Innovating Clinical Trial Design in IPF: Lessons from LTI-03

REIN Therapeutics

Brian Windsor, Ph.D.| IPF Summit August 21, 2025

Forward Looking Statements

This presentation and various remarks we make during this presentation contain forward-looking statements of Rein Therapeutics, Inc. ("Rein", the "Company", "we", "our" or "us") within the meaning of the Private Securities Litigation Reform Act of 1995, including statements with respect to: Company's RENEW Phase 2 clinical trial of LTI-03, including with respect to the timing of the trial and the assumption that Company will raise the funds necessary to conduct the trial; future expectations, plans and prospects for the Company; the sufficiency of the Company's cash resources; and the potential commercial opportunity of LTI-03 and LTI-01. We use words such as "anticipate," "believe," "estimate," "expect," "hope," "intend," "may," "plan," "predict," "project," "target," "potential," "would," "can," "could," "should," "continue," and other words and terms of similar meaning to help identify forward-looking statements, although not all forward-looking statements contain these identifying words. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including risks and uncertainties related to: the ability of the Company to obtain the cash resources to fund the RENEW Phase 2 clinical trial and the Company's operations for the necessary periods of time, and the Company's ability to manage unplanned cash requirements; changes in applicable laws or regulations; the possibility that the Company may be adversely affected by other economic, business, and/or competitive factors, including risks inherent in pharmaceutical research and development, such as: adverse results in the Company's drug discovery, preclinical and clinical development activities, the risk that the results of preclinical studies and early clinical trials may not be replicated in later clinical trials, including the RENEW Phase 2 clinical trial of LTI-03, or that partial results of a trial will be indicative of the full results of the trial, the Company's ability to enroll patients in its clinical trials, and the risk that any of its clinical trials may not commence, continue or be completed on time, or at all; and decisions made by the U.S. Food and Drug Administration and other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies with respect to our development candidates; as well as the risks and uncertainties discussed in the "Risk Factors" section of the Company's Annual Report on Form 10-K for the year ended December 31, 2024, which is on file with the United States Securities and Exchange Commission (the "SEC"), and in the subsequent filings that the Company files with the SEC. These forward-looking statements should not be relied upon as representing the Company's view as of any date subsequent to the date of this presentation, and we expressly disclaim any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

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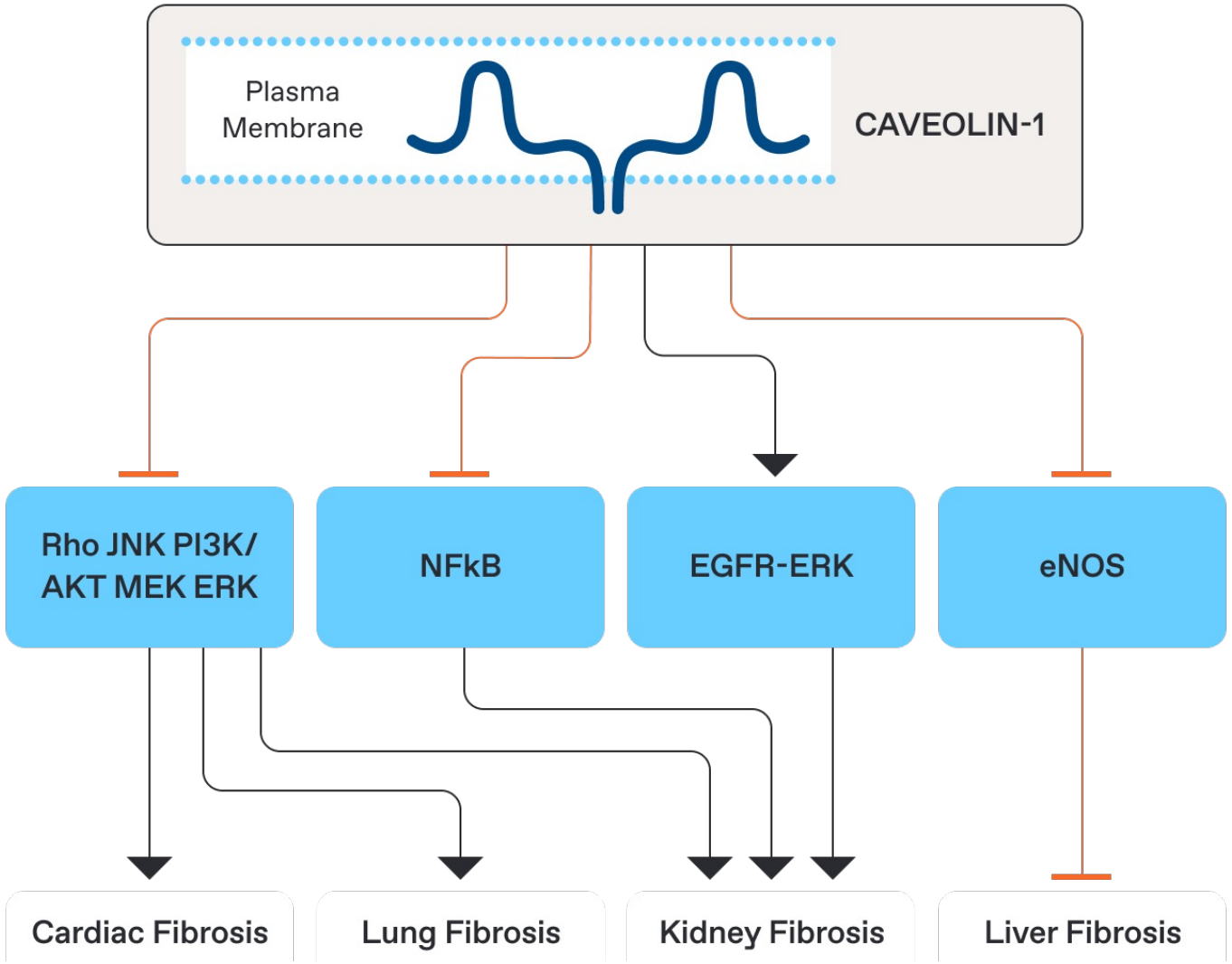
LTI-03: A Novel Treatment with Potential to Reverse the Course of IPF

