ASX Announcement

Fibrosis symposium presentation material

MELBOURNE Australia 21st February 2017: AdAlta Limited (ASX: 1AD), the biotechnology company advancing AD-114, its lead i-body candidate for the treatment of idiopathic pulmonary fibrosis (IPF) and other human fibrotic diseases towards clinical development, is pleased to release the material that will be presented in Melbourne today at an R&D briefing meeting on fibrosis for analysts and investors.

Fibrosis accounts for 45% of all diseases globally in the developed world and represents a large unmet medical need.

Speakers and topics on the agenda at the symposium include:

- Dr Robert Peach, Non-Executive Director, AdAlta’s Board, Receptos story – From NZ to the US, a Phase III antibody and an $8B acquisition
- Associate Professor Michael Foley, La Trobe University, AD-114 a novel i-body for the treatment of fibrosis
- Associate Professor Glen Westall, Alfred Hospital, Pulmonary fibrosis – current state of play in Idiopathic Pulmonary Fibrosis (IPF)
- Dr Muh Geot Wong, Kolling Institute Renal fibrosis and chronic kidney disease
- Professor Erica Fletcher, University of Melbourne, eye fibrosis, causes, diseases and treatments
- A closing panel chaired by Stuart Roberts, including Dr Brian Richardson, Dr John Westwick and Dr Robert Peach
- Sam Cobb, CEO of AdAlta will provide an update on company activities

Highlights from the symposium will be made available to shareholders during the coming week.

To find out more about AdAlta, contact Sam Cobb, CEO, Tel: (03) 9479 5159 or email enquiries@adalta.com.au.
Notes to editors

AdAlta Limited (ASX:1AD) is an Australian based drug development company headquartered in Melbourne. The Company is focused on using its proprietary technology platform to generate i-bodies, a new class of protein therapeutics, with applications as therapeutic drugs to treat diseases. AdAlta is developing its lead i-body candidate, AD-114, for the treatment of idiopathic pulmonary fibrosis (IPF) and other human fibrotic diseases, for which current therapies are sub-optimal and there is a high-unmet medical need. AD-114 has strong pre-clinical results for IPF, demonstrating both anti-fibrotic and anti-inflammatory activity in human lung tissue and indicating greater efficacy than existing approved IPF drugs. The i-body is a human analogue of the antigen binding domain of the shark antibody, which combines the advantages of monoclonal antibodies (high target specificity and affinity) with the beneficial stability features of small molecules. In addition to stability, the i-body has a long binding loop that is a feature of shark antibodies not present in either human or next generation antibodies. This feature enables the i-body to recognise and bind to a diverse range of different therapeutically-relevant drug targets, including those that are difficult/intractable to access by current antibody therapies. These include clinically important targets such as G-protein coupled receptors (GPCRs) and ion channels.

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Analyst and investor fibrosis briefing

A new class of protein therapeutics to treat human disease

February 2017
AdAlta’s inaugural investor and analyst briefing aims to educate analysts and investors on our R&D technology platform as it relates to the science and the commercial opportunity to deliver value to shareholders.

AD-114 for idiopathic pulmonary fibrosis remains a core priority for the business.

AdAlta’s focus is the completion of Phase I clinical studies and securing a global licensing deal for our lead i–body candidate.

Additional applications for the i-body platform in a range of other fibrotic diseases will also be discussed in detail.
Analyst & investor fibrosis briefing

- Recent international partnerships and collaborations have independently assessed and validated our technology
- Expert presentation by non-executive Director Dr Robert Peach will outline what it takes to get an antibody to Phase III and an $8B acquisition
- AdAlta Chief Scientific Officer Mick Foley will outline AD-114 data in various therapeutic areas of fibrosis
- Presentations by leading researchers in lung, kidney and eye fibrosis will provide an overview of the clinical and commercial opportunities in this therapeutic area
- AdAlta’s world class SAB John Westwick and Brian Richardson and AdAlta’s non-executive Director Robert Peach will be available to answer specific questions and to discuss what it takes to get a fibrosis drug to the clinic and a deal
## Agenda

<table>
<thead>
<tr>
<th>Speaker</th>
<th>Topic</th>
<th>Details</th>
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<tbody>
<tr>
<td>Robert Peach</td>
<td>From NZ to the US, a Phase III antibody and an $8B acquisition</td>
<td>Robert will discuss the Receptos story and what it takes to get an $8B acquisition</td>
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<tr>
<td>Mick Foley</td>
<td>AD-114 a novel i-body for the treatment of fibrosis</td>
<td>Mick will provide a summary of AD-114 data in therapeutic areas of lung, liver and eye fibrosis</td>
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<tr>
<td>Glen Westall</td>
<td>Pulmonary fibrosis – current state of play in Idiopathic Pulmonary Fibrosis</td>
<td>Glen will discuss what is IPF, how it is diagnosed, what the current treatments and their limitations and the drug development pipeline</td>
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<td>Muh Geot Wong</td>
<td>Renal fibrosis and chronic kidney disease</td>
<td>Muh Geot will discuss what happens with chronic kidney disease, how it is diagnosed, what the current treatments and their limitations and the drug development pipeline</td>
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## Agenda

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<tr>
<td>Erica Fletcher</td>
<td>Eye Fibrosis, causes, diseases and treatments</td>
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<td>Erica will discuss eye fibrosis and the various diseases including wet-AMD, what the current treatments and the drug development pipeline</td>
</tr>
<tr>
<td>PANEL</td>
<td>DISCUSSION: Getting a fibrosis drug to the clinic and a deal</td>
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<td>The panel includes a number of drug development experts who have significant experience taking a drug from the research bench, through the clinic and providing to patients.</td>
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<td>The panel will discuss what it takes to get a fibrosis drug to the clinic.</td>
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<td>They will also discuss what it takes to get a deal with a pharmaceutical company.</td>
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<tr>
<td>Sam Cobb</td>
<td>AdAlta Investor Update</td>
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<td></td>
<td>Sam will provide investors an update on AdAlta’s achievements since the oversubscribed IPO in August and upcoming milestones</td>
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Receptos story – From NZ to the US, a Phase III antibody and an $8B acquisition

Robert Peach
Dr Robert Peach

Dr Peach has over 25 years of drug discovery and development experience in the pharmaceutical and biotechnology industry. In 2009 he co-founded Receptos, becoming Chief Scientific Officer and raising $59M in venture capital and $800M in an IPO and three subsequent follow-on offerings.

In August 2015 Receptos was acquired by Celgene for $7.8B. His extensive drug discovery and development experience in autoimmune and inflammatory diseases, and cancer has resulted in multiple drugs entering clinical trials and 3 registered drugs. He currently serves on the Board of Directors of Innate Immunotherapeutics and Avalia Immunotherapies and is a consultant for several other biotechnology companies.

Robert is the co-author of 70 scientific publications and book chapters, and 17 patents. He was educated at the University of Canterbury and the University of Otago, New Zealand.
Receptos Story – From NZ to the US, and an $8B Acquisition
Robert Peach, Ph.D.
Receptos experience

Starting a biotechnology company in San Diego
  - Licensing assets
  - Raising venture capital
  - Hiring staff and building a productive culture

Ozanimod: a small molecule drug for treating relapsing multiple sclerosis and inflammatory bowel diseases
  - Clinical data
  - Market analyses

Strategies that lead to an $8B acquisition
The Path Towards Receptos – Key Roles

1991-2000  Discovery and development of Orencia and Nulojix at Bristol-Myers Squibb; Seattle and Princeton

2000-2003  Director Antibody Discovery at IDEC. Rituxan (anti-CD20) for autoimmune diseases

2003-2007  Senior Director, Oncology Discovery at merged Biogen Idec. Multiple programs advanced into clinic. In-licensing, acquisition, VC investments

2007-2009  Co-founder and VP Biology at Apoptos. Oncology assets licensed from Burnham Institute

2009-2015  Co-founder and Chief Scientific Officer of Receptos
Receptos Start-Up: 2009

Starting with a failure: Apoptos

Receptos was founded in 2009 with technology licenses from The Scripps Research Institute™

Focus primarily on autoimmune disease drug discovery and development, and a structure-based drug design technology platform

2009: A tough time raising $25M in venture capital
- Venrock, Arch, Lilly, Flagship

$34M in 2010
- Polaris, Venrock, Arch, Lilly, Flagship

20 scientists, 1 business development, 1 accountant, 1 admin
- Deep experience, multiple skill sets, cultural “fit”
- No CEO, CMO, CFO etc
Receptos Location: Torrey Pines Mesa in San Diego
What did we License from Scripps?

