Novel Therapeutics for Fibrotic Disease: Has Their Time Finally Arrived?

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The contents of this presentation are not meant to be comprehensive, but to encourage a spirited dialogue. Feedback, comments and corrections are welcome.
Nearly 50% of All Deaths in the Developed World are Associated with Some Type of Chronic Fibroproliferative Disease

- Fibrosis—the accumulation of extracellular matrix components in organs or tissues—is a leading cause of morbidity and mortality worldwide.
- Fibrosis alters the architecture of organs and tissues, thereby disrupting normal function.
- Fibrosis can affect almost any organ or tissue and is associated with a wide variety of diseases and injuries.
- Despite the high prevalence of fibrosis and its enormous impact on human health, there are currently no FDA-approved agents that can prevent, arrest, or reverse fibrosis.

Fibrosis Offers Large Patient Populations with High Unmet Need, However...

♦ Fibrosis has historically not been covered by Pharma.

♦ Fibrosis spans multiple organs and tissues and does not necessarily fit neatly into any single therapeutic category.

♦ Fibrosis often progresses very slowly necessitating long clinical trials.

♦ The natural history of fibrosis is often heterogeneous and difficult to predict necessitating large clinical trials.

♦ Most fibrotic indications currently lack non-invasive clinical endpoints.

♦ A fundamental challenge in the development of an antifibrotic agent is that extracellular matrix synthesis is not an aberrant process.
Bristol-Myers Squibb to Acquire Amira Pharmaceuticals – Acquisition Marks BMS's Entrance into Fibrotic Diseases

Jul 21, 2011

Bristol-Myers Squibb Company (NYSE:BMY) and Amira Pharmaceuticals, Inc., announced today that the companies have signed a definitive agreement under which Bristol-Myers Squibb will acquire privately held Amira Pharmaceuticals, a small-molecule pharmaceutical company focused on the discovery and early development of new drugs to treat inflammatory and fibrotic diseases.

Under the terms of the agreement, Bristol-Myers Squibb will acquire all of Amira Pharmaceuticals' issued and outstanding shares of capital stock and stock equivalents in an all-cash transaction for a purchase price of $325 million upfront and potential additional milestone payments totaling $150 million. Bristol-Myers Squibb will secure Amira Pharmaceuticals' fibrosis program, including the lead asset AM152, an orally available lysophosphatidic acid 1 (LPA1) receptor antagonist which has completed Phase I clinical studies and is now poised for Phase IIa proof-of-confidence studies for the treatment of idiopathic pulmonary fibrosis (IPF) and systemic sclerosis (SSc), or scleroderma. Bristol-Myers Squibb will also obtain Amira Pharmaceuticals' preclinical autotaxin program, which may be useful in the treatment of neuropathic pain and cancer metastases. Bristol-Myers Squibb plans to retain Amira Pharmaceuticals' scientists who work on both of these programs and they will remain located in San Diego.

"As part of the continued execution of our focused BioPharma strategy, Bristol-Myers Squibb has identified fibrotic diseases as an area of high unmet medical need that complements our research efforts in several of our therapeutic areas," said Elliott Sigal, executive vice president, chief scientific officer and president, Research and Development, Bristol-Myers Squibb.

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Source: www.bms.com
Biogen Idec to Acquire Stromedix – Stromedix Brings Highly Differentiated Candidate for Treatment of Fibrosis

Feb. 14, 2012

Biogen Idec and Stromedix, Inc. today announced that they have entered into a definitive agreement under which Biogen Idec will acquire Stromedix Inc., a privately held biotechnology company focused on innovative therapies for fibrosis and organ failure.

Stromedix’s lead candidate, STX-100, is a novel humanized monoclonal antibody that selectively disrupts the TGF-β pathway, which plays a central role in fibrotic disease. STX-100 exhibited significant anti-fibrotic activity in preclinical animal models of fibrotic disease and demonstrated an attractive safety and tolerability profile in a Phase 1 trial. Stromedix has also identified a series of clinical biomarkers that reflects the biological activity of STX-100. STX-100 is entering a Phase 2 trial in patients with idiopathic pulmonary fibrosis (IPF). STX-100 has potential in several additional fibrotic indications given its selective mechanism of action.

“Fibrotic organ failure, and in particular IPF, is a terrible disease with a high mortality rate, and there are no effective treatments at this time,” said Douglas E. Williams, EVP, R&D of Biogen Idec. “With a well-established understanding of the fundamental biology and tremendous unmet medical need, fibrosis is one of the most exciting and dynamic areas of drug development today,” said Michael Gilman, Ph.D., Founder and CEO of Stromedix.

Source: www.biogenidec.com
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Biogen Idec will make an upfront cash payment of $75 million and additional contingent value payments of up to $487.5 million based on the achievement of certain development and approval milestones across multiple indications.
Gilead Sciences to Acquire Arresto BioSciences – Deal Adds Pipeline Candidates for Fibrotic Diseases

December 20, 2010

Gilead Sciences, Inc. and Arresto Biosciences, Inc., a privately-held, development-stage biotechnology company focused on medicines to treat fibrotic diseases and cancer, today announced the signing of a definitive agreement pursuant to which Gilead will acquire Arresto. Under the terms of the agreement, Gilead will acquire Arresto for $225 million and potential future payments based on achievement of certain sales levels. Gilead anticipates that the deal would close in the first quarter of 2011, subject to satisfaction of certain closing conditions, and plans to finance the acquisition through available cash on hand.

Arresto develops medicines that target enzymes involved in the synthesis of the extracellular matrix, which appear to play a role in the etiology of a variety of fibrotic diseases and cancer. The company’s lead product is AB0024, a humanized monoclonal antibody (mAb) targeting the human lysyl oxidase-like-2 (LOXL2) protein. The company recently initiated a Phase I study evaluating AB0024 in patients with idiopathic pulmonary fibrosis (IPF). A Phase I study of AB0024 in patients with advanced solid tumors is also ongoing.

“Arresto's research and development expertise is well aligned with Gilead's areas of focus, including our ongoing clinical program for ambrisentan in IPF,” said Norbert W. Bischofberger, PhD, Gilead’s Executive Vice President, Research and Development and Chief Scientific Officer. “We look forward to working with the team from Arresto to advance the development of novel therapies for serious fibrotic diseases and explore their potential for the treatment of tumors.”
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Gilead paid $225 million in upfront cash primarily for AB0024 (now GS6624), which was in Phase I trials for IPF and advanced solid tumors.

