Recent insights in the management of IPF

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The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Fibrosis — A Common Pathway to Organ Injury and Failure

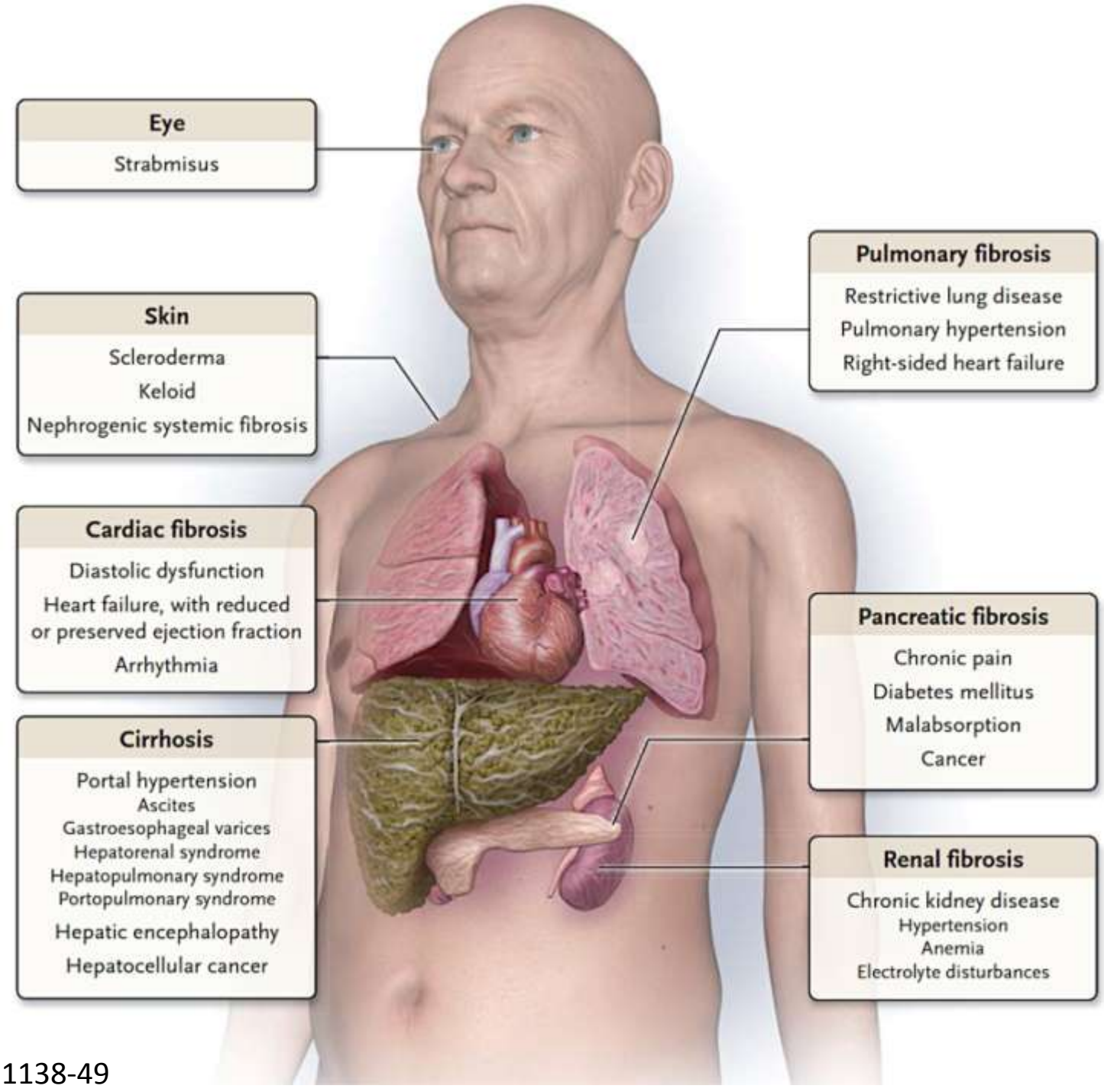
Don C. Rockey, M.D., P. Darwin Bell, Ph.D., and Joseph A. Hill, M.D., Ph.D.

*"Fibrosis and resultant organ failure account for at least **one third of deaths** worldwide.*

*Since fibrosis is common and has adverse effects in all organs, it is an **attractive therapeutic target**.*

*Contrary to the widely held perception that scar tissue is permanent, the available evidence points to the **highly plastic nature of organ fibrosis**."*

NEJM 2015; 372: 1138-49

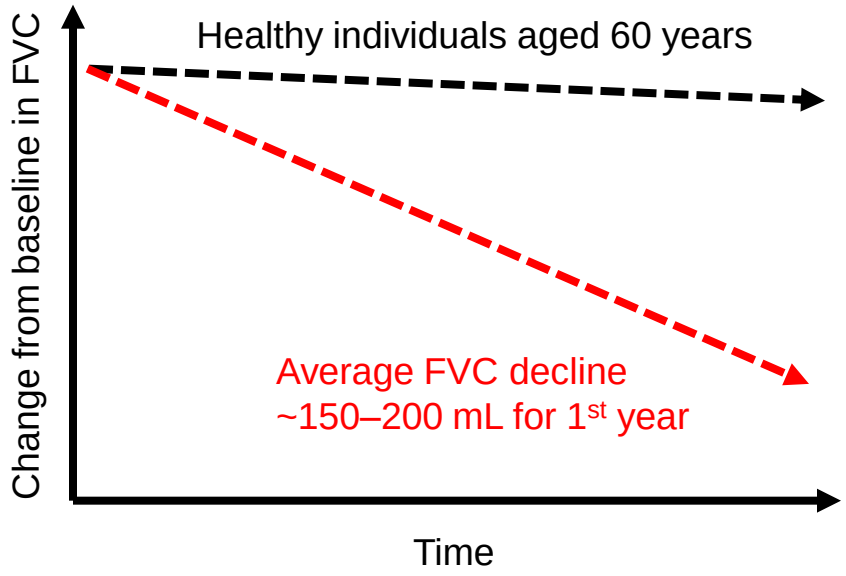


NEJM 2015; 372: 1138-49

Introduction

- IPF is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause that leads to irreversible loss in lung function; average FVC decline ~150–200 mL in 1st year[1]
- 5-year survival rate of 20–40%[2]
- Pirfenidone and nintedanib were approved for IPF in 2014[3–4]
  - Both slow the rate of decline in FVC
  - No drugs to date have been shown to abort disease progression or improve any objective measurements of disease status[5–6]
- The need for novel IPF treatments persists

Natural course of lung function in patients with mild to moderate impairment



Adapted from Raghu G, *Eur Respir J*; 50:1701209.

FVC, forced vital capacity; IPF idiopathic pulmonary fibrosis.

1. Raghu G, *Eur Respir J.* 2017;50:1701209; 2. Olson AL, et al. *Am J Respir Crit Care Med.* 2007;176(3):277–84; 3. Esbriet US prescribing information. Available at: https://www.accessdata.fda.gov/ drugsatfda_docs label/2014/022535s000lbl.pdf (accessed March 2018); 4. Ofev US prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205832s000lbl.pdf (accessed March 2018); 5. King TE, Jr, et al. *N Engl J Med.* 2014;370(22):2083–92; 6. Richeldi L, et al. *N Engl J Med*. 2014;370(22):2071–82.

Medical Therapy in Idiopathic Pulmonary Fibrosis

Katerina M. Antoniou[1] Wim Wuyts[2] Marlies Wijsenbeek[3] Athol U. Wells[4]

Semin Respir Crit Care Med 2016;37:368–377.

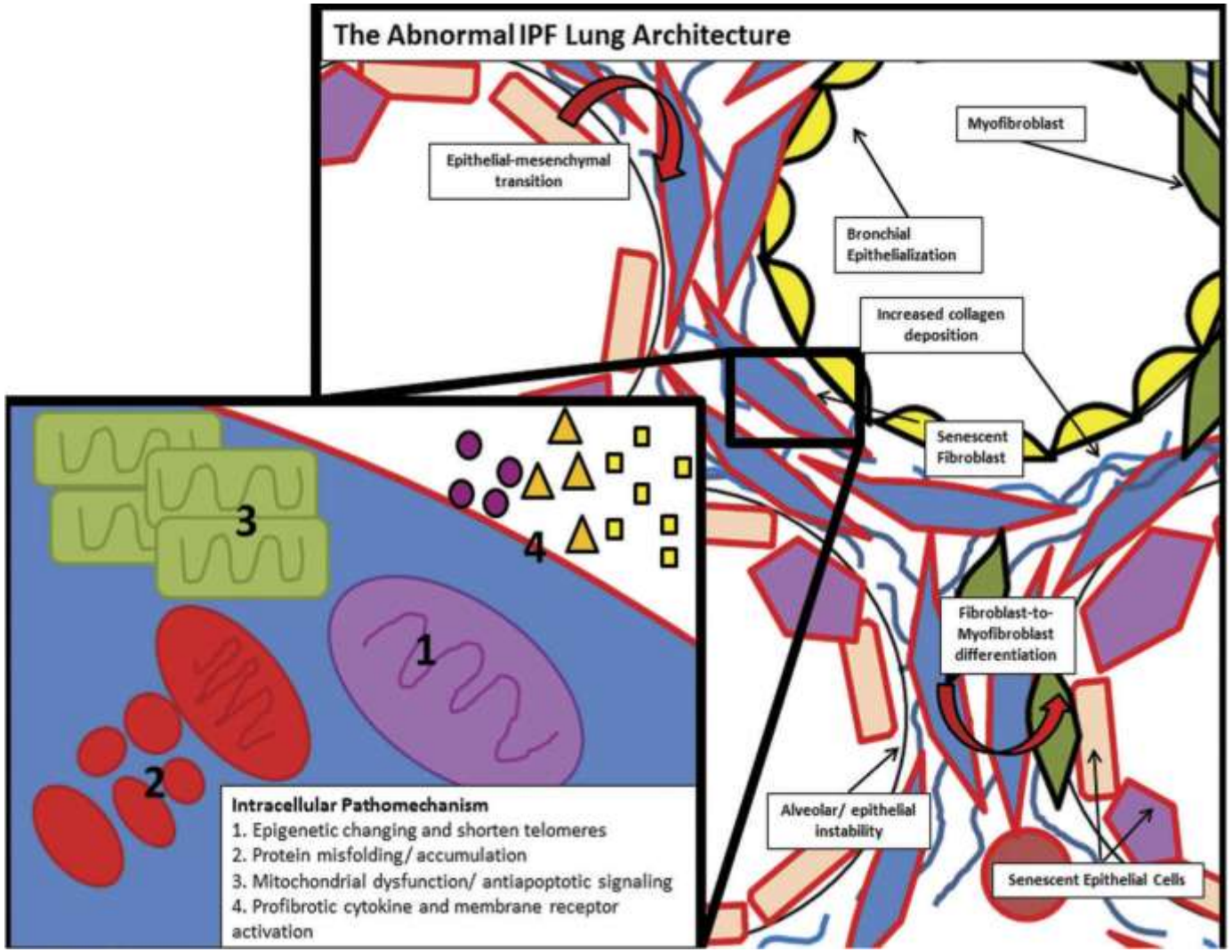
Abstract

Medical therapy for idiopathic fibrosis remains controversial. Idiopathic pulmonary fibrosis (IPF) was uniformly a disease that progressed inexorably, typically leading to death within 3 to 5 years from onset of symptoms. Until recently, lung transplantation was the only effective transplant option. Within the past decade, several placebo-controlled trials failed to show benefit in patients with IPF. However, within the past 2 years, two novel antifibrotic agents (pirfenidone and nintedanib) were approved by the Food and Drug Administration (FDA) in the United States and European Medicines Agency (EMA) based upon pivotal studies that showed benefit (specifically slowing of the rate of disease progression) with both agents. Short-term outcomes (12 months) showed less deterioration of physiological parameters (e.g., change in forced vital capacity), although survival benefit has not convincingly been established with either agent. Nonetheless, these agents bring a glimmer of hope to patients with this deadly disease. The appropriate indications for initiating therapy, best candidates for therapy, and possible role for combination therapy remain controversial. Additional studies using agents that attenuate or abrogate profibrotic cytokines and chemokines may provide even further improvement in the future.

