

Review

# A Review of the Current Landscape of Anti-Fibrotic Medicines

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**ABSTRACT:** Fibrosis is defined as the excessive accumulation and disorganized deposition of extracellular matrix components, affecting any organ in the human body. Fibrotic diseases of the vital organs such as lung, heart, kidney and liver can be chronic, progressive, irreversible and fatal. Although fibrotic diseases account for 45% of the mortality in the Western world, the available treatment options are limited in numbers, efficacy and safety. There is certainly a lack of progress in developing novel anti-fibrotics even though the market size for fibrotic diseases is estimated to be ~\$30B and several pharmaceutical companies have active R&D programmes in this field. We reviewed the current efforts in developing novel anti-fibrotic medicines focusing on lung, heart, kidney, liver and skin fibrosis. Our analysis revealed an estimated 83% attrition rate from Phase 2 to Phase 3 trials across the five fibrotic diseases. The possible reasons for the slow pace and high attrition rates in developing new anti-fibrotics are discussed and potential solutions are proposed.

**Keywords:** Fibrosis; Drug discovery; Pharmaceutical; Pharmacology



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## 1. Introduction

Fibrosis is defined as excessive accumulation and disorganized deposition of extracellular matrix (ECM) components in tissues, following injury. Fibrosis has been shown to be a critical driver in the pathophysiology of several chronic and progressive inflammatory and metabolic diseases. It may occur in any organ or tissue, affecting single organs or multiple organs as in systemic sclerosis (SSc). The accumulation of ECM in the tissues in a disorganized fashion is the main cause of dysfunction in the affected tissue and can ultimately lead to organ failure which can be fatal. The main four vital organs that may be affected by fibrosis are lung, heart, liver and kidney—all of which have high mortality rates. Another organ which can be affected is the skin, which may not necessarily cause mortality but can lead to significant morbidity. The annual combined incidence of fibrosis-related diseases affecting these five organs is estimated to be 5000 per 100,000 people per year, causing huge disease burden. It is estimated that fibrotic diseases account for ~45% of mortality in Western countries [1]. The incidence of fibrotic diseases especially in the lung and heart are expected to increase because of COVID-19 infections [2,3].

Despite these overwhelming statistics, there are only three drugs that are approved and licensed for fibrotic diseases: pirfenidone and nintedanib for lung fibrosis and resmetirom for liver fibrosis. There is certainly a lack of progress in developing novel anti-fibrotics even though the market size of fibrotic diseases is estimated to be ~\$30B and several pharmaceutical companies have active R&D programmes in this field [4].

The aim of this paper is to review the current drug development activities for novel anti-fibrotic medicines in five major fibrotic conditions (lung, heart, kidney, liver and skin) and to discuss the bottlenecks and potential solutions to them.

## 2. Major Fibrotic Conditions

### 2.1. Lung Fibrosis

Fibrosis of the lung can be observed at the end stage of various parenchymal lung diseases including idiopathic pulmonary fibrosis (IPF), fibrotic interstitial lung disease (fILD) and fibrotic hypersensitivity pneumonitis (fHP) which are grouped under the umbrella term of “progressive pulmonary fibrosis” [5]. Prevalence of IPF is estimated to be 0.33–2.51 per 10,000 persons in Europe and 2.40–2.98 per 10,000 persons in North America. Prevalence of non-IPF PPF is estimated to be 0.22–2.0 per 10,000 persons in Europe and 2.8 per 10,000 persons in North America [6]. Autoimmune connective tissue disease, smoking, family history, radiation, chemotherapy, asthma, allergic airway inflammation, exposure to substances such as asbestos or silica dust, sarcoidosis and viral infections such as COVID-19 have been suggested as etiological factors for non-IPF PPF [7]. Family history has been suggested to be a contributing factor also to IPF [8]. Diagnosis of fibrosis using radiological techniques such as thin-section computerized tomography has recently been recognized as key to the appropriate categorization of pulmonary fibrosis [9].

Fibrotic lung diseases are characterized by progressive worsening of dyspnea and lung function and are associated with a poor prognosis and high mortality. The median survival in patients with IPF and non-IPF PPF without a lung transplant have been reported to range from two to five years [10,11]. The age-standardized mortality rate for IPF vary from 0.5 to 12 per 100,000 population per year with regional differences [12].

Fibrosis in the lung has been suggested to be initiated by repeated sub-clinical injury to epithelial cells and subsequent destruction of the alveolar-capillary basement membrane [13]. This process triggers an inflammatory response which results in the recruitment and infiltration of immune cells such as macrophages, and the release of pro-inflammatory and pro-fibrotic cytokines and chemokines such as tumor necrosis factor (TNF)- $\alpha$ , transforming growth factor (TGF)- $\beta$ , monocyte chemoattractant protein (MCP)1/CCL2, macrophage inhibitory protein (MIP)1 $\alpha$ /CCL3, and T-helper (Th)2-chemokines such as CCL17, CCL18 and CCL22 [13]. This leads to trans-differentiation (transformation) of various cell types such as fibroblasts, epithelial cells, endothelial cells, fibrocytes, mesenchymal stem cells and/or pericytes to myofibroblasts; the origin of myofibroblasts in lung fibrosis has been widely studied and debated [13]. Myofibroblasts in comparison to their cells of origin have increased proliferation and ECM production capacity and adopt the ability to contract due to their alpha smooth muscle actin ( $\alpha$ -SMA) contractile stress fibers. In physiological wound healing, myofibroblasts are removed from the wound once the healing process is complete by undergoing apoptosis. However, in fibrosis (often referred to as aberrant wound healing), myofibroblasts lose their apoptotic potential, leading to their prolonged existence and excessive proliferation, plus the subsequent excessive accumulation of ECM proteins [14]. Under physiological conditions, the ECM not only determines the tissue architecture of the lung but also provides mechanical stability and the elastic recoil required for pulmonary function. It also regulates and controls myofibroblast transformation [15,16]. However, during fibrosis this balance is lost, and remodeling of the lung is dysregulated which leads to tissue destruction and loss of function [15].

Current clinical management of IPF is comprised of anti-fibrotic drugs (pirfenidone, nintedanib), anti-inflammatory/anti-tussive drugs (oral corticosteroids and opioids) to decrease cough and improve quality of life, anti-acids/proton pump inhibitors to reduce gastroesophageal reflux and lung transplantation [17]. Current clinical management of non-IPF PPF involves the removal of the underlying cause (e.g., limiting the occupational exposure to substances), treatment of underlying disease (e.g., immunosuppressants for systemic sclerosis, rheumatoid arthritis), anti-inflammatory/anti-tussive drugs (oral corticosteroids and opioids) and lung transplantation. The use of anti-fibrotic drugs (pirfenidone, nintedanib) in non-IPF PPF is debated [18]. Nintedanib is approved in many countries for ILD due to systemic sclerosis (SSc-ILD), but pirfenidone is not [19].

### 2.2. Cardiac Fibrosis

Fibrosis in the heart can be observed in several cardiovascular conditions such as heart failure (HF), hypertension, myocarditis and ischemic or non-ischemic cardiomyopathy. Fibrotic changes can be observed in the myocardium or the valves, or both [20].

Heart failure has an estimated global prevalence of 64 million and this number is projected to increase due to the ageing population. It is estimated that approximately 30–50% of patients with HF suffer from HF with preserved ejection fraction (HFpEF) which has a median survival rate of 2.1 years [21]. Although several therapies exist for HF with reduced ejection fraction (HFrEF) (e.g., beta adrenoceptor blockers, drugs targeting renin angiotensin aldosterone system, and sodium-glucose co-transporter 2 inhibitors), no treatment has been shown to be efficacious for HFpEF. The

etiological and risk factors for HFpEF are age, myocardial infarction, aortic stenosis, valvular disease, diabetes, obesity, chronic kidney disease, hypertension, atrial fibrillation, chronic obstructive pulmonary disease, iron deficiency, alcohol consumption, anthracyclines and anemia [22]. The pathophysiology of HFpEF is complex and comprises several pathological mechanisms such as endothelial dysfunction, chronic inflammation, and cardiomyocyte dysfunction. Among these mechanisms, fibrosis is a common outcome regardless of etiology and all pathophysiological mechanisms converge on fibrosis [23].

The pathophysiology of cardiac fibrosis shares several features with lung fibrosis. Cardiomyocyte death after injury such as ischemia or due to other disease leads to an inflammatory response and transformation of cardiac resident fibroblasts to  $\alpha$ -SMA-positive myofibroblasts [24]. Resident and circulating mesenchymal cell progenitors, pericytes, endothelial cells and epicardial epithelial cells have also been suggested as possible sources for myofibroblasts [24]. Pro-inflammatory and pro-fibrotic mediators released by monocytes, macrophages, lymphocytes, endothelial cells and mast cells during fibrosis include TGF- $\beta$ , TNF- $\alpha$ , IL-6, platelet-derived growth factor (PDGF), IL-4, IL-1 $\beta$ , histamine, endothelin-1 (ET-1) and MCP-1. Mast cells release several proteases such as chymase and tryptase which are shown to be pro-fibrotic. Chymase has been suggested to exert fibrogenic actions through generation of angiotensin II or through activation of the TGF- $\beta$  pathway. It should be noted that chymase-induced angiotensin II generation is not affected by angiotensin converting enzyme (ACE) inhibitors which may explain the progression of cardiac fibrosis despite ACE inhibition [24]. Proliferation of myofibroblasts leads to excessive accumulation of fibrillar collagen in the cardiac interstitium which is the hallmark of cardiac fibrosis. Myocardial infarction causes the death of a significant number of cardiomyocytes, resulting in their replacement with disorganized fibrillar collagen containing fibrous tissue, since the adult human heart has negligible regenerative capacity [24]. Loss of functional myocardial tissue leads to ventricular stiffness and diastolic dysfunction initially, followed by cardiac remodeling, ventricular dilation and systolic failure [25]. Fibrotic ventricular remodelling can also promote arrhythmogenesis through impaired conduction and subsequent generation of re-entry circuits [26].

The current clinical management of HFpEF is comprised of management of associated conditions (i.e., diabetes, atrial fibrillation, obesity, chronic kidney disease, myocardial ischemia, hyperlipidemia), lifestyle modifications and pharmacotherapy to manage the symptoms (i.e., diuretics, sodium-glucose co-transporter 2 (SGLT2) inhibitors, mineralocorticoid receptor antagonists (MRA) and ACE inhibitors). There are no approved drugs for treatment of cardiac fibrosis.

### 2.3. Liver Fibrosis

Autoimmune hepatitis, biliary obstruction, iron overload, non-alcoholic fatty liver diseases (such as non-alcoholic steatohepatitis; NASH), viral hepatitis B & C and alcoholic liver disease are chronic diseases of the liver that have fibrosis in the core of their pathogenesis. Chronic liver diseases are estimated to cause 2 million deaths per year hence are the 11th leading cause of death worldwide [27]. Alcohol is the leading cause of end stage liver failure, globally and is responsible for almost 60% of cirrhosis cases in Europe, North and Latin America [28]. Another significant fibrotic liver disease is NASH which affects a quarter of the global adult population with considerable variation depending on geographic region, ethnicity, genetic variants and lifestyle factors [29]. The percentage of total deaths from all causes attributable to NASH increased from 0.10% to 0.17% in the last three decades [30].