- GPCR structural biology technology platform
- Established industry partnerships that raised $20M in non-dilutive capital
- Small molecule compound “hits” identified in a high through-put screen targeting the activation of a protein called sphingosine 1-phosphate 1 receptor (S1P1R)
- Receptor is expressed on lymphocytes and is involved in controlling the trafficking of these cells out of lymphoid tissues
- Biological rationale suggested an ability to impact pathology associated with multiple autoimmune diseases, including multiple sclerosis and inflammatory bowel diseases (ulcerative colitis, Crohn’s disease)
- Clinical proof of concept established for this mechanism of action
Drug Discovery Goals: Best in Class and Rapid Development

- Develop an oral daily pill that could be dosed chronically and had a superior safety profile to “same class” multiple competitor drugs, including Gilenya, that was close to completing clinical development
  - Cardiac toxicity including 1st dose heart rate monitoring
  - Prolonged drug activity
  - Induction of fibrosis
- Rapid preclinical development
  - 1 year to identify clinical candidate
  - 10 months to file an IND (November 2010)
  - Phase 1 SAD/MAD began 1 month after IND approved (January 2011)
Optimal potency, selectivity, oral bioavailability, absorption, distribution, metabolism, excretion, toxicity, pharmacokinetic and pharmacodynamic properties
RADIANCE Phase 2/3 Trial Overview
Relapsing Multiple Sclerosis
SPA Agreement with FDA

Interim analysis of Phase 2 (Nov 2013) gated initiation of Phase 3 (Dec 2013)
Phase 2 Primary Endpoint: Mean Cumulative Number of GdE Lesions From Wk 12 to Wk 24

- Placebo (N=88)
- RPC1063 0.5 mg (N=87)
- RPC1063 1 mg (N=83)

86% decrease p < 0.0001
First Dose Effect on Mean Heart Rate Hours 1 to 6: Comparison to Gilenya*

*Data estimated from Novartis material at MSBoston2014; not a head to head comparison
Current Clinical Trial Status in Relapsing Multiple Sclerosis

Two large phase 3 registrational trials ongoing

- Worldwide
- 1,300 patients per trial
- 1 year of dosing
- 2 years of dosing

Compared to Avonex, a currently approved drug

- $100,000/patient; $130M/trial
- Clinical development completed in 2017
- New Drug Application and approval with FDA/Europe in 2018
RPC1063 is Active in a Therapeutic SCID Mouse Model of Inflammatory Bowel Disease

CD4^+ CD45RB^{high} T-Cell Adoptive Transfer: Histopathology

Chronic, transmural colitis responsive to immunotherapy
Phase 2 Ulcerative Colitis: Proportion of Patients in Remission at Week 8 (April 2015)

Primary Endpoint

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Placebo (N=65)</th>
<th>Ozanimod 0.5 mg (N=65)</th>
<th>Ozanimod 1 mg (N=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of Patients in Remission</td>
<td>6.2%</td>
<td>13.8%</td>
<td>16.4%</td>
</tr>
<tr>
<td>p</td>
<td>0.1422</td>
<td>0.0482</td>
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The Relapsing Multiple Sclerosis Market is Valued at ~$16B

2013 MS Market: ~$16B

- **INFs 43%**
  - **Gilenya® 12%**
  - **Tecfidera® 11%**
  - **Copaxone® 27%**
  - **Aubagio® 1%**

**MARKET SIZE**
- 11% CAGR (2009 – 2013)
- **Interferon-b ($6.8B)** characterized by flu-like symptoms and injections from weekly to every-other day
- **Copaxone® ($4.3 B)** is similar in efficacy to INFs; trades off flu-like symptoms for daily injections
- **Tysabri® ($1.7B)** has superior efficacy but PML risk limit uptake
- **Gilenya® ($1.9B)** *first oral* with significant improvement in ARR reduction compared to ABCRs (launched 3Q10)
- **Tecfidera® ($0.9B)** newest oral to RMS market (launched 2Q13)
- Safe and efficacious therapies
- More tolerable & convenient therapies
- Agents that halt or reverse damage

**CURRENT THERAPIES***
- **Interferon-b ($6.8B)**
  - characterized by flu-like symptoms and injections from weekly to every-other day
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- More tolerable & convenient therapies
- Agents that halt or reverse damage

**UNMET NEEDS**
- Safe and efficacious therapies
- More tolerable & convenient therapies
- Agents that halt or reverse damage

Source: Datamonitor, Credit Suisse Analyst Reports, Company Annual Reports and Q4 2013 Reports
Oral Share of RMS IMS Scripts Rapidly Increasing

*Gilenya*® and *Tecfidera*® drive rapid increases in oral market share gains

Note: RMS Therapies Include Avonex®, Betaseron®, Copaxone®, Rebif®, Gilenya®, Aubagio® & Tecfidera®;
Orals = Gilenya®, Aubagio® & Tecfidera®; ABCRs = Avonex®, Betaseron®, Copaxone® & Rebif®

Source: IMS Scripts NPA
RPC1063 Poised to be Next S1P$_{1,5}$R Modulator into RMS Market

**Phase II**

- **Ceralifimod** (ONO / Merck Serono)
  - Positive Phase 2 outcome
  - AV blocks; hepatotoxicity
  - Merck Serono terminated license in June 2014

- **Siponimod / BAF-312** (Novartis)
  - Phase 3 for SPMS
  - Phase 2 for Dermatomyositis and Polymyositis

- **Ponesimod** (Actelion)
  - Positive Phase 2 psoriasis data
  - P2 RMS extension study ongoing, announced no Phase 3
  - RMS without partnership

**Phase III**

- **RPC1063** (Receptos)
  - Phase 3

**MT-1303** (Mitsubishi Tanabe)
- Phase 2 in RMS and psoriasis
RMS Market Valued at $16B and Growing
Marketing Strategy for RMS Includes Competing Head to Head with Tecfidera® in Front Line While “Beating” Gilenya® in Later Lines

Positioning of MS Treatment Options

1st Line Treatment
- Cycling
- New therapies will be introduced

2nd Line Treatment
- 1st line failures
- Tolerability Issues

Last Line Treatment
- Salvage treatment

- Beta Interferons / Copaxone® ($11B)
- RPC1063 Tecfidera® ($0.9B)
- Gilenya® ($1.9B)
- Aubagio® ($0.2B), Laquinimod
- Daclizumab
- JC virus negative patients

- Lemtrada™ Ocrelizumab
- Tysabri® ($1.5B)
In Market Research, RPC1063 Profile Viewed More Favorably Than Tecfidera® on Efficacy and Tolerability and Gilenya® on Safety

- Majority of physicians had a positive view of RPC1063 on all metrics tested compared to currently marketed orals
- When shown patient profiles, physicians selected RPC1063 more frequently than any marketed RMS therapy

Note: For purposes of the survey, respondents were provided with a product profile for RPC1063 that assumed efficacy equal to Gilenya® with specified improvements in safety profile; Actual clinical results for late stage trial and the FDA marketing label for RPC1063, if approved, may be different than the profile that was assumed for market research; Pricing and reimbursement were assumed to be equal among RPC1063 and all other RMS treatments

Source: ZS Associates, Neurologist Survey, N = 75; ZS Associate, Neurologist Interview Study, N = 21; Market research was sponsored by Receptos
The UC Market Opportunity for RPC1063 in the US: Gastroenterologists Position RPC1063 in Early Lines Against Immunosuppressants as well as Last Line Against Anti-TNFs

Positioning of UC Treatment Options in Market Research Outcomes

- RPC1063 scored higher on key safety attributes than anti-TNFs
- Most physicians would use RPC1063 earlier in UC treatment algorithm than anti-TNFs, Entyvio® and tofacitinib
- RPC1063 rated highly differentiated from Entyvio® and tofacitinib on key attributes tested

