ILD Collaborative

Project ECHO

Update on Emerging Treatments for Pulmonary Fibrosis and Active Clinical Trials

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Emerging treatments for PF

Conflicts of interest

Site PI for the following studies which will be discussed:

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

Emerging treatments for PF

Anti-fibrotic trials – ongoing areas of investigation:

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

nintedanib / pirfenidone switching, combining

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

When there's concern that the antifibrotic is ineffective

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

Does switching help?

nintedanib / pirfenidone switching, combining

How do you even 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)

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

PROGRESSION trial

Eligibility:

Stable dose of pirfenidone or nintedanib prescribed as first-line therapy for at least 6 months

Worsening of respiratory symptoms AND fibrosis according to PFTs, CT

Intervention – 24 weeks of:

- **pirfenidone 2403 mg per day in combination with nintedanib 300 mg per day**
- **switch from one monotherapy to alternative**
- **cont current therapy**

Enrollment : 378 participants

Will likely complete study in 2023

Primary Outcome Measure : Slope of the decline in FVC

Expanded indications for nintedanib / pirfenidone

Expanded indications for nintedanib being investigated

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

Expanded indications for nintedanib / pirfenidone

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**
- **Chronic HP**

Semi-novel anti-fibrotics

- **LYT-100 - deupirfenidone**

  Phase II; Enrolling; 1:1:1:1; 26 wks

  240 participants, rate of FVC change

- **AP01 - nebulized pirfenidone**

  Phase Ib published in Thorax in 8/23

  Avalyn – also making inhaled nintedanib, inhaled combo

Novel anti-fibrotics

Clinical trial info : www.clinicaltrials.gov

Many phase I and II trials

<u>Phase III Trials:</u>

Treprostinil	**UT**	**PGI2 analog**
BI 1015550	**BI**	**PDE4B inhibitor**
BMS-986278	**BMS**	**LPA1 antagonist**

Novel anti-fibrotics

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 - treprostinil

INCREASE study : 16-week randomized controlled trial to evaluate inhaled treprostinil in patients with ILD and pulmonary hypertension documented by RHC

Inhaled treprostinil up to 12 breaths (72 µg) qid vs. placebo

Primary endpoint : Δ 6MWT distance

Lab observations : treprostinil reduces recruitment of fibrocytes to sites of vascular remodeling, suppresses fibroblast activity including 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.

