NDF RESEARCH

Providing independent research coverage of
ASX-listed Life Science companies

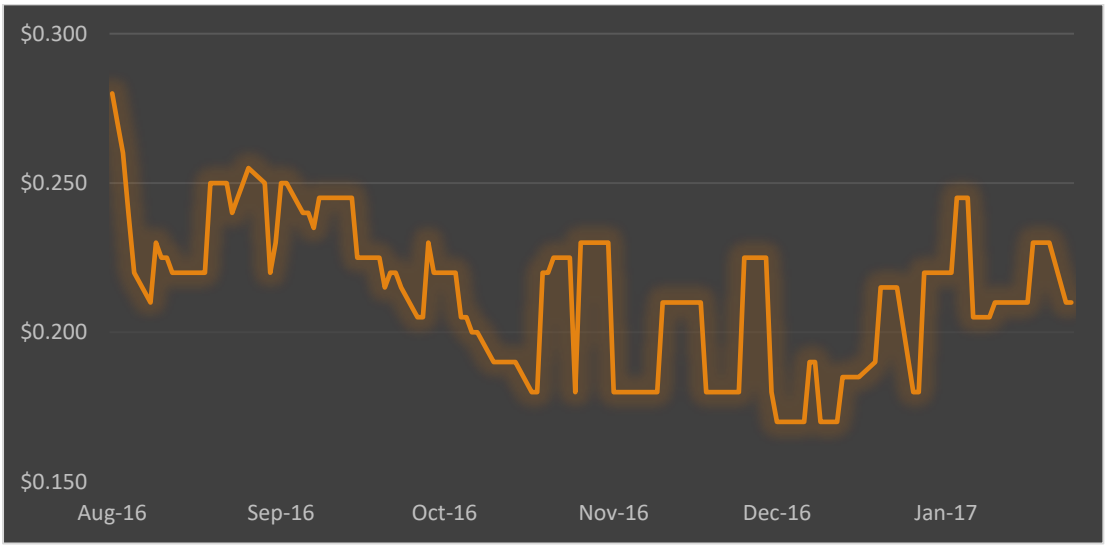
# AdAlta (ASX: 1AD)

**Update note – Monday 20 February 2017**

## I-bodies continue to make progress

Since our initiation note on 13 September 2016 AdAlta has made significant progress with its AD-114 i-body drug candidate. AdAlta announced new *in vivo* data on the effectiveness of AD-114 in lung and liver fibrosis in early January 2017, while later that month the drug gained Orphan Drug status for Idiopathic Pulmonary Fibrosis from the FDA. As of November 2016, the company has a technology development arrangement in place with a German company called XL-protein GmbH for improving the half-life of its i-bodies through a technology called 'PASylation', and it also has its first commercial collaboration following an agreement to work with a Dutch company called Crossbeta Biosciences on a potential Alzheimer's therapy. Coming up for AdAlta is completion of manufacturing scale-up for AD-114, which would show potential partners that AdAlta can make its drug in simple bacterial systems, and then the preparation for AD-114's first clinical study, expected to kick off in early 2018. Our 60-cent price target and Buy recommendation for AdAlta stays in place.

| Rating | Risk | Current price | Target price |
|---|---|---|---|
| Buy | Speculative | $0.21 | $0.60 |




**Stock details**

Daily Turnover: ~A$9,300
Market Cap: A$21.2m
Shares Issued: 101.1m
52-Week High: $0.28
52-Week Low: $0.17

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**Please note:** Please refer below for risks related to AdAlta as well our General Advice Warning, disclaimer and full disclosures. Also please be aware that the investment opinion in this report is current as at the date of publication but that the circumstances of the company may change over time, which may in turn affect our investment opinion.

# About NDF Research

NDF is an independent equity research firm based in Sydney, Australia. It focuses on Life Science companies that are publicly traded on the Australian Securities Exchange (ASX). This Exchange hosts one of the world's premier equity markets for biotech and medical device companies, and is home to world-beating companies such as CSL and ResMed and emerging pioneers such as Mesoblast and Impedimed.

NDF's Founder and Senior Analyst, Stuart Roberts, has been involved in Life Sciences since 2002 as a sell-side analyst as well as an executive of two ASX-listed immuno-oncology drug developers.

NDF believes that ASX-listed companies have been largely overlooked in the global Life Sciences boom that began in late 2008, partly because of insufficient quality research. NDF's goal is to provide such research, and introduce investors around the world to potential future billion dollar companies from 'Down Under'.

To learn more about the Life Sciences sector on the ASX and our firm, please visit ndfresearch.com.

