Idiopathic pulmonary fibrosis: An opportunity for inhaled therapies

A look at the pipeline for inhaled drugs for this high unmet need

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Definition and prevalence

Of unknown cause, idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease characterized by inflammation that results in scarring (fibrosis) of the lungs [1]. It is the most common of the interstitial lung diseases, also known as ILDs, a group of diseases that number more than 200. IPF occurs primarily in older adults, predominantly in their 60s and 70s, and is associated with a poor prognosis [2]. Over time, increased scarring of the lung tissue leads to impaired gas exchange in the lungs, often requiring supplemental oxygen to maintain adequate oxygen saturation (Figure 1). Due to this, patients with IPF typically have difficultly breathing, often have a dry cough and experience shortness of breath while performing normal activities.

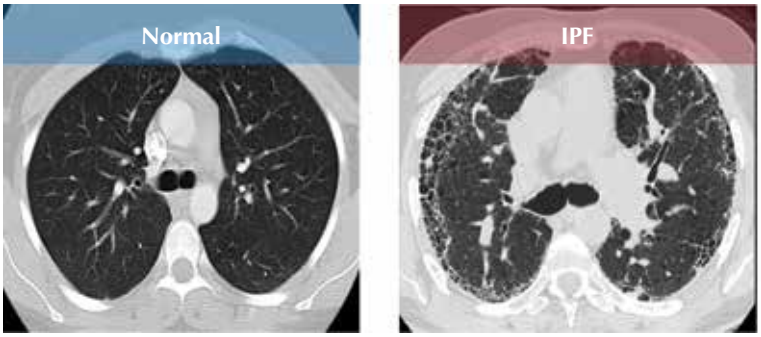
The overall incidence of IPF varies substantially from country to country due to differing diagnostic criteria, disease reporting mechanisms and data collection. The most comprehensive study, to date, suggests an incidence range of 3-9 per 100,000 population, with the highest incidences occurring in North America and the European Union [4]. According to the Pulmonary Fibrosis Foundation, in the United States alone, it is estimated that more than 200,000 people are living with IPF today and approximately 50,000 new cases are diagnosed each year [5].

Disease progression and currently available treatments

The course of IPF is hard to predict and can vary widely depending on gender, age, physiology, forced vital capacity (FVC) and smoking history

Figure 1

Normal lung vs. IPF lung. The normal lung, made up of a matrix rich in elastin, is replaced with one rich in fibrillar collagen—an important contributor to fibrotic lung diseases. Lung lesions are also present, either alveolar (with a pattern common to interstitial pneumonia) or honeycomb in nature [3]. Image courtesy of Bellerophon Therapeutics.



- Fibrotic Interstitial Lung Disease (fILD) is a broad category of diffuse lung diseases characterized by variable amounts of inflammation and fibrosis
- Idiopathic Pulmonary Fibrosis (IPF) is the largest and most serious of these diseases
- Patients with fILD have thickening and scarring of the air sacs in the lungs, and often require supplemental oxygen to maintain adequate oxygen saturation

[2]. Once there is a concrete diagnosis, the median survival time is approximately 2-3 years, which translates to 40,000 people dying annually in the US [4] due to IPF.

Available treatments today include pharmacological therapy based on small-molecule drugs and non-pharmacological therapy such as supplemental oxygen, pulmonary rehabilitation and, as a last resort, lung transplantation. It is recommended that last option be considered for all IPF patients who meet the selection criteria (dependent on severity) and do not have significant contraindications [6]. In the US, IPF is the leading cause of lung transplantation; about 35% of the 2,714 people in the US who underwent a lung transplant in 2019 had IPF. Unfortunately, only 1,000 lungs [approximately] are available per year for IPF patients, thus most people living with the disease will never receive a transplant [7].

For the majority of IPF patients, pharmacological therapy offers the best hope for slowing the decline of the condition. To date, there are only two therapies approved by the United States Food and Drug Administration (FDA):

Ofev® nintedanib (Boehringer Ingelheim, Ingelheim Am Rhein, Germany), a multiple receptor tyrosine kinase inhibitor approved by the FDA in 2014, blocks signaling pathways implicated in the pathogenesis of IPF [8]. In clinical trials, nintedanib demonstrated an ability to slow the progression of lung decline (as measured by FVC) vs. placebo. In addition, the trials demonstrated nintedanib is associated with a reduced time to first acute IPF exacerbation. This oral medication is taken twice a day (150 mg BID) [8].

