FIRST REPORT MANAGED CARE

Nerandomilast in Fibrotic Lung Diseases: A Clinical Evidence and Market Access Series

Part 1: Idiopathic Pulmonary Fibrosis Phase 3 Trial Results and PDE4B Inhibition Mechanism

Executive Summary

Idiopathic pulmonary fibrosis (IPF) is a progressive, high-burden disease with no new US Food and Drug Administration (FDA)-approved therapies in more than a decade. Existing antifibrotics offer limited benefit, are highly costly, and are frequently discontinued due to tolerability issues, leaving a persistent gap in care and cost containment.

Nerandomilast, a selective phosphodiesterase 4B (PDE4B) inhibitor, is the first investigational agent in 10 years to demonstrate a statistically significant difference in slowing lung function decline in IPF compared with placebo in the Phase 3 FIBRONEER-IPF trial. In this trial, which permitted patients to be on background antifibrotic therapy, treatment with nerandomilast 18 mg twice daily preserved forced vital capacity (FVC) by 68.8 mL versus placebo over 52 weeks.

Nerandomilast showed a favorable safety and tolerability profile in both the FIBRONEER-IPF trial and in a second Phase 3 trial of patients with progressive pulmonary fibrosis (PPF), with lower discontinuation rates and manageable adverse events, positioning it as a potentially more durable treatment option.

Consistent efficacy across subgroups—including autoimmune interstitial lung disease (ILD) and fibrotic hypersensitivity pneumonitis—suggests broader utility beyond IPF, supporting simplified utilization strategies across progressive fibrosing ILDs.

With Breakthrough Therapy designation and a differentiated mechanism of action, nerandomilast may represent statistically significant Phase 3 efficacy results. For payers, it offers an opportunity to evaluate new clinical trial data—delivering on outcomes, persistence, and potential cost offsets in a historically static landscape.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a relentlessly progressive interstitial lung disease (ILD) of unknown etiology associated with irreversible scarring of lung tissue, declining respiratory function, and premature mortality.[1,2] The disease predominantly affects middle-aged and older men. Though classified as idiopathic, several factors have been reported to increase disease risk, including aging, exposure to metal and wood dust, air pollution, and smoking, likely through complex interactions with genetic predispositions.[1]

IPF carries a high symptom burden characterized by severe breathlessness, cough, and fatigue that increases as patients near death, resulting in deteriorating physical, social, and emotional well-being and poor quality of life (QoL).[3]

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Despite its severity, the treatment landscape has remained stagnant for more than a decade. Pirfenidone and nintedanib, the first-generation antifibrotic therapies approved more than 10 years ago, have been shown to slow disease progression and modestly extend survival in patients with IPF.[4] However, despite these advances, the majority of IPF trials in the past decade have failed to meet their primary endpoints, underscoring a persistent and urgent unmet need for therapies that can more effectively halt disease progression and improve survival.[4] While the treatment landscape is beginning to evolve, only a limited number of novel options have advanced to Phase 3 testing.[4]

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Recent Phase 3 data for nerandomilast, a novel phosphodiesterase 4B (PDE4B) inhibitor, suggest the potential to change this paradigm. With statistically significant efficacy in slowing lung function decline, as measured by the absolute change from baseline in forced vital capacity (FVC), and a favorable safety profile, nerandomilast may represent the first meaningful therapeutic advancement for IPF since the approvals of pirfenidone and nintedanib in 2014.[5,6]

This document discusses nerandomilast, an investigational treatment that has not been approved by the FDA. The efficacy and safety of nerandomilast have not been established.

