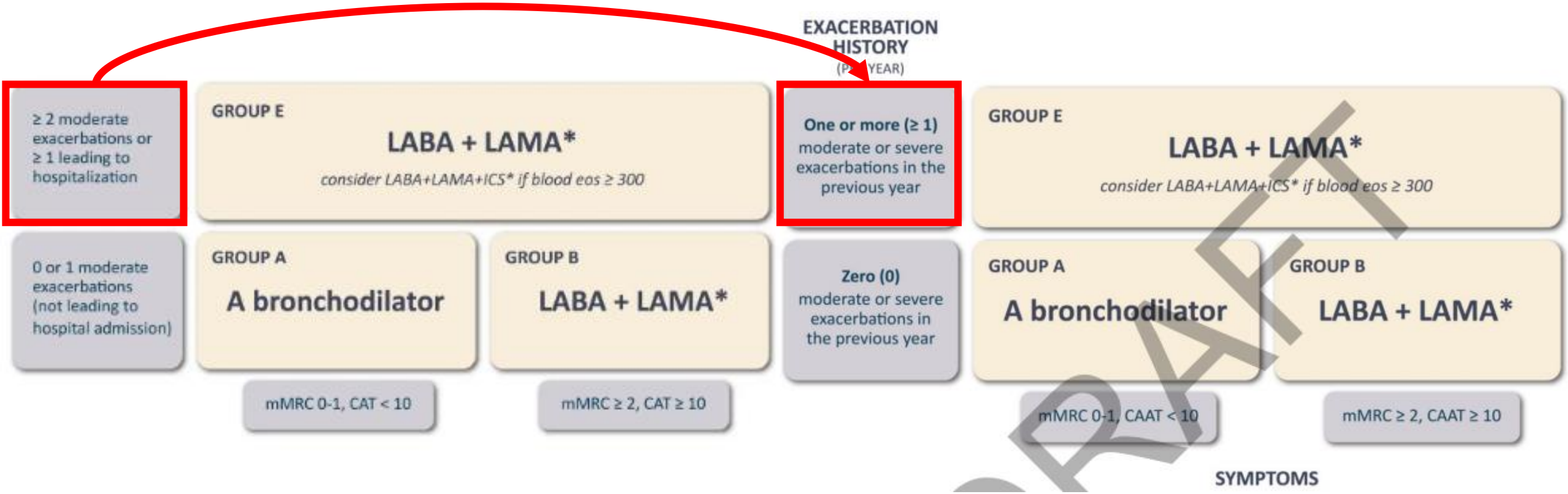
COPD 약물치료

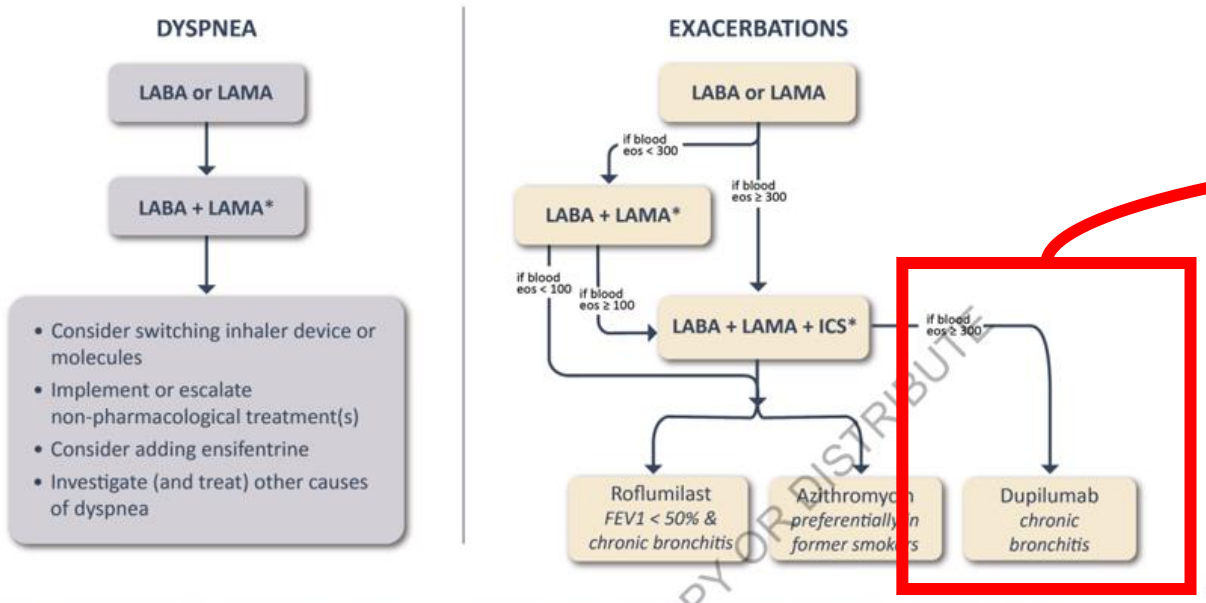
국민건강보험 일산병원 호흡기내과 정은기

GOLD 2025

GOLD 2026

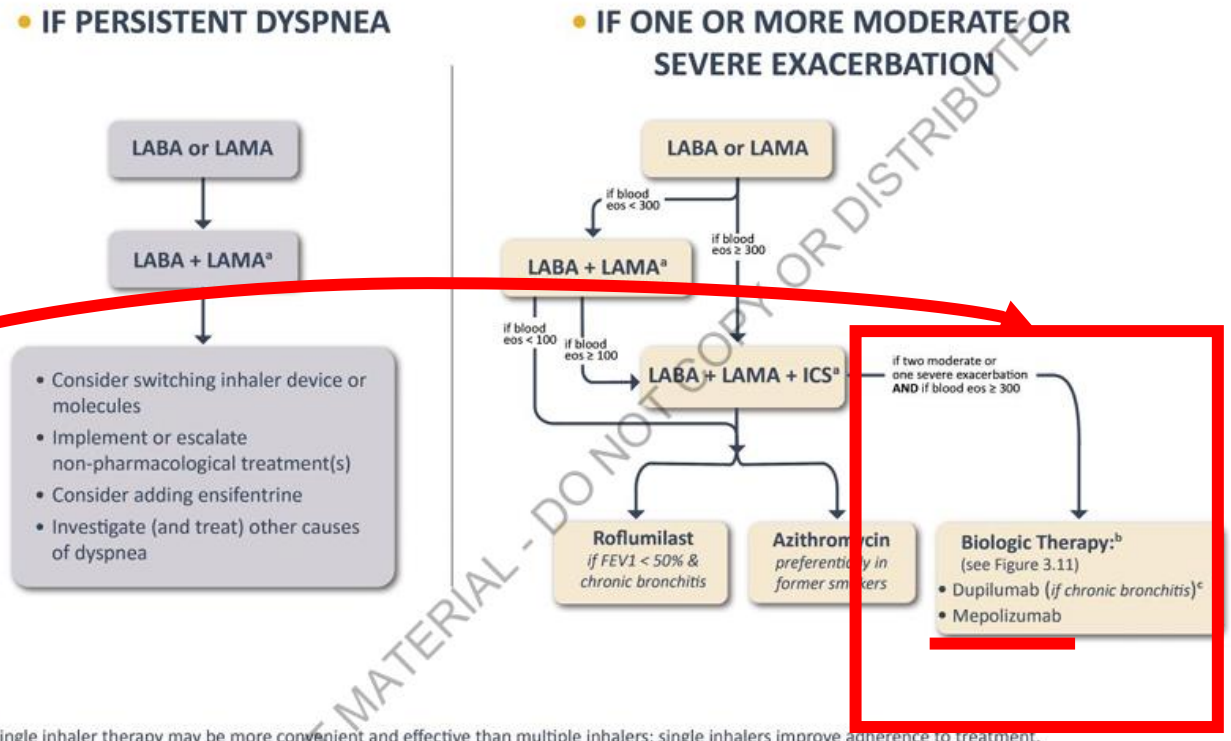


GOLD 2025



*Single inhaler therapy may be more convenient and effective than multiple inhalers; single inhalers improve adherence to treatment.
Consider de-escalation of ICS if pneumonia or other considerable side-effects. In case of blood eos ≥ 300 cells/µl de-escalation is more likely to be associated with the development of exacerbations.
Exacerbations refers to the number of exacerbations per year.

GOLD 2026



[a]Single inhaler therapy may be more convenient and effective than multiple inhalers; single inhalers improve adherence to treatment.
[b]Listed in order of approval in the US.
[c]Patient-reported history of chronic bronchitis (chronic productive cough) for 3 months in the year up to screening, absent other known causes.
Consider de-escalation of ICS if pneumonia or other considerable side-effects. In case of blood eosinophils ≥ 300 cells/µl de-escalation is more likely to be associated with the development of exacerbations.

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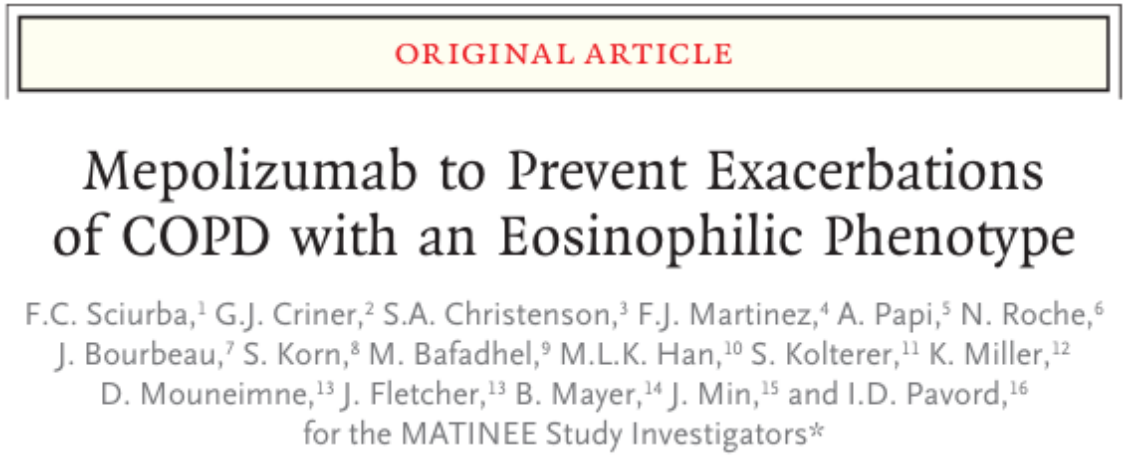
- Ensifentrine, Triple therapy, ICS

- **Oral medication**

- Azithromycin, Phosphodiesterase-5 Inhibitor (with PH), OM-85

Biologics – Mepolizumab


ORIGINAL ARTICLE

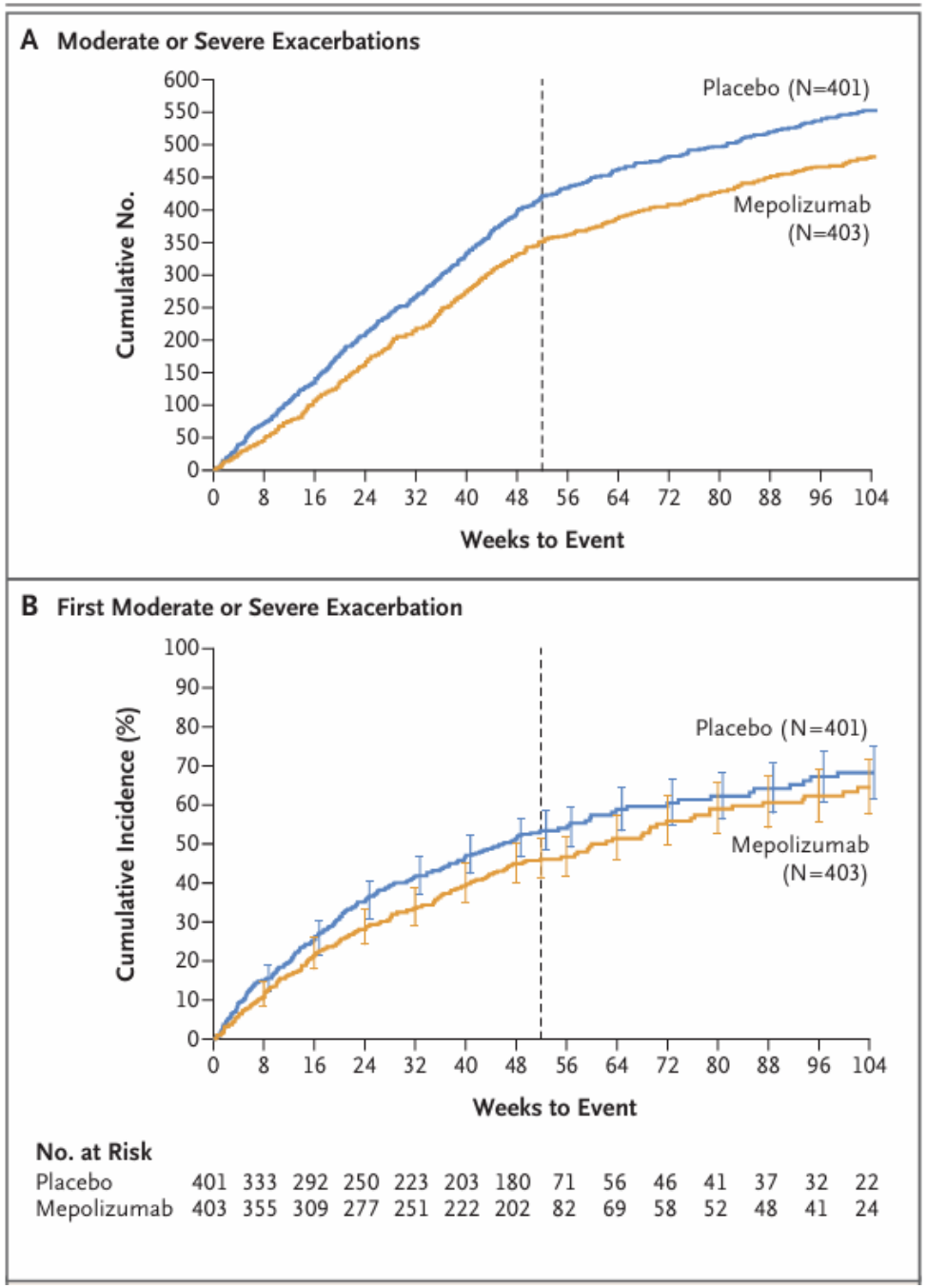
Mepolizumab to Prevent Exacerbations of COPD with an Eosinophilic Phenotype

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

- **Study Design:** A phase 3, multicenter, randomized, double-blind, placebo-controlled trial
- **Participants:** Patients with COPD (FEV1 20-80%), triple therapy, history of exacerbations (≥ 2 moderate or ≥ 1 severe in the previous year), eosinophilic phenotype (BEC ≥ 300 cells/uL)
- **Intervention:** Mepolizumab 100 mg or placebo SC every 4 weeks.
- **Primary Endpoint:** The annualized rate of moderate or severe COPD exacerbations.

Table 2. Primary and Secondary Efficacy End Points.*

End Point	Mepolizumab (N=403)	Placebo (N=401)
Primary end point		
Annualized rate of moderate or severe exacerbations (95% CI) — events/yr	0.80 (0.70–0.91)	1.01 (0.89–1.15)
Rate ratio vs. placebo (95% CI)	0.79 (0.66–0.94)	—
P value	0.01	—
Secondary end points		
Time to first moderate or severe exacerbation		
Kaplan–Meier median time to first moderate or severe exacerbation (95% CI) — days	419 (332–530)	321 (262–396)
Estimated risk of a moderate or severe exacerbation up to wk 104 (95% CI) — %	64.5 (57.5–71.4)	68.3 (61.4–74.9)
Hazard ratio for the first moderate or severe exacerbation up to wk 104 vs. placebo (95% CI)	0.77 (0.64–0.93)	—
P value	0.009	—
Response, defined as a decrease in the CAT score†‡		
No. of patients with a response (%)	162 (41)	180 (46)
No. of patients without a response (%)	220 (56)	206 (52)
Odds ratio of response vs. placebo (95% CI)	0.81 (0.60–1.09)	—
Relative risk of response vs. placebo (95% CI)§	0.92 (0.81–1.05)	—
Response, defined as a decrease in the SGRQ total score¶		
No. of patients with a response (%)	195 (50)	179 (46)
No. of patients without a response (%)	186 (48)	206 (52)
Odds ratio of response vs. placebo (95% CI)	1.17 (0.87–1.57)	—
Relative risk of response vs. placebo (95% CI)§	1.04 (0.91–1.20)	—
Response, defined as a decrease in the E-RS–COPD total score‖		
No. of patients with a response (%)	123 (31)	137 (34)
No. of patients without a response (%)	271 (67)	254 (64)
Odds ratio of response vs. placebo (95% CI)	0.82 (0.60–1.12)	—
Relative risk of response vs. placebo (95% CI)§	0.87 (0.72–1.04)	—
Annualized rate of exacerbations resulting in emergency department visit, hospitalization, or both		
Events/yr (95% CI)	0.13 (0.10–0.18)	0.20 (0.15–0.27)
Rate ratio vs. placebo (95% CI)	0.65 (0.43–0.96)	—



Biologics – Dupilumab 1

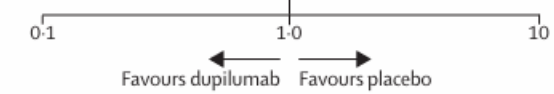
Dupilumab for chronic obstructive pulmonary disease with type 2 inflammation: a pooled analysis of two phase 3, randomised, double-blind, placebo-controlled trials

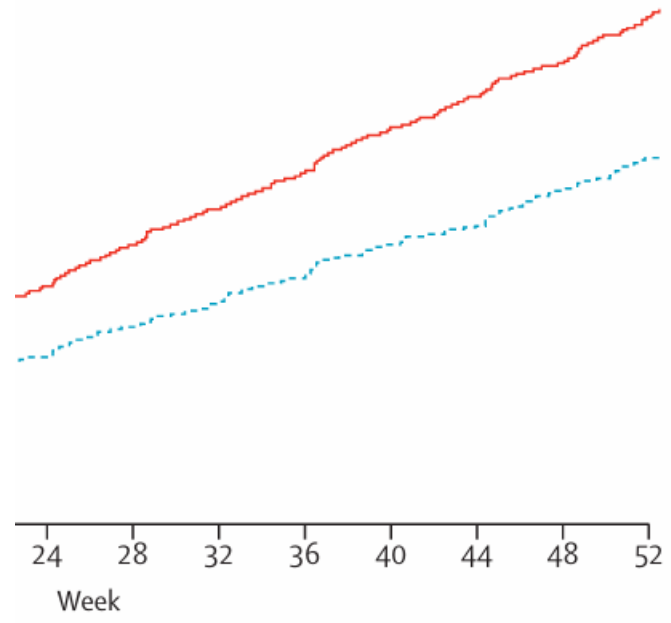
Surya P Bhatt, Klaus F Rabe*, Nicola A Hanania, Claus F Vogelmeier, Mona Bafadhel, Stephanie A Christenson, Alberto Papi, Dave Singh, Elizabeth Laws, Paula Dakin, Jennifer Maloney, Xin Lu, Deborah Bauer, Ashish Bansal, Raolat M Abdulai, Lacey B Robinson*

- **Study Design:** Pooled analysis of two replicate multicentre, randomised, double-blind, placebo-controlled Phase 3 trials (BOREAS and NOTUS).
- **Participants (n=1,874)**: 40-85y, 10PYs, Moderate ~ very severe COPD (FEV1 30-70%), BEC ≥ 300 cells/µL at screening, ≥ 2 moderate or ≥ 1 severe exacerbations in the previous year despite triple therapy, excluding asthma.
- **Intervention:** 1:1 randomised
  - **Dupilumab 300 mg** SC every 2 weeks.
  - **Placebo** SC every 2 weeks.
- **Primary Endpoint:** Annualised rate of moderate or severe COPD exacerbations

A

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





886	866	854	843	829	810	791	709
896	881	864	849	835	820	802	777

Figure 1: **Moderate to severe exacerbations in dupilumab and placebo groups**
(A) Mean cumulative number of moderate or severe exacerbations during the 52-week treatment period. (B) Annualised moderate or severe exacerbations by demographic, disease characteristic, and biomarker subgroups. BODE=BMI, airflow obstruction, dyspnoea, and exercise capacity. COPD=chronic obstructive pulmonary disease. HR=hazard ratio. NA=not available. ppb=parts per billion. *Included 14 patients in the placebo group and 12 patients in the dupilumab group in the pooled intention-to treat population who had multiple races, including Black or African American.

