ISSN 1443-850X

Bioshares

8 November 2013
Edition 528

Delivering independent investment research to investors on Australian biotech, pharma and healthcare companies.

	Bioshares Portfolio
Year 1 (May '01 - May '02)	21.2%
Year 2 (May '02 - May '03)	-9.4%
Year 3 (May '03 - May '04)	70.6%
Year 4 (May '04 - May '05)	-16.3%
Year 5 (May '05 - May '06)	77.8%
Year 6 (May '06 - May '07)	17.4%
Year 7 (May '07 - May '08)	-36%
Year 8 (May '08 - May '09)	-7.4%
Year 9 (May '09 - May '10)	50.2%
Year 10 (May '10 - May'11)	45.4%
Year 11 (May '11 - May '12)	-18.0%
Year 12 (May '12 - May '13)	3.1%
Year 13 (May '13 - Current)	63.2%
Cumulative Gain	**481%**
Av. annual gain (13 yrs)	**20.1%**

Bioshares is published by Blake Industry & Market Analysis Pty Ltd.

Blake Industry & Market Analysis Pty Ltd
ACN 085 334 292
PO Box 193
Richmond Vic 3121
AFS Licence
No. 258032

Enquiries for *Bioshares*
Ph: (03) 9326 5382
Fax: (03) 9329 3350
Email: info@bioshares.com.au

David Blake - Editor
Ph: (03) 9326 5382
Email: blake@bioshares.com.au
Mark Pachacz - Research Principal
Ph: 0403 850 425
Email: pachacz@bioshares.com.au

Individual Subscriptions (48 issues/year)
$400 (Inc.GST)
Edition Number 528 (8 November 2013)

Antisense Therapeutics Approaching Major Inflexion Point

The field of antisense drug development has been receiving positive attention over the last year with the success of the leader in the field Isis Pharmaceuticals. Antisense Therapeutics (ANPDA: $0.17; *to revert to ANP when 10:1 stock consolidation is completed*) has licensed the Isis technology and has a number of programs it is seeking to move through significant milestones over the next 12 months. Its most valuable asset is the drug candidate ATL1103, which is being investigated in a Phase II trial for the treatment of acromegaly. With interim results due by year's end, this is a stock worth evaluating.

ANP is working on three main programs. The first is ATL1103 for the treatment of acromegaly. The second is ATL1102, which may return to clinical investigation for the treatment of multiple sclerosis. And the third is the use of ATL1102 for stem cell mobilization in patients undergoing chemotherapy, which is due to enter the clinic in coming months.

ATL1103 – Phase II trial Underway in Acromegaly

Acromegaly is a disorder that results from too much insulin-like growth factor (IGF-1) production in the body resulting in excessive growth of the hands, feet, face and organs in the body. ATL1103 has been designed to block the growth hormone receptor expression which directly reduces IGF-1 levels in tissues.

ANP is currently conducting a Phase II trial in 24 people with acromegaly. Interim results (of IGF-1 levels) are expected to be available by the end of this year. The company expects the trial to be fully enrolled by the end of 2013.

In this trial patients will receive one of two doses, 200mg or 400mg. Patients will start with a 600mg dose in the first week, then one or two injections a week of 200mg for 12 weeks. Final results from the trial are expected in Q2 2014.

The company completed a Phase I trial with this compound in 2011. In the trial, healthy volunteers were used, the dose was smaller, and the duration of therapy was shorter. The highest dosed volunteers received 250mg four times in the first week, and then only weekly doses of the 250mg for two weeks. That trial showed that the mean fall in IGF-1 levels in all the trial participants was 7%.

To have a commercially viable product, a fall of around 30% in IGF-1 levels is required. In this Phase II trial, there will be some variability in results with smaller patients receiving a higher dose per kg. The trial should elicit some clear information of the potential of ATL1103 in treating people with acromegaly.

The result should be particularly clear as the biomarker, IGF-1, is actually the endpoint in the trial. The result is also being compared against a clear baseline .

Cont'd over

– Antisense Therapeutics cont'd

After three months of treatment, equilibrium levels of the drug in the body are expected to be achieved. It should be noted that antisense drugs accumulate in the tissue, particularly the liver, where IGF-1 is produced, and take some time to get to equilibrium levels in the body. ATL1103 has a half-life of around one month in the body.

