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Efficacy of NS-863, a novel orally bioavailable selective PDGFR inhibitor, in preclinical rat models of PAH and PH-ILD

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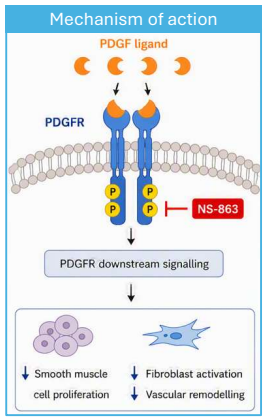
Background

Pulmonary arterial hypertension (PAH) and pulmonary hypertension associated with interstitial lung disease (PH-ILD) are severe disorders with pulmonary vascular remodeling. Platelet-derived growth factor (PDGF) signaling via the PDGF receptor (PDGFR) plays a central role in pulmonary vascular remodeling through the proliferation and migration of vascular smooth muscle cells.

NS-863 is a novel orally bioavailable selective PDGFR inhibitor. Based on the results of a Phase 1 trial, which demonstrated good safety and tolerability, Phase 2 trials for PAH and PH-ILD are scheduled to begin in 2026 worldwide.

Phase 2 study for PAH: NCT07441200
Phase 2 study for PH-ILD: NCT07441278



Aim

To evaluate the pharmacological profile and efficacy of NS-863 in vitro and in animal models of PAH and PH-ILD

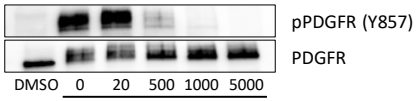
In vitro Profile of NS-863

■ **NS-863 demonstrated high selectivity for PDGFR kinase.**

Compound	Kinase inhibition IC_{50} (nmol/L)		
	PDGFRβ	KIT	Fold
NS-863	130	110,000	850
Imatinib	76	40	0.53

NS-863 was assessed for its inhibitory effect on 277 kinases or kinase signaling pathways. Other than PDGFRα and PDGFRβ, only discoidin domain receptor tyrosine kinases 1 and 2 were inhibited by ≥70% at a concentration of 5 µmol/L.

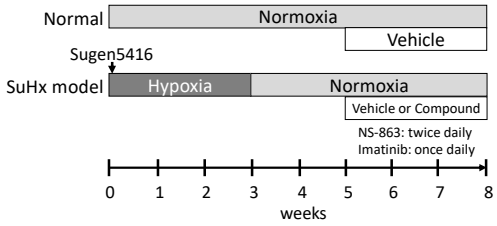
■ **NS-863 inhibited PDGFR phosphorylation in human pulmonary arterial smooth muscle cells**

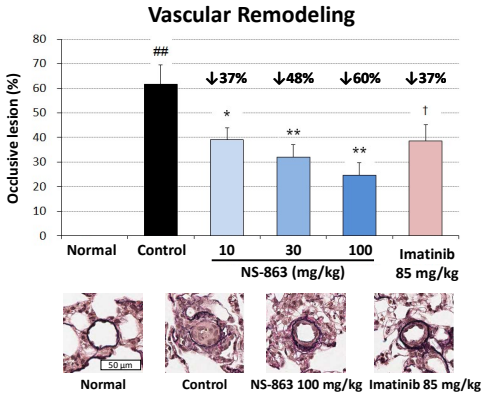


■ **NS-863 inhibited hPASMC proliferation with weak suppression of hematopoiesis.**

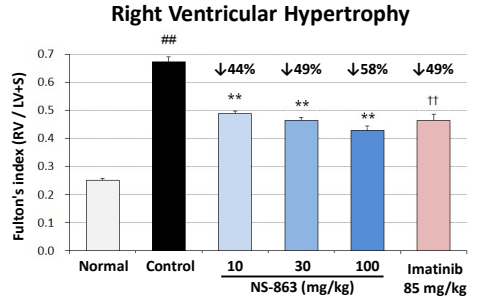
Compound	PDGF-BB-stimulated proliferation of hPASMC IC_{50} (nmol/L)	Reticulocyte colony formation IC_{50} (nmol/L)	Megakaryocyte colony formation IC_{50} (nmol/L)
NS-863	120	5,200	> 100,000
Imatinib	140	230	3,600

NS-863 effectively improved PAH pathology in the SuHx rat model.

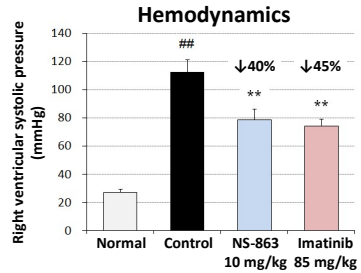




The mean + standard error of the mean for each condition (normal group, n = 8; control group, n = 6; compound group, n = 7) are shown. ## p<0.01 vs. normal (Student's t-test); † p<0.05 vs. control (Student's t-test); * p<0.05, ** p<0.01 vs. control (Williams' multiple comparison test).