*Ferry at the end of a rainbow on Sydney Harbour, August 2014*

# In this report

# Financial summary

| | |
|---|---|
| Code | 1AD |
| Analyst | Stuart Roberts |
| Date | 15 February, 2017 |
| Share price | $0.2100 |
| Market capitalisation | $21m |
| Year end | 30 June |

| | |
|---|---|
| Rating | BUY |
| Price target | $0.600 |
| Upside/downside | 185.7% |
| Valuation | $0.352 / $0.851 |
| Valuation method | Probability-weighted DCF |
| Risk | Speculative |

**PROFIT AND LOSS (A$m)**

| Y/e June 30 (A$m) | FY15A | FY16A | FY17E | FY18E | FY19E |
|---|---|---|---|---|---|
| Revenue | 0.8 | 0.7 | 0.4 | 0.6 | 14.9 |
| **EBITDA** | **-1.4** | **-1.2** | **-4.4** | **-5.6** | **7.4** |
| D&A | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **EBIT** | **-1.4** | **-1.2** | **-4.4** | **-5.6** | **7.4** |
| Net interest | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Pre-tax profit | **-1.4** | **-1.2** | **-4.3** | **-5.6** | **7.4** |
| Tax | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| NPAT | -1.4 | -1.2 | -4.3 | -5.6 | 7.4 |
| Minority interests | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Net profit after minorities | -1.4 | -1.2 | -4.3 | -5.6 | 7.4 |

**BALANCE SHEET (A$m)**

| Y/e June 30 | FY15A | FY16A | FY17E | FY18E | FY19E |
|---|---|---|---|---|---|
| Cash | 0.0 | 0.5 | 6.9 | 1.7 | 8.7 |
| Current receivables | 0.1 | 0.9 | 0.1 | 0.1 | 0.7 |
| Inventories | 0.0 | 0.0 | 0.0 | 0.0 | 0.5 |
| Other current assets | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Current assets** | **0.1** | **1.4** | **7.0** | **1.8** | **10.0** |
| PPE | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Intangible assets | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Other non-current assets | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Non-current assets** | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Total assets** | 0.1 | 1.4 | 7.0 | 1.8 | 10.0 |
| Payables | 0.3 | 0.2 | 0.5 | 0.5 | 0.9 |
| Debt | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Other liabilities | 0.0 | 0.0 | 0.1 | 0.1 | 0.1 |
| **Total liabilities** | 0.3 | 0.2 | 0.6 | 0.6 | 1.0 |
| Shareholders' equity | -0.2 | 1.2 | 6.4 | 1.2 | 9.0 |
| Minorities | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Total shareholders funds** | **-0.2** | **1.2** | **6.4** | **1.2** | **9.0** |
| **Total funds employed** | **0.1** | **1.4** | **7.0** | **1.8** | **10.0** |
| **W/A shares on issue** | 2 | 8 | 101 | 101 | 101 |

**CASH FLOW (A$m)**

| Y/e June 30 | FY15A | FY16A | FY17E | FY18E | FY19E |
|---|---|---|---|---|---|
| NPAT plus discontinued ops. | -1.4 | -1.2 | -4.3 | -5.6 | 7.4 |
| Non-cash items | 0.0 | 0.0 | 0.4 | 0.4 | 0.4 |
| Working capital | 0.0 | 0.0 | 0.9 | 0.0 | -0.7 |
| Other operating cash flow | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Operating cashflow** | **-1.4** | **-1.2** | **-3.1** | **-5.2** | **7.1** |
| Capex | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Investments | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Other investing cash flow | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Investing cashflow** | **0.0** | **0.0** | **0.0** | **0.0** | **0.0** |
| Change in borrowings | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Equity raised | 1.0 | 1.6 | 9.5 | 0.0 | 0.0 |
| Dividends paid | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Other financing cash flow | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Financing cashflow** | **1.0** | **1.6** | **9.5** | **0.0** | **0.0** |
| **Net change in cash** | **-0.3** | **0.5** | **6.4** | **-5.2** | **7.1** |
| **Cash at end of period** | 0.0 | 0.5 | 6.9 | 1.7 | 8.7 |

**EARNINGS (A$m)**

| Y/e June 30 | FY15A | FY16A | FY17E | FY18E | FY19E |
|---|---|---|---|---|---|
| Net profit ($m) | -1.4 | -1.2 | -4.3 | -5.6 | 7.4 |
| EPS (c) | -66.2 | -14.1 | -4.3 | -5.5 | 7.3 |
| *EPS growth (%)* | N/A | N/A | N/A | N/A | N/A |
| P/E ratio (x) | -0.3 | -1.5 | -4.9 | -3.8 | 2.9 |
| CFPS (c) | -66.9 | -14.2 | -3.0 | -5.2 | 7.0 |
| Price/CF (x) | -0.3 | -1.5 | -6.9 | -4.1 | 3.0 |
| DPS ( c ) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| *Yield (%)* | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% |
| Franking (%) | N/A | N/A | N/A | N/A | N/A |
| EV/EBITDA | -15.4 | -17.7 | -3.3 | -3.5 | 1.7 |
| EV/EBIT | -15.4 | -17.7 | -3.3 | -3.5 | 1.7 |

**PROFITABILITY RATIOS**

| Y/e June 30 | FY15A | FY16A | FY17E | FY18E | FY19E |
|---|---|---|---|---|---|
| EBITDA/revenue (%) | N/A | N/A | N/A | N/A | 49.8% |
| **EBIT/revenue (%)** | N/A | N/A | N/A | N/A | 49.8% |
| Return on assets (%) | -1536.0% | -84.1% | -61.9% | -310.3% | 74.7% |
| Return on equity (%) | 790.2% | -99.6% | -67.7% | -464.2% | 82.6% |
| Return on funds empl'd (%) | 790.2% | -99.6% | -67.7% | -464.2% | 82.6% |
| Dividend cover (x) | N/A | N/A | N/A | N/A | 0% |
| Effective tax rate (%) | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% |

