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REVIEW

Idiopathic Pulmonary Fibrosis, Today and Tomorrow: Certainties and New Therapeutic Horizons

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) represents a clinical and therapeutic challenge characterized by progressive fibrosis and destruction of the lung architecture. The pathogenesis of IPF has been long debated; while it is generally believed that repeated lung injury and abnormal wound repair are the main pathogenetic mechanisms, clear understanding of disease development and efficacious treatment remain important unmet needs. Indeed, current standard of care (i.e., the antifibrotic drugs pirfenidone and nintedanib) can slow down lung function decline and disease progression without halting the disease. In the last 2 decades, several clinical trials in IPF have been completed mostly with negative results. Yet, unprecedented numbers of clinical trials of pharmacological interventions are currently being conducted. In this review, we summarize and critically discuss the current and future treatment landscape of IPF, with emphasis on the most promising developmental molecules.

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Key Summary Points

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic lung disease with unknown origin and without therapeutic drugs able to halt disease progression. Indeed, the two available anti-fibrotic agents, pirfenidone and nintedanib, have the effect on slowing the decline of forced vital capacity

In the last 2 decades, many clinical trials have attempted to provide the scientific community with new drugs for IPF; there have been numerous failures, but many other molecules are currently under investigation

Alveolar macrophages, fibroblasts, and epithelial cells are the main targets of the treatments being investigated in clinical trials

Inhaled molecules and others aimed at treating symptoms related to IPF, such as cough, are also gaining attention

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic lung disease of unknown cause and with poor survival that typically affects patients aged ≥ 60 years [1], with predilection for male subjects with a smoking history. The global incidence and prevalence of IPF are in the range of 0.09 and 1.30 per 10,000 people [2].

In the last decade, our understanding of disease pathogenesis has improved significantly. Genetic factors, aging and exposure to environmental/occupational pollutants are believed to interact with each other to determine disease development [2]. The combination of these three elements causes cellular damage and the abnormal activation of alveolar epithelial cells, which secrete a plethora of profibrotic cytokines, including transforming growth factor-beta (TGF-β). The epithelial injury promotes the proliferation and migration of fibroblasts in the interstitium and their differentiation into myofibroblasts, which secrete excessive amount of extracellular matrix (ECM), leading to parenchymal remodeling [2, 3].

The median survival of patients with IPF without treatment is around 3 years [4], but patient registry and real-world studies suggest improved prognosis; in a European registry, the median survival of patients with IPF on antifibrotic therapy was 123.1 months versus a median survival of 68.3 months with any other treatments [1], whereas in a Korean registry the median survival among patients treated with antifibrotics was 54 months versus 34 months in patients not treated with antifibrotics [5].

Before 2014, a combination of immunosuppressants including prednisone and azathioprine, as well as N-acetylcysteine, was the standard of care for IPF [6]. However, the FDA-sponsored PANTHER-IPF trial showed that, compared with placebo, the so-called "triple therapy" was associated with increased likelihood of hospitalization, treatment-related severe adverse events, and death [7].

To date, two drugs have been approved for IPF, nintedanib and pirfenidone. Although with different mechanisms of action, both drugs have been shown to slow down the forced vital capacity (FVC) decline over time and, ultimately, to reduce respiratory hospitalizations and mortality [8]. Conversely, neither drug has shown effectiveness in relieving symptoms, and few patients experience safety and tolerability issues, mainly gastrointestinal [8, 9].

Comorbidities and complications, such as acute exacerbations, pulmonary hypertension and lung cancer, contribute to the high mortality rate of IPF [9, 10].

Acute exacerbations (Fig. 1) occur in 10% of patients per year and are usually treated with corticosteroids, although without clear evidence of efficacy. Phase III trials, involving the use of intravenous cyclophosphamide in addition to the steroid and thrombomodulin alfa, have failed [11, 12].

Therapeutic strategies for IPF are scarce, and more efficacious and better tolerated drugs are urgently needed.

In this review, we summarize and critically discuss current and developmental treatments for IPF.

Ethical Approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

CURRENT THERAPIES

Pirfenidone

Although the precise mechanism of action is unknown, pirfenidone is a molecule that inhibits fibroblast proliferation and collagen synthesis by regulating TGF-β [13]. Pirfenidone was approved for the treatment of IPF in Europe in 2011 and in the US in 2014 [14, 15]. In the phase 3, randomized, double-blind, placebo-controlled trials CAPACITY 004 and 006, the results indicated that pirfenidone had a favorable risk-benefit profile and was a suitable treatment option for individuals with IPF. The first study demonstrated

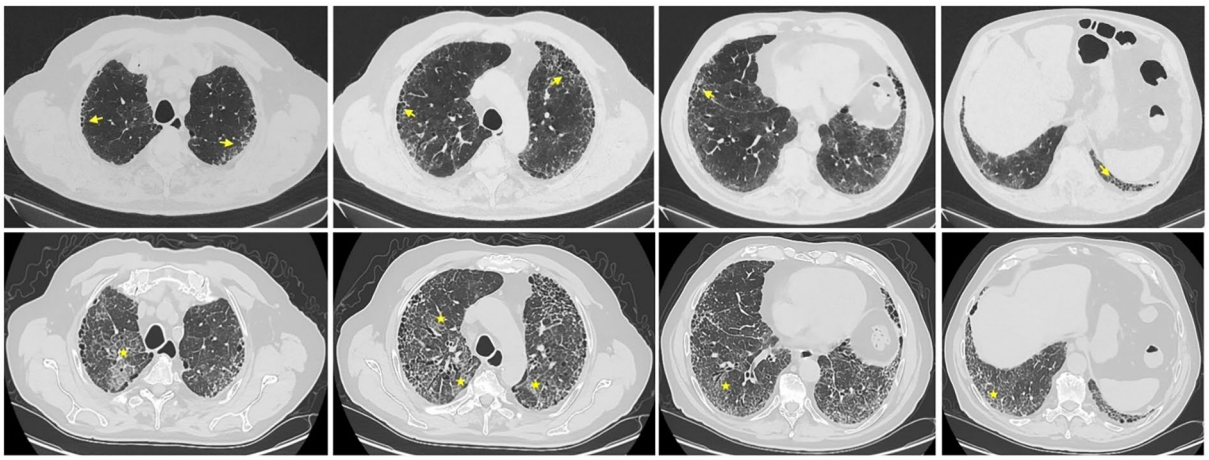

Fig. 1 Acute exacerbation of idiopathic pulmonary fibrosis (IPF). Extensive ground glass opacities (stars) superimposed on a background of reticulation, traction bronchiectasis and honeycombing (arrows) in a 75-year-old man

that pirfenidone helped reduce the decline in FVC, while in study 006, the difference between the groups in the change in FVC at week 72 was not statistically significant. However, a consistent effect of pirfenidone was observed up until week 48 as well as in an analysis across all study time points [13]. In 2014, ASCEND, a the phase 3, randomized, double-blind, placebo-controlled trial, demonstrated that, in the group treated with pirfenidone, compared to the placebo group, there was a 47.9% relative reduction in the proportion of patients who experienced an absolute decline of ≥ 10 percentage points in the predicted forced vital capacity (FVC) or who passed away. Additionally, there was a 132.5% relative increase in the proportion of patients with no decline in FVC. Furthermore, pirfenidone helped slow the decline in the 6-min walk distance and enhanced progression-free survival. No significant differences were observed between the groups in terms of dyspnea scores or mortality rates from any cause or IPF [16]. Since this work, which recruited patients with IPF and with a mild-to-moderate physiological impairment, several studies have demonstrated its efficacy even in advanced disease stages [17].

Gastrointestinal and skin-related adverse events (AEs) are the most common causes of dose reduction and treatment discontinuation [15] (Table 1).

Nintedanib

Nintedanib is an oral triple-tyrosine kinase inhibitor (TKI). Initially approved as a second-line agent for non-small cell lung cancer, nintedanib also exerts anti-fibrotic properties [18]. In IPF, nintedanib is approved for the treatment of mild-to-moderate disease [14], although post hoc analyses have suggested a similar beneficial effect in more advanced disease [19]. The efficacy of nintedanib was evaluated in the multinational, randomized, double-blind, placebo-controlled phase III trials INPULSIS-1 and INPULSIS-2 [20] and in the open-label long-term extension INPULSIS-ON [21], subsequently confirmed in post hoc analyses. In both the INPULSIS trials, nintedanib significantly reduced the rate of decline in FVC over the 52 weeks. In INPULSIS-1, no significant difference was observed between nintedanib and placebo in the time to the first acute exacerbation, with similar proportions of patients experiencing at least one investigator-reported event. In contrast, INPULSIS-2 showed a significant delay in the first acute exacerbation with nintedanib, and fewer patients in this group had at least one investigator-reported exacerbation compared to placebo (3.6% vs 9.6%). The pooled analysis found no significant difference in time to the first investigator-reported exacerbation, but a sensitivity

Table 1. Current therapies for IPF

Drug	Mechanism of action	Route of administration	Year of approval for IPF	Efficacy	Most common adverse events	References
Pirfenidone	Partially unknown but likely related to inhibition of TGF-β1 and pro-inflammatory cytokines (e.g., TNF-α)	Oral	2008 Japan, 2011 Europe, 2014 USA	- Reduction of lung function decline in terms of FVC (in the ASCEND CT −235 ml with pirfenidone vs −428 ml with placebo at 52-week follow-up, relative difference of 45.1%) - Reduction of disease progression - Reduction of all-cause hospitalization	Nausea, diarrhea and skin rash	[15, 82, 83]
Nintedanib	Tyrosine kinase inhibition	Oral	2014 USA, 2015 Europe	- Reduction of lung function decline in terms of FVC (in the INPULSIS-1 CT −114.7 ml with nintedanib vs −239.9 ml with placebo, in the INPULSIS-2 CT −113.6 ml with nintedanib vs −207.3 ml with placebo at 52-week follow-up, relative difference of 44–57%) - Reduction of disease progression - Reduction of acute exacerbations - Less deterioration of patient quality of life (observed in INPULSIS-2 CT)	Diarrhea, nausea, vomiting, weight loss, liver enzyme elevation	[20, 84, 85]

ASCEND 52-week, randomized, double-blind, placebo controlled, phase III study which evaluated the efficacy and safety of pirfenidone in patients affected by IPF, *CT* clinical trial, *FVC* forced vital capacity, *GI* gastrointestinal, *INPULSIS-1 and INPULSIS-2* 52-week, randomized, double-blind, placebo-controlled, phase III studies which evaluated the efficacy and safety of nintedanib in patients affected by IPF, *IPF* idiopathic pulmonary fibrosis, *TGF-β1* transforming growth factor-beta1, *TNF-α* tumor necrosis factor-alpha

analysis on the time to the first adjudicated acute exacerbation (confirmed or suspected) indicated a significant benefit of nintedanib over placebo [20]. In INPULSIS-1, the adjusted mean change in the total St. George's Respiratory Questionnaire (SGRQ) score (a measure of health-related quality of life) from baseline to week 52 did not differ significantly between groups. In INPULSIS-2, however, the increase in total SGRQ score was significantly lower (consistent with less deterioration in health-related quality of life) with nintedanib than with placebo (2.80 vs 5.48 points; $P = 0.02$). The prespecified pooled analysis found no significant difference in the adjusted mean change in total SGRQ score between the two groups [20].