“Arresto’s research and development expertise is well aligned with Gilead’s areas of focus, including our ongoing clinical program for ambrisentan in IPF,” said Norbert W. Bischofberger, PhD, Gilead’s Executive Vice President, Research and Development and Chief Scientific Officer. “We look forward to working with the team from Arresto to advance the development of novel therapies for serious fibrotic diseases and explore their potential for the treatment of tumors.”

Source: www.gilead.com/pr_1509319
Pfizer to Acquire Excaliard – *Lead Program Includes Novel Compound for Prevention/Treatment of Skin Scarring*

November 22, 2011

Pfizer Inc.(NYSE: PFE) and Excaliard Pharmaceuticals, Inc. announced today that they have entered into a definitive agreement under which Pfizer will acquire Excaliard, a privately owned biopharmaceutical company focused on developing novel drugs for the treatment of skin fibrosis, more commonly referred to as skin scarring. The acquisition is expected to close before the end of the year.

Excaliard’s lead product, EXC 001, an antisense oligonucleotide in phase 2, is designed to interrupt the process of fibrosis by inhibiting expression of connective tissue growth factor (CTGF). CTGF is a growth factor that can be over expressed in damaged skin or tissue following surgery or traumatic injury and lead to disfiguring skin scarring. The phase 2 program for EXC 001 has thus far produced positive clinical results in reducing scar severity. Upon completion of the acquisition, Pfizer plans to continue development of EXC 001 to address unmet medical needs in patient groups who suffer from excessive skin scarring.

“The acquisition of Excaliard is part of our corporate research and development strategy to actively complement our robust internal project pipeline with innovative and differentiated drugs from biotech partners,” said Mikael Dolsten, president, Worldwide Research and Development, Pfizer.
Sanofi and GSK have Both Recently Established Research Units Focused Specifically on Fibrosis

♦ Fibrosis and Wound Repair was one of the five Therapeutic Strategy Units (TSU) created as part of Sanofi’s new R&D model.
  • By studying the mechanisms that trigger the development of tissue fibrosis, Sanofi strives to produce innovative new agents to treat and/or prevent fibrosis and preserve organ function. Potential indications include pulmonary fibrosis, primary biliary cirrhosis, liver fibrosis, healing phenomena and wound repair. Existing alliances and partnerships include Regeneron, Regulus, KaloBios, Harvard, MIT, Stonybrook and Scripps.

♦ GSK recently established a Fibrosis Drug Performance Unit (DPU).
  • The Fibrosis DPU is focused on the delivery of new medicines for lung fibrosis (e.g. Idiopathic Pulmonary Fibrosis), hepatic and renal fibrosis (all causes), and skin fibrosis including abnormal scarring conditions of the skin. Central to our strategy is a close collaboration with a network of academic experts in the UK and beyond who closely participate in strategy and drug development.

Source: Sanofi partnering brochure 2010; www.burrillreport.com
What Recent Discoveries, Innovations, or Other Events Have Piqued Pharma’s Interest in Fibrosis?

♦ **COMMERCIAL:** has Pharma simply been forced to look outside its traditional therapeutic categories for novel indications which don’t have competition from generic products?

♦ **EPIDEMIOLOGY:** has Pharma simply begun to appreciate the fact that fibrotic diseases represent a huge patient population with a high level of unmet need?

♦ **SCIENTIFIC:** has our understanding of the biology of fibrosis improved sufficiently to justify investment in this area now?

♦ **CLINICAL:** has the clinical and/or regulatory environment changed such that clinical trials of an antifibrotic agent are now feasible?
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Fibrosis Affects Most Organs and Tissues and is a Leading Cause of Morbidity and Mortality

**LIVER**
- NASH
- Congenital hepatic fibrosis
- Alcoholic liver disease
- HCV/HBV
- Primary sclerosing cholangitis
- Idiopathic portal HTN
- Autoimmune hepatitis
- Primary biliary cirrhosis

**EYES**
- Dry eye
- Diabetic macular edema
- Diabetic retinopathy
- Glaucoma
- AMD

**LUNG**
- Asthma
- Cystic fibrosis
- IPF
- COPD
- Pulmonary arterial HTN
- ARDS

**HEART**
- Congestive heart failure
- Atherosclerosis
- Endomyocardial fibrosis
- Myocardial infarction

**KIDNEY**
- FSGS
- IgA nephropathy
- Transplant nephropathy
- Diabetic nephropathy
- Lupus nephritis

**SKIN**
- Scleroderma
- Keloids
- Hypertrophic scars
- Eosinophilic fasciitis
- Dermatomyositis

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Fibrosis Insight Briefing
### Fibrotic Diseases Include Many Indications with Large Patient Populations and High Levels of Unmet Need

<table>
<thead>
<tr>
<th>Indication</th>
<th>Population Size</th>
<th>Current Treatment</th>
<th>Unmet Need</th>
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<tbody>
<tr>
<td>Hepatitis C</td>
<td>HCV affects 1-2% of the US population (5.3 million).</td>
<td>Interferon, anti-virals.</td>
<td>10–30% will eventually develop hepatic cirrhosis and these pts have a 20 fold increased risk of HCC.</td>
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<tr>
<td>Nonalchoholic Steatohepatitis (NASH)</td>
<td>Liver biopsy is required to make a definitive diagnosis of NASH; estimates from biopsy series indicate the US prevalence of NASH is ~3-5% (~12 million).</td>
<td>No therapy of proven benefit for NASH; modification of risk factors (e.g. obesity, hyperlipidemia, diabetes) is recommended.</td>
<td>Up to 15% of people with NASH will develop cirrhosis; incidence of HCC at 5 years may be as high as 15%.</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>20-30% of all diabetics will develop nephropathy (~5.2 million in the US).</td>
<td>Strict glycemic control; antihypertensive therapy with ACE inhibitors and ARBs.</td>
<td>Current treatments may slow disease progression but unmet need remains for a drug that can halt or reverse disease progression.</td>
</tr>
<tr>
<td>Heart failure</td>
<td>In developed countries, ~2% of adults suffer from heart failure and 6–10% of adults over 65 (~6 million in US).</td>
<td>Lifestyle modifications; pharmacotherapy; surgery; medical devices; transplant.</td>
<td>Average survival after hospitalization for a first episode of HF remains poor (e.g. in Scotland in 2002 the median survival was 2.3 years in men and 1.7 years in women).</td>
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Source: UpToDate
### Fibrotic Diseases Also Include *Orphan Indications* with a High Level of Unmet Need