Keywords

- idiopathic pulmonary fibrosis
- pirfenidone
- nintedanib

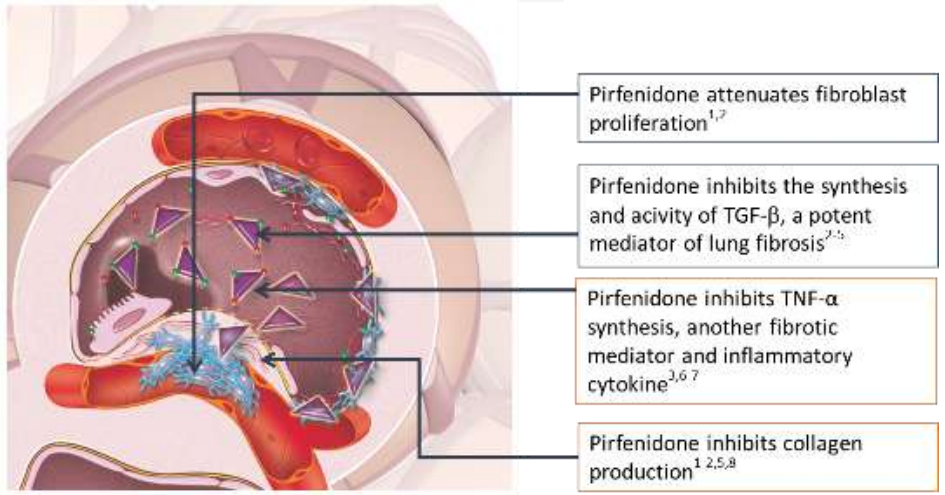
Targeting of established and novel pharmacologic pathways in IPF



Kareem Ahmad and Steven D. Nathan. EXPERT REVIEW OF RESPIRATORY MEDICINE 2018

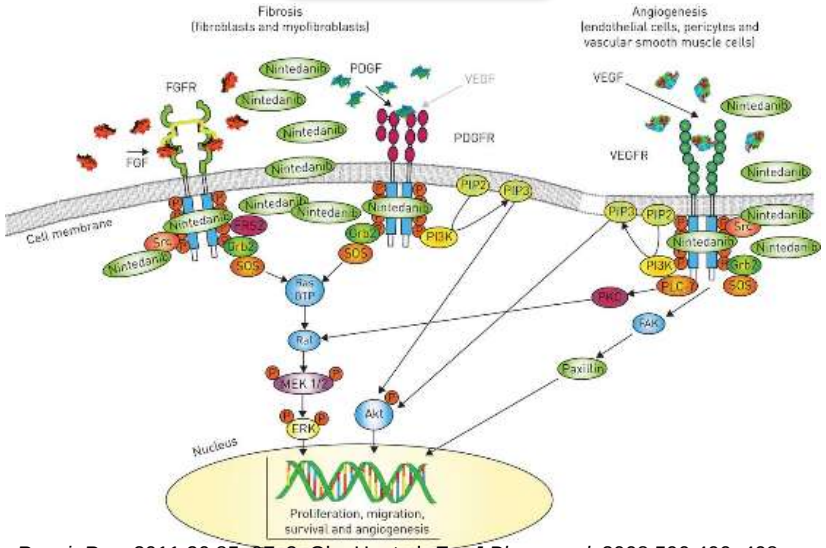
Combination therapy: Rationale for combination of antifibrotics

Pirfenidone[1-8]



Data from animal and *in vitro* studies

Nintedanib[9]



1. Di Sario A, et al. *J Hepatol*. 2012;37:584–591; 2. Schaefer CJ, et al. *Eur Respir Rev*. 2011;20:85–97; 3. Oku H, et al. *Eur J Pharmacol*. 2008;590:400–408; 4. Liu H, et al. *Am J Transplant*. 2005;1256–1263; 5. Nakayama S, et al. *Life Sci*. 2008;82:210–217; 6. Oku H, et al. *Eur J Pharmacol*. 2002;446:167–176; 7. Grattendick KJ, et al. *Int Immunopharmacol*. 2008;8:679–687; 8. Iyer SN, et al. *J Pharmacol Exp Ther*. 1999;289:211–218; 9. Wollin L, et al. *Eur Respir J*. 2015;45:1434–1445

ERJ Express. Published on November 15, 2018 as doi: 10.1183/13993003.01060-2018

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

No relevant pharmacokinetic drug-drug interaction between nintedanib and pirfenidone

Luca Richeldi, Sophie Fletcher, Huzaifa Adamali, Nazia Chaudhuri, Sabrina Wiebe, Sven Wind, Kathrin Hohl, Andrew Baker, Rozsa Schlenker-Herceg, Susanne Stowasser, Toby M. Maher

Nintedanib and pirfenidone are two drugs approved for patients with idiopathic pulmonary fibrosis (IPF). Since nintedanib and pirfenidone act in different ways, combining them is a potentially attractive treatment option. Our study sought to confirm that these drugs do not adversely affect the concentration of each other when given together in patients with IPF. Our analysis confirmed that the concentration of each drug does not change when they are given in combination. Further studies will be required to evaluate the clinical benefit of using these drugs in combination.

Antifibrotic combination therapy trials in IPF

- **Two trials combining pirfenidone and nintedanib were completed in 2017**

	Nintedanib added to stable pirfenidone (NCT02598193; Roche)[1,2]	Pirfenidone added to stable nintedanib (NCT02579603; BI)[3]
Design	Exploratory multicentre, open-label, single-arm	Open-label, randomised, parallel-group
Enrolment	89	105
Duration	24 weeks	12 weeks
Primary outcome	**Patients (%) who complete 24 weeks of combination treatment on pirfenidone (1602–2403 mg/day) and nintedanib (200–300 mg/day)**	**Patients (%) with on-treatment GI AEs from baseline to Week 12**

BI, Boehringer Ingelheim

1. Flaherty K, et al. Poster presented at ERS 2017: PA2805;
2. Flaherty K, et al. *Eur Respir J*; accepted for publication; 3. Vancheri C, et al. *Am J Respir Crit Care Med*. 2018;197:356–363

Trials of Pirfenidone and nintedanib in combination

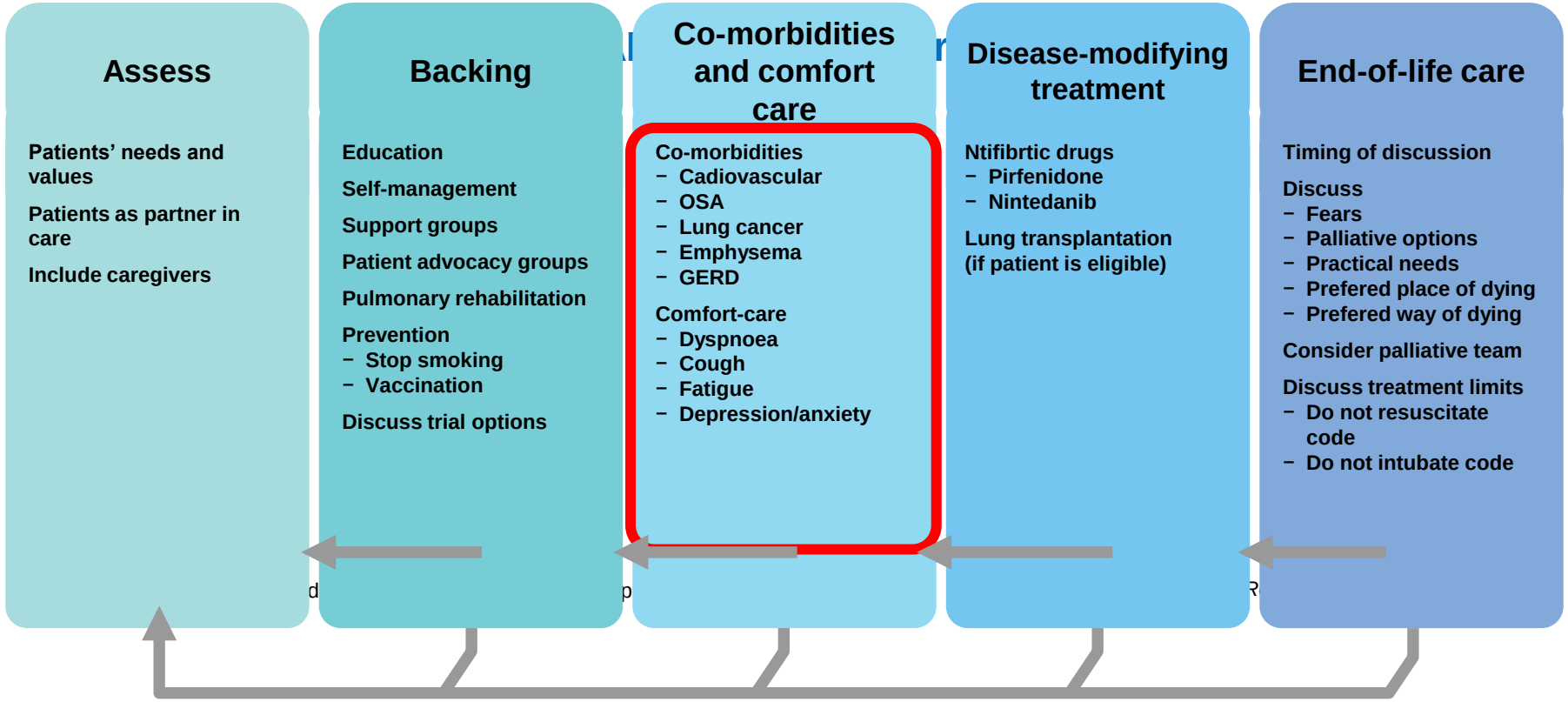
Trials of pirfenidone and nintedanib in combination

- Nintedanib added to pirfenidone[4] and pirfenidone added to nintedanib (INJOURNEY)[5]
  - Safety and tolerability profile similar to Phase III trials, with a slightly higher discontinuation rate
  - Short duration, no placebo controls
  - No robust efficacy data

1. Parker J, et al. ATS 2017;195:A7606; 2. Raghu G, et al. *Lancet Respir Med.* 2017;5:22–32;
3. Clinicaltrials.gov identifier: NCT02550873; 4. Flaherty KR, et al. *Eur Respir J.* 2018;52:1800230;
5. Vancheri C, et al. *Am J Respir Crit Care Med*. 2018;197:356–363

Importance of accounting for comorbidities in patients with IPF

- The move towards a **holistic** approach for management of IPF
  - Including a focus on quality of life and best supportive care
- We need to take comorbidities into account when treating IPF



Modifiable Comorbidities in IPF management

Comorbidity	Key Points	Recent Relevant Publication(s)
OSA/Sleep Disorders	• High incidence of sleep apnea, up to 88% of IPF patients • Treatment improves QOL and outcomes (worsening ischemic heart disease) • Architectural distortion, abnormal respiratory pattern, nocturnal desaturation are common	Mermigkis C, et al. Chest. 2017
Pulmonary Hypertension (PH)	• Entails poor functional status and survival • Treatment directed at PH has lacked efficacy and potentially can be harmful • Oxygen is only supported intervention • Possible role for earlier intervention	Collum SD, et al. Canadian Respiratory Journal. 2017
GERD	• Possible causative relationship • Not conclusive if prophylaxis is beneficial in regards to progression • Occult disease should be treated as it is associated with worse outcomes	Fidler L, et al. Chest. 2018
Exercise Intolerance/ Deconditioning	• Regular activity/exercise is beneficial for quality of life and outcomes • Referral to pulmonary rehabilitation should be done in early disease for greatest benefit	Vainshelboim B. Breathe. 2016
Venous Thromboembolism (VTE)	• Higher incidence of VTE in IPF patients • No optimal anticoagulant, pre-emptive AC is associated with increased mortality • AC shown to improve mortality in AE-IPF	Kreuter M, et al. Eur Respiratory Journal. 2016

OSA- Obstructive Sleep Apnea, QOL- Quality of Life, GERD- Gastroesophageal Reflux Disease, AC- Anticoagulation

Proton Pump Inhibitors in IPF: A Call for Clinical Trials

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[1] *Department of Radiation Oncology, Baylor College of Medicine, Houston, TX, United States,* [2] *Section of Pulmonary and Critical Care Medicine, Department of Medicine, Baylor College of Medicine, Houston, TX, United States*

The recent FDA approval of two drugs, pirfenidone and nintedanib, for the treatment of idiopathic pulmonary fibrosis (IPF) has fueled interest in the development of additional drugs to treat the disease or its major clinical complications including cough and acute exacerbations. Since 2015, there are at least a dozen active interventional studies that are testing the efficacy of novel pharmacotherapies, exercise or stem cells in modifying the disease process in IPF. Additionally, there are combinatorial studies evaluating the effectiveness of pirfenidone or nintedanib in combination with other agents. However, there remains an urgent need for clinical trials to prospectively evaluate the efficacy of existing drugs with promising retrospective data, such as proton pump inhibitors (PPIs), in IPF. Several retrospective cohorts have provided tantalizing data supporting the beneficial effect of PPIs in patients with well-defined IPF. This review provides the general outlook of pharmacotherapies in IPF, and highlights preclinical and retrospective clinical data to make a case for randomized controlled clinical trials of PPIs in IPF.

Laparoscopic anti-reflux surgery for the treatment of idiopathic pulmonary fibrosis (WRAP-IPF): a multicentre, randomised, controlled phase 2 trial

Findings Between June 1, 2014, and Sept 30, 2016, we screened 72 patients and randomly assigned 58 patients to receive surgery (n=29) or no surgery (n=29). 27 patients in the surgery group and 20 patients in the no surgery group had an FVC measurement at 48 weeks (p=0·041). Intention-to-treat analysis adjusted for baseline anti-fibrotic use demonstrated the adjusted rate of change in FVC over 48 weeks was –0·05 L (95% CI –0·15 to 0·05) in the surgery group and –0·13 L (–0·23 to –0·02) in the non-surgery group (p=0·28). Acute exacerbation, respiratory-related hospitalisation, and death was less common in the surgery group without statistical significance. Dysphagia (eight [29%] of 28) and abdominal distention (four [14%] of 28) were the most common adverse events after surgery. There was one death in the surgery group and four deaths in the non-surgery group.