Liver fibrosis pathophysiology is like that of lung and cardiac fibrosis but with distinct differences. The main source for myofibroblasts in the liver are hepatic stellate cells, formerly known as lipocytes, Ito cells or perisinusoidal cells [31,32]. It should be noted that myofibroblasts can also originate from cells other than hepatic stellate cells in the liver such as portal myofibroblasts and hematopoietic stem cells [33,34]. Another difference is the regenerative property of the liver. After an acute injury such as viral hepatitis, parenchymal cells can regenerate and replace the necrotic cells. However, if the injury persists such as in chronic alcohol abuse, eventually liver regeneration fails, and the hepatocytes are replaced with ECM. The third difference is the main pro-fibrotic cytokine; PDGF, which is mainly produced by Kupffer cells, is the predominant mitogen but other cytokines and chemokines such as TGF- $\beta$ , TNF- $\alpha$  and ET-1 are also involved [35].

During the progression of fibrosis in the liver, functioning hepatocytes are replaced with stiff, disorganized ECM. Eventually collagen bands in the liver join up and lead to the formation of new vascular connections between portal fields and central veins, known as bridging fibrosis. This leads to frank cirrhosis with typical features like portal hypertension and liver failure which can progress to hepatocellular carcinoma.

The current clinical management of NASH is comprised of lifestyle modifications, anti-fibrotic drug treatment (resmetirom), other pharmacotherapy (pioglitazone, vitamin E) and bariatric surgery [36]. The current clinical management of chronic liver disease includes lifestyle modifications (i.e., dietary changes, alcohol abstinence, weight management), management of underlying disease (i.e., antivirals for viral hepatitis, immunosuppressants for autoimmune hepatitis), management of complications of cirrhosis (ascites, variceal bleeding, hepatic encephalopathy and hepatorenal syndrome) and liver transplantation [37].

#### 2.4. Kidney Fibrosis

Kidney or renal fibrosis, characterized by glomerular (called glomerulosclerosis) and interstitial (called tubulointerstitial) fibrosis, represents the final stage of chronic kidney disease (CKD). As CKD progresses, patients can advance to end-stage renal disease (ESRD), necessitating renal replacement therapies such as dialysis or transplantation. Various diseases, including glomerulonephritis, metabolic disorders like diabetes mellitus and atherosclerosis, obstructive nephropathy, interstitial nephritis, and cystic nephropathies such as polycystic kidney disease, can lead to CKD. However, kidney fibrosis is the common end result of all these conditions [38].

CKD is one of the most prominent causes of morbidity and mortality affecting an estimated 843.6 million individuals worldwide. Its prevalence is estimated to be 10.4% among men and 11.8% among women globally with significant differences due to geography and income levels [39]. The number of deaths caused by CKD doubled from 0.6 million in 1990 to 1.4 million in 2019 [40]; this increase has been attributed to an ageing population and increased incidence of diabetes mellitus.

Kidney fibrosis is similar to lung, heart and liver fibrosis and is characterized by excessive accumulation of ECM proteins by myofibroblasts. The origin of myofibroblasts in the kidney is suggested to be resident fibroblasts, pericytes, mesenchymal stem cell (MSC)-like cells, epithelial cells, endothelial cells and circulating bone marrow-derived cells [41]. The injured tubular cells and infiltrated immune inflammatory cells release profibrotic mediators such as TGF- $\beta$ , PDGF, FGF2 and HER2 in the fibrotic niche [42] which leads to the transformation and activation of myofibroblasts. Other mediators such as angiotensin II (Ang-II), nuclear factor-kappa B (NF $\kappa$ B) and plasminogen activator inhibitor-1 (PAI-1) have also been suggested to be involved in the renal fibrotic niche. Tubular epithelium plays an important role in this process as these cells, following repetitive injury, release mediators to recruit inflammatory cells and activate myofibroblast differentiation, proliferation, and matrix secretion [42]. A unique feature of CKD is a pathology called vascular rarefaction which is a consequence of kidney fibrosis. It is caused by the apoptosis, detachment, and dysfunction of endothelial cells and characterized by a decrease in capillary density leading to ischemic and hypoxic conditions [43]. Continuous deposition of ECM results in fibrous scars and distorts the fine architecture of kidney tissues, leading to the collapse of renal parenchyma, which is comprised of tubular atrophy, capillary loss and podocyte depletion, ultimately resulting in the irreversible loss of kidney function [44].

The current clinical management of CKD includes management of co-morbidities (i.e., diabetes, hypertension and hyperlipidemia), diet, lifestyle modifications, dialysis and kidney transplantation. There are no approved anti-fibrotic drugs for CKD or kidney fibrosis [45].

#### 2.5. Skin Fibrosis

Dermal fibrosis can be observed in a wide spectrum of skin diseases such as scleroderma, nephrogenic fibrosing dermopathy, mixed connective tissue disease, scleromyxedema, scleroderma and eosinophilic fasciitis. Exposure to chemical/physical agents or trauma to the skin are also potential causes of fibrotic skin disease such as keloid and hypertrophic scars [46–48].

Scleroderma can be categorized into two main types, localized (exclusive to the skin and underlying tissues) and systemic (initial skin fibrosis, followed by fibrosis of other organs). Localised scleroderma (LoS) is a rare disease, with an incidence of 0.4–2 per 100,000 individuals, with >90% of cases being diagnosed in children [49,50]. LoS is clinically characterised by the formation of ‘morphea’ on the trunk and/or limbs, which is the result of the thickening of the skin & underlying tissues, caused by excessive collagen deposition in these areas [51].

Systemic sclerosis (SSc) is a multisystem autoimmune and vascular disease of unknown etiology which results in fibrosis of various organs. The global prevalence of SSc is estimated to be 19 per 100,000 persons [52]. The commonly accepted pathogenesis of SSc involves vascular injury (i.e., capillary loss and arteriolar stenosis) and aberrant activation of vascular cells (i.e., endothelial cells) which are secondary to autoimmune attacks and unknown environmental factors. This dual vasculopathy leads to tissue hypoxia, inflammation, activation of pro-fibrotic pathways and eventual tissue

fibrosis [53]. Due to multiple organ involvement, SSc has the highest mortality rate among any of the autoimmune rheumatic diseases [54]. Current clinical management of SSc is organ-based. For the skin fibrosis, a wide variety of immunosuppressants have been used, but only a few have been studied in randomized clinical trials [55].

It is estimated that 100 million people in the developed world are affected by some sort of cutaneous scarring, following burn injury, trauma, or surgery every year. The types of scars with the highest incidence are hypertrophic (incidence of 32–72%) and keloid scars (0.09–16%, depending on ethnic background). These types of scars can result in itching, pain, loss of function, contractures, disfigurement, and diminished quality of life [56–58]. Like other fibrotic diseases, the pro-fibrotic microenvironment secondary to tissue injury and inflammation drives the transformation of fibroblasts, fibrocytes, pericytes, smooth muscle cells and epithelial cells to myofibroblasts [59]. Current clinical management of cutaneous scars includes steroid injection, laser therapy, bleomycin or 5-fluorouracil injection, cryotherapy and surgical removal of the scar tissue [58].

### 3. Approved Drugs

#### 3.1. Pirfenidone

Pirfenidone (Table 1) was the first approved anti-fibrotic drug. It was first approved in Japan in 2008, followed by the EU in 2011, Canada in 2012 and the USA in 2014 and is now available as a generic medication for the treatment of IPF. It was first reported in patents in the 1970s. The demonstration of its anti-fibrotic properties in a hamster model of bleomycin-induced lung fibrosis in the 1990s provided support for its development to treat IPF [60]. Its exact molecular target is unknown but several targets such as TGF $\beta$ , TNF, IL-10, p38 $\alpha/\gamma$  and MRC5 have been suggested [60].

**Table 1.** The names, indications, route of administration and mechanisms of action of the drugs that have been approved for fibrotic diseases.

Drug Name	Indications	Route of Administration	Mechanism of Action
Pirfenidone	IPF, PPF	Oral	Unknown
Nintedanib	IPF, PPF, SSc-ILD	Oral	Antagonist of VEGFR1-3, PDGFR $\alpha$ , FGFR1-2, LCK, Flt-3 kinase
Resmetirom	NASH	Oral	THR- $\beta$ agonism

Pirfenidone has been shown to inhibit the production and release of pro-fibrotic and pro-inflammatory cytokines such as TGF- $\beta$ , TNF- $\alpha$  and IL-6 and to prevent TGF- $\beta$ -induced transformation of lung fibroblasts to myofibroblast [60]. In both bleomycin-induced and transplant-induced lung fibrosis models pirfenidone has been shown to reduce fibrosis and dysfunction [61].

Pirfenidone has been studied in several clinical trials with IPF patients. A recent systematic review and meta-analysis in 2021 of nine randomized controlled trials showed that pirfenidone has been beneficial to prolong the progression-free survival and improve lung function in patients with IPF. Main side effects of the drug are gastrointestinal reactions, photosensitivity and skin rashes [62,63]. Pirfenidone has been recommended to be administered in adults in titration starting with 801 mg/day reaching up to 2403 mg/day in two weeks [64].

Pirfenidone has also been tested *in vitro* and *in vivo* for other fibrotic conditions which were mostly positive [60]. However, these pre-clinical results have not been translated to clinics.

#### 3.2. Nintedanib

Nintedanib (Table 1) was the second approved anti-fibrotic drug. It was approved for the treatment of IPF in 2014 and for FILD in 2020. It was discovered during a compound screening campaign to identify inhibitors of VEGF receptor 2 (VEGFR2) with the aim of developing angiogenesis inhibitors for the treatment of cancer [65]. Nintedanib targets pro-angiogenic and pro-fibrotic pathways mediated by the VEGFR family, the fibroblast growth factor receptor (FGFR) family, the platelet-derived growth factor receptor (PDGFR) family, as well as lymphocyte-specific protein tyrosine kinase (Lck) and Flt-3 kinases [65].

Nintedanib has been shown to inhibit PDGF- and VEGF-induced proliferation and motility of human lung fibroblasts. It also prevents TGF- $\beta$ -induced transformation of lung fibroblasts to myofibroblasts, leading to a reduction in TGF- $\beta$ -stimulated collagen secretion and deposition. Nintedanib was found to have no effect on epithelial-mesenchymal transition (EMT) of human alveolar type II epithelial cells, and did not induce apoptosis in human lung

fibroblasts [66]. In bleomycin- and silica-induced lung fibrosis models in vivo, nintedanib reduced both fibrosis and inflammation in a preventive model and to a lesser extent in therapeutic model [66].