5-Aminosalicylates

Immunosuppressants and Corticosteroids

1st Line Treatment

2nd Line Treatment

3rd Line Treatment

Last Line Treatment

~370K Moderate to Severe

~750K Moderate-to-Severe Patients

Positioning based on Receptos sponsored market research. Respondents were provided with a product profile for RPC1063 and vedolizumab that assumed comparable efficacy improved to anti-TNFs with specified improvements in safety profile. Actual clinical results for late stage trial and the FDA marketing label for RPC1063, if approved, and vedolizumab, approved in May 2014, may be different than the profile that was assumed for market research; pricing and reimbursement were assumed to be equal among RPC1063 and all other UC treatments

Source: Kantar 2013, US Gastroenterologist Quantitative Survey (N = 101)
### Market Research Results:
**US Gastroenterologist Estimated RPC1063 Patient Share in IBD**

<table>
<thead>
<tr>
<th>Ulcerative Colitis</th>
<th>Treatment Algorithm</th>
<th>Crohn’s Disease</th>
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<tbody>
<tr>
<td><strong>RPC1063 Patient Share</strong></td>
<td>First Line</td>
<td><strong>Current Treatment Choice by Line</strong></td>
</tr>
<tr>
<td>7% *</td>
<td>5ASA</td>
<td>6-MP, AZA</td>
</tr>
<tr>
<td>13.0%</td>
<td>Corticosteroids</td>
<td>6-MP, AZA</td>
</tr>
<tr>
<td>18.0%</td>
<td>6-MP, AZA</td>
<td>Biologics</td>
</tr>
<tr>
<td>24.0%</td>
<td>Biologics</td>
<td>Biologics</td>
</tr>
</tbody>
</table>

**Note:** *Physicians were asked to estimate first line RPC1063 peak patient share IF clinical trial data was available demonstrating improvement to 5-ASAs. Receptos applies appropriate discounts to market research results for the purposes of financial modeling.*

**Source:** Kantar 2013, US Gastroenterologist Quantitative Survey (N = 101)
Receptos: 2015

IPO (NASDAQ: RCPT) in May 2013. $83M raised. $14/share
Additional 3 capital raises in 2014, totaling ~$700M. Each raise over-subscribed
110 employees and growing
Phase 3 clinical trials in relapsing multiple sclerosis and phase 2 in inflammatory bowel diseases (UC and Crohn’s disease)
Phase 2 in EoE
Preclinical program in T2D/NASH
Discovery chemokine receptor program
Acquired July 2015 for $7.8B
$232/share
Key Strategies and Lessons Learnt

- Hire the “right” people and on an “as needed” basis. Wear lots of hats and preserve $$
- Build a productive, creative, rewarding culture
- Focus, don’t waste time or money. Understand the critical path activities
- Do rigorous science
- Don’t partner early
- Enact bold (but not reckless) clinical development plans
- Understand the competition and where your drug might fit in the market place
- Under promise and over deliver
- Build relationships: FDA, CRO’s, consultants, KOL’s, investors, pharma/biotech
- Raise money when you can
- Maintain optionality
Kaikoura
AD-114 a novel i-body for the treatment of fibrosis

Mick Foley, CSO AdAlta Limited
m.foley@adalta.com.au
Mick is the founding scientist of AdAlta and a key inventor of AdAlta’s lead i-body candidate AD-114.

Upon completion of his PhD he was awarded a Wellcome Training Fellowship and worked at the Walter and Elisa Hall Institute. In 1995 Mick was awarded an ARC QEII Fellowship where he established the phage display of antibodies and peptide technology as a means of answering fundamental questions of immunity to infectious diseases.

Mick is an internationally recognized leader in phage display, the technology used to screen the i-body library to identify new drug candidates. Having published over 70 scientific publications Mick has received funding from ARC, NHMRC and NIH (US).
Investment in AdAlta is subject to investment risk, including possible loss of income and capital invested. AdAlta does not guarantee any particular rate of return or performance, nor do they guarantee the repayment of capital.

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Developing i-bodies as improved therapies for the treatment of fibrosis
- a condition that is prevalent in 45-50% of all diseases

Fibrosis can occur in many tissues of the body as a result of inflammation or damage
- it can result in scarring of vital organs causing irreparable damage and eventual organ failure

AdAlta’s initial focus is on lung fibrosis

Collectively fibrosis represents a large unmet clinical need
i-body technology

AdAlta is developing a new technology platform that produces unique proteins known as i-bodies, that mimic the shape of shark antibody binding domain and engineers their key stability features into a human protein, for therapeutic intervention in disease.

The single domain antigen binding region of shark antibodies is extremely stable and has a long binding loop not present in either human or next generation antibodies.

**Advantages of i-bodies**

- High target specificity and high affinity for their target
- Small proteins; 10% the size of a typical human antibody
- Highly stable to proteases, high temperatures and low pH
- Long loop that can bind to a diverse range of therapeutically relevant targets including those that are difficult for current antibody therapies
- **Human protein** – reduced risk of immune response

![Diagram](image)
AD-114 lead program in Idiopathic Pulmonary Fibrosis (IPF)

- AD-114 is lead i-body candidate in pre-clinical development
  - Demonstrates both anti-fibrotic and anti-inflammatory activity in the lung
  - Important for arresting and modifying the disease and tackling the treatment of idiopathic pulmonary fibrosis (IPF); this is the primary indication

**Idiopathic Pulmonary Fibrosis**
A chronic, highly lethal and rare disease.
50-70% mortality rate
>135,000 people in US alone
World wide sales ~$4.2B by 2020

Source: Evaluate Pharma, Orphan Drug Report 2015
CXCR4 and idiopathic pulmonary fibrosis (IPF)

Patients that rapidly progress express more CXCR4 compared to slow IPF progressors

CXCR4 +ve cells (fibrocytes) significantly elevated in stable IPF patients, and further increased during acute exacerbations

Fibrocytes not correlated with lung function but an independent predictor of early mortality

- 7.5 months with more than 5% fibrocytes
- 27 months with less than 5% fibrocytes

AD-114 binds to lung tissue from patients with fibrosis

AD-114 was used for Immunohistochemical (IHC) staining of normal and diseased lung tissues to verify expression of CXCR4 in situ

AD-114 does not bind lung tissue from normal lungs

AD-114 binds to lung tissue from lungs with fibrosis
Migration/invasion specifically reduced with IPF lung fibroblasts

AD-114 specifically inhibited migration of slow and rapid IPF fibroblast migration but did not have any effect on normal fibroblasts.

AD-114 has greater in vitro efficacy compared to the only approved therapies Nintedanib and Pirfenidone for IPF treatment.

<table>
<thead>
<tr>
<th>MIGRATION</th>
<th>No effect on normal fibroblasts</th>
<th>Inhibits slow IPF progressors</th>
<th>Inhibits fast IPF progressors</th>
</tr>
</thead>
<tbody>
<tr>
<td>i-body AD-114</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Nintedanib (Boehringer)</td>
<td>✗</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Pirfenidone (Roche)</td>
<td>✔</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Other CXCR4 drug (Sanofi)</td>
<td>✔</td>
<td>✗</td>
<td>✗</td>
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</tbody>
</table>

- Normal fibroblasts
- Slow/stable IPF progresor fibroblasts
- Rapid IPF progresor fibroblasts

For personal use only
AD-114 prevents fibrosis in Bleomycin-induced mouse model of lung fibrosis
Prophylactic or Preventative setting

AD-114 reduces collagen content and inflammatory cell infiltration in the Bleomycin mouse model and demonstrates a similar architecture to that of the normal lung
AD-114 significantly reduced the Ashcroft score compared to the Bleomycin treated mice.

The negative i-body at the same dose as AD-114 had no effect on preventing fibrosis.

