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Taladegib (ENV-101) for the Treatment of Idiopathic Pulmonary Fibrosis: A Randomised, Double-Blind, Placebo-Controlled Phase 2a Trial

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Conflict of Interest Disclosure

Dr. Toby Maher has stock options from Qureight and has received consulting fees from Boehringer Ingelheim, Roche/Genentech, AbbVie, Amgen, AstraZeneca, Bayer, Bridge Bio, Bristol-Myers Squibb, CSL Behring, Endeavor BioMedicines, Galapagos, Galecto, GSK, IQVIA, Merck, Pfizer, Pliant, PureTech, Sanofi, Trevi, and Vicore.

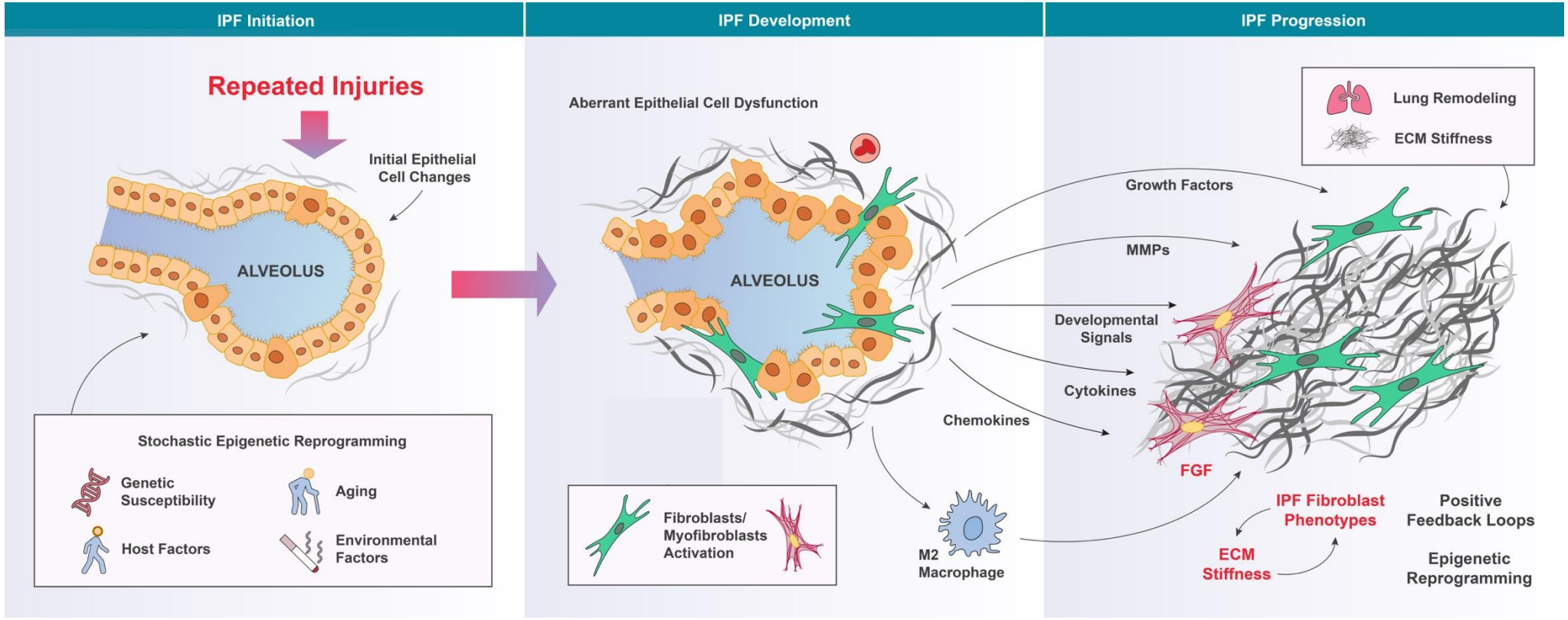
Dr. Maher has also participated on a data safety monitoring board or advisory board for Fibrogen, United Therapeutics, Nerre, IQVIA, and AstraZeneca.