	Placebo (n=936)*	Dupilumab (n=938)*	Difference *vs* placebo (95% CI)†	Nominal p value‡
Primary outcome				
Annualised rate of moderate or severe COPD exacerbation during the 52-week treatment period§	1·156	0·794	0·687 (0·595 to 0·793)	<0·0001
Secondary or other outcomes				
Change in pre-bronchodilator FEV_1 from baseline to week 12 compared with placebo, L	0·064 (0·013)	0·147 (0·013)	0·083 (0·053 to 0·112)	<0·0001
Change in pre-bronchodilator FEV_1 from baseline to week 52 compared with placebo, L	0·059 (0·015)	0·133 (0·015)	0·073 (0·040 to 0·107)	<0·0001
Change in pre-bronchodilator FEV_1 from baseline to week 12 compared with placebo in patients with baseline FeNO ≥20 ppb¶, L	0·089 (0·027)	0·219 (0·027)	0·131 (0·074 to 0·187)	<0·0001
Change in pre-bronchodilator FEV_1 from baseline to week 52 compared with placebo in patients with baseline FeNO ≥20 ppb¶, L	0·104 (0·029)	0·210 (0·029)	0·106 (0·042 to 0·170)	0·0012
Change from baseline to week 52 in SGRQ total score compared with placebo	−6·579 (0·640)	−9·945 (0·636)	−3·366 (−4·953 to −1·778)	<0·0001
Proportion of patients with SGRQ improvement ≥4 points at week 52 compared with placebo‖	370/830 (44·6%)	427/830 (51·5%)	1·311 (1·070 to 1·607)	0·0089
Change in Evaluating Respiratory Symptoms in COPD total score from baseline to week 52 compared with placebo	−1·605 (0·200)	−2·519 (0·201)	−0·914 (−1·438 to −0·389)	0·0006
Annualised rate of moderate or severe COPD exacerbation compared with placebo during the 52-week treatment period in patients with baseline FeNO ≥20 ppb¶	1·321	0·729	0·552 (0·434 to 0·701)	<0·0001
Annualised rate of severe COPD exacerbation compared with placebo during the 52-week treatment period	0·124	0·084	0·674 (0·438 to 1·037)	0·073

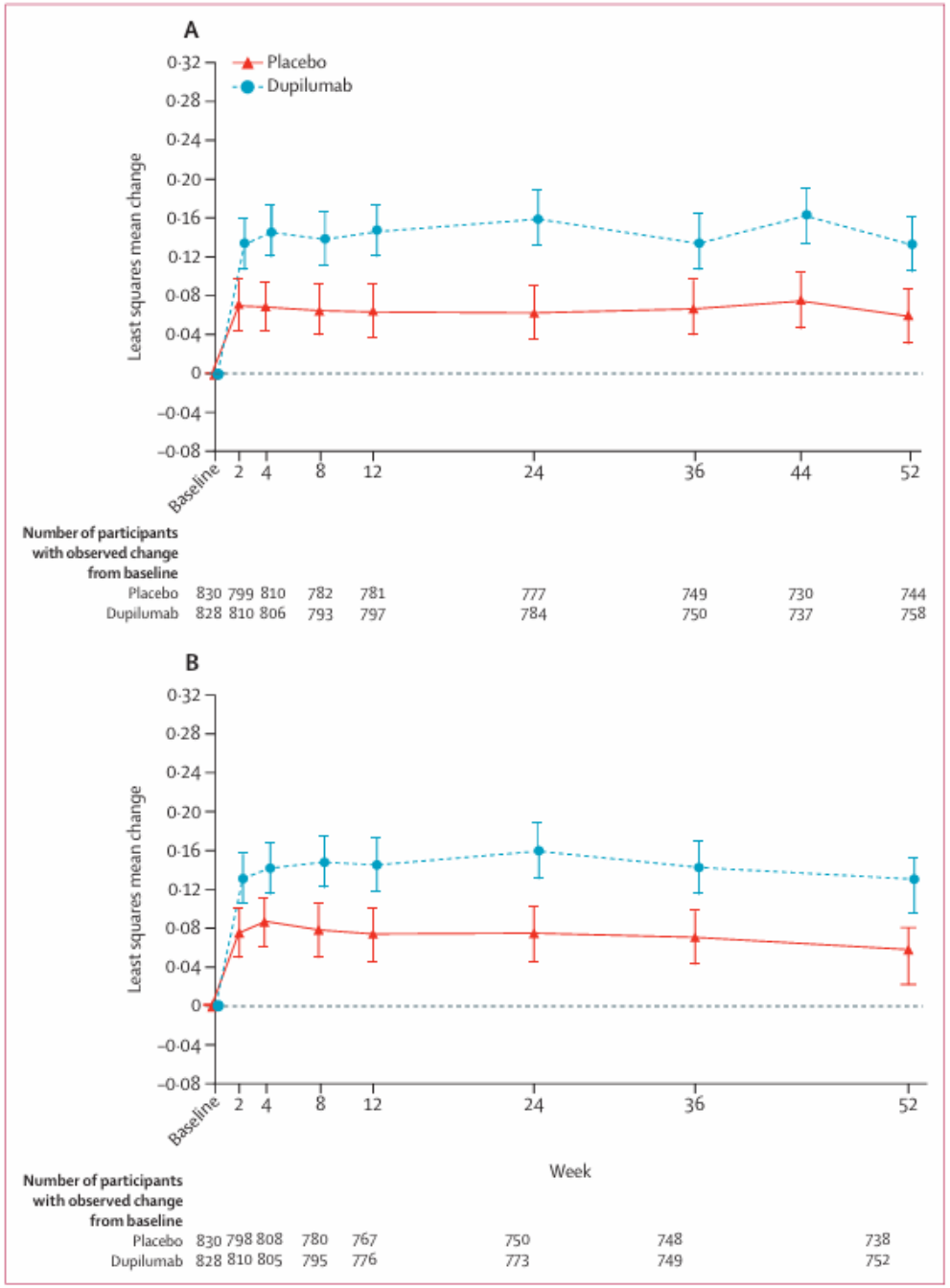


Figure 2: **Change in lung function from baseline to week 52**
(A) Change in pre-bronchodilator FEV_1. (B) Change in post-bronchodilator FEV_1. Error bars show 95% CI.

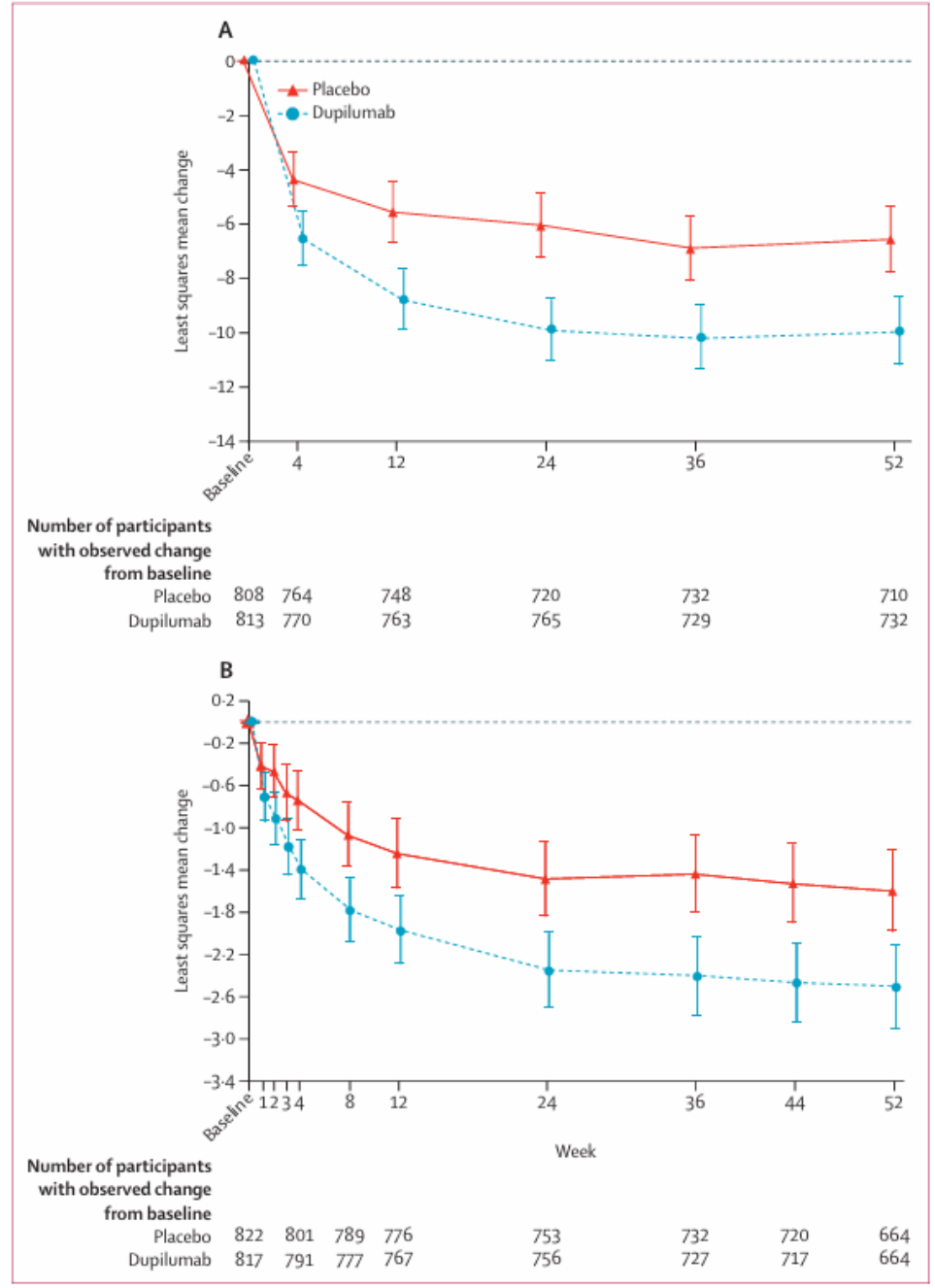


Figure 3: **Change in patient-reported outcomes from baseline to week 52**
(A) Change in St George's Respiratory Questionnaire total score. (B) Change in Evaluating Respiratory Symptoms in COPD total score. Error bars show 95% CI. COPD=chronic obstructive pulmonary disease.

Biologics – Dupilumab 2

Effect of Dupilumab on Health-Related Quality of Life and Respiratory Symptoms in Patients With COPD and Type 2 Inflammation

BOREAS and NOTUS

Surya P. Bhatt, MD, MSPH; Klaus F. Rabe, MD, PhD; Nicola A. Hanania, MD; Claus F. Vogelmeier, MD; Mona Bafadhel, MD, PhD; Stephanie A. Christenson, MD; Alberto Papi, MD; Dave Singh, MD; Elizabeth Laws, PhD; Paula Dakin, MBChB; Jennifer Maloney, MD; Xin Lu, PhD; Deborah Bauer, MS; Ashish Bansal, MD; Raolat M. Abdulai, MD, MMSc; and Lacey B. Robinson, MD, MPH

- **Study Design:** Prespecified pooled analysis of two multicentre, randomised, double-blind, placebo-controlled Phase 3 trials (BOREAS and NOTUS).
- **Participants (n=1,874)**
- **Intervention:** 1:1 randomized, Dupilumab 300 mg or Placebo SC every 2 weeks.
- **Primary Endpoints**
  - Change from baseline to Week 52 in **SGRQ total score** (Quality of Life).
  - Change from baseline to Week 52 in **E-RS:COPD total score** (Respiratory Symptoms).

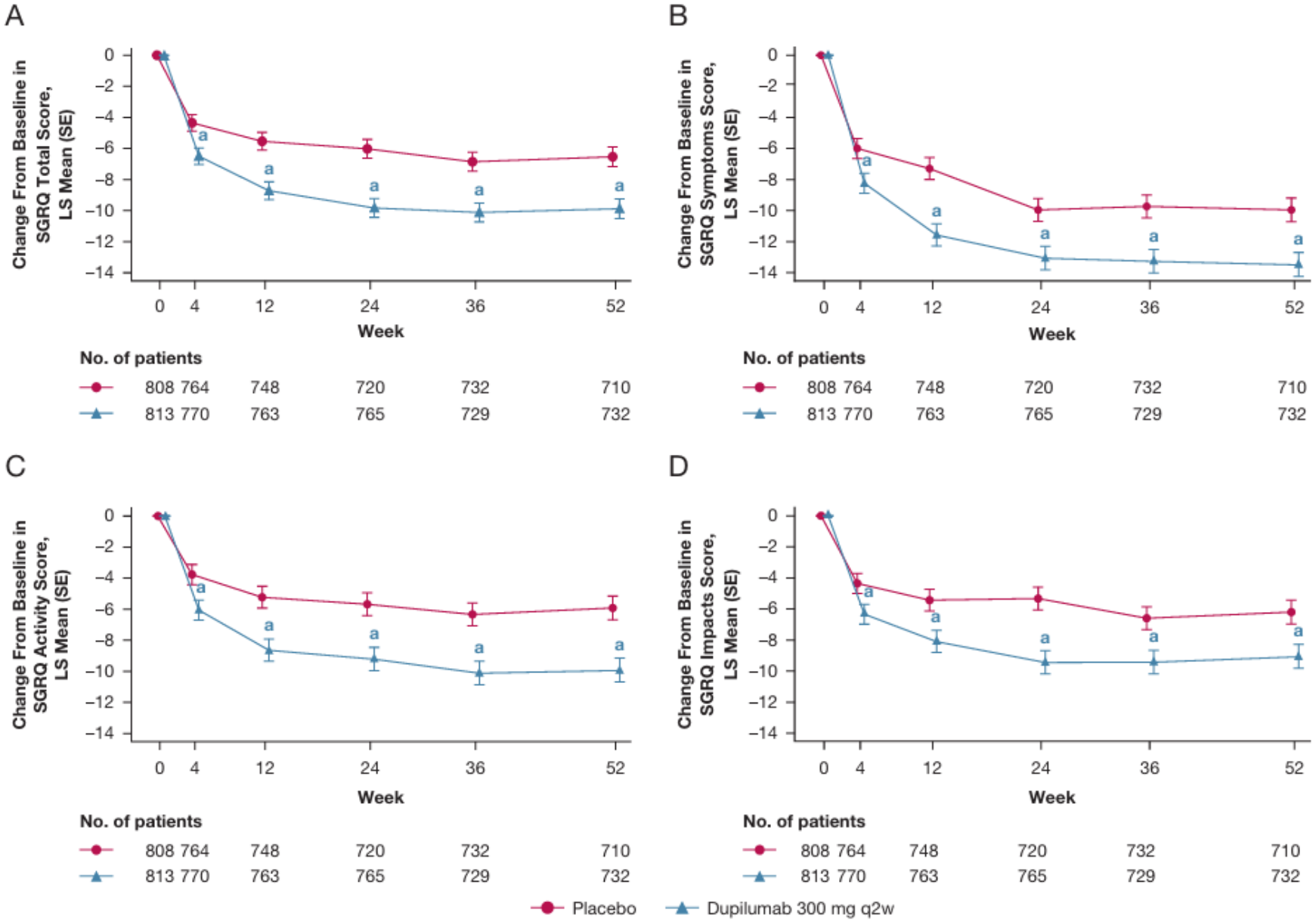


Figure 1 – *A-D, Change over time for SGRQ score in pooled intention-to-treat population with an opportunity to reach week 52. SGRQ total score (A), symptoms domain score (B), activity domain score (C), and impacts domain score (D).* [a]P < .05 *vs placebo;* P *values reported for the pooled analysis were nominal. LS = least squares; q2w = every 2 weeks; SGRQ = St. George's Respiratory Questionnaire.*