Caveolin-1 Regulates Proteins Involved in Multiple Fibrosis-Related Pathways in the Lung and Other Organs

- Caveolin-1 (Cav1) is a regulator of cellular homeostasis
- Cav1 regulates many proteins involved in **multiple fibrosis pathways**
- Cav1 effects its regulation through interacting at the **Caveolin Scaffolding Domain (CSD)**, a 20 amino acid region that binds proteins and affects trafficking through phosphorylation
- Cav1 is lost in a fibrotic state—it is dramatically downregulated both at the transcript and protein level and thus loses its ability to properly regulate proteins involved in fibrosis[1]
- This is not limited to the lung. Cav1 is involved in fibrosis in the heart, skin, kidney, liver, and other organs

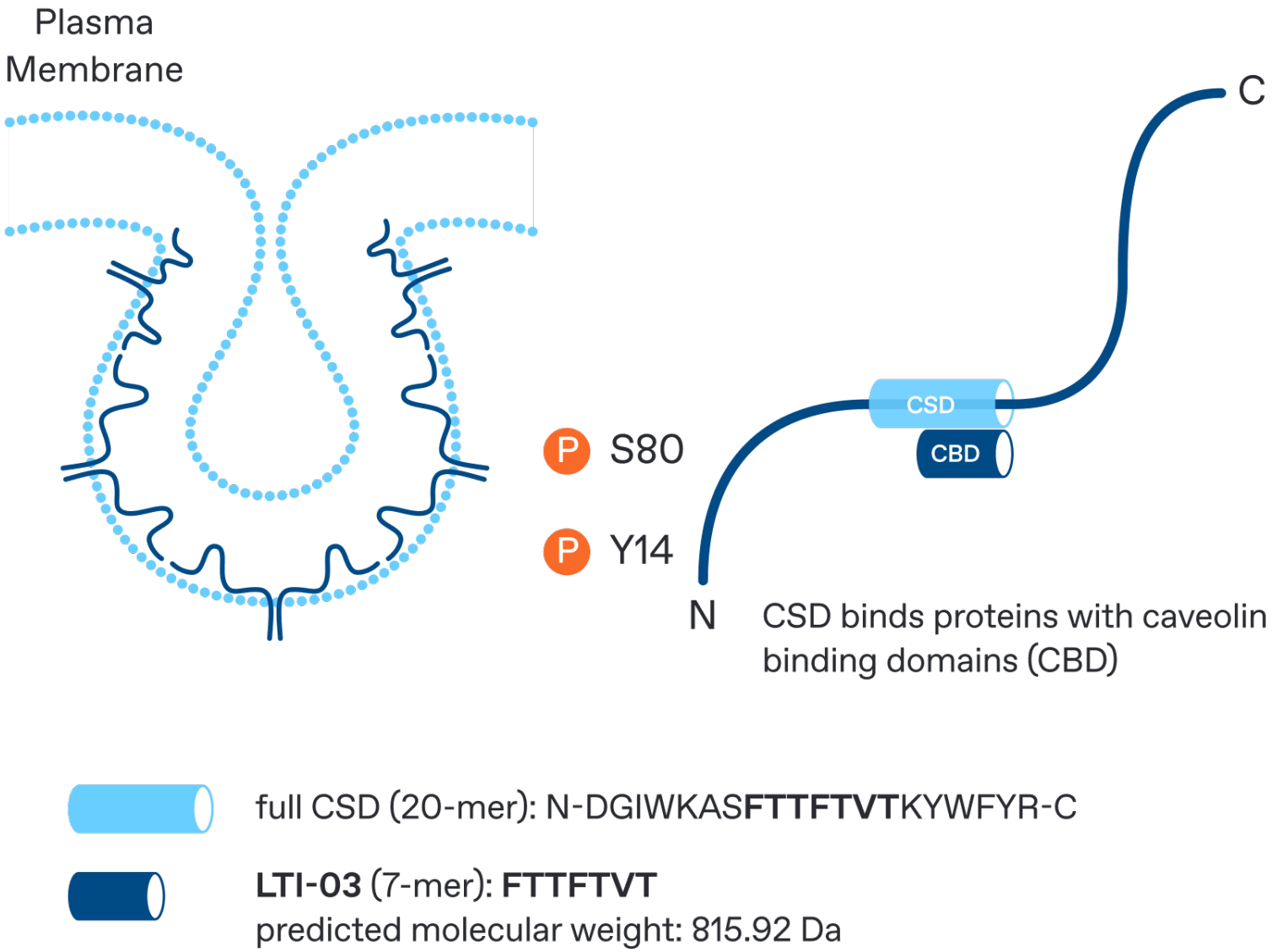


[1]Wang XM et al. Caveolin-1: a critical regulator of lung fibrosis in idiopathic pulmonary fibrosis. J Exp Med. 2006 Dec 25;203(13):2895-906.

