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Bioshares

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Edition 557

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

Companies covered: BNO, MSB, QRX

	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 - May '14)	26.6%
Year 14 (May '14 -)	0.6%
Cumulative Gain	**353%**
Av. Annual gain (14 yrs)	**16.1%**

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Bionomics Surprises Market with US$20 Million Upfront Alzheimer's Disease Deal

Bionomics (BNO: $0.575) has signed an impressive research collaboration and licensing deal with Merck for its preclinical Alzheimer's disease program. Under the terms of the deal, Bionomics will receive US$20 million up front and up to US$506 million in future milestone payments plus royalties (not disclosed) from any product sales.

Merck will fund all of the future R&D with the collaboration and the next step in the program is now up to Merck said Bionomics CEO Deborah Rathjen. Prior to this deal, Bionomics had been preparing the lead compound, BNC375, for Phase I studies under an IND. BNC375 has achieved positive efficacy results in animal models. The program is also backed up by a number of other compounds that will also be evaluated by Merck.

It's the second deal with Merck in two years, following on from the research collaboration signed last year for Merck to evaluate Bionomics compounds for the treatment of chronic pain. That was a two year research program and if Merck exercises its option to progress the agreement, Bionomics may stand to receive up to US$172 million in future payments.

There are six good reasons that Merck has licensed access to Bionomics Alzheimer's disease program. The first is that Merck has a strong interest in the Alzheimer's disease field, with one of the leading programs in the world with is BACE inhibitor that has entered into Phase III trials. The second is that there is a paucity of Alzheimer's disease programs, as evidence by the small number of recent deals in this area (see table). The third is that Merck knows the capabilities of the Bionomics R&D team through the pain

Cont'd over

Recent Alzheimer's Disease Drug Development Deals

Date	Company	Partner	Stage of Development	Up Front US$M	Total Potential Deal Value US$M	Mechanism of Action or Target
June 2014	Bionomics	Merck	Preclinical	$20	$526	Modulation of alpha-7 nicotine receptor
December 2013	Orion Corporation	J&J	Phase IIa	$31	Undisc.	Alpha-2C adrenoceptor antagonist
December 2013	Proteostasis Therapeutics	Biogen Idec	Preclinical	Undisc.	$200	Modulation of protein homeostasis pathw ays
March 2013	Lundbeck	Otsuka	Due to start Phase III	$150	$675	Selective serotonin 5-HT6 receptor antagonist
September 2011	Evotec	Roche	Preclinical	$10	$830	Selective monoamine oxidase-B inhibitor
August 2010	Alectos Therapeutics	Merck	Discovery	Undisc.	$289	Modulation of O-GlcNAcase enzyme to
October 2008	Affiris	GSK	Phase I & Preclinical	$28	$560	Beta amyloid vaccine

collaboration started last year. The fourth is that Bionomics has shown positive results in a range of animal studies. The Bionomics program is working on a novel mode of action. And the sixth is that Forum Pharmaceuticals has achieved positive Phase IIb results with its alpha-7 potentiator (see below) and has moved into a 1,600 patient Phase III trial.

The Bionomics Alzheimer's Program

Bionomics started its Alzheimer's disease program in 2010. The program is based on modulating the alpha-7 nicotine acetyl choline receptor in brain. Modulating this receptor may improve cognition and also reduce inflammation in the brain. Both these outcomes may be beneficial in treating Alzheimer's disease.

There are two ways to modulate the alpha-7 receptor. One way is to turn it on (potentiators) and leave in on, which is the approach that is being trialed by Forum Pharmaceuticals (currently in a Phase III trial). However leaving this receptor constantly switched on may lead to desensitization and drug tolerance. There is also the increased risk of gastrointestinal effects and cardiac side effects. Bionomics is taking the approach of modulating this receptor, using an approach called positive allosteric modulation.