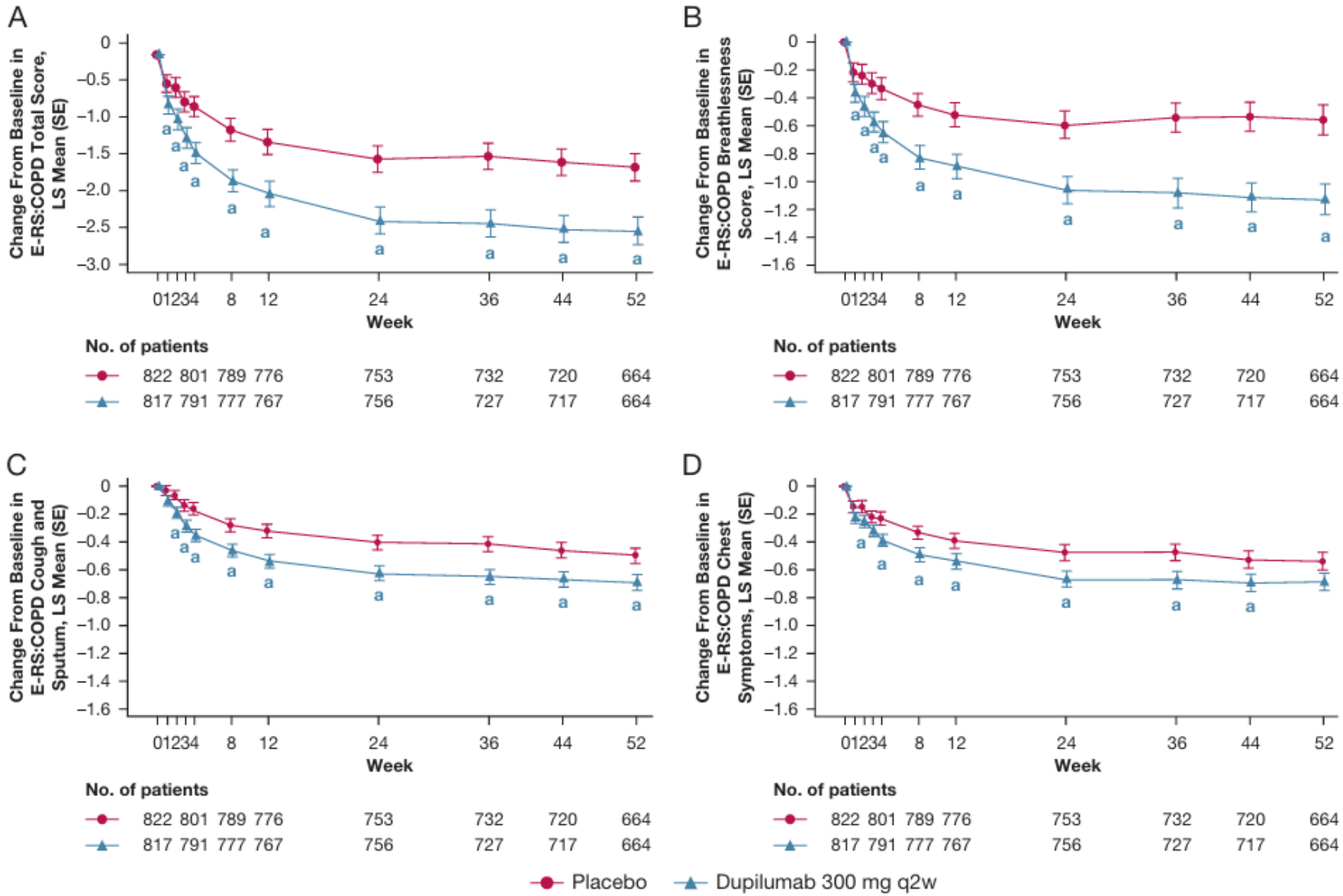


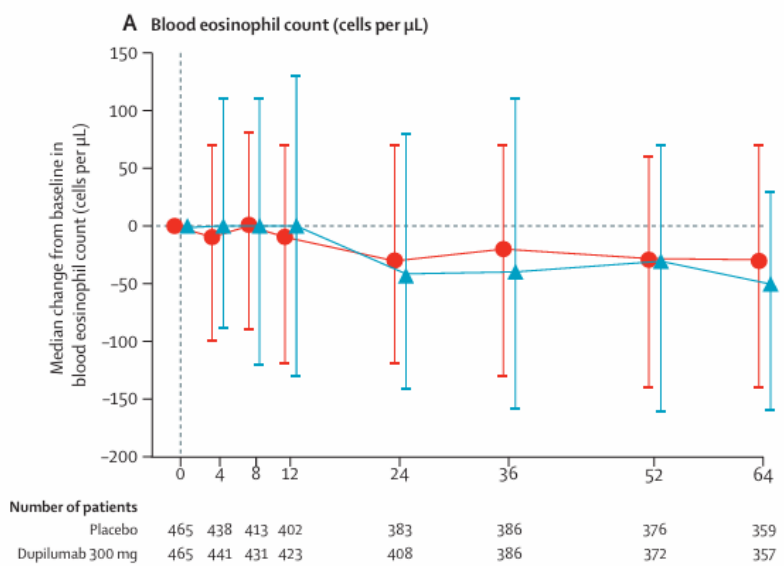
Figure 2 – *A-D, Change over time for E-RS:COPD score in pooled intention-to-treat population with an opportunity to reach week 52. E-RS:COPD total score (A), breathlessness (B), cough and sputum (C), and chest symptoms (D) domain scores.* [a]P < .05 *vs placebo;* P *values reported for the pooled analysis were nominal. E-RS:COPD = Evaluating Respiratory Symptoms in COPD; LS = least squares; q2w = every 2 weeks.*

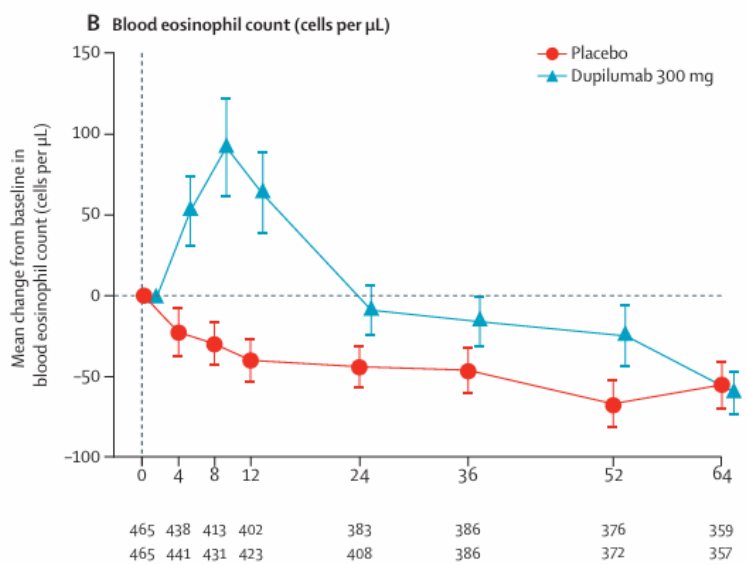
Biologics – Dupilumab 3

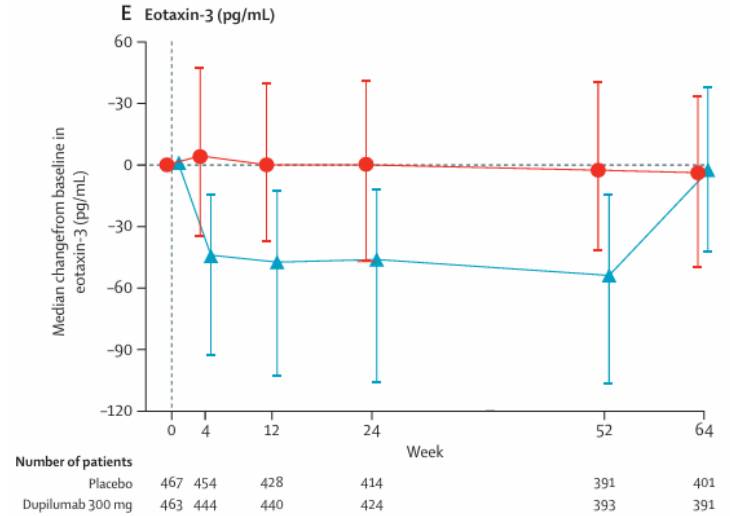
Type 2 inflammation biomarkers and their association with response to dupilumab in COPD (BOREAS): an analysis of a randomised, placebo-controlled, phase 3 trial

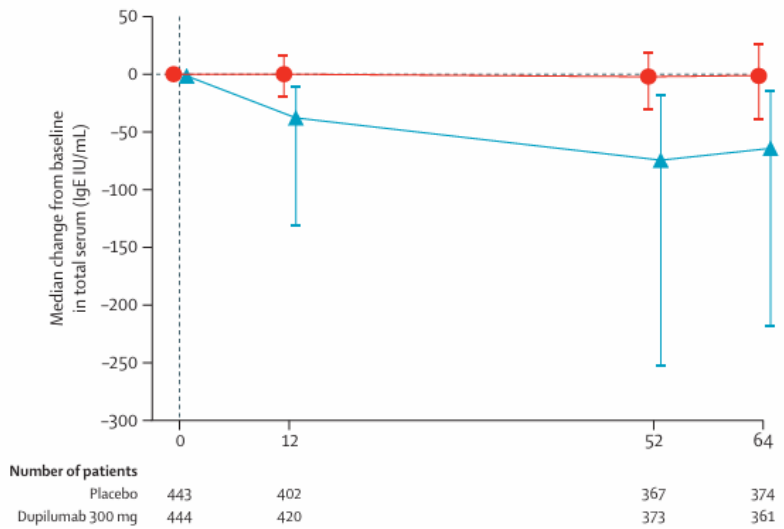
Stephanie A Christenson, Nicola A Hanania, Surya P Bhatt, Mona Bafadhel, Klaus F Rabe, Claus F Vogelmeier, Alberto Papi, Dave Singh, Elizabeth Laws, Paula Dakin, Ashish Bansal, Xin Lu, Deborah Bauer, Jennifer Maloney, Lacey B Robinson, Raolat M Abdulai

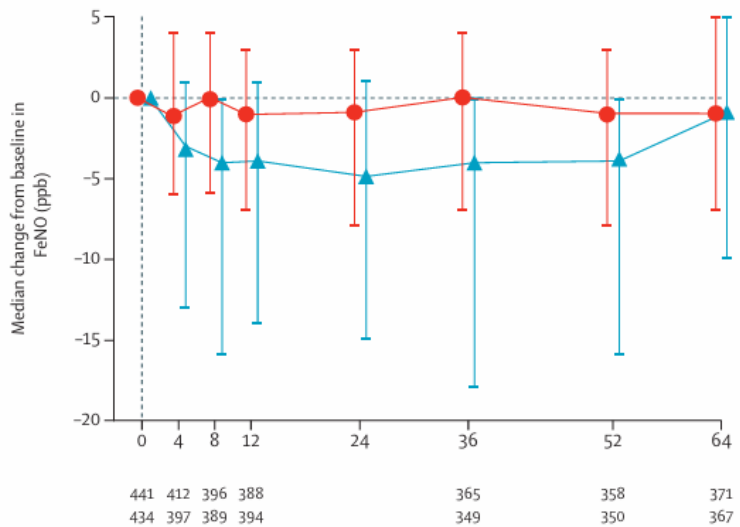
Study Design: Post-hoc analysis of the BOREAS Phase 3 trial.
Participants (N=939): COPD with **Type 2 inflammation** (Blood Eosinophil ≥300 cells/µL).
Intervention: Dupilumab 300 mg q2w vs. Placebo (52 weeks).
Endpoints: Change in biomarkers (FeNO, IgE, Eotaxin-3, PARC). Predictive value of baseline biomarkers for clinical efficacy (exacerbation reduction).

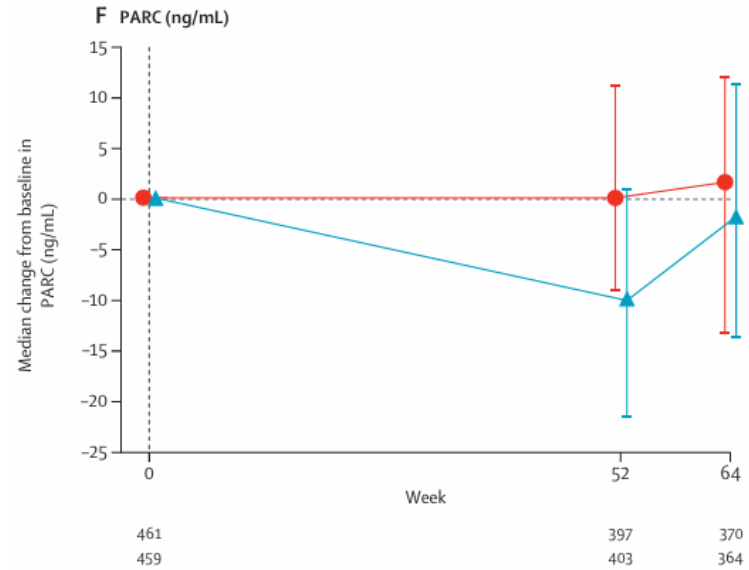

A Blood eosinophil count (cells per µL)
Median change from baseline in blood eosinophil count (cells per µL)
150
100
50
0
−50
−100
−150
−200
0 4 8 12 24 36 52 64
Number of patients
Placebo 465 438 413 402 383 386 376 359
Dupilumab 300 mg 465 441 431 423 408 386 372 357

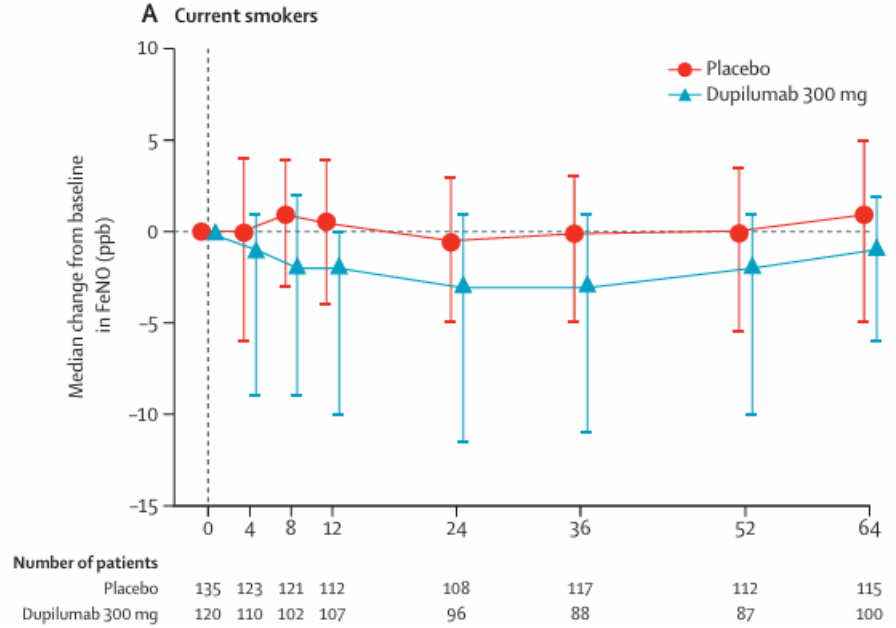

B Blood eosinophil count (cells per µL)
Placebo
Dupilumab 300 mg
Mean change from baseline in blood eosinophil count (cells per µL)
150
100
50
0
−50
−100
0 4 8 12 24 36 52 64
465 438 413 402 383 386 376 359
465 441 431 423 408 386 372 357

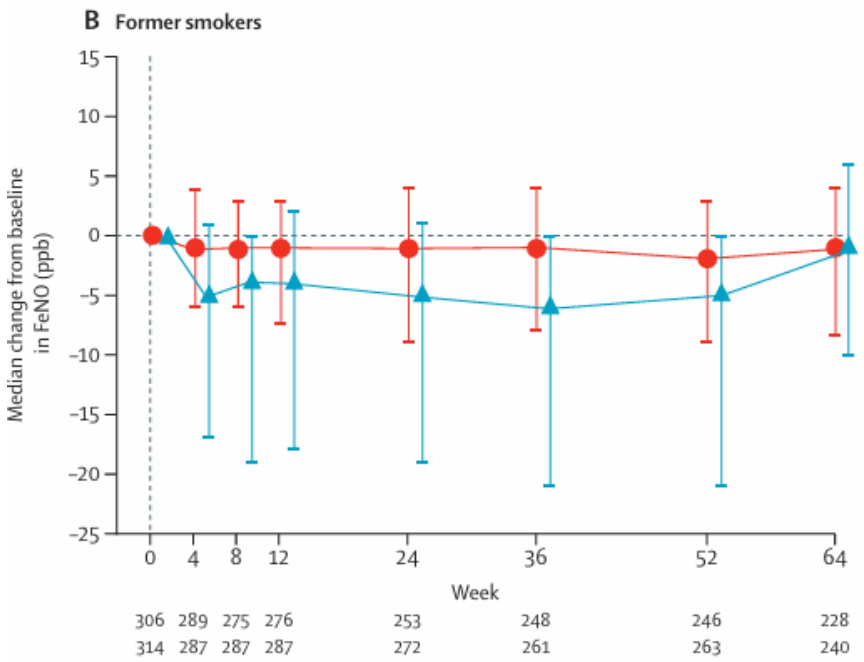

E Eotaxin-3 (pg/mL)
Median changefrom baseline in eotaxin-3 (pg/mL)
60
−30
0
−30
−60
−90
−120
0 4 12 24 52 64
Week
Number of patients
Placebo 467 454 428 414 391 401
Dupilumab 300 mg 463 444 440 424 393 391


C Total serum IgE (IU/mL)
Median change from baseline in total serum (IgE IU/mL)
50
0
−50
−100
−150
−200
−250
−300
0 12 52 64
Number of patients
Placebo 443 402 367 374
Dupilumab 300 mg 444 420 373 361


D FeNO (ppb)
Median change from baseline in FeNO (ppb)
5
0
−5
−10
−15
−20
0 4 8 12 24 36 52 64
441 412 396 388 365 358 371
434 397 389 394 349 350 367


F PARC (ng/mL)
Median change from baseline in PARC (ng/mL)
15
10
5
0
−5
−10
−15
−20
−25
0 52 64
Week
461 397 370
459 403 364





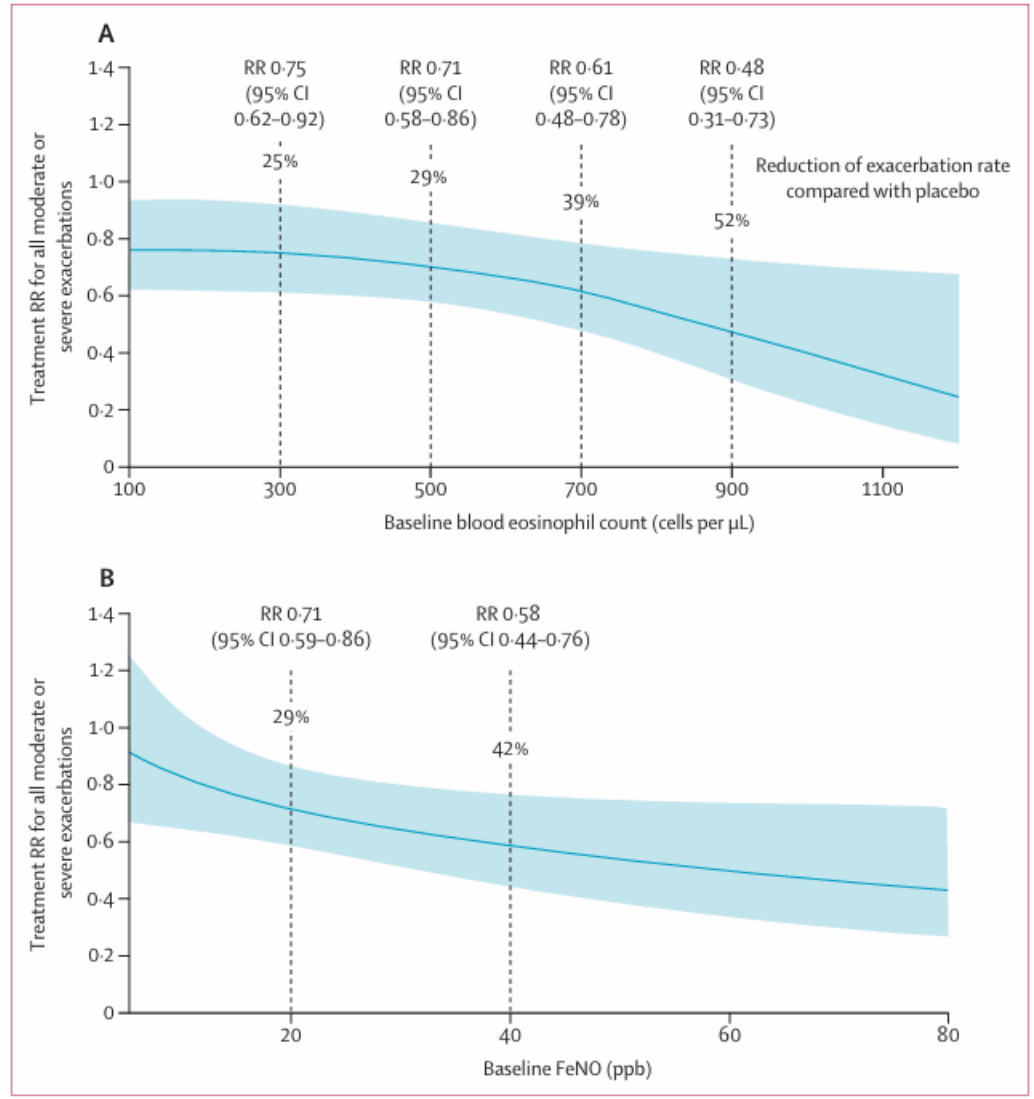


Figure 3: **Treatment rate of moderate or severe exacerbations by continuous baseline blood eosinophil count (A) and continuous baseline FeNO concentration (B)**