AD-114 prevents fibrosis in Bleomycin-induced mouse model of lung fibrosis
Prophylactic or Preventative setting
AD-114 prevents fibrosis in Bleomycin-induced mouse model of lung fibrosis

Therapeutic setting

AD-114 reduces collagen content and inflammatory cell infiltration in the Bleomycin mouse model and demonstrates a similar architecture to that of the normal lung.
AD-114 prevents fibrosis in Bleomycin-induced mouse model of lung fibrosis

Therapeutic setting

- AD-114 significantly reduced the Ashcroft score compared to the Bleomycin treated mice
- AMD3100 (CXCR4 antagonist) also reduced the Ashcroft score compared to the Bleomycin treated mice
AD-114 and non-alcoholic steatohepatitis (NASH)

- Non-alcoholic steatohepatitis (NASH) is a pandemic, metabolic disease which has both inflammatory and fibrotic components
- AD-114 is lead i-body candidate in pre-clinical development
  - Demonstrates both anti-fibrotic and anti-inflammatory activity in the liver
  - Important for arresting and modifying the disease and tackling the treatment of NASH

NASH
A chronic disease with high levels of morbidity and mortality
About 3-5% of adults in the United States have NASH
Sales of drugs for the treatment of fibrosis caused by NASH are estimated to be US$1.6 billion by 2020.
AD-114 prevents fibrosis in a mouse model of liver fibrosis
Therapeutic setting

AD-114 significantly reduces hepatocellular ballooning, a key feature required for the diagnosis of NASH
AD-114 prevents fibrosis in a mouse model of liver fibrosis

- AD-114 decreased serum ALT levels and non-alcoholic fatty liver disease (NAFLD) score compared with the vehicle or disease model group.
- The improvement in serum ALT levels suggests that i-body ameliorated hepatocellular injury and inflammation preventing progression of disease.
- Hepatocyte ballooning was significantly decreased compared with the vehicle or diseased group.
- AD-114 possess hepatoprotective and anti-NASH effects.
Infections or inflammation in the eye result in impairment of visual function and can ultimately lead to fibrosis. Complications from common eye diseases that can result in fibrosis occur in age related macular degeneration (AMD) and diabetic retinopathy.

AD-114 is lead i-body candidate in pre-clinical development
- Demonstrates both anti-fibrotic and anti-leakage activity in the eye
- Important for arresting and modifying the disease and tackling the treatment of eye fibrosis

**Eye Fibrosis**
AMD is the commonest cause of severe visual impairment in people over the age of 50 years in the developed world.
>1m in AU and 2m in USA with AMD
Market research estimates that the market size for AMD will be over US$10 billion by 2023 while the market size for diabetic retinopathy will be US$10 billion in 2022.
AD-114 prevents eye fibrosis

Mouse choroidal neo-vascularization model (CNV):
- Laser burn to the retina
  - Induces subretinal haemorrhage
  - Contraction of retinal tissue
  - Alteration in microglia and glial response
  - Alteration in gene expression

IVT injection of single dose of i-body
- Improves retinal retraction and reduces lesion size
- Fibrosis gene expression reduced

AD-114 reduces contraction and lesion size in eye fibrosis mouse model
AD-114 reduces lesion size and number

AD-114 is able to reduce the number and size of the lesion in both preventative and therapeutic models of wet-AMD (CNV)

AD-114 is able to significantly reduce fibrosis as measured by trichrome staining in both preventative and therapeutic models of wet-AMD (CNV)
AdAlta summary

- Powerful proprietary technology platform to develop a pipeline of i-bodies for the treatment of a wide range of human diseases
  - Extreme stability of i-body similar to single domain shark antibody
  - Long loop of i-body binds deep in GPCR pocket and has functional activity

- Advanced lead candidate AD-114 with significant pre-clinical validation
  - has specificity for diseased human tissue with effects only shown on IPF tissue and no effects displayed on normal lung tissue nor any evidence of off target effects;
  - is more effective than existing IPF approved drugs showing greater in vitro efficacy compared to the only approved therapies Nintedanib and Pirfenidone;
  - demonstrates both anti-fibrotic and anti-inflammatory effects in multiple animal models in multiple areas of fibrosis; and
  - is a novel mechanism of action for fibrosis making AD-114 a potential “first in class” therapy.
Pulmonary fibrosis – current state of play in Idiopathic Pulmonary Fibrosis

A/Prof Glen Westall
Lung Fibrosis Service, Alfred Hospital
NHMRC Centre of Research Excellence: Lung Fibrosis
Dr Glen Westall received his undergraduate medical training at King’s College Medical School in London, UK, before training in general and respiratory medicine at the Royal Brompton Hospital in London and the Alfred Hospital in Melbourne. His clinical interests include advanced lung disease, bronchoscopy and lung transplantation. He is physician-in-charge of the Paediatric Lung Transplant program at the Alfred.

Glen's research interests parallel his clinical expertise in advanced lung disease and lung transplantation. He has subsequently developed a wider interest into how activation of the innate immune system early post-lung transplant influences clinical outcomes. Establishing a research platform in pulmonary xenotransplantation has resulted in the award of an internationally competitive Career Development Award. Clinically, Glen is a principal and co-investigator on numerous studies in lung transplantation and bronchoscopic lung volume reduction.
Lung Fibrosis

Scaring of the Lung

Lungs become stiff

Lungs shrink in size

Normal CXR

Lung Fibrosis
Interstitial lung disease (ILD) classification

- Diseases of known cause
- Idiopathic interstitial pneumonias
- Granulomatous lung diseases
- Other

Multiple subtypes – over 200 types of disorder in total!

Adapted from ATS/ERS. Am J Respir Crit Care Med. 2002;165:277.
Idiopathic Pulmonary Fibrosis (IPF)

Represents 50% of all Fibrotic Lung Conditions

Male:Female 1.5:1
Age of Presentation 66 yrs
Smoking history 70%

Australian IPF Cases 5000-10,000

Diagnosed by MDT Meeting
IPF Diagnosis: Multi-Disciplinary Team (MDT) meeting

- Communication between clinician, radiologist and when appropriate pathologist
- Clinical data
  - Presentation, Exposures, Smoking status, Associated disease, Lung function and Radiologic findings
Traditional Therapy for IPF: historical view

- Uncontrolled Chronic Inflammation
  - Corticosteroids
  - Cyclophosphamide
  - Azathioprine
- N-acetylcysteine (NAC)
# 2011 Evidence Based Guidelines: Treatment recommendations

<table>
<thead>
<tr>
<th>Agent</th>
<th>For</th>
<th>Against</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td></td>
<td>Strong +</td>
</tr>
<tr>
<td>Colchicine</td>
<td></td>
<td>Strong +</td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td></td>
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</tr>
<tr>
<td>Corticosteroid and imm-mod</td>
<td></td>
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</tr>
<tr>
<td>Interferon gamma</td>
<td></td>
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<td>Bosentan</td>
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</tr>
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<td>Etanercept</td>
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<tr>
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<tr>
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</tr>
</tbody>
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## 2011 Evidence Based Guidelines: Treatment recommendations

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</table>
2014: A big year for lung fibrosis!

Pirfenidone approved by FDA

Reduction in mortality and decreased FVC

![Graph showing reduction in mortality and decreased FVC](image)

47% reduction in proportion of patients with a decline in FVC

**Adverse Events**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Pirfenidone (N=278)</th>
<th>Placebo (N=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>47 (17.2)</td>
<td>30 (11.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>44 (16.0)</td>
<td>24 (8.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>44 (16.0)</td>
<td>20 (7.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22 (8.0)</td>
<td>10 (3.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>25 (9.1)</td>
<td>10 (3.6)</td>
</tr>
<tr>
<td>IPF deaths</td>
<td>60 (22.0)</td>
<td>20 (7.3)</td>
</tr>
</tbody>
</table>

NEJM 2014; 370: 2083
2014: A big year for lung fibrosis!

