Phase 1 Safety, Tolerability, and Pharmacokinetics of NS-863 Supporting Development for Pulmonary Arterial Hypertension and Pulmonary Hypertension Associated with Interstitial Lung Disease

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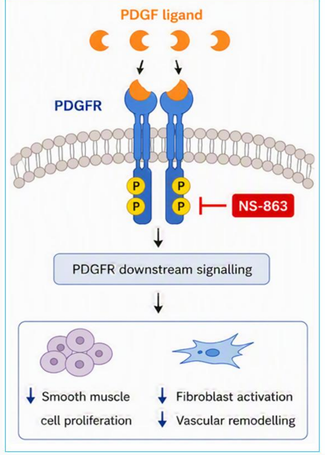
Background

Pulmonary Arterial Hypertension (PAH) and pulmonary hypertension associated with interstitial lung disease (PH-ILD) are progressive, life-threatening disorders characterised by vascular remodelling[1]. Platelet-derived growth factor (PDGF) signalling contributes to these pathobiological processes[2].

NS-863 is a novel, orally administered, selective PDGF receptor (PDGFR) inhibitor designed to maintain efficacy while improving the risk–benefit profile. In preclinical studies, NS-863 potently and selectively inhibited PDGFR signalling *in vitro*. In rat models of PAH and PH-ILD, NS-863 markedly attenuated pulmonary vascular and right ventricular remodelling, with less myelosuppressive effects.

NS-863: A Novel, Oral, Selective PDGFR Inhibitor

1. Mechanism of Action



2. Target Selectivity

Inhibition Activity IC_{50} (nmol/L)		
Kinase	NS-863	Imatinib
PDGFRβ	130	76
KIT	110,000	40

~850-fold selectivity for KIT versus PDGFRβ

Kinase panel:
Only PDGFRα/β and DDR1/2 showed >70% inhibition among 277 kinases at 5 μM.

Focused target profile, rather than broad PDGFR/KIT/CSF1R inhibition

3. Differentiated Preclinical Profile

In Vitro Haematopoietic Inhibition

IC_{50} (nmol/L)	NS-863	Imatinib
Reticulocyte Colony Formation	5,200	230
Megakaryocyte Colony Formation	> 100,000	3500

In Vivo Disease Model

SuHx-induced PAH rat model
- ✓ Reduced RV hypertrophy (RVH), RV systolic pressure, and occlusive lesions
- ✓ Prolonged survival

Comparable efficacy to imatinib, with no reduction in RBC

Bleomycin-induced PH-ILD rat model
- ✓ Reduced RVH and occlusive lesions

Purpose

To characterise the safety, tolerability and pharmacokinetics (PK) of NS-863 following single and multiple dosing in healthy adults, and to support optimal regimen selection for global Phase 2 studies in PAH and PH-ILD.

Method

Phase 1 study was conducted in healthy Japanese and White adults (n=133; NS-863, n=103; Placebo, n=30).

- Part A – Single ascending dose (SAD) (3.48–232 mg, fasting) : 57 Japanese and White participants, including 6 females
- Part B – Food effect (232 mg, crossover): 16 Japanese participants in a crossover design
- Part C – Multiple ascending dose (MAD) (13.92–116 mg BID, 7 days) : 30 Japanese and White participants

Assessments: PK, adverse events (AEs), vital sings, electrocardiogram, clinical laboratory tests.

Key Results

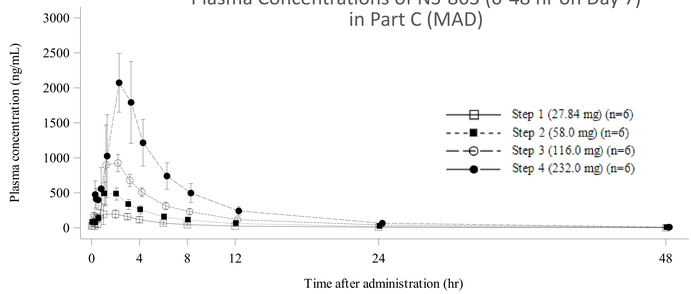
Pharmacokinetics

- C_{max} and AUC increased single
- and multiple linearly at doses 232 mg/day for both doses.
- Steady state was reached within 3–4 days.

Race, Sex, and Food Effects

- No significant differences based on race or sex were observed.
- C_{max} and AUC_{inf} following a non-fasting dose decreased by approximately 37% and 12%, respectively, without any clinically meaningful impact.

Plasma Concentrations of NS-863 (0-48 hr on Day 7) in Part C (MAD)



Safety and Tolerability

- No safety issues were observed at doses up to 232 mg/day (116 mg BID). All adverse drug reactions were mild and resolved within 1 week.
- No clinically significant changes in vital signs, electrocardiograms or laboratory values, including platelet counts, were observed.

Part	Adverse Drug Reaction	Dose	Severity	Action	Outcome
B	Feeling abnormal	232 mg	Mild	No	Recovered
B	Headache	232 mg	Mild	No	Recovered
C	Diarrhoea	116 mg BID	Mild	No	Recovered
C	Headache	116 mg BID	Mild	No	Recovered
C	Petechiae	116 mg BID	Mild	Drug Withdrawn	Recovered

Conclusion

Phase 1 Results

- NS-863 demonstrated a favourable safety and tolerability profile at doses up to 232 mg (single dose) and 116 mg BID for 7 days (multiple dose).
- Plasma exposure was dose-proportional after both single and multiple dosing.
- No clinically meaningful differences were observed by race, sex, or food intake.

Next Step: Global Phase 2 Studies

- Two global Phase 2 studies: NS-863 58 or 116 mg BID vs. placebo for 24 weeks; primary endpoint: pulmonary vascular resistance (PVR)
- Approximately 135 (PAH) and 177 (PH-ILD) participants will be enrolled across approximately 100 sites in North America, Latin America, Europe, and Asia Pacific, with study initiation planned for 2026.

  PAH Study: NCT07441200
  PH-ILD Study: NCT07441278

References:
1. Leopold JA, et al. Int J Mol Sci. 2016;17(5):761. 2. Perros F, et al. Am J Respir Crit Care Med. 2008;178(1):81-88

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