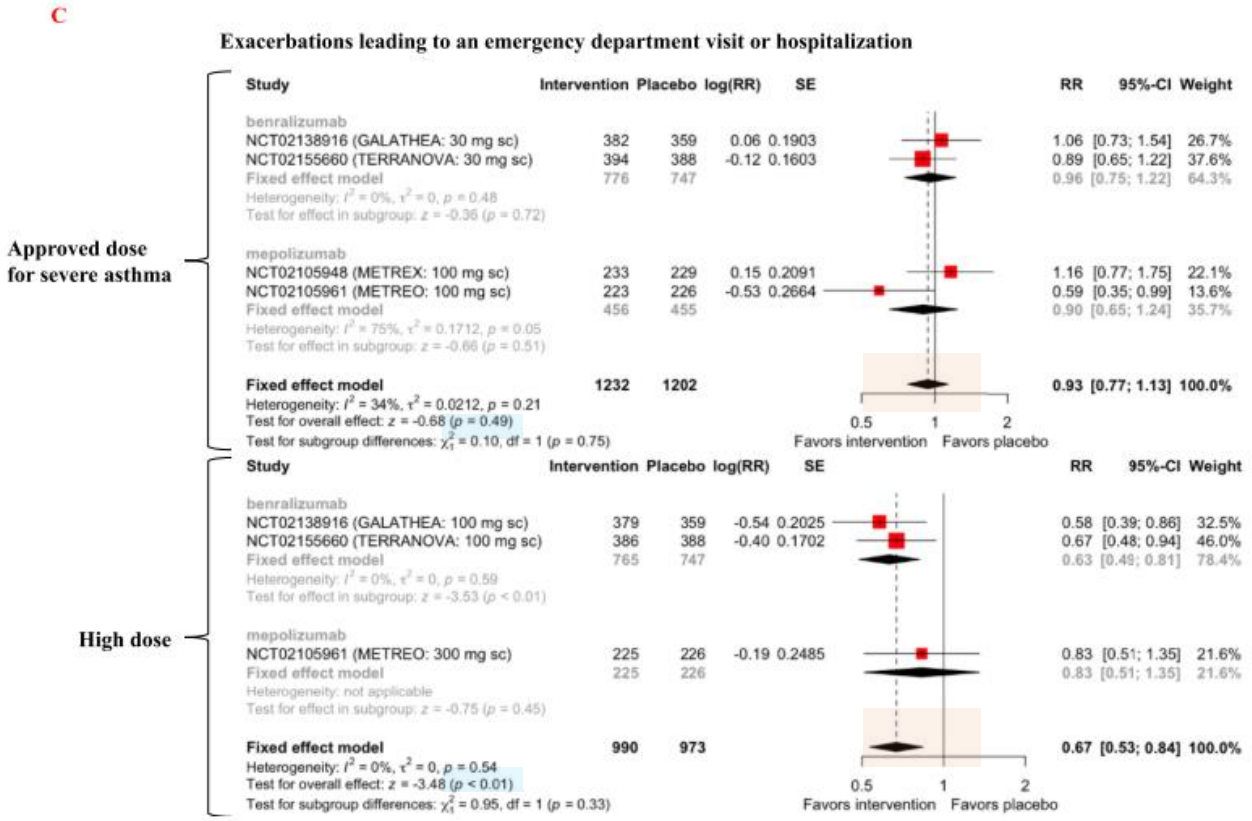
[a] Department of Respiratory Medicine and Allergology, Oko-cho, Kohasu, Nankoku, Kochi, 780-8505, Japan
[b] Department of Environmental Medicine, Kochi Medical School, Kochi University, Oko-cho, Kohasu, Nankoku, Kochi, 780-8505, Japan

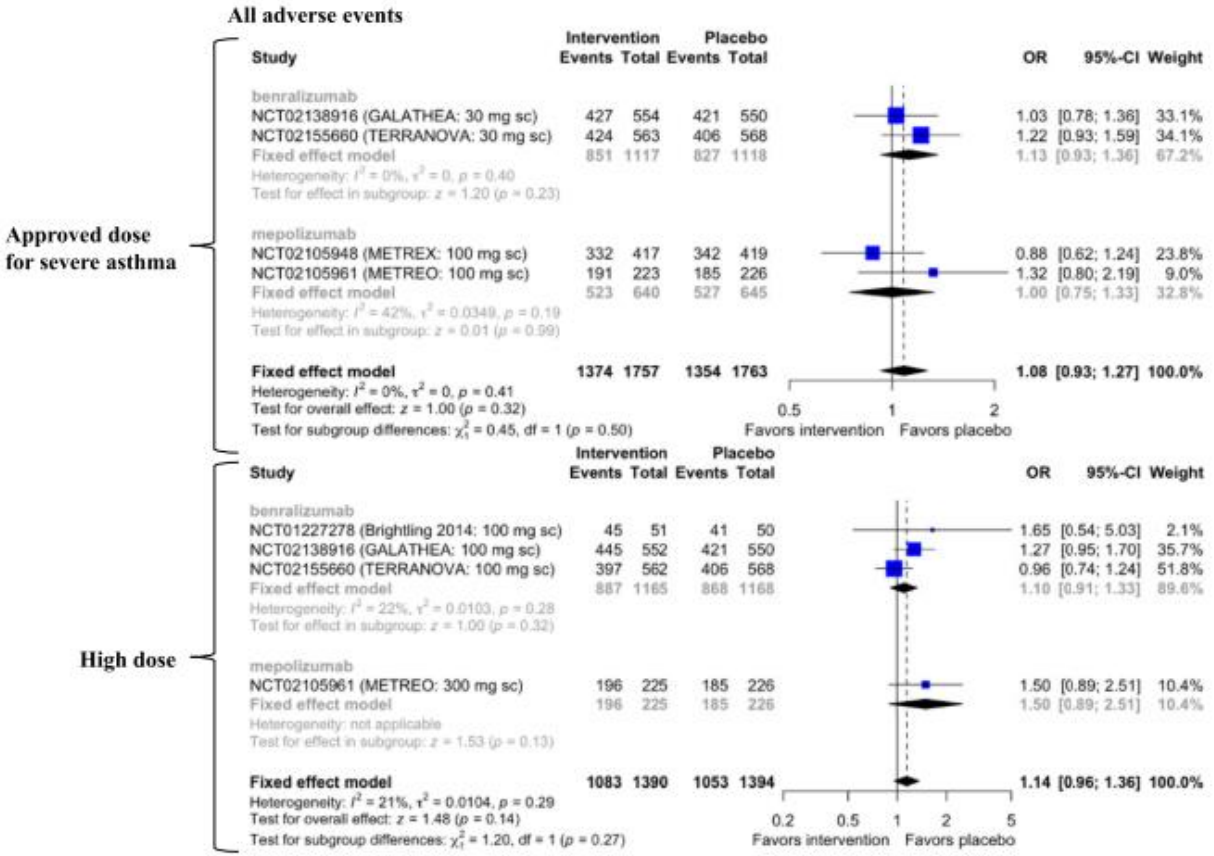
Study	METREX1		METREO1			Brightling et al.2		GALATHEA3			TERRANOVA3			
Inclusion criteria for eosinophils	Peripheral blood Eos ≥ 150/μL at screening or ≥300/μL during the previous year					Sputum Eos ≥3%		Peripheral blood Eos ≥ 220/μL at baseline						
	Mepo 100 mg	Placebo	Mepo 100 mg	Mepo 300 mg	Placebo	Benra 100 mg	Placebo	Benra 30 mg	Benra 100 mg	Placebo	Benra 10 mg	Benra 30 mg	Benra 100 mg	Placebo
n	233	229	223	225	226	51	50	382	379	359	377	394	386	388
Age	65 ± 8	65 ± 9	65 ± 9	65 ± 9	66 ± 9	63 ± 8	65 ± 8	66 ± 8	66 ± 8	66 ± 8	65 ± 8	66 ± 8	65 ± 8	65 ± 8
Female (%)	36	34	41	30	31	31	42	29	31	28	33	32	35	35
Current smoker (%)	27	31	25	32	28	33	42	37	34	32	29	27	28	30
Ex-smoker (%)	70	64	73	66	71	67	58	63	66	68	71	73	72	70
GOLD group D (%)	94	95	95	97	96	–	–	–	–	–	–	–	–	–
Exacerbations in the previous year	2.6 ± 1.3	2.5 ± 1.2	2.5 ± 1.2	2.7 ± 1.4	2.7 ± 1.5	1.6 ± 1.0	1.6 ± 1.0	2.3 ± 1.2	2.3 ± 1.2	2.4 ± 1.4	2.3 ± 1.0	2.2 ± 1.0	2.3 ± 1.0	2.3 ± 1.0
Post-BD % predicted FEV1	45 ± 15	43 ± 15	47 ± 15	45 ± 16	46 ± 15	44 ± 16	50 ± 18	42 ± 11	44 ± 12	43 ± 13	44 ± 12	43 ± 12	43 ± 12	43 ± 11
Geometric mean Eos (/mm^3)	260	290	300	310	310	–	–	–	–	–	–	–	–	–
Baseline mean Eos (/mm^3)	–	–	–	–	–	249 ± 193	230 ± 165	451 ± 281	459 ± 277	450 ± 283	518 ± 420	503 ± 389	504 ± 404	493 ± 360
ICS/LABA/LAMA (%)	100					50	41	72.3	69.1	67.4	57.3	56.9	61.4	59.0
ICS/LABA (%)	–					10	10	18.8	21.1	24.0	34.7	32.3	34.5	34.3
LABA/LAMA (%)	–					–		8.6	9.8	8.6	7.7	10.7	4.1	6.4
Current asthma (%)	excluded					excluded		4.5	6.9	5.0	1.6	4.3	3.1	4.1
Previous history of asthma (%)	excluded for never smokers with a history of asthma					–		6.8	10.0	8.1	4.8	5.3	7.3	7.2

