WHISTLE-PF: Study Design of a Phase 2b, Multi-Center, Randomized, Double-Blind Controlled Trial of ENV-101 (Taladegib) in Patients With Idiopathic Pulmonary Fibrosis

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Aberrant Hh signaling promotes fibrosis in IPF

- Aberrant Hh signaling results in the formation of myofibroblasts, which drive lung fibrosis in IPF[1]
- Inhibiting the Hh pathway is a novel therapeutic approach in IPF, with the potential to reverse disease progression[2]

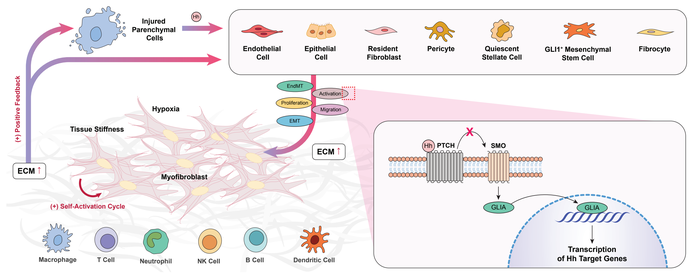


Figure 1. Hedgehog signaling pathway-mediated fibrogenesis. Prolonged and repetitive stimuli lead to consistent injury of parenchymal and epithelial cells. Epithelial cell injury results in Hh secretion. Epithelial cell Hh initiates crosstalk with immune and mesenchymal cells. Immuno-epithelial crosstalk results in the recruitment of various inflammatory cells. Precursor cell types, including resident fibroblasts, quiescent stellate cells, pericytes, bone marrow-derived fibrocytes/MSCs, endothelial cells undergoing EndMT, epithelial cells undergoing EMT, and GLI1+ MSCs, which are responsive to the Hh ligand, contribute to the myofibroblasts' activation, proliferation, differentiation, and sustained ECM production. This process is accompanied by the activation of the Hh signaling pathway (Hh/PTCH/SMO/GLIA), resulting in increased tissue stiffness, hypoxia, and tissue remodeling.

Adapted from Hu Y, et al.[3]

ENV-101 (taladegib) is a small molecule Hh inhibitor

Background

- Safety, tolerability, and therapeutic potential of ENV-101 in IPF were investigated in a 18-week, Phase 2a, randomized, double-blind placebo-controlled trial conducted at 16 centers in Australia, Canada, Malaysia, Mexico, and South Korea (NCT04968574)[4]
- Phase 2a data showed that there were no ENV-101–related serious AEs, related grade 3 or grade 4 AEs, or deaths in the trial
- In patients with IPF, treatment with ENV-101 for 12 weeks improved lung function (ppFVC, Figure 2), reduced lung fibrosis, and increased lung capacity
- Data from this trial supported further evaluation of the safety and efficacy of ENV-101 in the current Phase 2b WHISTLE-PF trial (NCT06422884)

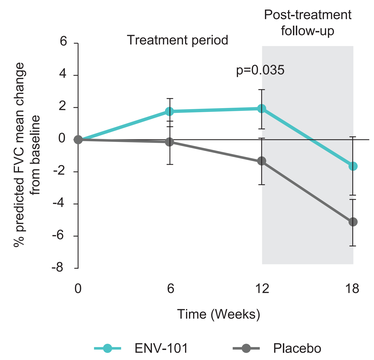
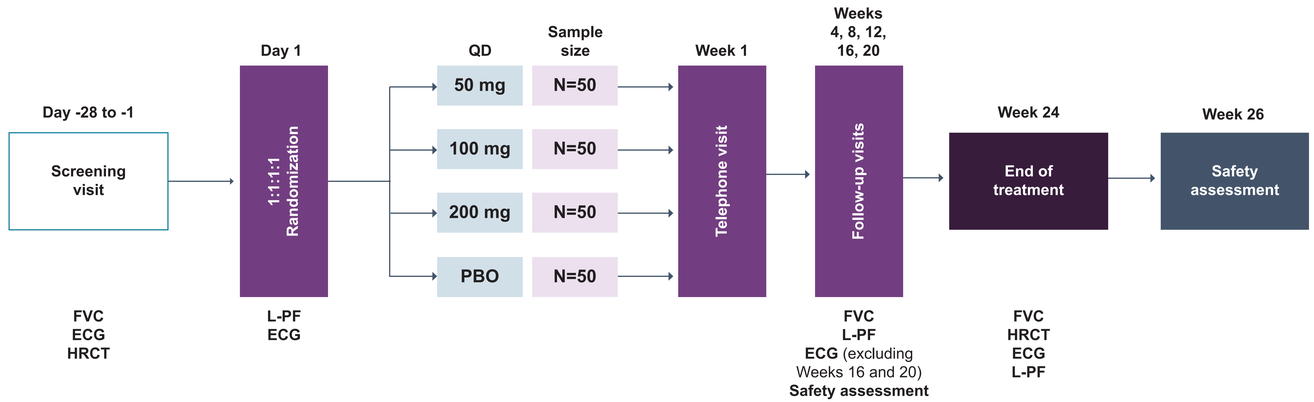


Figure 2. Mean change from baseline in secondary efficacy endpoint for lung function. Shown is the mean change from baseline at Weeks 6, 12, and 18 for ENV-101 and placebo for ppFVC.