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<td>IPF</td>
<td>100,000 IPF pts in US; 30,000 new cases/year.</td>
<td>None in the US. Pirfenidone in EU and Japan.</td>
<td>Median survival is 2-3 years; 5-year mortality rate 50%-70%.</td>
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<tr>
<td>Systemic Sclerosis</td>
<td>SSC prevalence estimated at 65,000 in US, of which ~70% have pulmonary involvement (PAH and/or ILD).</td>
<td>No curative therapy short of lung transplantation.</td>
<td>42% pts with SSc ILD will die within 10 years.</td>
</tr>
<tr>
<td>IgA Nephropathy</td>
<td>~2500 new cases/year in the US.</td>
<td>No FDA approved drugs but a number of treatments are used off-label (ACEIs, ARBs, immunosuppressive therapy).</td>
<td>Up to 50% may progress to ESRD, but often takes 20-25 years.</td>
</tr>
<tr>
<td>Chronic renal allograft nephropathy</td>
<td>The exact incidence of chronic renal allograft nephropathy is unknown, but over 17,000 kidney transplants were performed in 2008 (US).</td>
<td>Treatment is limited to modifications of immunosuppressive regimens (i.e. calcineurin inhibitor sparing) and aggressive control of blood pressure and hyperlipidemia.</td>
<td>Renal allograft failure is one of the most common causes of end-stage renal disease accounting for 25-30% of patients awaiting renal transplantation.</td>
</tr>
</tbody>
</table>

Source: UpToDate
A Major Obstacle to the Development of Antifibrotic Agents has been the Lack of Non-Invasive Clinical Endpoints

♦ A major difficulty in developing antifibrotic therapies is the lack of accurate and established techniques to estimate fibrosis regression in response to therapy.

♦ Biopsy is currently the gold standard for assessing fibrosis, but has several limitations:
  • Biopsy is an invasive technique; for example, 20% of liver biopsy patients experience pain and 0.5% experience major complications such as bleeding or hemobilia.
  • Biopsy is prone to sampling variability due to the small size of the biopsy.
  • Interpretation of results are subject to inter- and intra-observer variation.

♦ An important goal for researchers studying fibrosis is the development of noninvasive techniques to measure fibrosis.
  • Promising candidates for liver fibrosis include serum markers (e.g. Fibrotest) and imaging based on ultrasound (e.g. FibroScan), CT, and MRI.

♦ Kinemed is developing quantitative methods for measuring changes in tissue collagen synthesis and breakdown.

♦ Epistem and GSK recently announced a three-year collaboration to identify key biomarkers of fibrotic disease.

♦ BG Medicine has developed a blood test for the pro-fibrotic molecule galectin-3 (i.e. the BGM Galectin-3 test for heart failure).

What Recent Discoveries, Innovations, or Other Events Have Piqued Pharma’s Interest in Fibrosis?

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♦ CLINICAL: has the clinical and/or regulatory environment changed such that clinical trials of an antifibrotic agent are now feasible?
Fibrosis Results from a Wound-Healing Response to Acute or Chronic Injury

1 Injury
2 Platelet activation and fibrin clot formation
3 Inflammation and migration
4 Angiogenesis and myofibroblast proliferation and activation
5 Wound contraction and re-epithelialization
6 Regeneration of damaged tissues

Myofibroblasts are the Primary Source of Collagen and the Key Cellular Mediators of Fibrosis

- Myofibroblasts are derived from at least three sources:
  - Expansion and activation of resident tissue fibroblasts.
  - Epithelial and/or endothelial mesenchymal transition (EMT/EdMT).
  - Tissue migration of bone marrow-derived circulating fibrocytes.
- Myofibroblasts are activated by a variety of mechanisms, including:
  - Paracrine signals derived from lymphocytes and macrophages (e.g. TGFβ, CTGF, IL-13 and PDGF).
  - Autocrine factors secreted by myofibroblasts (e.g. TGFβ).
  - Pathogen-associated molecular patterns (PAMPS) produced by pathogens that interact with pattern recognition receptors (i.e. TLRs) on fibroblasts.
- Intrinsic changes in the activation status of epithelial cells and fibroblasts can promote growth factor–independent fibrosis.
  - For example, Wnt–β-catenin signaling is constitutively active in some ATII epithelial cells in IPF patients and mice with bleomycin-induced pulmonary fibrosis.

Interventions Aimed at Multiple Points of Attack Could Potentially be Antifibrotic

♦ Eliminate the cause(s) of injury and their mediators:
  • Control of the underlying etiology is the most effective antifibrotic treatment.

♦ Reduce inflammation and the immune response:
  • Persistent inflammation may precede or accompany fibrosis and drugs that target inflammation (i.e. steroids) can have antifibrotic effects.
  • However, fibrosis develops despite steroid treatment in many patients.
  • Moreover, some fibrotic diseases (i.e. IPF) appear to be driven primarily by inflammation-independent mechanisms.

♦ Reduce fibrogenesis by inhibiting matrix synthesis:
  • TGF-β1 is the most potent inducer of collagen I and other matrix components.
  • Connective tissue growth factor (CTGF) is another potent fibrogenic signal.

♦ Reverse fibrosis by:
  • Increasing matrix degradation by activating endogenous matrix-degrading enzymes (e.g. MMPs) or administering such enzymes using gene therapy.
  • Stimulating apoptosis of stellate cells; clearance by apoptosis is one of the key features of the liver’s endogenous response to scar removal.
  • BM or cell transplantation; BMCs may degrade liver matrix by increasing MMP expression of MMPs.
Fresolimumab (Genzyme/Sanofi) – a Human Monoclonal Antibody that Inactivates All Forms of TGF-β

♦ TGF-β is a pleiotropic cytokine that affects cell proliferation, differentiation, and apoptosis and is involved in a multitude of homeostatic functions.

♦ TGF-β is also a master regulator of fibrosis:
  • Stimulates fibroblast proliferation.
  • Stimulates conversion of fibroblasts to myofibroblasts which produce collagen.
  • Induces expression of ECM genes.
  • Inhibits metalloproteinase expression.
  • May also induce EMT.

♦ TGF-β gain of function mice develop progressive fibrosis resembling systemic sclerosis.