Adapted from Gvaramia et al, Matrix Biology, 2013

LTI-03: the Critical Portion of the CSD Region of Cav1
Mimics the Regulatory Activity of Cav1, Affecting a Wide Range of Proteins Involved in Fibrosis

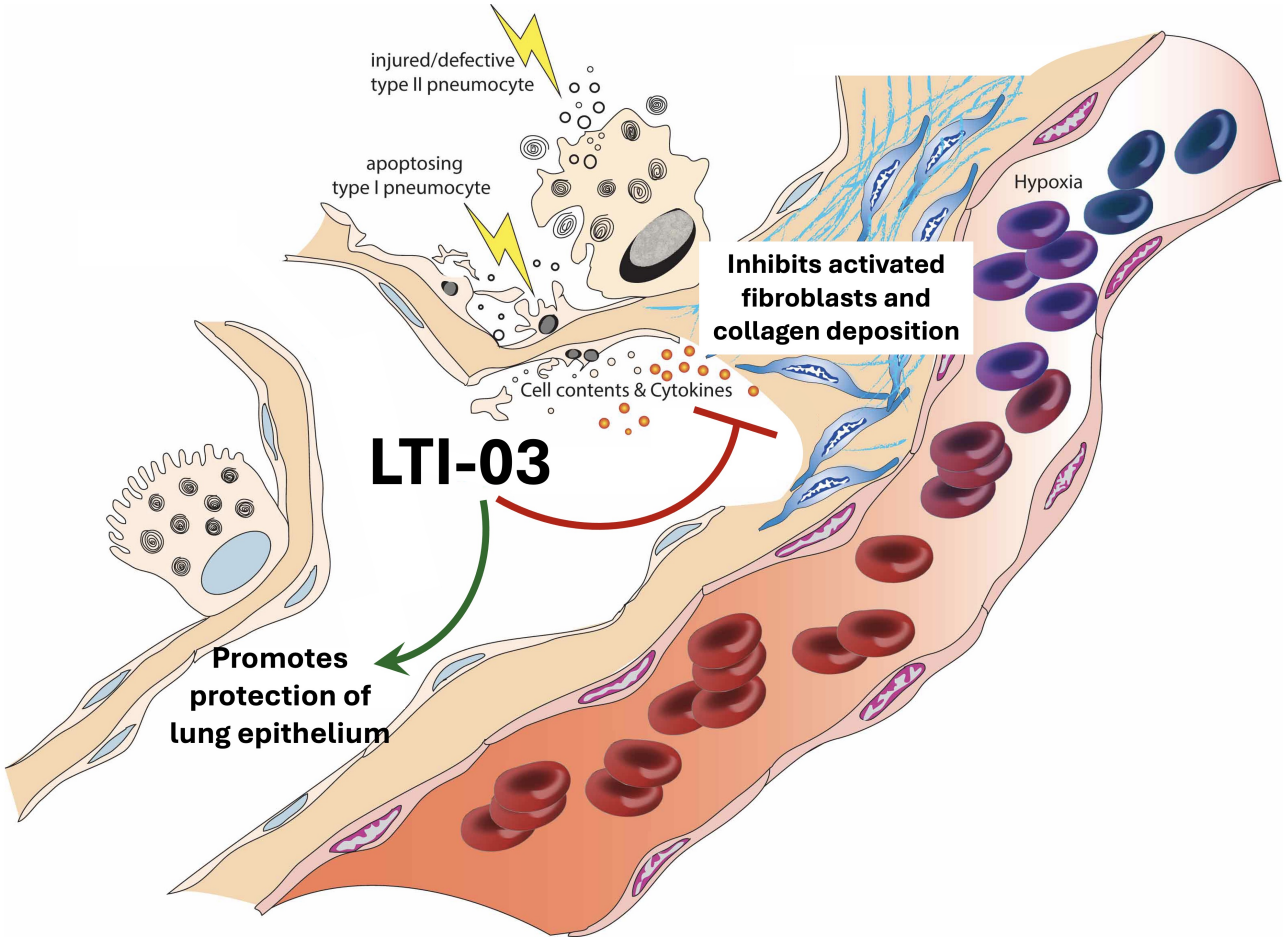
- LTI-03 is a seven amino acid peptide comprising a portion of the Cav1 CSD. Substitution/deletion analysis revealed it is the smallest CSD fragment that retains functionality
- This hydrophobic peptide can enter cells, and it may be acting both at the cell membrane and intracellularly
- Studies have shown that the LTI-03 peptide can affect phosphorylation of dozens of profibrotic proteins
- LTI-03 is dosed direct to the lungs by dry powder inhaler, and studies have shown that intact peptide can be detected in the lungs 24 hours after administration



For a review on CSD/CBD binding domain list, see: Byrne et. al. PLOS One 2012

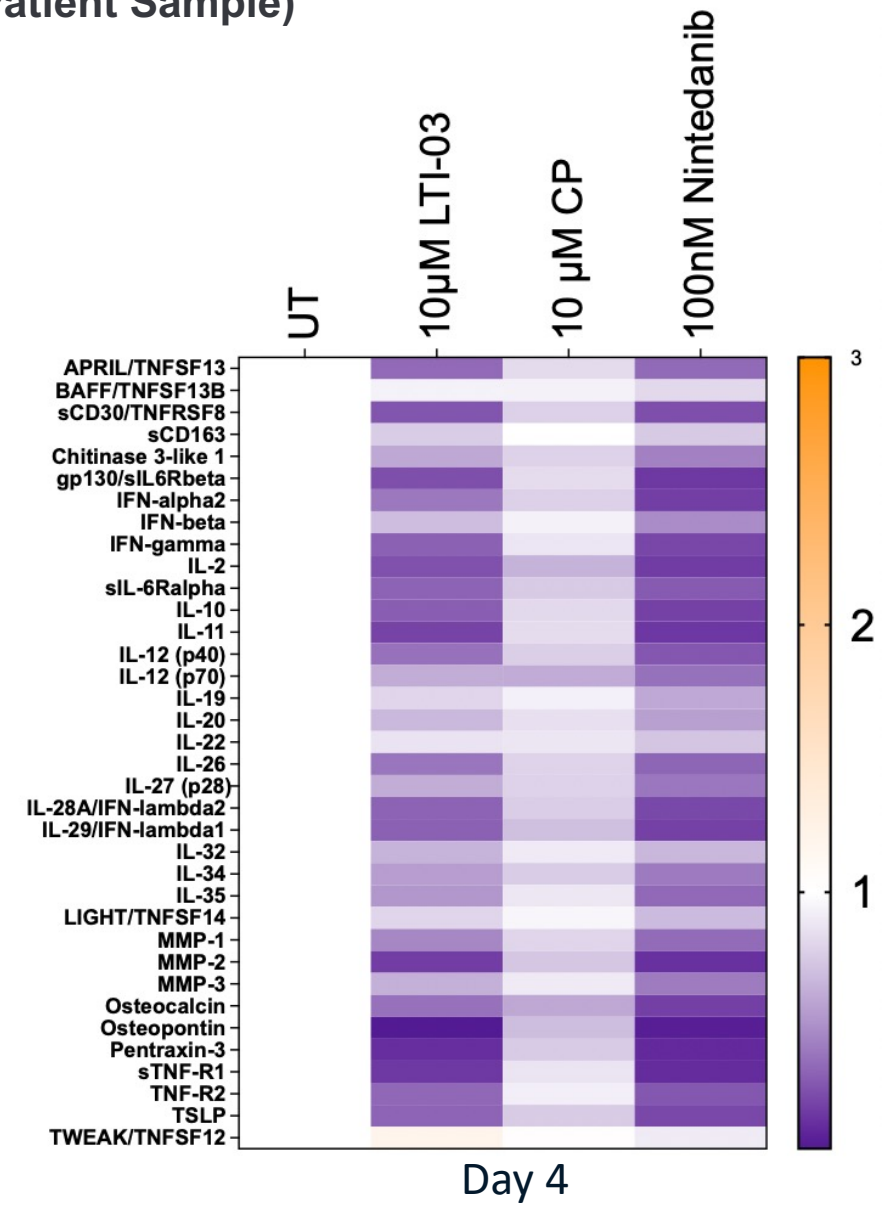
LTI-03's Dual Mechanism: Potent Antifibrotic Activity Combined with Epithelial Protection

