Endotype-Driven Selection of Biologics in Label-Free Airway Disease

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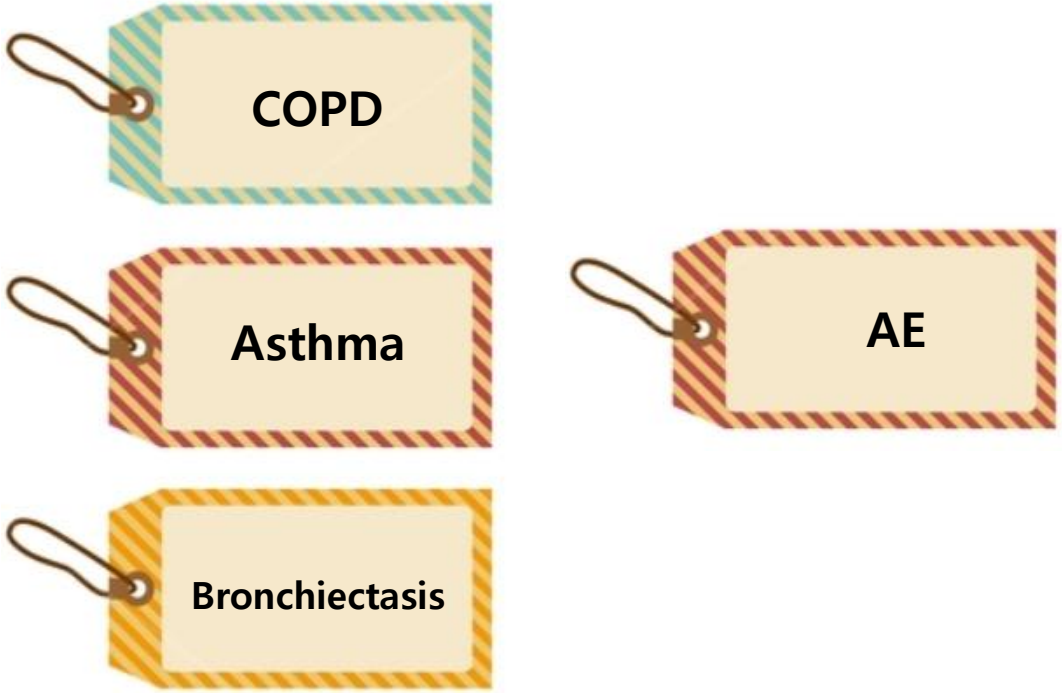
Label-free

- Label-free is a technique that **doesn't require additional labels** to identify or detect components or entities.

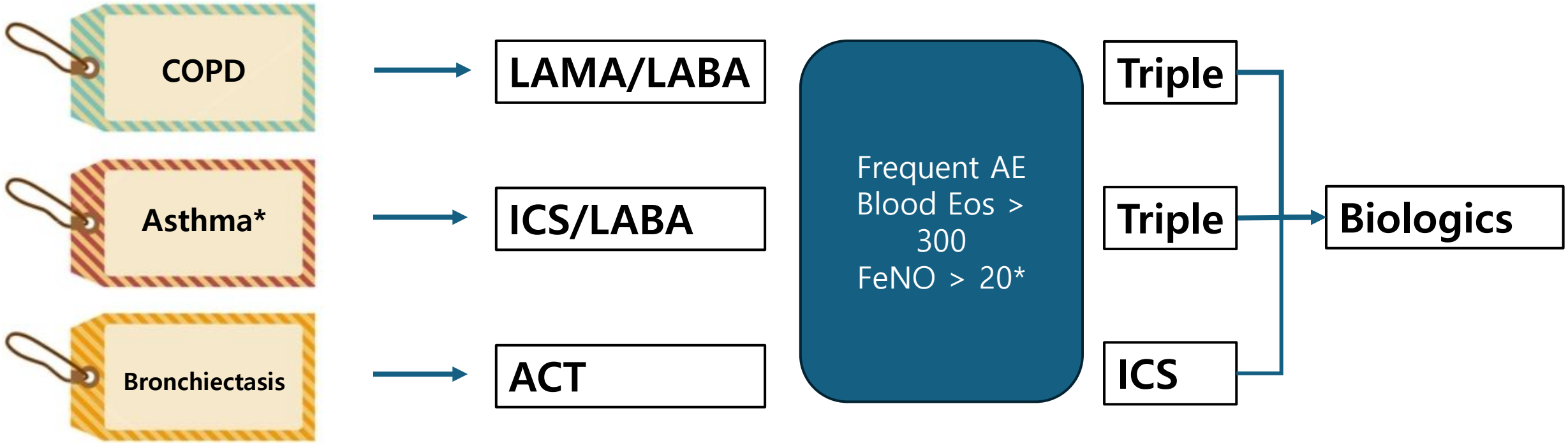
Type of labels in airway disease

- Disease label
  - COPD
  - Asthma
  - Bronchiectasis
- Status label
  - Stable
  - Exacerbation status



Label tag-driven treatment

If not controlled → Biomarker-driven Tx



Label free-driven treatment ?

Airway disease

FeNO > 20*
Blood Eos > 300
Sputum Eos 증가

ICS

AFL 존재

LAMA/ LABA

Frequent AE
Blood Eos > 300
FeNO > 20*
Sputum Eos 증가

Biologics

Sputum secretion

ACT

진단명: Chronic <u>T2-high (FENO, Bloo Eos, ets.)</u> airway disease with <u>AFL</u>

Type of labels in airway disease

- **Disease label**
  - **COPD**
  - **Asthma**
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  - **Stable**
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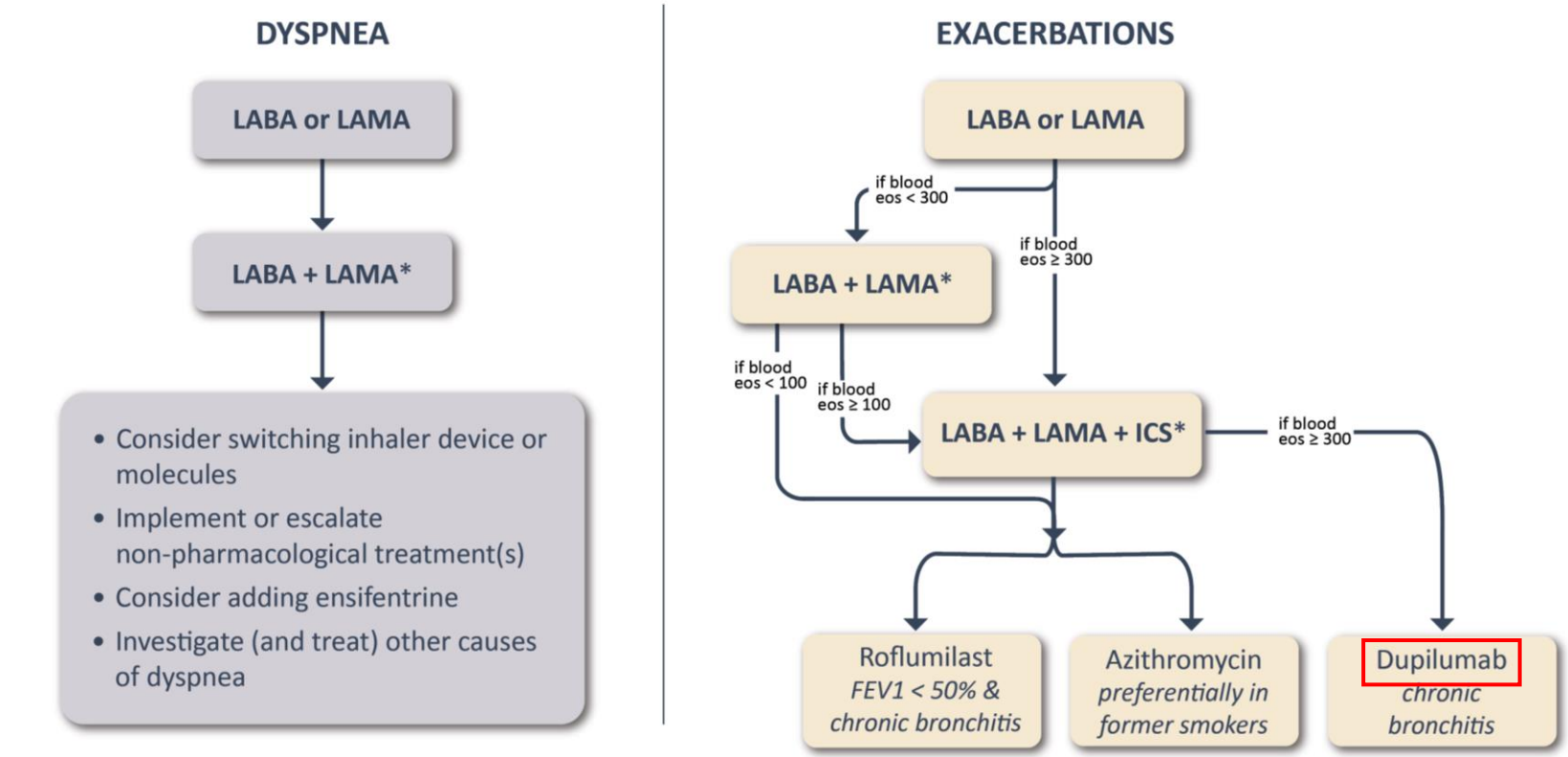
Follow-up Pharmacological Treatment

Figure 3.9



*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.

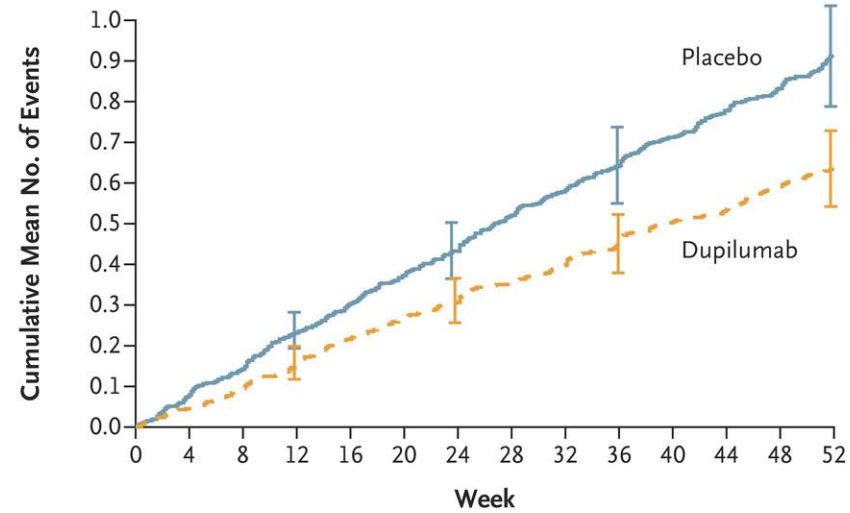
Exacerbations refers to the number of exacerbations per year.

CLINICAL TRIAL

Design: In a phase 3, international, double-blind, randomized, placebo-controlled trial, the efficacy and safety of dupilumab were evaluated in patients with COPD and an absolute blood eosinophil count of ≥300 per microliter.

Intervention: 939 current or former smokers 40 to 80 years of age, who had symptomatic COPD and were at increased risk for exacerbations despite the use of standard inhaled triple therapy, received add-on therapy with either subcutaneous dupilumab (300 mg) or placebo every 2 weeks for 52 weeks. The primary end point was the annualized rate of moderate or severe exacerbations of COPD during the trial.

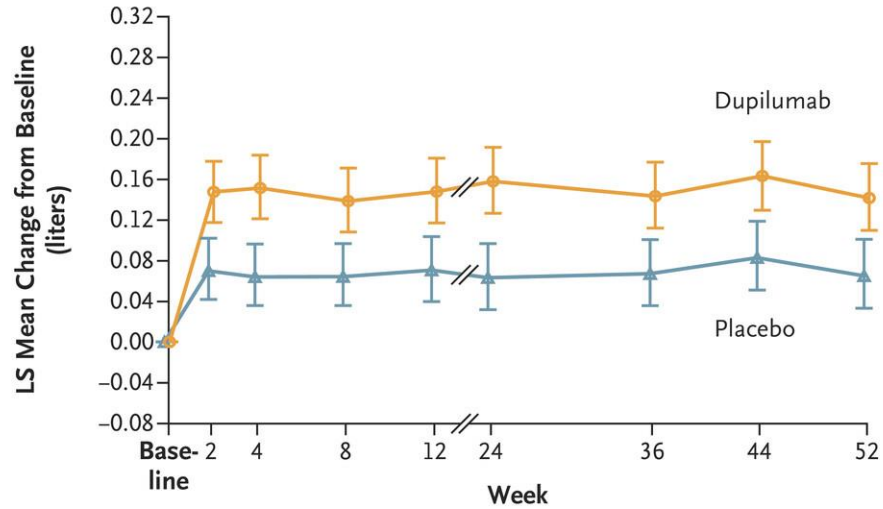
A Cumulative Moderate or Severe COPD Exacerbations



No. at Risk

Placebo	471	470	466	461	457	457	456	451	451	449	445	442	441	437
Dupilumab	468	467	465	464	462	460	458	457	456	454	451	450	448	437

B Prebronchodilator FEV_1



No. of Patients with Data

Placebo	471	455	459	439	439	435	415	404	420
Dupilumab	467	457	454	446	449	443	415	410	426

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

End Point	Placebo (N=471)	Dupilumab (N=468)	P Value
Primary end point			
Annualized rate of moderate or severe exacerbations of COPD			
Adjusted annualized rate of moderate or severe exacerbations — events per yr (95% CI)	1.10 (0.93 to 1.30)	0.78 (0.64 to 0.93)	
Rate ratio vs. placebo (95% CI)	—	0.70 (0.58 to 0.86)	<0.001
Secondary and other end points			
Change in prebronchodilator FEV_1 from baseline to wk 12			
Least-squares mean change (95% CI) — liters	0.077 (0.042 to 0.112)	0.160 (0.126 to 0.195)	
Least-squares mean difference vs. placebo (95% CI) — liters	—	0.083 (0.042 to 0.125)	<0.001
Change in prebronchodilator FEV_1 from baseline to wk 52			
Least-squares mean change (95% CI) — liters	0.070 (0.033 to 0.107)	0.153 (0.116 to 0.189)	
Least-squares mean difference vs. placebo (95% CI) — liters	—	0.083 (0.038 to 0.128)	<0.001
Change in prebronchodilator FEV_1 from baseline to wk 12 among patients with a baseline F_ENO ≥20 ppb			
Least-squares mean change (95% CI) — liters	0.108 (0.038 to 0.177)	0.232 (0.164 to 0.299)	
Least-squares mean difference vs. placebo (95% CI) — liters	—	0.124 (0.045 to 0.203)	0.002
Change in prebronchodilator FEV_1 from baseline to wk 52 among patients with a baseline F_ENO ≥20 ppb			
Least-squares mean change (95% CI) — liters	0.120 (0.047 to 0.192)	0.247 (0.176 to 0.318)	
Least-squares mean difference vs. placebo (95% CI) — liters	—	0.127 (0.042 to 0.212)	0.003

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

End Point	Placebo (N=471)	Dupilumab (N=468)	P Value
Primary end point			
Annualized rate of moderate or severe exacerbations of COPD			
Adjusted annualized rate of moderate or severe exacerbations — events per yr (95% CI)	1.10 (0.93 to 1.30)	0.78 (0.64 to 0.93)	
Rate ratio vs. placebo (95% CI)	—	0.70 (0.58 to 0.86)	<0.001
Annualized rate of moderate or severe exacerbations of COPD among patients with a baseline F_ENO ≥20 ppb			
Adjusted annualized rate of moderate or severe exacerbations — events per yr (95% CI)	1.12 (0.83 to 1.50)	0.70 (0.51 to 0.96)	
Rate ratio vs. placebo (95% CI)	—	0.62 (0.45 to 0.87)	0.005

* End points are listed in the order in which they were hierarchically tested.

