Update in IPF

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CLINICAL STUDY DESIGN

The Pulmonary Fibrosis Foundation Patient Registry

Rationale, Design, and Methods

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Meta-Analysis > Ann Am Thorac Soc. 2024 Mar;21(3):486-498.
doi: 10.1513/AnnalsATS.202305-402OC.

The Impact of Occupational Exposures on the Risk of Idiopathic Pulmonary Fibrosis: A Systematic Review and Meta-Analysis

Sheiphali A Gandhi [1], Bohyung Min [2], Jane C Fazio [3], Kerri A Johannson [2], Craig Steinmaus [4], Carl J Reynolds [5], Kristin J Cummings [6]

Affiliations + expand

PMID: 38096107 PMCID: PMC10913770 (available on 2025-03-01)
DOI: 10.1513/AnnalsATS.202305-402OC

- through July 2023
- Five exposure categories were analyzed:

  VGDF : vapors, gas, dust, fumes
- The pooled OR was increased for
  - VGDF : 1.8 PAF of 21% population attributable fraction (PAF)
  - metal dust : 1.6 and 7%
  - wood dust: 1.6 and 3%
  - agricultural dust: 1.8 and 14%
  - silica dust: 1.8 and 4% for.
- **Conclusions:**

Our findings indicate that 21% of IPF cases (or approximately one in five) could be prevented by removal of occupational exposure

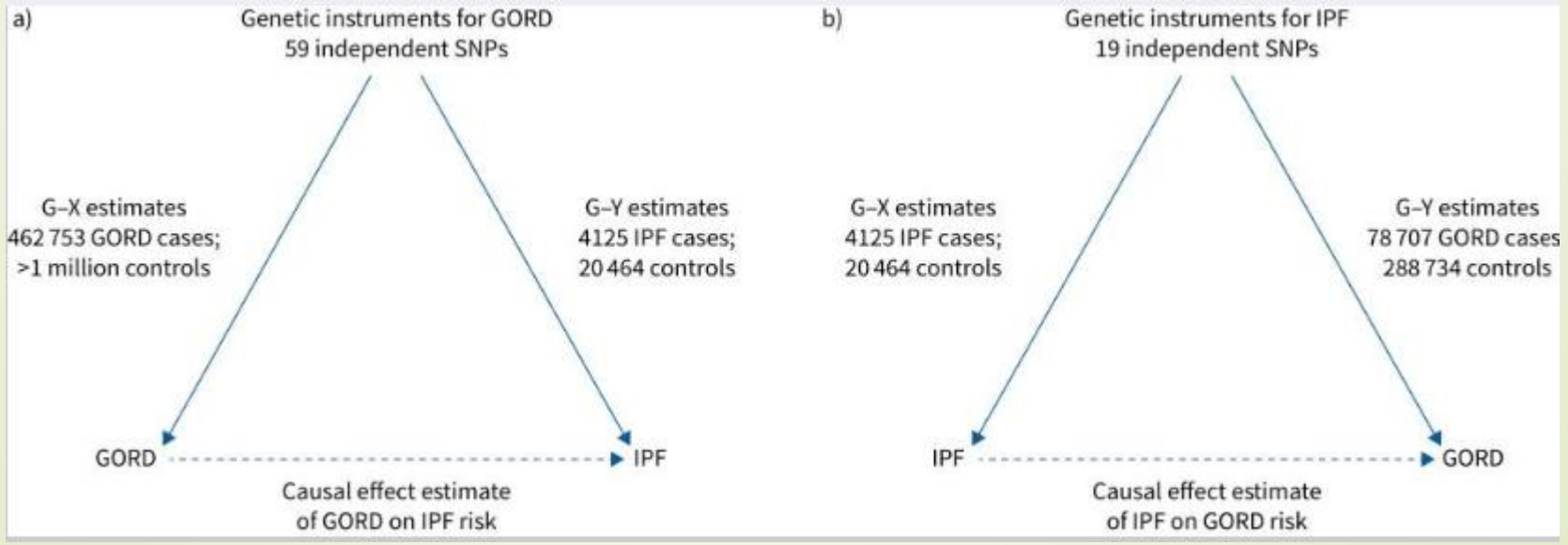
› Gut. 2022 Jun;71(6):1053-1061. doi: 10.1136/gutjnl-2020-323906. Epub 2021 Jun 29.

Multitrait genetic association analysis identifies 50 new risk loci for gastro-oesophageal reflux, seven new loci for Barrett's oesophagus and provides insights into clinical heterogeneity in reflux diagnosis

Meta-Analysis › Eur Respir J. 2023 May 25;61(5):2201585. doi: 10.1183/13993003.01585-2022. Print 2023 May.

