

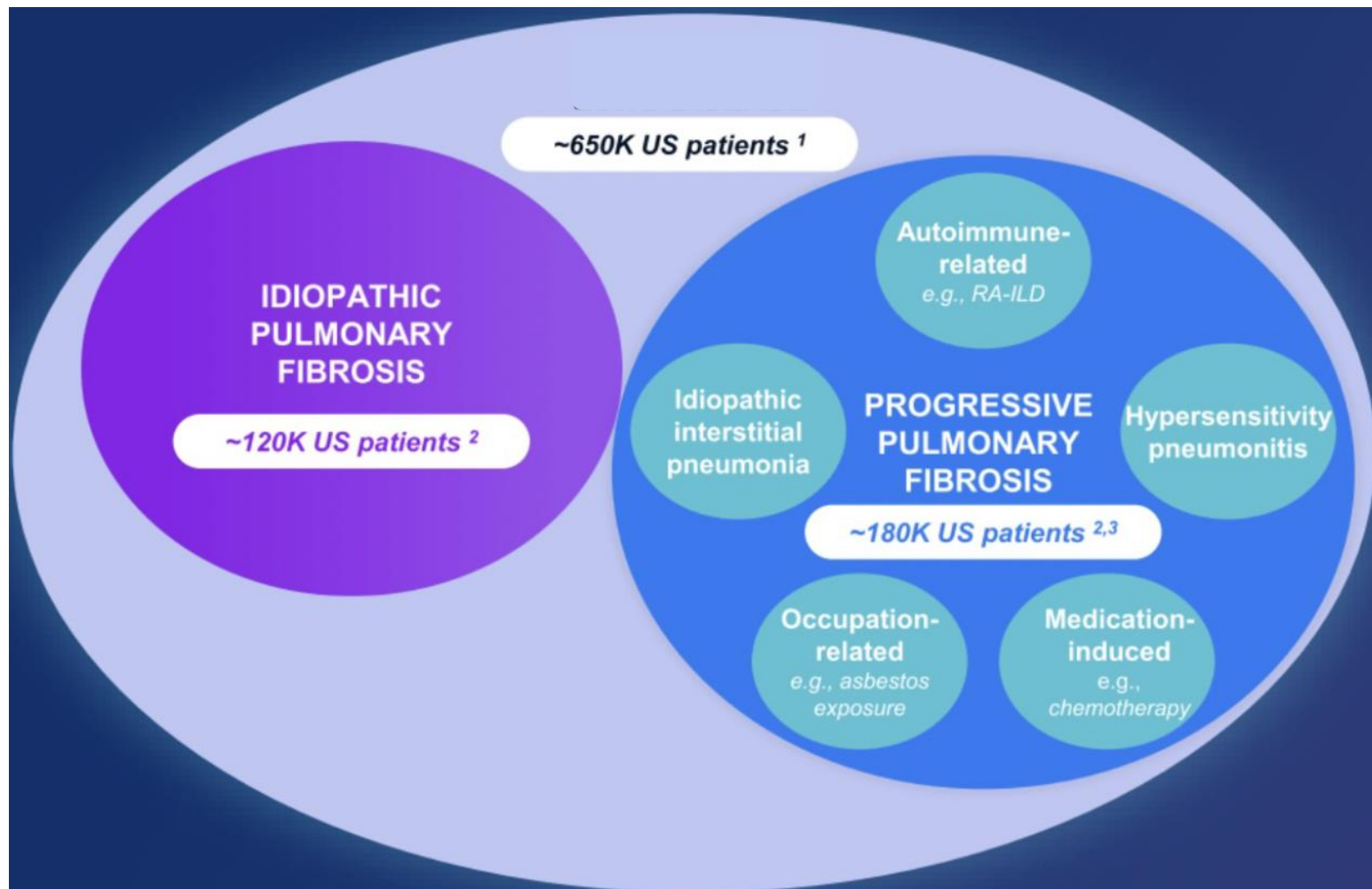
Lung Directed Combination Therapies



SPRAYE™ inhaled combination powders for
Pulmonary Fibrosis - Engineered particles
maximizing drug delivery to where it matters

“Smooth-as-Silk”

Interstitial Lung Diseases



¹Jeganathan et al., 2024; ²Avalyn Market Research; ³Olson et al., 2021. PPF, previously referred to as Progressive Fibrosing ILD (PF-ILD)