**LIQUIDITY AND LEVERAGE RATIOS**

| Y/e June 30 | FY15A | FY16A | FY17E | FY18E | FY19E |
|---|---|---|---|---|---|
| Net debt/(cash) ($m) | 0 | 0 | -7 | -2 | -9 |
| **Net debt/equity (%)** | 20.2% | -41.6% | -107.2% | -138.6% | -97.0% |
| Net interest cover (x) | N/A | N/A | N/A | N/A | N/A |
| Current ratio (x) | 0.3 | 6.4 | 11.8 | 3.0 | 10.4 |

**INTERIMS**

| Y/e June 30 ($m) | 2H15A | 1H16A | 2H16A | 1H17F | 2H17F |
|---|---|---|---|---|---|
| Revenue | 0.8 | 0.2 | 0.6 | 0.0 | 0.4 |
| **EBITDA** | **-0.4** | **-0.7** | **-0.5** | **-2.3** | **-2.1** |
| D&A | **0.0** | **0.0** | **0.0** | **0.0** | **0.0** |
| **EBIT** | **-0.4** | **-0.7** | **-0.5** | **-2.3** | **-2.1** |
| Net interest | **0.0** | **0.0** | **0.0** | **0.0** | **0.0** |
| Pre-tax profit | -0.4 | -0.7 | -0.4 | -2.3 | -2.1 |
| Tax | **0.0** | **0.0** | **0.0** | **0.0** | **0.0** |
| NPAT | -0.4 | -0.7 | -0.4 | -2.3 | -2.1 |
| Minority interests | **0.0** | **0.0** | **0.0** | **0.0** | **0.0** |
| Net profit after minorities | -0.4 | -0.7 | -0.4 | -2.3 | -2.1 |

**VALUATION**

| | Base | Optimistic |
|---|---|---|
| Value of AdAlta technology | 30.5 | 81.5 |
| Value of tax losses | 2.1 | 2.1 |
| Corporate overhead | -5.5 | -5.5 |
| Cash now (A$m) | 8.8 | 8.8 |
| Cash to be raised (A$m) | 0.0 | 0.0 |
| Option exercises (A$m) | 0.0 | 0.0 |
| Total value (A$m) | 35.9 | 86.9 |
| Total diluted shares (million) | 102.1 | 102.1 |
| Value per share | $0.352 | $0.851 |
| Valuation midpoint | $0.602 | |
| Share price now (A$ per share) | $0.210 | |
| Upside to midpoint | 186.4% | |

# Solid new pre-clinical data on AD-114

**AdAlta already had some promising *in vivo* and *in vitro* data on AD-114 in Idiopathic Pulmonary Fibrosis.** We knew from a PCT patent application[1] which was published in July 2016 that AD-114 was potentially powerful in Idiopathic Pulmonary Fibrosis (IPF):

- In the standard Bleomycin mouse model of IPF[2], AD-114 was able to reduce collagen content and inflammation in the lungs, as well as reduce fibroblast migration to the lungs, to the point where the lung tissue was almost normalised[3].
- *In vitro*, the drug also seems to work on both IPF 'slow progressors' and 'fast progressors'[4], the difference being test subjects whose lung function declines slowly and have a relatively low level of fibrocytes in their lungs, as against test subjects whose lung function declines quickly and have a high level of fibrocytes[5].

**For AD-114 in IPF, just got a whole lot better, in terms of the *in vivo* evidence**. In January 2017 AdAlta reported further favourable pre-clinical data on the effectiveness of AD-114 in IPF. Prior to January, AdAlta had been able to assert that AD-114 reduces collagen deposition in the Bleomycin mouse model due to the use of an assay called 'Sircol'. However, this assay is somewhat controversial[6]. To double-check the reduced collagen claim, and at the request of the FDA ahead of the grant of Orphan Drug status, AdAlta repeated the work using a visual assessment scale called Ashcroft[7] and an assay for hydroxyproline, in which collagen is abundant. It also measured collagen gene expression, looking for two genes called Col1A and Col3A. The results confirmed what AdAlta had said all along, that collagen came down markedly after just 14 days of AD-114 treatment.

**AD-114 CAN MARKEDLY REDUCE COLLAGE IN ANIMAL MODELS OF IPF**

**AdAlta now has evidence that AD-114 works in liver fibrosis.** We noted in our 13 September 2016 report on AdAlta that AD-114's target, CXCR4, was a key player in NASH, that is Nonalcoholic Steatohepatitis[8]. NASH, a fibrotic disease characterised by fat build-up in the liver, is understood to affect around 2-3% of the general population of most Western countries, however at the moment there are no treatment options for patients[9]. That has led to significant interest by pharma companies in developing new drugs for NASH. AdAlta is now potentially a player in the NASH drug development game, as well as drugs for a related disorder called non-alcoholic fatty liver disease (NAFLD), with evidence from *in vivo* work that AD-114 can act against liver fibrosis.