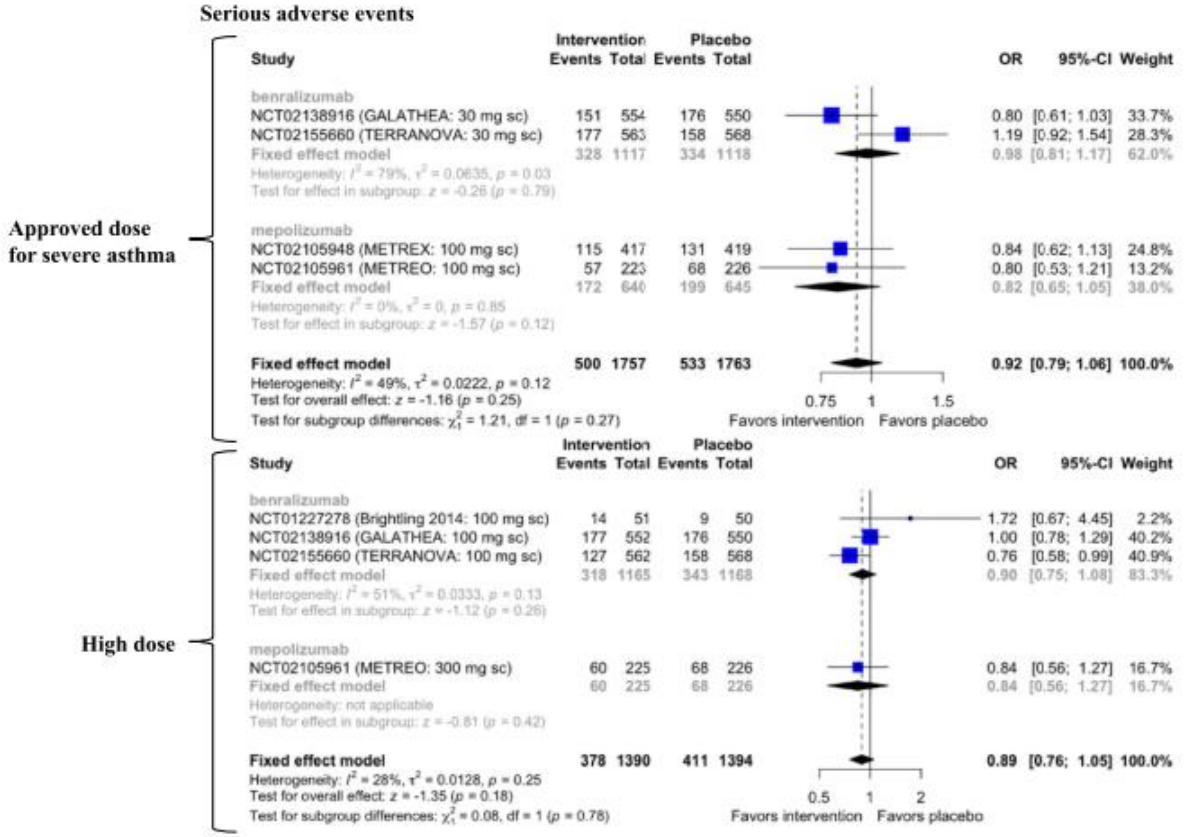
Heliyon. 2022 Jun 16;8(6):e09736.





Heliyon. 2022 Jun 16;8(6):e09736.





Heliyon. 2022 Jun 16;8(6):e09736.

Anti-Ig-E (omalizumab)

Omalizumab in asthma

Monoclonal antibody	MOA	IgG format affinity for target (K_d)	Effect on eosinophils	Clinical effects
Omalizumab (Xolair®)	Anti-IgE	Humanized IgG_1 $K_d = 2.7$ nM (Meno-Tetang & Lowe, 2005; Arm et al., 2014) $K_d = 7.7$ nM (Arm et al., 2014)	Sputum: • Reduction post allergen challenge but not statistically significant compared with placebo (Fahy et al., 1997) • Reduction in patients with mild to moderate allergic asthma (Djukanović et al., 2004) • Nonsignificant reduction compared with placebo in patients with severe allergic asthma (Takaku et al., 2013) Lung tissue: • Statistically significant reduction in lung tissue eosinophils in patients with mild to moderate asthma (Djukanović et al., 2004) and in patients with severe allergic asthma (Riccio et al., 2012) Blood: • Reduction in blood eosinophils post allergen challenge (Fahy et al., 1997) and in patients with moderate to severe allergic asthma (Massanari et al., 2010)	Statistically significant reduction in the number of asthma exacerbations, improvements in lung function and symptoms for patients with moderate to severe allergic asthma (Busse et al., 2001; Solèr et al., 2001)

Pharmacol Ther. 2017 Jan;169:57-77.

Omalizumab in COPD

October 2007, Vol 132, No. 4_MeetingAbstracts

Abstract: Poster Presentations | October 2007

ROLE OF ANTI-IGE ANTIBODY IN COPD

Mary L. Zaremba, APRN, BC*; Nipurn J. Shah, MD, FCCP; Syed V. Ali, MD, FCCP; Sridhar P. Reddy, MD MPH FCC
St. Clair Pulmonary & Critical Care PC, St. Clair, MI

Chest. 2007;132(4_MeetingAbstracts):533a. doi:10.1378/chest.132.4_MeetingAbstracts.533a

- A small observational study
- Patients with COPD + elevated IgE
- Omalizumab was given 3 mo

- Symptom score improved (2 -> 1.34, $p<0.01$)
- Satisfaction score improved (6 → 9.41, $p<0.01$)

- Total number of patients, exacerbation rates, side effect, type of questionnaire
  : not mentioned in the abstract

https://doi.org/10.1378/chest.132.4_MeetingAbstracts.533a

Omalizumab in ACO

Journal of ASTHMA

http://tandfonline.com/ijas
ISSN: 0277-0903 (print), 1532-4303 (electronic)

J Asthma, 2016; 53(10): 1048–1050
 DOI: 10.1080/02770903.2016.1178281

Taylor & Francis
Taylor & Francis Group

PHARMACOTHERAPY

Omalizumab treatment in asthma-COPD overlap syndrome

Tugba Songul Tat, MD[1] and Aykut Cilli, MD[2]

[1]*Department of Internal Medicine, School of Medicine, Akdeniz University, Antalya, Turkey and* [2]*Department of Pulmonary Medicine, School of Medicine, Akdeniz Universitv. Antalva. Turkev*

	Pretreatment	Posttreatment
FEV_1 /FVC (%)		
Case 1	44	41
Case 2	62	62
Case 3	65	64
FEV_1 (l,%)		
Case 1	1.01 (34)	0.96 (33)
Case 2	1.52 (54)	1.15 (42)
Case 3	2.46 (62)	2.52 (64)
Asthma Control Test (ACT)		
Case 1	6	23
Case 2	7	20
Case 3	5	23
Level of asthma symptom control		
Case 1	Uncontrolled	Partly controlled
Case 2	Uncontrolled	Partly controlled
Case 3	Uncontrolled	Partly controlled
Hospitalization for asthma in the past year		
Case 1	3	1
Case 2	0	0
Case 3	3	0
Asthma exacerbations in the past year		
Case 1	6	1
Case 2	2	0
Case 3	6	1

J Asthma. 2016 Dec;53(10):1048-50.

[Original Research **Asthma**]

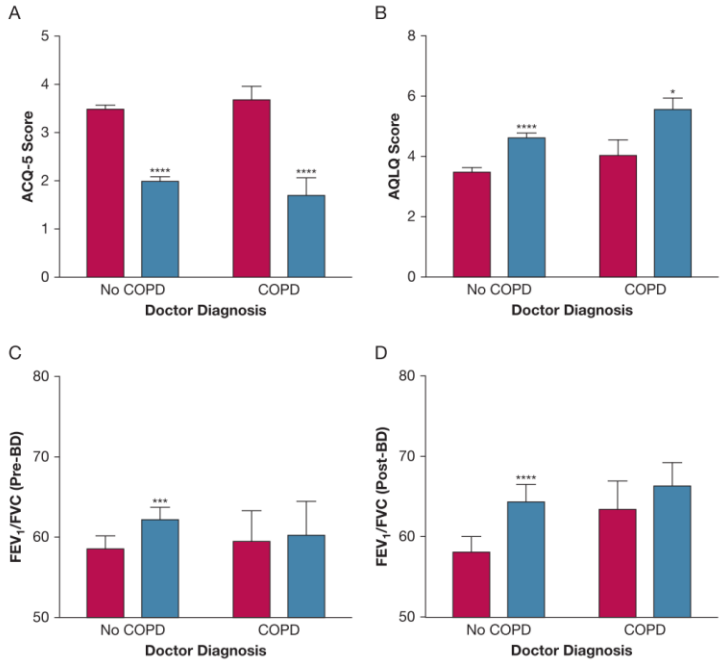
CHEST

Omalizumab Treatment Response in a Population With Severe Allergic Asthma and Overlapping COPD

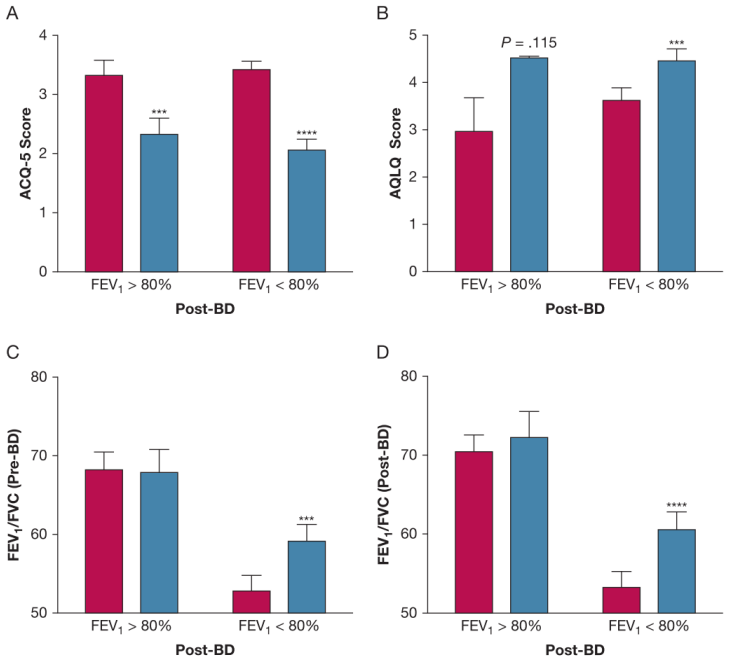
Steven Maltby, PhD; Peter G. Gibson, MBBS; Heather Powell, MMedSc; and Vanessa M. McDonald, PhD, B Nurs, RN