Aims / Learning Objectives

1. Explore the role of the hedgehog signaling pathway in the pathophysiology of idiopathic pulmonary fibrosis (IPF) and its potential as a therapeutic target

2. Describe the efficacy, safety, and tolerability of taladegib in this Phase 2a randomized controlled trial of patients with IPF

Initiation, Development, and Progression of Idiopathic Pulmonary Fibrosis

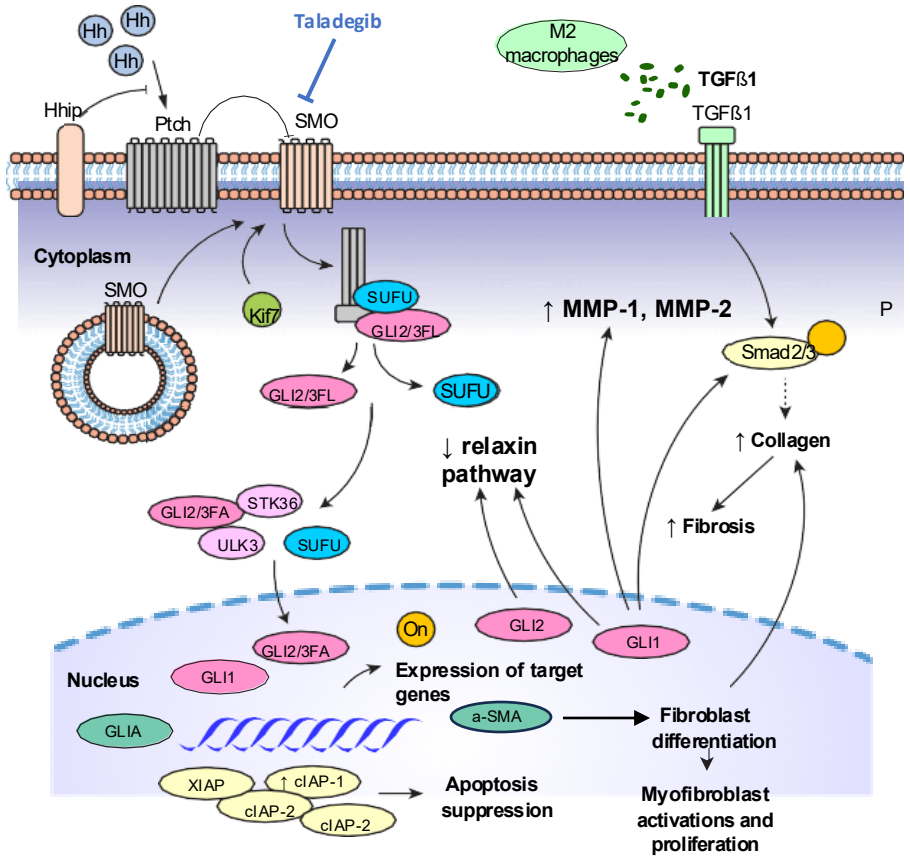


A complex interplay of genetic and environmental risk factors, aging-associated processes, and epigenetic reprogramming causes IPF

ECM, extracellular matrix; FGF, fibroblast growth factor; IPF, idiopathic pulmonary fibrosis; MMPs, matrix metalloproteinases; TGFβ, transforming growth factor beta.

Adapted from: Pardo A, Selman M. The interplay of the genetic architecture, aging, and environmental factors in the pathogenesis of idiopathic pulmonary fibrosis. Am J Respir Cell Mol Biol *2021;64:163–172.*

The Hedgehog Signaling Pathway Drives Fibrosis in IPF



- **Taladegib** is an orally available, small molecule Smoothened (SMO) antagonist that **inhibits the hedgehog (Hh) signaling pathway**
- The **Hh signaling pathway** is essential for proper cell differentiation in embryonic development and disease states
- **Persistent and aberrant activation of Hh signaling in IPF** occurs through the upregulation of sonic Hh and downstream effectors, **inducing multiple pro-fibrotic pathways**
- **Inhibition of the Hh pathway** results in regulation of the myofibroblast population via inhibition of the epithelial-mesenchymal transition and initiation of apoptosis of pathogenic myofibroblasts, which **has the potential to reverse the course of the disease**

1. Kurita Y, et al. Pirfenidone inhibits myofibroblast differentiation and lung fibrosis development during insufficient mitophagy. Respir Res. 2017;18(1):114

A Phase 2a Randomized, Double-Blind, Multicenter, Placebo-Controlled 12-Week Trial in Patients With IPF

1. Men and women >40 years old
2. IPF diagnosis based upon 2018 ATS/JRS/ERS/ALAT guidelines and centrally read chest HRCT
3. % predicted FVC >50%
4. Percent predicted DL_{CO} ≥35%
5. Life expectancy >12 months
6. Not taking antifibrotics