[1] See *CXCR4 binding molecules*, WO/2016/109872.
[2] Bleomycin, an antitumor antibiotic, causes lung injury in patients (see Arch Toxicol. 1991;65(2):81-94), and the drug is therefore useful in modelling pulmonary fibrosis in mice (See PLoS One. 2013;8(4):e59348. Epub 2013 Apr 2).
[3] See example 18 of WO/2016/109872.
[4] This 'fast progressor' and 'slow progressor' distinction was first identified by a group at McMaster University in Canada in 2009 – see Am J Respir Crit Care Med. 2009 Apr 1;179(7):588-94. Epub 2009 Jan 16.
[5] See example 21 of WO/2016/109872.
[6] Sircol is a simple colorimetric method for the determination of collagen concentration based on the binding of a dye called Sirius Red to the collagen. The trouble with Sircol is that it can be interfered with by non-collagenous proteins such as serum (see Acta Biomater. 2010 Aug;6(8):3146-51. Epub 2010 Feb 6).
[7] Biotechniques. 2008 Apr;44(4):507-11, 514-7.
[8] Clin Sci (Lond). 2015 Feb;128(4):257-67.
[9] Dig Dis. 2010;28(1):155-61. Epub 2010 May 7.

- In an animal model of liver disease (which we understand to be the Stelic model[10]), AD-114 was able to reduce serum alanine aminotransferase (ALT) by around a third. ALT is an enzyme found mostly in the cells of the liver and kidney which is released into the blood when the liver is damaged, making it a useful test for early detection of liver damage. This suggests at the very least that AD-114 is hepatoprotective[11].
- AD-114 reduced the NAFLD score;
- There was significantly less 'hepatocellular ballooning' – in NASH, liver cells tend to enlarge as a result of damage to the cytoskeleton. The degree of ballooning is a key indicator of risk of disease progression[12].

# AD-114 is now an Orphan Drug in IPF

**AD-114 was granted Orphan Drug status by the FDA for IPF in January 2017.** In the US an Orphan Drug, as per the Orphan Drug Act of 1983, is one that treats a disease that affects less than 200,000 people in the United States. Having Orphan Drug status brings a new drug substantial benefits in terms of the path to market, namely

- US Federal tax credits for up to 50% of the research costs;
- seven years of US market exclusivity for the approved indication, where there aren't patents pending to take the exclusivity further[13];
- waivers of PDUFA fees[14];
- research grants to defray clinical development costs[15]; and
- protocol assistance from the FDA.

Many Orphan Drugs get Fast Track and Priority Review[16], and the FDA often shows flexibility in considering Orphan Drugs[17]. The gaining of Orphan Drug status means that the FDA's people have done substantial due diligence on the drug and deemed it worthy of ongoing investment of Agency time and resources.

**ORPHAN DRUGS ARE OFTEN EASIER TO DEVELOP THAN MAINSTREAM DRUGS**

**Why an IPF indication for AD-114 is still valuable even after Esbriet and Ofev.** Two drugs gained FDA approval for the treatment of IPF in 2014[18]:

- Roche's Esbriet[19], which works by to work by interfering with the production TGF-β and TNF-a;

[10] Where neonatal male mice are exposed to streptozotocin to induce liver steatosis with diabetes, then fed a high-fat diet. See Med Mol Morphol. 2013 Sep;46(3):141-52. Epub 2013 Feb 22. For a recent overview of animal models for fibrotic liver diseases see J Clin Transl Hepatol. 2015 Mar; 3(1): 53–66.
[11] ALT doesn't predict NASH or NAFLD very well – see Liver Int. 2013 Oct;33(9):1398-405. Epub 2013 Jun 13.
[12] World J Gastroenterol. 2014 Nov 28; 20(44): 16474–16479.
[13] This is better than the usual five years exclusivity granted to non-orphan new chemical entities.
[14] The Prescription Drug User Fee Act of 1992 allows the FDA to collect fees from drug developers in order to review drug approval applications by a set 'PDUFA date'. The Act is renewed every five years. With President Obama's renewal of PDUFA in July 2012 (PDUFA V) the fees which drug developers pay to the FDA rose to US$1.96m for the initial application, US$0.53m for the annual 'establishment fee' (for the drug's manufacturing facility) and US$0.1m for the annual 'product fee' for the drug itself. Orphan Drugs are free of these fees.
[15] Orphan Products Grants Program provides up to $200,000-$300,000 per year for three years.
[16] Fast Track designation from the FDA provides benefits such as scheduled meetings to seek FDA input into development plans, the option of submitting an NDA in sections rather than all at one, and, and the option of requesting evaluation of studies using surrogate endpoints. Priority Review mean that the FDA will decide whether to approve drugs within six months of the application's submission, rather than the usual 10 months or so.
[17] A 2011 study from the National Organization for Rare Diseases found, in examining 135 non-cancer FDA-approved Orphan Drugs, that in 90 of these approvals that Agency had shown flexibility when reviewing the drug's application, and had been willing to customise the approval process in 58 of them. Source: *Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs* by Frank Sasinowski, 2011 report from the National Association of Rare Diseases.
[18] Indeed, both drugs were approved on the same day – 15 October 2014.
[19] Generic name pirfenidone, see www.esbriet.com.

- Boehringer Ingelheim's Ofev[20], a tyrosine kinase inhibitor.

At first glance two drugs would appear to be enough for a US patient population of only 100,000. What that view ignores is that fact that before Esbriet and Ofev there were no drugs at all indicated for IPF, which is why both compounds were granted Breakthrough Therapy Designation by the FDA in July 2014.Consequently any new drug was a step forward, even in the drugs came with drawbacks.

