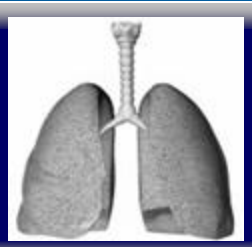
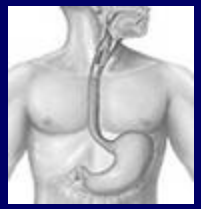
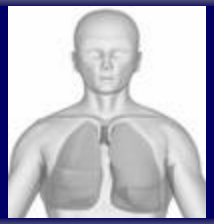
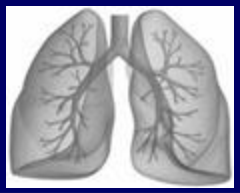



Emerging Treatments for Pulmonary Fibrosis and Active Clinical Trials

Peter LaCamera, MD

Division of Pulmonary, Critical Care and Sleep Medicine
St. Elizabeth's Medical Center

Assistant Professor of Medicine, Tufts University
Boston, MA

Conflicts of interest:

Site PI for the following studies which will be discussed:

- **BMS-986278 phase II**
- **FIBRONEER**
- **ALOFT**

Current state (10+ years)

IPF J84.112

nintedanib (Ofev) or pirfenidone (Esbriet)

PF-ILD (PPF) J84.170 (INBUILD '19)

- o A decline in the relative ppFVC of ≥10%, OR
- o A decline in the relative ppFVC of ≥5% to <10% along with worsening symptoms or CT, OR
- o Worsening symptoms along with an increased extent of fibrosis on CT

nintedanib (Ofev) with/without immunosuppressant(s)

Worsening Despite an Anti-Fibrotic

Current options:

- For IPF…switch?
- For PPF…intensify immunosuppressants?

Anti-fibrotic trials – ongoing areas of investigation:

- Nintedanib / pirfenidone switching, combining
- Expanded indications for nintedanib / pirfenidone
- Novel anti-fibrotics

Anti-fibrotic trials – ongoing areas of investigation:

- **nintedanib / pirfenidone switching, combining**

How do you know if an anti-fibrotic is working?

Well, you usually don't

Consider rate of pre-treatment FVC loss c/w rate of FVC loss while on treatment (if sufficient data available) – is there an improvement?

While on treatment, if rate of FVC loss > 200 mL / year, at minimum entertain idea that anti-fibrotic isn't effective
(trials demonstrated that on average those with IPF lose < 200 mL / year while on treatment)

Anti-fibrotic trials – ongoing areas of investigation:

- **nintedanib / pirfenidone switching, combining**

When do you consider switching from a med that is generally being tolerating?

When there's concern that antifibrotic is ineffective

Ongoing side effects taken into consideration – the more bothersome the side effects, the lower the threshold to change

Does switching help?

Anti-fibrotic trials – ongoing areas of investigation:

- **nintedanib / pirfenidone switching, combining**

Combined Therapy (pirfenidone + nintedanib)

3 small, short studies investigating safety, tolerability, exploratory efficacy

Anti-fibrotic trials – ongoing areas of investigation:

- **nintedanib / pirfenidone switching, combining**

Management of Progressive Disease in Idiopathic Pulmonary Fibrosis (PROGRESSION)

Goal:
Evaluate the efficacy and tolerance of combined pirfenidone and nintedanib as compared to "switch monotherapy“ in patients with worsening IPF despite receiving either pirfenidone or nintedanib

Management of Progressive Disease in Idiopathic Pulmonary Fibrosis (PROGRESSION)

Eligibility:
- **Stable dose of pirfenidone or nintedanib**
- **Worsening**

Intervention – 24 weeks of:
- **pirfenidone 2403 mg / d in combination with nintedanib 300 mg / d**
- **switch from one monotherapy to alternative**
- **cont current therapy**

Enrollment : 378 participants

Primary Outcome Measure : Slope of the decline in FVC

Results hopefully in ‘25

Anti-fibrotic trials – ongoing areas of investigation:

Expanded indications for nintedanib being investigated

- BOS in setting of HST
- Progressive Fibrosing Coal Mine Dust-Induced Interstitial Lung Disease
- BOS following lung transplant
- Occupational Progressive Pneumoconiosis
- Radiation Pneumonitis
- ILD following COVID-19
- Myositis - progressive fibrosing ILD