Esbriet® pirfenidone (Genentech, South San Francisco, California, US), was also approved by the FDA in 2014, and similar to nintedanib, demonstrated statistically significant improvement in FVC compared to placebo. The dosage is three capsules or tablets, three times per day (801 mg TID, or 2403 mg/day) [9]. Pirfenidone is an antifibrotic, anti-inflammatory and antioxidant compound with beneficial effects in the lung, liver, kidney and heart, but its specific mechanism of action (MoA) in the treatment of IPF is unknown [10]. It is noteworthy that both nintedanib and pirfenidone only slow the rate of decline. Currently, there are no therapies that stabilize or reverse fibrosis, only medications that attenuate disease progression [9].

While both of these oral treatments have helped thousands of patients, they have well documented systemic adverse events (AEs). In the case of nintedanib, these include diarrhea (60% of cases), elevated liver enzyme levels (more than three times the normal range) drug-induced liver injury, numerous drug-to-drug interactions, arterial thromboembolic events, bleeding events and other gastrointestinal disorders such as nausea and diarrhea [11]. Pirfenidone, likewise, causes gastrointestinal side effects, has many drug-to-drug interactions and can cause significant hepatoxicity in some patients, warranting liver function tests for the first six months of therapy [12].

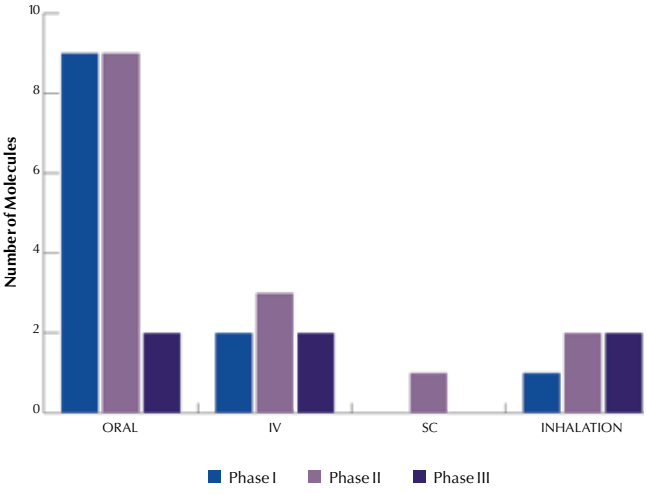
Considerations for inhaled therapy

Unlike oral or intravenous therapies, inhaled therapies deliver drugs directly to the airways. For diseases of the lung, this is the therapeutic site of action and can thereby provide high pulmonary drug levels and rapid onset of action. Several desirable features include enhancing organ specificity, avoiding first-pass metabolism and reducing systemic side effects due to lower systemic exposure [13]. To achieve a comparable potency, the amount of drug that needs to be inhaled may be orders of magnitude lower than the oral or injectable route of administration (RoA) [14]. In some cases, this may translate into greater efficacy as some drugs may be limited by systemic side effects [14].

In the case of IPF, reformulating nintedanib or pirfenidone as an inhaled therapy delivered directly to the lungs of IPF patients may eliminate some of the aforementioned side effects while enhancing efficacy. Various studies have shown that both pirfenidone and nintedanib can be reformulated as inhalable therapies delivering greater drug to the lung and, potentially, be safer [15, 16]. Pirfenidone, in particular, has been studied in pre-clinical animal models

Figure 2

IPF pipeline segregated according to route of administration. Content adapted from the Pulmonary Fibrosis Drug Development Pipeline [21], Pulmonary Fibrosis Clinical Trials [39] and clinicaltrials.gov [26] (accessed June 21, 2021) but may not be comprehensive.



IV = intravenous; SC = subcutaneous

Table 1

Inhaled drugs in the pipeline for IPF. Content excerpted from the Pulmonary Fibrosis Drug Development Pipeline [21], Pulmonary Fibrosis Clinical Trials [39] and clinicaltrials.gov [26] (accessed June 21, 2021) but may not be comprehensive.