- Both compounds have serious side effects - typically around 60% of Esbriet patients will experience gastrointestinal upset, 40% will experience fatigue and 25% will find that their skin is more sensitive to the sun (photosensitivity)[21]. For Ofev the common adverse events are diarrhea (60%) and nausea (25%)[22].
- The drugs don't stabilise or reverse lung function decline, only slow the rate of decline by around half over a twelve-month period[23]

**Where AD-114 may be the next step forward for IPF**. Obviously, it is early days for AdAlta's development of AD-114 in IPF but there is the potential for a differentiated product:

**AD-114 IS DIFFERENT FROM THE EXISTING IPF DRUGS**

- Ofev isn't specific to disease fibroblasts; AD-114 is;
- Esbriet can't work on both fast and slow progressors (the clinical data seems to suggest its effectiveness is in slow progressors[24]); AD-114 can

We estimate that the global market opportunity for IPF is probably US$1-3bn, so commercially there is room for other drugs.

**Various companies are going after new IPF drugs, but none are late stage**. We see AdAlta benefiting from the relatively early-stage nature of the remaining IPF competition:

- **Curis**. This company, which is mostly focused on new cancer drugs, developed Genentech's Erivedge (vismodegib) for the treatment of advanced Basal Cell Carcinoma. Genentech has now taken Erivedge into the clinic as a potential IPF treatment. Erivedge works by targeting the Hedgehog signaling pathway, and Hedgehog is understood to play a role in IPF as well[25].
- **FibroGen**. This company's work on Connective Tissue Growth Factor (CTGF) has led to Pamrevlumab, an anti-CTGF antibody that performed well in an open-label Phase 2 study in IPF[26]. A placebo-controlled Phase 2 trial has completed enrolment.
- **Galapagos**. This company is one of the pioneers of drugs that work through the JAK1 pathway - its filgotinib JAK1 inhibitor is in Phase 3 in Rheumatoid Arthritis. Its GLPG1690 autotaxin inhibitor is in Phase I in IPF. Autotaxin is an enzyme which generates lysophosphatidic acid (LPA), known to be a mediator of fibroblast recruitment in IPF[27].
- **Global Blood Therapeutics**. This company, focused on blood-based disorders, is in Phase 3 in sickle cell disease and IPF with GBT440, a haemoglobin modifier[28].

[20] Generic name nintedanib, see www.ofev.com.
[21] Am J Respir Crit Care Med. 1999;159(4 Pt 1):1061–1069.
[22] Am Health Drug Benefits. 2015 Mar; 8(Spec Feature): 101–104.
[23] Drug Des Devel Ther. 2015; 9: 6407–6419.
[24] N Engl J Med. 2014 May 29;370(22):2083-92. Epub 2014 May 18.
[25] Am J Physiol Lung Cell Mol Physiol. 2012 Dec 1;303(11):L978-90. Epub 2012 Sep 28.
[26] Eur Respir J. 2016 May;47(5):1481-9. Epub 2016 Mar 10.
[27] Am J Respir Cell Mol Biol. 2012 Nov; 47(5): 563–565.
[28] The drug's usefulness may be in increasing haemoglobin-oxygen affinity - see Physiol Rep. 2016 Sep;4(17). pii: e12965.

- **Pulmatrix**. This company is a developer of pulmonary therapeutics based on a platform called ISPERSE for engineering inhaled small particles. PUR1900 is an ISPERSE formulation of an anti-fungal for cystic fibrosis patients. PUR1500, for IPF, is an iSPERSE formulation of a 'kinase inhibitor with established anti-angiogenesis activity'.

# Liver fibrosis is a significant market opportunity

**NASH and NAFLD are shaping up to be billion-dollar drug markets**. When fat molecules build up inside liver cells, to the point where more than 5% of the liver by weight is fat, the result is Non-Alcoholic Fatty Liver Disease (NAFLD). The 'Non-Alcoholic' means that the fat build up isn't primarily the result of drinking. The presence of fat in the liver may be almost asymptomatic in most cases, which is why it took until 1980 for it to be first described in the literature[29]. That said, 30%-or-so of the US population has this condition[30], and there are comparable figures in other Western world jurisdictions[31]. Consequently, NAFLD has turned into a serious disease burden as the most common cause of liver problems. The cutting edge of this disease burden is non-alcoholic steatohepatitis, or NASH, in which the fat build-up is accompanied by damaging liver inflammation, leading to fibrosis and from there in some instances to cirrhosis. The mechanism by which NAFLD progresses to NASH is currently unknown, however that transition is the subject of much research interest given that perhaps 3% of the US population has NASH[32], which is 9-10 million people. The large market opportunity, and the fact that no drug has ever been approved for NASH – meaning that the 'standard of care' is effectively low-calorie and low fat diets, and physical activity – has also prompted large and small pharma companies around the world to start developing pipelines of NASH drug candidates.

**3% OF THE US POPULATION MAY HAVE NASH**

**There are three broad approaches being pursued for future NASH drugs**. One approach involves metabolic modifers that, by restoring insulin sensitivity and normal glucose metabolism, can bring fat in the liver down. Another group of compounds are focused on blunting the inflammation ultimately behind the fibrosis. A third approach, and so far the least pursued due to what science doesn't yet know about how fibrosis works, has been drugs that directly act on fibrosis mechanisms such as the build-up of collagen. AdAlta's AD-114 is anti-inflammatory but also has a direct anti-fibrotic effect due to CXCR4's role in promoting fibrocyte migration[33].