Mepolizumab (METREX/METREO)

Phase 3, Randomized placebo-controlled, double-blind parallel-group trial

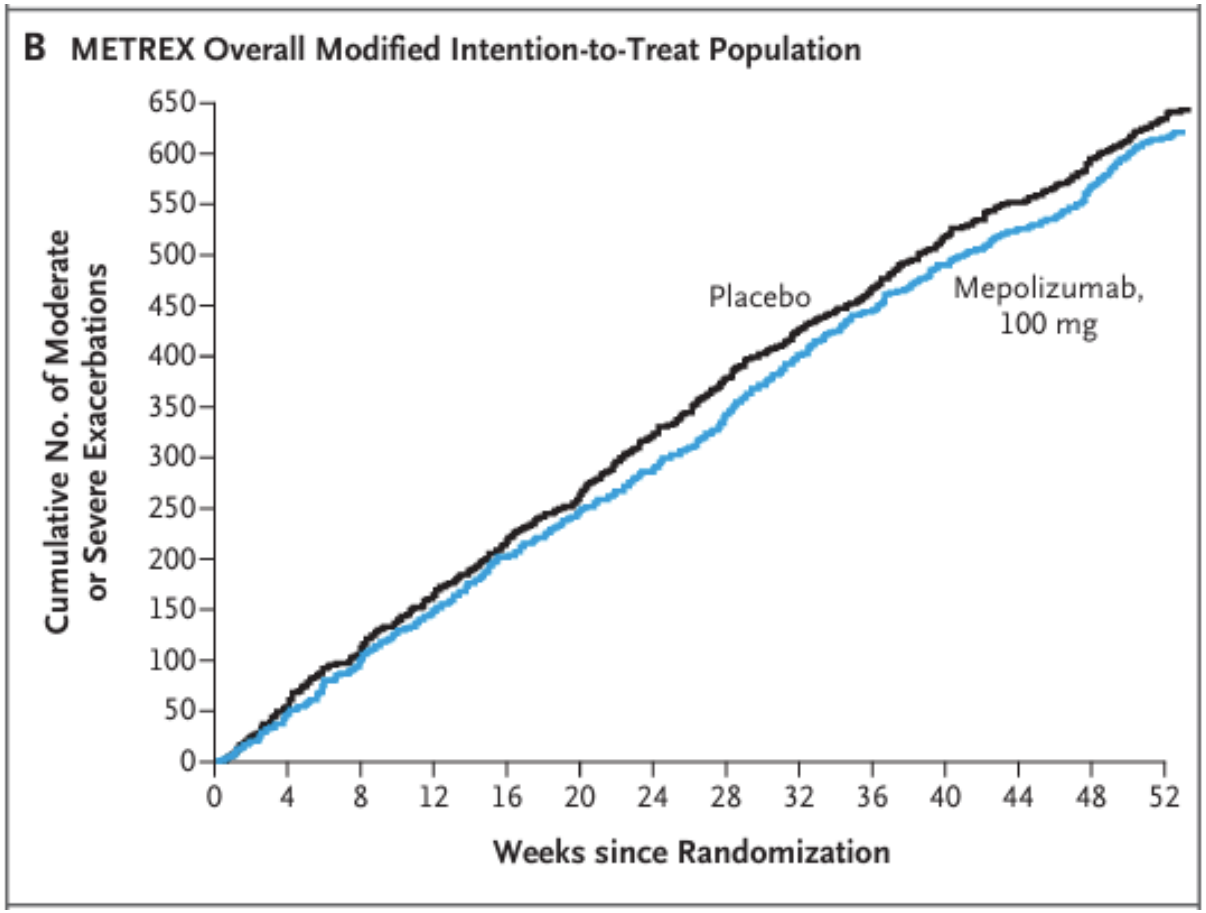
METREX
Inclusion
Adults (with COPD ≥ 40 years) who had a history of mod-to-severe AE while taking triple inhaler therapy

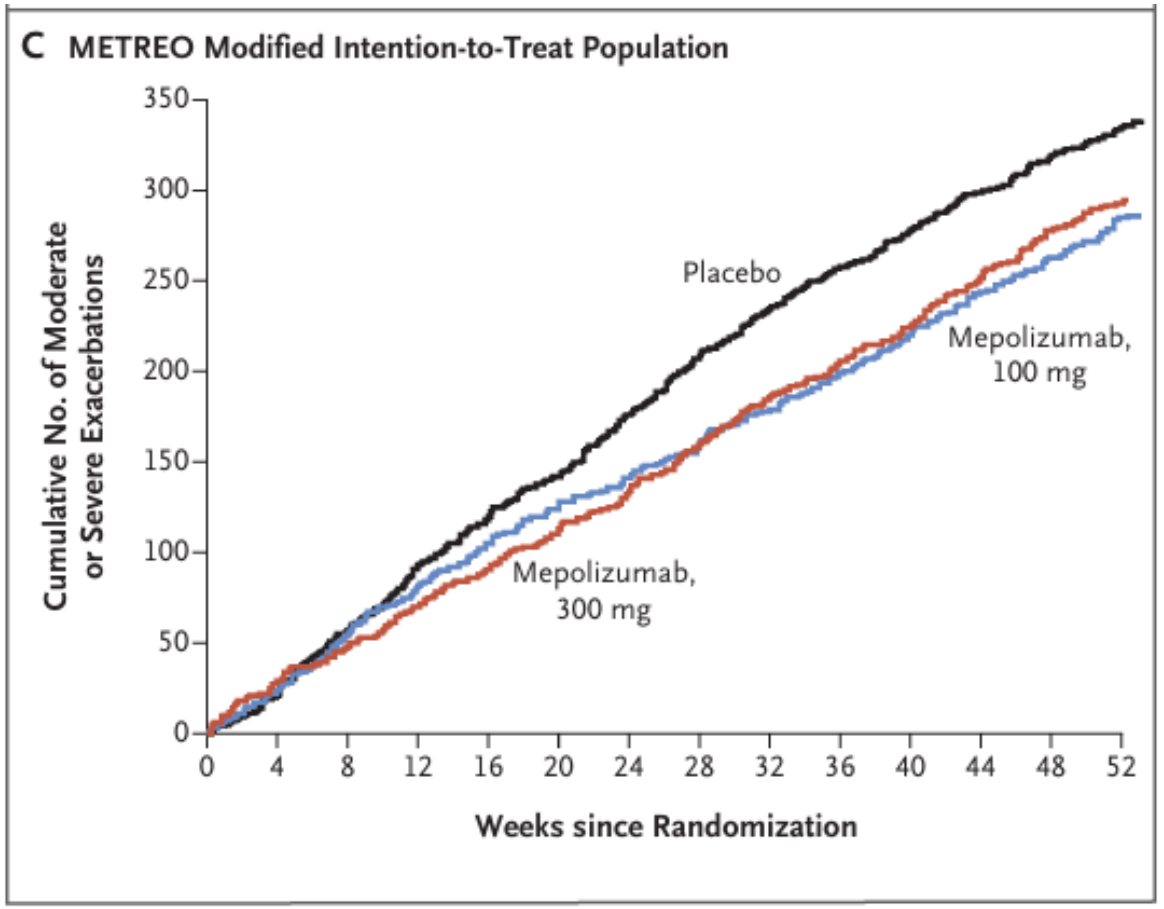
METREX
- Subgroup analysis according to blood eos

METREO
- All patients had a blood eos ≥ 150 at screening or ≥ 300 during the previous year

Primary outcome
-Annual rate of mod-to-severe AE

Mepolizumab (METREX/METREO)

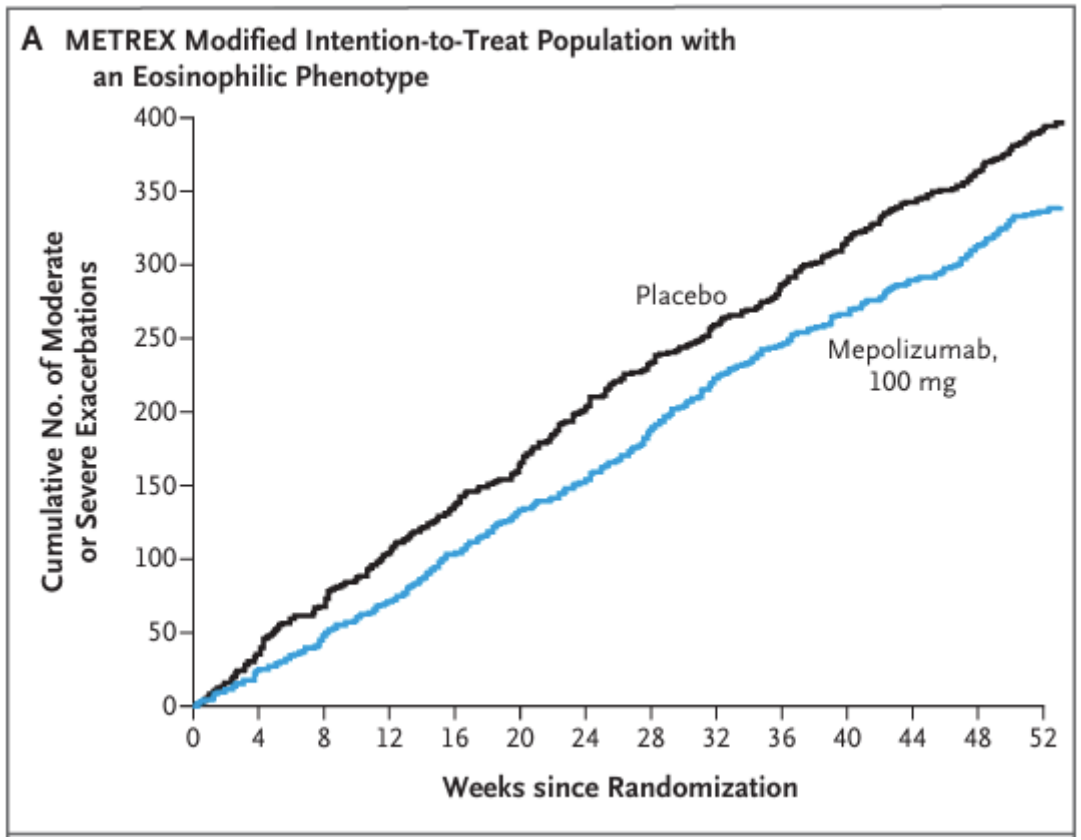




0.98 (0.85 to 1.12)

0.80 (0.65 to 0.98) / 0.86 (0.70 to 1.05)

Eos count ≥150 at screening or ≥300 at any point in the previous year



Issued: 06 September 2024, London UK

GSK announces positive results from phase III trial of *Nucala* (mepolizumab) in COPD

- Primary endpoint met with a statistically significant and clinically meaningful reduction in annualised rate of moderate/severe exacerbations vs. placebo with data up to two years

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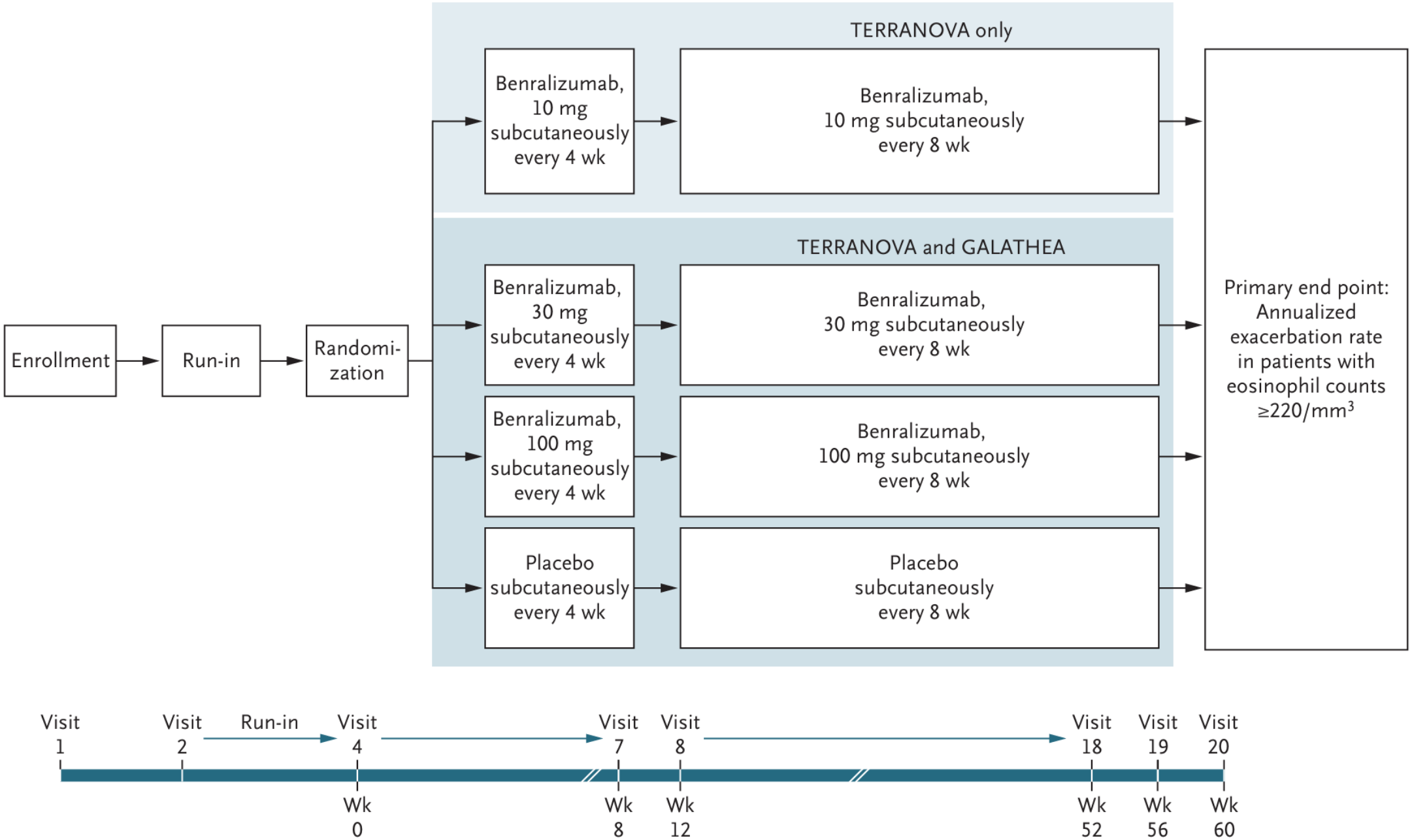
GSK plc (LSE/NYSE: GSK) today announced positive headline results of MATINEE, the phase III clinical trial evaluating *Nucala* (mepolizumab), a monoclonal antibody that targets interleukin-5 (IL-5) in adults with chronic obstructive pulmonary disease (COPD).

