New Therapies for fibrotic ILD

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Financial Disclosure Information

Relationship	Commercial Interest for past three years
Advisory Committee/ Consultant	Abvie, Boehringer Ingelheim, Bristol Myers Squibb, DevPro, Excalibur, Hoffman-LaRoche, IQVIA, Lung Therapeutics, Novartis, Sanofi, Shionogi, twoXR, Veracyte
Study support/Steering Committees	Bayer, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, DevPro, Nitto, Novartis, Patara/Respivant, ProMedior/Roche
DSMB/Adjudication Committee	Biogen, Boehringer Ingelheim
CME programs	Academy for Continuing Healthcare Learning, Boehringer Ingelheim, France Foundation, Paradigm, Peer View, United Therapeutics, UpToDate, Vindico

Short time for a huge topic so…

- IPF
  - Numerous studies ongoing
  - Recent Phase III studies terminated
  - Phase III study coming shortly
  - Phase III studies launching
  - Novel study designs in process
- PPF
  - Recent recommendations regarding anti-fibrotic therapy
  - Phase III study(ies) coming

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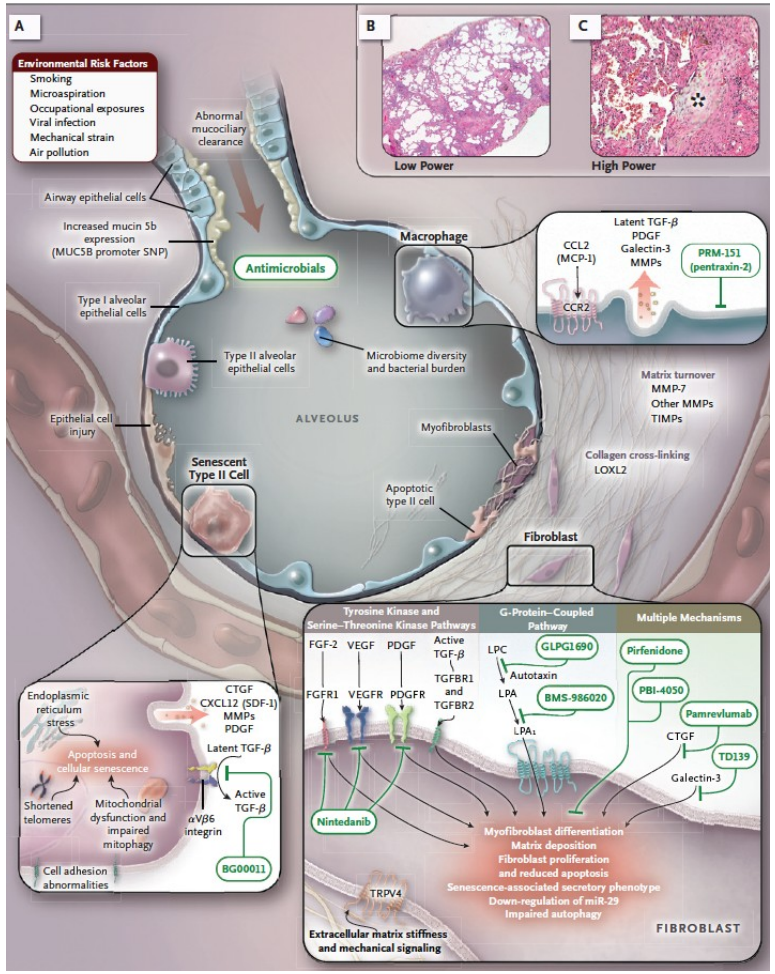
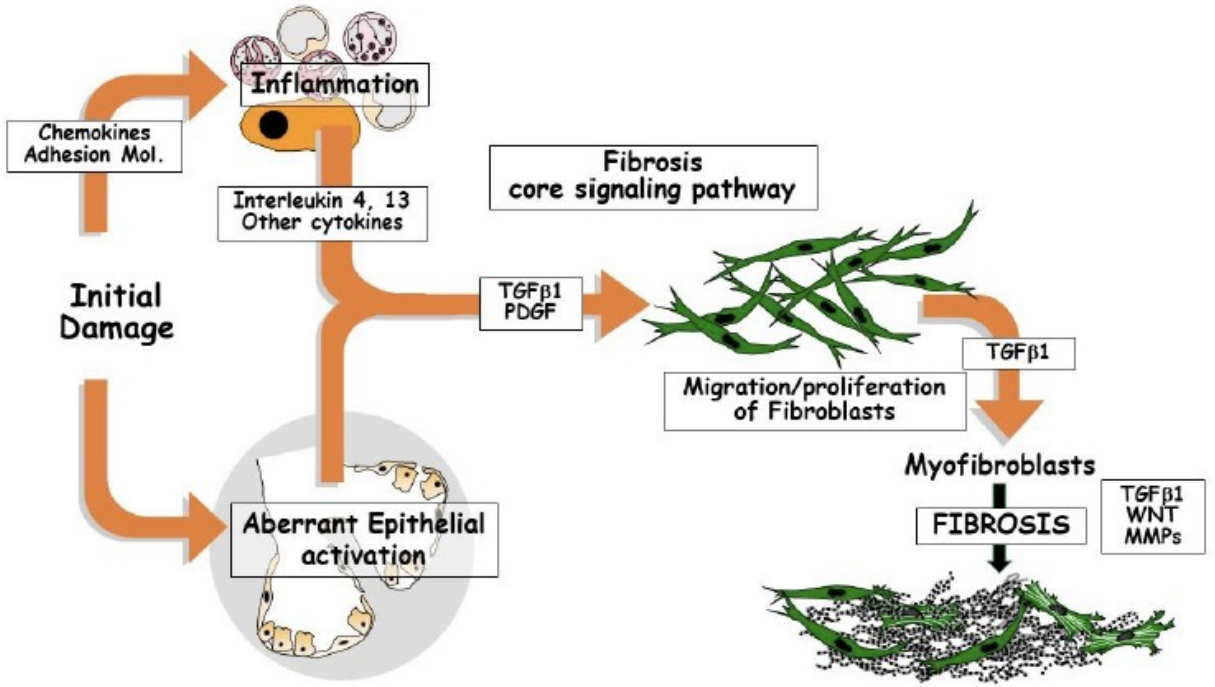
Numerous potential therapeutic targets for IPF and PPF

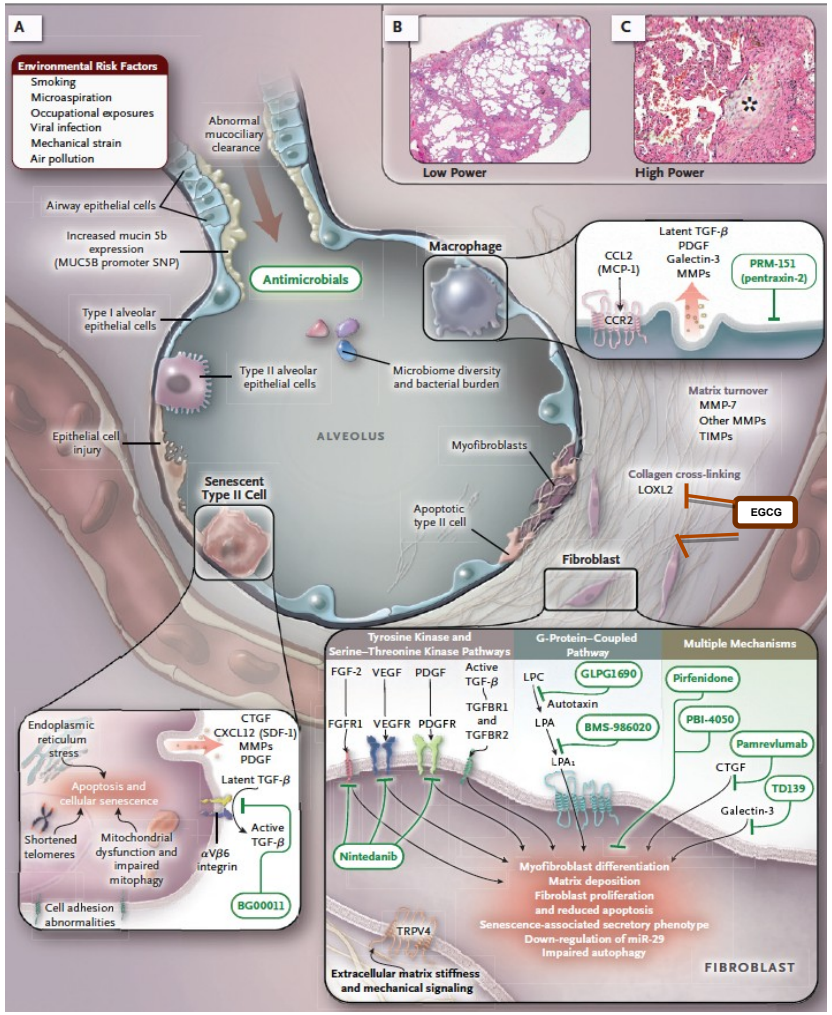


Lederer DJ, Martinez FJ. *N Engl J Med*. 2018;378:1811-1823



Selman M & Pardo A
Eur Respir J 2021; 58(3): 2004507

IPF therapeutic options are rapidly increasing



Lederer DJ, Martinez FJ. *N Engl J Med*. 2018;378:1811-1823

Evaluation of Efficacy and Safety of Pamrevlumab in Patients With Idiopathic Pulmonary Fibrosis

Inhaled Nitric Oxide (iNO) in Idiopathic Pulmonary Fibrosis (IPF).