Randomization

1:1

16 study sites in Australia, Canada, Malaysia, Mexico, and South Korea

Taladegib 200 mg po QD (n=21)

12 weeks of treatment

Placebo po QD (n=20)

Safety follow-up

Baseline 6 12 18
Weeks

PRIMARY ENDPOINT

Overall safety of taladegib

SECONDARY ENDPOINTS

Change from baseline to Week 12 on lung function (% predicted FVC and FVC mL)

Patient-reported outcomes (UCSD SOBQ)

KEY EXPLORATORY ENDPOINT

HRCT at Week 12 (total lung capacity, %QILD, %QLF, %QGG)

ALAT, Latin American Thoracic Association; ATS, American Thoracic Society; DL_{CO}, diffusing capacity of lungs for carbon monoxide; ERS, European Respiratory Society; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; JRS, Japanese Respiratory Society; po, orally; QD, once a day; QGG, quantitative ground glass; QILD, quantitative interstitial lung disease; QLF, quantitative lung fibrosis; UCSD SOBQ, University of California, San Diego Shortness of Breath Questionnaire.

Maher TM, et al. *Lancet Respir Med*. Published online September 30, 2025

The Taladegib and Placebo Arms Were Well-Matched and Typical of IPF Population at Baseline

	Overall (N=41)	Taladegib (n=21)	Placebo (n=20)
Age, years, mean (SD)	70.4 (7.46)	69.7 (9.05)	71.2 (5.46)
Sex			
Female	7 (17%)	3 (14%)	4 (20%)
Male	34 (83%)	18 (86%)	16 (80%)
Race			
American Indian or Alaska Native	1 (2%)	0	1 (5%)
Asian	17 (42%)	10 (48%)	7 (35%)
White	19 (46%)	9 (43%)	10 (50%)
Other	4 (10%)	2 (10%)	2 (10%)
Ethnicity			
Hispanic or Latino	13 (32%)	7 (33%)	6 (30%)
Not Hispanic or Latino	23 (56%)	10 (48%)	13 (65%)
Other	5 (12%)	4 (19%)	1 (5%)
BMI (kg/m^2), mean (SD)	26.369 (3.3)	26.277 (3.4)	26.465 (3.3)
Time since IPF diagnosis, months (SD)	15.9 (20.4)	14.3 (20.1)	17.6 (21.1)
Prior antifibrotic therapy			
Pirfenidone	7 (17%)	4 (19%)	3 (15%)
Nintedanib	0	0	0
Baseline FVC (mL), mean (SD)	2718 (679)	2658 (742)*	2778 (624)
Baseline % predicted FVC, mean (SD)	82.8 (18.4)	80.6 (19.5)*	85.1 (17.4)
Baseline % predicted DL_{CO}, corrected for hemoglobin, mean (SD)	58.7 (16.7)	57.4 (16.4)†	60.1 (17.4)†
UCSD SOBQ score, mean (SD)	33.0 (24.3)	43.1 (24.9)	22.4 (19.0)

*n=20. †n=18.

BMI, body mass index; DL_{CO}, diffusing capacity of lungs for carbon monoxide; FVC, forced vital capacity; UCSD SOBQ, University of California, San Diego Shortness of Breath Questionnaire.

Safety of Taladegib

	Overall (N=41)	Taladegib (n=21)	Placebo (n=20)
Any TEAE	33 (81%)	18 (86%)	15 (75%)
Severe TEAE	4 (10%)	4 (19%)	0
Grade ≥3 TEAE	7 (17%)	5 (24%)	2 (10%)
Treatment-related grade ≥3 AE	0	0	0
Treatment-related AE†	18 (44%)	15 (71%)	3 (15%)
Treatment-emergent SAE	8 (20%)	6 (29%)	2 (10%)
Treatment-related SAE	0	0	0
TEAE leading to study drug interruption‡	8 (20%)	7 (33%)	1 (5%)
TEAE leading to dose reduction	5 (12%)	5 (24%)	0
TEAE leading to study withdrawal	1 (2%)	1 (5%)	0
TEAE leading to study drug discontinuation	4 (10%)	4 (19%)	0
TEAE leading to hospitalisation	4 (10%)	4 (21%)	0
TEAE leading to death	0	0	0

