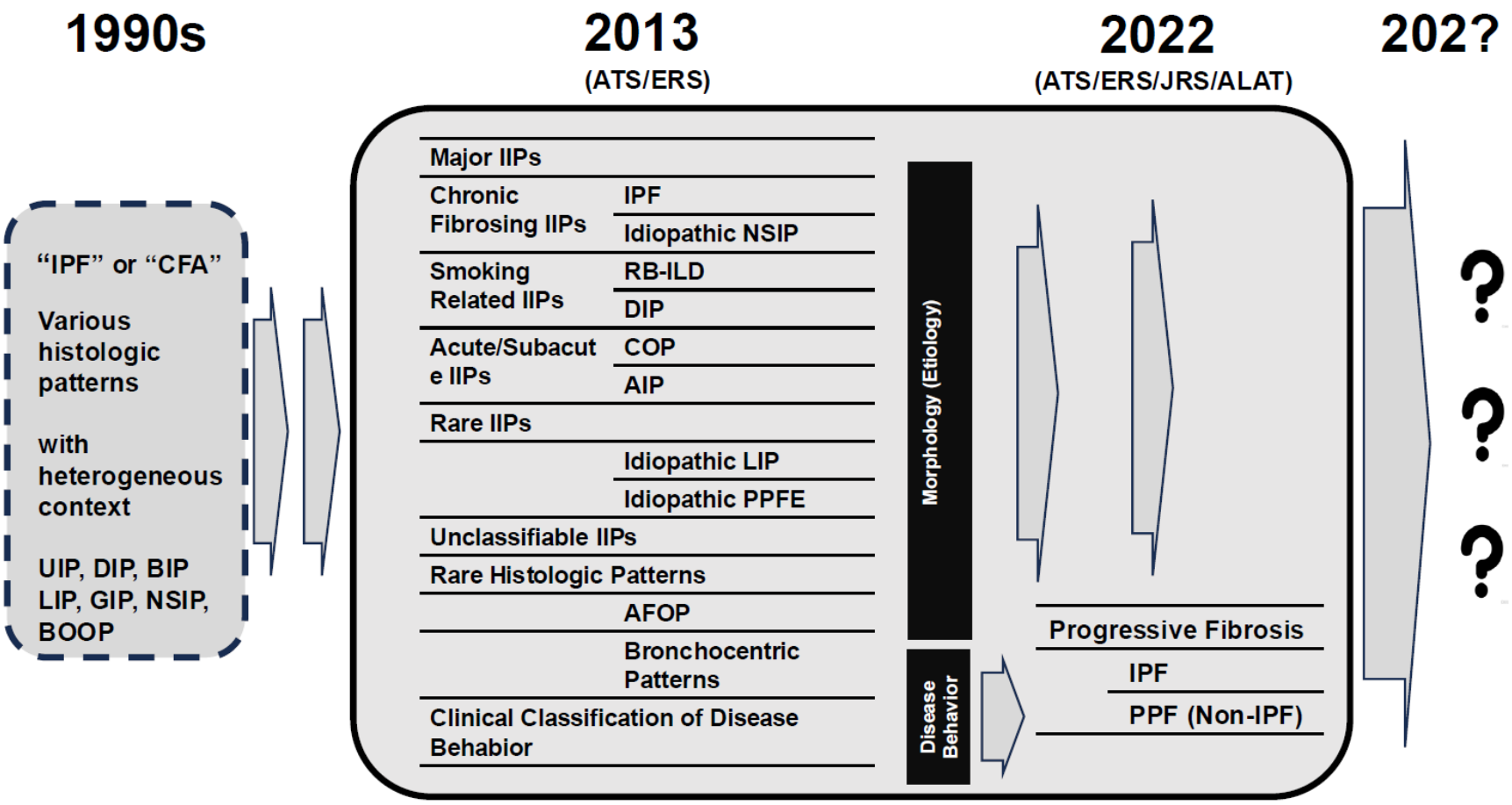
Recent update in ILD

Division of Pulmonology and Critical Care Medicine
Inje University Haeundae Paik Hospital
Ji Hoon Jang

INJE UNIVERSITY HAEUNDAE PAIK HOSPITAL

Where we are heading…?

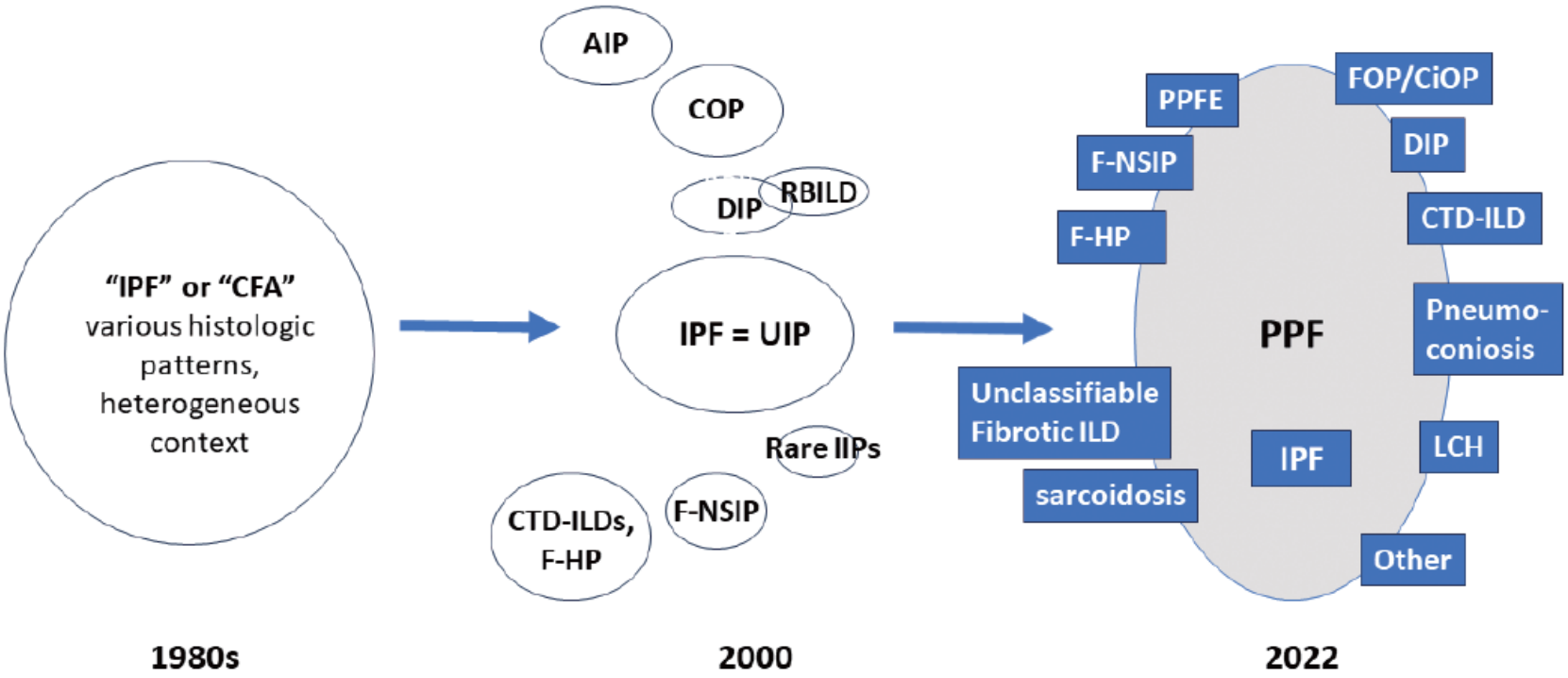
INJE UNIVERSITY
HAEUNDAE PAIK HOSPITAL



JPTM Journal of Pathology and Translational Medicine

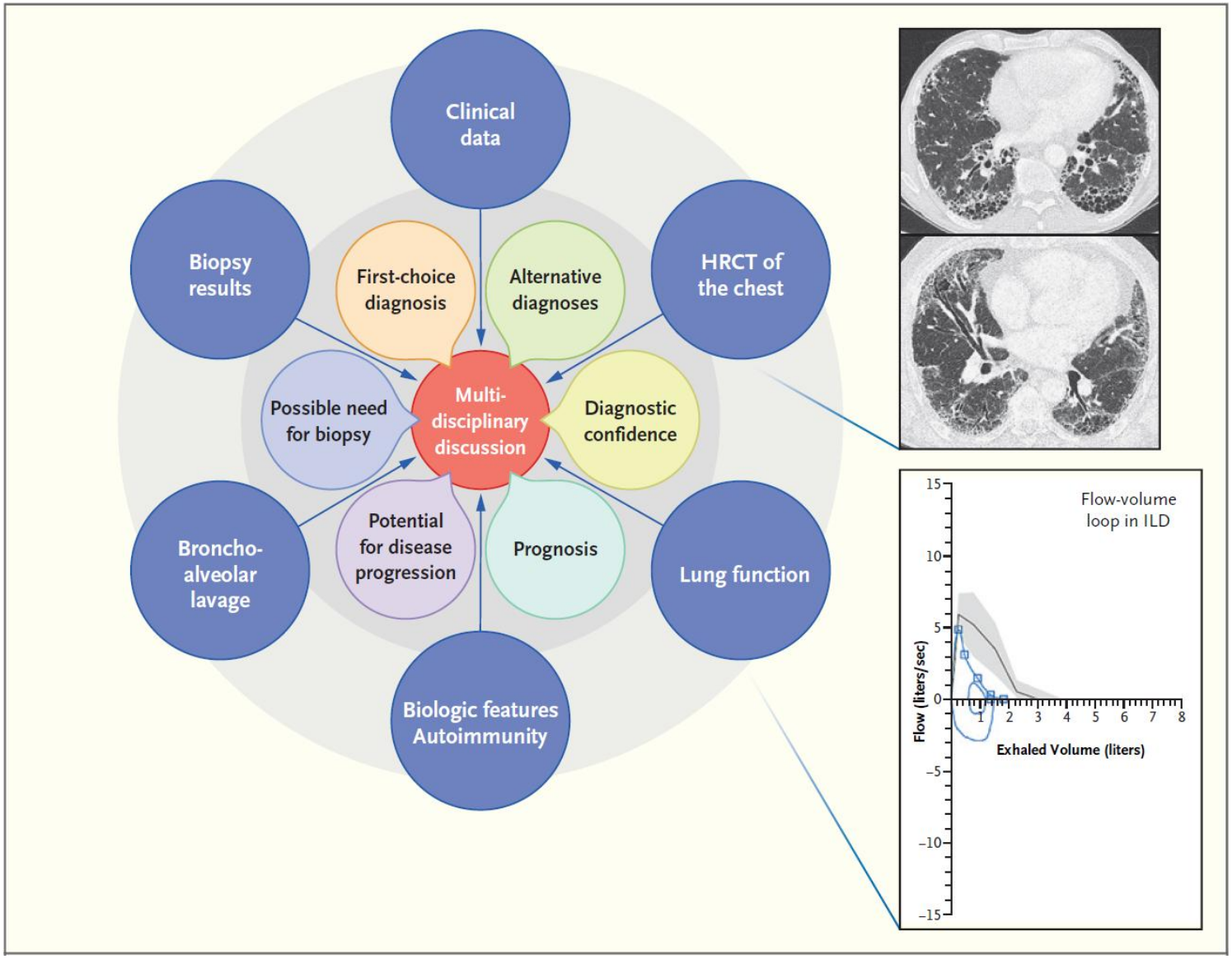
Diagnosis of interstitial lung diseases: from Averill A. Liebow to artificial intelligence

Conceptual Evolution of Pulmonary Fibrosis



J Pathol Transl Med. 2024 Jan;58(1)