Zephyrus II: Efficacy and Safety Study of Pamrevlumab in Participants With Idiopathic Pulmonary Fibrosis (IPF)

Treating People With Idiopathic Pulmonary Fibrosis With the Addition of Lansoprazole (TIPAL)

Autoantibody Reduction for Acute Exacerbations of Idiopathic Pulmonary Fibrosis (STRIVE-IPF)

LYT-100 in Patients With Idiopathic Pulmonary Fibrosis (IPF) (ELEVATE)

Saracatinib in the Treatment of Idiopathic Pulmonary Fibrosis (STOP-IPF)

A Study Evaluating the Safety and Efficacy of ENV-101 in Subjects With Idiopathic Pulmonary Fibrosis (IPF)

A Multicenter Trial to Evaluate the Efficacy, Safety and Tolerability of HZN-825 in Subjects With Idiopathic Pulmonary Fibrosis

Evaluation of Oral ORIN1001 in Subjects With Idiopathic Pulmonary Fibrosis (IPF)

Jaktinib Dihydrochloride Monohydrate in Idiopathic Pulmonary Fibrosis

Human Autologous Lung Stem Cell Transplant for Idiopathic Pulmonary Fibrosis (HALT-IPF)

A Study to Evaluate the Efficacy and Safety of Recombinant Human Pentraxin-2 (rhPTX-2; PRM-151) in Participants With Idiopathic Pulmonary Fibrosis (STARSCAPE)

GKT137831 in IPF Patients With Idiopathic Pulmonary Fibrosis (GKT137831)

Tolerability, Pharmacokinetics and Efficacy of ZSP1603 in Patients With Idiopathic Pulmonary Fibrosis （IPF）

Safety, Efficacy and Pharmacokinetics of C21 in Subjects With IPF

Safety of Cultured Allogeneic Adult Umbilical Cord Derived Mesenchymal Stem Cell Intravenous Infusion for IPF

Efficacy and Safety Study of Orvepitant for Chronic Cough in Patients With Idiopathic Pulmonary Fibrosis (IPF-COMFORT)

Study of Efficacy and Safety of Inhaled Treprostinil in Subjects With Idiopathic Pulmonary Fibrosis (TETON)

Clinical Efficacy and Safety of Autologous Lung Stem Cell Transplantation in Patients With Idiopathic Pulmonary Fibrosis

Phase II Study of HEC585 in Patients With IPF

Morphine Sulfate/Placebo for the Treatment of PulmonAry Fibrosis Cough (PAciFy Cough)

A Study Measuring the Effectiveness, Safety, and Tolerability of BMS-986278 in Participants With Lung Fibrosis

ClinicalTrials.gov Identifier: NCT04308681

Recruitment Status : Recruiting
First Posted : March 16, 2020
Last Update Posted : August 15, 2022

See Contacts and Locations

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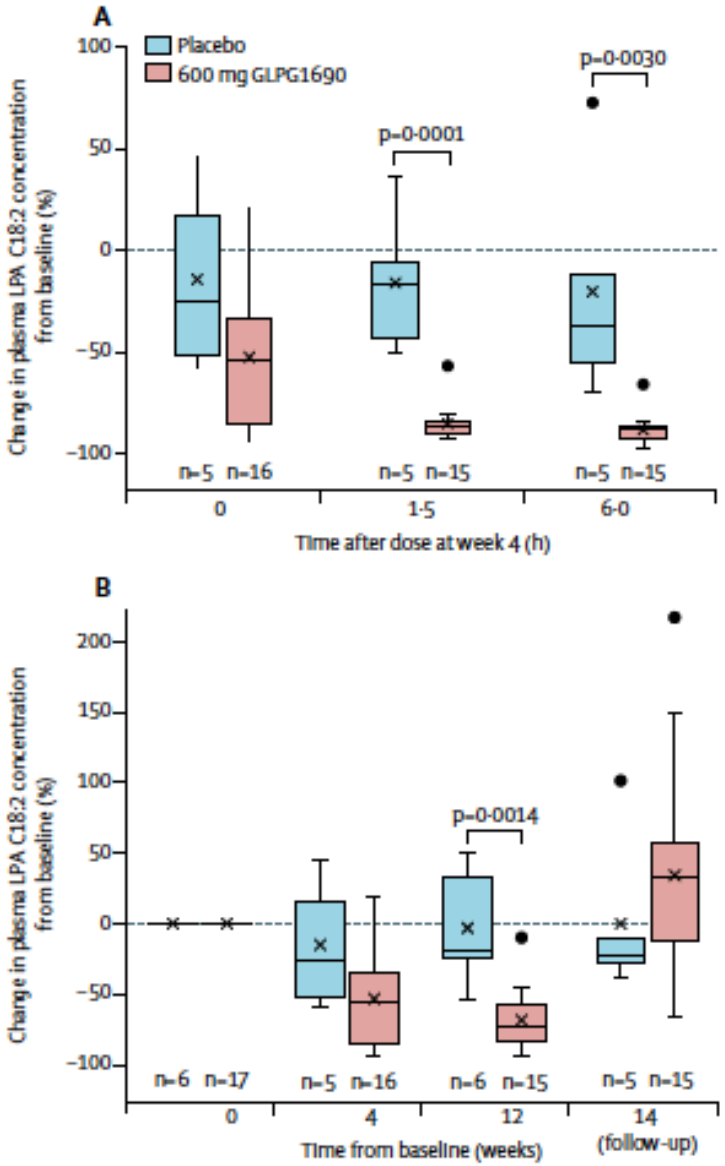
Phase 2a Trial of a novel autotaxin inhibitor



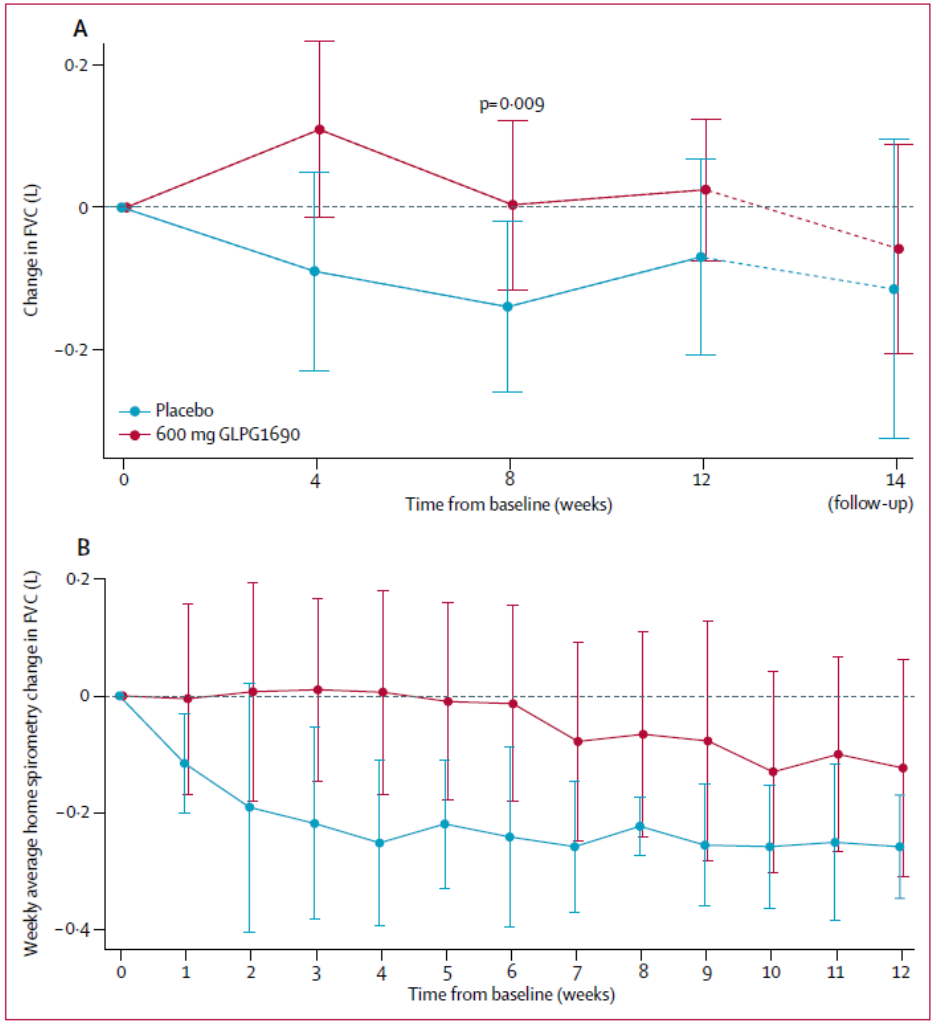
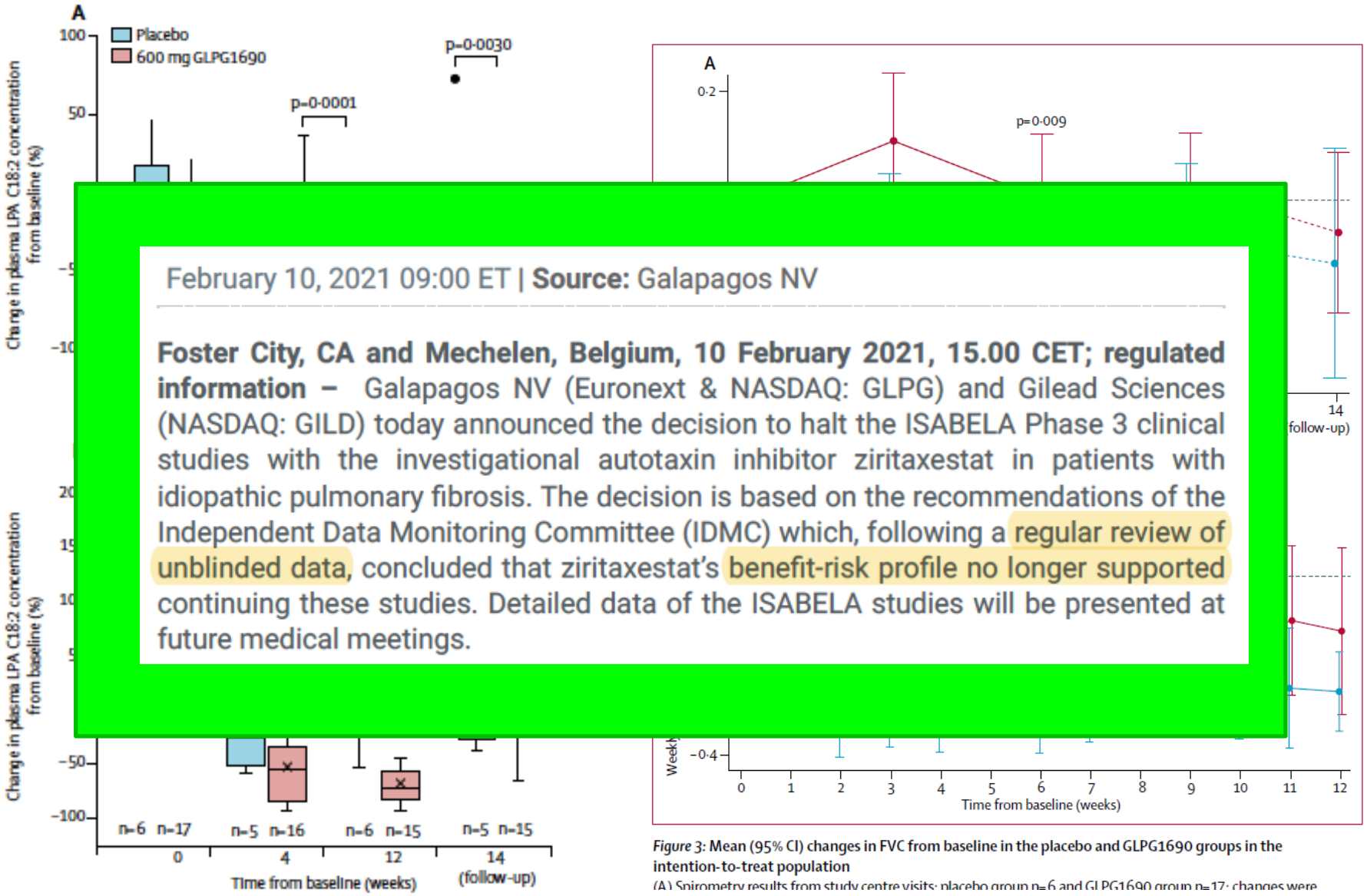


Figure 3: Mean (95% CI) changes in FVC from baseline in the placebo and GLPG1690 groups in the intention-to-treat population

(A) Spirometry results from study centre visits: placebo group n=6 and GLPG1690 group n=17; changes were

Maher TM et al. *Lancet Respir Med* 2018; 6: 627-35

Phase 2a Trial of a novel autotaxin inhibitor



February 10, 2021 09:00 ET | **Source:** Galapagos NV

Foster City, CA and Mechelen, Belgium, 10 February 2021, 15.00 CET; regulated information – Galapagos NV (Euronext & NASDAQ: GLPG) and Gilead Sciences (NASDAQ: GILD) today announced the decision to halt the ISABELA Phase 3 clinical studies with the investigational autotaxin inhibitor ziritaxestat in patients with idiopathic pulmonary fibrosis. The decision is based on the recommendations of the Independent Data Monitoring Committee (IDMC) which, following a regular review of unblinded data, concluded that ziritaxestat's benefit-risk profile no longer supported continuing these studies. Detailed data of the ISABELA studies will be presented at future medical meetings.