The trial recruited COPD patients with broad clinical presentations of chronic bronchitis and/or emphysema, who were receiving optimised inhaled maintenance therapy. Participants were also required to have evidence of type 2 inflammation characterised by raised blood eosinophil count.[1] MATINEE met its primary endpoint with the addition of *Nucala* to inhaled maintenance therapy, and study results showed a statistically significant and clinically meaningful reduction in the annualised rate of moderate/severe exacerbations versus placebo with patients treated for up to 104 weeks.

https://www.gsk.com/en-gb/media/press-releases/gsk-announces-positive-results-from-phase-iii-trial-of-nucala-mepolizumab-in-copd/



Criner et al. N Engl J Med. 2019;381(11):1023-1034. PMID: 31112385.

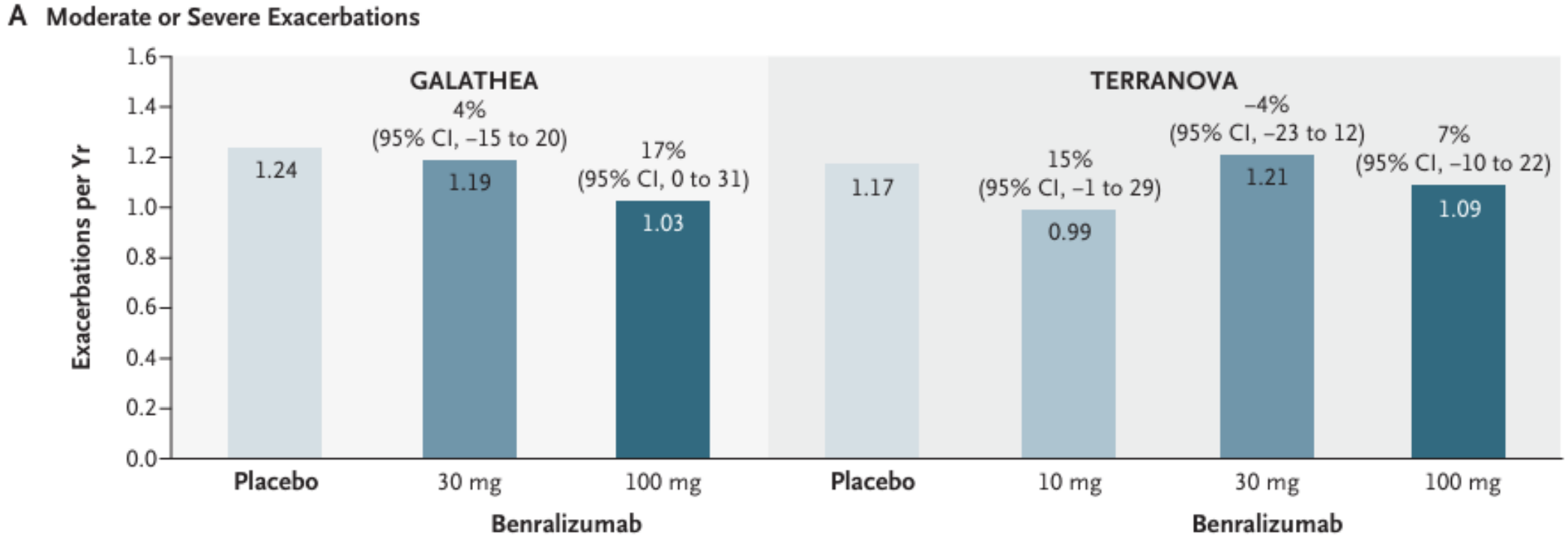


Table 2. Analysis of Efficacy in Patients with Baseline Blood Eosinophil Counts of 220 per Cubic Millimeter or Greater.*

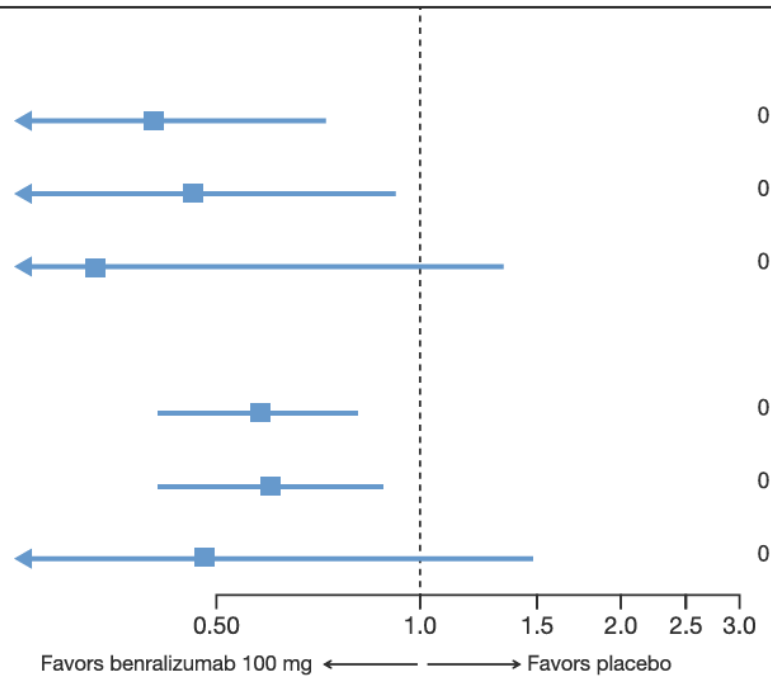
End Point	GALATHEA			TERRANOVA			
	Benralizumab, 30 mg (N=382)	Benralizumab, 100 mg (N=379)	Placebo (N=359)	Benralizumab, 10 mg (N=377)	Benralizumab, 30 mg (N=394)	Benralizumab, 100 mg (N=386)	Placebo (N=388)
Exacerbations							
Estimated annual rate (95% CI) — exacerbations/yr	1.19 (1.04–1.36)	1.03 (0.90–1.19)	1.24 (1.08–1.42)	0.99 (0.87–1.13)	1.21 (1.08–1.37)	1.09 (0.96–1.23)	1.17 (1.04–1.32)
Rate ratio, benralizumab vs. placebo (95% CI)†	0.96 (0.80–1.15)	0.83 (0.69–1.00)	—	0.85 (0.71–1.01)	1.04 (0.88–1.23)	0.93 (0.78–1.10)	—
Unadjusted P value	0.65	0.05	—	0.06	0.66	0.40	—

Criner et al. N Engl J Med. 2019;381(11):1023-1034. PMID: 31112385.

A post-hoc analysis of GALATHEA and TERRANOVA study

1) ≥3 COPD exacerbations in the previous year
2) Triple therapy
3) baseline blood Eos ≥300 cells/μL

	Exacerbation events		Crude rate			
	Benralizumab	Placebo	Benralizumab	Placebo	Rate ratio (95% CI)	*p* values
30 days						
Moderate/severe	14	62	1.67	4.55	0.40 (0.22, 0.72)	0.0022
Moderate	11	45	1.31	3.30	0.46 (0.24, 0.91)	0.0247
Severe	3	17	0.36	1.25	0.33 (0.08, 1.30)	0.1133
90 days						
Moderate/severe	48	127	1.93	3.74	0.58 (0.41, 0.81)	0.0017
Moderate	40	103	1.61	3.03	0.60 (0.41, 0.87)	0.0071
Severe	8	24	0.32	0.71	0.48 (0.16, 1.43)	0.1862



Singh et al. Int J Chron Obstruct Pulmon Dis. 2023;18:1595-1599. PMID: 37533773

RESOULTE study

ClinicalTrials.gov

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Active, not recruiting

Efficacy and Safety of Benralizumab in Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD) With a History of Frequent Exacerbations (RESOLUTE)

ClinicalTrials.gov ID NCT04053634

Sponsor AstraZeneca

Information provided by AstraZeneca (Responsible Party)

Last Update Posted 2025-03-25

https://clinicaltrials.gov/study/NCT04053634?rank=1&tab=table

Overview | Arms and interventions | Documents | Contacts

Official Title

A Multicenter, Randomized, Double-blind, Chronic-dosing, Parallel-group, Placebo-controlled Phase 3 Study to Evaluate the Efficacy and Safety of Benralizumab 100 mg in Patients with Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD) with a History of Frequent COPD Exacerbations and Elevated Peripheral Blood Eosinophils (RESOLUTE)

eosinophils (≥300/μL)

Medical condition
Chronic Obstructive Pulmonary Disease

Phase
Phase 3

Healthy volunteers
No

Study drug
-

Sex
All

Actual Enrollment
689

Study type
Interventional

Age
40 Years - 85 Years

Date
Study Start Date: 26 Aug 2019
Estimated Primary Completion Date: 21 Aug 2025
Estimated Study Completion Date: 21 Aug 2025

Study design
Allocation: Randomized
Endpoint Classification: -
Intervention Model: Parallel Assignment
Masking: -
Primary Purpose: Treatment

Verification:
Verified 01 Feb 2025 by AstraZeneca

Sponsors
AstraZeneca

Collaborators
-

Arms	Assigned Interventions
Experimental: Benralizumab **Administrated subcutaneously (SC) every 4 weeks for the first 3 doses, then every 8 weeks**	Biological/Vaccine: Benralizumab Benralizumab solution for injection in accessorized prefilled syringe (APFS) will be administered subcutaneously (SC) every 4 weeks for the first 3 doses - Weeks 0, 4 and 8, and then every 8 weeks until the end of treatment.
Placebo Comparator: Placebo **Administrated subcutaneously every 4 weeks for the first 3 doses, then every 8 weeks**	Biological/Vaccine: Placebo Matching placebo will be administered subcutaneously with accessorized prefilled syringe (APFS) every 4 weeks for the first 3 doses - Weeks 0, 4 and 8, and then every 8 weeks until the end of treatment.

Type of labels in airway disease

- **Disease label**
  - COPD
  - **Asthma**
  - Bronchiectasis
- Status label
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5 *Investigate* further and provide *patient support*

- Investigate for comorbidities/differential diagnoses and treat/refer as appropriate
  - Consider: CBC, CRP, IgG, IgA, IgM, IgE, fungal precipitins; CXR and/or HRCT chest; DLCO; DEXA scan
  - Skin prick testing or specific IgE for relevant allergens, if not already done
  - Consider screening for adrenal insufficiency in patients taking maintenance OCS or high dose ICS
  - If blood eosinophils ≥300/µl, look for and treat non-asthma causes, including parasites (e.g. Strongyloides serology, or stool examination)
  - If hypereosinophilia e.g. ≥1500/µl, consider causes such as EGPA
  - Other directed testing (e.g. ANCA, CT sinuses, BNP, echocardiogram) based on clinical suspicion
- Consider need for social/psychological support
- Involve multidisciplinary team care (if available)
- Invite patient to enroll in registry (if available) or clinical trial (if appropriate)

6 Assess the *severe asthma phenotype*

Could patient have Type 2 airway inflammation?

yes

Type 2 airway inflammation

- Consider adherence tests
- Consider increasing the ICS dose for 3-6 months
- Consider add-on non-biologic treatment for specific Type 2 clinical phenotypes, e.g. AERD, ABPA, chronic rhinosinusitis, nasal polyposis, atopic dermatitis

Is add-on Type 2 biologic therapy available/ affordable?

yes

no

If add-on Type 2-targeted biologic therapy is NOT available/affordable

- Consider higher dose ICS, if not used
- Consider other add-on therapy (e.g. LAMA, LM/LTRA, low dose azithromycin)
- As last resort, consider add-on low dose OCS, but implement strategies to minimize side-effects
- Stop ineffective add-on therapies

Go to section **10**

no

Type 2 inflammation

- Blood eosinophils ≥150/µl and/or
- FeNO ≥20 ppb and/or
- Sputum eosinophils ≥2%, and/or
- Asthma is clinically allergen-driven

(Repeat blood eosinophils and FeNO up to 3x, at least 1-2 weeks after OCS or on lowest possible OCS dose)

*Note: these are **not** the criteria for add-on biologic therapy (see **8**)*

No evidence of Type 2 airway inflammation

- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects
- Avoid exposures (tobacco smoke, allergens, irritants)
- Consider investigations (if available and not done)
  - Sputum induction
  - High resolution chest CT
  - Bronchoscopy for alternative/additional diagnoses
- Consider trial of add-on treatments (if available and not already tried)
  - LAMA
  - Low dose azithromycin
  - Anti-IL4Rα* if taking maintenance OCS
  - Anti-TSLP* (but insufficient evidence in patients on maintenance OCS)
  - As last resort, consider add-on low dose OCS, but implement strategies to minimize side-effects
- Consider bronchial thermoplasty (+ registry)
- Stop ineffective add-on therapies

Not currently eligible for T2-targeted biologic therapy

Go to section **10**

7 Consider *other* treatments

8 Consider *add-on biologic Type 2-targeted* treatments

- Consider add-on Type 2-targeted biologic therapy for patients with exacerbations or poor symptom control on high dose ICS-LABA, who have evidence of Type 2 inflammation*
- Consider **local payer eligibility criteria***, **comorbidities** and **predictors of response** when choosing between available therapies
- Also consider cost, dosing frequency, route (SC or IV), patient preference

Which biologic is appropriate to start first?

	Eligibility	*Predictors of asthma response*
Anti-IgE *(omalizumab)*	*Is the patient eligible for **anti-IgE** for severe allergic asthma?** • Sensitization on skin prick testing or specific IgE • Total serum IgE and weight within dosage range • Exacerbations in last year	*What factors may predict good asthma response to anti-IgE?* • Blood eosinophils ≥260/µl ++ • FeNO ≥20 ppb + • Allergen-driven symptoms + • Childhood-onset asthma +
Anti-IL5 / Anti-IL5R *(benralizumab, mepolizumab, reslizumab)*	*Is the patient eligible for **anti-IL5 / anti-IL5R** for severe eosinophilic asthma?** • Exacerbations in last year • Blood eosinophils, e.g. ≥150/µl or ≥300/µl	*What factors may predict good asthma response to anti-IL5/5R?* • Higher blood eosinophils +++ • More exacerbations in previous year +++ • Adult-onset of asthma ++ • Nasal polyposis ++
Anti-IL4Rα *(dupilumab)*	*Is the patient eligible for **anti-IL4Rα** for severe eosinophilic/Type 2 asthma?** • Exacerbations in last year • Blood eosinophils ≥150 and ≤1500/µl, or FeNO ≥25 ppb, or taking maintenance OCS	*What factors may predict good asthma response to anti-IL4Rα?* • Higher blood eosinophils +++ • Higher FeNO +++
Anti-TSLP *(tezepelumab)*	*Is the patient eligible for **anti-TSLP** for severe asthma?** • Exacerbations in last year	*What factors may predict good asthma response to anti-TSLP?* • Higher blood eosinophils +++ • Higher FeNO +++

no / *no* (between each biologic)

