Ente Ospedaliero Cantonale

Update Pneumologia 2025

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AGENDA

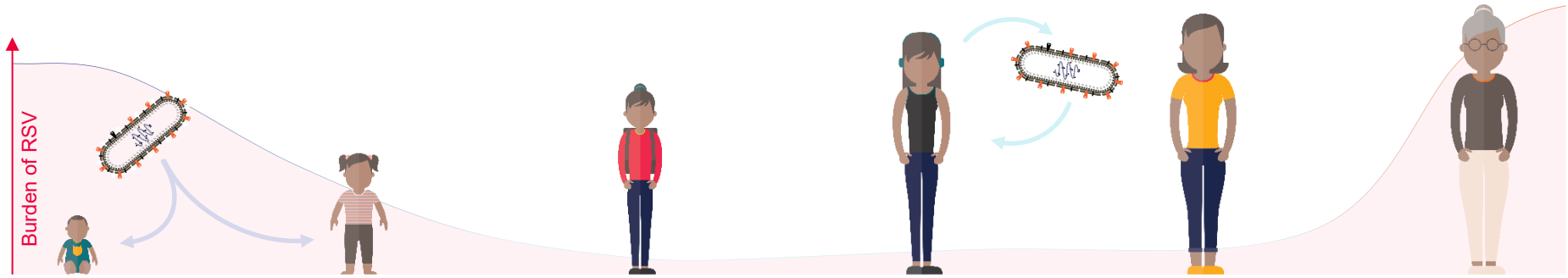
- Guidelines GOLD 2025:
  - Prevention: *RSV* vaccination
  - Biologics in COPD

- New therapeutic perspectives for pulmonary fibrosis: *Nerandomilast* in IPF and PPF-ILD

- Pulmonary hypertension: revolution thanks to *Sotatercept*

RSV is a disease of all ages

- Incidence between 45-59/100’000 *RSV* hospitalisation
- Annual incidence of *RSV* infection range 3-10% among older



Most children will have been infected with RSV by age 2 years[1–3]

Immune response after natural infection is incomplete and is short-lived[4,5]

RSV reinfections may occur throughout life[5]

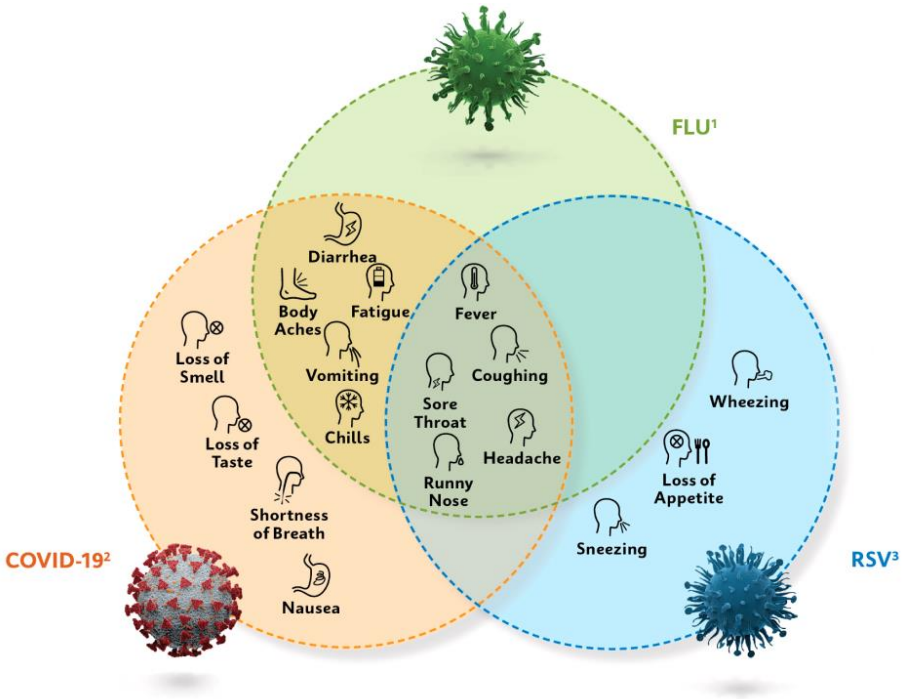
Older adults are at high risk of severe RSV infection. Those with certain comorbidities are at even greater risk[6,7]

The figure is for illustrative purposes only

1. Andeweg SP *et al. Sci Rep*. 2021;11(1):8953; 2. Sarna M *et al. J Infect Dis*. 2018;217(3):418–427; 3. Pasittungkul S *et al. Int J Infect Dis*. 2022;125:177–183; 4. Openshaw PJM *et al. Annu Rev Immunol* 2017;35:501–532; 5. Walsh E *et al. Clin Chest Med* 2017;38(1):29–36; 6. Branche AR *et al. Clin Infect Dis* 2022;74(6):1004–1011; 7. Centers for Disease Control and Prevention (CDC), 2023. RSV in Older Adults and Adults with Chronic Medical Conditions. https://www.cdc.gov/rsv/high-risk/older-adults.html (accessed January 2024)

Background: *RSV*

- *RSV* causes **serious lower respiratory tract infections (LRTIs)** in **older adults** and those with **chronic lung disease**.
- *RSV* as a trigger in ~ up to 28 **% of acute COPD exacerbations** (AECOPD)
- 2 – 4x increased risk of hospitalization for adults with COPD
- **Induce**: airway inflammation, mucus hypersecretion, reduced clearance and increased risk of bacterial infection
- Consequence: **lung function decline** and **disease progression**



GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE

GOLD 2025: Prevention

Vaccination for Stable COPD

Figure 3.6

People with COPD should receive all recommended vaccinations in line with the relevant local guidelines:

- Yearly influenza vaccination **(Evidence B)**
- SARS-CoV-2 (COVID-19) vaccination based on WHO and CDC updated recommendations **(Evidence B)**
- Either one dose of 21-valent pneumococcal conjugate vaccine (PCV21) or one dose PCV20, as recommended by the CDC **(Evidence B)**. Pneumococcal vaccination has been shown to reduce the incidence of community-acquired pneumonia and exacerbations for people with COPD **(Evidence B)**
- Respiratory syncytial virus (RSV) vaccination for individuals aged ≥ 60 years and/or with chronic heart or lung disease, as recommended by the CDC **(Evidence A)**
- Tdap (dTaP/dTPa) vaccination to protect against pertussis (whooping cough) for people with COPD that were not vaccinated in adolescence, as recommended by the CDC **(Evidence B)**
- Zoster vaccine to protect against shingles for people with COPD aged > 50 years, as recommended by the CDC **(Evidence B)**

- *RSV* is recommended but not yet refunded…

Infobox 2

Recommandations de vaccination contre le VRS pour les adultes âgés de 75 ans et plus et pour les personnes à risque accru de complications âgées de 60 ans et plus

L'**OFSP et la CFV recommandent actuellement** la vaccination contre le VRS avec **1 dose de vaccin, et la prochaine dose au plus tôt tous les deux ans**[1]**:**

1. comme **vaccination complémentaire** pour toutes les personnes âgées de **75 ans et plus**
2. comme **vaccination des groupes à risque** pour les personnes **âgées de 60 à 74 ans** présentant un **risque accru** d'une forme grave de la maladie au VRS. Ces personnes comprennent:

   a) **Les patients** souffrant de **maladies chroniques *telles que:***

   - un déficit immunitaire (dû à une affection médicale ou à un traitement immunosuppresseur)
   - des maladies pulmonaires (par ex., bronchopneumopathie chronique obstructive, emphysème, asthme)
   - des maladies cardiovasculaires (par ex., insuffisance cardiaque congestive, maladie coronarienne)
   - des affections neurologiques ou neuromusculaires
   - des troubles rénaux
   - des troubles hépatiques
   - des troubles hématologiques
   - un diabète

   b) **Personnes fragiles** et personnes **résidant dans des maisons de retraite** ou d'autres **établissements de soins de longue durée**

En outre, la vaccination contre le VRS peut être envisagée pour les patients **âgés de 18 à 59 ans** présentant un **déficit immunitaire grave** (dû à une affection médicale ou à un traitement immunosuppresseur) ou pour ceux présentant d'autres affections sous-jacentes dont le médecin traitant estime qu'elles présentent un **risque très élevé** de maladie grave à VRS. **Il est à noter que** chez les personnes âgées de moins de 60 ans, cette recommandation se situe en dehors de l'autorisation de Swissmedic. Elle est donc assujettie aux principes d'une utilisation hors étiquette (off-label) et n'est pas prise en charge par l'assurance obligatoire des soins (AOS).

La vaccination contre le VRS devrait idéalement être administré entre la **mi-octobre et la mi-novembre.** Elle peut également être administrée plus tard, si possible avant le début de l'épidémie saisonnière de VRS. La vaccination contre le VRS peut être effectuée en même temps, avant ou après la vaccination contre la grippe et/ou le COVID-19.

Tous les vaccins autorisés en Suisse pour les personnes âgées de 60 ans ou plus peuvent être utilisés.

1 L'intervalle de temps recommandé actuellement entre une 1ère dose de vaccin contre VRS et une dose suivante est basée sur les données disponibles jusqu'en octobre 2024. L'intervalle entre les doses peut être modifié si les données futures sur la durée de protection justifient un ajustement.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults

A. Papi, M.G. Ison, J.M. Langley, D.-G. Lee, I. Leroux-Roels, F. Martinon-Torres, T.F. Schwarz, R.N. van Zyl-Smit, L. Campora, N. Dezutter, N. de Schrevel, L. Fissette, M.-P. David, M. Van der Wielen, L. Kostanyan, and V. Hulstrøm, for the AReSVi-006 Study Group*

N ENGL J MED 388;7 NEJM.ORG FEBRUARY 16, 2023

Clinical Infectious Diseases

MAJOR ARTICLE

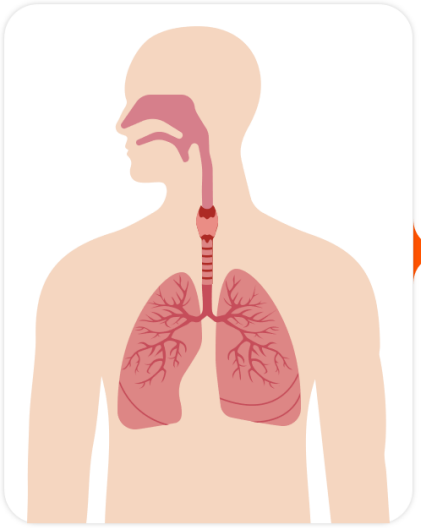
Efficacy and Safety of Respiratory Syncytial Virus (RSV) Prefusion F Protein Vaccine (RSVPreF3 OA) in Older Adults Over 2 RSV Seasons

Michael G. Ison,[1,a] Alberto Papi,[2,a] Eugene Athan,[3,4] Robert G. Feldman,[5] Joanne M. Langley,[6] Dong-Gun Lee,[7] Isabel Leroux-Roels,[8] Federico Martinon-Torres,[9,10,11] Tino F. Schwarz,[12] Richard N. van Zyl-Smit,[13] Céline Verheust,[14] Nancy Dezutter,[14] Olivier Gruselle,[14] Laurence Fissette,[14] Marie-Pierre David,[14] Lusine Kostanyan,[14] Veronica Hulstrøm,[14] Aurélie Olivier,[14] Marie Van der Wielen,[14,©] and Dominique Descamps[14]; for the AReSVi-006 Study Group[b]

CID 2024:78 (15 June) • Ison et al

Mechanism of action:

- Stimulates the production of neutralizing antibodies that bind to the *RSV* surface protein F
- Blocks entry into cells



RSV-ARI*

RSV-LRTD*

RSV-LRTD* in participants with ≥1 comorbidity of interest†

Severe RSV-LRTD*

Vaccine efficacy

	Season 1[1‡]	Seasons 1–2[2§]	Seasons 1–3[3§]
RSV-ARI*	71.7% (95% CI: 56.2, 82.3)	52.7% (95% CI: 40.0, 63.0)	51.1% (95% CI: 40.3, 60.2)
RSV-LRTD*	82.6% (96.95% CI: 57.9, 94.1)	67.2% (97.5% CI: 48.2, 80.0)	62.9% (97.5% CI: 46.7, 74.8)
RSV-LRTD* in participants with ≥1 comorbidity of interest†	94.6% (95% CI: 65.9, 99.9)	66.7% (95% CI: 41.8, 82.0)	NR
Severe RSV-LRTD*	94.1% (95% CI: 62.4, 99.9)	78.8% (95% CI: 52.6, 92.0)	67.4% (95% CI: 42.4, 82.7)

- Vaccine efficacy of 83.7% in preventing a first episode of *RSV*-associated lower respiratory tract disease with at least 2 signs or symptoms
- Vaccine efficacy of 82.4% with at least 3 signs or symptoms

- Vaccine efficacy of 68.4% against *RSV* acute-respiratory disease

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Efficacy and Safety of an mRNA-Based RSV PreF Vaccine in Older Adults

Wilson E et al. DOI: 10.1056/NEJMoa2307079

CLINICAL PROBLEM

Older adults are at increased risk for respiratory syncytial virus (RSV)–associated complications and death. An mRNA-based RSV vaccine, mRNA-1345, encoding the stabilized RSV prefusion F glycoprotein appeared to be safe and immunogenic in adults in a phase 1 clinical trial, but additional data are needed.