Affecting the action of the alpha-7 receptor may also have a role in treating other diseases, including multiple sclerosis, Parkinson's disease, schitzophrenia and ADHD, as well as improving memory. Targeting the alpha-7 receptor, which focuses on treating the memory impairment associated with Alzheimer's disease, is distinctly different to the main approach in inhibiting beta amyloid which forms the plaques in the brain that are biological hallmark of this disease.

The Merck Deal

What makes this deal impressive is the size of the upfront payment to Bionomics, of US$20 million, which has exceeded our expectations. The agreement is a classic small biotech-pharma deal, highlighting the quality of the Bionomics program, and the demand for access to credible R&D programs in the Alzheimer's drug development field.

The potential market for an effective treatment for Alzheimer's disease is valued at billions of dollars a year. Whilst affecting the alpha-7 receptor may not inhibit the progression of the underlying disease, but improve cognition, that remains a very large market potential, particularly if the such a drug may have an effect in other diseases such as Parkinson's, ADHD and schizophrenia. If targeting this receptor is also successful in inhibiting inflammation in the brain, then this approach may also inhibit disease progression and have an effect in multiple sclerosis.

In additional to the up front and milestone payments, Bionomics will be entitled to receive royalties from future product sales. Given the high up front payment, we would expect a lower royalty entitlement, of 4%-5%.

Alzheimer's Disease: A Tough Area of Drug Development

Rathjen correctly said that Alzheimer's disease has been a frustratingly difficult area in which to develop new drugs, with no new drug for the disease being approved in over 10 years.

The drugs that are approved, such as Aricept, have only minimal benefit, slowing the symptoms of disease progression for only around six months. Bionomics has compared its drug candidate to Aricept in preclinical studies and has it has shown to have improved efficacy. Alzheimer's disease is an under-researched area of drug development, because of the difficulty, as evidenced by the low number of commercial deals in this space, and the number of clinical failures.

In Australia, two other companies developing drug candidates with potential in treating Alzheimer's disease are Neuren Pharmaceuticals and Innate Immunotherapeutics.

Neuren's lead compound, NNZ-2566, is a synthetic analogue of the neuroprotective peptide glypromate, and is believed to play a role in maintaining cognitive health in the brain. Innate Immunotherapeutics is working on an immune system modulator that is achieving positive effects in patients with secondary progressive multiple sclerosis. That drug candidate's potential to reduce inflammation in the central nervous system may also see that drug candidate having a role in treating Alzheimer's disease in the future.

Cont'd on page 5

Current Leading Alzheimer's Disease Programs

Company	Stage of Development	Patients to be Enrolled	Mechanism of Action or Target
Merck	Phase III trials underw ay	1960	Beta secretase inhibitor (BACE) in mild (prodromal) AD
Eli Lilly	Phase III trials underw ay	2100	Beta amyloid antibody in mild AD
Forum Pharmaceuticals	Phase III trials underw ay	1600	Potentiator of alpha-7 nicotine receptor
AstraZeneca	Looking for partner for Phase III	-	Beta secretase inhibitor (BACE)
AZTherapies	Due to commence Phase III	-	Combination therapy, existing drugs
AFFiRis/GSK	Positive Phase II results	-	Beta amyloid vaccine

Mesoblast: Publication of MPCs with LVADs Trial Results

Mesoblast (MSB: $4.59) has reported the publication of results in the journal Circulation from a randomised Phase II trial of its mesenchymal precursor stem cells (MPC) in patients with end-stage heart failure who received a left ventricular assist device (LVAD). The trial was an investigator led trial sponsored by the National Heart, Lung, and Blood Institute (NHLBI), an institute of US National Institutes of Health.

The rationale for the trial was to evaluate the role that MPCs could play alongside the deployment of LVADs in end stage heart failure patients, but specifically to see if MPCs could be improve heart function so that a patient could be weaned off the device, even for a short time.