Drug Name	Molecule Type	Mechanism of Action	Status
Pirfenidone	Small molecule	Cytokine inhibitor; Collagen inhibitor	Phase I
Galectin-3 inhibitor	Small molecule	Galectin-3 inhibitor	Phase II
Nucleic acid medicine	Oligonucleotide	Suppress the expression of transforming growth factor-beta 1 (TGF-β1)	Phase II
Treprostinil	Small molecule	Prostacyclin receptor agonist, Peroxisome proliferator-activated receptor delta agonist and AP2Y purinoceptor	Phase III (*Approved for Pulmonary arterial hypertension*)
Nitric oxide	Small molecule	Regulation of pulmonary vasomotor tone by several mechanisms	Phase III

comparing low-dose intranasal and high-dose oral administration and has been shown to have comparable amelioration of lung immune cell infiltration and inflammatory and fibrotic markers [17]. It has also been studied as an aerosol in healthy adult sheep with favorable pulmonary pharmacokinetics [18]. Ninetanib, on the other hand, was reformulated as a solution for nebulization and was able to deliver superior pulmonary anti-fibrotic activity, as well as lower local and systemic drug levels with a substantially lower dose [11].

Currently, both pirfenidone and nintedanib are being developed as inhaled formulations. Pirfenidone is being developed as a nebulized solution. A recent Phase I /II study that explored the 50 mg dose once daily or 100 mg twice daily, demonstrated no loss of lung function as measured by FVC over 24 weeks for the higher dose group. This drug is expected to enter Phase III trials to confirm improved tolerability and long-term efficacy [19]. After successful preclinical studies in two lung injury models, aerosolized nintedanib was expected to begin Phase I trials during 2021 [20].

Inhaled treatments in the IPF clinical pipeline

The Pulmonary Fibrosis Foundation maintains a database of molecules and clinical programs in development for IPF. While it may not be comprehensive, as of June 2021, it listed 33 programs—13 in Phase I, 14 in Phase II and 6 in Phase III (Figure 2). Eight of the 33 are studying drugs already marketed for other indications while 25 represent new molecular entities (NMEs).

Yet despite the advantages of inhaled therapies, the database lists only five programs (including pirfenidone) in development via the inhaled route (Table 1). Of those, three are not already marketed for other indications:

- An "aerosolized" siRNA-based oligonucleotide
- A dry powder inhaler (DPI) of a galectin-3 inhibitor
- Nitric oxide (delivered as a gas proprietary pulsatile delivery system/portable canister)

Earliest along the development path is a novel RNAi therapeutic agent that inhibits the progression of pulmonary fibrosis by selectively suppressing the expression of the transforming growth factor beta 1 (TGF-β1) protein. Preclinical studies in mice evaluated the *in vitro* suppression of TGF-β1 expression and *in vivo* reduction in TGF-β1 and collagen levels in the lungs [22]. The *in vitro* suppression was evaluated in human lung-derived cell lines as well as in rat, mouse and cynomolgus monkey cell lines. For the *in vivo* studies in mice, lung tissue was evaluated for TGF-β1 protein levels and collagen deposition after intratracheal administration. Researchers concluded that this novel oligonucleotide had the potential to prevent the progression of pulmonary fibrosis [22]. A Phase 1 trial in 34 patients evaluating single and multiple doses in aerosolized form (unspecified) is expected to conclude late in 2021 [23].

A small molecule in a DPI format is in development that inhibits galectin-3 (Gal-3). The Gal-3 protein impedes fibrosis by targeting macrophages, fibroblasts and epithelial cells that promote tissue scarring and inflammation. The molecule was evaluated in preclinical studies investigating Gal-3 expression *in vitro* and *in vivo* in naïve and bleomycin-treated mice. It demonstrated that TGF-β1-induced and bleomycin-induced lung fibrosis were dramatically reduced in mice deficient in Gal-3, indicating that Gal-3 is an essential mediator of TGF-β1-induced lung fibrosis [24]. A Phase IIa study of this molecule at various doses was completed to assess safety,

tolerability and PK/PD in 24 patients with IPF who underwent bronchoalveolar lavage (BAL). Results showed that the Gal-3 inhibitor was well tolerated at all doses with concentrations in BAL macrophages >567-fold higher than systemic exposure. Gal-3 expression on BAL macrophages was significantly lower in the 3 mg dose group (% change of approximately 53%) and 10 mg dose group (% change of approximately 79%) compared to placebo, with a concentration-dependent inhibition [25]. A Phase IIb placebo-controlled study in 500 patients is being conducted across more than 100 centers in the US, Canada, the United Kingdom and Israel, evaluating 3 mg once daily for 52 weeks. An initial, unblinded data readout is anticipated in 2022 [26]. The therapy has received Orphan Drug Designation from the FDA and the European Medicines Agency (EMA).