CLINICAL TRIAL

Design: An ongoing, phase 2–3, international, double-blind, randomized, placebo-controlled trial assessed the efficacy and safety of the mRNA-1345 vaccine in preventing RSV-associated lower respiratory tract disease in adults ≥60 years of age.

Intervention: 35,541 participants were assigned to receive a single intramuscular injection of mRNA-1345 or saline placebo. The two primary efficacy end points were the prevention of a first episode of RSV-associated lower respiratory tract disease with ≥2 signs or symptoms and with ≥3 signs or symptoms within 14 days to 12 months after injection.

RESULTS

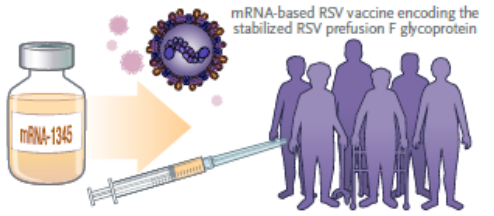
Efficacy: During a median follow-up of 112 days, the mRNA-1345 vaccine showed efficacy against RSV-associated lower respiratory tract disease with ≥2 and with ≥3 lower respiratory signs or symptoms.

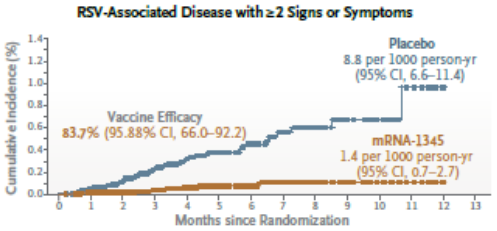
Safety: Solicited local and systemic adverse reactions were reported more often with the mRNA-1345 vaccine than with placebo; most adverse reactions were mild to moderate in severity and were transient. The incidence of serious adverse events did not differ between the groups.

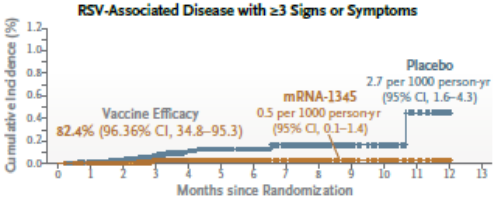
LIMITATIONS AND REMAINING QUESTIONS

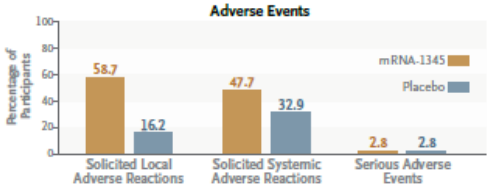
- Participants with certain immunocompromising conditions were excluded from the trial.
- There were low case numbers in some subgroups, including participants ≥80 years of age and frail participants.
- Ongoing follow-up will assess the duration of protection from the vaccine, and the need for and appropriate timing of a booster are under study.

Links: Full Article | NEJM Quick Take | Editorial







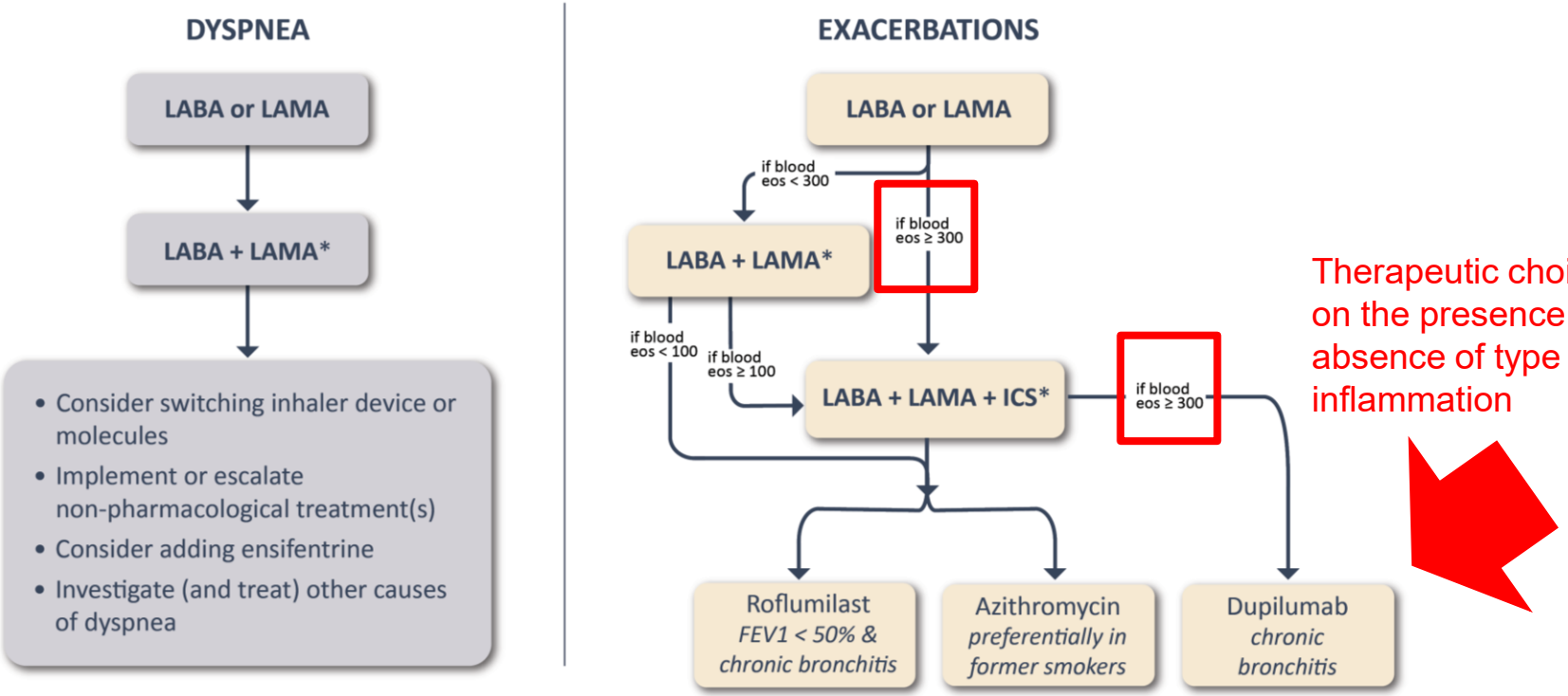


CONCLUSIONS

Among adults ≥60 years of age, a single dose of the mRNA-1345 vaccine led to a lower incidence of RSV-associated lower respiratory tract disease than placebo and resulted in no apparent safety concerns.

GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE

GOLD 2025: Biologics in COPD



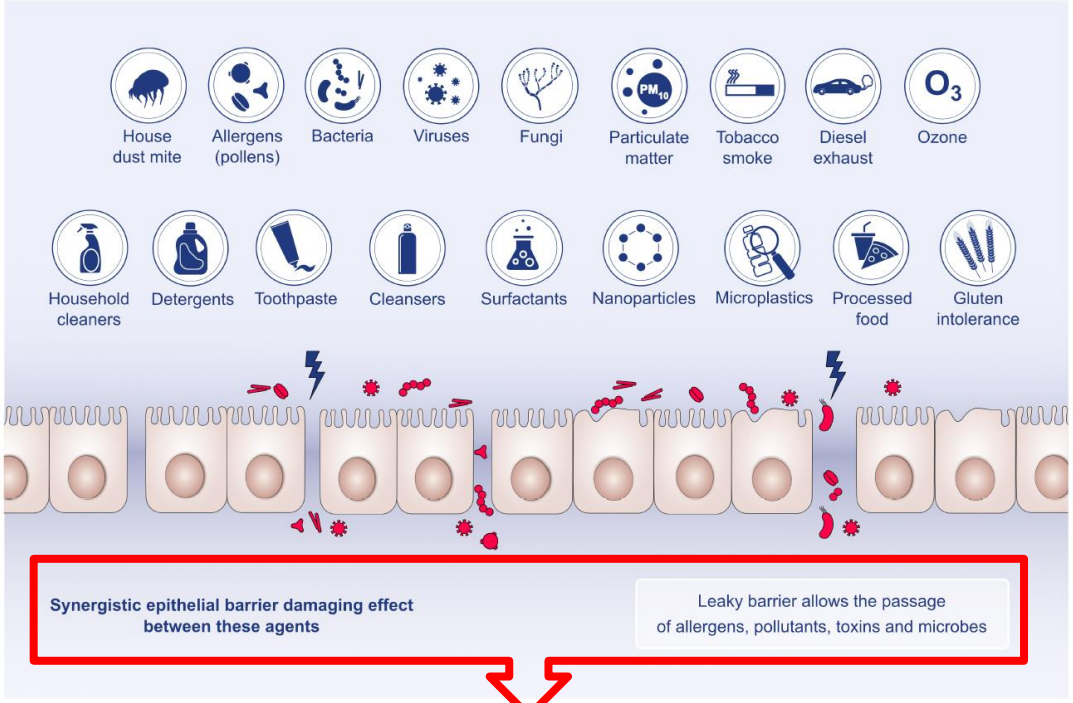
*Single inhaler therapy may be more convenient and effective than multiple inhalers; single inhalers improve adherence to treatment.

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.