Pulmonary Fibrosis Market Opportunity



US Market Prevalence

~650,000 patients
with ILDs¹

~120,000 IPF
patients²

~180,000 PPF
patients³

>\$4B

Ofev® global
revenue in 2024

Approved Oral Medicines



Annual Brand Pricing

> \$150k / yr

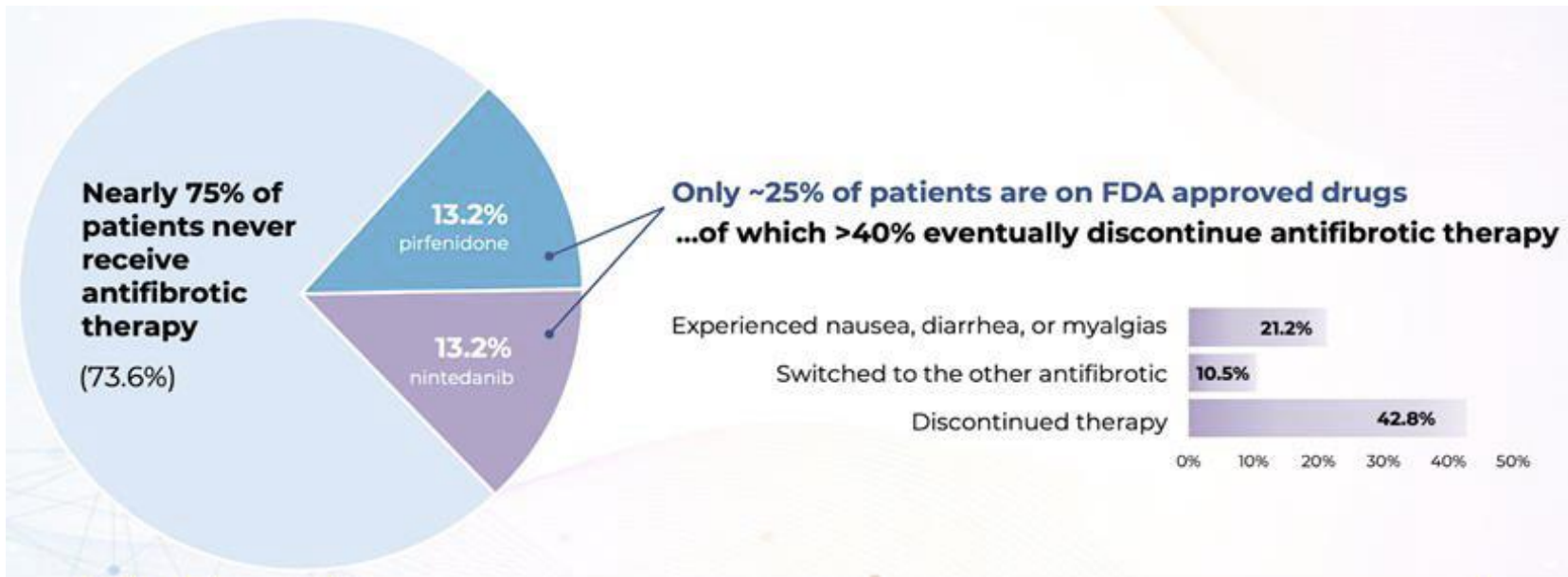
Implied US Market Size

\$42B+

Inhaled Combination Drugs

The Future of Pulmonary Fibrosis Treatment

Oral antifibrotics pirfenidone and nintedanib are modestly effective and poorly tolerated, leading to low adoption and high discontinuation rates. Few patients can handle their combined GI side effects. Nerandomilast, a recently approved **oral PDE4 inhibitor** is safer for combination use.



1. Oral monotherapies deliver modest efficacy and are limited by tolerability
2. GI toxicity from oral therapies limits mechanism-based combination stacking
3. A lung targeted approach can widen the therapeutic index at the site of disease

Solution

Targeted Delivery to the Lung

Local delivery maximizes exposure at the site of disease

Pathology in ILDs is largely in the lung parenchyma. Systemic delivery distributes drug throughout the body, with only a fraction reaching the lungs.

Reduced systemic exposure / toxicity

Risks of systemically delivery include off-target effects in organs where signaling is important. Restricting exposure to the lung can reduce systemic side effects.

