SNUH 분당서울대학교병원
SEOUL NATIONAL UNIVERSITY BUNDANG HOSPITAL

COPD KOREA: Year in review 2024
COPD medical treatment

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- Oral medication
  - Steroid, bisoprolol, NAC, mirtazapine
- Inhaler
  - Ensifentrine, treprostinil, ICS, NAC, nebulized interferon beta-1
- Biologics
  - Dupilumab, tezepeblumab, tozorakimab

Oral medication

- Steroid
  - STARR2 study
- Bisoprolol
  - The BICS study
- N-acetylcysteine
- Mirtazapine
  - BETTER-B study

Prednisolone for AECOPD, eosinophil guided

Blood eosinophil-guided oral prednisolone for COPD exacerbations in primary care in the UK (STARR2): a non-inferiority, multicentre, double-blind, placebo-controlled, randomised controlled trial

Sanjay Ramakrishnan, Helen Jeffers, Beverly Langford-Wiley, Joanne Davies, Samantha J Thulborn, Mahdi Mahdi, Christine A'Court, Ian Binnian, Stephen Bright, Simon Cartwright, Victoria Glover, Alison Law, Robin Fox, Adam Jones, Christopher Davies, David Copping, Richard EK Russell, Mona Bafadhel

Lancet Respir Med 2024 Jan; 12: 67–77

Oral prednisolone-STARR2 design

STARR2 design

From Nov 6, 2017, to April 30, 2020

Participants

- Recruited from **14 primary care practices in the UK**
- Diagnosis of COPD with **≥ 1 exacerbation in the prior year**
- Screened after alerting study team or practice of **symptoms c/w COPD exacerbation**
- Randomized if **clinical review by PCP** confirmed a COPD exacerbation

Randomization - Blood eosinophil-guided treatment (BET) vs standard care treatment (ST)

BET arm n=47
- Eos ≥ 2%: prednisolone 30 mg daily x 14 days
- Eos < 2%: matching placebo daily x 14 days

ST arm n=46
- prednisolone 30 mg daily x 14 days

+ doxycycline 200 mg daily x 7 days

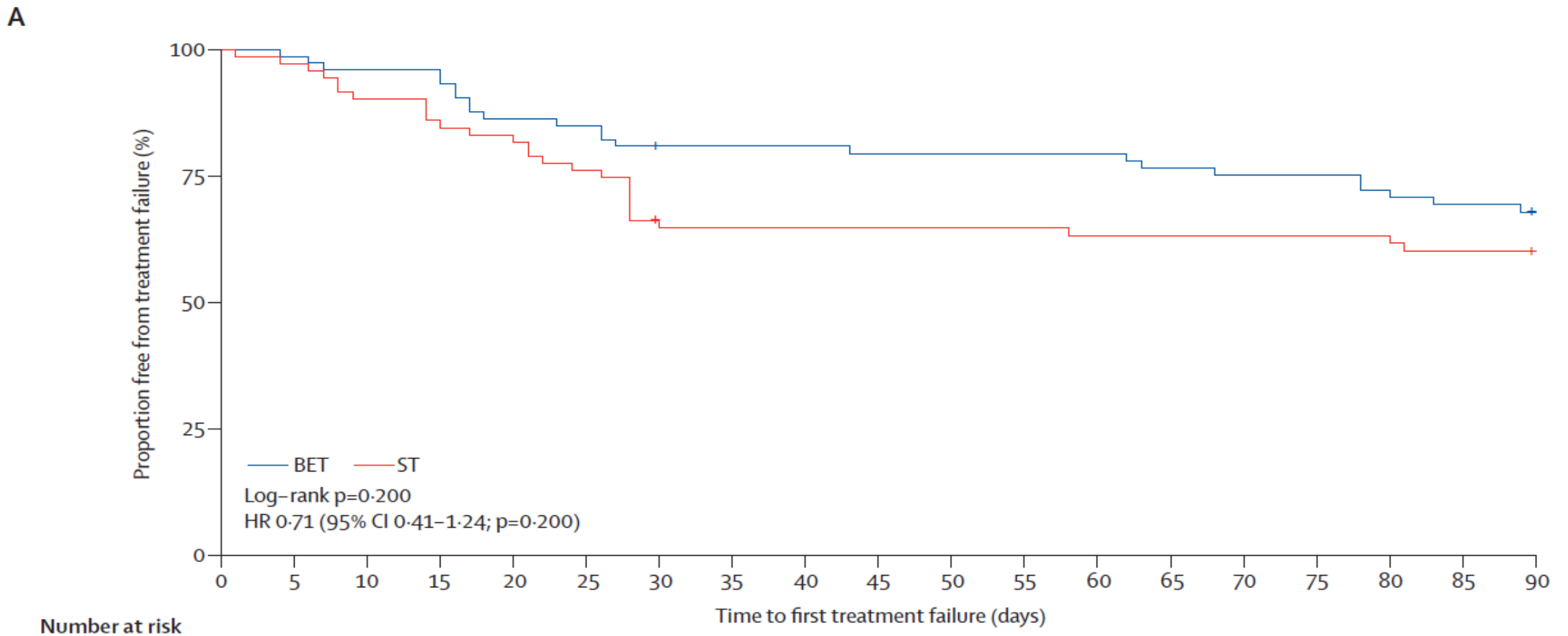
Primary outcome - Treatment failure

Need for re-treatment of exacerbation, hospitalization for any cause or death within 30 days

ATS 2024

Lancet Respir Med 2024 Jan; 12: 67–77

No difference of time to first treatment failure



Lancet Respir Med 2024 Jan; 12: 67–77

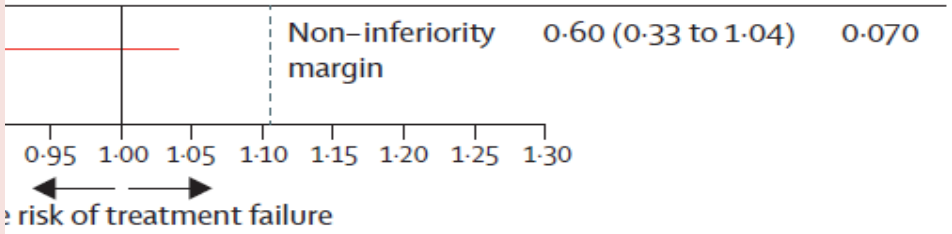
BET was non-inferior to ST

B

	Standard care treatment group (n=71)	Blood eosinophil-directed group (n=73)	p value
Change in COPD Assessment Test score	7 (6 to 8)	8 (6 to 10)	0·271
Change in FEV_1, L	0·14 (0·07 to 0·21)	0·17 (0·10 to 0·24)	0·548
Change in VAS total, mm*	126 (99 to 152)	127 (103 to 150)	0·971
Change in VAS cough, mm	25 (19 to 31)	26 (20 to 32)	0·828
Change in VAS dyspnoea, mm	22 (15 to 29)	23 (17 to 29)	0·772
Change in VAS sputum production, mm	26 (19 to 33)	24 (18 to 30)	0·726
Change in VAS sputum purulence, mm	26 (18 to 34)	25 (19 to 31)	0·857
Change in VAS wheeze, mm	27 (21 to 33)	26 (21 to 32)	0·933
Geometric mean change in leukocytes (95% CI), 10^9 cells per L	2·7 (1·5 to 3·9)	1·7 (0·9 to 2·5)	0·167
Geometric mean change in neutrophils (95% CI), 10^9 cells per L	1·8 (0·9 to 2·7)	1·3 (0·7 to 1·9)	0·313
Geometric mean change in eosinophils (95% CI), 10^9 cells per L	−0·2 (−0·3 to −0·1)	−0·2 (−0·2 to −0·1)	0·535
Median Change in C-reactive protein, g/L	−10 (IQR −32 to −4)	−5 (IQR −15 to −3)	0·058

Data are mean (95% CI) unless otherwise stated. A negative value in FEV_1, COPD Assessment Test score, and VAS indicates worsening (reduction). COPD=chronic obstructive pulmonary disease. VAS=visual analogue scale. *VAS total is the total of each of the VAS domains.

Events in BET Events in ST RR (95% CI) p value



Lancet Respir Med 2024 Jan; 12: 67–77

No difference lung function nor symptom

	Standard care treatment group (n=71)	Blood eosinophil-directed group (n=73)	p value
Change in COPD Assessment Test score	7 (6 to 8)	8 (6 to 10)	0·271
Change in FEV_1, L	0·14 (0·07 to 0·21)	0·17 (0·10 to 0·24)	0·548
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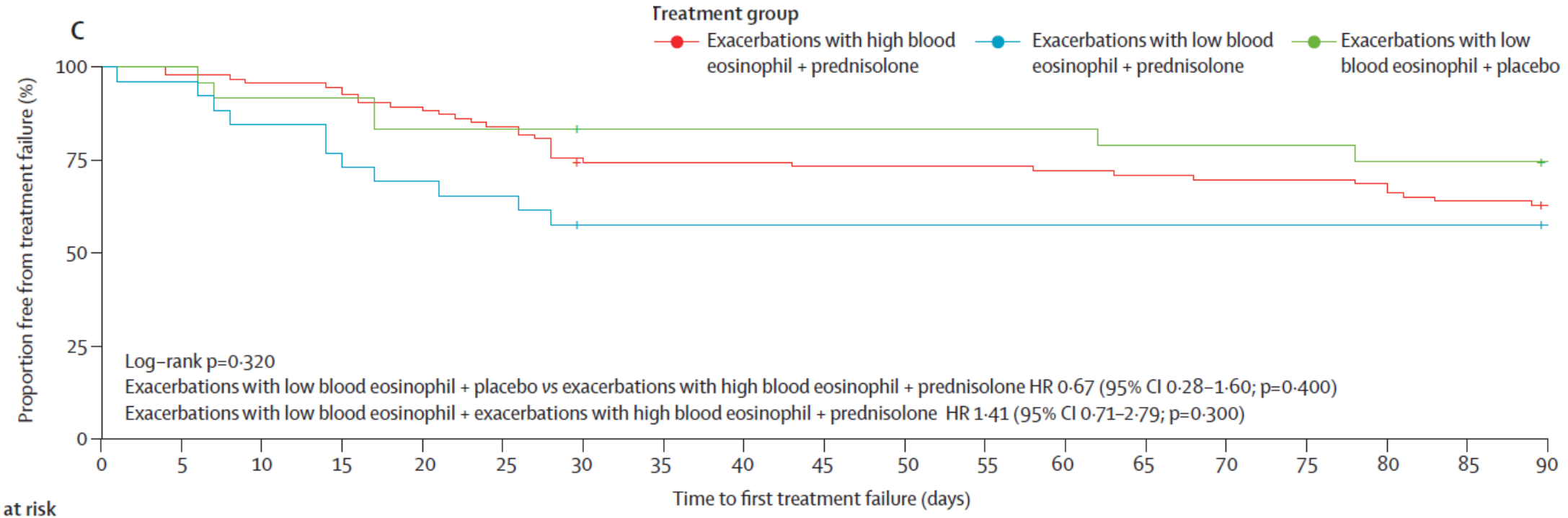
Median Change in C-reactive protein, g/L	−10 (IQR −32 to −4)	−5 (IQR −15 to −3)	0·058

Low (<2%) eosinophil count + placebo (n=24)	Low (<2%) eosinophil count + prednisolone (n=26)	High (≥2%) eosinophil count + prednisolone (n=94)	p value
−2 (−6 to 2)	7 (5 to 9)	9 (7 to 10)	0·120
−0·05 (−0·17 to 0·07)	−0·09 (−0·26 to 0·08)	0·19 (0·13 to 0·25)	0·124*
100 (61 to 139)	117 (74 to 160)	137 (115 to 158)	0·265
23 (12 to 33)	26 (16 to 37)	26 (21 to 32)	0·826
22 (12 to 32)	18 (5 to 30)	25 (19 to 30)	0·476
15 (6 to 24)	26 (13 to 39)	28 (22 to 33)	0·101
20 (9 to 30)	27 (14 to 39)	27 (21 to 33)	0·490
20 (13 to 28)	20 (13 to 30)	30 (24 to 35)	0·105
−0·4 (−1·6 to 0·7)	2·5 (0·8 to 4·3)	2·9 (2·0 to 3·8)	0·003
−0·6 (−1·4 to 0·3)	1·3 (−0·2 to 2·8)	2·2 (1·5 to 2·8)	0·001*
0·0 (−0·1 to 0·1)	0·0 (−0·1 to 0·1)	−0·3 (−0·4 to −0·2)	<0·001*
−5 (−9 to −4)	−20 (−50 to −6)	−8 (−17 to −3)	0·058

Lancet Respir Med 2024 Jan; 12: 67–77

Low eos+steroid tend to more treatment failure



Number at risk (number censored) Treatment group																		
Exacerbations with high blood eosinophil + prednisolone	94 (0)	92 (0)	90 (0)	89 (0)	84 (0)	79 (0)	71 (6)	64 (6)	64 (6)	63 (6)	63 (6)	63 (6)	62 (6)	61 (6)	60 (6)	60 (6)	59 (6)	55 (6)	54 (60)
Exacerbations with low blood eosinophil + placebo	24 (0)	24 (0)	22 (0)	22 (0)	20 (0)	20 (0)	20 (1)	19 (1)	19 (1)	19 (1)	19 (1)	19 (1)	18 (1)	18 (1)	18 (1)	18 (1)	17 (1)	17 (1)	17 (18)
Exacerbations with low blood eosinophil + prednisolone	26 (0)	25 (0)	22 (0)	20 (0)	18 (0)	17 (0)	15 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (1)	14 (15)

Lancet Respir Med 2024 Jan; 12: 67–77

Bisoprolol for COPD at high-risk AE

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Research

JAMA | Original Investigation

Bisoprolol in Patients With Chronic Obstructive Pulmonary Disease at High Risk of Exacerbation

The BICS Randomized Clinical Trial

Graham Devereux, MD; Seonaidh Cotton, PhD; Mintu Nath, PhD; Nicola McMeekin, PhD; Karen Campbell, MSc; Rekha Chaudhuri, MD; Gourab Choudhury, MD; Anthony De Soyza, PhD; Shona Fielding, PhD; Simon Gompertz, MD; John Haughney, MD; Amanda J. Lee, PhD; Graeme MacLennan, MSc; Alyn Morice, MD; John Norrie, MSc; David Price, MD; Philip Short, MD; Jorgen Vestbo, MD; Paul Walker, MD; Jadwiga Wedzicha, MD; Andrew Wilson, MD; Olivia Wu, PhD; Brian J. Lipworth, MD

JAMA. 2024 May 19 ;332(6):462-470.

Bisoprolol- The BICS study design

- **Participants**
  - 76 UK sites (45 primary care & 31 secondary care)
  - Diagnosis with COPD with ≥2 exacerbation history in prior year
  - Exclusion
    - Asthma, resting HR<60/min, BP<100mmHg, medication with CCB, anti-arrhythmic drug
    - Condition for which b-blocker are guideline recommended (HF, recent ACS)
- **Randmomization (double blind RCT)**
  - Bisoprolol: 1.25mg tablets (Tiofarma B.V) for 52 weeks, 4 up titration (7wks)-> 1.25mg, 2.5mg, 3.75mg, 5mg
  - Placebo
- **Primary outcome**
  - Patients reported AECOPD requiring steroid and antibiotics within 52 weeks

JAMA. 2024 May 19 ;332(6):462-470.

Study flow and baseline of BICS

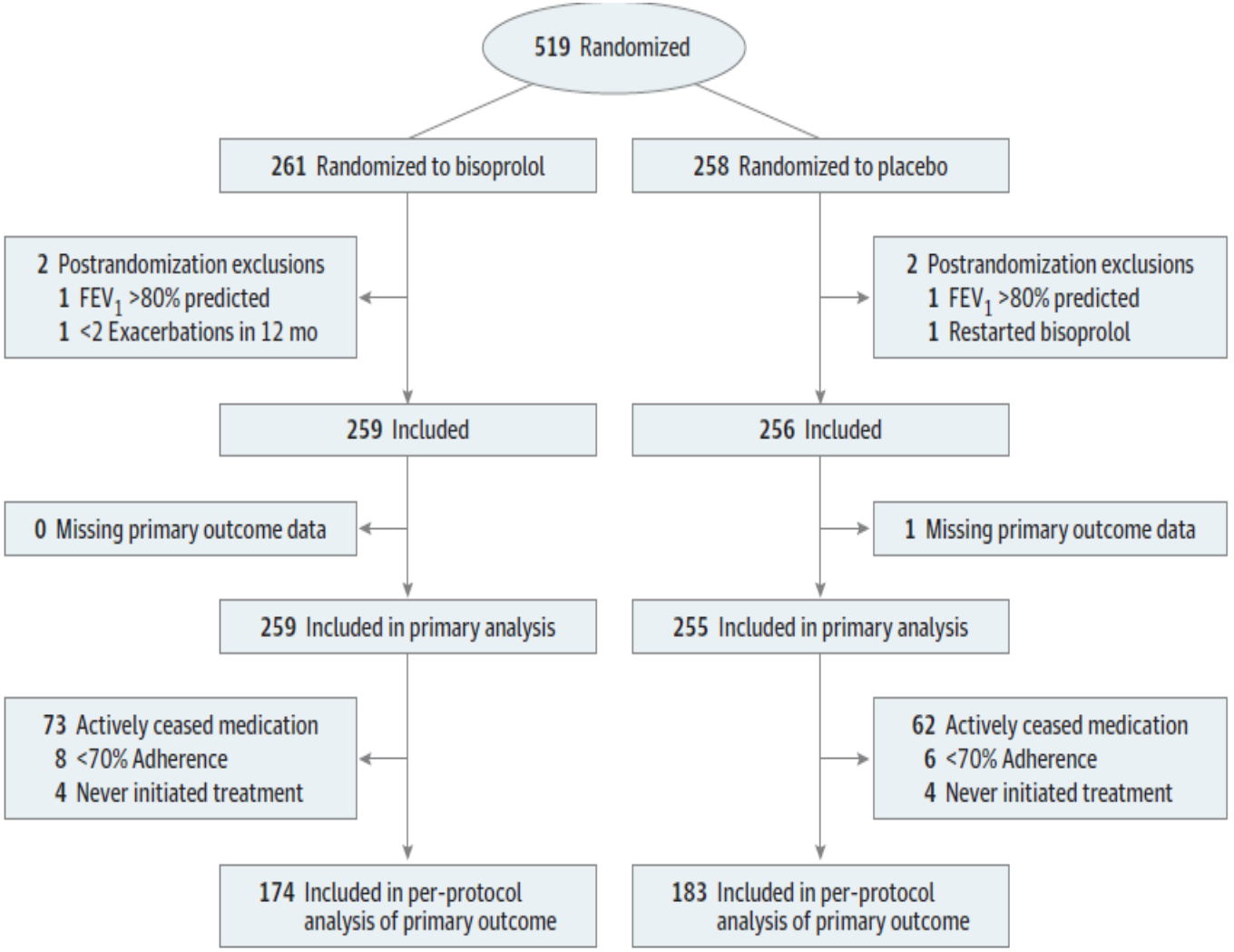


Table 1. Baseline Characteristics of Patients

	No. (%)	
	Bisoprolol (n = 259)	Placebo (n = 256)
Age, mean (SD), y	67.7 (8.0)	67.7 (7.7)
Male, No. (%)	134 (51.7)	140 (54.7)
Female, No. (%)	125 (48.3)	116 (45.3)
Body mass index, mean (SD) [No.]	26.4 (5.7) [258]	27.2 (6.6) [254]
Currently smokes, No. (%)	78 (30.1)	82 (32.0)
Pack-years smoking, mean (SD) [No.]	45.1 (24.4) [259]	45.2 (26.0) [255]
Exacerbations in last 12 mo, mean (SD)[a]	3.5 (1.8)	3.6 (2.1)
Exacerbations with hospitalization in last 12 mo, mean (SD)	0.4 (0.8)	0.5 (1.1)
COPD assessment test, mean (SD)[c]	22.7 (8.1)	22.0 (8.0)
Resting heart rate, mean (SD), /min	82.2 (11.8)	80.3 (12.4)
Systolic blood pressure, mean (SD), mm Hg	137.0 (18.9)	135.8 (17.7)
Diastolic blood pressure, mean (SD), mm Hg	79.9 (10.7)	79.6 (9.5)
Hypertension, No. (%)	73 (28.2)	79 (30.9)
Anxiety or depression treated in last 5 y, No. (%)	71 (27.4)	77 (30.1)

JAMA. 2024 May 19 ;332(6):462-470.