Expanded indications for pirfenidone being investigated

- Fibrotic Lung Disease After COVID-19
- Radiation Pneumonitis
- Fibroproliferative ARDS
- Checkpoint inhibitor-related pneumonitis
- Silicosis
- CTD-ILD
- Occupational Pneumoconiosis

Anti-fibrotic trials – ongoing areas of investigation:

Semi-novel anti-fibrotics

- **LYT-100 - deupirfenidone**
  phase II ongoing
  press release in 12/24 suggested favorable results

- **AP01 - nebulized pirfenidone**
  phase II ongoing

Anti-fibrotic trials – ongoing areas of investigation:

- **Novel anti-fibrotics**

Many phase I and II trials

Phase III Trials:

Treprostinil (UT)	**PGI2 analog**
Nerandomilast (BI 1015550)	**PDE4B inhibitor**
Admilparant (BMS-986278)	**LPA1 antagonist**

Subject-centric clinical trial – protocol features attractive to patients

- 2:1 randomization
- 52+ week study
- Open-label extension
- Reasonable study visit duration
- Transportation offered
- Stipend provided
- If phase III, promising phase II results
- PO vs. IV administration
- Background pirfenidone / nintedanib allowed

Novel Anti-fibrotics

BI 1015550 (nerandomilast) **BI** **PDE4B inhibitor**

Existing PDE4 inhibitors:

apremilast (Otezla) - psoriasis, psoriatic arthritis, Behcet's

roflumilast (Daliresp) – COPD, psoriasis

PDE4B

Hydroyzes cAMP, inhibition results in increased intracellular cAMP

High expression in lung, immune cells

Inhibition:

- **Blocks airway inflammation / hyperactivity in response to allergens**
- **Inhibits TGF-β-induced differentiation into myofibroblasts**
- **Inhibits injury-induced neutrophil recruitment**
- **Reduces inflammatory responses of monocytes and macrophages**
- **Inhibition of TNF-α production**