Eligible for none? Return to section 7

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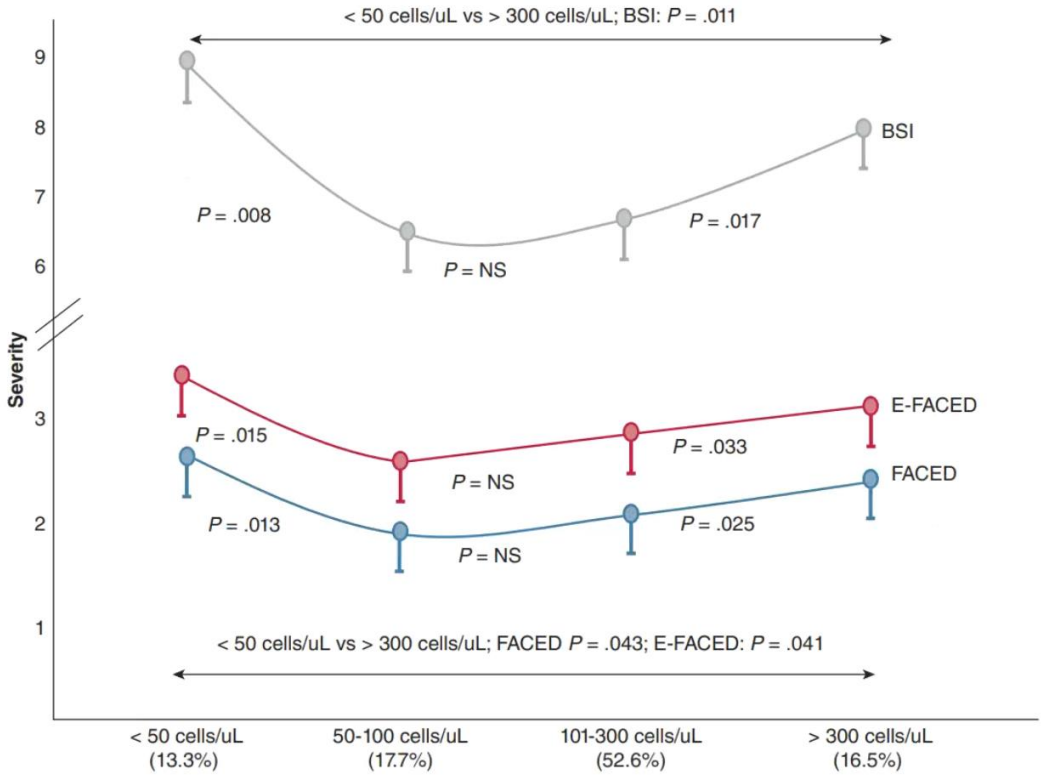
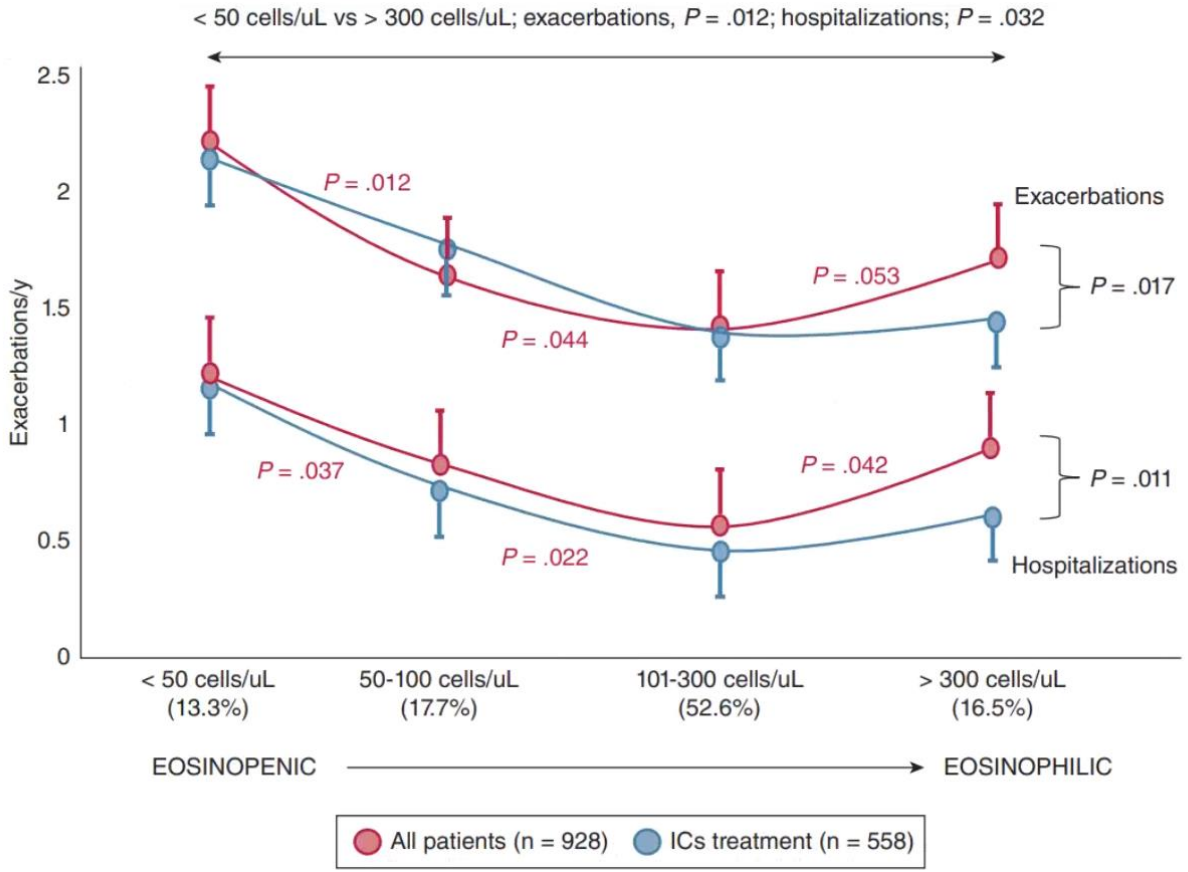
Eosinophilic inflammation, ICS, and AE





Martinez-Garcia. CHEST. 2023 In press.

Biologics

450 patients in Hannover Clinic

11% ≥3% eos

21 patients with refractory disease

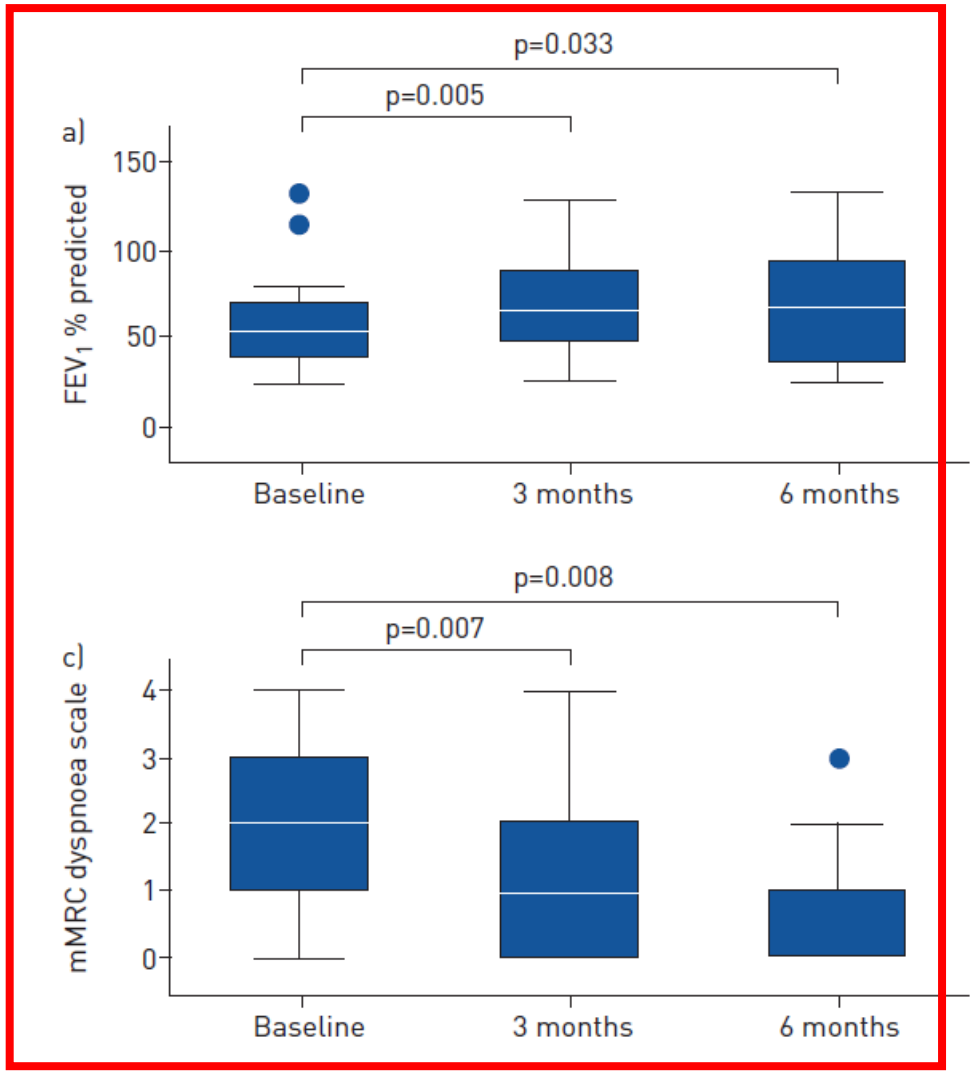
- Frequent or severe AE requiring OCS in the previous year
- Chronic airflow limitation
- Reduced QoL
- Reproducible peripheral eos ⩾300

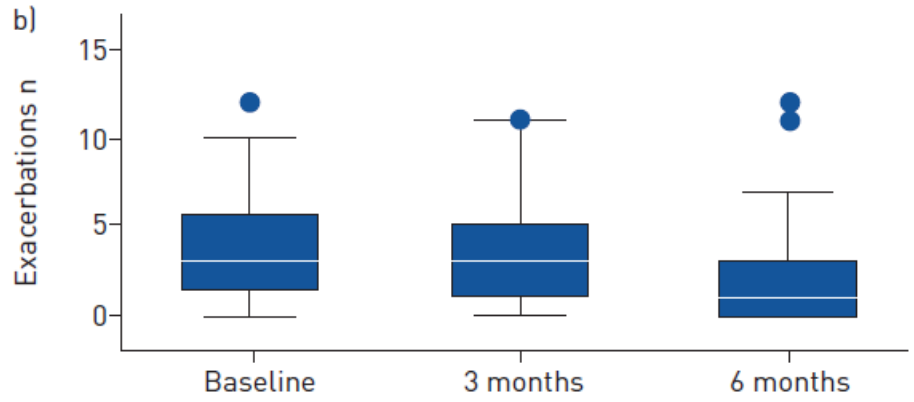
Recommended vaccinations, pulmonary rehabilitation, daily chest physiotherapy with adjunct nebulised mucolytics and triple inhalers

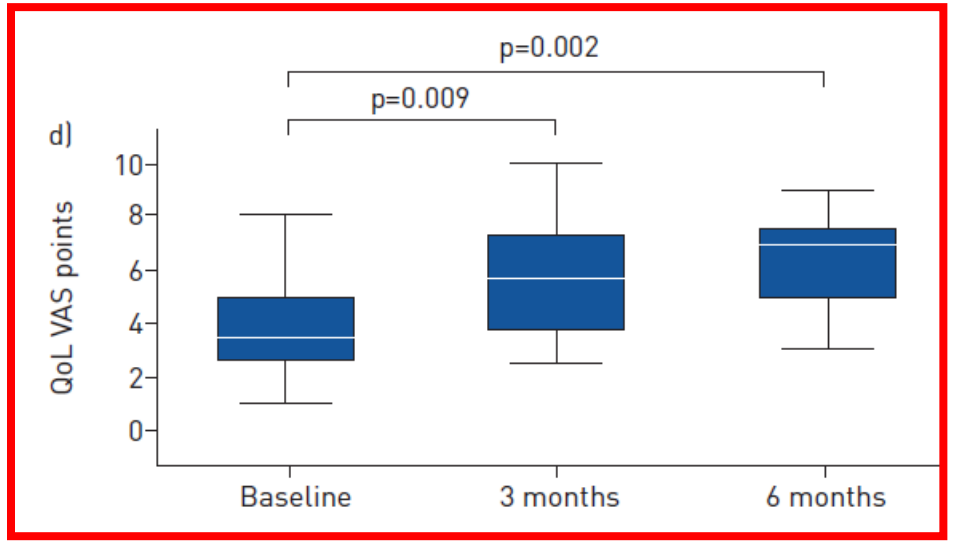
9 - Benralizumab

12 - mepolizumab

Rademacher. Eur Respir J 2020; 55: 1901333







Significant improvement in FEV_1, Dyspnea (mMRC), and QoL, but not AE

Rademacher et al. Eur Respir J 2020; 55: 1901333

Label free-driven treatment ?

FeNO > 20*
Blood Eos > 300
Sputum Eos 증가

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AFL 존재

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Biologics

Sputum secretion

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Phase 2 Acute exacerbations treated with BenRAlizumab (ABRA) trial

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

Abra?

"Abracadabra"는 흔히 마술사들이 사용하는 신비로운 주문으로 잘 알려져 있습니다. 그 기원과 사용은 매우 흥미로운데요:

1. **어원**:
   - 이 단어는 고대 언어에서 유래되었을 가능성이 높습니다. 특히 아람어, 라틴어, 혹은 헤브라이어에서 파생되었다고 추정됩니다.
   - 아람어에서 "abra"는 "만들다" 또는 "창조하다"를, "cadabra"는 "말로"를 의미한다고 해석할 수 있습니다. 즉, "말로써 무언가를 창조하다"라는 뜻이 담겨 있을 수 있습니다.
2. **역사적 사용**:
   - 중세 시대에 "Abracadabra"는 실제로 마법 주문으로 사용되었으며, 질병을 물리치거나 악령을 쫓아내기 위해 사용되었습니다.