Current diagnostic approach to ILDs

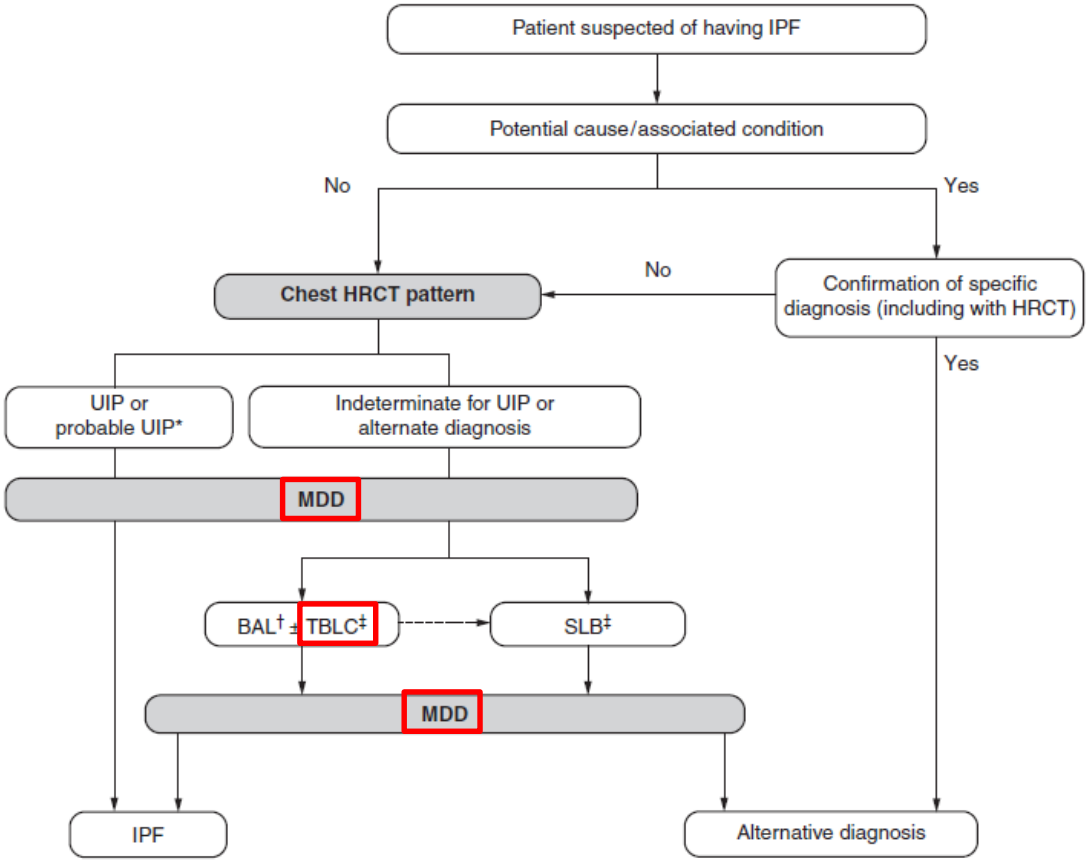


N Engl J Med 2020;383

ATS Journals

Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline



Am J Respir Crit Care Med. 2022 May 1;205(9)

ATS Journals

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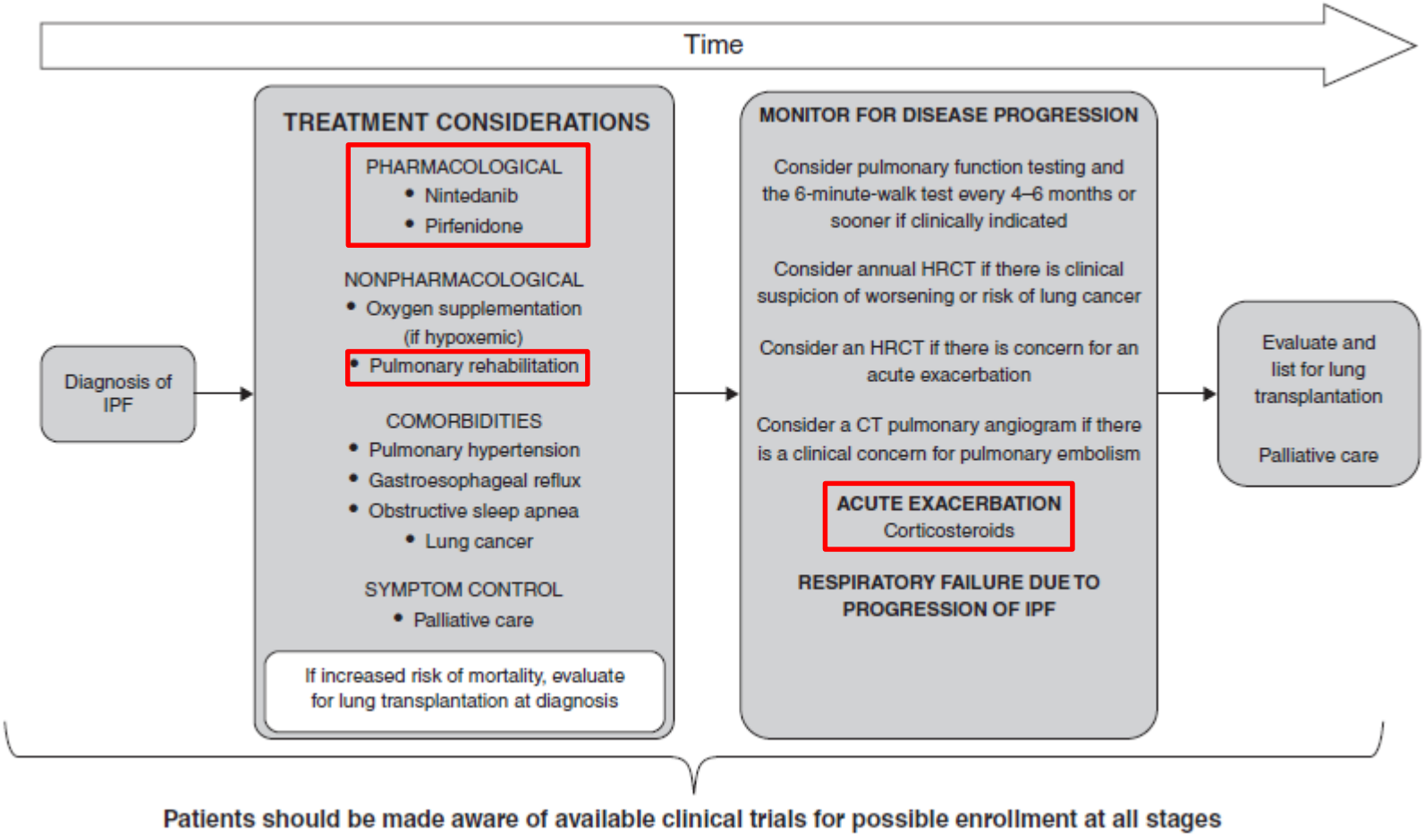

Am J Respir Crit Care Med. 2022 May 1;205(9)

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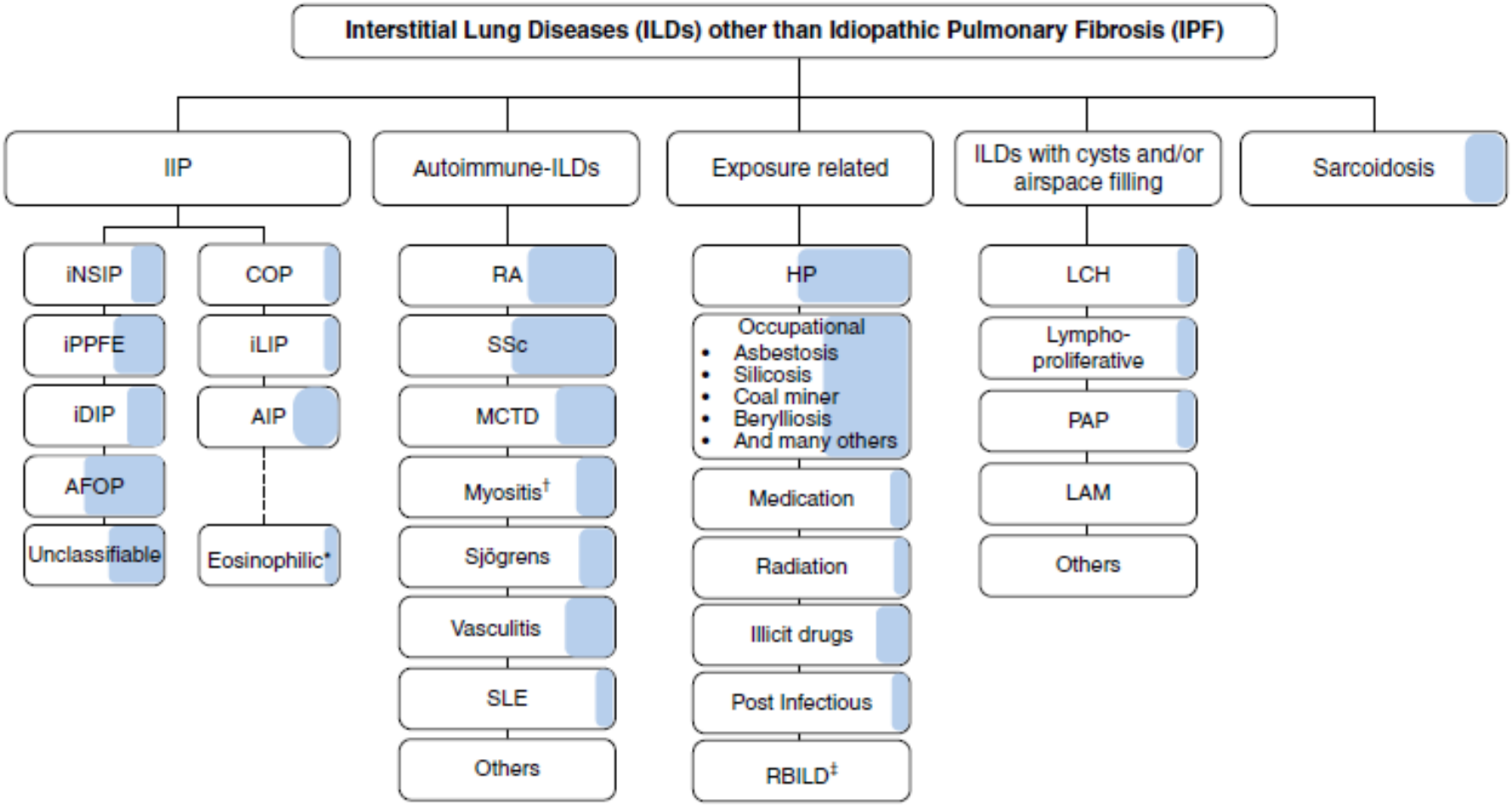


Am J Respir Crit Care Med. 2022 May 1;205(9)

ATS Journals

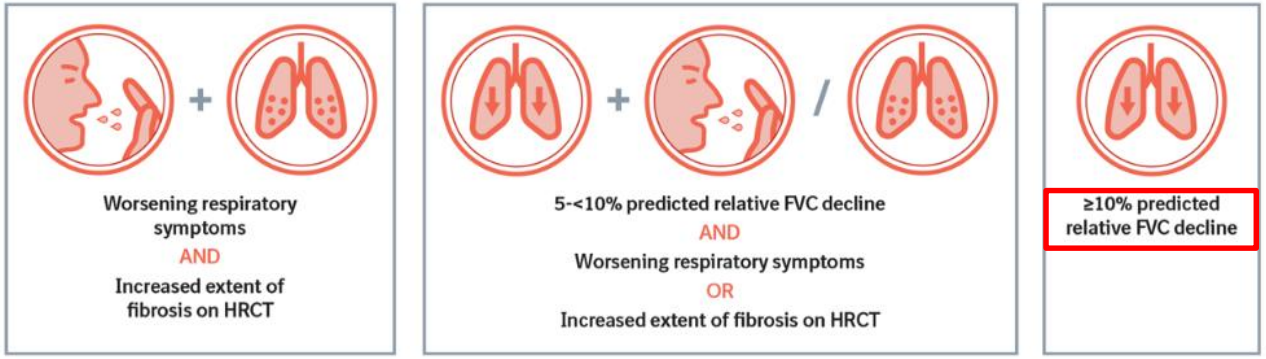
Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

ORIGINAL ARTICLE

Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

K.R. Flaherty, A.U. Wells, V. Cottin, A. Devaraj, S.L.F. Walsh, Y. Inoue, L. Richeldi, M. Kolb, K. Tetzlaff, S. Stowasser, C. Coeck, E. Clerisme-Beaty, B. Rosenstock, M. Quaresma, T. Haeufel, R.-G. Goeldner, R. Schlenker-Herceg, and K.K. Brown, for the INBUILD Trial Investigators*



Definition of PPF

In a patient with ILD of known or unknown etiology other than IPF who has radiological evidence of pulmonary fibrosis, PPF is defined as at least two of the following three criteria occurring within the past year with no alternative explanation*:

1 Worsening respiratory symptoms

2 Physiological evidence of disease progression (either of the following):
- a. Absolute decline in FVC ⩾5% predicted within 1 yr of follow-up
- b. Absolute decline in D_{LCO} (corrected for Hb) ⩾10% predicted within 1 yr of follow-up

3 Radiological evidence of disease progression (one or more of the following):
- a. Increased extent or severity of traction bronchiectasis and bronchiolectasis
- b. New ground-glass opacity with traction bronchiectasis
- c. New fine reticulation
- d. Increased extent or increased coarseness of reticular abnormality
- e. New or increased honeycombing
- f. Increased lobar volume loss

Am J Respir Crit Care Med. 2022 May 1;205(9)

ORIGINAL ARTICLE

Validation of Proposed Criteria for Progressive Pulmonary Fibrosis

Janelle Vu Pugashetti[1,2*], Ayodeji Adegunsoye[3*], Zhe Wu[4,5], Cathryn T. Lee[3], Anand Srikrishnan[6], Sahand Ghodrati[2], Vivian Vo[2], Elisabetta A. Renzoni[4,5], Athol U. Wells[4,5], Christine Kim Garcia[7], Felix Chua[4,5], Chad A. Newton[6‡], Philip L. Molyneaux[4,5‡], and Justin M. Oldham[1‡]