Novel anti-fibrotics - treprostinil

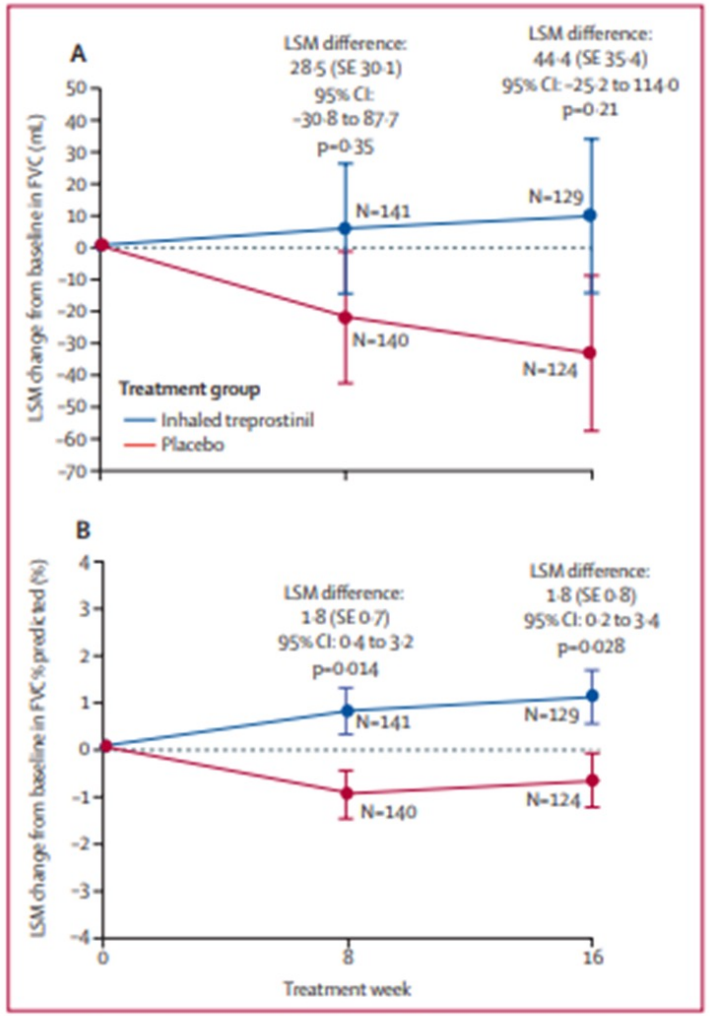

Figure 1: Change in FVC at week 8 and week 16 for the overall population

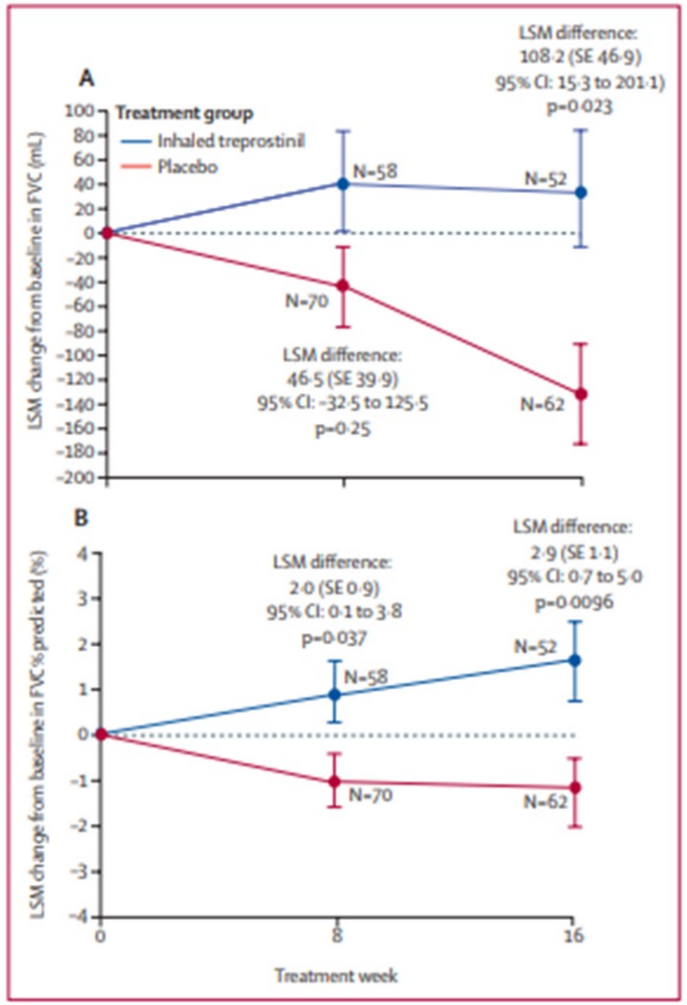

Figure 2: Change in FVC at week 8 and week 16 for patients with idiopathic interstitial pneumonia

N Engl J Med. 2021 Jan 28;384(4):325-334.

Novel anti-fibrotics - treprostinil

TETON / TETON-PPF

Nebulized treprostinil qid vs. placebo

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

Primary outcome : change in absolute FVC

For PFF study, broad range of immunosuppressants allowed

Enrolling

Open-label extension available

Novel anti-fibrotics - treprostinil

TETON / TETON-PPF

- 2:1 randomization
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Novel anti-fibrotics - BI 1015550

Existing PDE4 inhibitors:

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

roflumilast (Daliresp) – COPD, psoriasis

BI 1015550

A PDE4B inhibitor and a clinical drug candidate for the oral treatment of idiopathic pulmonary fibrosis

UNIQUE MECHANISM OF ACTION

Preferentially inhibits PDE4B

- Inhibition (IC_{50}) of PDE4B at **10 nmol/l**
- IC_{50} for inhibition of
  PDE4D 91 nmol/l
  PDE4A 248 nmol/l
  PDE4C 8,700 nmol/l

IC_{50}: concentration required for 50% inhibition

POTENTIALLY IMPROVED TOLERABILITY

Low emetic potential

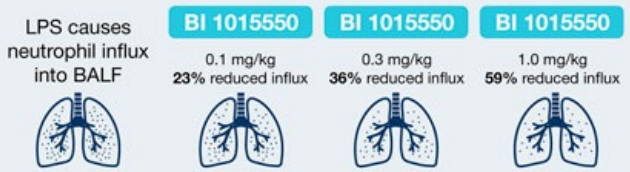
- 0.1 emetic events per animal at 0.5 mg/kg and 0.3 events per animal at 6 mg/kg (~10 x ED_{50})
- For comparison, roflumilast resulted in 0.7 emetic events per animal at 10 × ED_{50}

ED_{50}, dose inhibiting 50% of neutrophil influx into BALF

ANTI-INFLAMMATORY

Inhibits release of pro-inflammatory cytokines *in vitro*

Inhibits migration of neutrophils into BALF in *Suncus murinus*



BALF, bronchoalveolar lavage fluid

ANTIFIBROTIC

Active in murine models of lung fibrosis

Synergises with nintedanib to inhibit profibrotic activity of primary lung fibroblasts from patients with IPF