Copilot

Study design

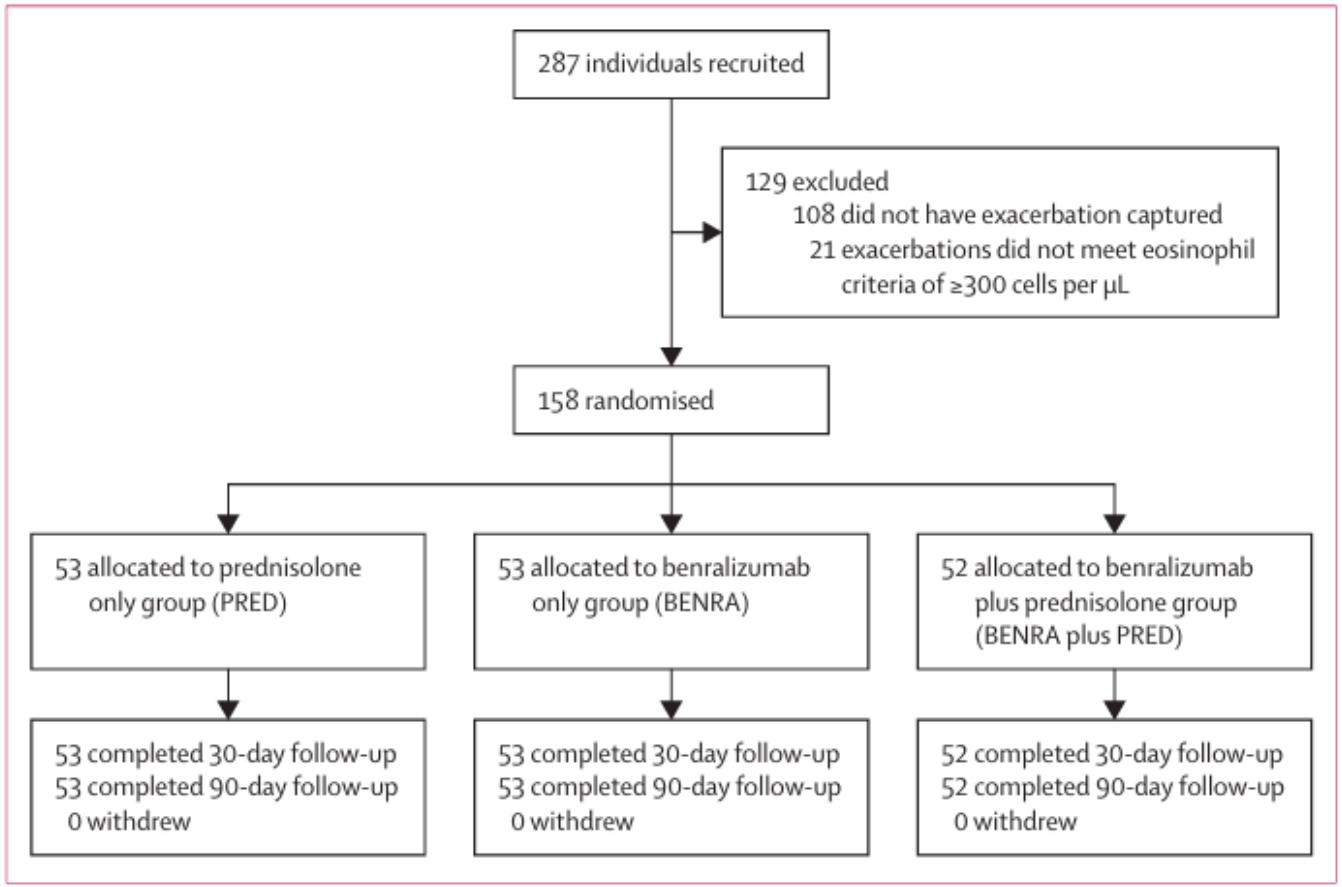
A double-blind, double-dummy, active placebo-controlled randomized trial

1. Study population
1) Adults (aged >= 18 years)
2) COPD (smokers at least 10 PY, FEV1/FVC < 0.7
3) Asthma (never or ex-smokers < 10 PY, variable AFL)

2. Exposure – BENRA vs. PD vs. BENRA + PD

3 Primary outcomes
1) % of treatment failures over 90 days
- Composite of death, hospitalization, and re-treatment requiring systemic CS or antibiotics

2) VAS symptoms at day 28



Ramakrishnan et al., Lancet Respir Med. 2025;13(1):59-68. PMID: 39615502.

A single admin of high-dose BENRA vs. PD (5days)

VS.

A single admin of high-dose BENRA vs. PD (5days)

VS.

2,842,543원/펜 x 3.3펜 = 938만원

20원 x 6T x 5일 = 600원

15,633배 가격

15,633배 정도 가격차이가 나는 자동차 2개만 알려줘

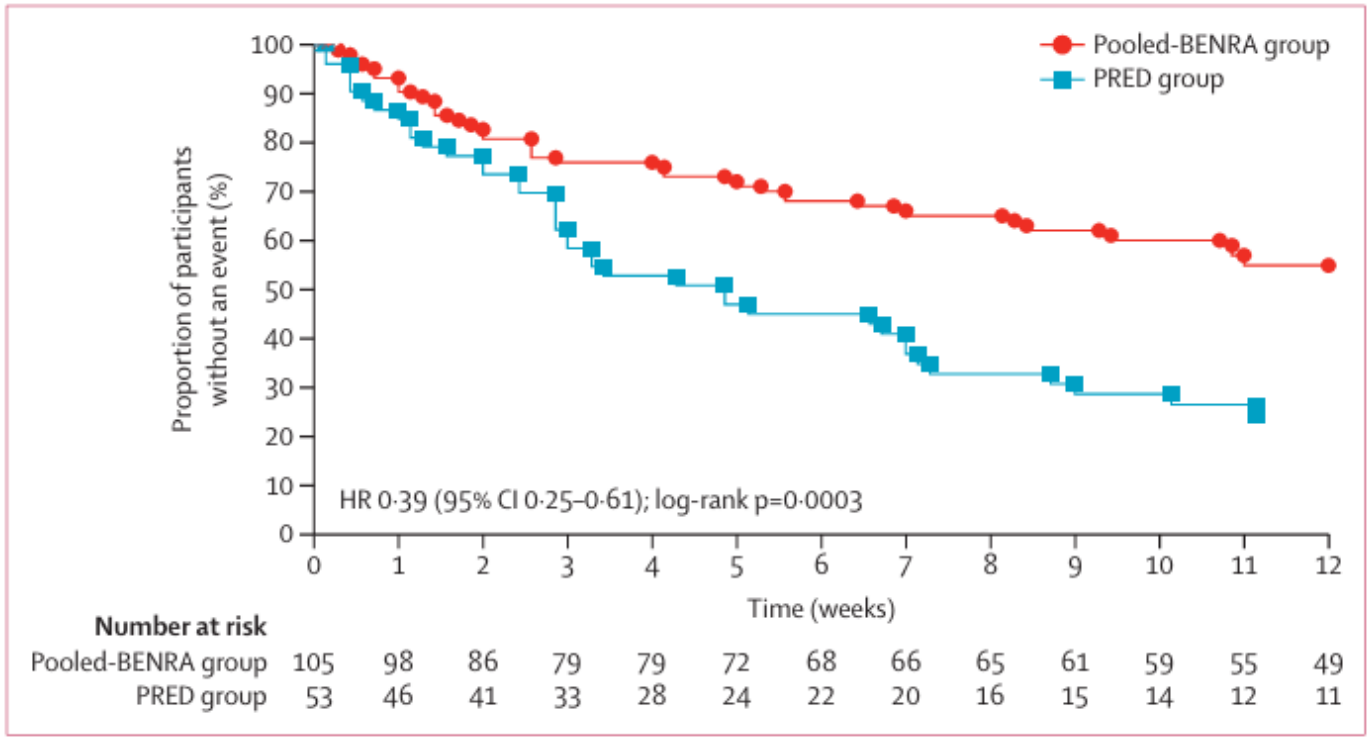
자동차 가격 차이가 15,633배 정도 나는 예를 들어보자면, 다음과 같은 비교가 가능합니다:

1. **타타 나노 (Tata Nano)**: 인도에서 출시된 초저가 자동차로, 약 2,000달러(한화 약 260만 원) 정도의 가격으로 판매되었습니다.
2. **롤스로이스 스웹테일 (Rolls-Royce Sweptail)**: 세계에서 가장 비싼 자동차 중 하나로, 약 1,300만 달러(한화 약 170억 원)에 달하는 가격으로 알려져 있습니다.

VS.

Copilot

Treatment failure over 90days



	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

Ramakrishnan et al., Lancet Respir Med. 2025;13(1):59-68. PMID: 39615502.

VAS change

	PRED group (n=53)	Pooled-BENRA group (n=105)	p value
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

	Pooled-BENRA group events (n/N; %)	PRED group events (n/N; %)	HR (95% CI)	Log-rank p value
Primary analysis				
Intention-to-treat population	47/105 (44·8%)	39/53 (73·6%)	0·39 (0·25–0·61)	0·0003
Adjudicated diagnosis				
Asthma	23/53 (43·4%)	25/35 (71·4%)	0·44 (0·25–0·78)	0·0037
COPD	19/36 (52·8%)	10/13 (76·9%)	0·43 (0·20–0·93)	0·027
Asthma and COPD	5/14 (35·7%)	3/5 (60·0%)	0·69 (0·16–2·91)	0·611
FEV_1 strata				
≥50% predicted normal	32/78 (41·0%)	27/40 (67·5%)	0·51 (0·30–0·85)	0·0087
<50% predicted normal	15/27 (55·6%)	12/13 (92·3%)	0·18 (0·07–0·47)	0·0012
Smoking history				
Current smoker	6/11 (54·5%)	4/4 (100%)	0·25 (0·05–1·15)	0·055
Ex-smoker	23/53 (43·4%)	19/27 (70·4%)	0·48 (0·26–0·89)	0·017
Non-smoker	18/41 (43·9%)	16/22 (72·2%)	0·45 (0·23–0·89)	0·018
Gender				
Male	13/41 (31·7%)	22/31 (71·0%)	0·39 (0·19–0·77)	0·0050
Female	34/64 (53·1%)	17/22 (77·3%)	0·45 (0·25–0·81)	0·0066
Age, years				
<50	11/34 (32·4%)	9/13 (69·2%)	0·38 (0·16–0·93)	0·028
≥50	36/71 (50·7%)	30/40 (75·0%)	0·49 (0·30–0·80)	0·0080
Eosinophils, cell per µL				
300–500	25/55 (45·5%)	13/16 (81·3%)	0·39 (0·20–0·77)	0·0048
>500	22/50 (44·0%)	26/37 (70·3%)	0·49 (0·27–0·86)	0·012
Fractional exhaled nitric oxide, parts per billion				
≤30	22/39 (56·4%)	12/17 (70·6%)	0·61 (0·30–1·23)	0·16
>30	23/63 (36·5%)	25/34 (73·5%)	0·36 (0·20–0·65)	0·0003

Benralizumab – life threatening AE

Patient 1 – MV
Patient 2 – VV-ECMO
Patient 3 – VV-ECMO
Patient 4 - MV

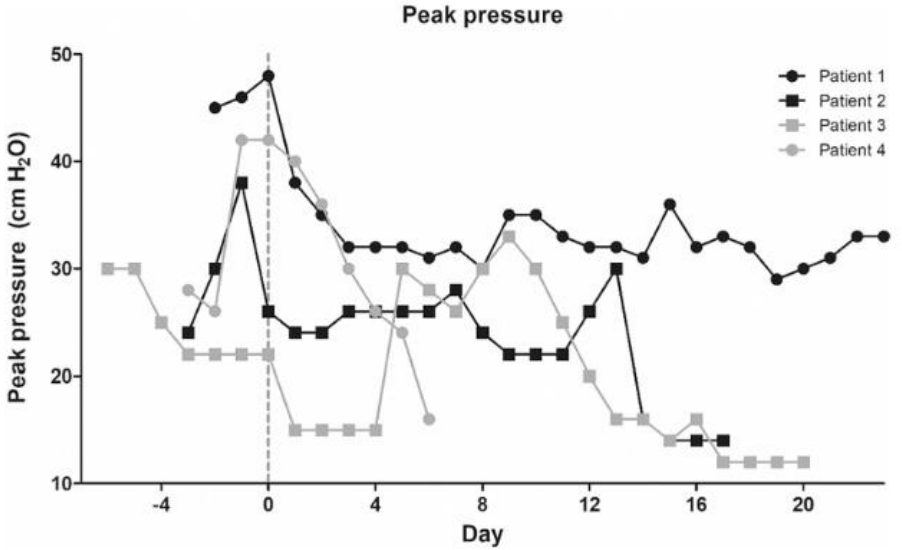


FIGURE 1 | Ventilator peak pressures are shown for the individual patients. On day 0 benralizumab was administered.

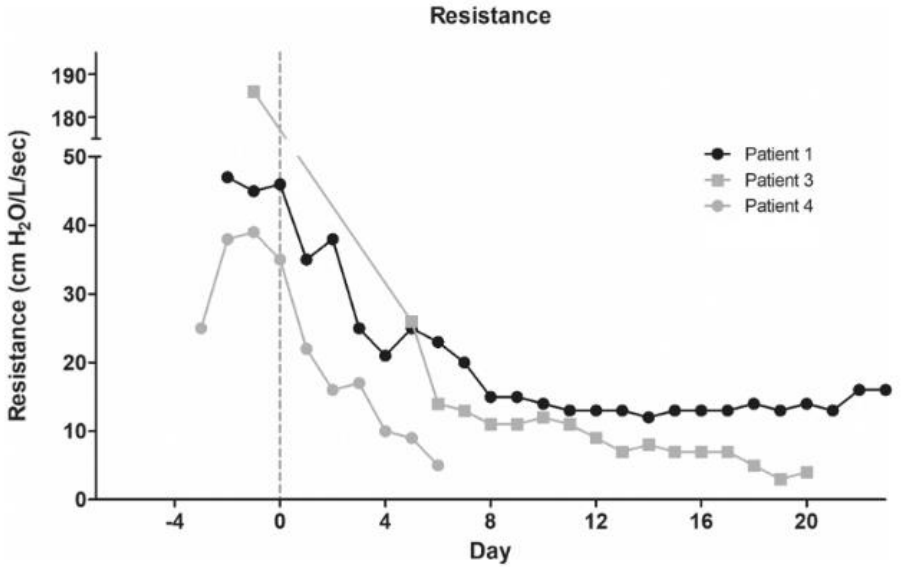


FIGURE 2 | Respiratory system resistance is shown for three patients. On day 0 benralizumab was administered. For patient 2, resistance values are missing because the ventilator's specifications did not allow for this measurement.

Conemans et al. Respirol Case Rep. 2025;13(3):e70117. PMID: 40078572

Table. **Reported Cases of Severe Asthma Exacerbation Requiring Invasive Mechanical Ventilation Treated with Biologics.**

Author (year)	Age/ Sex	Previous control of asthma	Comorbidities	Smoking history	Usual asthma treatment	Blood eosinophils (/μL)	IgE levels (kIU/L)	VV-ECMO	Biologics (day after intubation)	Time for improvement after administration	Duration of tracheal intubation
Milger K3 (2019)	41/M	Using SABA several times for several weeks	–	N.A.	SABA	low	584	+	Omalizumab (8, 22)	Within 48 hours	24 days
Benes J4 (2021)	25/F	Without hospitalization	Childhood asthma	Current smoker	–	100	2,087	+	Omalizumab (8)	90 minutes	10 days
Slevogt H5 (2022)	41/M	–	–	N.A.	N.A.	N.A.	2,200	–	Omalizumab (3, 6, 7, 10, 11)	24 hours later	14 days
Tello K6 (2019)	43/F	Exacerbation 2 months ago	–	N.A.	ICS/LAMA/ LABA	180	N.A.	–	Mepolizumab (7)	48 hours later	15 days
Binachon A2 (2020)	61/F	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	+	Mepolizumab	N.A.	N.A.
Barbarot N7 (2022)	31/M	Without hospitalization	Atopic dermatitis	Current smoker	SABA	210	N.A.	+	Mepolizumab (20)	48 hours later	30 days
Rodrigues HC8 (2023)	25/F	–	Childhood asthma	–	–	2,680	N.A.	–	Mepolizumab (4)	48 hours later	11 days
Grasmuk-Siegl E9 (2024)	43/M	Severe exacerbation with ICU-admission	Obesity with obstructive sleep apnoea	N.A.	ICS/LABA, oral theophylline, mepolizumab	1090	293	+	Tezepelumab (13)	Within 24 hours	33 days
Pérez de Llano L10 (2021)	23/M	2 severe exacerbations per year	Childhood asthma	Current smoker	He had stopped maintenance	600	N.A.	–	Benralizumab (4)	4 days later	13 days
Montagnolo F11 (2024)	24/F	Severe exacerbation with hospitalization	–	–	ICS/LABA, leukotrien reseptor antagonist	720	N.A.	+	Benralizumab (6)	5 days later	13 days
Our case	52/M	Without hospitalization	Childhood asthma	Ex-smoker	–	3,226	1,069	–	Benralizumab (2)	Within 6 hours	4 days

VV-ECMO: veno-venous extracorporeal membrane oxygenation, ICU: intensive care unit, SABA: short-acting β-agonists, ICS/LAMA/LABA: inhaled corticosteroids/long-acting murcarinic antagonists/long-acting beta agonists, ICS/LABA: inhaled corticosteroids/long-acting beta agonists, N.A.: not available.