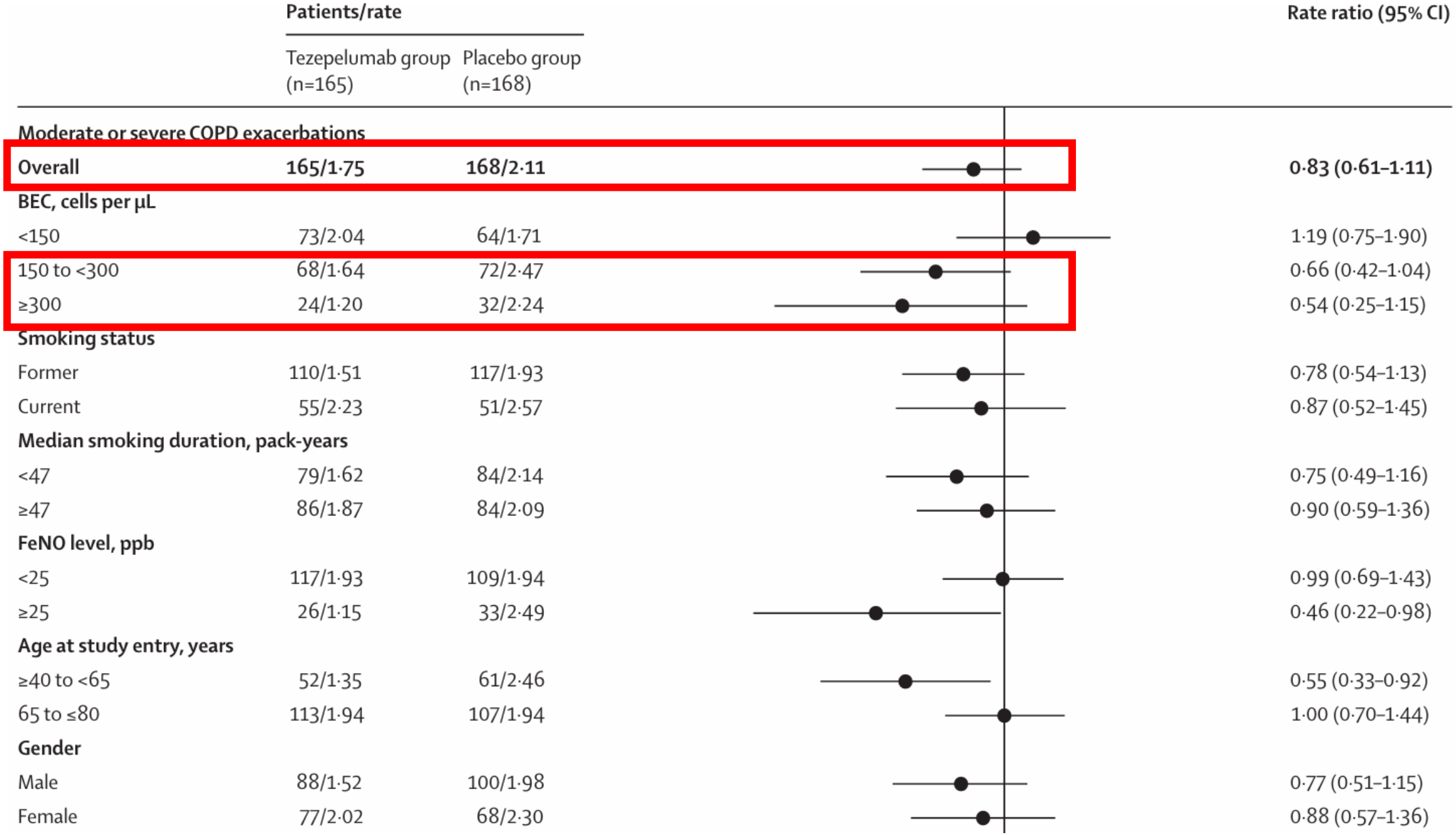
Percentages refer to reduction of exacerbation rate compared with placebo, which is shown by the solid blue line. The blue area curves indicate 95% CI. FeNO=fractional exhaled nitric oxide. ppb=parts per billion. RR=rate ratio.

Biologics - Tezepelumab

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

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

- **Study design:** Multicentre, Double-blind, Randomized, Placebo-controlled.
- **Participants (n=333):** Adults (40–80 years) with moderate-to-very severe COPD receiving triple therapy (≥12 months) who had ≥ 2 moderate or severe exacerbations in the prior year; asthma was excluded.
- **Intervention:** Tezepelumab 420 mg SC q4w vs. Placebo, 1:1. 52 weeks.
- **Primary endpoint:** The annualised rate of moderate or severe COPD exacerbations.


Patients/rate
Tezepelumab group (n=165)
Placebo group (n=168)
Rate ratio (95% CI)
Moderate or severe COPD exacerbations
Overall 165/1·75 168/2·11 0·83 (0·61–1·11)
BEC, cells per µL
<150 73/2·04 64/1·71 1·19 (0·75–1·90)
150 to <300 68/1·64 72/2·47 0·66 (0·42–1·04)
≥300 24/1·20 32/2·24 0·54 (0·25–1·15)
Smoking status
Former 110/1·51 117/1·93 0·78 (0·54–1·13)
Current 55/2·23 51/2·57 0·87 (0·52–1·45)
Median smoking duration, pack-years
<47 79/1·62 84/2·14 0·75 (0·49–1·16)
≥47 86/1·87 84/2·09 0·90 (0·59–1·36)
FeNO level, ppb
<25 117/1·93 109/1·94 0·99 (0·69–1·43)
≥25 26/1·15 33/2·49 0·46 (0·22–0·98)
Age at study entry, years
≥40 to <65 52/1·35 61/2·46 0·55 (0·33–0·92)
65 to ≤80 113/1·94 107/1·94 1·00 (0·70–1·44)
Gender
Male 88/1·52 100/1·98 0·77 (0·51–1·15)
Female 77/2·02 68/2·30 0·88 (0·57–1·36)

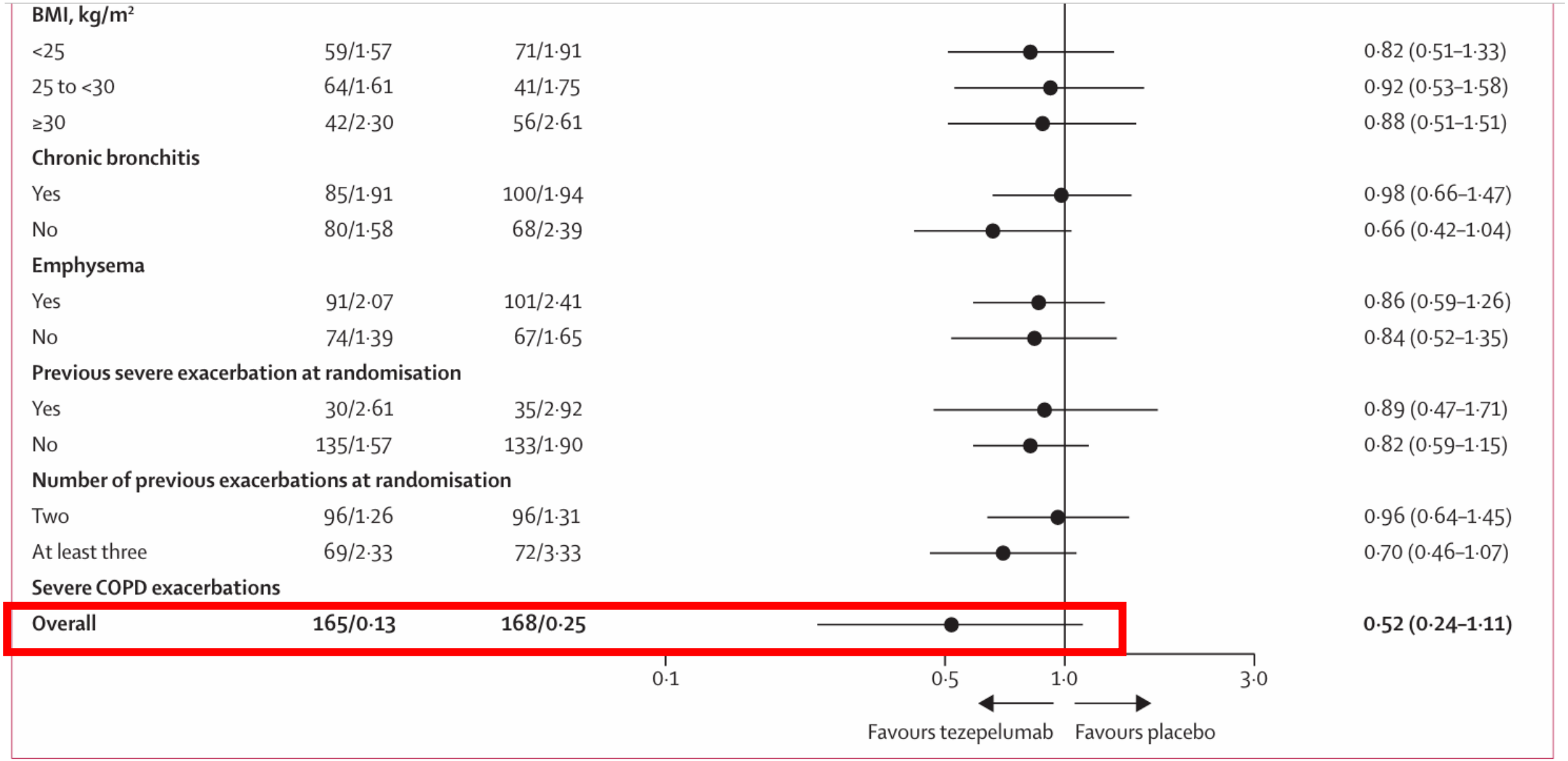


Figure 2: **The annualised rate of moderate or severe COPD exacerbations (primary endpoint; full analysis set) for the overall population and in prespecified patient subgroups by baseline demographics and clinical characteristics, and the annualised rate of severe COPD exacerbations (secondary endpoint; full analysis set)**

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

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

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

Biologics - Tezepelumab

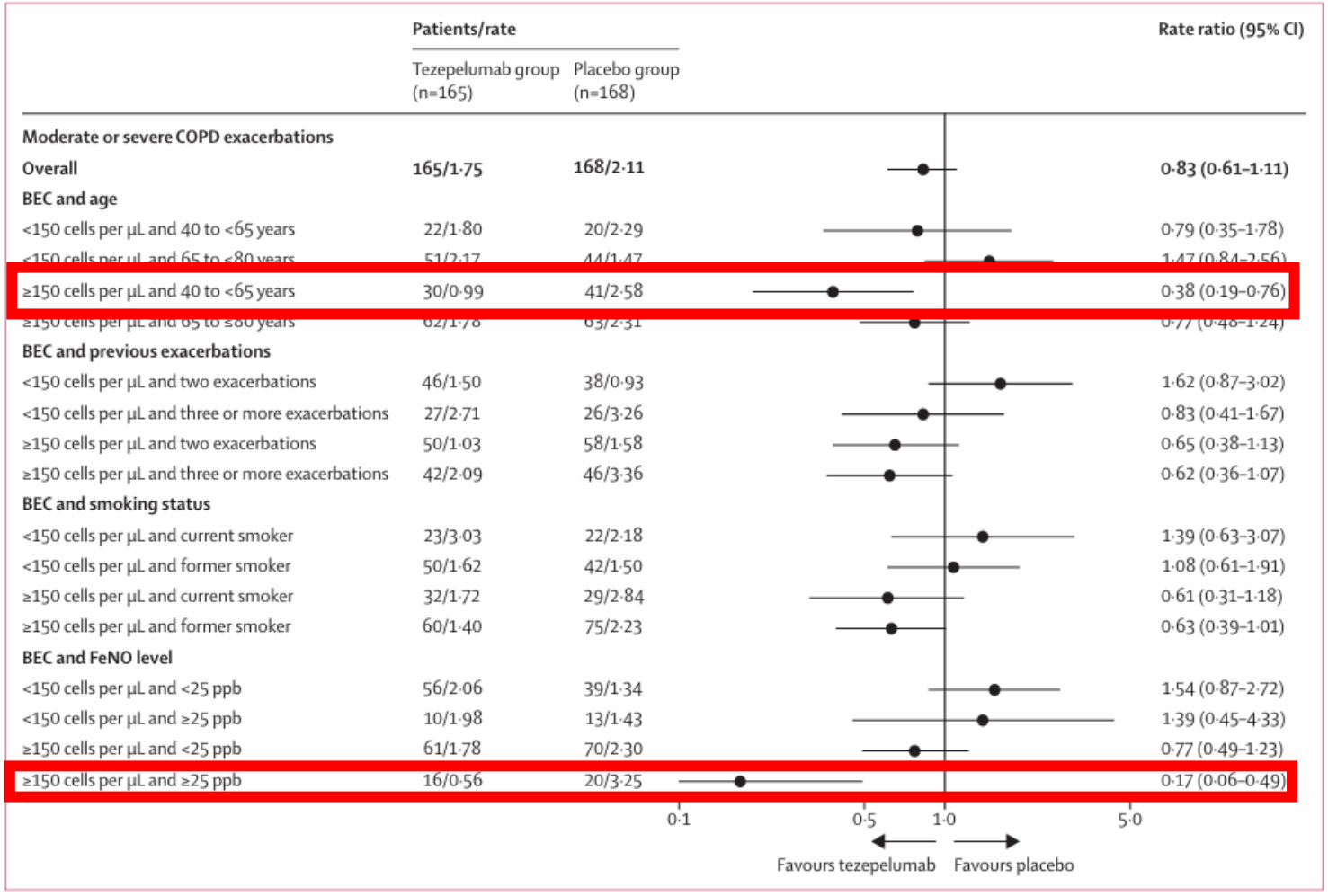


Figure 3: **Post-hoc analysis of the annualised rate of moderate or severe COPD exacerbations in patients grouped by baseline BEC and baseline age, previous exacerbations, smoking status, or FeNO level (full analysis set)**
BEC=blood eosinophil count. COPD=chronic obstructive pulmonary disease. FeNO=fractional exhaled nitric oxide. ppb=parts per billion.

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

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

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

Biologics – Benralizumab

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

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

- **Study Design:** Double-blind, Double-dummy, active placebo-controlled randomized trial
- **Participants (n=158):** Asthma or COPD exacerbation with **BE ≥ 300 cells/µL**

- **Intervention**
  - **Pooled-BENRA:** Benralizumab 100mg SC (single dose) ± Prednisolone.
  - **Standard of Care (PRED):** Prednisolone 30mg x 5 days + Placebo injection.
  - 1:1:1 [Benra, Benra + PRED, PRED]

- **Primary Endpoint:** Treatment failure at 90 days & Total VAS symptom score at Day 28.

Biologics – Benralizumab

	PRED group (n=53)	Pooled-BENRA group (n=105)	p value
Number of patients with treatment failure at 90 days	39 (74%)	47 (45%)	..
Odds ratio (95%CI) *vs* PRED group	..	0·26 (0·13 to 0·56)	0·0005
Change in total VAS symptoms from exacerbation to day 28			
Mean change (95% CI) in mm	103 (75 to 132)	152 (131 to 173)	..
Least-square mean difference *vs* PRED group	..	49 (14 to 84)	0·0065
Change in total VAS cough from exacerbation to day 28			
Mean change (95% CI) in mm	23 (16 to 30)	34 (28 to 39)	..
Least-square mean difference *vs* PRED group	..	10 (2 to 19)	0·020
Change in total VAS dyspnoea from exacerbation to day 28			
Mean change (95% CI) in mm	27 (19 to 34)	34 (28 to 39)	..
Least-square mean difference *vs* PRED group	..	7 (−2 to 16)	0·133
Change in total VAS wheeze from exacerbation to day 28			
Mean change (95% CI) in mm	23 (16 to 29)	36 (32 to 41)	..
Least-square mean difference *vs* PRED group	..	14 (6 to 22)	<0·001
Change in total VAS sputum purulence from exacerbation to day 28			
Mean change (95% CI) in mm	13 (7 to 18)	24 (20 to 28)	..
Least-square mean difference *vs* PRED group	..	11 (4 to 18)	0·002
Change in total VAS sputum volume from exacerbation to day 28			
Mean change (95% CI) in mm	17 (11 to 23)	26 (21 to 30)	..
Least-square mean difference *vs* PRED group	..	9 (2 to 17)	0·016

The VAS was measured on a 100 mm scale for which 0 indicated the best symptoms and 100 indicated the worst symptoms. For VAS the minimal clinical important difference is 9. All analyses were adjusted for randomisation stratification factors namely diagnostic label, steady state FEV_1 predicted, number of exacerbations in the previous year, and smoking status. The PRED group indicates the prednisolone only group. The pooled-BENRA group indicates the benralizumab alone and the benralizumab plus prednisolone groups pooled together.