- Data from the Australian Xolair Registry
- Compare treatment responses in ACO vs severe asthma alone.
- Assessed at baseline and after 6 months of omalizumab treatment.
- Several different definitions of asthma-COPD overlap.
  - physician diagnosis of COPD
  - FEV1 < 80%
    → stratified based on smoking history

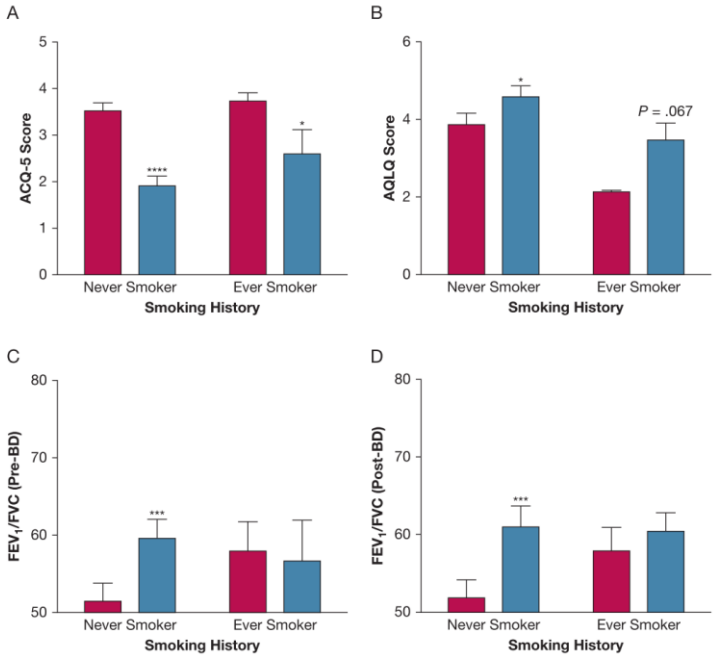
Chest. 2017 Jan;151(1):78-89.



Physician diagnosed ACO



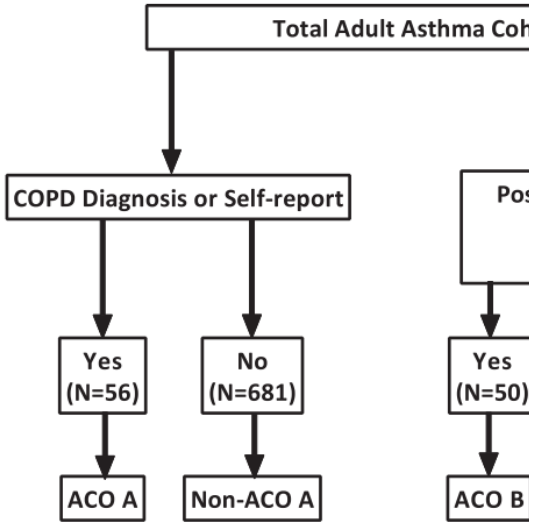
FEV1 < 80%



Ever smoker vs never-smoker

Chest. 2017 Jan;151(1):78-89.

Omalizumab effecti asthma-COPD overl analysis of PROSPE



Original Article

Omalizumab Effectiveness by Biomarker Status in Patients with Asthma: Evidence From PROSPERO, A Prospective Real-World Study

Thomas B. Casale, MD[a], Allan T. Luskin, MD[b], William Busse, MD[c], Robert S. Zeiger, MD, PhD[d,e], Benjamin Trzaskoma, MS[f], Ming Yang, PhD[f], Noelle M. Griffin, PhD[f,*], and Bradley E. Chipps, MD[g] *Tampa, Fla; Madison, Wis; and San Diego, Pasadena, South San Francisco, and Sacramento, Calif*

What is already known about this topic? Omalizumab efficacy has been demonstrated in controlled research settings, but knowledge of its effectiveness in a real-world setting, including the use of biomarkers or clinical characteristics to guide response, is limited.

What does this article add to our knowledge? Omalizumab initiation in patients with moderate to severe allergic asthma in a real-world setting yielded a positive treatment response, measured by multiple parameters, in 87% of patients independent of baseline characteristics or biomarker levels.

How does this study impact current management guidelines? These data suggest that once the decision to treat with omalizumab has been made, biomarker levels may not be predictive of treatment outcomes.

BACKGROUND: Omalizumab has demonstrated efficacy in clinical trials of patients with asthma, but real-world data are needed.
OBJECTIVE: To assess outcomes after omalizumab initiation in patients with asthma in a real-world setting.
METHODS: Patients aged 12 years and older with allergic asthma who were candidates for omalizumab on the basis of physician-assessed need were enrolled in a US-based, prospective, single-arm, 48-week multicenter study, the Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab. Monthly assessments included exacerbations, health care utilization, asthma control test (ACT), and adverse events. At baseline, 6 months, and end of study, biomarkers (blood eosinophils and fractional exhaled nitric oxide) were collected and spirometry performed.
RESULTS: Of 806 enrollees, 801 (99.4%) received omalizumab and 622 (77.2%) completed the study. The exacerbation rate significantly improved from a mean of 3.00 ± 3.28 in the 12 months before baseline to 0.78 ± 1.37 through month 12 ($P < .001$) and was similar in adults and adolescents; there was a reduction of 81.9% in the percentage of patients with 1 or more hospitalizations. Lung function remained generally unchanged. A mean improvement of 4.4 ± 4.9 in ACT scores was observed. Eighty-seven percent of patients were responders on the basis of clinical improvement in exacerbations, lung function, or ACT scores. Baseline biomarker status was associated with ACT scores and lung function improvement, but the magnitude of this

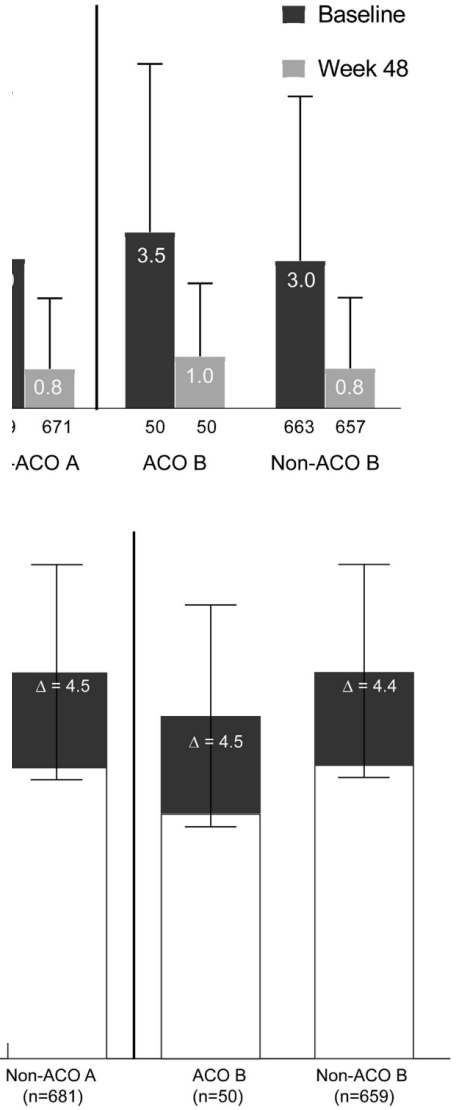


FIG 1. **A,** Mean exacerbation at baseline and week 48. **B,** Mean change *(gray bar)* in ACT score from baseline *(white bar)* at week 48 of omalizumab treatment in ACO and asthma cohorts.

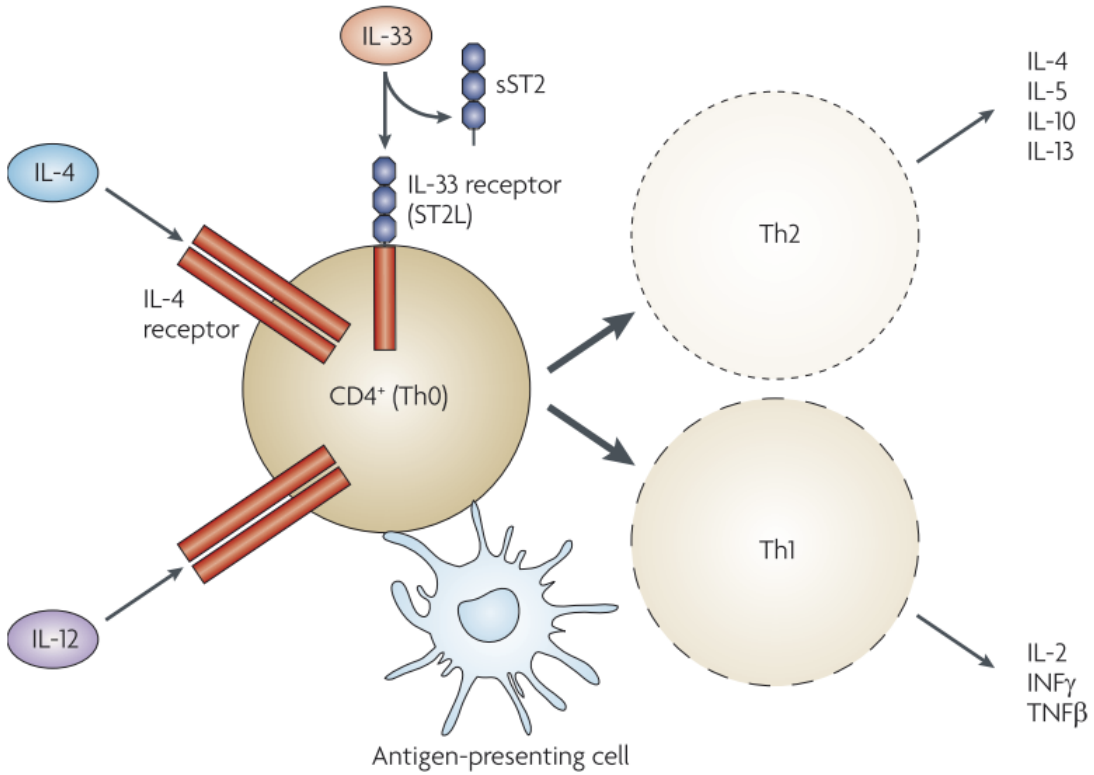
J Allergy Clin Immunol. 2019 Apr;143(4):1629-1633.e2.