Higher local concentrations

For effective antagonism, drug concentration at the receptor must exceed receptor occupancy thresholds. Lung delivery achieves higher local concentration in alveolar and interstitial spaces, especially in fibrotic foci.

Precedent in other inhaled therapies

Many respiratory diseases (e.g. asthma, COPD, pulmonary infections) use inhalation to deliver drugs to the lungs. The same general principles apply to ILDs (aerosol particle size, penetration to distal airways, retention, clearance).

Pharmacokinetic advantages

Lungs can act as a depot, allowing slower release into nearby interstitial tissue while limiting washout into the circulation. Alveolar epithelium is relatively thin, facilitating absorption into nearby tissue.

Reduced dose

Because a lower total dose may be needed (less “waste” into other tissues), inhalation could improve therapeutic index and potentially reduce toxicity.

DPI is the Preferred Format

Convenience and Adherence Matter

- Portable, fast and patient-friendly compared to nebulized workflows
- Supports broad commercial adoption if efficacy and tolerability are credible
- Creates a clean strategic fit for fixed-dose combinations

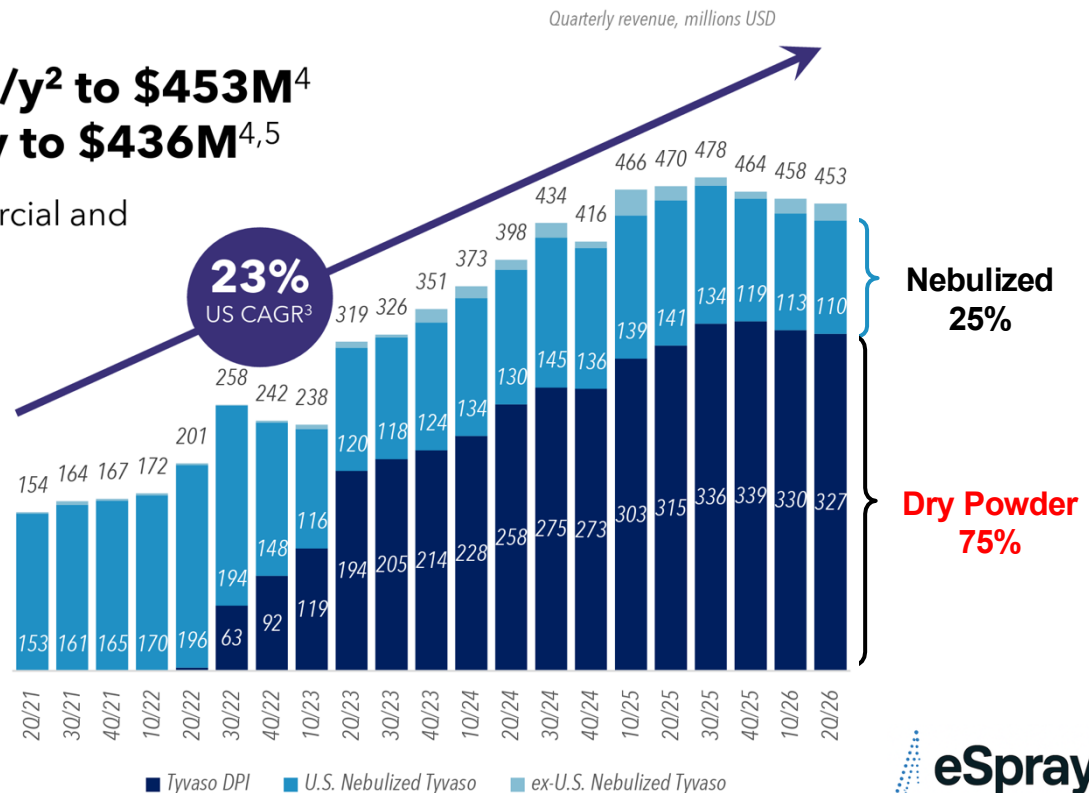


W/W¹ Combined Revenue ▼4% y/y² to \$453M⁴
U.S. Combined Revenue ▼4% y/y to \$436M^{4,5}

- **Record Tyvaso DPI** starts, referrals, commercial and total patients
- **Most prescribed** prostacyclin in the U.S.⁴

TYVASO DPI[®]
 (treprostinil) INHALATION
 POWDER

TYVASO[®]
 (treprostinil) INHALATION
 SOLUTION



1. w/w = worldwide. 2. y/y = year over year. 3. CAGR = compound annual growth rate calculated from 2Q/21 to 2Q/26.
 4. Data reflective of combined Tyvaso DPI + Nebulized Tyvaso. 5. Totals may not add due to rounding.

