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In this edition...
Osprey Medical has made commendable progress in expanding its product offerings. It has added the CINAVERT dye injection product which can be used as a standalone product or in conjunction with its CINCOR dye capture system.The company is also conducting a trial of a limb recovery system, to treat chronic infections in mostly diabetic patients. Neuren Pharmaceuticals has made changes at the corporate level with Acrux CFO Jon Pilcher set to join his former boss Richard Treagus at the New Zealand company in August. The changes will see certain admin and IR functions based in Melbourne. Neuren is a challenging stock valuation-wise. The drug industry track record with TBI trials is poor, hence generous US Army funding, but its programs in Fragile X and Rett Syndromes have appeal.
Companies Covered: CGS, OSP, NEU

	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 - current)	-1.8%
Cumulative Gain	**239%**
Av. annual gain (11 yrs)	**17.8%**

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Bioshares

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

Osprey Expands Product Portfolio

US-based Osprey Medical (OSP: $0.40) is commercialising research from Melbourne's Baker IDI Heart and Diabetes Institute. The core technology is the CINCOR system, which helps capture damaging imaging dyes used in coronary procedures. This product has just moved into a pivotal clinical study. However, Osprey continues to commercialise new inventions from the Baker Institute, with the latest being a novel technology to prevent limb amputations.

Limb Recovery

Cardiologist Dr David Kaye and his team at the Baker Institute have invented a new way to treat infections in the leg. It involves recirculating the blood flow in the leg, isolating that circulation from the rest of the body. In this way, a high level of antibiotics can be used to treat chronic infection and prevent leg amputation. Preclinical studies have shown that antibiotics can penetrate not only into soft tissue but also bone tissue with this system, treating chronic infections.

Using this system, the antibiotic used can either then be diluted eventually into the rest of the body, or if it is potentially damaging to the kidneys, then the blood from the leg can be drained from the body as the general blood circulation to the leg is returned. Dr Kaye said at a recent briefing that the patient can tolerate this loss of blood.

A five patient study commenced earlier this year, with three patients enrolled to date at the Royal Melbourne Hospital. The study is expected to be completed by the end of this year. This year the company also expects to move into a larger 20 patient randomised trial as well, which is scheduled to be completed in mid 2014.

This program is supported by a $1.1 million Victorian Government Market Validation Program grant. According to the company, advanced limb infections in diabetics affects over 300,000 people each year in the US and Australia.

CINCOR System Trial

In March this year the company started its pivotal study (called PRESERV) with its CINCOR System product. This trial was due to start in 2012. Rather than starting recruitment in August last year it started in December. This was because the company incorporated a second product into the CINCOR System. That second product is called the CINAVERT System. CINAVERT is a pressure adjustment valve on the delivery catheter, which does not allow excessive dye to injected into the vein or artery during the imaging procedure.

The company has completed two clinical studies. The first was in 41 patients, showing that the CINCOR system can reduce CIN events by 50% based on historical CIN events. Last year the company also completed a trial with CINAVERT in 53 patients showing that 38% less dye was injected when the CINAVERT system was used, whilst not affecting the quality of the imaging.

Cont'd over

There are now eight sites open now that are recruiting patients in the PRESERV trial, including one in Germany, with around 30 hospitals seeking ethics approval to start enrolling patients into the trial.

The trial will enrol 600 patients undergoing a coronary procedure, such as a stent implant, where imaging dye needs to be injected to perform the procedure. Each patient has chronic kidney disease and is at a high risk of sustaining irreversible kidney damage, called Contrast Induced Nephropathy (CIN). In this patient population, 20% will develop CIN when undergoing a stent implant. This trial will cost $8-$10 million, using proceeds raised at the IPO.

A positive aspect from this trial is that the effectiveness of this product can be quickly measured. This is by measuring changes in a blood protein three days after the procedure, which quickly assesses whether the patient has developed CIN. The trial is expected to be completed next year with a 510(k) regulatory submission to be made to the FDA by the end of 2014. The standard approval process for a 510(k) product takes 90 days.

CINAVERT

Osprey intends to also sell the CINAVERT system as a standalone product. Dr Kaye believes that CINAVERT could become the standard of care when injecting dyes for cardiac procedures.

One of the applications for CINAVERT is for patients who have had a heart attack and are undergoing an emergency imaging and stenting procedure. For scheduled procedures, CIN can be reduced by increasing the level of fluids prior to the procedure. However this is not possible for heart attack patients. Heart attack patients are 10 times more likely to develop CIN than non-heart attack patients.

In *Bioshares'* view however, it will be more difficult to secure patent protection around the CINAVERT product. Osprey has filed patents relating to the delivery profile of the dye into the blood vessel.