Bisoprolol did not reduce self-reported AECOPD

Figure 2. Primary and Secondary Outcomes Expressed as Adjusted Incidence Rate Ratios (IRRs) or Hazard Ratios (HRs)

	No. of events		
	Bisoprolol (PY = 257)	Placebo (PY = 248)	Adjusted IRR or HR (95% CI)
Primary outcome			
COPD exacerbations (IRR)	526	513	0.97 (0.84-1.13)
Secondary outcomes			
COPD hospital admissions (IRR)	71	68	1.00 (0.67-1.50)
Non-COPD hospital admissions (IRR)	47	32	1.47 (0.88-2.55)
All-cause mortality (HR)	11	13	0.77 (0.34-1.73)

2.03/yr 2.01/yr

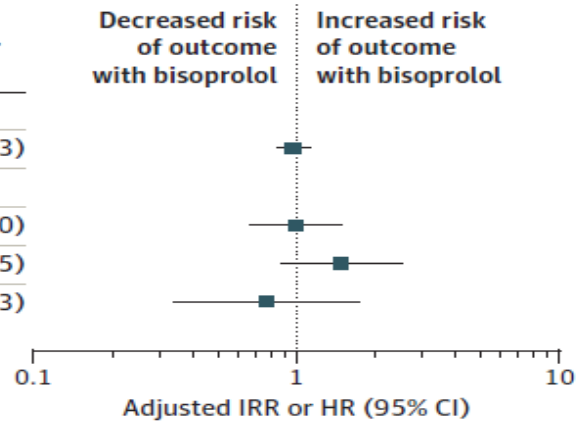


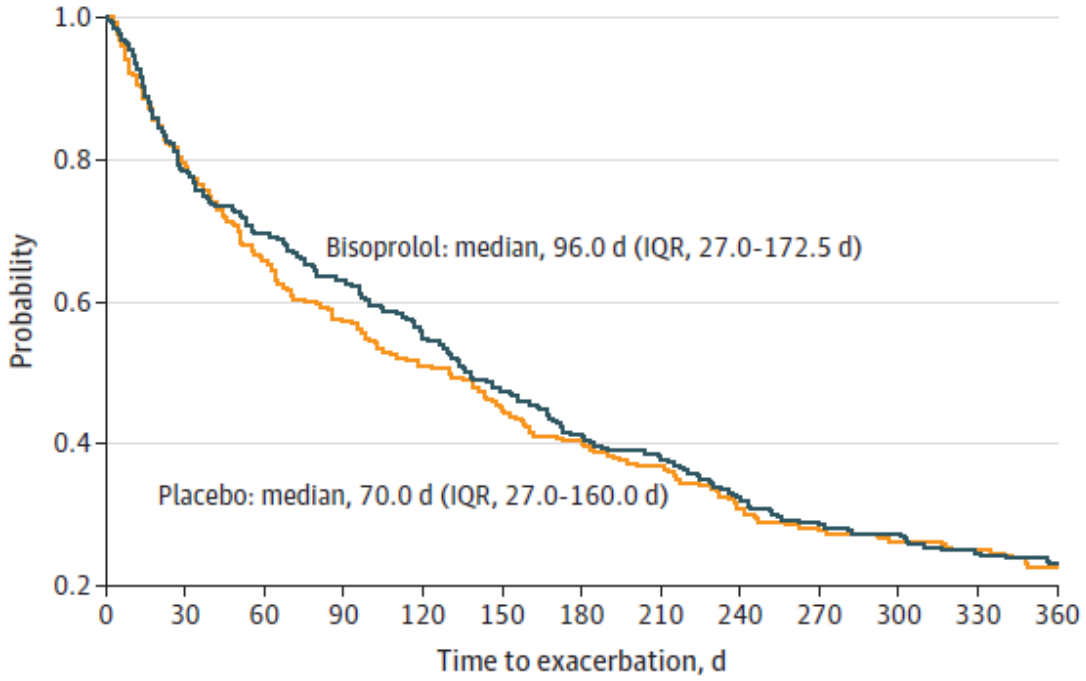
Table 2. Secondary Outcomes for Patients Randomized to Bisoprolol and Placebo

	FEV_1 % predicted			CAT score[a]			TDI[b]		
	Bisoprolol, %	Placebo, %	Adjusted mean difference (95% CI)[c]	Bisoprolol, %	Placebo, %	Adjusted mean difference (95% CI)[c]	Bisoprolol	Placebo	Adjusted mean difference (95% CI)[d]
Baseline									
Mean (SD) [No.]	49.3 (19.0) [256]	51.3 (19.1) [251]	NA	22.7 (8.12) [259]	22.0 (8.04) [255]	NA	NA	NA	NA
26 wk									
Mean (SD) [No.]	47.8 (18.8) [92]	47.0 (19.3) [87]	−0.75 (−3.61 to 2.10)	20.3 (8.85) [219]	18.7 (9.25) [222]	1.64 (0.05 to 3.23)	−0.83 (2.78)	−0.34 (2.91)	−0.62 (−1.16 to −0.07)
P value			.61			.04			.03
52 wk									
Mean (SD) [No.]	43.3 (20.8) [30]	53.1 (18.9) [21]	−4.53 (−10.2 to 1.16)	19.4 (8.86) [207]	19.8 (9.40) [202]	−0.59 (−2.26 to 1.07)	−1.73 (3.66)	−1.01 (3.58)	−0.73 (−1.44 to −0.01)
P value			.13			.48			.05

JAMA. 2024 May 19 ;332(6):462-470.

Bisoprolol did not reduce self-reported AECOPD

Figure 3. Freedom From Exacerbation of Chronic Obstructive Pulmonary Disease in the 2 Trial Groups



Placebo													
No. at risk	255	203	168	146	130	115	103	94	79	72	67	64	58
No. of events	0	54	87	109	125	141	153	161	176	184	188	191	197
Bisoprolol													
No. at risk	259	203	180	163	145	123	107	99	84	75	71	64	60
No. of events	0	56	79	96	117	136	153	161	176	185	188	195	199

JAMA. 2024 May 19 ;332(6):462-470.

High dose N-acetylecysteine on AECOPD

nature communications

Article

https://doi.org/10.1038/s41467-024-51079-1

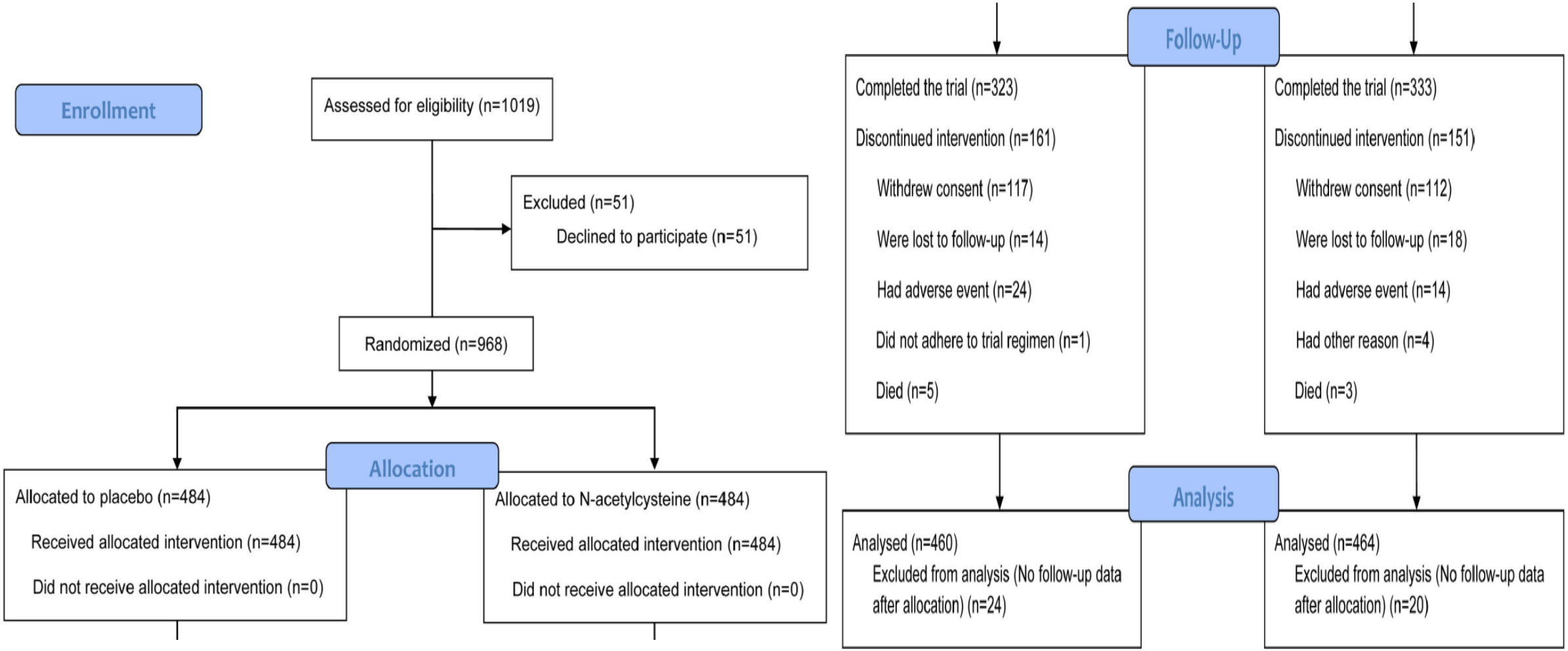
Effect of high-dose *N*-acetylcysteine on exacerbations and lung function in patients with mild-to-moderate COPD: a double-blind, parallel group, multicentre randomised clinical trial

Nature Communications 2024 July 15:8468

High dose N-acetylecysteine study design

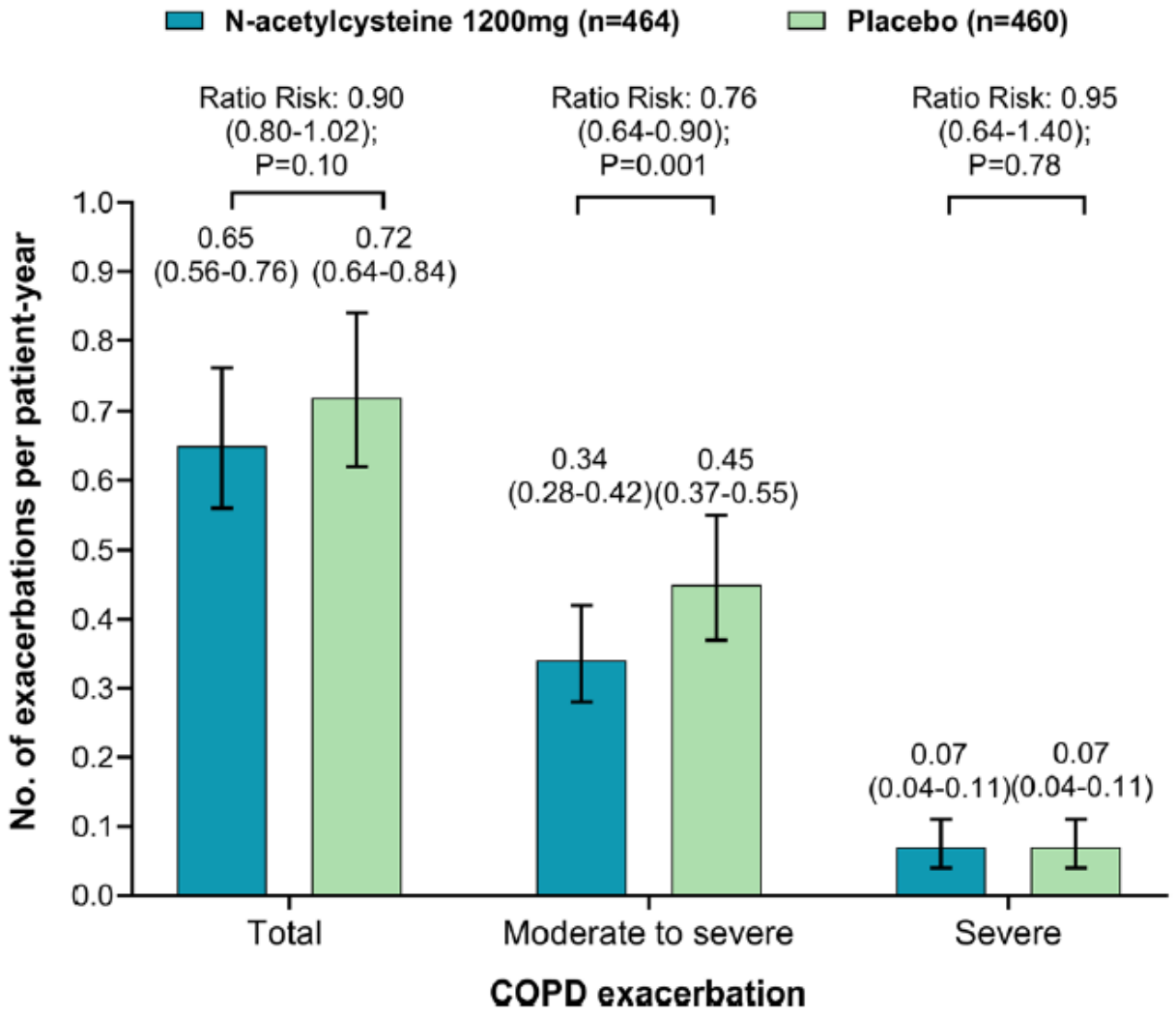
- **Participants**
  - China 24 site, from Sep 2017 to Jan 2022
  - Diagnosis with COPD with mild to moderate (GOLD stage 1-2)
  - Exclusion
    - AECOPD within 1month, long term use steroid or antibiotics, long term use oxygen
    - Long term treatment of NAC over 3months before trial, lung cancer, bronchiectasis, pneumoconiosis, asthma, ILD, other restrictive lung disease
- **Randmomization (double blind RCT, 1:1)**
  - High dose NAC: 600mg twice daily for two years
  - Placebo for two years
- **Primary outcome**
  - coprimary outcomes were the annual rate of total (mild, moderate and severe) exacerbations and the difference in FEV1 before bronchodilator use at 24 months from baseline

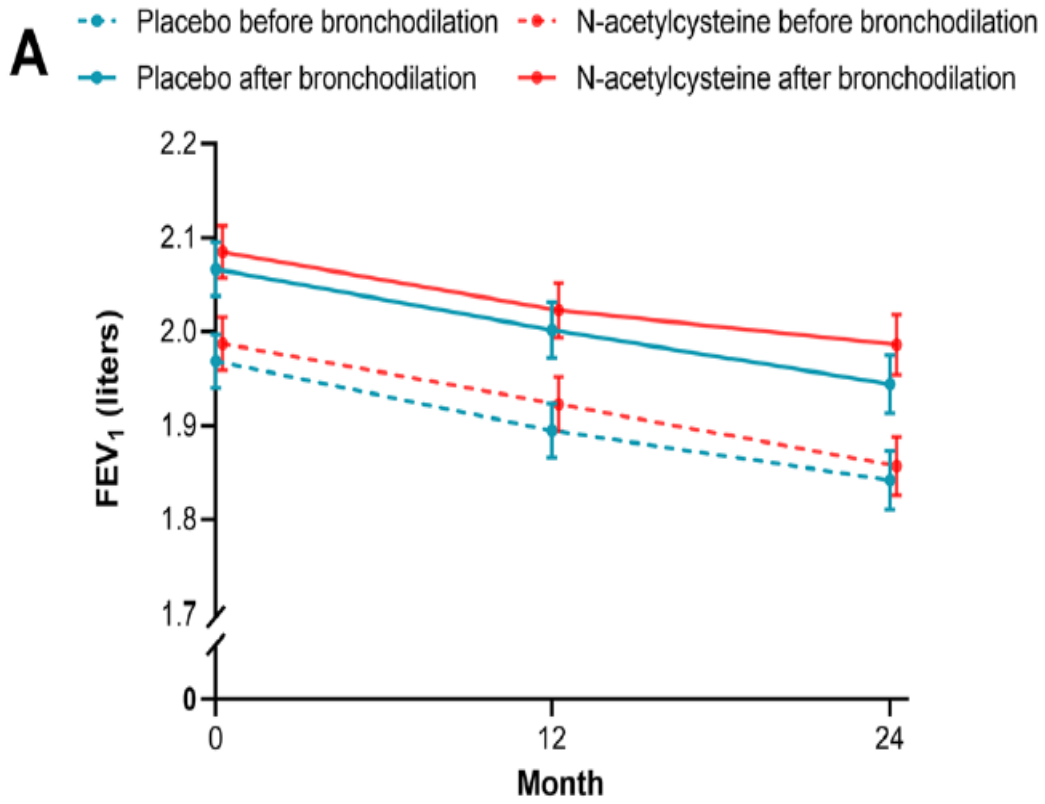
Study flow chart of high dose NAC on AECOPD



Nature Communications 2024 July 15:8468

No difference of AE rate and FEV1 decline rate





Nature Communications 2024 July 15:8468

Mirtazapine to reduce breathlessness in COPD or ILD

Mirtazapine to alleviate severe breathlessness in patients with COPD or interstitial lung diseases (BETTER-B): an international, multicentre, double-blind, randomised, placebo-controlled, phase 3 mixed-method trial

*Irene J Higginson, Sarah T Brown, Adejoke O Oluyase, Peter May, Matthew Maddocks, Massimo Costantini, Sabrina Bajwah, Charles Normand, Claudia Bausewein, Steffen T Simon, Karen Ryan, David C Currow, Miriam J Johnson, Simon P Hart, Hannah Mather, Malgorzata Krajnik, Silvia Tanzi, Luca Ghirotto, Charlotte E Bolton, Piotr Janowiak, Elena Turola, Caroline J Jolley, Geraldine Murden, Andrew Wilcock, Bobbie Farsides, Julia M Brown, BETTER-B consortium**