♦ Fresolimumab is a human monoclonal antibody that inactivates all forms of TGF-β.

♦ In Phase I trials, fresolimumab was safe and well tolerated in patients with primary focal segmental glomerulosclerosis, IPF, and renal cancer.

♦ According to Adis, fresolimumab has entered Phase 2 trials for fibrosis in the US.

FG 3019 (Fibrogen) – a Fully Human Monoclonal Antibody Targeting Connective Tissue Growth Factor (CTGF)

- CTGF is a downstream mediator of TGF-β which stimulates matrix production by fibroblasts and myofibroblast differentiation.
- CTGF is induced by TGF-β, angiotensin II, endothelin, thrombin, AGE, and oxidative stress.
- CTGF is over-expressed in patients with diabetic nephropathy, chronic allograft nephropathy, scleroderma, lung fibrosis and hepatic fibrosis.
- FG 3019 inhibits fibrosis in animal models of diabetes, kidney fibrosis, and radiation-induced pulmonary fibrosis.
- Phase II trials of FG 3019 for patients with liver fibrosis (due to chronic hepatitis B infection) and IPF are currently underway.
- A Phase II trial in patients with diabetic nephropathy was terminated in January, 2011, as was a Phase I trial in patients with glomerulonephritis (2009).

Source: www.fibrogen.com/CTGF_Biology
FibroGen Recently Announced Promising Preliminary Data from an Open-label Phase 2 Study of FG-3019 in Patients with IPF

♦ **May 3, 2012** – Combined 6-month preliminary pulmonary function and HRCT data are available for over half of the patients (N = 54) who remain in the study.

♦ Key preliminary findings from the first dose group include:
  - Disease severity at baseline, measured as the FVC percent predicted, ranged from 42.5-86.0%, with a median of 63%. These data suggest that patients enrolled in the FibroGen trial on average have greater disease severity than those enrolled in several recent IPF clinical trials with other experimental therapies.
  - A substantial proportion of the patients who entered the trial with FVC percent predicted values above the median (i.e., > 63%) are experiencing stable disease or improvement in pulmonary function, as evidenced by increasing or stable FVC measurements during the study and comparable effects on FVC percent predicted values over the same period.
  - Computer-generated HRCT data suggest that patients who entered the trial with disease severity above the median exhibit, on average, an improvement in lung fibrosis compared to baseline in two different measures of the extent of tissue scarring in the lung.

♦ Based on these preliminary results, FibroGen plans to expand the ongoing open-label Phase 2 study:
  - A second, higher dose group will be added as higher doses of FG-3019 appear to be associated with a more robust biological and clinical response.
  - Patients in the first dose group who are exhibiting stable or improved lung function will have the option of continuing FG-3019 treatment for another year to determine whether maintenance of lung function continues.

Source: Biospace.com
EXC 001 (Pfizer) – an Antisense Oligonucleotide Targeting Connective Tissue Growth Factor (CTGF)

♦ EXC 001 is an antisense oligonucleotide which targets connective tissue growth factor (CTGF), a gene known to be over-expressed in damaged skin or tissue following a traumatic event.

♦ Pfizer is developing EXC 001 for the treatment of fibrotic diseases including scarring.

♦ EXC 001 (intradermal injection) is in Phase II development for the reduction of skin scarring in the US.

♦ EXC 001 was initially being developed by Excaliard Pharmaceuticals, but Excaliard was acquired by Pfizer in November of 2011 for an undisclosed upfront payment and contingent payments based on clinical milestones.

Source: ADIS R&D Insight
Although Developers have Been Working on TGF-β and CTGF for Years, Little Progress Has Been Made Against These Targets

♦ TGF-β and CTGF are clearly key mediators of fibrosis, but both molecules are also involved in numerous biological processes aside from fibrosis. Therefore, safety and tolerability are key concerns when considering systemic blockade of either molecule.

♦ In Phase I trials, fresolimumab was safe and well tolerated in patients with FSGS, IPF, and renal cancer. Likewise, FG 3019 appears to have been safe and well tolerated in Phase 1 trials.

♦ However, treatment with an anti-TGF-β antibody in a mouse model of myocardial infarction resulted in increased mortality suggesting that systemic blockade of TGF-β might not be a viable antifibrotic strategy.

♦ In addition, trials of FG 3019 have been discontinued in a number of fibrotic indications including diabetic nephropathy and glomerulonephritis.

BMS 986202/AM152 (BMS) – a Lysophosphatidic Acid Receptor (LPAR) Antagonist

- Lysophosphatidic acid (LPA) is a bioactive phospholipid implicated in numerous biological processes including proliferation, survival, motility and differentiation.
- Fibrosis is associated with increased production of LPA and LPAR subtypes in a number of organs.
- Moreover, LPAR deletion or inhibition inhibits fibrosis in animal models of kidney, lung, vascular, and dermal fibrosis.

- AM152 is an oral small-molecule LPA1 receptor antagonist developed by Amira Pharmaceuticals.
- Preclinical data have shown that AM 152 reduces the fibrotic activity of fibroblasts in vitro and reduces fibrosis in numerous animal models (e.g. bleomycin induced pulmonary fibrosis, UUO induced renal fibrosis, systemic sclerosis, scleroderma).
- A Phase I trial was completed in May 2011 and AM 152 was safe and well tolerated at therapeutic doses.
- *Amira Pharmaceuticals was acquired by BMS in July of 2011 for $325 million in upfront cash, plus $150 million in future milestones.*

STX-100 (Biogen) – a Humanized Monoclonal Antibody Targeting Integrin αvβ6

♦ TGF-β is tightly regulated in the lung by the integrin αvβ6.
  • αvβ6 is expressed at low levels on healthy alveolar epithelial cells but is highly induced by lung injury or fibrosis.
  • Inhibition of αvβ6 may allow localized, injury-specific inhibition of TGF-β activation.

♦ STX-100 is a monoclonal antibody targeting integrin αvβ6 which was originally developed by Biogen Idec.
  • STX-100 exhibits significant anti-fibrotic activity in preclinical models of lung, kidney and liver disease and cancer.

♦ Stromedix acquired STX-100 from Biogen and was developing this agent for IPF and tubular atrophy in kidney transplant recipients.
  • STX 100 was granted orphan drug status by the US FDA for the treatment of chronic allograft nephropathy in 2008 and for IPF in 2010.
  • A Phase 2 trial for patients with IPF has begun recruiting.