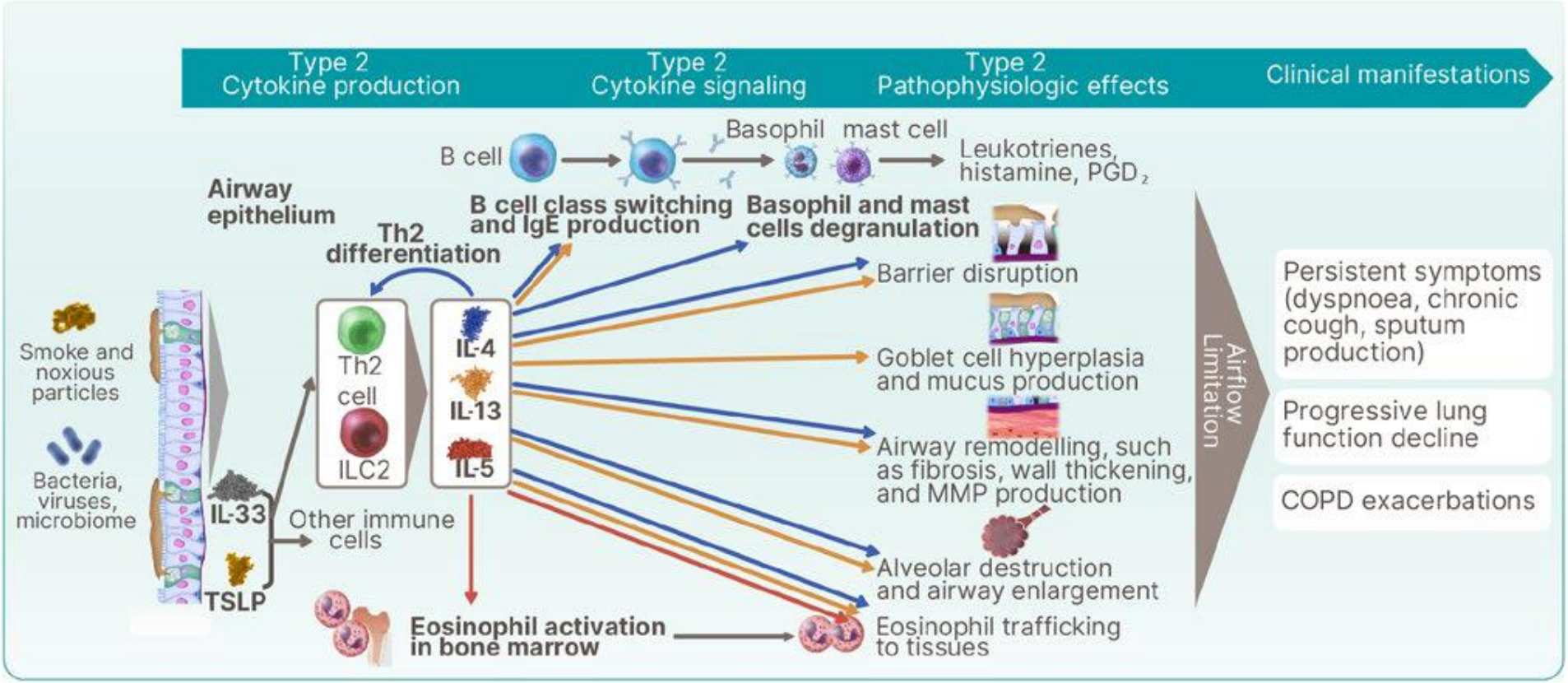
Background & Rationale:

- Around 10-40% of COPD patients demonstrate increased Eosinophilic inflammation
- Elevated Blood Eosinophil Counts is associated with higher exacerbation risk



Production of «danger» signals: IL-33, IL-25 and Thymic Stromal Lymphopoietin (TSLP)

Understanding type 2 in COPD

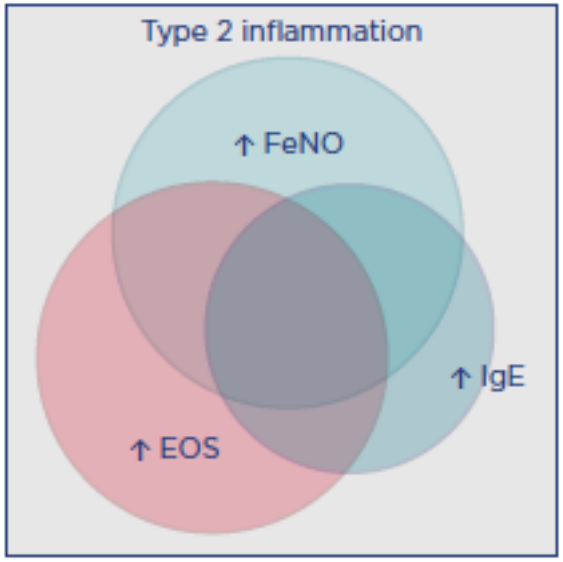


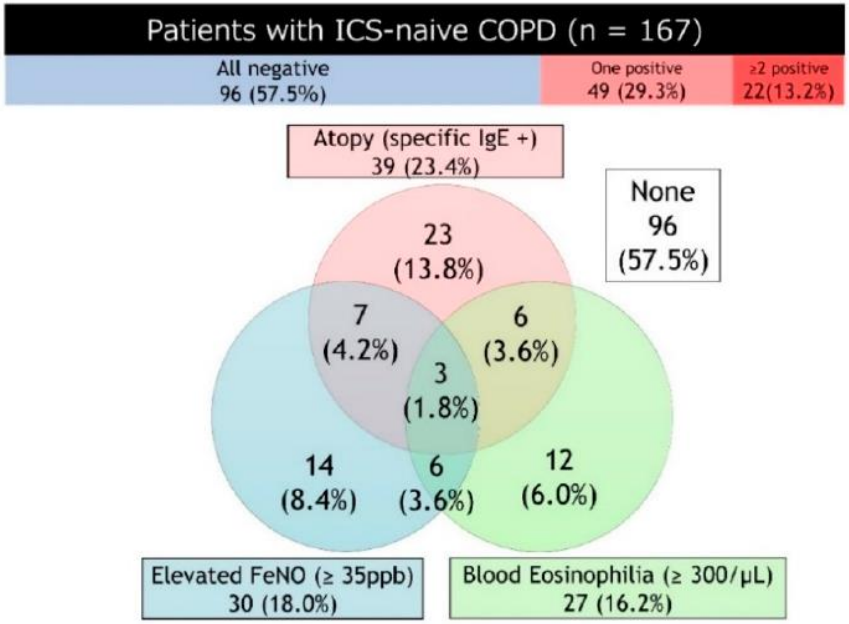
Biomarkers in type 2 inflammation

- Eosinophil:
  - Eos expectoration (> 3%, GOLD standard)
  - Blood Eosinophilia
  - Tissue Eosinophilia

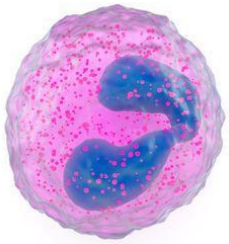
- exhaled Nitric Oxide Fraction (FeNO)

- Ig E





In clinical practice:



- Pheriperal BEC is the main biomarker of type 2 inflammation:
  - **cut-off ≥ 150 cells/µl in asthma**
  - **cut-off ≥ 300 cells/µl in COPD**
  - Easily obtainalble
  - Minimally invasive
  - Inexpensive
- CAVE:
  - Temporal fluctuation
  - Sub-optimal sensitivity and specificity
  - Influenced by systemic Corticosteroids

FeNO: exhaled Nitric Oxyde Fraction

- Produced by L-arginine through the action of NO synthase present in the respiratory epithelium upon stimulation by IL-13
- Functions:
  - Bronchodilation
  - Vasodilation
- Cut-off: negative < 20 ppb, pathological > 50 ppb

- CAVE:
  - Incresed in cases of *Rhinovirus*, pollution
  - Reduced in case of smoking

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

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

Lancet Respir Med
2025; 13: 234–43

- Pooled Analysis of Two Phase 3 Trials (BOREAS + NOTUS)
- The aim: assess whether *Dupilumab*, added to maximal inhaled therapy (ICS + LABA + LAMA), reduces exacerbations and improves lung function / symptoms in COPD patients with type 2 inflammation.
- Population: COPD patients (current/ex smokers) with Eos ≥ 300/ul, asthma history excluded
- Intervention: *Dupilumab* 300 mg sc/2wks + inhaled therapy vs placebo + inhaled therapy

	Placebo (n=936)	Dupilumab (n=938)	Overall (n=1874)
Age, years	65·0 (8·3)	65·1 (8·0)	65·1 (8·2)
Sex			
Female	302 (32·3%)	320 (34·1%)	622 (33·2%)
Male	634 (67·7%)	618 (65·9%)	1252 (66·8%)
Region*			
Asia	66 (7·1%)	67 (7·1%)	133 (7·1%)
Latin America	256 (27·4%)	255 (27·2%)	511 (27·3%)
Eastern Europe	358 (38·2%)	361 (38·5%)	719 (38·4%)
High-income	256 (27·4%)	255 (27·2%)	511 (27·3%)
Race			
White	813 (86·9%)	815 (86·9%)	1628 (86·9%)
Black	10 (1·1%)	7 (0·7%)	17 (0·9%)
Asian	70 (7·5%)	74 (7·9%)	144 (7·7%)
American Indian or Alaskan Native	30 (3·2%)	25 (2·7%)	55 (2·9%)
Native Hawaiian or Pacific Islander	1 (0·1%)	1 (0·1%)	2 (0·1%)
Multiple	12 (1·3%)	16 (1·7%)	28 (1·5%)
Ethnicity			
Hispanic or Latino	278 (29·7%)	283 (30·2%)	561 (29·9%)
Non-Hispanic or non-Latino	650 (69·4%)	650 (69·3%)	1300 (69·4%)
Unknown	8 (0·9%)	5 (0·5%)	13 (0·7%)
Smoking status			
Former	654 (69·9%)	662 (70·6%)	1316 (70·2%)
Current	282 (30·1%)	276 (29·4%)	558 (29·8%)
Smoking history, pack-years	38 (22–50)	35 (22–48)	36 (22–50)
Emphysema	301 (32·2%)	289 (30·8%)	590 (31·5%)
BMI, kg/m²	27·7 (5·6)	27·8 (5·4)	27·8 (5·5)
Triple therapy (ie, inhaled corticosteroid, long-acting β2-agonist, and long-acting muscarinic antagonist)	919 (98·2%)	921 (98·2%)	1840 (98·2%)
Moderate or severe COPD exacerbations in the previous year	2·2 (0·9)	2·2 (1·0)	2·2 (1·0)
≥1 severe COPD exacerbation in the previous year	214 (22·9%)	242 (25·8%)	456 (24·3%)

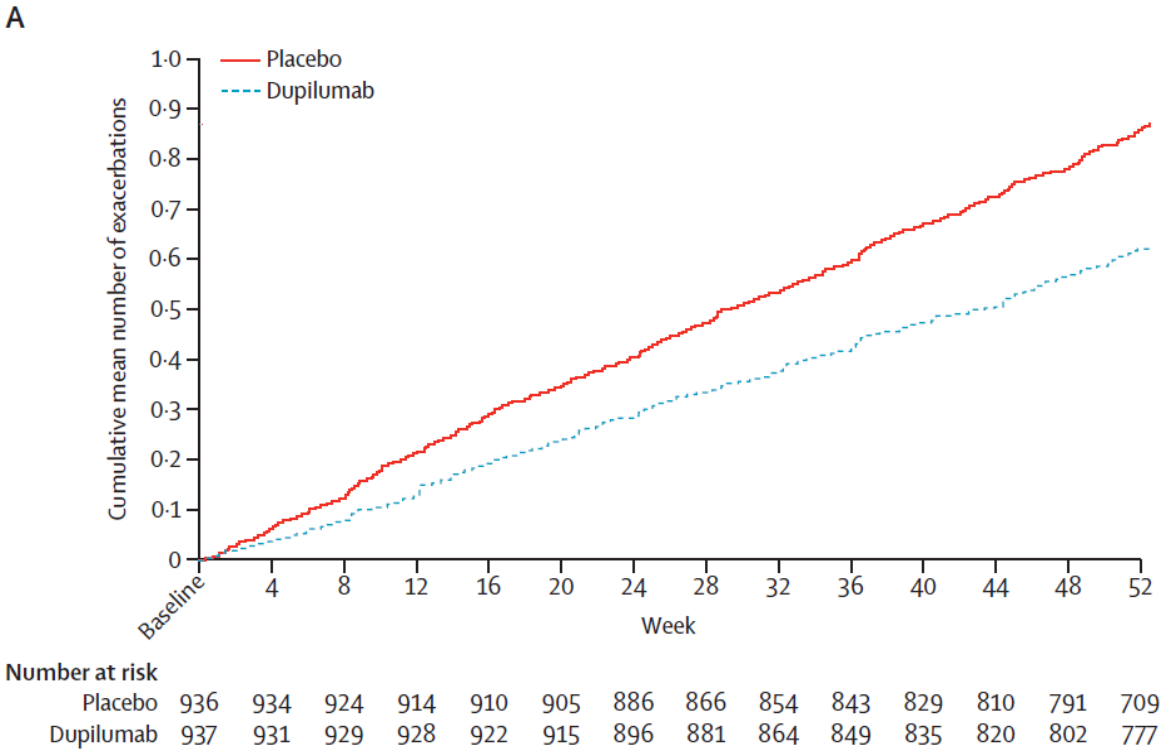
(Table 1 continues next column)

