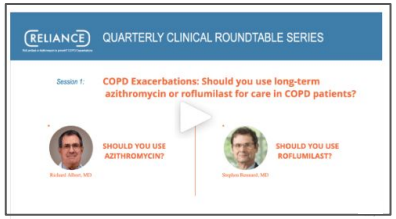
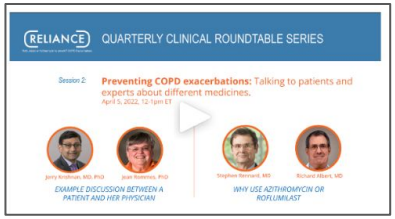
QUARTERLY CLINICAL ROUNDTABLE SERIES

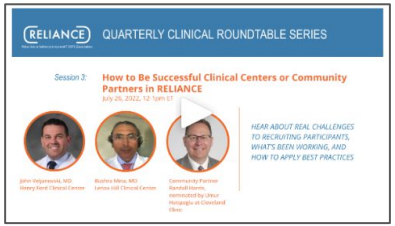
RofLumilast or Azithromycin to preveNT COPD Exacerbations



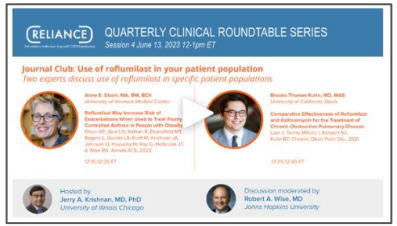
January 11, 2022 | COPD Exacerbations: Should you use long-term azithromycin or roflumilast for care in COPD patients?



April 5, 2022 | Preventing COPD exacerbations: talking to patients and experts about deciding between medicines.



July 26, 2022 | How to be successful Clinical Centers or Community Partners in RELIANCE



June 13, 2023 | Journal Club: Use of roflumilast in your patient population

Watch past events at
reliance-study.org/clinicians/#roundtable

Have an idea for a roundtable?
Put it in the chat!

RELIANCE
RofLumilast or Azithromycin to preveNT COPD Exacerbations

QUARTERLY CLINICAL ROUNDTABLE SERIES

Session 5 September 19, 2023 12-1pm ET

Journal Club: Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts: Challenges and Opportunities

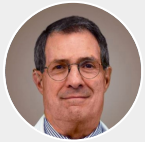
Surya P. Bhatt, MD, MSPH
University of Alabama at Birmingham

Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts
Bhatt SP, Rabe K, Hanania N, Vogelmeier C, Cole J, Bafadhel M, Christenson SA, Papi A, Singh D, Laws E, Mannent LP, Patel N, Staudinger HW, Yancopoulos GD, Mortensen ER, Akinlade B, Maloney J, Lu X, Bauer D, Bansal A, Robinson LB, Abdulai RM; BOREAS Investigators. N Engl J Med, 2023 Jul 20.

Hosted by
Jerry A. Krishnan, MD, PhD
University of Illinois Chicago

Discussion moderated by
Robert A. Wise, MD
Johns Hopkins University

Commentary by
Stephen Rennard, MD
University of Nebraska



Commentary by
Richard Albert, MD
University of Colorado

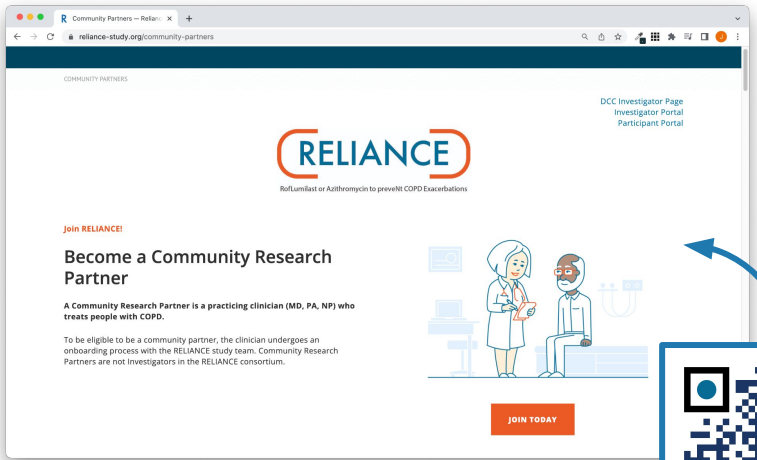
RELIANCE
RofLumilast or Azithromycin to preveNT COPD Exacerbations

QUARTERLY CLINICAL ROUNDTABLE SERIES

Session 5 September 19, 2023 12-1pm ET

1. Please mute yourself
2. **Put questions + comments in the chat**
3. Consider joining RELIANCE,
   or tell a colleague!
   a. Pragmatic clinical trial embedded in clinical practice, funded by PCORI
   b. Long-term azithromycin vs. roflumilast in patients with COPD associated with chronic bronchitis
   c. N=540 enrolled as of 9/13/2023
   d. ClinicalTrials.gov: NCT04069312

Learn more about RELIANCE and how to join
https://www.reliance-study.org/community-partners



RELIANCE

Surya P. Bhatt, MD, MSPH

University of Alabama at Birmingham

Professor of Medicine in the Division of Pulmonary, Allergy and Critical Care Medicine
Director, UAB Lung Imaging Lab

Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts

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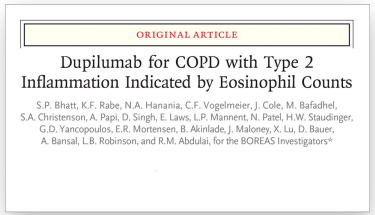
Challenges and Opportunities of Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts

RELIANCE Round Table Journal Club

Surya P. Bhatt, MD, MSPH
Professor of Medicine
Endowed Professor of Airways Disease
Director| UAB Lung Imaging Lab
Medical Director| Pulmonary Rehabilitation| Telehealth PR
Medical Director| Pulmonary Function & Exercise Physiology Lab
University of Alabama at Birmingham

The NEW ENGLAND JOURNAL of MEDICINE


ORIGINAL ARTICLE

Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts

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

September 19, 2023

UAB HEERSINK SCHOOL OF MEDICINE
The University of Alabama at Birmingham

Disclosures

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- R01 Grant from NHLBI (R01HL151421)
- R21 TrailBlazer Grant from NIBIB (R21EB027891)