Nintedanib approved by FDA

Reduction in mortality and decreased FVC

Intracellular inhibitor of multiple tyrosine kinases

NB: Not curative

Secondary end points not achieved

Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>INPULSiS1</th>
<th>Placebo</th>
<th>INPULSiS2</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>29 (16.4)</td>
<td>39 (22.0)</td>
<td>23 (13.1)</td>
<td>30 (18.4)</td>
</tr>
<tr>
<td>Any adverse event, excluding progression of idiopathic pulmonary fibrosis#</td>
<td>25 (14.4)</td>
<td>34 (20.0)</td>
<td>19 (11.2)</td>
<td>26 (15.0)</td>
</tr>
<tr>
<td>Adverse events leading to treatment discontinuation</td>
<td>8 (4.6)</td>
<td>10 (5.9)</td>
<td>7 (4.3)</td>
<td>8 (4.8)</td>
</tr>
<tr>
<td>Event</td>
<td>INPULSiS1</td>
<td>Placebo</td>
<td>INPULSiS2</td>
<td>Placebo</td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
<td>---------</td>
<td>-----------</td>
<td>---------</td>
</tr>
<tr>
<td>QTc</td>
<td>150 (51.3)</td>
<td>28 (16.8)</td>
<td>250 (48.2)</td>
<td>40 (26.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>26 (13.0)</td>
<td>13 (7.5)</td>
<td>35 (20.5)</td>
<td>26 (15.6)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>38 (21.3)</td>
<td>34 (19.7)</td>
<td>34 (20.5)</td>
<td>34 (21.5)</td>
</tr>
<tr>
<td>Cough</td>
<td>47 (26.2)</td>
<td>35 (20.7)</td>
<td>28 (16.2)</td>
<td>33 (20.0)</td>
</tr>
<tr>
<td>Progression of idiopathic pulmonary fibrosis#</td>
<td>31 (18.3)</td>
<td>21 (12.3)</td>
<td>23 (13.7)</td>
<td>49 (31.9)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>36 (13.1)</td>
<td>28 (16.3)</td>
<td>31 (18.9)</td>
<td>17 (11.9)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>22 (5.3)</td>
<td>27 (15.9)</td>
<td>23 (13.9)</td>
<td>23 (14.9)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>22 (16.0)</td>
<td>18 (11.3)</td>
<td>30 (18.5)</td>
<td>26 (16.3)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>26 (18.6)</td>
<td>14 (8.9)</td>
<td>42 (25.0)</td>
<td>10 (6.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>40 (27.3)</td>
<td>4 (2.6)</td>
<td>34 (20.0)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>23 (15.6)</td>
<td>10 (6.3)</td>
<td>37 (21.2)</td>
<td>20 (12.9)</td>
</tr>
<tr>
<td>Severe adverse events</td>
<td>21 (13.4)</td>
<td>17 (10.6)</td>
<td>19 (11.7)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>21 (13.4)</td>
<td>17 (10.6)</td>
<td>19 (11.7)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Fatal adverse events</td>
<td>21 (13.4)</td>
<td>17 (10.6)</td>
<td>19 (11.7)</td>
<td>2 (1.3)</td>
</tr>
<tr>
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<td>8 (4.8)</td>
</tr>
</tbody>
</table>

Study discontinuation 5%
Unmet clinical need: drugs in development

- Current drugs have limited efficacy and substantial side effects
- Other anti-fibrotic and anti-angiogenic agents currently in development with multiple targets
  - Inhaled Pirfenidone
  - WNT signaling
  - FG-3019
  - Zileutin
  - ACE inhibitors
  - Anti-\(\gamma\)6 integrin
  - Anti-IL13
  - Anti-IL13/IL4
  - Imatanib
  - LOXL-2
Clinical trials.gov

Phase 1
Dasatinib (oral Bcr-Abl TK inhibitor, BMS) + Quercetin
Vismodegib (hedgehog signalling pathway) + perfinidone (Genentech, Roche)
CC-90001 (Celgene, JNK inhibitor)
Mesenchymal stem cells

Phase 2
Rituximab
Tipelukast (medicnova)
STX-100 (αvβ6 integrin inhibitor, Biogen)
GBT440 (oxygen carrying capacity, Global blood therapeutics)
KD0125 (ROCK2 signalling inhibitor, Kardmon)
Lebrikizumab and perfinidone (Roche)
GLPG1690 (autotaxin inhibitor)

Phase 3
Bactrim
Cyclophosphamide (acute exacerbations)
Nintedanib and sildenafil (BI)
Perfinidone and sildenafil (Roche)
ART-123 (acute exacerbations) thrombomodilin

Phase 4
perfinidone + nintedanib
Drug Discovery and translational research

In-vitro science → Animal model → Human IPF Tissue → Clinical Trials

Assessment of human IPF tissue provides additional evidence of efficacy prior to clinical trials.
Alfred Tissue Bank

- National resource
- Collaborations (Academic and Commercial entity)
- Creation of pilot data
- Conduit: Alfred Lung Transplant Program (n=90)

ILD Explant Lungs

Normal Lungs donated for research (Donate Life)
CXCR4 Role in IPF

Very limited expression in normal or non-diseased tissues

CXCR4 is upregulated in IPF tissue
Summary

- Increasing understanding of the pathophysiology
- Treatments (albeit limited)
- Many Lung Fibrosis services/clinics

Need better therapies for a terminal disease!!
Renal fibrosis and chronic kidney disease
Novel therapeutic targets for kidney fibrosis

Professor Muh Geot Wong
Royal North Shore Hospital, University of Sydney Australia
George Institute for Global Health
Dr Wong is Renal Physician at the Royal North Shore hospital, Sydney, Australia. He is also a senior research fellow at the George Institute of Global Health and a senior clinical lecturer at the University of Sydney. His PhD entitled “Novel therapeutic options in models of nephropathy” was awarded in 2011.

His main area of research is in understanding the pathomechanisms of kidney tubulointerstitial fibrosis and biomarkers in predicting progression of chronic kidney disease particularly in diabetic kidney disease.

**DISCLOSURES**

- Speaker fees; Astra Zeneca
- The George Institute for Global Health holds research contracts for trials in cardiovascular and/or kidney disease with several organization including Boehringer Ingelheim, Merck, AbbVie, Roche, AstraZeneca, Servier, Astellas, Baxter, BMS, GSK, Janssen and Pfizer
Overview

- Residual risk of standard of care
- Mechanism of kidney fibrosis
- Novel therapies for kidney fibrosis
- Global market potential
Kidney Fibrosis

Kidney or renal fibrosis is seen in virtually all progressive kidney diseases including diabetic nephropathy, allograft nephropathy or aging.
Causes of end stage kidney disease over time

AUSTRALIA

USA

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Renin Angiotensin Aldosterone system
Residual risk of end stage renal disease on conventional therapy

Risk reduction, 28%
P=0.002

Imbalance between injury and repair

Genetic susceptibility

Kidney fibrosis

Inflammation

Mononuclear & T-cell infiltration

Inflammatory cytokines

Transcription factors

Fibroblast activation

EMT

EndoMT

RAAS & TGFβ

Hypoxia

Dysregulated autophagy

ER stress

Epigenetic modification

Kinases, proteases, ROS, enzymes, phospholipids

Insults
Chronic kidney disease associated pathways are shared between renal diseases

Martini S et al. JASN 2013
Monocyte infiltration
CCR2 inhibition
SSAO/VAP-1 inhibition
Tie2 receptors

NOX1/NOX4

LOXL2i

Stat 4 antagonists
PDE4 inhibitors
MCR inhibition

RASi

TGFβ/ CTGF

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**Novel therapies and status**

- Anti TGFB antibody (LY2382770): Negative Study
- Pirfenidone: Study withdrawn
- Nox1/4 inhibitor: negative trial
- Tranilast and analogues FT011: In Phase 1b Clinical Trial
- Anti-CTGF Antibodies FG3019: Studies terminated
- CCR2/MCP1 inhibition: Larger clinical trial with hard renal endpoints needed
- SSAO/ VAP1 inhibitors: Phase 1 Clinical Trial concluded. ? Results
- Tie2Rec activator: angiopoietin receptor, tyrosine kinase inhibitor - in development
- JAK-STAT inhibitors: in development
- LOX inhibitors: in development
- CXCR4 and AdAlta’s i-body?
CXCR4 promising therapeutic strategy for treatment of kidney fibrosis

- CXCR4 expression was increased in disease state compared with normal tissue.
- Collaboration between Kolling Renal Research and AdAlta i-body technology in exploring CXCR4 as therapeutic strategy to prevent the development of fibrosis.
Challenges for clinical trial in CKD/Fibrosis