	Placebo (n=936)	Dupilumab (n=938)	Overall (n=1874)
(Continued from previous column)			
Lung function			
Pre-bronchodilator FEV_1, L	1·4 (0·5)	1·3 (0·5)	1·3 (0·5)
Post-bronchodilator FEV_1, L	1·4 (0·5)	1·4 (0·5)	1·4 (0·5)
Post-bronchodilator FEV_1, predicted value	50·7% (12·8)	50·0% (13·0)	50·3% (12·9)
Post-bronchodilator FEV_1/FVC ratio	0·49 (0·12)	0·49 (0·12)	0·49 (0·12)
St George's Respiratory Questionnaire total score	49·8 (17·2)	50·2 (17·4)	50·0 (17·3)
Evaluating Respiratory Symptoms in COPD total score	13·1 (8·3–17·9)	12·7 (8·4–17·7)	13·0 (8·3–17·8)
Biomarkers of type 2 inflammation			
Baseline blood eosinophil count, cells per μL	330 (230–460)	340 (240–460)	330 (230–460)
Blood eosinophil category at randomisation			
<300 cells/μL	374 (40·0%)	364 (38·8%)	738 (39·4%)
≥300 cells/μL	562 (60·0%)	573 (61·1%)	1135 (60·6%)
Fractional exhaled nitric oxide	17 (10–30)	17 (10–29)	17 (10–30)
<20 ppb	494/865 (57·1%)	495/862 (57·4%)	989/1727 (57·3%)
≥20 ppb	371/865 (42·9%)	367/862 (42·6%)	738/1727 (42·7%)

Primary Endpoint: annualised rate of moderate or severe exacerbations

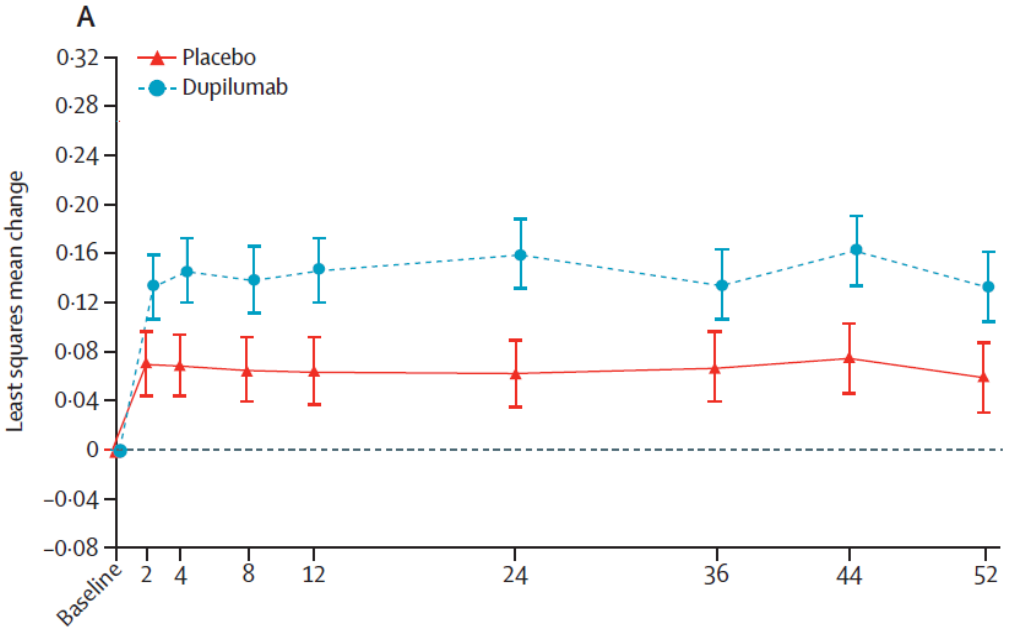
- **31%** Reduction in the annualised rate of moderate or severe exacerbation

(RR 0,69, 95% CI 0,595-0.793; p< 0.0001)

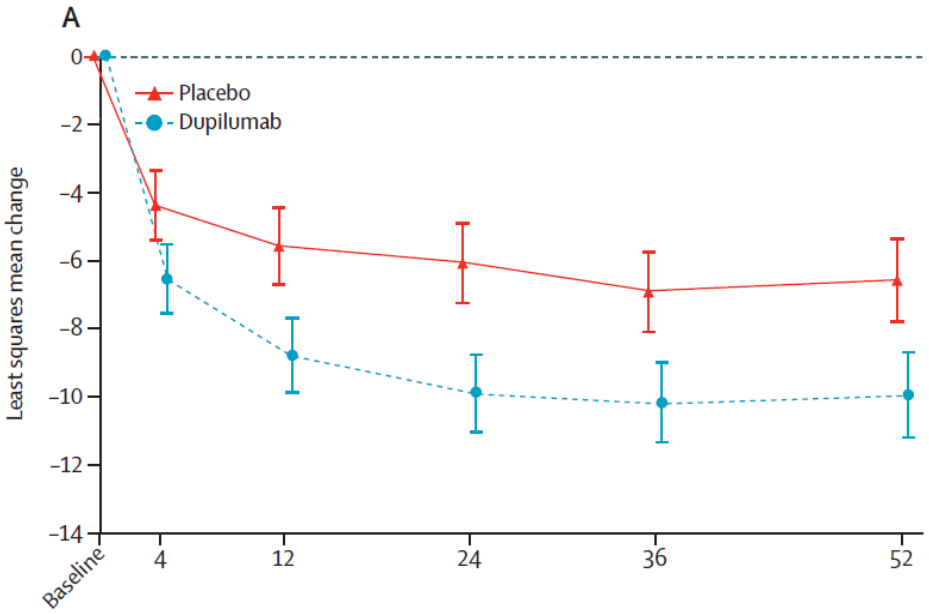


Secondary Endpoints

- Change of FEV_1 greater than placebo during the 52 wks
- + 83 mL (95% CI 0·053–0·112; p<0·0001)



- Improvement in SGRQ greater than placebo maintained until week 52 (−3·366, −4·953 to −1·778; p=<0·0001)
- MCID of -4 in 51% of patient in the *Dupilumab* group



Other results

- No statistically significant difference compared to placebo in reducing annualised rate of **severe** exacerbation
- Delayed time to first moderate or severe exacerbation
- *Dupilumab* reduced the average number of corticosteroid courses per patient by **~34 %** compared with placebo (0.639 vs 0.966 courses/year; 95 % CI)
- Adverse Event similar in the 2 groups

	Placebo (n=934)	Dupilumab (n=938)
Any treatment-emergent adverse event	663 (71·0%)	676 (72·1%)
Any treatment-emergent adverse event with a frequency ≥5%		
Nasopharyngitis	69 (7·4%)	73 (7·8%)
COVID-19	66 (7·1%)	65 (6·9%)
Upper respiratory tract infection	57 (6·1%)	50 (5·3%)
Headache	62 (6·6%)	73 (7·8%)
Any treatment-emergent severe adverse event	117 (12·5%)	108 (11·5%)
Any treatment-emergent serious adverse event	147 (15·7%)	125 (13·3%)
Any treatment-emergent adverse event leading to death	15 (1·6%)	19 (2·0%)
Any treatment-emergent adverse event leading to permanent intervention discontinuation	28 (3·0%)	32 (3·4%)
Major adverse cardiovascular event	16 (1·7%)	7 (0·7%)

Data are n (%).

Table 3: **Pooled treatment-emergent adverse events**

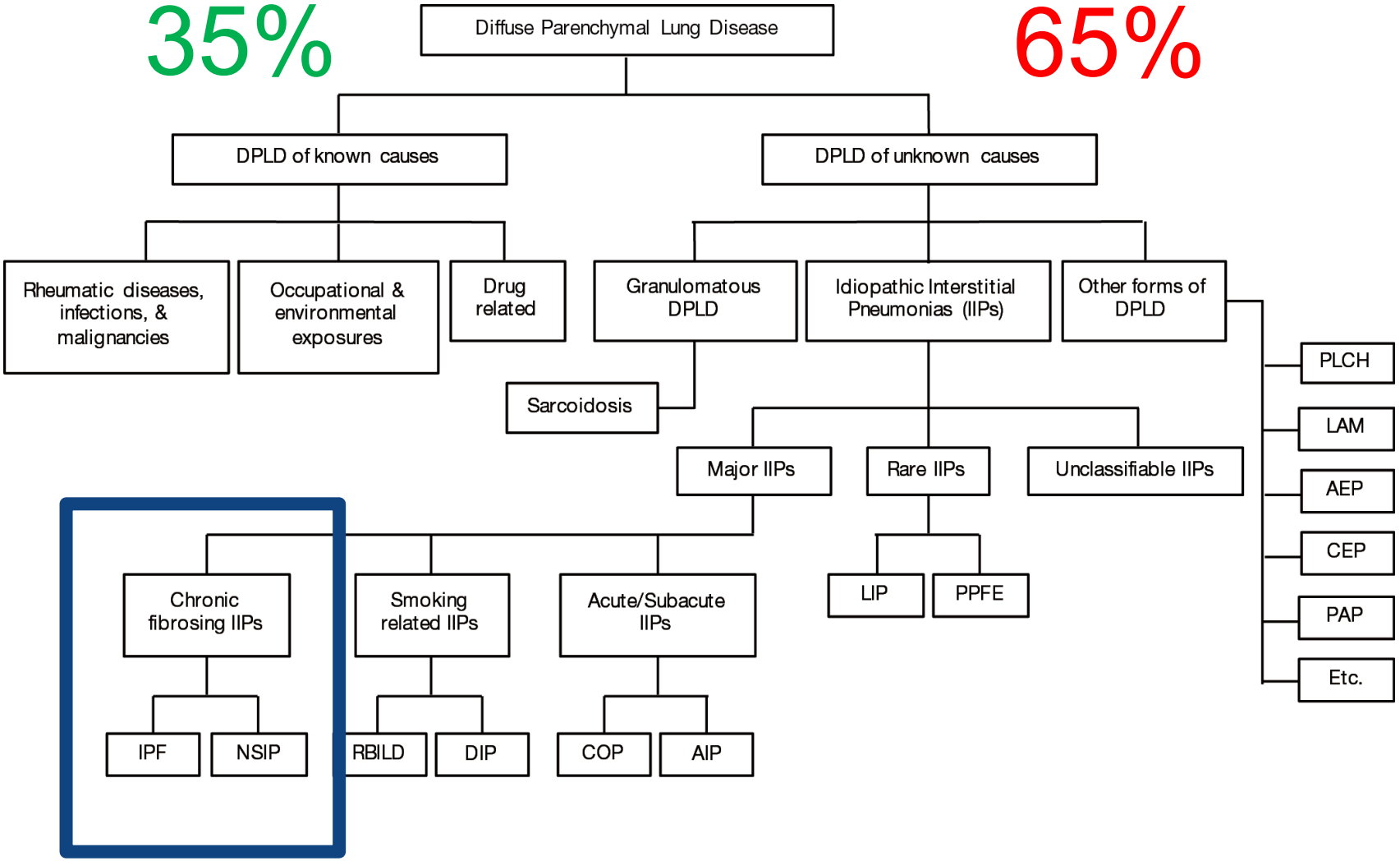
Take Home Message: GOLD 2025

- *RSV* is frequently associated with AECOPD
- *RSV* vaccination significantly prevent and reduce the risk of a LRTi
- It is reccomended for patients > 75 years or > 60 years with comorbidities (e.g Asthma, COPD,…)
- Add on treatment with *Dupilumab* demonstrate a clinical reduction in exacerbations in a selected COPD subgroup (with type 2 inflammation)
- Improvement in lung function over 52 weeks
- Support the precision medicine approach in COPD
- But some limitations:
  - Some endpoints were not emphasized (e.g SGRQ)
  - Effectiveness beyond 1 year