**The first drugs for NASH may be coming soon.** The US drug developer Intercept Pharmaceuticals[34] is currently in Phase 3 with Ocaliva, a metabolic modifier drug[35] which in Phase 2 demonstrated improved liver histology in 45% of the treated patients versus 21% in the placebo group[36]. Ocaliva was granted Breakthrough Therapy Designation by FDA for the treatment of NASH with liver fibrosis in January 2015. The drug targets the farnesoid X receptor (FXR), highly relevant in inflammatory disorders and fibrotic disease[37]. It gained its first approval in May

[29] Mayo Clin Proc. 1980 Jul;55(7):434-8.
[30] Am J Epidemiol. 2013 Jul 1;178(1):38-45. Epub 2013 May 23.
[31] Hepatology. 2016 Jul;64(1):73-84. Epub 2016 Feb 22.
[32] Dig Dis. 2010;28(1):155-61. Epub 2010 May 7.
[33] J Med Invest. 2013;60(1-2):127-37.
[34] New York, NY, Nasdaq: ICPT, www.interceptpharma.com.
[35] Ocaliva is obeticholic acid, a synthetic bile acid known to improve lipoprotein metabolism – see Diabetes Obes Metab. 2016 Sep;18(9):936-40. Epub 2016 Jun 6.
[36] Lancet. 2015 Mar 14;385(9972):956-65. Epub 2014 Nov 7.
[37] Diabetes Metab. 2008 Dec;34(6 Pt 2):685-91.

2016 for the treatment of a rare liver disease called primary biliary cholangitis (PBC). In February 2017 Intercept advised the market that the FDA had reduced the number of patients needed in the NASH Phase 3 before an interim analysis was allowed from 1,400 to 750. Moreover the Agency will now allow Intercept to only meet one of two co-endpoints: improvement in fibrosis or NASH resolution (defined as zero ballooning or residual/no inflammation)[38]. This Phase 3 is expected to be completed around 2019. Other programmes are following on behind this one, including major programmes from Gilead, Allergan and BMS as well as emerging programmes from companies like:

- **Genfit**[39], in Phase 3 with a PPAR agonist[40] called Elafibranor which in Phase 2 met its primary endpoint of NASH resolution without worsening of fibrosis, but only after adjusting for baseline severity and site heterogeneity[41]
- **Galmed Pharmaceuticals**[42]**,** in Phase 2b with Aramchol, a fatty acid / bile acid conjugate[43]**.**
- **Cempra**[44]**,** in Phase 2 with Solithromycin, a macrolide antibiotic with anti-inflammatory properties.
- **MediciNova**[45], in Phase 2 in both NASH and IPF with tipelukast, a leukotriene receptor antagonist.

**The deals are becoming attractive in NASH**. A notable feature of the NASH drug development space has been the high prices that pharma companies are willing to pay to get hold of promising programmes. Consider:

**DEALS AROUND NASH CAN BE IN THE HUNDREDS OF MILLIONS**

- **Gilead, January 2015.** Gilead obtained an FXR agonist called GS-9674 currently in Phase 2, from the German biotech Phenex Pharmaceuticals for a total deal package of US$470m. Gilead made a US$100m milestone payment paid to Phenex in January 2017.
- **Boehringer Ingelheim, May 2015**. Boehringer licensed PXS-4728A, an inhibitor of an adhesion molecule called VAP-1[46], from the Australian drug developer Pharmaxis[47] for €27.5m upfront and a total potential deal value of over A$750m.
- **Gilead, April 2016.** Gilead acquired GS-0976, an allosteric inhibitor of an enzyme called ACC that prevents fatty acid synthesis, for US$400m upfront and US$800m in milestones in April 2016[48]. GS-0976 is now in Phase 2.
- **Allergan, September 2016**. Allergan bought Tobira Therapeutics for US$1.7bn in September 2016. Tobira, whose main focuses were liver disease and inflammation, was in Phase 2 with Cenicriviroc, a dual inhibitor of the CCR2 and CCR5 pathways known to be relevant in both inflammation and fibrosis. The first two Cenicriviroc indications were NASH and another disease of the bile ducts of the liver called primary sclerosing cholangitis (PSC).

[38] See *Intercept jumps on NASH phase 3 protocol changes* by Ben Adams, Fierce Biotech, 10 February 2017.
[39] Loos, France, Euronext Paris: GNFT, www.genfit.com.
[40] PPAR is Peroxisome proliferator-activated receptor. PPARs are of nuclear receptor proteins that function as transcription factors and play an important role in metabolism. Elafibranor targets PPAR alpha and delta – see Hepatology. 2013 Dec;58(6):1941-52. Epub 2013 Oct 29.
[41] See the Genfit press release dated 26 March 2015 and headlined 'Genfit announces topline results from the Golden-505 trial in NASH'.
[42] Tel Aviv, Israel, Nasdaq: GLMD, www.galmedpharma.com.
[43] Clin Gastroenterol Hepatol. 2014 Dec;12(12):2085-91.e1. Epub 2014 May 9.
[44] Chapel Hill, NC, Nasdaq: CEMP, www.cempra.com.
[45] La Jolla, Ca., Nasdaq: MNOV, www.medicinova.com.
[46] Vascular Adhesion Protein-1 – see J Clin Invest. 2015 Feb 2; 125(2): 501–520.
[47] Sydney, Australia, ASX: PXS, www.pharmaxis.com.au.
[48] See the Nimbus Therapeutics press release dated 4 April 2016 and headlined *Gilead Sciences announces acquisition of Nimbus Therapeutics' Acetyl-CoA Carboxylase (ACC) program for NASH and other liver diseases.*