Error bars represent standard error; p values are for the comparison between arms at Week 12; shaded area represents the follow-up period. ENV-101 arm, n=15; placebo arm, n=19.

WHISTLE-PF is an international, multi-center, randomized, double-blind, placebo-controlled, 6-month, dose-ranging Phase 2b trial of ENV-101 in patients with IPF

Study Design



Study Objectives and Endpoints

	Objectives	Endpoints
Primary	• Characterize the efficacy of a range of doses of ENV-101 (50 mg, 100 mg, or 200 mg) orally once daily compared to PBO in patients with IPF at 24 weeks	• Change in ppFVC from baseline to Week 24, as compared to PBO
Secondary	• Characterize the safety of ENV-101 in patients with IPF • Characterize the effects of ENV-101 on patient-reported outcomes in patients with IPF • Characterize the effects of ENV-101 on lung capacity and lung fibrosis as measured by chest HRCT in patients with IPF	• Assessments of TEAEs through Week 24 • Effects of ENV-101 on L-PF scores • Effects of ENV-101 on HRCT-based quantitative measures of TLC, ILD, ground glass, and lung fibrosis
Exploratory	• Characterize the PK of ENV-101 in patients with IPF	• ENV-101 PK parameters, including Day 1 C_{max} and C_{min} steady state

Entry Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Patients ≥40 years old • IPF diagnosis based upon 2022 international guidelines and centrally read chest HRCT • Percent predicted FVC ≥45% • Percent predicted DL_{CO} ≥25% • Life expectancy >12 months • Either no background antifibrotic or stable background antifibrotic	• Evidence of other known causes of ILD • Lung transplant expected within 12 months of the screening visit • Evidence of clinically significant lung disease other than IPF • FEV1/FVC ratio <0.7 at screening • Acute exacerbation of IPF within 3 months prior to Day 1 • History of malignancy during the preceding 5 years from the screening visit • Smoking (including vaping) within 6 months of the screening visit, current smoker, or unwillingness to refrain from smoking during the duration of the study • Major surgery requiring hospitalization performed within 3 months prior to the screening visit or planned during the course of the trial • Occurrence of serious illness requiring hospitalization within 90 days prior to Day 1 • Patients of reproductive potential who are sexually active and unwilling to use birth control for the duration of the study and for 3 months after their final dose • Females who are pregnant or nursing • Patients with a history of a severe allergic reaction or anaphylactic reaction or known hypersensitivity to any component of ENV-101

Conclusion

- Potential of Hh pathway inhibition in the treatment of IPF will be further assessed in future studies
- WHISTLE-PF will evaluate the dose-ranging effects, safety, and efficacy of the novel Hhi ENV-101 in patients with IPF
- Patients with IPF are now enrolling into WHISTLE-PF

Abbreviations:
AEs, adverse events; **DL_{CO},** diffusing capacity of lungs for carbon monoxide; **ECG,** electrocardiogram; **ECM,** extracellular matrix; **EMT,** epithelial–mesenchymal transition; **EndMT,** endothelial–mesenchymal transition; **FEV1,** forced expiratory volume in 1 second; **FVC,** forced vital capacity; **Hh,** hedgehog; **Hhi,** Hh inhibitor; **HRCT,** high-resolution computed tomography; **ILD,** interstitial lung disease; **IPF,** idiopathic pulmonary fibrosis; **L-PF,** living with pulmonary fibrosis; **MSCs,** mesenchymal stem cells; **PBO,** placebo; **PK,** pharmacokinetics; **ppFVC,** percent predicted forced vital capacity; **PTCH,** Patched; **QD,** once a day; **SMO,** Smoothened; **TLC,** total lung capacity; **TEAEs,** treatment-emergent adverse events.

References:
1. Effendi WI, Nagano T. The hedgehog signaling pathway in idiopathic pulmonary fibrosis: resurrection time. *Int J Mol Sci* 2021;23:171; 2. Cigna N, Farrokhi Moshai E, Brayer S, et al. The hedgehog system machinery controls transforming growth factor-β-dependent myofibroblastic differentiation in humans: involvement in idiopathic pulmonary fibrosis. *Am J Pathol* 2012;181:2126-2137; 3. Hu Y, Peng L, Zhuo X, Yang C, Zhang Y. Hedgehog signaling pathway in fibrosis and targeted therapies. *Biomolecules* 2024;14(12):1485; 4. Maher TM, Goldin JG, Hood J, et al. ENV-101 for the treatment of idiopathic pulmonary fibrosis: a randomised, double-blind, placebo-controlled phase 2 trial. *Submitted.*