Added value of this study

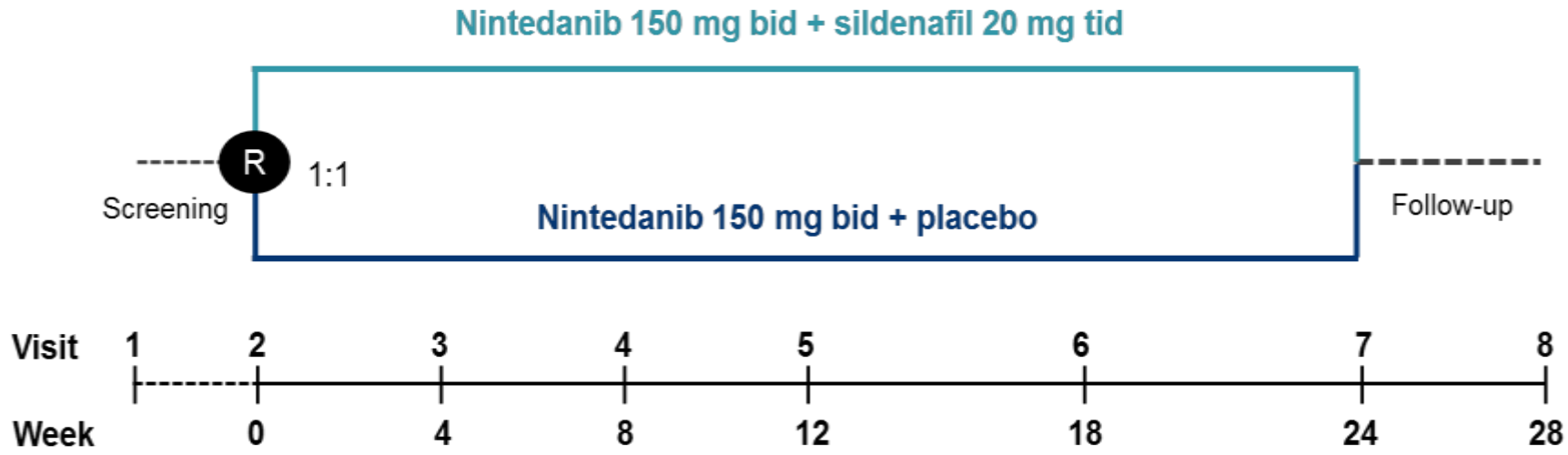
This phase 2 randomised, controlled trial aimed to determine whether normalisation of abnormal acid gastro-oesophageal reflux with laparoscopic anti-reflux surgery reduced the rate of disease progression. Laparoscopic anti-reflux surgery was safe and well tolerated but disease progression over 48 weeks—defined as change in forced vital capacity—did not reduce significantly. Respiratory-related hospitalisation and death were less common in the surgical group without statistical significance. These results provide the first prospective controlled data addressing this hypothesis.

Raghu G, et al. Lancet Respir Med 2018

Nintedanib plus sildenafil in IPF: INSTAGE study design

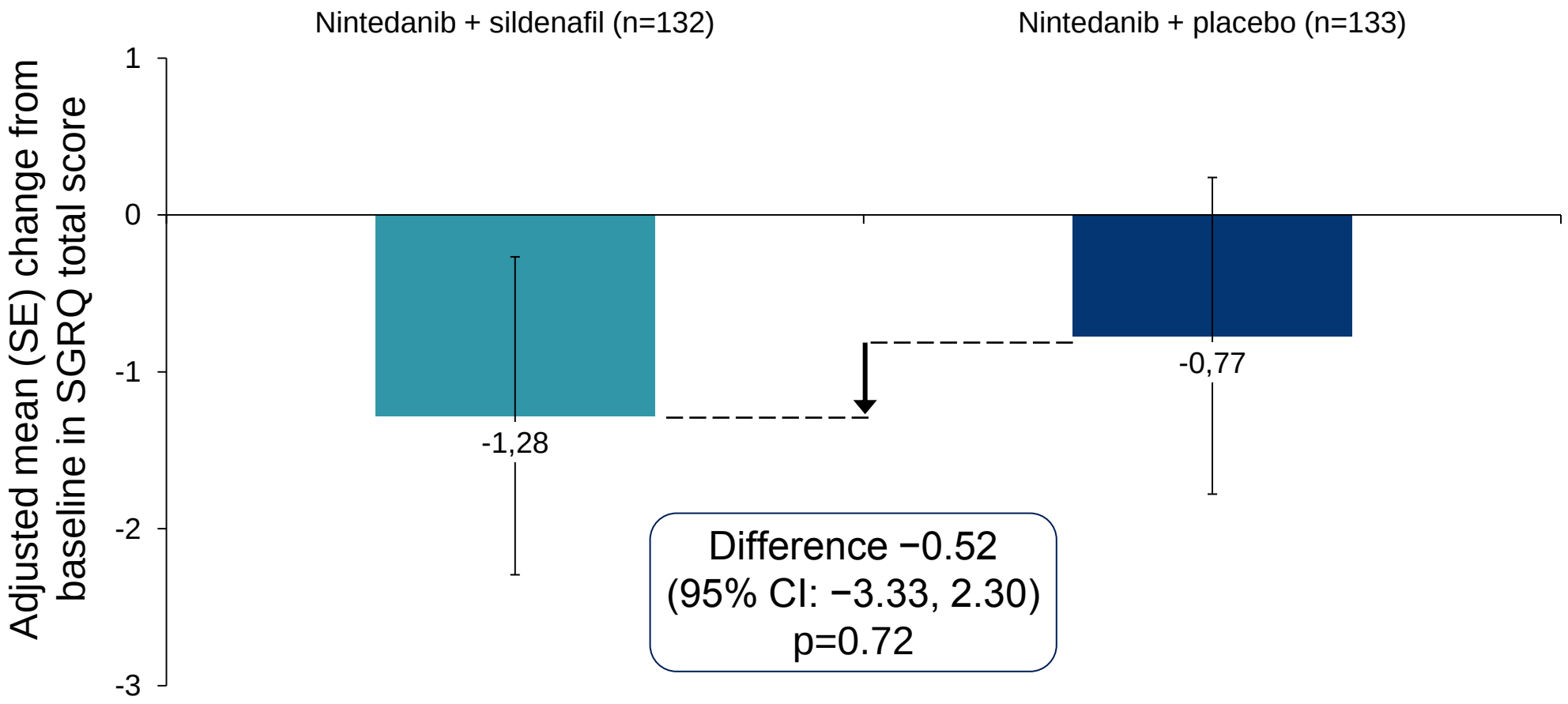
Objectives of INSTAGE® trial:

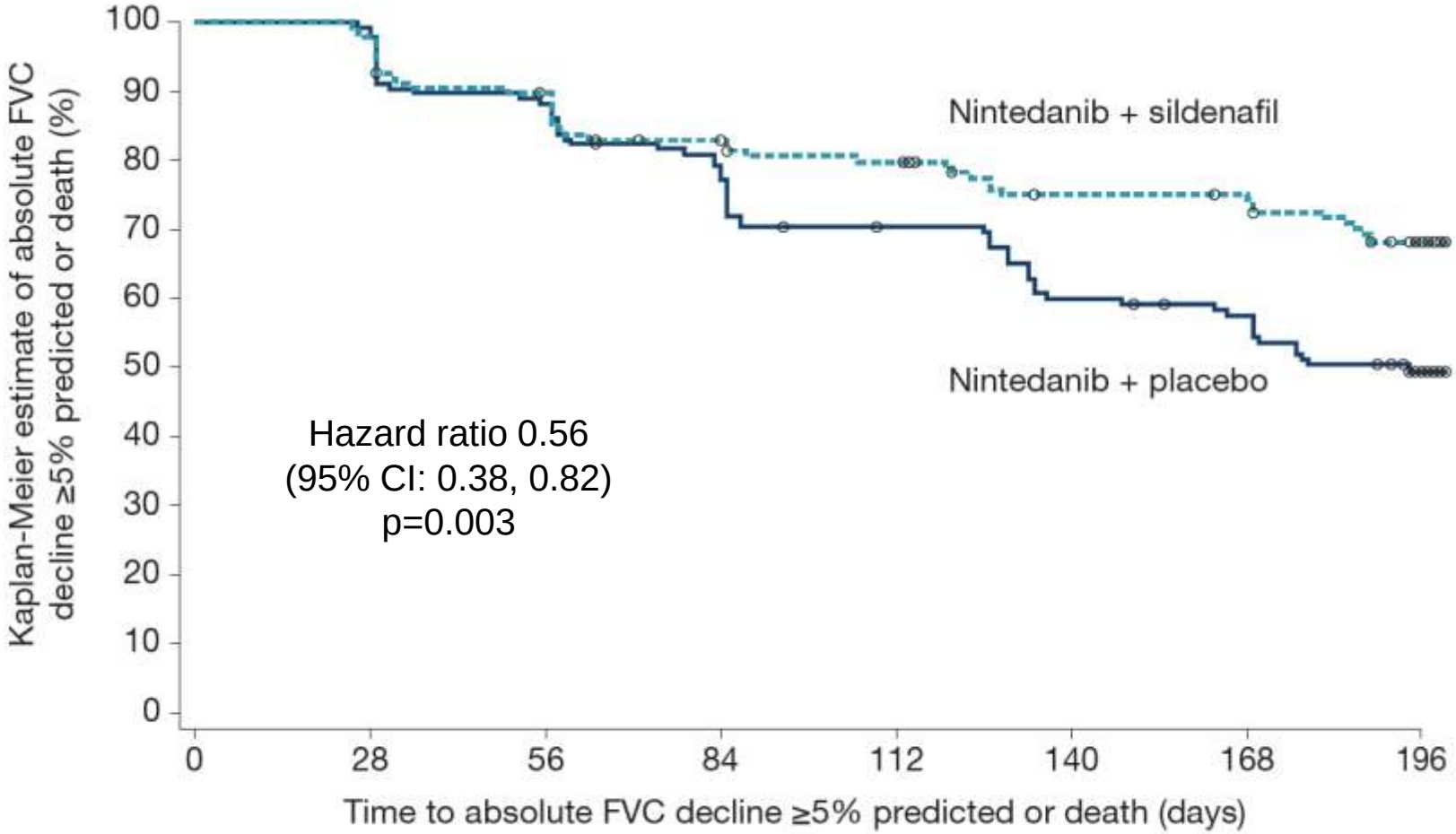
- Assess the efficacy and safety of combined treatment with nintedanib and sildenafil in patients with IPF and severely impaired gas exchange
- Enlarge the efficacy and safety database for nintedanib monotherapy with data from patients with IPF and severely impaired gas exchange
- Primary endpoint: change from baseline in SGRQ total score at Week 12



bid, twice a day; SGRQ, St George's Respiratory Questionnaire; tid, 3 times a day

Kolb M, et al. *N Engl J Med*. 2018;379:1722–1731

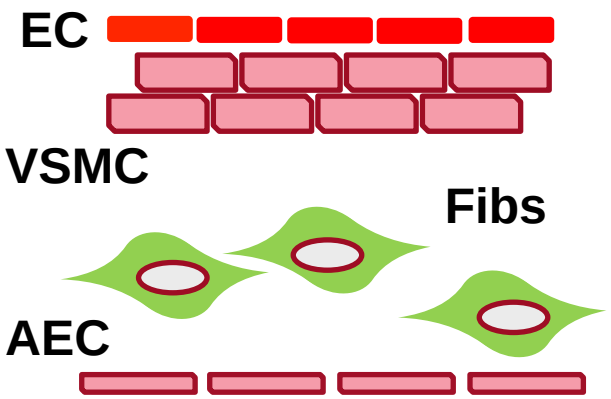

Nintedanib + sildenafil (n=132)
Nintedanib + placebo (n=133)
Adjusted mean (SE) change from baseline in SGRQ total score
1
0
-1
-2
-3
-1,28
-0,77
Difference −0.52
(95% CI: −3.33, 2.30)
p=0.72



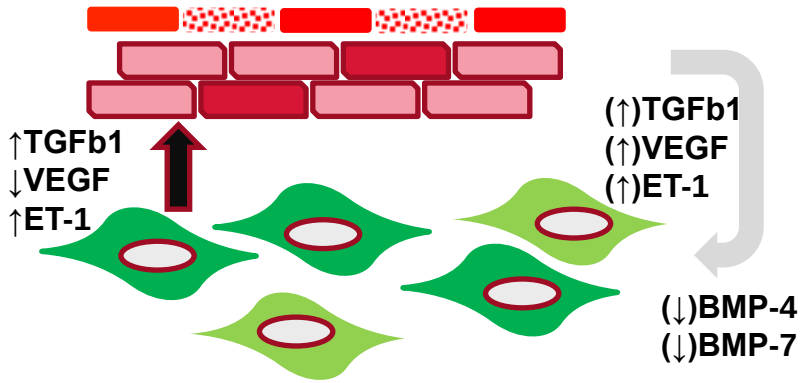
No. of patients								
Nintedanib + sildenafil	137	134	120	109	103	92	91	76
Nintedanib + placebo	136	135	120	107	93	79	73	57