Overview of TEAEs*

- All TEAEs considered related to the study drug were grade 1 or 2
- No serious AEs and no AEs leading to hospitalisation were considered related to taladegib

*TEAEs were defined as AEs that occurred from the first administration of study drug to the end of study visit or a follow-up period of 7 days for non-serious AEs or up to 30 days for SAEs. If a participant had multiple occurrences of a TEAE, the participant was counted only once.
†Study drug-related TEAEs were defined as TEAEs possibly or probably related to the study drug.
‡Participants with TEAEs leading to study drug interruption include those for whom the study drug was discontinued.
AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Maher TM, et al. *Lancet Respir Med*. Published online September 30, 2025

Most Common TEAEs Reported

TEAEs reported by >10% of taladegib–treated participants by System Organ Class*†

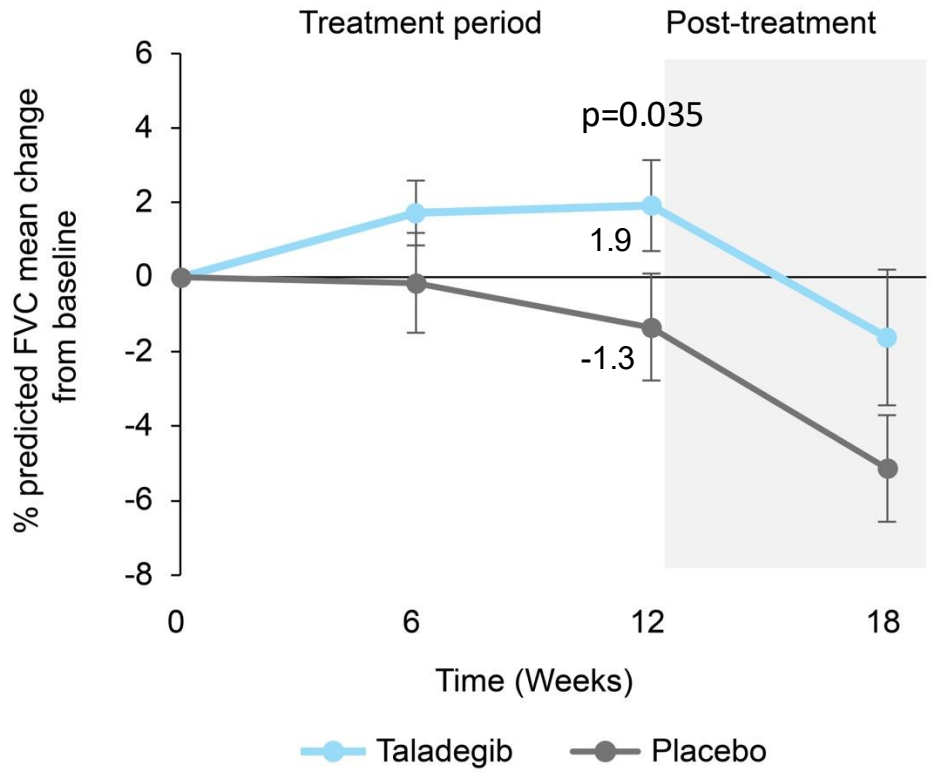
	Overall (N=41)	Taladegib (n=21)	Placebo (n=20)
Any TEAE	33 (81%)	18 (86%)	15 (75%)
Gastrointestinal disorders			
Diarrhea	7 (17%)	3 (14%)	4 (20%)
Nausea	4 (10%)	4 (19%)	0
Constipation	3 (7%)	3 (14%)	0
Nervous system disorders			
Dysgeusia	12 (29%)	12 (57%)	0
Headache	7 (17%)	4 (19%)	3 (15%)
Dizziness	4 (10%)	3 (14%)	1 (5%)
Musculoskeletal and connective tissue disorders			
Muscle spasms	12 (29%)	12 (57%)	0
Skin and subcutaneous tissue disorders			
Alopecia	11 (27%)	11 (52%)	0
Investigations			
Weight decreased	3 (7%)	3 (14%)	0
Metabolism and nutrition disorders			
Decreased appetite	3 (7%)	3 (14%)	0

The most common TEAEs in the taladegib arm are known Hh inhibitor class effects (dysgeusia, muscle spasms, alopecia)