Figure 3: Mean (95% CI) changes in FVC from baseline in the placebo and GLPG1690 groups in the intention-to-treat population

(A) Spirometry results from study centre visits: placebo group n=6 and GLPG1690 group n=17; changes were

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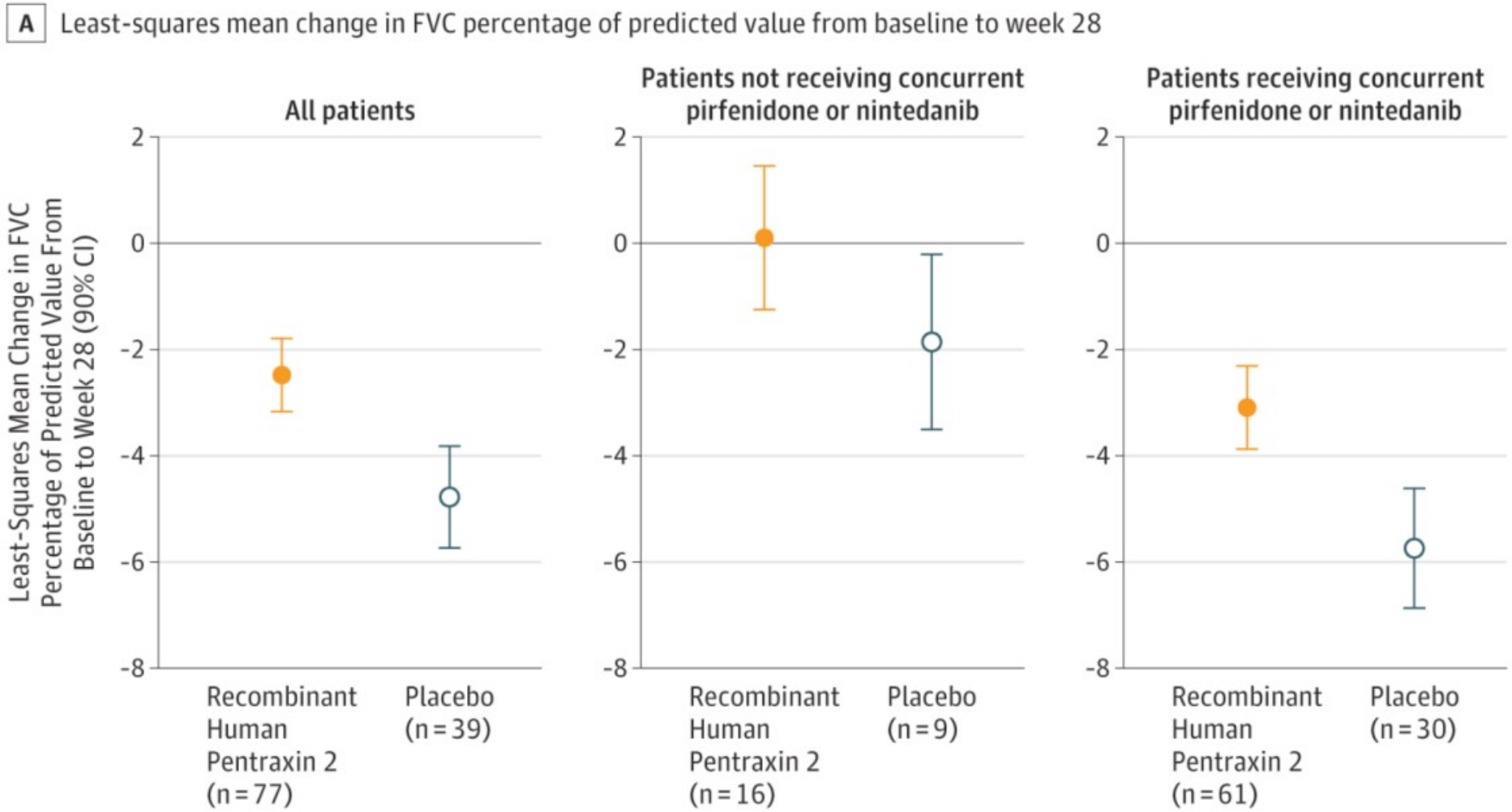
Pentraxin 2 efficacy in IPF as a function of concomitant antifibrotic therapy



Raghu G et al; JAMA 2018; 319: 2299-307

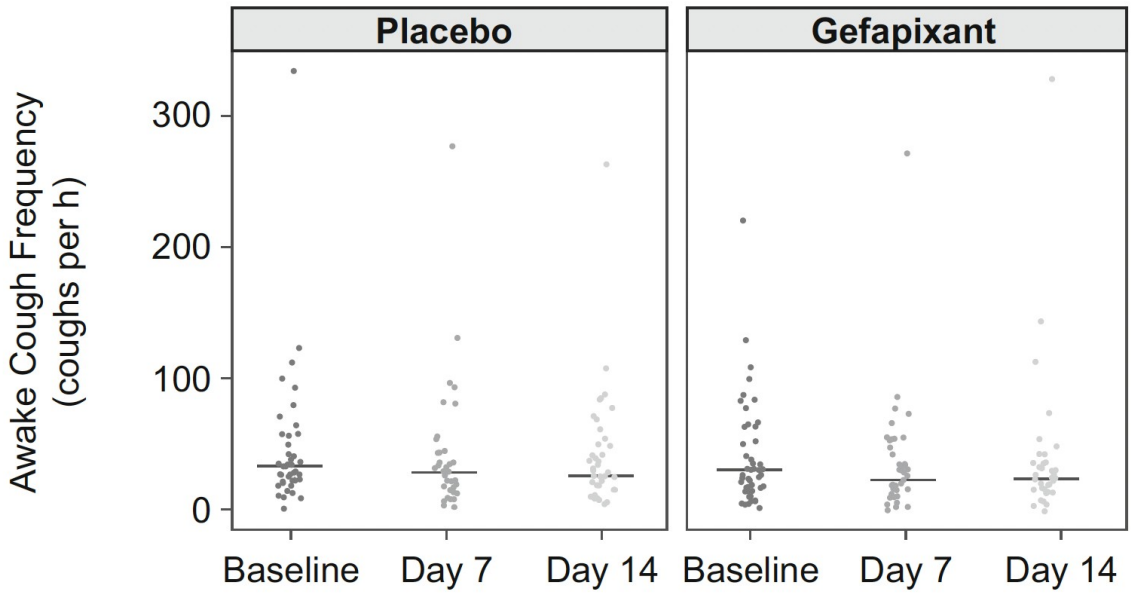
Pentraxin 2 efficacy in IPF as a function of concomitant antifibrotic therapy

Clinical success in idiopathic pulmonary fibrosis (IPF) has been elusive, and Roche's zinpentraxin alfa is the latest to fall by the wayside. The company today said it had discontinued the asset in IPF after the pivotal Starscape trial was stopped for futility, incurring a $400m write-off against the asset's acquired value. The next big hope in the disease is Fibrogen's pamrevlumab, with the first late-stage data due this year. Since the last time *Evaluate Vantage* carried out this analysis, Boehringer has taken BI 1015550 into phase 3 following promising mid-stage data, while Pliant posted a phase 2a win; both projects have been linked with improvements in forced vital capacity, a measure of lung function. Roche did not show an increase in FVC in its phase 2 trial of zinpentraxin, but merely demonstrated slightly less decline than with placebo. The phase 2 study of pamrevlumab tells a similar story, which might not bode well for Fibrogen. Still, plenty of others are vying for this space, with a crowded mid-stage pipeline. Recent entrants include autotaxin inhibitors from Blade and Bridge Biotherapeutics, cudetaxestat and BBT-877 respectively; Boehringer returned rights to the latter amid toxicity concerns, however.

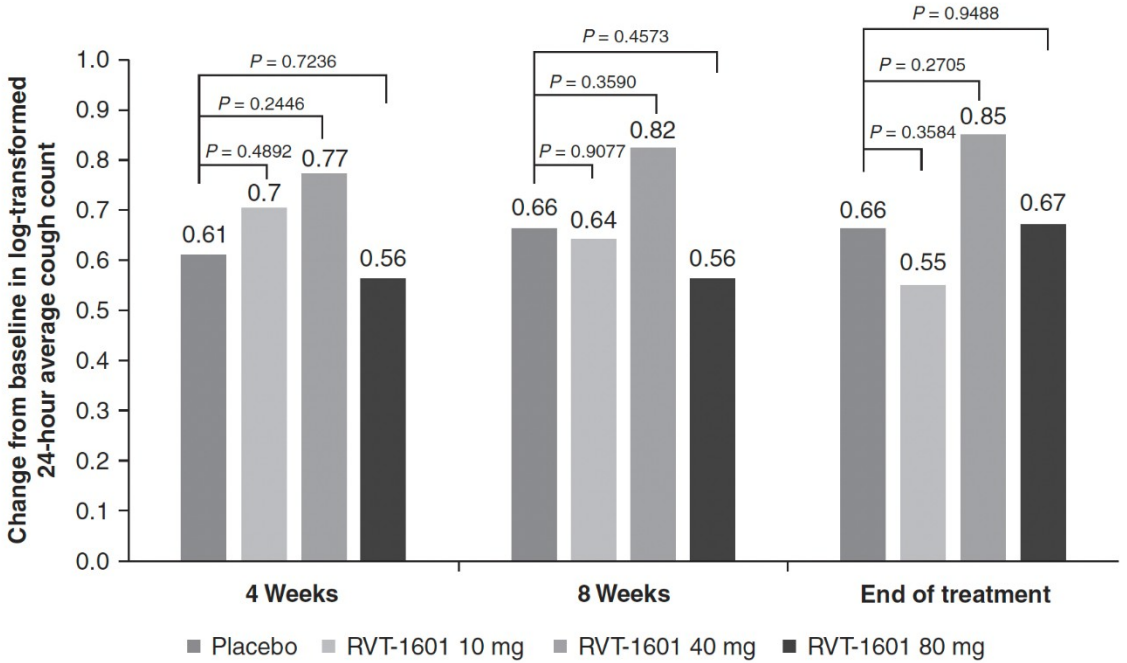
https://www.evaluate.com/vantage/articles/news/snippets/roche-adds-lung-fibrosis-disappointment