SPRAYE™ Inhalation Powders

Advantages over Ordered Mixtures (Lactose and FDKP Blends)

Provides higher delivery efficiency to the lungs

- Much, much more than simply using less drug (i.e. COGS reduction)

Enables delivery of higher lung doses (at least 20-fold higher than that of lactose blends)

Reduced variability for patients / increased dose consistency

- Low or no flow-rate dependence - most patients get their dose regardless of breathing profile
- Drug delivery to the lungs is much less dependent on anatomical differences in mouth and throat

Lower oropharyngeal deposition leads to lower off-target effects and improved tolerability

- Reduced throat deposition (local effects such as cough, candidiasis)
- Reduced dose to GI tract

Stabilization of amorphous drug using glass stabilization technology is impossible with blends

Delivery of fixed dose combinations without co-formulation effects that plague fixed-dose combinations ('multiparticulate nightmares' that result in differences in delivery efficiency of each drug in a combination). Blending a fixed dose combination is not as simple as it seems

Difficult to reverse engineer, especially when delivery efficiency high. Raises competitive bar

SPRAYE™ Inhaled Powders

Pipeline and Intellectual Property

Projects	SPRAYE™ Combos	Indications	Development Stage	Originator
Combo 1	Pirfenidone* Nintedanib	IPF PF-ILD, SSc-ILD	Combinations Formulated	Generic Boehringer
Combo 2	Ensifentrine** Nintedanib	IPF, PPF CFPE ("ILD Syndrome")	Combinations Formulated	MERCK Boehringer
Combo 3	Treprostinil Palmitil Nintedanib	Pan - ILD ONCE DAILY	Formulation Initiated	Insmed Boehringer

*Deupirfenidone

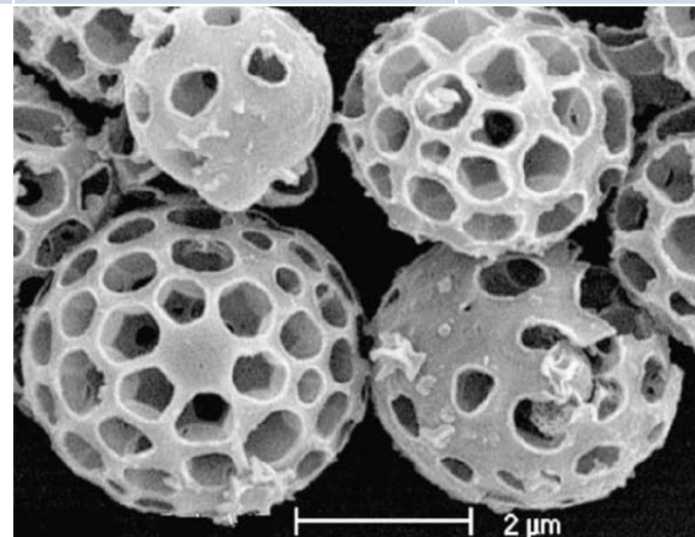
**Deuensifentrine

Intellectual Property - Patent Applications

Combo 1: US Utility & PCT Published, Provisional 7/26

Combo 2: PCT 5/26, Two Provisionals 7/26

Combo 3: US Utility & PCT Published, Provisional 7/26



Ensifentrine + Nintedanib SPRAYE™ Combination 2

ORAL Ofev® (nintedanib)

Approved to treat Pulmonary Fibrosis

Dose: 150 mg capsules twice daily

MOA: Inhibition of RTKs blocking fibroblast activation and proliferation



INHALED Ohtuvayre® (ensifentrine)

Approved to treat COPD

Dose: 3 mg nebulized twice daily

MOA: Inhibition of PDE3 & PDE4



ONE PUFF Twice Daily

Delivers both drugs in every particle simultaneously engaging all MOAs

- Ensifentrine inhaled dose is 3 mg
- Nintedanib inhaled dose range is 4-6 mg
- Combined dose of ensifentrine + nintedanib 7-9 mg



Why Now?