Table 2: **Primary endpoint for the PRED and the pooled-BENRA treatment groups**

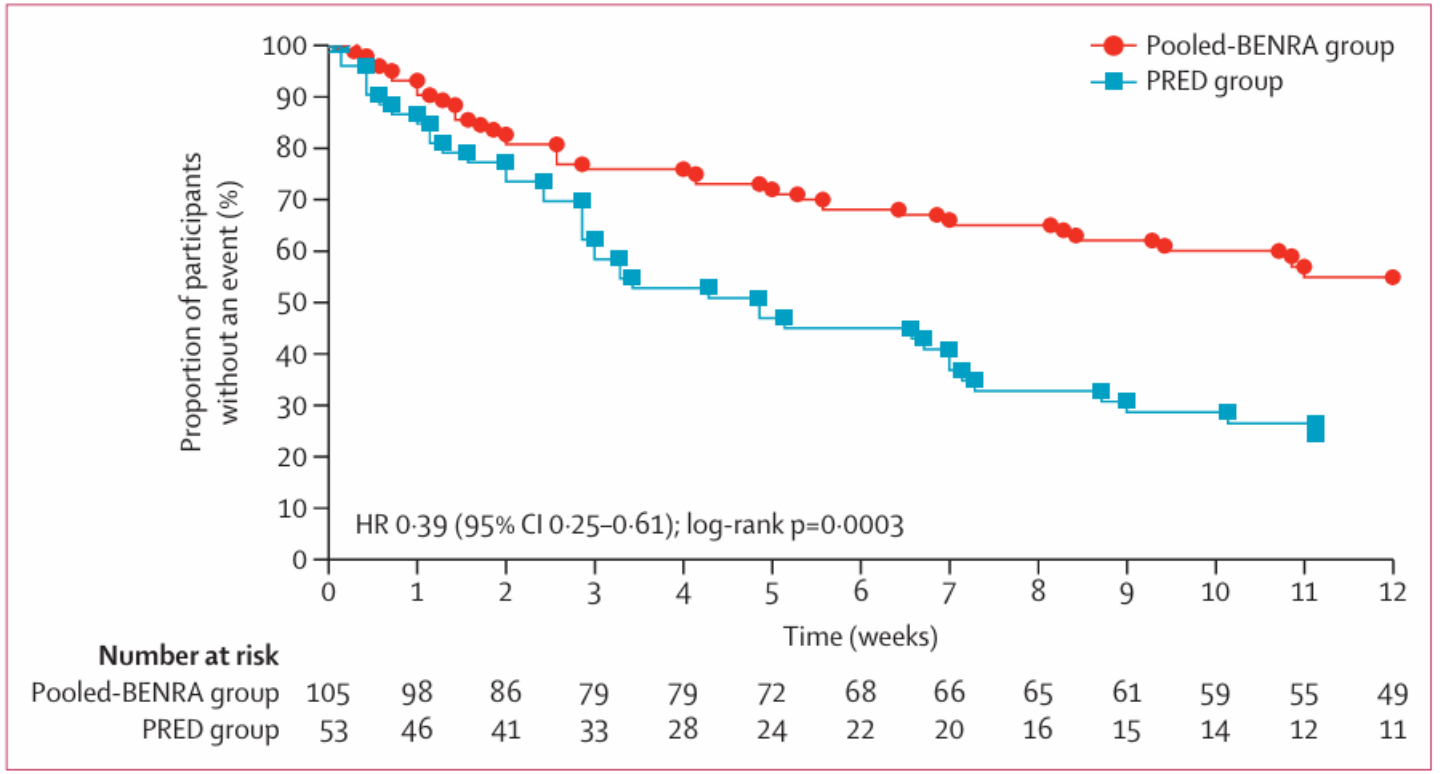


Figure 2: **Kaplan–Meier plot of time to first treatment failure event in the PRED and pooled-BENRA treatment groups**

The PRED group indicates the prednisolone only group (blue line). The pooled-BENRA group indicates the benralizumab alone and the benralizumab plus prednisolone groups pooled together (red line).

Biologics - Tozorakimab

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

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

- **Study Design:** Phase 2a, randomized, double-blind, placebo-controlled trial.
- **Participants (N=135):** Moderate-to-severe COPD with Chronic Bronchitis, History of ≥ 1 exacerbation in prior 24 months, On maintenance therapy (Dual or Triple).

- **Intervention (24 weeks):**
  - **Tozorakimab 600 mg** SC every 4 weeks.
  - **Placebo** SC every 4 weeks.
- **Primary Endpoint:** Change from baseline in **pre-bronchodilator FEV1** at Week 12.

TABLE 2 Efficacy data in the ITT population and in relevant subgroups

Subgroup	Treatment	Pre-BD FEV_1 (mL)		Post-BD FEV_1 (mL)		Time-to-first COPDCompEx event	
		Change from baseline to week 12, mean±SE	Difference *versus* placebo, mean (80% CI)	Change from baseline to week 12, mean±SE	Difference *versus* placebo, mean (80% CI)	Patients with an event, n (%)	HR (80% CI)
ITT population	Tozorakimab 600 mg (n=67)	19±26	24 (−15–63) p=0.216	41±36	67 (17–116) p=0.044	28 (41.8)	0.79 (0.57–1.11) p=0.186
	Placebo (n=68)	−5±25	N/A	−25±34	N/A	36 (52.9)	N/A
⩽1 exacerbation in the last 12 months	Tozorakimab 600 mg (n=41)	−14±31	−8 (−59–43) p=0.418	1±40	31 (−34–96) p=0.269	17 (41.5)	1.00 (0.63–1.60) p=0.495
	Placebo (n=35)	−5±32	N/A	−31±42	N/A	14 (40.0)	N/A
⩾2 exacerbations in the last 12 months	Tozorakimab 600 mg (n=26)	61±38	69 (9–130) p=0.072	103±50	124 (47–201) p=0.020	11 (42.3)	0.61 (0.37–1.00) p=0.098
	Placebo (n=33)	−8±34					
⩽1 moderate exacerbation in the 12 months before study enrolment	Tozorakimab 600 mg (n=38)	−5±43					
	Placebo (n=32)	2±45					
⩾2 moderate and/or ⩾1 severe exacerbation in the 12 months before study enrolment	Tozorakimab 600 mg (n=29)	47±44					
	Placebo (n=36)	−12±41					
Baseline BEC <150 cells·µL^{-1}	Tozorakimab 600 mg (n=37)	−12±32					
	Placebo (n=36)	12±31					
Baseline BEC ⩾150 cells·µL^{-1}	Tozorakimab 600 mg (n=30)	57±35					
	Placebo (n=32)	−25±35					
Current smokers	Tozorakimab 600 mg (n=24)	42±40					
	Placebo (n=32)	17±33					
Former smokers	Tozorakimab 600 mg (n=43)	5±31					
	Placebo (n=36)	−27±33					

BD: bronchodilator; BEC: blood eosinophil count; CI: confidence interval; COPDCompEx: CO
N/A: not applicable; SE: standard error.

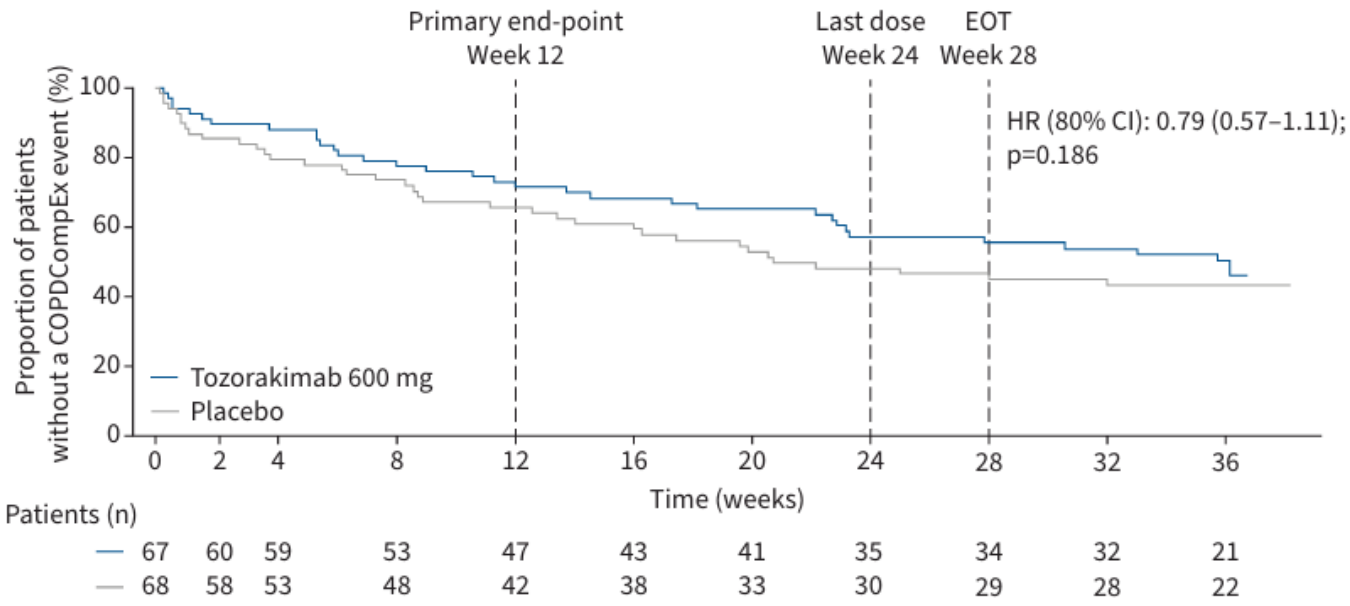


FIGURE 3 Kaplan–Meier plots of time-to-first COPD composite exacerbation (COPDCompEx) event in the intent-to-treat population. CI: confidence interval; EOT: end of treatment; HR: hazard ratio.

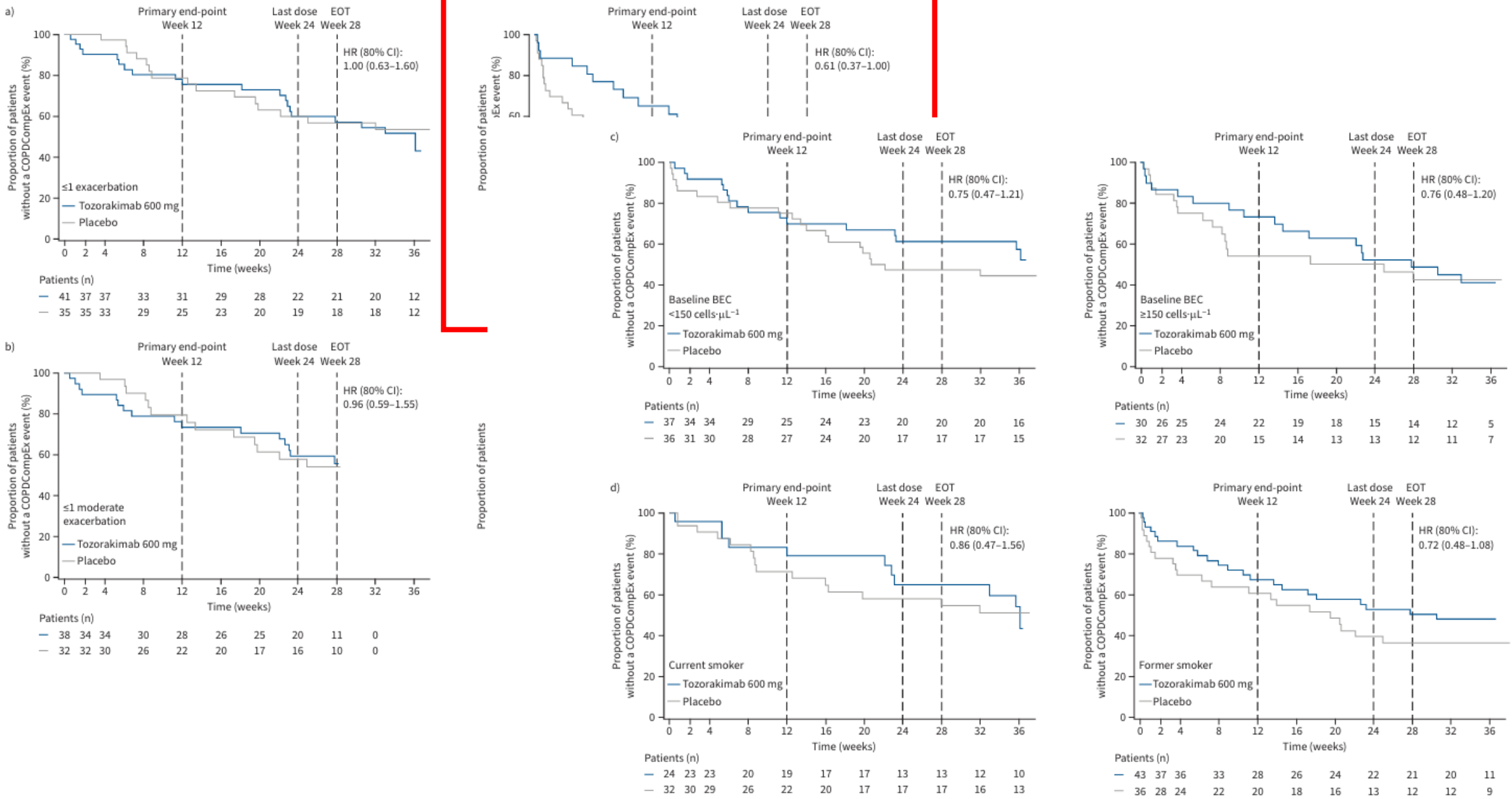


FIGURE 4 Kaplan–Meier plots of time-to-first COPD composite exacerbation (COPDCompEx) event by a) prespecified exacerbation history, b) *post hoc* exacerbation history, c) baseline blood eosinophil count (BEC) and d) current and former smoker subgroups. CI: confidence interval; EOT: end of treatment; HR: hazard ratio.

Inhaler – Ensifentrine

Effect of Dual Phosphodiesterase 3 and 4 Inhibitor Ensifentrine on Exacerbation Rate and Risk in Patients With Moderate to Severe COPD

Frank C. Sciurba, MD; Stephanie A. Christenson, MD; Tara Rheault, PhD, MPH; Thomas Bengtsson, MSc; Kathleen Rickard, MD; and Igor Z. Barjaktarevic, MD, PhD

- **Study Design:** Prespecified pooled analysis of two Phase 3, multicenter, randomized, double-blind, placebo-controlled trials (ENHANCE-1 & 2).
- **Participants (N=1,549):** Age 40–80, symptomatic Moderate to Severe COPD (post-BD FEV1 30–70%). Allowed background maintenance therapy (LAMA or LABA, but no dual/triple).
- **Intervention (24 weeks)**
  - **Ensifentrine 3 mg** nebulized suspension BID (twice daily).
  - **Placebo** nebulized suspension BID.
- **Primary Endpoint:** Rate of moderate to severe COPD exacerbations

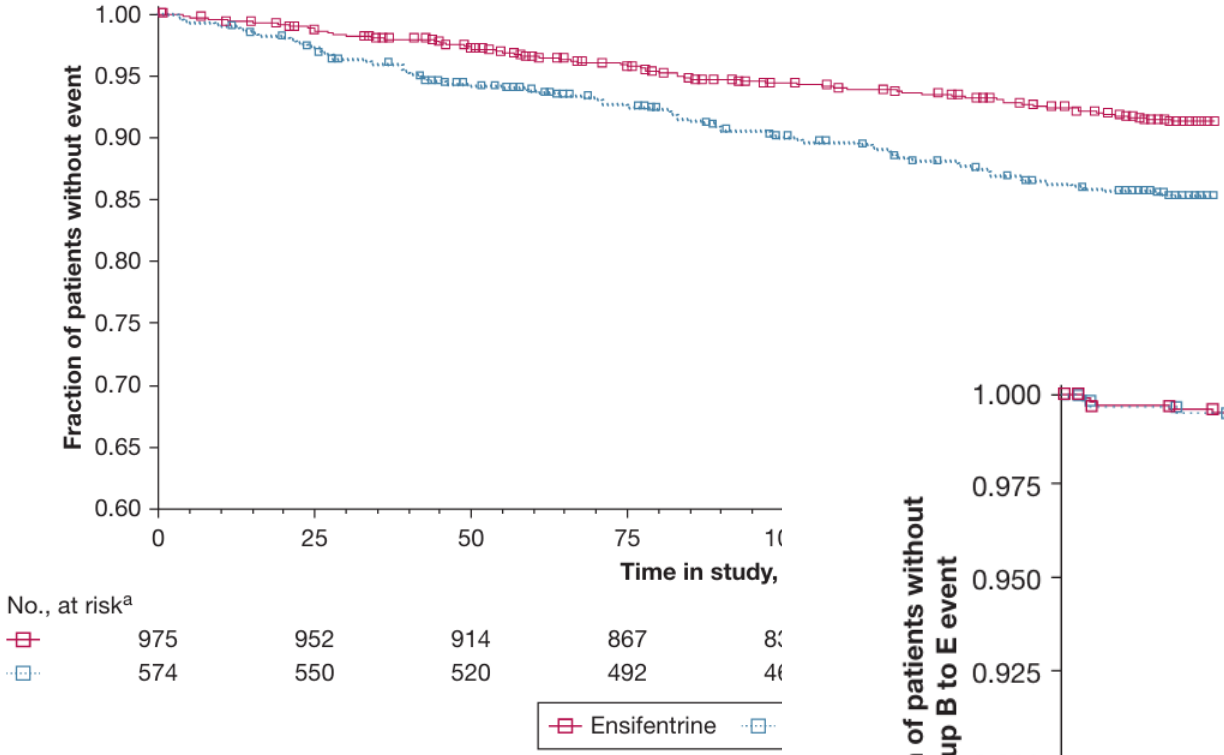


Figure 2 – *Kaplan-Meier plot showing time to first moderate to severe COPD exacerbation last exacerbation that occurred during the interval reported. HR = hazard ratio.*

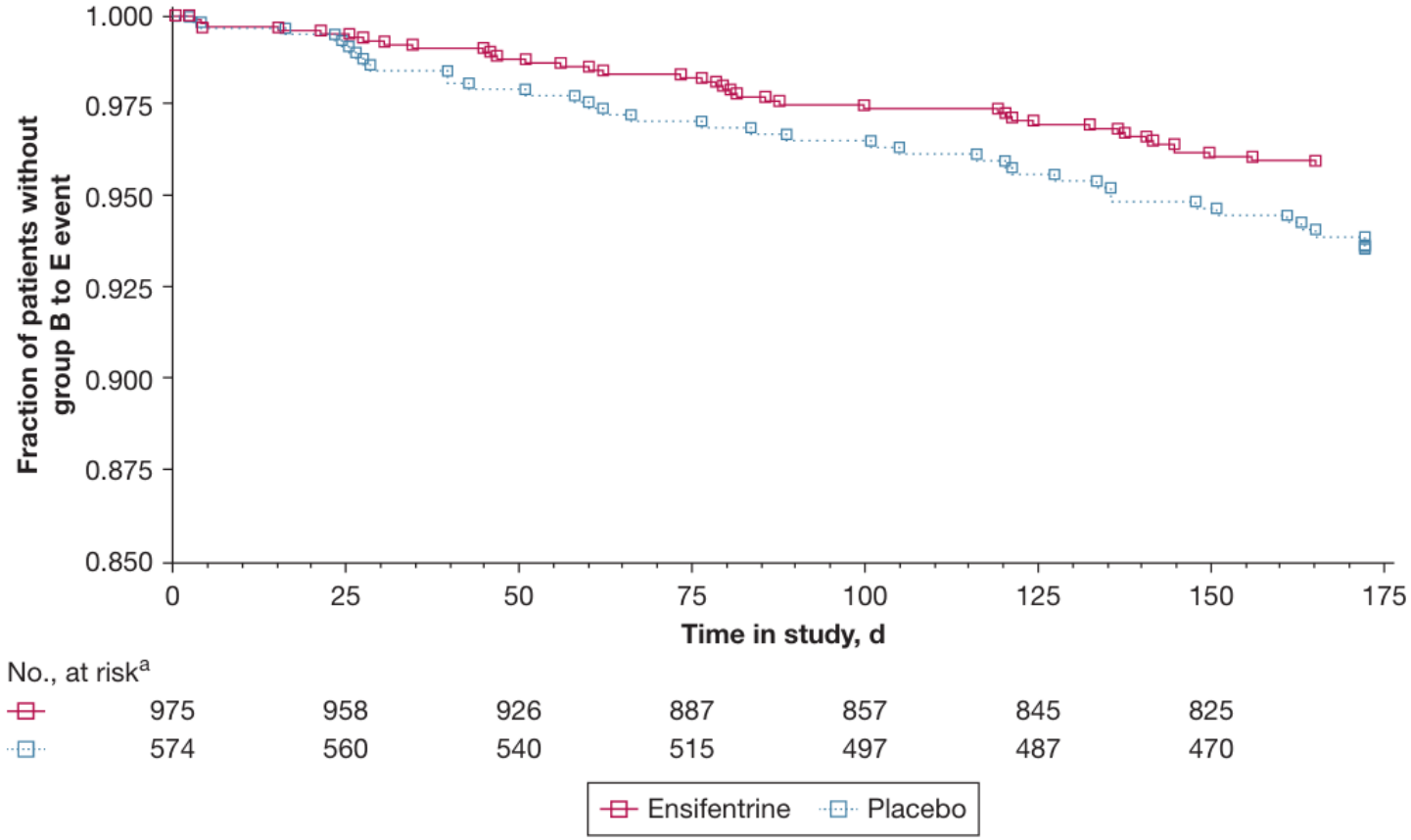


Figure 4 – *Kaplan-Meier plot showing time to first Global Initiative for Chronic Obstructive Lung Disease group B to E transition over 24 weeks.*
[a]Reported number at risk corresponds to the last exacerbation that occurred during the interval reported.