New therapeutic perspectives for pulmonary fibrosis: IPF and PF-ILD

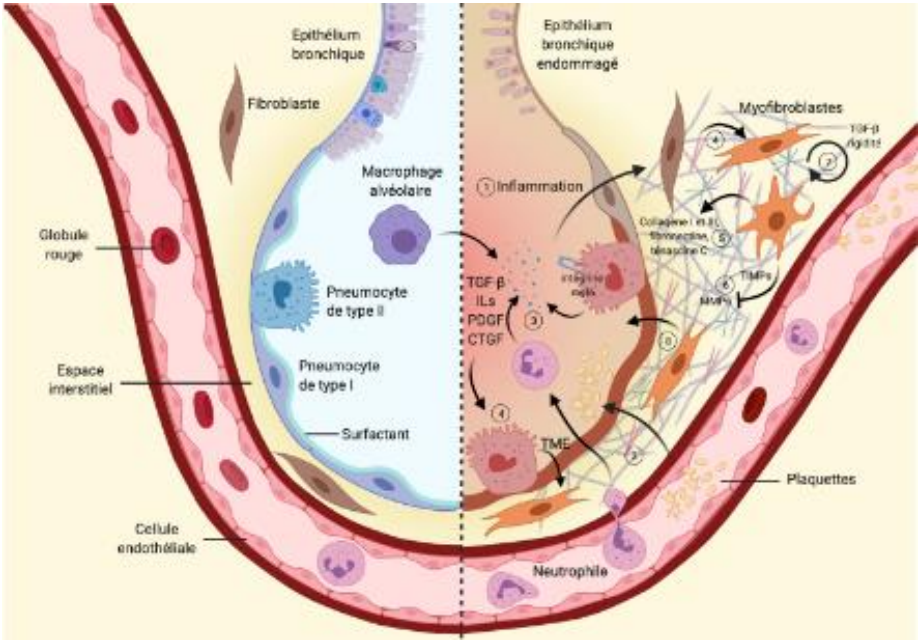
35%

65%



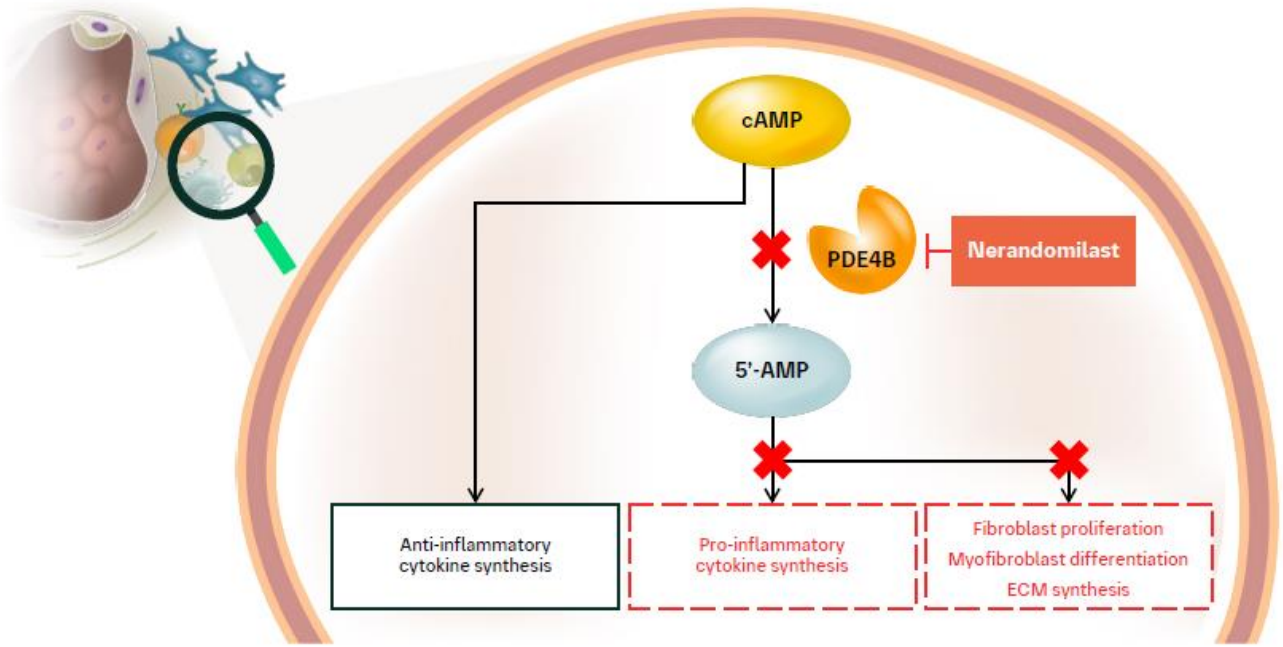
ILD: pathophysiology

- Epithelial injury:
  - Cellular and humoral AI, endothelial cell disfunction, alveolar macrophage activation
  - Trigger: Infections, Smoke, Dysbiosis, Reflux
  - Genetic mutations, susceptibility
- T cells, B cells, TGF-ß, PDGF, IL



- Common fibrotic pathways may exist
- Overgrowth, stiffening and scarring due to excess deposition of ECM component
- Repetitive cycles of injury and attempt to repair-deposit of non functional tissue
- Self-sustaining fibrosis: collagene-secreting myofibroblasts

PDE4B inhibition increases intracellular cAMP levels and is associated with antifibrotic and anti-inflammatory effects[1,2]



PDE4B mediates the breakdown of cAMP, which is a key second messenger that plays a role in regulating fibrotic and inflammatory pathways[1,2]

In preclinical studies, nerandomilast has shown promising antifibrotic effects via inhibition of fibroblast proliferation, myofibroblast differentiation and the expression of ECM proteins[2]

Anti-inflammatory effects were also demonstrated by inhibition of induced TNF-α and IL-2 synthesis (pro-inflammatory cytokines), and inhibition of induced neutrophil influx[2]

5'-AMP, adenosine 5'-monophosphate; cAMP, cyclic adenosine monophosphate; ECM, extracellular matrix; IL, interleukin; PDE4B, phosphodiesterase 4B; TNF, tumor necrosis factor
1. Kolb M *et al. Eur Respir Rev* 2023;32:220206; 2. Hermann FE *et al. Front Pharmacol* 2022;13:838449

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nerandomilast in Patients with Idiopathic Pulmonary Fibrosis

Luca Richeldi, M.D.,[1] Arata Azuma, M.D.,[2,3] Vincent Cottin, M.D.,[4]
Michael Kreuter, M.D.,[5,6] Toby M. Maher, M.D.,[7,8] Fernando J. Martinez, M.D.,[9]
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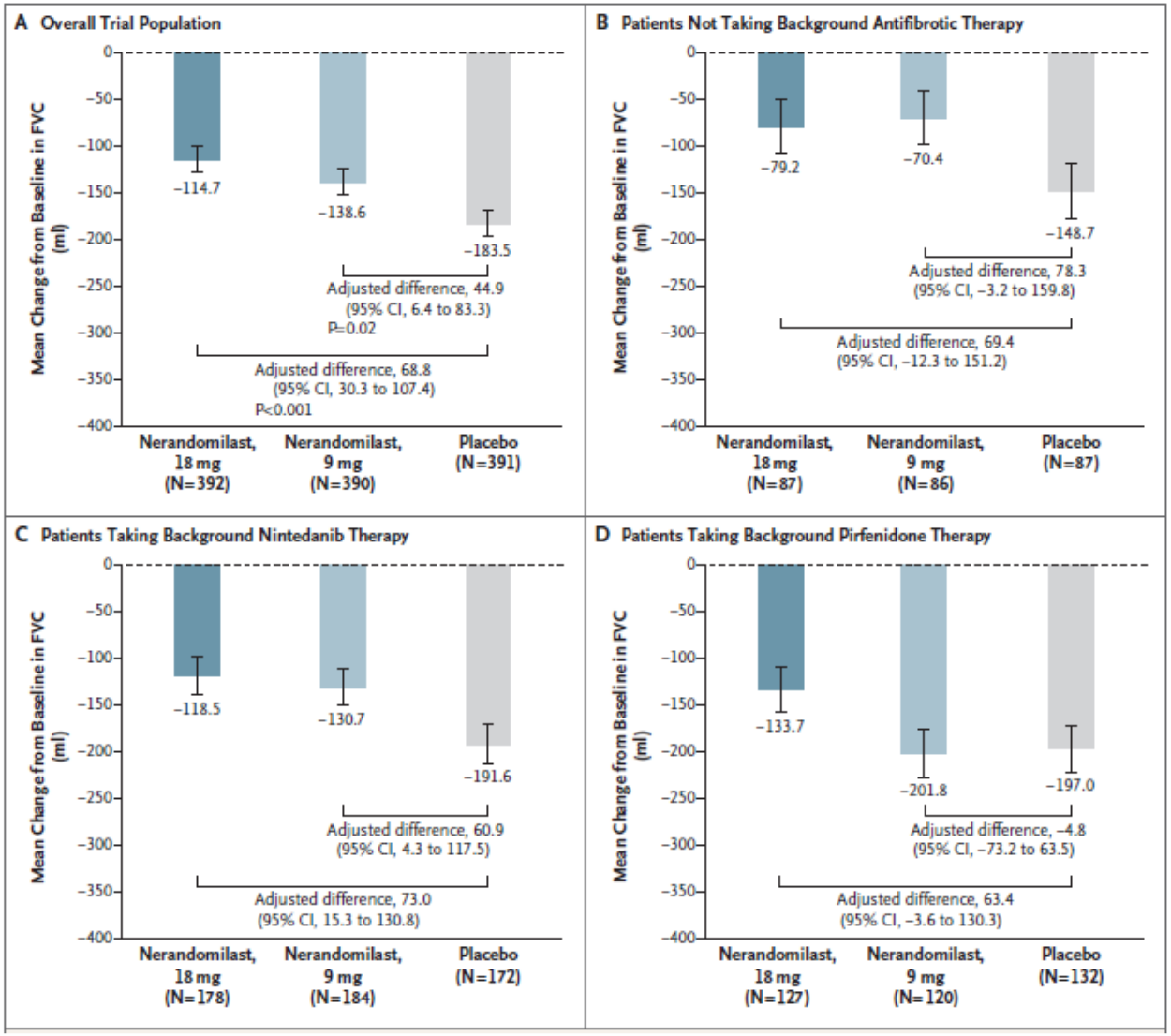
Emmanuelle Clerisme-Beaty, M.D.,[12] Maud Gordat, M.Sc.,[13]
Daniel Wachtlin, M.Sc.,[14] Yi Liu, Ph.D.,[15] Christina Schlecker, M.D.,[16]
Susanne Stowasser, M.D.,[12] Donald F. Zoz, M.D.,[17] and
Marlies S. Wijsenbeek, M.D.,[18] for the FIBRONEER-IPF Trial Investigators*

This article was published on May 18, 2025, at NEJM.org.