- **Allergan, September 2016**. The same day Allergan was buying Tobira it also acquired the earlier-stage Akarna Therapeutics for US$50m upfront plus undisclosed milestones. Akarna had a selective FXR agonist at preclinical.
- **Bristol-Myers Squibb, November 2016**. BMS licensed a suite of siRNA molecules targeting HSP-47[49] from the Japanese company Nitto Denko[50] for US$100m upfront. The lead molecule in this programme, ND-L02-s0201, is currently in Phase 1b study for the treatment of advanced liver fibrosis from either NASH on Hepatitis C infection.
- **Novartis, December 2016**. Novartis licensed Emricasan, an oral pan-caspase inhibitor in Phase 2 in NASH, from Conatus Pharmaceuticals[51] for US$50m upfront.

**NASH could be a serious opportunity for AdAlta.** We see the increasing levels of clinical and commercial activity in the NASH space as helping shape the market opportunity for AdAlta over the next three years. While the *in vivo* evidence on hepatocyte ballooning bodes well for NASH, there may also be an opportunity to target liver co-morbidities given how the drug seems to be hepatoprotective.

# AdAlta is improving the half-life of its i-bodies

ADALTA BELIEVES IT CAN LENGTHEN I-BODY HALF LIFE TO RIVAL MONOCLONALS

**The half-life of i-bodies needs to be improved to make them competitive with monoclonals**. One of the strengths of monoclonal antibodies is that they have a long serum half-life, in many cases greater than three weeks[52]. In developing i-bodies, AdAlta's scientists haven't been able to match that because of the small molecule size, which means that the protein is cleared from circulation via the kidneys at a rapid rate. A shorter half-life could be deleterious to the commercial prospects of i-bodies because generally, the less frequently a protein drug must be dosed, the more popular it is with physicians and patients alike. Consequently, AdAlta has sought for ways to increase half-life. A common approach with other therapeutic proteins where better half-life is needed is to 'PEGylate' the protein, that is, conjugate it to a polymer called polyethylene glycol which increases the molecular mass of the protein and, importantly, shields it from proteolytic enzymes. PEG is popular with protein drug engineers due to its well-established safety profile and its 'tunable' properties, meaning that the half-life can be raised or lowered in a predictable fashion. AdAlta used PEGylated i-bodies in some of its early *in vivo* work[53], but was concerned at the multiple conjugation and purification steps that would be required, which would raise the manufacturing cost of the drug. In November 2016, however, it moved towards what it considers to be a much better approach called 'PASylation'.

**What is PASylation?** PASylation, which originated around three years ago at the Technical University of Munich in Germany[54], is, as the name suggests, similar to PEGylation in that involves using a polymer to extend the half-life of the protein of interest. With PASylation the half-life extender is simply a long sequence of the small amino acids proline (P), alanine (A), and serine (S). PAS sequences have similar properties to PEG because they adopt a

[49] Heat shock protein 47, a collagen chaperone – see Nat Biotechnol. 2008 Apr;26(4):431-42. Epub 2008 Mar 30.
[50] Osaka, Japan, TSE: 6988, www.nitto.com. Nitto Denko is a conglomerate one of whose divisions is involved in the synthesis of nucleic acid medicines.
[51] San Diego, Ca., Nasdaq: CNAT, www.conatuspharma.com.
[52] Cancer Control. 2002 Mar-Apr;9(2):152-66.
[53] See *CXCR4 binding molecules*, WO/2016/109872, op. cit.
[54] Protein Eng Des Sel. 2013 Aug;26(8):489-501. Epub 2013 Jun 10.

random coil structure in aqueous solution, which generates the requisite change in hydrodynamic volume. The difference is that, unlike PEG, PAS can be fused onto the therapeutic protein at the genetic level, cutting out the coupling or conjugation steps. Like PEG, it is tunable, but unlike PEG, which is not metabolised by the body, PAS metabolises easily. Given that AdAlta intends to manufacture its i-bodies in simple-to-use and cheap-to-operate bacterial cell systems, PASylation is an ideal half-life extension technology. The results *in vivo* for PAS's commercial developer, XL-protein GmbH[55], have been stunning. For example, when XL-protein PASylated leptin, a satiety hormone potentially useful in the treatment of obesity, it improved the half-life in mice from around half an hour to more like 20 hours[56]. When XL-protein PASylated a protein called Coversin, a complement inhibitor being developed by the US biotech company Akari Therapeutics[57], it not only raised the half-life but, unexpectedly, improved the therapeutic ability of the original drug *in vivo*[58].

**AdAlta will now work with XL-protein on PASylation of AD-114**. AdAlta announced in November 2016 that it would collaborate with XL-protein on PASylation of AD-114. Encouragingly, AdAlta reported a 'dramatic extension' in half-life from animal work that XL had performed. Obviously AdAlta's manufacturing scale-up for AD-114 will now have to take account of PASylation, but if it can be shown that GMP bacterial systems can accommodate the entire PASylated protein, this will be a significant step forward in terms of engendering partner interest in i-bodies.