Matsuoka et al. Intern Med. 2025 Epub ahead of print. PMID: 39814383.

Dupilumab

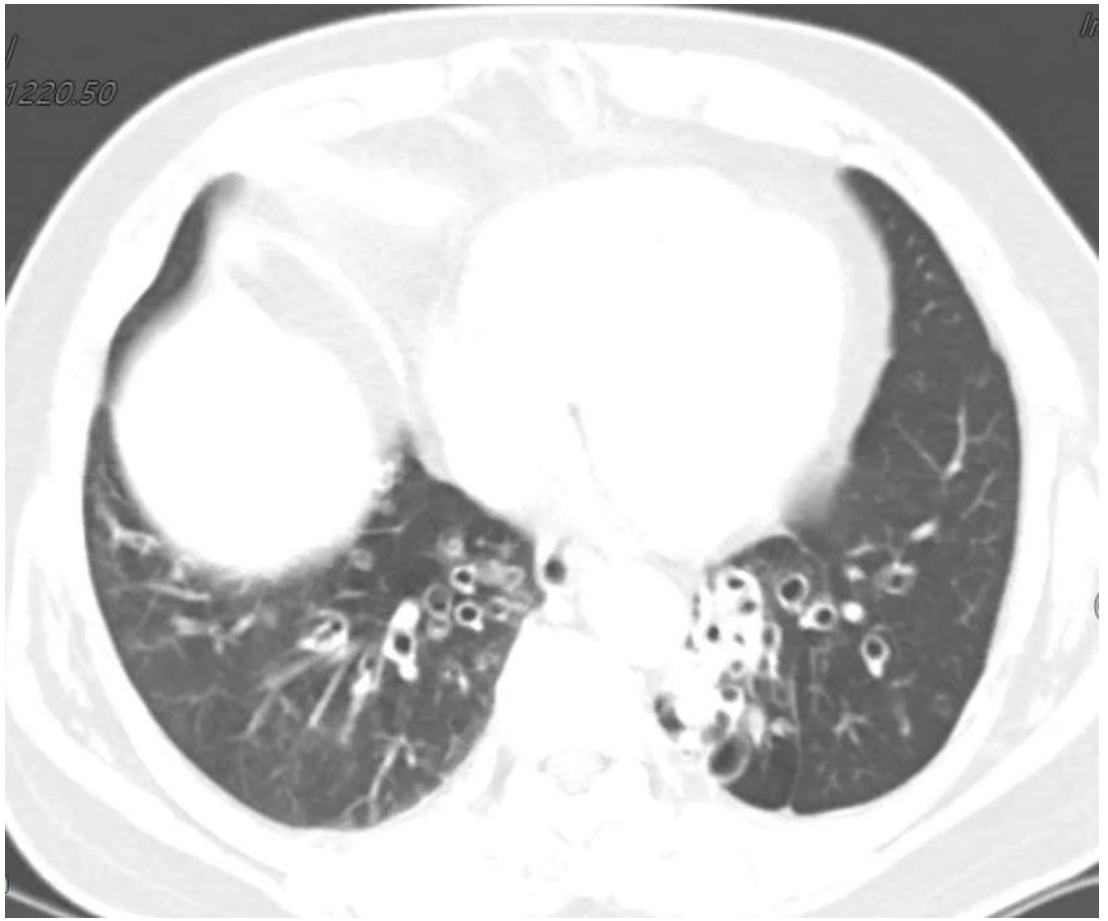
TABLE I. Daily progress

	Day 1																	
	ER	Admission	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9 (dupilumab SC)	Day 10	Day 11	Day 12	Day 13	Day 15 (discharge)	Day 22	Day 29	Day 36
Dyspnea			Improved						Worsened	Worsened	Improved							
O_2 supply	Room air → reservoir mask 15 L → NC 4 L	NC 2 L	NC 2 L	NC 2 L	NC 2 L	NC 2 L	NC 2 L	NC 2 L	NC 2 L	HFNC FiO_2 50%, 50 L	HFNC FiO_2 40%, 40 L	HFNC FiO_2 40%, 40 L	NC 5 L	NC 3 L	Quit			
SpO_2 (%)	88 → 97 → 94	96	97						94	94	97	99	99		98			
Systemic steroid, the equivalent dose of PD (mg)	50		50	50	50	30	30	30	60	60	60	40	30	20	15	10	5	Quit
Eosinophil (%)	11.3												2.2					
Eosinophil count (/mm^3)	1345												176					
Arterial blood gas test																		
pH	7.37*					7.42			7.37				7.41					
PaO_2 (mmHg)	58.0*					111.0			80.2				110.0					
$PaCO_2$ (mmHg)	45.0*					30.1			52.8				28.7					
Pre-BD FEV_1 (L)			0.86						0.71					1.15		2.08	2.03	2.46
Pre-BD FEV_1 (%pred)			35.1						28.9					47.3		85.5	83.4	101.0
Post-BD FEV_1 (L)			0.87						0.70					1.15		2.11	2.24	2.52
Post-BD FEV_1 (%pred)			35.7						28.8					47.3		86.6	91.7	103.6
FeNO (ppb)									55									

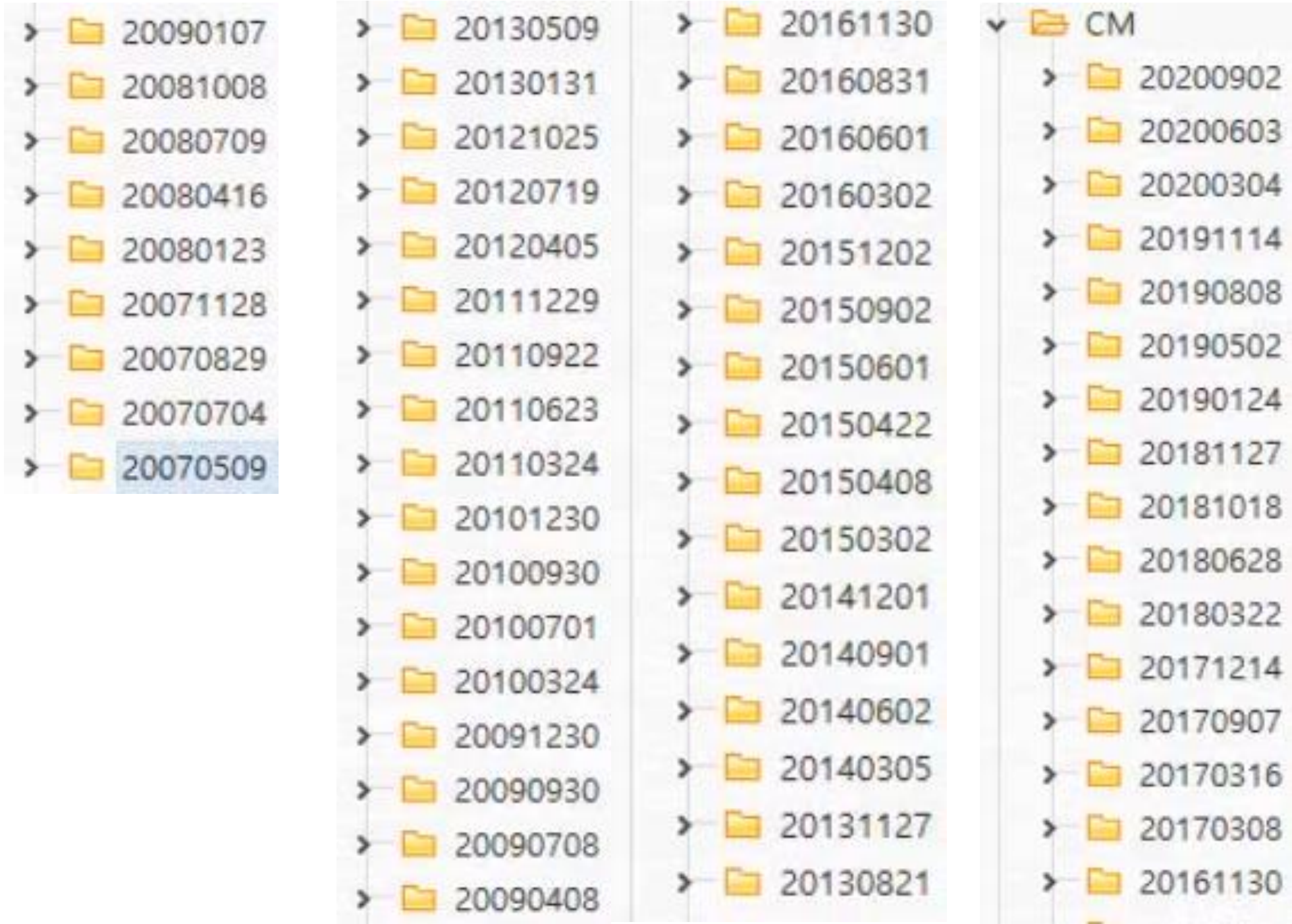
BD, Bronchodilator; *ER*, emergency room; *FeNO*, fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *HFNC*, high-flow nasal cannula; *NC*, nasal cannula; *$PaCO_2$*, arterial partial pressure of carbon dioxide; *PaO_2*, arterial partial pressure of oxygen; *PD*, prednisolone; *SpO_2*, peripheral oxygen saturation; *% pred*, % predicted value.
*At room air.

Kim and Lee et al. J Allergy Clin Immunol Pract. 2023 ;11(9):2922-2925. PMID: 37429420.

45/M – Hemoptysis, Never smoker



2004-04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20181018
20180628
20180322
20171214
20170907
20170316
20170308
20161130

2020.12.02

2020. 12. 02

■ 주관적 소견 (S)

DOE

■ 객관적 소견 (O)

chest: insp. crackles
BP: 150/93

Bronchiectasis
Hypertension
Gout

■ 진료계획

[투약]

NORVASC TAB 5mg (화이자) 1 T 1 회M 91일
ZYLORIC TAB 100mg (삼일) 1 T 1 회M 91일

[검사]

Spirometry with Flow-Volume Curve MVV and BDR
Chest PA and Lateral,Left

2020.12.02

		Pred	Act1	%(A1/P	Act2	%(A2/P	D%(A2/
FVC	[L]	5.15	2.37	46.0	2.34	45.4	-1.4
FEV 1	[L]	3.60	1.18	32.9	1.27	35.2	7.0
FEV 1 % FVC	[%]	73.64	49.90	67.8	54.15	73.5	8.5
FEV 1 % VC MAX	[%]	73.64	48.54	65.9	47.65	64.7	-1.9
PEF	[L/s]	8.19	4.11	50.2	5.45	66.5	32.6
MEF 75	[L/s]	7.52	1.23	16.3	1.33	17.6	8.3
MEF 50	[L/s]	4.09	0.50	12.2	0.51	12.6	2.8
MEF 25	[L/s]	1.49	0.19	12.9	0.13	8.8	-31.8
MMEF 75/25	[L/s]	3.33	0.40	12.1	0.37	11.0	-9.2
FVC IN	[L]	5.15	2.44	47.3	2.66	51.6	9.0
FIV1	[L]		2.26		2.57		13.7

치료

■ 진료계획

[투약]

ZYLORIC TAB 100mg (삼일) 1 T 1 회M 91일
DUKARB TAB 60/10mg (보령) 1 T 1 회WM 91일
CRESTOR TAB 5mg (아스트라) 1 T 1 회WM 91일
ANORO 62.5 ELLIPTA 30D/B (GSK) 1 BOX 1 회INM 1일

2024.10.15

2024. 10. 15

■ 주호소

* 주증상 호흡곤란, 발열

발생시기 : 5일 전

■ 현병력

Underlying BE, COPD, HTN, gout 등 있는 자.

내원 5일 전 발열, 기침, 누런 가래 등이 발생하여 금호동 내과병원에서 먹는 항생제와 주사 항생제 지속적으로 처방받았으나, 증상 호전되지 않고, 힘들어 본원 응급실 내원함.
desaturation 있어 HFNC 60%60L apply 하며 EICU 입원함.

* **중환자실 입실정보**

ICU admission : Unplanned

Surgical status at ICU admission : Emergent

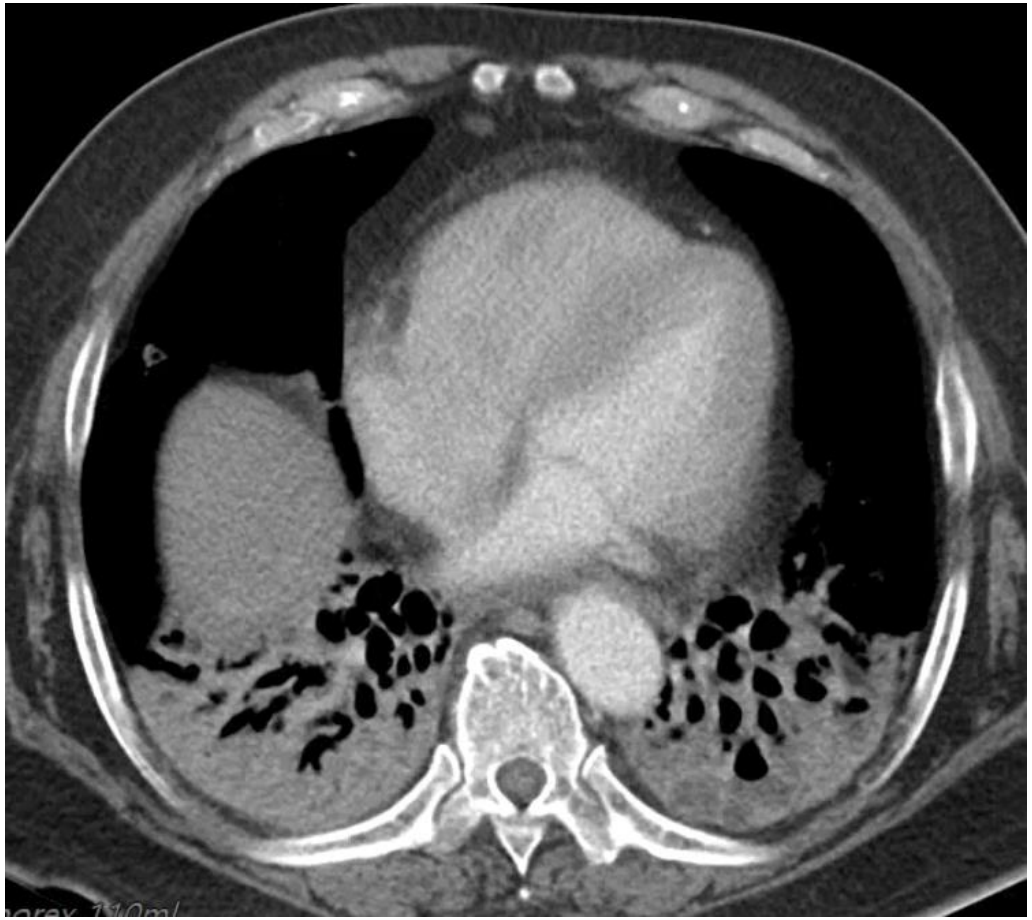
입실경로 : 병동

* **중환자실 입실사유**

Respiratory system

- Acute Resiratory failure on chronic pulmonary disease
  (pH < 7.35, PaCO2 >45 mmHg)

