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

Anita DiFrancesco[1], John Hood[1], Miguel de los Rios[1], Miguel Monterio[2], Elliott Bussell[2], Muhunthan Thillai[2], Simon LF Walsh[2,3]

1. Endeavor BioMedicines, San Diego, CA, United States; 2. Qureight Ltd, Cambridge, United Kingdom; 3. National Heart and Lung Institution, Imperial College, United Kingdom

Key Messages

ENV-101 (taladegib) is a small molecule Hh inhibitor with clinically validated efficacy in IPF patients

- **The ENV-IPF-101 (NCT04968574) trial was a randomized, double-blind, placebo-controlled Phase 2a study of ENV-101 (taladegib), a novel Hh signalling pathway inhibitor. Previously presented data showed that ENV-101 had an acceptable safety profile and improved lung function after 12 weeks of treatment**

Novel deep learning-based CT analysis technologies offer independent measures of IPF progression

- **Fibrotic tissue volume, airway volume, pulmonary vessel volume, and lung volume are all volumetric lung measures that change either during IPF disease progression or treatment response and predict mortality independently**
- **We evaluated the clinical utility of 3 newly developed deep learning models for quantifying lung volume (Lung8), pulmonary vessel volume (Vascul8), and fibrosis extent (Fibr8) on the baseline and follow-up CTs of treated and placebo patients**

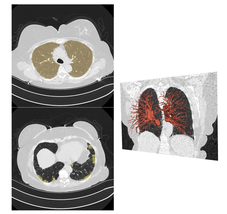
Results from post hoc CT analyses provide new evidence supporting ENV-101 activity and efficacy

- **Significant reduction in normalized pulmonary vessel volume (Vascul8) for patients in the treatment arm vs placebo**
- **Significant increase in lung volume (Lung8) and trend towards reduced fibrosis (Fibr8) for treated patients vs placebo**
- **Our analysis provides additional evidence that ENV-101 is reversing disease in IPF across multiple orthogonal endpoints given that a reduction in pulmonary vessel volume correlates with improved mortality and decreased disease burden in IPF[1,2]**
- **As a Hh pathway inhibitor, ENV-101 has the potential to exert a vascular effect, as captured by Vascul8**

Post Hoc Analysis Methods

A post hoc analysis of the Phase 2a study using deep learning-based image analyses

- The Qureight platform automated the segmentation of CT scans from 34 study patients (placebo = 18; ENV-101 = 16) using 3D Convolutional Neural Network-based algorithms trained on HRCT scans from IPF patients
- These algorithms quantified the lung volume (Lung8), pulmonary vessel volume (Vascul8), and fibrosis volume (Fibr8) from the CTs of study patients at baseline (t = 0) and 12 weeks. Example model outputs for lung and fibrosis volumes are shown opposite
- Group comparisons were performed with an independent samples t-test, and linear regression assessed variable relationships. Effect sizes were calculated using Hedge's g. A p-value < 0.05 was considered significant



Example: Example CT slices showing overlays in yellow for lung volume (top) and fibrosis volume (bottom). A 3D visualization of the pulmonary vessel segmentation is shown on the right. These segmentations can be used to calculate absolute volume, as well as fibrosis and vessel volume extent normalized to lung volume

Aberrant Hh Signaling Promotes Fibrosis in IPF

- Aberrant Hh signaling results in the formation of myofibroblasts, which drive lung fibrosis in IPF[3]
- Inhibiting the Hh pathway is a novel therapeutic approach in IPF, with the potential to reverse disease progression[4]

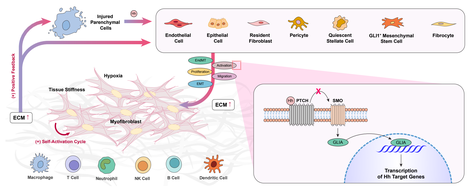
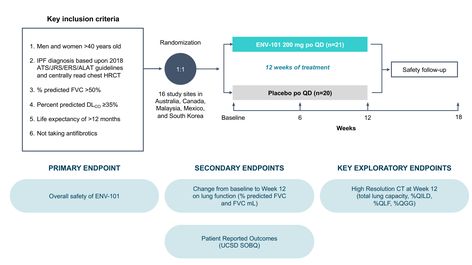


Figure 1. Hedgehog signaling pathway-mediated fibrogenesis. Prolonged and repetitive stimuli lead to consistent injury of parenchymal and epithelial cells. Epithelial cell injury results in Hh secretion. Epithelial cell Hh initiates crosstalk with immune and mesenchymal cells. Immuno-epithelial crosstalk 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.

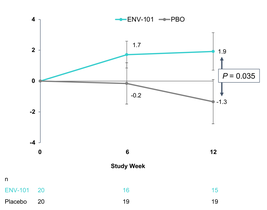
Adapted from Hu Y, et al.[5]

Phase 2a Study Design[6]



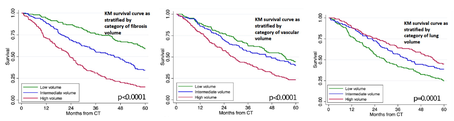
ENV-101 Continuously Improved Lung Function by Spirometry Through Week 12

% Predicted FVC Mean Change From Baseline



Exploratory endpoint measures also demonstrated a treatment effect, including an increase in Total Lung Capacity following ENV-101 treatment for 12 weeks, which correlated with FVC change

Lung, Fibrosis, Vasculopathy Models for Post Hoc Analysis[1]