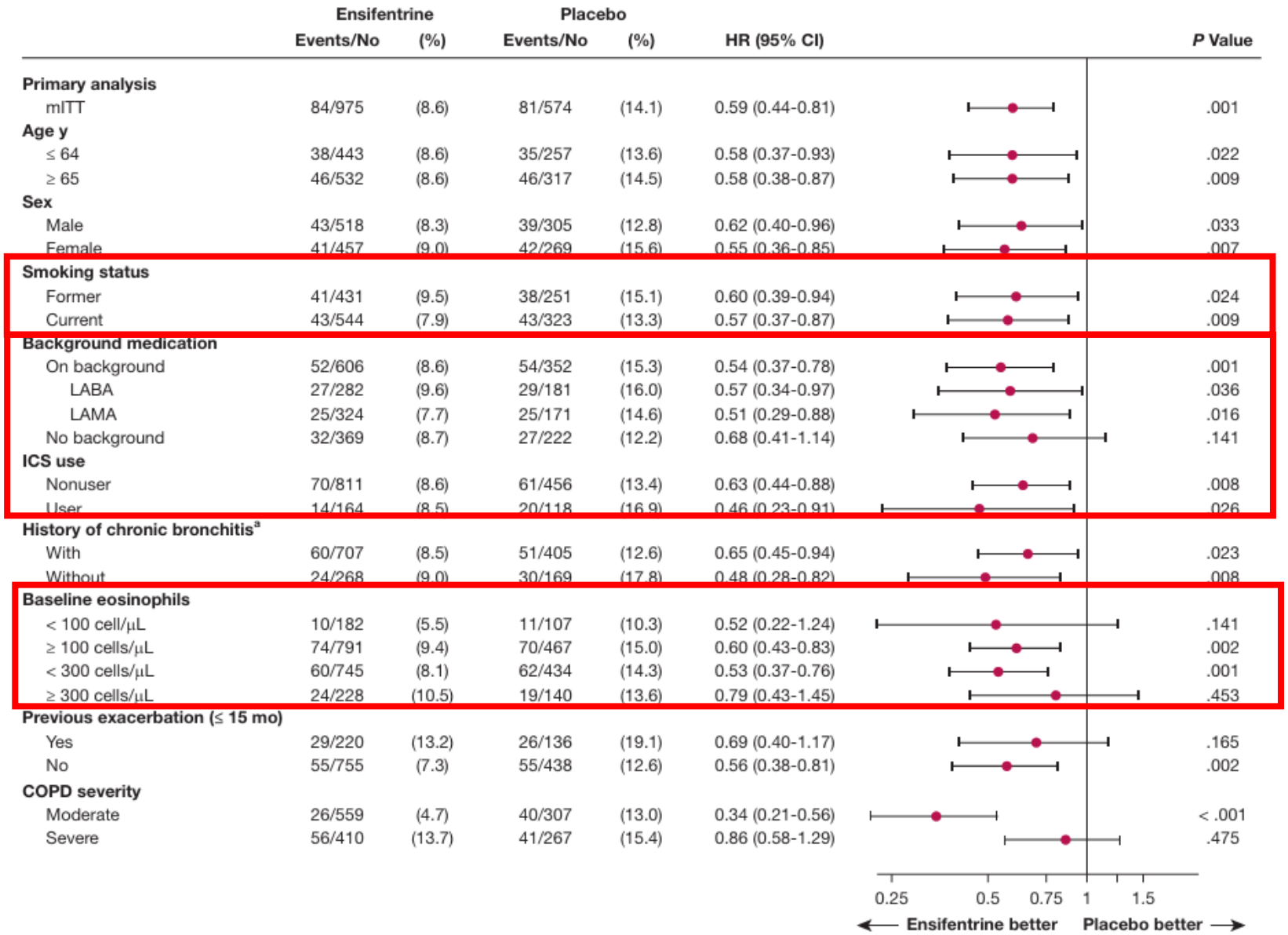


Figure 3 – *Forest plot showing HRs of time to first moderate to severe exacerbation by model covariate over 24 weeks.* [a]*Chronic bronchitis was defined as regular production of sputum for ≥ 3 months in 2 consecutive years in the absence of other conditions that may explain it.*[1] *Models for subgroup analyses adjusted for trial, background medication strata, and smoking status, except for subgroups based on background medication, ICS use, or eosinophil count of < 100 cells/μL that used only trial and smoking status. HR = hazard ratio; ICS = inhaled corticosteroid; LABA = long-acting β2-agonist; LAMA = long-acting muscarinic antagonist; mITT = modified intention-to-treat.*

Inhaler – Triple therapy 1

Effect of Triple Therapy on Cardiovascular and Severe Cardiopulmonary Events in Chronic Obstructive Pulmonary Disease
A *Post Hoc* Analysis of a Randomized, Double-Blind, Phase 3 Clinical Trial (ETHOS)

Dave Singh[1], Fernando J. Martinez[2], John R. Hurst[3], MeiLan K. Han[4], Chris P. Gale[5,6,7], Martin Fredriksson[8], Dobrawa Kisielewicz[9], Alec Mushunje[10], Charlotta Movitz[8], Nikki Ojili[11], Himanshu Parikh[11], Niki Arya[12], Karin Bowen[11], and Mehul Patel[10]

- **Study Design:** Multicentre, Double-blind, Randomized, Parallel-group
- **Participants (n=8,588)**: Moderate~Very Severe COPD, Exacerbation Hx
- **Intervention (1:1:1:1)**
  - **BGF 320 (Triple):** Budesonide 320 μg + Glycopyrrolate 18 μg + Formoterol 9.6 μg
  - **BGF 160 (Triple):** Budesonide 160 μg + Glycopyrrolate 18 μg + Formoterol 9.6 μg
  - **BFF (Dual, ICS/LABA):** Budesonide 320 μg + Formoterol 9.6 μg
  - **GFF (Dual, LAMA/LABA):** Glycopyrrolate 18 μg + Formoterol 9.6 μg
- **Endpoint: Time to first** MACE, CVAESI (cardiovascular adverse event of special interest), cardiac adverse event, and severe cardiopulmonary events.

** **Severe Cardiopulmonary Event:** MACE + Severe Exacerbation + Non-malignant respiratory death.

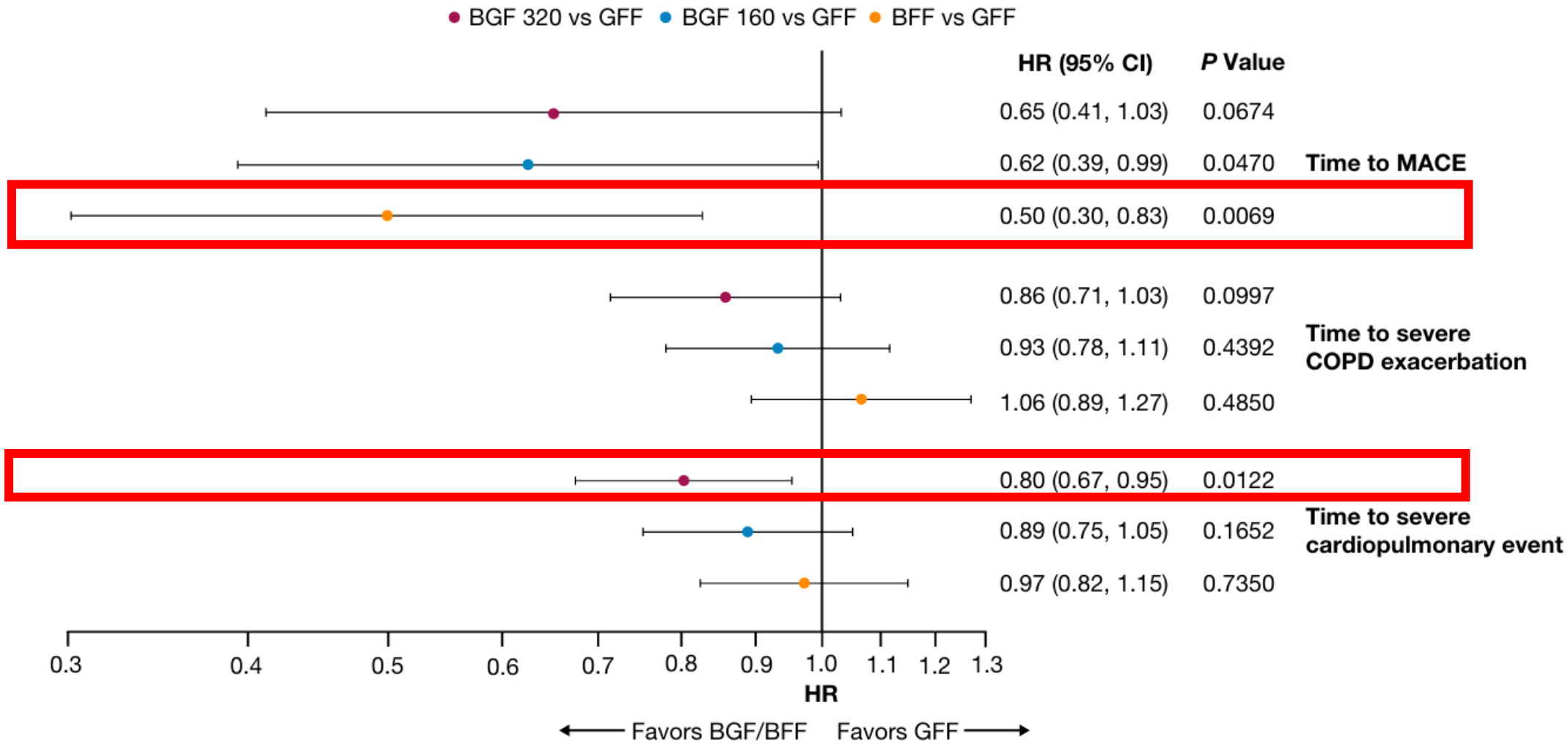


Figure 1. Hazard ratios (HRs) for time to severe cardiopulmonary events with BGF 320, BGF 160, and BFF versus GFF (modified intention-to-treat population). HRs and 95% CIs were calculated using Cox regression; *P* values are nominal and unadjusted for multiplicity. BFF = budesonide/formoterol fumarate 320/9.6 μg; BGF 160 = budesonide/glycopyrrolate/formoterol fumarate 160/18/9.6 μg; BGF 320 = budesonide/glycopyrrolate/formoterol fumarate 320/18/9.6 μg; CI = confidence interval; COPD = chronic obstructive pulmonary disease; GFF = glycopyrrolate/formoterol fumarate 18/9.6 μg; MACE = major adverse cardiac event. Adapted by permission from reference 15.

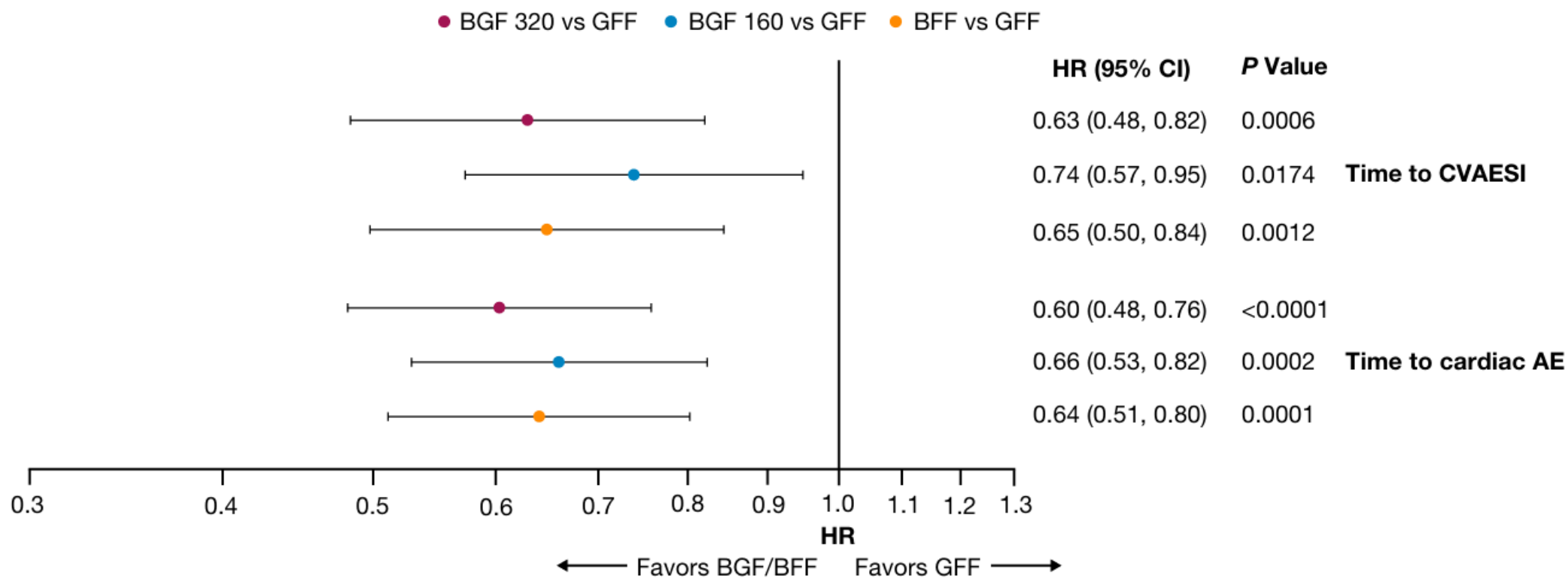
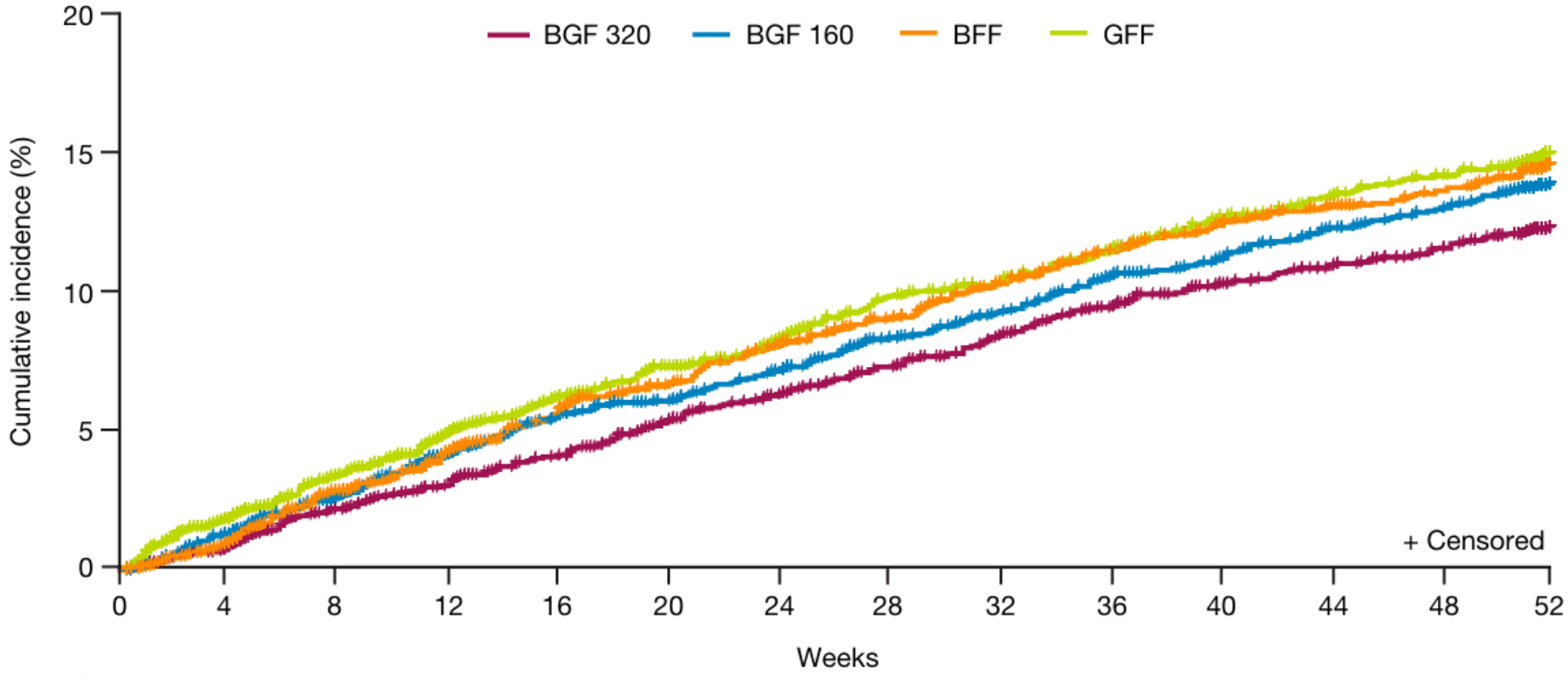


Figure 2. Hazard ratios (HRs) for time to first CVAESI and cardiac AE with BGF 320, BGF 160, and BFF versus GFF (modified intention-to-treat population). HRs and 95% CIs were calculated using Cox regression; *P* values are nominal and unadjusted for multiplicity. AE = adverse event; BFF = budesonide/formoterol fumarate 320/9.6 μg; BGF 160 = budesonide/glycopyrrolate/formoterol fumarate 160/18/9.6 μg; BGF 320 = budesonide/glycopyrrolate/formoterol fumarate 320/18/9.6 μg; CI = confidence interval; CVAESI = cardiovascular adverse event of special interest; GFF = glycopyrrolate/formoterol fumarate 18/9.6 μg. Adapted by permission from reference 15.