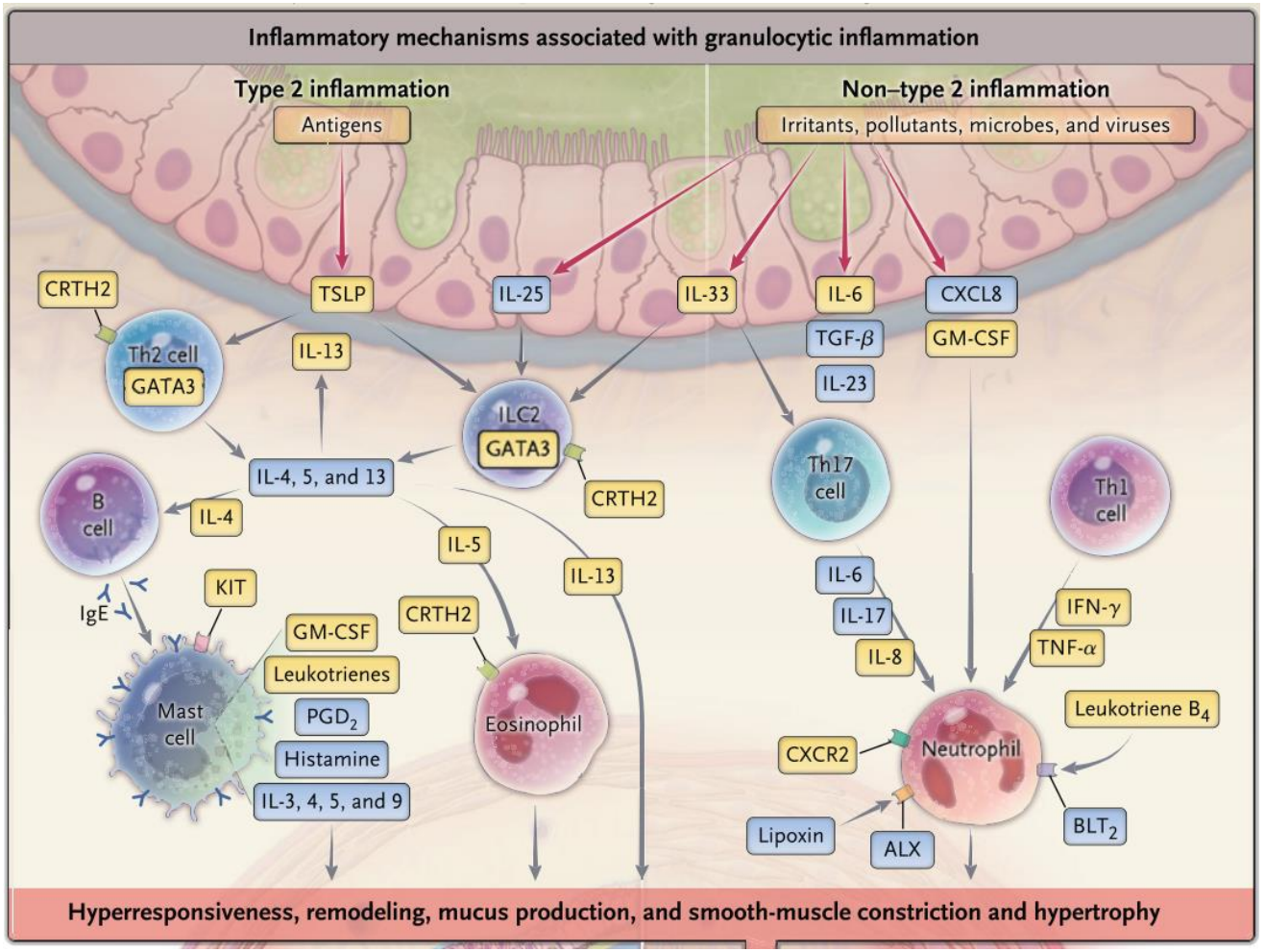
Omalizumab summary

- Little evidence in COPD alone.
- Potential benefit in ACO.

- No further clinical studies ongoing.

Anti IL-33/ST2





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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Itepekimab in Patients with Moderate-to-Severe Asthma

Michael E. Wechsler, M.D., Marcella K. Ruddy, M.D., Ian D. Pavord, M.D., Elliot Israel, M.D., Klaus F. Rabe, M.D., Ph.D., Linda B. Ford, M.D., Jorge F. Maspero, M.D., Raolat M. Abdulai, M.D., Chih-Chi Hu, Ph.D., Renata Martincova, M.D., Andreas Jessel, M.D., Michael C. Nivens, Ph.D., Nikhil Amin, M.D., David M. Weinreich, M.D., George D. Yancopoulos, M.D., Ph.D., and Helene Goulaouic, Ph.D.

Lancet Respir Med. 2021 Nov;9(11):1288-1298, N Engl J Med. 2021 Oct 28;385(18):1656-1668.

Itepekimab (Anti-IL-33)

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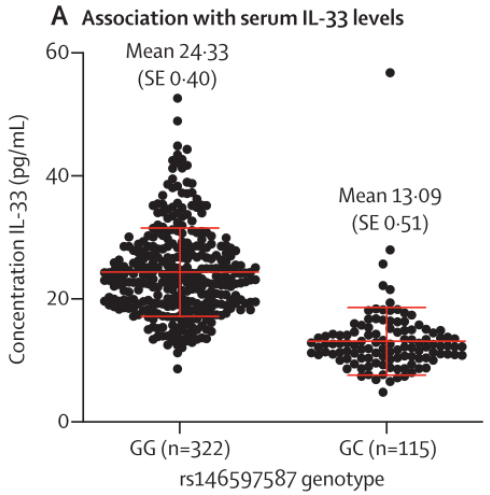
Lancet Respir Med. 2021 Nov;9(11):1288-1298

1. Genetic analyses of variants in the IL-33 pathway
   (previously associated with asthma risk)
   → characterized for COPD.

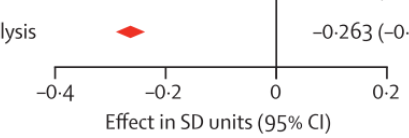
2. Double-blind, phase 2a RCT comparing itepekimab with placebo

- 83 study sites in ten countries.
- Moderate-to-severe COPD on triple or dual inhaler
- Aged 40–75 years
- Current or former smokers
- Primary endpoint : annualized rate of moderate-to-severe acute exacerbations of COPD



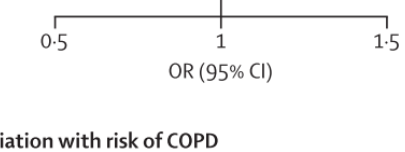
B Association with peripheral blood eosinophil counts

Study	Effect in SD units (95% CI)	p value	Effect in cells/µl (95% CI)	EAF	Number of samples with 146597587 genotype		
					GG	GC	CC
UKB_500K	−0·269 (−0·297 to −0·241)	$3·9 \times 10^{-78}$	−31·5 (−34·8 to −28·3)	0·0046	444707	4134	7
GHS_145K	−0·219 (−0·300 to −0·138)	$1·3 \times 10^{-07}$	−20·0 (−28·6 to −11·4)	0·0031	99833	579	1
Meta-analysis	−0·263 (−0·290 to −0·237)	$6·3 \times 10^{-84}$	−30·2 (−33·9 to −26·4)	0·0038	544540	4713	8



C Association with risk of asthma

Study	OR (95% CI)	p value	EAF	Number of cases			Number of controls		
				GG	GC	CC	GG	GC	CC
UKB_500K	0·562 (0·500 to 0·632)	$5·5 \times 10^{-22}$	0·0048	52875	314	1	268600	2796	4
GHS_145K	0·846 (0·659 to 1·085)	0·19	0·0032	14753	76	0	63268	396	1
Meta-analysis	0·605 (0·544 to 0·673)	$1·7 \times 10^{-20}$	0·0040	67628	390	1	331868	3192	5



D Association with risk of COPD

Study	OR (95% CI)	p value	EAF	Number of cases			Number of controls		
				GG	GC	CC	GG	GC	CC
UKB_500K	0·79 (0·649 to 0·960)	0·018	0·0051	11421	93	0	268600	2796	4
GHS_145K	0·804 (0·606 to 1·066)	0·13	0·0032	10782	56	0	63268	396	1
Meta-analysis	0·794 (0·676 to 0·933)	0·0049	0·0042	22203	149	0	331868	3192	5