Kolb M et al. Eur Respir Rev 2023; 32: 220206

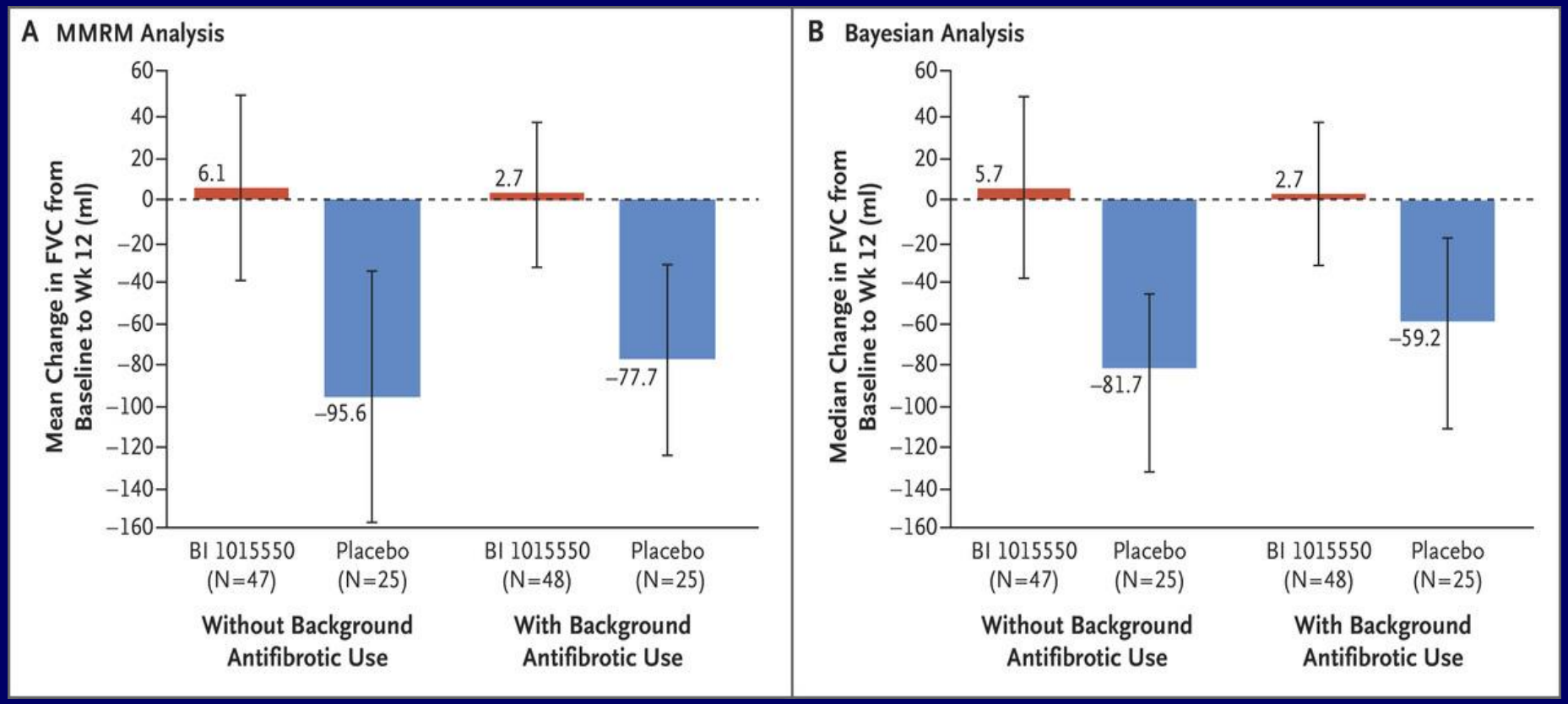
ORIGINAL ARTICLE

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

Luca Richeldi, M.D., Ph.D., Arata Azuma, M.D., Ph.D., Vincent Cottin, M.D., Ph.D., Christian Hesslinger, Ph.D., Susanne Stowasser, M.D., Claudia Valenzuela, M.D., Marlies S. Wijsenbeek, M.D., Ph.D., Donald F. Zoz, M.D., Florian Voss, Ph.D., and Toby M. Maher, M.D., Ph.D. for the 1305-0013 Trial Investigators*

June 9, 2022
N Engl J Med 2022; 386:2178-2187

Changes in FVC at Week 12 (18 mg)



FIBRONEER (IPF, PPF cohorts)

Oral BI 1015550 bid vs. placebo

Double-blind, 52 week RCT, 2:1 randomization (9, 18 mg doses of BI 1015550 being evaluated)

Primary outcome : change in absolute FVC

PPF cohort to transition to OLE this month, IPF cohort transitioned > 4 months ago

Boehringer's nerandomilast meets primary endpoint in pivotal phase-III FIBRONEER™-IPF study

Ingelheim, Germany, Mon, 09/16/2024 - 12:00

- Topline data from FIBRONEER™-IPF show that the investigational compound nerandomilast met its primary endpoint, which was the absolute change from baseline in Forced Vital Capacity [mL] at week 52 versus placebo.

