Direct Lung Administration of Nintedanib Reduces Lung Fibrosis in a Multi-Challenge Bleomycin Rat Model

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1 Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a life-limiting lung disease characterised by chronic cough and loss of lung function. Nintedanib is one of two oral treatments approved for disease management. Unfortunately, both are associated with substantial adverse effects often leading to dose reduction or discontinuation. Using the multi-challenge bleomycin rat model, the objectives of this study were to establish and compare inhaled and oral nintedanib pharmacokinetics and the anti-fibrotic treatment effects of each at different lung exposures.

4 Conclusion

These data support that only infrequent, short-duration nintedanib lung exposure (in the absence of a large, oral-equivalent AUC) is required for anti-fibrotic effect. Because very small inhaled doses achieved this pharmacokinetic parameter while largely avoiding the GI tract, liver and systemic exposure, oral-observed side effects may be substantially reduced enabling inhaled dose escalation for potential additional efficacy.

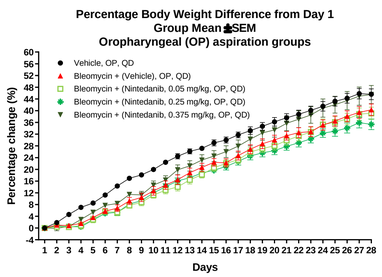
2 Results

Inhaled and Oral Nintedanib Pharmacokinetic Studies in Rats

		Lung Cmax		Lung AUC	
Route	Dose (mg/kg)	(µg/g)	Fold vs. Oral	(mg·hr/kg)	Fold vs. Oral
Oral	60	13.2	–	175.0	–
OP[a]	0.375	14.3	1.1	12.2	0.07
OP[b]	0.25	9.6	0.7	8.2	0.05
OP[b]	0.05	1.9	0.1	1.6	0.01
		Plasma Cmax		Plasma AUC	
		(µg/mL)	Fold vs. Oral	(mg·hr/L)	Fold vs. Oral
Oral	60	0.3400	–	0.8760	–
OP	0.375	0.0048	0.014	0.0030	0.0034
OP	0.25	0.0032	0.009	0.0015	0.0017
OP	0.05	0.0006	0.002	0.0003	0.0003

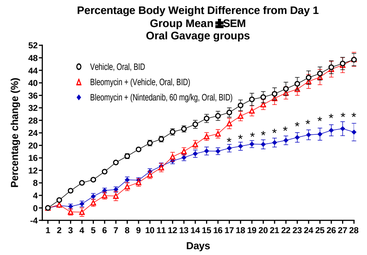
Compared to oral, small inhaled nintedanib dose levels delivered a shorter-duration, similar lung Cmax with very low local and systemic AUC.

Inhaled Nintedanib Improved Body Weight Gain



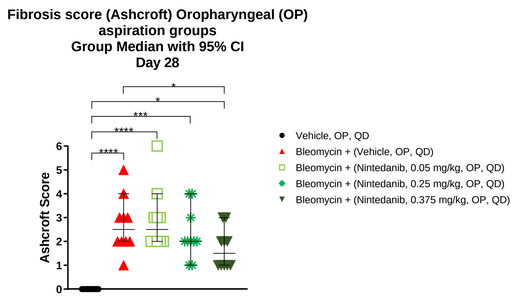
High dose inhaled nintedanib (0.375 mg/kg) improved body weight gain compared with bleomycin/vehicle group.

Oral Nintedanib Reduced Body Weight Gain



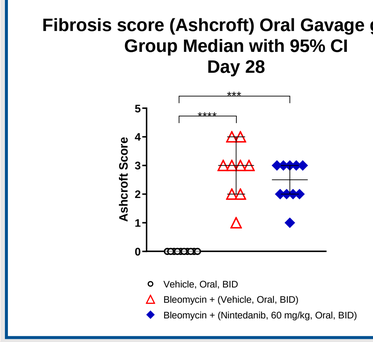
Oral nintedanib (60 mg/kg) reduced body weight gain compared to vehicle controls.

Inhaled Nintedanib Reduced Fibrosis in a Dose-Dependent Manner



Inhaled nintedanib reduced group median lung fibrosis; this reduction was statistically significant at 0.375 mg/kg versus bleomcyin/vehicle controls. Oral nintedanib also reduced group median fibrosis score, although the difference was not statistically significant. Inhaled (0.25 mg/kg and 0.375 mg/kg) and oral nintedanib also reduced lung inflammation (not shown).

Oral Nintedanib Slightly Reduced Lung Fibrosis



3 Methods

Studies were performed in male SD rats (250-300g). Nintedanib pharmacokinetic (PK) parameters were determined in lung and plasma following oral (60 mg/kg) and inhaled (0.1 and 0.5 mg/kg) administration. The multi-challenge fibrosis model was established administering OP bleomycin (1.66 units/kg) on Days 1, 2, 3, and 6. Inhaled nintedanib was administered QD by oropharyngeal aspiration (OP aspiration) from Day 8 to Day 27. Oral nintedanib was administered BID from Day 8 to Day 27. On Day 28, the right lung was inflation-fixed and scored for fibrosis using the modified Ashcroft scale (blind assessment on 6 lung sections per right lung) and inflammation. Apart from one animal in the bleomycin/vehicle (oral) control group there were no premature mortalities. N = 10 per group. Data presented as mean/SEM or median/95% CL. *P<0.05, **P<0.01, ***P<0.001, P<0.0001.