The patients enrolled in ANP's Phase II trial are generally patients who have not had their symptoms controlled well by existing therapies with IGF-1 levels from 30% to greater than100% higher than normal. The trial is being conducted in the UK, Spain and France.

To date no serious adverse events related to treatment have been reported in the ANP Phase II trial. If the trial results are good, then ANP will activate licensing discussions with potential partners. Acromegaly is orphan drug designation disease.

Market Need

Somatostatin agonists such as the drug Octeotride are effective in treating up to 65% of patients who require drug therapy. The remaining 35% can use the drug Somavert from Pfizer, which is a recombinant, pegylated (for longer half life) protein.

Somavert generates more than $200 million in annual sales in acromegaly, but it has its downsides. These include its high cost (around $60,000 a year), it needs to be reconstituted from a powder, and that it needs to be injected daily. It also has potential tumour growth complications.

In the highest dose in clinical trials, Somavert was shown to normalize IGF-1 levels in 82% of patients. Somavert also inhibits the growth hormone function (which forms IGF-1) by binding with the growth hormone receptors. ATL1103 achieves the same outcome by inhibiting the expression of this receptor with an antisense drug approach.

Licensing Deals in Acromegaly

In February this year, Roche licensed a potential next generation form of the drug Octreotide, called Octreolin, which is an orally available version of Octeotride.

Roche paid biotech company Chiasma US$65 million upfront with up to US$530 million in future milestone payments. Chiasma has developed a technology to coat drugs with its 'Transient Permeability Enhancer' technology which makes peptide and protein injectable drugs orally available. Octreolin is in Phase III clinical development.

The market for acromegaly is estimated to be worth $500 million a year.

Revisiting ATL1102 Multiple Sclerosis Application

ATL1102 had previously been licensed to Teva Pharmaceutical Industries for the treatment of multiple sclerosis. However Teva came across some toxicology issues with the compound and handed it back to ANP.

ANP is now conducting further toxicology testing of the compound with those results expected to be available early next year. If the compound clears these trials, then ANP will look to re-license with a view of moving the program into Phase IIb clinical trials again with a partner.

The toxicology issue is thought may have arisen because of a pre-existing health issue in the animals. Adverse events were seen at all doses. These toxicology studies are expected to cost only $300,000, with the study being conducted with existing drug supplies.

ATL1102 inhibits the VLA-4 protein linked to MS, achieving a similar outcome to the Biogen-Idec drug Tysabri. Tysabri generates sales of US$1.6 billion a year. CEO of ANP, Mark Diamond, believes that if this compound can clear the toxicology studies, then the compound potentially offers safety advantages over Tysabri.

This is because Tysabri binds to all VLA-4 receptors in the blood, whilst ATL1102 prevents expression of VLA-4 receptors found in the tissue. The immune suppression associated with Tysabri is linked to activation of the latent JC virus in B-cells in the blood.

It is thought that blinding to the VLA-4 receptor on these immune cells causes an intracellular signaling effect triggering the JC virus which gives rise to the fatal effect of PML (progressive multifocal leucoencephalopathy).

Antisense drugs work predominantly in tissue and are rapidly cleared from the blood stream, so therefore may not have the same side effects.

ATL1102 for Stem Cell Mobilisation in Cancer

A third program for ANP is the potential use of ATL1102 for use in cancer treatment, and more specifically, stem cell mobilisation prior to chemotherapy treatment. Patients undergoing chemotherapy treatment are given GCSF to help mobilise and collect bone marrow hematopoeitic cells that rebuild the immune system after chemotherapy.

It had previously been shown that Tysabri helped mobilize these stem cells. ANP looked at samples from its Phase II MS trial and found a similar effect, with CD34+ levels having increased by 50%. However, the problem with Tysabri is its long half-life and its safety issues.

ANP has shown in mouse studies that ATL1102 in combination with GCSF increased CD34+ stem cell levels by 100%. ANP expects to start a Phase I trial in volunteers at the start of next year

GCSF is effective in about 40%-60% of patients. The drug Mozobil from Genzyme also improves stem cell mobilisation, however there are about 10,000 patients a year who remain in need of better treatment.