Novel Anti-fibrotics

BMS-986278 (admilparant) BMS LPA1 antagonist

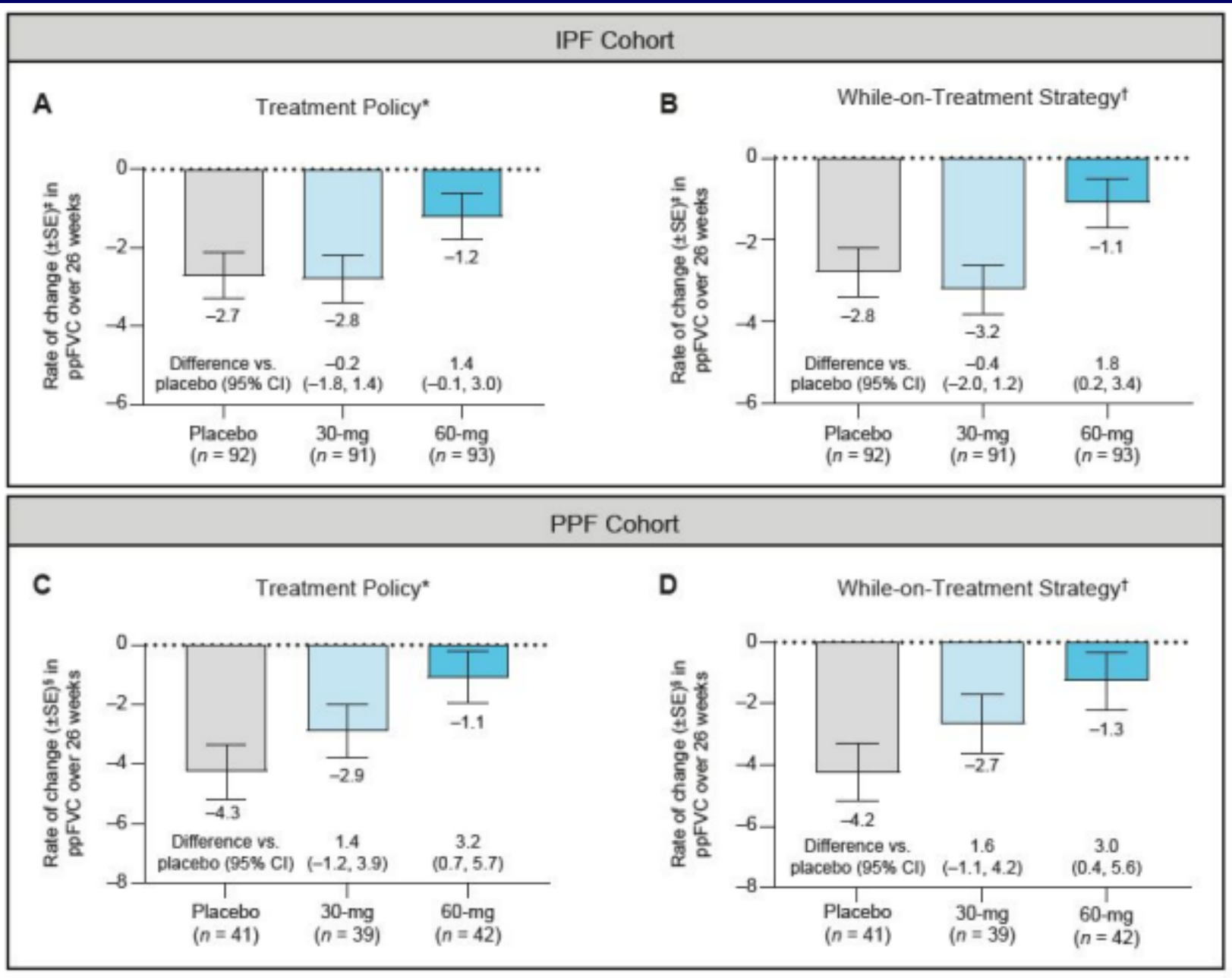
LPA – LPA1

- **Recruits fibroblasts and prevents their apotosis**
- **Promotes vascular leak**
- **Induces epithelial cell apotosis**

Tager AM et al. Nat Med. 2008 Jan;14(1):45-54.
Tager AM et al. Am J Respir Cell Mol Biol. 2012 Mar;46(3):355-64.

Efficacy and Safety of Admilparant (BMS-986278), an LPA(1) Antagonist in Pulmonary Fibrosis: A Phase 2 Randomized Clinical Trial.

Positive results reported at ATS ‘23, on-line pub 10/24



Corte TJ et al. Am J Respir Crit Care Med. 2024 Oct 11.

ALOFT-IPF / ALOFT-PPF

Oral BMS-986278 bid vs. placebo

Double-blind, 52 week RCT, 2:1 randomization (60, 120 mg being evaluated)

Primary outcome : change in absolute FVC

Enrollment opened

Open-label extension available

Novel Anti-fibrotics

Treprostinil	**United Therapeutics**	**PGI2 analog**

INCREASE study : evaluated inhaled treprostinil in patients with ILD and pulmonary hypertension (meant to be a traditional PH study)

Pre-clinical observations : reduces recruitment of fibrocytes to sites of vascular remodeling, suppresses fibroblast activity including synthesis and deposition of collagen and fibronectin

N Engl J Med. 2021 Jan 28;384(4):325-334.
Lancet Respir Med. 2021 Nov;9(11):1266-1274.

