# Inhaled Nintedanib: Predictive Sheep Model for Human Dose Selection and Tolerability Assessment

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## OBJECTIVES

While oral nintedanib slows IPF disease progression, associated side effects challenge compliance and prevent dose escalation for possible additional efficacy. To overcome these shortcomings and maximize effect, nintedanib was reformulated as a solution for nebulization and inhaled, direct-lung administration (AP02). To obtain early inhalation tolerability, guide human plasma pharmacokinetic sampling and assist estimation of the human ELF concentration/elimination profile (from a single human BAL sample), a large animal sheep model was first assessed (1).

## METHODS

Briefly, 0.06 mg/kg inhaled AP02 or 2.14 mg/kg oral nintedanib (gavage following $CuSO_4$-induced gastric groove closure; 2) were administered to 35 kg ventilated sheep. To confirm oral delivery, a glucose chaser was administered and blood glucose levels monitored (Figure 1 – $CuSO_4$ + glucose). Inhaled administration was performed using a ventilator-inline PARI eFlow® nebulizer (Figure 2).

Respiratory safety parameters were evaluated before and after administration. Serial plasma and bronchioalveolar lavage (BAL) samples were also collected. Measured nintedanib BAL concentrations were converted to lung epithelial lining fluid (ELF) levels using urea content (3) and plotted versus time to generate a concentration/elimination profile for human estimation (4).

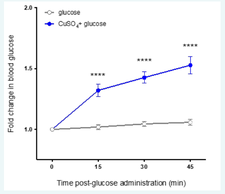



Figure 1. Oral Delivery Confirmation

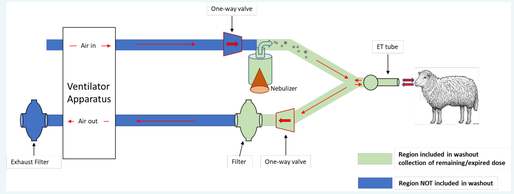
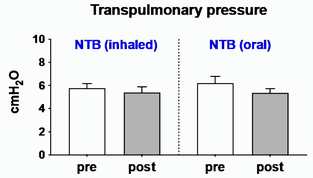


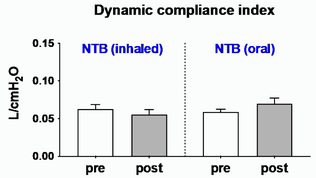

Figure 2. Sheep Nebulizer/Ventilator Circuit

## RESULTS

Tolerability:

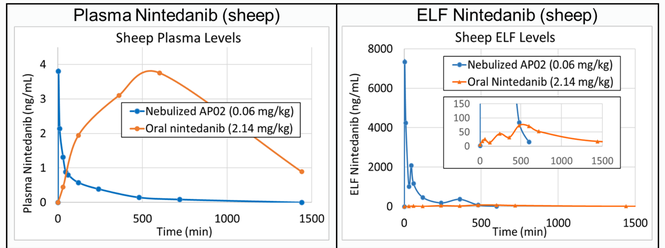
Lung function was assessed before and after each dosing. The mean (± SEM) values for each assessment are summarized below.




There were no significant lung function changes for either route of nintedanib (NTB) administration (pre- vs post-) as measured by mean transpulmonary pressures (airway resistance) or dynamic compliance.

Pharmacokinetics:




| | Sheep Plasma | | | Sheep Lung ELF | | |
|---|---|---|---|---|---|---|
| | Oral | Inhaled | Fold vs Oral | Oral | Inhaled | Fold vs Oral |
| Dose (mg/kg) | 2.14 | 0.06 | – | 2.14 | 0.06 | – |
| Cmax (ng/mL) | 3.8 | 3.8 | Equivalent | 74.0 | 7375 | +99.7 |
| AUC (mg·hr/L) | 0.058 | 0.005 | -11.6 | 1.2 | 5.4 | +4.5 |

Pharmacokinetic take-aways:

- Inhaled nintedanib exhibited a 10 minute lung epithelial lining fluid (ELF) elimination half-life and immediate plasma Tmax
- With an oral-similar plasma Cmax and 12-fold lower AUC, this 36-fold smaller inhaled dose delivers a 100-Fold and 5-Fold greater ELF Cmax and AUC
- Sheep ELF nintedanib concentration/elimination profile was later used to estimate human inhaled ELF Cmax and AUC from a single bronchioalveolar lavage sample

## CONCLUSIONS

- **Inhaled AP02 is well-tolerated in sheep and delivers an oral-superior lung dose with reduced systemic exposure**
  - **Promising to improve nintedanib safety, tolerability and compliance**
  - **Enables testing for additional IPF treatment effect in human trials**
- **An immediate inhaled plasma Tmax suggests efficient alveolar nintedanib aerosol deposition**
- **Inhaled PK profile supports nintedanib anti-fibrotic activity (5, 6, 7)**
  - **Only short-duration exposure is required for anti-fibrotic effect; activity that appears enabled by the high-delivered lung Cmax**
  - **Nintedanib exhibits concentration-dependent activity whereby the magnitude of the delivered lung Cmax (and associated AUC) defines the duration of residual drug effect (activity after drug is eliminated)**
  - **Data indicates nintedanib's residual activity lasts more than 24 hours**
- **Together with recent Phase 1 clinical study results, this data supports advancement of inhaled AP02 into longer-term clinical trials**

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