Patients at risk:

BGF 320	2137	2084	2006	1958	1905	1849	1808	1762	1724	1685	1636	1608	1576	1296
BGF 160	2121	2056	1990	1932	1872	1834	1798	1750	1712	1673	1638	1601	1576	1271
BFF	2131	2051	1957	1886	1817	1770	1730	1686	1641	1597	1561	1533	1508	1217
GFF	2120	2015	1903	1827	1753	1704	1658	1602	1579	1549	1511	1484	1458	1182

Figure 3. Kaplan-Meier curves for time to severe cardiopulmonary event (defined as a major adverse cardiac event, severe chronic obstructive pulmonary disease exacerbation, or death of a nonmalignant respiratory cause) with BGF 320, BGF 160, BFF, and GFF (modified intention-to-treat population). BFF = budesonide/formoterol fumarate 320/9.6 μg; BGF 160 = budesonide/glycopyrrolate/formoterol fumarate 160/18/9.6 μg; BGF 320 = budesonide/glycopyrrolate/formoterol fumarate 320/18/9.6 μg; GFF = glycopyrrolate/formoterol fumarate 18/9.6 μg. Adapted by permission from reference 15.

Inhaler – Triple therapy 2

Single-Inhaler Triple vs Long-Acting $Beta_2$-Agonist-Inhaled Corticosteroid Therapy for COPD

Comparative Safety in Real-World Clinical Practice

Samy Suissa, PhD; Sophie Dell'Aniello, MSc; and Pierre Ernst, MD

- **Study Design:** Observational cohort study using UK CPRD database.
- **Participants (N=20,510):** COPD patients initiating Triple therapy or LABA/ICS, LAMA-naive patients (to avoid withdrawal bias).

- **Intervention (1:1 PSM):**
  - **Single-Inhaler Triple Therapy** (LAMA/LABA/ICS).
  - **LABA/ICS**
- **Primary Endpoint:** Incidence of MACE (Major Adverse Cardiovascular Events: MI, Stroke, All-cause death) over 1 year.

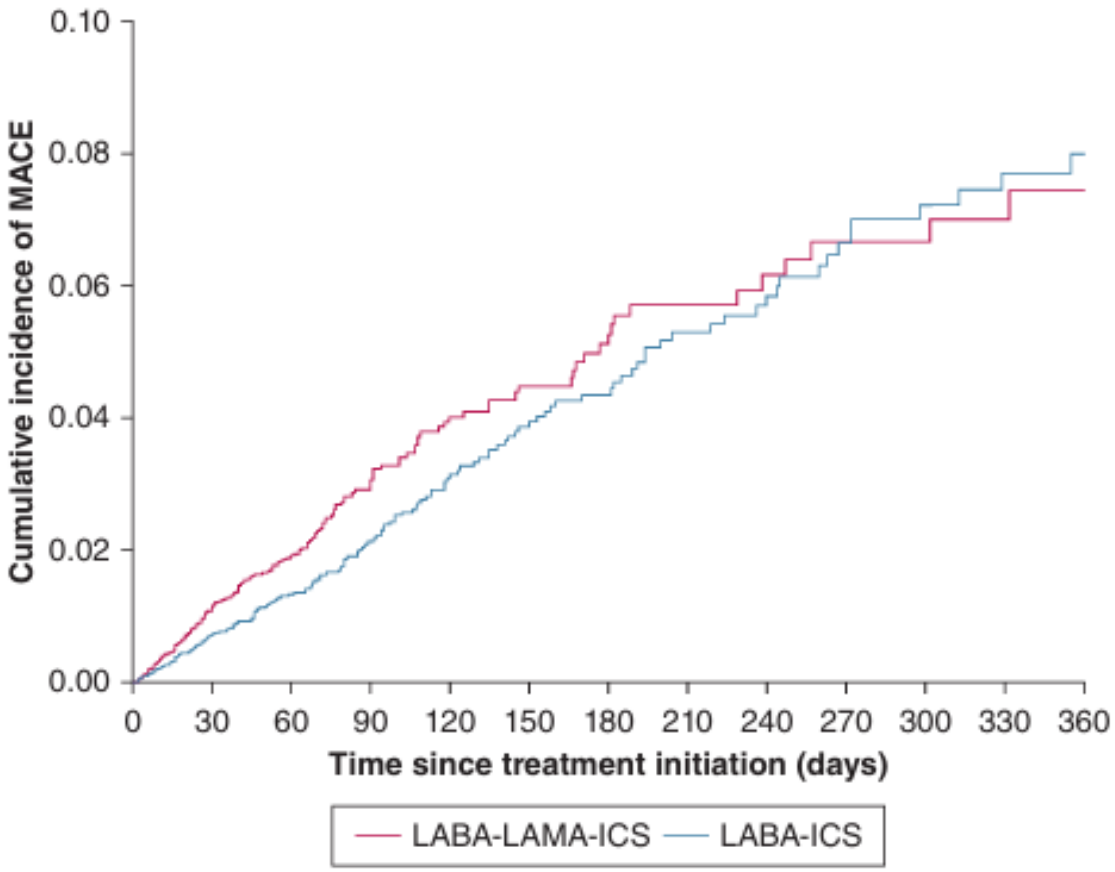


Figure 2 – *One-year as-treated cumulative incidence of MACE for the triple therapy and LABA-ICS matched groups, estimated using the Kaplan-Meier method. ICS = inhaled corticosteroid; LABA = long-acting beta$_2$-agonist; LAMA = long-acting muscarinic antagonist; MACE = major adverse cardiovascular event.*

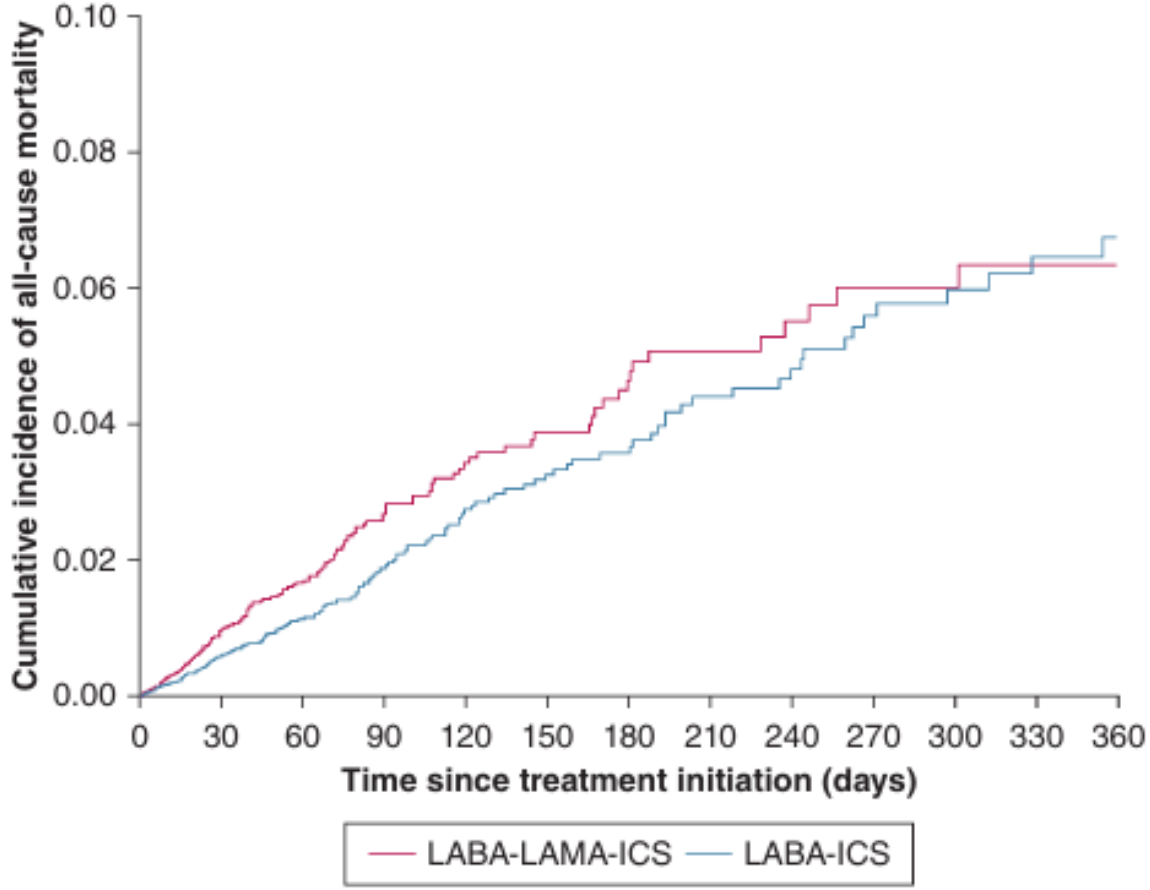


Figure 3 – *One-year as-treated cumulative incidence of all-cause death for the triple therapy and LABA-ICS matched groups, estimated using the Kaplan-Meier method. ICS = inhaled corticosteroid; LABA = long-acting beta$_2$-agonist; LAMA = long-acting muscarinic antagonist.*

Inhaler – ICS

The effect of different inhaled corticosteroid and long-acting bronchodilator combinations on the airway microbiome in patients with severe COPD: a randomised trial (MUSIC)

Hollian Richardson, Daniela Alferes De Lima Headley, Clare Clarke, Abirami Veluchamy, Petra Rauchhaus, Jennifer Pollock, Thomas Pembridge, Diane Cassidy, Holly R. Keir, Simon Finch, Furrah Hussain, Margaret Band, Andrew Smith, Manish Patel, Mohammad Paracha, Gourab Choudhury, Devesh Dhasmana, Rekha Chaudhuri, Philip M. Short and James D. Chalmers

- **Study Design:** Multicenter, randomized, open-label, controlled trial.
- **Participants (n=61):** Severe COPD (FEV1 <50%) or Frequent exacerbators.
- **Intervention (3 months):**
  - **FS500:** Fluticasone/Salmeterol 500/50 µg.
  - **FS250:** Fluticasone/Salmeterol 250/50 µg.
  - **BF400:** Budesonide/Formoterol 400/12 µg.
  - **AF** (Control arms).
- **Endpoint:** Bacterial load in oropharyngeal swabs (FS500 vs. BF400).

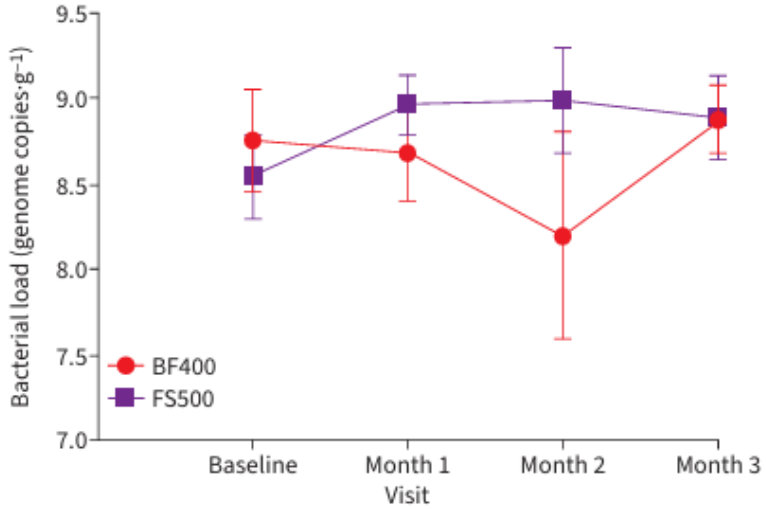


FIGURE 2 Mean±SE bacterial load in oropharyngeal swabs at each time-point in the study for fluticasone/salmeterol 500/50 µg (FS500) and budesonide/formoterol 400/12 µg (BF400).

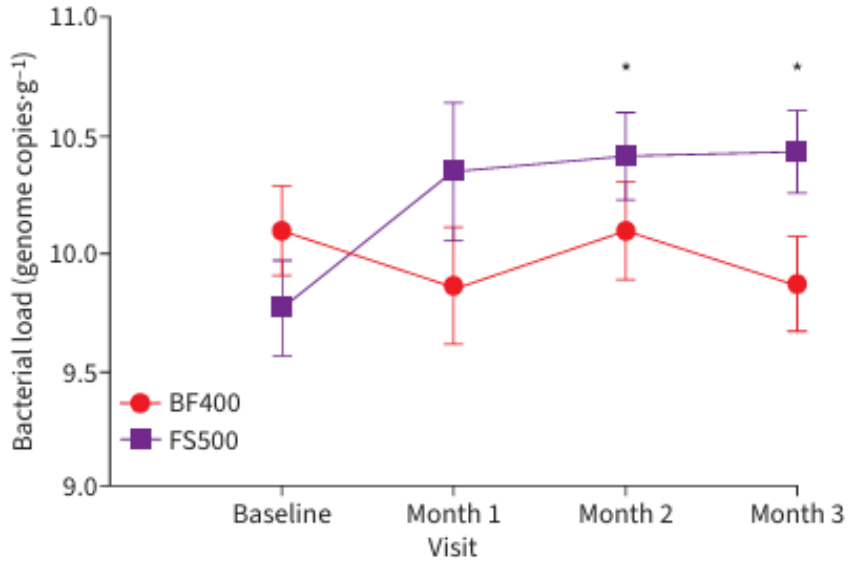


FIGURE 3 Mean±SE bacterial load in sputum at each time-point in the study for fluticasone/salmeterol 500/50 µg (FS500) and budesonide/formoterol 400/12 µg (BF400). *: time-points with significant differences $p<0.05$.

Oral medication - Azithromycin

Original research

Identifying azithromycin responders with an individual treatment effect model in COPD

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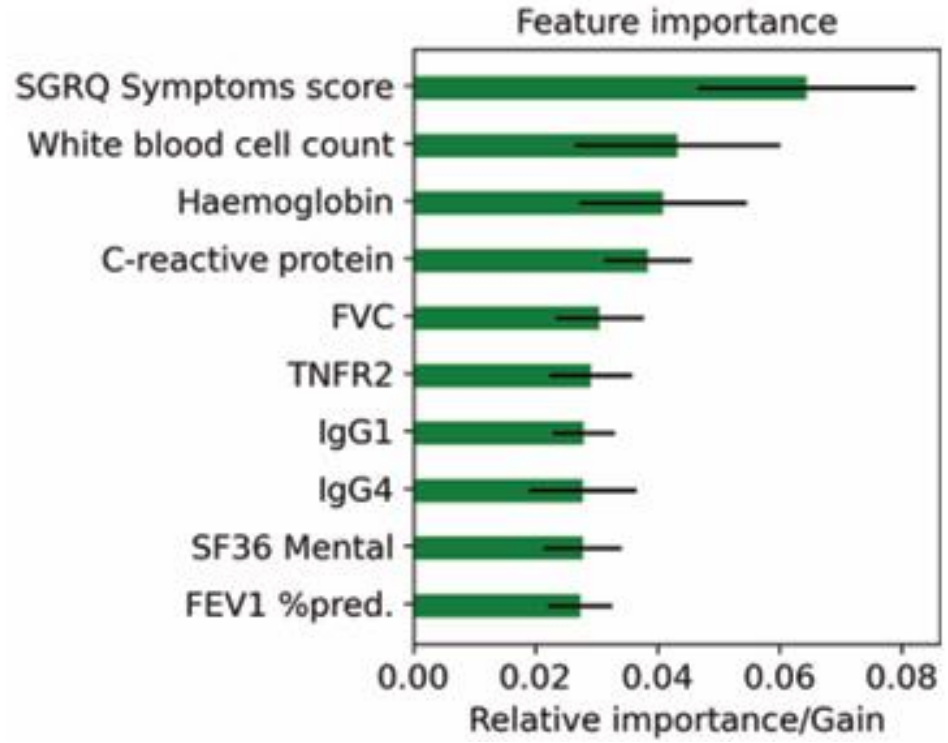

- **Study Design:** Post-hoc analysis of MACRO trial (Development set) and COLUMBUS trial (Validation set) using Causal Forest machine learning model.
- **Participants** (MACRO n=1,025, COLUMBUS n=83)**:** COPD patients with a history of exacerbations
- **Intervention (12m):** Azithromycin (250mg daily or 500mg 3x/week) vs. Placebo.
- **Primary Endpoint:** Individual Treatment Effect on annual exacerbation rate.

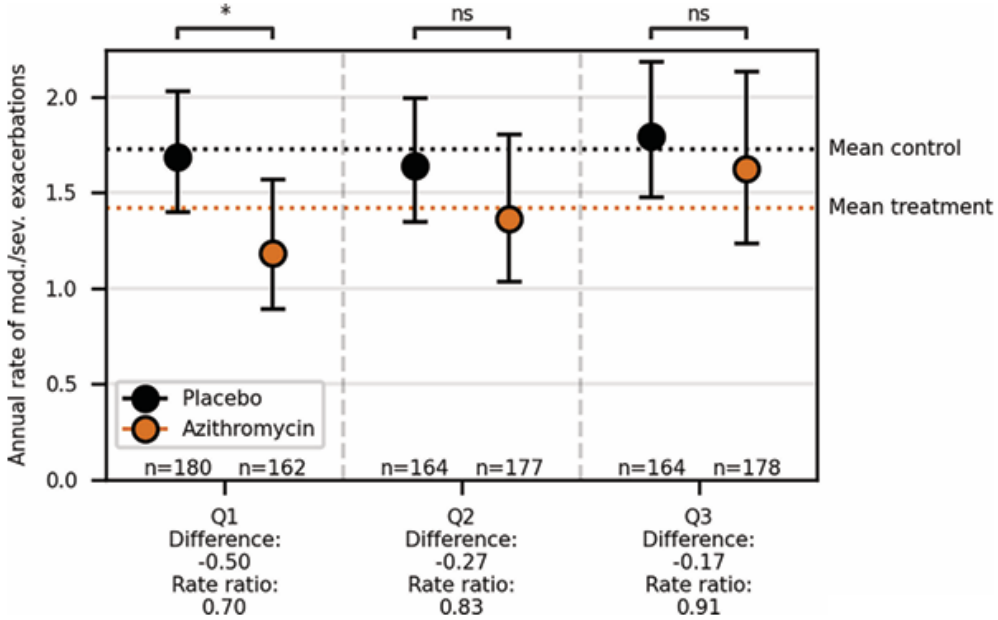

Figure 2 Tertile discretisation of the internal test set in MACRO. Subjects of the internal test set were rankec most favourable predicted ITE—that is, most negative- to least favourable predicted ITE) and subsequently div observed treatment effect, the annual rate of moderate to severe exacerbations was compared between treate tertile. ITE, individual treatment effect; ns, non-significant; Q1, quantile 1; Q2, quantile 2; Q3, quantile 3.