♦ On February 14, Stromedix was acquired by Biogen for an upfront payment of $75 million with additional contingent value payments of up to $487.5 million.

GS 6624/AB0024 (Gilead) – a Humanized Monoclonal Antibody Targeting Lysyl Oxidase-Like 2 (LOXL2)

- LOXL2 promotes crosslinking of fibrillar collagen, a major component of the ECM.
- LOXL2 is over-expressed in lung tissue of patients with IPF.
- In the bleomycin mouse model of pulmonary fibrosis, treatment with a LOXL2 mAb reduced lung fibrosis, decreased expression of TGF-β, and reduced the number of activated fibroblasts.
- GS 6624 was originally developed by Arresto Biosciences, prior to its acquisition by Gilead.
- Phase II clinical trials in myelofibrosis, pancreatic cancer and colorectal cancer are underway in the US.
- Gilead has initiated a phase I sequential dose-escalation study of GS 6624 in patients with IPF.
- Gilead is planning a phase I/IIa pilot trial to assess the safety and tolerability of GS 6624 in patients with fibrosis of the liver.
- **In December of 2010, Gilead paid $225 million in upfront cash to acquire Arresto Biosciences.**

Source: Nat Med. 2010 Sep;16(9):1009-17.
PRM-151 (Promedior) – Recombinant Human Pentraxin-2/Human Serum Amyloid P

♦ PRM 151 is a recombinant form of Pentraxin-2 (PTX-2), a naturally circulating human protein which can inhibit fibrosis by blocking the differentiation of monocytes into fibrocytes.

♦ Promedior is developing PRM151 for the treatment of fibrotic diseases and tissue remodeling in the eye, lung and kidney.

♦ A subconjunctival formulation is in phase II trials for prevention of scarring following trabeculectomy in patients with glaucoma.

♦ An IV formulation is in Phase I trials for IPF.

PTX-2 simultaneously controls the initiation and progression of fibrosis and promotes healing and resolution. In the presence of PTX-2, recruited monocytes are signaled by the PTX-2 coated cellular debris to differentiate into regulatory macrophages, locally shifting the cellular equilibrium to resolution and healing. The regulatory macrophages secrete IL-10 to inhibit myofibroblast-driven scar tissue production and shift the ratio of TIMP/MMP expression resulting in increased break down of scar tissue.

Source: www.promedior.com; ADIS R&D Insight
Promedior Presented PC Data at ARVO Demonstrating that Pentraxin-2 Suppressed Fibrosis, Neovascularization, and Vascular Leakage

May 7, 2012

In studies presented at the Association for Research in Vision and Ophthalmology (ARVO), the effects of intraocular injections of rPTX-2 on subretinal neovascularization, vascular leakage and collagen deposition were investigated. These studies showed that intraocular injections of rPTX-2 suppressed neovascularization, vascular leak and collagen deposition which correlated with reduced monocyte/macrophage numbers in the retina in animal models of retinal disease.

Further, the studies showed:

- There was a significant and dose dependent reduction in the mean area of neovascularization after injection of 2μg (40%), 5μg (43%) or 20μg (50%) of rPTX-2, but not 0.2μg.
- Compared to eyes injected with vehicle, those injected with rPTX-2 had a significant increase in mRNA of IL-10, which is an anti-inflammatory cytokine produced by regulatory macrophages.
- Mice with ischemia-induced retinal neovascularization treated with rPTX-2 had significantly fewer CXCR4+, CCR2+ and F4/80+ cells in the retina compared to controls, but no difference in CX3CR1+ cells in ischemic retina. This resulted in a substantial increase in the ratio of regulatory (CX3CR1+) to inflammatory (CCR2+) macrophages remaining in the retina, thereby promoting healing.
Galecto Biotech and Galectin Therapeutics are Both Developing Galectin Antagonists for the Treatment of Fibrosis

- Galectins (galactoside binding lectins) are a group of proteins which have been shown to be involved in a number of disease processes.

- Galectin-3 plays key roles in fibrosis:
  - Galectin-3 promotes myofibroblast activation and differentiation and promotes collagen synthesis.
  - Galectin-3 promotes activation of macrophages which in turn cause activation of myofibroblasts.
  - Galectin-3 KO mice develop less severe fibrosis in animal models of liver, renal and pulmonary fibrosis.

- Galectin Therapeutics is developing carbohydrate polymers which inhibit Galectins 1 and 3 for the treatment of fibrosis and cancer.
  - GR-MD-02 is in preclinical development for NASH and post-transplant fibrosis.

- Galecto Biotech was launched in January of 2012.
  - Galecto’s lead compound is TD139, a galectin-3 inhibitor that blocked fibrosis in an animal model of IPF.
  - A clinical trial of TD139 is expected to start in 15 months and a POC trial is within 27 months.

Source: www.galectintherapeutics.com; www.galecto.com; Biocentury January 2, 2012
More Recently Discovered Molecules and Pathways May Provide More Promising Targets for an Antifibrotic Agent

- However, products targeting these newly discovered pathways remain highly risky as they have yet to be tested in proof of concept clinical trials.

- The preclinical data looks very promising, and even more so when it comes from multiple models, but preclinical models of fibrosis are not very predictive of results in humans.

- For example, most of the preclinical data supporting a role for LPA in IPF comes from the bleomycin mouse model of pulmonary fibrosis. However, the belomycin model is primarily an inflammatory model of pulmonary fibrosis while human IPF appears to be driven by inflammation-independent pathways.

- Wound healing is a fundamental biological process involving multiple redundant pathways. Therefore, targeting a single molecule or pathway may not be sufficient to prevent or arrest fibrosis.
Intedanib is an orally active receptor tyrosine kinase (RTK) inhibitor which inhibits kinases involved in both angiogenesis and fibrosis (i.e. VEGFR 1-3, FGFR 1-3 and PDGFR).

Intedanib is in Phase III trials for non-small cell lung cancer, ovarian cancer and IPF.
- Two phase III trials for IPF were initialed in May 2011.
- Both trials will enroll 485 patients and will assess the effect of intedanib on Forced Vital Capacity (FVC) decline over 52 weeks.

Phase II development is underway for a variety of other cancers.

*In the Phase II TOMORROW (To Improve Pulmonary Fibrosis with BIBF 1120) trial, intedanib decreased the annual rate of decline in FVC by 68% compared to placebo in patients with IPF.*
- Intedanib treatment also reduced the incidence of acute exacerbations and produced a small increase in QOL, as measured by SGRQ.
- The most common adverse events included diarrhea, nausea, vomiting, abdominal pain and reversible increases of liver transaminases.

