Population pharmacokinetics of nerandomilast in patients with idiopathic pulmonary fibrosis and progressive pulmonary fibrosis

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Background

Mechanism of Action

- Nerandomilast (JASCAYD®) is an orally administered, preferential inhibitor of the phosphodiesterase-4B (PDE4B) isoenzyme
- PDE4B hydrolyzes and inactivates cyclic adenosine monophosphate

Therapeutic Indication

- Approved by the U.S. FDA and China's CDE for the treatment of idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF)
- IPF is a specific type of interstitial lung disease (ILD) and PPF is associated with a subset of ILDs distinct from IPF
- Both IPF and PPF lead to lung scarring that progresses over time, with a median survival time of 3-5 years

Chemical and Metabolic Properties

- Nerandomilast (R-enantiomer) contains a chiral sulfoxide group and undergoes a minor level of metabolic chiral inversion following oral administration
- The resulting S-enantiomer is pharmacologically inactive
- Both nerandomilast and the S-enantiomer were characterized in this analysis

Objectives

The objective of this analysis was to support dose selection of nerandomilast in patients with IPF and patients with PPF. To achieve this, the parent-metabolite relationship between nerandomilast and the S-enantiomer was characterized.

Methods

Clinical Trial Data Sources and Population Characteristics

- A total of 1,653 subjects from six Phase 1 and two Phase 3 trials were included: 109 healthy volunteers, 770 patients with IPF, and 774 patients with PPF [1, 2]
- Quantifiable plasma concentrations corresponding to nerandomilast (n=8,414) and the S-enantiomer (n=822) were included
- Baseline age ranged from 18–90 years (median 69 years), body weight from 31.2–143 kg (median 73.7 kg), and estimated glomerular filtration rate (eGFR) from 15.8–135 mL/min/1.73 m² (median 85.2 mL/min/1.73 m²)

Population Pharmacokinetic (PK) Model Development and Simulation

- A population PK model incorporating both nerandomilast and the S-enantiomer was developed to characterize their dose-exposure relationship. Model performance was evaulated by assessing the precision of parameter estimates, goodness-of-fit plots, and simulation-based diagnostics
- The PK of nerandomilast was described by a three-compartment model with sequential zero- and first-order absorption and linear elimination; the S-enantiomer PK was described by a one-compartment model with five transit compartments and a separate dosing compartment to describe an apparent fraction of S-enantiomer in the administered dose (Figure 1)
- Population simulations using the final PK model evaluated steady-state exposures at dose levels of 9 and 18 mg twice daily (BID) in subpopulations of interest; virtual population was generated by empirically sampling with replacement 1,000 representative patients from the Phase 3 analysis dataset

Results

Parameter Estimation Strategy

- A sequential modeling approach was used, in which nerandomilast parameters were estimated first and subsequently fixed in the parent-metabolite model where S-enantiomer parameters were estimated

Relevant Covariate Effects

- **Nerandomilast**
  - Concomitant pirfenidone increased nerandomilast CL/F by 48% (95% confidence interval (CI): 40-56%), leading to reduced exposure; concomitant nintedanib use had a negligible effect on CL/F
  - Nerandomilast CL/F was 24.8% lower (95% CI: 18.4-30.7%) in patients with IPF or PPF than in healthy volunteers
  - Nerandomilast CL/F was 10% lower (95% CI: 2.9-16.7% in Chinese subjects and 14.3% lower (95% CI: 6.2% to 21.7%) in Japanese subjects than in non-Chinese/non-Japanese subjects
  - Nerandomilast CL/F was estimated to increase with increasing eGFR and decrease with increasing bilirubin
  - Nerandomilast V2/F was 60% higher (95% CI: 37-87%) in patients with IPF or PPF than in healthy volunteers
  - Nerandomilast V2/F was lower in females, Chinese subjects, and Japanese subjects
  - Effect of body weight was included on all nerandomilast clearance and volume parameters using the fixed allometric exponents of 0.75 and 1, respectively
- **S-enantiomer**
  - No covariates were included on S-enantiomer parameters as covariate effects were assumed to be consistent and accounted for via fixed nerandomilast parameters

Exposure Differences

- Simulation-based evaluations showed that differences in nerandomilast exposure between IPF and PPF populations were driven by baseline demographic and clinical covariates, such as sex, body weight, Japanese ethnicity, and especially concomitant pirfenidone use in the IPF population, rather than disease-specific effects (Figure 2)