Sildenafil

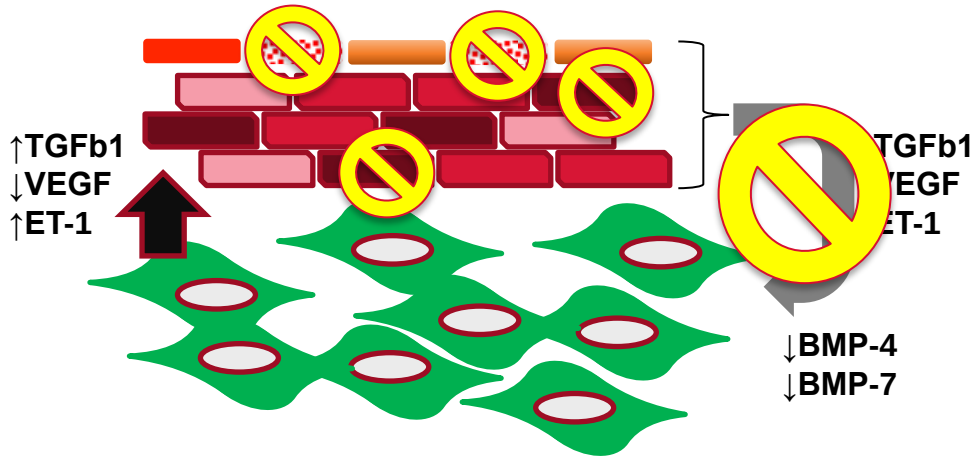
Normal

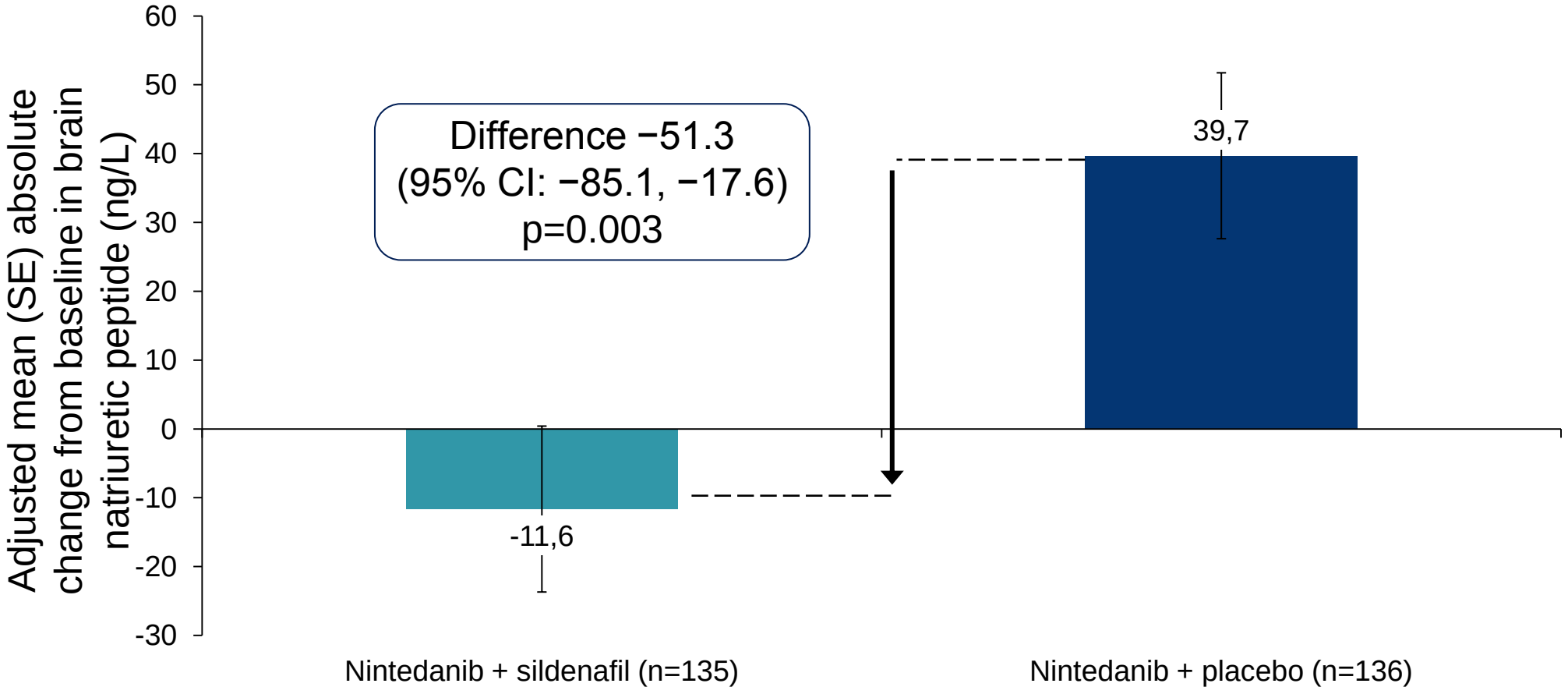


Early fibrosis / no PH



Advanced fibrosis and PH




Adjusted mean (SE) absolute change from baseline in brain natriuretic peptide (ng/L)
60
50
40
30
20
10
0
-10
-20
-30
Difference −51.3
(95% CI: −85.1, −17.6)
p=0.003
39,7
-11,6
Nintedanib + sildenafil (n=135)
Nintedanib + placebo (n=136)

Nintedanib plus sildenafil in IPF

Strengths:

- Similar effect on FVC at Weeks 12 and 24 vs INPULSIS trial
- Manageable safety profile in more advanced disease
- No new safety signals
- Less risk of absolute FVC decline of

Limitations:

- Primary endpoint of change in SGRQ from baseline to Week 12 not met
- Trial not powered to show differences in physiological outcomes
- Only 24-week study duration with primary endpoint at Week 12
- 6MWD, the standard outcome for PH, was not measured

PH, pulmonary hypertension

Jürgen Behr,[1] Steven D. Nathan,[2] Sergio Harari,[3] Wim Wuyts,[4] Nesrin Mogulkoç Bishop,[5] Demosthenes Borous,[6] Katerina Antoniou,[7] Julien Guiot,[8] Mordechai Kramer,[9] Klaus-Uwe Kirchgaessler,[10] Monica Bengus,[10] Frank Gilberg,[10] Athol U. Wells[11]

- **Baseline Characteristics of All Patients Randomized in a Phase IIb Trial of Sildenafil Added to Pirfenidone in Patients With Advanced Idiopathic Pulmonary Fibrosis and Risk of Pulmonary Hypertension**

- Screening/run-in failure occurred in 96/271 patients (35.4%), mainly based on eligibility criteria related to advanced IPF and risk of PH.
- All randomized patients (N=177) were included; mean age was 68.6 years, 75.7% were male and mean time from IPF diagnosis was 3.1 y

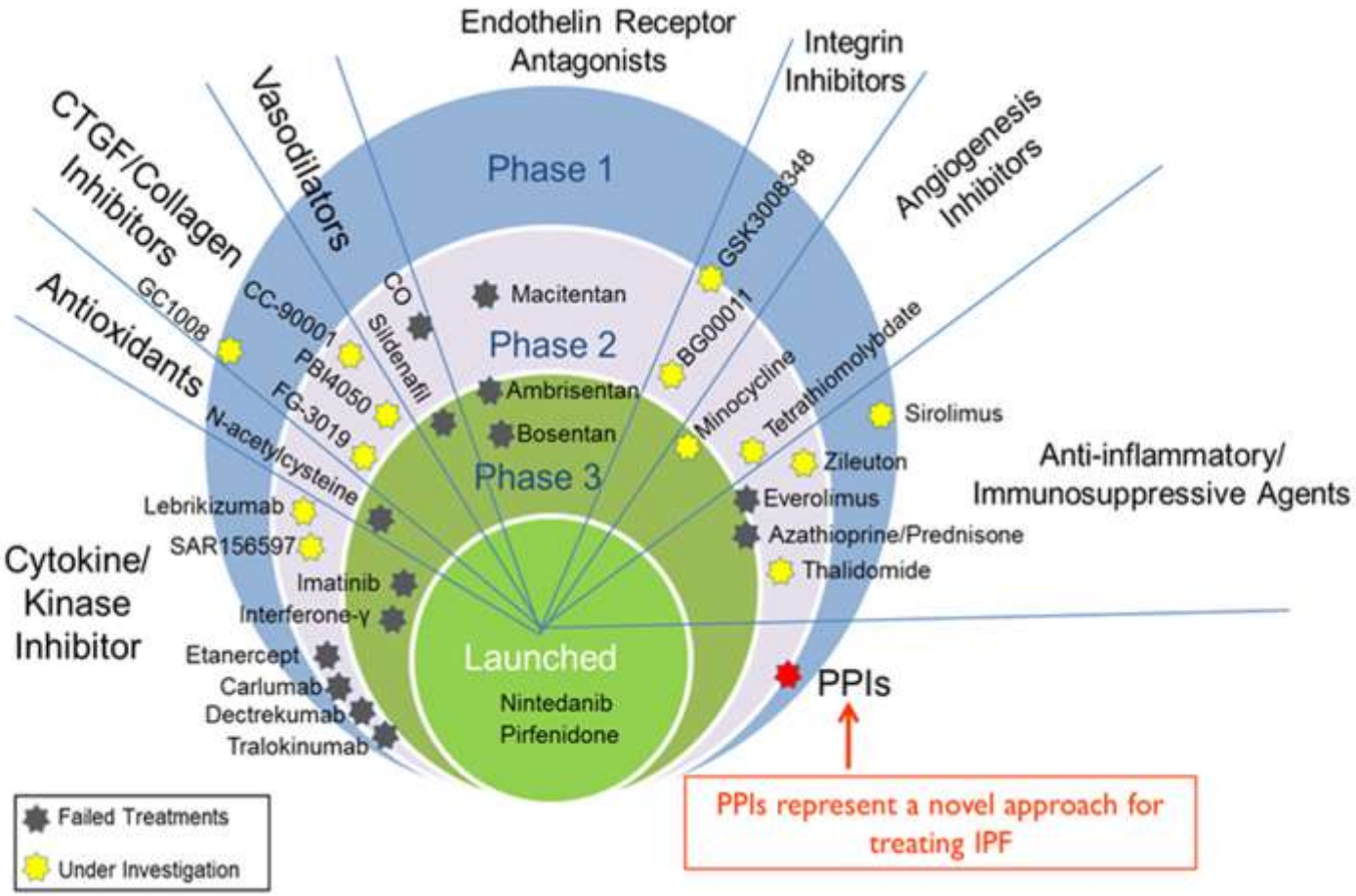
- ***Additional values reported in MA29957 included: mean mPAP on RHC was 28.1 mmHg (n=32), echocardiogram (ECHO) peak TRV was 3.5 m/s (n=158) and sPAP was 57.5 mmHg (n=157). Mean 6MWD was 290.7 m.***

Other Molecular Targets

- Coagulation (Warfarin)
- Collagen scaffold (LOXL2I: GS-6624)
- Renin-angiotensin System (losartan)
- Telomerase (Nandrolone decanoate)
- Hemoglobin modifiers (GBT440)
- Hormone analogs (Octreotide)

Other Anti-fibrotic Agents

- TD139 (Galectin-3 inhibitor)
- GSK2126458 (mTOR/PI3Kinhibitor)
- IW001 (Anti-Collagen Type V)
- PRM151 (Recombinant human serum amyloid P protein)
- GLPG1690 (Autotaxin inhibitor)
- Tipelukast (inhibitor of leukotriene receptor, lipoxygenase and PDE)
- Rituximab (anti-CD20 monoclonal antibody)
- BMS-986020 (inhibitor of lysophosphatidic acid receptor)



PRECLINICAL & PHASE 1 CLINICAL TRIALS IN IPF

Drug/Compound	Manufacturer	Pathway/Mechanism of Action	Stage of Development	Study	Publication
Dasatinib (Sprycel)/ Querecitin	BMS	Tyrosine kinase inhibitor/ Flavonoid	Pre-clinical		Schafer MJ, et. al
Navitoclax (ABT-263)	Abbot	Bcl-2 inhibitor	Pre-clinical		Zhu Y, et. al
GKT-831/GKT137831	Genkyotex	NADPH oxidase inhibitor	Pre-clinical		Hecker L, et al.
Torkinib (PP242/30)	Chemdea	mTOR inhibitor	Pre-clinical		Feldman ME, et. al
Sapanisertib (MLN0128/ INK128)	Millenium Pharm	mTOR inhibitor	Pre-clinical		Chang W, et. al
Palomid 529	Diffusion Pharm	mTOR inhibitor	Pre-clinical		Ferguson KT, et. al
Vorinostat (Zolinza)	Merck	HDAC inhibitor	Pre-clinical		Korfei, M, et. al
Romidepsin (Istodax)	Celgene	HDAC inhibitor	Pre-clinical		Conforti F, et. al
Fasudil	Asahi Kasei	ROCK inhibitor	Pre-clinical		Jiang C, et. al
GSK3008348	GSK	Anti-integrin avB6	Phase 1	NCT02612051	Maden, C.H., et al.
Omipalisib	GSK	mTor inhibitor	Phase 1	NCT01725139	Mercer PF, et. al
IW001	Immuneworks	Anti-col (V)	Phase 1	NCT01199887	Wilkes DS, et. al
Fresolimumab (GC1008)	Genzyme	Anti-TGF-β	Phase 1	NCT00356460	
Vismodegib (Erivedge)	Genentech	Hh cell signaling pathway inhibition	Phase 1	NCT00968981	Jia G, et. al

PHASE 2 CLINICAL TRIALS IN IPF

PRM-151	Promedior/BMS	Rh-pentraxin-2 protein	Phase 2	NCT02550873	Raghu G, et. al
SAR-156597	Sanofi	Anti IL-3/4/13	Phase 2	NCT01529853/ NCT02345070	Ercole R, et. al
FG3019 (Pamrevlumab)	Fibrogen	Anti-CTGF	Phase 2	NCT01890265	Raghu G, et. al
STX-100/BG00011	Biogen	Anti-integrin avB6	Phase 2	NCT01371305	Raghy G, et. al
PBI-4050	Prometric	CTGF expression inhibitor	Phase 2	NCT02538536	Parker J, et. al
Carlumab (CNTO 888)	Centocor	CCL2 inhibitor	Phase 2	NCT00786201	Raghu, G, et. al
VAY736	Novartis	Anti- BlyS/BAFF-R	Phase 2	NCT03287414	Dorner T, et. al
Tralokinumab	MedImmune	Anti- IL-13	Phase 2	NCT01629667	Parker JM, et. al
Lebrikizumab	Genentech	Anti-IL-13	Phase 2	NCT01872689	J.J Swigris, et. al
QAX576	Novartis	Anti-IL-13	Phase 2	NCT00532233	
Zileuton (Zyflo)	Cornerstone Therapeutics	LT inhibition	Phase 2	NCT00262405	
Tipelukast/MN-001	Medici Nova	LT inhibition	Phase 2	NCT02503657	
TD-139	Galecto/BMS	Galectin-3 inhibition	Phase 2	NCT02257177	Hirani N, et. al
Simtuzumab (GS-6624)	Gilead Sciences	Anti-LOXL2	Phase 2	NCT01769196	Raghu G, et. al
GLPG1690	Galapagos	LPA1/autotaxin inhibitor	Phase 2	NCT02738801	Maher TM, et. al
KD025 (SLX-2119)	Kadmon	ROCK2 inhibitor	Phase 2	NCT02688647	Zanin-Zhorov A, et. al
Tanzisertib (CC-930)	Celgene	JNK 1/2 inhibitor	Phase 2	NCT01203943	Van der Velden JL, et. al
CC-9001	Celgene	JNK 1 Inhibitor	Phase 2	NCT03142191	Bennett B, et. al
Imatinib mesylate (Gleevec)	Novartis	Tyrosine kinase inhibitor	Phase 2	NCT00131274	Daniels CE, et. al
Rituximab (Rituxan)	Genentech	Anti- CD 20	Phase 2	NCT01266317	Donahoe M, et. al