Diamond said the company has interest from oncologists in Australia to trial this therapy. Diamond does not expect any toxicity

Cont'd on page 4

Five Stock Wrap

Company	Novogen	**Code**	NRT	**CMP**	$0.23	**Cap'n ($M)**	$35.1	**Cash ($M) 30/6**	$2.7	**SI**	**0.3**

- Novogen discontinued its phenoxodiol drug development (as managed through 60% owned subsdiary MEI Pharma) in 2012
- Now developing super-benzopyrenes to treat ovarian and brain cancers, following acq. of Triaxial Pharmaceuticals for $2.9 m in Dec 2012
- Initiated a $5M Convertible Note (CN) funding arrangement with Hudson Bay Capital in July 2013; a second $1M CN followed in October
- In October, acquired anti-tropomysoin technology from Melbourne-based GenScreen
- Recently announced joint venture company, CanTx, Inc with Yale University. (NRT 85%; Yale 15%)
- Yale provides a peptide technology which localises nanoparticle 'sugar package' in and to tumour blood vessels
- Yale also provides cancer stem cell lines, against which NRT compounds can be tested for cytotoxic effect
- Expects to complete pre-clinical studies on lead super benzopyrene compound CS-6 (Trilexium) in 6-9 months
- IND filing and clinical trials for CS-6 to commence by end 2014
- Anti-tropomyosin program to identify lead compound in 3-4 months

Comment: NRT 'Mark 2' is a pre-clinical stage company; dilutive convertible note financing is an investment negative

Bioshares recommendation: **Sell** | Timing - Revisit in 12 months when IND is cleared

Company	Prima Biomed	**Code**	PRR	**CMP**	$0.038	**Cap'n ($M)**	$43.4	**Cash ($M) 30/9**	$31.4	**SI**	**1.9**

- Prima Biomed is developing CVac, a Dendritic cell immunotherapy, for the treatment of ovarian (ovca) and other cancers
- PRR announced results of Phase II trial in September; no difference in Progression Free Survival between treatment and control arms
- Analysis of subset of patients treated post-second remission showed a strong PFS signal
- PRR will submit a revised protocol for its larger 1,000 pt Phase III CANVAS trial, which has enrolled 113 to date (but only 76 randomised)
- Will now aim to treat 210 subjects at the second remission stage with an Overall Survival endpoint (not PFS)
- Study is powered to deliver significance once 105 events have been reached
- Results now expected in 2018
- A modified Phase III trial eases PRR's cash burden but need for cost savings will be an ongoing issue

Comment: A modified trial reduces the ovca economic opportunity; COGS & business model impose a high risk with this stock

Bioshares recommendation: **Sell** | Timing -

Company	Anteo Diagnostics	**Code**	ADO	**CMP**	$0.078	**Cap'n ($M)**	$60.1	**Cash ($M) 30/9**	$3.3	**SI**	**2.6**

- Anteo Diagnostics is commercialising a chemical reagent, Mix&Go, which improves the surface binding properties of proteins
- The technology can offer between a 4 fold and 50 fold decrease in the quantity of protein used in certain diagnostic tests
- The technology can potentially deliver an 8 fold saving in costs of antibodies (proteins) diagnostic products
- More than 80 companies have been collaborating with ADO to assess the technology; business model is to seek multiple licencees
- Sales have been minimal to date with no products yet to emerge which incorporate the Mix&Go technology
- One POC Dx product is progressing better than expected through the feasibility stage of development
- ADO has identified the bioseparations market as the next business sector to target
- ADO was awarded a $1.7 M Commercialisation Australia grant in June 2013

Comment: The 'Intel inside' business model requires patience, with a future tipping point effect a desirable event in the long term

Bioshares recommendation: **Speculative Hold Class B** | Timing -

Company	Biotron	**Code**	BIT	**CMP**	$0.088	**Cap'n ($M)**	$20.1	**Cash ($M) 30/9**	$3.5	**SI**	**1.0**

- Biotron is developing BIT225 to treat HCV and HIV co-infection; it has a novel mechanism of action, targeting the p7 protein on the virus
- Phase IIa trial showed that BIT225 twice daily in combo with ribavarin and peg-interferon reduced virus to undetectable levels after 28 days
- BIT's rationale for developing BIT225 is that it can address drug resistance issues that could emerge with other classes of HCV drugs
- Recently Gilead Sciences' sofusbuvir with ribavirin was recommended for approval by the FDA, for treating HCV genotypes 2 and 3
- Sofusbuvir with pegylated interferon was also recommended for approval for treating HCV genotypes 1 and 4
- Sofusbuvir cuts duration of treatment from 24 to 12 weeks, and delivers up to a 90% cure rate
- Gilead has a pan-genotype and interferon and ribavarin free regime of sofusbuvir and GS-5816 moving into Phase II
- Johnson & Johnson's simeprevir with peg-interferon and ribavarin for genotype 1, was also recommended for approval
- BIT intends to commence a 12 week trial of BIT225 in genotypes 1 and 3 subjects later in 2013