Osprey received clearance for the CINAVERT system in Australia and Europe in December last year and clearance to sell the product in the US is expected in mid 2013 under the claim of the controlled delivery of a dye. The company expects to launch the CINAVERT system in Texas and Australia this year.

In the US, the aim is to start with Texas and to get proof of commercial adoption. If that region can become cash flow positive, with only the label of controlled delivery of a dye, then it will expand into other regions.

Global Launch

The company received CE Mark clearance to sell the CINCOR system in Europe in 2011. However the company has a weak label, that being for removal of a dye. A stronger label that the company is seeking is for the reduction in CIN.

The company will aim for a worldwide launch of the full CINCOR system once the US trial is complete and approval in the US is received, importantly with CIN reduction claims. The company says that the claims the company can use are critical to sales. It plans to hire a sales force of around 30-35 people.

Reimbursement & Market

The company believes that incorporating the CINCOR system will reduce the number of patients who develop CIN. A CIN event costs a hospital between $12,000-$16,000, costs which the hospital can not recover.

Initially the company will be selling the system without hospital reimbursement, on a cost saving argument. While this is an appropriate approach, without reimbursement it will take longer to convince hospitals to adopt the system. The company has initiated hospital reimbursement in the US healthcare system.

A stent procedure costs around $15,000 and is fully reimbursable. The price of the CINCOR system (which will include CINAVERT) will be between $1500-$2000. The price of the CINAVERT system will be between $350-$450 per procedure.

The company believes that adding the CINAVERT system doubles the potential market for these products from around $600 million to $1.1-1.4 billion.

Summary

Osprey is a well managed company that is sufficiently funded for the next 18 months, holding $13.2 million in cash at the end of March. It is commercialising products that will reduce complications with coronary stenting and imaging procedures. These products will improve lives and reduce associated healthcare costs. Its challenge however is to convert global healthcare practises, which is a process that is not rapid. A key performance parameter to monitor will be the recruitment rate into the 600 patient PRESERV clinical study.

Osprey Medical is capitalised at $40 million.

Bioshares recommendation: **Speculative Hold Class A**

Bioshares

Neuren – Careful Assessment of Assets Required

The shares of Neuren Pharmaceuticals ($0.057) have increased 84% from four weeks ago and by 68% from March 31, 2013. The shares hit a recent peak of $0.074 on May 20, the day of the company's AGM. (The company's financial year ends on December 31.)

Recent Corporate Changes

At the company's AGM, Robin Congreve and Doug Wilson retired from the board, leaving the board to comprise of Richard Treagus as Executive Chairman, along with Larry Glass as MD and CEO, and with John Holaday (CEO QRxPharma), Bruce Hancox and Trevor Scott.

The company announced in April that certain investor relations and administrative function would be relocated to Australia and that it would consolidate all clinical development and clinical operations in the USA. Today the company announced that Acrux CFO Jon Pilcher would take of the role of CFO, commencing in August.

The company's largest shareholder, with a 19.3% stake, is Lang Walker through the Auckland Trust Company as trustee for Second Pacific Master Superannuation Fund.

Neuren's Technology and Programs

Neuren Pharmaceuticals is developing NNZ-2566 for the treatment of several neurological conditions including traumatic brain injury (TBI), Rett's Syndrome and more recently Fragile X Syndrome.

NNZ-2566 is a new molecular entity (NME). It is a peptidase-resistant analogue of the terminal tri-peptide of the growth factor IGF-1. The function of peptidase (or protease) molecules is to cleave or cause changes to peptide complexes.

The peptidase-resistance attribute of NNZ-2566 confers the molecule with a longer half life than would occur otherwise.

Neuren was unsuccessful in developing the NNZ-2566 predecessor molecule Glypromate, the naturally occurring terminal tri-peptide of the growth factor IGF-1, due to a poor indication selection (the patient population selected did not experience the anticipated cognitive decline following heart surgery).

The medical hypothesis driving the development of NNZ-2566 is that it delivers neuroprotective or neurological repair and restorative functions. Its treatment potential extends beyond TBI, concussion, Rett Syndrome and Fragile X Syndrome to non-convulsive seizures and autism spectrum disorders; to Parkinson's, Alzheimer's and Huntington's diseases; and to MS and diabetes, according to claims included in patents filed by Neuren.

In the TBI setting, NNZ-2566 works by inhibiting inflammatory cytokines, inhibiting microglial activation and inhibiting apoptosis (cell death). The function of microglial cells is to (when turned on) attack and dispose of foreign material in the central nervous system. TBI is one sense can be seen as form of uncontrolled inflammation, so damping the inflammatory response and apoptosis should limit the neurological damage caused by microglial cells.