Approximately 20–25% of patients do not tolerate nintedanib because of side effects [21], the most frequent being diarrhea, which is induced by a dysfunction in the intestinal absorption and secretion of water [22], followed by nausea, vomiting, weight loss and elevation in liver enzymes [9], 9 (Table 1). Diarrhea can be managed by using loperamide, an opioid receptor agonist [9]. Alternatively, diarrhea can be relieved from a reduced dose (100 mg twice daily) or temporal discontinuation of the drug [23].

Combination of Pirfenidone and Nintedanib

The potential role for a combination of both antifibrotics was previously suggested in two studies, also due to the absence of a relevant drug-drug interaction [24, 25]. However, these trials were not powered for efficacy; thus, definitive studies are needed to address this question.

Lung Transplant

Lung transplantation is a therapeutic option for patients with IPF that progress until respiratory failure. A key discussion point among experts is identifying the patients eligible for a transplant and the right time to evaluate them for inclusion on the transplant list. As we learn from the International Society of Heart and Lung Transplantation (ISHLT) consensus document of 2021, referral for lung transplantation is a complex process that should ideally begin before the need becomes urgent. Early referral allows time to introduce the concept of lung transplant, discuss its requirements and expected outcomes and address modifiable barriers like obesity, malnutrition, comorbidities or inadequate social support. It also provides time to review vaccination records and administer necessary vaccines before the immunosuppression [26]. Key considerations are also the risk of death, the likelihood of post-transplant survival and comorbidities that may lead to complications. Criteria for candidate selection and listing proposed by the International ISHLT represent a tool used by transplant centers [27, 28].

Whether it is better to perform a mono- or bilateral transplant is still being discussed; according to a meta-analysis, published in recent 2020, bilateral lung transplant does not lead to a survival advantage but is characterized by better residual lung function [29]. The main causes of post-transplant mortality are chronic lung allograft dysfunction and infections [27].

Currently, there is no upper age limit representing an absolute contraindication to transplantation. Age > 65 should be considered a relative contraindication (ISHLT guidelines) [30]. Furthermore IPF, one of the leading indications for transplantation, appears to have the highest prevalence among individuals > 70 years; thus, many centers in the USA and Europe have tried to offer transplantation to older patients with IPF, with contrasting results [31].

Recently, IPF has been considered an interesting field for testing new drugs. Many trials have been proposed, but many expectations have not been met.

Ziritaxestat, an autotaxin (ATX) inhibitor, which showed promising results in the phase IIa study, did not demonstrate a reduction in the annual rate of decline in FVC compared to placebo in the subsequent ISABELA 1 and ISABELA 2 trials, thus failing to meet the primary endpoint. Moreover, it failed to show benefits in any of the secondary outcomes. Additionally, a slightly increased all-cause mortality rate was observed with ziritaxestat compared to placebo in both trials [32] (Table 2). The reasons for the discrepancy between the results in the two phases of the molecule's development are

unknown. Contributing factors could include the limited number of patients enrolled in the phase IIa study, its shorter duration and the inability to administer standard therapies (pirfenidone and nintedanib) as well as the fact that ziritaxestat showed an increase in plasma levels of nintedanib, which could have led to an increase in adverse events recorded in the phase III trials. Furthermore, unusually, the ISABELA trials showed a greater functional decline in patients receiving standard of care compared to those not receiving it. The COVID-19 pandemic, which arose after the trials were initiated, may have contributed by often causing patients to miss clinic visits.

Recombinant human pentraxin-2 (PRM-151), which works by modifying neutrophil adhesion, the inhibition of the differentiation of monocytes into profibrotic macrophages and fibrocytes, and the promotion of phagocytosis of cell debris by macrophages, showed promising results in the phase II study, with a decrease in the decline in FVC percent predicted (ppFVC) and distance walked at 6MWT. Unfortunately, interim data analyses of the phase III randomized, placebo-controlled clinical trial (STARSCAPE) results showed a lack of efficacy, and the trial was terminated by the sponsor in the fourth quarter of 2022 [33] (Table 2). In this case as well, the SARS-CoV-2 pandemic could have played an unfavorable role, although mechanisms were put in place to minimize its impact on the study. In addition, the different patient samples and their functional characteristics, which obviously did not overlap, may have influenced the outcome, as well as the standard of care they were receiving. Compared with phase II, fewer patients in STARSCAPE were receiving pirfenidone (39.2% vs 52.6%), and more patients were receiving nintedanib (43.8% vs 25.9%).

Another failure concerns a drug on which many hopes were placed, namely pamrevlumab, which targets connective tissue growth factor (CTGF) with modulation of myofibroblast activation, extracellular matrix (ECM) deposition and fibrotic remodeling via tumor necrosis factor β (TGF-β) downstream signaling [34, 35]. The phase II PRAISE study had shown a reduction in the decline of FVC at 48 weeks in the treatment group compared with placebo. The ZEPHYRUS 1 phase III clinical trial, however, did not show a significant decrease in the rate of decline in FVC in the pamrevlumab randomized group compared with placebo and thus did not meet its primary outcome. Pamrevlumab also did not show significant benefits in any of the secondary or exploratory outcomes (Table 2). Based on the results of this study, the planned open-label extension was terminated, as was its companion trial (ZEPHYRUS 2) [35]. Again, the reasons for the failure are unclear, but factors such as the smaller cohort of patients involved in the phase II study, the enrollment of patients with worse respiratory conditions, poorer functional patterns and a greater latency between the diagnosis of IPF and enrollment in the study in the phase III trial may have contributed. Even in ZEPHYRUS 1, taking standard antifibrotic therapy was possible, which was prohibited in the previous study. Perhaps, compared to the previous two trials, this trial was less impacted by the COVID-19 pandemic. There was no increase in mortality with pamrevlumab, and patients were allowed to receive infusions of the study drug at home via a qualified home health care service, which likely improved adherence and willingness to continue treatment during the pandemic.

Despite the unsuccessful studies, the intriguing pathophysiological mechanisms of IPF continue to be a source of inspiration regarding new therapeutic frontiers.

NEW TRIALS AND FUTURE PERSPECTIVES

Lung tissue affected by IPF is damaged by organ aging, such as cellular senescence, telomere shortening and epigenetic changes, and mitochondrial and autophagic dysfunctions [9]. Aging contributes to the pathogenesis of the disease by reducing type 2 alveolar epithelial cells (AEC2s), involved in damage repair [36]. The subsequent activation of a series of cytokines and chemokines (e.g., tumor necrosis factor-α and interleukin-1) perpetuate the damage, and secretion of profibrotic mediators, such as TGF-β, leads to the activation of connective tissue

Table 2 Non-exhaustive list of negative trials

Drug	Mechanism of action	Route of administration	Trial acronym/ NCT/UMIN/ ACTRN no.	Status/year of completion	Phase and duration	Satisfaction with outcomes	Security profile notes	Next developments	References
Ziritaxestat (GLPG1690)	Inhibition of ATX, which stimulates LPA production, with pro-fibrotic effects	Oral	FLORA/ NCT02738801	Completed/2018	Phase IIa/12-week RCT	FVC improvement compared with placebo	–	Twin phase III trials: NCT03711162 (ISABELA-1) and NCT03733444 (ISABELA-2), both stopped in FEB/2021 due to benefit-risk profile	[9, 27, 86]
Recombinant Human Pentraxin-2 (PRM-151)	- Modification of neutrophil adhesion - Inhibition of the differentiation of monocytes into profibrotic macrophages and fibrocytes - Promotion of phagocytosis of cell debris by macrophages	Intravenous	NCT02550873	Completed/2017	Phase II/28-week RCT + 76-week open-label crossover extension	Slowdown of the decline of ppFVC and distance walked at 6MWT	–	Phase III trial, stopped in February 2023 because of futility (STARSCAPE; NCT04552899)	[87–89]

Table 2 continued

Drug	Mechanism of action	Route of administration	Trial acronym/ NCT/UMIN/ ACTRN no.	Status/year of completion	Phase and duration	Satisfaction with outcomes	Security profile notes	Next developments	References
Pamrevlumab	Target CTGF with modulation of myofibroblast activation, ECM deposition and fibrotic remodeling via TGF-β downstream signaling	Intravenous	PRAISE/NCT01890265	Completed/2020	Phase II/48-week RCT	Reduction in FVC decline at 48 weeks in the treatment group compared with placebo	–	Phase III trial in IPF ZEPHYRUS I (NCT03955146) did not reach the primary endpoint. The planned open-label extension was terminated as well as its companion trial ZEPHYRUS 2; (NCT04419558)	[34, 90]

ATX autotaxin, *CTGF* connective tissue growth factor, *ECM* extracellular matrix, *LPA* plasma lysophosphatidic acid, *ppFVC* percent predicted forced vital capacity, *RCT* randomized controlled trial, *TGF*-β transforming growth factor-beta

growth factor (CTGF), fibroblast growth factor (FGF), insulin-like growth factor (IGF) and platelet-derived growth factor (PDGF), all fibrogenic molecules [9].