Compound	Company	Structure/ route of admin	Stage of Development	Mechanism of Action	Background Therapy
PRM-151	Promedior/ BMS	mAb/IV	Phase II	Rh-pentraxin-2 protein	Pirfenidone or Nintedanib allowed
SAR-156597	Sanofi	mAb/SC	Phase II	Anti IL-4/IL-13	Pirfenidone or Nintedaib allowed
FG3019	Fibrogen	mAb/IV	Phase II	Anti-CTGF	Pirfenidone or Nintedanib allowed only in the sub study
STX-100/BG00011	Biogen	mAb/SC	Phase II	Anti-integrin avB6	Pirfenidone allowed
PBI-4050	Prometric	Sm/oral	Phase II	CTGF expression inhibitor	Pirfenidone or Nintedanib allowed
TD139	Galecto./BMS	Sm/Inhalation	Phase II	Galectin-3 inhibitor	Not allowed
MN-001/ Tipelukast	MediciNova	Sm/oral	Phase II	Leukotriene receptor antagonist	Nintedanib allowed
KD025	Kadmon	Sm/oral	Phase II	ROCK2 inhibitor	Not allowed
CC-90001	Calgene	Sm/oral	Phase II	JNK1 inhibitor	NA
GLPG-1690	Galapagos	Sm/oral	Phase II	Autotaxin inhibitor	NA

Cardinal Phase II Trials

- PBI-4050[1]
  - Phase II, open-label study showed PBI-4050 was well tolerated with a good safety profile
  - Potential drug–drug interactions with pirfenidone
- Simtuzumab[2]
  - Phase II trial showed no improvement in progression-free survival
- PRM-151[3]
  - Phase II trial to evaluate the efficacy of PRM-151

Promising Phase II studies

- Autotaxin inhibitor (GLPG1690)
- Recombinant human pentraxin 2 (PRM-151)
- Pamrevlumab (anti-CTGF)
- Anti-integrin-αvβ6 (BG00011; STX-100)
- PBI4050

Research

JAMA | Preliminary Communication

Effect of Recombinant Human Pentraxin 2 vs Placebo on Change in Forced Vital Capacity in Patients With Idiopathic Pulmonary Fibrosis
A Randomized Clinical Trial

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Editorial

Supplemental content

IMPORTANCE Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic lung disease with poor prognosis. Approved therapies do not halt disease progression.

OBJECTIVE To determine the effect of recombinant human pentraxin 2 vs placebo on change from baseline to week 28 in mean forced vital capacity (FVC) percentage of predicted value.

DESIGN, SETTING, AND PARTICIPANTS Phase 2, randomized, double-blind, placebo-controlled trial conducted at 18 sites in 7 countries of eligible patients with IPF (N = 117, aged 40-80 years, FVC ≥50% and ≤90% predicted, ratio of forced expiratory volume in the first second/FVC >0.70, diffusing capacity for carbon monoxide [Dlco] ≥25% and ≤90% predicted, and distance of ≥150 m on the 6-minute walk test). Study period was August 2015-May 2017.

INTERVENTIONS Patients were randomized to receive either recombinant human pentraxin 2 (10 mg/kg intravenous every 4 weeks, n = 77) or placebo (n = 39) for 24 weeks, and stratified by concurrent IPF treatment status.

MAIN OUTCOMES AND MEASURES The primary end point was the least-squares mean change in FVC percentage of predicted value from baseline to week 28 (minimal clinically important difference, decline of 2%-6%). Secondary end points included mean change in lung volumes (total, normal, and interstitial lung abnormalities) on high-resolution computed tomography (HRCT) and 6-minute walk distance (minimal clinically important difference, 24-45 m).

RESULTS Of 117 randomized patients, 116 received at least 1 dose of study drug (mean age, 68.6 years; 81.0% men; mean time since IPF diagnosis, 2.8 years), and 111 (95.7%) completed the study. The least-squares mean change in FVC percentage of predicted value from baseline to week 28 in patients treated with recombinant human pentraxin 2 was −2.5 vs −4.8 for those in the placebo group (difference, +2.3 [90% CI, 1.1 to 3.5], P = .001). No significant treatment differences were observed in total lung volume (difference, 93.5 mL [90% CI, −27.7 to 214.7]), quantitative parenchymal features on HRCT (normal lung volume difference, −1.2% [90% CI, −4.4 to 1.9]; interstitial lung abnormalities difference, 1% [90% CI, −2.2 to 4.3]), or measurement of Dlco (difference, −0.4 [90% CI, −2.6 to 1.7]). The change in 6-minute walk distance was −0.5 m for patients treated with recombinant human pentraxin 2 vs −31.8 m for those in the placebo group (difference, +31.3 m [90% CI, 17.4 to 45.1], P < .001). The most common adverse events in the recombinant human pentraxin 2 vs placebo group were cough (18% vs 5%), fatigue (17% vs 10%), and nasopharyngitis (16% vs 13%).

CONCLUSIONS AND RELEVANCE In this preliminary study, recombinant human pentraxin 2 vs placebo resulted in a slower decline in lung function over 28 weeks for patients with idiopathic pulmonary fibrosis. Further research should more fully assess efficacy and safety.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT02550873

JAMA. doi:10.1001/jama.2018.6129
Published online May 20, 2018.

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JAMA® Journal of the American Medical Association

Raghu G, van den Blink B, Hamblin MJ, et al.

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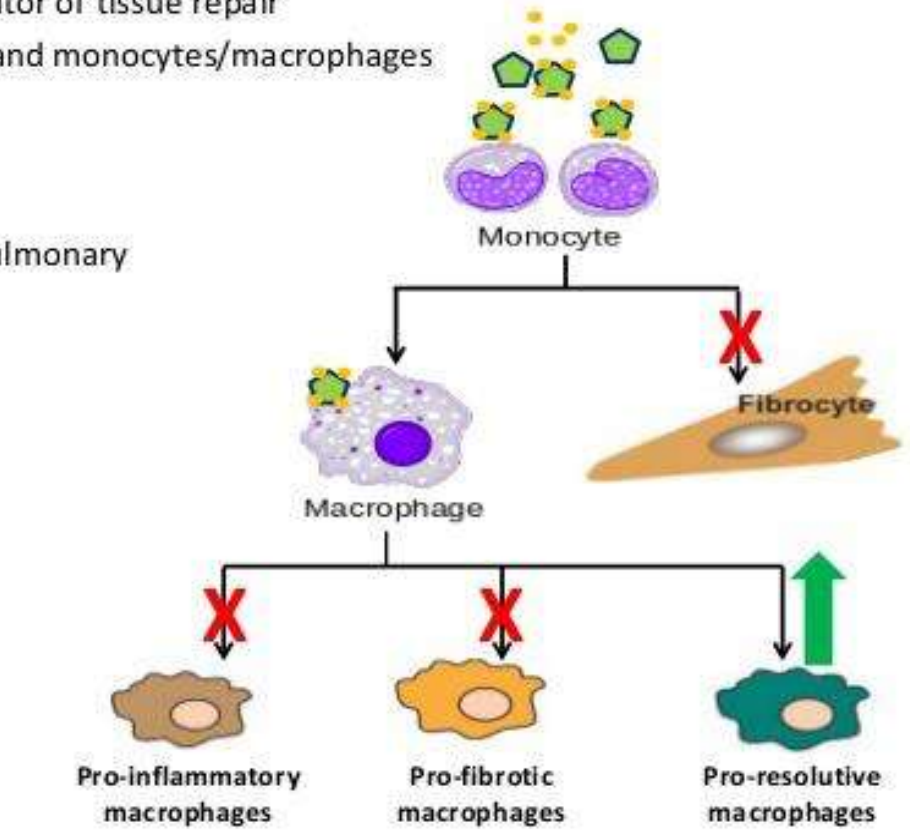
Published online May 20, 2018

Available at jama.com and on The JAMA Network Reader at mobile.jamanetwork.com

Recombinant human pentraxin 2 in IPF: effect on FVC

PRM-151: Recombinant Human Pentraxin-2 (PTX-2)

- PTX-2 ( ) is an endogenous regulator of tissue repair
- PTX-2 binds to damaged tissue ( ) and monocytes/macrophages
- PTX-2 prevents and reverses fibrosis in pre-clinical models
- PTX-2 levels are low in MF patients
  - Also low in patients with renal, pulmonary and liver fibrosis

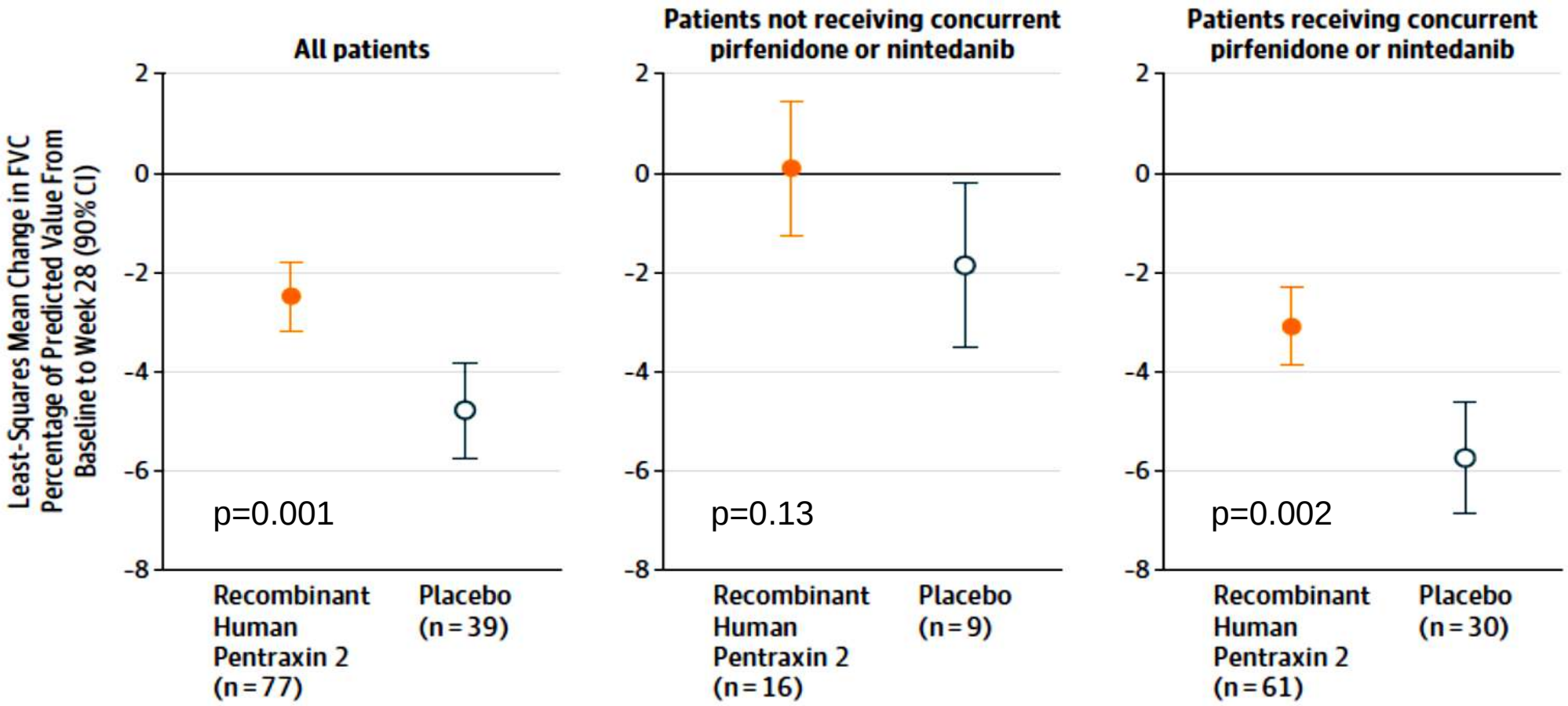


MF, myelofibrosis

Raghu G. et al. *JAMA.* 2018;319:2299–2307

Recombinant human pentraxin 2 in IPF: change in FVC (primary outcome)

Least-squares mean change in FVC percentage of predicted value from baseline to Week 28



CI, confidence interval

Raghu G. et al. *JAMA.* 2018;319:2299–2307

Conclusions

- A significant treatment effect for rhPTX-2 versus placebo was observed for change in FVC percentage of predicted value
- No appreciable decline from baseline to Week 28 in the LS mean 6-minute walk test was observed for rhPTX-2–treated patients
  - Placebo-treated patients had a mean decline of 32 m in the 6-minute walk test
  - This result is the first clinical trial over the last 25 years to show stabilization in the 6-minute walk test as a result of IPF treatment
- RhPTX-2 was well tolerated, with no notable difference in AE rate between treatment groups
- This study supports further evaluation of safety and efficacy of rhPTX-2 in patients with IPF