Like pirfenidone, nintedanib has been investigated in several randomized clinical trials. A meta-analysis of these trials in 2022 demonstrated that nintedanib reduced the rate of decline by ~50% in lung function across subjects with different forms of lung fibrosis [67]. A more recent meta-analysis showed a reduction in risk of death compared to placebo in IPF and other forms of progressive pulmonary fibrosis [68]. A meta-analysis of the safety of the drug has shown that it was associated with a higher risk of adverse events especially diarrhea, nausea, vomiting and weight loss, but it was also associated with a lower risk of cough and dyspnea in IPF and fibrotic-ILD patients [69]. Nintedanib has been recommended to be administered in adults at 300 mg daily [64].

Nintedanib has been shown to reduce fibrosis in animal models of other organs such as liver and kidney in both preventive and therapeutic models [70,71], but these results have not been translated to clinic.

### 3.3. Resmetirom

Resmetirom has recently been approved for the treatment of non-cirrhotic NASH (Table 1). It is a selective thyroid receptor beta (THR- $\beta$ ) agonist. It was discovered through a compound screening campaign to identify selective THR- $\beta$  agonists. THR- $\beta$  agonists are known to reduce hepatic lipid levels in metabolic disorders.

Another THR- $\beta$  agonist, CS271011, has been shown to lower the levels of serum triacylglycerol and cholesterol without causing liver injury, to alleviate liver steatosis and hepatic lipid accumulation, and to improve hepatic biochemical indices in a diet-induced obese (DIO) mouse model [72]. It should be noted that this particular model does not produce liver fibrosis. In DIO-NASH animal models, where the animals develop liver fibrosis, resmetirom has been shown to reduce liver weight, hepatic steatosis, plasma alanine aminotransferase activity, liver and plasma cholesterol, blood glucose & liver  $\alpha$ -SMA expression, and to down-regulate the genes involved in fibrogenesis [73].

In a Phase 2 trial of adults with NASH, resmetirom has been shown to reduce hepatic fat and increased the resolution of liver fibrosis [74]. In two Phase 3 trials, resmetirom was shown to reduce hepatic fat, liver stiffness/fibrosis and biomarkers of liver fibrosis and injury [75,76]. Resmetirom has been recommended to be administered in adults at 80–100 mg daily [75,76].

## 4. Anti-Fibrotic Compounds under Development

The compounds which are currently in clinical development are discussed in this section. Any trials with solo treatment with pirfenidone, nintedanib or resmetirom are not included. The trials are grouped according to their target class and then ranked according to their progress status (from the most to the least advanced). Where a positive result from a Phase 2/3/4 study is reported, the peer-reviewed publication that supports that conclusion is quoted where possible. Any negative result or terminated trial, unless it is published, is noted as it is stated at Clinical Trials Gov website.

### 4.1. Compounds Targeting Cytokines and Their Pathways

As several pro-fibrotic growth factors are involved in the pathophysiology of fibrosis, it is not surprising to observe that several compounds that are being developed, are antagonists of pro-fibrotic factors (e.g., TGF) or agonists of anti-fibrotic growth factors (e.g., FGF) (Table 2). Among the growth factors, the most frequently trialed target is TGF- $\beta$  which carries certain challenges in therapeutic translation as discussed by others [77]. Foremost is the risk of systemic inhibition of TGF- $\beta$  response which is required for physiological homeostasis (e.g., wound healing, immune response, vascular effects). Therefore, upstream tissue specific targets such as integrins [78] and downstream fibrotic-tissue specific targets like CTGF [79] are pursued. Among the FGF subtypes, FGF-19 [80] and FGF-21 [81] are the choice of targets in fibrosis. The list of trials in the growth factors space (Table 2) reveals that the FGF-21 analogs efruxifermin and pegozafermin are the most advanced drug candidates; this could be attributed to the suggestion that FGF-21 ameliorates fibrosis by multiple mechanisms [82]. It should be noted that most of the FGF-21 analogs have been developed for the treatment of obesity and T2DM [83] hence their use in NASH and MASH.

**Table 2.** The names, indications, route of administration (RoA), mechanisms of action and the latest status of the compounds that target growth factors. The year next to Clinical Trial number (NCT) denotes the date of the last available update. DKD, diabetic kidney disease; FSGS, focal segmental glomerulosclerosis; HTS, hypertrophic scarring; IPF, idiopathic pulmonary fibrosis; mAb, monoclonal antibody; MASH, metabolic dysfunction-associated steatohepatitis; NASH, non-cirrhotic nonalcoholic steatohepatitis; SSc, systemic sclerosis.

Compound	Indications	RoA	Mechanism of Action	Latest Status
Efruxifermin	NASH/MASH	Subcutaneous	FGF-21 analog	Phase 3 recruiting NCT06215716 (2024)
Pegozafermin	MASH	Subcutaneous	FGF-21 analog	Phase 3 recruiting NCT06318169 (2024)
Aldafermin (NGM-282)	NASH	Subcutaneous	FGF-19 analog	Positive Phase 2 results [84] NCT04210245 (2023)
Disitertide (P144)	SSc skin	Topical	TGFβ1-inhibiting peptide	Positive Phase 2 results NCT00781053 (2013)
FT-011	SSc skin	Oral	Inhibition of TGFβ and PDGF	Positive Phase 2 results NCT04647890 (2023)
Bexotegrast (PLN-74809)	IPF	Oral	αvβ1/αvβ6 inhibitor	Positive Phase 2 results [85] NCT04396756 (2023) Phase 2 recruiting NCT06097260 (2024)
PF-06473871	HTS	Intradermal	Anti-CTGF antisense oligonucleotide	Positive Phase 2 results [86] NCT01730339 (2016)
HEC-585	IPF	Oral	Inhibition of TGFβR1	Phase 2 recruiting NCT05060822 (2023)
TTI-101	IPF	Oral	STAT3 inhibitor	Phase 2 recruiting NCT05671835 (2024)
SHR-1906	IPF	Intravenous	Anti-CTGF mAb	Phase 2 recruiting NCT05722964 (2023)
Axatilimab	IPF	Intravenous	Anti-CSF-1R mAb	Phase 2 recruiting NCT06132256 (2024)
STP-705	HTS	Intralesional	Anti-TGFβ/COX2 siRNA	Phase 2 not yet recruiting NCT05196373 (2023)
HLX-6018	IPF	Intravenous	Anti-GARP/TGF-β1 mAb	Phase 1 recruiting NCT06310746 (2024)
AGMB-447	IPF	Inhalation	ALK5 inhibitor	Phase 1 recruiting NCT06181370 (2024)
PMG-1015	IPF	Intravenous	Anti-amphiregulin mAb	Phase 1 recruiting NCT05895565 (2024)
TRK-250	IPF	Inhalation	TGFβ1 targeting siRNA	Phase 1 completed NCT03727802 (2023)
LEM-S401	HTS	Subcutaneous	Anti-CTGF siRNA	Phase 1 completed results not posted NCT04707131 (2023)
RXI-109	HTS	Intradermal	Anti-CTGF siRNA	Phase 1/2a completed unknown status NCT02246465 (2018)
STP-705	HTS	Intradermal	Anti-TGFβ1/COX2 siRNA	Phase 1/2a not yet recruiting NCT05196373 (2023)
BG-00011	IPF	Subcutaneous	anti-αvβ6 mAb	Phase 2 terminated due to safety NCT03573505 (2022)
Fresolimumab (GC-1008)	FSGS, SSc (skin)	Intravenous	TGFβ1/2/3 binding mAb	Negative Phase 2 results in FSGS [87] NCT01665391 (2015)  Positive Phase 2 results in SSc [88] NCT01284322 (2014)
Pamrevlumab	IPF,	Intravenous	CTGF binding mAb	Negative Phase 2 results

(FG-3019)	DKD			for both indications NCT00913393 (2019) NCT03955146 (2024)
Pegfelfermin (BMS-986036)	NASH	Subcutaneous	FGF-21 analog	Negative Phase 2 results [89] NCT03486912 (2022)
Metelimumab (CAT-192)	SSc (diffuse)	Intravenous	Anti-TGF- $\beta$ 1 mAb	Negative Phase 2 results [90] NCT00043706 (2015)
LY-2382770	DKD	Subcutaneous	Anti-TGF- $\beta$ 1 mAb	Phase 2 terminated due to lack of efficacy [91] NCT01113801 (2011)
BMT-101 (OLX-10010)	HTS	Intradermal	Anti-CTGF siRNA	Phase 2 terminated due to internal reasons NCT04012099 (2023)
MK-3655 (NGM-313)	NASH	Subcutaneous	FGF-R1 agonistic mAb (FGF-21 mimetic)	Phase 2 terminated due to business reasons NCT04583423 (2024)
IDL-2965	IPF	Oral	$\alpha$ v $\beta$ 1/ $\alpha$ v $\beta$ 3/ $\alpha$ v $\beta$ 6 inhibitor	Phase 1 terminated due to internal reasons NCT03949530 (2020)

#### 4.2. Compounds Targeting Kinases

A multitude of pro-fibrotic mediators such as TGF $\beta$ , CTGF, PDGF and FGF involve several kinases in their signalling cascades and their inhibition has been shown to be anti-fibrotic in preclinical models [92]. Kinases in general are druggable targets and most of the kinase inhibitors are orally bioavailable making them ideal drug candidates. Some of these kinase inhibitors work dually by inhibiting fibrotic pathways and also inflammatory pathways which can be a pro-fibrotic driver. Most of the kinase inhibitors in Table 3 were originally developed for cancer or auto-immune disease and out of 500 kinases encoded by the human genome, only 50 have so far been targeted for those therapeutic areas [93]. It is therefore predicted that more kinase inhibitors will be developed in the future. However, the overall safety profile of kinase inhibitors, particularly for non-cancer indications, still needs to be improved. The results from Phase 2 studies in fibrosis (Table 3) is mixed, some kinase inhibitors (i.e., baricitinib) seem to be progressing while others (i.e., selonsertib and tanzisertib) have efficacy and safety issues. No kinase inhibitor has progressed to Phase 3 yet.

**Table 3.** The names, indications, route of administration (RoA), mechanisms of action and the latest status of the compounds that target kinases. The year next to Clinical Trial number (NCT) denotes the date of the last available update. DKD, diabetic kidney disease; JAK, janus kinase; KHK, ketohehexokinase; TNIK, TRAF2 and NCK-interacting protein kinase; ROCK2, Rho associated coiled-coil containing protein kinase 2; PI3K, phosphoinositide 3-kinase; mTOR, mammalian target of rapamycin; MK2, MAP kinase-activated protein kinase 2; MAP3K19, mitogen-activated protein kinase 19; AMPK, 5' adenosine monophosphate-activated protein kinase; DDR2, discoidin domain receptor 2; JNK, c-Jun N-terminal kinase; ASK1, apoptosis signal-regulating kinase 1; MPAKK5, MAPK activated protein kinase 5; IPF, idiopathic pulmonary fibrosis; mAb, monoclonal antibody; NAFLD, non-alcoholic fatty liver disease; NASH, non-cirrhotic nonalcoholic steatohepatitis; SSc, systemic sclerosis.