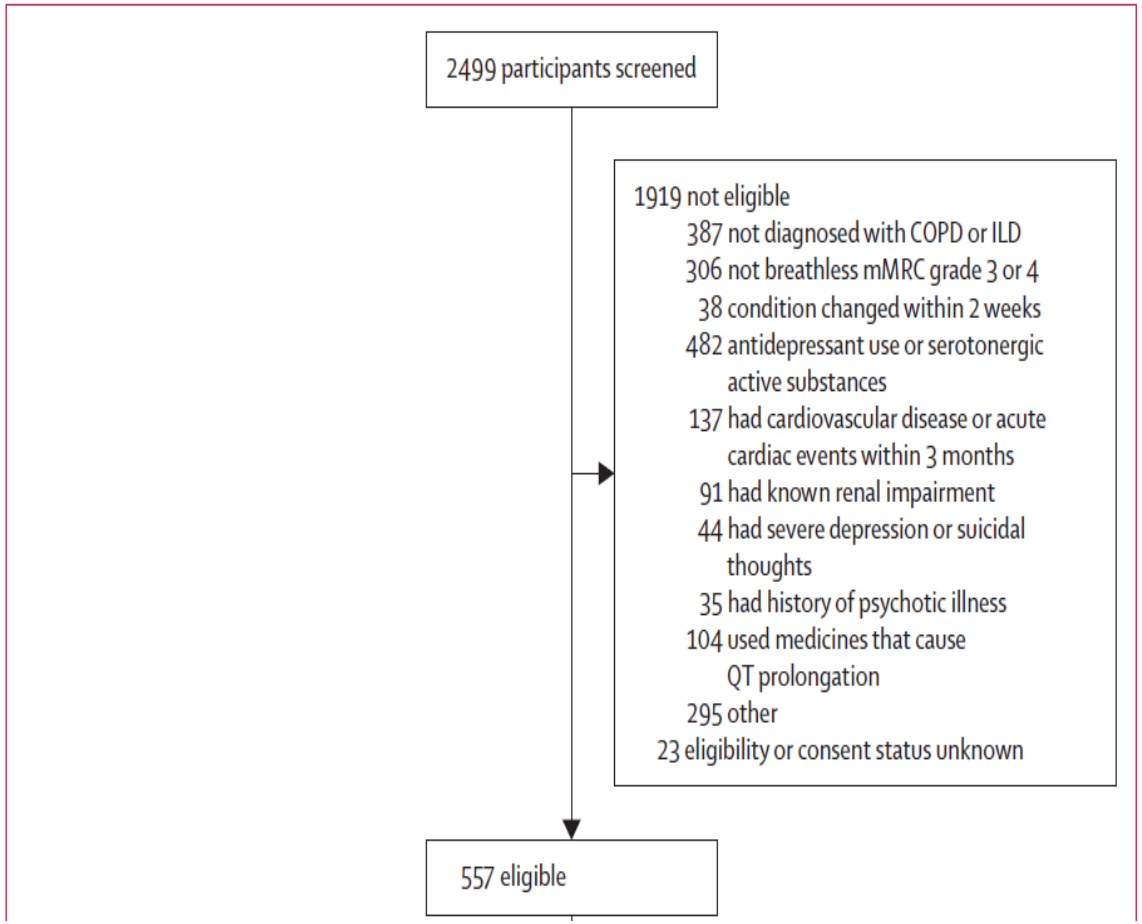
Lancet Respir Med 2024 Sep;12: 763–74

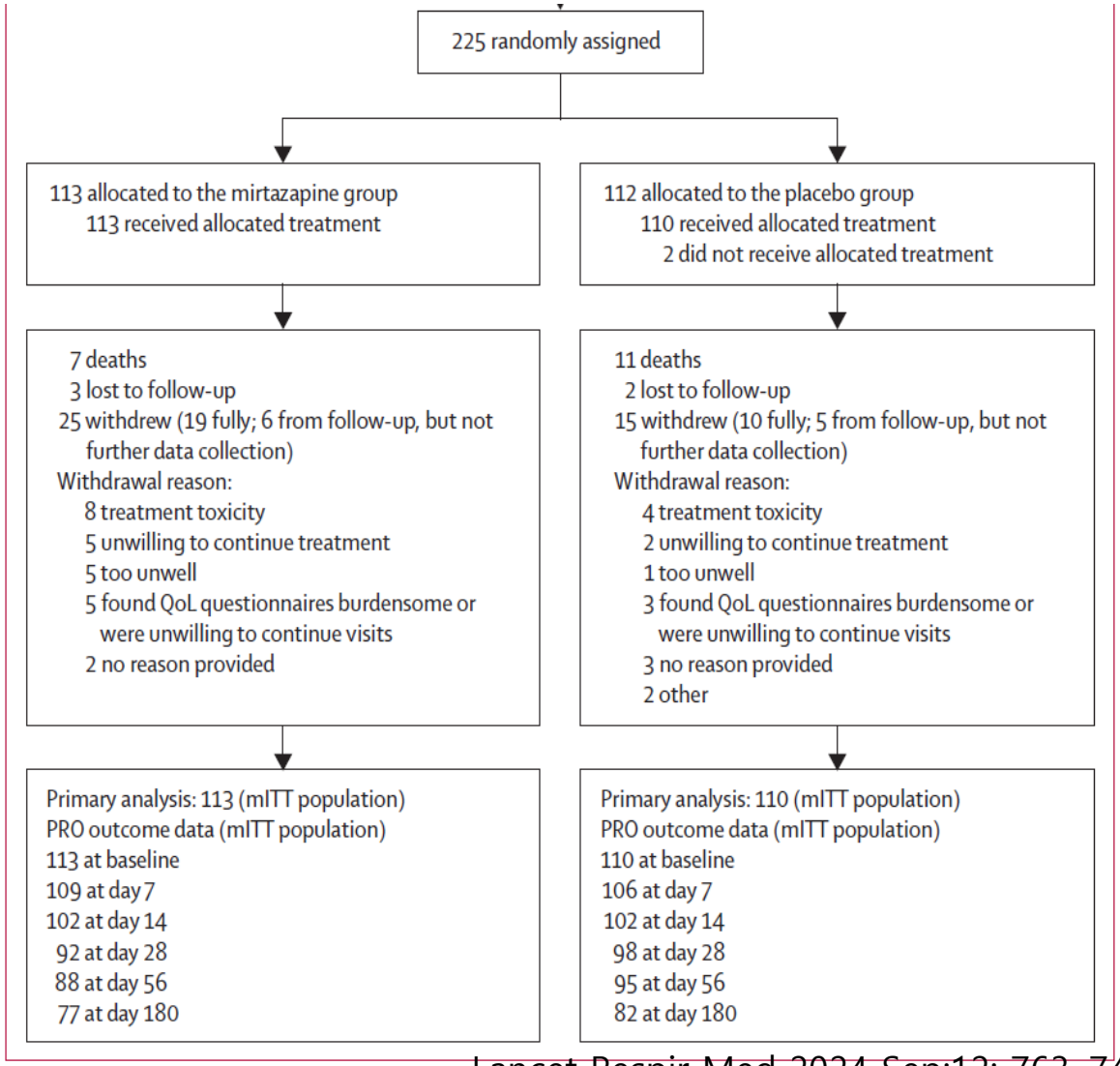
BETTER-B study design

- **Participants**
  - 16 centers in seven countries, Feb 4, 2021 and March 28, 2023
  - COPD or ILD with mmRC grade 3,4 (**71% with COPD**)
  - Exclusion
    - Existing antidepressant use (But opioid permit)
- **Randmomization (double blind RCT, 1:1)**
  - Oral mirtazapine 15mg ->45mg for 56 days, tapered at treatment end
  - Placebo for 56 days
- **Primary outcome**
  - Self reported worst breathlessness in the preceding 24 h measured on a 0–10 numerical rating scale (NRS), at 56 days post-treatment start, with follow-up to 180 days.

Lancet Respir Med 2024 Sep;12: 763–74

Flow chart of mirtazapine study





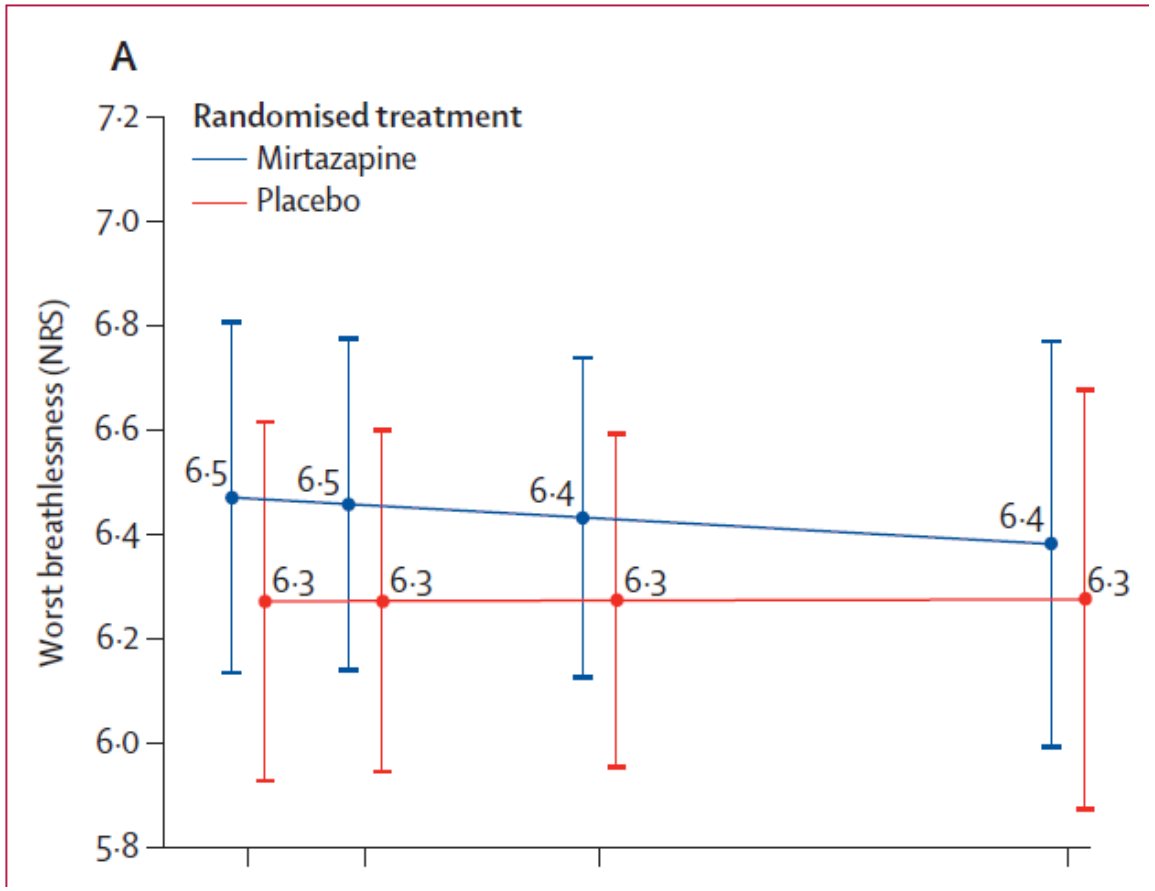
Lancet Respir Med 2024 Sep;12: 763–74

Baseline characteristics of mirtazapine study

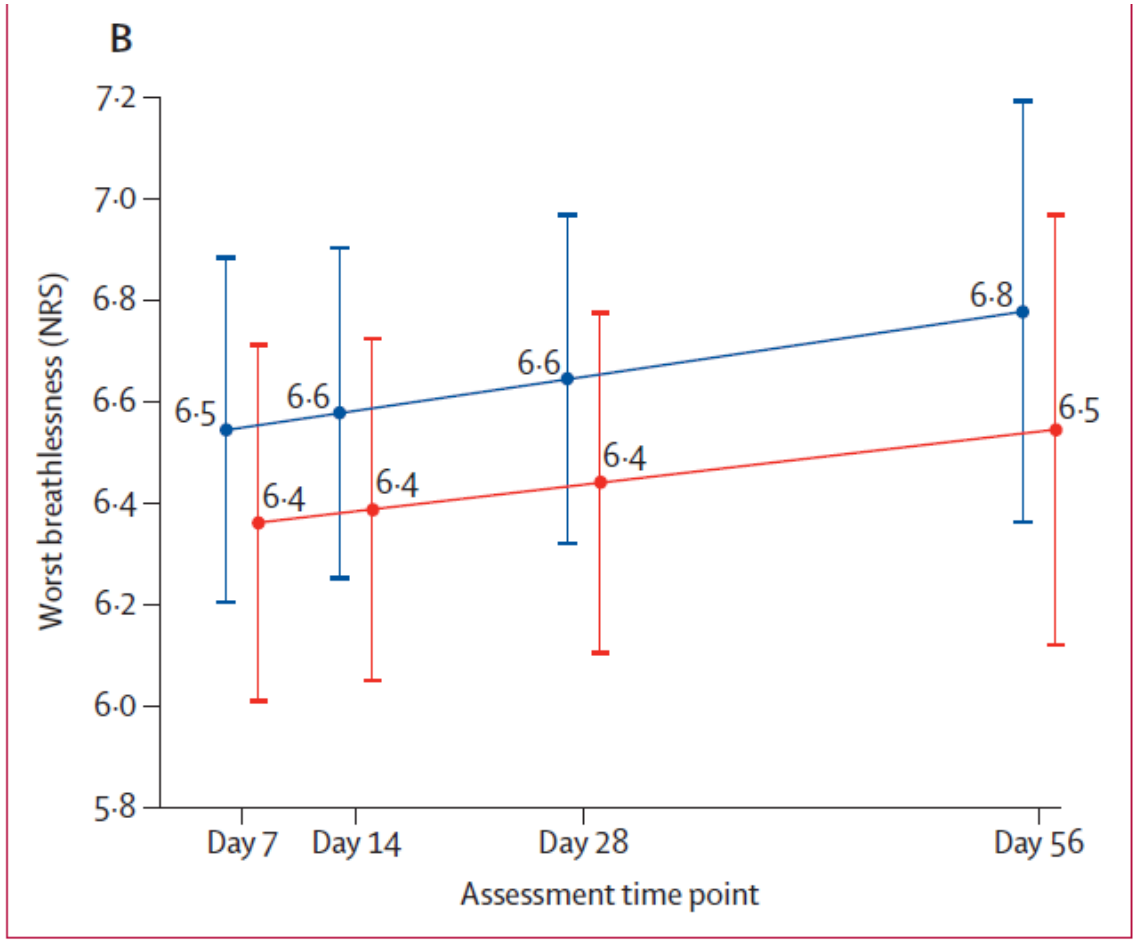
	Mirtazapine (n=113)	Placebo (n=112)	Total (n=225)
Age, years	74·0 (67·0–78·0)	73·0 (66·0–78·0)	74·0 (67·0–78·0)
Gender			
Male	73 (65%)	75 (67%)	148 (66%)
Female	40 (35%)	37 (33%)	77 (34%)
Ethnicity or origin*			
Europe (without Germany) (n=169)			
White—White British	46 (41%)	48 (43%)	94 (42%)
White—Irish	12 (11%)	10 (9%)	22 (10%)
White—Italian	16 (14%)	12 (11%)	28 (12%)
White—Slavic	2 (2%)	0	2 (1%)
White—Other†	6 (5%)	11 (10%)	17 (8%)
Black/African/Caribbean—Caribbean	0	1 (1%)	1 (<1%)
Black/African/Caribbean—Other	1 (1%)	0	1 (<1%)
Asian—Indian	2 (2%)	1 (1%)	3 (1%)
Other ethnic group—Don't know	1 (1%)	0	1 (<1%)
Primary diagnosis			
COPD	63 (56%)	61 (55%)	124 (55%)
ILD	50 (44%)	51 (46%)	101 (45%)
HADS anxiety score			
≤10	89 (79%)	88 (79%)	177 (79%)
>10	24 (21%)	24 (21%)	48 (21%)
HADS depression score			
≤10	88 (78%)	88 (79%)	176 (78%)
>10	25 (22%)	24 (21%)	49 (22%)
Taking opioids			
Yes	19 (17%)	17 (15%)	36 (16%)
No	94 (83%)	95 (85%)	189 (84%)
mMRC grade			
Grade 3	75 (66%)	74 (66%)	149 (66%)
Grade 4	38 (34%)	38 (34%)	76 (34%)
Comorbidities			
Yes	95 (84%)	86 (77%)	181 (80%)
No	18 (16%)	26 (23%)	44 (20%)
Charlson index summary score	1·8 (1·3)	1·6 (1·1)	1·7 (1·2)
Integrated Palliative Care Outcome Scale total score	20·8 (9·1)	21·1 (9·7)	20·9 (9·4)
Chronic Respiratory Questionnaire emotional score (7 items)	30·9 (8·6)	30·8 (8·5)	30·8 (8·5)

Lancet Respir Med 2024 Sep;12: 763–74

Mirtazapine no effect on worst breathlessness



Primary analysis



sensitivity analysis

Lancet Respir Med 2024 Sep;12: 763–74

Mirtazapine might cause adverse reaction

	Mirtazapine (n=113)	Placebo (n=110)	Total (n=223)
Number of adverse reactions	215	116	331
Number of participants with one or more adverse reactions	72 (64%)	44 (40%)	116 (52%)
Number of adverse reactions per participant*			
0	41 (36%)	66 (60%)	107 (48%)
1	19 (17%)	17 (15%)	36 (16%)
2	20 (18%)	15 (14%)	35 (16%)
3	13 (12%)	5 (5%)	18 (8%)
4	8 (7%)	4 (4%)	12 (5%)
5	5 (4%)	0	5 (2%)
6	2 (2%)	0	2 (1%)
7	1 (1%)	0	1 (<1%)
8	2 (2%)	2 (2%)	4 (2%)
10	1 (1%)	0	1 (<1%)
15	1 (1%)	0	1 (<1%)
22	0	1 (1%)	1 (<1%)
Number of serious adverse events	11	8	19
Number of participants with one or more serious adverse event	6 (5%)	7 (6%)	13 (6%)
Number of SUSARs	1	0	1
Number of participants with one or more SUSAR	1 (<1%)	..	1 (<1%)
Serious adverse event MedDRA term†			
Cardiac disorders	1/11 (9%)	2/8 (25%)	3/19 (16%)
General disorders and administration site conditions	1/11 (9%)	0	1/19 (5%)
Infections and infestations	3/11 (27%)	2/8 (25%)	5/19 (26%)
Injury, poisoning and procedural complications	1/11 (9%)	1/8 (13%)	2/19 (11%)
Metabolism and nutrition disorders	1/11 (9%)	0	1/19 (5%)
Musculoskeletal and connective tissue disorders	1/11 (9%)	0	1/19 (5%)
Respiratory, thoracic, and mediastinal disorders	3/11 (27%)	1/8 (13%)	4/19 (21%)
Gastrointestinal disorders	0	2/8 (25%)	2/19 (11%)

	Outcome data: mean (SD)			Treatment effect: mirtazapine vs placebo (95% CI)
	Mirtazapine	Placebo	Total	
Acute hospital nights	0·99 (4·39)	0·48 (2·07)	0·74 (3·45)	0·57 (–0·48 to 1·62)
Emergency department admissions	0·10 (0·33)	0·07 (0·36)	0·09 (0·35)	0·02 (–0·07 to 0·12)
Outpatient visits	1·66 (2·63)	1·32 (1·98)	1·49 (2·33)	0·38 (–0·25 to 1·02)
Hours of family care	72·90 (153·29)	58·46 (142·72)	65·71 (148·29)	14·99 (–24·81 to 54·79)

Table 4: Health-care use at the primary endpoint (day 56)

Inhaler

- Ensifentrine (nebulizer)
  - Phosphodiesterase 3 and 4 inhibitor
- Treprostinil
  - Pulmonary hypertension associated with COPD
  - PERFECT study
- ICS
  - Post hoc study of FLAME trial
- N-acetylcysteine
  - The NEWEST study
- Nebulised interferon beta-1

Ensifentrine-ENHANCE design

ENHANCE-1 and -2 design

Participants

- Post-bronchodilator **FEV_1 30-70% predicted**
- **mMRC dyspnea score ≥ 2**
- Maintenance inhaler therapy:
  - **None** (31% and 45% of participants in ENHANCE-1 and -2, respectively)
  - **LABA +/- ICS**
  - **LAMA +/- ICS**