Comment: The number of new and improved HCV drugs nearing FDA approval diminish the prospects for BIT225

Bioshares recommendation: **Sell** | Timing -

Company	Living Cell Technologies	**Code**	LCT	**CMP**	$0.089	**Cap'n ($M)**	$31.8	**Cash ($M) 30/9**	$4.76	**SI**	**NA**

- Living Cell Technologies is developing porcine islet cells (DIABECELL) to treat Type 1 diabetes
- The cells are encapsulated to prevent immune rejection and are transplanted into the abdomen to boost insulin production
- An 8 pt DOSING study showed 3/4 patients in the higher dose group sustaining HbA1c (blood sugar) <7% over the 52 week period
- 4/4 patients in the higher dose group saw unaware hypoglycemic events fall by >40%
- Program is now funded as a 50:50 joint venture (Diatranz Otsuka Limited (DOL)) with Otsuka Pharmaceutical Factory
- $25 M in JV funding has greatly reduced funding risk at the expense of reduction in share of potential revenues
- LCT is planning a 30-60 pt efficacy study in Australia, New Zealand and Singapore, as well as improved formulation of DIABECELL
- Limits to scalability of the LCT technology potentially confines revenue upside of DIABECELL to niche pt groups
- Company is also developing NTCELL for neurodegenerative conditions, leading with Parkinson's disease

Comment: While the trial number for the dosing trial was small, establishing dose effects was positive for LCT

Bioshares recommendation: **Speculative Hold Class C** | Timing - Consider once efficacy trial protocol is available

Bioshares Model Portfolio (8 November 2013)

Company	Price (current)	Price added to portfolio	Date added
Imugene	$0.020	$0.022	November 13
Oncosil Medical	$0.110	$0.155	September 13
Calzada	$0.073	$0.073	September 13
Invion	$0.110	$0.060	August 13
IDT Australia	$0.455	$0.260	August 13
Viralytics	$0.360	$0.300	August 13
Circadian Technologies	$0.250	$0.270	March 2013
Tissue Therapies	$0.235	$0.255	March 2013
Benitec Biopharma	$0.585	$0.40	November 2012
Somnomed	$1.23	$0.94	January 2011
Cogstate	$0.450	$0.13	November 2007
Universal Biosensors	$0.57	$1.23	June 2007

Portfolio Changes – 8 November 2013

IN:
No changes..

OUT:
No changes.

Board Renewal at Impedimed

The corporate renewal process which began at Impedimed (IPD: $0.165) with the appointment of Richard Carreon as CEO in July 2012, has continued with the recent appointment of the US-based David Adams to replace longstanding board member Mel Bridges. US-based Scott Ward joined the board earlier in May 2013, replacing Martin Kriewaldt. These board changes were flagged at Impedimed's AGM in 2012. Both Adams and Ward bring considerable experience gained in various roles at Medtronic.

Carreon and his team have been successful in greatly reducing the company's cash burn, down from $4.9 million for first half of FY2013 to $2.3 million for the second half of the same fiscal period.

Strategies for LDex in the US

The principle objective for Impedimed in the US is to gain a Category 1 CPT code in January 2016, with wording which supports the assessment of lymphedema over time. A CPT 1 code will facilitate the expansion of the company's LDex U400 product into the private health insurance market. The company will be aiming to increase its early adopters base to greater than 300 so that it has sufficient numbers for an independent survey of users that is used to inform the AMA's CPT process .

Another important element of its US strategy is that Impedimed will conduct a pivotal clinical trial of the LDex lymphodema detection and assessment system to establish how the product can make a difference to clinical practise. [*Previously, the company had relied on data from long term trials of another technology to support the case for the early detection of lymphodema, and not its own product.*] The trial is expected to run for five years and cost $2-$3 million to complete and beginning in 2014. However, Impedimed hopes to use data gained at the 1, 2, 3, and 4 year time points to obtain reimbursement as each year progressively demonstrates the benefits of both early detection and continuous assessment. If the company is successful in gaining the agreement of health insurers to incrementally lift the periods of coverage, then revenues can expect to flow sooner.