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The Idiopathic Pulmonary Fibrosis Challenge

Though considered a rare disease, the annual prevalence of IPF is rising globally.[7] A retrospective analysis based on a national cohort of US veterans determined that the annual prevalence of IPF increased from 276 cases per 100,000 in 2010 to 725 cases per 100,000 in 2019. The annual incidence likewise increased from 73 per 100,000 person-years in 2010 to 210 cases per 100,000 person-years in 2019.[7]

The disease is marked by insidious onset, diagnostic delays, and a heterogeneous but obstinately progressive course. Most patients experience disease-related mortality within two to seven years of diagnosis, often in the hospital setting due to respiratory failure related to either progression of the disease or acute exacerbation.[8]

Even with treatment, patients experience gradual but steady loss of lung function. The physical, emotional, and financial toll on patients and families is profound.[9] For health care systems, IPF contributes to frequent hospitalizations, high utilization of specialist care, and significant end-of-life costs.[9] The pressing need for therapies that can meaningfully slow progression, reduce symptom burden, and improve adherence remains unmet.

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The Treatment Landscape Stagnation

Approved more than a decade ago, pirfenidone and nintedanib remain the currently recommended first-line antifibrotic therapies for IPF.[10] Nintedanib, a tyrosine kinase inhibitor (TKI), targets multiple receptors involved in fibrogenesis to suppress fibroblast proliferation, migration, and differentiation.[11] Nintedanib is also approved in the US to treat other chronic fibrosing ILDs with a progressive phenotype and for systemic sclerosis-associated ILD.[12]

Pirfenidone exerts antifibrotic effects through several mechanisms, including attenuation of oxidative stress, downregulation of transforming growth factor beta-1 (TGF-β1), and inhibition of proinflammatory cytokine production and release.[11] Pirfenidone is only approved in the US to treat IPF.

While these agents modestly slow the annual rate of FVC decline, they do not appear to substantially alter the underlying disease trajectory and do not meaningfully improve survival.[11] Moreover, they are frequently associated with gastrointestinal side effects, such as nausea and diarrhea, which drive high discontinuation rates and impact real-world effectiveness.[13] Health-related quality of life (HRQoL) also remains substantially impaired despite treatment.[3,14] Patients experience persistent cough, dyspnea, fatigue, and progressive functional decline even with pharmacologic treatment, necessitating complementary disease management strategies including early integration of palliative care to help improve HRQoL.[3,14]

A 2025 qualitative, real-world study published in *BMJ Pulmonary Medicine* sought to better elucidate the lived experiences of patients in the US diagnosed with IPF, including the burden of the disease itself and how treatment with antifibrotics affects QoL.[15] Among the 106 surveyed patients with IPF, 59 had been treated with one or more antifibrotic—23% had taken pirfenidone, 32% had taken nintedanib, and 10% had taken both via switch. Of the 106 patients with IPF who participated in a survey, 87% reported ongoing dyspnea, and 78% reported fatigue, with more than 40% rating these symptoms as "very burdensome." These symptoms were associated with significant limitations in social engagement, daily functioning, and hobbies and activities.[15]

Among the 59 patients exposed to one or more antifibrotic therapies, 87% taking pirfenidone and 92% taking nintedanib reported at least one treatment-related side effect. Between 30% and 55% of participants agreed that the side effects of each antifibrotic significantly impacted their QoL, frequently leading to modifying, pausing, or discontinuing treatment.[15]

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Despite these limitations, 78% of patients in the study agreed with the statement that antifibrotic treatment "gives them hope,"[15] underscoring the emotional impact of the disease and the continued need for more effective and tolerable therapeutic options.

High patient out-of-pocket costs and the need for routine monitoring further compound the burden on patients and health care systems.[15] Antifibrotic therapy costs may be prohibitive for patients with high-deductible or coinsurance-based plans, with financial pressures linked to delayed treatment uptake and reduced medication persistence.[16] Ongoing pulmonary function assessments, the management of adverse events (AEs), and frequent hospitalizations for acute exacerbations lead to increased health care resource utilization and specialty care demands. The result is a fragmented standard of care with limited ability to preserve function or extend life in a meaningful way.