- Patients with CKD usually excluded from major trial
- Lack of intermediate endpoints/ biomarkers that regulatory agencies will accept for approval
- High trial failure rate
- Lack of coordination between scientists, investors, clinical trialists, pharma companies, regulatory authorities, policy makers and governments to develop novel strategies.
EMPA-REG


Primary outcome:
3-point MACE

CV death

Hospitalisation for heart failure

HR 0.86
(95% CI 0.74, 0.98)
p = 0.0082

↓ 14%

HR 0.42
(95% CI 0.49, 0.77)
p = 0.0001

↓ 38%

All-cause mortality

HR 0.68
(95% CI 0.53, 0.85)
p = 0.0017

↓ 35%

HR 0.68
(95% CI 0.53, 0.85)
p = 0.0001

↓ 32%

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### Effects of empagliflozin on renal outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident/worsening of nephropathy</td>
<td>0.61</td>
<td>0.53 – 0.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New onset macroalbuminuria</td>
<td>0.62</td>
<td>0.54 - 0.72</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Doubling creatinine or ESKD</td>
<td>0.54</td>
<td>0.40 - 0.75</td>
<td>0.0002</td>
</tr>
<tr>
<td>Doubling of serum creatinine</td>
<td>0.56</td>
<td>0.39 - 0.79</td>
<td>0.0009</td>
</tr>
<tr>
<td>ESKD</td>
<td>0.45</td>
<td>0.21 - 0.97</td>
<td>0.04</td>
</tr>
</tbody>
</table>

The impact of empagliflozin on the primary end-point was not diminished in patients with CKD compared to those without it (MACE HR 0.88, CV death HR 0.78, heart failure HR 0.59, all-cause mortality HR 0.80).
SGLT2 inhibition: glycosuria and natriuresis

LEADER study: Liraglutide in type 2 diabetes

Number needed to treat (NNT) in 3 years to prevent primary outcome=66, and to prevent death from any cause=98

Marso et al NEJM July 2016
Projecting the estimated number of patients receiving RRT from 2010 to 2030

**World**
- 2010: 2.62 million
- 2015: 3.13 million
- 2020: 3.78 million
- 2025: 4.53 million
- 2030: 5.44 million

**Region**
- **Asia**: (0.97 → 2.16)
- **North America**: (0.64 → 1.26)
- **Latin America**: (0.37 → 0.90)
- **Europe**: (0.53 → 0.83)
- **Africa**: (0.08 → 0.24)
- **Oceania**: (0.03 → 0.05)
Global “push”

- International Society of Nephrology (ISN) established working groups to establish and validate novel therapeutic targets to retard progression of CKD.

Four goals

- Improve the identification of “druggable” targets that are amenable to therapeutics
- Enhance the capacity for pre-clinical and early clinical development
- Broaden the availability of novel therapeutic approaches
- Increase investment in the development of therapies to limit CKD
Global Market Opportunity

- According to Decision Resources Group, the CKD market will achieve total sales of $11.7 billion in 2022.
- Erythropoietin-stimulating agents (ESAs), phosphate binders, calcium mimetics, active vitamin D analogues, antihypertensive agents, IV iron and emerging CKD therapies for the CKD non-dialysis and dialysis patient populations. This analysis takes into account the offset of increasing costs of new therapies by emerging availability of generic drugs.
- The launch and uptake of novel drugs during the next ten years will be the largest driver of market growth.
- Of the emerging therapies with novel mechanisms of action, the hypoxia-inducible factor-prolyl hydroxylase (HIF-PH) inhibitors will likely have the biggest impact on the CKD market.

### Late-Stage CKD: Key Metrics in Six Major Pharmaceutical Markets, 2012–2017

<table>
<thead>
<tr>
<th>2012 Patient Population</th>
<th>2012 Market Sales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late-stage CKD Population(^a)</td>
<td>2,356,913</td>
</tr>
<tr>
<td>Treated Population(^b)</td>
<td>1,446,904</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$1.88bn</strong></td>
</tr>
</tbody>
</table>

**Key events (2012–2017)**

- PA-21 launch in the US and EU – 2014
- Zerenex launch in the US and EU – 2014/2015
- Renagel/Renvela patent expiry in the US and EU – 2014
- Oral treatments included in the Medicare dialysis reimbursement bundle – 2016
- Velcalcetilde launch in the US and EU – 2016/2017

<table>
<thead>
<tr>
<th>2017 Market Sales</th>
</tr>
</thead>
<tbody>
<tr>
<td>US $1.27bn</td>
</tr>
<tr>
<td>SEU $391m</td>
</tr>
<tr>
<td><strong>Total</strong> $1.66bn</td>
</tr>
</tbody>
</table>

Source: GlobalData.
For the purposes of this report, the six major pharmaceutical markets = US and SEU (France, Germany, Italy, Spain, and UK).
\(^a\) = Stage 4 and 5 CKD prevalence cases; \(^b\) = patients treated for hyperphosphatemia and/or secondary hyperparathyroidism.
Summary

- An unmet need for new therapeutic options of kidney fibrosis
- Global recognition, demand and commercial opportunity to develop new therapeutics in CKD
- Promising novel targets needs clinical translation and hard renal outcomes
- Collaborative effort among scientists, clinicians, investors, trialists, pharma companies, regulatory authorities, policy makers and governments needed
Eye Fibrosis, causes, diseases and treatments

Professor Erica L Fletcher
Department of Anatomy and Neuroscience
The University of Melbourne
Email: elf@unimelb.edu.au
Erica Fletcher is Professor in the Department of Anatomy and Neuroscience, at The University of Melbourne where she heads the Visual Neuroscience Laboratory.

She is a clinically trained optometrist who holds both MSc and PhD degrees. She completed her PhD at The University of Melbourne and undertook postdoctoral training at the Max Planck Institute for Brain Research in Germany, funded by a CJ Martin Award from the NH&MRC.

Prof Fletcher was appointed to an academic position in 2000 at The University of Melbourne. Prof Fletcher’s research interests remain primarily focussed on understanding the causes of retinal disease.
The eye
Fibrosis and the eye

Definition:
- Scarring of the retina leading to vision loss

Diseases of the retina associated with fibrosis:

- Retinal vascular disease:
  - Diabetic retinopathy and Age related macular degeneration.

- Retinal detachment:
  - Fibrosis (PVR): 8-10% of all patients undergoing primary retinal detachment surgery.
The retina and its vasculature

{Image: Prof Erica Fletcher Univ Melb}

{Image: Friedlander, 2007 J Clin Invest}
Blindness: 50-100,000 Australians

- Refractive Error: 48%
- Cataract: 14%
- Glaucoma: 12%
- Diabetes and other Retinal: 10%
- Neuro-ophthalmic: 8%
- Retinitis Pigmentosa: 3%
- Others: 1.5%

{Image: Prof Robyn Guymer, CERA}
Age related macular degeneration

{Image: Prof Robyn Guymer, CERA}
First medical treatment for wet AMD
2002

{Image: Prof Robyn Guymer, CERA}
Anti-VEGF treatments

Vision (letters)

Month

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Untreated

Lucentis treatment

Incidence rates of legal blindness from AMD
Denmark population based observational registry study

Introduction of antiVEGF treatment

47% Reduction

Long term effects: A sting in the tail!

~50% of patients are legally blind
There is a problem: fibrosis

Risk of Scar in the Comparison of Age-related Macular Degeneration Treatments Trials

Ebenezer Daniel, MBBS, PhD, Cynthia A. Toth, MD, Juan E. Grunwald, MD, Glenn J. Jaffe, MD, Daniel F. Martin, MD, Stuart L. Fine, MD, Jiayan Huang, MS, Gui-shuang Ying, MD, PhD, Stephanie A. Hagstrom, PhD, Katrina Winter, BS, Maureen G. Maguire, PhD, for the Comparison of Age-related Macular Degeneration Treatments Trials Research Group

Results: Scar developed in 480 of 1059 eyes (45.3%) by 2 years.

versus occult CNV, blocked fluorescence (aHR, 1.4; CI, 1.1–1.8), foveal retinal thickness >212 μm (aHR, 2.4; CI, 1.7–3.6) versus <120 μm, foveal subretinal tissue complex thickness >275 μm (aHR, 2.4; CI, 1.7–3.6) versus ≤75 μm, foveal subretinal fluid (aHR, 1.5; CI, 1.1–2.0) versus no subretinal fluid, and subretinal hyperreflective material (SHRM) (aHR, 1.7; CI, 1.3–2.3) versus no SHRM. Eyes with elevation of the retinal pigment epithelium had lower risk (aHR, 0.8; CI, 0.5–0.9) versus no elevation. Drug, dosing regimen, and genotype had no statistically
Reduction in vision in wet AMD

- Abnormal growth of blood vessels
- Leakage of blood vessels
- Influx of inflammatory cells
- Tissue remodelling
- Scarring/vision loss

New targets:
- CXCR4

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Current drugs have limited efficacy with ~45% of patients being legally blind after 7 years.