*TEAEs were defined as AEs that occurred from the first administration of study drug to the end of study visit or a follow-up period of 7 days for non-serious AEs or up to 30 days for SAEs. If a participant had multiple occurrences of a TEAE, the participant was counted only once.
†System Organ Class and Preferred Term according to MedDRA version 24.0.
AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Maher TM, et al. *Lancet Respir Med*. Published online September 30, 2025

Treatment With Taladegib Improved Lung Function from Baseline

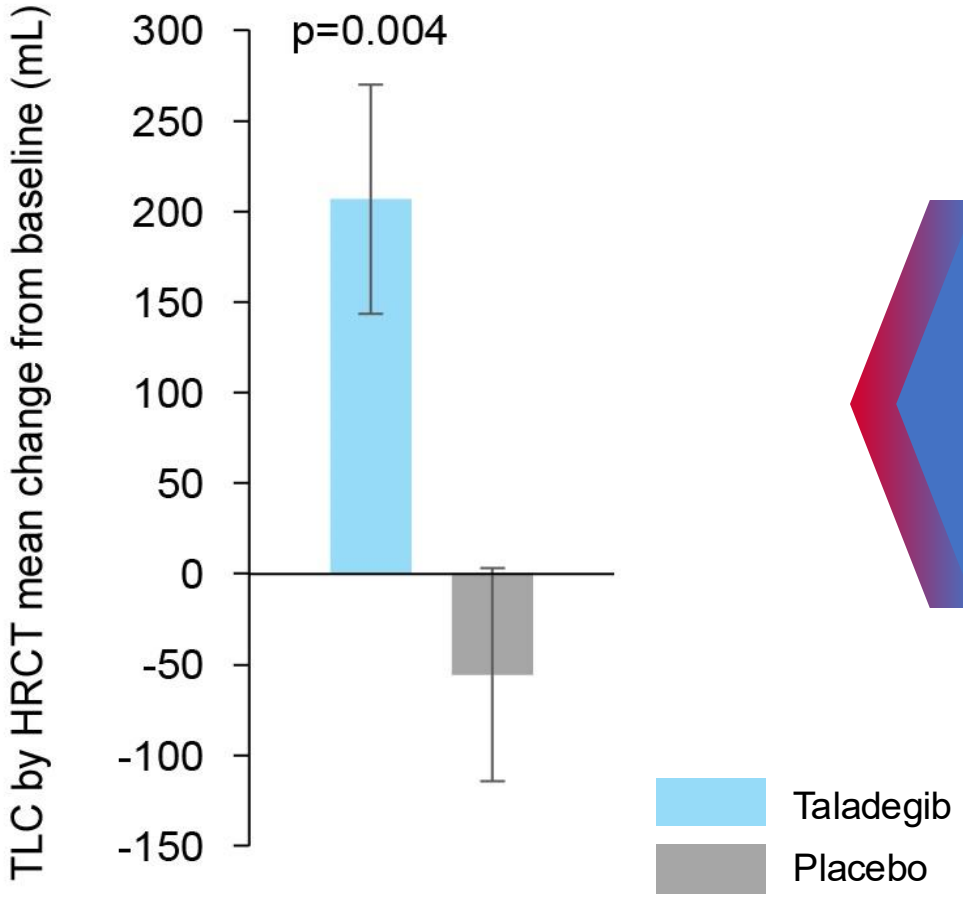
There was a significant difference in % predicted FVC after 12 weeks in the taladegib arm versus placebo (p=0.035)



Taladegib (n)	20	16	15	14
PBO (n)	20	19	19	17

FVC, forced vital capacity; PBO, placebo.
Maher TM, et al. *Lancet Respir Med*. Published online September 30, 2025