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The Innovation Gap

Despite the growing burden of IPF, the last 10 years have failed to deliver new US Food and Drug Administration (FDA)-approved therapies, leaving clinicians and patients dependent on legacy antifibrotics with modest efficacy and well-documented tolerability challenges.

This innovation drought is not due to a lack of investment. Over the past decade, numerous investigational therapies for IPF—including simtuzumab (lysyl oxidase-like 2 [LOXL2] inhibition) and pamrevlumab (anti-connective tissue growth factor [CTGF])—have failed to demonstrate efficacy in Phase 2 and 3 trials, despite promising early-phase data.[4,17,18] These repeated setbacks reflect the complexity of the disease pathophysiology, characterized by aberrant wound healing in a dysfunctional, aging lung epithelium, exaggerated fibroblast activation, and chronic inflammation.[19]

Methodological barriers have further compounded the challenge. Clinical trials in IPF struggle with disease heterogeneity, endpoint sensitivity, and the absence of reliable biomarkers—making it difficult to capture clinically meaningful improvement or predict treatment responders. These dynamics have contributed to a high rate of attrition and stagnated the therapeutic pipeline.[4,20]

A well-tolerated, disease-modifying therapy that performs consistently across ILDs could reduce reliance on dose modifications, improve persistence, and consolidate coverage strategies—addressing longstanding clinical and operational inefficiencies in IPF management.

Nerandomilast: A Novel Therapeutic Approach

Against this backdrop, nerandomilast has emerged as a promising exception. Preclinical and early-phase studies demonstrated not only a favorable safety profile with lower potential for gastrointestinal side effects, but also antifibrotic and anti-inflammatory activity through selective PDE4B inhibition, a mechanism distinct from the broad antifibrotic mechanisms of the current standard.[21]

There are four PDE4 enzymes: PDE4A, B, C and D. Nerandomilast is an oral PDE4 inhibitor that preferentially inhibits PDE4B, which is highly expressed in immune and structural cells involved in fibrogenesis.[12]

PDE4 is broadly expressed in immune system cells and its inhibition leads to reduced production of pro-inflammatory mediators and limits the recruitment of inflammatory cells. As a result, PDE4 inhibitors exhibit both anti-inflammatory and antifibrotic properties and may help mitigate pulmonary inflammation and fibrotic remodeling in patients with progressive fibrosing ILDs, such as IPF.[12]

This selectivity distinguishes nerandomilast from broader PDE4 inhibitors, which are often limited by gastrointestinal AEs.[12,22] By avoiding pan-PDE4 inhibition, nerandomilast seeks to retain antifibrotic and anti-inflammatory efficacy while improving tolerability,[22] which is a key consideration for a population prone to polypharmacy and multiple comorbidities.[3,23]

For payers, this shift is significant. A well-tolerated, disease-modifying therapy that performs consistently across ILDs could reduce reliance on dose modifications, improve persistence, and consolidate coverage strategies—addressing longstanding clinical and operational inefficiencies in IPF management.

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Clinical Development Journey: A Data-Driven Path Toward Differentiation

Nerandomilast's clinical program reflects a stepwise and risk-mitigated development path, underpinned by consistent signals of efficacy and tolerability across trial phases.[5]

Initial Phase 1 studies in healthy volunteers established a favorable safety and pharmacokinetic profile. AEs were mostly mild or moderate, with no new safety signals—positioning nerandomilast as a candidate with a potentially manageable side effect profile from the outset.[12]

Encouraged by this foundation, a Phase 2 proof-of-concept study enrolled 147 patients with IPF, including those on stable background antifibrotics.[24] Nerandomilast 18 mg twice daily significantly slowed lung function decline over 12 weeks compared to placebo—showing benefit regardless of background antifibrotic therapy use. The median FVC change in patients not on antifibrotics was +5.7 mL with nerandomilast vs -81.7 mL with placebo. Among those on background antifibrotics, nerandomilast still demonstrated a relative preservation in lung function compared to placebo (median +2.7 mL vs -59.2 mL).[24]

Importantly, nerandomilast was associated with lower rates of gastrointestinal side effects than historically observed with nintedanib, including lower rates of diarrhea, even among patients on dual therapy.[24,25] These early tolerability signals addressed one of the most significant barriers to persistence seen with current IPF treatments.