Therefore, research is moving towards cellular senescence, oxidative stress, mitochondrial dysfunction, alveolar macrophages, epithelial cells and fibroblasts themselves. The patient's choice should not be underestimated, with the need to identify those with a "rapid progressor" phenotype, which is clearly distinct from the "slow progressor" [37] and which actually responds better to anti-fibrosing treatment [38]. The challenge for researchers is to develop treatments that can further slow lung function decline and improve symptoms, preferably acting synergistically with the actual standard of care.

In our discussion, we will focus on the ongoing or recently concluded phase II and III trials on patients with an IPF diagnosis. In Table 3, we summarize the main trials underway in earlier phases.

TARGETING ALVEOLAR MACROPHAGES

Axatilimab

Axatilimab is an intravenous humanized monoclonal antibody that inhibits CSF-1R signlling and restrains macrophage development. It has proven to be a promising novel strategy for refractory chronic graft-versus-host disease (cGVHD) [39]. The main adverse effects recorded with the drug in patients treated for cGVHD after allogeneic hematopoietic cell transplantation are blood chemistry alterations, infections, musculoskeletal pain and asthenia [40].

MAXPIRe, a phase II, randomized, double-blind, placebo-controlled study, to evaluate the efficacy of the drug on patients affected by IPF (NCT06132256), is now recruiting (Table 3). The main eligibility criteria for the trial include a compatible high-resolution computed tomography (HRCT) of the chest, ppFVC ≥ 45%, forced expiratory volume in 1 s (FEV1)/FVC ≥ 0.7, and DLco percent predicted (ppDLco) ≥ 30% and ≤ 90% (corrected for hemoglobin) at screening visit. Participants are randomized to take axatilimab or placebo every 2 weeks during the 26-week treatment period. The first outcome of the study is the annualized rate of decline in morning pre-dose through FVC (ml) from baseline to week 26. Secondary outcomes are time to disease progression, the annualized rate of decline in ppFVC, change in SGRQ score and change in ppDLco (corrected for hemoglobin) from baseline to week 26. Completion of the study is expected in June 2025.

TARGETING FIBROBLASTS

BMS-986020 and Admilparant (BMS-986278)

BMS-986020 and BMS-986278 are LPA receptor 1 (LPA1) antagonists [9].

The first drug was blocked in phase II because of hepatobiliary toxicity [41]. The second, administered orally, was studied in a phase II trial aimed at patients affected by IPF and PPF (NCT04308681). The trial consisted of a 42-day screening period, a placebo-controlled, 26-week treatment period, an optional active-treatment extension (OTE) period for an additional 26 weeks and a post-treatment follow-up for 28 days. The IPF cohort included adult patients with a centrally read chest HRCT consistent with usual interstitial pneumonia (UIP) or probable UIP, ppFVC ≥ 40%, FEV1/FVC ≥ 0.7 and single-breath ppDLco ≥ 25% (corrected for hemoglobin). Patients were randomized at a ratio of 1:1:1 to receive 30 mg or 60 mg of admilparant or placebo, two times per day for 26 weeks in the placebo-controlled treatment phase. In the OTE, patients receiving active treatment continued to receive their assigned dosage of admilparant, and patients receiving placebo were randomized to receive 30 mg or 60 mg admilparant. The primary endpoint was to evaluate the rate of change in ppFVC from baseline to week 26. Secondary outcomes included AEs, treatment-emergent deaths, clinically significant changes in clinical laboratory results, electrocardiogram (ECG), physical examination and vital signs,

Table 3 New drugs in clinical trials for IPF and related conditions by mechanism of action and formulation

Drug	Mechanism of action	Route of administration	Trial acronym/NCT/UMIN/ACTRN no.	Status/end date	Phase and duration	Main results	Security profile notes	Primary outcome(s) achievement	Principal secondary outcome(s) achievement	Magnitude of the results	Next developments	References
Targeting alveolar macrophages												
Axatilimab	Inhibition of CSF-1R signaling with reduction of macrophage development	Intravenous	MAXPIRe/NCT06132256	Recruiting/June 2025 (estimated)	Phase II/26-week RCT	–	–	–	–	–	–	[39]
Venetoclax (ABT-199)	Inhibition of Bcl-2 Induction of apoptosis of MDMs and reversion of established fibrosis	Oral	NCT05976217	Completed/March 2024	Phase I/3-week open-label trial	Pending	–	–	–	–	–	–
Targeting fibroblasts												
BMS-986020	Antagonization of LPA receptor-1 (high levels of LPA can promote fibrosis)	Oral	NCT01766817	Completed/February 2016	Phase II/26-week RCT	Reduced FVC decline compared with placebo	Hepatobiliary SAE (study discontinued)	Mean rate of change in FVC (baseline-w26) ✓	Safety and tolerability: ✗ Mean change in QLF on HRCT (baseline-w26): ✗ Mean change in DLCO (baseline-w26): ✗ Mean change in dyspnea (baseline-w26): ✗	◎◎	–	[41]

Table 3 continued

Drug	Mechanism of action	Route of administration	Trial acronym/NCT/UMIN/ACTRN no.	Status/end date	Phase and duration	Main results	Security profile notes	Primary outcome(s) achievement	Principal secondary outcome(s) achievement	Magnitude of the results	Next developments	References
Admilparant (BMS-986278)	Antagonization of LPA receptor-1 (high levels of LPA can promote fibrosis)	Oral	NCT04308681 IPF and non-IPF ILDs	Completed/September 2023	Phase II/26-week RCT + optional 26-week active-treatment extension period	Reduced ppFVC decline compared with placebo	Incidence of GI events and treatment discontinuation similar to placebo Transient day 1 postdose blood pressure reductions: in all arms but greater with admilparant	Change in ppFVC (baseline-w26): ✓ *(with 60-mg dose)*	Safety and tolerability profile: ✓	●●◎	–	[43, 44, 91]
Nerandomilast	Preferential inhibition of PDE-4B, with reduction of level of PGE2, which regulates some fibroblast functions	Oral	FIBRONEER™-IPF (NCT05321069)	Completed/August 2024 *Topline data*	Phase III/52-week RCT	Positive absolute change from baseline in FVC at week 52 versus placebo	–	Absolute change in FVC baseline-w52: ✓	–	●●●	FIBRONEER™-ON (NCT06238622), open-label extension trial directed at patients with IPF and PPF (now recruiting)	[45, 46, 48, 49]
Ifetroban	Antagonism of TBXA2R, upregulated in fibroblasts of lung affected by IPF, with reduction of profibrotic signaling	Oral	NCT05571059	Recruiting/January 2026 (estimated)	Phase II/12-month RCT	–	–	–	–	–	–	[50]

Table 3 continued

Drug	Mechanism of action	Route of administration	Trial acronym/NCT/UMIN/ACTRN no.	Status/end date	Phase and duration	Main results	Security profile notes	Primary outcome(s) achievement	Principal secondary outcome(s) achievement	Magnitude of the results	Next developments	References
BBT-877	Inhibition of ATX, which stimulates LPA production, with pro-fibrotic effects	Oral	NCT05483907	Active, but not recruiting/February 2025 (estimated)	Phase II/24-week RCT	–	–	–	–	–	–	[27]
PMG1015	Target AREG, a downstream gene overexpressed by TGF-β during fibrosis, promoting FMT	Intravenous	NCT05895565	Recruiting/May 2025 (estimated)	Phase Ib 2-year RCT	–	–	–	–	–	–	[92, 93]
HNC1058	Inhibition of ATX, which stimulates LPA production, with pro-fibrotic effects	Oral	NCT05803850	Completed/March 2024	Phase I/RCT	Pending	–	–	–	–	–	[27]
SHR-1906	Antagonism towards CTGF	Intravenous	NCT05722964	Unknown status/May 2024 (estimated)	Phase II/28-week RCT	–	–	–	–	–	–	[34]
Epigallocatechin-3-gallate (EGCG)	Inhibition of TGFβ1 signaling and pro-inflammatory stress pathways Reduction of sFRP2 Consequent block of lung tissue pro-fibrotic signaling	Oral	NCT05195918	Recruiting/April 2026 (estimated)	Phase I/12 week-RCT	–	–	–	–	–	–	[94]

Table 3 continued

Drug	Mechanism of action	Route of administration	Trial acronym/NCT/UMIN/ACTRN no.	Status/end date	Phase and duration	Main results	Security profile notes	Primary outcome(s) achievement	Principal secondary outcome(s) achievement	Magnitude of the results	Next developments	References
SRN-001 (small interfering RNA—siRNA-drug)	Down-regulation of AREG, a downstream gene overexpressed by TGF-β during fibrosis, promoting FMT	Intravenous	NCT05984992	Completed/ May 2024 *Results not totally reliable*	Phase I/4-week RCT	Safety	No cytokine changes or anti-SRN-001 antibodies related to immunogenicity issues were observed	–	–	◦◎◎	–	[95]
Targeting epithelial cells												
Bexotegrast (PLN-74809)	Dual-selective inhibition of αvβ6 and αvβ1 integrins (activators of TGF-β), upregulated in IPF lungs	Oral	INTEGRIS-IPF/ NCT04396756	Completed/ February 2023	Phase IIa/12-week RCT	Added to IPF background treatment, compared to placebo: - Improved prevention of FVC decline (at w12 for the 80-mg and 320-mg doses) Reduced increase in QLF extent Decrease in integrin αvβ6 and PRO-C3 Reduced cough severity as assessed by visual analog scale Dose-dependent trend of reduction in the percentage of participants with relative and absolute decline > 10% of ppFVC *(last four in particular for the 160-mg and 320-mg doses at w12)*	Most common AE: diarrhea (primarily observed in patients taking background nintedanib) No dose relationship for TEAEs across the four doses studied	Safety and tolerability profile baseline-12w: ✓	–	◦◦◦	BEACON-IPF/NCT06097260: adaptive phase IIb RCT. Recently discontinued for imbalance in IPF-related AEs between the treatment and placebo groups (10% in both the 160 mg and 320 mg doses vs below 3%)	[52, 55, 96, 97]