Compound	Indications	RoA	Mechanism of Action	Latest Status
Baricitinib	DKD	Oral	Jak1/Jak2 inhibitor	Positive Phase 2 results NCT01683409 (2019)
F-351 (Hydronidone)	Liver (Hep B infection)	Oral	p38 kinase inhibitor	Positive Phase 2 results [94] NCT02499562 (2022) Phase 3 recruiting NCT05905172 (2022)
PF-06835919	NAFLD	Oral	KHK inhibitor	Positive Phase 2 results NCT03256526 (2019)
INS018-055	IPF	Oral	TNIK inhibitor	Phase 2 recruiting NCT05975983 (2024) Phase 1 completed NCT05154240 (2023)
RXC-007	IPF	Oral	ROCK2 inhibitor	Phase 2 recruiting NCT05570058 (2023)
Itacitinib	SSc (skin)	Oral	JAK1 inhibitor	Phase 2 recruiting NCT04789850 (2024)
Saracatinib	IPF	Oral	Dual Src/ Bcr-Abl tyrosine-kinase	Phase 2 active, not recruiting



			inhibitor	NCT04598919 (2024)
ZSP-1603	IPF	Oral	Triple tyrosine kinase inhibitor	Phase 1/2 recruiting NCT05119972 (2023)
Omipalisib (GSK2126458)	IPF	Oral	PI3K–mTOR inhibitor	Phase 1 completed NCT01725139 (2016)
HEC-68498	IPF	Oral	PI3K–mTOR inhibitor	Phase 1 completed NCT03502902 (2019)
MMI-0100	IPF	Inhalation	MK2 inhibitor	Phase 1 completed NCT02515396 (2017)
MG-S-2525	IPF	Oral	MAP3K19 inhibitor	Phase 1 completed NCT03650075 (2020)
Gleevec (Imatinib)	IPF, SSc (skin), Liver (advanced)	Oral	BCR-ABL tyrosine kinase inhibitor	Negative Phase 2 results in IPF NCT00131274 (2010) Mixed Phase 2 results in SSc (reviewed in [95]) Phase 1/2 completed in liver, results unknown NCT05224128 (2022)
Sorafenib (BAY43-9006)	skin (keloid)	Oral	Multiple serine/threonine tyrosine kinase inhibitor	Phase 2 study terminated NCT01425216 (2016)
Nilotinib	SSc-skin	Oral	BCR-ABL, KIT, PDGF, LYN and DDR2 inhibitor	Phase 2 study completed, inconclusive results NCT01166139 (2017)
Dasatinib	SSc-ILD, IPF, NASH	Oral	Pan-SRC kinase inhibitor	Negative Phase 2 in SSc-ILD NCT00764309 (2012) Phase 1 in IPF completed NCT02874989 (2020) Phase 1/2 in NAFLD in combination with quercetin recruiting NCT05506488 (2023)
Tanzisertib (CC-930)	IPF	Oral	JNK/p38 kinase inhibitor	Phase 2 terminated due to unfavorable benefit-risk profile NCT01203943 (2019)
PXL-770	NAFLD	Oral	AMPK inhibitor	Negative Phase 2 results NCT03763877 (2021)
Selonsertib (GS-4997)	NASH, DKD	Oral	ASK1, MPAKK5 inhibitor	Phase 3 in NASH terminated due to lack of efficacy NCT03053050 (2020) Negative results from Phase 2 in DKD NCT02177786 (2019) NCT04026165 (2022)
CC-90001	NASH, IPF	Oral	JNK1/MAPK8 inhibitor	Phase 2 in both indications terminated due to change of business objectives NCT04048876 (2023) NCT03142191 (2023)
Belumosudil	SSc-skin IPF	Oral	ROCK2 inhibitor	Phase 2 in SSc-skin terminated due to strategic decision NCT04680975 (2023) Negative results from Phase 2 in IPF NCT02688647 (2022)

### 4.3. Compounds Targeting PPARs

NASH/NAFLD are multi-system metabolic diseases affecting cardiovascular and renal systems and increasing the incidence of T2DM and hepatic cancer. Agonists of peroxisome proliferator-activated receptors (PPARs) have the potential to treat all these aspects of NASH/NAFLD. PPARs have three subtypes (PPAR $\alpha$ , PPAR $\delta$ (/β), PPAR $\gamma$ ) whose agonists have been recognized to lower lipid levels and increase insulin sensitivity. PPAR $\gamma$  agonists have been approved for the treatment of T2DM. PPAR agonists have been shown to reduce or prevent liver fibrosis in pre-clinical models [96]. Among the drug candidates listed in Table 4, lobeglitazone is the most advanced while its long-term safety remains to be elucidated.

**Table 4.** The names, indications, route of administration (RoA), mechanisms of action and the latest status of the compounds that target peroxisome proliferator-activated receptors (PPARs). The year next to Clinical Trial number (NCT) denotes the date of the last available update. NAFLD, non-alcoholic fatty liver disease; NASH, non-cirrhotic nonalcoholic steatohepatitis; PBC, primary biliary cholangitis.

Compound	Indications	RoA	Mechanism of Action	Latest Status
Lobeglitazone	NAFLD	Oral	PPAR $\gamma$ agonist	Positive anti-fibrotic effect in a Phase 4 study [97] NCT02285205 (2016)
Pemafibrate	NAFLD	Oral	PPAR $\alpha$ agonist	Positive antifibrotic effect in Phase 2 study [98] NCT03350165 (2021)
Lanifibranor	NASH, NAFLD	Oral	PPAR $\alpha$ / $\delta$ / $\gamma$ pan agonist	Positive anti-fibrotic effect in Phase 2 studies [99,100] NCT03008070 (2023) Several Phase 2 and 3 studies recruiting (reviewed in [101])
Pioglitazone	NAFLD	Oral	PPAR $\gamma$ agonist	Mixed anti-fibrotic effect in Phase 2-4 studies (reviewed in [101])
Saroglitazar	NAFLD	Oral	PPAR $\alpha$ / $\gamma$ dual agonist	Several Phase 2-4 studies recruiting (reviewed in [101])
Elafibranor	NASH	Oral	PPAR $\alpha$ / $\delta$ dual agonist	Positive anti-fibrotic effect in Phase 2 [102] NCT01694849 (2022), but not in Phase 3 NCT02704403 (2022)
Rosiglitazone	NASH	Oral	PPAR $\gamma$ agonist	No anti-fibrotic effect in Phase 2 study NCT00492700 (2007) NCT00699036 (2009) Phase 4 terminated due to discontinuation of the drug NCT01406704 (2011)
Chiglitazar	NASH	Oral	PPAR $\alpha$ / $\delta$ / $\gamma$ pan agonist	Phase 2 completed, no results yet NCT05193916 (2024)
Fenofibrate	NASH	Oral	PPAR $\alpha$ agonist	Negative results from Phase 2 studies (reviewed in [101])
Seladelpar	PBC	Oral	PPAR $\delta$ agonist	Phase 2 terminated due to unexpected histological findings NCT03551522 (2022)

#### 4.4. Compounds Targeting Endothelin Receptors

Endothelin receptors (type A and B) are expressed on vascular and pulmonary smooth muscle cells in the cardiovascular system, lungs and kidneys [103]. Endothelin receptor antagonists have been shown to be vasodilators and anti-fibrotic. Bosentan, a dual ET-A and -B antagonist has been approved for the treatment of pulmonary artery hypertension. In preclinical models, bosentan has been shown to be anti-fibrotic in the lungs [104]. In clinical trials (Table 5) however endothelin receptor antagonists have failed show clinical efficacy in IPF which has been further confirmed by meta-analysis [105]. Attention has now seemed to turn to kidney and liver fibrosis with some positive results.

**Table 5.** The names, indications, route of administration (RoA), mechanisms of action and the latest status of the compounds that target endothelin receptors. The year next to Clinical Trial number (NCT) denotes the date of the last available update. CDK, chronic kidney disease.

Compound	Indications	RoA	Mechanism of Action	Latest Status
Atrasentan	CDK	Oral	Endothelin A receptor antagonist	Positive results from Phase 3 study [106] NCT01858532 (2019)
Zibotentan (ZD-4054)	CDK, liver cirrhosis	Oral	Endothelin A receptor antagonist	Positive results from Phase 2 study in CDK [107] (combined with SGLT2 inhibitor dapagliflozin) NCT04724837 (2024)  Phase 2 in liver cirrhosis recruiting (combined with dapagliflozin) NCT06269484 (2024)
Ambrisentan	IPF	Oral	Endothelin A receptor antagonist	Negative results from Phase 2 study [108] NCT00768300 (2014)
Bosentan	IPF	Oral	Endothelin A and B receptor antagonist	Negative results from Phase 2 study [109] NCT00391443 (2015)
Macitentan (ACT-064992)	IPF	Oral	Endothelin A and B receptor antagonist	Negative results from Phase 2 study [110] NCT00903331 (2014)

#### 4.5. Compounds Targeting Phosphodiesterases

Phosphodiesterases (PDEs) regulate the intracellular concentrations of second messenger cyclic nucleotides cyclic adenosine monophosphate (cAMP) and/or cyclic guanosine monophosphate (cGMP). There are 11 types of PDEs with differential affinity for cAMP and/or cGMP. There have been previous reports stating that increasing cAMP or cGMP levels may have anti-fibrotic effect in preclinical models [111,112]. PDE inhibitors, which elevate intracellular cyclic nucleotide levels, therefore have been pursued as anti-fibrotic agents. There have been some positive results with the PDE5 inhibitor sildenafil (which elevates cGMP levels and is approved for the treatment of erectile dysfunction, pulmonary artery hypertension and lower urinary tract symptoms) in cardiac fibrosis and with PDE2 and PDE4B inhibitors (which elevate cAMP levels) in NASH and IPF, respectively (Table 6).

**Table 6.** The names, indications, route of administration (RoA), mechanisms of action and the latest status of the compounds that target phosphodiesterases (PDEs). The year next to Clinical Trial number (NCT) denotes the date of the last available update. IPF, idiopathic pulmonary fibrosis; NASH, non-alcoholic steatohepatitis; CDK, chronic kidney disease.

Compound	Indications	RoA	Mechanism of Action	Latest Status
Sildenafil	Cardiac	Oral	PDE5 inhibitor	Positive results from Phase 3 study [113] NCT00975494 (2009)
BI-1015550	IPF	Oral	PDE4B inhibitor	Positive results from Phase 2 study [114] NCT04419506 (2022)  Follow-up long-term Phase 2 recruiting NCT06238622 (2024)
ZSP-1601	NASH	Oral	PDE2 inhibitor	Positive results from Phase 1/2 study [115] NCT04140123 (2021)
CTP-499	CDK	Oral	Pan-PDE inhibitor	Phase 1 completed [116] NCT01460199 (2013)
Pentoxifylline	CDK	Oral	Pan-PDE inhibitor	Phase 4 completed, results unknown NCT03664414 (2019)

#### 4.6. Compounds Targeting the Immune System

Both innate and adaptive immune systems play important roles in the pathophysiology of fibrosis [117]. Several drug candidates which were initially developed for auto-immune/inflammatory diseases have been trialed for fibrotic diseases (Table 7). While most of these studies have reported negative results, the most advanced drug candidate is currently an anti-CD20 mAb (divozilimab) for SSc.