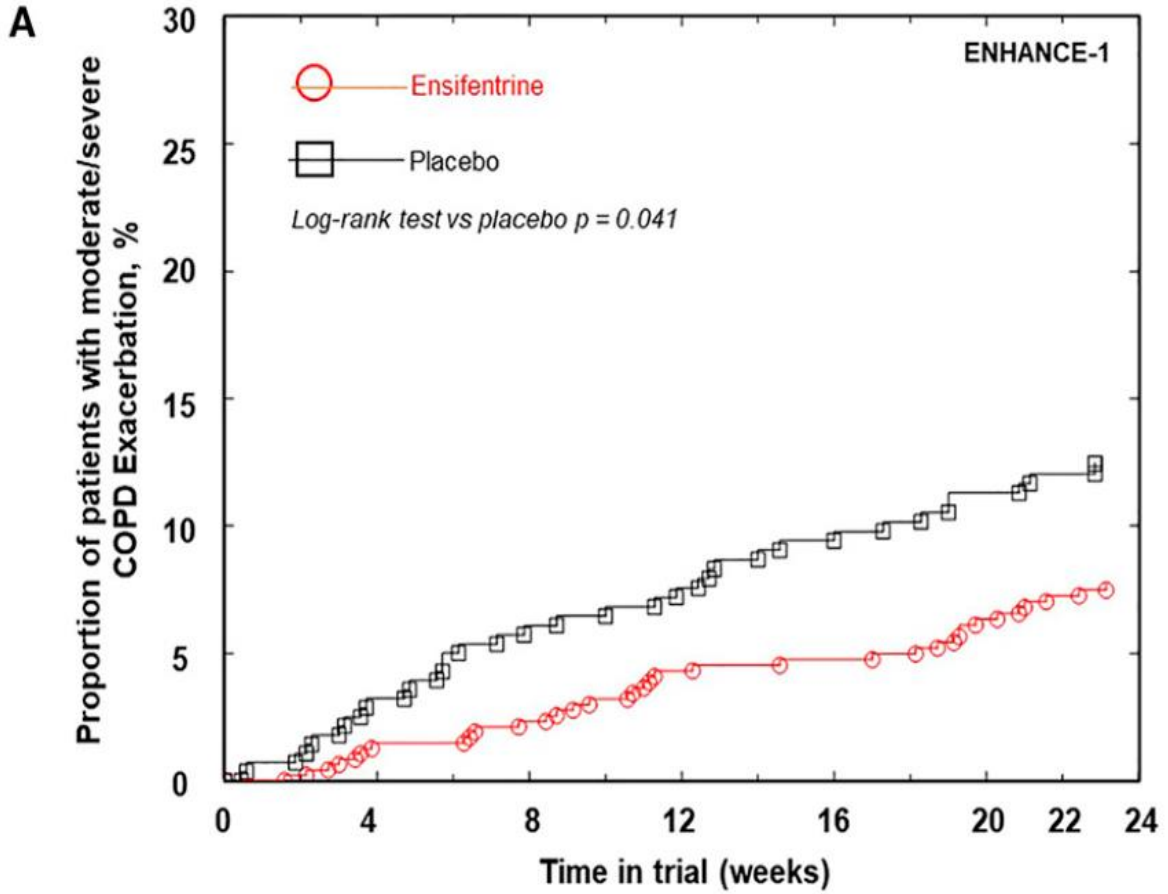
Randomization

Ensifentrine 3 mg twice daily through a nebulizer vs **placebo**

Primary outcome

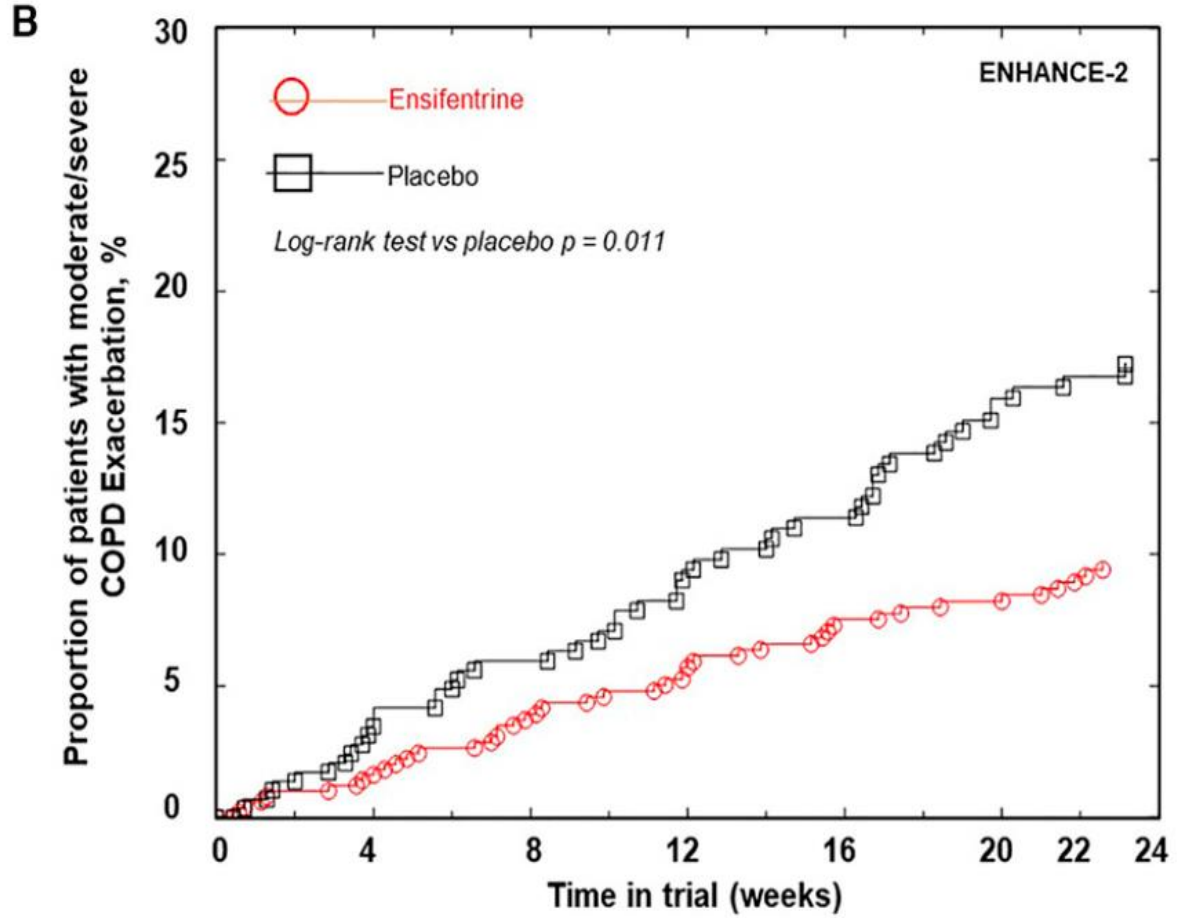
Baseline-to-week 12 change in FEV_1 during the 12 hours after dosing (**FEV_1 AUC_{0-12h}**)

Ensifentrine associated with decreased AE



Number at Risk

Ensifentrine	477	466	453	431	422	412	404	279
Placebo	283	270	258	250	243	235	232	155



Number at Risk

Ensifentrine	498	481	443	422	399	390	380	278
Placebo	291	275	257	232	218	201	196	151

Am J Respir Crit Care Med. 2023 Aug 15;208(4):406-416.

Ensifentrine(Ohtuvayre) approved by FDA

NEJM Journal Watch

DRUG WATCH | GENERAL MEDICINE, AMBULATORY MEDICINE, HOSPITAL MEDICINE

DRUG/DEVICE INFORMATION

August 13, 2024

Ensifentrine: Newly Approved for Maintenance Treatment in Patients with Chronic Obstructive Pulmonary Disease

Steven T. Kariya, MD

Steven T. Kariya, MD

Contributing Editor
NEJM JOURNAL WATCH GENERAL MEDICINE

Biography | Disclosures | Summaries

Ensifentrine (Ohtuvayre) is a novel phosphodiesterase 3 and 4 inhibitor — administered by nebulizer — that was approved by the U.S. FDA for maintenance treatment of COPD (June 26, 2024, Verona pharma)

Careful consideration and adverse reaction of Ohtuvayre

Notable points from the official prescribing information

Ensifentrine is officially approved for maintenance treatment in adults with COPD, without reference to its specific role among other agents. It is administered as 3-mg vials via standard jet nebulizers twice daily. It is not indicated for managing acute exacerbations of COPD or acute bronchospasm. Because "psychiatric adverse reactions, including suicidality" have been reported, clinicians are advised to "carefully weigh risks and benefits" in patients with histories of depression or suicidal thoughts.[3]

Table 1. Adverse Reactions with OHTUVAYRE with incidence ≥ 1% and More Common than Placebo in Patients with COPD in the Pooled 24-Week Safety Population (ENHANCE-1 and ENHANCE-2)

Adverse Reaction	OHTUVAYRE N=975 n (%)	Placebo N=574 n (%)
Back pain	18 (1.8%)	6 (1.0%)
Hypertension	17 (1.7%)	5 (0.9%)
Urinary tract infection	13 (1.3%)	6 (1.0%)
Diarrhea	10 (1.0%)	4 (0.7%)

U.S. Food and Drug Administration. Prescribing information for Ohtuvayre. FDA 2024 Jun 26; [e-pub].

Inhaled Treprostinil in pulmonary HTN with COPD

EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
S.D. NATHAN ET AL.

Inhaled treprostinil in pulmonary hypertension associated with COPD: PERFECT study results

Steven D. Nathan, Rahul Argula, Maria G. Trivieri, Sameh Aziz, Elizabeth Gay, Boris Medarov, Joseph Parambil, Amresh Raina, Michael G. Risbano, Thenappan Thenappan, Jose Soto Soto, Heidi Bell, Victoria Lacasse, Prakash Sista, Michael Di Marino, Aimee Smart, Brittanie Hawkes, Elizabeth Nelson, Todd Bull, Victor Tapson and Aaron Waxman

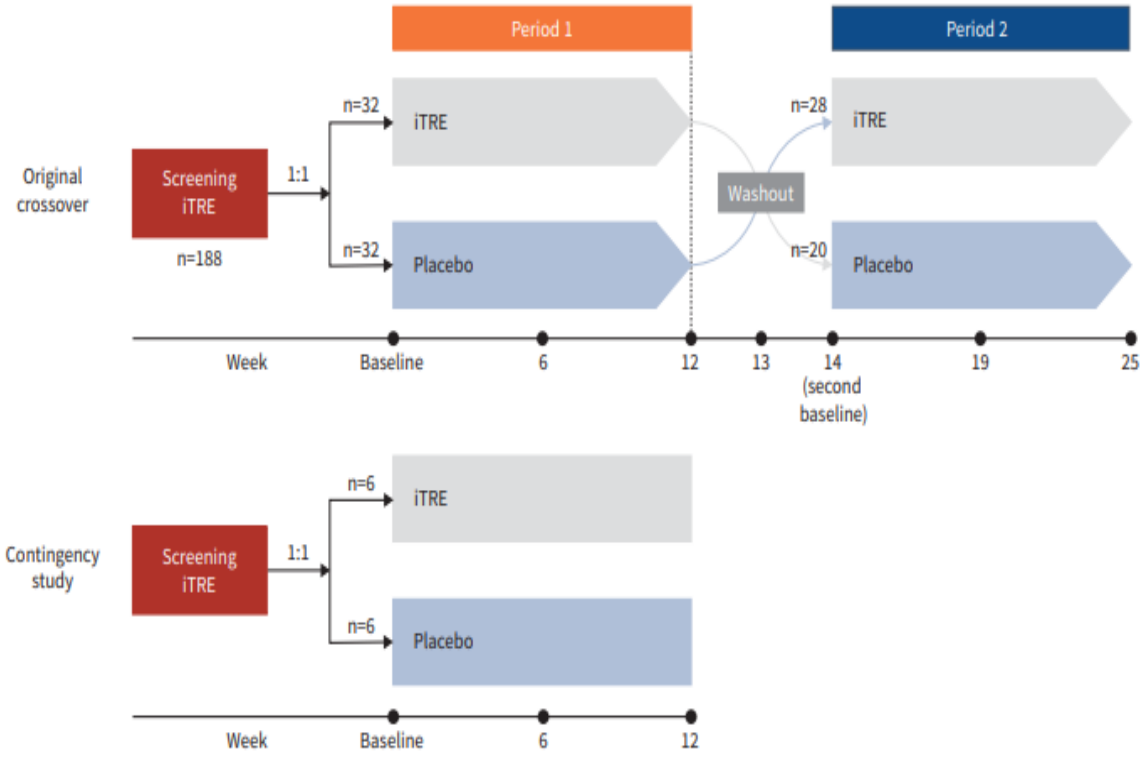
Eur Respir J 2024 April; 63: 2400172

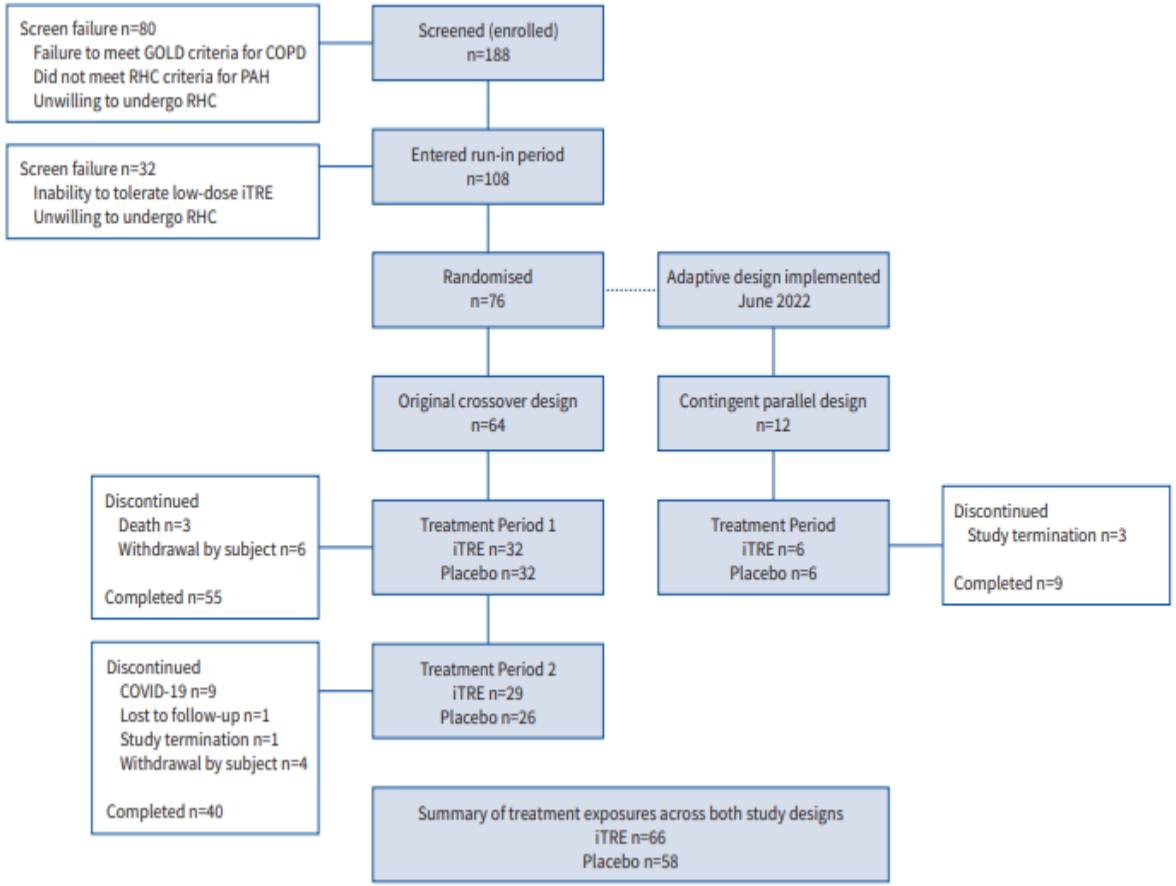
PERPECT study design

- **Participants**
  - Patients with PH-COPD (mean pulmonary arterial pressure ≥30mmHg and pulmonary vascular resistance ≥ 4WU)
  - Resting saturation ≥90% with or without supplemental oxygen, supplemental oxygen not exceed 10L/min, 6MWD ≥ 100m
  - Exclusion: group 1, 2, 4, or 5 PH as well as any evidence of ILD or CPFE
- **Randmomization (double blind RCT, 1:1)**
  - Inhaled treprostinil (iTRE) 72ug 4 times daily for 14-18 days
  - Placebo
- **Primary outcome**
  - 6min walk distance at week 12

Eur Respir J 2024 April; 63: 2400172

PERPECT STUDY flow chart





Eur Respir J 2024 April; 63: 2400172

No benefit but harmful effect of iTRE

SNUH 분당서울대학교병원 SEOUL NATIONAL UNIVERSITY BUNDANG HOSPITAL

TABLE 2 6-min walk distance (6MWD) (week 12) for the full analysis set

	Original crossover		Contingent parallel	
	iTRE (n=60)	Placebo (n=52)	iTRE (n=6)	Placebo (n=6)
Baseline#				
Patients (n)	38	42	3	4
6MWD (m)				
Mean±SD	222.71±77.80	228.60±75.21	232.33±85.29	277.50±76.97
Median	234.00	242.50	268.00	293.00
Minimum¶–maximum	64.0–396.0	78.0–358.0	135.0–294.0	180.0–344.0
Week 12+				
Patients (n)	38	42	3	4
6MWD (m)				
Mean±SD	218.24±74.29	223.45±87.22	252.67±42.16	296.00±81.01
Median	224.00	233.50	276.00	289.50
Minimum–maximum	61.0–373.0	43.0–416.0	204.0–278.0	217.0–388.0
Change from baseline§				
Patients (n)	38	42	3	4
6MWD (m)				
Mean±SD	−4.47±39.01	−5.14±50.71	20.33±116.99	18.50±42.49
Median	0.00	0.00	8.00	24.50
Minimum–maximum	−85.0–78.0	−176.0–124.0	−90.0–143.0	−35.0–60.0

iTRE: inhaled treprostinil. #: baseline is defined as the last non-missing value preceding the start of treatment; ¶: there were a few patients who had a drop in their 6MWD between screening and baseline visits such that their baseline 6MWD values were below the inclusionary lower limit; +: includes study week 12 of blinded treatment by study treatment; §: change from baseline=post-baseline value−baseline value.

TABLE 3 Treatment-emergent adverse events (TEAEs): safety population

	Enrolled	Randomised	
	iTRE (run-in) (n=108)	iTRE# (blinded) (n=66)	Placebo (blinded) (n=58)
Total TEAEs	165	178	122
Subjects with ⩾1 TEAEs	67 (62.0)	47 (71.2)	38 (65.5)
SAEs	10	26	20
Subjects with ⩾1 SAEs	9 (8.3)	17 (25.8)	6 (10.3)
TEAEs related to study treatment	115	77	32
Subjects with ⩾1 TEAEs related to study treatment	48 (44.4)	29 (43.9)	15 (25.9)
TEAEs leading to treatment discontinuation	15	11	6
Subjects with ⩾1 TEAEs leading to treatment discontinuation	11 (10.2)	8 (12.1)	3 (5.2)
TEAEs leading to study discontinuation	24	14	12
Subjects with ⩾1 TEAEs leading to study discontinuation	16 (14.8)	10 (15.2)	2 (3.4)

Data are presented as n or n (%). iTRE: inhaled treprostinil; SAE: serious adverse event. #: number of subjects exposed to iTRE during 12-week blinded treatment period only, including washout period.

Eur Respir J 2024 April; 63: 2400172

Blood eosinophil for assessing ICS response

[COPD Original Research]

CHEST

Rethinking Blood Eosinophils for Assessing Inhaled Corticosteroids Response in COPD

A Post Hoc Analysis From the FLAME Trial

Alexander G. Mathioudakis, PhD; Sebastian Bate, MMath; Pradeesh Sivapalan, PhD; Jens-Ulrik Stæhr Jensen, PhD; Dave Singh, MD; and Jørgen Vestbo, DMSc

CHEST 2024; 166(5):987-997

Post HOC analysis from the FLAME trial

- **FLAME (the Fluticasone Salmeterol on COPD exacerbation Trial) study**
  - 52wks, double-anonymized, non-inferiority RCT, N=3,362
  - LAMA(glycopyrronium)/LABA(indacaterol) vs LABA(salmeterol)/ICS(fluticasone propionate)
  - 4 weeks run in period while ICS or OCS not permitted, with BEC measured before and after

- **Post hoc analysis**
  - Participants on ICS at baseline, who had within 3 days prior to the first BEC measurement (BEC on ICS)
  - BEC change (BEC on ICS-BEC off ICS)
    - Negative: BEC suppression during ICS treatment

- **Primary outcomes**
  - Moderate or severe AE and severe AE

CHEST 2024; 166(5):987-997

Baseline characteristics of post hoc analysis

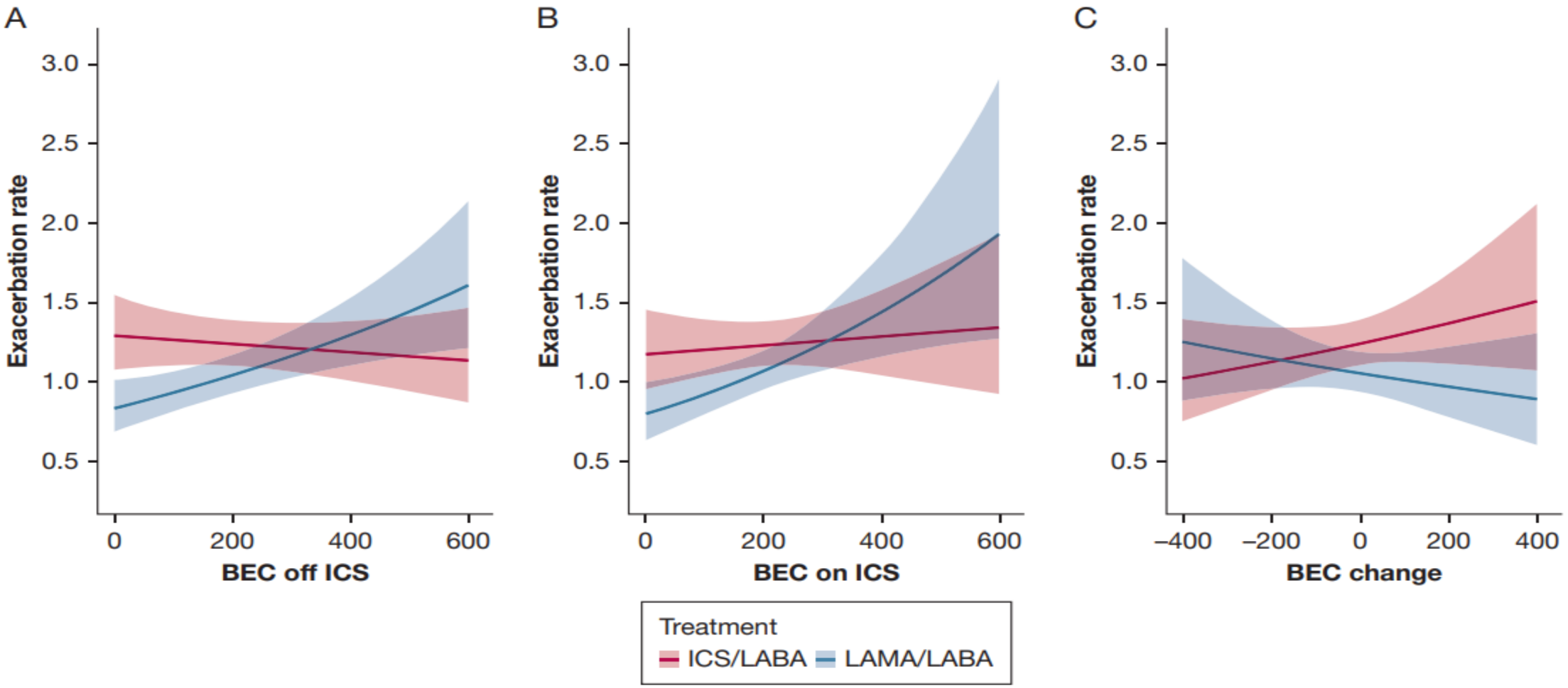
TABLE 1] Baseline Characteristics of the Participants Included in This Post Hoc Analysis