Unlike TBI, an acute condition, Fragile X Syndrome and Rett Syndrome are chronic neuro-development disorders. Fragile X Syndrome is caused by a genetic mutation (fmr1). Its symptoms include large testes, anxiety, attention deficit and intellectual disability. Rett Syndrome is also caused by a genetic mutation (MeCP2). Between the ages of 6 and 18 months, the usually female subjects display a very rapid decline in hand use and spoken communication. Subjects also suffer seizures, develop spasticity and exhibit abnormal movements.

These chronic syndromes appear to share a 'common biology' according to Neuren, in that they occur because of dysfunctional neurons. The company has shown in pre-clinical studies that NNZ-2566 improves signal transmission between neurons in a Rett Syndrome model (and also increases dendrite length and branching).

In a Fragile X Syndrome model, NNZ-2566 normalises the activation of pathways which control signalling between neurons. A quite striking effect of NNZ-2566 in the Fragile X mouse model was the complete reversion to normal size of over-sized testes. Other data from a study of NNZ-2566 in the Fragile X mouse model show marked positive effects in bevy of behavioural tests.

Cash Position

The company retained cash of NZ$4.2 million ($3.6 million) at the end of April. At the Neuren AGM, the company's chairman said Neuren was 'not under any immediate pressure to raise funds and we are confident that we have the full support and commitment of our major shareholders in the event that additional equity funding is considered necessary.'

Neuren has almost 300 million options outstanding with an average exercise price of 2.7 cents

The company has access to significant US Army funding of US$26 million for its TBI program and has also received funding support from the International Rett Syndrome Foundation.

TBI and Concussion Trials

The company's lead program is NNZ-2566 for the treatment of TBI which is being evaluated in a 260 patient Phase II trial. To date, 109 subjects have been enrolled, with 68% emanating from just three sites. Recruitment for the trial has been slow due to the trial site approval process related to the US Army. Ten of the 18 sites in the trial fall under an exception from informed consent (EFIC) protocol. These sites must receive approval from the Secretary of the US Department of Defense.

The TBI trial is a randomized, placebo controlled trial in which NNZ-2566 is administered intravenously.

The primary endpoint of the trial is safety (adverse events and serious adverse events) up to three months from discharge from hospital. Efficacy endpoints include evidence of efficacy in modi-

Cont'd over

fying outcomes on the Glasgow Outcome Scale and improvements in cognitive and neuro-psychological functioning. The Glasgow Outcome Scale is a standardized system for scoring patients with brain damage.

A Phase II trial of NNZ-2566 (oral solution) in 132 concussion subjects will be initiated at two-to-three US military facilities at a date that is yet to be determined.

The oral formulation of NNZ-2566 will be administered twice daily for seven days within 24 hours of concussion in either a 35 mg/kg dose or a 70 mg/kg dose.

Rett Syndrome

Neuren has enrolled three subjects in a randomized, placebo controlled Phase II trial in 60 females diagnosed with Rett Syndrome, although it anticipates that 48 will complete the dosing. The trial is being conducted at two sites in the US.

NNZ-2566 will be administered in an oral solution for 14 days following three days in which either 35 mg/kg or 75mg/kg twice a day is titrated.

The endpoints of the trial include safety, seizure activity and caregiver and clinician assessments of symptom severity and behaviour.

The trial is being supported with a US$600,000 grant from the International Rett Syndrome Foundation.

Results are expected in mid 2014.

Fragile X Syndrome

Neuren is currently in the planning phase for a 60 subject Phase II trial in Fragile X Syndrome subjects. It is aiming to commence a trial in mid 2013 and complete enrolment by late 2014.

NNZ-2566 will be administered in an oral solution for 28 days to subjects who will receive either 35 mg/kg or 75mg/kg twice a day after initial titration. A cross-over to the treatment will take place for the placebo arm.

Issues for the TBI Program

The assets of Neuren Pharmaceuticals can be divided into three parts. The first are the US Army funded TBI and concussion programs, the second the Rett and Fragile X Syndrome programs and the third, the NNZ-2591 and Motiva compounds.

While supported by non-dilutive funding, the longer term future development of the TBI and concussion programs will in all likelihood remain outside the financial capability of Neuren. The value and deal structure for a potential licensee will be conditioned by the time and expense and probability of success of Phase III programs.

The consideration for investors to bear in mind is that the history of the development of drugs for the treatment of TBI has been unsuccessful. According to Andrew Maas of the University Hospital in Antwerp, all 33 Phase III trials in TBI conducted between 1980 and 2009 failed. If NNZ-2256 delivered clear positive Phase II results, a prospective partner might prefer to license the compound and commit to more Phase II studies, rather than go headlong into a Phase III program.

