What is Idiopathic Pulmonary Fibrosis?

Idiopathic pulmonary fibrosis (IPF) belongs to the rare group of serious lung diseases collectively called interstitial lung diseases (ILD) characterised by damage to functional parts of the lung such as the alveolar tissue, bronchioles, bronchi and blood vessels. IPF is the most common of ILDs, representing 50% of all fibrotic lung conditions (see below for patient numbers worldwide).

The term ‘idiopathic’ literally means ‘of no known cause’ although it is known that the disease is more common in smokers. IPF results from continued injury to the lung through exposure from irritants, causing dysfunctional inflammation and scarring that does not properly repair but rather produces an environment that promotes persistent and progressive scarring or fibrosis.

This continual fibrosis results in the thickening of the tissue in the lung, impairing breathing and causing an inefficiency in the amount of oxygen being delivered throughout the body. The amount of scar tissue irreversibly increases over time. The lungs of IPF patients become stiff and shrink in size, with patients typically having half the normal lung volume. IPF is commonly fatal.

Symptoms, Diagnosis and Prognosis

Many patients experience no symptoms during the early stages of IPF. The most common indications are shortness of breath or laboured breathing, a persistent cough and a crackling “Velcro-like” sound when breathing.

IPF is often challenging to diagnose, with diagnosis of IPF performed by a multi-disciplinary team consisting of respiratory physicians, radiologists and pathologists. The team reviews the patient’s clinical data including physical examination, lung function tests, blood tests and appearance of the lung in a CT scan (see figure to the right) before reaching a consensus regarding the diagnosis.

The course of the disease varies greatly, ranging from a lengthy progression over several years to an acute exacerbation, rapid decrease in lung function and death.

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Current IPF treatments

- **Pirfenidone**
- **Nintedanib**

### IPF Therapy Sales (US$)

- **Japan**: $47.3m
- **EU**: $190.8m
- **US**: $669.2m

Estimates 2025

- **Japan**: $2.34bn
- **EU**: $824.4m
- **US**: $81.2m

Source: GlobalData IPF Forecast 2016
Current IPF treatment options

The treatment of IPF was greatly improved in 2014 with the United State’s FDA approval of two anti-fibrotic agents — Pirfenidone and Nintedanib. Despite different modes of action, Pirfenidone and Nintedanib are deemed by respiratory clinicians to be equally effective, with both compounds slowing the reduction in lung volume that is characteristic in IPF patients. But these compounds only slow the progression of the disease, they do not act as a cure and cannot halt or reverse the decline in lung function.

Despite their benefits to lung function, Pirfenidone and Nintedanib are also associated with significant side effects. Treatment with Pirfenidone can result in a rash and nausea while also increasing sensitivity to sunlight, making the patient highly prone to sunburn and skin cancer, which is highly relevant in Australia. Nintedanib demonstrated significant gastro-intestinal side effects including nausea and diarrhea.

Developing new IPF therapies

The world urgently needs improved treatment of IPF. A range of agents are currently being developed to combat IPF, targeting various pathways. But as of April 2017 there were no drugs reported to be in Phase III trials for IPF. Summary data for earlier stage studies/trials are detailed in the table (see right) based on publicly available information.

A novel target

Independent studies (Moeller et al, American Journal of Respiratory and Critical Care Medicine, Vol 179, 2009) have shown that chemokine receptor type 4 (CXCR4) positive cells (fibrocytes) can be significantly elevated in IPF patients and are an independent predictor of early mortality. Patients with more than 5% fibrocytes had on average just 7.5 months to live compared to patients with less than 5% fibrocytes who had on average 27 months to live.

AdAlta’s unique approach

AdAlta has developed an i-body (see box below right for further information) called AD-114. AD-114 has been shown to specifically bind to CXCR4. This data has been peer reviewed and published in the Journal of Biological Chemistry (June 2016).

AD-114 binds to the diseased lung tissue from IPF patients but not to normal lung tissue. Extensive pre-clinical experiments have been performed in the lab (in vitro) and in animal models (in vivo), showing dramatic positive effects of AD-114. AD-114 has demonstrated both anti-inflammatory and anti-fibrotic activity in animal models.

CXCR4 is a novel disease target pathway in IPF and AD-114 would be a “first in class” drug for treatment for this “orphan disease” indication. Drugs are recognised by industry participants as “first in class” when, for example, they use a new and unique mechanism of action for treating a medical condition.

Orphan diseases affect up to 200,000 Americans and are often fatal, having few or no drug treatment options. Both classifications offer the potential to positively impact speed to approval, in that the majority of these drugs meet an unmet clinical need. AdAlta was granted orphan status for AD-114 in January 2017.

AdAlta’s AD-114 represents a UNIQUE pathway not currently addressed by approved drugs or those drug candidates in the clinic.