Tanzisertib/JNK CC-930 (Celgene) – an Orally-Administered JNK Inhibitor

- c-Jun N-terminal kinase (JNK) is a member of the MAP kinase family which is involved in the regulation of proliferation, cell death, inflammation and metabolism.
- JNKs are activated in response to stress stimuli such as inflammatory cytokines, bacterial products, oxidative stress and irradiation.
- JNK is also activated by profibrotic mediators including PDGF, TGF-β, and angiotensin II.
- A modestly selective JNK inhibitor has shown efficacy in animal models of renal fibrosis, hepatic fibrosis, and asthma.
- Tanzisertib is an orally active JNK inhibitor which is in phase II development for IPF and discoid lupus erythematosus in North America.
- Tanzisertib has been granted orphan drug status by the FDA for IPF.

SAR156597 (Sanofi) and QAX 576 (Novartis) – Monoclonal Antibodies Targeting IL-4 and IL-13

- IL-4 and IL-13 promote the development of a pro-fibrotic subpopulation of macrophages that secrete TGF-β and other mediators of fibrosis.
- SAR 156597 is a bispecific interleukin 4/interleukin 13 monoclonal antibody being developed by Sanofi for the treatment of IPF.
- SAR156597 is in Phase I development, presumably in France.
- SAR156597 was granted orphan drug status by the US FDA for idiopathic pulmonary fibrosis in September 2011.
- QAX 576 is an anti-interleukin-13 monoclonal antibody.
- Novartis is conducting Phase II trials of QAX 576 in patients with rapidly progressing IPF, eosinophilic oesophagitis and keloids.

Source: J Exp Med. 2011 Jul 4;208(7):1339-50; AdisInsight
Carlumab (Janssen Biotech) – a Monoclonal Antibody Against CC-Chemokine Ligand 2 (CCL2)

♦ By virtue of their effects on inflammatory cells, fibroblasts and endothelial cells, chemokines are essential regulators of fibroproliferative processes in a variety of tissues.
♦ CC chemokines have been implicated in the pathogenesis of pulmonary, renal, and hepatic fibrosis.
♦ Blocking or genetically deleting CCL2 provides significant protection from bleomycin-induced pulmonary fibrosis.
♦ Carlumab is a mAb against CCL2/MCP-1 which is being developed for the treatment of IPF.
♦ Janssen is conducting a Phase II study to evaluate the safety and effectiveness of IV carlumab versus placebo in patients with idiopathic pulmonary fibrosis.

Inhibitors of Receptor Tyrosine Kinases, Map Kinases, Cytokines and Chemokines Might All be Repurposed as Antifibrotic Agents

♦ Broadly acting inhibitors of receptor tyrosine kinases may have a better chance of blocking fibrosis than interventions aimed at individual molecules or pathways. However, safety and tolerability are likely to be an issue with any such broadly acting drugs.

♦ Moreover, the receptor tyrosine kinase inhibitor Gleevec/imatinib did not affect survival or lung function in a randomized, placebo-controlled trial of patients with mild to moderate IPF followed for 96 weeks.

♦ Interventions targeting cytokines and chemokines may have a role in some fibrotic indications. However, targeting a single molecule or pathway may not be sufficient to prevent or arrest fibrosis.

♦ Interventions targeting IL-4/IL-13 failed in asthma, likely because of redundancy in the pathways responsible for inflammation in these patients. As in asthma, there are currently no biomarkers available which would allow clinicians to select individual patients who might benefit most from a given targeted intervention.
MiRNAs are short, single-stranded RNA molecules that regulate gene expression and play a role in disease pathways.

Modulation of miRNAs can affect protein expression of specific miRNA targets.

MicroRNA-21 Promotes Fibrosis of the Kidney by Silencing Metabolic Pathways.

What goes up must come down: the emerging role of microRNA in fibrosis.

MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts

In 2008, Sanofi and Regulus signed a deal to collaborate on four microRNA targets for the treatment of fibrosis.

Regulus received $25 million upfront with the potential for up to $750 million more in milestone payments.
Heart Disease: Fibrosis

Cardiac myocytes are normally surrounded by a fine network of collagen fibers. In response to pathological stress, cardiac fibroblasts and extracellular matrix proteins accumulate disproportionately and excessively. Cardiac fibrosis, which results in stiffening of the ventricular walls, diminished contractility and abnormalities in cardiac conductance, is a common consequence of numerous forms of heart disease, including pathological hypertrophy, volume overload and myocardial infarction. Phenotypically transformed fibroblast-like cells, termed myofibroblasts, are primarily responsible for fibrous tissue formation at the site of infarction. Thus, reversal of this process represents an important therapeutic target in post-MI management and heart failure. Fibrosis is also commonly associated with numerous other tissue disorders, such as liver, kidney and lung disease.

One of miRagen’s lead miRNAs, miR-29, has been shown to regulate multiple components of the fibrotic response.
There are Plenty of Interesting Anti-fibrotic Targets, both Old and New

♦ Developers have been working on TGF-β and CTGF for years, but relatively little progress has been made against these targets.

♦ More recently discovered molecules and pathways may offer more promising antifibrotic targets. However, products targeting these newly discovered pathways remain highly risky as they have yet to be tested in proof of concept clinical trials.

♦ Repurposed anti-inflammatory agents and cancer drugs may be useful for some fibrotic disease. However, not all fibrotic indications are driven by inflammation and one RTKI (Gleevec/imatinib) has already failed to show a benefit in IPF.

♦ Wound healing is a fundamental biological process involving multiple redundant pathways. Therefore, targeting a single molecule or pathway may not be sufficient to prevent or arrest fibrosis.

♦ There is a growing belief that multi-agent combination therapy may be required to successfully treat fibrosis; will fibrosis be like RA or cancer?
What Recent Discoveries, Innovations, or Other Events Have Piqued Pharma’s Interest in Fibrosis?

- COMMERCIAL: has Pharma simply been forced to look outside its traditional therapeutic categories for novel indications which don’t have competition from generic products?

- EPIDEMIOLOGY: has Pharma simply begun to appreciate the fact that fibrotic diseases represent a huge patient population with a high level of unmet?

- SCIENTIFIC: has our understanding of the biology of fibrosis improved sufficiently to justify investment in this area now?