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FDA Breakthrough Therapy Designation

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This designation recognizes therapies for serious or life-threatening conditions that show preliminary clinical evidence of substantial improvement over existing options.[27] It reflects the agency's recognition of both the magnitude of unmet need in IPF and the agent's early promise. It also allows for enhanced regulatory engagement, including intensive guidance on an efficient drug development program, and potentially accelerated timelines for review and approval.[27]

Advancement to Phase 3: Robust Trial Design, Diverse Populations

Building on Phase 2 findings, nerandomilast advanced to two parallel, placebo-controlled Phase 3 trials under the FIBRONEER program:

- **FIBRONEER-IPF**, enrolling 1177 patients with IPF, the majority of whom were on background antifibrotic therapy.[6]
- **FIBRONEER-ILD**, enrolling 1176 patients with progressive fibrosing ILDs other than IPF, including autoimmune ILDs and hypersensitivity pneumonitis.[5]

Both trials employed rigorous, placebo-controlled designs with a 52-week duration and stratification by background antifibrotic use—ensuring generalizability to real-world patient populations.[5,6]

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The FIBRONEER-IPF trial's primary endpoint, absolute change in FVC from baseline at 52 weeks, met statistical significance.[6] Patients in the nerandomilast 18 mg arm experienced a mean FVC decline of 114.7 mL compared to 183.5 mL in the placebo group, representing an adjusted treatment difference of 68.8 mL (P<0.001). Even among those on existing antifibrotics, nerandomilast added incremental benefit,[6] suggesting potential value as both an adjunctive or switch option for patients with suboptimal response or poor tolerability to standard therapy.

The FIBRONEER-ILD trial similarly met its primary endpoint.[5] At week 52, the nerandomilast 18 mg group experienced an annual rate of FVC decline of 98.6 mL versus 165.8 mL in the placebo arm, for an adjusted treatment difference of 67.2 mL (P<0.001). Consistent effects were observed regardless of background antifibrotic use,[5] supporting nerandomilast's broader applicability beyond IPF and reinforcing its potential role in unified ILD management strategies.

In both trials, nerandomilast maintained a favorable safety profile.[5,6] Diarrhea was the most commonly reported AE but led to treatment discontinuation in 2.6% and 6.1% of patients in the 18 mg groups of FIBRONEER-ILD and FIBRONEER-IPF, respectively—rates significantly lower than those observed in clinical trials of currently approved antifibrotics. Serious AEs occurred at similar rates between active and placebo arms, and no new safety signals were identified.[5,6] Collectively, these findings suggest nerandomilast may reduce treatment discontinuation, improve adherence, and mitigate the need for dose reductions or treatment interruptions that often complicate real-world antifibrotic use.

For a disease area long defined by narrow options and persistent tolerability challenges, nerandomilast may be an opportunity to improve clinical outcomes while simplifying utilization pathways.

From a managed care standpoint, nerandomilast's clinical trajectory is meaningful. The consistent efficacy across ILD phenotypes, favorable tolerability profile, and relevance in both monotherapy and combination settings speak directly to unmet needs in access management.[5,6,28] For a disease area long defined by narrow options and persistent tolerability challenges, nerandomilast may be an opportunity to improve clinical outcomes while simplifying utilization pathways.