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- Nuvaira
- Sanofi/Regeneron

Advisory Board/Consulting

- Sanofi, Regeneron, GSK, Boehringer Ingelheim

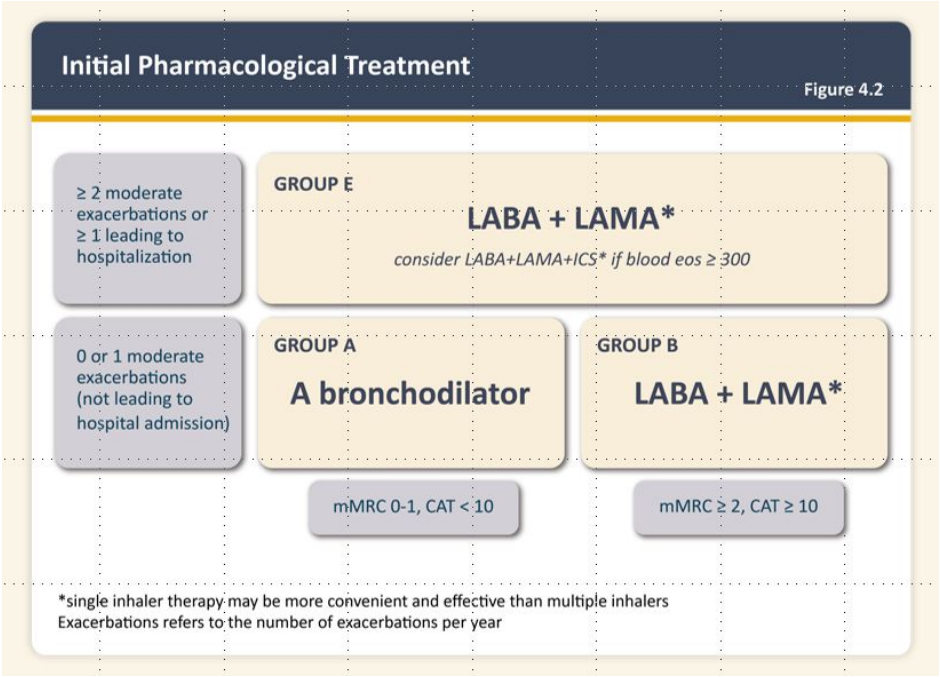
National Heart, Lung, and Blood Institute

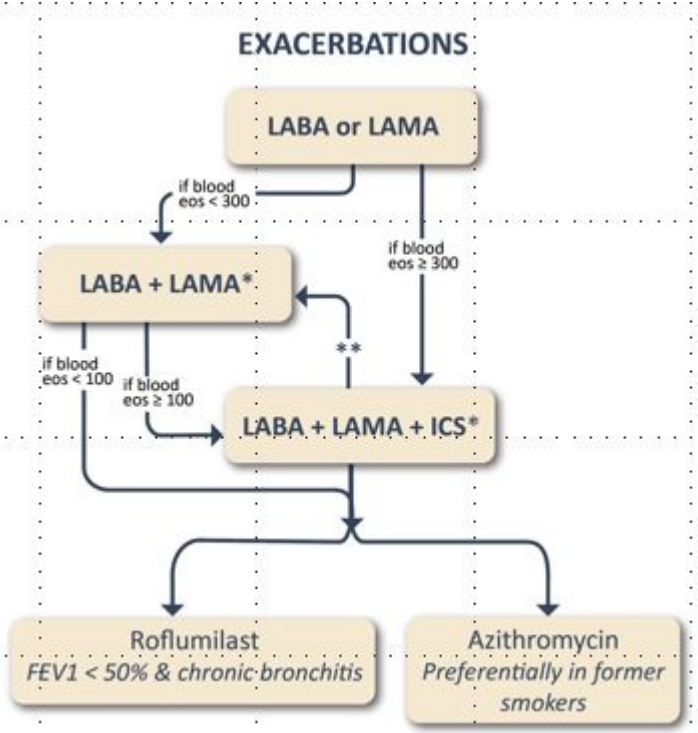
National Institute of Biomedical Imaging and Bioengineering

Background

- 50% of patients continue to have persistent symptoms and exacerbations despite optimization of existing therapy
- COPD exacerbations are associated with:
  - High morbidity
  - Lung function decline and emphysema progression
  - Increased risk of death