A Phase III trial is currently underway investigating NO as a treatment for fibrotic ILDs, including IPF, through targeted vasodilation of only the well-ventilated alveoli, thereby preventing ventilation perfusion mismatch (V/Q) and oxygen desaturation. Two Phase II trials demonstrated clinically meaningful benefit in moderate to vigorous physical activity (MVPA) with a low incidence of adverse events in both active and placebo groups, enabling immediate transition into a pivotal Phase III trial with MVPA as the primary endpoint [27]. In the Phase II trials, pulsed NO, in cartridges at doses of 30, 45 or 75 mcg/kg of ideal body weight per hour, was delivered by a small, lightweight device that can be operated on a standalone basis or be connected directly to a patient's oxygen supply via a tri-lumen cannula. The device has been granted Orphan Drug Designation for IPF by the FDA.

Phase I and II drugs: Opportunities to reformulate drug for pulmonary indications

In the Phase I and II stages, there are 27 drugs in clinical trials of which 20 are small molecules (Figure 3) [21]. Seven of these drugs are products already marketed for other indications and are undergoing studies for treatment of IPF. Interestingly, the trials for all seven of these are funded by the US National Institutes of Health (NIH), university grants or other non-profit organizations. Among the seven large molecule drugs, there are proteins, monoclonal antibodies, nucleic acids, stem cells and plasma therapies. Excluding these, of the 20 remaining drugs in the pipeline, only three are in an inhaled form (all previously discussed). This leaves 17 drugs (85%) of the pipeline utilizing an oral/IV/SC route of administration.

Given the market experience with inhaled drugs to date—whether nebulized, liposomal, metered dose dry or aerosol inhalers (MDIs), micronized or spray-dried DPIs—there appears to be a viable opportunity to reformulate some of these pipeline drugs for inhaled delivery to increase efficacy and tolerability.

The earlier a drug is in its development, the greater the opportunity to reformulate it as an inhaled drug with the least impact to the clinical development timeline. It may be feasible that while the molecule is in Phase I (and sometimes in Phase II), an inhaled formulation can be concurrently developed. A decade ago, a reformulation would have meant a delay of years to a clinical program or starting from scratch with a new program altogether. With the advent of newer modeling imaging techniques, such as functional respiratory imaging (FRI), the delay can be minimized significantly. FRI offers three-dimensional models of human lungs and computational fluid dynamics to simulate functional changes within airways and predict the deposition of inhaled drugs [28]. It is a validated technique that uses aerosol delivery performance profiles, patients' high-resolution computed tomography (HRCT) lung scans, and patient-derived inhalation profiles to simulate lung deposition of inhaled drugs [29].

Use of *in silico* modeling does not obviate the multiple regulatory requirements for inhaled drugs, such as inhaled toxicity studies, but can provide considerable data whereby drug developers can make informed decisions on trends or signals of possible efficacy for an inhaled formulation. These models have advanced significantly in the past decade and can be a tool for validating a hypothesis about the efficacy of a given molecule on lung drug targets.

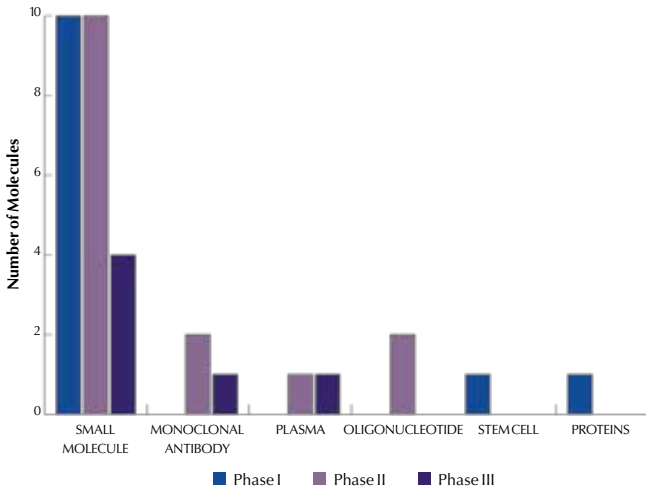
It is not an understatement to say the challenges and complexities are extensive in reformulating large molecules into an inhalable form. Yet, it is certainly possible, as shown by the approval of various large molecules in inhalable formulations: (1) a protein biologic, dornase alfa/DNase I, Pulmozyme® (Genetech) in 1993 for cystic fibrosis, (2) human insulin, Exubera® (Pfizer, New York, NY, US), approved in 2006 although discontinued in 2007 and, (3) human insulin, Afrezza® (Mannkind, Danbury, CT, US) approved in 2014 [30]. Given the scarcity of large molecules for inhalation, it is fair to say that once the rationale for pulmonary delivery has been established, the efficacy of these therapies depends upon the properties of the molecule, its ability to be formulated for inhalation and the performance of the formulation in a suitable device.