- Other drugs act strictly as an antifibrotic, only addressing the lung scarring, and ultimately only slowing the progression of the disease
- LTI-03 acts to both inhibit profibrotic activity and to preserve epithelial progenitor cells, allowing for potential lung regeneration and restoration
- LTI-03 works to impact multiple fibrosis pathways—this multi-pathway approach is critical for better therapy



Antifibrotic Activity: Single dose LTI-03 inhibits multiple profibrotic proteins similar to Ofev®
(Every 12hrs in Precision Cut Lung Slices (PCLS)—Single Patient Sample)

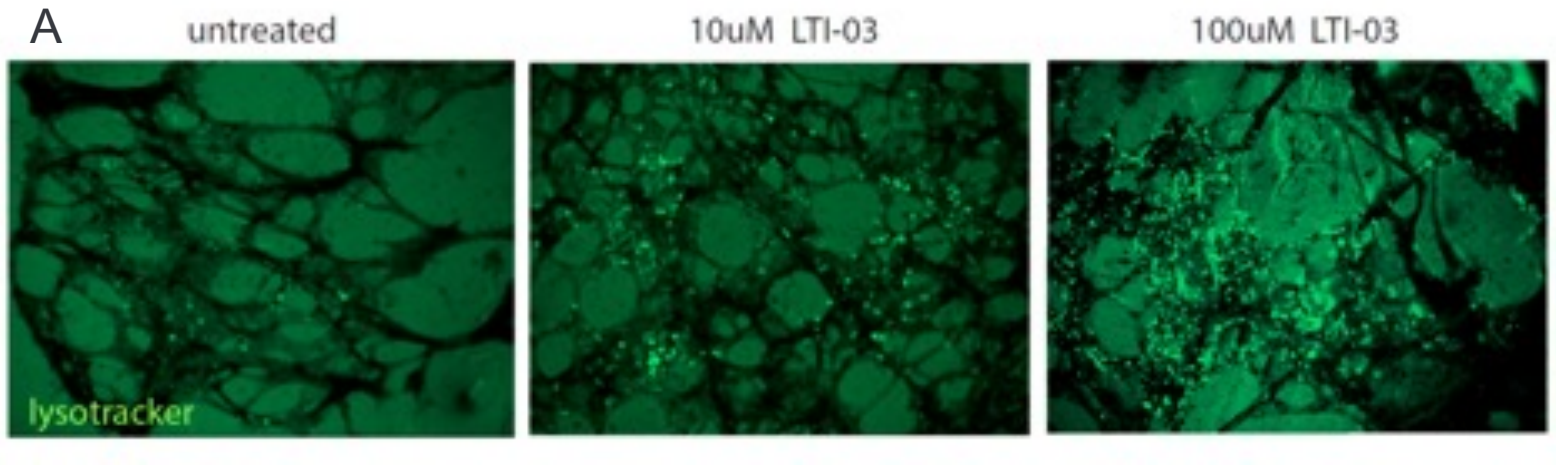
- As an **antifibrotic**, LTI-03 inhibits large panels of profibrotic proteins in a manner similar to the standard of care drug Ofev® (nintedanib)
  - Darker purple = more inhibition of the protein
- The PCLS tissue culture system uses actual biopsied tissue from an IPF lung (removed due to lung transplant), preserving all cell types in the IPF lung
- 10 µM LTI-03 is equivalent to an approximate dose of 1 mg in a dry powder inhaler. Phase 1b trial tested 5mg and 10mg, both of which were safe and well tolerated
- The equivalent human dose of 100nM nintedanib is very poorly tolerated, with significant GI side effects

