Hedgehog Pathway Inhibition Improves Lung Function and Reduces Lung Fibrosis in Patients with IPF: Results from a Randomized, Double-blind, Placebo-controlled Phase 2 Trial of ENV-101

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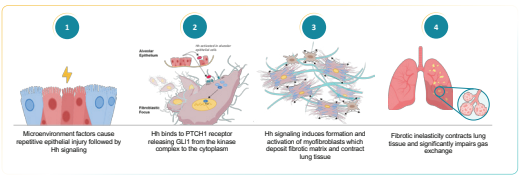
Constant Aberrant Activation of the Hedgehog Signaling Pathway Drives Pathophysiologic Fibrosis in IPF

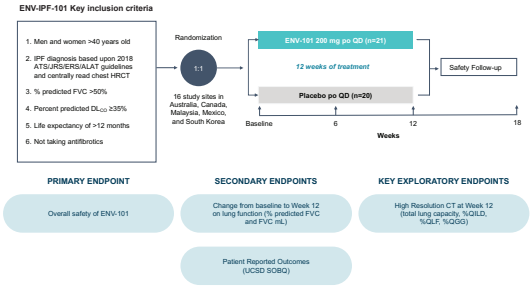
Myofibroblasts deposit fibrotic matrix as well as contract and remodel lung tissue in IPF, resulting in an inelastic, contracted lung and loss of lung function[1,2]



ENV-101 blocks the Hh pathway, causing myofibroblasts to undergo apoptosis, eliminating the driver of IPF pathology and enabling resolution of the wound remodeling disorder

- In IPF, the Hh pathway is dysregulated, with sustained activation of Hh signaling by SHH, perpetuating the presence and activity of myofibroblasts and contributing to the progressive fibrotic process.[1] SHH induces expression of multiple apoptosis suppressors in myofibroblasts and increases secretion of fibrotic proteins, including collagen and fibronectin.[2] These activities lead to pathological changes in lung structure that progress over time.[1]
- ENV-101 (taladegib) is a potent, selective, orally available inhibitor of SMO,[3-5] a key transmembrane protein of the Hh signaling pathway, that prevents the propagation of SHH signaling implicated in the pathogenesis and progression of IPF.

A Phase 2a Randomized, Double-blind, Multicenter, Placebo-controlled 12-week Trial in Patients with IPF



Baseline Demographics

Characteristic	ENV-101 (n=21)	Placebo (n=20)
Age (years, mean)	69.7 ± 9.0	71.2 ± 5.5
Male	86%	80%
BMI (kg/m^2, mean)	26.3 ± 3.4	26.5 ± 3.3
Mean ± SD % predicted FVC	80.6 ± 19.5 (n=20)	85.1 ± 17.4
Mean ± SD baseline DLco (mL/min/mmHg)	22.1 ± 2.5 (n=18)	22.6 ± 2.6 (n=18)
Time since IPF diagnosis (years, mean)	1.2	1.5
Previous antifibrotic treatment (pirfenidone)	19%	15%

ENV-101 Safety Profile

AE, n(%)	ENV-101 (n=21)	Placebo (n=20)
Any TEAE	**18 (85.7)**	**15 (75.0)**
Related to study drug	15 (71.4)	3 (15.0)
Treatment-related SAEs	0	0
Treatment-related AE Grade 3 or 4	0	0
TEAE leading to dose interruption	7 (33.3)	1 (5.0)
TEAE leading to withdrawal	1 (4.8)	0
TEAE leading to medication discontinuation	4 (19.0)	0
TEAE leading to death	0	0

Most common ENV-101–related TEAEs:

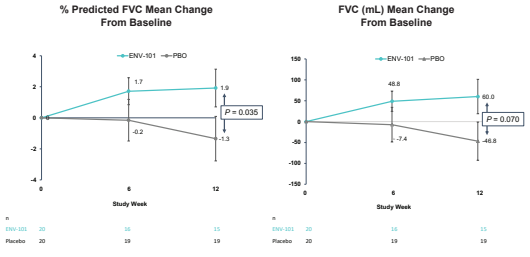
1. Dysgeusia (57%)
2. Alopecia (52%)
3. Muscles spasms (43%)

(On-target TEAEs observed with all Hh inhibitors)