Pharmacological Treatment of COPD

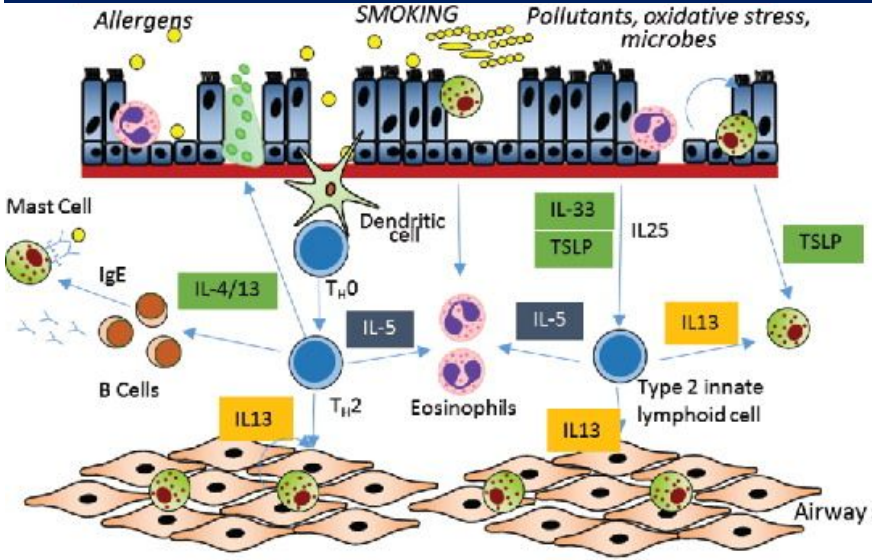




Agusti et al. Am J Respir Crit Care Med. 2023; 207(7):819-837

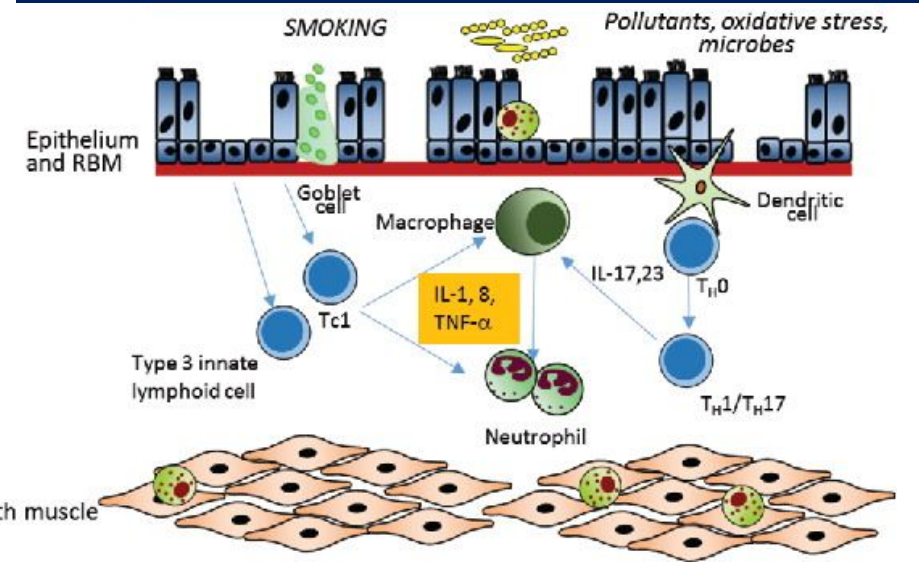
COPD Endotypes

Eosinophil Predominant T2



Present in 20-40% of COPD

Neutrophil Predominant T1 & T17



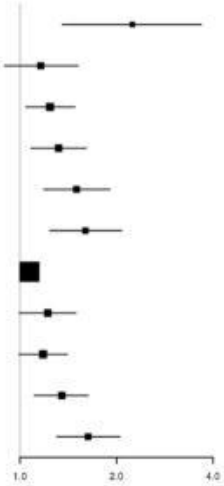
Majority of COPD

Yousuf et al. COPD. 2018;15(2):99-107

Blood Eosinophils and Exacerbations

COPDGene

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



ECLIPSE

Eosinophil Cutoff	< n	≥ n	IRR	95% CI
continuous cells/uL	NA	1895	1.46	1.09-1.93
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340 cells/uL	1584	311	1.22	1.06-1.40
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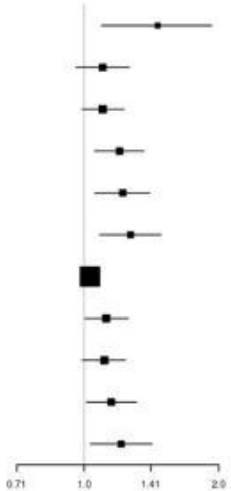
4 %	1476	419	1.15	1.01-1.31
5 %	1660	235	1.21	1.03-1.42



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

Blood Eosinophils and Exacerbations

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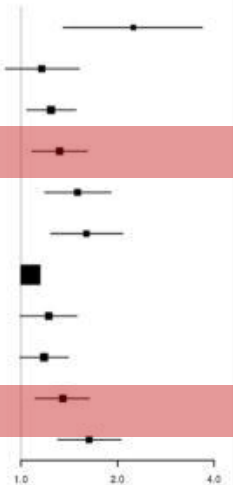

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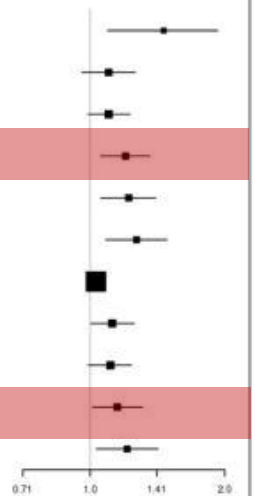
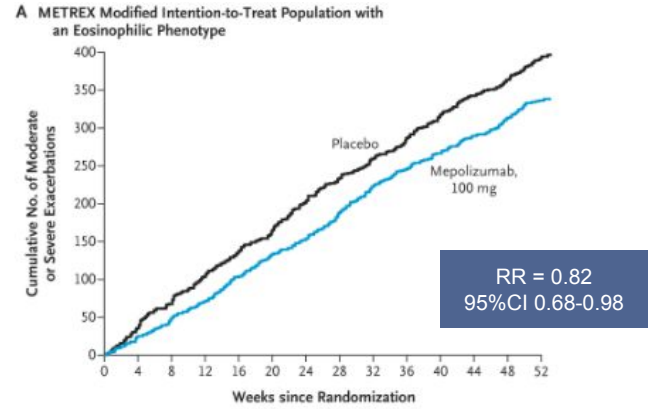


22%-24% population

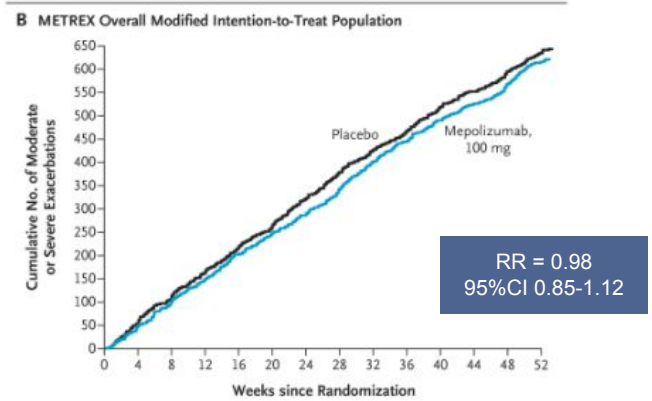
Yun et al. J Allergy Clin Immunol. 2018; 141(6):2037-2047.e10

Anti IL-5 Ab: Mepolizumab

Metrex (Stratified by Eos)