While the primary endpoints of the trial related to safety events, the secondary endpoint was the functional status and ventricular function while weaned from LVAD support at 90 days following the intervention (i.e placement of the LVAD and delivery of MPCs or control). Functional status was defined as the ability to tolerate weaning from LVAD support for 30 minutes without hypofusion occurring.

The trial enrolled 30 patients who were randomized 2:1 to the treatment arm (24 million MPCs) and the control arm, which received the cryoprotective media alone. Across the trial, 10 patients were in a bridge to transplantation group and 20 were indicated as destination therapy patients.

Trial Results

The trial showed that 50% of patients in the treatment group were able to tolerate weaning at 90 days, compared to 20% in the control group. However, this was not statistically significant (p=0.24). Furthermore, the duration of the wean (for those who could tolerate it) was greater in the MPC group than in the control arm.

There was no difference at 90 days between the MPC arm and the control arm for the left ventricular ejection fraction at the conclusion of the temporary wean (for those who could tolerate it).

Outcomes at the 12 month mark generally showed similarity between the MPC arm and the control arm across a number of measures, including the ability to tolerate temporary weaning and the use of drug regimes. However, 85% of MPC patients tolerated one or more temporary weans over the 12 months, compared to 40% of the control group (p=0.03).

In terms of safety at the 90 day mark, no patient developed a primary safety event, defined as infectious myocarditis, myocardial rupture, neoplasm, hypersensitivity reaction, and immune sensitization. (It should be noted that over the first 90 days, three patients in the control arm died, and over 12 months, six patients in the MPC arm died. These deaths were attributed to LVAD failure, multi-system organ failure, pump thrombus and sepsis.)

Over 12 months, major bleeding rates were similar for both groups, as were hospitalisation rates.

Limitations of the Trial

The authors of the study report noted several limitations with the trial, which was exploratory in nature. The efficacy endpoints of weaning, LVEF and Six Minute Walk at 90 days were based on the comparison of 10 MPC treated patients and two patients in the control group, clearly limiting the value of the results obtained.

They also noted that an absence of an effect of the therapy at 12 months would appear to suggest that a higher dose of MPCs could be evaluated, alongside redosing after 90 days to promote a more durable effect.

Comments

The value of this trial, while lacking measures of significance on many of the reported outcomes, is that is lays the foundation for Mesoblast to commit to another study in a larger patient group that would receive a higher dose of MPCs, or even more than one dose of MPCs.

The market opportunity for treating end-stage heart failure patients is significant, with an estimated 10% of 6 million people in the USA diagnosed with heart failure falling into the endstage category. However, there is only a much smaller number of endstage heart failure patients who receive LVADS as either a destination therapy or as a bridge to transplant, which we estimate to be between 3,000-4,000 per year in the US. These low numbers are a sign that the technology is open to adjunct therapies such as Mesoblast's MPCs which might improve the efficacy and safety of LVAD implants in end-stage heart failure patients.

Committing to a further trial in the area of LVAD intervention in heart failure is consistent with Mesoblast's strategy of building a broad portfolio of therapeutic product opportunities.

Mesoblast is capitalised at $1.5 billion and retained cash of $241 million at March 31, 2014.

Bioshares previous recommendation in edition 537 was to buy Mesoblast stock opportunistically below $5. The stock has been trading below $5 from April 7. A struggling share price is on balance likely to mean that opportunities to buy the stock below $4 will arise in the medium term. Any absence of robust data from randomised and blinded clinical trials will play its way into a softer Mesoblast share price going forward. On the other hand, strategic asset acquisitions by Mesoblast in the biopharmaceuticals space could trigger upwards movements in the share price.

Bioshares recommendation: **Speculative Class A - Look to Buy Opportunistically Below $4**

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QRxPharma Update on July 7 General Meeting and July 9 FDA EOR Meeting

Shareholders associated with Lang Walker ("The Walker Group"), which represents shareholding interests of 10% (16.4 million of 164.2 million shares) in QRxPharma, called a General Meeting of the company to vote on replacing directors Dr Gary Pace and Dr Peter Farrell with Dr Richard Treagus and Mr Bruce Hancox.

