ENV-101, a Novel Hedgehog Inhibitor, Increases Lung Function and Reduces Lung Fibrosis in Patients with Idiopathic Pulmonary Fibrosis: Results from a Randomized, Double-blind, Placebo-controlled Phase 2 Trial

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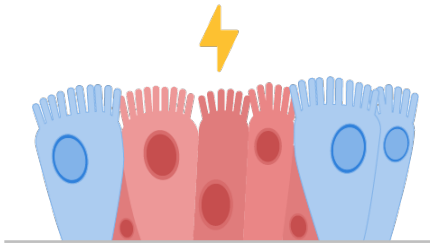
Constant Aberrant Activation of the Hh Pathway Drives Pathophysiologic Fibrosis in IPF

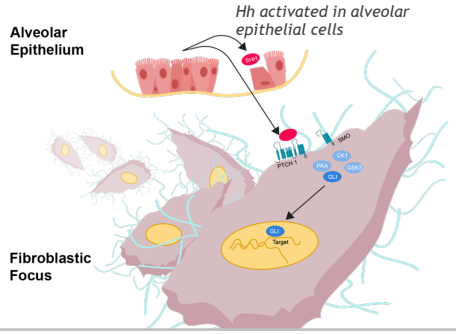
Myofibroblasts deposit fibrotic matrix as well as contract and remodel lung tissue in IPF, resulting in an inelastic, contracted lung and loss of lung function[1,2]

1



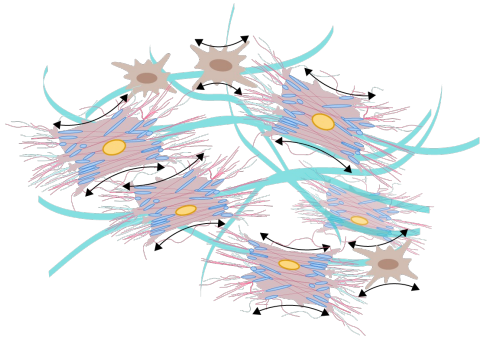
Microenvironment factors cause repetitive epithelial injury followed by Hh signaling

2



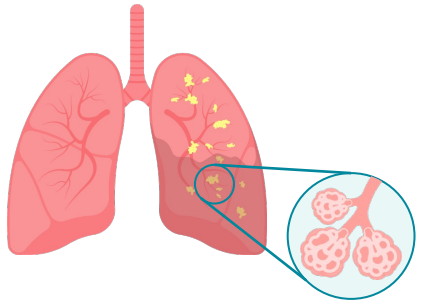
Hh binds to PTCH1 receptor releasing GLI1 from the kinase complex to the cytoplasm

3



Hh signaling induces formation and activation of myofibroblasts which deposit fibrotic matrix and contract lung tissue

4



Fibrotic inelasticity contracts lung tissue and significantly impairs gas exchange

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

Hh, hedgehog; IPF, idiopathic pulmonary fibrosis.

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-L990.

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

Key inclusion criteria

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 of >12 months
6. Not taking antifibrotics

Randomization

1:1

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

ENV-101 200 mg po QD (n=21)

12 weeks of treatment

Placebo po QD (n=20)

Safety Follow-up

PRIMARY ENDPOINT

Overall safety of ENV-101

SECONDARY ENDPOINTS

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

Patient-Reported Outcomes (UCSD shortness of breath questionnaire)

KEY EXPLORATORY ENDPOINTS

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

Clinicaltrial.gov Identifier: NCT04968574

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; JRS, Japanese Respiratory Society; po, orally; QD, once a dayQGG, quantitative ground glass; QILD, quantitative interstitial lung disease; QLF, quantitative lung fibrosis; ; UCSD, University of California San Diego.

Patient 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%

BMI, body mass index; SD, standard deviation.

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. Muscle spasms (43%)