Characteristic	LABA/LAMA (n = 673)	LABA/ICS (n = 659)
Age, y	64.1 ± 8.0	64.3 ± 7.8
Female sex	180 (26.7)	192 (29.1)
Active tobacco use	241 (35.8)	240 (36.4)
COPD severity, spirometric stages		
GOLD I – mild	0 (0)	0 (0)
GOLD II – moderate	206 (30.6)	179 (27.2)
GOLD III – severe	406 (60.3)	422 (64.0)
GOLD IV – very severe	56 (8.3)	54 (8.2)
Baseline treatment		
LABA	586 (87.1)	597 (90.6)
LAMA	389 (57.8)	395 (59.9)
LABA + LAMA + ICS	362 (53.8)	382 (58.0)
Postbronchodilator FEV_1, % predicted	43.7 (9.4)	43.4 (9.3)
Postbronchodilator ratio of FEV_1 to FVC, %	41.1 (9.5)	41.4 (9.8)
Exacerbations during the preceding year		
1	533 (79.2)	510 (77.4)
≥ 2	140 (20.8)	149 (22.6)

CHEST 2024; 166(5):987-997

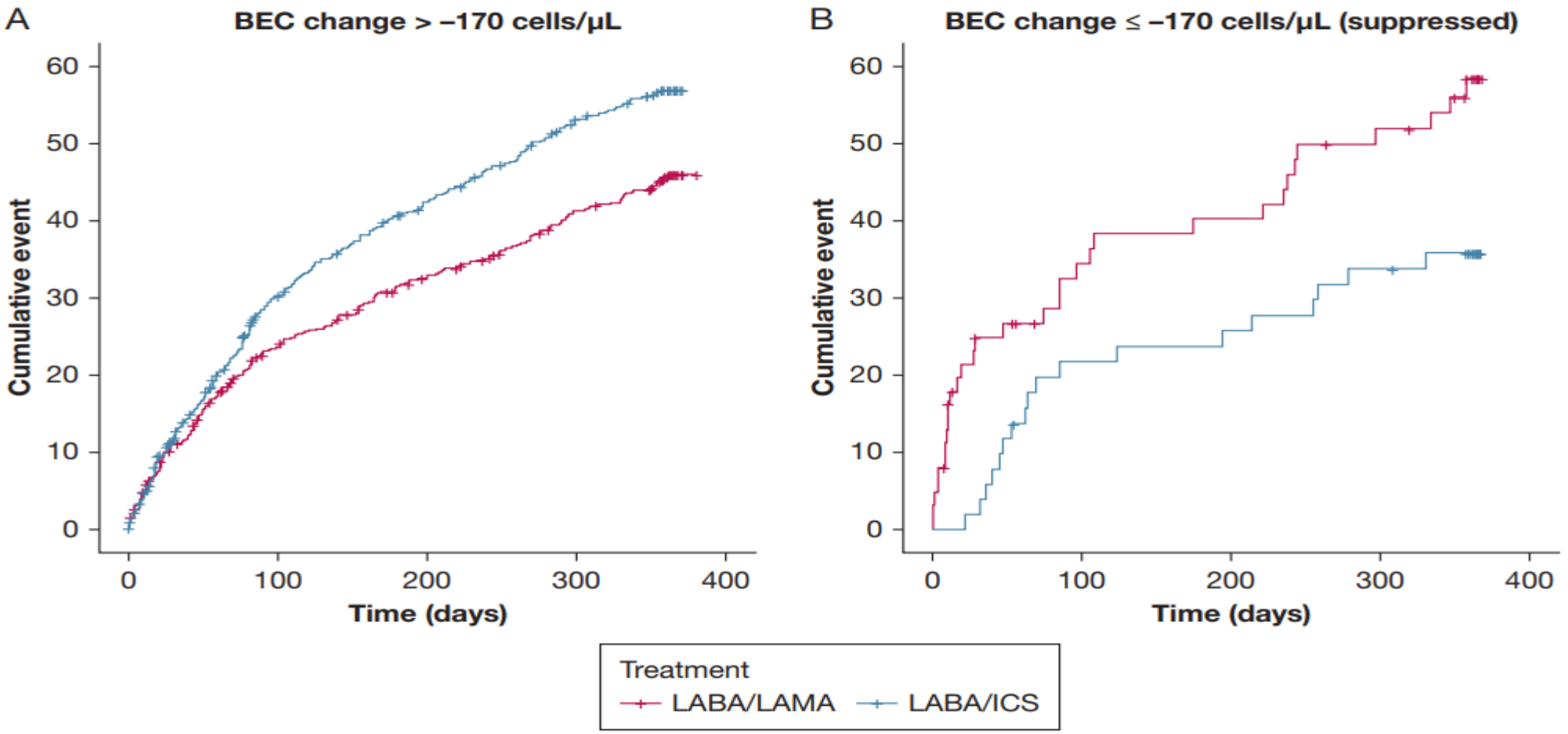
BEC off ICS related to superior response to ICS/LABA

Moderate or severe AE rate



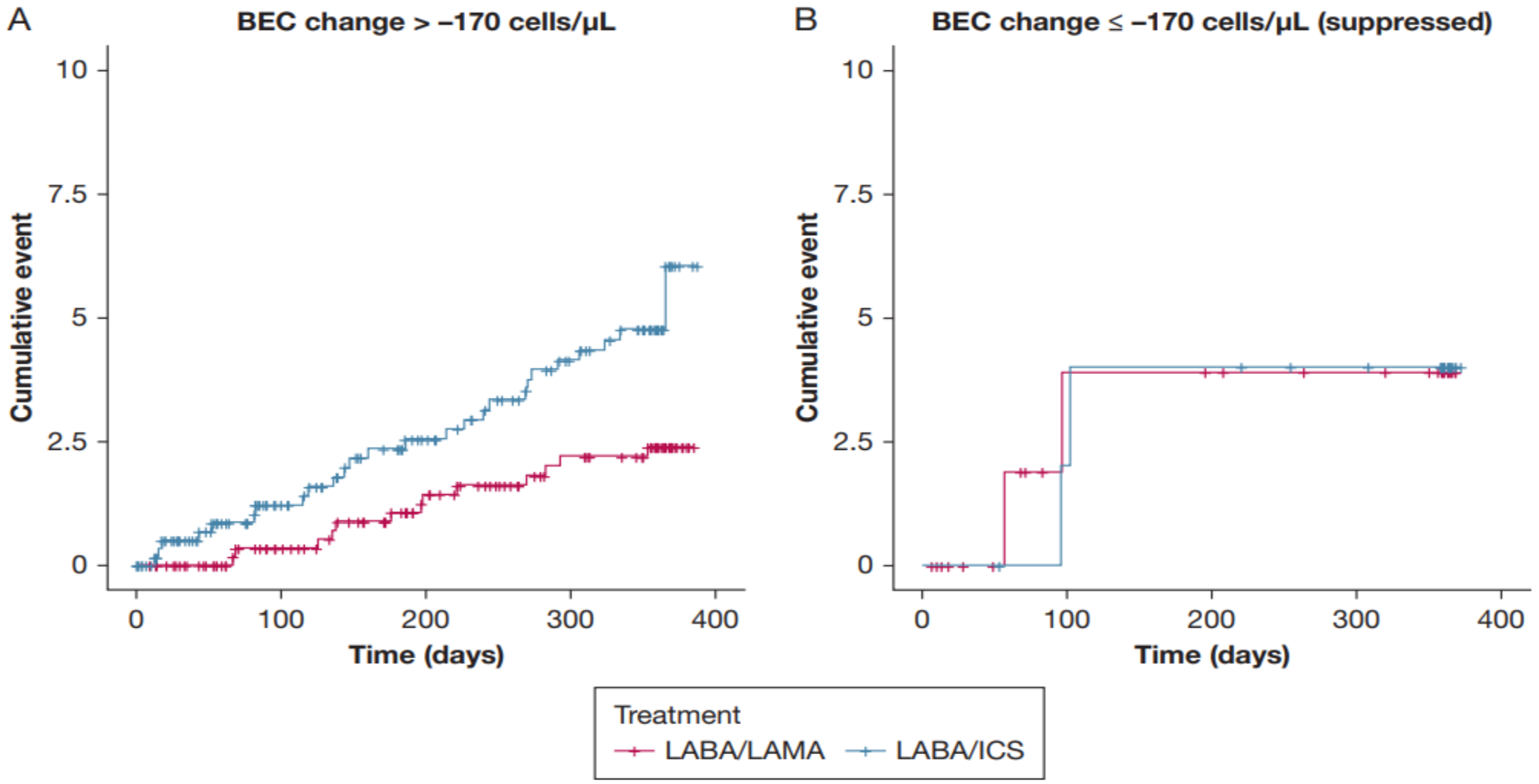
CHEST 2024; 166(5):987-997

Time to first moderate or severe AE by BEC change



CHEST 2024; 166(5):987-997

Time to first pneumonia episode by BEC change



CHEST 2024; 166(5):987-997

Nebulized N-acetylcysteine on phlegm of COPD

RESEARCH Open Access

The effect of nebulized N-acetylcysteine on the phlegm of chronic obstructive pulmonary disease: the NEWEST study

Chin Kook Rhee[1], Seong Yong Lim[2], Won-Yeon Lee[3], Ji Ye Jung[4], Yong Bum Park[5], Chang Youl Lee[6], Yong Il Hwang[7], Jin Woo Song[8], Won-Il Choi[9], Kwang Ha Yoo[10*], Ki Uk Kim[11], Yu-Il Kim[12], Tae-Hyung Kim[13], Seong Ju Park[14], Kyeong-Cheol Shin[15], Soo-Jung Um[16], Hyoung Kyu Yoon[17], Ho Sung Lee[18], Deog Kyeom Kim[19], Ah Young Leem[4] and on Behalf of the Korean Pulmonary Rehabilitation Study Group[20]

BMC Pulm Med 24, 434 (2024).

NEWEST study design

- **Participants**
  - Patients with COPD with CAT phlegm score ≥2, current or ex smoker
  - Exclusion: pregnant, treated with nebulized NAC, newly prescribed drug
  -
- **Prospective, single arm, open label, phase IV multi center trial**
  - 4mL of Mucomyst (0.8g NAC) with normal saline, three times daily for 12 weeks
- **Primary outcome**
  - Change in CAT phlegm score at 12wks compared to the baseline
  - Assessment: baseline, 4, 8, and 12 weeks of treatment using CAT, SGRQ-C

Table 1 Baseline characteristics ($n=91$)

Characteristics	Mean ± SD or number (%)
Age	71.42 ± 8.20
Male	89 (97.80%)
BMI	23.13 ± 3.14
Smoking status	
Current	18 (19.78%)
Ex	73 (80.22%)
Pack years	40.32 ± 35.18
Duration of COPD (yr)	5.69 ± 5.27
FVC (L)	3.94 ± 8.20
FVC (%)	75.44 ± 18.00
FEV_1 (L)	2.22 ± 5.62
FEV_1 (%)	58.50 ± 19.43
FEV_1/FVC	0.53 ± 0.13
CAT phlegm	3.47 ± 1.06
CAT total	18.68 ± 7.55
SGRQ-C	43.05 ± 22.23

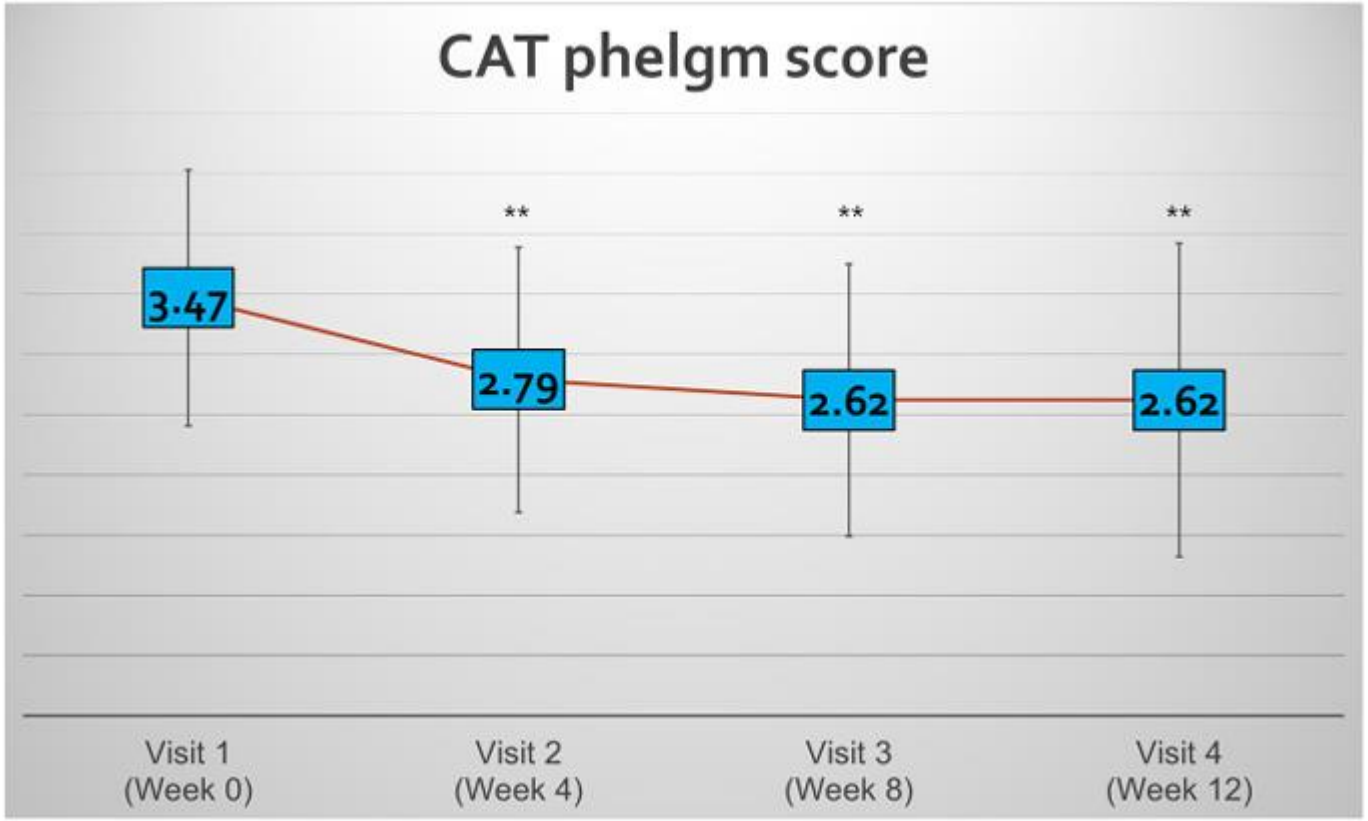


Table 4 The compliance of nebulized NAC ($n = 90$)

Group	Number (%)
Compliance < 50%	11 (12.22%)
50% ≤ Compliance < 60%	4 (4.44%)
60% ≤ Compliance < 70%	9 (10.00%)
70% ≤ Compliance < 80%	10 (11.11%)
80% ≤ Compliance < 90%	10 (11.11%)
90% ≤ Compliance	46 (51.11%)

NAC N-acetylcysteine

Table 5 Adverse events of nebulized NAC ($n = 99$)

Type of adverse events	Number of cases (%)	Total count
General disorders and administration site conditions	6 (6.06)	7
Chest discomfort	4 (4.04)	4
Chest pain	1 (1.01)	1
Pyrexia	1 (1.01)	1
Swelling face	1 (1.01)	1
Gastrointestinal disorders	1 (1.01)	1
Nausea	1 (1.01)	1
Metabolism and nutrition disorders	1 (1.01)	1
Decreased appetite	1 (1.01)	1
Nervous system disorders	1 (1.01)	1
Dizziness	1 (1.01)	1
Respiratory, thoracic, and mediastinal disorders	1 (1.01)	1
Dyspnea	1 (1.01)	1

NAC N-acetylcysteine

Nebulised interferon-ß1a in viral AECOPD

Monk *et al. Respiratory Research* (2024) 25:228
https://doi.org/10.1186/s12931-024-02854-7