**Table 7.** The names, indications, route of administration (RoA), mechanisms of action and the latest status of the compounds that target immune system. The year next to Clinical Trial number (NCT) denotes the date of the last available update. NASH, non-alcoholic steatohepatitis; CDK, chronic kidney disease; TLR4, toll-like receptor 4; CCL, chemokine (C-C motif) ligand; IL, interleukin; SSc, systemic sclerosis; ILD, interstitial lung disease; mAb, monoclonal antibody; BAFF, B-cell activating factor; CD, cluster of differentiation; TNF, tumor necrosis factor; TNFSF, TNF superfamily; CCR, C-C chemokine receptor.

Compound	Indications	RoA	Mechanism of Action	Latest Status
JKB-121	NASH	Oral	TLR4 antagonist	Negative results from Phase 2 study NCT02442687 (2019)
JKB-122	NASH	Oral	TLR4 antagonist	Phase 2 study completed, no results posted NCT04255069 (2020)
Bindarit	CDK	Oral	Inhibitor of CCL2/7/8	Phase 2 study completed, no results posted NCT01109212 (2016)
Tocilizumab	SSc ILD	Intravenous/ Subcutaneous	Anti-IL6 mAb	Phase 2-3 study comparing tocilizumab and rituximab in SSC ILD completed; no results posted NCT05963048 (2023) Negative results from Phase 3 study in SSc [118] NCT02453256 (2020)
Rituximab	SSc ILD	Intravenous	Anti-CD20 mAb	Phase 2-3 study comparing tocilizumab and rituximab in SSC ILD completed; no results posted NCT05963048 (2023)
Divozilimab	SSc	Intravenous	Anti-CD20 mAb	Phase 3 recruiting NCT05726630 (2023)

	(skin and ILD)			
Belimumab/ Rituximab combination	SSc (skin)	Intravenous/ subcutaneous	Belimumab: Anti-BAFF mAb Rituximab: Anti-CD20 mAb	Phase 2 recruiting NCT03844061 (2024)
Ianalumab	SSc (skin)	Subcutaneous	Anti-BAFF mAb	Phase 2 recruiting NCT06470048 (2024)
Tulisokibart	SSc-ILD	Intravenous	Anti- TNFSF15/TL1A mAb	Phase 2 recruiting NCT05270668 (2024)
Efzofitimod	SSc-ILD	Intravenous	Fc fusion protein	Phase 2 recruiting NCT05892614 (2024)
Foralumab	NASH	Oral	Anti-CD3 mAb	Phase 2 withdrawn NCT03291249 (2019)
Pomalidomide	SSc-ILD, IPF	Oral	Anti-TNF and Anti-IL-2	Phase 2 in SSc-ILD withdrawn NCT01559129 (2023) Phase 2 in IPF terminated NCT01135199 (2023)
Cenicriviroc	NASH	Oral	CCR2/5 antagonist	Negative results from Phase 2 studies NCT02217475 (2019) NCT03028740 (2022) NCT03059446 (2022)
RN1003	HTS	Intradermal	Human IL-10	Phase 2 study completed, results not posted NCT00984646 (2009)
Interferon gamma	IPF	Intravenous/ Subcutaneous	Interferon gamma	Phase 3 study terminated due to lack of efficacy NCT00075998 (2009)

#### 4.7. Compounds Targeting FXR

The farnesoid X receptor (FXR) is involved in regulation of several physiological mechanisms in the human gut such as bile acid synthesis and enterohepatic circulation, lipid and glucose metabolism, inflammation, fibrosis, gut barrier integrity and intestinal microbiota [119]. Since these mechanisms are involved in the pathogenesis of NASH, several FXR agonists have been developed (Table 8). Among them TERN-101 and vonafexor have been reported to be the most advanced.

**Table 8.** The names, indications, route of administration (RoA), mechanisms of action and the latest status of the compounds that target farnesoid X receptor (FXR). The year next to Clinical Trial number (NCT) denotes the date of the last available update. NASH, non-alcoholic steatohepatitis.

Compound	Indications	RoA	Mechanism of Action	Latest Status
TERN-101	NASH	Oral	FXR agonist	Positive results from Phase 2 study NCT04328077 (2022)
Vonafexor	NASH	Oral	FXR agonist	Positive results from Phase 2 study [120] NCT03812029 (2023)
Cilofexor	NASH	Oral	FXR agonist	Phase 2 active, not recruiting NCT04971785 (2024)
PX-102	NASH	Oral	FXR agonist	Phase 1 completed NCT01998672 (2014) NCT01998659 (2014)
Obeticholic acid (OCA)	NASH	Oral	FXR agonist	Phase 3 terminated NCT02548351 (2023) Negative results from Phase 3 study NCT03439254 (2023)
Nidufexor	NASH	Oral	FXR agonist	Phase 2 terminated NCT02913105 (2021)

EDP-305	NASH	Oral	FXR agonist	Phase 2 terminated due to strategic decision NCT04378010 (2023)
Tropifexor	NASH	Oral	FXR agonist	Phase 2 terminated due to business reasons NCT04065841 (2024)

#### 4.8. Compounds Targeting Prostaglandins

Prostaglandins are synthesized from the lipid arachidonic acid, which is present in all cellular membranes, by cyclooxygenase 1 and 2 (COX-1 and COX-2) and prostaglandin synthases [121]. Among the four prostaglandins, prostaglandin I<sub>2</sub> (PGI<sub>2</sub>, prostacyclin) has been shown to exert anti-fibrotic effects in preclinical models of lung and kidney fibrosis [122,123], with subsequent clinical trials taking place in IPF and CDK with prostacyclin analogs (Table 9). Treprostinil, one of the inhalation formulations of prostacyclin, is the most advanced among this group. In contrast to prostacyclin, prostaglandin D<sub>2</sub> (PGD<sub>2</sub>) is a pro-inflammatory and pro-fibrotic mediator which is synthesized by hematopoietic PGD synthase (hPGDS) [124]. ZL-2102, a selective hPGDS inhibitor has been developed for COPD, asthma and IPF [125] (Table 9).

**Table 9.** The names, indications, route of administration (RoA), mechanisms of action and the latest status of the compounds that target prostaglandins. The year next to Clinical Trial number (NCT) denotes the date of the last available update. IPF, idiopathic pulmonary fibrosis; PAH, pulmonary arterial hypertension; CDK, chronic kidney disease; hPGDS, hematopoietic prostaglandin D synthase.

Compound	Indications	RoA	Mechanism of Action	Latest Status
Treprostinil	IPF	Inhalation	Prostacyclin analogue	Phase 3 recruiting NCT04708782 (2024)
Iloprost	PAH-IPF	Inhalation/oral	Prostacyclin analogue	Phase 2/3, unknown status NCT00439543 (2007) Phase 2 completed, no results posted NCT00109681 (2010)
Beraprost	CDK	Oral	Prostacyclin analogue	Phase 2, unknown status NCT01796418 (2013)
ZL-2102	IPF	Oral	hPGDS inhibitor	Phase 1, unknown status NCT02397005 (2019)

#### 4.9. Anti-Diabetic Compounds

There are currently several therapeutics marketed for type 2 diabetes mellitus (T2DM): dipeptidyl peptidase-4 inhibitors (DPP-4is, gliptins), glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter type 2 inhibitors (SGLT2s, gliflozins). Glucose-dependent insulinotropic polypeptide (GIP) receptor agonists have also been developed but have not reached the market. Recently compounds that have dual activity have been developed [126] such as tirzepatide (LY3298176) [127], survodutide (BI-456906) [128] and pemvidutide (ALT-801) [129] which have agonistic activity on the GIP receptor and the GLP-1 receptor; and DD-01 [130] and cotadutide [131] which have agonistic activity on the GLP-1 receptor and the glucagon receptor. There have also been development of triple agonists (GIP/GLP-1/glucagon receptor) such as efocipegtrutide (HM-15211) [132], LY3437943 [133] and SAR-441255 [134]. Most of these compounds have shown efficacy in improving fibrosis markers in clinical trials of liver fibrosis, but not in kidney or cardiac fibrosis (Table 10).

**Table 10.** The names, indications, route of administration (RoA), mechanisms of action and the latest status of anti-diabetic compounds. The year next to Clinical Trial number (NCT) denotes the date of the last available update. NASH, non-alcoholic steatohepatitis; MASH; metabolic dysfunction-associated steatohepatitis; MAFLD, metabolic dysfunction-associated fatty liver disease; GLP, glucagon-like peptide; GIP, glucose-dependent insulinotropic polypeptide; SGLT2, sodium-glucose transport protein 2; CDK, chronic kidney disease.

Compound	Indications	RoA	Mechanism of Action	Latest Status
Tirzepatide (LY3298176)	NASH	Subcutaneous	Dual GLP-1/GIP receptor agonist	Positive results from Phase 2 study [135] NCT04166773 (2024)
Semaglutide	NASH	Subcutaneous	GLP-1 agonist	Phase 3 recruiting NCT04822181 (2024)
Efocipegtrutide (HM-15211)	NASH	Subcutaneous	GIP, GLP-1 and glucagon receptor agonist	Phase 2 recruiting NCT04505436 (2024)
DD-01	MASLD/MASH	Subcutaneous	Dual GLP-1 and glucagon receptor agonist	Phase 2 recruiting NCT06410924 (2024)
Pemvidutide (ALT-801)	MASH	Subcutaneous	Dual GLP-1 and glucagon receptor agonist	Phase 2 recruiting NCT05989711 (2024)
Survodutide (BI-456906)	NASH	Subcutaneous	Dual GLP-1 and glucagon receptor agonist	Positive Phase 2 results [136] NCT04153929 (2022) Phase 2 recruiting NCT06309992 (2024)
Dapagliflozin	Myocardial fibrosis, cirrhosis, CDK	Oral	SGLT2 inhibitor	Phase 2 in myocardial fibrosis completed, no effect on fibrosis [137] NCT03782259 (2023) Phase 2 in cirrhosis recruiting NCT06269484 (2024) Phase 2 in CKD terminated due to lack of efficacy [138] NCT03036150 (2021)
Canagliflozin	CDK	Oral	SGLT2 inhibitor	Phase 2 terminated due to lack of efficacy [139] NCT02065791 (2019)
Cotadutide (MEDI-0382)	NASH	Subcutaneous	Dual GLP-1/glucagon receptor agonist	Phase 2 completed, no results posted NCT05364931 (2024)

#### 4.10. Other Compounds

There have been several clinical trials with other compounds, most of which have given negative results (Table 11). Positive results were seen in Phase 2 studies with a fatty acid synthase inhibitor (denifanstat) in NASH, a dual GPR-40/80 antagonist (PBI-4050) in IPF, a mineralocorticoid receptor antagonist (finerenone) in DKD and a cyclophilin inhibitor (rencofilstat) in NASH (Table 11). There are also several Phase 1-2-3 studies which are recruiting with various targets ranging from NADPH-oxidase to autotaxin (Table 11).