Late stage clinical development drugs: Opportunity for post-commercialization reformulations

As previously mentioned, there are six drugs in Phase II, two of which are large molecules in intravenous (IV) form—one a protein and one a monoclonal antibody (Mab) (Figure 3). Both molecules

Figure 3

IPF pipeline segregated according to molecule type. Content adapted from the Pulmonary Fibrosis Drug Development Pipeline [21], Pulmonary Fibrosis Clinical Trials [39] and clinicaltrials.gov [26] (accessed June 21, 2021) but may not be comprehensive.



act by either suppressing or blocking proteins contributing to pulmonary fibrosis—proteins found specifically in the lung. They have advanced to late stage clinical trials, after showing a positive effect on lung function in earlier stage trials.

Human pentraxin-2 protein is a recombinant human serum amyloid P/pentraxin 2 protein, produced in a Chinese hamster ovary cell expression system, which has been shown to reduce TGF-β1-induced and bleomycin-induced lung fibrosis in preclinical models [31]. Phase II trials showed that long term treatment (up to 76 weeks) produced positive effects on the percentage of predicted FVC and a 6-minute walking distance test [32]. The drug has been granted Orphan Drug Designation by the FDA and EMA [33].

Pamrevlumab is a fully humanized monoclonal antibody that blocks the activity of connective tissue growth factor (CTGF), a pro-inflammatory protein that promotes wound healing as well as fibrosis. Preclinical studies of CTGF in IPF have clearly defined its pro-fibrotic effect and demonstrated its contribution to lung fibrosis [34]. In Phase IIb trials, pamrevlumab showed significantly reduced decline in FVC. The FDA has granted the drug Orphan Drug Designation for IPF [35].

Reformulating a drug in Phase III occurs extremely infrequently as it can delay or jeopardize an entire clinical development program. However, should these drugs prove to be efficacious and receive regulatory approval, a more viable strategy could be to invest in a reformulation after commercialization.

Opinion and a challenge to the industry

As previously stated, IPF is a debilitating, progressive disease with a poor prognosis. The two approved pharmacological therapies have shown to slow disease progression, but do not stabilize or reverse fibrosis, yet cause noteworthy side effects in many patients [9, 11, 12]. Therefore, there is a real and urgent need for disease-modifying therapies for IPF patients.

The current pipeline of 33 IPF drugs includes eight that are already marketed for other indications and 25 new molecular entities, yet few are inhalation products. It is understandable not to pursue drug reformulation during Phase II or III, as doing so would compromise drug development timelines. However, it may be possible to reformulate Phase I and pre-clinical drugs (not mentioned in this article) without substantially compromising timelines. This is especially true for small molecules (83% of the IPF Phase I pipeline). Even with larger molecules, there has been progress in the last decade in manufacturing technologies such as spray drying that allow for these molecules to be formulated as DPIs [36]. Molecules that were previously thought to be unsuitable for spray drying—biologics, peptides, proteins and, more recently, nucleic acid-based vaccines—have been successfully formulated as dry powders [37, 38]. As witnessed by the growing number of inhalable spray-dried inhalation products that are commercially available, this technology has been proven to be robust and scalable for pharmaceutical development.

Inhalable formulations may provide considerable advantages for patient care, access, administration and distribution compared to intravenous formulations. Advantages versus oral formulations for diseases of the lung include reduced systemic side effects due to use of lower doses and potentially greater efficacy [13, 14]. Why then, given the availability of the technology and manufacturing knowledge, and the inherent medical advantages of inhaled drugs, are manufacturers pursuing conventional oral and IV formulations? Reasons may include greater convenience and adherence for an oral therapy compared to some inhaled therapies, such as nebulization that can take longer to administer. Also, as discussed, development of inhaled therapies can be more challenging and costly, especially when taking into account additional factors such as influence of the delivery device and patient inhalation technique, which add complexity to overall development.

Notwithstanding, there remain significant opportunities for pharmaceutical developers to pursue inhaled formulations of drugs, especially those for indications that have high unmet needs such as IPF, PAH, cystic fibrosis and other rare lung diseases and thereby provide safer, more tolerable and more efficacious products.

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