2024.10.25



Lab

검사명	단위	2024-10-15 13:42
WBC	*10^3/μL	8.8
RBC	*10^6/μL	4.47
Hemoglobin(Hb)	g/dL	14.0
Hematocrit(Hct)	%	43.8
MCV	fl	▲97.9
MCH	pg	31.3
MCHC	g/dL	32.0
RDW	%	▲15.7
Platelet	*10^3/μL	325
PCT	%	0.197
MPV	fl	▼6.1
Platelet Distribution Width	fL	15.9
Seg neutrophil	%	66.3
Band	%	0
Lymphocyte	%	▼17.6
Monocyte	%	▲15.6
Eosinophil	%	▼0.2

검사명	단위	2024-10-15 13:26	2024-10-15 17:04
Oxygen saturation	%		
Total hemoglobin	g/dL		
Hematocrit(Hct)	%		
Lactate	mmol/L		
pH/ ER		7.43	▼7.33
pCO2/ ER	mmHg	43	▲59
pO2/ ER	mmHg	▼46	95
HCO3- concentration/ ER	mmol/L	▲28.5	▲31.1
Base excess(B)/ ER	mmol/L	▲3.7	▲3.6
Oxygen content/ ER	mL/dL	▼15.9	18.2
Oxygen saturation/ ER	%	▼80.7	95.4
ctCO2/ ER	mmol/L	▲29.8	▲32.9
Total hemoglobin/ ER	g/dL	14.3	13.6
Hematocrit(Hct)/ ER	%	46	44
Ionized calcium/ ER	mmol/L	▼1.12	1.19
Sodium/ ER	mmol/L	▼126	▼131
Potassium/ ER	mmol/L	5.0	4.8
Chloride/ ER	mmol/L	104	101
Anion Gap/ ER		▼-2	▼4
Glucose/ ER	mg/dL	▲100	▲98
Lactate(ER-POCT)		▲0.9	0.5

▼7.33	▼7.30	▼7.26	7.39	▼7.34
▲62	▲68	▲78	▲56	▲62
81	▼74	91	▼69	84
▲32.7	▲33.5	▲35.0	▲33.9	▲33.4

치료

- ICU 입원
- HFNC FiO_2 60% 60L/min
- 항생제 (piperacillin/tazobactam + levofloxacin)

Legionella urinary Ag			Negative		
Pneumoniae urinary Ag			Negative		
Adenovirus				Negative	
Bocavirus				Negative	
Enterovirus				Negative	
Rhinovirus				Negative	
Influenza A				Negative	
Influenza B				Negative	
Metapneumovirus				Negative	
RSV A				Negative	
RSV B				Negative	
Parainfluenza 1				Negative	
Parainfluenza 2				Negative	
Parainfluenza 3				Negative	
Parainfluenza 4				Negative	
Coronavirus NL63				Negative	
Coronavirus 229/OC43				Negative	
Mycoplasma pneumoniae					Negative
Legionella pneumophila					Negative
Streptococcus pneumoniae					Positive
Haemophilus influenzae					Positive
Bordetella pertussis					Negative
Chlamydia pneumoniae					Negative
Bortella parapertussis					Negative

환자의 예후를 개선하기 위해 추가할 수 있는 약은?

Macrolide

Long-term inhaled Antibiotics vs. macrolide

	Inhaled antibiotics	Macrolide
Studies	RESPIRE 1,2 (≥ 2 AE) ORBIT 2-4 (≥ 2 AE) AIR-Bx 1-2 Nebulized tobramycin, ceftazidime, gentamicin, colistin	BAT (≥ 3AE) – AZIT 250mg QD BLESS (≥ 2 AE) – ETM 400mg BID Daily EMBRACE (≥ 1AE) – AZIT 500mg TIW
Outcomes		
AE	Improved Rate ratio = **0.81(0.67-0.97)** Time to first AE (HR) = **0.83(0.69-0.99)** Severe AE – Rate ratio = **0.43(0.24-0.78)**	Improved Adjusted incidence rate ratio = **0.49(0.36-0.66)** Time to first AE (HR) = **0.46(0.34-0.61)** *P. Aeruginosa* – **IRR, 0.36(0.18-0.72)**
QoL	No effect	Improved QoL measured by the **SGRQ (mean improvement 2.93 points [0.03-5.83])**
FEV_1	No improvement (Toward to deterioration) (−2.00 to 0.26%pred)	No improvement (toward to improvement) (67 mL at 1 year, −22-112)

Laska, Lancet Respir Med. 2019;7(10):855-869.
Chalmers, Lancet Respir Med. 2019;7(10):845-854.

2024. 11. 04

■ 주관적 소견 (S)

산소 감량 후에도 괜찮아요 금요일 쯤 퇴원하고 싶어요

■ 객관적 소견 (O)

【검사명】 【단위】 2024-11-03 06:32

CRP(C-reactive protein)(응급) (mg/dL):▲0.54

■ 진단명 (A)

#. ARDS type 1 & type 2 combined
d/t pneumonia
#. underlying COPD, bronchiectasis

2024. 11. 06

On-duty 기록

■ 치료 및 경과

낮에 O2-밤에 NIV 유지 중

■ 환자상태

both lung wheezing
NP 3 L/min에서 SpO2 87% HR 120

■ 진료계획

knee arthralgia 관련 OS/RM 협진
AE 악화로 산소 증량, steroid 투여

2024. 11. 11

Off-duty 기록

■ 진료계획

1. COPD/BE AE에 대해 2024.11.06 호흡곤란 악화, wheezing 악화 등으로 mPd 40 mg 투여하면서 호전 경과입니다. 11/12부터 mPd 20 mg 으로 감량하였습니다.
항생제는 따로 투여하지 않았고 영상 혹은 가래증상 악화는 없었습니다.

Macrolide, Triple inhaler, Roflumilast, furosemide로 퇴원

“숨이 너무 차서 죽을 것 같아요.”

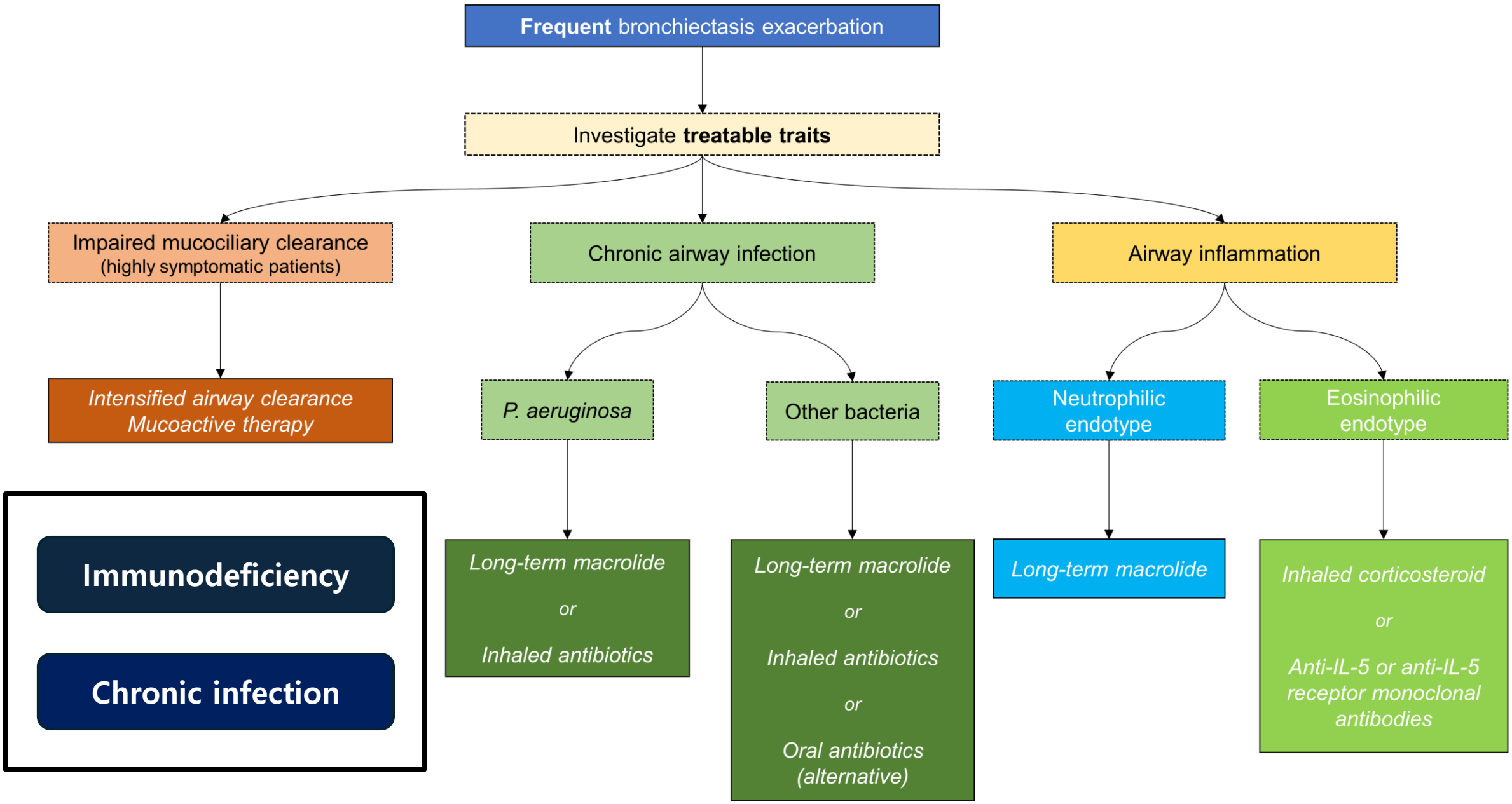
어떤 검사를 해볼 수 있을까요?

Macrolide를 썼으니 기다려보자고 할까요?

Long-term inhaled Antibiotics vs. macrolide

	Inhaled antibiotics	Macrolide
Studies	RESPIRE 1,2 (≥ 2 AE) ORBIT 2-4 (≥ 2 AE) AIR-Bx 1-2 Nebulized tobramycin, ceftazidime, gentamicin, colistin	BAT (≥ 3AE) – AZIT 250mg QD BLESS (≥ 2 AE) – ETM 400mg BID Daily EMBRACE (≥ 1AE) – AZIT 500mg TIW
Outcomes		
AE	Improved Rate ratio = **0.81(0.67-0.97)** Time to first AE (HR) = **0.83(0.69-0.99)** Severe AE – Rate ratio = **0.43(0.24-0.78)**	Improved Adjusted incidence rate ratio = **0.49(0.36-0.66)** Time to first AE (HR) = **0.46(0.34-0.61)** *P. Aeruginosa* – **IRR, 0.36(0.18-0.72)**
QoL	No effect	Improved QoL measured by the **SGRQ (mean improvement 2.93 points [0.03-5.83])**
FEV_1	No improvement (Toward to deterioration) (−2.00 to 0.26%pred)	No improvement (toward to improvement) (67 mL at 1 year, −22-112)

Laska, Lancet Respir Med. 2019;7(10):855-869.
Chalmers, Lancet Respir Med. 2019;7(10):845-854.

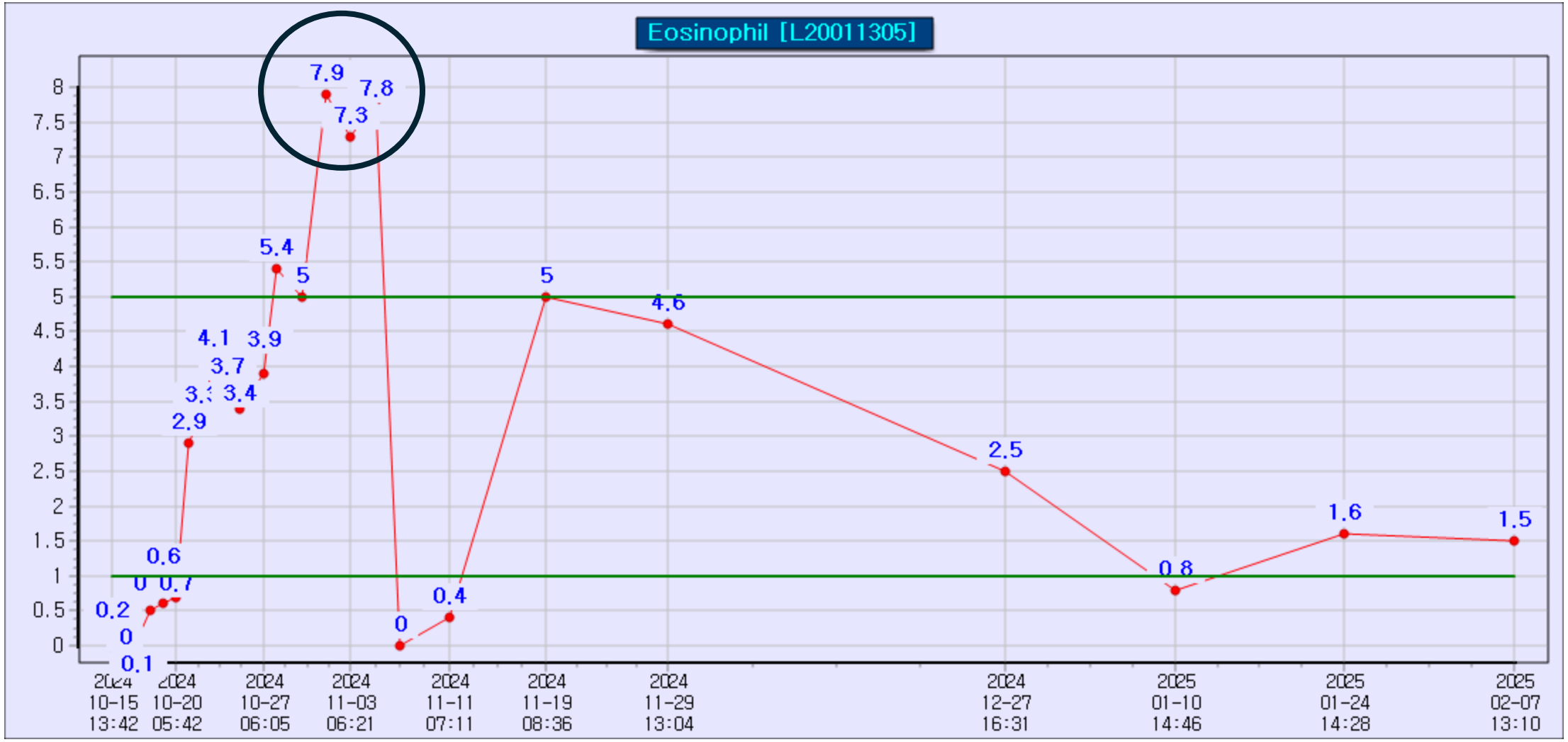


Choi et al. Ann Transl Med. 2023;11(1):25

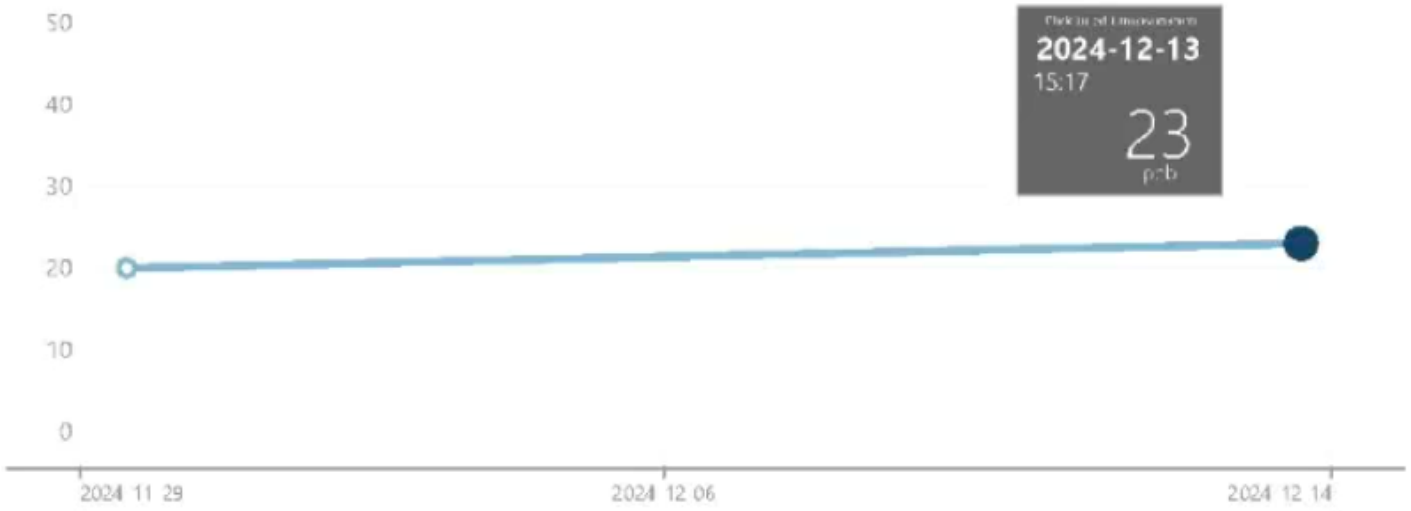
(1-3)-β-D-Glucan	pg/mL	Negative ...				
TB Realtime PCR				Negative		
NTM realtime PCR				Negative		
결핵균 및 리팜핀 내성 PCR(MTB)					Negative	
결핵균 및 리팜핀 내성 PCR(RIF)					해당없음	
Aspergillus Ab IgG	mg/L		Negative ...			
Aspergillus Ag	Index		Negative ...			