Raghu G et al; JAMA 2018; 319: 2299-307

Cough as a therapeutic target



Martinez FJ et al Pulm Ther; 2021; 7: 471-86



Martinez FJ et al AJRCCM; 2022; 205: 1084-92

	Azithromycin ($n = 15$)			Placebo ($n = 12$)			Between-Period Difference in Change*	
	Before	After	*P* Value	Before	After	*P* Value	Mean Difference (95% CI)	*P* Value
Cough Index, /h								
Total	4.5 (3.4–5.9)	3.7 (2.8–4.3)	0.73	5.7 (2.7–9.7)	4.1 (2.4–7.4)	0.04	−3.9 (−10.2 to 2.3)	0.19
Wake	6.2 (4.4–8.2)	6.0 (4.7–9.5)	0.62	7.4 (3.5–13.7)	6.1 (2.6–11)	0.20	−7.0 (−16.4 to 2.4	0.13
Sleep	0.6 (0.1–1.1)	0.8 (0.2–1.3)	0.58	1.0 (0.5–2.1)	0.5 (0.2–0.7)	0.04	−2.9 (−7.5 to 1.6)	0.17
Cough Attack Index, /h								
Total	0.7 (0.5–0.9)	0.8 (0.2–1.3)	0.48	1.2 (0.5–1.8)	0.7 (0.1–1.0)	0.12	−0.35 (−1.1 to 0.4)	0.29
Wake	0.9 (0.7–1.3)	1.1 (0.2–1.0)	0.81	1.5 (0.6–2.5)	0.8 (0.2–1.2)	0.15	−0.8 (−1.9 to 0.4)	0.16
Sleep	0.1 (0–0.4)	0.2 (0–0.5)	0.92	0.4 (0.2–0.6)	0.1 (0–0.35)	0.04	−0.4 (−0.6 to −0.1)	0.02

Guler SA et al *AATS*; 2021 18: 2018-26

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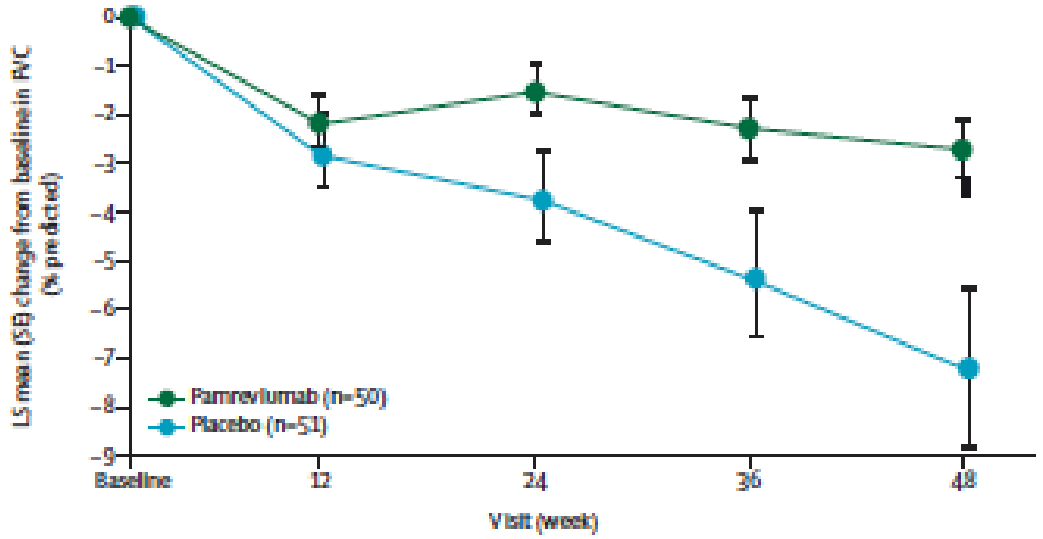
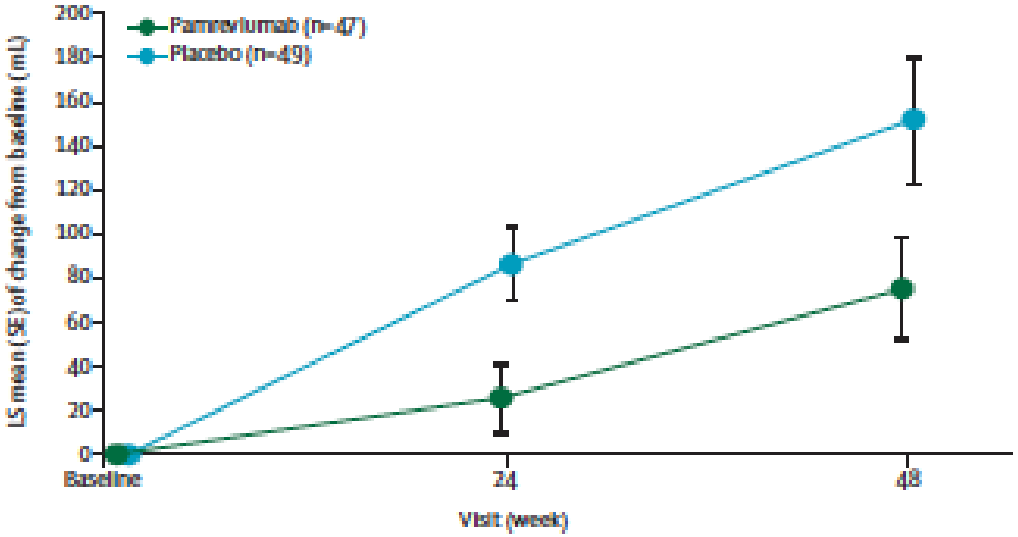
Pamrevlumab program expects results later this year



Pamrevlumab	−2·2 (0·6)	−1·5 (0·5)	−2·3 (0·7)	−2·7 (0·6)
Placebo	−2·8 (0·8)	−3·8 (0·9)	−5·3 (1·3)	−7·2 (1·7)
Absolute difference	0·6 (0·9)	2·3 (1·1)	3·0 (1·5)	4·5 (1·8)
95% CI	(−1·3 to 2·5)	(0·1 to 4·4)	(0·1 to 6·0)	(0·9 to 8·0)
Relative difference	22·2%	59·8%	57·0%	62·4%
p value	0·51	0·042	0·044	0·014



Pamrevlumab	24·8 (16·0)	75·4 (23·2)
Placebo	86·4 (17·3)	151·5 (29·3)
Absolute difference	−61·6 (23·6)	−76·2 (36·7)
95% CI	(−107·8 to −15·4)	(−148·2 to −4·2)
Relative difference	−71·3%	−50·3%
p value	0·009	0·038

Richeldi L et al. *LRM.* 2020; 8: 25-33.

Pamrevlumab program expects results later this year

The late-stage IPF pipeline			
Project	**Company**	**Mechanism**	**Trial details**
Zinpentraxin alfa (RG6354/ PRM-151)	Roche (ex Promedior)	Recombinant human serum amyloid P	Starscape stopped for futility Q4 2022
Pamrevlumab	Fibrogen	Anti-CTGF antibody	Zephyrus-1 data due mid-2023; Zephyrus-2 data due mid-2024
BI 1015550	Boehringer Ingelheim	Phosphodiesterase 4 inhibitor	NCT05321069 ends Nov 2024
Tyvaso	United Therapeutics	Prostacyclin mimetic	Teton & Teton 2 end Jun 2025
Source: Evaluate Pharma & clinicaltrials.gov.			

https://www.evaluate.com/vantage/articles/news/snippets/roche-adds-lung-fibrosis-disappointment

Richeldi L et al. *ERM.* 2020; 8: 25-33.