Table 3 continued

Drug	Mechanism of action	Route of administration	Trial acronym/NCT/UMIN/ACTRN no.	Status/end date	Phase and duration	Main results	Security profile notes	Primary outcome(s) achievement	Principal secondary outcome(s) achievement	Magnitude of the results	Next developments	References
			IPF-201/NCT04072315	Completed/July 2022	Phase IIa/28-days, non-randomized trial	Decrease in anti-αvβ6 cystine knot peptide (knottin) PET-CT-radiotracer distribution after a single dose	–	- Effect on αvβ6 PET: ✓	Safety and tolerability profile: ✓	⊛⊛◎	w	
Stem cells												
REGEND001	Lung tissue regeneration	By bronchoscopy	NCT06081621	Active, not recruiting/July 2025 (estimated)	Phase II/24-week RCT	–	–	–	–	–	–	–
Allogenic human cells (hMSC)	Regulation of fibrotic processes Control of lung damage and repair mechanisms	Intravenous	AETHER/NCT02013700	Terminated/November 2016	Phase I/60-week RCT	Safety of a single infusion of human mesenchymal stem cells in patients with mild-moderate IPF Group receiving 1 × 10^8 hMSC: slower progression in QLF and smaller decrease in DLCO than subjects receiving 2 × 10^7 hMSC	*See the previous and the next boxes*	Safety and tolerability: ✓	Difference in absolute decline of ppFVC: ✓/✗ *(average absolute decline in ppFVC and* DLCO *by the end of the study below a decline of FVC ≥ 10% or ≥ 15% in the absolute* DLCO *over 3 to 6 months)*	⊛⊛◎	–	[98, 99]

Table 3 continued

Drug	Mechanism of action	Route of administration	Trial acronym/NCT/UMIN/ACTRN no.	Status/end date	Phase and duration	Main results	Security profile notes	Primary outcome(s) achievement	Principal secondary outcome(s) achievement	Magnitude of the results	Next developments	References
Lung spheroid stem cells (LSCs)	Attenuation of the progression and severity of pulmonary fibrosis Protection of alveolar structures Increase of angiogenesis *(Rat model)*	Intravenous	HALT-IPF/NCT04262167	Recruiting/March 2027 (estimated)	Phase I/24-month RCT	–	–	–	–	–	–	[100]
Human umbilical cord tissue-derived mesenchymal stem cells (VUM02)	Reduction of lung inflammation Improvement of lung function through paracrine KGF	Intravenous	DEVIF-I/NCT06230822	Recruiting/December 2026 (estimated)	Phase I/24-week single-arm, open-label clinical trial	–	–	–	–	–	–	[101]
Senotherapy												

Table 3 continued

Drug	Mechanism of action	Route of administration	Trial acronym/NCT/UMIN/ACTRN no.	Status/end date	Phase and duration	Main results	Security profile notes	Primary outcome(s) achievement	Principal secondary outcome(s) achievement	Magnitude of the results	Next developments	References
Dasatinib (TKI) + Quercetin (flavonoid)	Apoptosis of senescent vs non-senescent cells	Oral	NCT02874989	Completed/June 2019	Phase I/3-week open label trial	- Good retention rates - Potential safety of the drug	No adverse changes in clinical chemistries	- Retention rates and completion rates for planned clinical assessments: ✓	Initial safety estimates and AE reports ✓/✗ *(majority of events consistent with placebo control arms of phase III RCTs, except for potentially higher reporting of cough, nausea, headache and fatigue)* Change in functional and reported health measures: ✓/✗ *(improved 6-min walk distance, 4-m gait speed, and five repeated chair-stand times; pulmonary function not changed)*	◎◎	–	[102]

Table 3 continued

Drug	Mechanism of action	Route of administration	Trial acronym/NCT/UMIN/ACTRN no.	Status/end date	Phase and duration	Main results	Security profile notes	Primary outcome(s) achievement	Principal secondary outcome(s) achievement	Magnitude of the results	Next developments	References
					Phase I, single-blind, single-center, randomized, placebo-controlled pilot confirmatory trial	Good drug tolerance	- Most common non-serious AEs: fatigue, nausea, headache, diarrhea, decreased appetite and feeling unwell - No reported cases of myelosuppression, a common AE related to dasatinib	Safety and tolerability: ✓ Inform study feasibility for future efficacy trials: ✓	–	◦◎◎	–	[103]
Inhaled drugs												
Treprostinil	Inhibition of PDE-5, causing vasodilation of both pulmonary and systemic blood vessels, thereby reducing pulmonary artery pressure and improving systemic oxygenation	Inhaled (aerosol)	INCREASE/NCT02630316 *Directed towards IPF and non-IPF ILDs*	Completed/December 2019	Phase III/16-week RCT	Improved 6MWD in the treatment group compared with placebo. Post hoc analysis: fewer disease progression events after an initial event continuing the drug than in the placebo group	Most frequent AEs: cough, headache, dyspnea, dizziness, nausea, fatigue and diarrhea	- Change in the peak 6MWD at week 16: ✓	Change in NT-proBNP concentration at week 16 ✓ Time to clinical worsening ✓	◦◦◎	TETON program: two replicate, phase III/52-week RCTs. *Directed towards IPF.* RIN-PF-301/NCT04708782: recruiting, completion expected in June 2025. RIN-PF-303/NCT05255991: active, not recruiting, completion expected in July 2025.	[58, 104]

Table 3 continued

Drug	Mechanism of action	Route of administration	Trial acronym/NCT/UMIN/ACTRN no.	Status/end date	Phase and duration	Main results	Security profile notes	Primary outcome(s) achievement	Principal secondary outcome(s) achievement	Magnitude of the results	Next developments	References
ARO-MMP7	Reduction of MM7, overexpressed in IPF by aberrant basaloid cells	Inhaled	NCT05537025	Recruiting/March 2025 (estimated)	Phase I/IIa/85-day RCT	–	–	–	–	–	–	[62, 105]
Aerosolized pirfenidone (AP01)	Take advantage of the action of pirfenidone by increasing pulmonary deposition and reducing systemic effects	Inhaled (aerosol)	ATLAS/ACTRN12618001838202 *(New Zealand trials registry)*	Completed/*date not available*	Phase Ib/24-week, randomized, open-label trial	- Good safety profile - AEs less frequent than with oral pirfenidone in other clinical trials - Stable mean ppFVC in the 100 mg twice-daily (the highest dose) group	Most common treatment-related AEs, mild/moderate: cough, rash, nausea, throat irritation, fatigue and taste disorder, dizziness and dyspnea	Absolute change from baseline to w24 in ppFVC: ✓/✗ *(100 mg two times a day dose group: significantly less loss of ppFVC compared with the 50 mg once per day group at 48 weeks)*	- Change from baseline in PROs (KBILD, LCQ): ✓ *(stable over 48 weeks in both doses of 50 mg BID and 100 mg BID)* - Extent of fibrosis: ✓/✗ *(changes in QLF scores from HRCT correlated well with changes in FVC for the 100 mg two times a day group)*	◎◎	Phase II/52-week RCTs (NCT06329401). *Directed towards PPF.* Recruiting, completion expected in April 2026	[106]

Table 3 continued

Drug	Mechanism of action	Route of administration	Trial acronym/NCT/UMIN/ACTRN no.	Status/end date	Phase and duration	Main results	Security profile notes	Primary outcome(s) achievement	Principal secondary outcome(s) achievement	Magnitude of the results	Next developments	References
BNC-1021 (then named TRK250) (siRNA drug)	Target TGF-β1 mRNA, reducing TGF-β1 expression and collagen production	Inhaled	NCT03727802	Completed/April 2022	Phase I/4-week RCT	- Safety and good tolerance for every dose tested (4 single doses of 2, 10, 30 and 60 mg or multiple rising doses of 10, 30, and 60 mg once per week for 4 weeks) - Low or virtually non-existent systemic exposure	AEs: mild or moderate (one of the more common: cough), except for one severe case with acute exacerbation	Incidence and severity of adverse events: ✓ *(no significant AEs)*	PKs: ✓ (all the bioanalytical results below the lower limit of quantification)	◎◎	–	[107]
AGMB-477	Lung-restricted inhibition of ALK5 (TGFβR1)	Inhaled	NCT06181370	Recruiting/March 2025 (estimated)	Phase I/8-week RCT	–	–	–	–	–	–	[108]
LTI-03	Promotion of survival of cells capable of producing healthy lung tissue Stop of the production of scar-like material	Inhaled	NCT05954988	Active, not recruiting/February 2025 (estimated)	Phase I/14-days RCT	–	–	–	–	–	–	[109]
CEFFE (cell-free fat extract)	Tissue repair and regeneration	Inhaled	NCT05883293	Recruiting/December 2024 (estimated, not updated)	Phase I/12-month open-label clinical trial	–	–	–	–	–	–	[110]

Table 3 continued

Drug	Mechanism of action	Route of administration	Trial acronym/NCT/UMIN/ACTRN no.	Status/end date	Phase and duration	Main results	Security profile notes	Primary outcome(s) achievement	Principal secondary outcome(s) achievement	Magnitude of the results	Next developments	References
Lip@VP (verteporfin + pirfenidone-loaded nanoparticles)	Inhibition of the fluidization of airway epithelium Inhibition of fibroblast overactivation Reduction of cytokine secretion	Aerosol	–	–	*Mice model study*	- Inhibition of honeycomb cyst and interstitium remodeling - Improvement of respiratory index	–	–	–	–	–	[111]
Other drugs												
Sufenidone	–	Oral	NCT06125327	Recruiting/December 2027 (estimated)	Phase II/III/52-week RCT	–	–	–	–	–	–	–
INS018_055 (also named ISM001-055)	Inhibition of TNIK, novel target identified by AI	Oral	NCT05938920	Completed/August 2024 *Topline data*	Phase IIa/12-week RCT	Good tolerance and safety Dose-dependent improvement in FVC and ppFVC	Most frequent AE: diarrhea, abnormal liver function	Percentage of patients who have at least 1 TEAE: ✓	Change in FVC and ppFVC: ✓ *(dose-dependent improvement to w12)* Change in LCQ: ✓/✗ *(improvement for the highest dose (60 mg QD) group)*	⊙⊙◎	–	[63–65]
			NCT05975983	Recruiting/February 2026 (estimated)	Phase IIa/12-week RCT	–	–	–	–	–	–	