- Randomized, double-blind, placebo-controlled, multicenter phase III trial
- Population: 1177 IPF patient with or without background anti-fibrotic treatment (*nintedanib-pirfenidone*)
- Intervention: *Nerandomilast* (9-18 mg bid) vs placebo, 52 weeks
- Primary Endpoint: change in FCV decline over time
- Secondary Endpoint: first acute exacerbation, hospitalisation, death

Primary Endpoint

- Treatment with *Nerandomilast* resulted in a smaller decline in FVC compared to placebo
- 77% of patient with background therapy



Secondary Endpoint

Table 2. Time-to-Event End Points up to First Database Lock.*

End Point	Nerandomilast, 18 mg (N=392)	Nerandomilast, 9 mg (N=392)	Placebo (N=393)	Hazard Ratio (95% CI)	
				Nerandomilast, 18 mg, vs. Placebo	Nerandomilast, 9 mg, vs. Placebo
	number with event (percent)				
Key secondary end point					
First acute exacerbation, hospitalization for a respiratory cause, or death	85 (21.7)	79 (20.2)	80 (20.4)	1.17 (0.86–1.59)†	1.03 (0.75–1.41)‡
Other secondary end points					
Acute exacerbation or death	50 (12.8)	51 (13.0)	49 (12.5)	1.11 (0.75–1.65)	1.12 (0.76–1.67)
Hospitalization for a respiratory cause or death	75 (19.1)	68 (17.3)	73 (18.6)	1.13 (0.82–1.56)	0.98 (0.70–1.36)
Death	21 (5.4)	26 (6.6)	28 (7.1)	0.81 (0.46–1.43)	1.03 (0.60–1.76)
Absolute decline in percentage of predicted value of FVC of >10 percentage points from baseline or death	94 (24.0)	107 (27.3)	111 (28.2)	0.84 (0.64–1.10)	0.96 (0.74–1.25)
Absolute decline in percentage of predicted value of DLCO of >15 percentage points from baseline or death	59 (15.1)	59 (15.1)	66 (16.8)	0.88 (0.62–1.26)	0.98 (0.69–1.41)

- ***Nerandomilast*** **did not reduce the risk of acute exacerbation, respiratory hospitalization, or death** during the 52-week study period

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

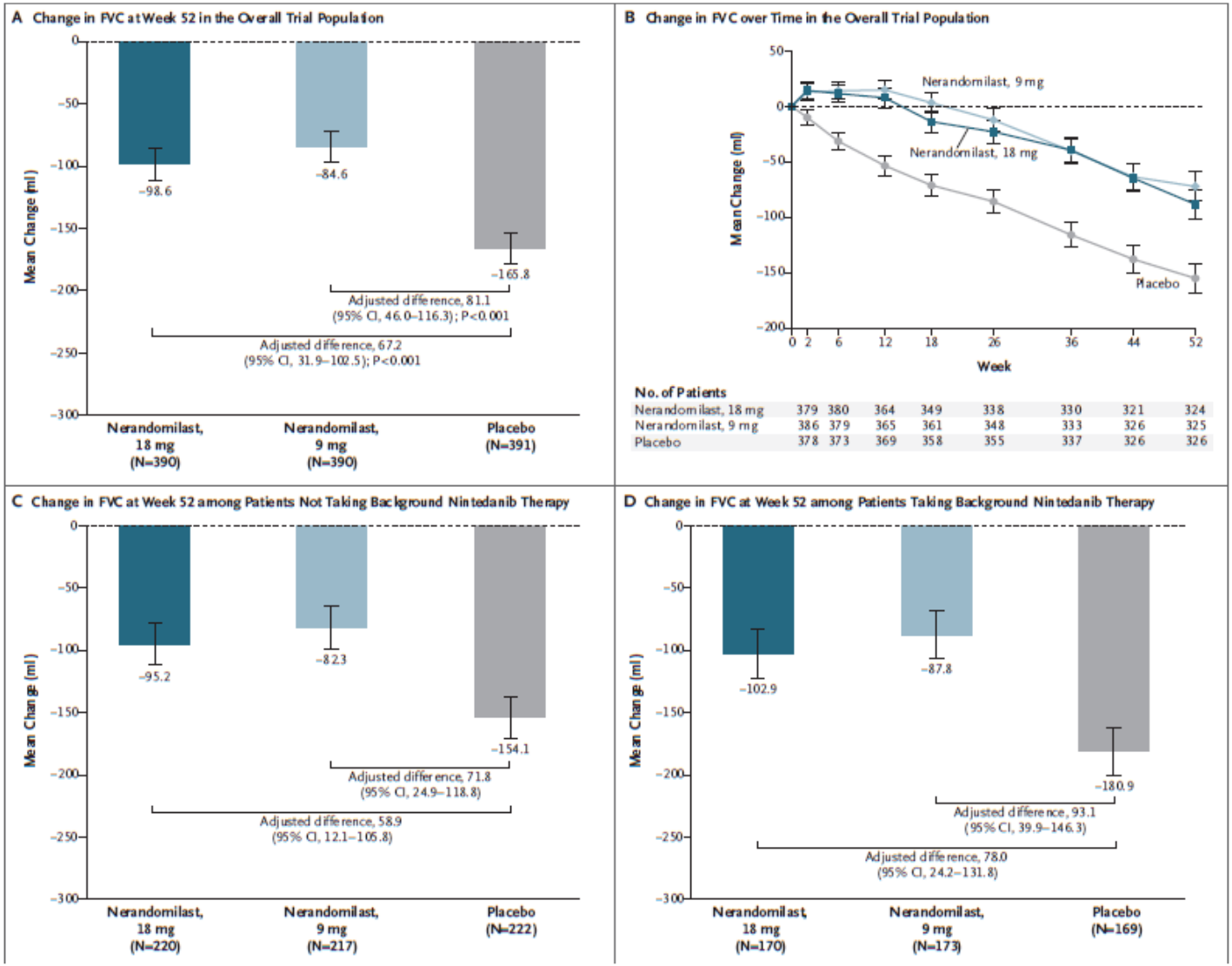
Nerandomilast in Patients with Progressive Pulmonary Fibrosis

Toby M. Maher, M.D.,[1,2] Shervin Assassi, M.D.,[3] Arata Azuma, M.D.,[4,5] Vincent Cottin, M.D.,[6] Anna-Maria Hoffmann-Vold, M.D.,[7,8] Michael Kreuter, M.D.,[9,10] Justin M. Oldham, M.D.,[11] Luca Richeldi, M.D.,[12] Claudia Valenzuela, M.D.,[13] Marlies S. Wijsenbeek, M.D.,[14] Emmanuelle Clerisme-Beaty, M.D.,[15] Carl Coeck, M.D.,[16] Hui Gu, Ph.D.,[17] Ivana Ritter, M.D.,[15] Arno Schlosser, M.Sc.,[18] Susanne Stowasser, M.D.,[15] Florian Voss, Ph.D.,[19] Gerrit Weimann, M.D.,[15] Donald F. Zoz, M.D.,[20] and Fernando J. Martinez, M.D.,[21] for the FIBRONEER-ILD Trial Investigators*

This article was published on May 19, 2025, at NEJM.org.

- Randomized, double-blind, placebo-controlled, multicenter phase III trial
- Population: 1176 PPF patients with or without background anti-fibrotic treatment (*nintedanib*)
- Intervention: *Nerandomilast* (9-18 mg bid) vs placebo, 52 weeks
- Primary Endpoint: change in FCV decline over time
- Secondary Endpoint: first acute exacerbation, hospitalisation, death

Primary Endpoint

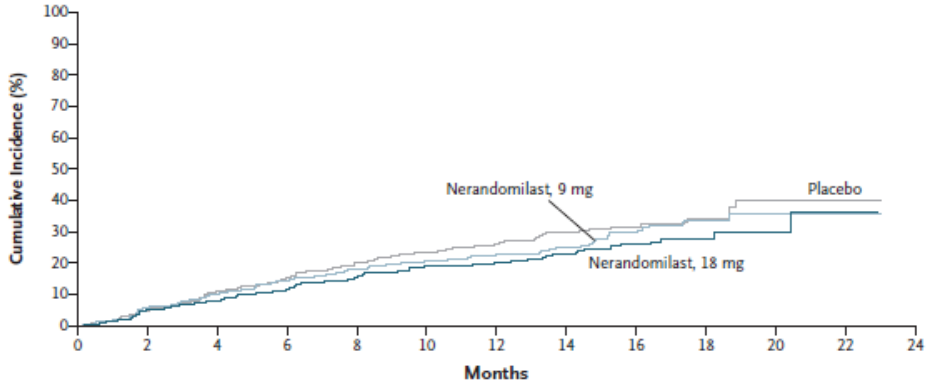


Secondary Endpoints

- 23% lower relative risk of first exacerbation/hospitalization/death but not statistical significance

- 52% lower relative risk of death

A Time to a First Key Secondary End-Point Event up to First Database Lock

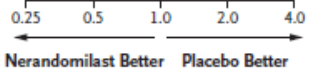


No. at Risk

Nerandomilast, 18 mg	391	370	353	338	321	305	261	198	92	38	25	1	0
Nerandomilast, 9 mg	393	368	350	332	317	307	259	199	95	37	25	5	0
Placebo	392	373	348	329	310	296	245	184	83	38	23	2	0

B Analyses of Key Secondary End Point and Related Secondary End Points up to First Database Lock

End Point	Nerandomilast	Placebo	Hazard Ratio (95% CI)	P Value
	no. with event/no. of patients			
Key secondary end point				
Nerandomilast, 18 mg	95/391	122/392	0.77 (0.59–1.01)	0.06
Nerandomilast, 9 mg	110/393	122/392	0.88 (0.68–1.14)	0.34
Acute exacerbation of ILD or death				
Nerandomilast, 18 mg	48/391	83/392	0.59 (0.41–0.84)	
Nerandomilast, 9 mg	65/393	83/392	0.78 (0.56–1.08)	
Hospitalization for respiratory cause or death				
Nerandomilast, 18 mg	84/391	110/392	0.75 (0.56–1.00)	
Nerandomilast, 9 mg	97/393	110/392	0.83 (0.63–1.10)	
Death				
Nerandomilast, 18 mg	24/391	50/392	0.48 (0.30–0.79)	
Nerandomilast, 9 mg	33/393	50/392	0.60 (0.38–0.95)	



Safety Endpoints

- In both studies discontinuation rates are comparable between *Nerandomilast* and placebo
- The most frequently side effect is diarrhea 36-41%
- More pronounced in *Nintedanib* background patient group (51-62%)
- Treatmen-related discontinuation incidence low