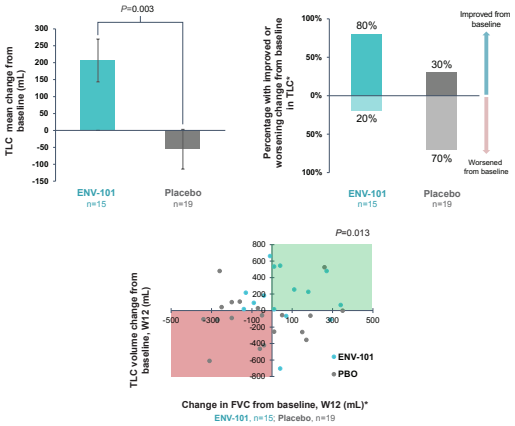
No clinically significant findings on labs, vital signs, ECGs, or physical exam.
5 patients discontinued ENV-101 treatment:

- 1 AE-related (dysgeusia, decreased appetite)
- 1 lost to follow-up post IPF exacerbation on Study Day 9
- 3 withdrew consent

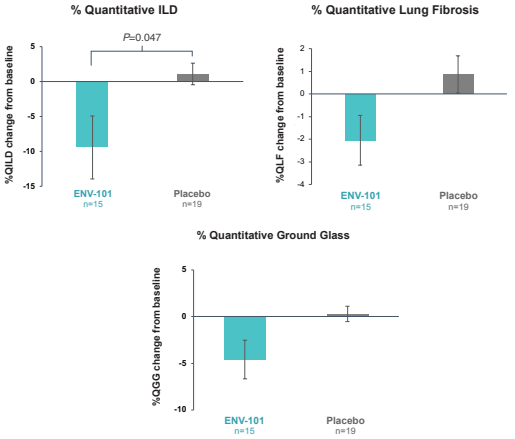
ENV-101 Continuously Improved Lung Function by Spirometry Through Week 12



Treatment with ENV-101 Increased Total Lung Capacity by HRCT and Was Correlated with Change in FVC



ENV-101 Treatment Led to Reduction of Interstitial Lung Disease and Lung Fibrosis by HRCT at Week 12



These HRCT results provide preliminary clinical evidence to support the proposed antifibrotic MOA of ENV-101

Conclusion

- **In patients with IPF, treatment with ENV-101 for 12 weeks improved lung function associated with an increase in lung capacity and a reduction in fibrosis**
- **There were no ENV-101–related safety signals, serious adverse events, or grade 3/4 adverse events**
- **Results support the continued development of ENV-101 in a planned Phase 2 dose-ranging trial in patients with IPF (WHISTLE-PF Trial)**

Statistical Methods:
If normality assumption was satisfied for the efficacy endpoint, the paired t-test was used to analyze the change from baseline at each timepoint. Two sample t-tests were used to compare efficacy endpoints between treatment arms at each timepoint. Generalized estimating equations were used to estimate mean values over time as well as changes from baseline over time for outcomes FVC, UCSD SOBQ, and DLco for each treatment arm. If normality assumption was violated, the non-parametric analog was used to assess treatment effect. Wilcoxon rank sum test was used to compare efficacy endpoints between treatment arms.

***Post hoc analyses**

Abbreviations:
AE, adverse event; **ALAT,** Latin American Thoracic Association; **ATS,** American Thoracic Society; **BMI,** body mass index; **CT,** computed tomography; **DL_{CO},** diffusing capacity of lungs for carbon monoxide; **ECG,** electrocardiogram; **ERS,** European Respiratory Society; **FVC,** forced vital capacity; **HRCT,** high resolution CT; **IPF,** idiopathic pulmonary fibrosis; **JRS,** Japanese Respiratory Society; **PBO,** placebo; **PO,** orally; **PPF,** progressive pulmonary fibrosis; **QD,** once a day; **QGG,** quantitative ground glass; **QILD,** quantitative interstitial lung disease; **QLF,** quantitative lung fibrosis; **SAE,** serious adverse event; **SD,** standard deviation; **SHH,** sonic hedgehog; **SMO,** smoothened; **TEAE,** treatment-emergent adverse event; **TLC,** total lung capacity; **UCSD SOBQ,** University of California, San Diego shortness of breath questionnaire; **W12,** week 12.

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J. Hood is the CEO of Endeavor BioMedicines.

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1. Effendi WI, Nagano T. *Int J Mol Sci* 2021;23(1):171. **2.** Bolaños AL, et al. *Am J Physiol Lung Cell Mol Physiol* 2012;303(11):L978-990. **3.** Lauressergues E, et al. *Pharmacol Res Perspect* 2016;4(2):e00214. **4.** Jin G, et al. *Arch Pharm Res* 2017;40(12):1390-1393. **5.** Gampala S, Yang JY. *Cells* 2021;10(11):3135.