Table 3 continued

Drug	Mechanism of action	Route of administration	Trial acronym/NCT/UMIN/ACTRN no.	Status/end date	Phase and duration	Main results	Security profile notes	Primary outcome(s) achievement	Principal secondary outcome(s) achievement	Magnitude of the results	Next developments	References
Leramistat	Avoid outright inhibition of inflammatory cytokine cascades and promotion of a pro-repair environment	Oral	NCT05951296	Recruiting/September 2024 (estimated, not updated)	Phase II/12-week RCT	–	–	–	–	–	–	[66, 112]
TTI-101	Inhibition of STAT3, key regulatory protein, at the center of pulmonary fibrosis development	Oral	REVERT-IPF/NCT05671835	Recruiting/July 2025 (estimated)	Phase II/12-week RCT	–	–	–	–	–	–	[69]
TDI01	Inhibition of ROCK2, which contributes to lung injury	Oral	NCT06102083	Not yet recruiting/March 2026 (estimated)	Phase II/24-week + 52-week extension RCT	–	–	–	–	–	–	[113]
Vixarelimab	Target OSMRβ, which mediates signaling of IL-31 and OSM, key cytokines implicated in fibrosis	Subcutaneous	NCT05785624	Recruiting/August 2027 (estimated)	Phase II/52-week RCT *Directed towards IPF and systemic sclerosis-associated ILD*	–	–	–	–	–	–	[72]
CHF10067	Monoclonal antibody	Intravenous	NCT05513950	Completed/June 2024	Phase I/84-day RCT	Pending	–	–	–	–	–	–

Table 3 continued

Drug	Mechanism of action	Route of administration	Trial acronym/NCT/UMIN/ACTRN no.	Status/end date	Phase and duration	Main results	Security profile notes	Primary outcome(s) achievement	Principal secondary outcome(s) achievement	Magnitude of the results	Next developments	References
Artesunate	Inhibition of cell proliferation and migration Induction of programmed cell death Suppression of inflammatory responses Mitigation of oxidative stress Improvement of vascular permeability and repair Regulation of airway remodeling	Oral	DIAMOND/NCT05988463	Not yet recruiting/November 2026 (estimated)	Phase I/12-week open label RCT	–	–	–	–	–	–	[114]
Atezolizumab	Block of the interaction between PD-1 and PD-L1, binding to the last one	Intravenous	NCT05515627	Recruiting/April 2026 (estimated)	Phase I/24-week open-label clinical trial	–	–	–	–	–	–	–

Table 3 continued

Drug	Mechanism of action	Route of administration	Trial acronym/NCT/UMIN/ACTRN no.	Status/end date	Phase and duration	Main results	Security profile notes	Primary outcome(s) achievement	Principal secondary outcome(s) achievement	Magnitude of the results	Next developments	References
For IPF-related cough												
N115	Reduction of inflammatory agents in the lungs and nasal passages, allowing nasal nitric oxide to increase bronchodilatation	Nasal spray	NCT06037408	Completed/May 2024	Phase III/21-day RCT	Percent decrease in coughing episodes per 24 h from baseline to day 21 Improvement in FEV1/FVC ratio	No mild, moderate or serious AEs No safety concerns or abnormal changes in vital signs, blood chemistry, hematological parameters	Percent change in coughing episodes per day from baseline to day 21: ✓	Percent change in FEV1/FVC ratios from baseline to day 21: ✓	●●◎	–	[115]
Extended-Release Nalbuphine (NAL ER)	Antagonism of μ-opioid and κ-opioid receptors	Oral	CANAl/NCT04030026	Completed/May 2022	Short-term phase II/3-week crossover RCT	75.1% reduction in daytime objective cough frequency during NAL ER treatment period compared to the placebo period 76.1% reduction in 24 h objective cough frequency with NAL ER compared to 25.3% reduction with placebo	Nausea, fatigue, constipation, dizziness: more frequent with NAL ER than with placebo	Effect of Nalbuphine ER on the mean daytime cough frequency compared to placebo: ✓	Change from baseline in 24-hour cough at day 22 of treatment ✓	●●◎	CORAl/NCT05964335: phase II/6-week RCT. Recruiting, completions expected in April 2025	[78, 79]

Table 3 continued

Drug	Mechanism of action	Route of administration	Trial acronym/NCT/UMIN/ACTRN no.	Status/end date	Phase and duration	Main results	Security profile notes	Primary outcome(s) achievement	Principal secondary outcome(s) achievement	Magnitude of the results	Next developments	References
Suplatast tosilate (ME-015)	Stabilization of ion channels in the neuronal lung endings that mediate cough Reduction of neural inflammation and hyperactivity	Oral	COSMIC-IPF/NCT05983471	Recruiting/September 2025 (estimated)	Phase II/14-day RCT	–	–	–	–	–	–	[80]
For acute exacerbations of IPF												
Azithromycin (+ methylprednisolone)	Immunomodulatory and anti-inflammatory effect	Oral	NCT05842681	Not yet recruiting/June 2024 (estimated, not updated)	RCT	–	–	–	–	–	–	–

Table 3 continued

Drug	Mechanism of action	Route of administration	Trial acronym/NCT/UMIN/ACTRN no.	Status/end date	Phase and duration	Main results	Security profile notes	Primary outcome(s) achievement	Principal secondary outcome(s) achievement	Magnitude of the results	Next developments	References
To counteract nintedanib-related diarrhea												
Faecal microbiota transplantation	Normalization of the recipient's gut microbiota	By colonoscopy	BIOFEV/NCT05755308	Not yet recruiting/April 2026 (estimated)	12-week RCT	–	–	–	–	–	–	[116]

6MWD 6-min walking distance, *6MWT* 6-min walk test, *AEs* adverse events, *AI* artificial intelligence, *ALK5* activin receptor-like kinase 5, *ACTRN* Australian and New Zealand Clinical Trial Registry, *AREG* amphiregulin, *Bcl-2* B-cell lymphoma 2, *CSF-1R* colony stimulating factor-1 receptor, *CTGF* connective tissue growth factor, *ER* extended release, *FI-lab* frailty index based on laboratory test, *FMT* fibroblast to myofibroblast transition, *fsFRP2* fibroblast secreted frizzle-like receptor protein 2, *Gal-3* galectin-3, *GI* gastrointestinal, *IL-31* interleukin-31, *ILD* interstitial lung disease, *IPF* idiopathic pulmonary fibrosis, *KBILD* King's brief interstitial lung disease, *LCQ* Leicester Cough Questionnaire, *LSCs* lung spheroid stem cells, *MDMs* monocyte-derived macrophages, *MM7* matrix metalloproteinase 7, *mRNA* messenger ribonucleic acid, *NCT* National Clinical Trial, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *OSM* Oncostatin M, *OSMRβ* oncostatin m receptor beta, *PD-1* programmed cell death protein 1, *PDE-4B* phosphodiesterase-4B, *PDE-5* phosphodiesterase-5, *PD-L1* programmed death-ligand 1, *PET-CT* positron emission tomography and computed tomography, PGE2 Prostaglandin E2, *PPF* progressive pulmonary fibrosis, *ppFVC* percent predicted forced vital capacity, *PRO-C3* N-terminal type III collagen propeptide, *QD* Quaque Die, *QLF* quantitative lung fibrosis, *RCT* randomized controlled trial, *ROCK2* Rho-associated protein kinase 2, *SAE* serious adverse event, *STAT3* signal transducer and activator of transcription 3, *TBXA2R* thromboxane-prostanoid receptor, *TEAEs* treatment emergent adverse events, *TGF-β* transforming growth factor-beta, *TGF-βR1* transforming growth factor-beta receptor 1, *TNIK* Traf2 and Nck-interacting kinase, *UMIN* University Hospital Medical Information Network, *w* week, – not relevant/not available, ✓ met, ✗ not met, ✓/✗ uncertain/not unequivocally interpretable, ◎◎◎ no relevance (findings lacking scientific relevance, with no potential to contribute to disease treatment, even in future scenarios), ●◎◎ low relevance (early results, findings from more advanced studies that, however, have shown significant limitations), ●●◎ medium relevance (promising results, concerning key parameters, such as respiratory function and the radiological extent of the disease, also in early-phase studies), ●●● high relevance (positive results regarding multiple key parameters in phase II studies, or positive outcomes in phase III studies, which could represent a groundbreaking contribution to the treatment of the disease)

acute exacerbations, other spirometric parameters and plasma drug concentration. Results, published in a paper, showed that the rate of decline in ppFVC was lower after 26 weeks of administering 60 mg of BMS-986278 twice daily compared to the placebo. This effect was observed regardless of whether antifibrotic treatment was used concurrently. BMS-986278 was safe and well tolerated, with the incidences of gastrointestinal adverse events and treatment discontinuation similar to those seen with the placebo [42–44] (Table 3).

Nerandomilast (BI 1015550)

Phosphodiesterases 4 (PDE4), which include four isoforms (PDE4-A, PDE4-B, PDE4-C and PDE4-D) with different distributions in the organism, are enzymes implicated in inflammation and mediate the degradation of the secondary messengers adenosine-3′,5′-cyclic monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). Inhibition of this pathway leads to reduced levels of prostaglandin E2, which regulates some fibroblast functions [9, 45, 46].

Nerandomilast (BI 1015550) is an oral preferential PDE4-B inhibitor which has shown antifibrotic effects in vitro and in vivo, inhibiting TGFβ1-induced myofibroblast transformation and ECM deposition, and has a synergistic action compared to nintedanib. Diarrhea, nausea and headache, followed by depression and suicidal ideation and behavior, are the most frequent side effects of this therapy [47].