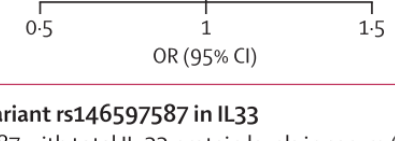
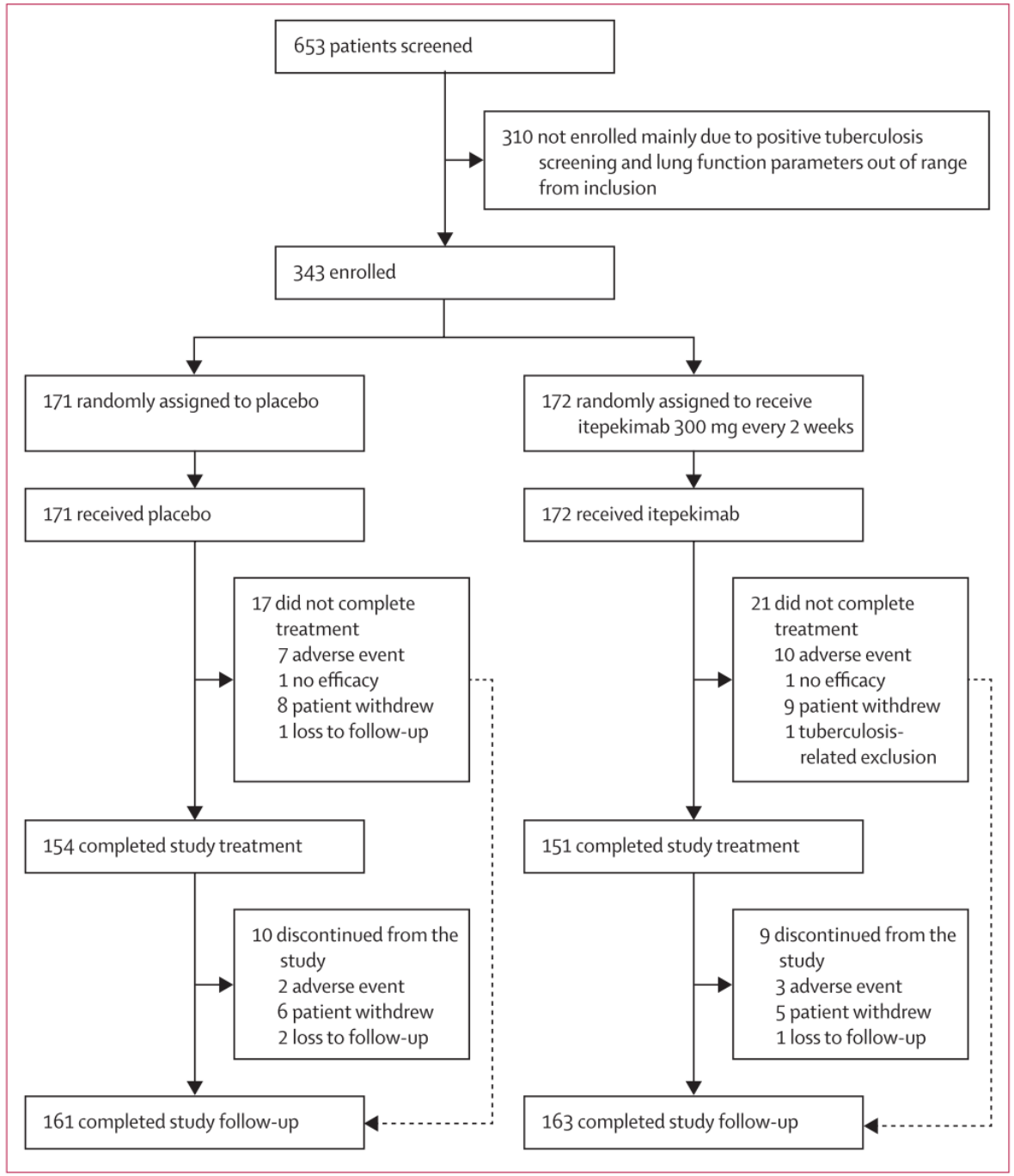


Figure 1: **Genetic association results for the rare splice-acceptor variant rs146597587 in IL33**

Genetic associations of IL-33 rare loss of function variant rs146597587 with total IL-33 protein levels in serum (A), peripheral blood eosinophil counts (B), asthma risk (C), and COPD (D). The effect allele for rs146597587 is the C allele. The GC genotype denotes heterozygous carriers, the GG genotype denotes homozygous non-carriers, and the CC genotype denotes homozygous carriers. COPD=chronic obstructive pulmonary disease. OR=odds ratio. EAF=effect allele frequency.


653 patients screened
310 not enrolled mainly due to positive tuberculosis screening and lung function parameters out of range from inclusion
343 enrolled
171 randomly assigned to placebo
172 randomly assigned to receive itepekimab 300 mg every 2 weeks
171 received placebo
172 received itepekimab
17 did not complete treatment
7 adverse event
1 no efficacy
8 patient withdrew
1 loss to follow-up
21 did not complete treatment
10 adverse event
1 no efficacy
9 patient withdrew
1 tuberculosis-related exclusion
154 completed study treatment
151 completed study treatment
10 discontinued from the study
2 adverse event
6 patient withdrew
2 loss to follow-up
9 discontinued from the study
3 adverse event
5 patient withdrew
1 loss to follow-up
161 completed study follow-up
163 completed study follow-up

	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

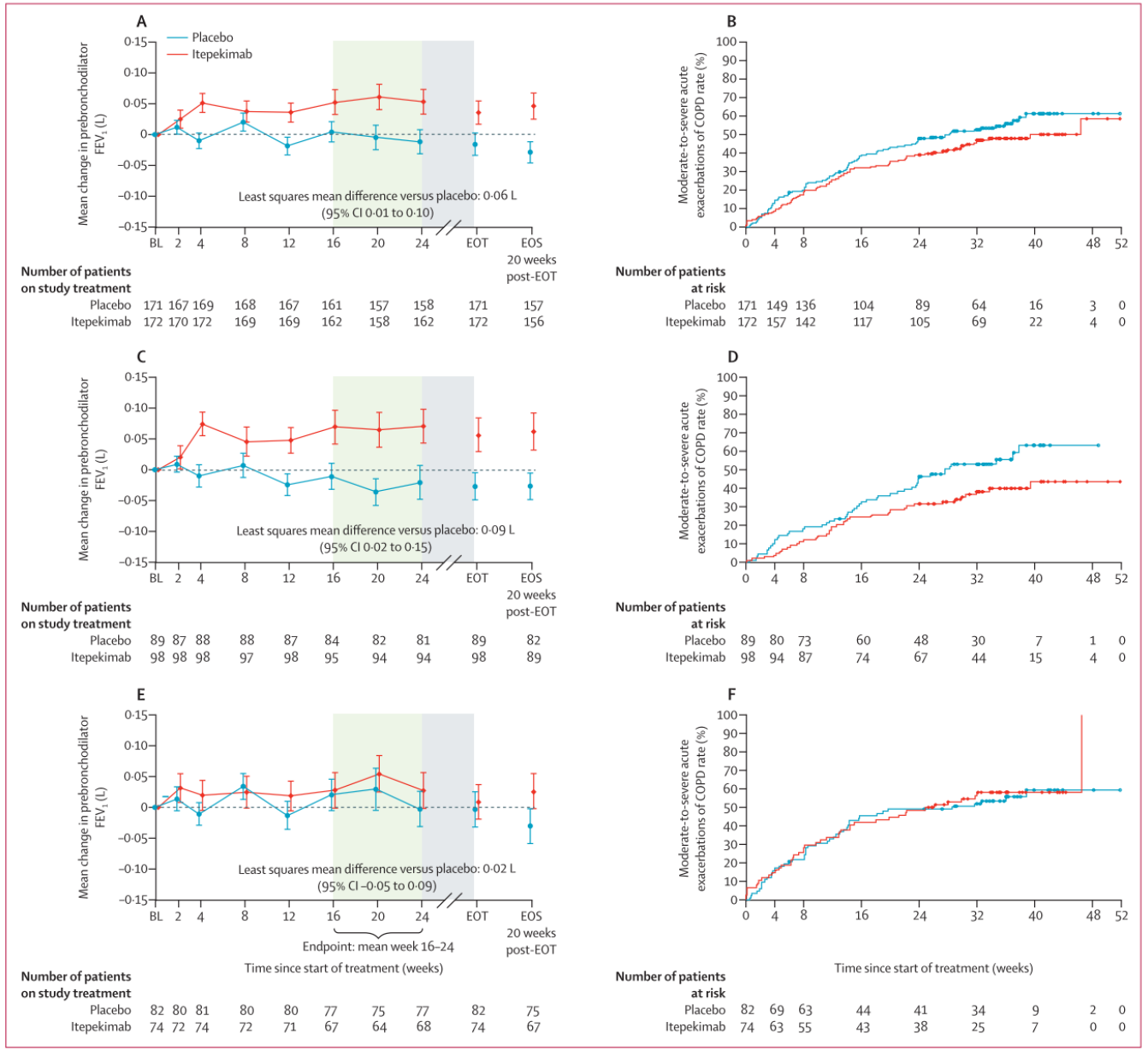
Eosinophil counts are based on values at the baseline visit. The p value for interaction for baseline blood eosinophils is 0·88 for moderate-to-severe acute exacerbations and 0·055 for prebronchodilator FEV_1, and for smoking status, it is 0·023 for moderate-to-severe acute exacerbations and 0·17 for 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**

Overall

Former smoker

Current smoker



	Placebo group (n=171)	Itepekimab group (n=172)
Any TEAE	136 (80%)	135 (78%)
Any severe TEAE	35 (20%)	26 (15%)
Any serious TEAE	36 (21%)	29 (17%)
Any TEAE leading to death	2 (1%)	3 (2%)
Any TEAE leading to permanent treatment discontinuation	7 (4%)	9 (5%)
TEAEs occurring in ≥5% of patients		
Nasopharyngitis	29 (17%)	28 (16%)
Bronchitis	14 (8%)	18 (10%)
Upper respiratory tract infection	15 (9%)	13 (8%)
Headache	23 (13%)	14 (8%)
Hypertension	11 (6%)	3 (2%)
COPD worsening	14 (8%)	11 (6%)

Data are n (%). TEAEs are defined as events occurring from the first administration of study treatment to the end of the post-treatment period by Medical Dictionary for Regulatory Activities preferred term. COPD=chronic obstructive pulmonary disease. TEAE=treatment-emergent adverse event.