The causal relationship between gastro-oesophageal reflux disease and idiopathic pulmonary fibrosis: a bidirectional two-sample Mendelian randomisation study

Carl J Reynolds [1], Fabiola Del Greco M [2], Richard J Allen [3 4], Carlos Flores [5 6 7 8], R Gisli Jenkins [9], Toby M Maher [9 10], Philip L Molyneaux [9], Imre Noth [11], Justin M Oldham [12], Louise V Wain [3 4], Jiyuan An [13], Jue-Sheng Ong [14], Stuart MacGregor [14], Tom A Yates [15], Paul Cullinan [9], Cosetta Minelli [9]



Methods:

Estimate the causal effect of GERD on IPF risk and of IPF on GERD risk, using genetic data from the largest GERD (78 707 cases and 288 734 controls) and IPF (4125 cases and 20 464 controls) genome-wide association meta-analyses currently available.

Results:

GERD increased the risk of IPF, with an OR of 1.6 (95% CI 1.04-2.49; p=0.032).

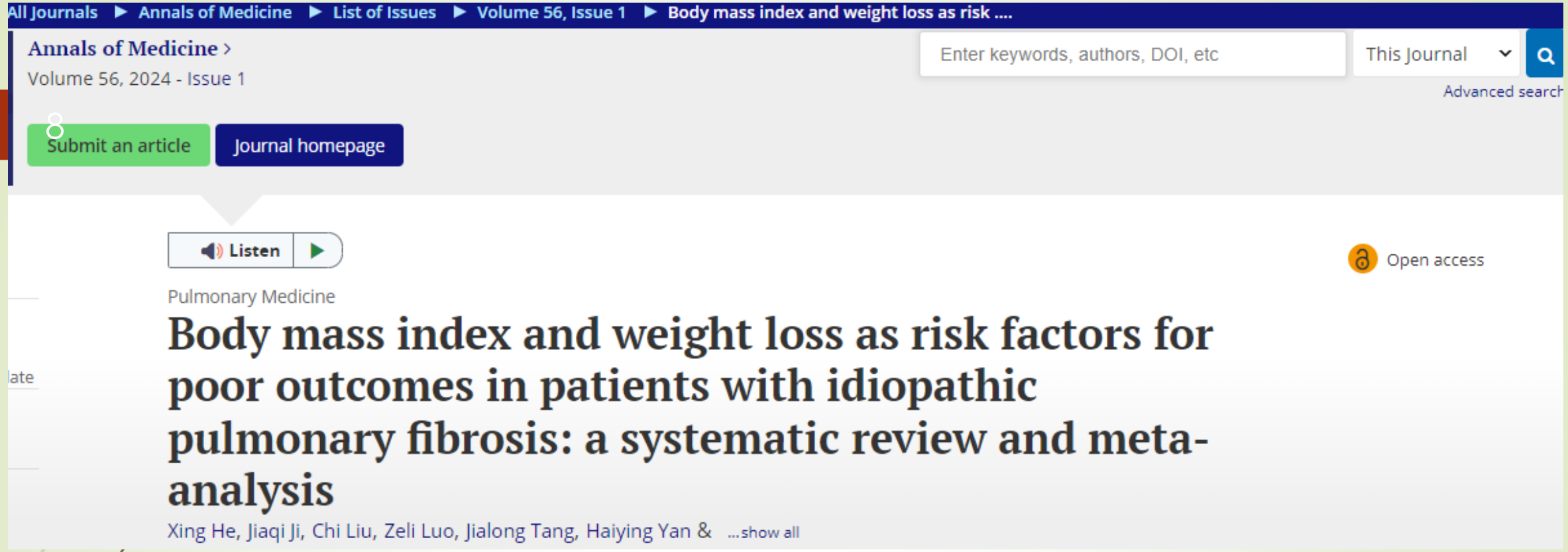
Conclusions:

GERD increases the risk of IPF, but found no evidence that IPF increases the risk of GERD

