Absolute oral bioavailability of nerandomilast (BI 1015550) in healthy male study participants

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Objectives

To assess the absolute oral bioavailability of a single oral dose of nerandomilast by simultaneously administering an IV ^{14}C microtracer in healthy male study participants.

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Introduction

- Nerandomilast (BI 1015550), a preferential inhibitor of phosphodiesterase 4B, is being investigated in the Phase III FIBRONEER™ clinical trials as a potential treatment for idiopathic pulmonary fibrosis and progressive pulmonary fibrosis.[1,2]
- To provide potentially insightful pharmacokinetic information such as the extent of absorption or the first-pass effect, this study assessed the absolute oral bioavailability of a single oral dose of 18 mg nerandomilast using a microtracer approach.

Methods

- This non-randomized, open-label, single-period, single-arm, Phase I study examined the absolute bioavailability of 18 mg nerandomilast as a tablet formulation for oral administration using an IV microtracer approach in healthy male participants.
- A microtracer of 10 µg ^{14}C-labeled nerandomilast (R) mixed with 90 µg unlabeled nerandomilast in 10 mL solution was administered intravenously 1.5 h after the administration of a single oral dose of 18 mg nerandomilast in tablet form (T).
- Concentrations of nerandomilast in plasma were determined using a validated LC-MS/MS assay, and concentrations of ^{14}C nerandomilast in plasma were determined using a validated UPLC + AMS method.
- The absolute bioavailability of the oral dose was estimated by the ratio of adjusted gMeans for the dose-normalized $AUC_{0-\infty}$ (gMean ratio of T/R; dose normalization implemented as $AUC_{0-\infty}$ /dose) using a statistical model of an analysis of variance on the logarithmic scale, including the 'formulation' as fixed effect and 'subject' as random effect.

Primary endpoint

- $AUC_{0-\infty}$ of ^{14}C-nerandomilast after IV administration and $AUC_{0-\infty}$ of nerandomilast after oral administration.

Additional objectives

- The safety and tolerability of nerandomilast were assessed based on the following parameters: safety laboratory tests, 12-lead ECG, vital signs, local tolerability of injection site, and assessment and monitoring for adverse events.

Baseline demographics

8
Healthy male participants
(six White, one Asian, one multiple race)

22.6 kg/m² (1.9)
BMI, mean (SD)

28.9 years (13.9)
Age, mean (SD)

Pharmacokinetics

- Upon dose normalization, $AUC_{0-\infty}$ of the oral dose was 118.27 h · nmol/L/mg, and $AUC_{0-\infty}$ of the IV dose was 161.69 h · nmol/L/mg.
- The absolute bioavailability of a single oral dose of 18 mg nerandomilast was estimated as 73.15% (90% CI: 67.32%, 79.48%) (Table).

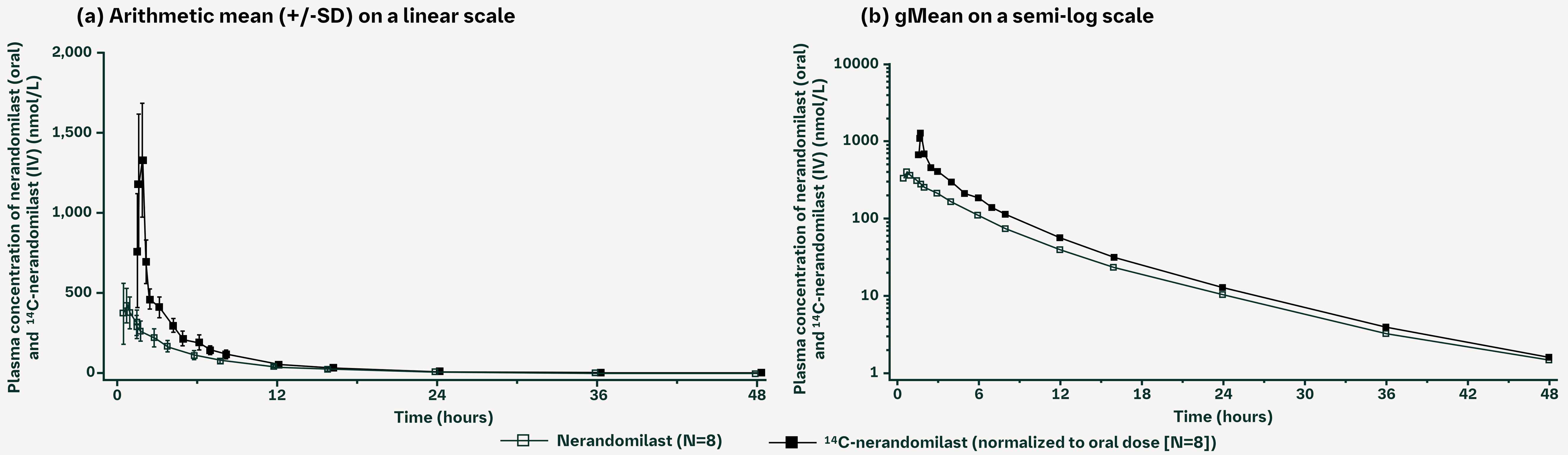
Table. Absolute oral bioavailability of nerandomilast