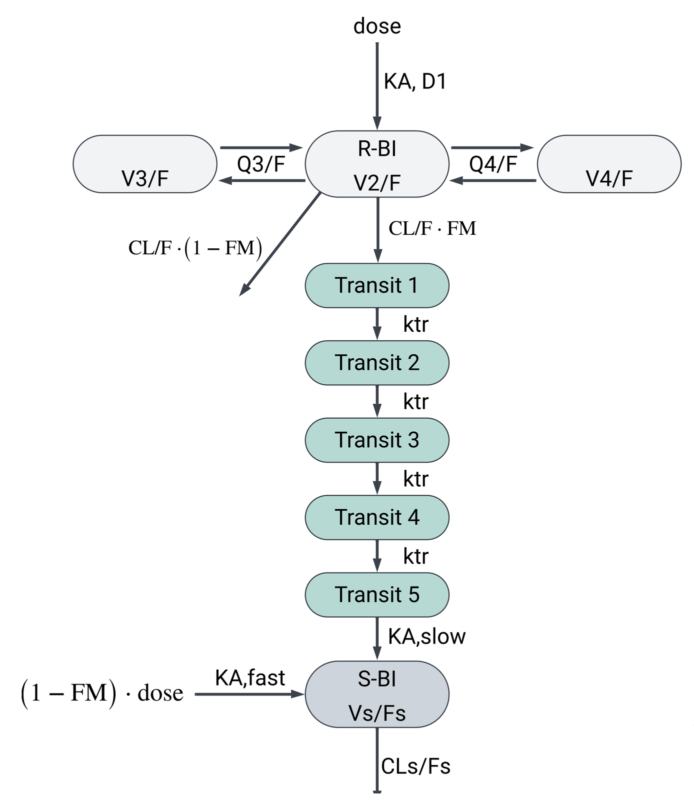

Figure 1. Combined enantiomer compartmental model structure. R-BI: nerandomilast; S-BI: S-enantiomer; CL/F: apparent clearance of nerandomilast (central compartment); D1: duration of zero-order absorption; FM: fraction of nerandomilast converted to the S-enantiomer; KA: first-order absorption rate constant.; KA,fast: absorption rate of S-enantiomer from the administered dose; KA,slow: absorption rate of S-enantiomer into the central compartment from the 5th transit compartment; ktr: transit (distribution) rate constant between S-enantiomer transit compartments; CLs/Fs: apparent clearance of S-enantiomer (central compartment); Q3/F, Q4/F: apparent intercompartmental clearance of nerandomilast (central-peripheral 1; central-peripheral 2); V2/F, V3/F, V4/F: apparent volumes of distribution of nerandomilast (central; peripheral 1; peripheral 2).

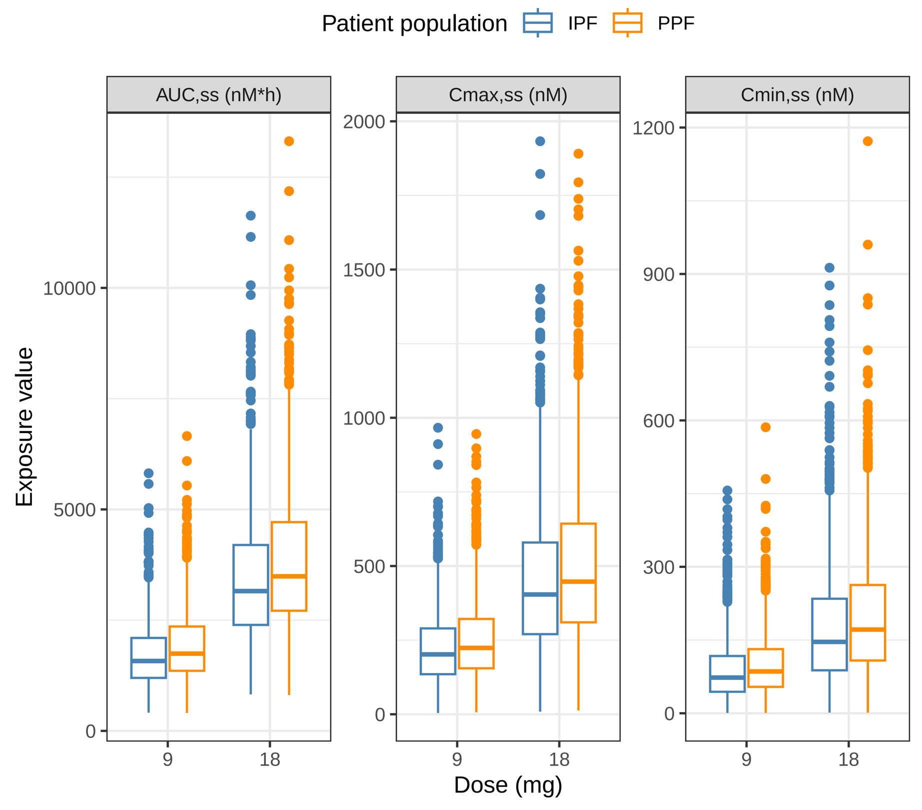

Figure 2. Boxplots of simulated nerandomilast exposure versus dose stratified by exposure metric and patient population. AUC,ss: area under the concentration-time curve for a dosing interval at steady state; Cmax,ss: maximum concentration in the dosing interval at steady state; Cmin,ss: minimum concentration in the dosing interval at steady state.