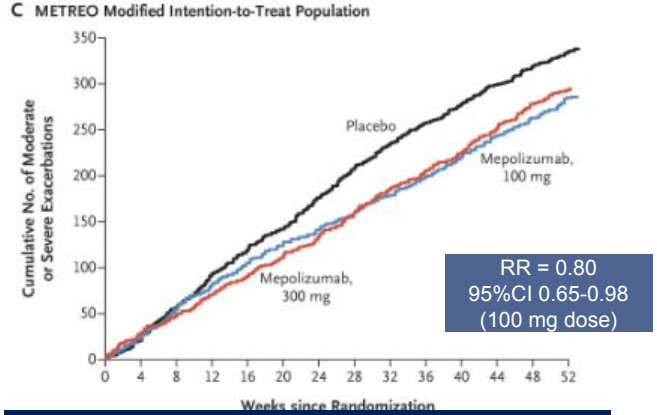


RR = 0.82
95%CI 0.68-0.98



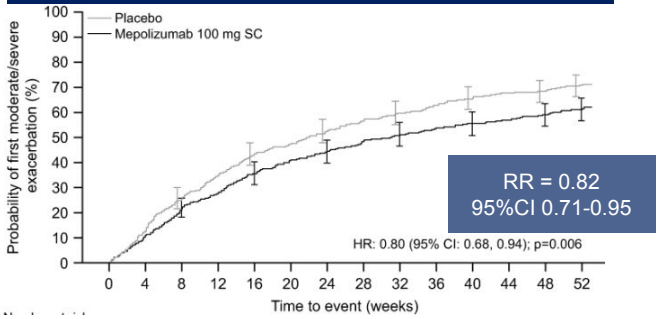
RR = 0.98
95%CI 0.85-1.12

Metreo (All high Eos)



RR = 0.80
95%CI 0.65-0.98
(100 mg dose)

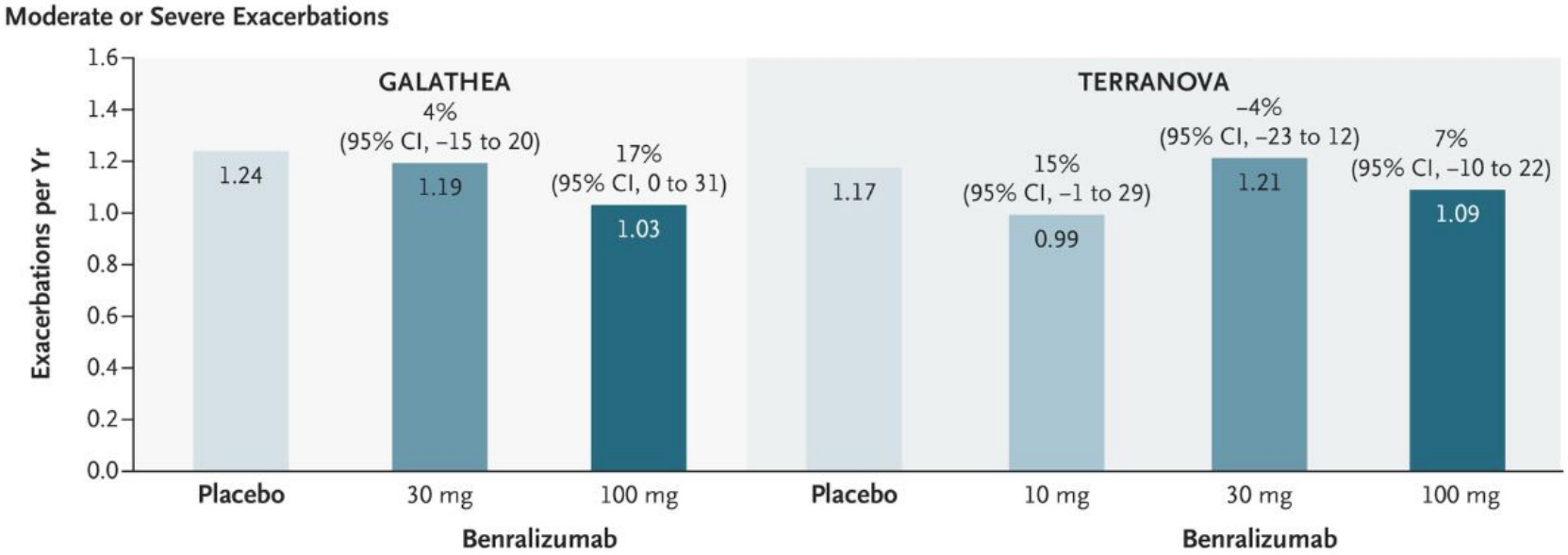
Pooled Analysis (High Eos)