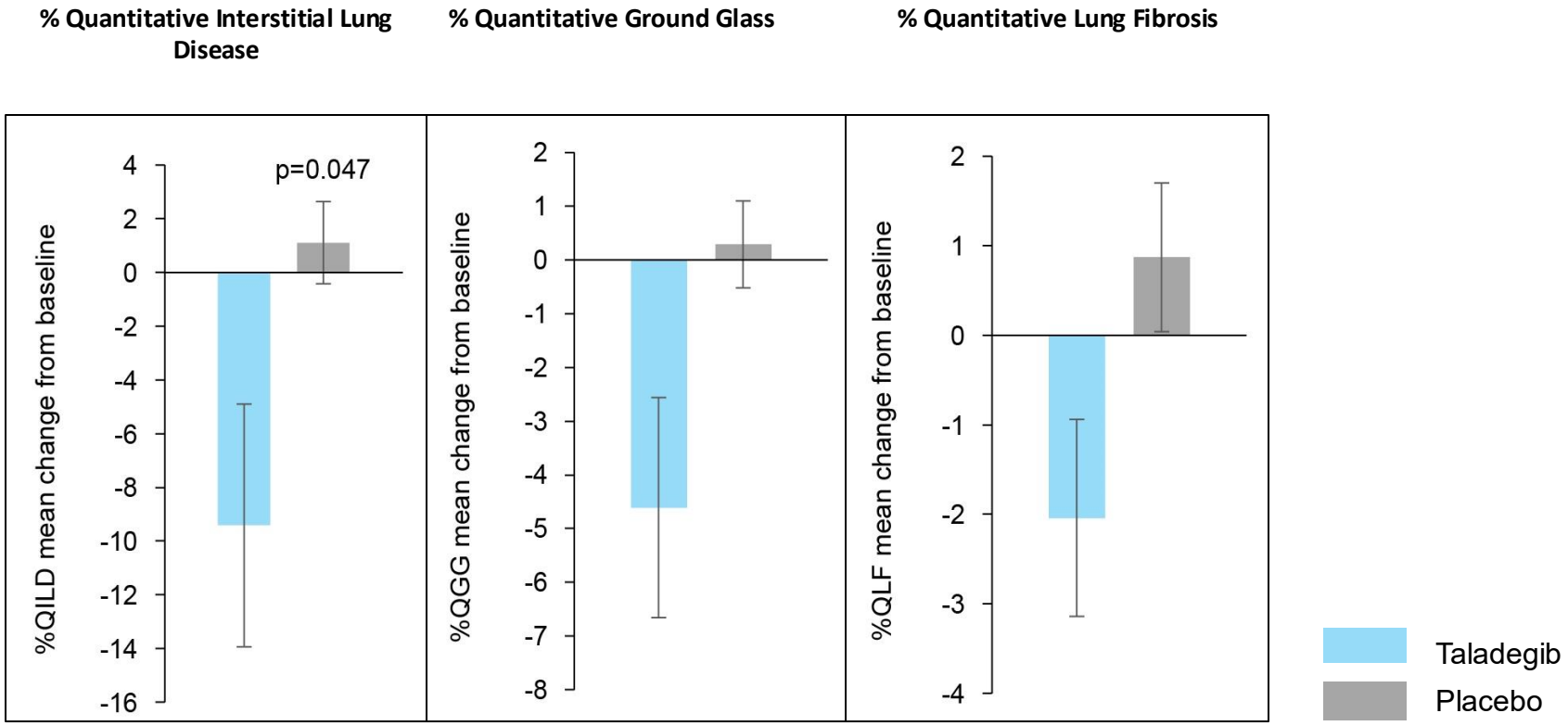
Treatment With Taladegib Led to an Increase in Total Lung Capacity as Measured by HRCT



There was a significant difference in TLC measured by HRCT after 12 weeks in the taladegib arm versus placebo (257.0 mL; p=0.004)

HRCT, high-resolution computed tomography; TLC, total lung capacity.
Maher TM, et al. *Lancet Respir Med*. Published online September 30, 2025