The phase I trial demonstrated safety and tolerability of the drug in male adults and patients with IPF regardless of gender. In the phase II study, nerandomilast, administered orally at a dosage of 18 mg twice day, has been shown to prevent the decline in FVC (ml) over 12 weeks and has a good safety profile both as a single therapy and in association with the usual antifibrotic treatment.

The main inclusion criteria of the phase III, multicenter, double-blind, randomized, placebo-controlled trial FIBRONEER-IPF/1305-0014 (NCT05321069) were age ≥40 years, being on a stable therapy with nintedanib or pirfenidone or not on antifibrotic treatment, ppFVC ≥ 45% and ppDLco ≥ 25% (corrected for hemoglobin) at visit 1, using contraceptives in the case of women of childbearing potential (WOCBP). Patients were randomized in a 1:1:1 ratio to receive 9 mg or 18 mg of nerandomilast or placebo twice per day. The primary endpoint was the absolute change from baseline in FVC in ml at week 52, and the secondary endpoint was the time to first IPF acute exacerbation and first hospitalization for respiratory cause or death over the duration of the trial [48]. Topline data, recently published by Boehringer Ingelheim Co., showed that the investigational compound nerandomilast met its primary endpoint [49] (Table 3).

FIBRONEER-ON, an open-label extension trial of the long-term safety and efficacy of BI 1015550, taken orally in patients with IPF and Progressive Pulmonary Fibrosis (PPF) (NCT06238622), is now recruiting patients (Table 3). The primary outcome of the study is to assess the occurrence of any adverse event over the course of the extension trial. Secondary outcomes include absolute change from baseline in FVC and ppFVC over time, time to absolute decline in ppFVC of > 10% from baseline, time to first (acute) IPF/PPF exacerbation, first hospitalization for respiratory cause or death, time to absolute decline in ppFVC predicted of > 10% from baseline or death, and time to relative decline in ppFVC of > 10% from baseline or death. Among the main inclusion criteria are the completion of treatment in one of the parent trials (1305-0014 or FIBRONEER-ILD/1305-0023, a phase III study directed at patients with PPF) without prematurely discontinuing treatment permanently according to the protocol (i.e., completed treatment with or without temporary treatment interruption), being a WOCBP using highly effective methods of birth control and, for France, being a fertile male patient using acceptable methods of birth control. Exclusion criteria include having any disease that may put the patient at risk when participating in this trial, manifestation of suicidality, clinically relevant severe depression, occurrence of malignant neoplasm (other than appropriately treated basal cell carcinoma or in situ squamous cell carcinoma of the skin or in situ carcinoma of the uterine cervix) at visit 1, being in a lung

transplant program with an already assigned date, body mass index (BMI) < 18.5 kg/m^2 with an additional, unexplained, and clinically significant (> 10%) weight loss during the parent trial, an ongoing adverse event of special interest (AESI) at visit 1 (except for latent tuberculosis) leading to temporary treatment interruption in the parent trial, and necessity or desire to take restricted medications or any drug considered likely to interfere with the safe conduct of the trial. Every participant takes nerandomilast as tablets for up to 1 year and 10 months. The participants may also continue their regular treatment for pulmonary fibrosis during the study. The study is expected to be completed by May 2027.

Ifetroban

Ifetroban is an antagonist of thromboxane-prostanoid receptor (TBXA2R) that is upregulated in fibroblasts of lungs affected by IPF. In in vivo studies, treatment with ifetroban reduced profibrotic signaling, protected mice from lung fibrosis in three preclinical models (bleomycin, Hermansky-Pudlak mice and radiation-induced fibrosis) and markedly enhanced fibrotic resolution after bleomycin treatment [50]. A randomized, double-blind, placebo-controlled, phase II study (NCT05571059) is now recruiting (Table 3). Inclusion criteria are age ≥ 40 years, being on a stable antifibrotic therapy or being naïve to pirfenidone and nintedanib, receiving a stable dose for pulmonary hypertension (PH) if in monotherapy for its treatment, ppFVC ≥ 40% and ppDLco ≥ 25% to < 80% (corrected for hemoglobin). Patients who participate in the trial will be randomized to receive oral ifetroban at 250 mg once a day or placebo for 12 months. The primary outcome is the change in FVC from baseline (ml) over 52 weeks. Secondary outcomes include time to first acute IPF exacerbation, first hospitalization for respiratory cause, death (including time to the first occurrence of any of these components of the composite endpoint), the proportion of patients with acute exacerbations of lung fibrosis, change from baseline in quality of life assessed with the Shortness of Breath Questionnaire (SOBQ), change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms Dyspnea/Cough/Fatigue domain score and incidence of treatment-emergent AEs. Study completion is expected in January 2026.

BBT-877

BBT-877 is an autotaxin (ATX) inhibitor being considered in a phase II, randomized, double-blind, placebo-controlled, 24-week trial (NCT05483907). The study is currently active but not recruiting (Table 3). Inclusion criteria are a chest HRCT compatible with IPF, the ability to walk at least 150 m during the 6-min walking test (6MWT) at screening, a resting oxygen saturation of ≥ 89% using a maximum of 6 l/min of supplemental oxygen at sea level and up to 8 l/min at altitude during screening, ppFVC ≥ 45%, FEV1/FVC ≥ 0.7, ppDLco ≥ 30% (corrected for hemoglobin), absence of IPF improvement in the previous year and a stable antifibrotic treatment if on therapy. Patients are randomized to take 200 mg of BBT-877 twice daily or placebo for 24 weeks plus follow-up for 4 weeks. The primary outcome of the study is change from baseline in FVC (ml) after 24 weeks of treatment. Secondary outcomes are the reduction in ppFVC decline, change from baseline in DLco and 6MWT, change in IPF impacts and symptoms from the patient perspective and safety of BBT-877 compared to placebo; furthermore, the potential effect of BBT-877 on pharmacokinetics (PK) of each antifibrotic and the potential effect of antifibrotic on PK of BBT-877 will be evaluated. Study completion was expected in February 2025. During phase 1 clinical trial, the results of which have been reported as an abstract, only mild adverse events were noted [51].

TARGETING EPITHELIAL CELLS

Bexotegrast (PLN-74809)

Bexotegrast, also named PLN-74809, is an oral, small molecule, dual-selective inhibitor of αvβ6 and αvβ1 integrins.

INTEGRIS-IPF (NCT04396756) was a randomized, double-blind, placebo-controlled, phase IIa trial. Its results, published as an article, showed a positive safety and tolerability profile for bexotegrast of up to 12 weeks. The most common adverse event was diarrhea, primarily observed in those taking background nintedanib. No relationship between the dose of bexotegrast (40, 80, 160, 320 mg) and incidence of diarrhea was observed [52]. The findings also indicate that adding bexotegrast to an approved IPF background treatment enhanced the prevention of FVC deterioration for the 80- and 320-mg doses compared to pirfenidone or nintedanib combined with a placebo, without additional toxicity [52]. The potential added benefit of bexotegrast for IPF was supported by initial radiographic evidence showing a reduced increase in quantitative lung fibrosis (QLF) extent compared to placebo, reduced cough severity as assessed by visual analog scale, and a dose-dependent trend of a reduction in the percentage of participants with relative and absolute decline > 10% of ppFVC in particular for the 160- and 320-mg doses. A significant decrease in integrin αvβ6 (ITGB6, a biomarker previously linked to disease progression) levels was observed with bexotegrast compared to placebo [52, 53]. Additionally, the analysis revealed that circulating levels of PRO-C3 (N-terminal type III collagen propeptide, also elevated in patients with IPF and associated with disease progression) were reduced in a dose-dependent manner in participants receiving 80, 160 and 320 mg bexotegrast compared to placebo [52, 54].

IPF-201 (NCT04072315) was a phase IIa, non-randomized, open-label clinical trial evaluating αvβ6 receptor occupancy of PLN-74809 in the lungs of up to 12 participants with IPF, as measured by PET/CT with anti-αvβ6 cystine knot peptide (knottin) radiotracer. The data, published as an article, showed that, after a single dose administration of PLN-74809, there is a decrease in tracer distribution in the lungs compared with the pre-drug PET/CT scan. No treatment-emergent adverse events related to bexotegrast were reported [55] (Table 3).

BEACON-IPF was an adaptive phase IIb, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of bexotegrast for the treatment of IPF (NCT06097260) (Table 3). Patients could take antifibrotic therapy with nintedanib or pirfenidone or not. The study consisted of an up to 35-day screening period, a 52-week treatment period and a 14-day safety follow-up period. Inclusion criteria were age ≥ 40 years, ppFVC ≥ 45%, ppDLco ≥ 30% and < 90% (corrected for hemoglobin), not being treated with antifibrotics or being on a stable dose of pirfenidone or nintedanib. Patients were randomized to take bexotegrast at a dosage of 160 mg or 320 mg or placebo for 52 weeks. The primary outcome was change from baseline in absolute FVC (ml) over 52 weeks. Secondary outcomes were time to disease progression, change from baseline in L-PF dyspnea and cough domain/total score, proportion of participants with treatment-emergent/serious AEs, time to disease progression, change from baseline in King's brief interstitial lung disease (K-BILD) questionnaire total score, absolute change from baseline in Quantitative Lung Fibrosis (QLF) score (%), safety and tolerability of bexotegrast. The latest news, announced in a statement by the sponsoring pharmaceutical company, Pliant Therapeutics, dated March 3, 2025, revealed that after a predefined data assessment and recommendation from the study's independent Data Safety Monitoring Board (DSMB), along with a secondary evaluation and advice from an external panel of experts, the BEACON-IPF trial has been halted. Despite preliminary signs of effectiveness on FVC measurement, a disparity in unreviewed adverse events related to IPF between the treatment and placebo groups led to the trial's termination. The proportion of IPF-associated adverse events in both dosage groups was similar (around 10%). The discrepancy between the active treatment and placebo seems to have stemmed from a particularly low (under 3%) rate of IPF-related adverse events in the placebo group. By contrast, in the Phase IIa INTEGRIS-IPF study (average exposure period of around 16 weeks), adverse events linked to IPF were similar among participants receiving bexotegrast at all dosage levels (7%) and those given a placebo (10%). The company intends to conduct a thorough review of the complete data from the BEACON-IPF trial and determine the

next steps for bexotegrast's progression. Once the comprehensive analysis is finalized, offering greater insight into the risk-benefit profile and therapeutic range of bexotegrast, the company will explore further Phase 2b trials with reduced dosages for pulmonary fibrosis [56].