GERD should be considered in future studies of IPF

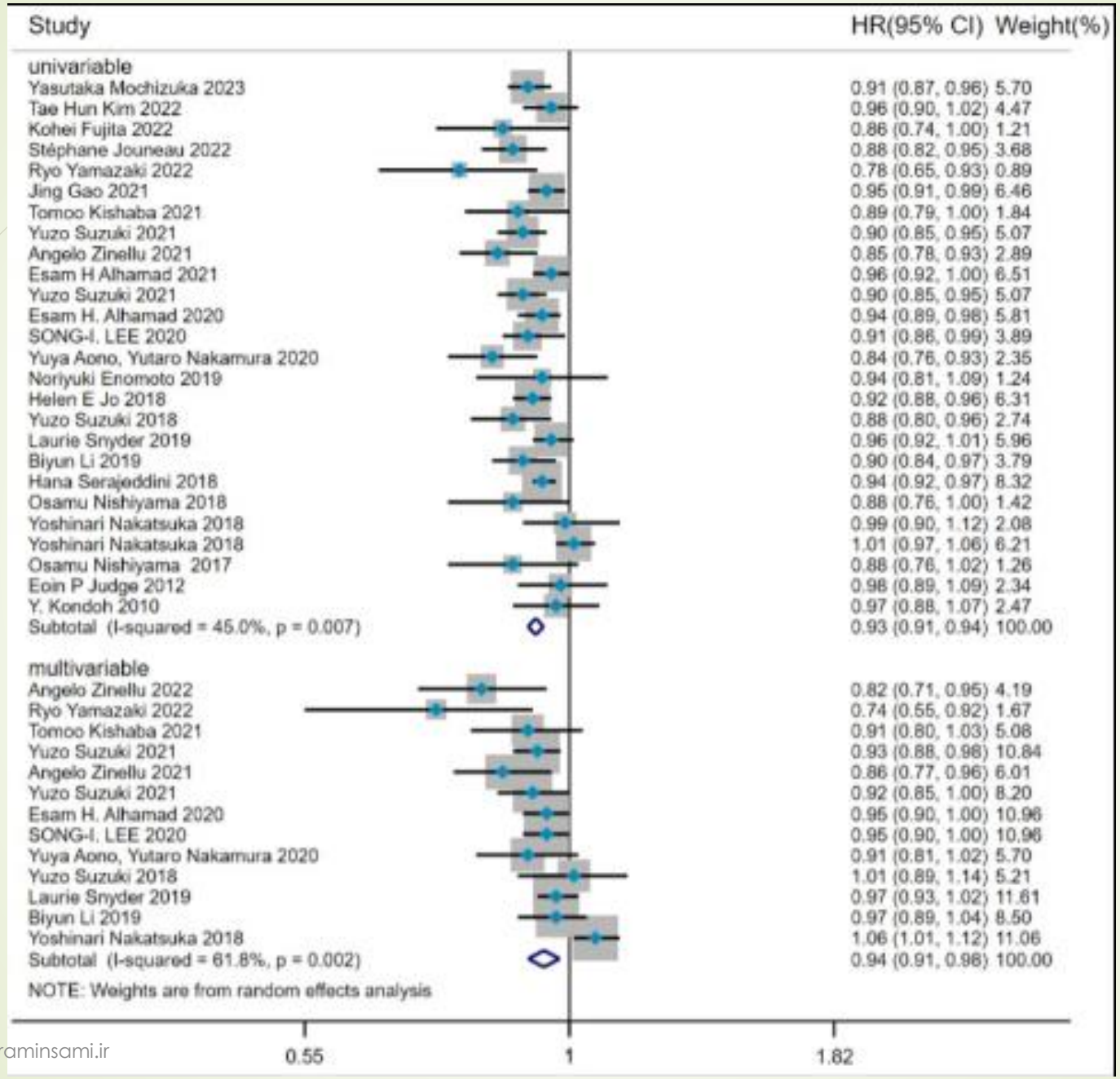
Interest in it as a potential therapeutic target should be renewed

The mechanisms underlying the effect of GERD on IPF should also be investigated.



Age
FVC
DLCO
TLC
oxygen partial pressure
alveolar-arterial oxygen gradient
6MWD
CRP

- ✓ up August 2023.
- ✓ 18,343 IPF patients
- ✓ baseline BMI was a predictive factor for IPF mortality (HR = 0.93, 95%CI = [0.91, 0.94]).
- ✓ BMI no predictive value for acute exacerbation or hospitalization
- ✓ Weight loss was identified as a risk factor for IPF mortality (HR = 2.74, 95% CI = [2.12, 3.54]



The forest plot pooled the hazard ratio of BMI predicting mortality in IPF.