IgG	mg/dL	▲1805
IgA	mg/dL	335
IgM	mg/dL	56
IgD	mg/dL	< 1.29

AFB S/C (-/-), Fungus C (-), Gram S/C (-/-)


Eosinophil [L20011305]
8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
7.9
7.8
7.3
5.4
5
4.1
3.9
3.7
3.4
2.9
0.6
0
0.7
0.2
0
0.1
0
0.4
5
4.6
2.5
0.8
1.6
1.5
2024 10-15 13:42
2024 10-20 05:42
2024 10-27 06:05
2024 11-03 06:21
2024 11-11 07:11
2024 11-19 08:36
2024 11-29 13:04
2024 12-27 16:31
2025 01-10 14:46
2025 01-24 14:28
2025 02-07 13:10

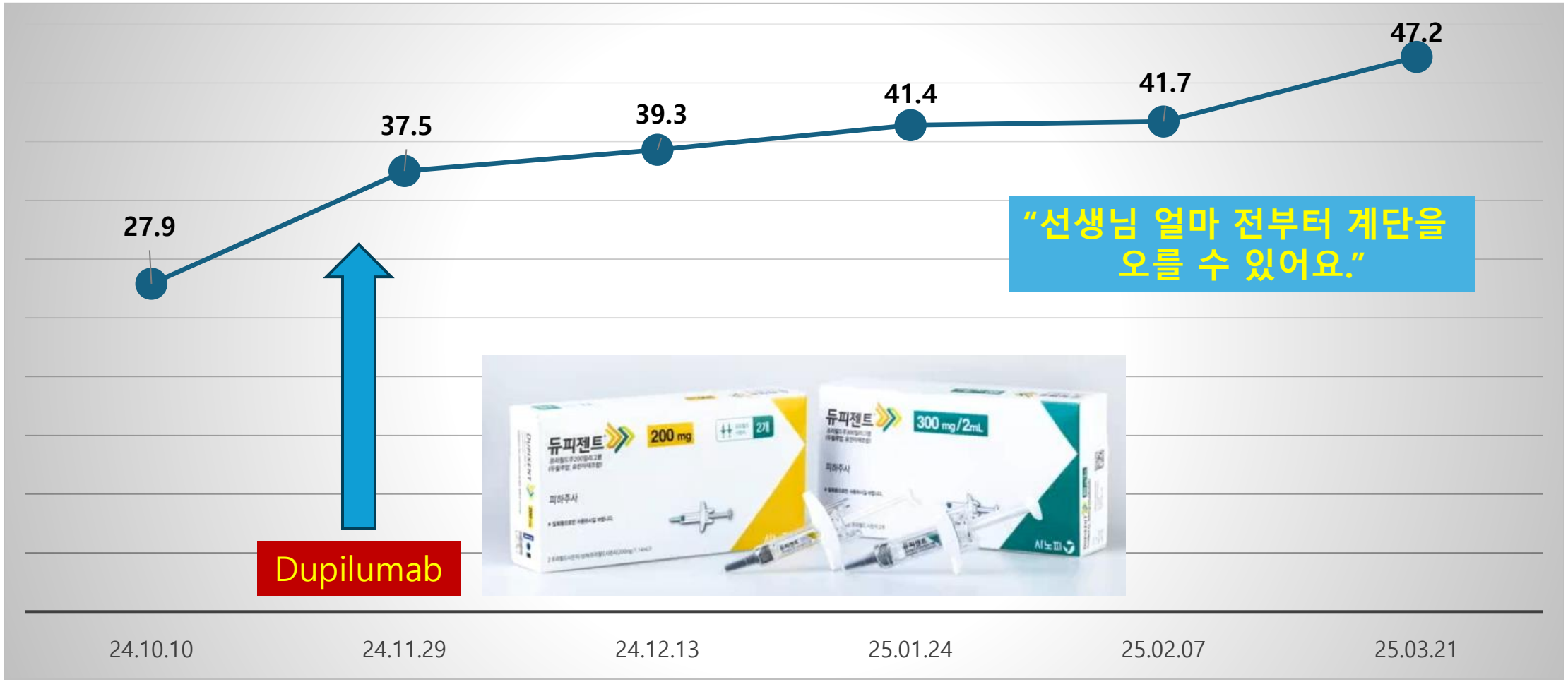
FeNO



TIMESTAMP	NO [ppb]	Mode	COMMENT	SIGNATURE
2024-12-13 오후 3:17	23	10s		
2024-11-29 오후 1:31	20	10s		

Biologics를 사용하면 효과가 있을까요?

FEV_1 %predicted



악화 전

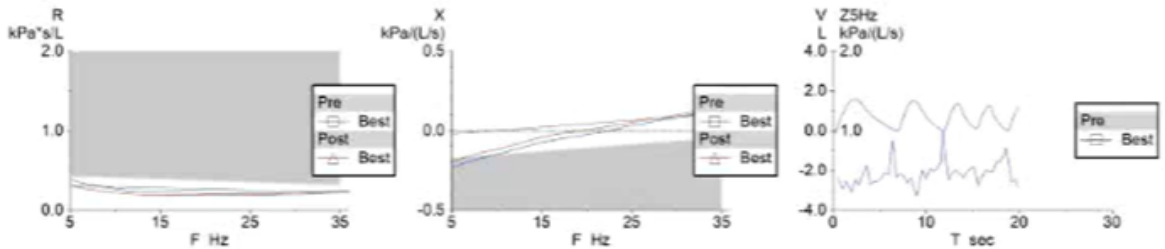
iOS

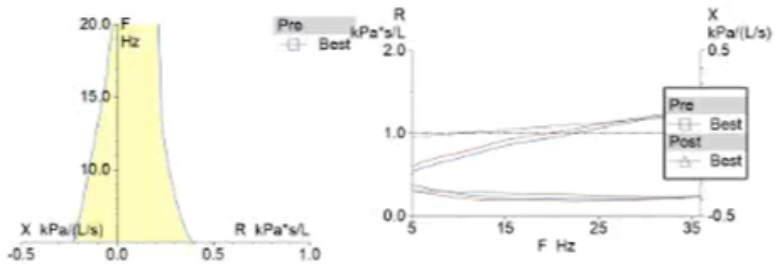
- Distal airway obstruction
  - R5, R5-20, Freq, AX 증가
  - X5 감소

X5

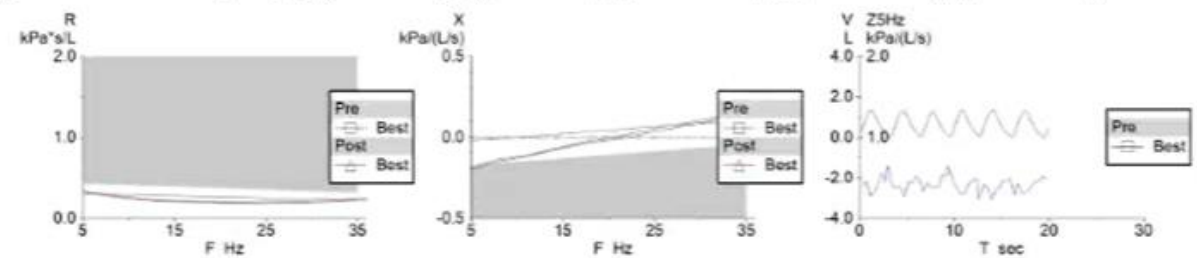
R5, R5-20, Freq, AX

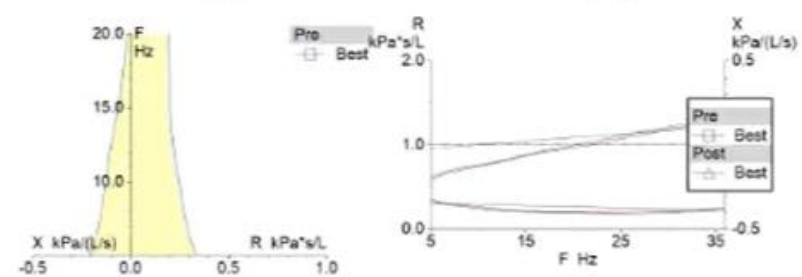
		PRED	PRE(BEST)	%PRED	POST(BEST)	%PRED	%CHG
R5Hz	kPa/(L/s)	0.30	0.39	127	0.31	102	−20
R10Hz	kPa/(L/s)	0.29	0.27	93	0.22	77	−17
R15Hz	kPa/(L/s)	0.28	0.23	81	0.19	68	−16
R20Hz	kPa/(L/s)	0.26	0.21	81	0.19	71	−11
X5Hz	kPa/(L/s)	−0.02	−0.23	1086	−0.20	943	−13
X10Hz	kPa/(L/s)	0.00	−0.15	−66006	−0.12	−52199	−21
X15Hz	kPa/(L/s)	0.02	−0.07	−343	−0.04	−190	−45
X20Hz	kPa/(L/s)	0.04	−0.02	−57	0.00	6	−111
Z5Hz	kPa/(L/s)		0.45		0.37		−18
Fres.	1/s		22.30		19.65		−12
AX	kPa/L		1.76		1.25		−29
D5−20%	%		44.84		39.21		−13
CO5Hz			0.8		0.8		5
CO20Hz			1.0		1.0		1
Di5−20	kPa/(L/s)		0.17		0.12		−30
VT	L	0.69	1.14	166	1.01	147	−11





		PRED	PRE(BEST)	%PRED	POST(BEST)	%PRED	%CHG
R5Hz	kPa/(L/s)	0.30	0.34	111	0.34	112	1
R10Hz	kPa/(L/s)	0.29	0.25	85	0.26	90	6
R15Hz	kPa/(L/s)	0.28	0.20	73	0.21	77	5
R20Hz	kPa/(L/s)	0.26	0.19	73	0.20	77	5
X5Hz	kPa/(L/s)	−0.02	−0.22	1059	−0.19	903	−15
X10Hz	kPa/(L/s)	0.00	−0.14	−60693	−0.12	−53186	−12
X15Hz	kPa/(L/s)	0.02	−0.07	−325	−0.06	−267	−18
X20Hz	kPa/(L/s)	0.04	−0.02	−46	−0.00	−7	−86
Z5Hz	kPa/(L/s)		0.41		0.39		−4
Fres.	1/s		22.00		20.23		−8
AX	kPa/L		1.63		1.34		−17
D5−20%	%		42.89		40.72		−5
CO5Hz			0.8		0.9		2
CO20Hz			1.0		1.0		−0
Di5−20	kPa/(L/s)		0.15		0.14		−4
VT	L	0.65	1.25	192	1.21	185	−3



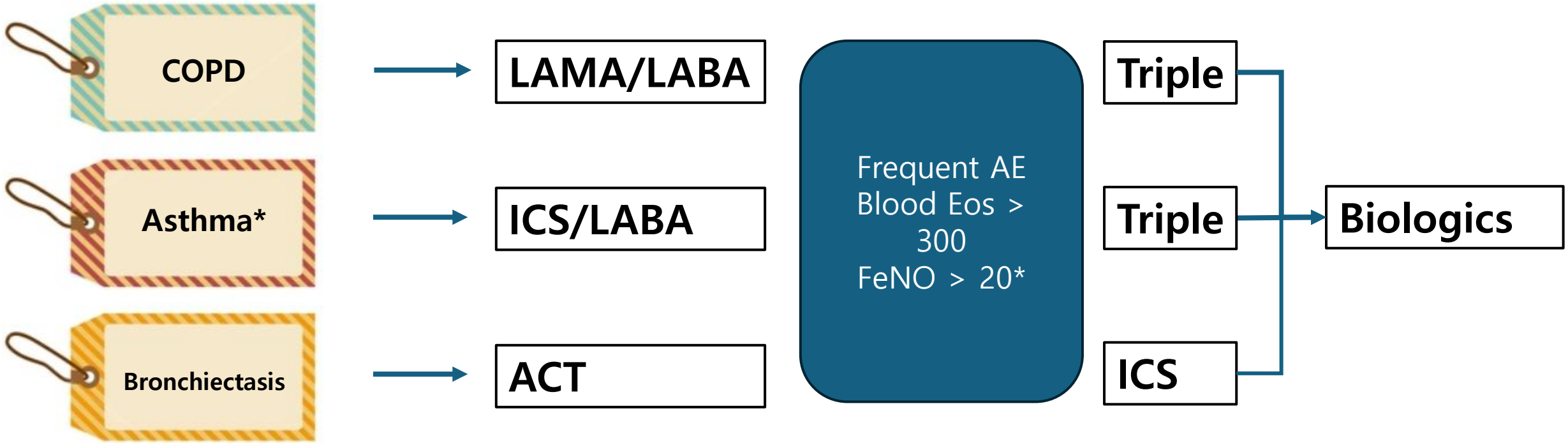


R5, R5-20, Freq, AX 증가 → 감소
X5 감소 → 증가

Summary

Label tag-driven treatment

If not controlled → Biomarker-driven Tx



Label free-driven treatment ?

Airway disease

FeNO > 20*
Blood Eos > 300
Sputum Eos 증가

ICS

AFL 존재

LAMA/ LABA

Frequent AE
Blood Eos > 300
FeNO > 20*
Sputum Eos 증가

Biologics

Sputum secretion

ACT

진단명: Chronic <u>T2-high (FENO, Bloo Eos, ets.)</u> airway disease with <u>AFL</u>