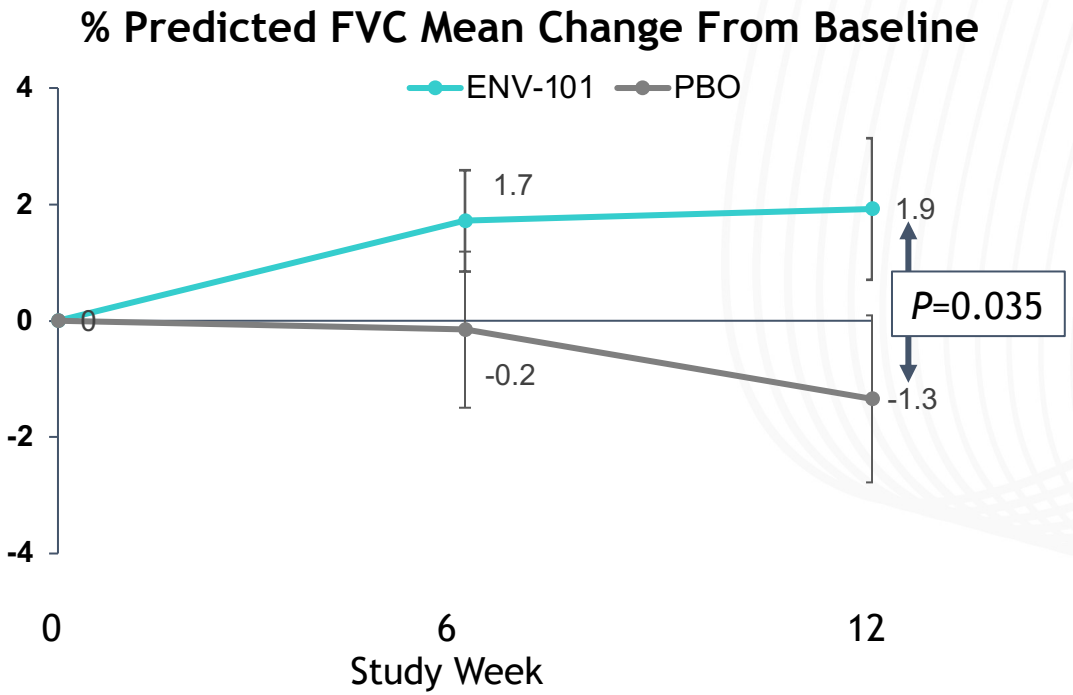
  (On-target TEAEs observed with all Hh inhibitors)
- No clinically significant findings on labs, vital signs, ECGs, or physical exam

5 patients discontinued ENV-101 treatment

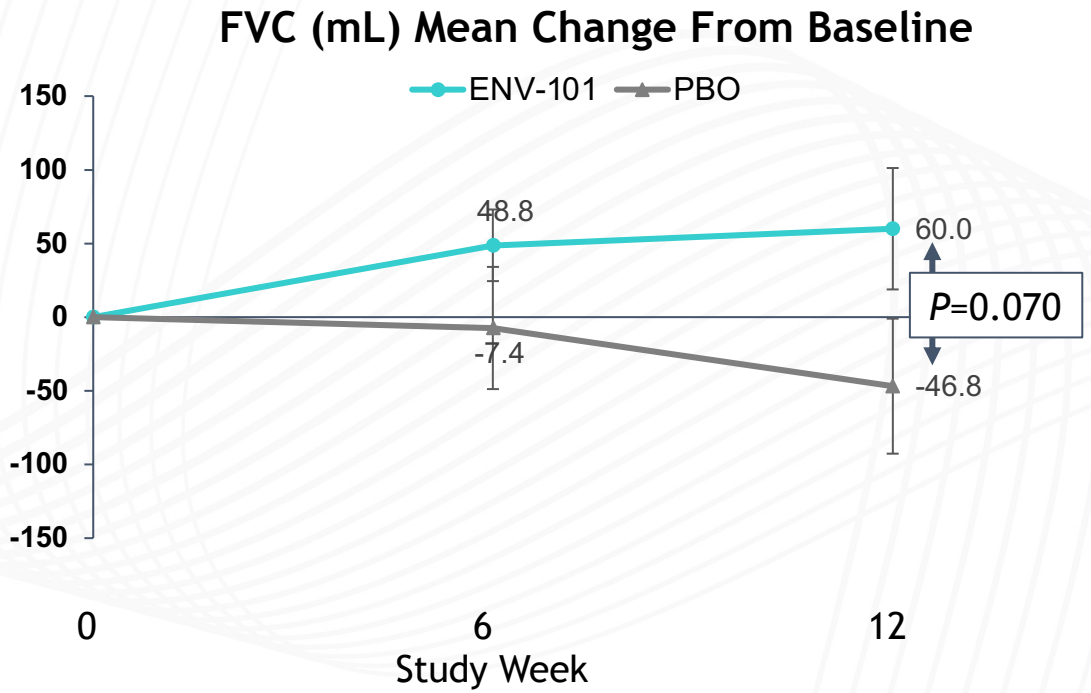
- 1 AE-related (dysgeusia, decreased appetite)
- 1 lost to follow-up post IPF exacerbation on Study Day 9
- 3 withdrew consent

AE, adverse event; ECG, electrocardiogram; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