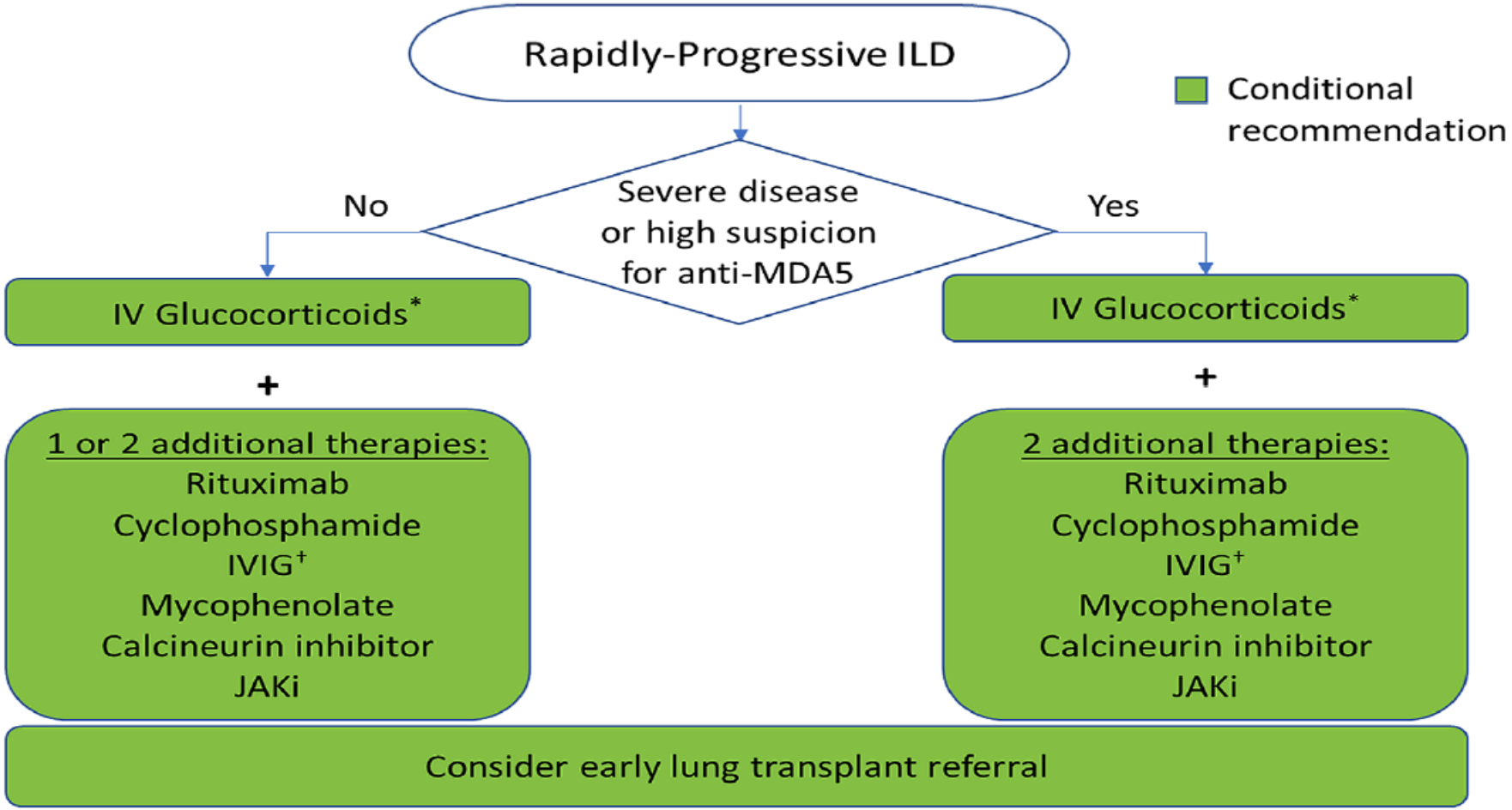
Table 2. Risk of Death or Lung Transplantation after Satisfying Proposed Progressive Pulmonary Fibrosis Criteria in U.S. Test and UK Validation Cohorts

PPF Criterion	U.S. Cohort (*n* = 828)			UK Cohort (*n* = 513)				Combined Cohort
	n	HR (95% CI)	*P* Value	*n*	HR (95% CI)	*P* Value	*P* Value*	HR (95% CI)
⩾10% relative FVC decline	404/828	3.11 (2.37–4.08)	<0.001	241/513	3.34 (2.35–4.73)	<0.001	0.702	3.11 (2.51–3.85)
Excluding those with concurrent ⩾10% relative FVC decline								
5–9% relative FVC decline	291/577	2.87 (2.04–4.03)	<0.001	183/366	2.36 (1.53–3.63)	<0.001	0.428	2.58 (1.98–3.35)
5–9% absolute FVC decline	146/535	2.50 (1.70–3.68)	<0.001	80/328	2.02 (1.22–3.33)	0.006	0.461	†
⩾10% absolute D_{LCO} decline	203/624	1.93 (1.41–2.65)	<0.001	43/394	0.91 (0.45–1.81)	0.779	0.057	†
⩾15% relative D_{LCO} decline	253/611	2.28 (1.65–3.13)	<0.001	116/366	2.19 (1.43–3.35)	<0.001	0.893	2.20 (1.71–2.83)
CT progression of fibrosis	135/524	1.81 (1.27–2.59)	0.001	62/324	2.43 (1.45–4.08)	0.001	0.577	1.99 (1.49–2.66)
5–9% relative FVC decline and worsening symptoms	190/574	2.68 (1.94–3.72)	<0.001	133/356	2.14 (1.41–3.27)	<0.001	0.420	2.42 (1.87–3.12)
5–9% absolute FVC decline and worsening symptoms	86/541	2.41 (1.58–3.67)	<0.001	44/323	1.89 (1.01–3.52)	0.046	0.542	†
5–9% relative FVC decline and ⩾15% relative D_{LCO} decline	129/596	2.40 (1.70–3.40)	<0.001	67/368	2.29 (1.42–3.70)	<0.001	0.725	2.29 (1.73–3.02)
⩾10% absolute D_{LCO} decline and worsening symptoms	126/648	1.85 (1.32–2.59)	<0.001	29/396	0.87 (0.37–2.00)	0.736	0.094	†
CT progression of fibrosis and worsening symptoms	93/525	2.26 (1.56–3.28)	<0.001	51/324	2.62 (1.54–4.48)	<0.001	0.961	2.32 (1.72–3.14)
CT progression of fibrosis and 5–9% relative FVC decline	50/493	1.63 (0.99–2.70)	0.055	25/302	1.33 (0.62–2.85)	0.467	0.402	†
CT progression of fibrosis and 5–9% absolute FVC decline	27/487	1.93 (1.01–3.71)	0.047	10/293	1.30 (0.38–4.39)	0.675	0.439	†
CT progression of fibrosis and ⩾10% absolute D_{LCO} decline	35/486	2.13 (1.23–3.67)	0.007	9/288	1.00 (0.23–4.29)	0.988	0.324	†

Am J Respir Crit Care Med. 2023 Jan 1;207(1)

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) Guideline for the Treatment of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Diseases



Arthritis Rheumatol. 2024 Aug;76(8)

Recent guideline update 3

INJE UNIVERSITY
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Contents lists available at ScienceDirect

Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv

Guideline

Japanese guidelines for the treatment of idiopathic pulmonary fibrosis 2023:Revised edition☆

Chronic stage

Drug therapy
- Corticosteroid monotherapy (CQ1)
- Corticosteroid + Immunosuppressant agents combination therapy (CQ2)
- Inhaled N-acetylcysteine (NAC) monotherapy (CQ3)
- Pirfenidone monotherapy (CQ4)
- Nintedanib monotherapy (CQ5)
- Pirfenidone + Inhaled NAC combination therapy (CQ6)
- Pirfenidone + Nintedanib combination therapy (CQ7)

Non-drug therapy
- Oxygen therapy (CQ8-1, CQ8-2) For resting hypoxemia
- Pulmonary rehabilitation (CQ9)

Acute exacerbation
- Corticosteroid therapy (including pulse therapy) (CQ10)
- Immunosuppressant agents (CQ11)
- Neutrophil elastase inhibitor (CQ12)
- PMX-DHP therapy (CQ13)
- Recombinant thrombomodulin (CQ14)
- Newly administer antifibrotic drugs (CQ15)
- Non-invasive ventilation therapy (HFNC, NPPV) (CQ16)

Complicated lung cancer
- Surgical treatment (CQ17)
- Prophylactic administrations for acute postoperative exacerbation (CQ18)
- Cytotoxic anticancer drugs (CQ19)
- Molecular targeted therapeutic drugs (CQ20-1, CQ20-2) Bevacizumab
- Immune checkpoint inhibitors (CQ21)

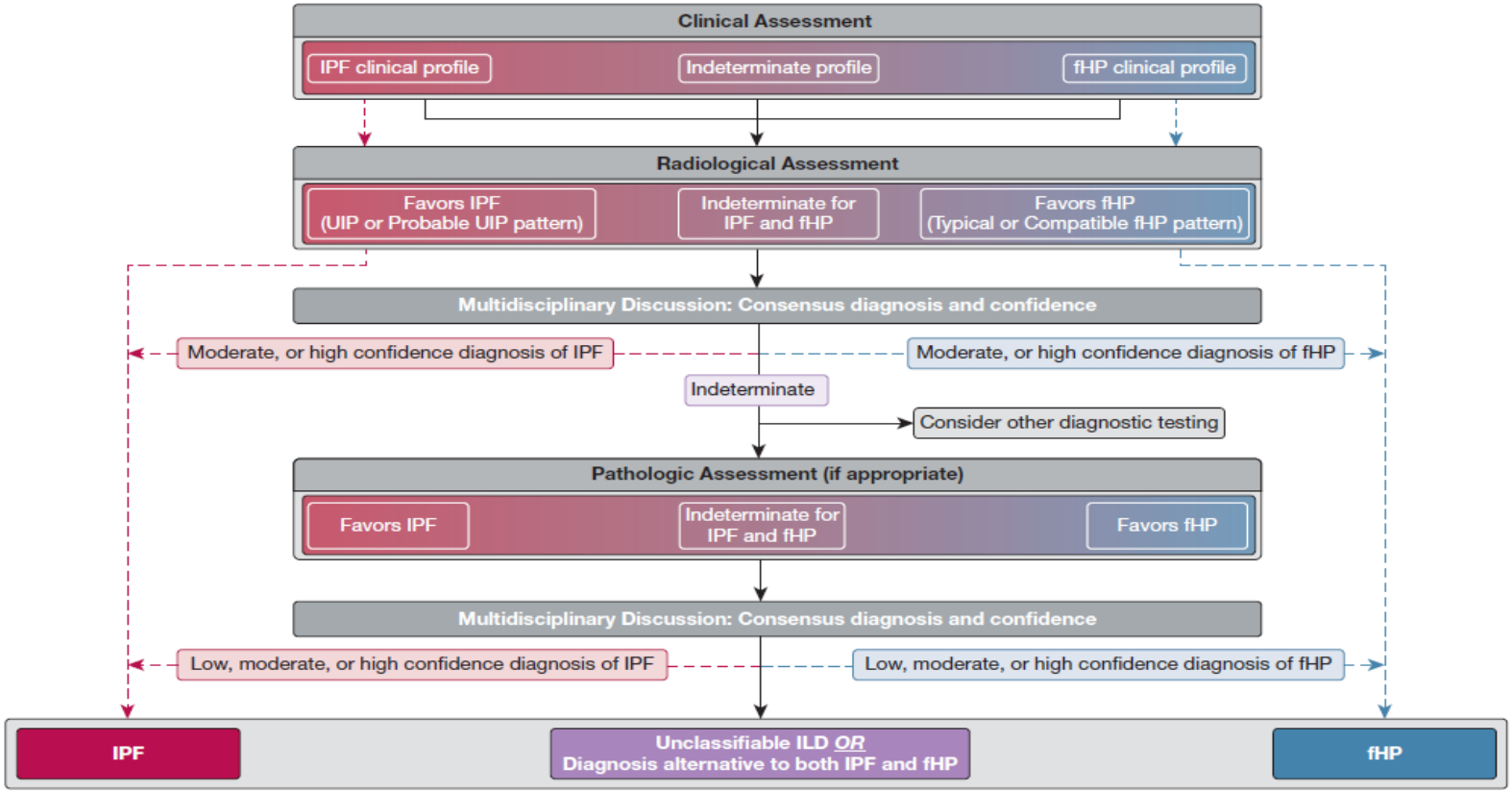
Pulmonary hypertension
- Pulmonary vasodilators (CQ22)