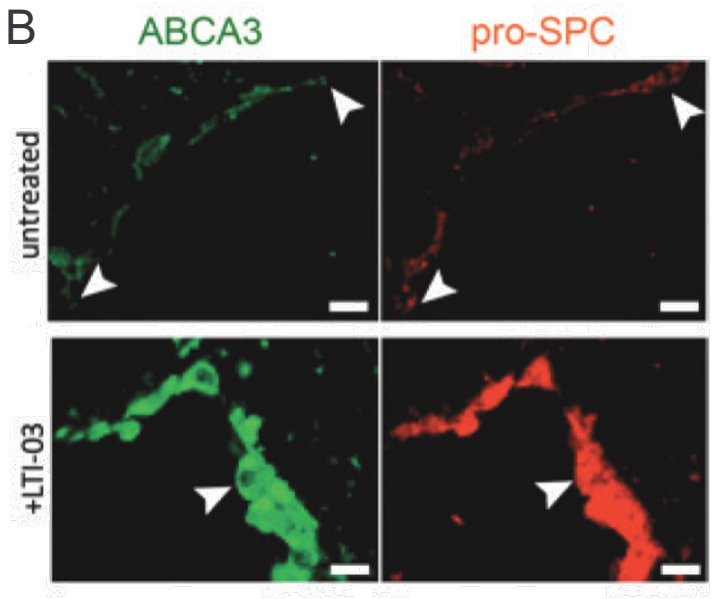


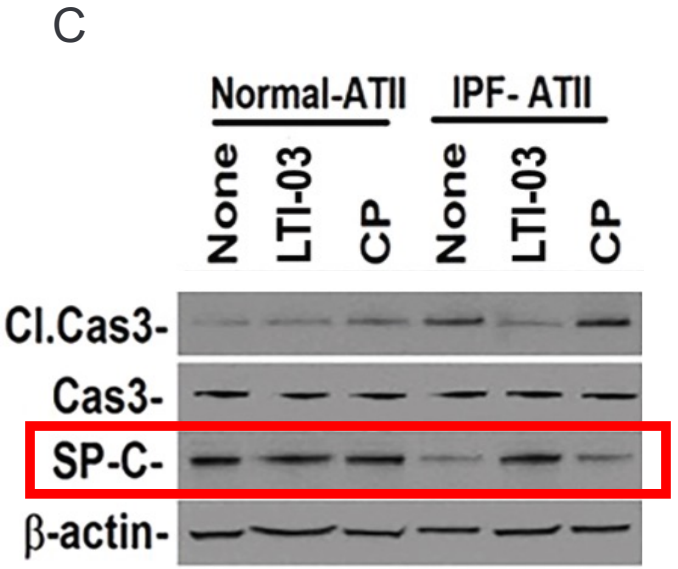
Regenerative Activity: LTI-03 Preserves Critical Progenitor Cells in the Lung

(PCLS Studies. Effects 48 Hours After Administration)

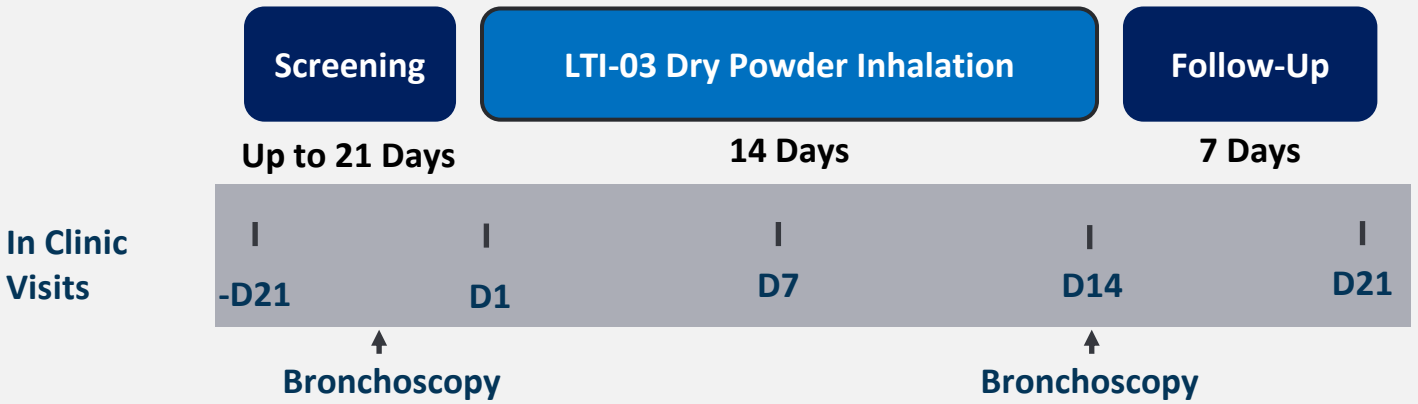
- Lysotracker dye (Panel A, bright green dots) localizes to AEC2 cells, the progenitor cells of the lung, which are responsible for making new lung tissue. LTI-03 resulted in an increase in staining, meaning an increase in these critical progenitor cells
- Increases in lysotracker staining (Panel B) also correlated with increases in surfactant protein C (pro-SPC) and ABCA3 (the pro-SPC transporter)
- Western blots (Panel C) confirm that in the IPF lung SPC levels are diminished, but that LTI-03 causes levels to increase







Phase 1b Clinical Trial Design—Focus on Safety, Tolerability, and Biomarkers (Status: Complete)



Study Design

- IPF diagnosis ≤ 3 years; no previous antifibrotic therapy w/in 2 months of baseline
- 24 patients total (18 active, 6 placebo)
  - Low (2.5mg BID) and high (5mg BID) dose cohorts, sequential daily dosing for 14 days
- Bronchoscopy at screening and Day 14
- Primary endpoint: Safety/tolerability
- Key exploratory endpoints: Biomarkers (blood, BAL, brushings)

Robust Biomarker Evaluation for De-Risking of LTI-03
Several Markers Linked to Lung Function

- All of the biomarkers selected for evaluation
  - ✓ Have literature suggesting their involvement
  - ✓ Are primarily found in important cell types in the IPF lung
  - ✓ Were shown in preclinical studies to be attenuated by LTI-03
- Attenuation of markers in the Phase 1b trial would demonstrate
  - ✓ That LTI-03 is reaching important cells in the deeply fibrosed lung
  - ✓ Surrogate target engagement
  - ✓ That LTI-03 is positively affecting pathogenic factors in the IPF lung