Other anti-fibrotic and anti-angiogenic agents currently in development with multiple targets:

- Platelet-Derived Growth Factor Receptor
- Anti-\(\alpha\varepsilon\beta1\) integrin
- Anti-\(\alpha\varepsilon\beta3\) integrin
- Androgen Receptor Agonist
- Angiopoietin 2 (ANGPT2) Inhibitor, Placental Growth Factor (PGF) Inhibitor, Vascular Endothelial Growth Factor A (VEGFA) Inhibitor
- Sphingosine 1-Phosphate (S1P) Inhibitor
- C5 Complement Inhibitor
- Sodium Hydrogen Exchange Isoform-3 (NHE-3) Inhibitor
- Connective Tissue Growth Factor (CTGF) Inhibitor
Fibrosis of the retina

- Fibrosis is a major factor leading to vision loss in a number of conditions including:
  - Treatment-resistant age related macular degeneration;
  - End stage diabetic retinopathy; and
  - Surgical repair of retinal detachment and trauma.

- Few if any current treatments

- Common causes including role of immune cells, tissue remodelling that is similar to fibrosis in other regions of the body
Getting a fibrosis drug to the clinic and a deal

Stewart Roberts (chair)
Dr Brian Richardson
Dr John Westwick
Dr Robert Peach
Stuart Roberts has been involved in the healthcare and biotechnology sector since the early 2002, initially as a sell-side analyst doing equities research in the sector in Australia, then, from the start of 2015, as an executive inside biotech companies, before he returned to equities research with the founding of NDF Research in June 2016.
Brian Richardson

Brian was most recently a member of The Leadership Team and The Global Head of The Musculoskeletal Disease Therapeutic Area at The Novartis Institutes for Biomedical Research having previously held several other senior positions during a 42 year career in the pharmaceutical industry.

Research conducted in Brian’s laboratories has led to the discovery, development and introduction of several new therapies.

John Westwick

John has extensive experience in drug discovery in the Pharmaceutical Industry and as a Professor of Pharmacology. With over 14 years at Novartis Institutes for Biomedical Research, John was responsible for the build-up and leadership of all aspects of drug discovery and early development from target validation to the completion of proof of concepts in the respiratory area, which included severe asthma, Chronic Obstructive Pulmonary Disease (COPD), cystic fibrosis, pulmonary arterial hypertension, and pulmonary fibrosis.

John has had 13 positive proof of concepts in respiratory, which include a number of compounds and monoclonal antibodies which are now in phase III clinical trials.

Robert Peach

Dr Peach has over 25 years of drug discovery and development experience in the pharmaceutical and biotechnology industry. In 2009 he co-founded Receptos, becoming Chief Scientific Officer and raising $59M in venture capital and $800M in an IPO and three subsequent follow-on offerings.

In August 2015 Receptos was acquired by Celgene for $7.8B. His extensive drug discovery and development experience in autoimmune and inflammatory diseases, and cancer has resulted in multiple drugs entering clinical trials and 3 registered drugs.
Drug development pathway

- What does it take to get a fibrosis drug to the clinic?
- What does orphan drug designation mean?
- Which fibrosis indication?
# Fibrosis deals: IPF, NASH, Renal

<table>
<thead>
<tr>
<th><strong>IPF</strong></th>
<th><strong>NASH</strong></th>
<th><strong>RENAL</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sep-15 acquired by Roche</td>
<td>May-15 acquired by BI</td>
<td>Sep-14 acquired by Shire</td>
</tr>
<tr>
<td>$105m + $475m milestones</td>
<td>$40m + $750m milestones</td>
<td>$75m + $483m milestones</td>
</tr>
<tr>
<td>phase I asset</td>
<td>phase I asset</td>
<td>phase I asset</td>
</tr>
<tr>
<td>Aug-15 acquired by BMS</td>
<td>April-16 acquired by Gilead</td>
<td>August-14 acquired by Mallinckrodt</td>
</tr>
<tr>
<td>$150m + $1.25b milestones</td>
<td>$400m + $800m milestones</td>
<td>$5.6B</td>
</tr>
<tr>
<td>phase IIa asset</td>
<td>phase I asset</td>
<td></td>
</tr>
<tr>
<td>Nov-14 acquired by BMS</td>
<td>Sep-16 acquired by Allergan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$1.695B acquisition</td>
<td></td>
</tr>
<tr>
<td></td>
<td>phase I &amp; III assets</td>
<td></td>
</tr>
</tbody>
</table>
i-bodies – a new class of protein therapeutics to treat human disease

February 2017

Sam Cobb, CEO and Managing Director
AdAlta Limited (ASX:1AD)

s.cobb@adalta.com.au
Sam Cobb

- Sam is the founding CEO of AdAlta and has over fifteen years’ experience in business development and commercialisation of early stage scientific technologies.
- Prior to AdAlta, Sam was the Business Development Director at the Co-operative Research Centre for Diagnostics. Sam has also worked for the biotech start up companies Sensologix Inc and Nephrogenix Pty Ltd and at the University of Queensland’s technology commercialisation companies, Uniquest Pty Ltd and IMBcom Pty Ltd.
- Sam has a Bachelor of Science, a Masters of Intellectual Property Law and has completed the Australian Institute of Company Directors course.
Disclaimer

Investment in AdAlta is subject to investment risk, including possible loss of income and capital invested. AdAlta does not guarantee any particular rate of return or performance, nor do they guarantee the repayment of capital.

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Corporate and investment summary

- A drug discovery and development company focused on using its proprietary technology platform to generate a new class of protein therapeutics, known as i-bodies, for treating a wide range of human diseases

**Investment highlights**

- Initial focus on treating fibrosis – high unmet medical need
- Advanced lead fibrosis drug candidate AD-114 with significant pre-clinical validation
- Fully funded for phase 1 development of lead fibrosis drug and i-body pipeline
- Early commercialisation potential
- Experienced team with strong track record of drug development and ability to deliver

**Capital structure**

<table>
<thead>
<tr>
<th>ASX code</th>
<th>1AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shares on issue*</td>
<td>101,037,617</td>
</tr>
<tr>
<td>Share price (31 January)</td>
<td>AU$0.21</td>
</tr>
<tr>
<td>Market capitalisation</td>
<td>AU$21m</td>
</tr>
<tr>
<td>Current cash</td>
<td>AU$8.77m</td>
</tr>
<tr>
<td>Trading Range</td>
<td>AU$0.31 to $0.165</td>
</tr>
</tbody>
</table>

* 50.9m shares escrowed for 6-24 months from listing

**Major Shareholders**

<table>
<thead>
<tr>
<th>Shareholder</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yuuwa Capital LP</td>
<td>53.5</td>
</tr>
<tr>
<td>Platinum Asset Management</td>
<td>7.97</td>
</tr>
<tr>
<td>Citycastle Pty Ltd</td>
<td>5.26</td>
</tr>
<tr>
<td>La Trobe University</td>
<td>3.01</td>
</tr>
<tr>
<td>Robin Beaumont</td>
<td>1.82</td>
</tr>
<tr>
<td>Other shareholders</td>
<td>28.44</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>100%</td>
</tr>
</tbody>
</table>

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Fibrosis: unmet medical need with multiple indications

- Developing i-bodies as improved therapies for the treatment of fibrosis
  - a condition that is prevalent in 45-50% of all diseases
- Fibrosis can occur in many tissues of the body as a result of inflammation or damage
  - it can result in scarring of vital organs causing irreparable damage and eventual organ failure
- AdAlta’s initial focus is on lung fibrosis