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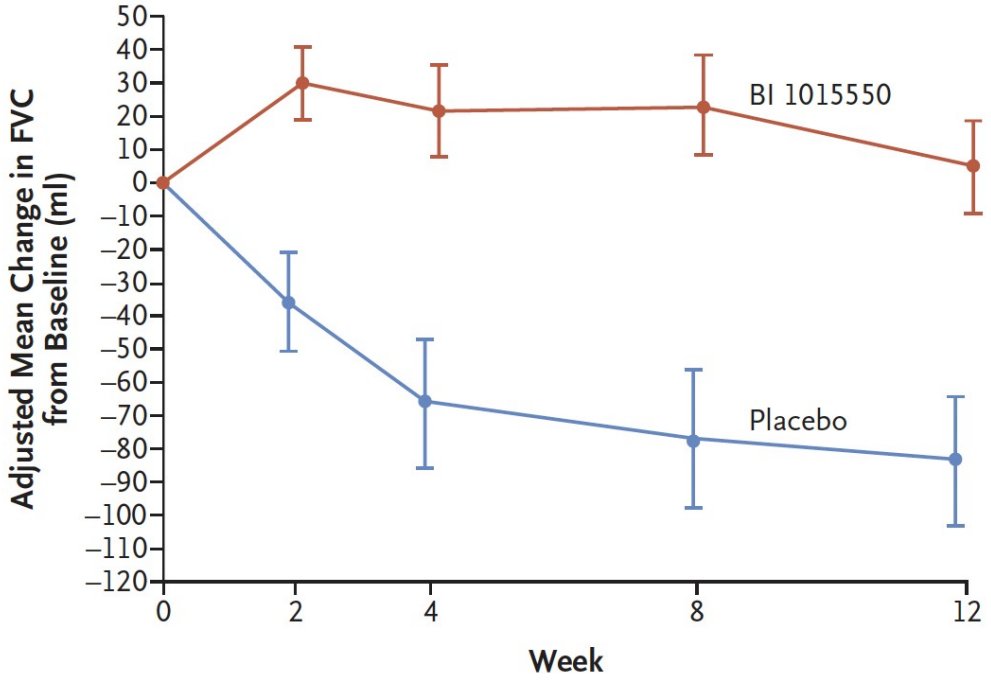
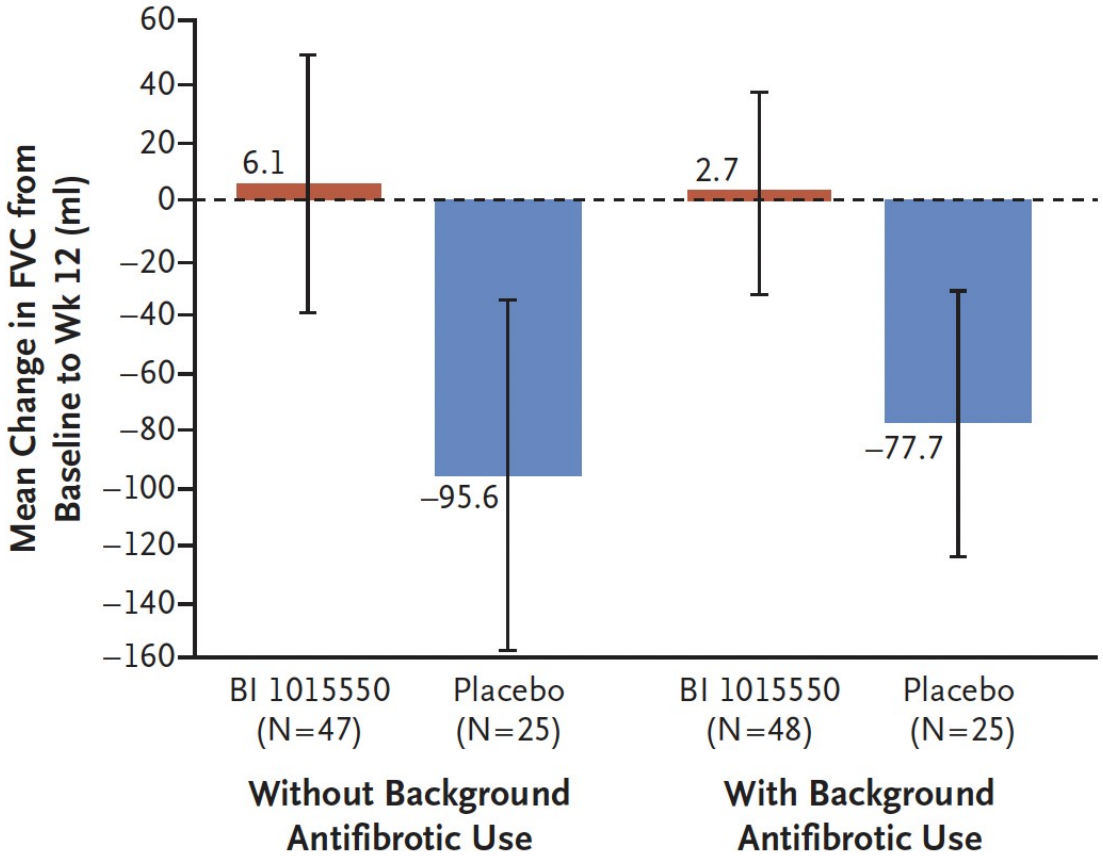
Source: Evaluate Pharma & clinicaltrials.gov.

https://www.evaluate.com/vantage/articles/news/snippets/roche-adds-lung-fibrosis-disappointment

PDE4 inhibitor preserves FVC on top of antifibrotics



No. of Patients				
BI 1015550	90	89	87	81
Placebo	49	50	50	49



Richeldi L et al. *NEJM* 2022; 386: 2178-87

FIBRONEER Phase III Study design

Two separate double-blind, randomized, placebo-controlled Phase III studies in patients with IPF (FIBRONEER-IPF, NCT05321069)[1] and chronic PF-ILD / PPF (FIBRONEER ILD, NCT05321082)[2]

R
1:1:1

In both studies, patients are randomized to receive 1:1:1 BI 1015550 18 mg BID or 9 mg BID or placebo

A 52-week treatment period is followed by a variable treatment period.

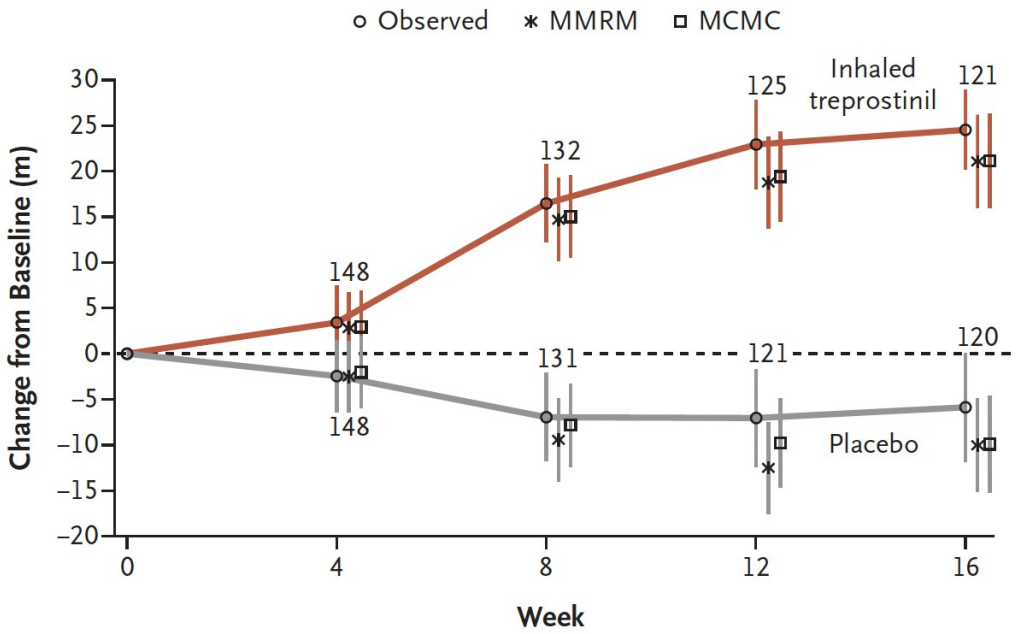
- n≈321 per treatment group for FIBRONEER-IPF[1]
- n≈347 per treatment group for FIBRONEER-ILD[2]

Part A of the study will run for 52 weeks and will be followed by Part B, a variable treatment period beyond week 52, during which patients will continue to receive blinded treatment until all patients have completed Part A. BID, 2x daily; IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis.

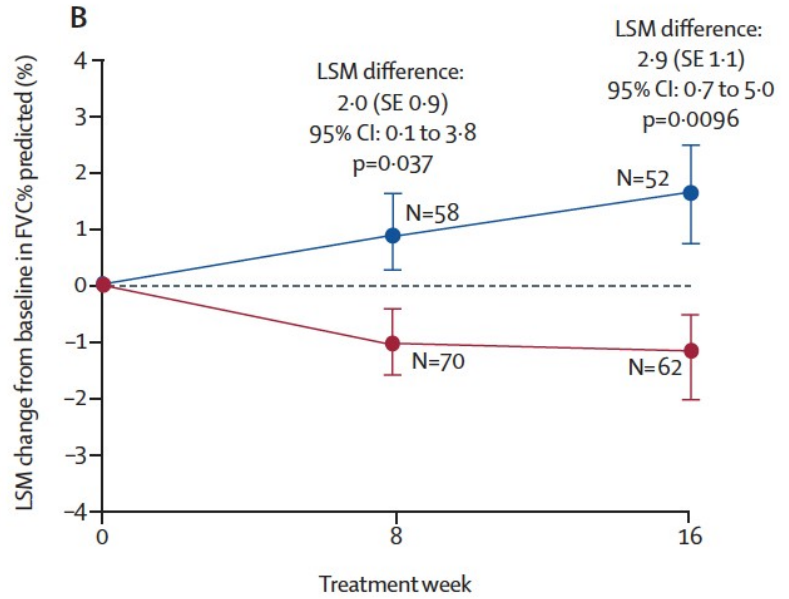
1. NCT05321069. Available here: https://clinicaltrials.gov/ct2/show/NCT05321069. Captured August 2022; 2. NCT05321082. Available here: https://clinicaltrials.gov/ct2/show/NCT05321082. Captured August 2022.

Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

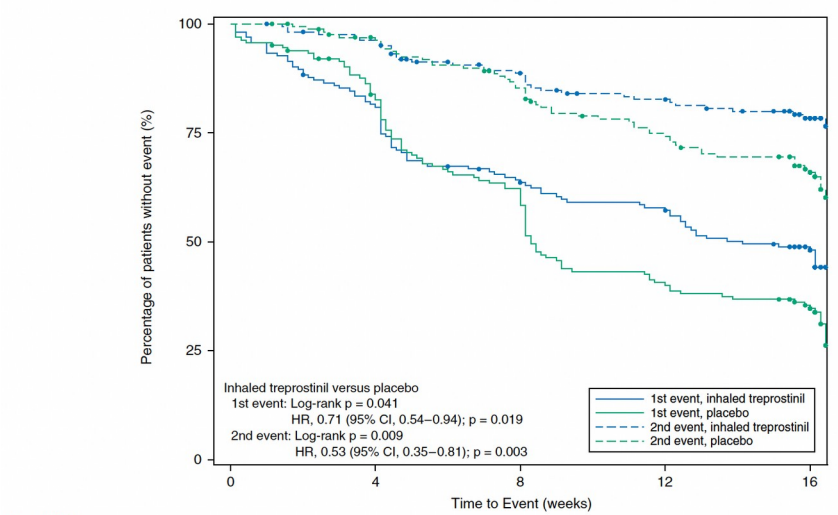
Aaron Waxman, M.D., Ph.D., Ricardo Restrepo-Jaramillo, M.D., Thenappan Thenappan, M.D., Ashwin Ravichandran, M.D., Peter Engel, M.D., Abubakr Bajwa, M.D., Roblee Allen, M.D., Jeremy Feldman, M.D., Rahul Argula, M.D., Peter Smith, Pharm.D., Kristan Rollins, Pharm.D., Chunqin Deng, M.D., Ph.D., Leigh Peterson, Ph.D., Heidi Bell, M.D., Victor Tapson, M.D., and Steven D. Nathan, M.D.