Such a history provides a reason for why the US Army has committed funds to researching novel approaches because the pharmaceutical industry is reluctant to do so. If NNZ-2256 delivered positive Phase II results a question that could then arise is what commitment the US Defense Department might provide to support Phase III trials. The commercialisation pathway is unclear at this stage and may remain unclear for quite some time.

Formulation and Administration

Much more work must be done to determine the preferred routes of administration and formulations of NNZ-2566 in the TBI and concussion settings and indeed all treatment settings. While the IV administration of NNZ-2566 may be suitable for TBI and concussion, it is unsuitable for the treatment of chronic diseases. However, it will be some time before the trials of oral formulations yield the first of any data which validates that route of administration.

Summary

The challenge for investors is to properly value the component assets of Neuren Pharmaceuticals. While the TBI and concussion programs (with US Army funding) are the most advanced and have delivered benefits such as an oral formulation of benefit to the chronic programs, their ultimate value must factor in high failure rates.

On the other hand, the chronic disease settings represent digestible projects for Neuren to tackle. The patient groups are homogenous (i.e. they exist because of genetic mutations) and fall into the Orphan Drug category for drug development.

While Neuren has expressed a view that it is not under any immediate pressure to raise funds, a more realistic view would be that the company will seek fresh capital sometime in the next 12 months.

Bioshares' recommendation is to hold back on taking a position in Neuren until its funding position is secured, its corporate changes have been allowed to settle and when further details about the treatments it is developing for chronic conditions of Rett and Fragile X Syndrome have been articulated.

Neuren Pharmaceuticals is capitalised at $70 million and retained cash of $3.6 million at the end of April.

Bioshares recommendation: **Sell**

Bioshares

Bioshares Model Portfolio (24 May 2013)

Company	Price (current)	Price added to portfolio	Date added
Atcor Medical	$0.073	$0.082	May 2013
Circadian Technologies	$0.245	$0.270	March 2013
Tissue Therapies	$0.120	$0.255	March 2013
Allied Healthcare	$0.040	$0.026	February 2013
Psivida	$3.04	$1.550	November 2012
Benitec	$0.014	$0.016	November 2012
Nanosonics	$0.490	$0.495	June 2012
QRxPharma	$1.19	$1.66	October 2011
Somnomed	$0.93	$0.94	January 2011
Cogstate	$0.360	$0.13	November 2007
Clinuvel Pharmaceuticals	$1.90	$6.60	September 2007
Universal Biosensors	$0.75	$1.23	June 2007

Portfolio Changes – 24 May 2013

IN:
No changes

OUT:
No changes

Cogstate's Test to be Part of Unique Alzheimer's Disease Trial

Cogstate's (CGS: 36 cents) cognition test has been selected to be included in what CEO Brad O'Connor has called a 'cutting edge' Alzheimer's disease trial.

While only a small trial involving 220 people, it will assess two experimental drugs to see if they can slow down the onset of this disease in a patient population that will definitely develop Alzheimer's disease, before any symptoms are even apparent.

The two drugs in the trial being evaluated are gantenerumab from Roche and solanezumab from Eli Lilly, both antibody drugs that bind to beta amyloid.

Amyloid binding antibody drugs have failed in Phase III trials recently. However there were some signs of efficacy when treating earlier stage patients. In this trial, 120 of the patients carry a gene that means they will definitely develop the disease. A further 90 do not carry the gene but one of their parents do.

The study is a Phase II/III trial with over 30 sites required worldwide because of the rare genetic makeup of these patients. The trial will take two years to complete. There will be three arms in the study, including one placebo group.

The study is important because if one or both of these drugs can show inhibition of disease at such an early stage before any symptoms are visible, then presumably it may bring back these potential blockbuster drugs into full scale clinical development for early stage disease.

If that happens then it's a positive step forward for Cogstate, because it arguably has the most sensitive test for picking up early stage disease, as demonstrated in the Melbourne-based long-term aging study, AIBL.

Cogstate's test is the only computerised test being used in this trial. The long-term standard pencil and paper tests will also be used. The patients will have their brains imaged to detect amyloid plaque build-up, and will have their cognitive function tested at seven times during the trial with the Cogstate test.

Cogstate will not be paid for its involvement in this study. However O'Connor said the data coming out of this study will be very valuable to Cogstate.

Cogstate is capitalised at $28 million and held $3.8 million in cash at the end of March.

Bioshares recommendation: **Speculative Buy Class A**
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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

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