RR = 0.82
95%CI 0.71-0.95

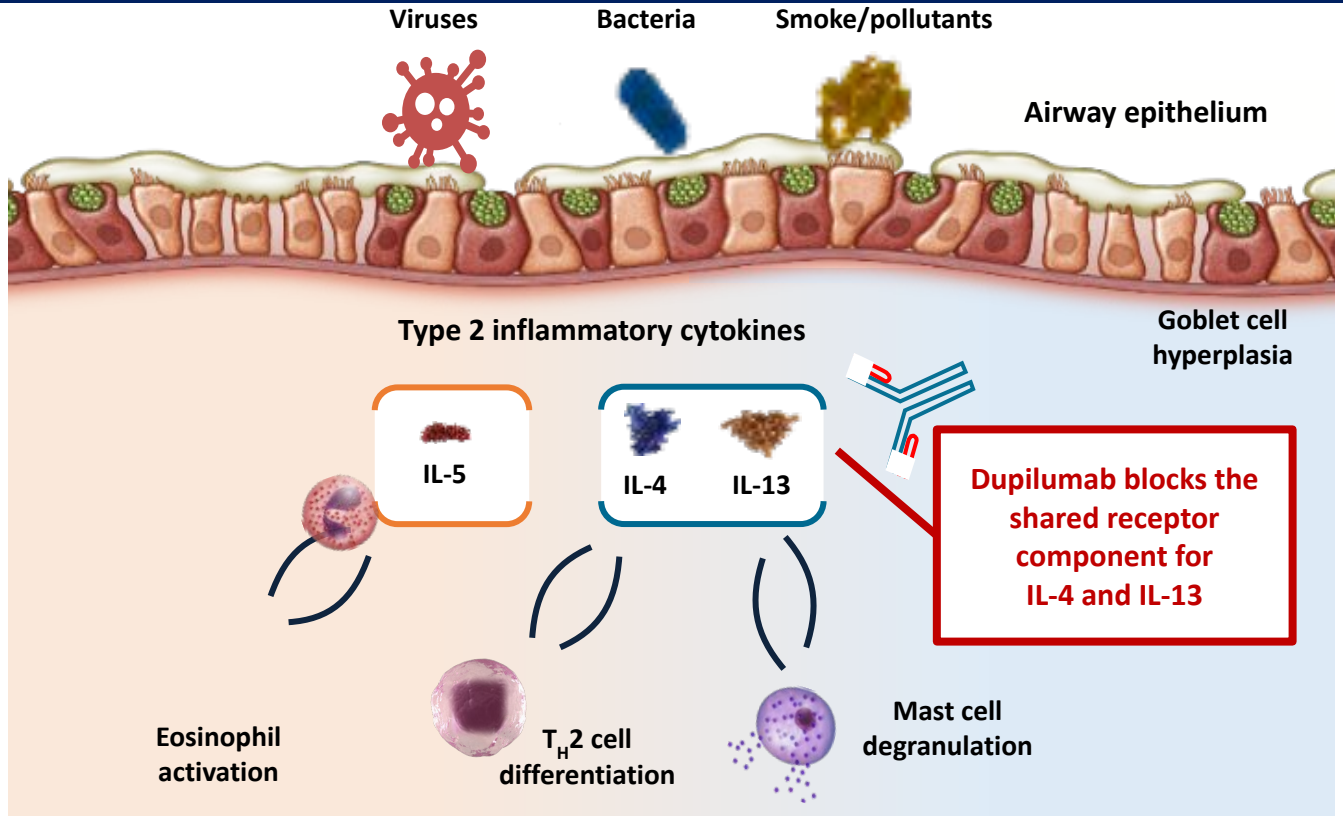
Pavord et al. N Engl J Med. 2017; 377(17):1613-1629
Pavord et al. Int J Chron Obstruct Pulmon Dis. 2021; 16:1755-1770

Anti IL-5R: Benralizumab



Criner et al. N Engl J Med. 2019; 381(11):1023-1034

Dupilumab Mechanism of Action



Boreas: Key Eligibility Criteria

Age
40-80 years

Physician diagnosis of COPD
Current or former smoker
FEV_1/FVC <0.70
FEV_1%pred >30% to ≤70%

High exacerbation risk
≥2 moderate or ≥1 severe exacerbation in prior 12 months

At least 1 exacerbation on ICS+LAMA+LABA

Blood Eosinophils at screening ≥300 cells/µL

On ICS+LAMA+LABA

MRC dyspnea ≥2

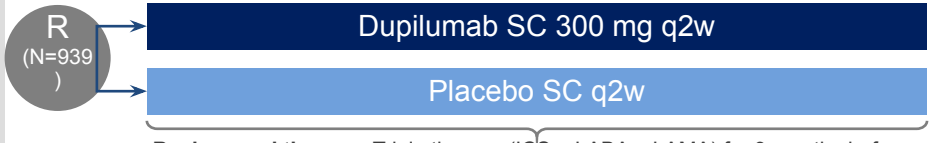
Chronic bronchitis

No past or current diagnosis of asthma

BOREAS Study Design

BOREAS: Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Phase 3 Study (NCT03930732)

Study population
Patients aged 40-80 years with COPD with moderate to severe airflow limitation and high risk for exacerbation and with evidence of type 2 inflammation



Primary endpoint
Annualized rate of moderate or severe acute exacerbations of COPD

Screening (4 weeks) | Baseline | Intervention (52 weeks) | Follow-up (12 weeks)

Efficacy Endpoints

Primary Endpoint

Annualized rate of moderate or severe exacerbations of COPD over the 52-week treatment period

Secondary Endpoints

- Change in pre-BD FEV_1 from baseline to week 12
- Change in pre-BD FEV_1 from baseline to week 52
- Change in pre-BD FEV_1 from baseline to week 12 among patients with a baseline FeNO ≥20 ppb
- Change in pre-BD FEV_1 from baseline to week 52 among patients with a baseline FeNO ≥20 ppb
- Change in SGRQ total score from baseline to week 52
- SGRQ total score improvement ≥4 points at week 52
- Change in E-RS–COPD total score from baseline to week 52
- Annualized rate of moderate or severe exacerbations of COPD among patients with a baseline FeNO ≥20 ppb