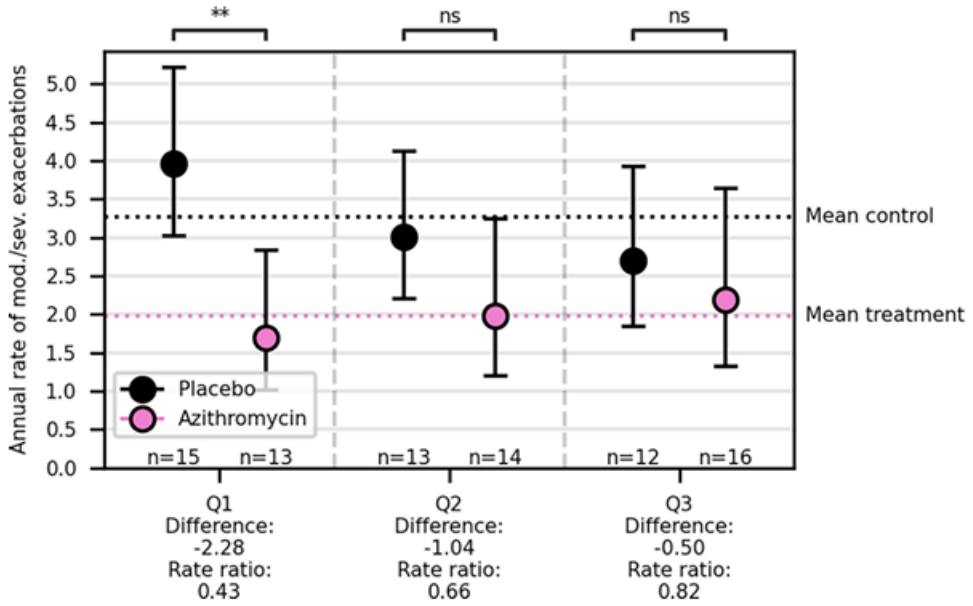

Figure 3 Tertile discretisation of the COLUMBUS external validation cohort. Subjects of the external test set were ranked according to their predicted ITE (most favourable to least favourable) and divided into tertiles. The observed treatment effect was evaluated by comparing annual exacerbation rates between treated and untreated subjects within each tertile. ITE, individual treatment effect; ns, non-significant; Q1, quantile 1; Q2, quantile 2; Q3, quantile 3.

Oral medication – PDE5i

Association of Phosphodiesterase-5 Inhibitor Treatment With Improved Survival in Pulmonary Hypertension Associated With COPD in the Pulmonary Vascular Research Institute GoDeep Meta-Registry

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- **Study Design:** Retrospective analysis of the PVRI GoDeep meta-registry (multicenter, international).
- **Participants (N=836):** Patients with COPD and PH diagnosed by right heart catheterization.
- **Intervention:**
  - **PDE5 Inhibitor (PDE5i) treatment** (n=418).
  - **Control:** No PH-targeted therapy.
- **Primary Endpoint:** Transplant-free survival (Time from diagnosis to death or transplantation).

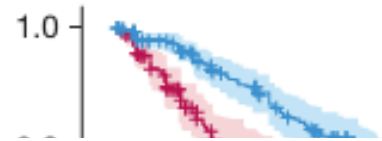
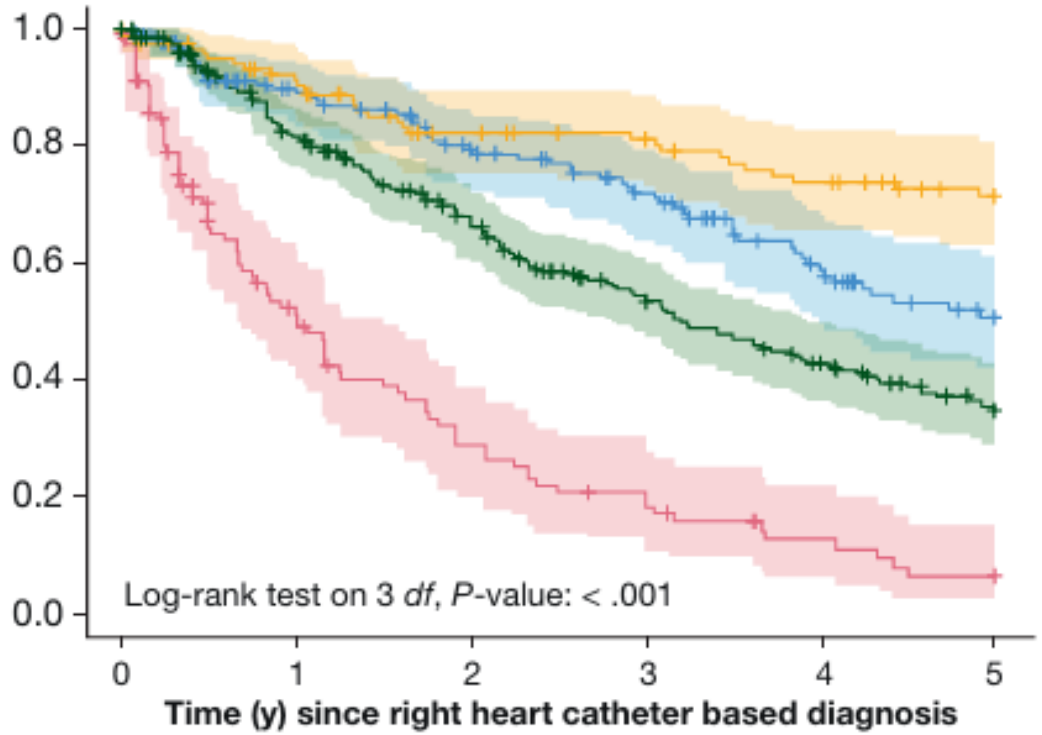


Figure 4 – *Kaplan-Meier overal*
95% CIs for patients with COPL
with PDE5i therapy or not bein
monary hypertension-targeting
freedom; PDE5i = phosphodieste
pulmonary hypertension.



At risk

Treatment, PVR	0	1	2	3	4	5
	228	124	102	84	59	39
	129	47	25	16	8	4
	130	103	85	79	69	59
	288	202	149	107	81	56

Figure 5 – *Kaplan-Meier overall survival curves with 95% CIs for patients being treated with PDE5i therapy or not being treated by any PH-targeting drugs, dichotomized for the patients with PVR of ≤ 5 WU and those with PVR of > 5 WU. df = degrees of freedom; PDE5i = phosphodiesterase-5 inhibitors; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; WU = Wood unit.*

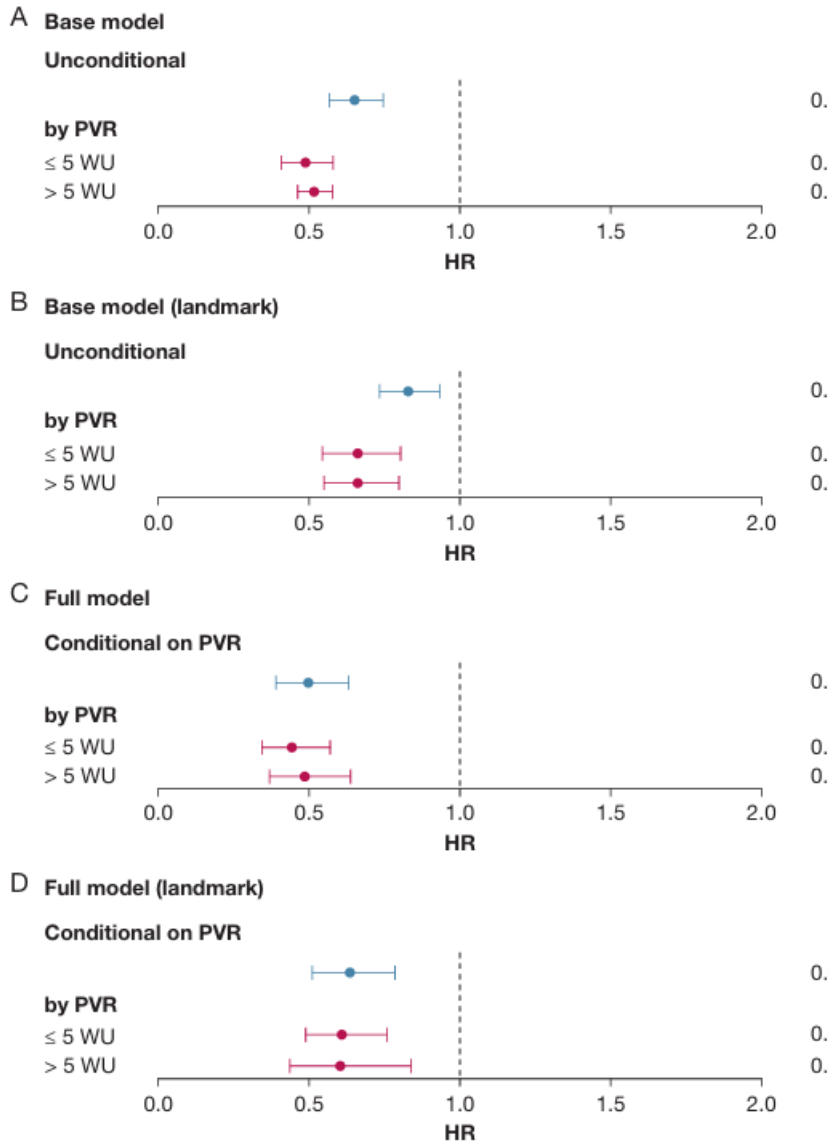


Figure 6 – *Forest plot showing HRs for patients receiving phosphodiesterase-5 inhibitor (PDE5i) treatment treatment from Cox proportional hazards models. The diagrams show the estimates with 95% CIs. The P the base model. The unconditional estimate is the HR of PDE5i not adjusted for any covariable except groups are from the base model including the interaction term of the dichotomized PVR and PDE5i treatm only. B, Results from the base model similar to (A), but after applying the landmark approach. C, Results on PVR is adjusted for a linear relationship between PVR and the log hazard, which is part of the full mod are obtained as for (A). This model is based on imputed data for variables with missing values in the cova to (C), but after applying the landmark approach. HR = hazard ratio; PVR = pulmonary vascular resi*

A

Treatment	untreated	treated	Overall
No.	418	418	836
Metabolic Syndrome	113 (27%)	145 (35%)	258 (31%)
Cardiovascular Disease	205 (49%)	224 (54%)	429 (51%)
Renal Comorbidities	77 (18%)	81 (19%)	158 (19%)
Cancer	61 (15%)	72 (17%)	133 (16%)
Sleep Apnea Syndrome	47 (11%)	68 (16%)	115 (14%)
Oxygen Treatment	180 (43%)	264 (63%)	444 (53%)
FEV_1% predicted < 80%	363 (87%)	344 (82%)	707 (85%)
FEV_1% predicted < 80% & FEV_1 to FVC ratio < 0.7	314 (75%)	290 (69%)	604 (72%)
FEV_1% predicted < 50%	214 (51%)	177 (42%)	391 (47%)
FEV_1% predicted < 30%	91 (22%)	62 (15%)	153 (18%)
D_{LCO}% predicted ≤ 50%			
Yes	128 (72%)	185 (81%)	313 (77%)
Missing	240 (57%)	189 (45%)	429 (51%)

B

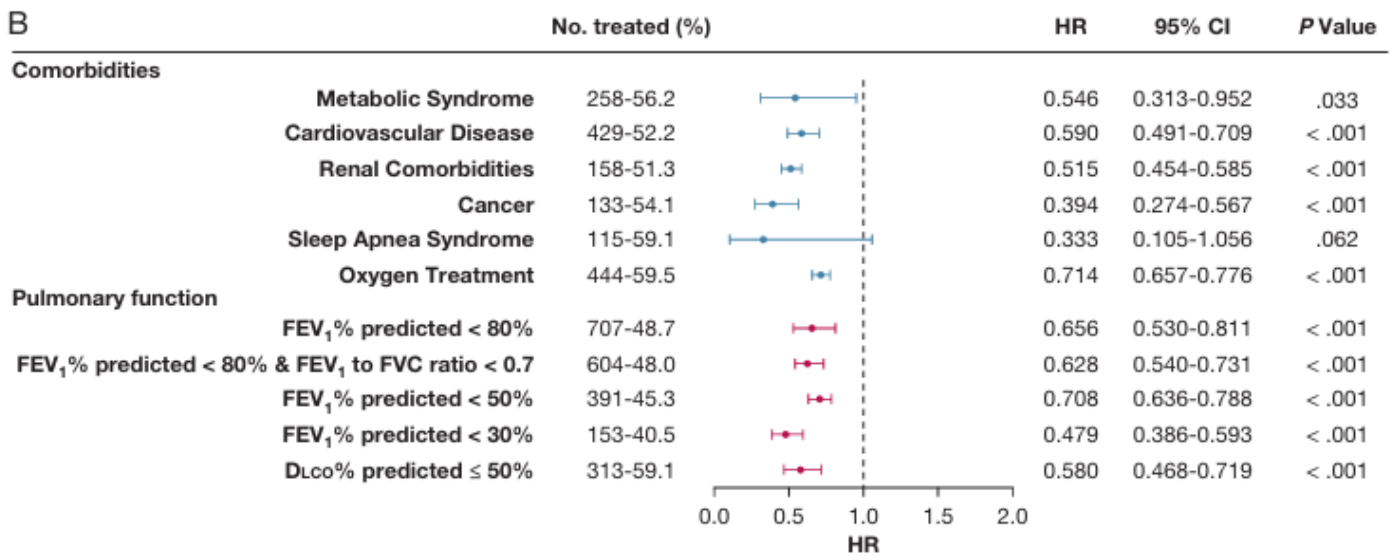


Figure 7 – *Relationship between phosphodiesterase-5 inhibitor (PDE5i) treatment and comorbidities and pulmonary function impairment. A, Contingency table. B, Forest plot showing results from the base model applied to subgroups defined by comorbidities and pulmonary function impairment. The HRs refer to patients receiving PDE5i treatment compared with patients not receiving PDE5i treatment from Cox proportional hazards models. The diagram shows the estimates with 95% CIs. The P values are from Wald z tests. D_{LCO} = diffusing capacity of the lungs for carbon monoxide; HR = hazard ratio.*

Oral medication – OM-85

OM-85 and Respiratory Symptoms in Korean Chronic Obstructive Pulmonary Disease: A Multicenter Observational Study

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- **Study Design:** Prospective, multicenter, observational, single-arm study.
- **Participants (n=323):** Korean COPD patients prescribed OM-85.

- **Intervention:** OM-85 (Broncho-Vaxom) 7mg daily for 3 months.
- **Primary Endpoint:** Changes in respiratory symptoms (CAT, mMRC) and QoL (SGRQ) over 6 months. (3m tx, 3m fu)

Table 2. Comparison of symptoms and quality of life scores between baseline and 3 or 6 months of treatment in 323 COPD patients who received OM-85 for 3 months

Variable	Time	Number	Mean±SD	p-value
mMRC	Baseline	314	1.60±0.90	
	3 months	314	1.62±0.93	0.593
	6 months	308	1.57±0.89	0.771
CAT	Baseline	319	9.81±7.79	
	3 months	319	8.97±7.58	0.001
	6 months	319	8.69±7.35	0.001
SGRQ	Baseline	321	1,113.26±707.66	
	3 months	321	1,082.19±712.96	0.234
	6 months	323	1,048.36±752.31	0.074
SGRQ%	Baseline	321	34.74±22.08	
	3 months	321	33.78±22.25	0.234
	6 months	323	32.72±23.48	0.074
Symptoms	Baseline	321	45.25±19.54	
	3 months	321	44.11±19.81	0.210
	6 months	323	42.04±20.29	0.004
Activity	Baseline	321	49.45±26.54	
	3 months	321	47.83±27.66	0.167
	6 months	323	46.26±28.34	0.038
Impact	Baseline	321	22.41±24.74	
	3 months	321	21.88±23.83	0.567
	6 months	323	21.48±25.32	0.467

COPD: chronic obstructive pulmonary disease; SD: standard deviation; mMRC: modified Medical Research Council; CAT: COPD Assessment Test; SGRQ: St. George's Respiratory Questionnaire.

Table 3. Comparison of clinical outcomes according to baseline CAT ≥10

Measure	Time point	CAT <10	CAT ≥10	Group effect (F/Wald χ^2, df, p-value)	Time effect (F/Wald χ^2, df, p-value)	Time×Group (F/Wald χ^2, df, p-value)
CAT	Baseline	4.82±2.30	17.53±6.84	F=354.9, df=1, p<0.001	F=18.03, df=2, p<0.001	F=32.80, df=2, p<0.001
	3 months	4.98±3.31	15.07±8.13			
	6 months	5.42±3.98	13.82±8.35			
CAT responder*	Baseline	-	-	χ^2=30.5, df=1, p<0.001	χ^2=11.6, df=1, p=0.001	χ^2=0.10, df=1, p=0.749
	3 months	47/197 (23.9)	69/126 (54.8)			
	6 months	58/197 (29.4)	79/126 (62.7)			
mMRC	Baseline	1.24±0.59	2.16±0.99	F=111.15, df=1, p<0.001	F=0.71, df=2, p=0.492	F=2.47, df=2, p=0.086
	3 months	1.28±0.68	2.14±1.01			
	6 months	1.29±0.69	2.03±0.99			
SGRQ	Baseline	24.14±11.73	51.38±24.21	F=13.00, df=1, p <0.001	F=4.318, df=2, p=0.014	F=8.09, df=2, p<0.001
	3 months	24.89±13.42	47.71±25.96			
	6 months	25.22±15.62	44.42±28.42			
SGRQ responder†	Baseline	-	-	χ^2=15.7, df=1, p<0.001	χ^2=10.5, df=1, p=0.001	χ^2=4.6, df=1, p=0.032
	3 months	47/197 (23.9)	57/126 (45.2)			
	6 months	57/197 (28.9)	59/126 (46.8)			
Acute exacerbation	Baseline	0.08±0.29	0.14±0.39	F=8.412, df=1, p=0.004	F=6.88, df=2, p=0.001	F=0.034, df=2, p=0.966
	3 months	0.02±0.13	0.06±0.24			
	6 months	0.01±0.11	0.06±0.25			

Values are presented as mean±standard deviation or number (%).
*Defined as a patient who showed a decrease of ≥2 points in the CAT score from baseline. †Defined as a patient with a decrease of ≥4 points from baseline in the total SGRQ score.
CAT: COPD Assessment Test; mMRC: modified Medical Research Council; SGRQ: St. George's Respiratory Questionnaire.

- Mepolizumab: Exacerbations ↓ , quality of life, improved symptoms ~~↑~~
- Dupilumab: Exacerbations ↓ , type 2 inflammatory biomarkers ↓ ,
  lung function ↑ , quality of life ↑

- Tezepelumab: Exacerbations ~~↓~~ (overall population)
  Potential efficacy (BEC ≥ 150 cells/ul)

- Benralizumab: treatment failure ↓ , improved symptoms ↑
  more than standard care (steroid) in acute eosinophilic exacerbations

- Tozorakimab: lung function ~~↑~~, exacerbations ~~↓~~ (overall population)
  Potential efficacy (≥ 2 exacerbations)

- Ensifentrine: exacerbations ↓, delays the time to first exacerbation
  + LAMA, LABA, ICS

- Triple therapy: cardiovascular events ↓
  severe cardiopulmonary events ↓ than dual tx.
  Real world - major adverse cardiovascular events ↑
  (single-inhaler triple therapy > LABA-ICS)

- ICS: High-dose fluticasone significantly increased sputum bacterial load compared to budesonide.

- Azithromycin: responder
  SGRQ ↓ , Hb ↓ ,
  WBC ↑ , CRP ↑ , FVC ↑

- PDE5 Inhibitor (with PH): transplant-free survival ↑

- OM-85: respiratory symptoms ↑ ,
  quality of life ↑ (CAT score ≥ 10)