Simulated efficacy of nerandomilast on forced vital capacity decline in idiopathic pulmonary fibrosis and progressive pulmonary fibrosis across background antifibrotic therapies

Samuel P. Callisto[1], Kyle Baron[1], Elias Clark[1], Curtis Johnston[1*], Nikolas Onufrak[2*], Sonja Hartmann[2*], Steve Choy[2]
[1]*Metrum Research Group, Boston, MA, U.S.A.*, [2]*Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, U.S.A.*
[*]Affiliation during time of analysis

Introduction

IPF and PPF Pathophysiology

- Idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF) are chronic, fibrosing interstitial pneumonias primarily affecting older adults [1, 2]
- Activated epithelial cells secrete cytokines, driving excessive extracellular matrix (ECM) deposition, lung distortion, and irreversible functional loss [3]

Current Standard of Care

- Antifibrotic (AF) medications pirfenidone (IPF) and nintedanib (IPF/PPF) demonstrate forced vital capacity (FVC) preservation through slowed disease progression without halting FVC decline
- Side effects and poor tolerability limit long-term adherence and combination treatment

Nerandomilast Mechanism of Action

- Nerandomilast (JASCAYD®) is a selective phosphodiesterase 4 isoenzyme B (PDE4B) inhibitor recently approved by the U.S. FDA and China's CDE for the treatment of both IPF and PPF
- Blockade of PDE4B elevates intracellular cyclic adenosine monophosphate (cAMP), thereby reducing pro-fibrotic growth factors and inflammatory cytokines, exerting dual antifibrotic and immunomodulatory effects [4]

Objectives

- Develop an exposure-response (ER) model capable of describing the effect of nerandomilast on absolute FVC using data collected throughout clinical development
- Identify optimal doses for individuals taking background AF treatment using simulations

Methods

Data Source and Efficacy Analysis Population

- The analysis was based on pooled data from two Phase 3 trials: Study 1305-0014 (IPF) and Study 1305-0023 (PPF) which included 2,353 patients contributing 20,937 FVC observations over 52 weeks in patients receiving either 9 mg nerandomilast twice daily (BID), 18 mg nerandomilast BID, or placebo [5, 6]
- The population was predominantly male (69.3%) with a median age of 69 years (range: 26 to 90 years) and a median baseline FVC of 2520 mL (range: 750-5940 mL)
- Background AF treatment was common: 44.5% of patients used nintedanib and 16.2% used pirfenidone

Absolute FVC ER Model

- A longitudinal mixed-effects ER model incorporating disease progression was developed to link individual model-derived nerandomilast steady-state minimum concentrations ($C_{min,ss}$) with changes in individual absolute FVC (FVC_i) using the following equation:

$$FVC_i = base_i - \alpha_i \cdot time + \beta_i \cdot \sqrt{C_{min,ss,i}}$$

- Baseline FVC ($base_i$): Included covariate effects for age, height, sex, background AF treatment, and underlying diagnosis (IPF vs. PPF)
- Disease Progression (α_i): Modeled the rate of FVC decline (mL/week) as influenced by height, background AF treatment, and the square-root of individual model-derived $C_{min,ss}$ ("disease-modifying effect")
- Drug Effect (β_i): Represented the "offset" drug effect (initial benefit) driven by the square-root of individual model-derived $C_{min,ss}$
- Inter-individual Variability (IIV): Random effects were estimated for $base_i$, α_i, and β_i

Simulation Methodology

- Typical Value Simulations: Conducted using 300 simulation replicates with parameter sets excluding IIV drawn from the uncertainty distribution for each iteration to summarize the range of median FVC responses across background AF scenarios
- Population Simulations: 300 replicates of 1000 virtual patients generated by sampling with replacement from the IPF and PPF study population, incorporating IIV and residual unexplained variability (RUV), to generate prediction intervals that reflect the expected range of outcomes in the broader patient population