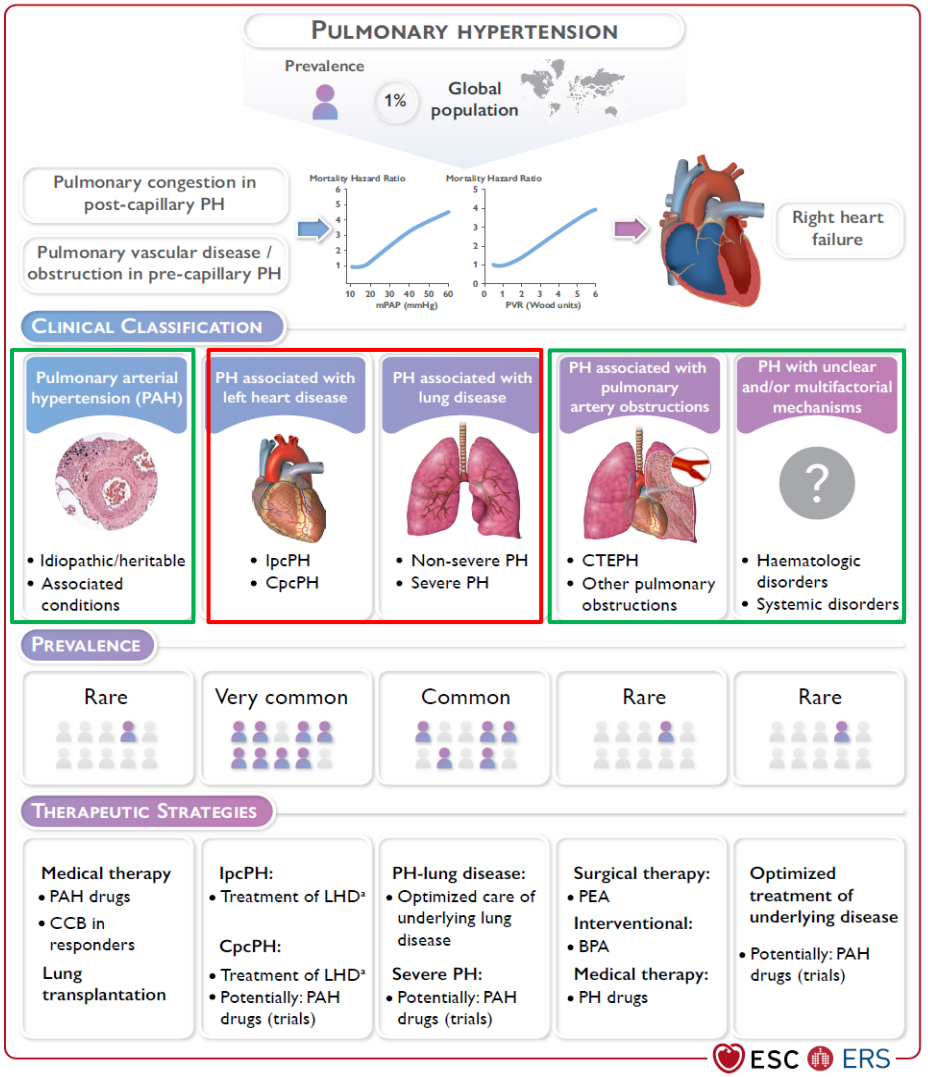
Conclusion and take home message:

- *Nerandomilast* can slow lung function decline in IPF and PPF-ILD as add-on treatment or in naïve patient
- But…the treatment does not stop progression…
- In IPF:
  - did not reduce risk of acute exacerbation, hospitalization or death
- In PPF-ILD:
  - positive trend in fewer respiratory events
  - lower relative risk of death

Pulmonary hypertension: revolution thanks to *Sotatercept*

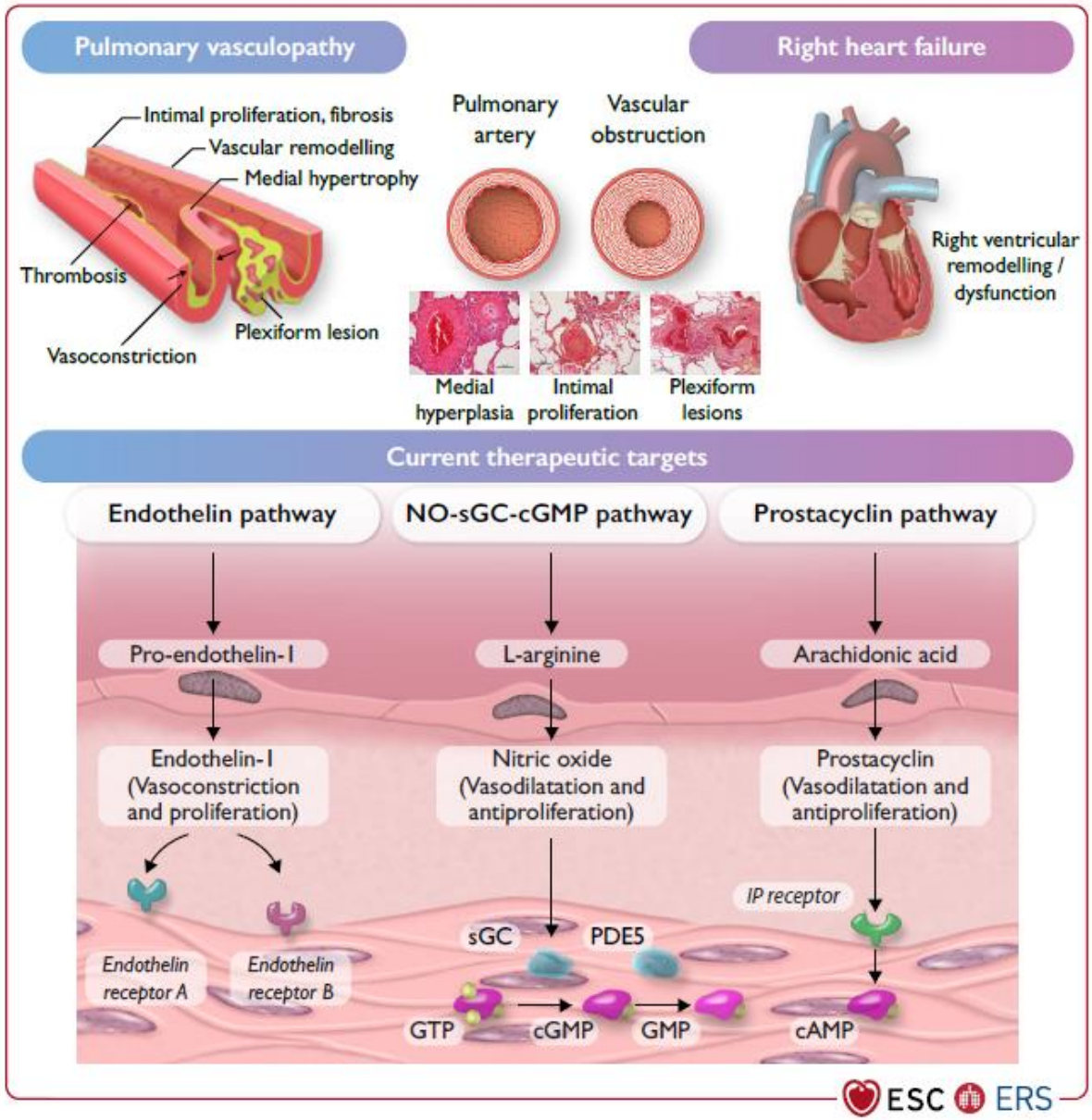
- 1% prevalence World
  - Group 2 and 3
- PH associated with increase in mortality

- Incidence $6/10^6$
  - Group 1-4-5
  - Target treatment



ESC European Society of Cardiology
European Heart Journal (2022) 00, 1–114
https://doi.org/10.1093/eurheartj/ehac237

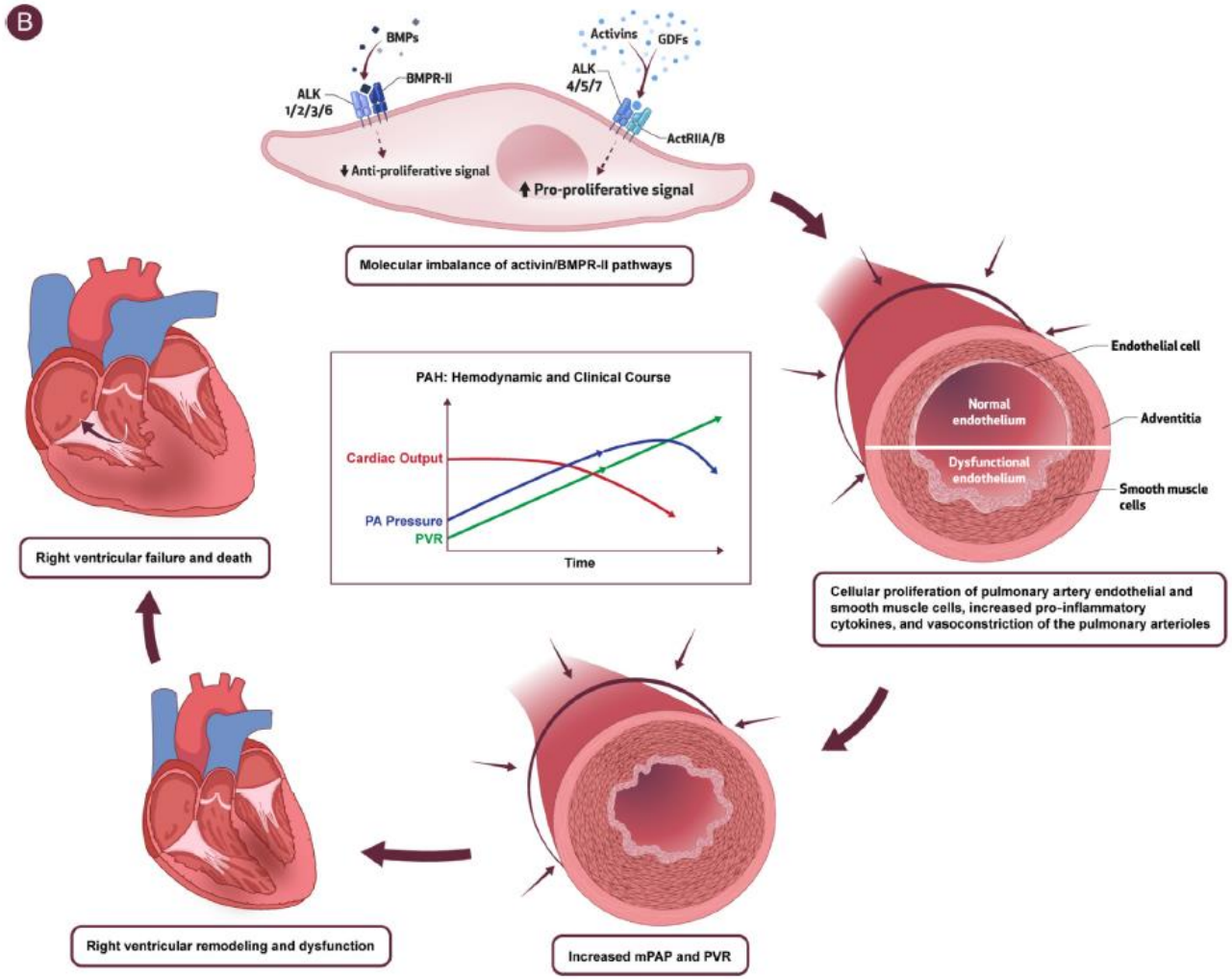
- Despite therapies acting on the 3 pathways 5 years mortality remains high 40%



ESC European Society of Cardiology
European Heart Journal (2022) 00, 1–114
https://doi.org/10.1093/eurheartj/ehac237

Another pathway involved in PAH

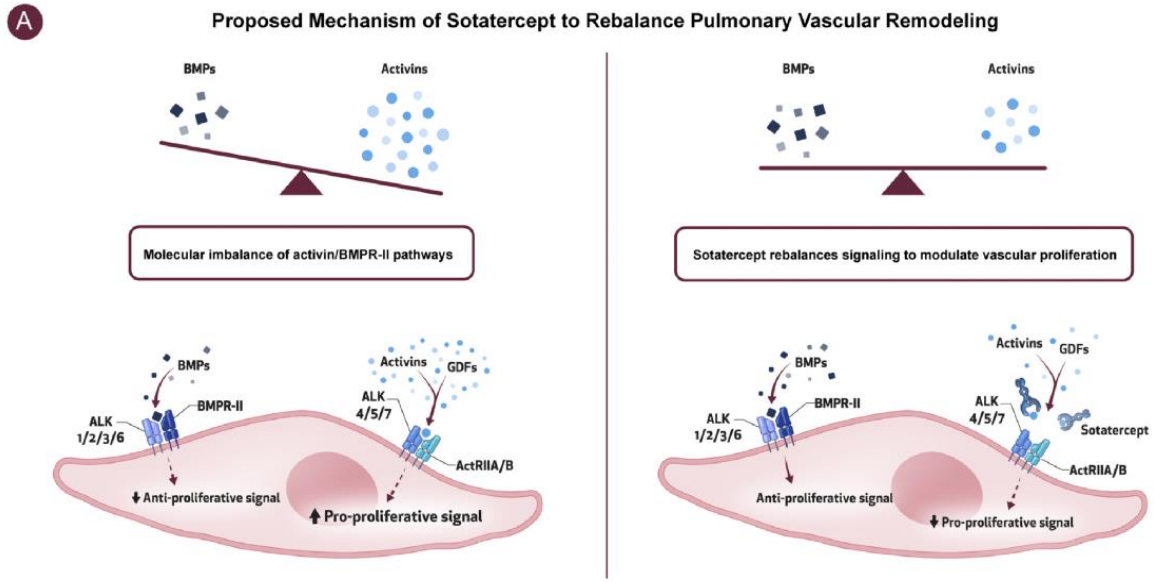
- Dysregulation of growth factor
- Molecular imbalance of Activines (pro-proliferative) and BMP (anti-proliferative signaling)
- Balance is critical to cellular differentiation, proliferation and apoptosis in pulmonary vessels