ECM homeostasis is maintained by a fine balance between production and metabolism of ECM components which is controlled by matrix metalloproteinases (MMPs) and their inhibitors, tissue inhibitors of metalloproteinases (TIMPs). Regulation of MMPs and TIMPs have been attractive strategies for the development of anti-fibrotic drugs. MMPs and TIMPs are often co-expressed in response to multiple stimuli including inflammatory cytokines, growth factors, glucocorticoids or retinoids [140,141]. Some of the candidate molecules listed in this section either directly act on MMP/TIMPs (e.g., MMP7 siRNA) or indirectly by regulating their expression such as recombinant human gene-2 relaxin (serelaxin) [142], angiotensin type 2 receptor agonists [143,144], lysophosphatidic acid receptor 1 antagonists [145], autotaxin antagonists [146] and angiotensin converting enzyme inhibitors [147].

**Table 11.** The names, indications, route of administration (RoA), mechanisms of action and the latest status of other compounds. The year next to Clinical Trial number (NCT) denotes the date of the last available update. NASH, non-alcoholic steatohepatitis; IPF, idiopathic pulmonary fibrosis; GPR, G-protein coupled receptor; DKD, diabetic kidney disease; NAFLD, non-alcoholic fatty liver disease; LT, leukotriene; PDE, phosphodiesterase; 5-LO, 5-lipoxygenase; SCD1, stearoyl CoA desaturase 1; ACC, acetyl-CoA carboxylase; HSP, heat shock protein; ATX, autotaxin; SSc, systemic sclerosis; ILD, interstitial lung disease; HTS, hypertrophic scarring; ACE, angiotensin converting enzyme; tRNA, transfer RNA; HCM, hypertrophic cardiomyopathy; TMG2, tissue transglutaminase 2; LPAR, lysophosphatidic acid receptor; NOX, NADPH oxidase; MMP, matrix metalloproteinase; PPAR, peroxisome proliferator-activated receptor; SGLT, sodium glucose transport protein; GR, glucocorticoid receptor; sGC, soluble guanylate cyclase.

Compound	Indications	RoA	Mechanism of Action	Latest Status
Denifanstat (TVB-2640)	NASH	Oral	Fatty acid synthase inhibitor	Anti-fibrotic effect in Phase 2 study [148] NCT03938246 (2021)
PBI-4050	IPF	Oral	GPR-40 agonist and GPR-84 antagonist	Positive results when combined with pirfenidone in Phase 2 study [149] NCT02538536 (2019)
Finerenone	DKD	Oral	Mineralocorticoid receptor antagonist	Disease progression slowed in Phase 2 study NCT02540993 (2023)
Rencofilstat (CRV-431)	NASH	Oral	Cyclophilin inhibitor	Positive results in Phase 2 study [150] NCT04480710 (2022)
Serelaxin	SSc (diffuse)	Subcutaneous	TGF- $\beta$ 1 and TIMP-1 inhibitor, MMP promoter	Negative results in Phase 3 study [151] NCT00704665 (2008)
Belapectin	NASH	Oral	Galectin-3 inhibitor	Negative results from Phase 2 study [152] NCT02462967 (2020)
GB-1211	NASH	Oral	Galectin-3 inhibitor	Phase 2 study withdrawn due to change in strategy NCT04607655 (2021)
GB-0139	IPF	Inhaled	Galectin-3 inhibitor	Negative results from Phase 2 study NCT03832946 (2024)
Epeleuton	NAFLD	Oral	$\omega$ -3 fatty acid	Negative results from Phase 2 study [153] NCT02941549 (2022)
Tipelukast	IPF	Oral	LT-R antagonist, PDE3/4 and 5-LO inhibitor	Phase 2 completed No results posted NCT02503657 (2022)
Compound 21	IPF	Oral	TGF- $\beta$ 1 and TIMP-1 inhibitor	Phase 2 completed No results posted NCT04533022 (2024)
LY3540378	HFpEF	Subcutaneous	Relaxin analogue	Phase 2 completed No results posted NCT05592275 (2024)
Aramchol	NASH	Oral	SCD1 inhibitor	Phase 2 suspended after meeting primary endpoint NCT04104321 (2022)
PF-05221304	NAFLD	Oral	ACC inhibitor	Phase 2 study completed, fibrosis was not measured [154] NCT03248882 (2020)
Namodenoson (CF-102)	NAFLD	Oral	Adenosine 3 receptor agonist	Phase 2 study completed, fibrosis was not measured [155] NCT02927314 (2020)
BMS-986263	NASH	Intravenous	Anti-HSP47 siRNA	Phase 2 terminated due to lack of efficacy NCT04267393 (2024)
GLPG-1205	IPF	Oral	GPR-84 antagonist	Negative results from

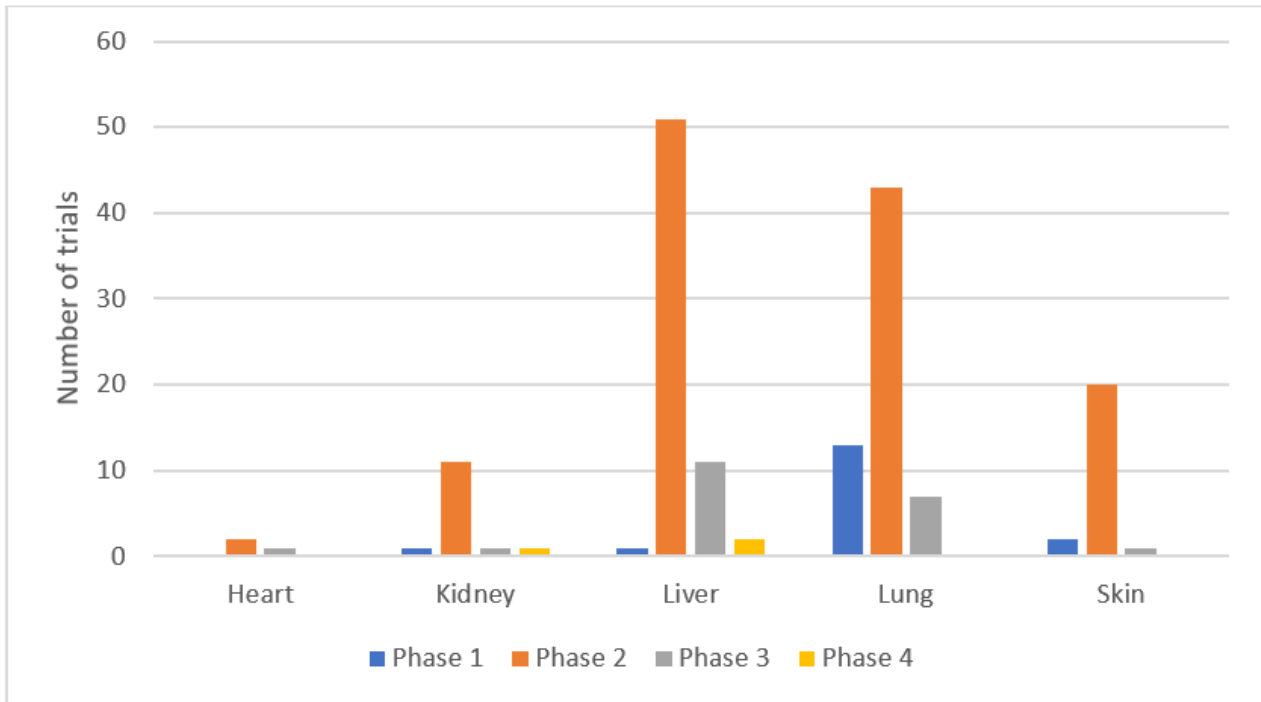


				Phase 2 study [156] NCT03725852 (2021)
Ziritaxestat (GLPG-1690)	IPF	Oral	ATX inhibitor	Phase 3 discontinued due to lack of efficacy [157] NCT03711162 (2022) NCT03733444 (2022)
Zinpentraxin (PRM-151)	IPF	Intravenous	Recombinant human pentraxin 2	Phase 2 terminated due to lack of efficacy NCT04552899 (2024)
spironolactone	HCM with fibrosis	Oral	Aldosterone antagonist	Negative results from Phase 2 study [158] NCT00879060 (2021)
Vixarelimab	IPF, SSc-ILD	Subcutaneous	Oncostatin M receptor beta (OSMR $\beta$ ) mAb	Phase 2 recruiting NCT05785624 (2024)
AZD3427	HFpEF	Subcutaneous	Relaxin analogue	Phase 2 recruiting NCT05737940 (2024)
Bersiporocin (DWN-12088)	IPF	Oral	Prolyl-tRNA synthetase inhibitor	Phase 2 recruiting NCT05389215 (2024)
Ifetroban	IPF	Oral	Thromboxane receptor antagonist	Phase 2 recruiting NCT05571059 (2024)
Enalaprilat	HTS	Intralesional	ACE inhibitor	Phase 2 not yet recruiting NCT05259137 (2024)
Sufenidone (SC-1011)	IPF	Oral	Pirfenidone analogue	Phase 2/3 recruiting NCT06125327 (2023)
GSK3915393	IPF	Oral	TMG2 inhibitor	Phase 2 recruiting NCT06317285 (2024)
LTI-03	IPF	Inhalation	Caveolin-1 peptide	Phase 1 recruiting NCT05954988 (2023)
BI-1819479	IPF	Oral	ATX inhibitor	Phase 2 not yet recruiting NCT06335303 (2024)
BBT-877	IPF	Oral	ATX inhibitor	Phase 2 recruiting NCT05483907 (2024)
HZN-825	SSc (skin)	Oral	LPAR1 antagonist	Phase 2 recruiting NCT04781543 (2024)
BMS-986278	IPF	Oral	LPAR1 antagonist	Phase 2 recruiting NCT06003426 (2024)
GKT-137831	IPF	Oral	NOX inhibitor	Phase 2 recruiting NCT03865927 (2024)
AK-3280	IPF	Oral	Pirfenidone analogue	Phase 2 not yet recruiting NCT05424887 (2022)
ARO-MMP7	IPF	Inhalation	MMP7 siRNA	Phase 2 recruiting NCT05537025 (2024)
HEC-585	IPF	Oral	Pirfenidone analogue	Phase 2 recruiting NCT05060822 (2023)
Pemafibrate (K-877-ER) and Tofogliflozin (CSG452)	NASH	Oral	Pemafibrate: PPAR $\alpha$ agonist Tofogliflozin: SGLT inhibitor	Phase 2 recruiting NCT05327127 (2024)
GH-509	NASH/NAFLD	Oral	Undisclosed	Phase 1/2 recruiting NCT05784779 (2023)
Ibutamoren (LUM-201)	NAFLD	Oral	Growth hormone secretagogue	Phase 2 recruiting NCT05364684 (2024)
GSK4532990 (ARO-HSD)	NASH	Subcutaneous	Anti-17 hydroxysteroid dehydrogenase siRNA	Phase 2 recruiting NCT05583344 (2024)
Mirocorilant (CORT-118335)	MASH	Oral	GR-antagonist	Phase 2 recruiting NCT06108219 (2024)
Avenciguat (BI-685509)	SSc (skin, ILD)	Oral	sGC activator	Phase 2 recruiting NCT05559580 (2024)

## 5. Analysis of Clinical Studies

### 5.1. Distribution According to the Organ

Out of 172 clinical trials we have identified, the highest proportion were in liver (65 [37.8%]) and lung (64 [37.2%]) fibrosis. The trials in heart, kidney and skin were relatively lower: there were 5 (2.9%) trials in heart, 14 (8.1%) in kidney and 24 (14%) in skin fibrosis. These results suggest that more candidate drugs are pursued in lung and liver fibrosis than skin, heart or kidney. There were 17 (10.1%) Phase 1, 130 (77.4%) Phase 2, 22 (13.1%) Phase 3 and 3 (1.8%) Phase 4 studies indicating a steep decrease from Phase 2 to Phase 3 studies. There were 130 Phase 2 and 22 Phase 3 trials suggesting an attrition rate of 83%. The distribution of each phase divided by organ is shown in Figure 1, which suggests that while there is more activity in Phase 2 trials in liver fibrosis, when compared to the other organs, there seems to be more Phase 1 activity in lung fibrosis.