Validated: PDE4 biology, Inhaled assets, DPI adoption

- **PDE4** inhibitor pathway clinically validated and commercially relevant
- Inhaled prostacyclins set to expand into IPF/PPF with TETON readouts
- Inhaled antifibrotics and device adoption de-risk the modality shift
- A practical way to combine mechanisms in one lung-targeted regimen



Jascayd[®] nerandomilast
PDE4 Inhibitor
Approved for **IPF, PPF** Q425
Oral Dose: 9 or 18 mg BID
Cost of treatment: **\$195K** /year



Ohtuvayre[®] ensifentrine
PDE3/**PDE4** Inhibitor
Approved for **COPD** 6/24
Inhaled Nebulized Dose: 3 mg BID
Cost of treatment: **\$35K** /year



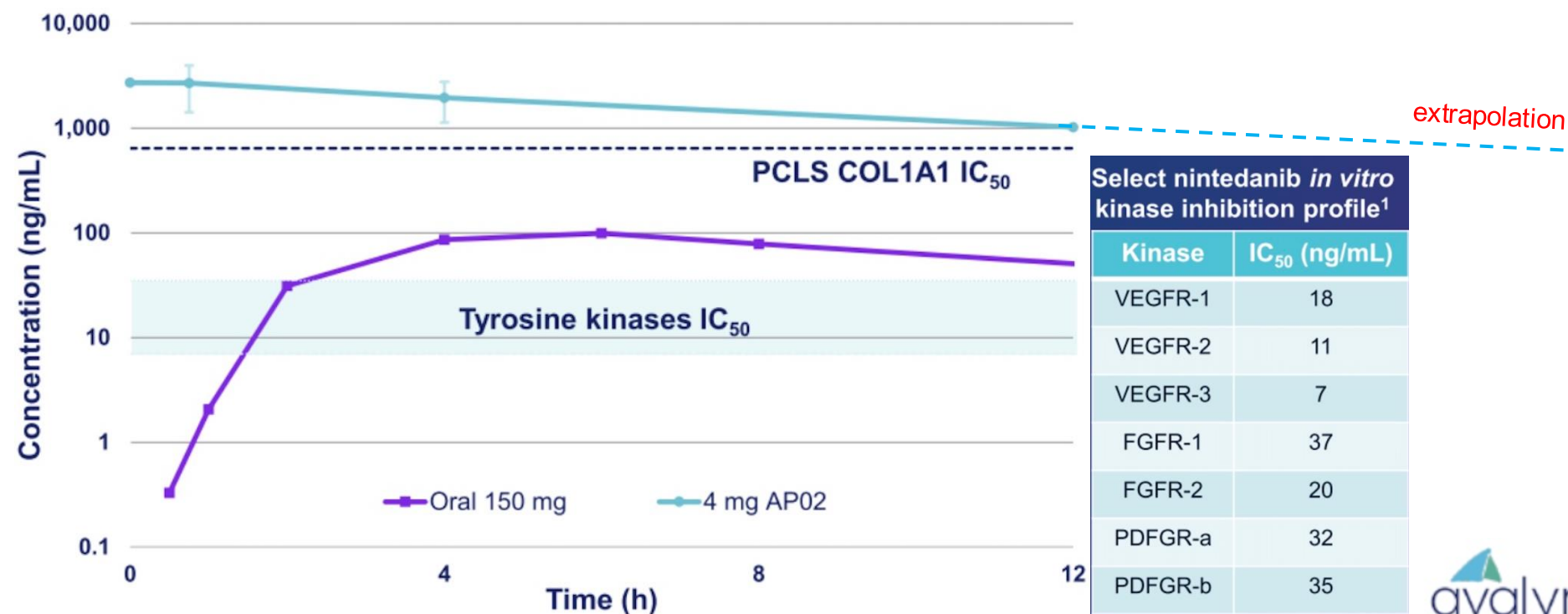
Tyvaso[®] treprostinil
Prostacyclin analog
Approved for **PAH, PH-ILD, IPF** in '27
Inhaled Nebulized Dose: 48-64 µg QID
Cost of treatment: **\$285K** /year

Inhaled Nintedanib Substantially Improves Lung Exposure

Once Daily Potential

Oral nintedanib (100-150 mg BID) limited by debilitating gastrointestinal side effects
Inhalation can achieve substantially higher lung levels with just 4 mg widening the therapeutic index due to reduction in systemic exposure and resulting toxicity