- CLINICAL: has the clinical and/or regulatory environment changed such that clinical trials of an antifibrotic agent are now feasible?
Pirfenidone (InterMune) was the First Antifibrotic Agent to be Approved for Any Fibrotic Disease

♦ Pirfenidone is an orally active, small molecule that inhibits the synthesis of TGF-β, TNF-α, and other mediators of fibrosis and inflammation.

♦ Pirfenidone has antifibrotic activity in animal models of lung, heart, kidney, and liver fibrosis.

♦ Shionogi launched pirfenidone in Japan as Pirespa, in December 2008.

♦ In February 2011, Esbriet/pirfenidone was approved by the European Commission for treatment of patients with IPF, representing the first approval of a treatment for IPF in this region.

♦ **Despite an expert panel voting in favor of its approval, the FDA sent InterMune a complete response letter in 2010 indicating that it wants an additional Phase III trial.**

**FIGURE 3.** Summary of activities observed in animal models and cell-based assays. ECM: extracellular matrix.

Pirfenidone Achieved its Primary Endpoint of Change in Predicted FVC in Only One of Two Pivotal Trials

♦ The CAPACITY program comprised two almost identical double-blind placebo controlled trials assessing the effects of pirfenidone on change in forced vital capacity (FVC) over a 72-week period.

♦ One study (004) was positive and matched the level of benefit observed in two previous Japanese trials (one Phase III, one Phase II).

♦ The other study (006) did not meet the primary endpoint, but positive trends were observed in FVC and a number of secondary end points.

♦ Following discussions with the FDA, InterMune initiated an additional Phase III trial (ASCEND) to enable approval of pirfenidone in the US, again using change in FVC as the primary endpoint.

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Despite having so far failed to gain approval in the US, pirfenidone has helped establish a regulatory path for antifibrotic agents and the treatment of IPF.

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Fibrosis Insight Briefing
Despite Having Only Modest Effects on IPF, Analysts Forecast Sales of Pirfenidone to Reach $1.15 Billion by 2020

**Box 1 | Market for idiopathic pulmonary fibrosis**

Analysing the market for idiopathic pulmonary fibrosis (IPF) is Uma Yasothan, IMS Health, London, UK.

In February 2011, the European Commission approved pirfenidone for use in adults with mild-to-moderate IPF, and the drug is expected to be launched in the European Union (EU) in September 2011. This follows on from its launch in Japan in December 2008. According to data from IMS MIDAS 2011, pirfenidone had sales of US$4.4 million in the year after its launch, and the compound annual growth rate in sales since its launch is an impressive 470%, with total sales of $45 million. However, although it received a vote in favour of approval from a US Food and Drug Administration (FDA) advisory committee in March 2010, the FDA declined approval in May 2010, asking for further data, which is anticipated to come from another Phase III trial that is underway in the United States.

The commercial potential of pirfenidone will be substantial if the benefits that have been observed in Phase III trials translate well to patient outcomes in clinical practice. Pirfenidone has been awarded orphan drug status and has extensive intellectual property protection, which could augment its long-term commercial potential. However, factors that could restrict its uptake include the need for comprehensive monitoring of liver function and dose adjustment in patients with liver complications, allergic reactions such as rash and challenges with reimbursement. Analysts’ peak sales estimates worldwide are in the range of $1.15 billion by 2020, with sales estimates 5 years after launch in the EU of ~$500 million annually.6,9.

Despite Having Only Modest Effects on IPF, Analysts Forecast Sales of Pirfenidone to Reach $1.15 Billion by 2020

InterMune launched pirfenidone in Germany in September 2011. The Institute for Quality and Efficiency in Health Care (IQWiG) initially concluded that no additional benefit is provided by pirfenidone. However, Germany's Federal Joint Committee (G-BA) recently granted the additional benefit. In April, France's Transparency Commission (CT) issued a favorable opinion for reimbursement of pirfenidone.

Idiopathic Pulmonary Fibrosis is Quickly Becoming a Crowded Space in Which to Play!

Undoubtedly, the EMA’s recent approval of pirfenidone has helped to stimulate Pharma’s interest in IPF, but what other factors have convinced Pharma to settle on IPF as the preferred indication for which to develop an antifibrotic agent?
IPF is a Chronic, Progressive, Lung Disease which is Fatal and for which No Treatment has Been Approved in the US

- IPF is a chronic, progressive lung disease characterized by fibrosis of the supporting framework (interstitium) of the lungs.
- The primary symptoms of IPF are exercise-induced breathlessness and chronic dry cough.
- There are no specific laboratory abnormalities in IPF, although routine spirometry reveals decreases in both FVC and FEV1.
- Aside from pirfenidone in the EU and Japan, no other drugs are approved for IPF.
- Therefore, treatment is typically palliative and includes supplemental oxygen and pulmonary rehabilitation.

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Unmet need is extremely high for patients with IPF: median survival is 2-3 years; 5-year mortality rate is 50-70%. In addition, first responders to the World Trade Centers on 9/11 are at increased risk of developing IPF.

Unlike Other Types of Fibrosis, IPF Can be Diagnosed Non-Invasively with High Resolution CT (HRCT)

♦ An important change over the last 5-10 years is that fibrotic lung diseases such as IPF are now more clearly classified and easily recognizable by clinicians.

♦ HRCT is now routinely employed and is the gold standard for diagnosis of IPF.

♦ Diagnostic criteria include the presence of honeycombing and reticular change (UIP pattern), and the absence of any other feature which is characteristic of other interstitial lung diseases.

♦ HRCT is becoming more widely available, cheaper, and easier to read, even for non-radiologist physicians.

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- HRCT is becoming more widely available, cheaper, and easier to read, even for non-radiologist physicians.

The use of HRCT to accurately diagnose IPF was an extremely important advance as IPF was often misdiagnosed in the past. In addition, guidelines established by the American Thoracic Society and European Respiratory Society (ATS/ERS) have enabled standardization of clinical trials.

Progression of IPF Can Also be Assessed Non-Invasively by Measuring Changes in Forced Vital Capacity (FVC)

- Forced vital capacity (FVC) is a standard spirometric measure of pulmonary function.
- Change in serial measures of lung volume (FVC or VC) is a widely accepted reflection of disease progression in patients with IPF and a commonly used primary endpoint in clinical trials.
  - A decline in FVC as small as 2–6% represents a clinically important change.
- Several studies have identified change in percent-predicted FVC as an independent predictor of mortality in patients with IPF.
  - 1-year risk of death was more than two fold higher in patients with a 24-week decline in FVC between 5% and 10%.