STEM CELLS

REGEND001

REGEND001 is a cell therapy product made from bronchial basal cells with ability to regenerate lung tissue.

Results of the phase I trial, published in abstract form, demonstrated that REGEND001 is safe and well tolerated at all dose levels, with no dose-limiting toxicities reported. The most commonly observed adverse events associated with cell therapy included fever, hemoptysis and leukocytosis, likely linked to the bronchoscopic procedures performed [57].

A randomized, double-blind, placebo-controlled phase II clinical study (NCT06081621) has completed the recruiting phase (Table 3). The main eligibility criteria were age between 40 to 75 years, tolerating bronchoscopy and lung function tests. Patients are randomized to 1–1.5 × 10^6 bronchial basal cells/kg administered by bronchoscopy or to placebo. The primary outcome is the ratio of subjects with improvement of DLco after 12 and 24 weeks of treatment; the secondary is the change from baseline in DLco. Other outcomes concern lung function, prognosis, symptoms, laboratory and instrumental tests, and AEs. The completion of the study is expected in July 2025.

INHALED DRUGS

As we know, one of the main problems with currently available anti-fibrosing therapy is represented by side effects. The idea of topical inhalation therapy is fascinating: avoiding systemic AEs, a higher concentration of the drug is guaranteed at the level of alveoli.

Treprostinil

The INCREASE trial (NCT02630316) investigated the efficacy of treprostinil, an inhaled form of PDE-5 inhibitor, in IPF and non-IPF ILD. It showed an improvement in terms of FVC (ml) at 16 weeks compared to placebo in patients with ILD associated with pulmonary hypertension (PH), particularly in subjects with IPF [58]. A post hoc analysis of 326 patients showed that patients who received inhaled treprostinil were less likely to have disease progression events after an initial event compared to the placebo group (a 15% or more decline in 6MWT, a 10% or more decline in FVC, acute exacerbation, cardiopulmonary hospitalization, lung transplantation or death) [59]. The most frequent adverse events included cough, headache, dyspnea, dizziness, nausea, fatigue and diarrhea [58].

The TETON program consists of two replicate phase III, randomized, controlled clinical trials directed toward patients with IPF. RIN-PF-301 (NCT04708782) is now recruiting, while RIN-PF-303 (NCT05255991) has completed the recruiting phase (Table 3). The main inclusion criteria are age ≥ 40 years, ppFVC ≥ 45% at screening, if in antifibrotic therapy being on a stable and optimized dose, if WOCBP being non-pregnant, non-lactating and avoiding pregnancy, and finally male partners using contraception. Patients may be randomized to inhaled treprostinil (6 mcg/breath) or placebo administered four times daily (QID). Primary endpoint is the change in absolute FVC at week 52. Secondary endpoints include time to clinical worsening, time to first acute exacerbation of IPF, overall survival, change in ppFVC and change in the K-BILD. Study completion is expected in June/July 2025. Patients who complete week 52 will be eligible to enter an open-label extension study [60].

ARO-MMP7

In IPF, matrix metalloproteinase 7 (MMP7) is overexpressed by aberrant basaloid cells. MMP7 activity promotes fibrosis and inflammation [61]. ARO-MMP7 is an RNA interference (RNAi)

treatment designed to reduce their expression (62).

A phase I/IIa study, currently in the recruiting phase, will evaluate safety and pharmacodynamic data of ARO-MMP7 inhalation solution in healthy subjects and patients with IPF (NCT05537025) (Table 3). The eligibility criteria include individuals aged ≥ 45 years who are deemed fit to safely undergo bronchoscopy, have stable IPF at screening with a minimum life expectancy of ≥ 12 months and, for female participants, who are not pregnant or breastfeeding. Both male and female participants of reproductive potential must agree to use highly effective contraception and not to donate eggs/sperm during the study and for at least 90 days after the study ends or after their final dose of the study medication. Participants will be randomly assigned to receive either ARO-MMP7, delivered via inhalation of a nebulized solution, or a placebo. The primary outcome is the number of participants with treatment-emergent adverse events (TEAEs) from the first dose of study drug through the end of the study (up to 85 days, or until sputum MMP7 protein concentration is ≥ 70% of the baseline value, whichever is later). Secondary outcomes are change from baseline in FEV1, FVC, DLco over time and pharmacokinetic parameters of the study drug. The estimated completion of the study was March 2025.

OTHER DRUGS

Sufenidone (SC1011)

A randomized, double-blind, placebo-controlled study using a phase II/III adaptive seamless design to evaluate the efficacy and safety of SC1011 in patients with IPF (NCT06125327) is recruiting (Table 3). The main inclusion criteria are a combination of HRCT and lung biopsy consistent with IPF assessed by central reviewers, ppDLco of 30%–90% (corrected for hemoglobin) and ppFVC ≥ 50%. Participants are randomized to receive oral SC1011 twice daily or placebo for 52 weeks. The primary outcome is to evaluate the annual rate of decline in FVC over 52 weeks. Secondary outcomes are change from baseline in SGRQ total score and time to first acute IPF exacerbation. The completion of the study is expected in December 2027.

INS018_055 (Also Known as ISM001-055)

INS018_055 is a potent and selective small molecule, an inhibitor of TNIK, which is proposed as a novel target with high affinity for IPF treatment by Insilico Medicine's AI target discovery engine platform, PandaOmics [63].

As announced by the company, the phase I study (NCT05154240) demonstrated safety and good tolerance by healthy volunteers. No deaths or SAEs were reported during the study [64].

Two phase IIa, randomized, double-blind, placebo-controlled studies, directed to patients with IPF (NCT05938920, NCT05975983), are respectively completed (August 2024) and in the recruitment phase with completion expected by February 2026 (Table 3). The inclusion criteria are age ≥ 40 years, being in stable clinical condition, if on active antifibrotic therapy, having taken it at a stable dose for ≥ 8 weeks prior to visit 1, ppFVC ≥ 40%, ppDLco ≥ 25% and < 80% (corrected for hemoglobin), and FEV1/FVC > 0.7. The active treatment arm is divided into three groups, one which is administered once daily at a low dose (30 mg), one which gives the drug twice daily at a low dose (60 mg in total) and one with a once daily treatment at a high dose (60 mg) for up to 12 weeks. Patients in the other arm are randomized to take a placebo once or twice a day up to 12 weeks. The primary outcome is the percentage of patients who have at least one TEAE. Secondary outcomes are data about the pharmacokinetics of the molecule under study, relative change in FVC (ml), percentage change in FVC, absolute and relative change in ppFVC, change in ppDLco, Leicester Cough Questionnaire (LCQ), distance traveled at 6MWT, number of acute IPF exacerbations and number of days hospitalized for acute IPF exacerbations.

The favorable topline outcomes of the NCT05938920 study, released by the company, showed that the medication was well tolerated

across all dosing groups. Most drug-related side effects were mild or moderate, with the most frequent adverse events being diarrhea and abnormal liver function. The pharmacokinetic profile of INS018_055 in patients with IPF aligned with phase I study findings in healthy individuals, exhibiting a half-life of 7–12 h. Patients treated with INS018_055 showed a dose-dependent improvement in lung function at all dosages by the 12-week mark (mean improvement of 98.4 ml in FVC from baseline at the highest dose of 60 mg QD, mean decline of – 62.3 ml in FVC from baseline in the placebo group). A similar dose-dependent trend was also observed in ppFVC (mean improvement of 3.05% from baseline at the highest dose of 60 mg QD, with a mean decline of – 1.84% in ppFVC for the placebo group). There was also a change in LCQ for the highest dose (60 mg QD) group [65].

Leramistat

Leramistat acts avoiding outright inhibition of inflammatory cytokine cascades and promoting a pro-repair environment [66, 67].

A phase II, double-blind, placebo-controlled study (NCT05951296) is now enrolling (Table 3). Key inclusion criteria are ppFVC ≥ 45%, ppDLco ≥ 25% and ≤ 80% (corrected for hemoglobin), a minimum distance on 6MWT of 150 m, FEV1/FVC > 0.70, if on antifibrotics, taking nintedanib or pirfenidone at a stable dose, and a life expectancy of at least 12 months. Patients are randomized to take leramistat or placebo once daily. The primary outcome is the change from baseline in FVC versus placebo up to week 12. Secondary outcomes are change from baseline in ppFVC and ppDLco, time to the first exacerbation, FEV1, any disease progression understood as decline in ppFVC ≥ 10%, decline in ppDLco ≥ 15%, lung transplantation or death. Patients are randomized to leramistat or placebo. Information about the expected end date of the study has not been updated.

From what we learned from a note published by the company regarding a phase 2b study that aims to evaluate leramistat in patients with rheumatoid arthritis, the AE rate was similar between groups receiving leramistat and placebo, and most AEs were mild in nature and resolved without treatment [68].

TTI-101

TTI-101 is an orally delivered, small molecule, direct inhibitor of STAT3, a key regulatory protein and a central node in the development of pulmonary fibrosis [69].

REVERT-IPF (NCT05671835) is a phase II, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics and efficacy of TTI-101 in participants with IPF over 12 weeks (Table 3). Inclusion criteria are a chest HRCT performed within 12 months prior to providing informed consent and reviewed by central review, ppFVC > 40%, FEV1/FVC ≥ 0.7 and ppDLco ≥ 25% (hemoglobin corrected), an oxygen saturation ≥ 88% with an oxygen support up to 4 l/min at rest, a life expectancy of at least 12 months, if on nintedanib, taking a stable dose of the drug and, if having previously discontinued it, having respected a 6-week washout period before screening. Patients can be randomized to take TTI-101 400 mg/day, 800 mg/day or placebo for 12 weeks. The primary outcome is the number of participants with an AE with a 16-week time frame. Secondary outcomes concern the pharmacokinetics of the molecule under study. The study is now recruiting, and completion is expected in July 2025.