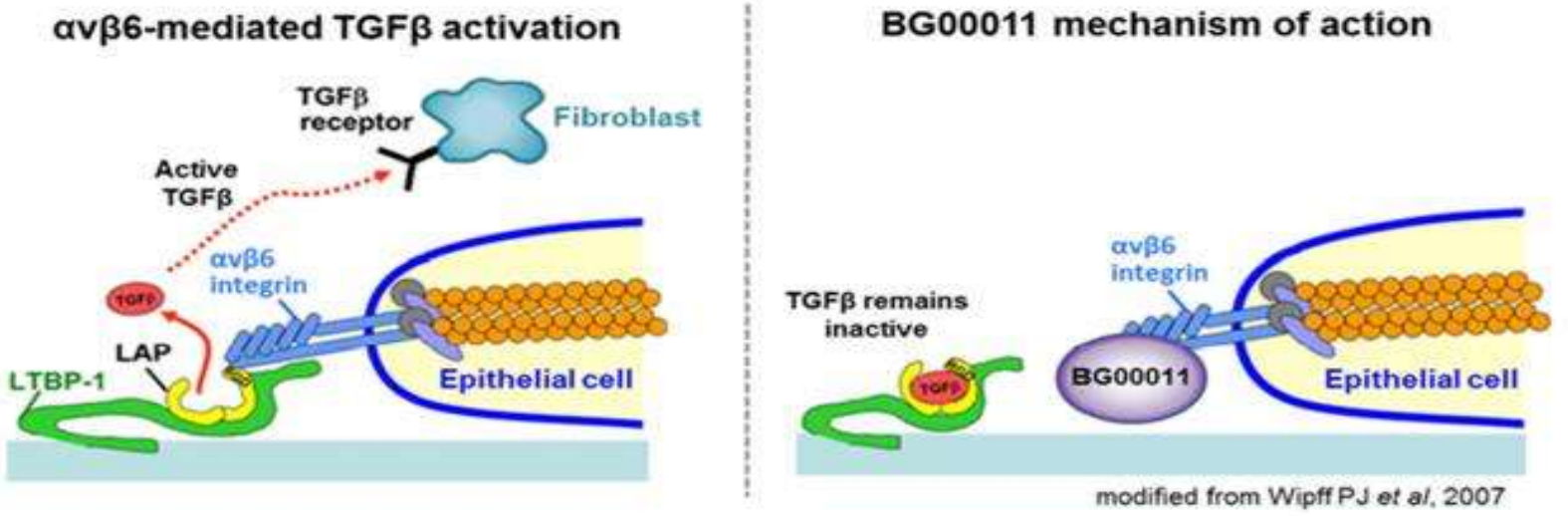
BIOGEN STUDY

- This Phase 2b study is designed to evaluate the treatment effect (change in Forced Vital Capacity (FVC) of BG00011 administered SC once weekly for 52 doses in subjects with mild to moderate IPF who may or may not be receiving protocol-defined background therapies (i.e., nintedanib or pirfenidone)

- In the previously completed, Phase 2a study (203PF201) in subjects with IPF, BG00011 demonstrated proof of biological activity by altering biomarkers in the lung. Therefore, the current study is being conducted to evaluate the clinical efficacy and safety of BG00011. The primary analysis will be conducted after 52 weeks of placebo-controlled treatment with BG00011

Biogen

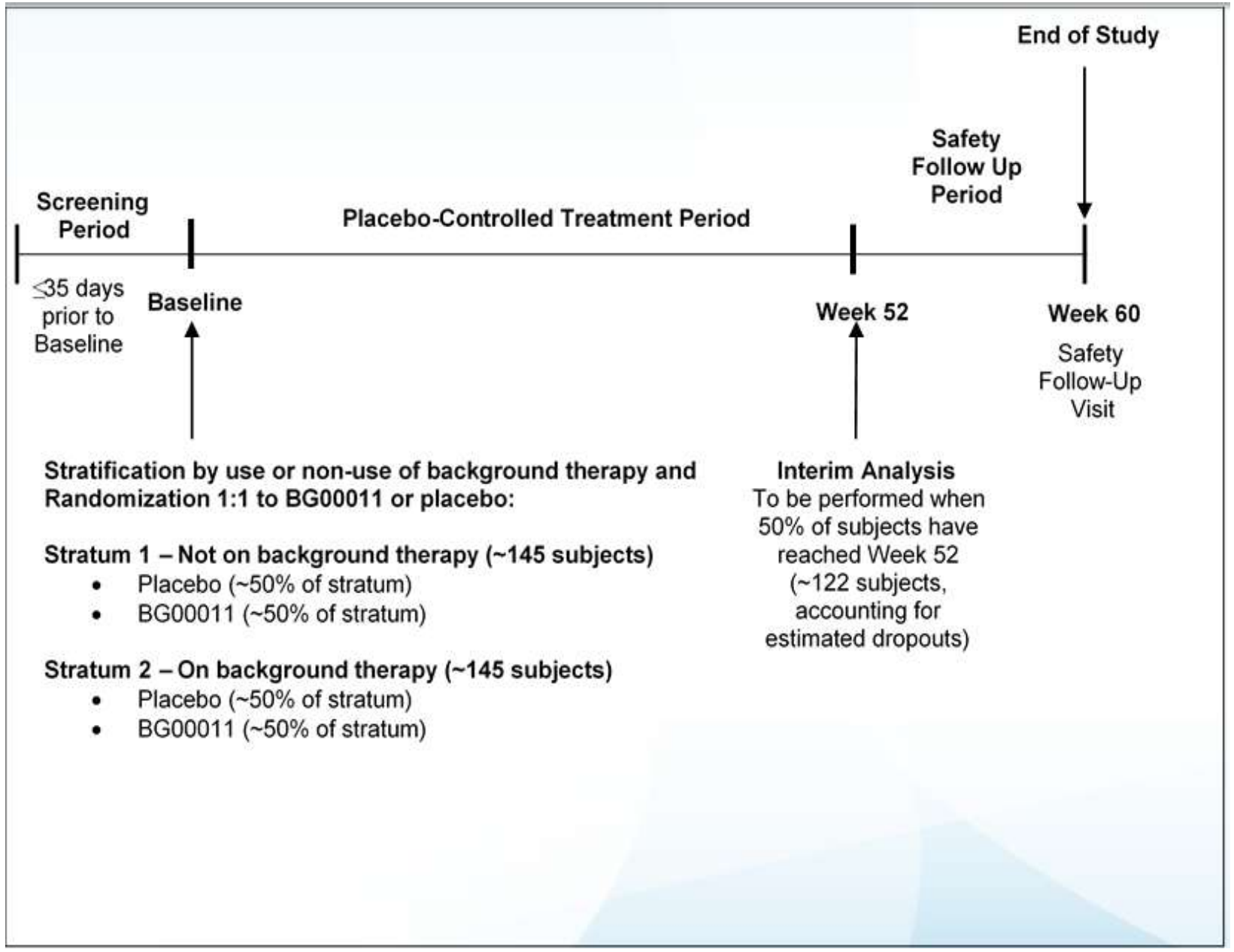
- Mechanisms: BG00011 is a mAb that binds to αvβ6 integrin and inhibits ligand binding. By blocking the binding of αvβ6 to latent TGF-β, BG00011 prevents αvβ6 -mediated TGF-β activation, thereby decreasing TGF-β signalling.
- Studies carried out in αvβ6 -deficient mice and with αvβ6 -blocking mAbs suggest that αvβ6 -mediated activation of TGF-β can prevent the development of fibrosis in the lung, kidney, and liver.



αvβ6 = alpha v beta 6; LAP = latency-associated peptide; LTBP-1 = latent transforming growth factor-beta binding protein-1; mAb = monoclonal antibody; RGD = arginine-glycine-aspartic acid; TGF-β = transforming growth factor-beta.

αvβ6 expression is up-regulated on epithelial cells during tissue injury and fibrosis. αvβ6 binds to an RGD motif in the LAP region of the latent TGF-β precursor protein leading to local activation of TGF-β. Anti-αvβ6 mAb interferes with this binding and blocks TGF-β activation [Weinreb 2004].

Study Design



Safety, tolerability, pharmacokinetics, and pharmacodynamics of GLPG1690, a novel autotaxin inhibitor, to treat idiopathic pulmonary fibrosis (FLORA): a phase 2a randomised placebo-controlled trial

Toby M Maher, Ellen M van der Aar, Olivier Van de Steen, Lisa Allamassey, Julie Desrivot, Sonia Dupont, Liesbeth Fagard, Paul Ford, Ann Fieuw, Wim Wuyts

Summary

Background Idiopathic pulmonary fibrosis (IPF) causes irreversible loss of lung function. People with IPF have increased concentrations of autotaxin in lung tissue and lysophosphatidic acid (LPA) in bronchoalveolar lavage fluid and exhaled condensate. GLPG1690 (Galapagos, Mechelen, Belgium) is a novel, potent, selective autotaxin inhibitor with good oral exposure. We explored the effects of GLPG1690 in patients with IPF.

Findings Between March 24, 2016, and May 2, 2017, 72 patients were screened., of whom 49 were ineligible and 23 were enrolled in eight centres (six in Ukraine and two in the UK). Six patients were assigned to receive placebo and 17 to receive GLPG1690. 20 patients completed the study after one in each group discontinued because of adverse events and one in the GLPG1690 group withdrew consent. Four (67%) patients in the placebo group and 11 (65%) in the GLPG1690 group had treatment-emergent adverse events, most of which were mild to moderate. The most frequent events in the GLPG1690 group were infections and infestations (ten events) and respiratory, thoracic, and mediastinal disorders (eight events) with no apparent differences from the placebo group. Two (12%) patients in the GLPG1690 group had events that were judged to be related to treatment. Serious adverse events were seen in two patients in the placebo group (one had a urinary tract infection, acute kidney injury, and lower respiratory tract infection and the other had atrioventricular block, second degree) and one in the GLPG1690 group (cholangiocarcinoma that resulted in discontinuation of treatment). No patients died. The pharmacokinetic and pharmacodynamic profiles of GLPG1690 were similar to those previously shown in healthy controls. LPA C18:2 concentrations in plasma were consistently decreased. Mean change from baseline in forced vital capacity at week 12 was 25 mL (95% CI –75 to 124) for GLPG1690 and –70 mL (–208 to 68 mL) for placebo.

Lancet Respir Med 2018

Published Online
May 20, 2018
http://dx.doi.org/10.1016/S2213-2600(18)30181-4

Added value of this study

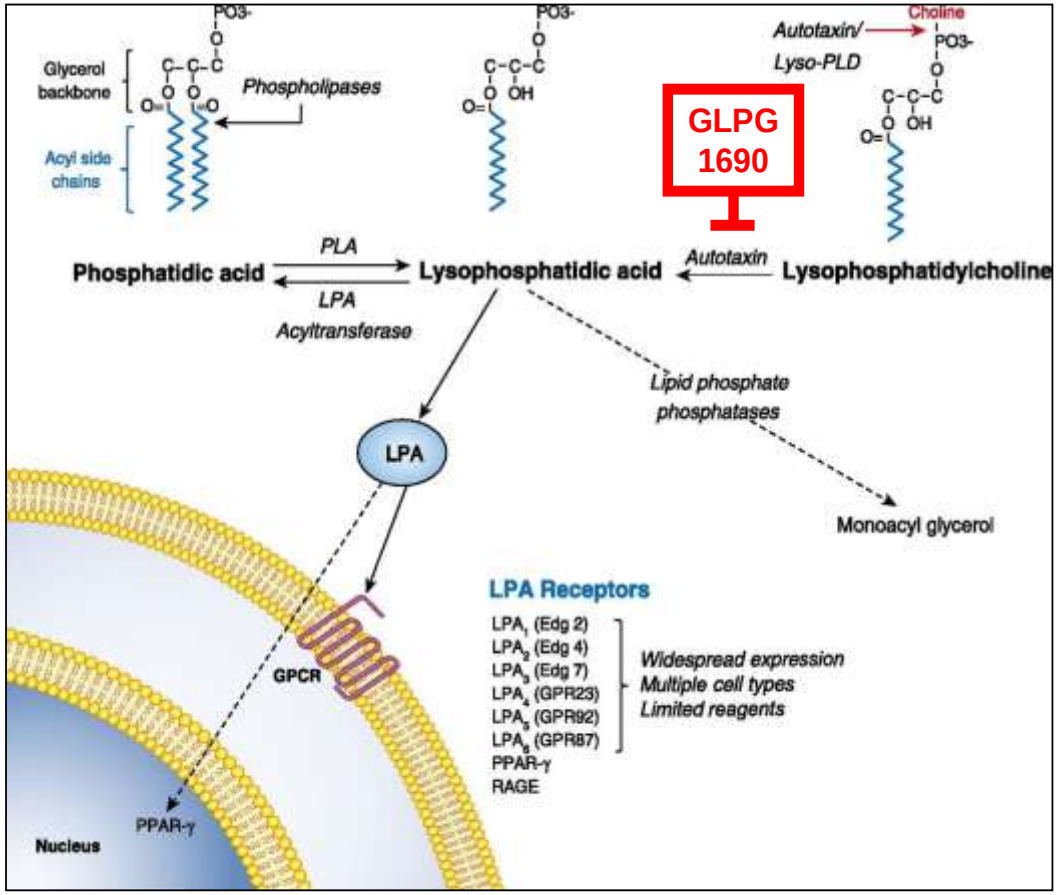
We believe this study to be unique among IPF clinical trials because it reports phase 2 results, including innovative endpoints, for a treatment with a novel mechanism of action in IPF. This small proof-of-concept study was intended to bridge the gap between the early pharmacokinetic and pharmacodynamic findings for GLPG1690 (Galapagos, Mechelen, Belgium) and assess its characteristics in people with IPF before moving to larger trials.

Implications of all the available evidence

Our results and the previous preclinical and phase 1 data support the further development of GLPG1690 for the treatment of patients with IPF. Longer-term data will provide further insights into the potential of GLPG1690 to address the unmet need in the treatment of IPF, including therapies with improved tolerability that are able to halt disease progression.