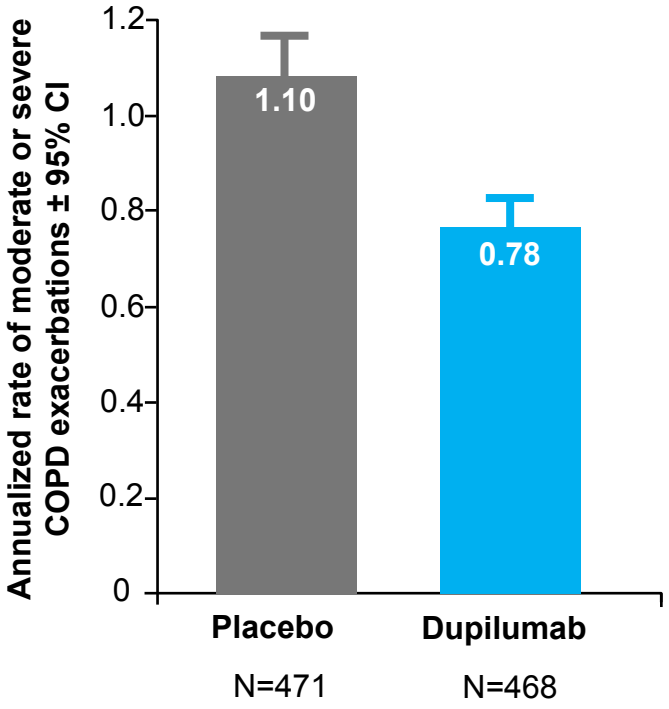
Baseline Characteristics

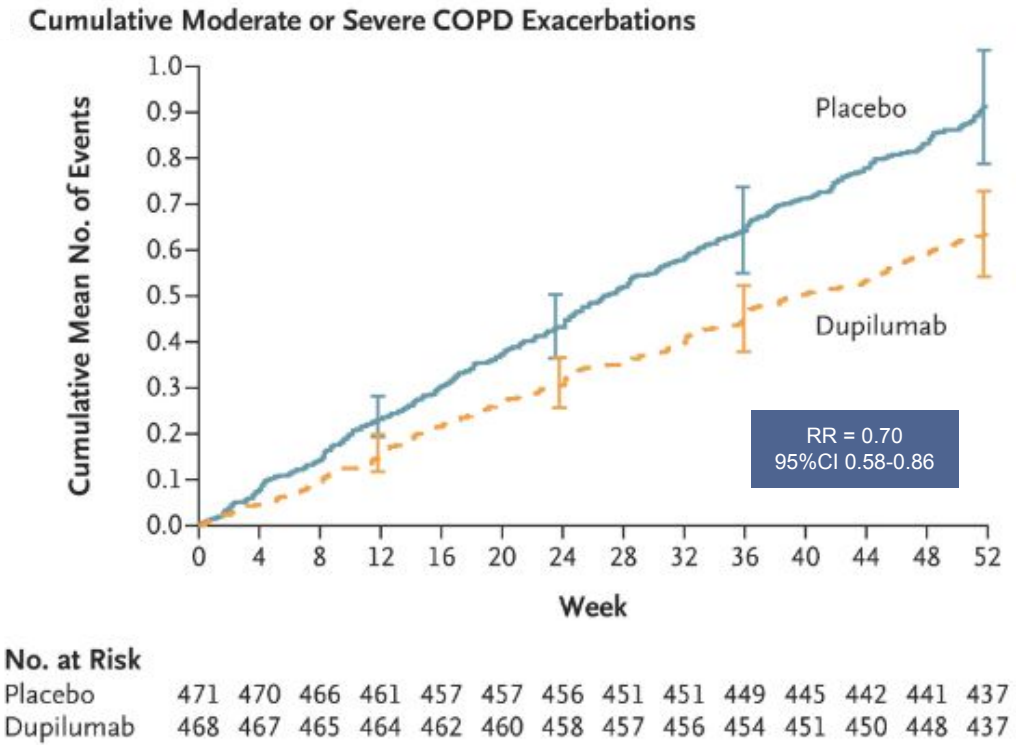
Characteristic	Placebo (N = 471)	Dupilumab (N = 468)	All (N = 939)
Age, mean (SD) — years	65.2 (8.1)	65.0 (8.0)	65.1 (8.1)
Male, no. (%)	322 (68.4)	298 (63.7)	620 (66.0)
Race — White, no. (%)	397 (84.3)	393 (84.0)	790 (84.1)
Ethnicity – Hispanic or Latino, no. (%)	129 (27.4)	132 (28.2)	261 (27.8)
Smoking status			
Former smoker, no. (%)	323 (68.6)	334 (71.4)	657 (70.0)
Current smoker, no. (%)	148 (31.4)	134 (28.6)	282 (30.0)
Pack-years, mean (SD)	41.4 (24.4)	39.6 (22.3)	40.48 (23.4)
BMI, mean (SD) – kg/m^2	27.7 (5.7)	27.5 (5.4)	27.6 (5.6)
Background medication			
Triple therapy (ICS+LAMA+LABA), no. (%)	461 (98.3)	455 (97.4)	916 (97.6)
Inhaled corticosteroid, high dose, no. (%)	126 (26.8)	131 (28.0)	257 (27.4)

Baseline Characteristics

Characteristic	Placebo (N = 471)	Dupilumab (N = 468)	All (N = 939)
Type 2 inflammation biomarkers			
Blood eosinophil count at randomization – cells/μL, mean (SD)	408 (331)	394 (261)	401 (298)
Post-BD Fe_{NO} level, ppb, mean (SD)	23.5 (22.0)	25.2 (22.8)	24.3 (22.4)
FE_{NO} level ≥20 ppb, no. (%)	188 (42.5)	195 (45.0)	383 (43.8)
FE_{NO} level <20 ppb, no. (%)	254 (57.5)	238 (55.0)	492 (56.2)
Moderate-severe COPD exacerbations in 1-year prior, mean (SD)	2.3 (1.0)	2.2 (1.1)	2.30 (1.0)
Lung function			
Post-BD FEV_1 (L), mean (SD)	1.41 (0.5)	1.39 (0.5)	1.40 (0.5)
Post-BD FEV_1 % predicted mean (SD)	50.6 (13.0)	50.57 (13.3)	50.60 (13.1)
Post-BD FEV_1/FVC, mean (SD)	0.49 (0.11)	0.49 (0.12)	0.49 (0.12)
SGRQ total score, mean (SD)	48.4 (17.8)	48.4 (17.0)	48.4 (17.4)
E-RS: COPD total score, mean (SD)	13.0 (6.9)	12.9 (7.2)	12.9 (7.1)