***Table 3*: TEAEs in the safety population**

Study to Assess the Efficacy, Safety, and Tolerability of SAR440340/REGN3500/Itepekimab in Chronic Obstructive Pulmonary Disease (COPD) (AERIFY-1)

ClinicalTrials.gov Identifier: NCT04701983

Recruitment Status : Recruiting
First Posted : January 8, 2021

Sponsor:
Sanofi

Collaborator:
Regeneron Pharmaceuticals

Information provided by (Res
Sanofi

Study Design

Go to

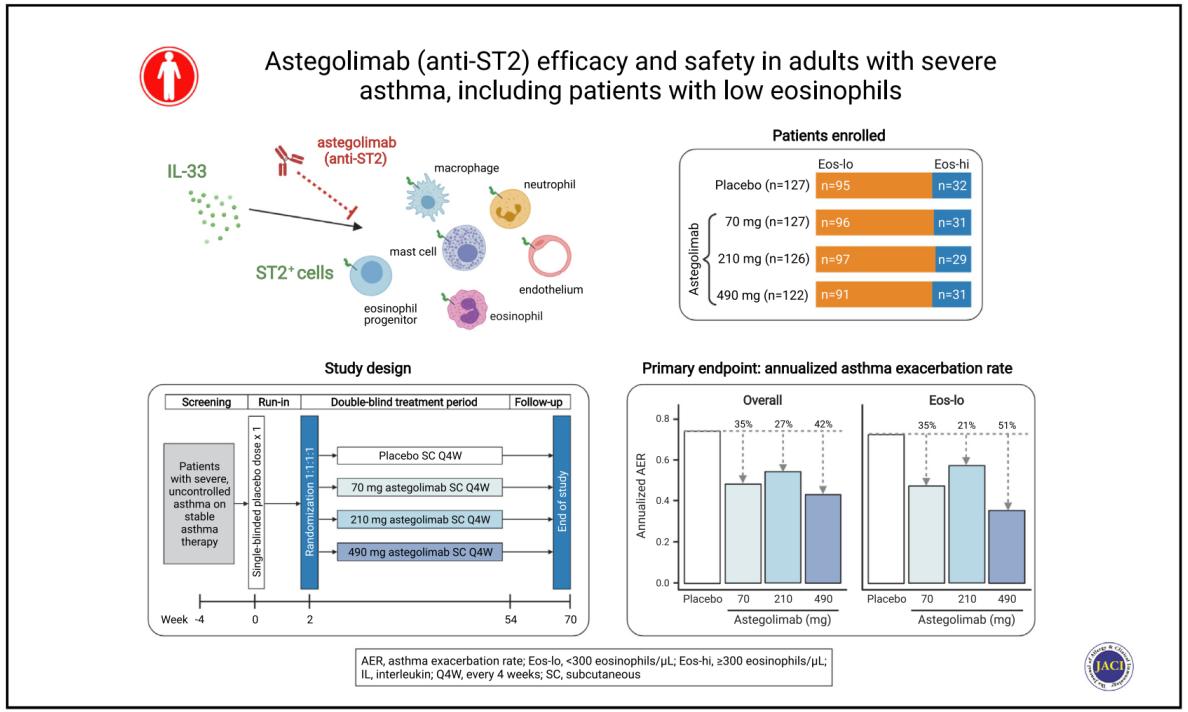
Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	960 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	Randomized, Double-blind, Placebo-controlled, Parallel Group Phase 3 Study to Evaluate the Efficacy, Safety, and Tolerability of SAR440340/REGN3500/Itepekimab (Anti-IL-33 mAb) in Patients With Moderate-to-severe Chronic Obstructive Pulmonary Disease (COPD)
Actual Study Start Date :	December 16, 2020
Estimated Primary Completion Date :	June 13, 2024
Estimated Study Completion Date :	October 31, 2024

Astegolimab (Anti-ST2)

Astegolimab (anti-ST2) efficacy and safety in adults with severe asthma: A randomized clinical trial

Steven G. Kelsen, MD,[a] Ioana O. Agache, MD, PhD,[b] Weily Soong, MD,[c] Elliot Israel, MD,[d] Geoffrey L. Chupp, MD,[e] Dorothy S. Cheung, MD,[f] Wiebke Theess, PhD,[f] Xiaoying Yang, PhD,[f] Tracy L. Staton, PhD,[f] David F. Choy, BS,[f] Alice Fong, PharmD,[f] Ajit Dash, MD, PhD,[f] Michael Dolton, PhD,[f] Rajita Pappu, PhD,[f] and Christopher E. Brightling, FMedSci, PhD[g] *Philadelphia, Pa; Brasov, Romania; Birmingham, Ala; Boston, Mass; New Haven, Conn; South San Francisco, Calif; and Leicestershire, United Kingdom*

GRAPHICAL ABSTRACT



J Allergy Clin Immunol. 2021 Sep;148(3):790-798.

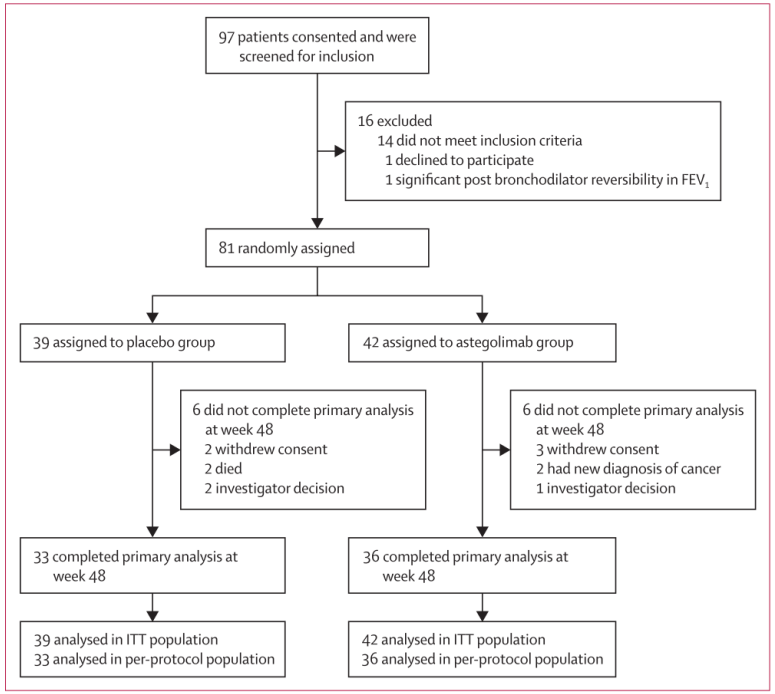
Astegolimab, an anti-ST2, in chronic obstructive pulmonary disease (COPD-ST2OP): a phase 2a, placebo-controlled trial

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**

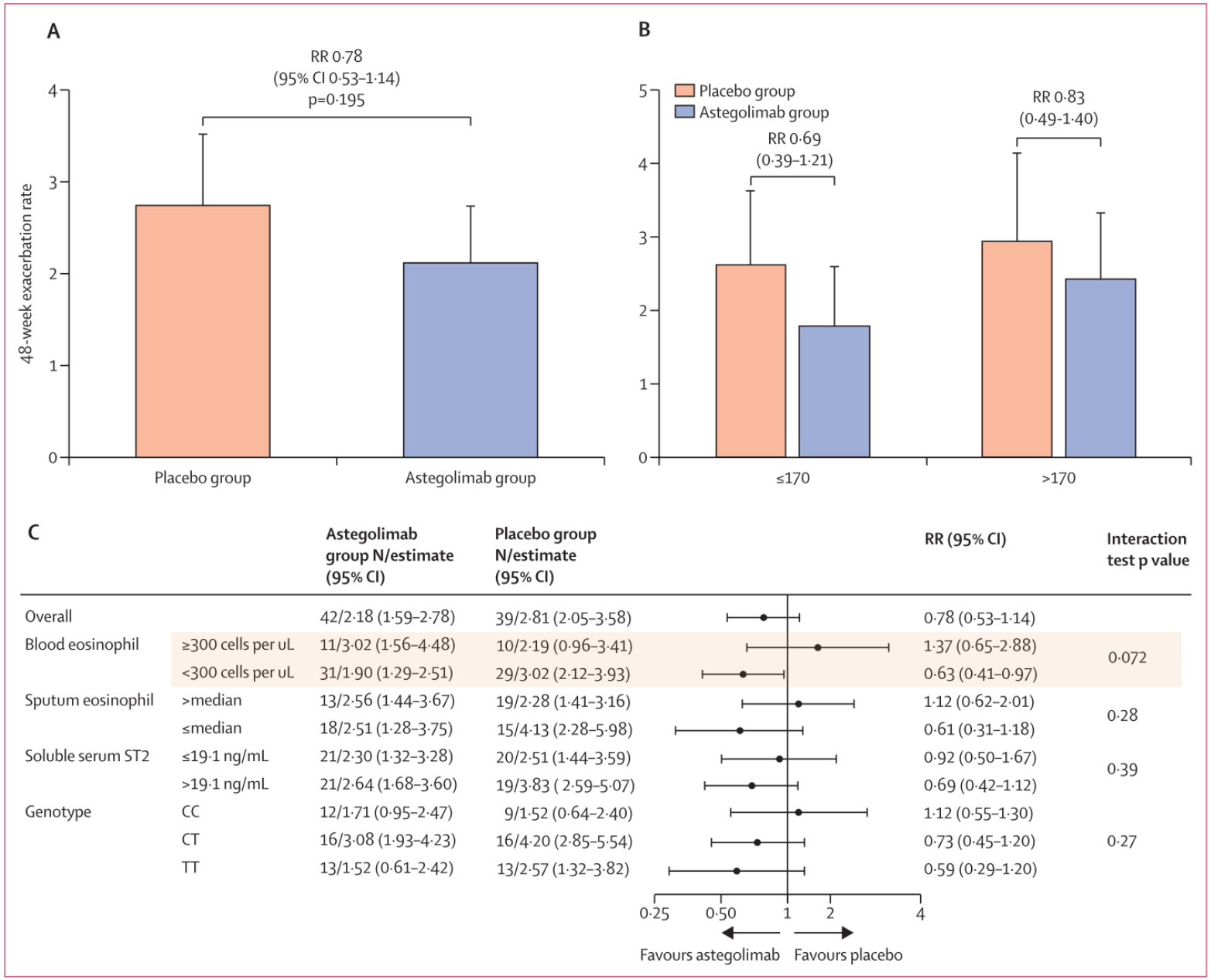
- Single-center, phase 2a RCT
- Aged ≥ 40
- Moderate-to-very severe COPD
- ≥ two acute exacerbations of COPD
- ≥ 10PY of smoking Hx.
- mMRC ≥ 2

- 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.