	N	Nerandomilast 18 mg oral tablet (T)		^{14}C-nerandomilast 10 µg IV (R)		Comparison of oral and IV administration			
		Adjusted		Adjusted		Ratio T/R (%)	90% CI		Intra-individual gCV (%)
		gMean	gSE	gMean	gSE		Lower limit (%)	Upper limit (%)	
$AUC_{0-\infty,norm}$ (h · nmol/L/mg)	8	118.27	1.07	161.69	1.07	73.15	67.32	79.48	8.8

An analysis of variance model accounting for 'subject' as a random effect and 'formulation' as a fixed effect was applied to the dose-normalized AUC ($AUC_{0-\infty,norm}$), to determine the absolute oral bioavailability of nerandomilast for a single oral dose of 18 mg nerandomilast compared with an IV microtracer infusion of 10 µg ^{14}C-nerandomilast (~40 kBq) administered 1.5 h after the oral dose at the assumed oral t_{max}.

- Nerandomilast 18 mg oral tablet was rapidly absorbed upon oral administration.
- The plasma concentration–time profiles of nerandomilast following the oral dose and ^{14}C-nerandomilast following the IV dose declined in a multiphasic fashion at a similar rate in the disposition phase (Figure).

Figure. Mean drug plasma concentration–time profiles of nerandomilast after single oral administration of 18 mg nerandomilast tablet vs ^{14}C-nerandomilast after single IV infusion of 10 µg ^{14}C-nerandomilast



Time scales have been slightly shifted for clarity.

Safety

- No on-treatment adverse events were reported for any participant during this study. Safety laboratory tests and the evaluation of vital signs and ECG revealed no clinically relevant findings.

Conclusions

- Nerandomilast 18 mg oral tablet, which corresponds to one of the therapeutic doses being investigated in the Phase III pivotal trials, had an oral bioavailability of 73.15% (90% CI: 67.32%, 79.48%).
- Nerandomilast was well tolerated by the healthy male participants in this study.

Abbreviations
AMS, accelerator mass spectrometry; $AUC_{0-\infty}$, area under the concentration–time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity; BMI, body mass index; CI, confidence interval; ECG, electrocardiogram; gCV, geometric coefficient of variation; gMean, geometric mean; gSE, geometric standard error; h, hour; IV, intravenous; kBq, kilobecquerel; LC-MS/MS, liquid chromatography tandem mass spectrometry assay; $_{norm}$, dose-normalized; R, reference treatment; SD, standard deviation; T, test treatment; t_{max}, time from (last) dosing to the maximum measured concentration of the analyte in plasma; T/R, ratio of the geometric means for T and R; UPLC, ultra-performance liquid chromatography.

References
1. Richeldi L, et al. BMJ Open Respir Res 2023; 10:e001563;
2. Maher TM, et al. BMJ Open Respir Res 2023; 10:e001580.

Disclosures
XT was employed at Boehringer Ingelheim and was not an FDA employee at the time of this work. NW is employed by Boehringer Ingelheim. SB and RT are contracted to Boehringer Ingelheim for this study.

XT is a current employee of the U.S. Food and Drug Administration (Silver Spring, MD, USA). The content reflects the views of the authors and should not be construed to represent the FDA's views or policies.

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