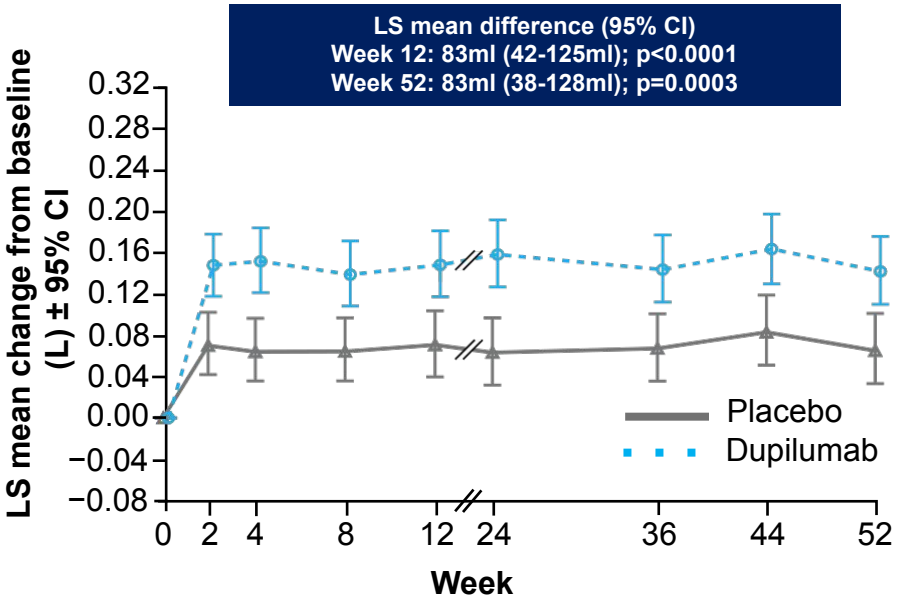
Primary Outcome: Annualized Rate of Exacerbations



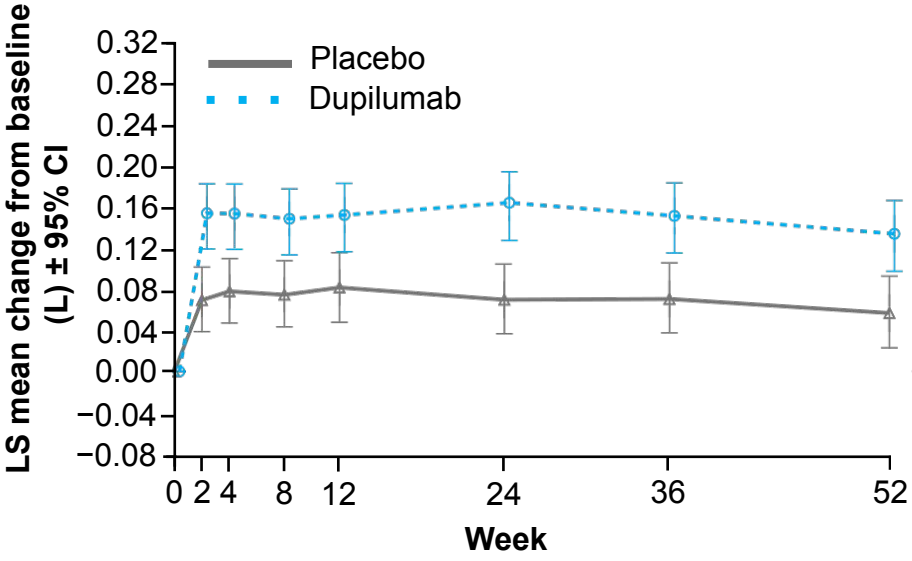


Change in Lung Function Over Time

Pre-BD FEV_1



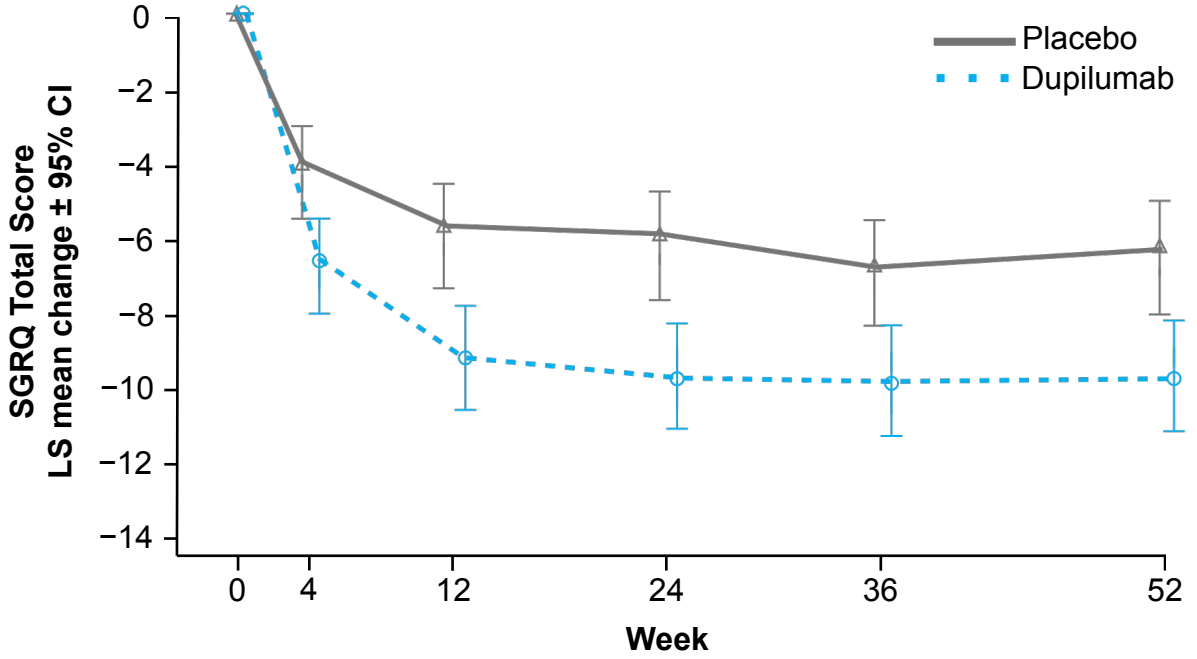
Post-BD FEV_1



No. of participants with observed change from baseline

Placebo	471	455	459	439	439	435	415	404	420	471	456	458	439	431	410	417	417
Dupilumab	467	457	454	446	449	443	415	410	426	468	457	454	448	436	434	417	423