Advanced stage
- Opioid administration (for symptom relief) (CQ23)
- Lung transplantation (CQ24)

Respir Investig. 2024 May;62(3)

CHEST

Integration and Application of Clinical Practice Guidelines for the Diagnosis of Idiopathic Pulmonary Fibrosis and Fibrotic Hypersensitivity Pneumonitis

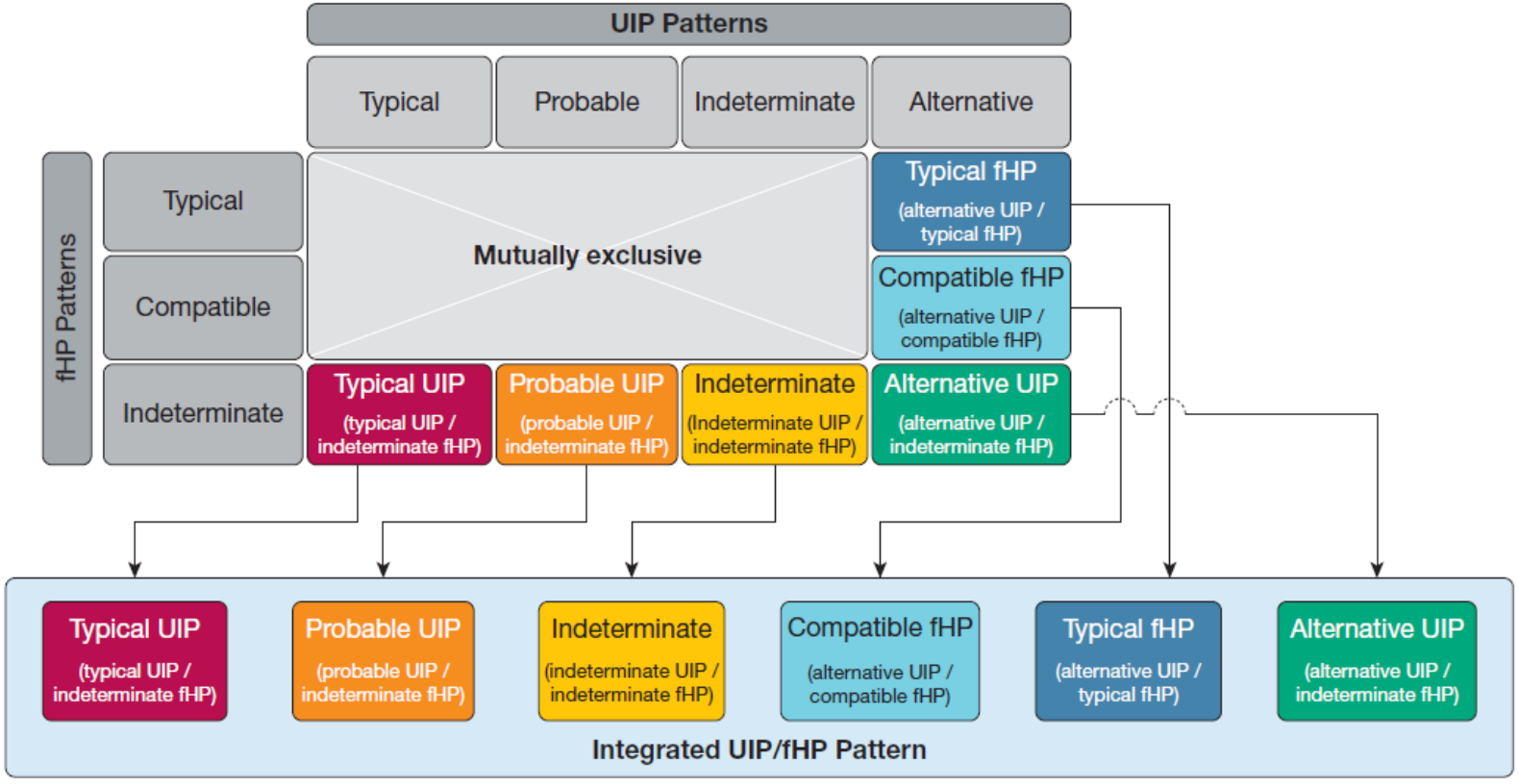


Chest. 2022 Sep;162(3)

[Diffuse Lung Disease Original Research]

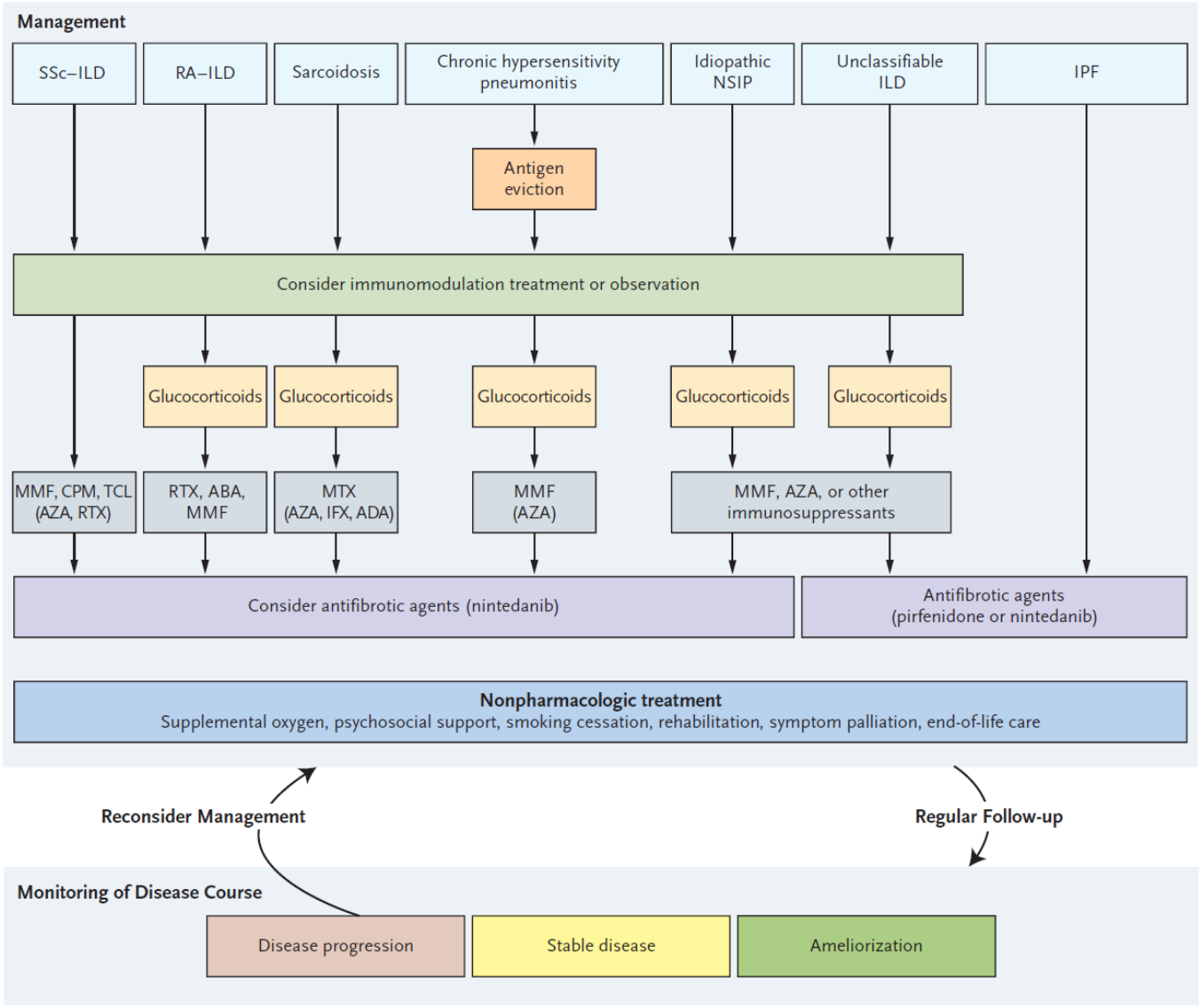
CHEST

Integration and Application of Radiologic Patterns From Clinical Practice Guidelines on Idiopathic Pulmonary Fibrosis and Fibrotic Hypersensitivity Pneumonitis



Chest. 2023 Dec;164(6)

Treatments?



N Engl J Med 2020;383

Generic war in 2025 for Nintedanib

품목	제약사	효능 효과	심의 결과
오페브연질캡슐 100,150밀리그램	한국베링거인겔하임㈜	1. 특발성 폐섬유증 2. 전신경화증 연관 간질성 폐질환 3. 진행성 폐섬유증	급여의 적정성이 있음 대상 1. 전신경화증 연관 간질성폐질환 2. 진행성 폐섬유증

Major Global Clinical Trials for IPF

Target	Drug	Sponsor	n	Phase	ID
rhPTX-2	Zinpentraxin Alfa (PRM-151, WA42294)	Hoffmann-La Roche	700, 658	III	NCT04594707, NCT04552899
CTGF	Pamrevlumab (FG-3019、FGCL-3019-091, 095)	FibroGen	340	III	NCT03955146, NCT04419558
Agonist of DP1, EP2 and IP receptors	**Inhaled Treprostinil**	United Therapeutics	792, 396	III	NCT 04905693, NCT04708782
PDE4 Inhibitor	**Nerandomilast (BI 1015550)**	Boehringer Ingelheim	147	III	NCT04419506
Tyrosine kinase inhibitor	TAS-115	Taiho	50	III	JapicCTI-183898
LPA1 Antagonist	BMS-986278	Bristol-Myers Squibb	360	III	NCT04308681
HSP47 siRNA	ND-L02-s0201	Nitto Denko Corporation	120	II	NCT03538301
FXIIa mAb	Garadacimab (CSL312)	CSL Behring	80	II	NCT05130970
AT2 agonist	C21	Vicore Pharma AB	60	II	NCT04533022
Lysophosphatidic acid receptor 1 antagonist,	HZN-825	Horizon Therapeutics, Ireland DAC	360	II	NCT05032066
Dual-selective inhibitor of αvβ6 and αvβ1 integrins	PLN-74809	Pliant Therapeutics,Inc.	112	II	NCT04396756
Hedgehog signaling pathway inhibitor	Taladegib (ENV-IPF-101)	Endeavor Biomedicines,Inc.	60	II	NCT04968574
Inhibitor of JAK1, JAK2 and JAK3	Jaktinib Dihydrochloride Monohydrate (ZGJAK005)	Suzhou Zelgen Biopharmaceuticals Co.,Ltd	90	II	NCT04312594
Dual NADPH oxidase NOX1/NOX4 inhibitor	GKT137831,	University of Alabama at Birmingham	60	II	NCT03865927
Galectin-3 inhibitor	GB0139	Galecto Biotech AB	426	II	NCT03832946
TGFα, β inhibitors	HEC585	Sunshine Lake Pharma Co., Ltd.	270	II	NCT05060822