Waxman A et al *NEJM.* 2021; 384: 325-34



Nathan SD et al *LRM.* 2021; 9: 1266-74



No. at Risk:

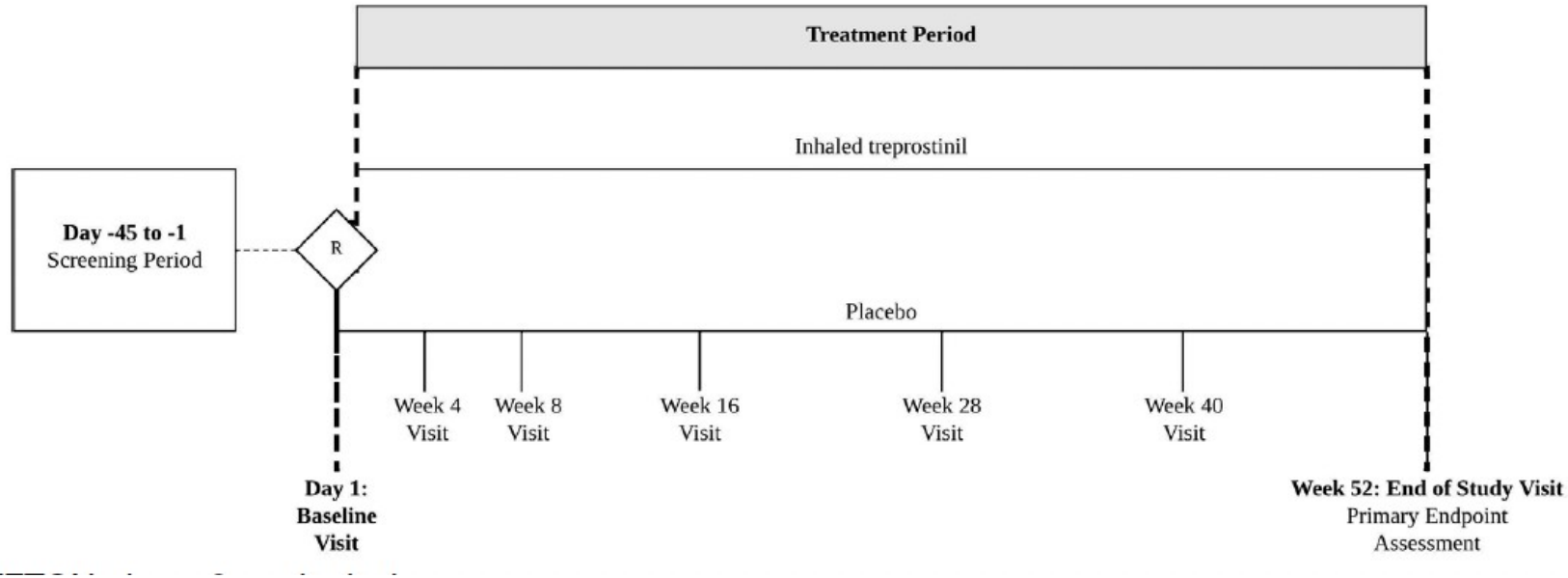
1st event, inhaled treprostinil	163	132	102	91	61
1st event, placebo	163	132	98	64	49
2nd event, inhaled treprostinil	163	155	135	122	92
2nd event, placebo	163	152	132	113	84

Nathan SD et al *AJRCCM.* 2022; 205: 198-207

BMJ Open Respiratory Research

Study design and rationale for the TETON phase 3, randomised, controlled clinical trials of inhaled treprostinil in the treatment of idiopathic pulmonary fibrosis

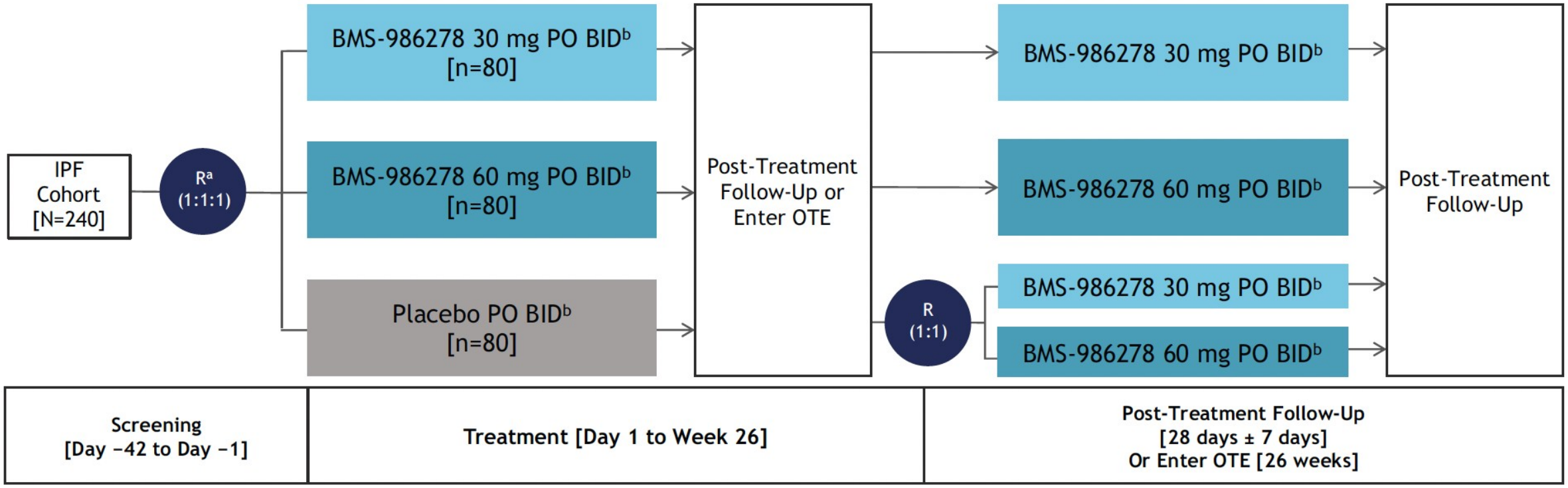
Steven D Nathan,[1] Jurgen Behr,[2] Vincent Cottin,[3] Lisa Lancaster,[4] Peter Smith,[5] CQ Deng,[5] Natalie Pearce ,[5] Heidi Bell,[5] Leigh Peterson,[5] Kevin R Flaherty[6]



Nathan SD et al. *BMJ Open Resp Res* 2022; 9: e001310

clinicaltrials.gov: NCT04308681

BMS-986278 (LPA_1 antagonist) Ph2 Study: PF-ILD Cohort



Corte TJ et al. *BMJ Open Resp Res* 2021; 8: e001026

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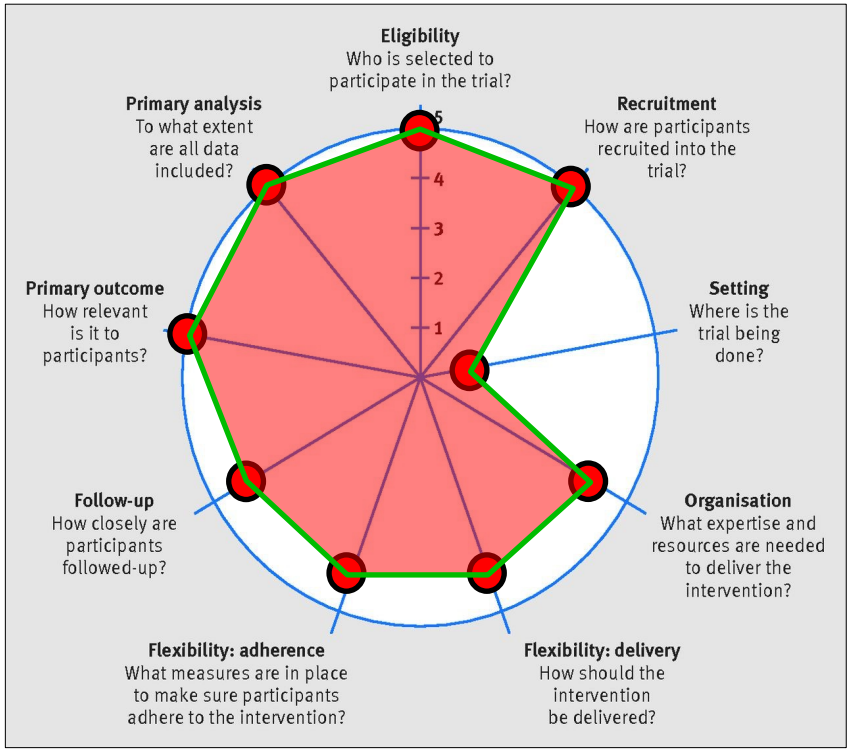
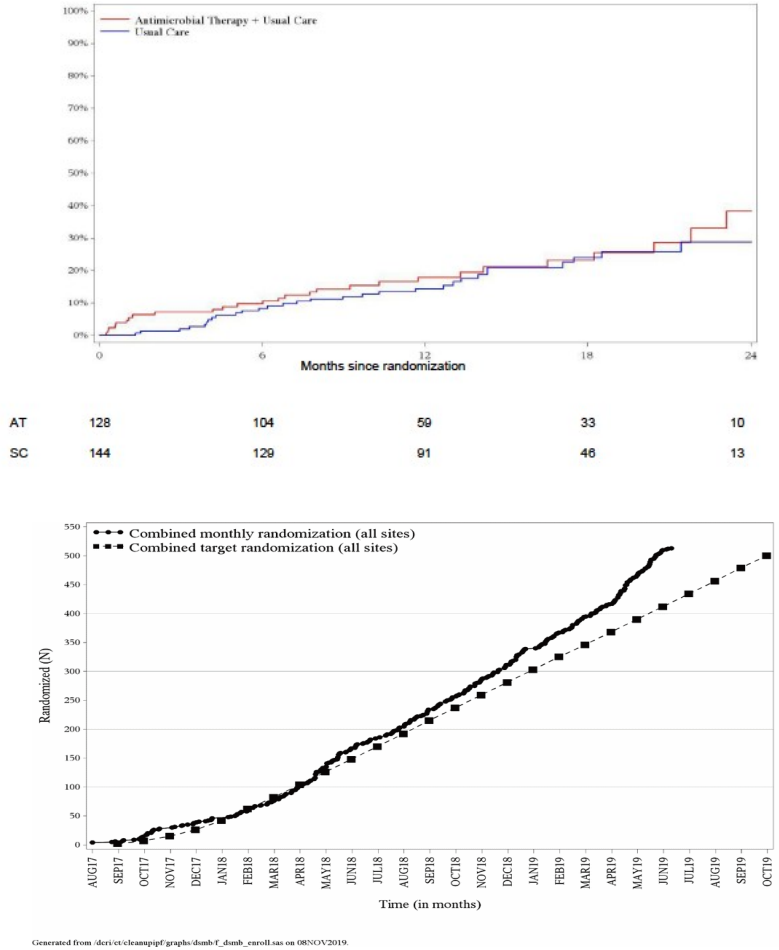
Innovative study designs facilitate study conduct



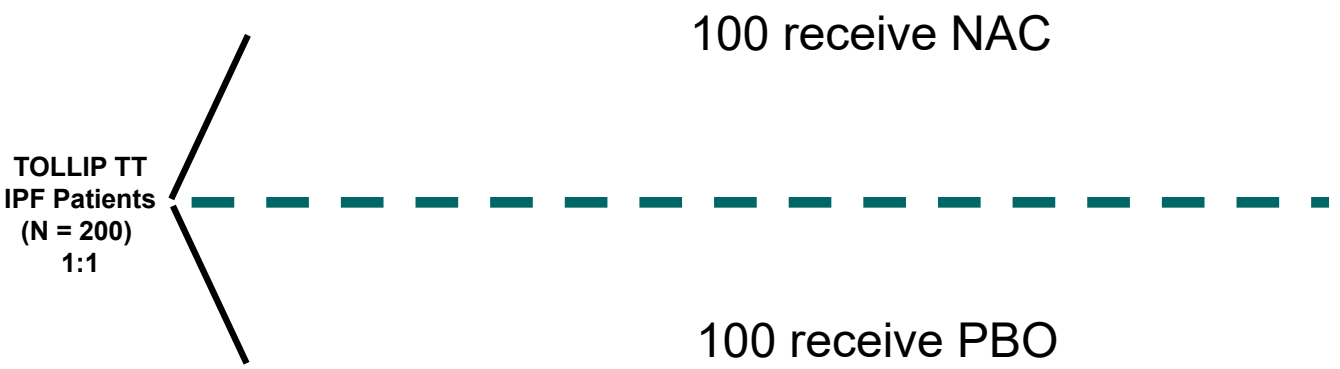
Anstrom KJ et al; *Respir Res*. 2020 Mar 12;21(1):68.