St. George's Respiratory Questionnaire

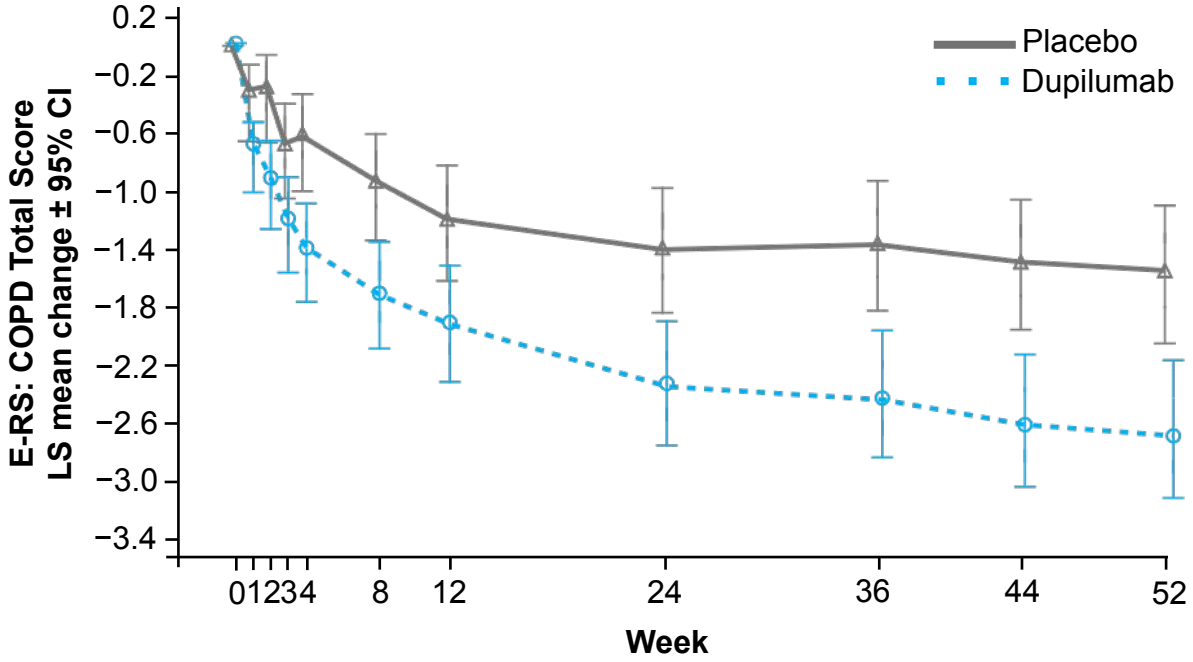


Week 52
LS mean difference (95% CI)
−3.4 (−5.5 to −1.3)
P=0.0017

No. of participants with observed change from baseline

Placebo	461	439	430	407	414	400
Dupilumab	461	444	436	434	407	415

Symptoms (E-RS:COPD)



Week 52
LS mean difference (95% CI)
−1.1 (−1.8 to −0.5)
P=0.0012

No. of participants with observed change from baseline

Placebo	467	454	448	443	424	414	404	379
Dupilumab	461	446	435	439	428	412	403	380

Important Subgroups

	Exacerbations	ΔFEV_1 (ml)
Active smokers	0.75 (95%CI 0.52-1.07)	57 (95%CI -6 to 120)
FeNO ≥20 ppb	0.63 (96%CI 0.45-0.87)	124 (95% CI, 45 to 203)
Age ≥65 years	0.74 (95%CI 0.57-0.95)	63 (95%CI 15-110)
High dose ICS	0.72 (95%CI 0.51-1.01)	104 (95%CI 1-207)
FEV_1 <50% predicted	0.71 (95%CI 0.55-0.92)	94 (95%CI 27-161)
Eos ≥500 cells/μL	0.51 (95%CI 0.35-0.74)	142 (95%CI 60-223)

Treatment-Emergent Adverse Events in the Safety Population

	Placebo (N = 470)	Dupilumab (N = 469)
Most common TEAEs (≥ 5%), no. (%)		
Nasopharyngitis	45 (9.6)	44 (9.4)
Headache	32 (6.8)	38 (8.1)
Upper respiratory tract infection	46 (9.8)	37 (7.9)
Chronic obstructive pulmonary disease	28 (6.0)	27 (5.8)
Diarrhea	17 (3.6)	25 (5.3)
Back pain	16 (3.4)	24 (5.1)
COVID-19	27 (5.7)	19 (4.1)
Hypertension	28 (6.0)	17 (3.6)

Conclusions

- Dupilumab reduced the annualized rate of moderate-to-severe exacerbations by 30% compared to placebo
- Dupilumab improved patient reported lung function and patient reported outcomes:
  - 83 mL improvement in FEV_1
  - Significant improvement in quality of life
  - Significant improvement in severity of symptoms
- Safety results were consistent with the known safety profile of dupilumab

Discussion

	MACRO	REACT	PANTHEON	BOREAS
Intervention	Azithromycin	Roflumilast	N-acetyl cysteine	Dupilumab
Key inclusion criteria	FEV_1 <50% pred 10 pack-years	CB FEV_1 <50% pred 20 pack-years	Non-smokers also included	Type 2 inflammation 10-pack-years
Background therapy	49% triple therapy 10% on no controller therapy	70% triple therapy	ICS/LABA 47% 26% on no controller therapy	97% triple therapy
Exacerbation risk	1 exacerbation or on O2 therapy	2 exacerbations	2 exacerbations	2 moderate or 1 severe exacerbation
Chronic bronchitis	60% (this group had less benefit)	100%	-	100%
Asthma	Excluded	Excluded	Excluded	Excluded
Efficacy	HR 0.73 (95%CI 0.63-0.84) IRR 0.83 (95% CI 0.72-0.95)	IRR 0.86 (95%CI 0.74-0.99) ▼Severe exacerbations	IRR 0.78 (95%CI 0.67-0.90)	IRR 0.70 (95%CI 0.58-0.86)
Safety	Hearing impairment QTc prolongation excluded	Diarrhea Weight loss	Safe	Safe

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Q&A

Robert A. Wise, MD
Johns Hopkins University

Attendees:

Add questions or your feedback on today's roundtable in the chat.

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RELIANCE Commentary

Stephen Rennard, MD
University of Nebraska

Richard Albert, MD
University of Colorado

Attendees:

Add questions, feedback on today's roundtable, or topic requests for the next roundtable in the chat.

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Thank you!