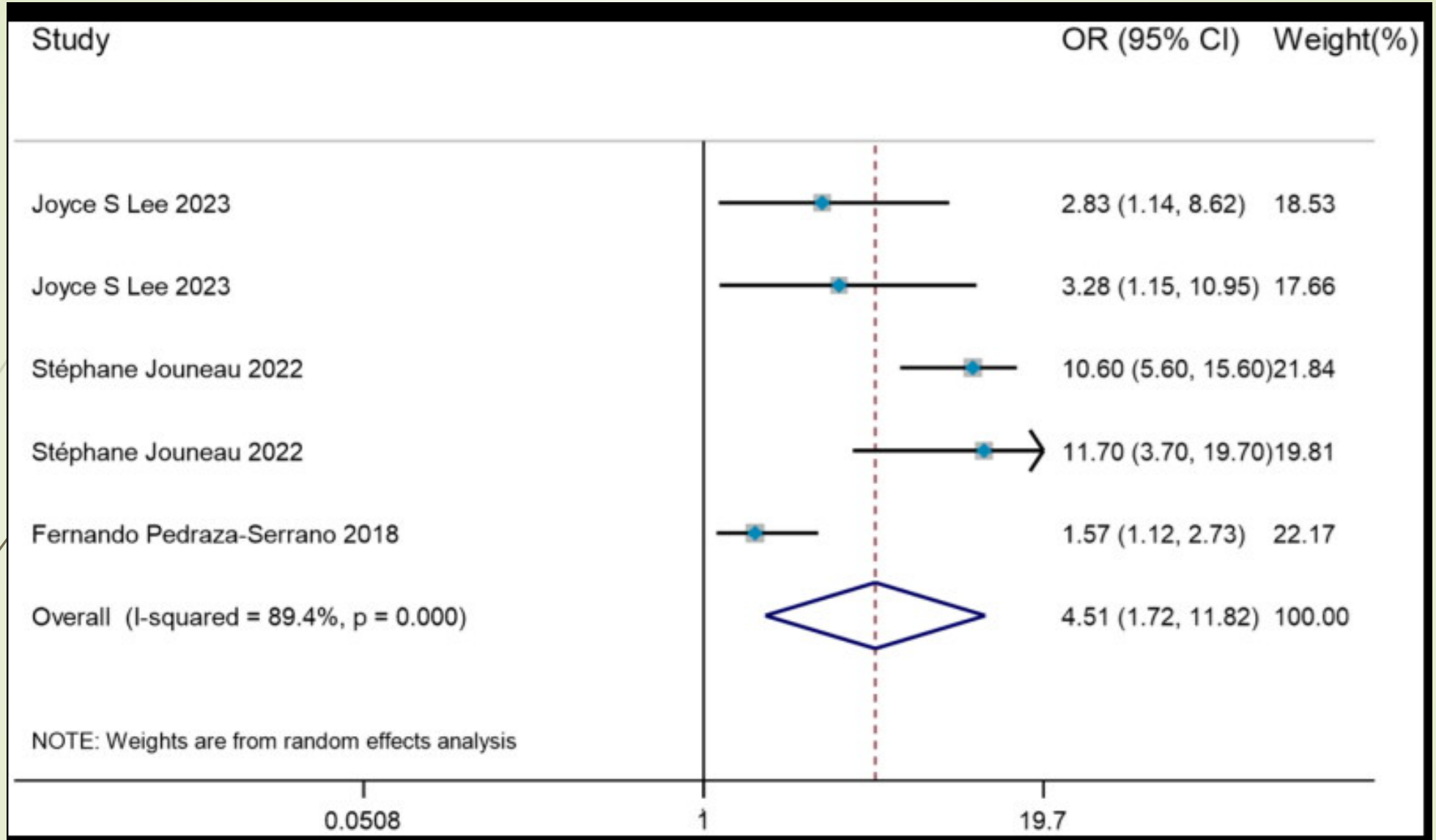


Figure 5. The forest plot pooled the odds ratio of weight loss predicting mortality in IPF.

Conclusion:

Low baseline BMI and weight loss in the course of IPF may indicate a high risk of mortality in patients with IPF

So it is meaningful to monitor and manage the nutritional status of IPF patients, and early intervention should be conducted for low BMI and weight loss.

Meta-Analysis > BMC Pulm Med. 2024 Jan 27;24(1):58. doi: 10.1186/s12890-024-02861-w.

A comprehensive comparison of the safety and efficacy of drugs in the treatment of idiopathic pulmonary fibrosis: a network meta-analysis based on randomized controlled trials

Xiaozheng Wu [1], Wen Li [1], Zhenliang Luo [1], Yunzhi Chen [2]

24 studies
6208 patient
13 drugs.

