

1. Introduction

Our signature technology platform – dry-powder formulations including Technosphere® technology and inhalation devices – offer rapid and convenient delivery of medicines to the deep lung where they can exert an effect locally or enter the systemic circulation, depending on the target indication.

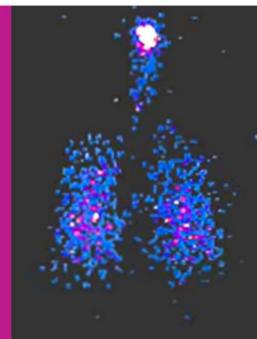
Oral nintedanib (Ofev®) is approved for the treatment of various pulmonary fibrotic diseases including Idiopathic Pulmonary Fibrosis (IPF), however its use and its effectiveness are significantly limited by its poor tolerability, especially with GI and neurologic adverse events. Nintedanib DPI is being developed to overcome these safety issues and to potentially improve on the efficacy of the oral formulation. About 60% of the nominal dose is deposited in the lungs.

- In a rat PD bleomycin study, **Nintedanib DPI** appeared to **mitigate inflammation and fibrosis** comparable to oral nintedanib at **substantially lower doses**
- Only 5% of oral nintedanib is bioavailable, and we can likely deliver much higher relevant lung concentrations without or with minimal GI or neurologic intolerability
- As a result, our hypothesis is that **Nintedanib DPI** may provide **better efficacy** and **improved tolerability** vs. oral nintedanib

Technosphere Technology

Extremely Versatile Platform With Competitive Advantages

- Two FDA-approved products on the platform
- Extensive distribution of powder throughout lung utilizing FDKP
- Deep lung delivery
- Requires very little inhalation effort to empty the cartridge



Radioactivity Distribution 0 to 3-min Scintigraphs	Percent of emitted dose, Mean (SD)
Delivered to left lung	31.7% (± 7.5%)
Delivered to right lung	27.2% (± 4.9%)
Deposited on oropharynx	30.0% (± 7.1%)
Swallowed (stomach)	10.7% (± 6.1%)

Figure 1: Technosphere deposition
Data on File at MannKind

2. Study Design

[Study Details | A Study to Evaluate Safety, Tolerability and Pharmacokinetics of MNKD-201 in Healthy Volunteers | ClinicalTrials.gov \(NCT06532942\)](#)

A single-ascending and multiple-ascending phase-1 study of nintedanib DPI in healthy volunteers older than 40 years old was just completed in the US, with a primary objective of characterizing its safety, tolerability, and pharmacokinetics profiles.

- Population: Healthy adults ≥ 40 and ≤ 65 years of age with normal lung function and no known respiratory issues
- Sample size: 40 enrolled, 24 in Part A (SAD) and 16 in Part B (MAD)
- Duration of trial intervention: 1 day in Part A and up to 7 days in Part B

Single- and Multiple-Ascending Doses

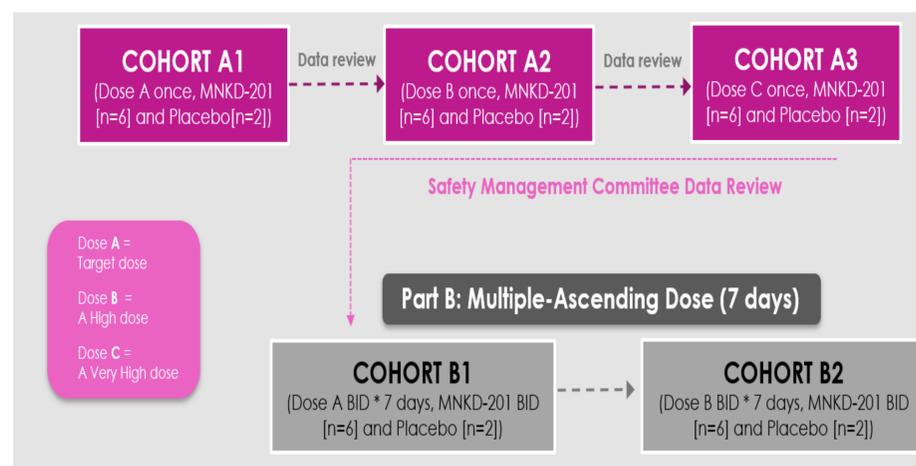


Figure 2: Phase-1 study design

3. Study Objectives

Primary: to evaluate the safety and tolerability of single and multiple ascending doses of nintedanib DPI versus placebo in healthy adult participants

Secondary:

- To evaluate the pharmacokinetics (PK) of nintedanib DPI following single- and multiple-ascending doses in healthy adult participants
 - ❖ Maximum plasma nintedanib DPI concentration (C_{max})
 - ❖ Time to maximum concentration (t_{max}) Terminal elimination half-life (t_{1/2})
 - ❖ Area under the plasma concentration-time curve (AUC) from time zero (from the start of inhalation time) to the last measurable concentration (AUC_{0-t})
- To evaluate the effect of nintedanib DPI versus placebo on pulmonary function immediately post-dose
 - ❖ Changes in FEV1 before and after dosing (pre-dose and 5, 15, 30, 60, 90 and 120 minutes post-dose)

4. Results and Discussion

Topline Results of the phase-1 study will be available in 4Q '24.

The study is still blinded. Dosing in all cohorts has been completed. All doses tested are well tolerated. There are no SAE's and discontinuations. Mild reversible cough has been reported by some participants.

Study design for the next study phase is being planned now. Our goal is an adaptive seamless operationally design of phase 2/3, pending discussions with the FDA, EMA, and other Health Authorities.