Martinez FJ et al. *JAMA* 2021; 325: 1841-51

Prospective tReatment EffiCacy in IPF uSIng genOtype for Nac Selection (PRECISIONS) trial

- Randomized, double-blinded, phase III multicenter clinical trial of N-acetylcysteine in idiopathic pulmonary fibrosis patients with a TT (favorable) TOLLIP genotype
- Screen 800 to identify 200 patients with TT genotype
- Randomize those 1:1

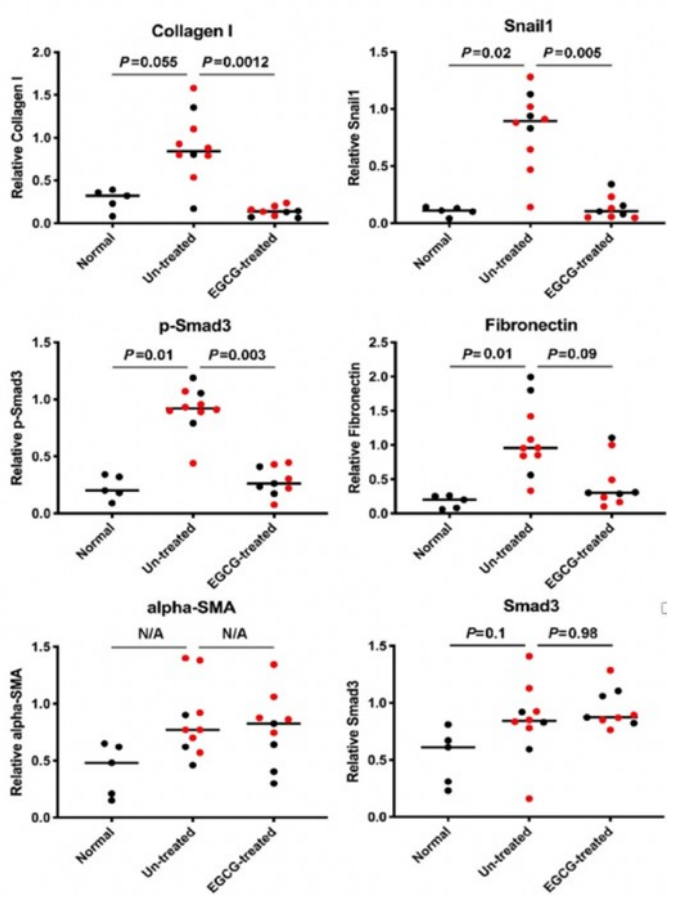


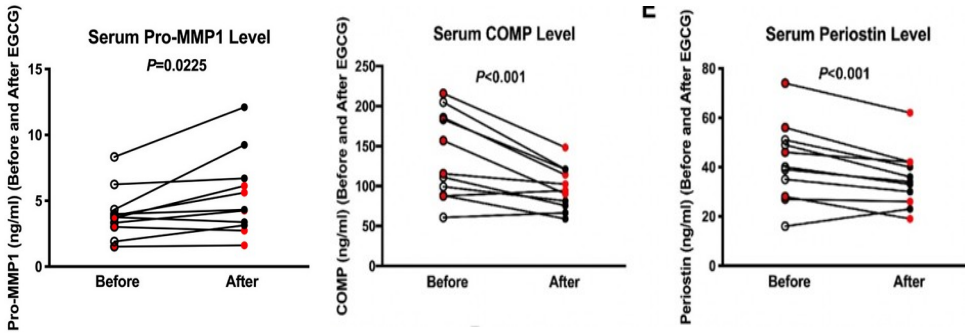
Primary endpoint - Time to categorical decline of relative 10% decline in FVC, or DLCO, first respiratory hospitalization, transplant or death from any cause

PFF repository for prevalent cases – 20 - 30 centers
Incident cases will take time

EGCG reverses TGFb-1 driven pro-fibrotic state in pulmonary fibrosis patients

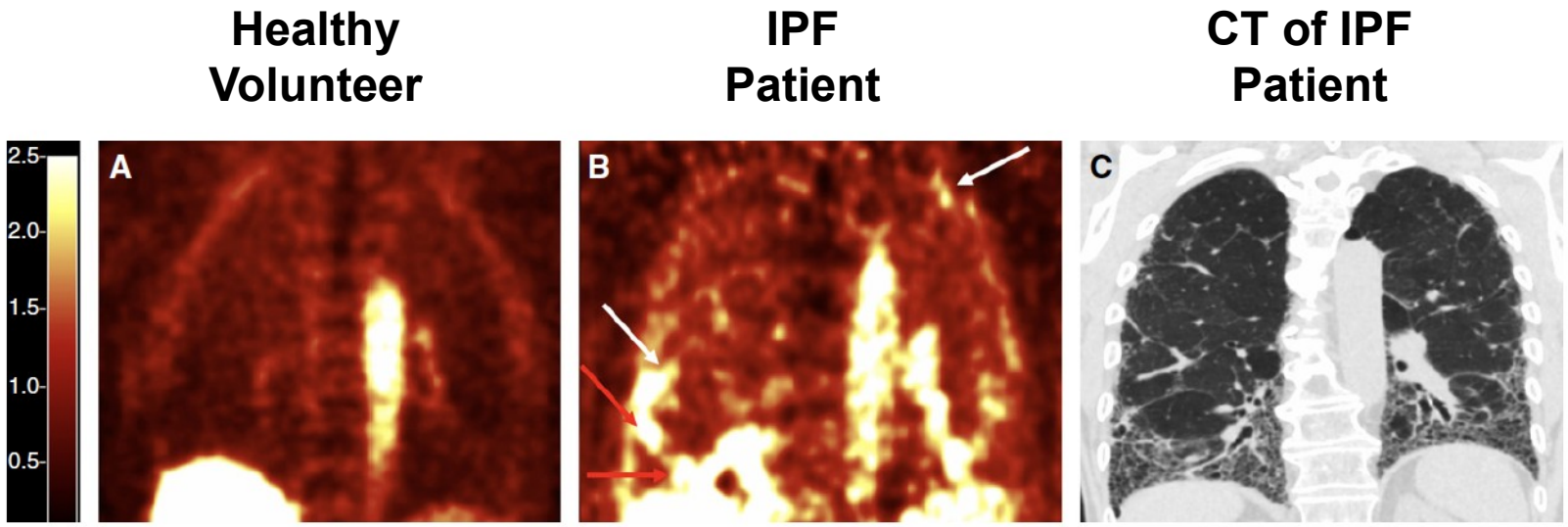
Patients to undergo surgical lung biopsy for interstitial lung disease were given EGCG 600 mg daily for 14 days prior to biopsy





Chapman HA et al *NEJM* 2020; 382:1068-70

^{68}Ga-CBP8 Detects Increased Collagen in IPF patients and *Active Disease*



Montesi et al, *Am J Respir Crit Care Med*. 2019; 200:258-261

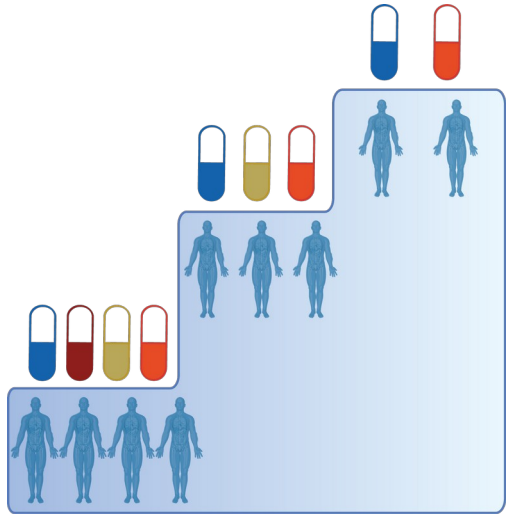
Novel trial design concepts

Master Protocol* design

- Umbrella
- Basket
- Platform

Adaptive design (elements)

- Sample size re-estimation
- Population/prognostic enrichment strategy
- Treatment arm selection
- Adaptive patient allocation
- Adaptive endpoint selection
- Group sequential design
- Adaptive hypothesis



A **platform** trial is designed to evaluate multiple investigational drugs in a single disease population in a perpetual manner, with treatments allowed to enter or leave the platform on the basis of a decision algorithm

*Also termed “complex clinical trials” by EU Clinical Trials Facilitation and Coordination Group (CTFG)

Platform design initiated with LTP001

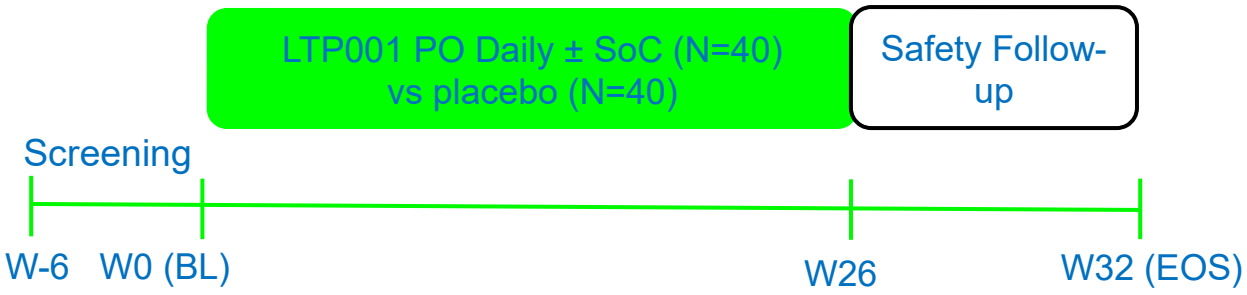
Treatment:
- LTP001 vs placebo (1:1) x 26 weeks

Patient population:
- Diagnosis of IPF (per ATS/ERS guidelines 2018)
- FVC ≥ 45% predicted
- ± SoC (stable pirfenidone or nintedanib or neither)

Primary endpoint:
Change from baseline in FVC %predicted at 26 weeks

Secondary endpoints:
- Safety and tolerability
- Progression free survival
- DLCO/ Hb
- 6MWD
- Patient reported outcomes
- PK