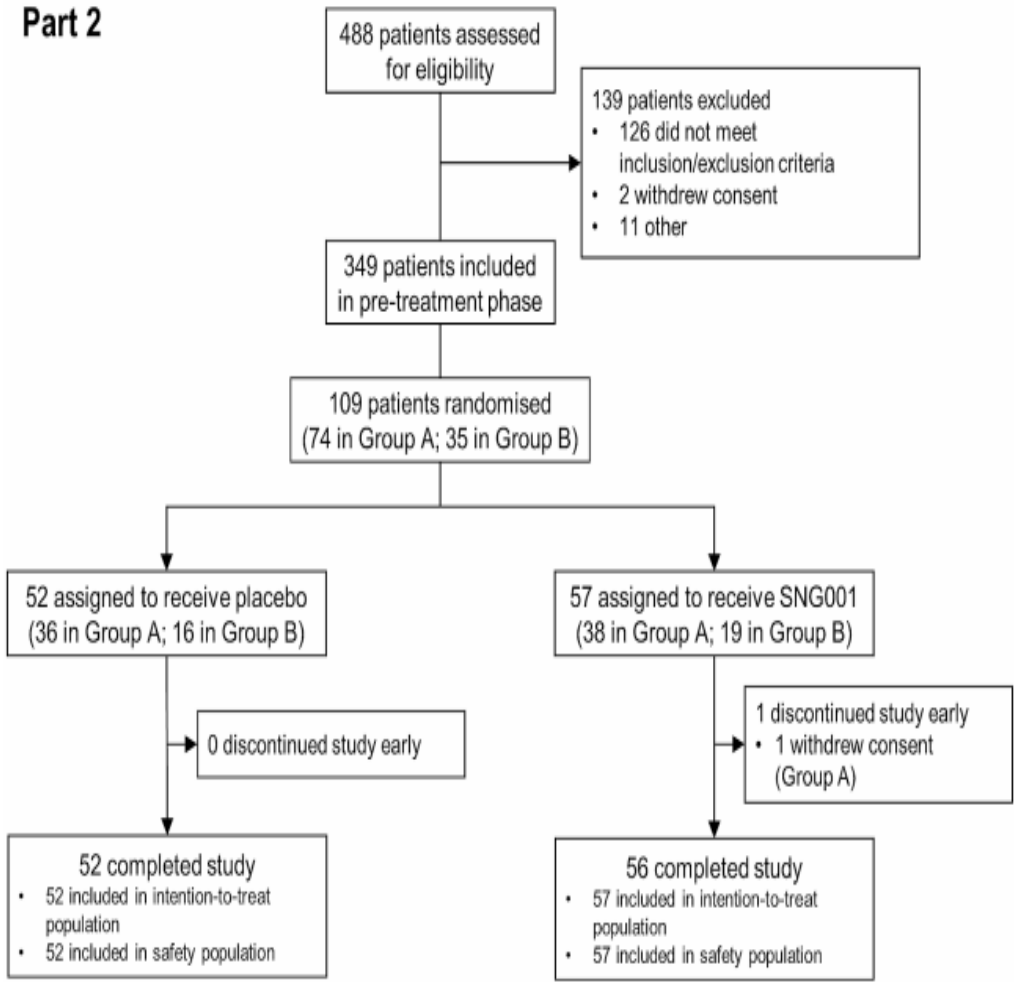
Respiratory Research

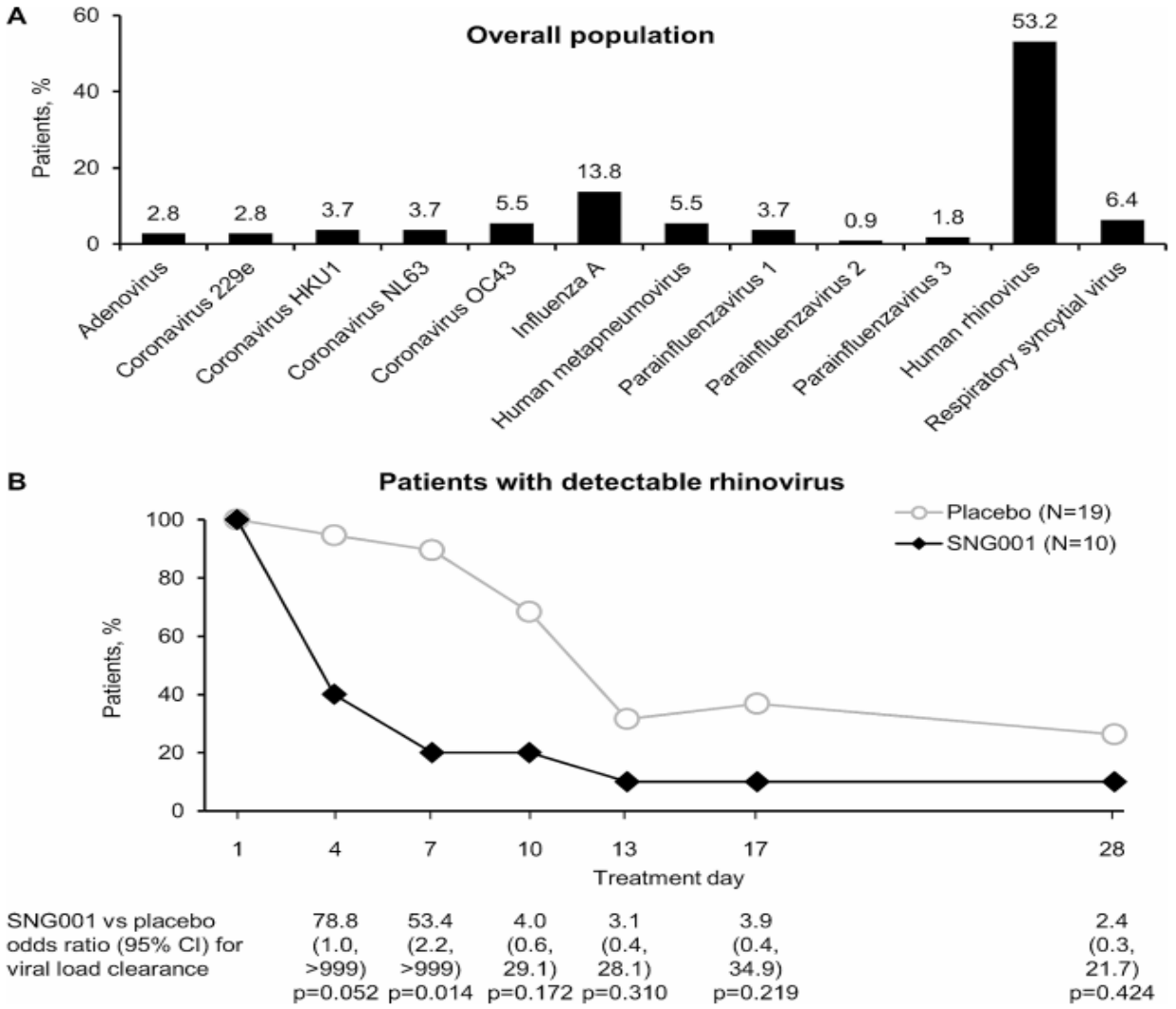
RESEARCH Open Access

Nebulised interferon beta-1a (SNG001) in the treatment of viral exacerbations of COPD

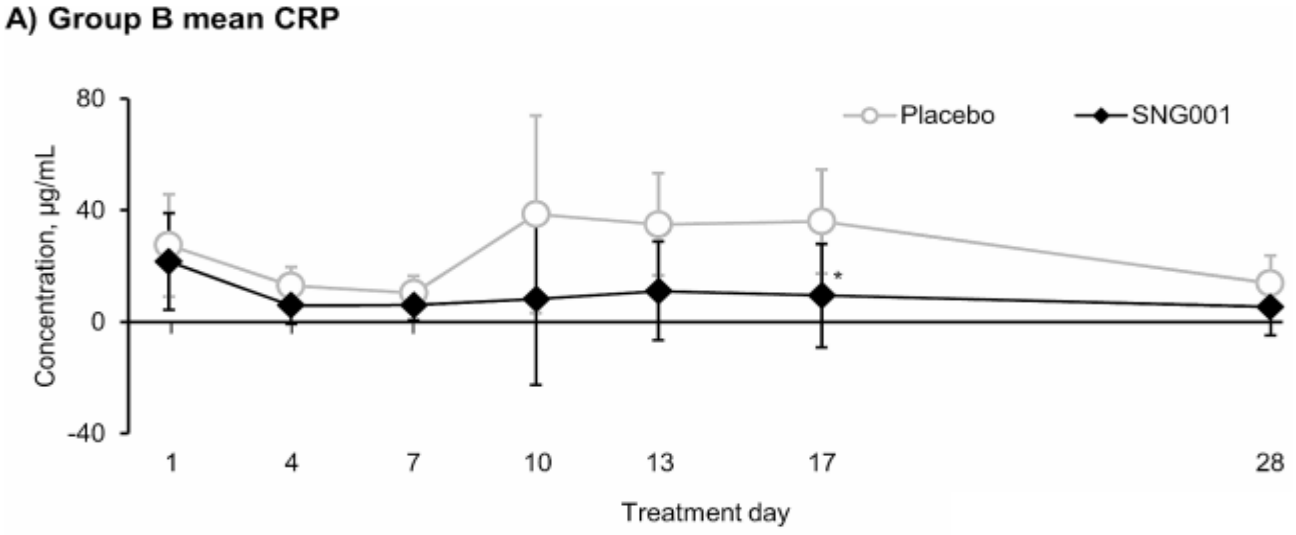
Phillip D. Monk[1*], Jody L. Brookes[1], Victoria J. Tear[1], Toby N. Batten[2], Clare Newall[2], Marcin Mankowski[1,3], Michael G. Crooks[4], Dave Singh[5], Rekha Chaudhuri[6,7], Brian Leaker[8], Kerry Lunn[1], Sophie Reynolds[1], Sarah Dudley[1], Felicity J. Gabbay[3], Stephen T. Holgate[9], Ratko Djukanovic[9] and Thomas MA Wilkinson[9]

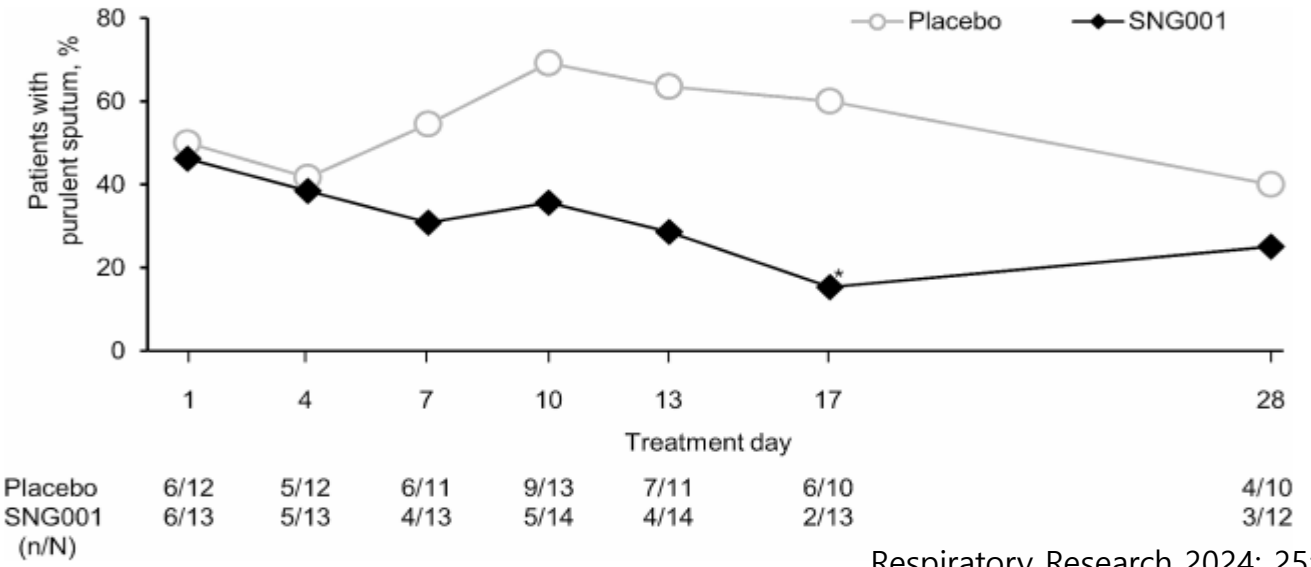
Study flow and virus detection rate





Nebulised Interferon-b1a decreased CRP, sputum





Respiratory Research 2024; 25:228

Biologics

- Dupilumab (IL-4 and IL-13 inhibitor)
  - BOREAS study (2023)
  - NOTUS study (2024)
- Tezepelumab
  - Phase 2a COURSE study
- Anti IL-33
  - Phase 1 study, Tozorakimab

Dupilumab-BOREAS design

BOREAS design

Participants

- **Blood eosinophil count ≥ 300/μL** at screening visit
- **≥ 2 moderate or ≥ 1 severe COPD exacerbations** in prior year
- On **triple inhaler therapy** for ≥ 3 months before randomization
- **Chronic bronchitis** symptoms for ≥ 3 months in prior year
- **No asthma** as a current or past diagnosis

Randomization

Dupilumab 300 mg SC every 2 weeks vs **placebo**

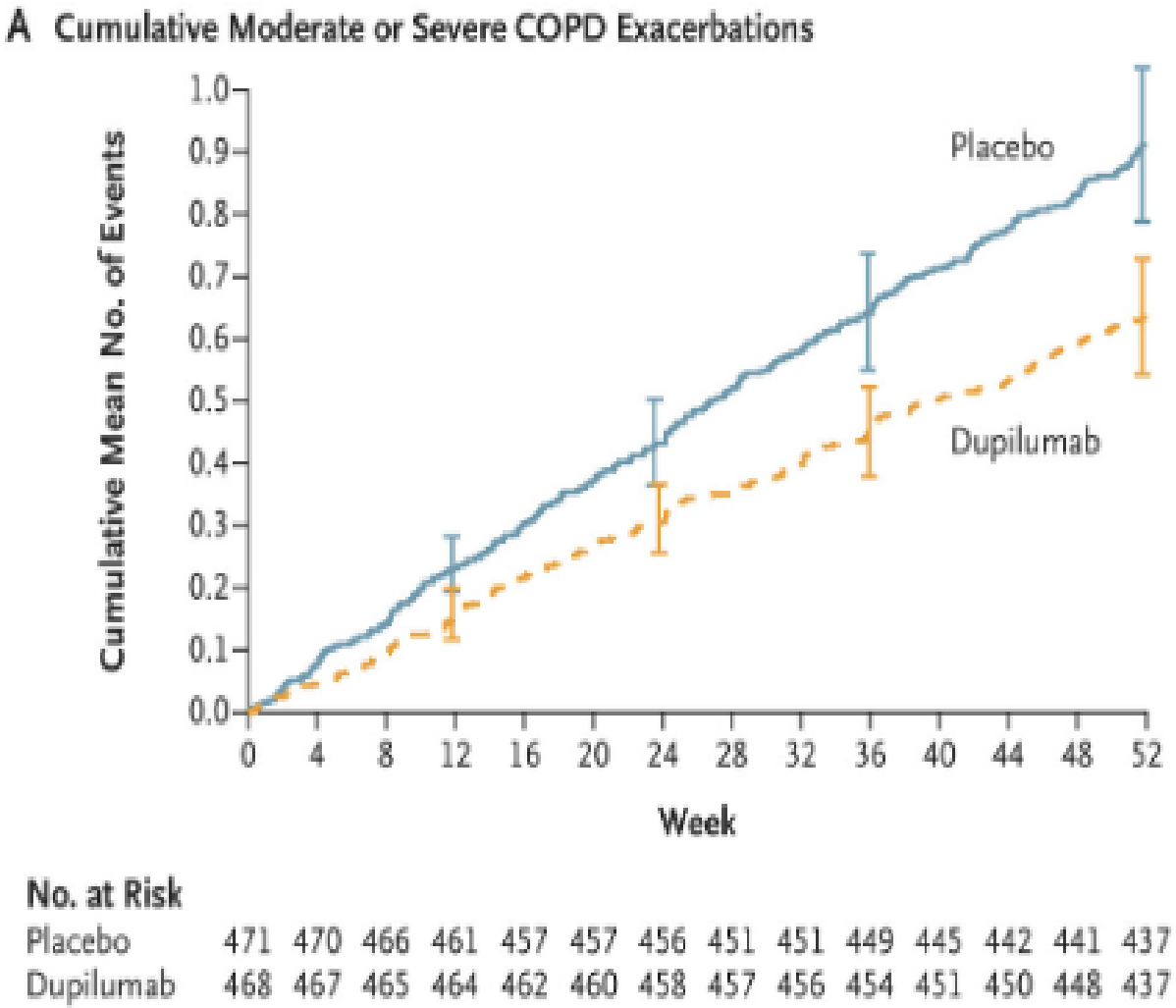
Primary outcome

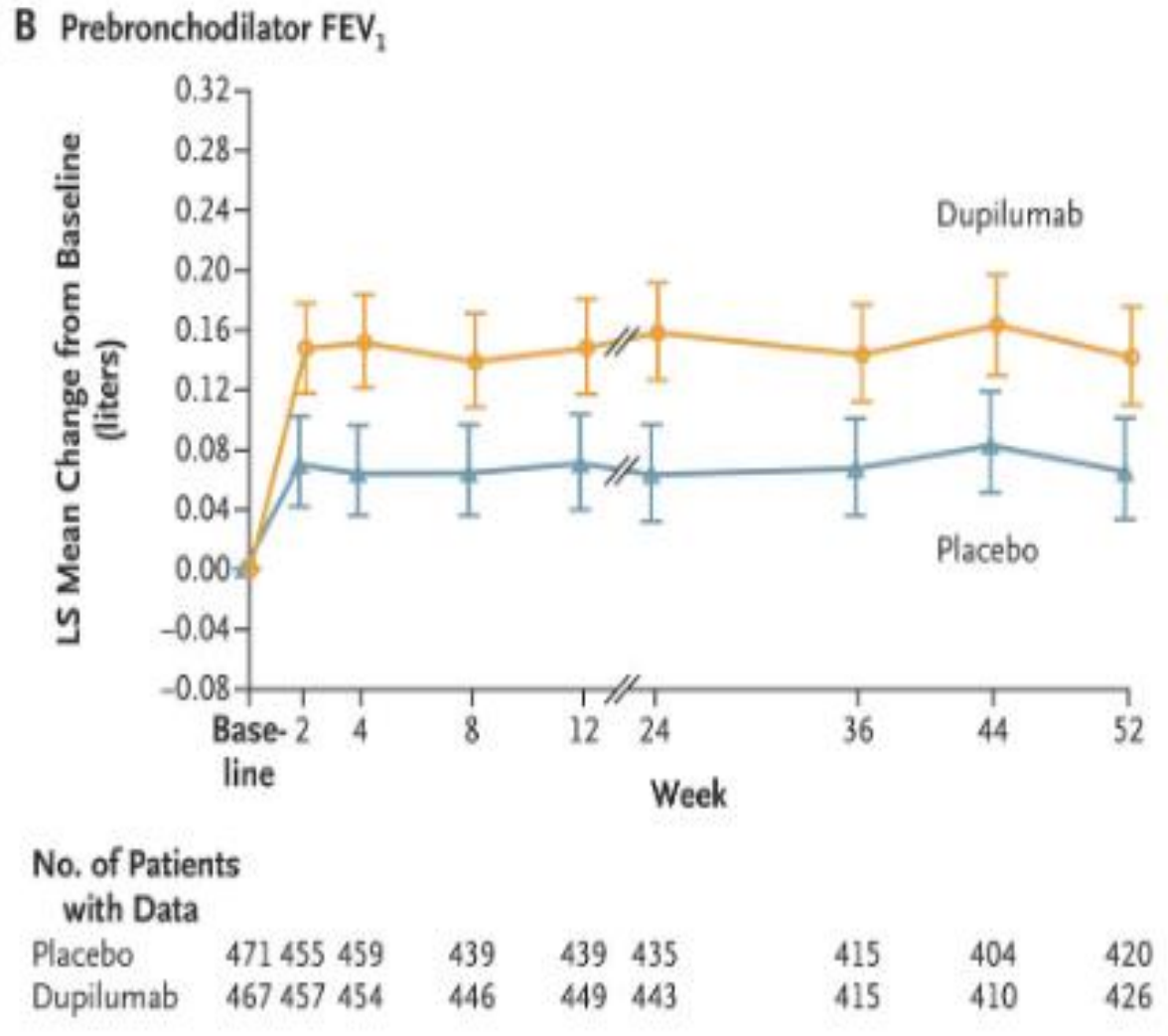
Annualized **rate of moderate or severe COPD exacerbations** for 52 weeks

ATS 2024

N Engl J Med 2023 Jul 20;389(3):205-214

Dupilumab fewer exacerbation, better lung function





N Engl J Med 2023 Jul 20;389(3):205-214

Dupilumab for COPD with type 2 inflammation

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dupilumab for COPD with Blood Eosinophil Evidence of Type 2 Inflammation

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

N Engl J Med. 2024 Jun 27;390(24):2274-2283.

NOTUS trial (Dupilumab for COPD)

- **Participants**
  - Multicenter,
  - 40-85yr, COPD with triple inhaler at least 3 months and stable at least 1month, ≥ 2 moderate or severe AE, at least one exacerbation within background triple inhaler therapy
  - Current or former smoker, mmRC ≥ 2 for 3 months, BEC ≥ 300 cells/mL
- **Randmomization (double blind RCT, 1:1)**
  - Dupilumab 300mg SQ, 2 weeks during 52 weeks
  - Placebo SQ 2 weeks during 52 weeks
- **Primary outcome**
  - Annualized rate of moderate or severe exacerbations
  - Secondary outcome: FEV1 and SGRQ change

N Engl J Med. 2024 Jun 27;390(24):2274-2283.