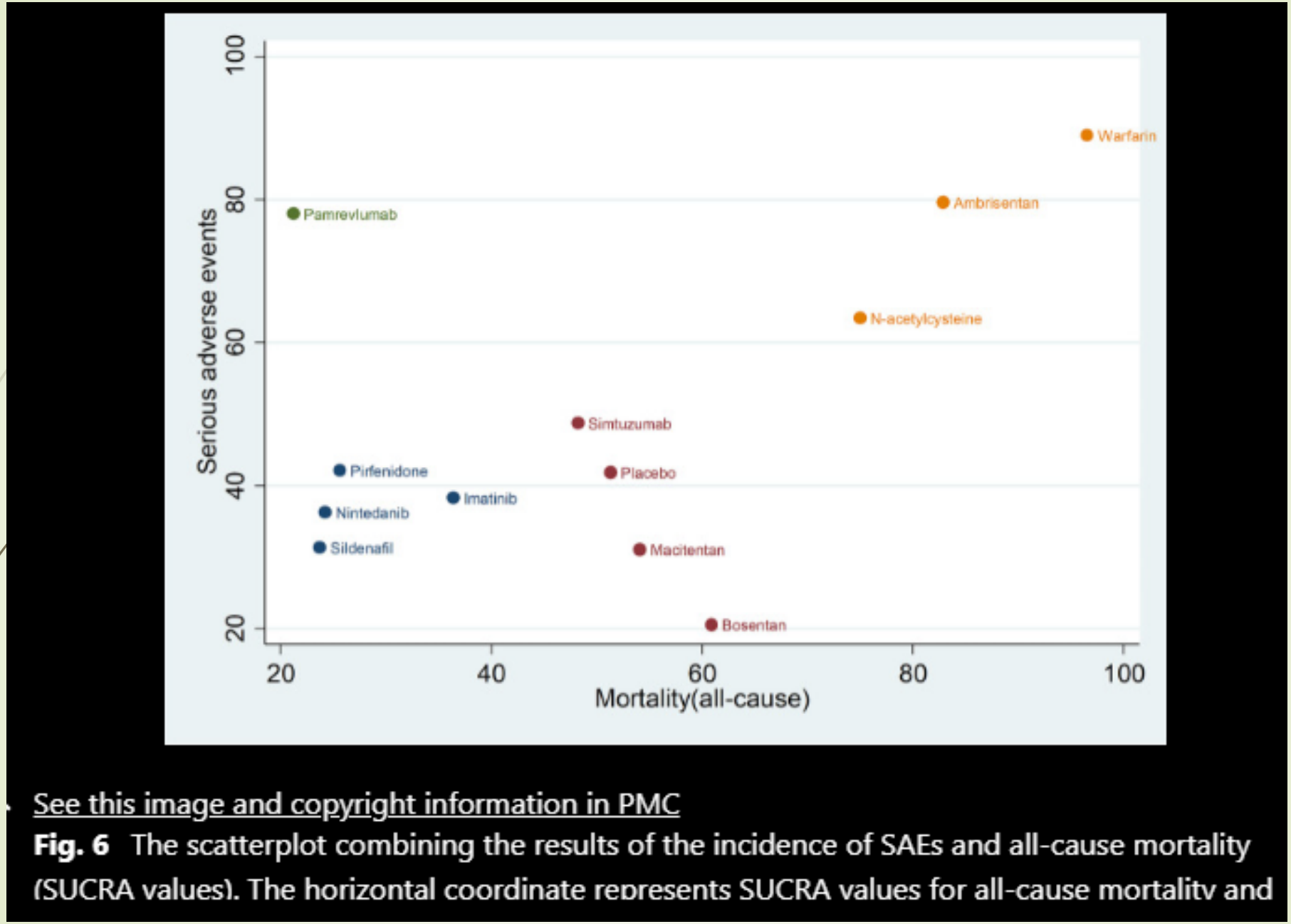


Fig. 6 The scatterplot combining the results of the incidence of SAEs and all-cause mortality (SUCRA values). The horizontal coordinate represents SUCRA values for all-cause mortality and

Pamrevlumab : antibody to inhibit the activity of connective tissue growth factor (CTGF)

Fig. 10 The scatterplot combining the results of FVC (% predicted)absolute change from baseline and the proportion of patients with decline in FVC≥10% predicted(SUCRA values). The

Adv Ther. 2023; 40(9): 3937–3955.
Published online 2023 Jun 30. doi: 10.1007/s12325-023-02565-3
PMCID: PMC10427557
PMID: 37391667

Efficacy and Safety of Pirfenidone in Advanced Versus Non-Advanced Idiopathic Pulmonary Fibrosis: Post-Hoc Analysis of Six Clinical Studies

Jürgen Behr,[✉1] Steven D. Nathan,[2] Ulrich Costabel,[3] Carlo Albera,[4] Wim A. Wuyts,[5] Marilyn K. Glassberg,[6] Harold Haller, Jr,[7] Giuseppe Alvaro,[8] Frank Gilberg,[8] Katerina Samara,[8] and Lisa Lancaster[9]

- Data were included from the following studies of pirfenidone:

ASCEND (NCT01366209)

CAPACITY 004 [NCT00287716]

CAPACITY 006 [NCT00287729]

RECAP (NCT00662038)

PASSPORT (NCT02699879)

SP-IPF (NCT02951429)

FVC < 50% and/or DLco < 35%

- In the pooled ASCEND/CAPACITY studies, the annual mean rate of FVC decline from baseline to Week 52 was significantly lower for pirfenidone versus placebo in advanced ($p = 0.0035$) and non-advanced IPF ($p = 0.0001$)

Rate of all-cause mortality over 52 weeks was numerically lower for pirfenidone versus placebo in advanced and non-advanced IPF.