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

Table 2. Summary of Primary and Secondary End Points.*

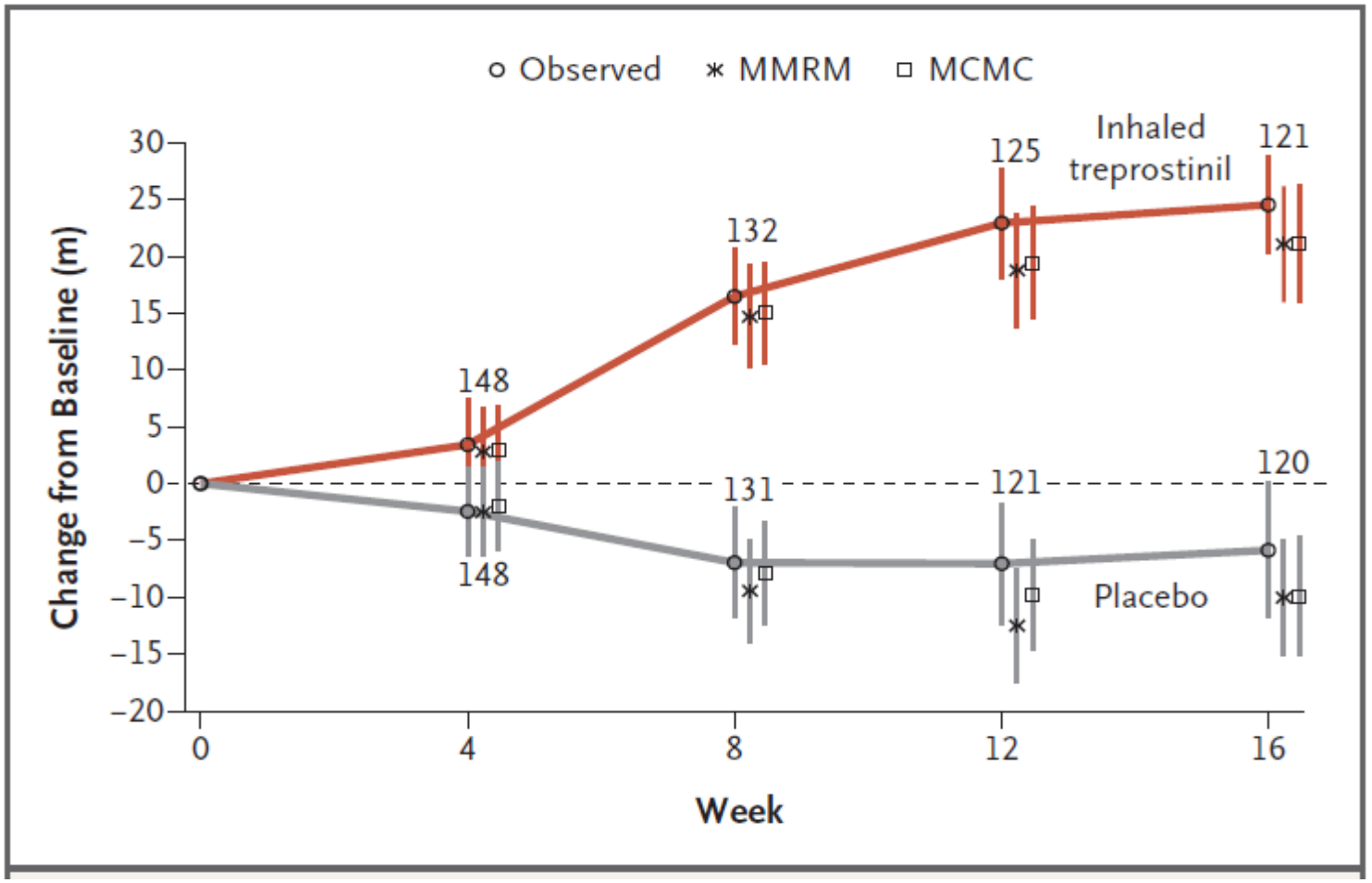
End Point	Inhaled Treprostinil (N=163)	Placebo (N=163)	Treatment Effect (95% CI)	P Value
Primary end point				
Change in peak 6-minute walk distance from baseline to wk 16 — m†	21.08±5.12	−10.04±5.12	31.12±7.25 (16.85 to 45.39)‡	<0.001
Secondary end points§				
Change in plasma concentration of NT-proBNP from baseline to wk 16¶				
Mean (±SD) change — pg/ml	−396.35±1904.90	1453.95±7296.20		
Median — pg/ml	−22.65	20.65		
Range — pg/ml	−11,433.0 to 5373.1	−5483.3 to 87,148.3		
Ratio to baseline	0.85±0.06	1.46±0.11	0.58±0.06 (0.47 to 0.72)‖	<0.001
Occurrence of clinical worsening — no. (%)			0.61 (0.4 to 0.92)**	0.04
Any event	37 (22.7)	54 (33.1)		
Hospitalization for cardiopulmonary indication	18 (11.0)	24 (14.7)		
Decrease in 6-minute walk distance of >15% from baseline	13 (8.0)	26 (16.0)		
Death from any cause	4 (2.5)	4 (2.5)		
Lung transplantation	2 (1.2)	0		
Least-squares mean change in peak 6-minute walk distance from baseline to wk 12 — m†	18.77±4.99	−12.52±5.01	31.29±7.07 (17.37 to 45.21)‡	<0.001
Least-squares mean change in trough 6-minute walk distance from baseline to wk 15 — m	9.3±5.5	−12.7±5.5	21.99±7.7 (6.85 to 37.14)‡	0.005††

N Engl J Med. 2021 Jan 28;384(4)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

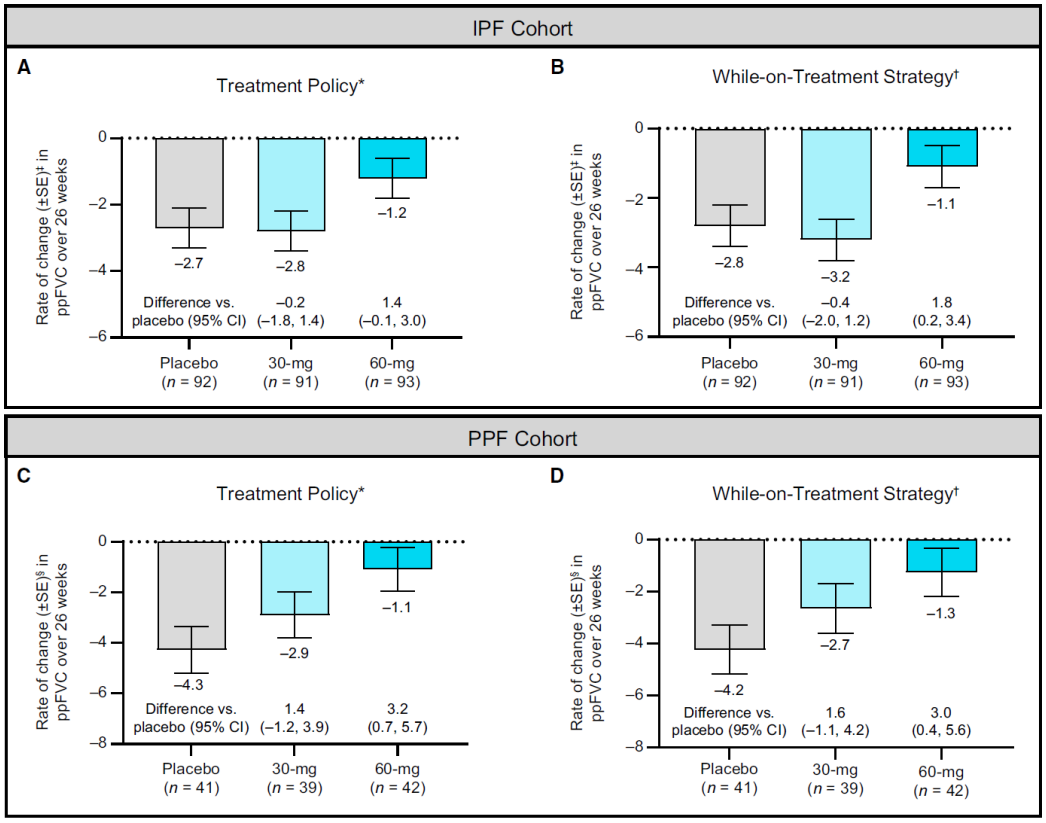


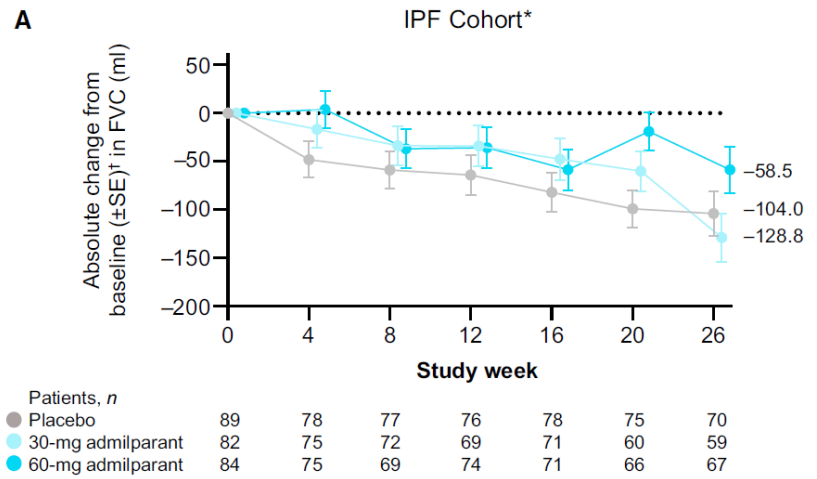
N Engl J Med. 2021 Jan 28;384(4)