Statistically Significant Biomarkers from Phase 1b Trial	
Associated with Fibroblasts/myofibroblasts cell-type	
Interleukin 11 (IL-11)	A predictor of prognosis and acute exacerbation in IPF patients
CXCL7	Proinflammatory and pro-fibrotic chemokine
Associated with Basal-like cell-type	
Thymic Stromal Lymphopoietin Protein (TSLP)	Expressed in fibroblasts and basal like epithelium of IPF UIP lesions
Galectin 7 (Gal7)	Highly expressed in Caveolin-1 deficient bronchiolized areas in the IPF lung

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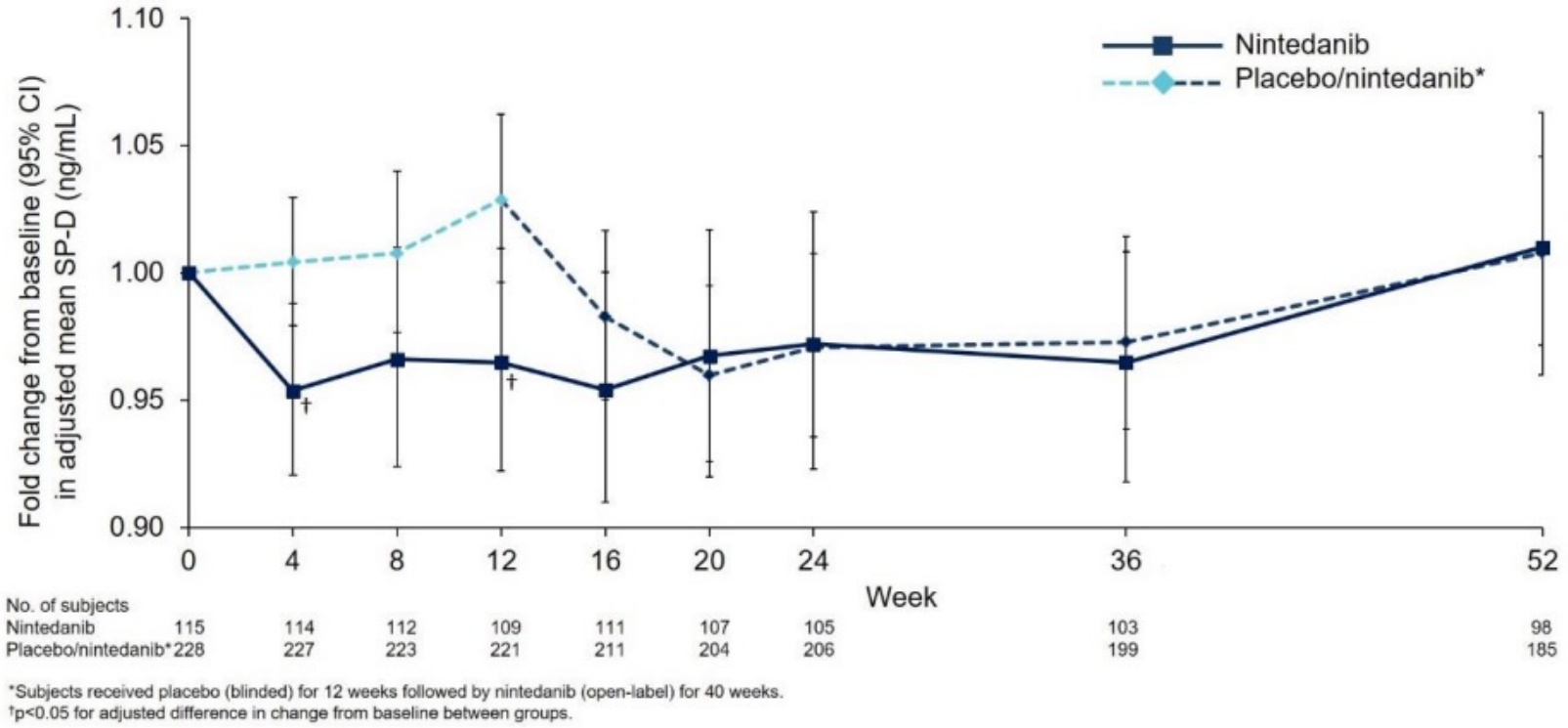
Surfactant Protein D (SPD) is an important biomarker for the approved IPF drug Ofev®* and now for LTI-03

- SPD is an indicator of epithelial cell health, an important cell type for proper lung function
- SPD has been significantly linked to decline in lung function
- SPD was reduced by 4% by Ofev over 12 weeks in the INMARK clinical trial
- LTI-03 (5 mg BID) decreased SPD by 5% over two weeks in the Phase 1b trial



Nintedanib versus placebo. Fold changes from baseline in SP-D at week 12 corresponded to a 4% decrease and 3% increase in the nintedanib and placebo groups, respectively (ratio 0.94 [95% CI: 0.89, 0.99]; p=0.024).

*Jenkins RG, Cottin V, Nishioka Y, et al. Effects of nintedanib on circulating biomarkers of idiopathic pulmonary fibrosis. ERJ Open Res 2024; in press

Surfactant Protein D (SPD) Reduction[1, 2]

Company	Trial	Compound	Percent Reduction	Duration of Treatment
REIN TX	Phase 1b	LTI-03	5%	2 weeks
Boehringer Ingelheim	INMARK (P2)	Nintedanib	4%	12 weeks
Roche	CAPACITY (P3)	Perfenidone	5%	12 weeks

The INMARK and CAPACITY trials were not conducted by the Company, no trials have been conducted comparing these compounds and the referenced trials had different trial designs, patient enrollment criteria and treatment regimens. In addition, the applicable measurements for the referenced trials were observed over different time periods and using different assays. As a result, the data from these trials may not be directly comparable.]