**i-bodies can also work with other half-life extension modalities**. The beauty of i-bodies is their flexibility. That means PASylation is only one of several approaches that AdAlta could take should the XL collaboration not work out as planned. For example, the company could develop an i-body that binds to serum albumin or FcRN, or create a bi-specific (as Ablynx have done) where one i-body binds to the target of interest and the other binds to albumin, thereby extending the half-life.

# Valuing AdAlta

We previously valued Adalta at $0.38 per share base case and $0.89 per share optimistic case using a probability-weighted DCF approach. With this note we are reducing our valuation slightly, to at $0.35 per share base case and $0.85 per share optimistic case, but only due to a change in our discount rate because the Australian ten year bond rate has risen slightly since September 2016. Our approach was as follows:

**WE VALUE ADALTA AT 35 CENTS BASE CASE AND 85 CENTS OPTIMISTIC CASE**

- Our WACC was 15.4% (Speculative – previously it was 14.5%)[59].
- We modelled a payoff only for AD-114 and allowed no value for the future AdAlta pipeline. We believe the building of this pipeline will allow us to gradually add value for future products.
- We assume another US$5-10m in expenditure for AdAlta to further develop AD-114;

[55] Friesing, Germany, privately held, www.xl-protein.com.
[56] Mol Pharm. 2015 May 4;12(5):1431-42. Epub 2015 Apr 10.
[57] New York, NY, Nasdaq: AKTX, www.akaritx.com. Coversin can potentially compete with Alexion's blockbuster complement inhibitor Soliris.
[58] Bioconjug Chem. 2016 Oct 19;27(10):2359-2371. Epub 2016 Sep 26.
[59] For a relevant discount rate, we use WACCs of between ~12% and ~16% depending on the risk for Life Science companies. This is derived from a RFR of the Australian ten year bond rate; a MRP of 7.5%-11.5% (7.5% for 'medium risk' companies, 9.5% for 'high risk' companies and 11.5% for 'speculative' companies like AdlAlta); and an ungeared beta of 1.1. We regard Life Science companies with existing businesses, or who have enough capital to reach the market with their products, as 'Medium' risk. Companies that have small revenue streams from marketed products but that are still potentially in need of capital are 'High' risk. Everything else is 'Speculative'.

- We model around 14 years of commercial exclusivity for AD-114.

**Risk weighting**

- We modelled AD-114 with a 20% probability of clinical success, which is roughly what its chances would be at Phase 2. We think this is reasonable give the *in vitro* evidence related to targeting and the fact that IPF is an Orphan disease, meaning that it can quickly transition to mid and late stage clinical development.

**Commercial outcomes**

- We assume that the product can license to a pharma partner in FY20 (base case) or FY19 (optimistic case) for US$30-50m upfront, US$150-300m in milestones and an 8-12% royalty.
- We assume a product launch in IPF and Wet AMD in FY23 (base case) or FY22 (optimistic case) in the US and FY24 (base case) or FY23 (optimistic case) in Europe.
- We assume peak sales for AD-114 of US$300-600m, initially from in IPF and Wet AMD. We believe this assumption is conservative given the market opportunity in both indications.

**Further capital**

- We assume no further capital needs to be raised, but that partnership and collaboration deals from 2018 can fund the company on an ongoing basis.

# Re-rating AdAlta

We see a number of events helping to re-rate AdAlta to our target price over the next 12-18 months:

- Publication of further *in vitro* and *in vivo* data showing the therapeutic of i-bodies in IPF and other fibrosis indications;
- Development of new i-body candidates;
- Potential partnerships or evaluation agreements around i-bodies;
- Completion of scale-up manufacturing of PASylated AD-114 for the Phase I in IPF;
- Initiation of the IPF Phase I.

**ADALTA WILL BE IN THE CLINIC WITH AD-114 BY 2018**

# Risks related to AdAlta

Risks specific to AdAlta. We see four major risks for AdAlta as a company and as a listed stock:

- *Manufacturing risk.* There is the risk that AdAlta may take longer to manufacture AD-114 than the time we have postulated in this note (ie to start in the clinic by 2018), particular given that PASylation is a relatively new modality for extending the half-life of protein therapeutics.
- *Timing risk*. There is the risk that the intended Phase I study of AD-114 may not happen as early as the beginning of 2018 for reasons other than manufacturing (eg delays in ethics approval for the study).
- *Regulatory ris*k. There is the risk that the FDA and other regulators may decline to approve AD-114 even if AdAlta considers the data submitted to be adequate.
- *Commercial risk*. There is the risk that AD-114 may not find significant usage in IPF as other therapies come onto the market between now and the end of AD-114's clinical development.

**Risks related to pre-revenue Life Science companies in general**.

- The stocks of biotechnology and medical device companies without revenue streams from product sales or ongoing service revenue should always be regarded as speculative in character.
- Since most biotechnology and medical device companies listed on the Australian Securities Exchange fit this description, the 'term' speculative can reasonably be applied to the entire sector.
- The fact that the intellectual property base of most biotechnology and medical device lies in science not generally regarded as accessible to the layman adds further to the riskiness with which the sector ought to be regarded.

***Caveat emptor***. Investors are advised to be cognisant of the abovementioned specific and general risks before buying any the stock of any biotechnology and medical device stock mentioned on this report, including AdAlta.

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