- In RECAP, the mean annual rate of FVC decline from baseline to Week 180 of pirfenidone treatment was similar in patients with advanced (- 141.5 mL) and non-advanced IPF (- 153.5 mL)
- the safety profile of pirfenidone in patients with advanced IPF was generally consistent with that of non-advanced IPF.
- **Conclusions**:

As such, the indication for pirfenidone in the EU has now been updated to include the treatment of adult patients with advanced IPF.

Adults

Upon initiating treatment, the dose should be titrated to the recommended daily dose of 2403 mg/day over a 14-day period as follows:

- Days 1 to 7: a dose of 267 mg administered three times a day (801 mg/day)
- Days 8 to 14: a dose of 534 mg administered three times a day (1602 mg/day)
- Day 15 onward: a dose of 801 mg administered three times a day (2403 mg/day)

The recommended maintenance daily dose of Esbriet is 801 mg three times a day with food for a total of 2403 mg/day.

Doses above 2403 mg/day are not recommended for any patient (see section 4.9).

Patients who miss 14 consecutive days or more of Esbriet treatment should re-initiate therapy by undergoing the initial 2-week titration regimen up to the recommended daily dose.

For treatment interruption of less than 14 consecutive days, the dose can be resumed at the previous recommended daily dose without titration.

Dose adjustments and other considerations for safe use

Gastrointestinal events: In patients who experience intolerance to therapy due to gastrointestinal undesirable effects, patients should be reminded to take the medicinal product with food. If symptoms persist, the dose of pirfenidone may be reduced to 267 mg – 534 mg, two to three times a day with food with re-escalation to the recommended daily dose as tolerated. If symptoms continue, patients may be instructed to interrupt treatment for one to two weeks to allow symptoms to resolve.

Photosensitivity reaction or rash: Patients who experience a mild to moderate photosensitivity reaction or rash should be reminded to use a sunblock daily and avoid exposure to the sun (see section 4.4). The dose of pirfenidone may be reduced to 801 mg each day (267 mg three times a day). If the rash persists after 7 days, Esbriet should be discontinued for 15 days, with re-escalation to the recommended daily dose in the same manner as the dose escalation period.

Patients who experience severe photosensitivity reaction or rash should be instructed to interrupt the dose and to seek medical advice (see section 4.4). Once the rash has resolved, Esbriet may be re-introduced and re-escalated up to the recommended daily dose at the discretion of the physician.

Hepatic function: In the event of significant elevation of alanine and/or aspartate aminotransferases (ALT/AST) with or without bilirubin elevation, the dose of pirfenidone should be adjusted or treatment discontinued according to the guidelines listed in section 4.4.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- History of angioedema with pirfenidone (see section 4.4).
- Concomitant use of fluvoxamine (see section 4.5).
- Severe hepatic impairment or end stage liver disease (see sections 4.2 and 4.4).
- Severe renal impairment (CrCl <30 ml/min) or end stage renal disease requiring dialysis (see sections 4.2 and 5.2).

EUROPEAN RESPIRATORY *journal*

Eur Respir J. 2023 Oct; 62(4): 2300262. PMCID: PMC10586233
Published online 2023 Oct 19. doi: 10.1183/13993003.00262-2023 PMID: 37857429

Gastrointestinal pirfenidone adverse events in idiopathic pulmonary fibrosis depending on diet: the MADIET clinical trial

Maria Molina-Molina,[1,2] Jessica Germaine Shull,[1] Vanesa Vicens-Zygmunt,[1,2] Pilar Rivera-Ortega,[3] Katerina Antoniou,[4]

Gastrointestinal AEs	SFA diet (n=37)	MUFA diet (n=49)	p-value
Unadjusted model (n=86)			
Number events/number patients	24/37	13/49	
Rate (95% CI)	64.9 (47.5–79.8)	26.5 (14.9–41.1)	0.001#
RR MUFA *versus* SFA (95% CI)	0.41 (0.23–0.67)		0.001
Adjusted model (n=74)			
Number events/number patients	24/37	10/37	
Rate (95% CI)	64.9 (47.5–79.8)	27 (13.8–44.1)	0.002#
RR MUFA *versus* SFA (95% CI)	0.42 (0.22–0.71)		0.003
Number of events, median (Q1; Q3)	1 (0; 2)	0 (0; 1)	0.001¶
Zero-inflated Poisson model			
Unadjusted OR MUFA *versus* SFA (95% CI)	0.11 (0.02–0.57)		0.009
Adjusted OR MUFA *versus* SFA+ (95% CI)	0.07 (0.01–0.51)		0.009

Meta-Analysis > Eur Rev Med Pharmacol Sci. 2024 Feb;28(3):1183-1193.
doi: 10.26355/eurrev_202402_35357.