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FVC is a reliable, valid, and responsive measure of clinical status in patients with IPF. However, it is currently unclear whether the FDA will approve an IPF drug without a mortality benefit.

Idiopathic Pulmonary Fibrosis is Quickly Becoming a Crowded Space in Which to Play!

Given the limited number of IPF patients available, recruiting for clinical trials is likely to be very competitive in the future. In addition, if pirfenidone is approved by the FDA novel agents may subsequently be compared to pirfenidone instead of placebo in clinical trials.
## Short Term View: What Other Indications Might Provide a Similar Path to Approval for an Antifibrotic Agent?

<table>
<thead>
<tr>
<th>Indication</th>
<th>Population Size</th>
<th>Unmet Need</th>
<th>Endpoints</th>
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<td>Systemic Sclerosis</td>
<td>SSC prevalence estimated at 65,000 in US, of which ~70% have pulmonary involvement (PAH and/or ILD).</td>
<td>No FDA approved drugs. 42% pts with SSc ILD will die within 10 years.</td>
<td>Rodnan skin score; forced vital capacity (FVC)</td>
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<td>IgA Nephropathy</td>
<td>~2500 new cases/year in the US.</td>
<td>No FDA approved drugs. Up to 50% may progress to ESRD, but often takes 20-25 years.</td>
<td>Proteinuria</td>
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<td>Radiation induced fibrosis (prophylaxis)</td>
<td>In pts with lung cancer, clinical pneumonitis occurred in 5-15%, while radiographic abnormalities were present in 66%.</td>
<td>May cause both cosmetic and functional impairment; can lead to death or deterioration in QOL.</td>
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<td>Chronic renal allograft nephropathy</td>
<td>The exact incidence of chronic renal allograft nephropathy is unknown, but over 17,000 kidney transplants were performed in 2008 (US).</td>
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Source: UpToDate
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Additional fibrotic indications may exist that, like IPF, offer orphan status, high unmet need, no FDA approved treatments, and non-invasive clinical endpoints.
Long Term View: What Advances are Required to Facilitate Trials in Indications with Much Larger Patient Populations (e.g. NASH)?

- Liver biopsy
- Serum markers
- Ultrasound (ARFI) and MRI
- Transient elastography
- Metabolic breath tests
- Hepatic venous pressure gradient (HVPG)

Long Term View: What Advances are Required to Facilitate Trials in Indications with Much Larger Patient Populations (e.g. NASH)?

Many simple biomarkers have low accuracy in predicting liver fibrosis while more advanced markers have an unacceptable cost benefit ratio.

Recent data indicate that the results from combination serum tests (e.g. Fibrotest, ELF) may be more accurate than biopsy in predicting risk of decompensation and overall survival.

The clinical acceptance of serum biomarkers is still low in the United States.

Transient elastography (e.g. FibroScan) is the most widely used noninvasive method for assessing the degree of liver fibrosis in Europe. Transient elastography to measure liver stiffness is rapid, noninvasive, reproducible, and acquires information from a much larger portion of the tissue than liver biopsy. Transient elastography best distinguishes between stages at either end of the fibrosis spectrum and its utility is limited in patients with narrow intercostals spaces or morbid obesity.

Long Term View: What Advances are Required to Facilitate Trials in Indications with Much Larger Patient Populations (e.g. NASH)?

Acoustic radiation force impulse (ARFI) imaging has shown excellent diagnostic accuracy in identifying significant fibrosis and cirrhosis in patients with various liver diseases.

Advantages of MRI include assessment of the entire liver parenchyma, lack of an acoustical window requirement, and operator independence.

Long Term View: What Advances are Required to Facilitate Trials in Indications with Much Larger Patient Populations (e.g. NASH)?

Although non-invasive techniques to measure fibrosis are an area of active research, tissue biopsy remains the gold standard for now.

Large Numbers of Patients, High Unmet Need, Interesting Targets and No Competition Make Fibrotic Diseases Very Appealing

- Fibrotic diseases collectively represent a huge patient population with a high level of unmet need. Moreover, numerous fibrotic diseases qualify as orphan diseases raising the prospect of lower clinical development costs and premium pricing.

- There are plenty of interesting anti-fibrotic targets, both old and new, but targeting a single molecule or pathway may not be sufficient to prevent or arrest fibrosis. This begs the question...is fibrosis going to be like RA or oncology?

- EMA approval of pirfenidone has helped to establish a regulatory path for antifibrotic agents in IPF and Pharma appears to have settled on IPF as the best indication for which to develop an antifibrotic agent. As a consequence, IPF is quickly becoming a crowded space in which to play.

- Given the limited number of IPF patients available, recruiting for clinical trials is likely to be very competitive in the future. In addition, if pirfenidone is approved by the FDA novel agents may subsequently be compared to pirfenidone instead of placebo in clinical trials. Therefore, we might soon need to consider fibrotic indications other than IPF.

- Additional fibrotic indications may exist that, like IPF, offer orphan status, high unmet need, no FDA approved treatments, and non-invasive clinical endpoints.

- Until non-invasive techniques to measure fibrosis are developed and validated, clinical trials requiring biopsies will remain difficult and expensive.
Things to Consider if You Have an IPF/Fibrosis Program, or Agents which Might be Repurposed as Antifibrotic Agents

♦ Existing fibrosis programs:
  • What’s the best indication in which to demonstrate POC?
  • What’s the best indication in which to gain regulatory approval?
  • What’s the best compound or intervention for my indication?
  • Will fibrosis be like RA or oncology?

♦ Existing IPF programs:
  • Is IPF the best indication for PoC?
  • If PoC comes later than for other IPF products, does it make sense to continue development for IPF (e.g. in combination?) or can PoC for IPF be extended to other fibrotic indications?
  • What other fibrotic indications should be considered for products currently seeking PoC in IPF?

♦ Agents that might be repurposed as antifibrotic therapies:
  • Which indication is the best fit for my product?
Defined Health: Upcoming Presentations

Cancer Progress by Defined Health

March 2013, New York
Dates to be advised soon!

www.cancerprogressbyDH.com

Therapeutic Insight by Defined Health at BIO-Europe Spring® 2013

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Barcelona, Spain

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