Impedimed is capitalised at $30 million and retained cash of $5.62 million at September 30, 2013.

Bioshares recommendation: **Speculative Buy Class B**

– Antisense Therapeutics cont'd

issues to arise as it will only be a one week trial with three doses, which is how the drug would potentially be used, prior to chemotherapy.

With such a short trial duration, Diamond believes this is one program the company could complete full clinical development on its own.

Share Consolidation and Loyalty Program

ANP has undertaken a 10 for one share consolidation. It is currently trading under the code ANPDA, which will revert to its previous code (ANP) on 20 November. The company has also launched a 'Loyalty Option Issue' whereby shareholders will receive one option for every three shares held for an upfront price of 1.2 cents on a post consolidation price.

The options will last for just over three years and will allow shareholders to convert those options to shares at a price of 27 cents. This loyalty program will raise $570,000 before costs, paying for the stem cell mobilization study.

Summary

ANP has a reasonable chance of getting positive results in this Phase II trial of ATL1103 in acromegaly. This is because it has achieved positive data from primate studies, and positive data in a Phase I trial. That IGF-1 is produced in the liver, which is where antisense drugs are known to accumulate, should also see the drug have a good opportunity to take effect.

ANP is capitalised at $25 million with $4 million in cash at the end of September (including the R&D rebate expected to be received). The company had a net loss in FY2013 of $2.5 million.

Bioshares recommendation: **Speculative Buy Class C**

Several small corrections have been made to the above commentary on ANP since it was published in the first edition.

How Bioshares Rates Stocks

For the purpose of valuation, Bioshares divides biotech stocks into two categories. The first group are stocks with existing positive cash flows or close to producing positive cash flows. The second group are stocks without near term positive cash flows, history of losses, or at early stages of commercialisation. In this second group, which are essentially speculative propositions, Bioshares grades them according to relative risk within that group, to better reflect the very large spread of risk within those stocks. For both groups, the rating "Take Profits" means that investors may re-weight their holding by selling between 25%-75% of a stock.

Group A

Stocks with existing positive cash flows or close to producing positive cash flows.

Buy	CMP is 20% < Fair Value
Accumulate	CMP is 10% < Fair Value
Hold	Value = CMP
Lighten	CMP is 10% > Fair Value
Sell	CMP is 20% > Fair Value

(CMP–Current Market Price)

Group B

Stocks without near term positive cash flows, history of losses, or at early stages commercialisation.

Speculative Buy – Class A
These stocks will have more than one technology, product or investment in development, with perhaps those same technologies offering multiple opportunities. These features, coupled to the presence of alliances, partnerships and scientific advisory boards, indicate the stock is relative less risky than other biotech stocks.

Speculative Buy – Class B
These stocks may have more than one product or opportunity, and may even be close to market. However, they are likely to be lacking in several key areas. For example, their cash position is weak, or management or board may need strengthening.

Speculative Buy – Class C
These stocks generally have one product in development and lack many external validation features.

Speculative Hold – Class A or B or C

Sell

Corporate Subscribers: Starpharma Holdings, Cogstate, Bionomics, Impedimed, QRxPharma, LBT Innovations, Mesoblast, Tissue Therapies, Viralytics, Phylogica, pSivida, Antisense Therapeutics, Benitec BioPharma, Allied Healthcare Group, Calzada, Atcor Medical, Invion, Circadian Technologies

Subscription Rates (inc. GST)

48 issues per year (electronic distribution): **$400**

For multiple email distributions within the same business cost centre, our pricing structure is as follows:	$630	2-3 email addresses
	$855	4-5 email addresses
	$1090	6-10 email addresses

To subscribe, post/fax this subscription form to:

Bioshares
PO Box 193 Richmond VIC 3121
Fax: +61 3 9329 3350

I enclose a cheque for **$** made payable to **Blake Industry & Market Analysis Pty Ltd**, or

Please charge my credit card **$** MasterCard ☐ Visa ☐

Card Number ☐☐☐☐ ☐☐☐☐ ☐☐☐☐ ☐☐☐☐

Signature _____ Expiry date _____

Subscriber details

Name _____

Organisation _____

Ph ( ) _____

Emails _____

_____

_____