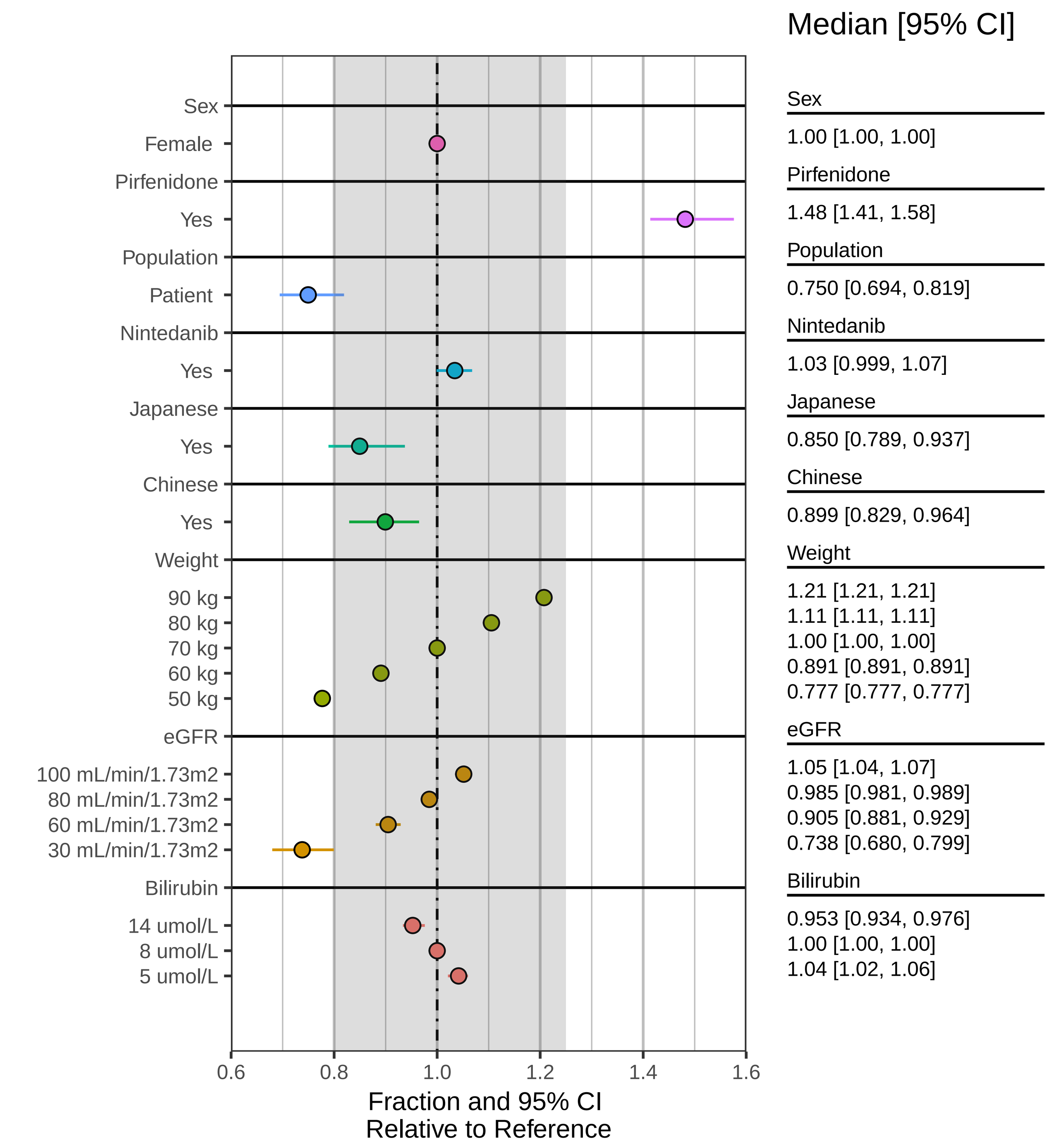

Figure 3. Covariate forest plot for nerandomilast apparent clearance (CL/F). Covariate effects in the reduced nerandomilast model were visualized by varying single covariates individually while keeping all other conditions constant. The colored circles represent the median, and the solid horizontal lines represent the 95% confidence interval (CI). eGFR: estimated glomerular filtration rate.

Conclusion

The PK of nerandomilast and the pharmacologically inactive S-enantiomer was well-described by the population PK model. Parameter estimates were generally precise, as reflected by narrow 95% CIs (median CI width ∼20% of estimate). Nerandomilast exposures were comparable across IPF and PPF patient populations, but were reduced with concomitant pirfenidone use. These results supported the justification of a single dosing strategy for the IPF and PPF patient populations.

References

[1] Richeldi, L. *et al.* Nerandomilast in patients with idiopathic pulmonary fibrosis. *N. Engl. J. Med.* **392** (2025):2193–2202.

[2] Maher, T.M. *et al.* Nerandomilast in patients with progressive pulmonary fibrosis. *N. Engl. J. Med.* **392** (2025):2203–2214.

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