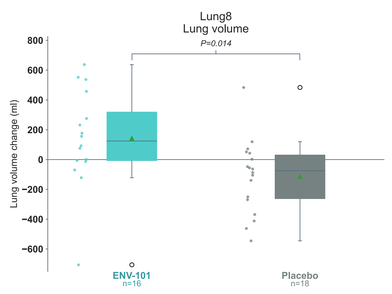


- Fibrosis/ILD scores in isolation or composite imaging metrics fail to optimize the prognostic utility of HRCT in IPF
- Increasing fibrosis extent, increasing vascular volume, and diminishing lung volume all associate with increased 2-year and 5-year mortality in IPF (controlling for disease severity, %ppFVC)
- Deep learning UNet-based CT segmentation models

Figures adapted from Thillai M, et al.[1]

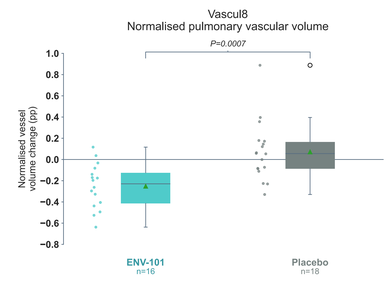
Results

Lung8 – Increased Lung Volume at 12 Weeks



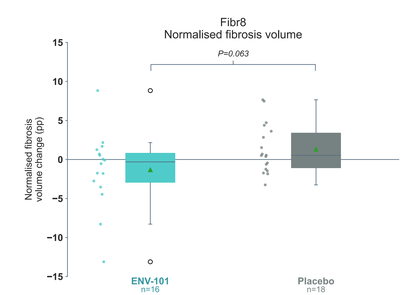
- Significant increase in lung volume change vs placebo (PBO: −113.07 mL vs ENV-101: 142.28 mL; p=0.014; effect size=0.87)
- Lung volume shows strong correlation with FVC (r=0.91, R^2=0.83)
- Larger effect size than % predicted FVC (p=0.03; effect size=0.78)

Vascul8 – Reduced Vessel Volume at 12 Weeks



- Significant reduction in normalised vessel volume vs placebo (PBO: 0.07pp vs ENV-101: -0.25pp; p=0.0007; effect size=-1.28)
- Larger effect size than % predicted FVC (p=0.03; effect size=0.78)
- First therapeutic to demonstrate a reduction in pulmonary vessel volume in IPF patients

Fibr8 – Reduced Fibrosis Extent at 12 Weeks



- Trend towards reduction in fibrosis vs placebo (PBO: 1.32pp vs ENV-101: −1.32pp; p=0.063; effect size=−0.64)
- Good negative correlation between Fibr8 normalised fibrosis volume % and ppFVC (r=-0.72, R^2 =0.52)

Conclusions

1. **In IPF, deep learning-based quantification of lung volume and pulmonary vascular changes may offer valuable insights that corroborate physiological improvement in lung function and measure treatment effects with a greater effect size than FVC, the current registrational endpoint in IPF**
2. **Utilization of deep learning models corroborates previous findings from the Phase 2a study of ENV-101 in patients with IPF:**
   - **Significantly improved lung volume**
   - **Reduced fibrosis extent**
3. **A new finding from this post hoc analysis demonstrated significantly reduced pulmonary vascular volume with a greater effect size than FVC**
4. **This post hoc analysis provides additional clinical evidence that ENV-101 is reversing disease across multiple lung compartments and orthogonal endpoints:**
   - **A reduction in pulmonary vessel volume has been correlated with improved mortality and decreased disease burden**
   - **To date, ENV-101 is the only therapeutic that has demonstrated a reduction in pulmonary vessel volume**
   - **The fact that this result was demonstrated in a 12-week study provides additional compelling support for the potential clinical utility of ENV-101 in patients with IPF**
   - **Result suggests new mechanistic insight given the known association of Hh inhibition with vascular repair effects**

Abbreviations:
ALAT, Latin American Thoracic Association; **ATS,** The American Thoracic Society; **CT,** computed tomography; **DL_{CO},** diffusing capacity of lungs for carbon monoxide; **ECM,** extracellular matrix; **EMT,** epithelial-mesenchymal transition; **EndMT,** endothelial to mesenchymal transition; **ERS,** European Respiratory Society; **FVC,** forced vital capacity; **Hh,** hedgehog; **HRCT,** high-resolution computed tomography; **IPF,** idiopathic pulmonary fibrosis; **JRS,** Japanese Respiratory Society; **MSCs,** mesenchymal stem cells; **PBO,** placebo; **po,** orally; **QD,** once a day; **pp,** percentage points, **QGG,** quantitative ground glass; **QILD,** quantitative interstitial lung disease; **QLF,** quantitative lung fibrosis; **UCSD SOBQ,** University of California San Diego Shortness of Breath Questionnaire.

References:
1. Thillai M, Oldham JM, Ruggiero A, et al. Deep learning-based segmentation of computed tomography scans predicts disease progression and mortality in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med.* 2024;210(4):465-472. 2. Jacob J, Bartholmai BJ, Rajagopalan S, et al. Mortality prediction in idiopathic pulmonary fibrosis: evaluation of computer-based CT analysis with conventional severity measures. *Eur Respir J.* 2017;49(1):1601011. 3. Effendi WI, Nagano T. The hedgehog signaling pathway in idiopathic pulmonary fibrosis: resurrection time. *Int J Mol Sci.* 2021;23:171. 4. 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. 5. Hu Y, Peng L, Zhuo X, Yang C, Zhang Y. Hedgehog signaling pathway in fibrosis and targeted therapies. *Biomolecules.* 2024;14(12):1485. 6. 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.*