Treatment with taladegib results in increased lung volume and regression of markers of ILD: a Phase 2a post hoc CT analysis using Brainomix e-Lung

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Key Messages

Taladegib (ENV-101) is a small molecule Hh inhibitor with statistically significant evidence of efficacy in patients with IPF

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

Previously published results from CT analyses provide unique evidence supporting the activity and efficacy of taladegib

- **UCLA algorithms (protocol-specified endpoint) showed significant improvements from baseline in TLC and a reduction in %QILD from baseline after 12 weeks of taladegib treatment. A post hoc analysis conducted by Qureight also showed a significant increase in lung volume (Lung8) and a trend toward reduction in fibrosis (Fibr8) after 12 weeks of taladegib treatment[1]**

Evaluation with the Brainomix 360 e-Lung platform further supports improvements in lung volume and a reduction in fibrosis, strengthening the cumulative evidence supporting the ability of taladegib to improve lung structure and reduce fibrosis

- **The taladegib and placebo groups were well matched at baseline, with slightly higher disease severity for the taladegib group (WRVS)**
- **12 weeks of taladegib treatment resulted in a significant increase in lung volume versus placebo**
- **There was a significant reduction in TDE versus placebo, a measure of the total burden of ILD in the lungs**
- **Treatment with taladegib led to a significant reduction in RVS versus placebo**
- **Improvements in e-Lung markers were in line with the observed improvement in FVC**

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

The Hedgehog Signaling Pathway Drives Fibrosis in IPF

Persistent and aberrant activation of Hh signaling in IPF occurs through the upregulation of sonic Hh and downstream effectors, inducing multiple pro-fibrotic pathways[2]

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

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Abbreviations
AI, artificial intelligence; **CT,** computed tomography; **FDA,** US Food and Drug Administration; **FVC,** forced vital capacity; **GGO,** ground-glass opacity; **Hh,** hedgehog; **HRCT,** high-resolution computed tomography; **ILD,** interstitial lung disease; **IPF,** idiopathic pulmonary fibrosis; **PBO,** placebo; **PPF,** progressive pulmonary fibrosis; **QCT,** quantitative computed tomography; **%QILD,** percent quantitative interstitial lung disease; **%QLF,** percent quantitative lung fibrosis; **RVS,** reticulovascular score; **SD,** standard deviation; **SMO,** Smoothened; **TDE,** total disease extent; **TLC,** total lung capacity; **UCLA,** University of California, Los Angeles; **WRVS,** weighted reticulovascular score.

Conflict of Interest Disclosure:
The presenting author has received honoraria and personal fees from Brainomix, Boehringer Ingelheim, Avalyn, AstraZeneca, Daiichi Sankyo, GSK, and Roche. The presenting author is a Senior Medical Director at Brainomix and holds stock options in the company.

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BRAINOMIX

Taladegib Is Being Investigated to Treat IPF

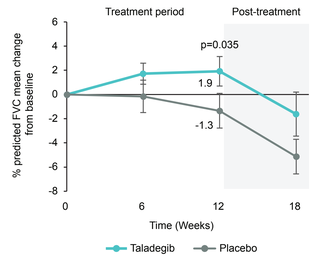
Taladegib is an orally available, small molecule SMO antagonist that inhibits the Hh signaling pathway

Previously presented data from a Phase 2a randomized, double-blind, multicenter, placebo-controlled 12-week trial in adults with IPF showed that taladegib had an acceptable safety profile, improved lung function, reduced lung fibrosis, and increased lung capacity after 12 weeks of treatment[3]

Exploratory endpoints of antifibrotic activity derived from chest HRCT included the change from baseline to week 12 in TLC, %QILD, and %QLF using a previously published algorithm from UCLA in partnership with Voiant Clinical[3,4]

Treatment With Taladegib Improved Lung Function From Baseline[4]

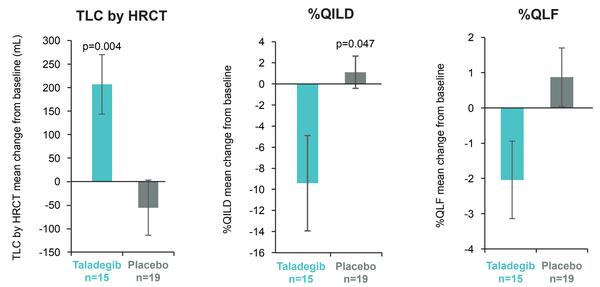
Figure 1. Taladegib led to significant improvements in % predicted FVC versus placebo from baseline to week 12



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

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

Figure 2. Taladegib led to improvements in radiographic measures of disease from baseline to week 12*



*UCLA/Voiant HRCT measurements

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

Results

Figure 3. The taladegib and placebo groups were well matched for disease severity at baseline

WRVS is a measure of peripheral fibrosis severity and a strong prognostic indicator

Baseline WRVS ≥15% indicates increased risk of FVC decline

Mean values at baseline:

- Taladegib: 15.5%
- Placebo: 14.2%

The taladegib arm had numerically more severe disease as measured by QCT biomarkers versus the placebo arm

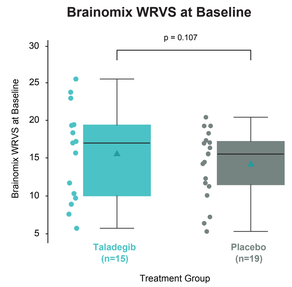
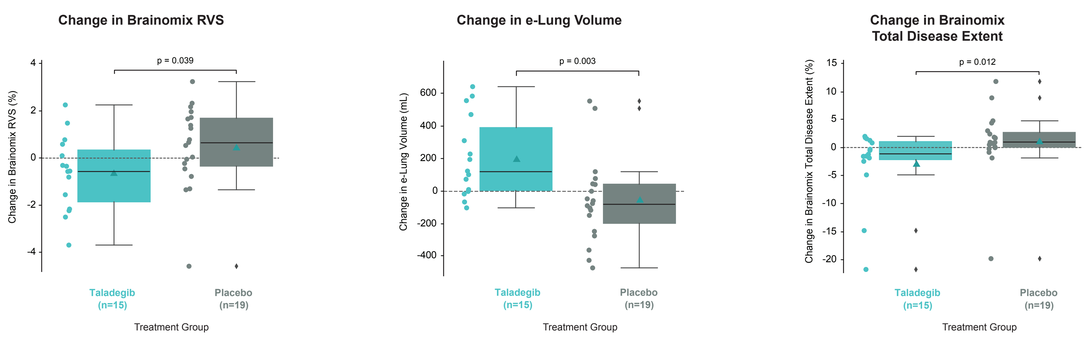


Figure 4. Treatment with taladegib demonstrated improvements from baseline in lung volume and surrogate measures of ILD severity versus placebo



Improvements were seen in RVS in the taladegib group (−0.7%) versus placebo (+0.5%) (p=0.039)

Mean rise in lung volume in the taladegib-treated group of +204 mL compared with a decline in the placebo group of −60 mL (p=0.003)

Significant difference in the mean change in TDE between taladegib (−2.9%) and placebo (+1.0%) (p=0.012)

Aims and Objectives

Assess the impact of taladegib on QCT measures of lung volume, ILD extent, and progression of fibrosis, applying the Brainomix e-Lung algorithm to baseline and 12-week HRCT scans in the Phase 2a trial

Methods

Brainomix 360 e-Lung Platform

Brainomix e-Lung is an FDA-cleared, AI-powered imaging software platform that automatically identifies and quantifies features on CT lung images, which can output configurable metrics that can be used to support the ILD clinical workflow, and is used prospectively in ILD clinical trials to provide outcome measures

e-Lung has been clinically validated to measure CT-based biomarkers in patients with ILD and PPF

Image Curation

Brainomix e-Lung performed quality control, image processing, and data analytics independently and blinded to the lung function data

Available chest CT scans were considered valid and were included in the analyses if they met the following criteria:

- Volumetric axial HRCT reconstruction with contiguous coverage of the lungs
- Non-contrast acquisition with full coverage of the lungs at full inspiration
- Slice thickness <3 mm and axial slice spacing <5 mm
- Absence of excessive artefacts such as noise, beam hardening, or motion

34 subjects (n=15 taladegib; n=19 placebo) were included in the analysis

e-Lung Processing

CT scans were processed using e-Lung (v2.3)

QCT biomarkers generated using e-Lung were:

- Lung volume (mL); the total volume of both lungs in mL
- RVS %; a surrogate measure of fibrosis severity
- WRVS %; a surrogate measure of peripheral fibrosis extent. WRVS >15% has been shown to be associated with risk of disease progression and mortality[5-7]
- TDE %; a measure of the total burden of ILD in the lungs as a sum of RVS and GGO

Statistical Methodology

QCT measurements are summarized with mean ± SD, while categorical variables are summarized using counts and percentages

The Wilcoxon rank sum method was used to determine statistical significance of any difference in QCT between groups, with a p-value <0.05 deemed to indicate statistical significance

Conclusions

Brainomix e-Lung analysis of the 12-week Phase 2a clinical trial found that **taladegib** treatment resulted in

- **Significant increase from baseline in lung volume** versus placebo (+204 mL vs −60 mL; p=0.003)
- **Significant reduction from baseline in TDE** versus placebo (−2.9% vs +1.0%; p=0.012)
- **Improvements from baseline in RVS** in the taladegib group (−0.7%) versus placebo (+0.5%) (p=0.039)

These data are **consistent** with previous results from the Phase 2a study and findings from the post hoc imaging analyses, reinforcing the potential role of **Hh pathway dysregulation in the pathophysiology of IPF and supporting the mechanism of action of taladegib to treat IPF**

With imaging results noted as early as 12 weeks, these results support further evaluation of QCT as an objective complement to FVC