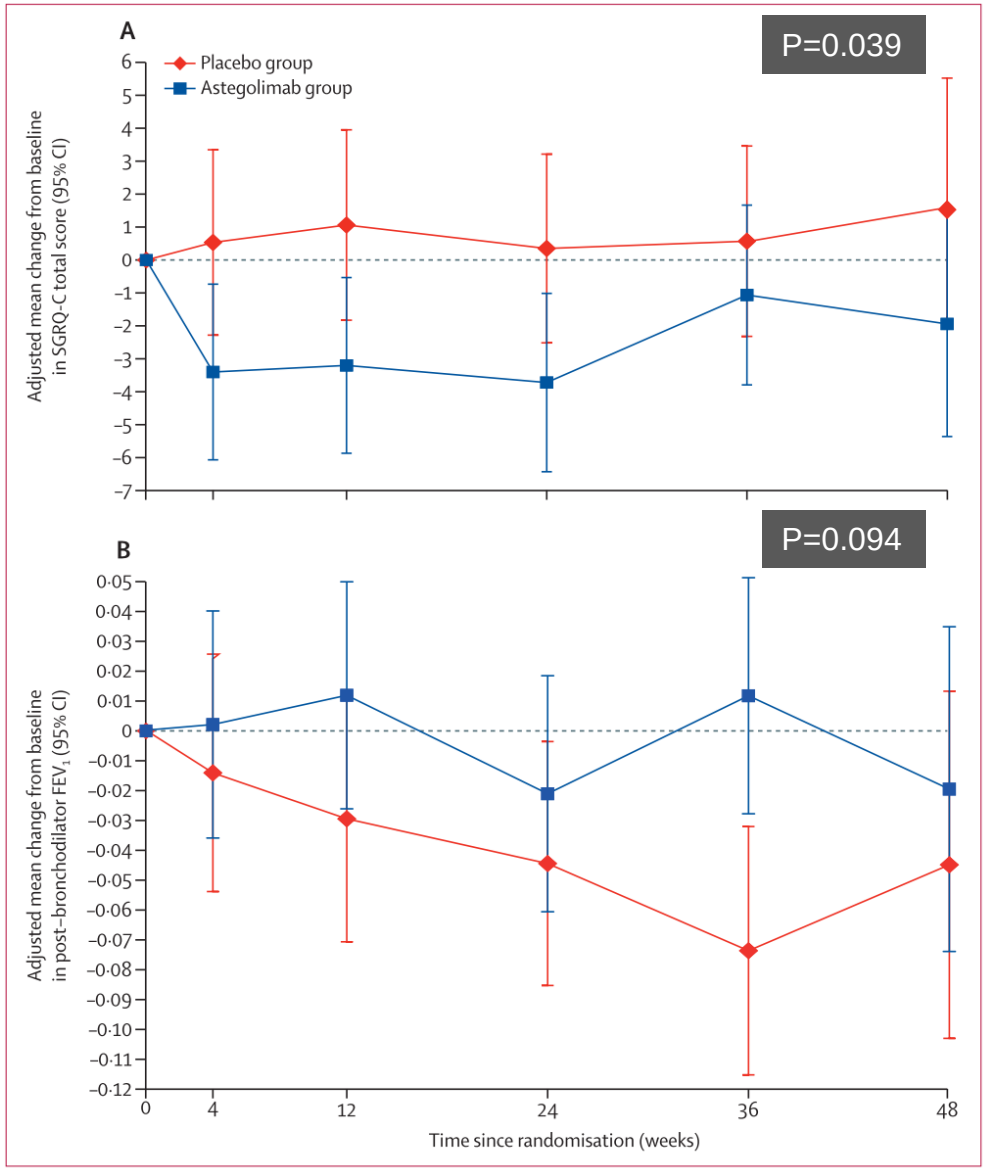
C

		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.

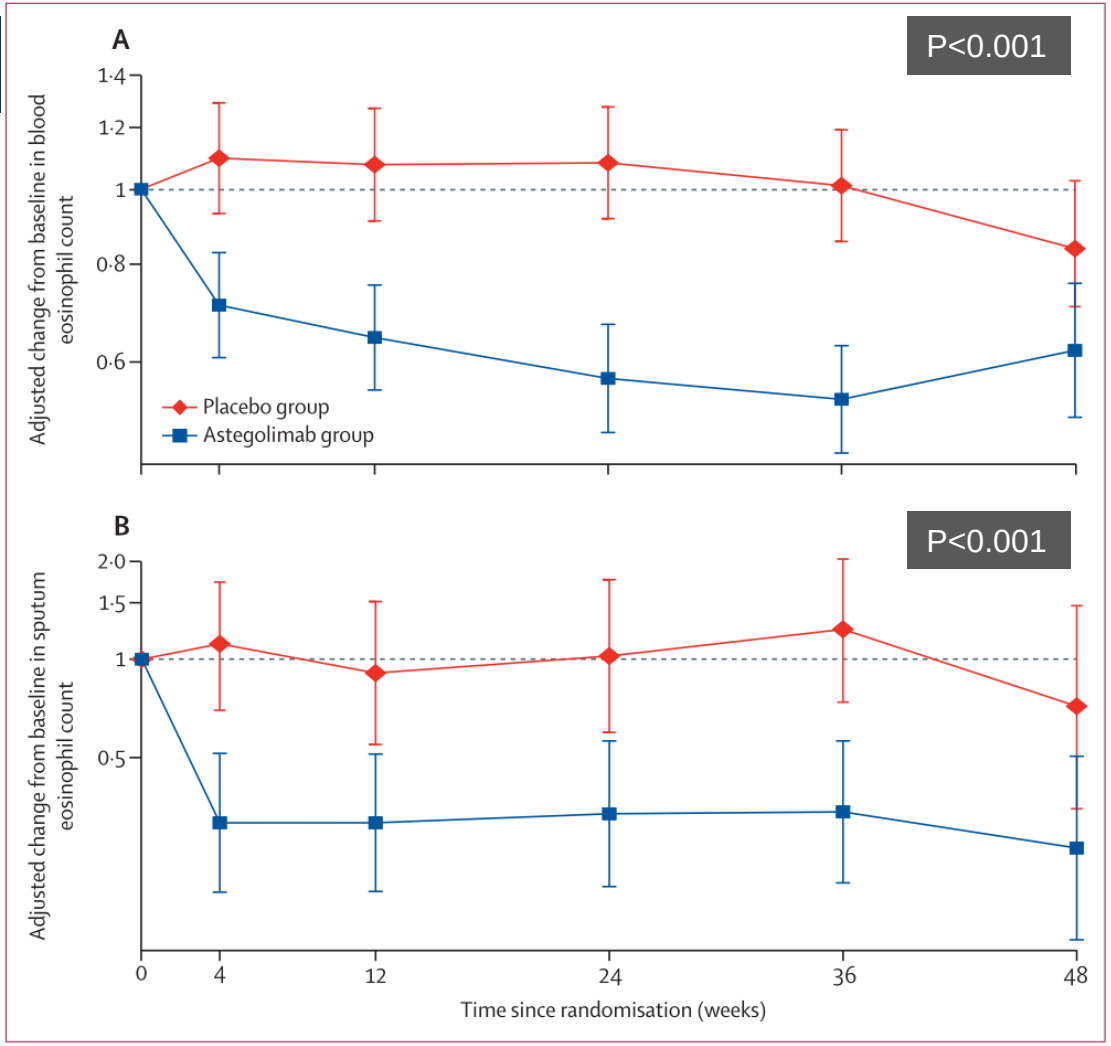
SGRQ-C

FEV$_1$



Blood eosinophil

Sputum eosinophil



A Study to Evaluate the Efficacy and Safety of Astegolimab in Participants With Chronic Obstructive Pulmonary Disease

ClinicalTrials.gov Identifier: NCT05037929

Recruitment Status : Recruiting
First Posted : September 8, 2021
Last Update Posted : January 18, 2023

See Contacts and Locations

Study Design

Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	930 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Double (Participant, Investigator)
Primary Purpose:	Treatment
Official Title:	A Phase IIb, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Astegolimab in Patients With Chronic Obstructive Pulmonary Disease
Actual Study Start Date :	October 5, 2021
Estimated Primary Completion Date :	May 1, 2024
Estimated Study Completion Date :	August 1, 2024

Future biologics
- Anti-TSLP
-Anti-IL-4R

Tezepelumab (anti-TSLP)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tezepelumab in Adults with Uncontrolled Asthma

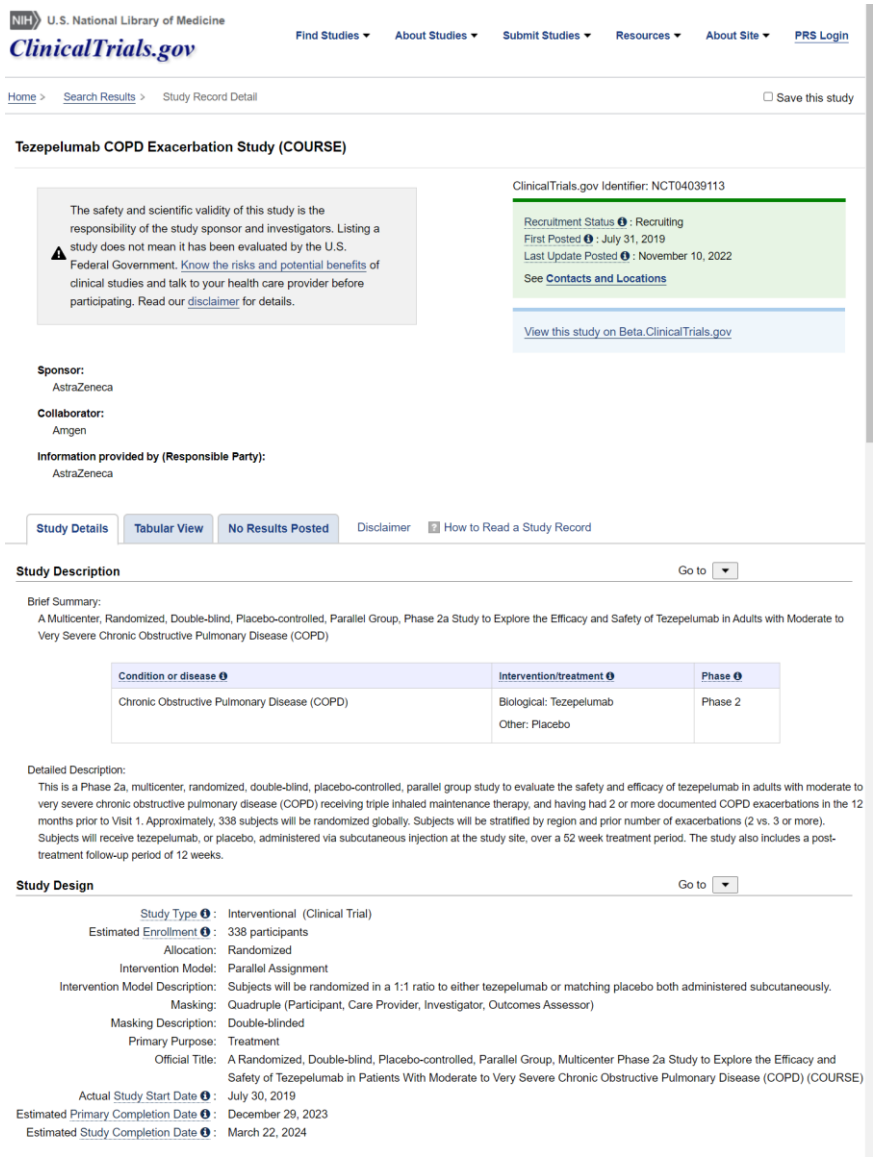
Jonathan Corren, M.D., Jane R. Parnes, M.D., Liangwei Wang, Ph.D., May Mo, M.S., Stephanie L. Roseti, A.P.N., M.S.N., Janet M. Griffiths, Ph.D., and René van der Merwe, M.B., Ch.B.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma

Andrew Menzies-Gow, M.D., Jonathan Corren, M.D., Arnaud Bourdin, M.D., Geoffrey Chupp, M.D., Elliot Israel, M.D., Michael E. Wechsler, M.D., Christopher E. Brightling, F.Med.Sci., Janet M. Griffiths, Ph.D., Åsa Hellqvist, M.Sc., Karin Bowen, M.Sc., Primal Kaur, M.D., Gun Almqvist, M.Sc., Sandhia Ponnarambil, M.D., and Gene Colice, M.D.