Nintedanib concentrations in ELF were compared to the PCLS IC_{50} and *in vitro* tyrosine kinase IC_{50} values

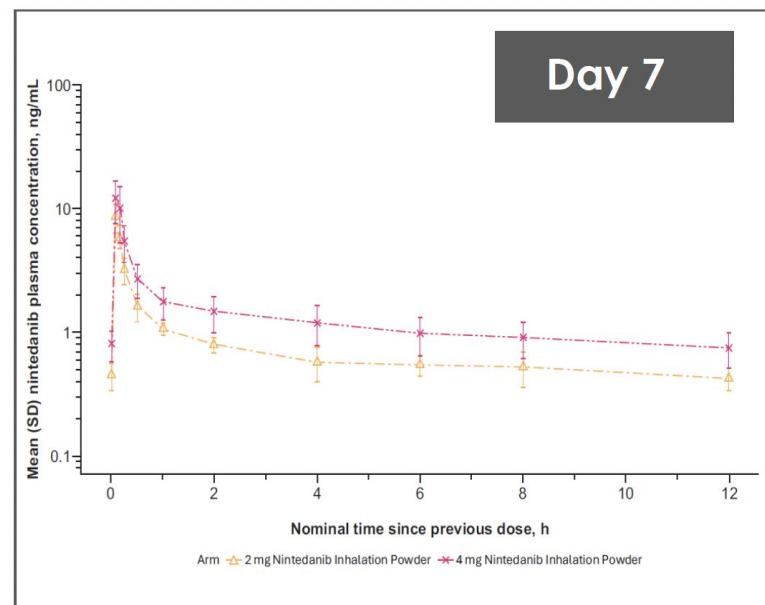
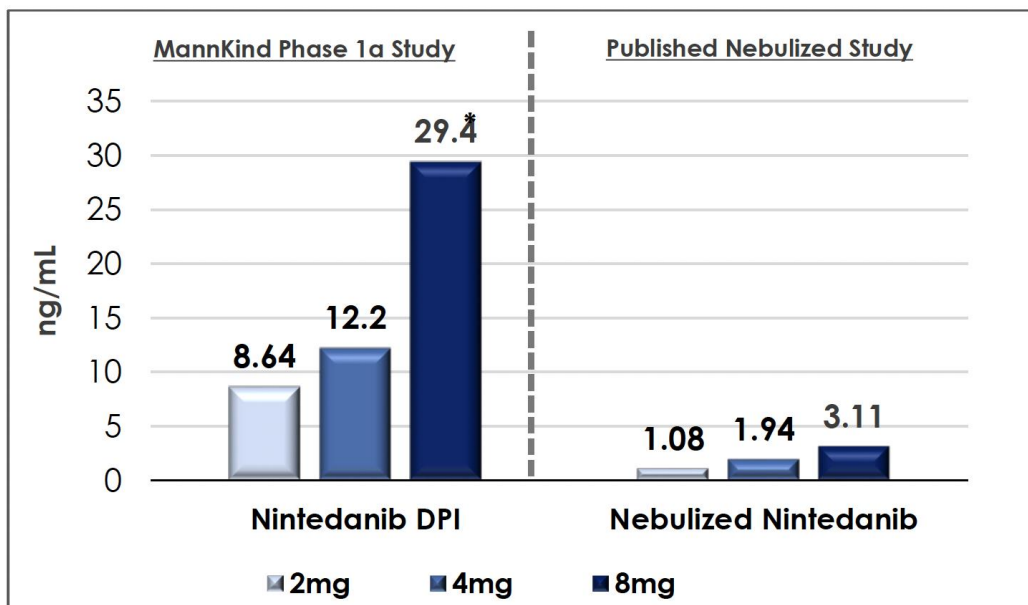


DPI versus Nebulization

Substantially Greater Lung Exposure with Same Doses

Phase 1a: Validated Efficient Deep-Lung Delivery of Nintedanib DPI

Rapid, dose-proportional exposure and favorable safety findings supported advancement into IPF patient studies



**Results for 8 mg Nintedanib DPI are from the 8 mg SAD Cohort (i.e., Day-1); Reference: Fares and Castagna. Safety and Pharmacokinetic Data for Inhaled Administration of Nintedanib Dry Powder Inhalation for Treatment of Pulmonary Fibrotic Diseases; J Aerosol Med Pulm Drug Deliv. 2026 Aug;39(4):185-197.*