The meeting will take place on Monday July 7, 2014 in Sydney.

Other significant shareholders of QRxPharma include Allen Gray with 20.9 million shares (12.7%) and former CEO John Holaday with 7.6 million shares (4.6%) (according to the most recently available company filings).

QRxPharma has recommended to shareholders to vote against this proposal.

History

On May 26, QRxPharma received a Complete Response letter from the US FDA regarding its New Drug Application for its moderate-to-severe pain drug Moxduo, on the basis that there was not sufficient evidence to approve the drug at this time.

This followed an FDA Advisory Panel meeting held on April 26 voting 14-0 against the recommending of Moxduo for approval.

John Holaday resigned as CEO of QRxPharma on May 2, and was replaced by COO Ed Rudnic.

An End-of-Review meeting with the FDA has been scheduled for July 9, in which the company will discuss with the FDA steps required to gain approval for Moxduo.

The Walker Group View

According to its members statement of June 12, The Walker Group proposal to add its nominees, Treagus and Hancox, to the QRxPharma board and replace incumbents Farrell and Pace, is based on its belief "that it is in the best interests of the Company and its shareholders that the Board, with the inclusion of new eyes and ears, consider all reasonable strategic alternatives as a means to restoring value to the Company and its underlying assets," and "In the absence of any company-specific information we are not able to expressly recommend any one particular strategy."

One of the Walker Group's criticisms was that "from recent information provided by the FDA to the members of the Advisory Committee is that it is very clear that the FDA has an entrenched and negative view of the suitability of Moxduo for marketing approval," despite QRxPharma's emphasis on the "positive feedback and extent of co-operation it has received from the FDA."

The Walker Group is also concerned that current shareholders will be severely diluted should fresh funding be brought into QRxPharma.

The QRX View

QRxPharma opposes the proposed board changes for the following reasons:

First, the Walker Group has not put forward an alternative strategy for the development of Moxduo. Second, the company is facing a critical period, which includes a series of discussions and meetings with the FDA, and therefore it argues that removing long standing directors "has the potential to adversely affect the Company's ability to navigate this period." Third, QRxPharma believes that the Walker Group may gain effective control of the company without paying a control premium.

Observations

QRxPharma's End-of-Review meeting with the FDA is scheduled after the General Meeting. It would be in the interests of all shareholders for the General Meeting to be deferred until after the End-of-Review meeting. Otherwise, shareholders are being asked to vote on changes to the board without highly relevant information at their disposal. There are several likely courses that FDA guidance can take at the EOR meeting. It may be that FDA guidance is so severe that QRxPharma is compelled to close down the development of Moxduo, sell residual assets, and return funds to shareholders. Other courses of action which permit a continuation of the development of Moxduo would likely impose varying degrees of development costs going forward.

In the interim, a commonsense measure for both QRxPharma and the Walker Group could be to have Richard Treagus, a former CEO of Acrux and current Executive Chairman of Neuren Pharmaceuticals, join the board so that he, as an experienced drug developer, can analyse and assess Moxduo's development history, regulatory filings and correspondence at a detailed level, which in turn should mean that the interests of all shareholders can be better served through the presence of newly installed but fully informed board member. QRxPharma has indicated it is receptive to Richard Treagus joining the board.

All shareholders of a company should reasonably be able to expect that if a certain shareholder group is seeking to gain control or exert influence over a company, especially without following the laws governing takeovers, that as a minimum it presents its plans and strategies up to all shareholders so that they can make an informed decision on the proposals that they are asked to vote on.

The development of Moxduo has been far from perfect from a regulatory point of view, but with it comes a strong lesson for investors that regulatory risk includes the risk that regulatory agencies can exercise the powers in arbitrary ways and that the relationships between drug developers and regulatory agencies can be subject to tensions and stresses that have the potential to derail a product from its progress to the market.