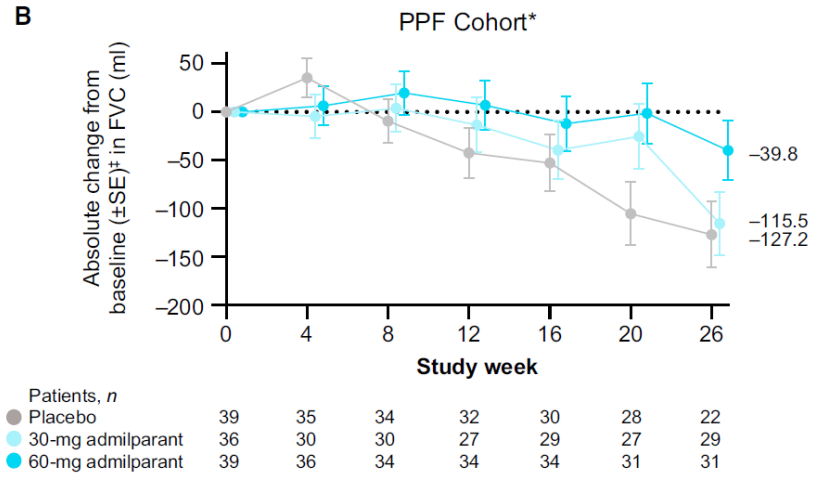
ORIGINAL ARTICLE

Efficacy and Safety of Admilparant, an LPA_1 Antagonist, in Pulmonary Fibrosis

A Phase 2 Randomized Clinical Trial





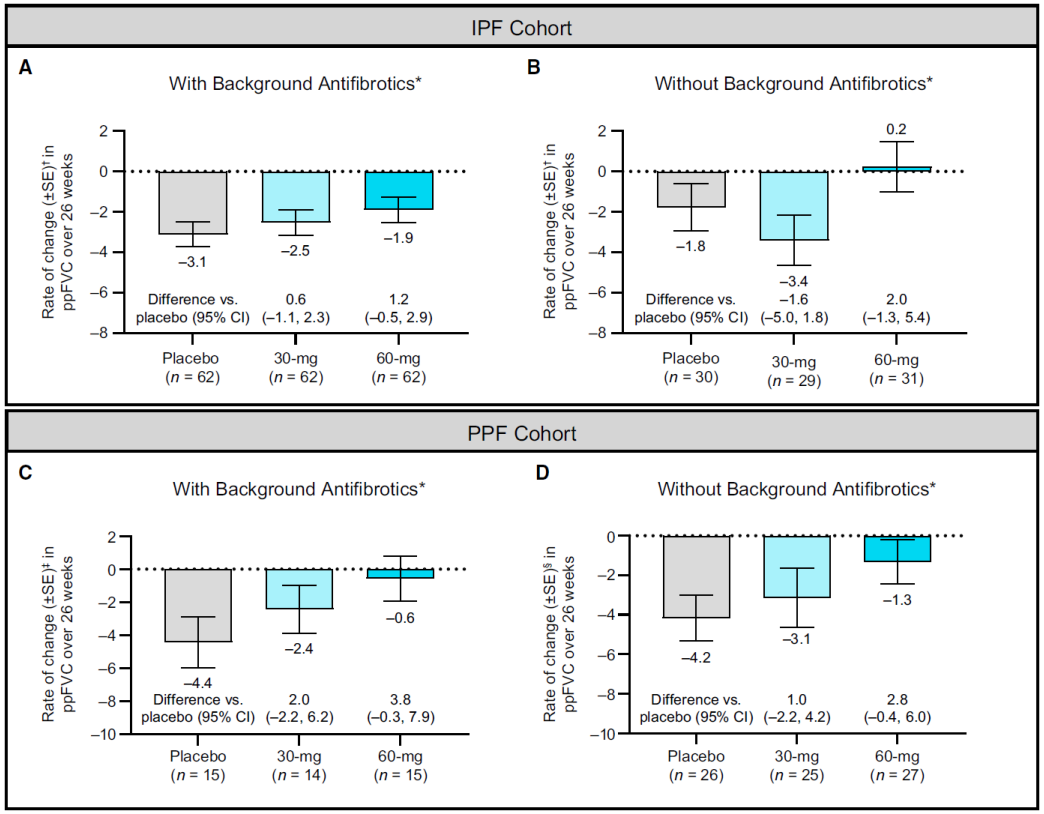


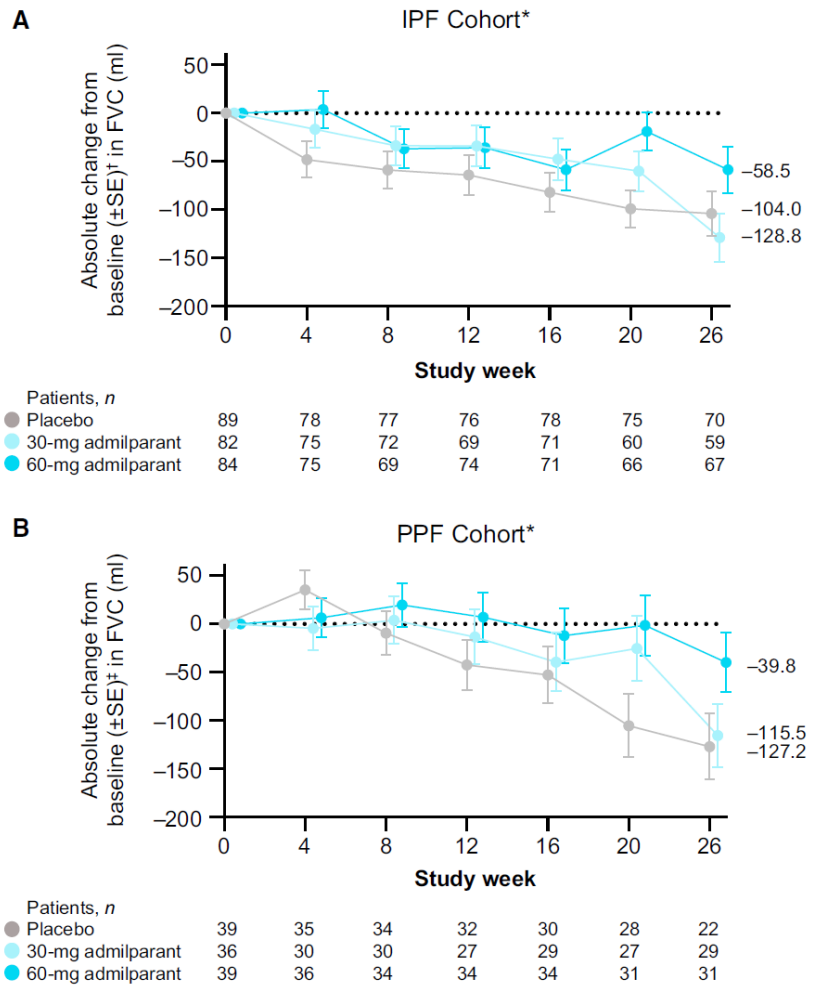
Am J Respir Crit Care Med. 2025 Feb;211(2)

ORIGINAL ARTICLE

Efficacy and Safety of Admilparant, an LPA_1 Antagonist, in Pulmonary Fibrosis

A Phase 2 Randomized Clinical Trial



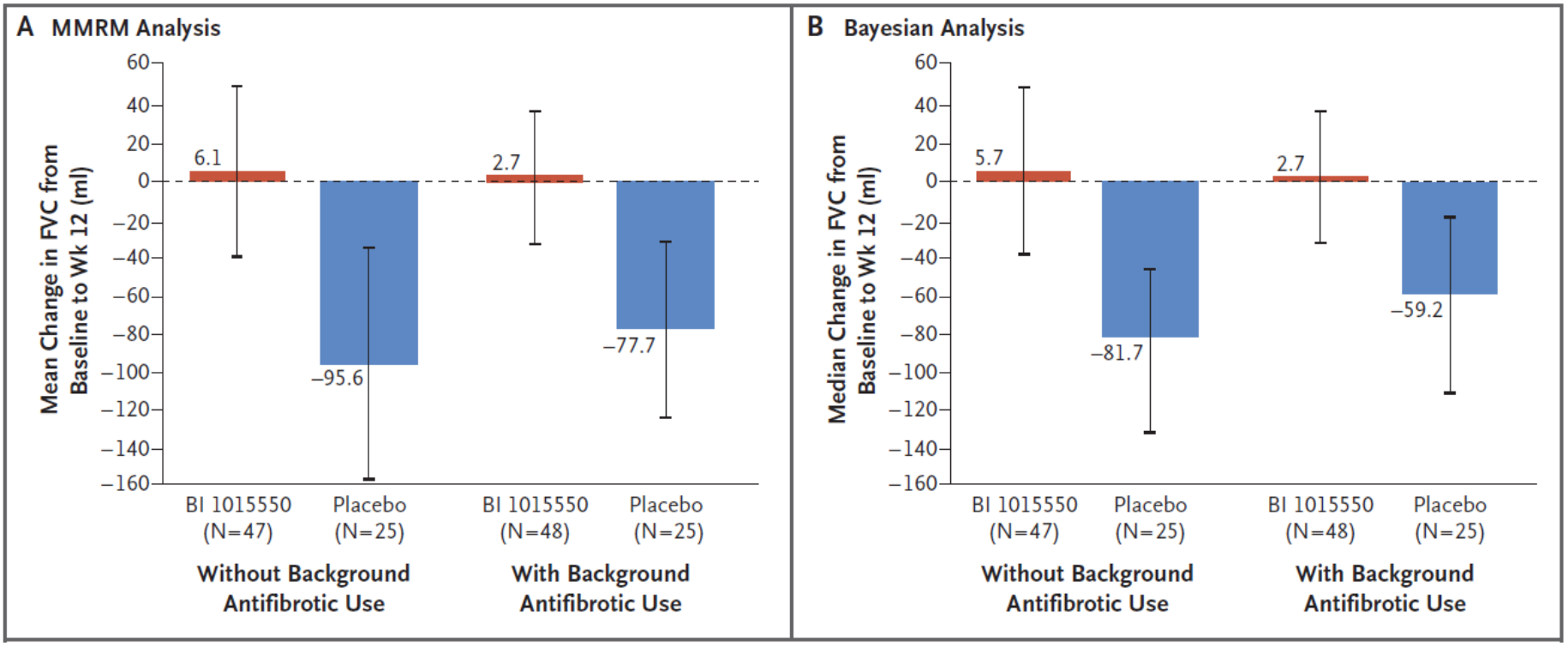


Am J Respir Crit Care Med. 2025 Feb;211(2)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of a Preferential Phosphodiesterase 4B Inhibitor for Idiopathic Pulmonary Fibrosis



N Engl J Med. 2022 Jun 9;386(23)

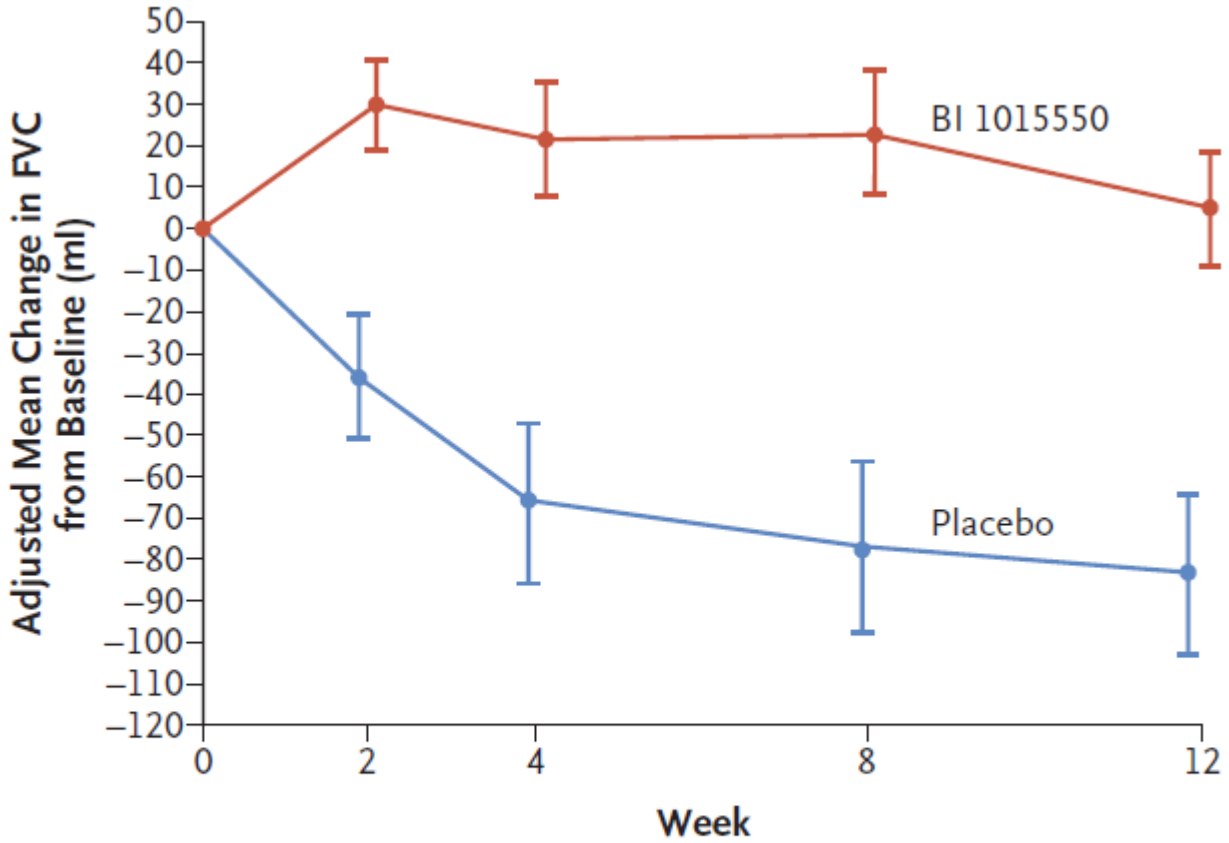
The NEW ENGLAND JOURNAL of MEDICINE

Trial of a
Inhibitor

A MMRM A

Mean Change in FVC from Baseline to Wk 12 (ml)

60
40
20
0
−20
−40
−60
−80
−100
−120
−140
−160



9.2

Placebo
(N=25)

round
: Use

N Engl J Med. 2022 Jun 9;386(23)

EUROPEAN RESPIRATORY JOURNAL
PERSPECTIVE
Y.H. KHOR ET AL.

Treatable traits: a comprehensive precision medicine approach in interstitial lung disease

Yet H. Khor[1,2,3,4], Vincent Cottin[5,6], Anne E. Holland[1,3,7,8], Yoshikazu Inoue[9], Vanessa M. McDonald[10,11,12], Justin Oldham[13,14], Elisabetta A. Renzoni[15,16], Anne Marie Russell[17,18,19], Mary E. Strek[20] and Christopher J. Ryerson[21,22]

To be considered a trait, a feature must meet three core attributes
1) Clinically important
2) Recognizable and measurable using identification markers (e.g. biomarkers, genetic tests, questionnaires, or phenotypic characteristics);
3) Treatable.

TABLE 1 Proposed candidate treatable traits in interstitial lung disease (ILD)

	Identification markers (recognisable and/or measurable features for a trait)	Proven or suspected associated health outcomes#			Treatment options (proven or potential treatments for a trait)	Major research priorities
		Symptoms and HRQoL	Disease progression	Prognosis		
Aetiological treatable traits						
Lung pathogenesis						
Immune dysregulation and inflammation	HRCT chest Histopathological features and cellularity of bronchoalveolar lavage	X		X	Immunosuppressive medications	Develop and validate therapeutic biomarkers of immune dysregulation and inflammation for clinical use
Progressive pulmonary fibrosis	Clinical progression Lung function HRCT chest	X	X	X	Antifibrotic medications	Optimise definition for progressive pulmonary fibrosis Develop effective treatments with high patient tolerability

Eur Respir J. 2023 July ; 62(1)

EUROPEAN RESPIRATORY JOURNAL
PERSPECTIVE
Y.H. KHOR ET AL.

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1) Clinically important
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3) Treatable.