Ikeda, K., Chiba, H., Nishikiori, H., Azuma, A., Kondoh, Y., Ogura, T., Taguchi, Y., Ebina, M., Sakaguchi, H., Miyazawa, S., Suga, M., Sugiyama, Y., Nukiwa, T., Kudoh, S., & Takahashi, H. (2020). Serum surfactant protein D as a predictive biomarker for the efficacy of pirfenidone in patients with idiopathic pulmonary fibrosis: a post-hoc analysis of the phase 3 trial in Japan. Respiratory Research, 21(1), 1

Maher, T. M., Gisli Jenkins, R., Cottin, V., Nishioka, Y., Noth, I., Selman, M., Song, J. W., Ittrich, C., Diefenbach, C., Stowasser, S., & White, E. S. (2024). Circulating biomarkers and progression of idiopathic pulmonary fibrosis: data from the INMARK trial. ERJ Open Research, 10(4). https://doi.org/10.1183/23120541.00335-2023

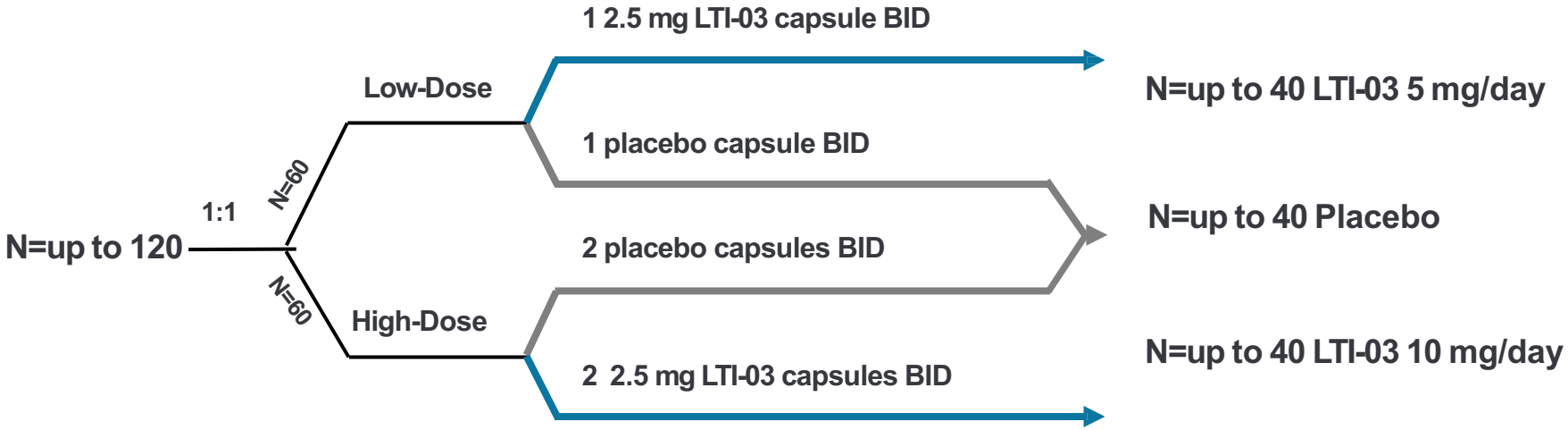
LTI-03 – Phase 2 Trial Measuring Lung Function

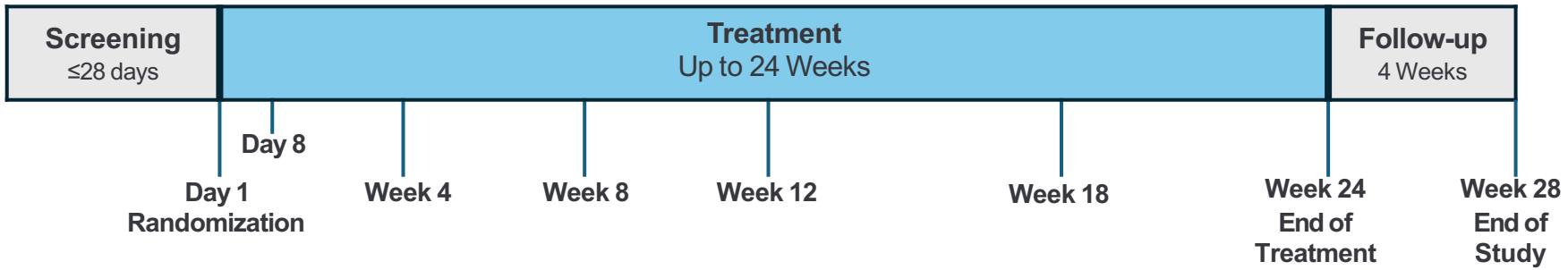
Primary endpoints

Safety and tolerability measured by incidence of treatment emergent adverse events

Efficacy of inhaled LTI-03 measured by:

- Change from baseline in FVC in mL
- Change from baseline in percent predicted FVC
- Change from baseline in lung fibrosis measure by HRCT





Select Competitive Landscape[1]

Company	Compound	Single or Multi-pathway	Mechanism	Target Cell Types	Clinical Stage
REIN TX	LTI-03	Multi-pathway	Caveolin-1 CSD mimic	Fibroblasts, type 2 Epithelial cells, Aberrant basaloid cells, Macrophages	P2
Boehringer Ingelheim	Nintedanib	Multi-pathway	Broad tyrosine kinase inhibitor	Fibroblasts	Approved
Roche	Perfenidone	Multi-pathway	unknown	Fibroblasts	Approved
Boehringer Ingelheim	Nerandomilast	Multi-pathway	PDE-4B inhibitor	Aberrant basaloid cells, Fibroblasts	P3
ENDEAVOR BioMedicines	ENV 101	Single	Sonic Hedgehog inhibitor	Fibroblasts	P2
vicore pharma	Buloxibutid	Single	Angiotensin II type 2 receptor agonist	Type 2 Epithelium	P2
avalyn pharma	APO-1	Multi-pathway	unknown	Fibroblasts	P2
tvardi THERAPEUTICS	TTI-101	Single	STAT3 inhibitor	Aberrant basaloid cells, Fibroblasts	P2

[1]Libra, A., Sciacca, E., Muscato, G., Sambataro, G., Spicuzza, L., & Vancheri, C. (2024). Highlights on Future Treatments of IPF: Clues and Pitfalls. International Journal of Molecular Sciences, 25(15). https://doi.org/10.3390/IJMS25158392