<table>
<thead>
<tr>
<th>Phase I</th>
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<tbody>
<tr>
<td>GlaxoSmithKline (NYSE: GSK)</td>
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<tr>
<td>Various Teva Pharmaceutical Industries Ltd (NYSE:TEVA) candidates</td>
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<tr>
<td>Vicemo Pharma</td>
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</tbody>
</table>
| Other companies with drugs in Phase I include: | • Samumed (SM-04646)  
• ImmuneWorks (IW001)  
• Pacific Therapeutics (PTL202) |

<table>
<thead>
<tr>
<th>Phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Various Bristol Myers Squibb (NYSE: BMY) candidates</td>
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<tr>
<td>Fibrogen Inc (NASDAQ: FGEN) candidates</td>
</tr>
<tr>
<td>Biogen Inc (NASDAQ: BIIB) candidates</td>
</tr>
<tr>
<td>Sanofi (NYSE: SNY) candidates</td>
</tr>
<tr>
<td>Various Hoffmann-La Roche (SIX: ROG) candidates</td>
</tr>
<tr>
<td>ProMetic Life Sciences Inc (TSE: PLI)</td>
</tr>
<tr>
<td>Kadmon Corp LLC (NYSE: KDMN)</td>
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<tr>
<td>Aimmune</td>
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</tbody>
</table>
| Other companies with drugs in Phase II or the intention to commence Phase II studies include: | • Afferent Pharmaceuticals [AF-219]  
• MediciNova Inc (tipelukast)  
• Celgene Corporation (CC-90001)  
• Galapagos (GLPG-1690)  
• Kasiak Research Pvt Ltd (Refacell-IPF) |

What is an i-body?

An i-body is a unique human protein that combines the advantages of small molecules (for stability) and antibodies (with a high affinity and specificity for treating certain illnesses) in one powerful treatment.

The i-body has a unique long loop that can bind to a diverse range of targets meaning that it has wide applicability across many diseases.
AD-114 makes encouraging progress to the clinic

Further Information
The following resources provide further information on IPF:

**Lung Foundation Australia Fact Sheet**

**IPF Registry Information**

**Introduction Video to IPF**
https://www.youtube.com/watch?v=1Kyo9HcyiQ0

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**Key data published in the Journal of Biological Chemistry June 2016**
AD-114 demonstrated to bind to CXCR4 with high affinity and specificity.

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**AD-114 binds more specifically to diseased human IPF tissue than normal lung tissue**

**AD-114 is more effective than existing approved IPF therapies Nintedanib and Pirfenidone**

**In an animal model of IPF, AD-114 significantly reduces key contributors to fibrosis**

**AD-114 was granted US FDA orphan drug status in January 2017**

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**Images of normal and fibrotic lung**

**A. Normal lung tissue**

**B. IPF diseased human lung tissue**

The red arrows left indicate binding of AD-114 to IPF diseased human lung (B) with limited binding to normal lung tissue (A). These studies confirm the significant binding of the i-body to diseased tissue.

**In vitro Migration Assay Results**

<table>
<thead>
<tr>
<th>Test Agent</th>
<th>No effect on normal fibroblasts</th>
<th>Inhibition of IPF progressor fibroblasts</th>
</tr>
</thead>
<tbody>
<tr>
<td>i-body AD-114</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Nintedanib (Boehringer)</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Pirfenidone (Roche)</td>
<td>✓</td>
<td>✗</td>
</tr>
</tbody>
</table>

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**Effect of AD-114 treatment on lung tissue of an IPF mouse model**

**A. Normal lung tissue**

**B. IPF diseased lung tissue**

This picture shows the lungs of a mouse given Bleomycin and then treated with AD-114 daily for 21 days. The lungs are now observed to have a similar architecture to that of the normal lung. AD-114 decreased the total collagen content in the lungs demonstrating the anti-fibrotic effect of the i-body in vivo. It shows very little collagen staining similar to the normal lung tissue as in Figure A.

**C. IPF disease lung tissue treated with AD-114**

In an animal model of IPF, AD-114 significantly reduces key contributors to fibrosis.

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**ADAlta exciting collaboration with The Alfred Hospital, Melbourne**

AdAlta has fostered a highly successful collaboration with The Alfred Hospital and the clinical research team led by Dr Glen Westall, an expert in lung fibrosis and IPF. The partnership provides access to specimens from IPF patients. These samples are a valuable resource to understand the influence of both CXCR4 and AD-114 on fibrosis. This research aims to investigate the mechanism and cell types involved in the anti-fibrotic effects observed upon treatment with AD-114 as well evaluating the potential application of AD-114 for the treatment of IPF.

“We are excited to continue working with AdAlta to further understand this complex fibrotic disease and how the Company’s novel i-body may play a role in the treatment of IPF, for which there is currently no cure.”
Dr Glen Westall, Respiratory Physician at The Alfred hospital.

Dr Glen Westall provides an overview of IPF, current treatments and unmet medical need in the AdAlta Fibrosis Briefing video series available on the AdAlta website www.adalta.com.au.

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**ADAlta signs manufacturing agreement to scale up production of AD-114**

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**First in man Phase I studies**

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**Toxicology studies to demonstrate safety of i-body AD-114**

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**AD-114 demonstrated to bind to CXCR4 with high affinity and specificity.**

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