**Figure 1.** The distribution of clinical trials divided by organs and phases.

The distribution of the trials divided by organ and their progress are shown in Tables 12–15. The distribution pattern of 17 Phase 1 trials (Table 12) correlates with Figure 1, suggesting that lung fibrosis has more activity in Phase 1 than the other organs, but the number of recruiting Phase 1 trials are relatively low.

**Table 12.** Distribution of 17 Phase 1 clinical trials in five major fibrotic diseases (heart, kidney, liver, lung and skin) according to their stages in clinical development. The percentages are shown in brackets.

Organ	Recruiting	Completed	Terminated Due to Business Reasons	Unknown Status
Heart	0 (0)	0 (0)	0 (0)	0 (0)
Kidney	0 (0)	1 (5.9)	0 (0)	0 (0)
Liver	0 (0)	1 (5.9)	0 (0)	0 (0)
Lung	4 (23.5)	7 (41.2)	1 (5.9)	1 (5.9)
Skin	0 (0)	2 (11.8)	0 (0)	0 (0)

The distribution of 130 Phase 2 trials (Table 13) shows that while there is more activity in liver fibrosis in this phase than the other organs (also shown in Figure 1), most of these trials either have negative results, are terminated due to business reasons or are completed but do not have results, which leaves only 13 trials with positive results and 13 recruiting trials. In contrast, lung fibrosis has 20 recruiting trials suggesting a high activity in this organ in Phase 2. There were 23 trials with positive results which would give an 18% success rate (82% attrition rate). If we compare the number of trials with positive results to those with negative results, only trials in skin fibrosis had more positive results than negative results.

**Table 13.** Distribution of 130 Phase 2 clinical trials in five major fibrotic diseases (heart, kidney, liver, lung and skin) according to their stages in clinical development. The percentages are shown in brackets.

Organ	Recruiting	Positive Results	Negative Results	Not Yet Recruiting	Terminated Due to Business Reasons	Completed Results Unknown
Heart	1 (0.8)	0 (0)	2 (1.5)	0 (0)	0 (0)	1 (0.8)
Kidney	0 (0)	3 (2.3)	6 (4.6)	0 (0)	0 (0)	2 (1.5)
Liver	13 (10)	13 (10)	16 (12.3)	0 (0)	5 (3.9)	4 (3.1)
Lung	20 (15.4)	2 (1.5)	14 (10.8)	3 (2.3)	1 (0.8)	4 (3.1)
Skin	5 (3.9)	5 (3.9)	4 (3.1)	3 (2.3)	2 (1.5)	1 (0.8)

Out of 22 Phase 3 trials, the recruiting trials are in liver (6), lung (2) and skin (1) (Table 14) suggesting a higher activity in liver fibrosis in Phase 3 than the other organs. Liver and lung fibrosis seem to have a similar number of trials with positive and negative results.

**Table 14.** Distribution of 21 Phase 3 clinical trials in five major fibrotic diseases (heart, kidney, liver, lung and skin) according to their stages in clinical development. The percentages are shown in brackets.

Organ	Recruiting	Positive Results	Negative Results	Not yet Recruiting	Terminated Due to Business Reasons	Completed Results Unknown
Heart	0 (0)	1 (4.5)	0 (0)	0 (0)	0 (0)	0 (0)
Kidney	0 (0)	1 (4.5)	0 (0)	0 (0)	0 (0)	0 (0)
Liver	6 (27.3)	1 (4.5)	4 (18.2)	0 (0)	0 (0)	0 (0)
Lung	2 (9.1)	0 (0)	3 (13.6)	0 (0)	0 (0)	2 (9.1)
Skin	1 (4.5)	0 (0)	1 (4.5)	0 (0)	0 (0)	0 (0)

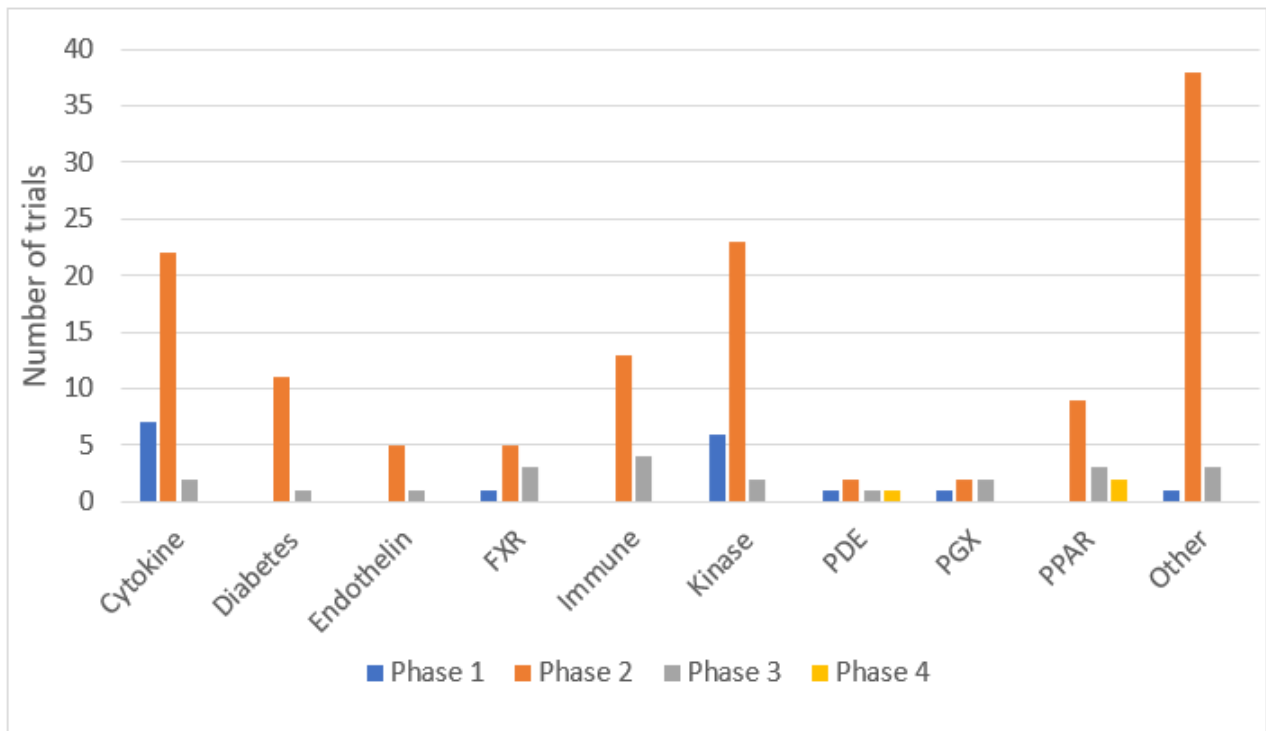
We have identified only 3 Phase 4 trials. The only one with positive results was lobeglitazone for liver fibrosis (Tables 4 and 15). One Phase 4 trial in liver fibrosis was terminated due to discontinuation of the drug (rosiglitazone, Tables 4 and 15) and one Phase 4 study in kidney fibrosis was completed but the results have not been posted or published (pentoxifylline, Tables 6 and 15).

**Table 15.** Distribution of 3 Phase 4 clinical trials in five major fibrotic diseases (heart, kidney, liver, lung and skin) according to their stages in clinical development. The percentages are shown in brackets.

Organ	Recruiting	Positive Results	Negative Results	Not Yet Recruiting	Terminated Due to Business Reasons	Completed Results Unknown
Heart	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Kidney	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33.3)
Liver	0 (0)	1 (33.3)	0 (0)	0 (0)	1 (33.3)	0 (0)
Lung	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Skin	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

## 5.2. Distribution According to Target Classes

When 172 trials were distributed according to their target classes, the highest number of trials were observed in cytokines (31 [18.5%]), kinases (31 [18.5%]) and other (42 [25%]) classes (Figure 2). With most trials in Phase 2, the most common target classes observed were in cytokines, kinases, anti-diabetic drugs, immune and other classes (Figure 2).



**Figure 2.** The distribution of clinical trials according to the target classes and the phases.

The distribution of 17 Phase 1 trials according to their target classes and progression is shown in Table 16. More than a third of completed Phase 1 trials were in “other” target class.

**Table 16.** Distribution of 17 Phase 1 clinical trials in ten target classes according to their stages in clinical development. The percentages are shown in brackets.

Target Class	Recruiting	Completed	Terminated Due to Business Reasons	Unknown Status
Cytokine	3 (17.7)	3 (17.7)	1 (5.9)	0 (0)
Anti-diabetic	0 (0)	0 (0)	0 (0)	0 (0)
Endothelin	0 (0)	0 (0)	0 (0)	0 (0)
FXR	0 (0)	1 (5.9)	0 (0)	0 (0)
Immune	0 (0)	0 (0)	0 (0)	0 (0)
Kinase	0 (0)	6 (35.3)	0 (0)	0 (0)
PDE	0 (0)	1 (5.9)	0 (0)	0 (0)
PGX	0 (0)	0 (0)	0 (0)	1 (5.9)
PPAR	0 (0)	0 (0)	0 (0)	0 (0)
Other	1 (5.9)	0 (0)	0 (0)	0 (0)

The distribution of 130 Phase 2 trials according to their target classes and progression is shown in Table 17. Although there were 17 trials recruiting in “other” target class, the number of trials with negative results (10) in this class was also high. The highest number of trials with positive results was in “cytokine” class. When we compare the numbers of trials with positive results to those with negative results, none of the target classes had more trials with positive results than those with negative results.

**Table 17.** Distribution of 130 Phase 2 clinical trials in ten target classes according to their stages in clinical development. The percentages are shown in brackets.