The phase 1 trial of TTI-101, directed at patients with advanced solid tumors, demonstrated no dose-limiting toxicities or fatal treatment-related adverse events (TRAEs). Diarrhea, mostly grade 1–2, was the only TRAE observed in ≥ 30% of subjects [70].

TDI01

TDI01 is an inhibitor of Rho-associated protein kinase-2 (ROCK-2), which has a specific role in monocyte migration and adhesion to endothelial cells and which contributes to lung injury [71].

A planned phase II, randomized, double-blind, placebo-controlled clinical study

(NCT06102083) is not yet recruiting (Table 3). The main inclusion criteria for the trial are age between 40 to 80 years, using effective contraceptive methods until 90 days after the last dose of the investigational product if patients are of reproductive potential, being in stable antifibrotic treatment for at least 12 weeks prior to visit 1, FEV1/FVC ≥ 0.70, ppFVC ≥ 45% and ≤ 90%, and ppDLco% ≥ 30% and ≤ 90% (corrected for hemoglobin) at screening. Participants will be randomized to take TDI01 at dose A once daily, TDI01 at dose B once daily or placebo once daily. Primary outcome is the change from baseline in FVC (ml) at week 24. Secondary outcomes are change from baseline in ppFVC and ppDLco (hemoglobin corrected), the proportion of subjects with an absolute decrease of ppFVC > 10%, time to first AE-IPF, time to disease progression, mean change in distance walked in the 6MWT and change in SGRQ. The completion of the study is expected in March 2026.

Vixarelimab

Vixarelimab is a fully human monoclonal antibody that targets oncostatin M (OSM) and oncostatin M receptor beta (OSMRβ), which mediates signaling of interleukin-31 (IL-31), two key cytokines implicated in pruritus, inflammation and fibrosis [72].

A phase II, randomized, double-blind, placebo-controlled study evaluating vixarelimab in patients with IPF and in patients with systemic sclerosis-associated ILD (NCT05785624) is now recruiting (Table 3). Inclusion criteria are ppFVC ≥ 45%, FEV1/FVC > 0.70, ppDLco ≥ 30% and ≤ 90% (corrected for hemoglobin), minimum 6MWT distance of 150 m with maximum use of supplemental oxygen at 6 l/min at sea level and up to 8 l/min at altitude while maintaining oxygen saturation of > 83% during the test. For the IPF cohort, additional criteria are age between 40 and 85 years and being on a stable dose if on antifibrotic treatment. Patients with IPF are randomized to receive vixarelimab or placebo subcutaneously once every 2 weeks for 52 weeks in the double-blind treatment period. The primary outcome is the absolute change in FVC from baseline. Regarding the cohort of patients with IPF, secondary outcomes are the absolute change from baseline in 6MWT distance, ppFVC and DLco (corrected for hemoglobin), time to disease progression, time to first AE-IPF, percentage of dead participants, change from baseline in quantitative lung fibrosis on HRCT and in Health-Related Quality of Life (HRQL), change from baseline in L-PF cough/dyspnea domain score, number of participants with AEs, serum concentrations of vixarelimab and number of participants with anti-drug antibodies (ADAs) to vixarelimab. The completion of the study is expected in August 2027.

In a phase 2a study directed at patients suffering from prurigo nodularis, vixarelimab was well tolerated by all subjects and no dose-limiting adverse experiences were observed, as well as no serious adverse events. There were no adverse drug-related signals for overall infections, immunological reactions, abnormal liver function, hematological changes, malignancies, injection-site reactions or cardiac toxicity [73].

IPF-RELATED COUGH

In the past, thalidomide has been proposed as an antitussive in IPF. Despite some good results, unfortunately, worldwide studies have never been carried out to recommend its use [74–76].

N115

N115 is a sodium pyruvate nasal spray that significantly reduces inflammatory agents, allowing nasal nitric oxide to reach bronchi and increase bronchodilation. Seven human clinical studies, conducted using a sodium pyruvate nasal spray, showed a decreased nasal inflammation, reduction in inflammatory cytokines, decrease in coughing and, when measured, an increase in lung function, including in patients with IPF.

A phase III, double-blind, randomized, placebo-controlled trial was recently concluded (NCT06037408). Inclusion criteria were an IPF-related cough, mild to moderate FEV1, abstaining from sexual intercourse or using contraceptives for the duration of the study. Participants were randomized to receive 20 mM sodium

pyruvate nasal spray treatment or placebo. The primary outcome was the percent change in coughing episodes per day from baseline to day 21. The secondary outcome was the percent change in FEV1/FVC ratios from baseline to day 21. The results of this study were published as a paper. The findings showed a significant decrease in the number of coughing episodes per 24 h in patients treated with N115. This was closely associated with an improvement in the FEV1/FVC ratio, which increased by 27.9% on day 22 for N115-treated patients compared to a 2.37% increase in the placebo group. No mild, moderate or serious adverse events were reported. Additionally, there were no safety concerns or abnormal changes in vital signs, blood chemistry or hematological parameters [77] (Table 3).

Extended-release Nalbuphine (NAL ER)

Nalbuphine is a μ-opioid antagonist and κ-opioid agonist, already studied for the treatment of prurigo nodularis, that can have a role in reducing cough in patients with IPF [78].

The results of a short-term phase II crossover trial (NCT04030026), which included two 22-day treatment periods (NAL ER to placebo and placebo to NAL ER) separated by a 2-week washout period, were published as a paper. The study showed a 75.1% reduction in daytime objective cough frequency during the NAL ER treatment period compared to the placebo period, with a 52.5 percentage point placebo-adjusted decrease from baseline at day 21. Additionally, there was a 76.1% reduction in 24-h objective cough frequency with NAL ER compared to a 25.3% reduction with placebo, yielding a 50.8 percentage point placebo-adjusted change. Nausea, fatigue, constipation and dizziness were reported more frequently with NAL ER than with placebo [79] (Table 3).

CORAL, a phase II, randomized, double-blind, placebo-controlled study (NCT05964335) evaluating NAL ER efficacy in reducing cough at 24 h is now ongoing and enrolling patients (Table 3). Inclusion criteria are a cough severity score ≥ 4 on CS-NRS (Cough Severity Numerical Rating Scale) during the screening period and baseline, a history of chronic cough for at least 8 weeks before screening, SpO2 ≥ 92%, ppFVC ≥ 40% and ppDLco ≥ 25% (corrected for hemoglobin). Trial participants are randomized to take NAL ER tablets 27 mg, 54 mg, 108 mg or placebo BID. The primary outcome was the effect of NAL ER on 24-h cough frequency (coughs per hour). Secondary outcomes concern tolerability and safety of the study drug, other efficacy parameters on cough and other symptoms felt by the patient, and the effect on disease exacerbations. Study completion is expected in April 2025.

Suplatast Tosilate (ME-015)

Orally administered ME-015 has been available for allergy-related conditions in Japan since 1995 with a very good safety and tolerability profile.

ME-015 is presumed to have an acute effect by stabilizing ion channels in the neuronal lung endings that mediate coughs. Second, it acts as a reactive oxygen species scavenger, thus reducing the hypersensitization of neuronal receptors to otherwise innocuous stimuli [80].

There is preclinical and exploratory clinical evidence suggesting that ME-015 may be effective in treating cough caused by IPF. COSMIC-IPF (NCT05983471), a phase II, double-blind, placebo-controlled clinical trial, is now enrolling patients (Table 3). The main inclusion criteria are age ≥ 18 years, having a cough attributed to IPF unresponsive to standard anti-tussive treatment, a life expectancy > 6 months, a stable medical condition, if on antifibrosis therapy, taking a stable dose of treatment, ppFVC ≥ 40%, FEV1/FVC ≥ 65%, and using contraception for WOCBP and male partners. Participants will be randomized to ME-015 2 × 100 mg capsules TID (three times per day) for 2 weeks or placebo. The primary outcome is the change from baseline to day 14 of the wake time cough frequency during 24 h. Secondary outcomes include change from baseline to day 14 of cough severity, cough-related quality of life and overall patient-reported health status, TEAEs and serious adverse events (SAEs) from baseline to day 14. The completion of the study is expected in September 2025.

A study that examined the effects of suplatast tosilate on antileukotriene non-responders with

mild-to-moderate persistent asthma demonstrated the absence of adverse effects during the entire research period [81].

CONCLUSION

Many things have changed over the years regarding awareness of IPF but much remains to be done. This report on the many ongoing trials and investigational drugs highlights the efforts made by pharmaceutical companies, researchers and doctors to prolong survival and improve the quality of life for patients suffering from this terrible disease, as well as the promising results in slowing lung function decline and thereby achieving progression-free survival in these patients. This review addresses the main disease targets known to date: fibroblasts, alveolar macrophages, epithelial cells, cellular senescence, oxidative stress and mitochondrial dysfunction. At the same time, it tries to counteract the main symptoms that afflict patients with IPF and to overcome the side effects of the two currently approved drugs.

There is certainly still much to understand about the pathogenesis and mechanisms underlying the development of IPF. Greater awareness of this will pave the way for the future of clinicians and researchers and, above all, for the patients.

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Declarations

Conflict of Interest. Elisabetta Cocconcelli declares consulting fees from Boehringer Ingelheim and Chiesi. Elisabetta Balestro declares consulting fees from Boehringer Ingelheim and Roche, speaker fees from Boehringer Ingelheim, and has been a trial investigator for Boehringer Ingelheim and Roche. Paolo Spagnolo reports grants from PPM Services, Roche, Boehringer Ingelheim and Chiesi; consulting fees from PPM Services and Novartis; honoraria from Boehringer Ingelheim; support for attending meetings from PPM Services; participation on a Data Safety Monitoring Board or Advisory Board from AstraZeneca, Trevi, Merck, Galapagos, Novartis and Structure Therapeutics. His wife is an employee of AstraZeneca. Giacomo Giulianelli, Giordano Fiorentù and Nicol Bernardinello have nothing to disclose. Nicol Bernardinello and Paolo Spagnolo are Editorial Board members of Pulmonary Therapy. Nicol Bernardinello and Paolo Spagnolo were not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

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