Bosentan and ambrisentan in the treatment of idiopathic pulmonary fibrosis: a meta-analysis

H-F Li [1], J-X Wang, Z-F Xie, L-H Li, B Li, F-F Huang, J Li, X-L Zhou

- ✓ meta-analysis until November 2021
- ✓ (6MWD), death, (DLCO), (FVC), hospitalization, IPF worsening, mean PAP, serious adverse events (SAEs), QOL
- ✓ 1,928 participants.
- ✓ The quality of evidence was high.
- ✓ The control group had significantly higher values for 6MWD, DLCO, and FVC compared to the ambrisentan treatment group. The rates of hospitalization and IPF worsening were considerably greater in comparison with the control group.

- ✓ The bosentan group exhibited significantly reduced rates of hospitalization and IPF worsening in comparison with the control group.

Conclusions

This research confirmed the effectiveness and safety of bosentan in improving symptoms (hospitalization and worsening of IPF) in sick persons with IPF (without increased death and SAEs) and confirmed the harmfulness of ambrisentan in such patients. The treatment of IPF requires more clinical evidence.

EUROPEAN RESPIRATORY *journal*
FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Effects of nintedanib on symptoms in patients with progressive pulmonary fibrosis

Marlies Wijsenbeek, Jeffrey J. Swigris, Yoshikazu Inoue, Michael Kreuter, Toby M. Maher, Takafumi Suda, Michael Baldwin, Heiko Mueller, Klaus B. Rohr, Kevin R. Flaherty on behalf of the INBUILD Trial Investigators

European Respiratory Journal 2024 63: 2300752; **DOI:** 10.1183/13993003.00752-2023

- Patients had a fibrosing ILD other than IPF of >10% extent on HRCT and met criteria for ILD progression within the prior 24 months.
- Patients were randomised 1:1 to receive nintedanib or placebo.
- Changes in Living with Pulmonary Fibrosis (L-PF) questionnaire scores from baseline to week 52
- In total, 663 patients were treated
- L-PF questionnaire impacts score decreased slightly in the nintedanib group and increased in the placebo group (−0.2 versus 4.6).
- Conclusion

Based on changes in L-PF questionnaire scores, nintedanib reduced worsening of dyspnoea, fatigue and cough and the impacts of ILD over 52 weeks in patients with PPF.

Clinical Trial > J Aerosol Med Pulm Drug Deliv. 2023 Dec;36(6):300-308.
doi: 10.1089/jamp.2023.0014. Epub 2023 Sep 22.

A Phase I Study of TRK-250, a Novel siRNA-Based Oligonucleotide, in Patients with Idiopathic Pulmonary Fibrosis

Hiroyuki Doi [1], Jun Atsumi [1], David Baratz [2], Yohei Miyamoto [1]

- TRK - 250 is a novel single-stranded oligonucleotide carrying a human Transforming growth factor-beta 1-targeting siRNA motif tethered by two proline linkers.
- Nonclinical studies have shown that TRK-250 may have potency to prevent the progression of pulmonary fibrosis.
- In the phase I study, 34 IPF patients were partially randomized to receive a placebo or TRK-250 in 4 single doses of 2, 10, 30, and 60 mg or multiple rising doses of 10, 30, and 60 mg once per week for 4 weeks by oral inhalation.
- no significant drug-related adverse events (AEs) were observed. The AEs were mild or moderate, except for one severe case with acute exacerbation.
- TRK-250 was not detected in the systemic circulation following inhalation, indicating low or virtually nonexistent systemic exposure.

Clinical Trial > BMJ Open Respir Res. 2023 Aug;10(1):e001563.
doi: 10.1136/bmjresp-2022-001563.