GLPG1690, a novel autotaxin inhibitor, to treat IPF: a Phase IIa study

Mechanism of action



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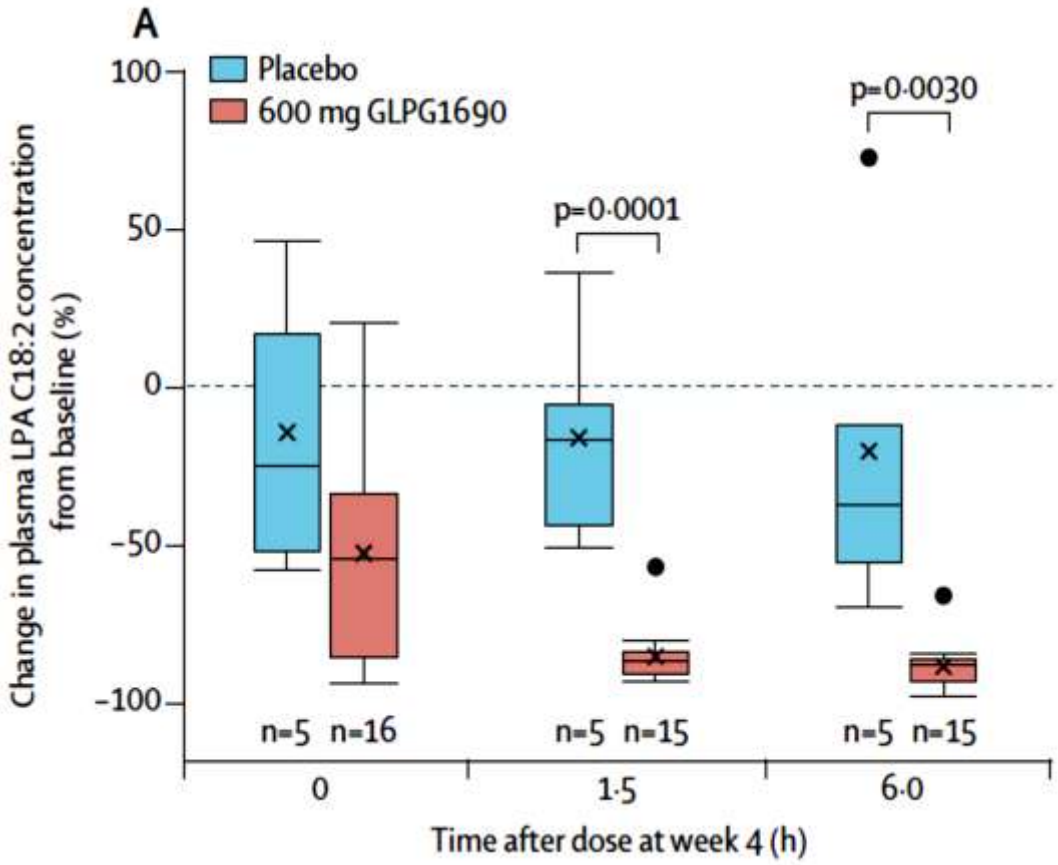
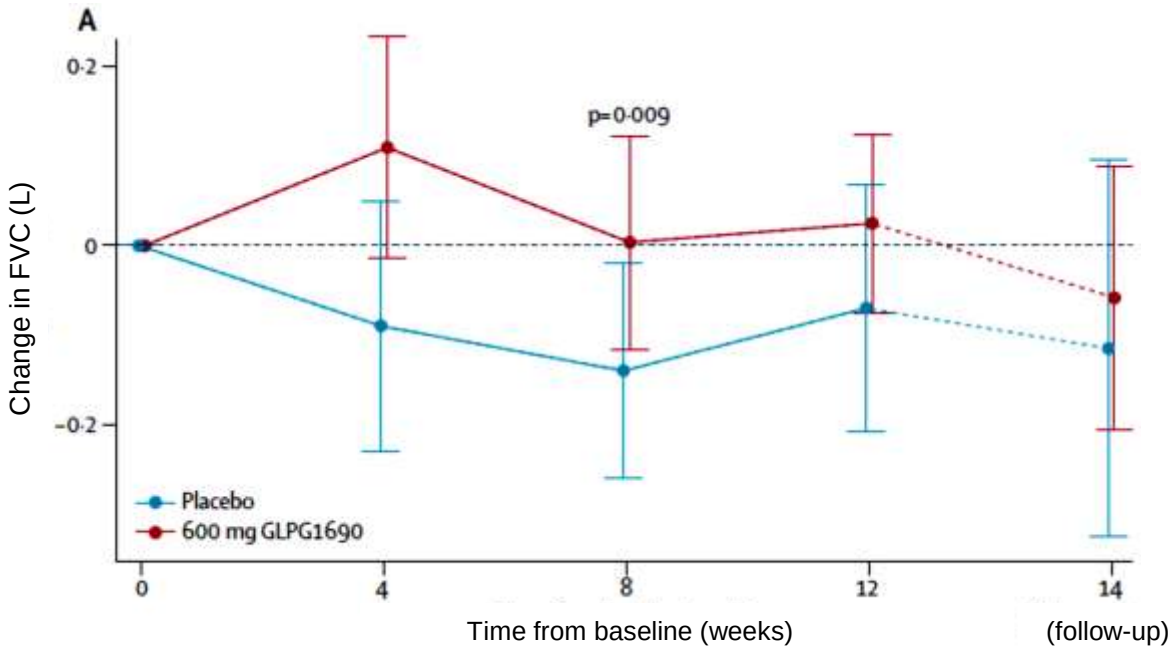


GPCR, G-protein-coupled receptor; LPA, lysophosphatidic acid; PLA, phospholipase A; PPAR, peroxisome proliferator activated receptor; RAGE, receptor for advanced glycation end products

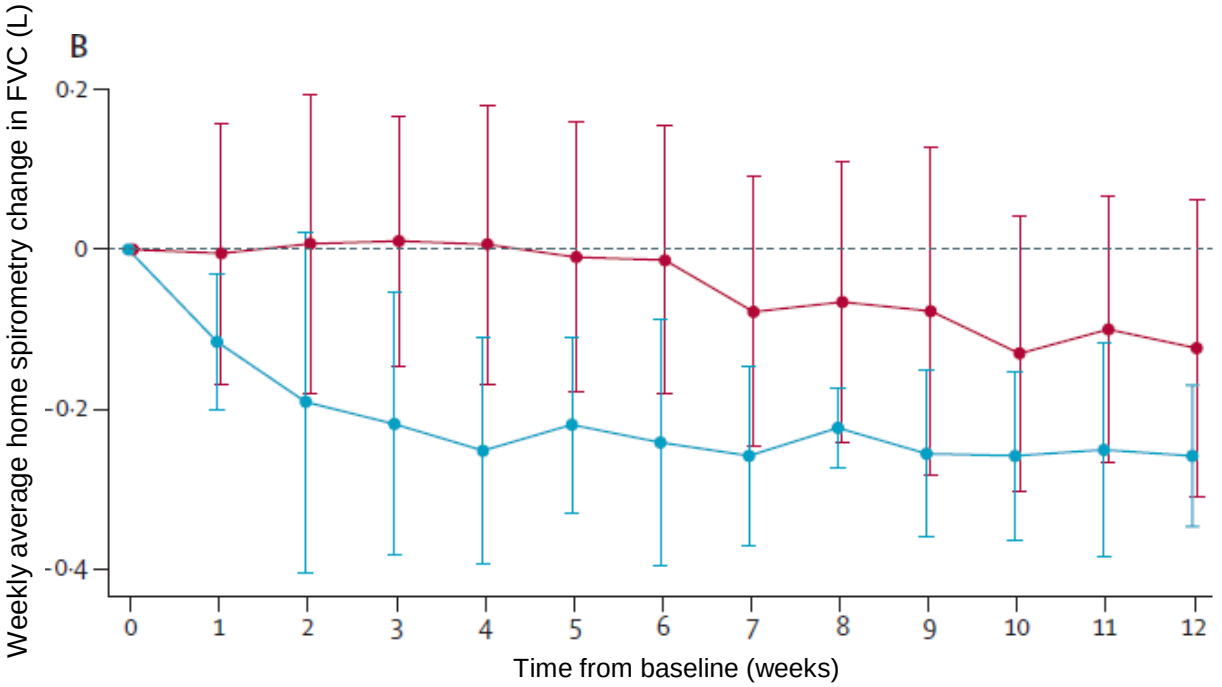
Knowlden S, et al. *J Immunol*. 2014;192:851–857;
Maher TM, et al. *Lancet Respir Med*. 2018;8:627–635

GLPG1690, a novel autotaxin inhibitor, to treat IPF: a Phase IIa study

Centre spirometry



Weekly home spirometry



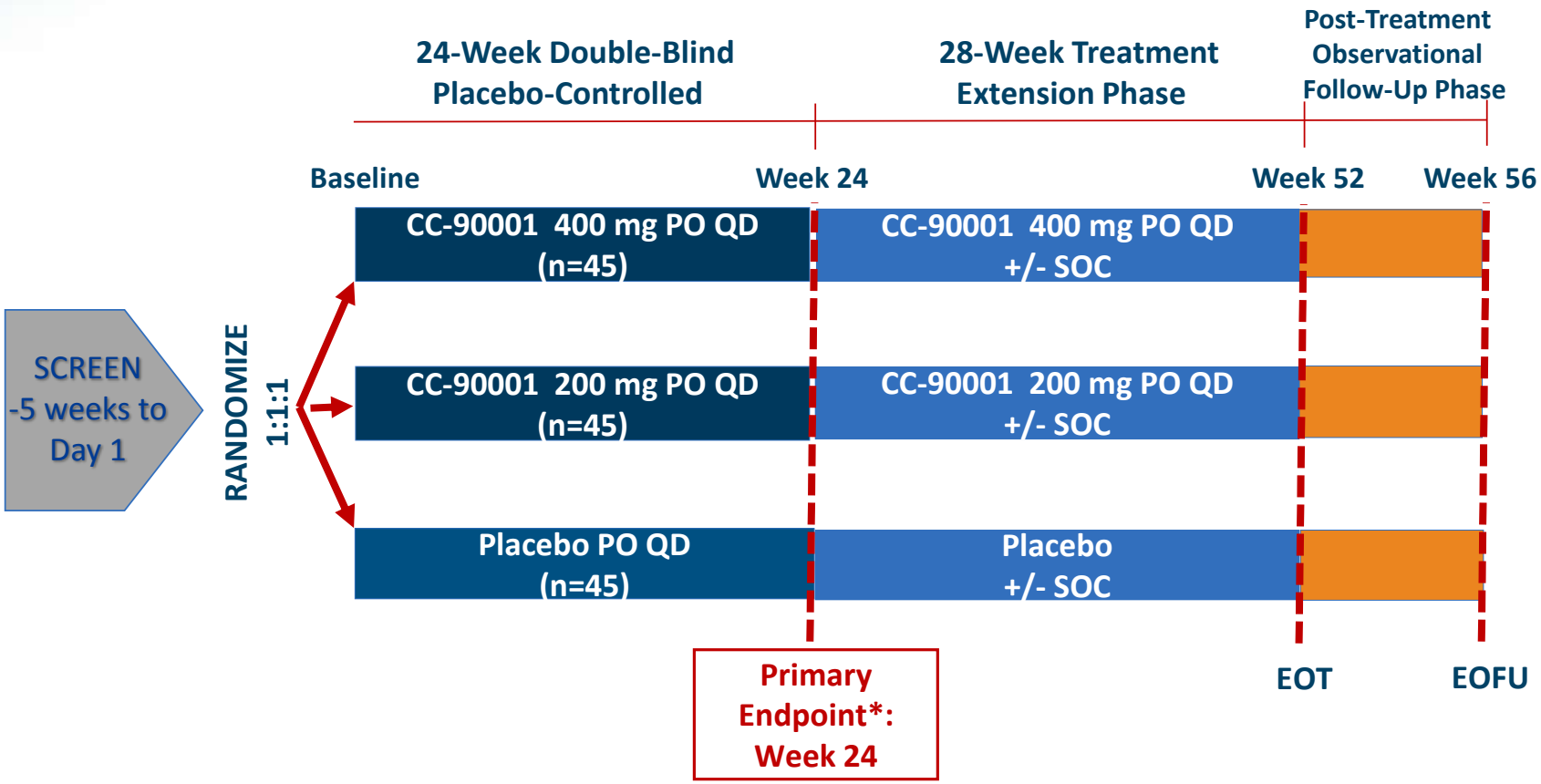
Maher TM, et al. *Lancet Respir Med*. 2018;8:627–635

Overview of JNK in IPF and CC-90001

- A kinase is an enzyme that catalyzes phosphorylation of its substrates.
- c-Jun N-terminal kinase (JNK), is a “stress-activated” kinase and is composed of 3 isoforms: JNK1, JNK 2, JNK3.
- JNK is rapidly activated in response to a variety of physical, chemical, and biological cellular stresses.[1]
- Activated JNK is detected in lungs of patients with IPF.[2]
- JNK is implicated in activation of the mitochondrial death pathway in epithelial cells[3] and collagen I production in fibroblasts[4]
- Inhibition or deletion of JNK, in particular JNK1, has been shown to be beneficial in animal models of fibrosis.[5,6]
- CC-90001 is a potent inhibitor JNK, with preferential selectivity towards JNK1.[7]

[1]Davis, Cell 2000;103:239; [2]Yoshida, J Pathol. 2002;198:388; [3]Lee, Am J Phyisol Lung Cell Mol Physiol 2005; 289:L521; [4]Lin 2013 Biochim Biophys Acta 2013; 1833:2823; [5]Kluwe, Gastroenterol. 2010;138:347; [6]Alcorn, Am J Respir Cell Mol. Biol. 2009; 40:422; [7]CC-90001 Investigator’s Brochure

Study Design



* Primary Endpoint: Percentage point change in % predicted FVC at week 24 compared to Baseline

Abbreviations: EOFU = end of follow-up; EOT = end of treatment; SOC = standard of care.