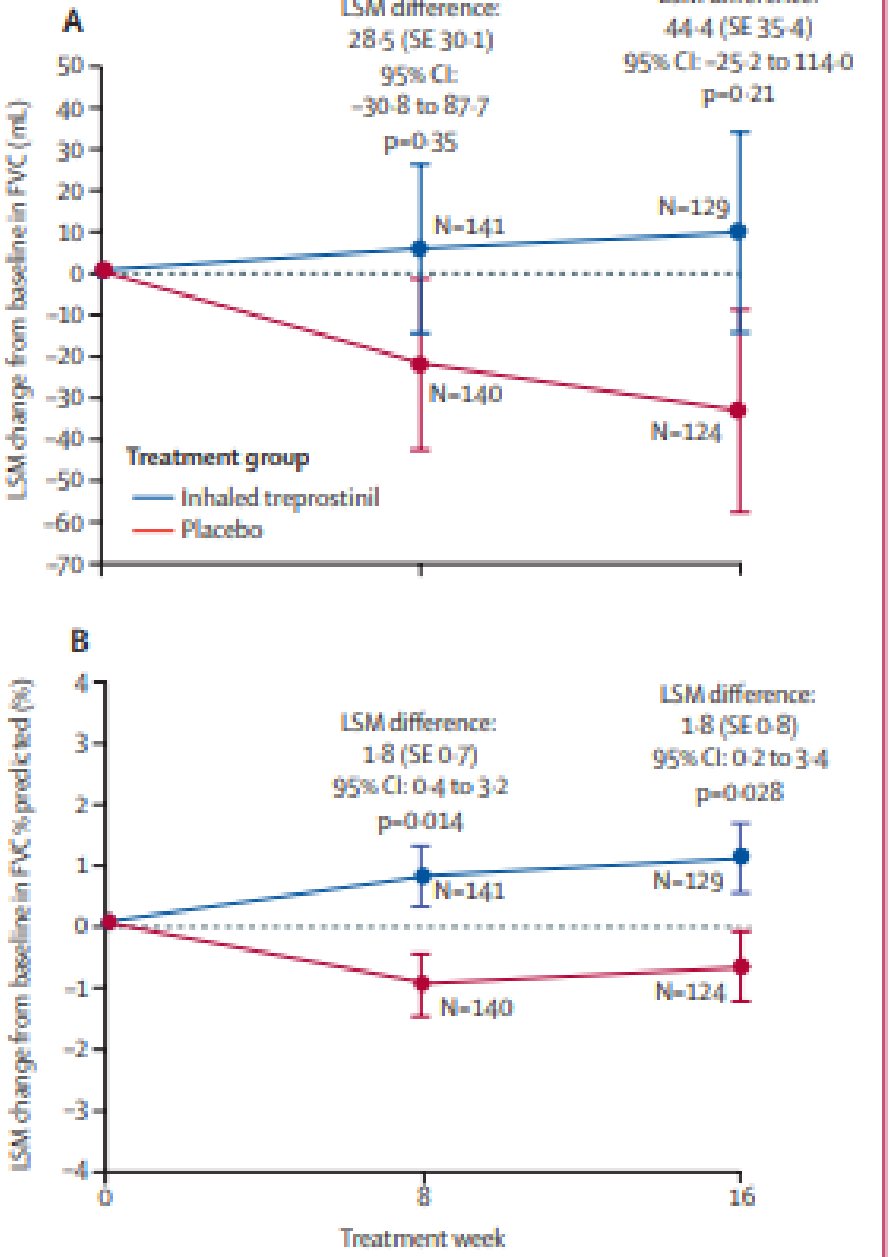


Figure 1: Change in FVC at week 8 and week 16 for the overall population

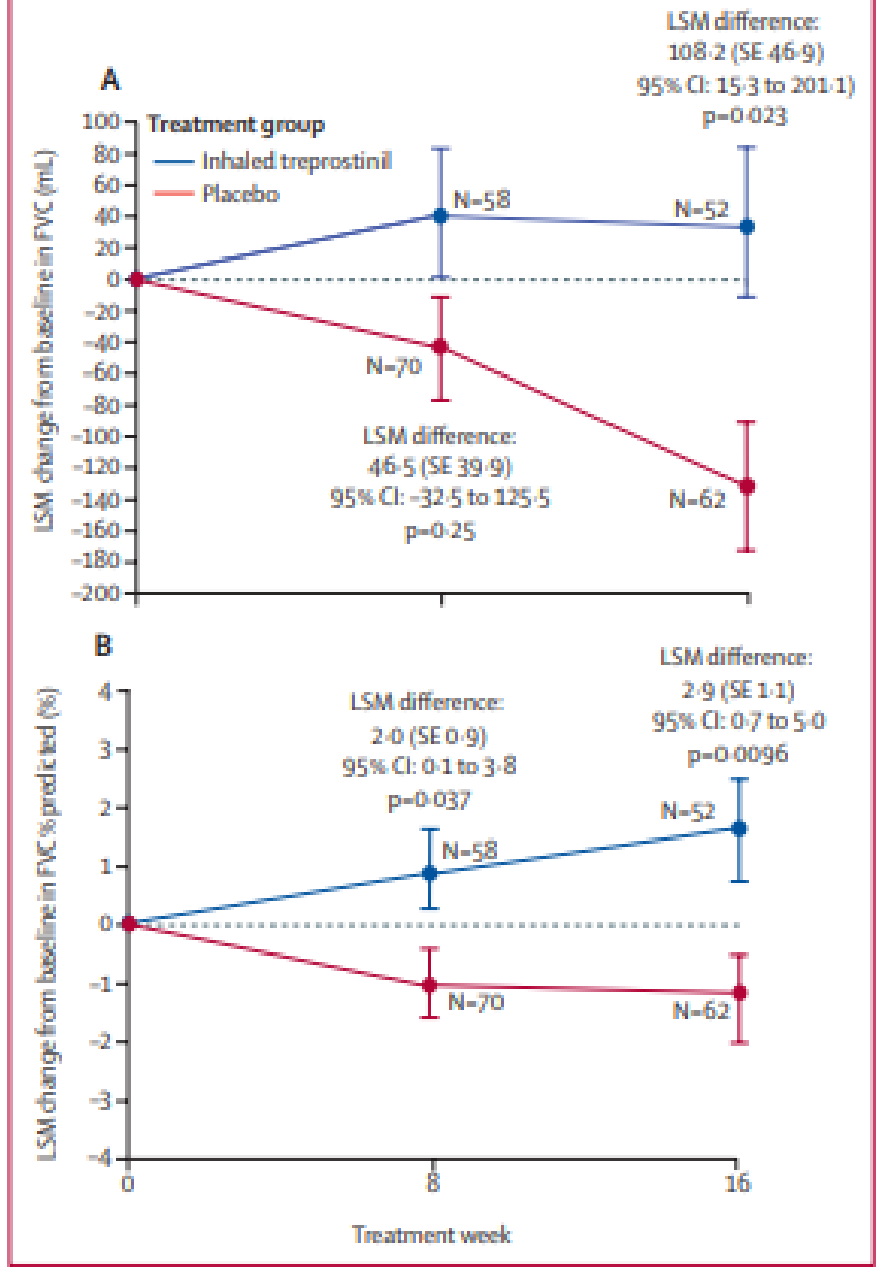


Figure 2: Change in FVC at week 8 and week 16 for patients with idiopathic interstitial pneumonia

TETON / TETON-PPF

Nebulized treprostinil qid vs. placebo

Double-blind, 52 week RCT, 1:1 randomization

Primary outcome : change in absolute FVC

Enrolling

Open-label extension available

Worsening Despite an Anti-Fibrotic

Current options:

- **For IPF…switch?**
- **For PPF…intensify immunosuppressants?**

Soon:

- **For IPF…replace (2+ options), combine (multiple potential combos)?**
- **For PPF…replace (unclear future options), combine (multiple potential combos), integrate AF management with immunosuppression adjustments?**

Anti-fibrotic trials – ongoing areas of investigation:

- **Nintedanib / pirfenidone switching, combining**
- **Expanded indications for nintedanib / pirfenidone**
- **Novel / Semi-novel anti-fibrotics**