Collectively fibrosis represents a large unmet clinical need
Global market interest in fibrosis treatments

Recent transactions confirm that big pharma are actively acquiring fibrosis assets at an early stage – typically based on Phase I results

<table>
<thead>
<tr>
<th>Date</th>
<th>Company</th>
<th>Target</th>
<th>Acquired by</th>
<th>Deal value (US$)</th>
<th>Deal commentary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sep-15</td>
<td>Adheron Therapeutics</td>
<td>SDP051</td>
<td>Roche</td>
<td>$105M upfront, plus $475M in milestones</td>
<td>SDP-51 at end of Phase I for IPF</td>
</tr>
<tr>
<td>Aug-15</td>
<td>Promedior</td>
<td>PRM-151</td>
<td>BMS</td>
<td>$150m upfront + $1.25B</td>
<td>Phase II IPF and myelofibrosis</td>
</tr>
<tr>
<td>Nov-14</td>
<td>Galecto Biotech AB</td>
<td>TD139</td>
<td>BMS</td>
<td>$444M</td>
<td>Option to acquire at end of clinical POC (no later than 60 days following Ph 1b for IPF completion)</td>
</tr>
<tr>
<td>Aug-14</td>
<td>Intermune</td>
<td>Esbriet / Pirfenidone</td>
<td>Roche</td>
<td>$8.3B</td>
<td>Approval in Europe / Japan, phase III in the US</td>
</tr>
<tr>
<td>Jun-13</td>
<td>MicroDose Therapeutx</td>
<td>MMI0100</td>
<td>Teva Pharmaceuticals</td>
<td>$40M upfront $125M milestones</td>
<td>MMI0100 was in pre-clinical development</td>
</tr>
<tr>
<td>Mar-12</td>
<td>Stromedix</td>
<td>STX100</td>
<td>Biogen Idec</td>
<td>$75M upfront $487.5M milestones</td>
<td>End of phase I for IPF</td>
</tr>
<tr>
<td>Jul-11</td>
<td>Amira / BMS</td>
<td>BMS-986020</td>
<td>BMS</td>
<td>$325M upfront $150M milestones</td>
<td>End of phase I for IPF</td>
</tr>
</tbody>
</table>

Source: Medtrack Pharma Intelligence, Informa (all IPF deals since 2011)
## AD-114 development: key milestones

<table>
<thead>
<tr>
<th>CY2017</th>
<th>CY2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>Q1</td>
</tr>
<tr>
<td>Q2</td>
<td>Q2</td>
</tr>
<tr>
<td>Q3</td>
<td></td>
</tr>
<tr>
<td>Q4</td>
<td></td>
</tr>
</tbody>
</table>

- **Manufacturing**
- **Toxicology studies**
- **Orphan designation**
- **Publication of data**
- **Other fibrosis indications**
- **BD and partnerships**
- **Partnering of lead candidate based on other benchmark deals**
- **Phase I**
Expected news flow next 12 months

**Q3 & Q4 2016**
- Commence manufacturing of material for toxicology testing with FujiFilm Diosynth Biotechnologies
- Additional AD-114 IPF fibrosis data
- Completion of evaluation of AD-114 with IPF clinicians Alfred Hospital
- Completion of AD-114 NASH animal study

**H1 2017**
- Orphan Drug Designation (US FDA)
  - Hypertrophic scarring animal results for AD-114
  - Manufactured material for toxicology testing available

**H2 2017**
- Eye fibrosis additional data, funded by NHMRC development grant
- Completion of other pre-clinical study animal models of AD-114
- AD-114 toxicology results
AdAlta business model – strategy to create value

i-body technology platform and library

Pharma & biotech partnerships
Revenues: Upfronts, FTEs, milestones & royalties

In-house pipeline of drug candidates
Invest up to key value inflection point

Licence to pharma
Revenues: major upfronts + milestones & royalties

i-bodies new drug class
Potential in multiple disease indications

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## Market benchmarks

### Fibrosis lead AD-114

<table>
<thead>
<tr>
<th>Company</th>
<th>Acquisition Date</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>adheron therapeutics</td>
<td>Sep-15</td>
<td>Acquired by Roche, $105m + $475m milestones, phase I asset</td>
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<td>Galecto Biotech AB</td>
<td>Nov-14</td>
<td>Acquired by BMS, $444m phase I asset</td>
</tr>
</tbody>
</table>

### Next gen antibodies

<table>
<thead>
<tr>
<th>Company</th>
<th>Date of Acq</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>argEN-X</td>
<td>Apr-16</td>
<td>Acquired by Abbvie, $40m upfront + $645m milestones &amp; royalties</td>
</tr>
<tr>
<td>piersis</td>
<td>Dec-15</td>
<td>Acquired by Roche, $6.4m upfront + $410m milestones &amp; royalties</td>
</tr>
<tr>
<td>Ablynx</td>
<td>Nov-15</td>
<td>Acquired by Novo-Nordisk, €9m upfront + €182m milestones &amp; royalties</td>
</tr>
</tbody>
</table>

### GPCRs

<table>
<thead>
<tr>
<th>Company</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEPTARES therapeutics</td>
<td>Acquired Feb-15 by Sosei, $400m Phase Ib asset + 7 pre-clinical leads</td>
</tr>
<tr>
<td>receptos</td>
<td>Acquired by Celgene July-15, $8b Ph III, Ph II and GPCR platform</td>
</tr>
<tr>
<td>Ablynx</td>
<td>April-16 with Boehringer, €8m payment for Ph1 GPCR nanobody (€125m milestones &amp; royalties)</td>
</tr>
</tbody>
</table>
Management and Board in place to deliver strategy

**Sam Cobb: Founding CEO and Director**
Extensive experience in raising equity, contract and grant funding
15 years of commercialisation and management experience

**Dr Robert Peach**
Founder and CSO of Receptos Inc, acquired by Celgene Corporation in 2015 for US$7.8bn
Deep experience in research and drug development

**Dr Paul MacLeman: Chairman**
Managing Director of a ASX listed IDT Australia Ltd
Founded biologics companies, experienced ASX listed executive

**Dr John Chiplin: Independent Director**
CEO of investment Company NewStar Ventures
Managing Director of acquired antibody company Arana Therapeutics

**Liddy McCall & Dr James Williams: Yuuwa Capital Directors**
Founders and investment Directors of Yuuwa Capital
Founders of iCeutica Inc (acquired 2011) and Dimerix Limited
Directors of several Australian biotech and Agritech companies
Multiple FDA, CE Mark and TGA approvals
Scientific Advisory Board

Internationally recognised with proven track record of drug development

**David McGibney: pre-clinical and clinical advisor**

20 years with Pfizer, including Head of European R&D

Ex Pfizer Ltd board member

Developed Viagra, and 10+ blockbuster drugs

**Brian Richardson: drug discovery and development expert**

Ex-Sandoz and Novartis (40+ years), including Head of Pre-clinical Research

Over 60 original peer reviewed research papers

**John Westwick: pulmonary drug discovery and development**

Over 14 years experience at Novartis, head of respiratory drug discovery

Five product launches and 13 positive proof of concepts in respiratory, including a number of antibodies which are now in phase III.

**Dr Mick Foley, AdAlta CSO**

Expert in phage display

NIH, NHMRC, ARC, Gates funding and over 70 scientific publications
AdAlta investment summary

- Powerful proprietary technology platform to develop a pipeline of i-bodies for the treatment of a wide range of human diseases
- Initial focus on treating Idiopathic Pulmonary Fibrosis and other fibrotic diseases - high unmet clinical need
- Advanced lead candidate with significant pre-clinical validation of AD-114 demonstrating anti-fibrotic and anti-inflammatory effects
- Early commercialisation opportunity
- Experienced management and Board to drive AD-114 development and secure technology platform partnerships and product licensing deals
- IPO August 2016 raised $10M to meet major milestones: clinical trials of AD-114 in lung fibrosis and development of i-body pipeline
Thank-you

Sam Cobb, CEO and Managing Director

s.cobb@adalta.com.au
www.adalta.com.au