Target Class	Recruiting	Positive Results	Negative Results	Not Yet Recruiting	Terminated Due to Business Reasons	Completed Results Unknown
Cytokine	5 (3.9)	6 (4.6)	7 (5.4)	2 (1.5)	2 (1.5)	0 (0)
Anti-diabetic	5 (3.9)	2 (1.5)	3 (2.3)	0 (0)	0 (0)	1 (0.8)
Endothelin	1 (0.8)	1 (0.8)	3 (2.3)	0 (0)	0 (0)	0 (0)
FXR	1 (0.8)	1 (0.8)	1 (0.8)	0 (0)	2 (1.5)	0 (0)
Immune	4 (3.1)	0 (0)	5 (3.9)	0 (0)	0 (0)	4 (3.1)
Kinase	5 (3.9)	4 (3.1)	9 (6.9)	1 (0.8)	3 (2.3)	1 (0.8)
PDE	1 (0.8)	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)
PGX	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.5)
PPAR	0 (0)	4 (3.1)	4 (3.1)	0 (0)	0 (0)	1 (0.8)
Other	17 (13.1)	4 (3.1)	10 (7.7)	3 (2.3)	1 (0.8)	1 (0.8)

The distribution of 22 Phase 3 trials according to their targets and progression is shown in Table 18. The trials with negative results were observed in FXR, immune, kinase, PPAR and other classes.

**Table 18.** Distribution of 22 Phase 3 clinical trials in ten target classes according to their stages in clinical development. The percentages are shown in brackets.

Target Class	Recruiting	Positive Results	Negative Results	Not Yet Recruiting	Terminated Due to Business Reasons	Completed Results Unknown
Cytokine	2 (9.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Anti-diabetic	1 (4.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Endothelin	0 (0)	1 (4.5)	0 (0)	0 (0)	0 (0)	0 (0)
FXR	0 (0)	1 (4.5)	2 (9.1)	0 (0)	0 (0)	0 (0)
Immune	1 (4.5)	0 (0)	2 (9.1)	0 (0)	0 (0)	1 (4.5)
Kinase	1 (4.5)	0 (0)	1 (4.5)	0 (0)	0 (0)	0 (0)
PDE	0 (0)	1 (4.5)	0 (0)	0 (0)	0 (0)	0 (0)
PGX	1 (4.5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4.5)
PPAR	2 (9.1)	0 (0)	1 (4.5)	0 (0)	0 (0)	0 (0)
Other	1 (4.5)	0 (0)	2 (9.1)	0 (0)	0 (0)	0 (0)

The distribution of 3 Phase 4 trials according to their targets and progression is shown in Table 19. As mentioned above, a Phase 4 trial with the PDE-inhibitor pentoxifylline was completed but the results have not been posted. PPAR agonist lobeglitazone gave a positive result but rosiglitazone was terminated due to discontinuation of the drug.

**Table 19.** Distribution of 3 Phase 4 clinical trials in ten target classes according to their stages in clinical development. The percentages are shown in brackets.

Target Class	Recruiting	Positive Results	Negative Results	Not Yet Recruiting	Terminated Due to Business Reasons	Completed Results Unknown
Cytokine	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Anti-diabetic	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Endothelin	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
FXR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Immune	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Kinase	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PDE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33.3)
PGX	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PPAR	0 (0)	1 (33.3)	0 (0)	0 (0)	1 (33.3)	0 (0)
Other	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

## 6. Discussion

The search for novel anti-fibrotic drugs has been underway for decades. The anti-fibrotic drug discovery field has two major impetuses: (1) Fibrotic diseases can cause significant morbidity, mortality and burden on patients and healthcare systems, and the patient numbers are significant. The numbers are suggested to increase because of COVID-

19 infections and increased prevalence of metabolic diseases. (2) The market size is significantly large: the anti-fibrotic drug market is estimated to have reached \$30B per annum. Despite these significant demands from the markets, patients and the healthcare providers, the number of approved anti-fibrotic drugs are limited in number, safety and efficacy, suggesting a slow pace of drug discovery in this field. We therefore reviewed and analyzed the current landscape of drugs being developed in five major fibrotic diseases with the aim of finding and exploring trends and raising questions for the possible reasons for the slow pace. Although there have been previous reviews on anti-fibrotic drug development in individual fibrotic diseases such as lung [159], liver [160,161], kidney [162], heart [163] and skin [164], the reviews of all major fibrotic diseases have been limited [165–167]. To our knowledge this is the first study that compares the clinical trial activity in different diseases and target classes and analyses attrition rates.

The analysis of 172 clinical trials identified in this study revealed that the majority of the studies are currently focusing on lung and liver fibrosis with less focus on skin, heart and kidney. The numbers of clinical trials in liver fibrosis might be skewed because of drugs for metabolic diseases such as PPAR agonists and anti-diabetic drugs being included. Nevertheless, this trend may be the result of previous success, particularly in lung fibrosis, which may have given impetus and clinical trial experience to that particular field. It is envisaged that the recent success with resmetirom will give a similar boost to the liver fibrosis field.

Our analysis also revealed that there was a steep decline in the number of trials from Phase 2 (130) to Phase 3 (22) in all five fibrotic diseases. This suggests attrition of candidate molecules in Phase 2 trials at a rate of ~83%. Similarly, the proportion of Phase 2 studies with positive results is 18%, suggesting an 82% attrition rate. Such high rates are not unexpected since attrition rates as high as 70–80% in Phase 2 is common across all therapeutic areas, although there have been some improvements in recent years [168,169]. Whether an 83% attrition rate at Phase 2 is higher than the industry norm would require more in-depth analysis. However, we think it is safe to conclude that the fibrosis field does suffer from a high attrition rate in Phase 2.

When we analyzed the attrition rates according to the organs, the number of Phase 2 trials with positive results were higher than those with negative results, in skin fibrosis only. This suggests that the trend of high attrition may not be uniform across diseases. When the attrition rates were analyzed against the target classes, no target class had a higher number of trials with positive results than those with negative results, suggesting that a target class cannot be singled out with our analysis.

High attrition in Phase 2 has been attributed to lack of efficacy, poor safety and poor commercial viability [170]. In our analysis, several of the Phase 2 studies with negative results stated that the primary endpoint of the study was not reached, while the candidate molecule was well tolerated by the patients, suggesting that the main driver in Phase 2 attrition in fibrosis field is the lack of efficacy.

The lack of efficacy in Phase 2 trials in the fibrosis field is a known and recognized problem [171–173]. This has been partly attributed to the timing of the treatment. The pathology of fibrosis is unique as it gives only a narrow window of opportunity for intervention. During the inflammatory phase the repetitive injury triggers inflammation which activates pro-fibrotic elements that lead to transformation of fibroblasts and other cells to myofibroblasts. Once the myofibroblasts have terminally differentiated and the ECM proteins are produced and deposited, the tissue injury becomes irreversible [174–176]. In hypertrophic scars it is possible to know the time of the injury, allowing intervention with anti-fibrotic treatment before the ECMs are deposited, and this results in less scarring [177]. It has been suggested that early diagnosis and intervention with anti-fibrotic drugs pirfenidone and nintedanib may result in improving outcomes in IPF [178]. Similarly in liver fibrosis, since early diagnosis and intervention is known to deliver better outcomes, population screening has been suggested [179]. In heart fibrosis, early identification and treatment of patients with HFpEF has been suggested to be important for achieving optimal outcomes [180]. It would be interesting to see whether the efficacy of new anti-fibrotic drug resmetirom would differ between early- and late-stage liver disease. Additional evidence to support the notion that early intervention can prevent fibrosis comes from studies we have conducted in Peyronie's disease (PD). PD is a fibrotic disease of the penis and can cause penile curvature, pain during erection and erectile dysfunction. The acute (inflammatory) phase of PD can last up to 6 months and usually presents with pain during erection. After the acute phase, pain subsides, and the chronic phase begins. Studies have shown that when treatment was given during the acute phase, before the fibrotic plaque was established, significant clinical improvement was observed [181]. For example, tamoxifen treatment or a combination of tamoxifen with a PDE5 inhibitor could prevent new fibrosis formation and negated the need for surgery [182–184]. When treatment was given during the chronic phase, however, there was no improvement [185]. These studies suggest that the design of the clinical trial, the correct patient inclusion and exclusion and timing of the treatment are of paramount importance.

To differentiate patients by early vs late fibrosis, clinical signs, symptoms and biomarkers that can differentiate the stages of fibrotic diseases are needed. As in the example of PD given above, the clinical symptom of pain, and a non-invasive easy way of measuring penile curvature, or penile ultrasound are ideal biomarkers for disease staging. However, this becomes more complicated in major fibrotic diseases as it becomes more difficult to diagnose fibrosis per se. For example, in liver fibrosis non-invasive clinical trial endpoints that are consistent for both Phase 2 and Phase 3 are still needed [172,186]. In cardiac fibrosis, again non-invasive biomarkers for fibrosis are needed, as endomyocardial biopsy, which is the gold standard for the diagnosis of myocardial fibrosis, has limitations in terms of clinical application [187].

Apart from study design and timing of the treatment, another factor that may be contributing to Phase 2 attrition is suggested to be the compensatory mechanisms in fibrosis. Fibrosis is fundamentally aberrant wound healing which has high levels of redundancy and compensatory mechanisms [188]. When a single target/pathway is inhibited, another pathway can take over/compensate for the loss of function. Therefore, one may need to target several pathways to achieve a meaningful functional response. This may be one of the reasons why we are seeing an increase in the combination of multiple drug candidates, in order to target different pathways, in the fibrosis field [189]. Another potential solution to this problem is the discovery of candidate molecules using a phenotypic approach rather than a target-based approach. Although historically older than the target-based approach, phenotypic drug discovery has recently re-emerged and has been shown to be more efficient in discovering first-in-class drugs than the target-based approach [190]. With the phenotypic approach, molecules are selected based on their action on a disease-associated phenotype rather than a single molecular target. This approach is target-agnostic and pathway-unbiased, making it a perfect alternative approach in the fibrosis field. There have been several compound screening campaigns using this approach for hypertrophic scars [191], lung [192], liver [193], kidney [194] & heart [195] fibrosis, and PD [196]. The drug combination (tamoxifen + PDE5 inhibitor) which was discovered through a phenotypic approach has been successfully translated into clinical outcomes in PD as mentioned above [182–184]. Further studies would be required to see whether other molecules that are identified using the phenotypic approach would find utility in the clinics.

### *Limitations*

Despite our best efforts to capture all the clinical trials in five major fibrotic diseases, it is possible that we may have missed some. This should not count as ignoring or dismissing any study in the field. We recognize and acknowledge that the field is active, and trials may have started or concluded while this manuscript was being prepared.

## **7. Conclusions**

Our analysis of the clinical trials in five major fibrotic diseases have revealed that the drug discovery and development activities in the field are focused on lung and liver, are slow paced and have high attrition in Phase 2. Better clinical trial design with better disease staging biomarkers and a phenotypic approach rather than a target-based approach are suggested to be potential solutions. To our knowledge, this is the first study that has estimated an 83% attrition rate in Phase 2 studies for major fibrotic diseases.

### **Author Contributions**

Conceptualization, A.R.L. and S.C.; Methodology, A.R.L. and S.C.; Investigation and Data Curation, D.S., D.C.S. and S.C.; Writing—Original Draft Preparation, S.C.; Writing—Review & Editing, A.R.L., S.L.H., K.M.F., D.S., D.C.S., S.C.; Supervision, A.R.L.

### **Ethics Statement**

Not applicable.

### **Informed Consent Statement**

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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