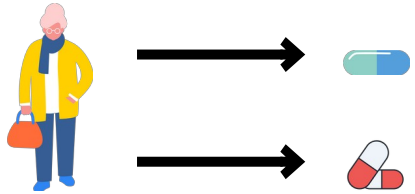
Selected exploratory endpoints:
- IPF Exacerbations
- HRCT quantitative lung fibrosis score
- Soluble Biomarkers
- Forced oscillation technique (FOT)



Interim Analysis:
- After ~half of patients have completed 26 weeks of treatment
- Consider sample size reassessment and need to add placebo participants

- Randomization ratio may be adjusted at IA pending entry of other compounds

REMAP Trials

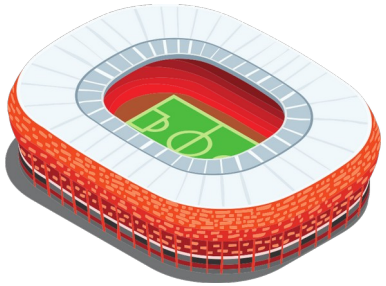


Randomised

Embedded

Multifactorial

Adaptive



Platform

Thanks to Derek C. Angus, MD, MPH, University of Pittsburgh Medical Center, for “REMAP”

REMAP-ILD

NHLI

NIHR | National Institute for Health and Care Research

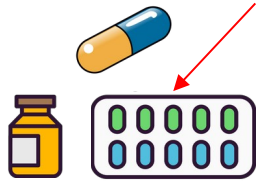
Multifactorial

DOMAINS

Factor

Anti-fibrotic

Pulmonary Rehab



Immunomodulatory

REGIMEN

REMAP-ILD

NHLI

NIHR | National Institute for Health and Care Research

Short time for a huge topic so…

- IPF
  - Numerous studies ongoing
  - Recent Phase III studies terminated
  - Phase III study coming shortly
  - Phase III studies launching
  - Novel study designs in process
- PPF
  - Recent recommendations regarding anti-fibrotic therapy
  - Phase III study(ies) coming

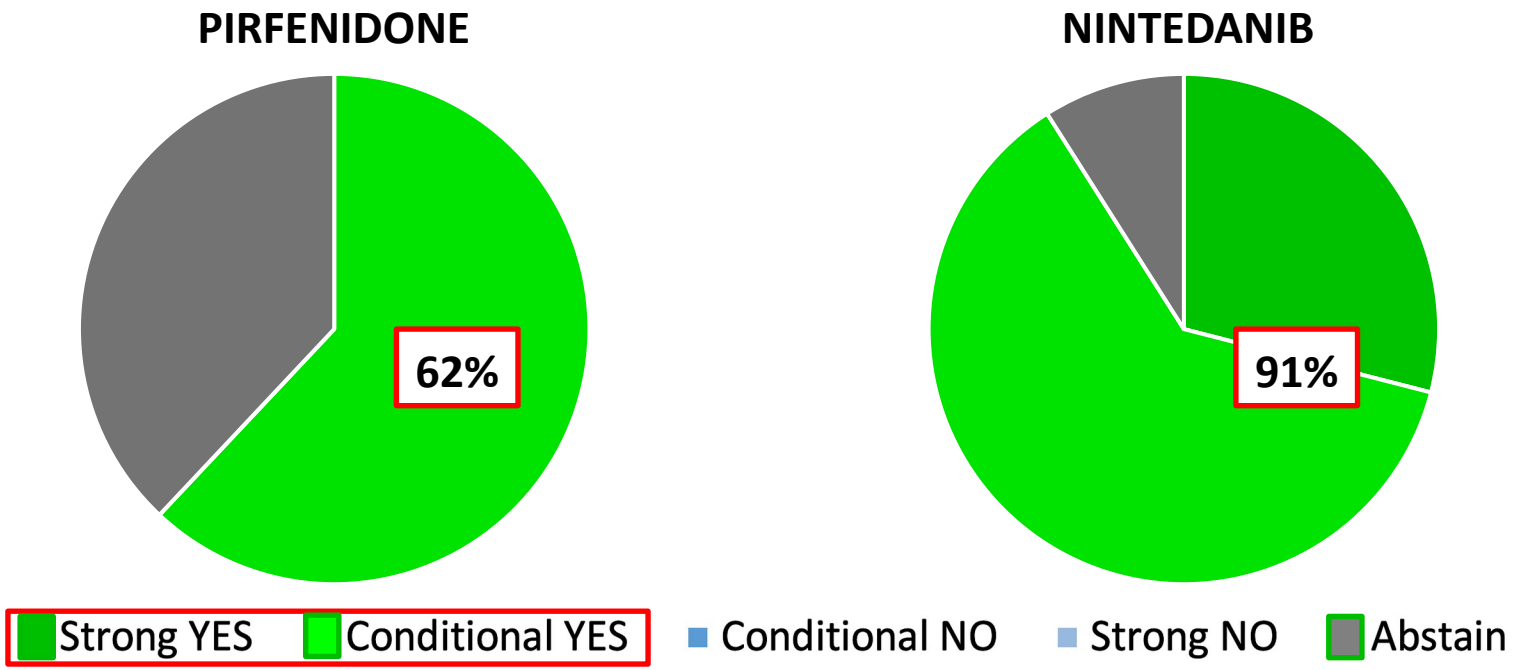
Should Patients with PPF Be Treated with Anti-Fibrotic Therapy?

AMERICAN THORACIC SOCIETY DOCUMENTS

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

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

Ganesh Raghu, Martine Remy-Jardin, Luca Richeldi, Carey C. Thomson, Yoshikazu Inoue, Takeshi Johkoh, Michael Kreuter, David A. Lynch, Toby M. Maher, Fernando J. Martinez, Maria Molina-Molina, Jeffrey L. Myers, Andrew G. Nicholson, Christopher J. Ryerson, Mary E. Strek, Lauren K. Troy, Marlies Wijsenbeek, Manoj J. Mammen, Tanzib Hossain, Brittany D. Bissell, Derrick D. Herman, Stephanie M. Hon, Fayez Kheir, Yet H. Khor, Madalina Macrea, Katerina M. Antoniou, Demosthenes Bouros, Ivette Buendia-Roldan, Fabian Caro, Bruno Crestani, Lawrence Ho, Julie Morisset, Amy L. Olson, Anna Podolanczuk, Venerino Poletti, Moisés Selman, Thomas Ewing, Stephen Jones, Shandra L. Knight, Marya Ghazipura, and Kevin C. Wilson; on behalf of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax



Raghu G et al, *Am J Respir Crit Care Med* 2022; 205: e18-e47

Short time for a huge topic so…

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- PPF
  - Recent recommendations regarding anti-fibrotic therapy
  - Phase III study(ies) coming

FIBRONEER Phase III Study design

Two separate double-blind, randomized, placebo-controlled Phase III studies in patients with IPF (FIBRONEER-IPF, NCT05321069)[1] and chronic PF-ILD / PPF (FIBRONEER ILD, NCT05321082)[2]

R 1:1:1

In both studies, patients are randomized to receive 1:1:1 BI 1015550 18 mg BID or 9 mg BID or placebo

A 52-week treatment period is followed by a variable treatment period.

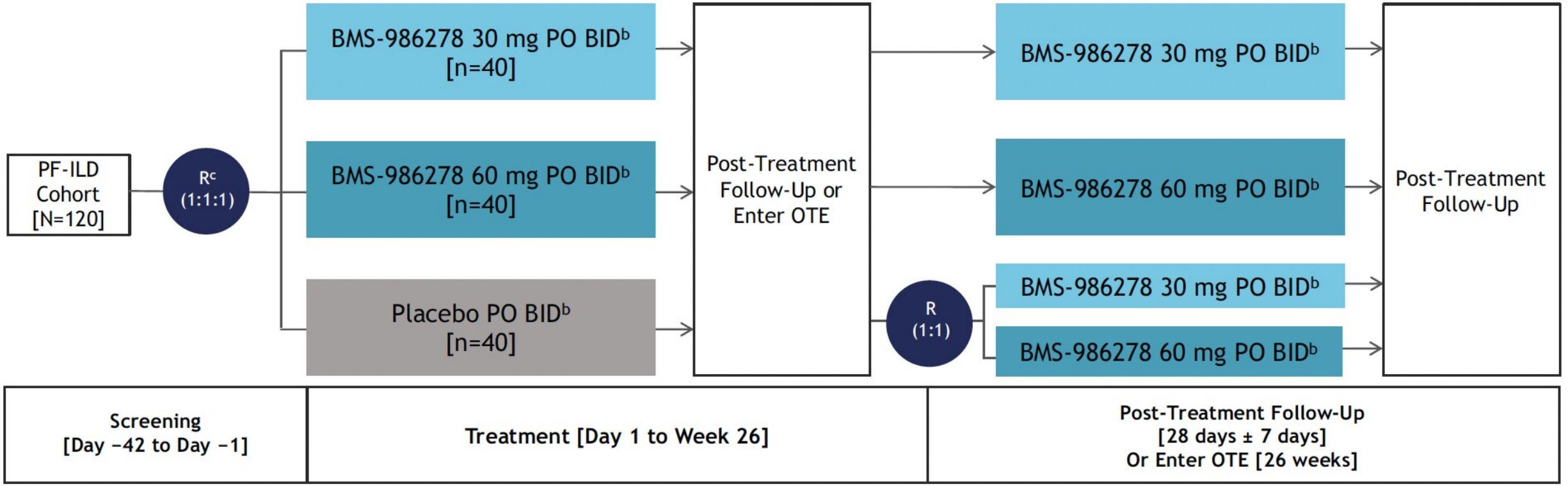
- n≈321 per treatment group for FIBRONEER-IPF[1]
- n≈347 per treatment group for FIBRONEER-ILD[2]

Part A of the study will run for 52 weeks and will be followed by Part B, a variable treatment period beyond week 52, during which patients will continue to receive blinded treatment until all patients have completed Part A. BID, 2x daily; IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis.

1. NCT05321069. Available here: https://clinicaltrials.gov/ct2/show/NCT05321069. Captured August 2022; 2. NCT05321082. Available here: https://clinicaltrials.gov/ct2/show/NCT05321082. Captured August 2022.

clinicaltrials.gov: NCT04308681

BMS-986278 (LPA_1 antagonist) Ph2 Study: PF-ILD Cohort



Corte TJ et al. *BMJ Open Resp Res* 2021; 8: e001026

Short time for a huge topic so…

- IPF
  - Numerous studies ongoing
    - Very rich pipeline
  - Recent Phase III studies terminated
    - Even negative studies instructive
  - Phase III study coming shortly
    - We are hopeful
  - Phase III studies launching
    - Active Phase III progress
  - Novel study designs in process
    - Much innovation in the space
- PPF
  - Recent recommendations regarding anti-fibrotic therapy
    - Remains controversial
  - Phase III study(ies) coming
    - Additional options will be imminent