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



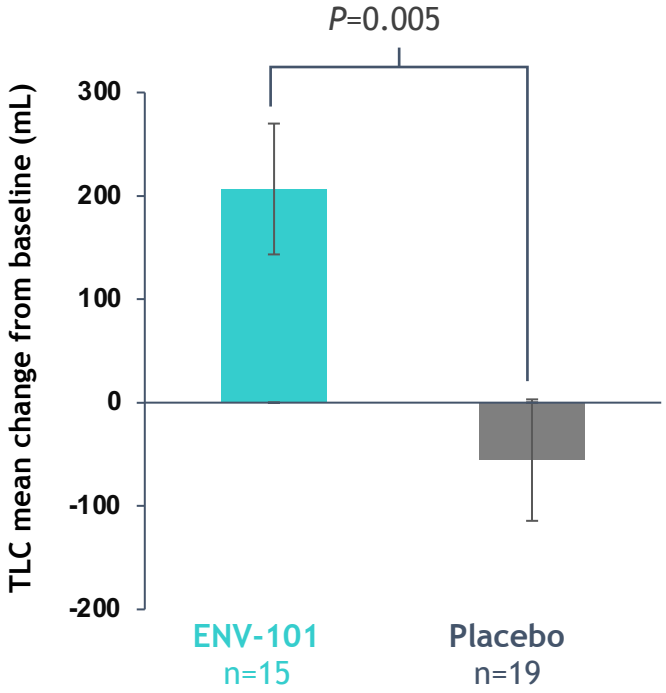
n			
ENV-101	20	16	15
Placebo	20	19	19

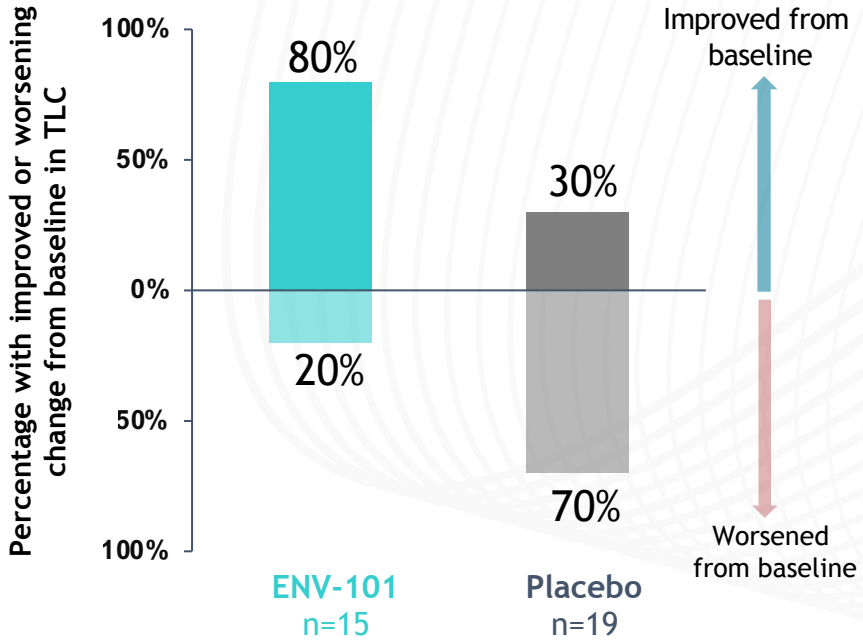


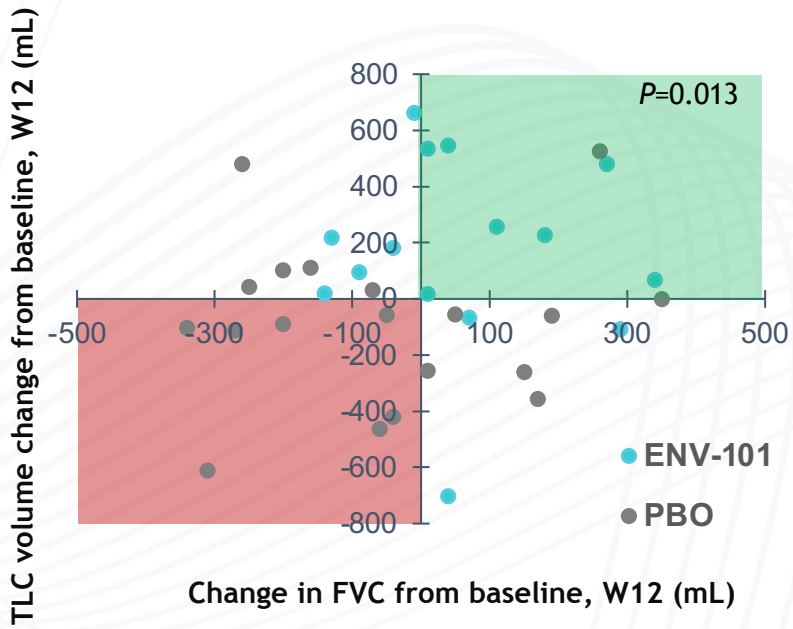
n			
ENV-101	20	16	15
Placebo	20	19	19

PBO, placebo.