Current management approach

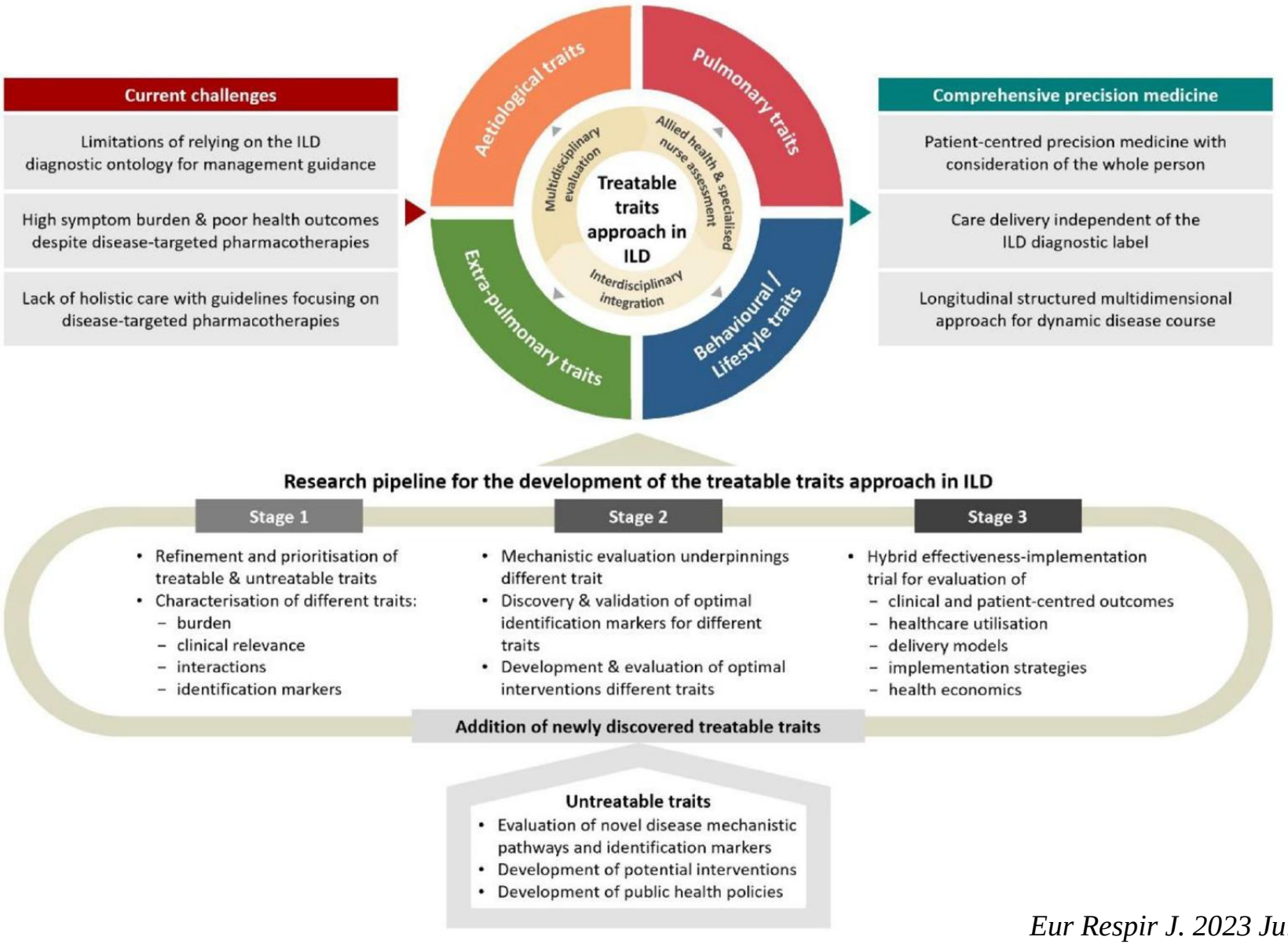
- Centred on the diagnosis of an ILD subtype with a standard approach for each subtype, with varying attention to and fragmented care beyond ILD (e.g. comorbidities)
- Management inadequately individualised to encompass different factors contributing patient outcomes

Treatable trait approach

- Coordinated evaluation of treatable traits related to aetiology, pulmonary and extra-pulmonary manifestations, and behavioural/lifestyle aspects present in individual patients
- Tailored management according to presence of treatable traits for each individual addressing heterogeneity

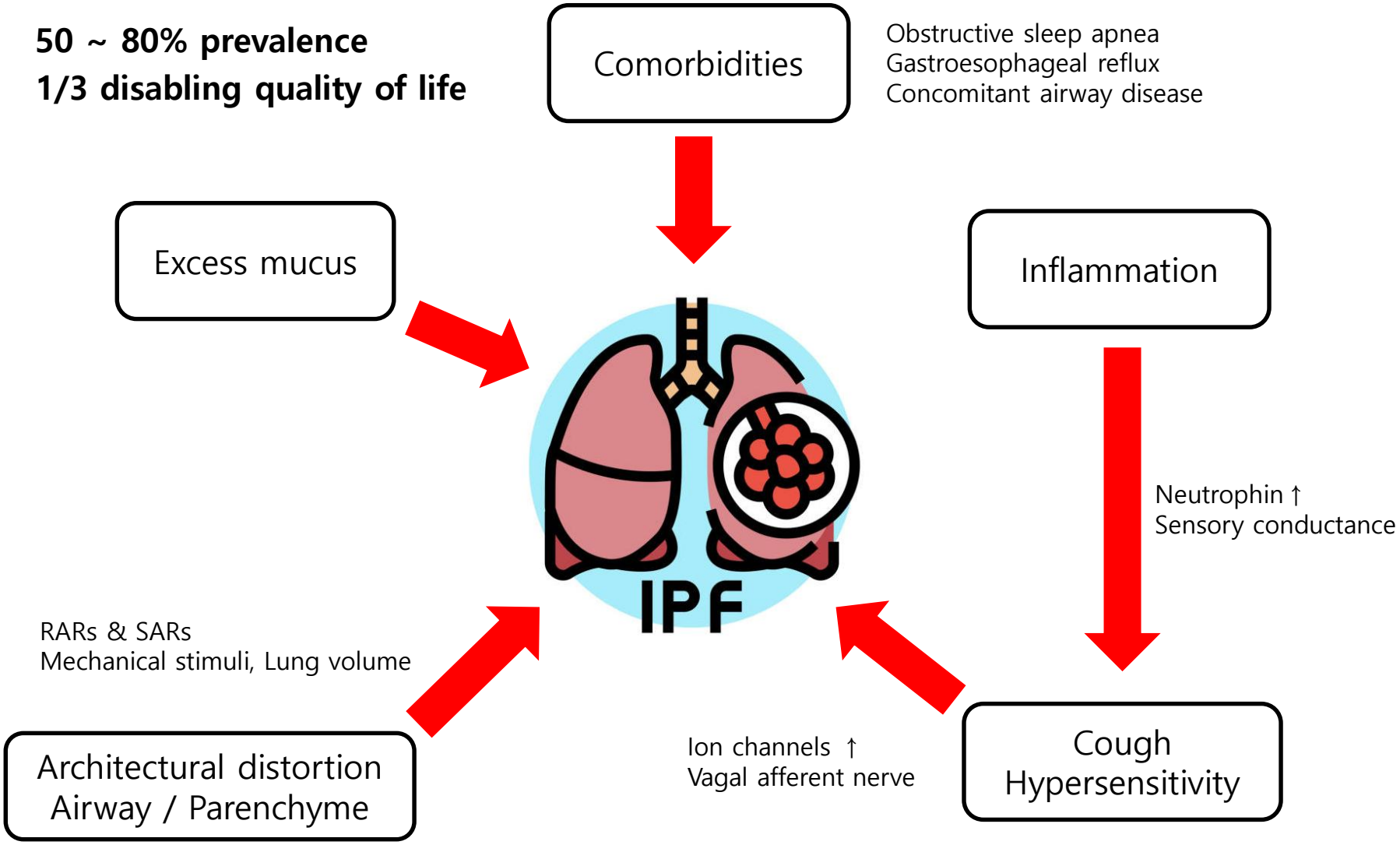
Eur Respir J. 2023 July ; 62(1)

Ongoing trend

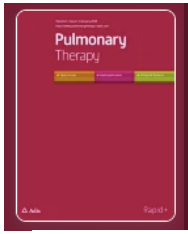


Eur Respir J. 2023 July ; 62(1)

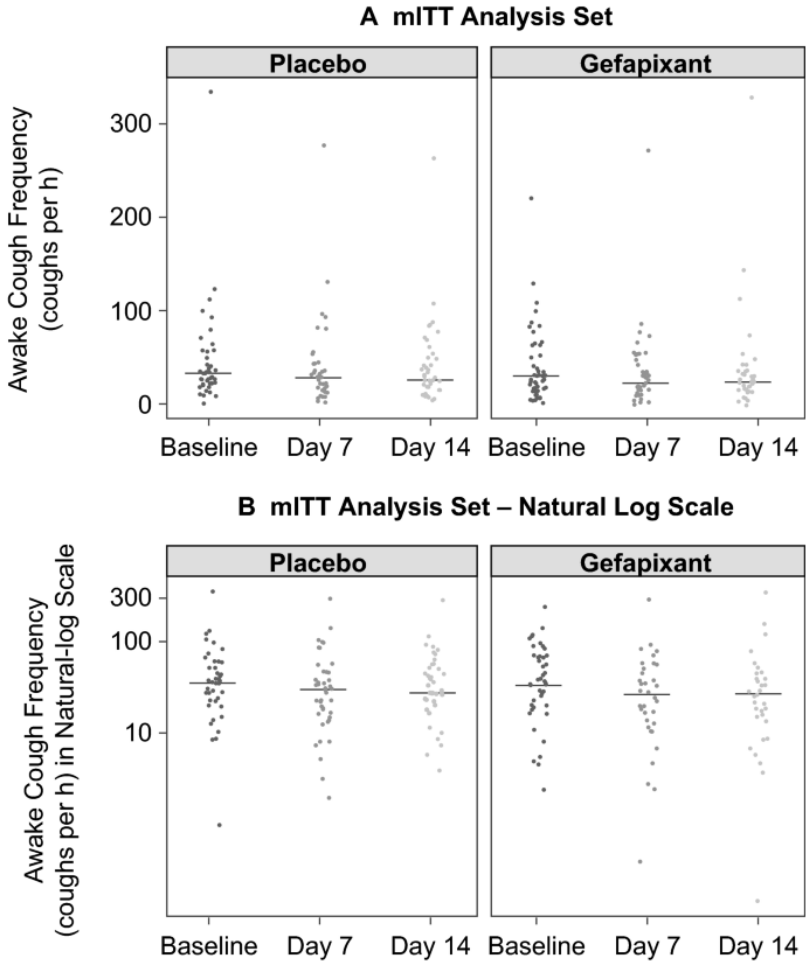
50 ~ 80% prevalence
1/3 disabling quality of life

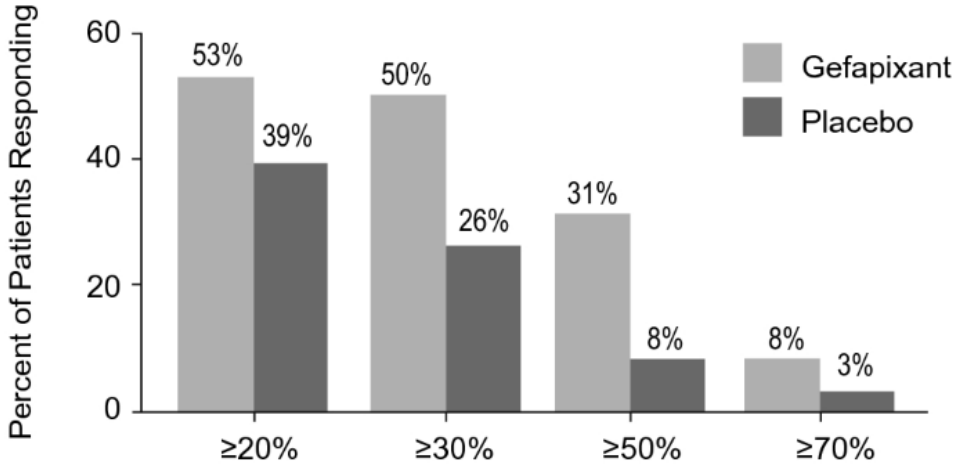


Expert Rev Respir Med. 2023 Dec;17(12)



Treatment of Persistent Cough in Subjects with Idiopathic Pulmonary Fibrosis (IPF) with Gefapixant, a P2X3 Antagonist, in a Randomized, Placebo-Controlled Clinical Trial



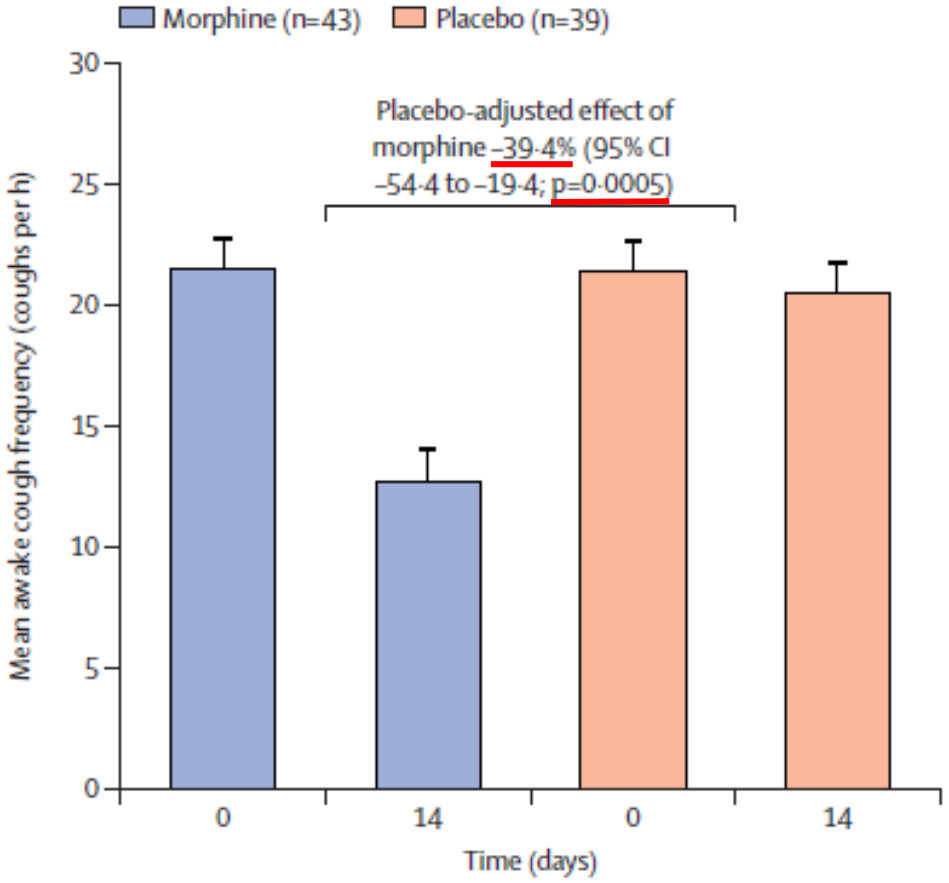


Pulm Ther. 2021 Dec;7(2)