Curr Opin Pulm Med 2017,

Pitfalls in developing new compounds for idiopathic pulmonary fibrosis

Steven D. Nathan[a] *and Fernando J. Martinez*[b]

KEY POINTS

- There are many lessons about the natural history of IPF that have been gleaned from prior clinical trial programs that provide a foundation for future clinical trial designs.
- The key element to a successful clinical trial in IPF is identifying the appropriate patient phenotype and the structure of the primary endpoint.
- Future clinical trials are encouraged to adopt novel approaches to patient selection and phenotypes as well as the endpoint(s) employed.
- IPF appears to be a disease that is primed to benefit from a precision medicine approach, but more research and knowledge pertaining to biomarkers is required before such an approach can be realized.
- Future studies of broader groups of patients with pulmonary fibrosis are encouraged, as are studies of patients with more severe disease.


Apoptosis Resistance
Epigenetics
Genetic predisposition
MUC5B
Abnormal mitochondria
Aging/ Senescence
Telomere Shortening
SNPs (eg.TOLLIP)
Decreased Autophagy/ Mitophagy
HHV
Microbiome
Bacterial overgrowth
Opportunistic organism
Hypoxic vasoconstriction
Endothelial Dysfunction
Coagulation cascade activation
CTGF
Thrombin
Factor X
VEGF
Increased proteostasis
Inhalant (eg. tobacco smoke)
Idiopathic Pulmonary Fibrosis
PGE2
Inflammatory cascade activation
Fibroblast/ Myofibroblast
TNFα
FGF
Pulmonary Hypertension
Myofibroblast differentiation
TGFβ
Alveolar epithelial cell type 2
Epithelial Injury
Abnormal Repair
Collagen Deposition
Lung Cancer
Venous Thromboembolism
OSA/ Sleep Disorders
GERD

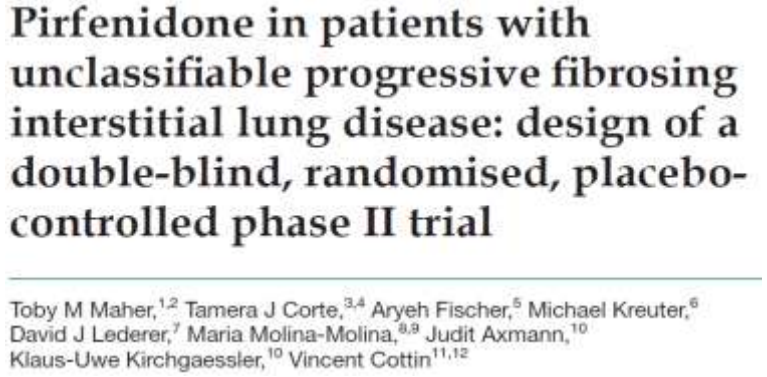
Current anti-fibrotic trials in grouped non-IPF disorders

Design of the PF-ILD trial: a double-blind, randomised, placebo-controlled phase III trial of nintedanib in patients with progressive fibrosing interstitial lung disease

Kevin R Flaherty,[1] Kevin K Brown,[2] Athol U Wells,[3] Emmanuelle Clerisme-Beaty,[4] Harold R Collard,[5] Vincent Cottin,[6] Anand Devaraj,[7] Yoshikazu Inoue,[8] Florence Le Maulf,[9] Luca Richeldi,[10] Hendrik Schmidt,[11] Simon Walsh,[12] William Mezzanotte,[4] Rozsa Schlenker-Herceg[13]

Exploring efficacy and safety of oral Pirfenidone for progressive, non-IPF lung fibrosis (RELIEF) - a randomized, double-blind, placebo-controlled, parallel group, multi-center, phase II trial

Jürgen Behr[1*], Petra Neuser[2], Antje Prasse[3], Michael Kreuter[4], Klaus Rabe[5], Carmen Schade-Brittinger[2], Jasmin Wagner[6] and Andreas Günther[6,7]



Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: design of a double-blind, randomised, placebo-controlled phase II trial

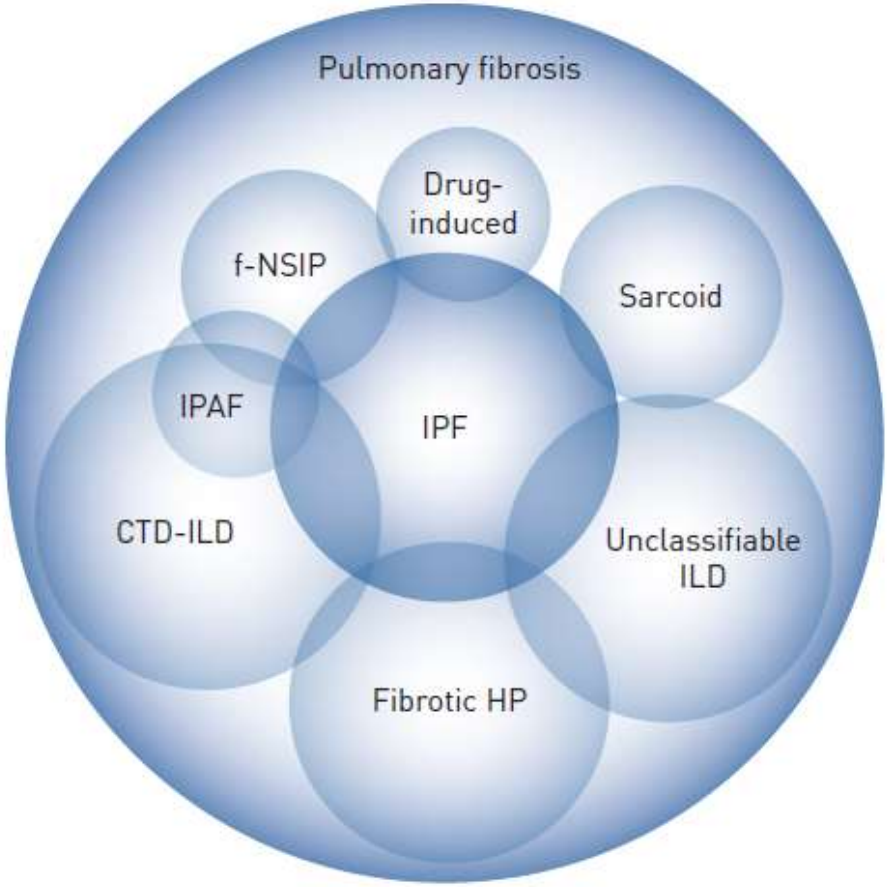
Toby M Maher,[1,2] Tamera J Corte,[3,4] Aryeh Fischer,[5] Michael Kreuter,[6] David J Lederer,[7] Maria Molina-Molina,[8,9] Judit Axmann,[10] Klaus-Uwe Kirchgaessler,[10] Vincent Cottin[11,12]

- IF THESE STUDIES ARE POSITIVE,
- WE WILL SEE THE DAWN OF CLASSIFICATION ACROSS ILD BY DISEASE BEHAVIOUR!

Flaherty KR, et al. *BMJ Open Respir Res*. 2017;4:e000212; Behr J, et al. *BMC Pulm M*ed. 2017;17:122;
Maher TM, et **al.** ***BMJ Open Respir Res*****. 2018;5:e000289**

“What’s in a name? That which we call IPF would behave the same with any other name.”

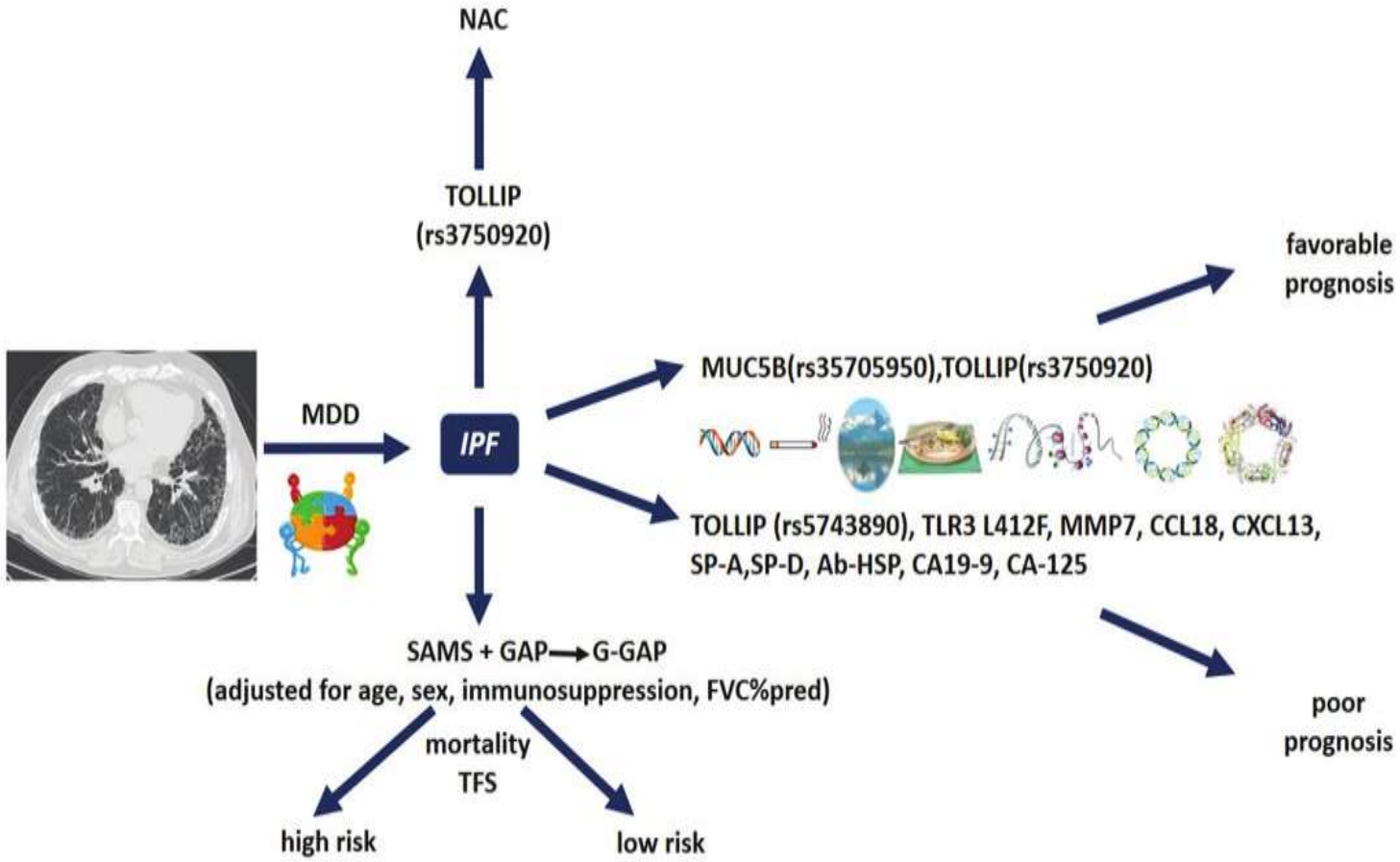
- “…it would be premature to propose an exact definition of the progressive fibrotic phenotype….Based on current knowledge…..it appears likely that a combination of HRCT features indicative of likely UIP, histologic features and emerging molecular data might eventually provide a baseline definition. At present, ***the progressive fibrotic phenotype can be designated only by observed disease progression, despite treatment*** considered to be appropriate in individual ILDs”



F-NSIP, fibrotic nonspecific interstitial pneumonia; HP, hypersensitivity pneumonitis

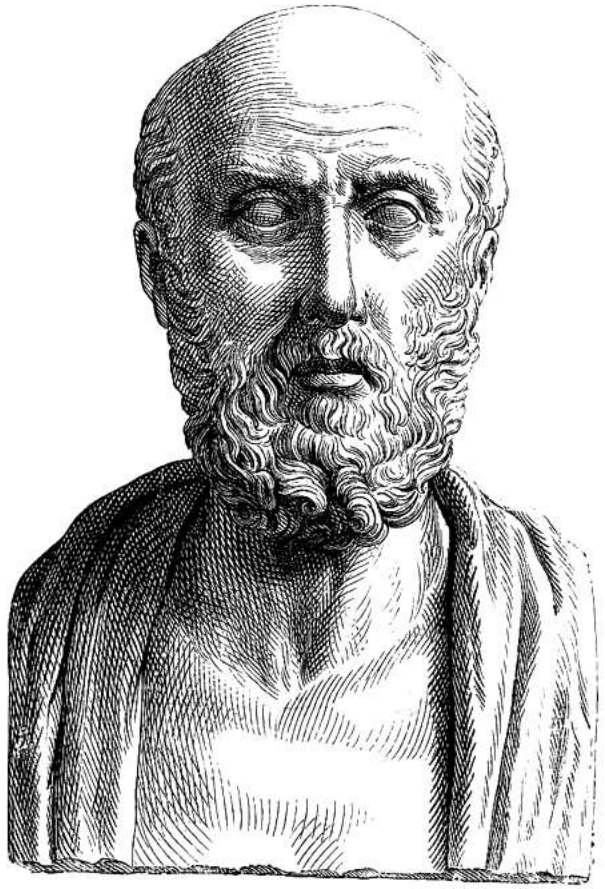
Wells AU, et al. *Eur Respir J*. 2018;6:154-60

Towards personalized therapy in IPF



Fingerlin TE, et al. *Nat Genet*. 2013;45:613-20; ,Herazo-Maya JD, et al. *Lancet Respir Med*. 2017;5:857-868; Karampitsakos T, et al. *Pneumon*. 2018;31:71-80

Splitting IPF & personalized medicine



"It's far more important to know what person the disease has than what disease the person has"

Give different ones [therapeutic drinks] to different patients, for the sweet ones do not benefit everyone, nor do the astringent ones, nor are all patients able to drink the same things
Hippocrates

IPF today

The future: Targeted therapy