Treatment with ENV-101 Increases Total Lung Capacity by HRCT and Is Correlated with Change in FVC at Week 12





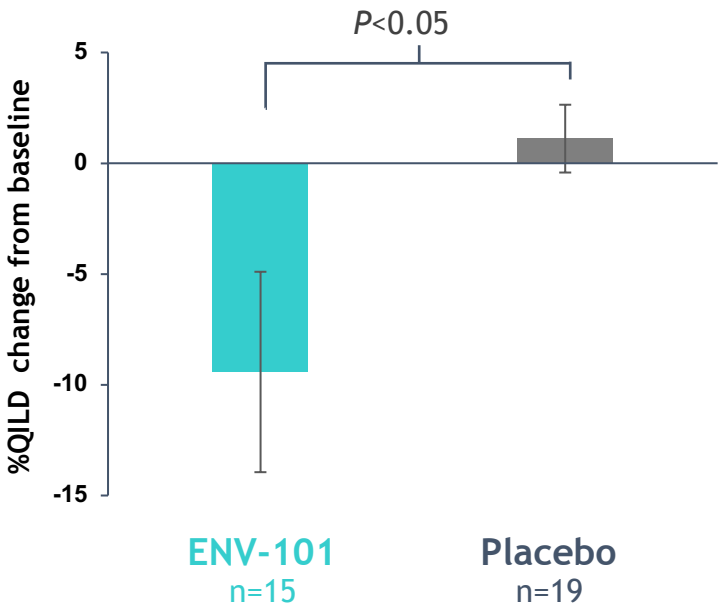


Treatment with ENV-101 led to a ~8% increase from baseline in total lung volume in 3 months

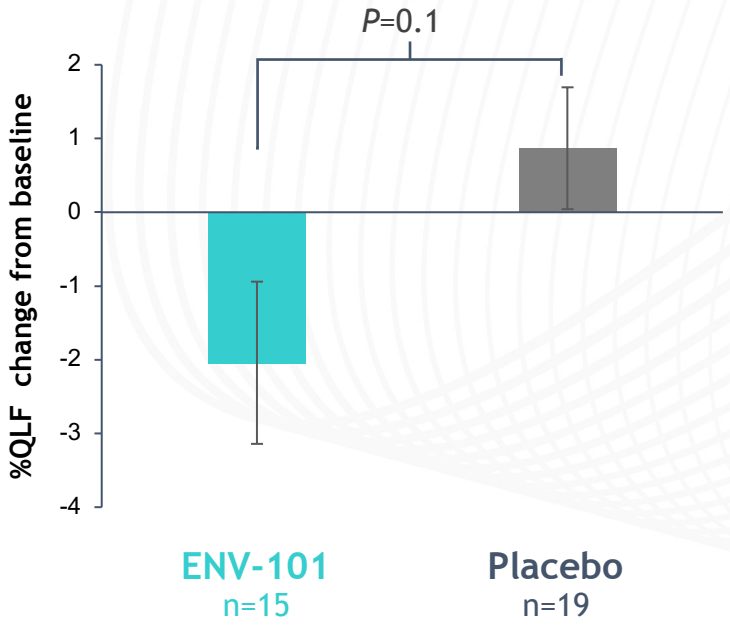
TLC, total lung capacity; W12, week 12.

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

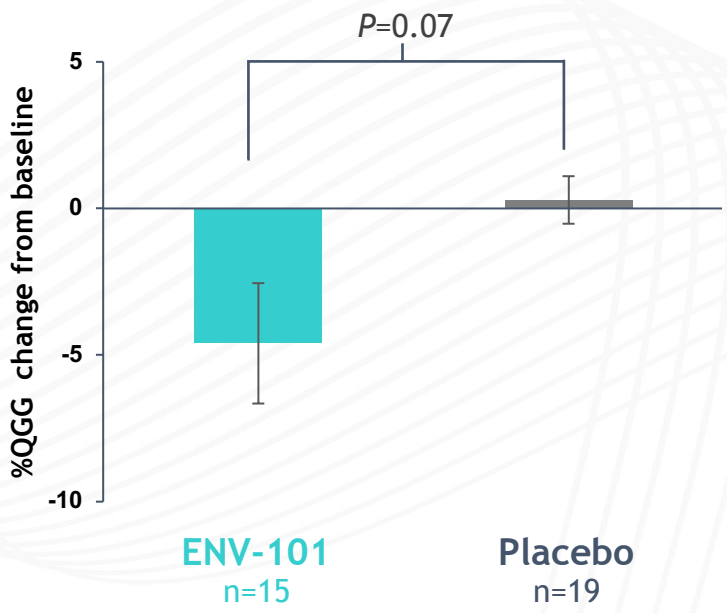
% Quantitative ILD



% Quantitative Lung Fibrosis



% Quantitative Ground Glass



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

Conclusions

- 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 or PPF (WHISTLE-PF Trial)

PPF, progressive pulmonary fibrosis.

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