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Tezepelumab COPD Exacerbation Study (COURSE)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT04039113

Recruitment Status : Recruiting
First Posted : July 31, 2019
Last Update Posted : November 10, 2022
See Contacts and Locations

View this study on Beta.ClinicalTrials.gov

Sponsor:
AstraZeneca

Collaborator:
Amgen

Information provided by (Responsible Party):
AstraZeneca

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

Study Description Go to

Brief Summary:
A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group, Phase 2a Study to Explore the Efficacy and Safety of Tezepelumab in Adults with Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD)

Condition or disease	Intervention/treatment	Phase
Chronic Obstructive Pulmonary Disease (COPD)	Biological: Tezepelumab Other: Placebo	Phase 2

Detailed Description:
This is a Phase 2a, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate the safety and efficacy of tezepelumab in adults with moderate to very severe chronic obstructive pulmonary disease (COPD) receiving triple inhaled maintenance therapy, and having had 2 or more documented COPD exacerbations in the 12 months prior to Visit 1. Approximately, 338 subjects will be randomized globally. Subjects will be stratified by region and prior number of exacerbations (2 vs. 3 or more). Subjects will receive tezepelumab, or placebo, administered via subcutaneous injection at the study site, over a 52 week treatment period. The study also includes a post-treatment follow-up period of 12 weeks.

Study Design Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	338 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Intervention Model Description:	Subjects will be randomized in a 1:1 ratio to either tezepelumab or matching placebo both administered subcutaneously.
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Masking Description:	Double-blinded
Primary Purpose:	Treatment
Official Title:	A Randomized, Double-blind, Placebo-controlled, Parallel Group, Multicenter Phase 2a Study to Explore the Efficacy and Safety of Tezepelumab in Patients With Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD) (COURSE)
Actual Study Start Date :	July 30, 2019
Estimated Primary Completion Date :	December 29, 2023
Estimated Study Completion Date :	March 22, 2024

N Engl J Med. 2017 Sep 7;377(10):936-946,
N Engl J Med. 2021 May 13;384(19):1800-1809

Dupilumab (Anti-IL4R)

The NEW ENGLAND JOURNAL of MEDICINE

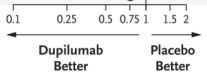
ORIGINAL ARTICLE

Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma

M. Castro, J. Corren, I.D. Pavord, J. Maspero, S. Wenzel, K.F. Rabe, W.W. Busse, L. Ford, L. Sher, J.M. FitzGerald, C. Katelaris, Y. Tohda, B. Zhang, H. Staudinger, G. Pirozzi, N. Amin, M. Ruddy, B. Akinlade, A. Khan, J. Chao, R. Martincova, N.M.H. Graham, J.D. Hamilton, B.N. Swanson, N. Stahl, G.D. Yancopoulos, and A. Teper

A Dupilumab, 200 mg Every 2 Wk, vs. Matched Placebo

Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	317	631	0.52 (0.41–0.66)
Eosinophil count			
≥300 cells/mm³	148	264	0.34 (0.24–0.48)
≥150 to <300 cells/mm³	84	173	0.64 (0.41–1.02)
<150 cells/mm³	85	193	0.93 (0.58–1.47)
Fe_{NO}			
≥50 ppb	71	119	0.31 (0.18–0.52)
≥25 to <50 ppb	91	180	0.39 (0.24–0.62)
<25 ppb	149	325	0.75 (0.54–1.05)



B Dupilumab, 300 mg Every 2 Wk, vs. Matched Placebo

Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	321	633	0.54 (0.43–0.68)
Eosinophil count			
≥300 cells/mm³	142	277	0.33 (0.23–0.45)
≥150 to <300 cells/mm³	95	175	0.56 (0.35–0.89)
<150 cells/mm³	83	181	1.15 (0.75–1.77)
Fe_{NO}			
≥50 ppb	75	124	0.31 (0.19–0.49)
≥25 to <50 ppb	97	186	0.44 (0.28–0.69)
<25 ppb	144	317	0.79 (0.57–1.10)

Figure 1. Forest Plots of the Risk of Severe Asthma Exacerbations in the Intention-to-Treat Population and in Subgroups Defined According to Baseline Blood Eosinophil Count and Baseline Fe_{NO}.

Fe_{NO} denotes fraction of exhaled nitric oxide, and ppb parts per billion.

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Pivotal Study to Assess the Efficacy, Safety and Tolerability of Dupilumab in Patients With Moderate to Severe COPD With Type 2 Inflammation (NOTUS)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT04456673

Recruitment Status : Recruiting
First Posted : July 2, 2020
Last Update Posted : December 21, 2022
See Contacts and Locations

View this study on Beta.ClinicalTrials.gov

Sponsor:
Sanofi

Collaborator:
Regeneron Pharmaceuticals

Information provided by (Responsible Party):
Sanofi

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

Study Description Go to

Brief Summary:

Primary Objective:

To evaluate the efficacy of dupilumab administered every 2 weeks in patients with moderate or severe Chronic Obstructive Pulmonary Disease (COPD) as measured by

- Annualized rate of acute moderate or severe COPD exacerbation (AECOPD)

Secondary Objectives:

To evaluate the effect of dupilumab administered every 2 weeks on

- Pre-bronchodilator forced expiratory volume in 1 second (FEV1) over 12 weeks compared to placebo
- Health related quality of life, assessed by the change from baseline to Week 52 in the St. George's Respiratory Questionnaire (SGRQ)
- Pre-bronchodilator FEV1 over 52 weeks compared to placebo
- Lung function assessments
- Moderate and severe COPD exacerbations
- To evaluate safety and tolerability
- To evaluate dupilumab systemic exposure and incidence of antidrug antibodies (ADA)

Condition or disease	Intervention/treatment	Phase
Chronic Obstructive Pulmonary Disease	Drug: Dupilumab SAR231893	Phase 3
	Drug: Inhaled Corticosteroid	
	Drug: Inhaled Long-Acting Beta Agonist	
	Drug: Inhaled Long-Acting Muscarinic Antagonist	
	Drug: Placebo	

Detailed Description:
Approximately 68 weeks including a 4-week screening period, a 52-week treatment period, and 12 weeks of follow-up

Study Design Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	924 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	A Randomized, Double-blind, Placebo-controlled, Parallel-group, 52-week Pivotal Study to Assess the Efficacy, Safety, and Tolerability of Dupilumab in Patients With Moderate-to-severe Chronic Obstructive Pulmonary Disease (COPD) With Type 2 Inflammation
Actual Study Start Date :	June 12, 2020
Estimated Primary Completion Date :	July 1, 2023

N Engl J Med. 2018 Jun 28;378(26):2486-2496.

Take home messages

- Failure of biologics targeting neutrophilic inflammations
  - Anti-IL-8/ Anti-CXCR2/ Anti-TNF-α/ Anti-IL-1/ Anti-17A
- Revolutionary outcomes of biologics targeting Th2 inflammation in asthma.
- Potential role of biologics targeting Th2 inflammation in COPD.
  - Anti-IL-5R (Benralizumab)/anti-IL-5 (Mepolizumab)
  - Anti-IgE (Omalizumab)
  - Anti-IL-33 (Itepekimab)/anti-ST2 (Astegolimab)
- Future biologics
  - Anti-TSLP/ Anti-IL-4R

Benralizumab	Mepolizumab	Omalizumab	Itepekimab	Astegolimab
• **Primary outcome** ↔ Moderate-to-severe AE • **Secondary outcome** ↔ FEV1 in the intervention group (↑in phase 2a trial) ↔ health status ↓ Blood and sputum eosinophils	• **Primary outcome** ↓ Moderate-to-severe AE COPD (eosinophilic COPD in METREX) ↔ Moderate-to-severe AE COPD (overall METREX, METREO) • **Secondary outcome** ↑ Time-to-first exacerbation (METREX+METREO) ↔ FEV1 ↔ SGRQ ↓ CAT (METREX+METREO) • Eosinophil count : potential biomarker for good responder	• Little evidence in COPD alone. • Potential benefit in ACO. • No further clinical studies ongoing.	• **Primary outcome** ↓ Moderate-to-severe AE COPD (Former smoker) • **Secondary outcome** ↑ FEV1 (Former smoker)	• **Primary outcome** ↓ Moderate-to-severe AE COPD (Blood eosinophil < 300) • **Secondary outcome** ↓ SGRQ ↔ FEV1 ↓ blood/sputum eosinophil count

Take home messages

- Failure of biologics targeting neutrophilic inflammations
  - Anti-IL-8/ Anti-CXCR2/ Anti-TNF-α/ Anti-IL-1/ Anti-17A
- Revolutionary outcomes of biologics targeting Th2 inflammation in asthma.
- Potential role of biologics targeting Th2 inflammation in COPD.
  - Anti-IL-5R (Benralizumab)/anti-IL-5 (Mepolizumab)
  - Anti-IgE (Omalizumab)
  - Anti-IL-33 (Itepekimab)/anti-ST2 (Astegolimab)
- Future biologics
  - Anti-TSLP/ Anti-IL-4R

Thank you for your attention!