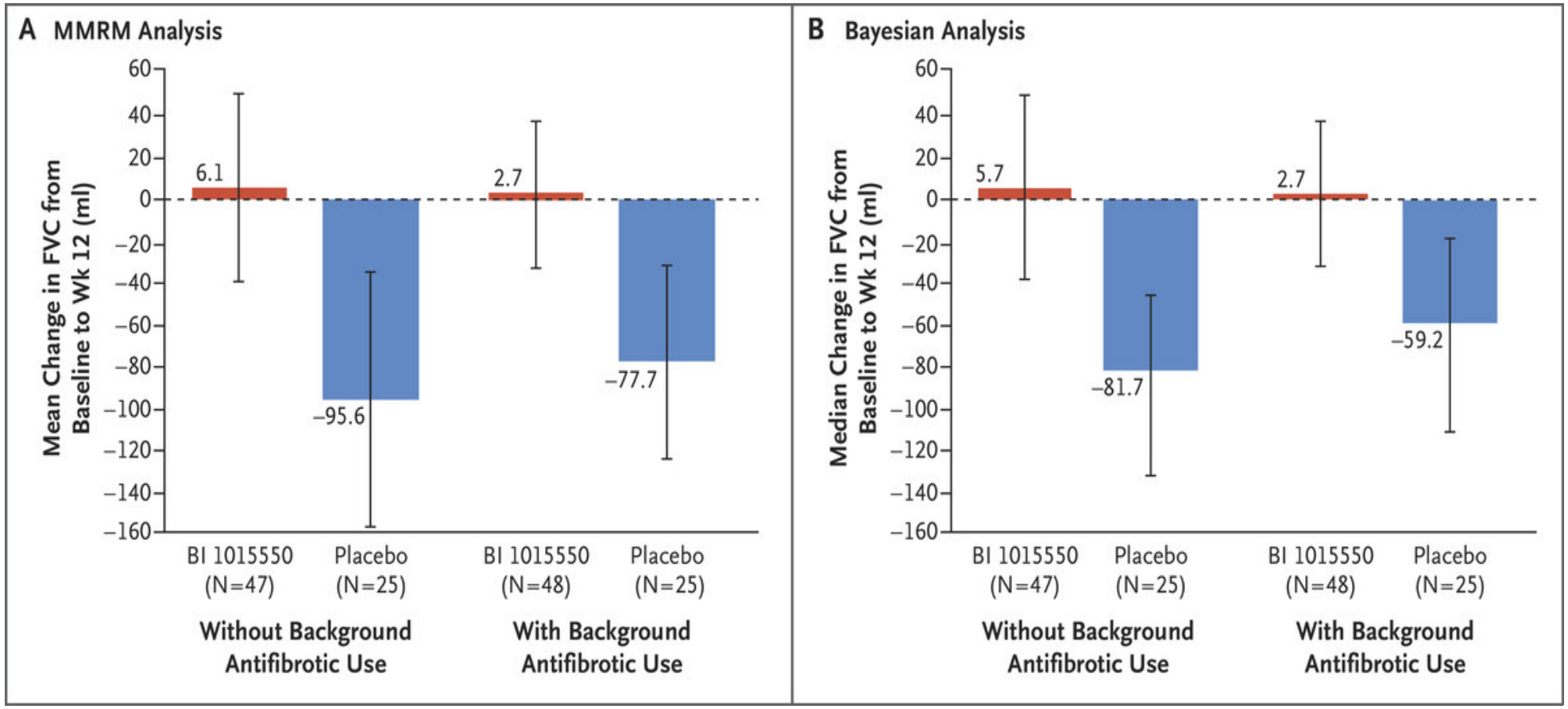
The unique preferential inhibition of PDE4B by BI 1015550 and its anticipated improved tolerability in humans, plus its anti-inflammatory and antifibrotic potential, suggest BI 1015550 to be a promising oral clinical candidate for the treatment of IPF and other fibrotic lung diseases

Herrmann FE, Hesslinger C, Wollin S-L, Nickolaus P. BI 1015550 is a PDE4B inhibitor and a clinical drug candidate for the oral treatment of idiopathic pulmonary fibrosis ***(full citation to be added)***

Front. Pharmacol., 20 April 2022

Novel anti-fibrotics - BI 1015550

Changes in FVC at Week 12



June 9, 2022

N Engl J Med 2022; 386:2178-2187

Novel anti-fibrotics - BI 1015550

FIBRONEER (IPF, PPF cohorts)

Oral BI 1015550 bid vs. placebo

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

Primary outcome : change in absolute FVC

PPF and IPF cohorts fully enrolled

Novel anti-fibrotics - BI 1015550

FIBRONEER

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- 52+ week study
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- Background pirfenidone / nintedanib allowed

Novel anti-fibrotics - BMS-986278

The lysophosphatidic acid receptor LPA1 links pulmonary fibrosis to lung injury by mediating fibroblast recruitment and vascular leak.

Tager AM, LaCamera P, Shea BS, Campanella GS, Selman M, Zhao Z, Polosukhin V, Wain J, Karimi-Shah BA, Kim ND, Hart WK, Pardo A, Blackwell TS, Xu Y, Chun J, Luster AD.

Nat Med. 2008 Jan;14(1):45-54.

Novel anti-fibrotics - BMS-986278

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

26 week, phase 2

Positive results reported at ATS ‘23, awaiting publication

Novel anti-fibrotics - BMS-986278

ALOFT-IPF / ALOFT-PPF

Oral BMS-986278 bid vs. placebo

Double-blind, 52 week RCT, 2:1 randomization (2 doses of BMS-986278 being evaluated)

Primary outcome : change in absolute FVC

For PFF study, broad range of immunosuppressants allowed

Enrollment has just opened

Novel anti-fibrotics - BMS-986278

ALOFT

- 2:1 randomization
- 52+ week study
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