Baseline characteristics of NOTUS trial

SNUH 분당서울대학교병원 SEOUL NATIONAL UNIVERSITY BUNDANG HOSPITAL

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Placebo (N=465)	Dupilumab (N=470)	Total (N=935)
Age — yr	64.9±8.5	65.2±8.1	65.0±8.3
Male sex — no. (%)	312 (67.1)	320 (68.1)	632 (67.6)
Race or ethnic group — no. (%)†			
White	416 (89.5)	422 (89.8)	838 (89.6)
Black	8 (1.7)	4 (0.9)	12 (1.3)
Asian	3 (0.6)	7 (1.5)	10 (1.1)
American Indian or Alaska Native	26 (5.6)	22 (4.7)	48 (5.1)
Native Hawaiian or Pacific Islander	0	1 (0.2)	1 (0.1)
Multiple	8 (1.7)	12 (2.6)	20 (2.1)
Not reported	4 (0.9)	2 (0.4)	6 (0.6)
Hispanic or Latino ethnic group — no. (%)			
Hispanic or Latino	149 (32.0)	151 (32.1)	300 (32.1)
Non-Hispanic or non-Latino	308 (66.2)	315 (67.0)	623 (66.6)
Unknown	2 (0.4)	0	2 (0.2)
Not reported	6 (1.3)	4 (0.9)	10 (1.1)
Smoking status — no. (%)			
Former smoker	331 (71.2)	328 (69.8)	659 (70.5)
Current smoker	134 (28.8)	142 (30.2)	276 (29.5)
Smoking history — pack-yr	42.1±30.2	38.6±23.7	40.3±27.2
Emphysema — no. (%)‡	150 (32.3)	134 (28.5)	284 (30.4)
Body-mass index§	27.8±5.6	28.1±5.3	27.9±5.4
Background medication — no. (%)			
Inhaled triple therapy¶	458 (98.5)	466 (99.1)	924 (98.8)
Inhaled high-dose glucocorticoid	134 (28.8)	127 (27.0)	261 (27.9)
Lung function			
Prebronchodilator FEV_1 — liters	1.38±0.50	1.35±0.49	1.36±0.50
Postbronchodilator FEV_1			
Volume — liters	1.46±0.50	1.43±0.49	1.45±0.49
Percent of predicted value	50.7±12.6	49.5±12.6	50.1±12.6
Postbronchodilator FEV_1:FVC	0.5±0.1	0.5±0.1	0.5±0.1
SGRQ total score‖	51.1±16.5	52.0±17.5	51.5±17.0
E-RS–COPD total score**	13.3±7.2	13.4±6.7	13.3±7.0
Biomarkers of type 2 inflammation			
Blood eosinophil count at randomization — per μl			
Mean	402±314	412±357	407±336
Median (interquartile range)	330 (220–470)	340 (230–460)	330 (220–460)
Category at randomization — no. (%)			
<300 cells/μl	188/465 (40.4)	184/469 (39.2)	372/934 (39.8)
≥300 cells/μl	277/469 (59.6)	285/469 (60.8)	562/934 (60.1)
Postbronchodilator F_ENO — ppb			
Mean	24.4±23.4	24.8±28.3	24.6±26.0
Median (interquartile range)	16 (10–30)	16 (10–27)	16 (10–29)
F_ENO — no./total no. (%)			
<20 ppb	240/423 (56.7)	257/429 (59.9)	497/852 (58.3)
≥20 ppb	183/423 (43.3)	172/429 (40.1)	355/852 (41.7)
No. of moderate or severe COPD exacerbations in previous yr	2.1±0.7	2.2±1.0	2.1±0.9

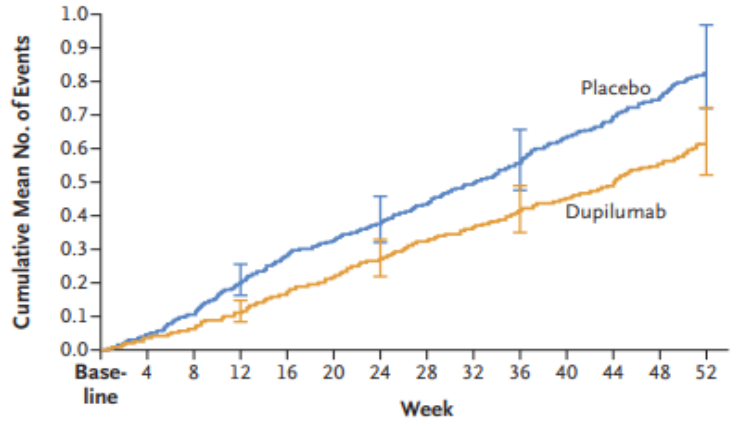
N Engl J Med. 2024 Jun 27;390(24):2274-2283.

Dupilumab reduced AE in COPD with type 2 inflammation

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

End Point*	Placebo (N = 465)	Dupilumab (N = 470)	P Value
Primary end point			
Annualized rate of moderate or severe exacerbations of COPD			
Adjusted annualized rate of moderate or severe exacerbations — no. of events/yr (95% CI)	1.30 (1.05 to 1.60)	0.86 (0.70 to 1.06)	
Rate ratio vs. placebo (95% CI)	—	0.66 (0.54 to 0.82)	<0.001
Secondary and other end points			
Change in prebronchodilator FEV_1 from baseline to wk 12			
Least-squares mean change (95% CI) — liters	0.057 (0.023 to 0.091)	0.139 (0.105 to 0.173)	
Least-squares mean difference vs. placebo (95% CI) — liters	—	0.082 (0.040 to 0.124)	<0.001
Change in prebronchodilator FEV_1 from baseline to wk 52†			
No. of patients	359	362	
Least-squares mean change (95% CI) — liters	0.054 (0.014 to 0.093)	0.115 (0.075 to 0.156)	
Least-squares mean difference vs. placebo (95% CI) — liters	—	0.062 (0.011 to 0.113)	0.02
Change in prebronchodilator FEV_1 from baseline to wk 12 among patients with a baseline F_ENO level ≥20 ppb			
No. of patients	183	172	
Least-squares mean change (95% CI) — liters	0.081 (0.008 to 0.153)	0.221 (0.148 to 0.294)	
Least-squares mean difference vs. placebo (95% CI) — liters	—	0.141 (0.058 to 0.223)	0.001
Change in prebronchodilator FEV_1 from baseline to wk 52 among patients with a baseline F_ENO level ≥20 ppb†			
No. of patients	132	132	
Least-squares mean change (95% CI) — liters	0.095 (0.011 to 0.179)	0.176 (0.091 to 0.261)	
Least-squares mean difference vs. placebo (95% CI) — liters	—	0.081 (−0.019 to 0.181)	0.11
Change in SGRQ total score from baseline to wk 52†			
No. of patients	359	362	
Least-squares mean change (95% CI)	−6.4 (−8.3 to −4.6)	−9.8 (−11.6 to −8.0)	
Least-squares mean difference vs. placebo (95% CI)‡	—	−3.4 (−5.8 to −0.9)	
SGRQ total score improvement ≥4 points at wk 52†			
No. of patients	359	362	
Percentage of patients (95% CI)	46.5 (41.3 to 51.8)	51.4 (46.1 to 56.6)	
Odds ratio vs. placebo (95% CI)‡	—	1.2 (0.9 to 1.6)	

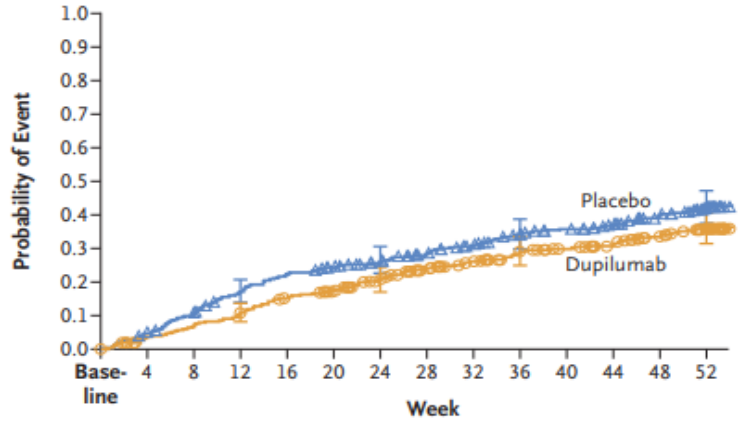
A Moderate or Severe COPD Exacerbations



No. at Risk

Placebo	465	464	458	453	453	448	430	415	403	394	384	368	351	303
Dupilumab	469	464	464	464	460	455	438	424	408	395	385	370	354	344

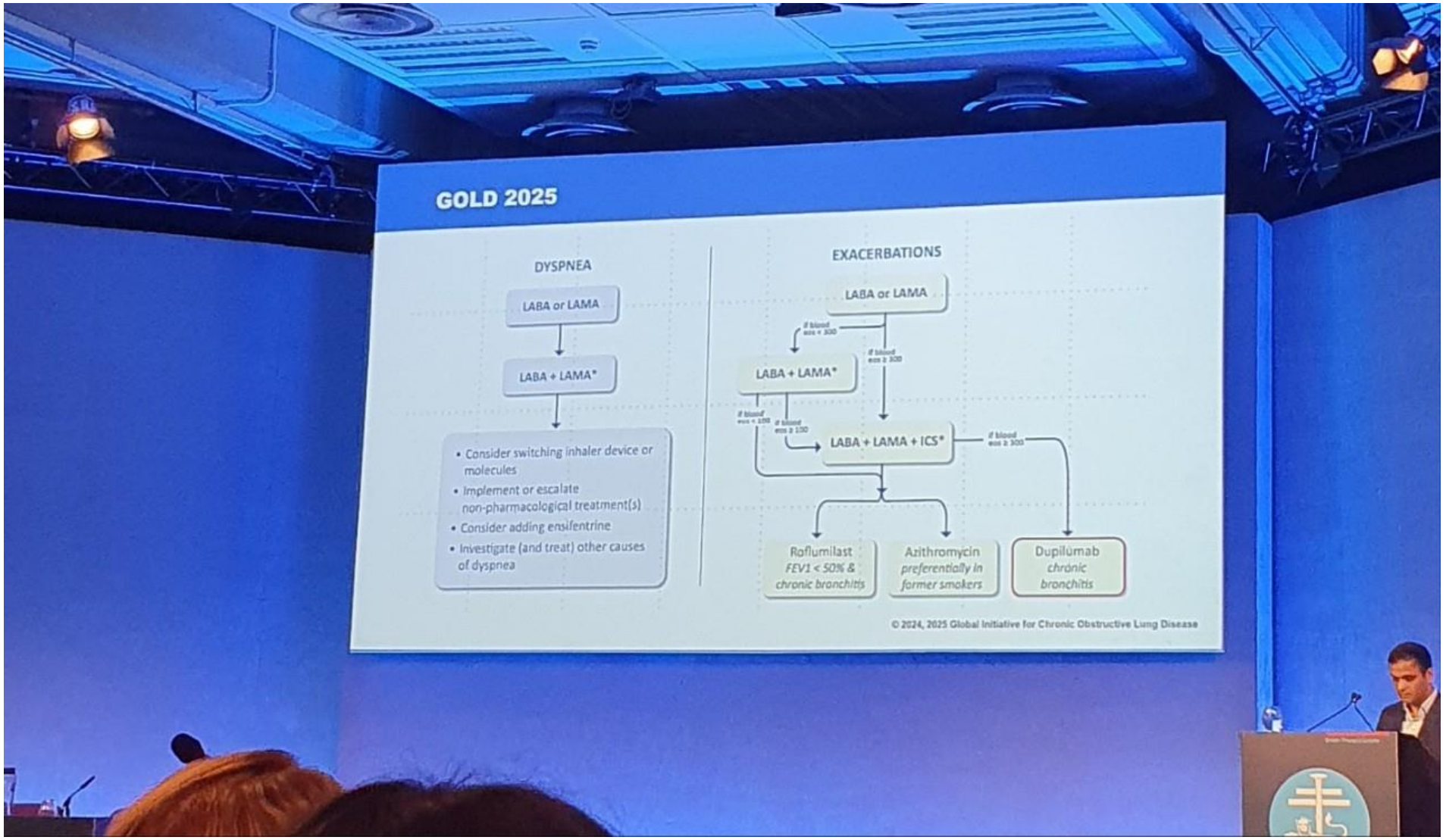
B Time to First Moderate or Severe COPD Exacerbation



No. at Risk

Placebo	465	442	414	378	355	339	319	301	282	262	248	232	211	149
Dupilumab	470	448	433	416	391	377	352	325	304	284	270	258	236	176

In GOLD 2025, Dupilumab will be added



외래경과 작성과: 호흡기내과 (2024-10-10)

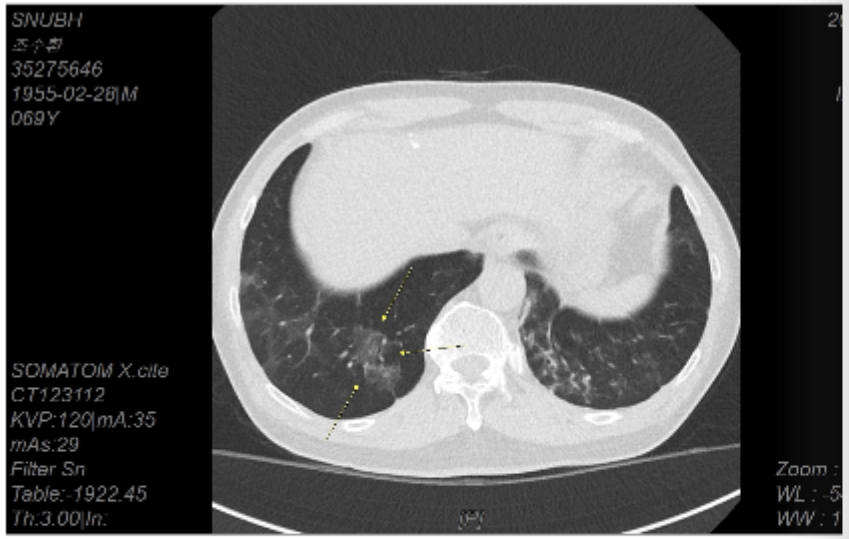
소견

COPD, Asthma (조영재 선생님) refer
NTM

Ex-smoker

S>
2주 전 객혈++

O>
BLLF rhonchi++



@ PFT

(2024-06) FEV1	2.47	0.94	38%	0.88	36%	-6%
(2023-07) FEV1	2.50	1.31	52%	1.33	53%	2% ,

DL104

(2022-07) FEV1 2.54 1.23 49% 1.22 48% -1% ,
DL89

==========

FVC	3.59	2.29	64%	2.31	64%	1%
FEV1	2.47	0.88	36%	0.85	35%	-3%
FEV1/FVC	70%	39%		37%		

@ FENO 16 (2022-07)->27

2024-10-03
[Conclusion]
Slightly increased multifocal bronchiolitis-like lesions in both lung (DDx. NTM)
-- with a new 5 mm nodule in RLL, probably inflammatory (se 2 image 94)

rec) consider 6 months f/u

@ AFB
(2024-07-04) S AFB -/NTM --> M. avium, DST
균주명 : Mycobacterium avium◑◑약제명 절대농도(㎍/ml) 판정결과◑----------◑Amikacin (16) ㎍/ml (S)◑Ciprofloxacin (16) ㎍/ml (-)◑Clarithromycin (2) ㎍/ml (S)◑Doxycycline (16) ㎍/ml (-)◑Moxifloxacin (4) ㎍/ml (R)◑Rifampin (2) ㎍/ml (-)◑Trimethoprime ◑/Sulfamethoxazole (2) ㎍/ml (-)◑Ethambutol (8) ㎍/ml (-)◑Linezolid (32) ㎍/ml (R)◑Streptomycin (64) ㎍/ml (-)◑----------◑◑MIC (Minimum Inhibitory Concentration)◑S (Susceptible), I (Intermediate), R (Resistant), IR (Inducible Resistant)◑◑항생제별 판정은 CLSI 기준에 따라 실시하였습니다.◑

(2024-07-04) S AFB -/NTM

Assessment & Plan

A>
COPD, asthma (SMC/AMC --> SNUBH 2022-04)
- On Trelegy from 2021-11~
Bronchiectasis
NTM isolation (2024-07)

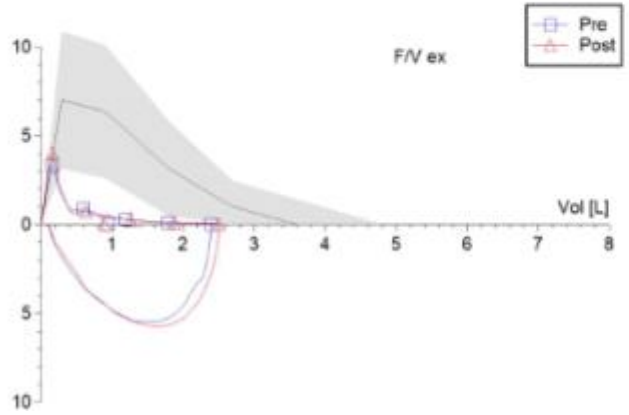
P>
1. NTM 치료 시작
2. Dupixent
3. 호흡기장애 진단서+

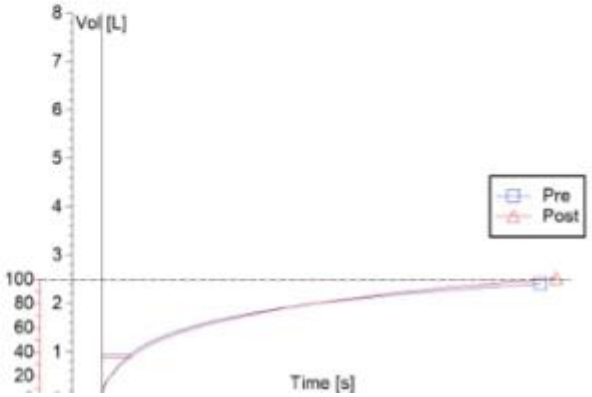
분당서울대학교병원

Age:	69.2 Years	Race:	Asian	Visit Date:	2024-06-13 16:00
Height:	164.0 cm	Weight:	60.0 kg	Physician:	
Date of Birth:	1955-02-28			Technician:	이주희

Spirometry

		PRE-RX		POST-RX		
	Pred	BEST	%PRED	BEST	%PRED	%CHG
FVC	3.59	2.39	67	2.50	70	5
FEV1	2.47	0.94	38	0.88	36	-6
FEV1/FVC	70	39		35		
FEF25-75%	2.44	0.25	10	0.22	9	-12
IsoFEF25-75		0.25		0.25		1
FEF75-85%	0.46	0.09	19	0.09	19	-0
PEF	7.00	3.33	47	4.03	57	21
FET100%		14.83		15.44		4
FIVC	3.59	2.30	64	2.42	67	5
FEV1	2.47	0.94	38	0.88	36	-6
FIV1						
FEF/FIF50		5		4		-18
Vol Extrap		0.04		0.04		-4
E ATS05		401		401		0
MVV	111					
f						





외래경과 작성과: 호흡기내과 (2024-12-05)

소견

COPD, Asthma (조영재 선생님) refer
NTM

Ex-smoker

S>
약은 잘 드시고, 흡입기도 잘 사용하고 계심.
Dupixent 하면서 많이 좋아지심.

외래경과　작성과: 호흡기내과 (2024-06-26,

소견

3월에 Pn로 입원 치료 COPD F/U

외부 CT; mild inflammation

chest P/E: RLLF wheezing (+)

S>
2층 계단만 올라가도 숨차고 호흡이 힘들다.
기침(+) 가래는 심하지 않다.

Assessment & Plan

COPD
s/p Pn

med for 3 months

CT reading

작성자 이

검체검사결과 (진단검사의학과)
의뢰처/진료과 : LIMR / LIMR 의뢰의사 : 이예진
(의뢰일시 : 2024-08-21 / 접수일시 : 2024-11-13 13:11 / 보고일시 : 2024-11-13 14:04)

검사명 :
일반혈액

검체명 :
EDTA BLD

항목명	검사결과	참고치	결과비고
WBC	4.53	4.0 ~ 10.0 ×10³/㎕	CBC 전 항목 동일한 검체로 재검한 결과임
RBC	4.04	4.2 ~ 5.7 ×백만/㎕	
Hb	12.6	13 ~ 17 g/dL	
Hct	40.0	39 ~ 52 %	
MCV	99.0	81 ~ 96 fL	
MCH	31.2	27 ~ 33 pg	
MCHC	31.5	32 ~ 36 g/dL	
RDW(CV)	12.6	11.5 ~ 14.5 %	
RDW(SD)	45.8	37 ~ 54 fL	
PDW	12.8	9.8 ~ 15.2 fL	
PLT	130	130 ~ 400 ×10³/㎕	
MPV	11.1	9.1 ~ 12.0 fL	
PCT	0.15	0.15 ~ 0.32 %	
Segmented neutrophil	62.0	50 ~ 75 %	
Lymphocyte	25.2	20 ~ 44 %	
Monocyte	7.5	2 ~ 9 %	
Eosinophil	4.9	1 ~ 5 %	
Basophil	0.4	0 ~ 2 %	
절대림프구수	1142	/㎕	
절대단구수	340	/㎕	
ANC	2809	/㎕	

기능검사결과
진료과/병동(의뢰처) : 호흡기내과 (폐센터) (외래)
(의뢰일: 2023-04-25 / 검사일: 2023-10-24 / 판독일시: 2023-10-26 10:07 / 결과보고일시: 2023-10-26 10:07)

임상진단명 :
Chronic obstructive pulmonary disease

임상소견 및 병력 :

검사명 :
PFT(기본 폐기능검사)

SNUBH Pulmonary Function Test Report

Date

Report	Ref	Pre Meas	Pre %Ref	Post Meas	Post %Ref	Post
FVC	3.79	2.68	71%	2.68	71%	-0%
FEV1	2.49	0.91	36%	0.90	36%	-1%
FEV1/FVC	68%	34%		34%		
PEF	7.35	2.61	36%	3.41	46%	31%
DLCO	14.8					
VA						

외래경과 작성과: 호흡기내과 (2024-07-23)

소견

3월에 Pn로 입원 치료 COPD F/U

외부 CT; mild inflammation

chest P/E: RLLF wheezing (+)

S>
훨씬 나으시다.
기침은 심하지는 않는다.
런닝머신 40분 -1시간 정도 합니다. 호흡힘든게 가라 앉았다.