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Bioshares Model Portfolio (27 June 2014)

Company	Price (current)	Price added to portfolio	Date added
pSivida	$4.400	$4.000	May 14
Invion	$0.071	$0.089	February 14
Impedimed	$0.185	$0.245	December 13
Analytica	$0.047	$0.025	December 13
Imugene	$0.014	$0.022	November 13
Oncosil Medical	$0.105	$0.155	September 13
IDT Australia	$0.190	$0.260	August 13
Viralytics	$0.275	$0.300	August 13
Tissue Therapies	$0.290	$0.255	March 2013
Somnomed	$1.46	$0.94	January 2011
Cogstate	$0.300	$0.13	November 2007

Portfolio Changes – 27 June 2014

IN:

No changes

OUT:

No changes

Recommendations:

– Bionomics cont'd

There have been over 100 clinical trial failures in the Alzheimer's disease field. It has been a graveyard for pharmaceutical group Eli Lilly, which has had three prominent Alzheimer's programs fail.

Eli Lilly failed with its Phase BACE inhibitor program last year, after evidence of liver toxicity. In 2012 it failed in Phase III trials with solanezumab, an antibody against the beta amyloid protein. And in 2010 it halted its Phase III Alzheimer's program with gamma secretase inhibitor which worsened cognition in some patients.

One of the positives to come out of the solanezumab trials was that there appeared to be some benefit in patients with earlier stage disease, and that is now the focus for many Alzheimer's disease drug developers. Eli Lilly is now conducting another Phase III study with solanezumab in 2100 patients with mild Alzheimer's disease.

A syndicate involving Elan, Johnson and Johnson and Pfizer also failed in the monoclonal antibody approach to beta amyloid in two Phase III trials in over 2,500 patients. The second trial failure was reported in 2012.

AstraZeneca is looking to partner its Phase III Alzheimer's program with another company that has more experience, and perhaps is willing to carry the cost of an expensive Phase III program.

Merck is leading the field in the BACE inhibitor approach. The company achieved an 84% drop in AB40 levels in the cerebral spinal fluid in clinical studies. It completed a lead-in 200 patient safety study in a Phase III program with its BACE inhibitor, which showed the drug was safe when taken for three months. That trial has moved into the Phase III part, with 1960 patients with mild disease to be enrolled overall. The final data for the primary outcome measure of cognition is expected to be collected by April 2017.

Earlier this year, Melbourne's Prana Biotechnology failed to achieve positive results with its metal chelator PBT-2 in a Phase IIb study.

Last month AZTherapies announced plans to start a Phase III study with a combination therapy for the prevention and treatment of patients with early stage Alzheimer's disease. The therapy combines two previously approved drugs that separately inhibit beta amyloid polymerization and act as an anti-inflammatory agent.

And earlier this month AFFiRis from Austria reported positive Phase II results where disease modification was achieved for at least 18 months in 47% of patients. AFFiRis is developing a vaccine against beta amyloid. The company said this is the first time that disease modification has been shown in a therapy for Alzheimer's disease. That trial involved 332 patients. The positive effects were also confirmed in changes in biomarkers associated with the disease.

AFFiRis entered into a US$560 million collaboration with GlaxoSmithKline in 2008 to develop this vaccine. That deal involved a US$28 million upfront payment.

Bionomics is capitalised at $240 million. It had $15.7 million in cash at the end of March.

A **Speculative Hold Class A** recommendation is placed on Bionomics, reflecting the mix of assets of different grades within the company, with the cancer drug development assets scoring less compared to the CNS assets scoring higher. One asset of concern for investors is the anxiety compound (BNC210/IW-2143) which was partnered with Ironwood Pharmaceuticals in early 2012 – evidence of its entry into a human clinical trial is hard to find, and until it does enter the clinic, then its value will weaken.

Bioshares recommendation: **Speculative Hold Class A**

Bioshares

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

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