Subgroup Insights and Clinical Relevance

Subgroup analyses by background therapy showed consistent FVC preservation with nerandomilast 18 mg resulting in adjusted FVC decline of:[6]

- -79.2 mL in patients without background antifibrotics vs -148.7 mL for the placebo group
- -118.5 mL in patients taking background nintedanib vs -191.6 mL for the placebo group
- -133.7 mL in patients taking pirfenidone vs -197.0 mL in the placebo group

The FIBRONEER-ILD trial included patients with a range of fibrosing ILDs, including autoimmune ILD and fibrotic hypersensitivity pneumonitis, and subgroup analyses reflected a generally consistent effect across ILD diagnoses, reinforcing nerandomilast's potential as a pan-ILD therapy.[5] Nerandomilast was also shown to slow ILD progression both in patients taking background nintedanib and in those not taking nintedanib.[5]

Though the trial was not powered to evaluate nerandomilast's efficacy in specific ILD subgroups, initial results highlight nerandomilast's potential role not only in IPF but across a spectrum of progressive fibrosing diseases.[5] For clinicians, this expands the range of treatable patients.

For payers managing diverse and comorbid populations, these subgroup data enable smarter segmentation strategies. Nerandomilast's consistent efficacy regardless of background therapy or

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ILD subtype introduces a rare opportunity: a single agent suitable across varied disease phenotypes, disease stages, and patient profiles. This may allow for more flexible coverage tiers, improves predictability of treatment response, and supports earlier, broader access—especially in cases where tolerability, comorbidity burden, or diagnostic uncertainty complicate treatment selection.

A First in a Decade

Nerandomilast represents the first investigational therapy since the approvals of pirfenidone and nintedanib to demonstrate significant Phase 3 efficacy in slowing lung function decline in progressive ILDs, including IPF.[5,6]

Nerandomilast represents the first investigational therapy since the approvals of pirfenidone and nintedanib to demonstrate significant Phase 3 efficacy in slowing lung function decline in progressive ILDs, including IPF.[5,6] These Phase 3 results may signal the end of a drought in meaningful therapeutic advancement in a disease characterized by rapid progression, poor prognosis, and limited options.[16] The success of nerandomilast in the FIBRONEER-ILD and FIBRONEER-IPF trials signals a shift in the innovation trajectory and represents the first Phase 3 success in this therapeutic area in over a decade.[5,6]

With a novel and selective mechanism targeting PDE4B, nerandomilast differs in mechanism from existing antifibrotics and offers systemic anti-inflammatory as well as antifibrotic effects.[12,22] This may confer broader utility not only in IPF, but also in other progressive fibrosing ILDs, and may enable its use as both an alternative and a complement to current therapies.[21,22]

From a clinical perspective, these results suggest nerandomilast could have the potential to address an important gap in care by serving patients who may be unable to tolerate current therapies due to gastrointestinal side effects or other limiting comorbidities. High discontinuation rates and poor adherence are well-documented challenges with existing antifibrotics,[16,28] making the favorable tolerability of nerandomilast a differentiating feature that may enhance persistence and optimize real-world outcomes.

Though new in mechanism, nerandomilast offers a familiar and payer-relevant value proposition: slowing disease progression, improving tolerability, and potentially reducing the need for adjunctive medications and frequent monitoring.[5]

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Conclusion

These Phase 3 results represent the first statistically significant efficacy demonstration in IPF trials in more than 10 years.[29] These findings may position nerandomilast as a differentiated antifibrotic with broad applicability across ILD phenotypes, including IPF, and enhanced tolerability, which may benefit a patient population largely consisting of older adults and those with multiple comorbidities.[3,5,6]

While longer-term data on survival and real-world adherence are still needed, current findings from the FIBRONEER-ILD and FIBRONEER-IPF trials are encouraging and support nerandomilast's potential to transform care for patients with progressive fibrosing lung diseases, including IPF.[5,6] Additional data on FVC decline and AEs are currently planned to be provided by an open-label extension study.[6]

In summary, nerandomilast represents a new treatment option after years of limited therapeutic advancement. These results also provide new clinical evidence for stakeholder evaluation, to ensure timely, evidence-based access to innovative therapies and close the long-standing treatment gap in IPF.

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