CAT score. 작성일:2024.07.23 09:55
(1) 기침:
[2]
(2) 가래:
[3]
(3) 가슴이 답답한 증상:
[3]
(4) 숨이 차는 증상:
[4]
(5) 외출시 어려움:
[2]
(6) 집에서 활동시 제약:
[2]
(7) 수면 영향:
[3]
(8) 체력 상태:
[3]

CAT score:22

* 누적 계산식 결과 (v1.0)
CAT score
2024.07.23, 22

O>
Expiratory mild wheezing+

Assessment & Plan

COPD with high eosinophil
s/p Pn

med for 3 months

P,
Dupixent 유지+

작성자 이예진 이예진

외래경과 작성과: 호흡기내과 (2024-08-21)

소견

3월에 Pn로 입원 치료 COPD F/U

외부 CT; mild inflammation

chest P/E: RLLF wheezing (+)

S>
바닷가도 걷고 수영도 좀 하고 그렇습니다.

CAT score. 작성일:2024.08.21 14:22
(1) 기침:
[1]
(2) 가래:
[1]
(3) 가슴이 답답한 증상:
[2]
(4) 숨이 차는 증상:
[3]
(5) 외출시 어려움:
[2]
(6) 집에서 활동시 제약:
[1]
(7) 수면 영향:
[1]
(8) 체력 상태:
[2]

CAT score:13

* 누적 계산식 결과 (v1.0)
CAT score
2024.08.21, 13
2024.07.23, 22

O>
Expiratory mild wheezing->거윈 안들림++

Assessment & Plan

A.
COPD with high eosinophil
s/p Pn

med for 3 months

P.
Dupixent 유지+++ -> 회송서써서 한달에 한번씩맞도록+

작성자 유은주/ 이예

기능검사결과

진료과/병동(의뢰처) : 호흡기내과 (폐센터) (외래)

'의뢰일: 2024-08-21 / 검사일: 2024-11-13 / 판독일시: 2024-11-14 09:40 / 결과보고일시: 2024-11-14 09:40)

임상진단명 :

Chronic obstructive pulmonary disease

임상소견 및 병력 :

검사명 :

기본폐기능검사(PFT)

SNUBH Pulmonary Function Test Report

Date

Report	Ref	Pre Meas	Pre %Ref	Post Meas	Post %Ref	Post
FVC	3.70	2.68	72%	2.73	74%	2%
FEV1	2.43	0.95	39%	1.02	42%	7%
FEV1/FVC	68%	36%		37%		
PEF	7.22	3.50	49%	4.05	56%	15%
DLCO	14.8					
VA						
DLCO/VA	3.46					
IVC						
TLC	5.58					
RV	2.40					
RV/TLC	43%					
FRC PL	3.57					
VC	3.70					
ERV	1.27					

Tezepelumab in COPD, phase 2a COURSE study

SNUH 분당서울대학교병원 SEOUL NATIONAL UNIVERSITY BUNDANG HOSPITAL

Boston CHEST 2024 October 6-9

Obstructive Lung Diseases

SESSION TITLE: Biologics in Obstructive Lung Disease: An Evolving Treatment Landscape

SESSION TYPE: Rapid Fire Original Inv

PRESENTED ON: 10/08/2024 01:45 pm - 02:30 pm

EFFICACY OF TEZEPELUMAB IN ADULTS WITH MODERATE TO VERY SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE BY BLOOD EOSINOPHIL COUNT AND SMOKING HISTORY: PHASE 2A COURSE STUDY

MEILAN K HAN STEPHANIE CHRISTENSON MARK T DRANSFIELD JEAN BOURBEAU MOHIT BHUTANI PARAMESWARAN K NAIR DAVE SINGH MONA BAFADHEL CHRISTOPHER E BRIGHTLING CHRISTOPHER S AMBROSE ALES KOTALIK ÅSA HELLQVIST GUN ALMQVIST NAVREET S SINDHWANI MONIKA GOLABEK NESTOR MOLFINO AND SANDHIA PONNARAMBIL

https://doi.org/10.1016/j.chest.2024.06.2822

Tezepelumab in COPD, phase 2a COURSE study

- **Participants**
  - Current or former smoker (40-80years)
  - Diagnosis with moderate to severe COPD
- **Randmomization (double blind RCT)**
  - Tezepelumab 420mg SQ every 4 weeks over 52wks
  - Placebo
- **Primary outcome**
  - Annualized rate of moderate or severe COPD exacerbation over 52 weeks by baseline BEC C (≥ 150 cells/mL or< 150 cells/mL) and smoking history at baseline evaluated two ways: 1) smoking status (current or former smoker); and 2) median number of pack-years (≥ 47 years or < 47 years)

https://doi.org/10.1016/j.chest.2024.06.2822

BECs over 150 cells associated reduction AE

https://doi.org/10.1016/j.chest.2024.06.2822

IL-33 antibody Tozorakimab for COPD

SNUH 분당서울대학교병원 SEOUL NATIONAL UNIVERSITY BUNDANG HOSPITAL

ARTICLE

A Randomized Phase I Study of the Anti-Interleukin-33 Antibody Tozorakimab in Healthy Adults and Patients With Chronic Obstructive Pulmonary Disease

Fred Reid[1,*], Dave Singh[2], Muna Albayaty[3], Rachel Moate[4], Eulalia Jimenez[5], Muhammad Waqas Sadiq[6], David Howe[7], Monica Gavala[8], Helen Killick[9], Adam Williams[10], Surekha Krishnan[11], Alex Godwood[7], Animesh Shukla[11], Lisa Hewitt[11], Alejhandra Lei[12], Chris Kell[7], Hitesh Pandya[1], Paul Newcombe[9], Nicholas White[10], Ian C. Scott[9] and E. Suzanne Cohen[13]

Clin Pharmacol Ther. 2024 Mar;115(3):565-575.

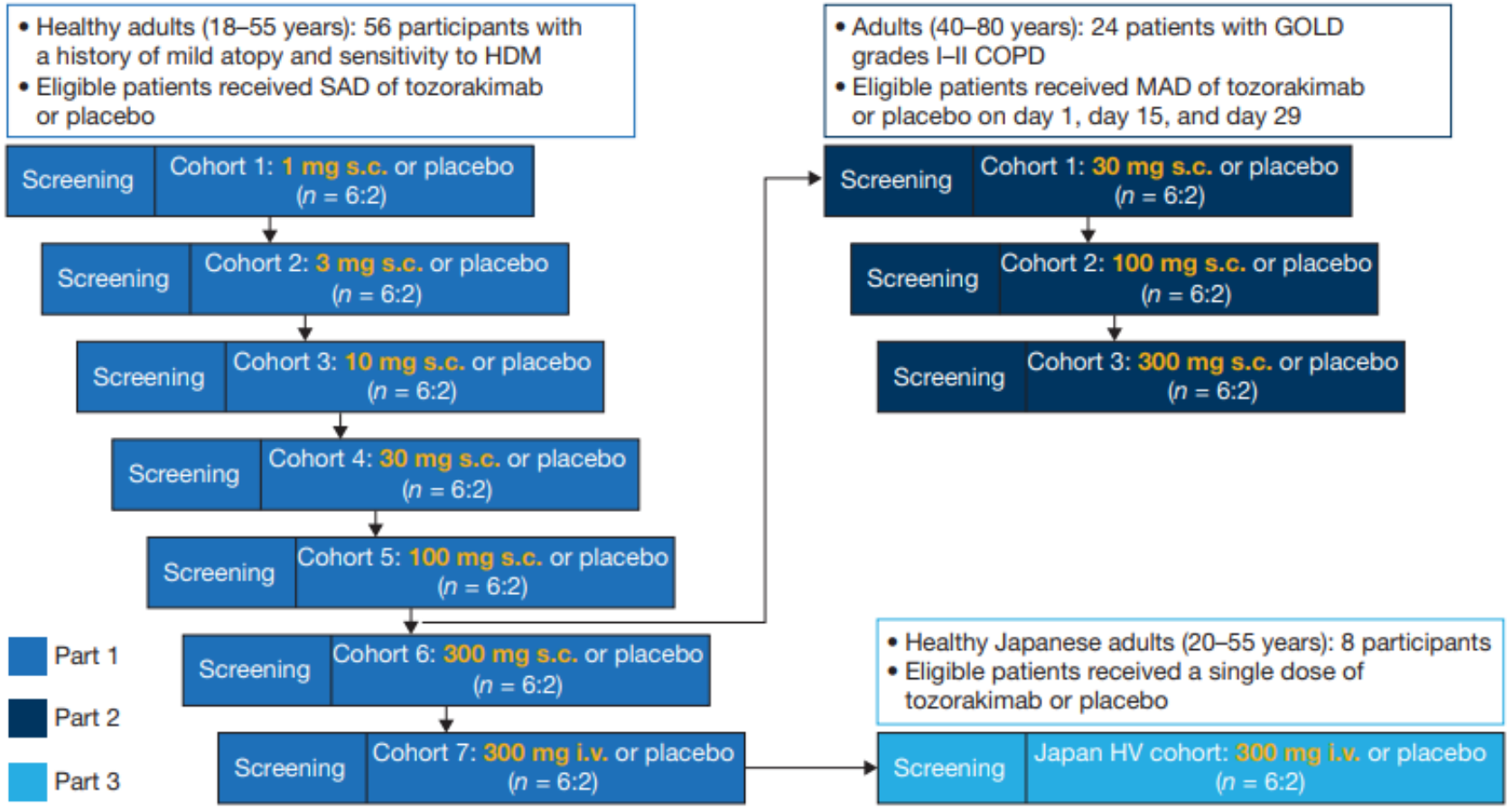
IL-33 antibody Tozorakimab for COPD

- **Participants and safety, PK and PD**
  - Part 1: 56 healthy participant with history of mild atophy-> single escalating dose of iv or SQ tozorakimab or placebo
  - Part 2: 24 patients with mild COPD ->multiple ascending doses of SQ tozorakimab or placebo
  - Part 3: 8 healthy Japanese participants ->single intravenous dose of tozorakimab or placebo

- **Primary outcome**
  - Safety data including vital sign, clinical laboratory parameters
  - PKs, immunogenicity, target engagement, PD biomarker

Clin Pharmacol Ther. 2024 Mar;115(3):565-575.

Study design of Tozorakimab phase 1a

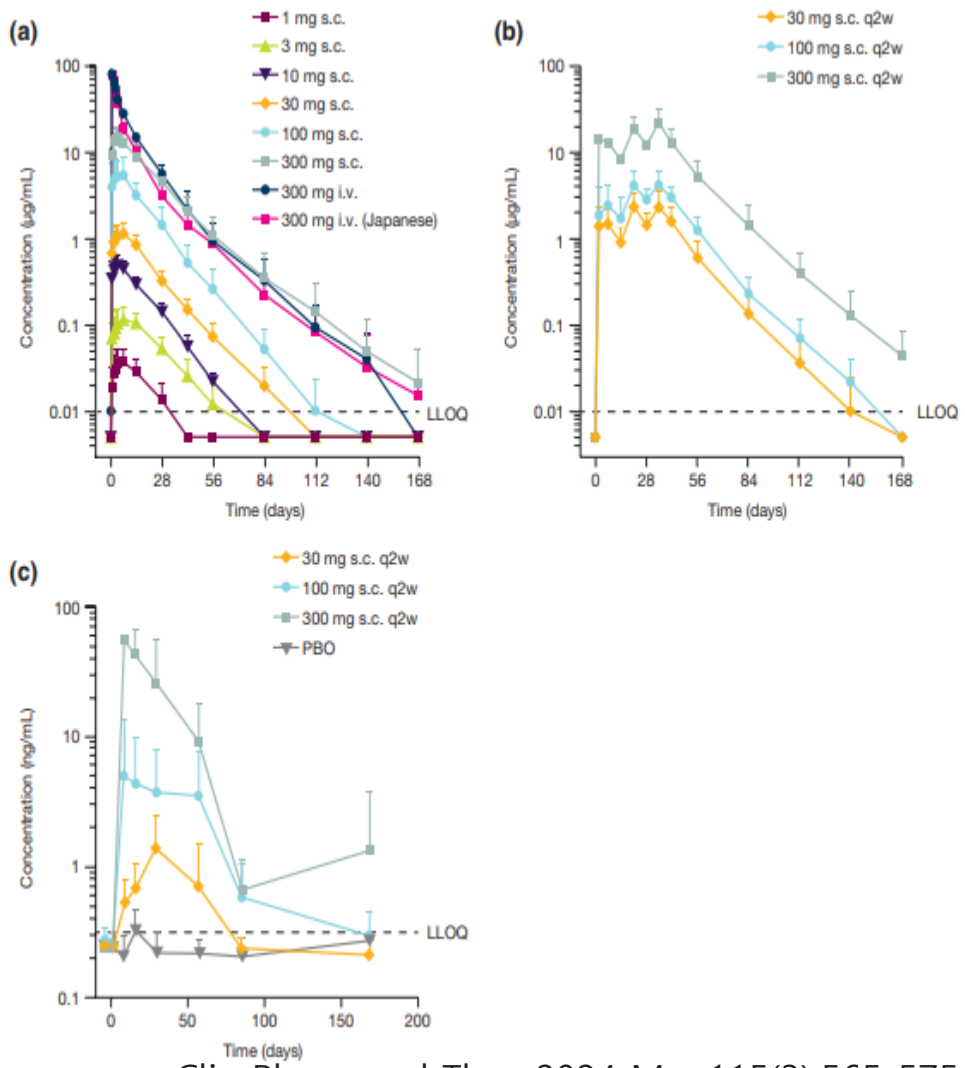


Clin Pharmacol Ther. 2024 Mar;115(3):565-575.

Safety and PK of Tozorakimab

Table 2 Summary of participants with TEAEs in the tozorakimab- and placebo-treated groups in each cohort of the as-treated population

	Part 1 SAD cohorts		Part 2 MAD cohorts		Part 3 Japanese cohort	
	Tozorakimab *n*=42	Placebo *n*=14	Tozorakimab *n*=18	Placebo *n*=6	Tozorakimab *n*=6	Placebo *n*=2
Participants with ≥1 TEAE	37 (88.1)	10 (71.4)	17 (94.4)	5 (83.3)	5 (83.3)	2 (100.0)
Participants with ≥1 TEAE of grade 3 severity	0 (0.0)	0 (0.0)	4 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)
Participants with ≥1 TESAE	0 (0.0)	0 (0.0)	3 (16.7)[a]	0 (0.0)	0 (0.0)	0 (0.0)
Participants with ≥1 TEAE leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration-site conditions	8 (19.0)	0 (0.0)	6 (33.3)	1 (16.7)	2 (33.3)	1 (50.0)
Influenza-like illness	3 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection-site reaction	1 (2.4)[b]	0 (0.0)	6 (33.3)	1 (16.7)	0 (0.0)	0 (0.0)
Catheter-site-related reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (50.0)
Immune system disorders	1 (2.4)	1 (7.1)	1 (5.6)	1 (16.7)	1 (16.7)	0 (0.0)
Seasonal allergy	1 (2.4)	1 (7.1)	1 (5.6)	1 (16.7)	1 (16.7)	0 (0.0)
Infections and infestations	25 (59.5)	6 (42.9)	10 (55.6)	2 (33.3)	0 (0.0)	1 (50.0)
Nasopharyngitis	20 (47.6)	4 (28.6)	2 (11.1)	0 (0.0)	0 (0.0)	1 (50.0)
Oral herpes	3 (7.1)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Lower respiratory tract infection	0 (0.0)	0 (0.0)	4 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinitis	0 (0.0)	0 (0.0)	6 (33.3)	2 (33.3)	0 (0.0)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	10 (23.8)	1 (7.1)	6 (33.3)	2 (33.3)	0 (0.0)	0 (0.0)
Cough	4 (9.5)	1 (7.1)	1 (5.6)	1 (16.7)	0 (0.0)	0 (0.0)
Rhinorrhea	2 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
COPD	0 (0.0)	0 (0.0)	3 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)



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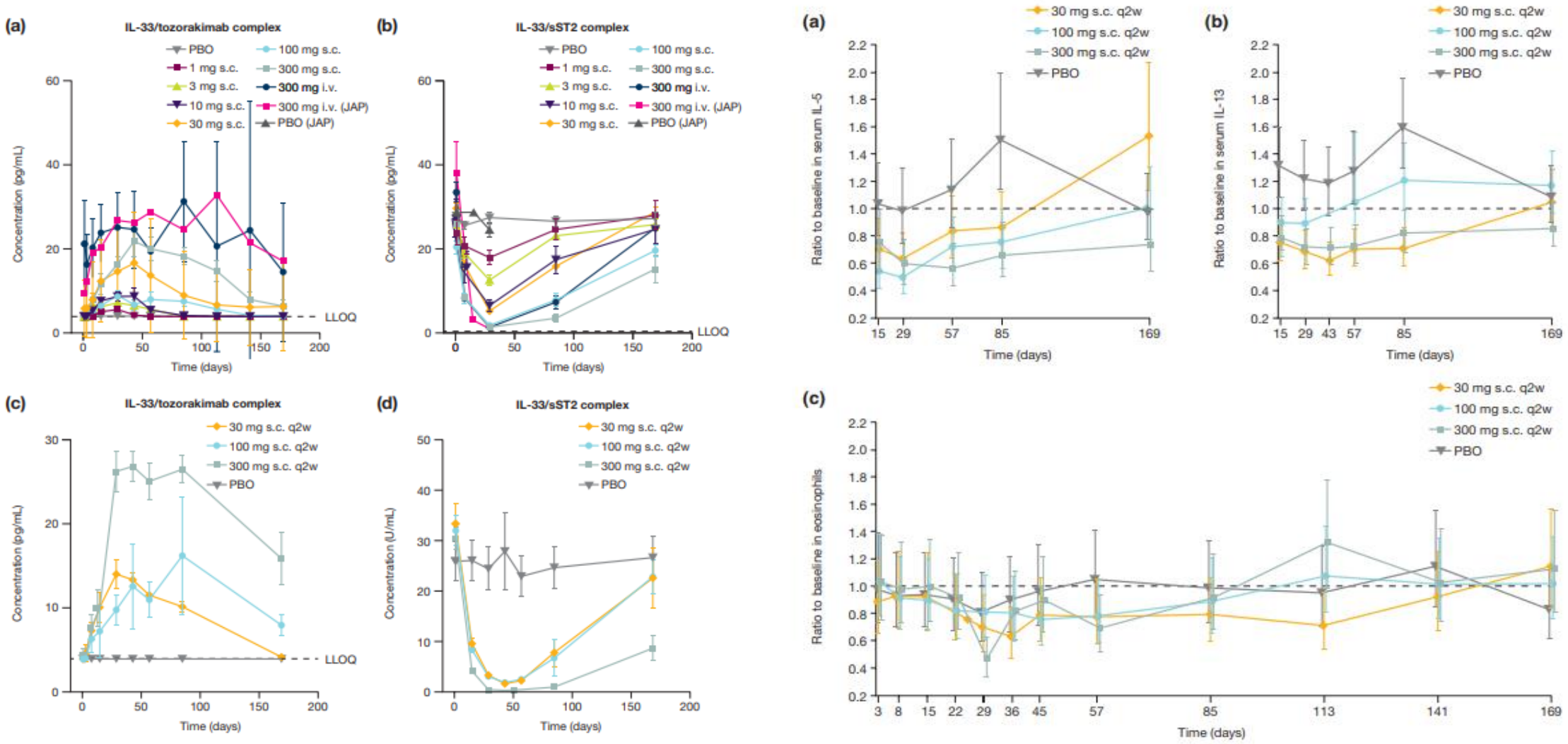
PD of Tozorakimab



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Summary 1

- Steroid : eosinophil guided steroid showed non inferior to standard therapy
- Bisoprolol did not reduce AECOPD in high-risk COPD patients
- High dose N-acetylcysteine
  - Long-term treatment with high dose NAC neither significantly reduced the annual rate of total AE nor improved lung function in patients with mild-to-moderate COPD
- Mirtazapine did not improve severe breathlessness in COPD

Summary 2

- Ensifentrine (nebulizer, phosphodiesterase 3 and 4 inhibitor)
  - Approved by the U.S. FDA for maintenance treatment of COPD
- Treprostinil (inhaled Treprostinil)
  - The study was terminated early d/t increased the risk of serious adverse events and mortality
- ICS
  - BEC measured on ICS is less predictive of treatment response
- Nebulized NAC is associated with decreased CAT phlegm score
- Nebulised interferon beta-1
  - Well-tolerated in patients with COPD, and upregulated lung antiviral defenses to accelerate viral clearance

Summary 3

- Dupilumab (IL-4 and IL-13 inhibitor)
  - In patients with COPD and type 2 inflammation (elevated BEC) dupilumab was associated with fewer AE and better lung function
- Tezepelumab (anti-TSLP)
  - Phase 2a study showed that patients with COPD with BEC ≥ 150 had less moderate or severe AE
- Anti IL-33
  - Tozorakimab significantly reduced serum IL-5 and IL-13 levels and tolerated in phase 1 study

Thank you for your attention