Results

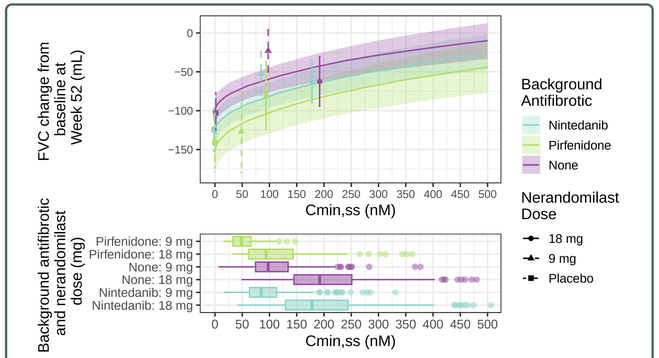

Figure 1. Preservation of FVC at Week 52 increases with nerandomilast $C_{min,ss}$. **Top:** Predicted FVC change from baseline at Week 52 vs. nerandomilast $C_{min,ss}$ colored by background AF. Lines and shaded regions represent the median and 95% CI from 300 population simulations; vertical bars show observed median response and 95% CI for AF/dose group. **Bottom:** Observed $C_{min,ss}$ by treatment and AF group. Boxplot shows medians as horizontal lines, inter-quartile range (IQR) as boxes, 1.5 × IQR as whiskers, and outliers as filled circles.

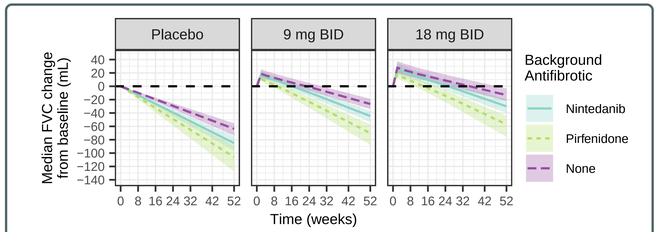

Figure 3. Nerandomilast slows IPF and PPF disease progression with or without background antifibrotic medication. Median (solid line) and 90% CI (shaded) from 300 typical value simulation replicates using observed covariate distributions. Reference line (dashed) indicates zero change from baseline.

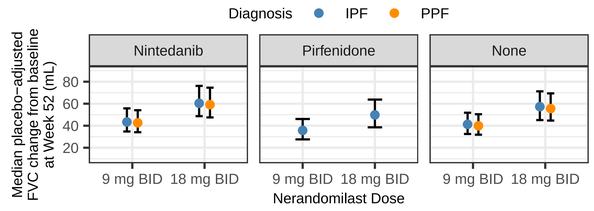

Figure 2. Change in FVC from baseline varies by nerandomilast dose and background antifibrotic medication, but not diagnosis. Median (solid line) and 90% CI (shaded) from 300 typical value simulation replicates using observed covariate distributions. Facet labels refer to background antifibrotic medication. Filled circle denotes observed values stratified by diagnosis and background antifibrotic.

Model Performance and Covariate Effects

- The ER model captured the overall trend of longitudinal FVC trajectories across all patient subgroups, including both IPF and PPF populations
- Key structural parameters were robustly identified with a relative standard errors (RSE) range of 0.1% to 34.4%
- The therapeutic benefit of nerandomilast was seen to elicit both an initial benefit, or "offset effect", and a long-term benefit, or "disease-modifying effect" mediated through a reduction in the rate of FVC decline, with both effects driven by the square-root of $C_{min,ss}$ (Figure 1)
- Older age, female sex, presence of background AF medication, and an underlying diagnosis of PPF (as compared to IPF) were associated with decreased baseline FVC, while taller height was associated with increased baseline FVC
- Taller height and presence of background AF medication were associated with increased rate of decline in FVC

Model-Predicted Efficacy Outcomes at Week 52

- Predicted placebo-adjusted change from baseline FVC (ΔFVC_{adj}) at Week 52 was consistent with reported Phase 3 results (Figure 2) [5, 6]

Impact of Background Antifibrotics and Covariates

- No disease-specific differences in nerandomilast efficacy were identified between IPF and PPF (Figure 2)
- Background pirfenidone use was associated with increased nerandomilast clearance, leading to 30.3–47.8% lower nerandomilast exposure and a corresponding reduction in FVC preservation (Figure 1)
- Increasing the dose from 9 mg to 18 mg BID in patients on pirfenidone provided efficacy comparable to the 9 mg dose group who received either nintedanib or no background AF medication (Figure 3)
- Effects were consistent across body weight, race, ethnicity subgroups, and on top of existing standard of care; therefore, dose adjustments were not warranted in any of these populations (results not shown)

Conclusions

- This model-based analysis confirms the presence of a positive ER relationship between nerandomilast and FVC preservation in patients with IPF and PPF
- The therapeutic benefit of nerandomilast is maintained regardless of underlying diagnosis (IPF vs. PPF) or demographic factors (body weight, sex, and race)
- Simulations support the use of 18 mg BID as providing enhanced clinical benefit across the broad patient population, while mitigating the reduced exposure observed with background pirfenidone use, ensuring a robust treatment response in patients on multi-drug regimens

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Disclosures

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