Design of a phase III, double-blind, randomised, placebo-controlled trial of BI 1015550 in patients with idiopathic pulmonary fibrosis (FIBRONEER-IPF)

Luca Richeldi [1], Arata Azuma [2 3], Vincent Cottin [4], Michael Kreuter [5 6], Toby M Maher [7 8], Fernando J Martinez [9], Justin M Oldham [10], Claudia Valenzuela [11], Maud Gordat [12], Yi Liu [13], Susanne Stowasser [14], Donald F Zoz [15], Marlies S Wijsenbeek [16]

- The oral preferential phosphodiesterase 4B inhibitor, BI 1015550, prevented a decline in forced vital capacity (FVC) in a phase II study in patients with IPF.
- This study design describes the subsequent pivotal phase III study of BI 1015550 in patients with IPF (FIBRONEER-IPF).
- In this placebo-controlled, double-blind, phase III trial, patients are being randomised in a 1:1:1 ratio to receive 9 mg or 18 mg of BI 1015550 or placebo two times per day over at least 52 weeks, stratified by use of background antifibrotics (nintedanib/pirfenidone vs neither).
- The primary endpoint is the absolute change in FVC at week 52. The key secondary endpoint is a composite of time to first acute IPF exacerbation, hospitalisation

Clinical Trial > Thorax. 2023 Sep;78(9):882-889. doi: 10.1136/thorax-2022-219391. Epub 2023 Mar 22.

Inhaled pirfenidone solution (AP01) for IPF: a randomised, open-label, dose-response trial

Alex West [1], Nazia Chaudhuri [2], Adam Barczyk [3], Margaret L Wilsher [4], Peter Hopkins [5], Ian Glaspole [6], Tamera Jo Corte [7 8], Martina Šterclová [9], Antony Veale [10], Ewa Jassem [11], Marlies S Wijsenbeek [12], Christopher Grainge [13], Wojciech Piotrowski [14], Ganesh Raghu [15 16 17], Michele L Shaffer [18], Deepthi Nair [18], Lisa Freeman [18], Kelly Otto [18], A Bruce Montgomery [19]

Randomized Controlled Trial > NEJM Evid. 2023 Aug;2(8):EVIDoa2300083.
doi: 10.1056/EVIDoa2300083. Epub 2023 May 22.

Nalbuphine Tablets for Cough in Patients with Idiopathic Pulmonary Fibrosis

Toby M Maher [1] [2], Cristina Avram [3], Enoch Bortey [4], Simon P Hart [5], Nikhil Hirani [6], Philip L Molyneux [2], Joanna C Porter [7] [8], Jaclyn A Smith [9], Thomas Sciascia [10]

Affiliations + expand

PMID: 38320144 DOI: 10.1056/EVIDoa2300083

Abstract

Nalbuphine for Cough with Idiopathic Pulmonary FibrosisIn patients with idiopathic pulmonary fibrosis, cough may have a negative impact on daily life. In a randomized, 22-day treatment period, placebo-controlled, crossover trial, extended-release nalbuphine (NAL ER), an opioid agonist-antagonist, was compared to placebo for cough control and adverse effects. During active treatment there was a 75.1% reduction in daytime objective cough frequency compared with 22.6% in the placebo treatment period. Nausea, fatigue, constipation, and dizziness were more common with NAL ER than with placebo.

Clinical Trial > Lancet Respir Med. 2024 Apr;12(4):273-280. doi: 10.1016/S2213-2600(23)00432-0. Epub 2024 Jan 15.

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

Zhe Wu [1], Lisa G Spencer [2], Winston Banya [3], John Westoby [3], Veronica A Tudor [3], Pilar Rivera-Ortega [4], Nazia Chaudhuri [5], Ira Jakupovic [3], Brijesh Patel [6], Muhunthan Thillai [7], Alex West [8], Marlies Wijsenbeek [9], Toby M Maher [10], Jacky A Smith [11], Philip L Molyneaux [12]

- phase 2, multicentre, randomised, double-blind, placebo-controlled in three specialist centres in the UK.

- Eligible patients aged 40-90 years had a diagnosis of idiopathic pulmonary fibrosis within 5 years, self-reported cough (lasting >8 weeks), and a cough visual analogue scale (VAS) score of 30 mm or higher.

- Patients were randomly assigned (1:1) to placebo twice daily or controlled-release morphine 5 mg orally twice daily for 14 days followed by crossover after a 7-day washout period.

- The primary endpoint was percentage change in objective awake cough frequency (coughs per h) from baseline as assessed by objective digital cough monitoring at day 14 of treatment in the intention-to-treat population,

- Between Dec 17, 2020, and March 21, 2023, 44 were enrolled
- Morphine reduced objective awake cough frequency by 39·4% (95% CI -54·4 to -19·4; p=0·0005) compared with placebo.
- Mean daytime cough frequency reduced from 21·6 (SE 1·2) coughs per h at baseline to 12·8 (1·2) coughs per h with morphine, whereas cough rates did not change with placebo.
- Adverse event: 40% in the morphine group and six 14% in the placebo group.
- The main side-effects of morphine were nausea and constipation

- **Interpretation:**

In patients with cough related to IPF , low dose controlled-release morphine significantly reduced objective cough counts over 14 days compared with placebo.