Phase 2 Trial Considerations in IPF for Small Biotech

Most Important Considerations for Smaller Biotech

- Direct relationships (sites, investigators, CRO)
- Ease of conduct (for patients and site)
- Experienced central read of HRCT

Considerations for IPF Phase 2 Trials for Smaller Biotech

- Diagnosis of IPF
  - Typically done at the site initially
    - Does not always meet the criteria for the trial
    - Compatible HRCT
  - Independent Central reader
    - May challenge the site – can result in problems
    - Problems can be mitigated by focusing on protocol HRCT endpoints

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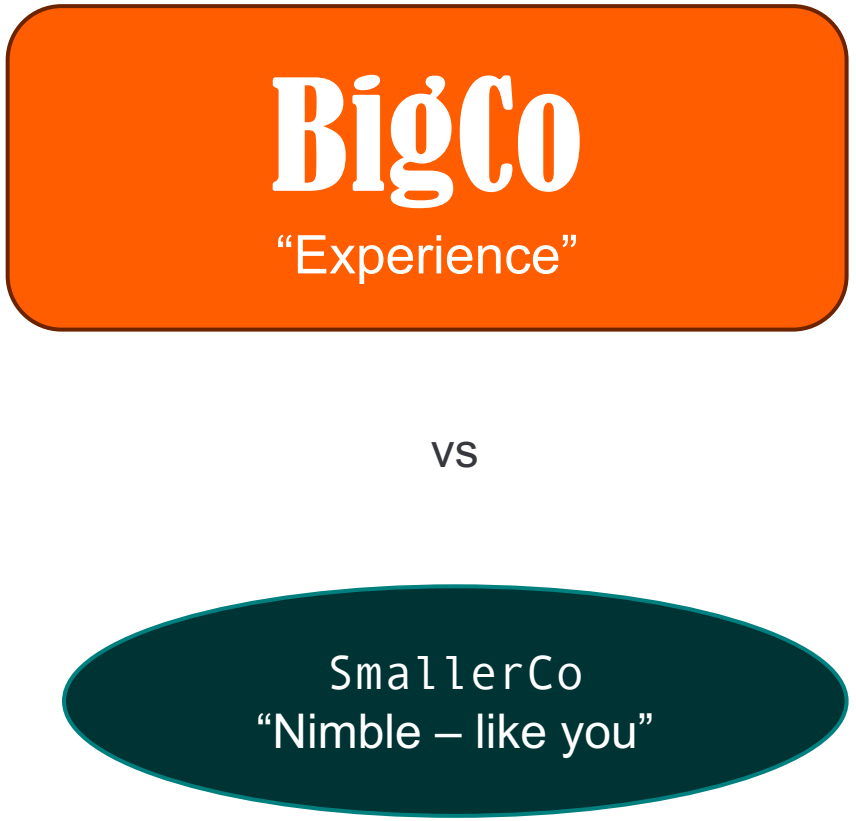
Considerations for IPF Phase 2 Trials for Smaller Biotech

- CRO Selection
  - Big or small
  - Move quickly, make decisions
  - Cost
  - Project Manager
  - Phone vs Email
  - Risk mitigation



Considerations for IPF Phase 2 Trials for Smaller Biotech

- Always a need for new investigators due to saturation
- Ease of conduct
  - Frequency of visits
  - Physical and logistical limitations: fit with clinic workflow
  - Time commitment
  - Explanation of trial (pts and their children)- printed and online material
  - Travel and time reimbursement important
  - Considerations for this pt population (e.g. pet care)
  - Details like paper questionnaires instead of electronic tablets

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Patient Support

What else do I need to consider?

- The study team will explain the possible benefits and risks of the study.
- You do not have to take part in the study if you do not want to.
- If you choose to take part in the study, you can stop participating at any time.
- All study medications and study-related tests will be provided at no cost to you.
- A team of doctors and nurses will monitor your health carefully during the study.
- An Institutional Review Board (IRB)/Ethics Committee (EC) has reviewed this study. An IRB/EC protects the rights, safety, and well-being of participants.

Who can take part?

You **may** be able to take part if you:

- are 40 years of age or older
- have been diagnosed with IPF within the past 5 years
- are willing and able to use an inhaler every day.

How do I get more information?

Please contact the study team using the details provided here. By contacting us, you are under no obligation to take part in the study.

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Patient Brochure, 18 Mar 2025 [V01 USA(en)]

We're striving to renew hope for people with idiopathic pulmonary fibrosis

RENEW
IPF CLINICAL STUDY

Patient Information

A clinical research study looking at an inhaled investigational medication for people with idiopathic pulmonary fibrosis (IPF).

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Considerations for IPF Phase 2 Trials for Smaller Biotech

- Lack of harmonization of regulatory approaches
  - View of 2/3 adaptive trials
  - Is it orphan or not? EU with more stringent criteria

Considerations for IPF Phase 2 Trials for Smaller Biotech

- Study Length and Design
  - Shorter studies not popular with pts
  - Placebo (less chance is better)
  - Open label extensions are wanted by pts
- Considerations of Inhaled Delivery
  - Device considerations
  - EU changing device regs
    - Previously had to show it was safe; now they are moving more towards a US approach where you must show drug/device safety
  - Education (materials, video)
  - Fewer systemic side effects

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Considerations for IPF Phase 2 Trials for Smaller Biotech

- Standard of Care
  - Much more harmonized than 15 years ago
  - Non-overlapping MOA offers competitive advantage
  - Not only have to allow it, but allow addition/removal

Considerations for IPF Phase 2 Trials for Smaller Biotech

- Remote Spirometry
  - Gets a lot of attention, pushed quite a bit
  - More expensive, not cost effective
  - Training of patients – it is hard for them to learn this
  - More reliable data when performed at the site
  - This population is highly motivated to see a doctor
  - Introduction of variability increases sample size requirements

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Nasdaq: RNTX