Cascino et al. The Journal of Heart and Lung Transplantation, Vol 44, No 1, January 2025

Sotatercept:

- **Is a new first-in-class therapy**
- **Novel mechanism of action** that target fundamental disease process
- Is a fusion protein combining activine type IIA receptor with a human IgG
- Act as a ligand trap for activins
- **Subcutaneous route**, initial dose of 0,3 mg/kg with escalation to 0,7 mg/kg



Sotatercept in pulmonary arterial hypertension: revolution, risk and the road ahead

Marius M. Hoeper [1,2]

Eur Respir J 2025; 66: 2501633

- PULSAR (phase 2): sotatercept (0.3 or 0.7 mg·kg^{-1} every 3 weeks) reduced PVR by ~2 and ~3 Wood units, respectively, and improved 6-min walk distance (6MWD) and N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) [9]. Benefits were sustained for up to 24 months in the open-label extension [10]. PULSAR included genetic testing for variants associated with PAH, and *BMPR2* mutation carriers – the most common subtype of HPAH – had similar improvements in PVR and 6MWD than noncarriers. Two patients with rare variants, one with an *ACVRL1* mutation (encoding activin receptor-like kinase-1 (ALK1), a type I receptor of the TGF-β superfamily, linked to hereditary haemorrhagic telangiectasia) and one with biallelic *EIF2AK4* mutations (associated with pulmonary veno-occlusive disease), also responded to sotatercept [11].
- STELLAR (phase 3): sotatercept (0.7 mg·kg^{-1} target dose) improved 6MWD by ~40 m *versus* placebo at 24 weeks, with additional improvements in haemodynamics, World Health Organization functional class (WHO FC) and NT-proBNP [12]. Clinical worsening risk at end of study was reduced by 84% (hazard ratio 0.16). *Post hoc* analyses showed that reductions in right ventricular afterload were driven largely by a decrease in mPAP, without a change in cardiac output, resulting in marked right ventricular reverse remodelling and less tricuspid regurgitation [13].
- ZENITH (phase 3): in WHO FC III–IV patients at high risk of death, sotatercept (0.7 mg·kg^{-1} target dose) reduced a composite endpoint of death from any cause, lung transplantation or PAH-related hospitalisation for at least 24 h by 76% (hazard ratio 0.24), again with improvements in haemodynamics, 6MWD, WHO FC and NT-proBNP [14].
- HYPERION (phase 3): this study has not been fully published. According to preliminary information, sotatercept reduced clinical worsening events in patients with PAH diagnosed ⩽1 year before inclusion (V.V. McLaughlin and co-workers: "Sotatercept for pulmonary arterial hypertension within the first year of diagnosis"; manuscript submitted.).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sotatercept for Pulmonary Arterial Hypertension within the First Year after Diagnosis

V.V. McLaughlin,[1] M.M. Hoeper,[2] D.B. Badesch,[3] H.A. Ghofrani,[4] J.S.R. Gibbs,[5] M. Gomberg-Maitland,[6] I.R. Preston,[7] R. Souza,[8] A.B. Waxman,[9] G. Kopeć,[10,11] G. Meyer,[12] K.M. Olsson,[2] W. Fu,[13] Y. Shi,[13] B. Miller,[13] S.S. Kim,[13] H.S. Mackenzie,[13] M. Brambatti,[13] M.J. Patel,[13] J. Koglin,[13] A.G. Cornell,[13] and M. Humbert,[14] for the HYPERION Trial Investigators*

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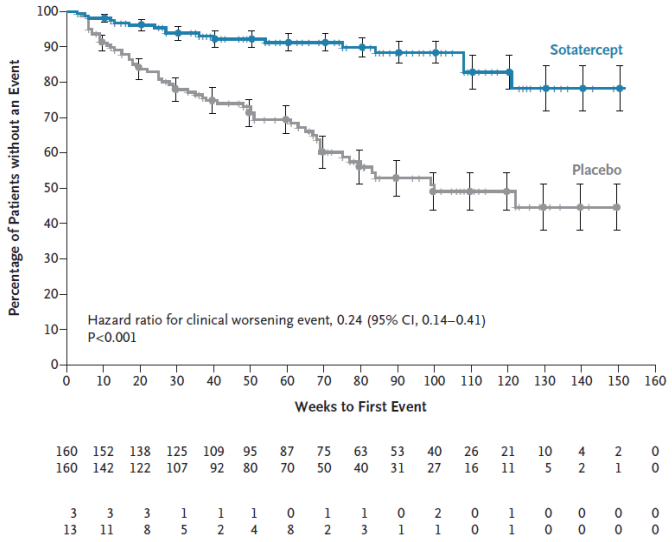
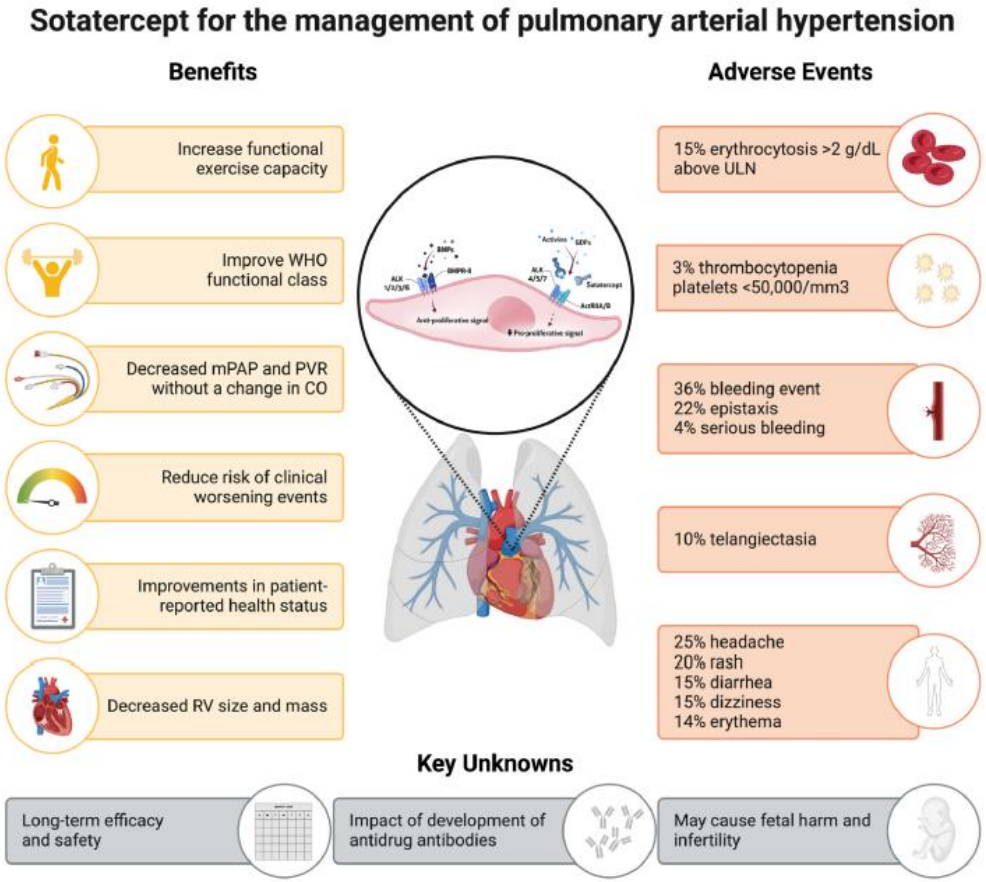
RESULTS

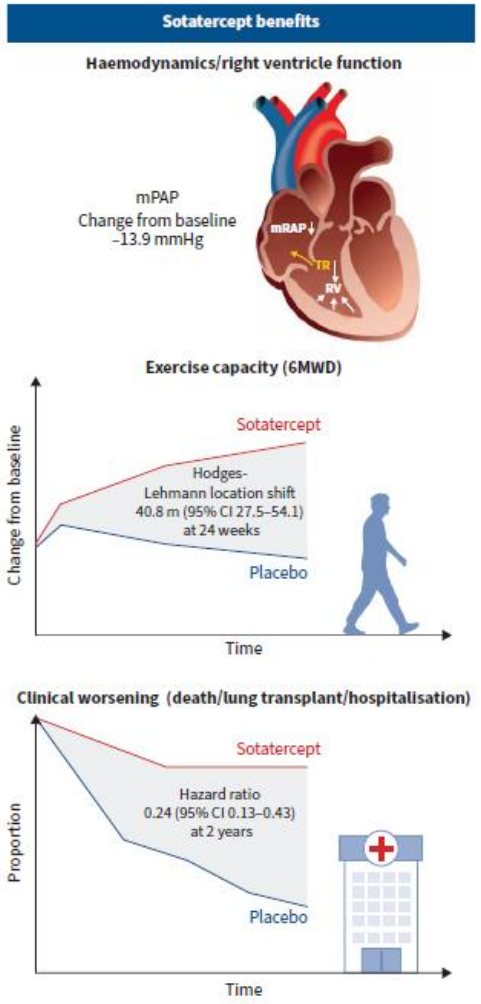
The trial was stopped early owing to loss of clinical equipoise after the reporting of positive results from previous sotatercept trials. A total of 320 patients were included (160 each in the sotatercept and placebo groups). The median duration of follow-up was 13.2 months. At least one primary end-point event occurred in 17 patients (10.6%) in the sotatercept group and in 59 patients (36.9%) in the placebo group (hazard ratio, 0.24; 95% confidence interval, 0.14 to 0.41; P<0.001). Deterioration in performance in exercise testing due to pulmonary arterial hypertension occurred in 8 patients (5.0%) in the sotatercept group and in 46 patients (28.8%) in the placebo group; unplanned hospitalization for worsening of pulmonary arterial hypertension occurred in 3 patients (1.9%) and 14 patients (8.8%), respectively; and death from any cause occurred in 7 patients (4.4%) and 6 patients (3.8%). No cases of atrial septostomy or lung transplantation occurred. The most common adverse events with sotatercept were epistaxis (31.9%) and telangiectasia (26.2%).



No. at Risk																		
Sotatercept	160	152	138	125	109	95	87	75	63	53	40	26	21	10	4	2	0	
Placebo	160	142	122	107	92	80	70	50	40	31	27	16	11	5	2	1	0	
No. of Events																		
Sotatercept	3	3	3	1	1	1	0	1	1	0	2	0	1	0	0	0	0	
Placebo	13	11	8	5	2	4	8	2	3	1	1	0	1	0	0	0	0	

Sotatercept ad add-on therapy





Take home message

- There is a new treatment add-on therapy for PAH
- *Sotatercept* my be a revolution in PAH showing promising signal of reverse pulmonary vascular and cardiac remodelling
- Its final location in the treatment PAH algorithm is a work in progress