Ensifentrine + Nintedanib SPRAYE™ Inhalation Powders

SPRAYE™ Inhalation Powders

- Ensifentrine Monotherapy 
- Nintedanib Monotherapy 
- Ensifentrine + Nintedanib 

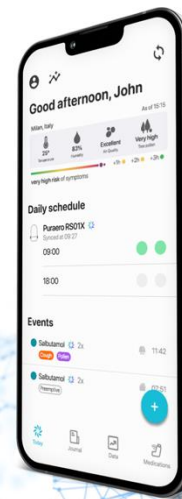


Inhalation Devices

EMPHASYS®



amcor



Clinical Development and Regulatory Strategy

AUS IRB / FDA 505(b)(2) / EMA Hybrid

Phase 1 in Australia

- Establish safety of doses and combination ratio of E to N in HV
- Establish maximum tolerated combination dose

Pre-IND meetings with FDA - building on Phase 1 data

- Agree on Phase 2/3 Pivotal study designs
- Address Combination Rule requirements
- Agree on acceptability of available toxicology data

Phase 2b in AUS, US, EU, Commonwealth

- File US IND and EU CTA
- Conduct Phase 2b (24 weeks)
- Add China and Commonwealth Countries (UK, Canada, NZ)

100 Participants (20 per arm) 4 Twice Daily Cohorts, 1 Once Daily Cohort



COPD *Fentrine Proliferation

Inhaled Dual PDE3/PDE4 Inhibitors



Verona Pharma
\$10B Acquisition

AirNexis

Haisco Pharmaceutical
\$40M Upfront
\$200M Series A (\$140M Pre)

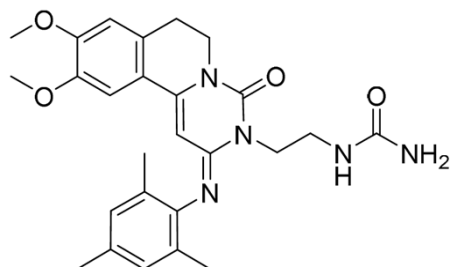
GSK

Hengrui
\$500M Upfront
(12 drugs)

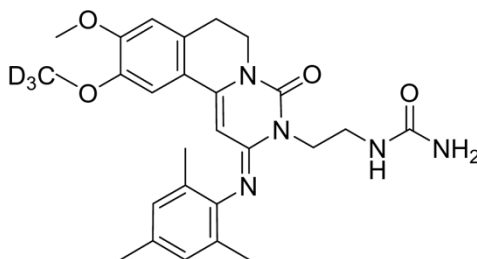
AstraZeneca

Sino Biopharma
\$200M Upfront

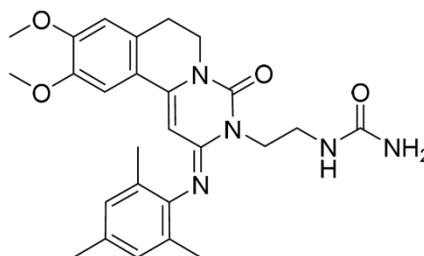
Ensifentrine



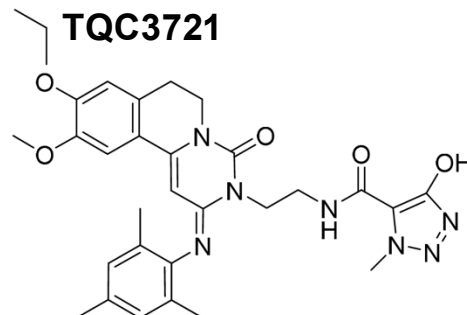
HSK39004 / AN01



HRS-9821 / GSK6582701



TQC3721



Molecule	PDE4B IC50	PDE3A IC50
Ensifentrine* (Merck / Verona)	110	0.25
HRS-9821* (GSK / Hengrui)	50	0.13
HSK39004/AN01 (AirNexis / Haisco)	N/A	0.17
TQC3721 (AstraZeneca / Sino Biopharma)	0.41	0.03
Nerandomilast ORAL (Boehringer-Ingelheim)	10	120,000
* Ensifentrine vs HRS-9821 is a head-to-head comparison		