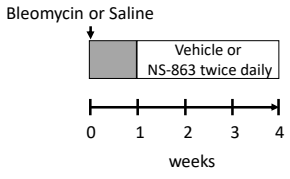
The mean + standard error of the mean for each condition (normal group, n = 8; control group, n = 6; compound group, n = 7) are shown. ## p<0.01 vs. normal (Student's t-test); †† p<0.01 vs. control (Student's t-test); ** p<0.01 vs. control (Williams' multiple comparison test).

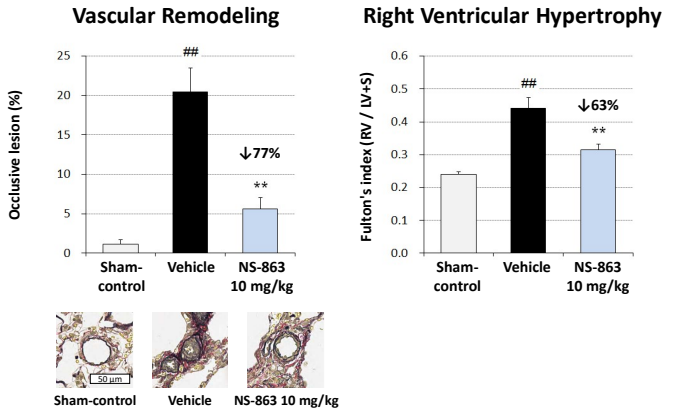


The mean + standard error of the mean for each condition (normal group, n = 5; control group, n = 7; compound group, n = 7) are shown. ## p<0.01 vs normal (Student's t-test); ** p<0.01 vs control (Dunnett's test).

■ **Phase 1-based PK simulations predicted that the planned Phase 2 dose range will achieve plasma exposures associated with efficacy in the SuHx model.**

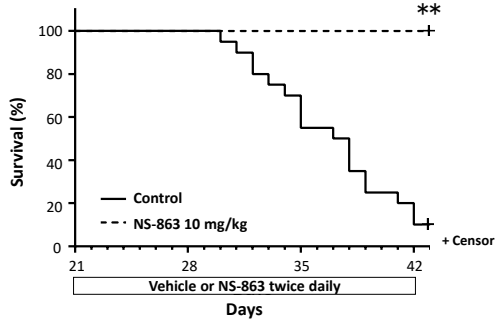
NS-863 effectively ameliorated PH in the bleomycin-induced PH-ILD rat model.





The mean + standard error of the mean for each condition (sham-control group, n = 8; vehicle group, n = 12; NS-863 group, n = 11) are shown. ## p<0.01 vs sham-control (Student's t-test); ** p<0.01 vs vehicle (Student's t-test).

NS-863 prolonged survival in the SuHx survival assessment model.



Kaplan–Meier survival curves.
** p<0.01 vs. control (log-rank test, n = 20).

Conclusion

- NS-863 demonstrated high selectivity for PDGFR kinase.
- NS-863 potently inhibited hPASMC proliferation with weak hematopoietic toxicity.
- In the PAH model, NS-863 demonstrated therapeutic effects on vascular remodeling, hemodynamics, and right ventricular hypertrophy, ultimately prolonging survival.
- NS-863 demonstrated therapeutic effects in the PH-ILD model.
- The exposures associated with efficacy observed in animal models will be achievable within the planned Phase 2 dose range.

Method

Sugen5416-hypoxia (SuHx)-induced PH model: Six-week-old male Sprague-Dawley rats were injected subcutaneously with Sugen5416 (20 mg/kg) and exposed to hypoxia (10% O_2) for 21 days. SuHx rats were subsequently maintained in normoxia for 14 days and treated with compounds for 21 days.

SuHx-induced PH rat survival assessment model: Six-week-old male F344/DuCrlCrlj rats were injected subcutaneously with Sugen5416 (20 mg/kg) and exposed to hypoxia (10% O_2) for 21 days. After returning to normoxia, rats were treated with NS-863 for 22 days and assessed for survival.

Bleomycin-induced PH-ILD model: Eight-week-old male Wistar rats received a single intratracheal administration of bleomycin (3 mg/kg). Sham-control rats received intratracheal administration of saline. NS-863 was administered for 21 days starting on Day 7 after bleomycin administration.

Conflict of Interest: All authors are employees of Nippon Shinyaku Co., Ltd.