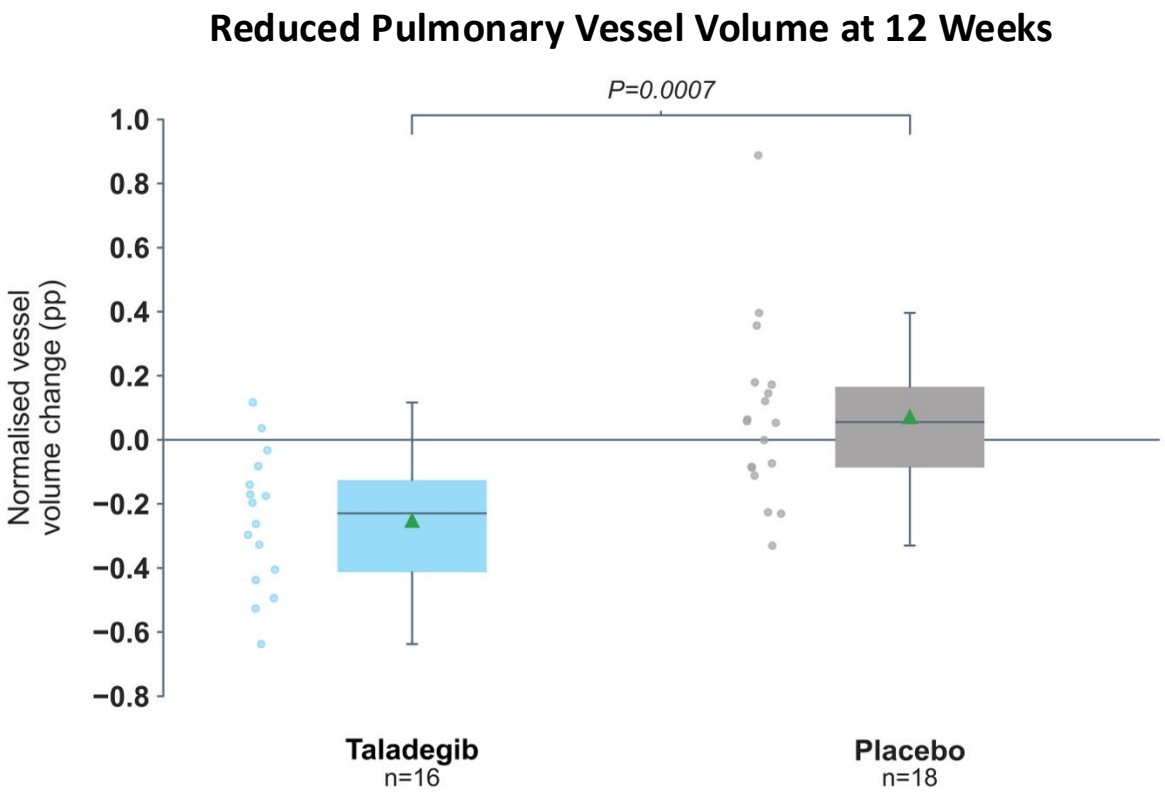
Taladegib Led to Improvements in Radiographic Measures of Disease From Baseline to Week 12



Taladegib treatment led to improvements in key measures of fibrosis, demonstrating the potential to reduce the extent of lung fibrosis

QGG, quantitative ground glass; QILD, quantitative interstitial lung disease; QLF, quantitative lung fibrosis.
Maher TM, et al. *Lancet Respir Med*. Published online September 30, 2025

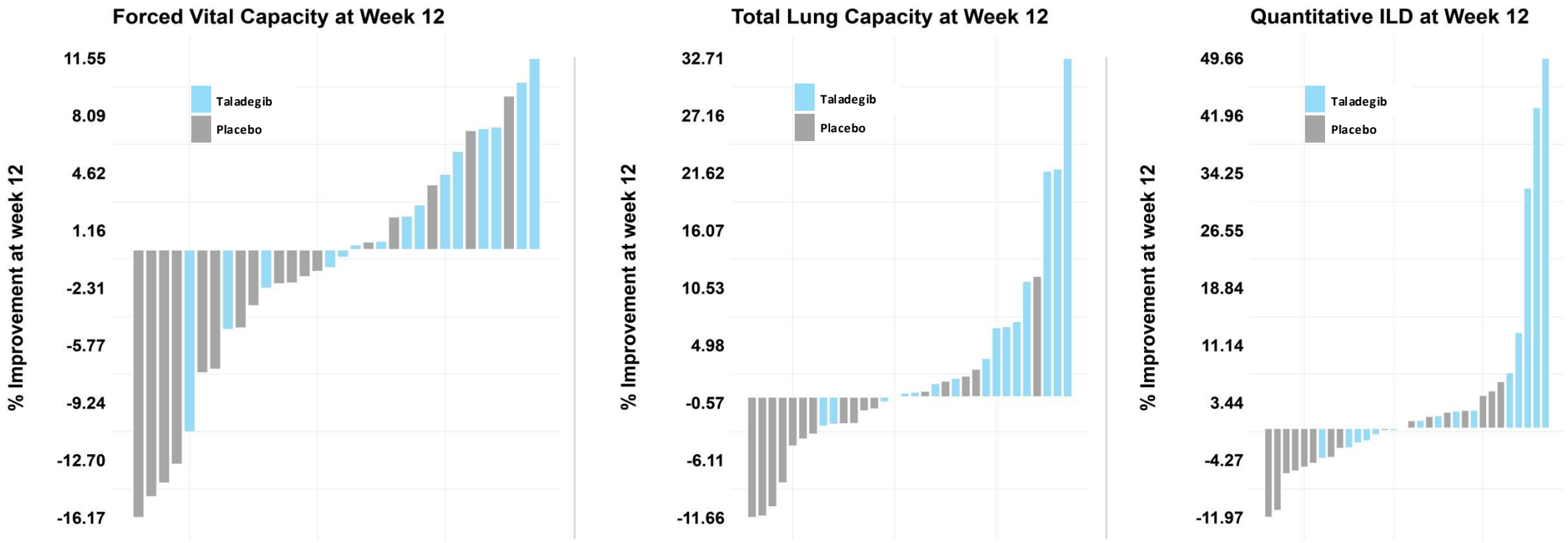
In a Post Hoc Analysis, Patients in the Taladegib Arm Demonstrated Reduction in Pulmonary Vessel Volume