Cough in IPF

The Lancet Respiratory Medicine
Volume 12, Issue 4, April 2024, Pages 273-280

Morphine for treatment of cough in idiopathic pulmonary fibrosis (PACIFY COUGH): a prospective, multicentre, randomised, double-blind, placebo-controlled, two-way crossover trial



Lancet Respir Med. 2024 Apr;12(4)

The Lancet Respiratory Medicine
Volume 12, Issue 4, April 2024, Pages 273-280

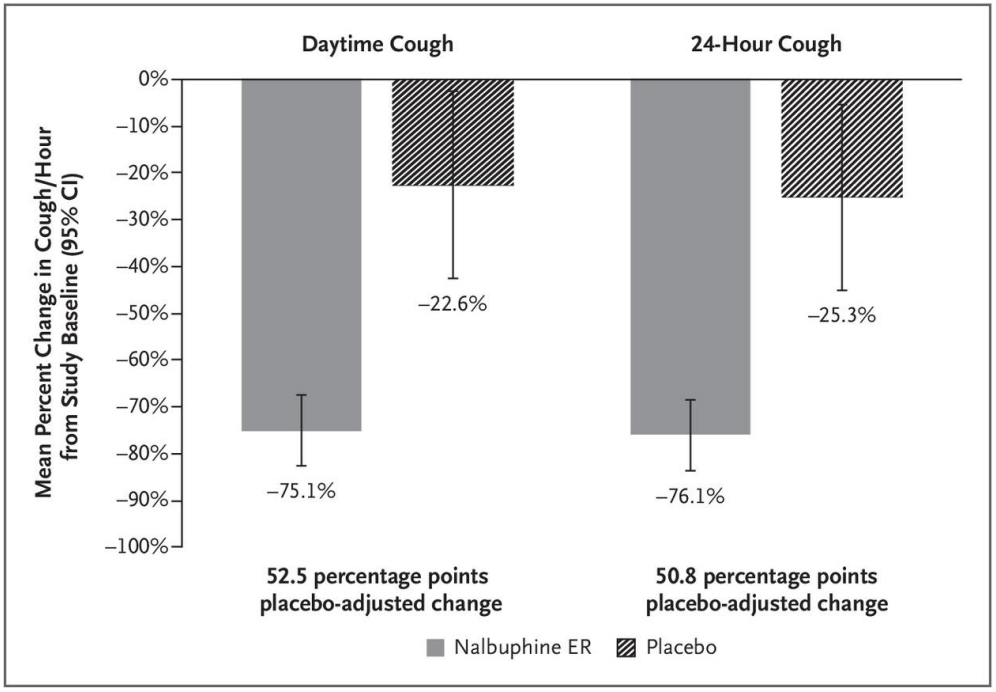
Morphine for treatment of cough in idiopathic pulmonary fibrosis (PACIFY COUGH): a prospective, multicentre, randomised, double-blind, placebo-controlled, two-way crossover trial

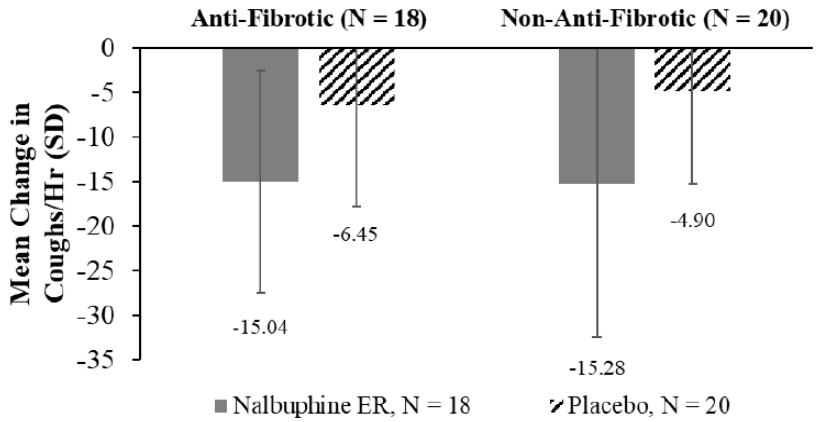
	Morphine			Placebo			Difference at 14 days	
	Baseline	Day 14	Change	Baseline	Day 14	Change	Placebo-adjusted effect of morphine (95% CI)*	p value
Awake cough frequency (coughs per h; ITT)	21·6 (1·2); n=43	12·8 (1·2); n=43	−40·8% (−54·2 to −23·6); p<0·0001	21·5 (1·2); n=39	20·6 (1·2); n=39	−4·3% (−21·8 to 17·0); p=0·66	−39·4% (−54·4 to −19·4)	0·0005
Awake cough frequency (coughs per h; per protocol)	24·2 (1·2); n=37	13·8 (1·2); n=37	−43·1% (−57·0 to −24·7); p<0·0001	23·6 (1·2); n=37	22·4 (1·2); n=37	−5·2% (−23·2 to 13·6); p =0·62	−40·3% (−55·9 to −18·9)	0·0009
Cough VAS†	61·5 (2·4); n=43	45·5 (3·7); n=43	−16·1 (−22·3 to −9·9); p<0·0001	57·7 (2·8); n=41	57·3 (2·7); n=41	−0·4 (−5·8 to 4·9); p=0·88	−14·6 (−22·8 to −6·5)	0·0004
LCQ‡	13·2 (0·5); n=43	15·0 (0·6); n=43	1·8 (0·9 to 2·8); p=0·0002	13·0 (0·5); n=41	13·6 (0·5); n=41	0·6 (−0·2 to 1·3); p=0·15	1·3 (0·4 to 2·3)	0·0047
Dyspnoea-12§	13·0 (1·2); n=43	12·9 (1·3); n=43	−0·1 (−1·9 to 1·6) p = 0·87	13·5 (1·4); n=41	14·3 (1·4); n=41	0·9 (−0·5 to 2·2); p=0·22	−1·2 (−3·1 to 0·8)	0·24
HADS anxiety¶	5·1 (0·5); n=43	5·2 (0·6); n=43	0·1 (−0·1 to 0·2); p=0·30	4·9 (0·6); n=40	5·0 (0·6); n=40	0·0 (−0·1 to 0·0); p=0·43	−0·2 (−0·9 to 0·6)	0·64
HADS depression¶	5·3 (0·6); n=43	5·3 (0·6); n=43	0·0 (0·0 to 0·0); p=0·68	5·5 (0·7); n=40	5·4 (0·7); n=40	−0·1 (−0·2 to 0·1); p=0·23	−0·2 (−1·0 to 0·6)	0·57
KBILD‖	58·2 (3·1); n=43	57·9 (3·1); n=43	−0·2 (−0·6 to 0·2); p=0·31	55·7 (3·3); n=40	55·9 (3·4); n=40	0·2 (−0·5 to 0·9); p=0·61	2·7 (−2·6 to 8·1)	0·32
L-IPF impacts**	60·9 (3·8); n=42	55·8 (3·8); n=42	−5·2 (−9·9 to −0·4); p=0·033	61·8 (4·0); n=40	60·1 (3·8); n=40	−1·7 (−5·5 to 2·1) p=0·38	−4·5 (−8·3 to −0·7)	0·019
L-IPF symptoms (total)**	40·9 (2·9); n=41	35·7 (3·1); n=41	−5·2 (−8·9 to −1·4); p=0·0078	40·9 (3·3); n=40	41·4 (3·4); n=40	0·5 (−2·5 to 3·4); p=0·75	−6·7 (−11·2 to −2·3)	0·0031
Dyspnoea domain	31·9 (3·7)	28·8 (3·6)	−3·1 (−7·9 to 1·8); p=0·22	32·1 (3·9)	31·9 (4·0)	−0·1 (−2·6 to 2·5); p=0·95	−1·5 (−6·2 to 3·2)	0·53
Cough domain	50·3 (3·7)	39·5 (3·8)	−10·8 (−16·9 to −4·8); p=0·0004)	50·1 (3·6)	49·6 (3·8)	−0·5 (−6·2 to 5·1); p=0·85	−11·9 (−18·7 to −5·1)	0·0006
Energy domain	44·2 (3·3)	44·8 (3·6)	0·6 (−4·3 to 5·6); p=0·81	44·5 (3·9)	47·9 (3·9)	3·4 (−1·3 to 8·2); p=0·16	−3·3 (−8·3 to 1·6)	0·19

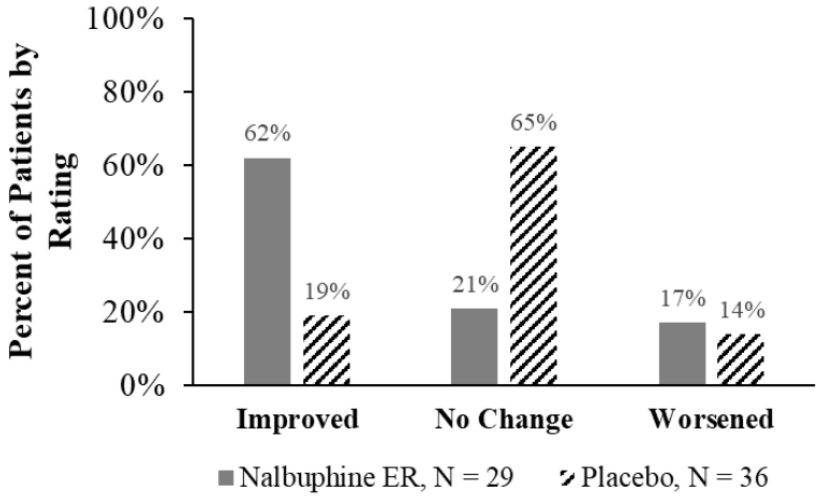
Lancet Respir Med. 2024 Apr;12(4)

NEJM Evidence

Nalbuphine Tablets for Cough in Patients with Idiopathic Pulmonary Fibrosis







NEJM Evid. 2023 Aug; 2(8)

NEJM Evidence

Nalbuphine Tablets for Cough in Patients with Idiopathic Pulmonary Fibrosis

Adverse Events	NAL ER* Twice Daily (n=38) — no. (%)	Placebo (n=40) — no. (%)	Total (n=41) — no. (%)
Patients with treatment-emergent adverse events leading to investigational product discontinuation			
Vomiting	2 (5.3)		2 (4.9)
Agitation	1 (2.6)		1 (2.4)
Anxiety	1 (2.6)		1 (2.4)
Bradycardia	1 (2.6)		1 (2.4)
Dyspnea	1 (2.6)		1 (2.4)
Headache	1 (2.6)		1 (2.4)
Insomnia	1 (2.6)		1 (2.4)
Lethargy	1 (2.6)		1 (2.4)
Mental disorder	1 (2.6)		1 (2.4)
Suicidal ideation	1 (2.6)		1 (2.4)
Vertigo	1 (2.6)		1 (2.4)
Treatment-emergent adverse events with 10% or greater frequency			
Nausea	16 (42.1)	0 (0)	16 (39.0)
Fatigue	12 (31.6)	3 (7.5)	15 (36.6)
Constipation	11 (28.9)	2 (5.0)	13 (31.7)
Dizziness	10 (26.3)	0 (0)	10 (24.4)
Somnolence	9 (23.7)	1 (2.5)	9 (22.0)
Vomiting	7 (18.4)	5 (12.5)	10 (24.4)
Dyspnea	6 (15.8)	2 (5.0)	8 (19.5)
Dry mouth	5 (13.2)	1 (2.5)	5 (12.2)
Headache	5 (13.2)	5 (12.5)	10 (24.4)
Anxiety	5 (13.2)	0 (0)	5 (12.2)
Decreased appetite	4 (10.5)	3 (7.5)	7 (17.1)
Depression	4 (10.5)	0 (0)	4 (9.8)

Total 9 discontinuation
6: on day 5
3: on day 14

51% of grade 1 or 2 AEs
→ resolved after 7 days

NEJM Evid. 2023 Aug; 2(8)

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