- Significant reduction in normalised vessel volume vs placebo (PBO: 0.07pp vs taladegib: -0.25pp; p=0.0007; effect size=-1.28)
- First therapeutic to demonstrate a reduction in pulmonary vessel volume in patients with IPF

DiFrancesco A et al. Deep Learning-Based Disease Severity Biomarkers on Computed Tomography: Post Hoc Analysis in a Phase 2a Placebo-Controlled Study of ENV-101 in Subjects With Idiopathic Pulmonary Fibrosis. Presented at the American Thoracic Society Annual Meeting. San Francisco. 2025.

Taladegib Reversed Functional and Structural Measures of IPF Disease



The statistical probability of taladegib improving these endpoints by chance was 0.00037

ILD, interstitial lung disease.
Data on File. Endeavor BioMedicines

Conclusions

- Therapies that can stop or reverse pulmonary fibrosis are an unmet need, as the long-term prognosis of patients with IPF remains poor
- Taladegib demonstrated an acceptable safety and tolerability profile
- Taladegib treatment was associated with improvement in lung function and key measures of fibrosis, whereas the placebo treatment was associated with progressive disease
- These findings provide proof of concept for the therapeutic potential of targeting the Hh signaling pathway to disrupt and potentially reverse the underlying pathologic processes in idiopathic pulmonary fibrosis
- These data support the continued development of taladegib as a therapy for patients with IPF in a Phase 2b trial (WHISTLE-PF)

Maher TM, et al. Lancet Respir Med. Published online September 30, 2025

THE LANCET
Respiratory Medicine

Articles

Taladegib for the treatment of idiopathic pulmonary fibrosis (ENV-IPF-101): a multicentre, randomised, double-blind, placebo-controlled, phase 2a trial

T M Maher, J G Goldin, J Hood, J Pitman, M de los Rios, B P Hobbs, A B Yu-Lin, I Buendia-Roldan, F Thien, J W Song, P C Perea, A Ramírez-Rivera, A DiFrancesco

Summary

Background The hedgehog (Hh) signalling pathway promotes fibrosis in idiopathic pulmonary fibrosis (IPF), an interstitial lung disease with a high mortality rate. Currently, there is no cure for IPF, and available anti-fibrotics only slow the rate of decline in lung function in IPF. We aimed to assess the safety and efficacy of taladegib (ENV-101), an Hh pathway inhibitor, in IPF in a phase 2a, proof-of-concept clinical trial.

Methods ENV-IPF-101 was a randomised, double-blind, placebo-controlled, phase 2a trial conducted at 16 clinical sites in Australia, Canada, Malaysia, Mexico, and South Korea for patients with IPF older than 40 years who were not treated with concurrent IPF therapy. Patients were randomly assigned to taladegib 200 mg or placebo equivalent once daily, orally for 12 weeks, with a 6-week follow-up. The primary outcomes were safety in the intention-to-treat population and change from baseline in forced vital capacity (FVC) in the efficacy-evaluable population. Exploratory outcomes were measures of fibrosis on high-resolution CT (HRCT) in the efficacy-evaluable population. This study is registered with ClinicalTrials.gov, NCT04968574.

Findings Between Aug 12, 2021, and July 28, 2023, 41 patients were randomly assigned to the taladegib group (n=21; three [14%] female and 18 [86%] male) or the placebo group (n=20; four [20%] female and 16 [80%] male). All

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