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Bioshares

8 August 2014
Edition 563

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

Companies covered: ACL, AVH, CUV, IVX, MVP, OSP, PAA

	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 -)	4.4%
Cumulative Gain	**370%**
Av. Annual gain (14 yrs)	**16.4%**

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Invion's Busy Months Ahead

Invion (IVX: $0.066 cents) has a busy few months ahead, with announcements expected for interim and final results from a number of Phase II clinical studies that are underway. Invion is focusing on the treatment of respiratory diseases, largely by repositioning proven therapeutics either for new indications of through improved methods of delivery.

The company's lead compound is nadalol, which the company has labelled INV102. It is a beta blocker that was originally brought to market by others as a treatment for conditions such as high blood pressure and migraine. It was specifically contraindicated for patients who also suffered asthma, as it was found that this drug would promote this condition (bronchoconstriction).

However, researchers, including Richard Bond, who is Professor of Pharmacology at the University of Houston, showed that by dosing only small amounts of this beta blocker and slowly increasing that dose, airway hyper-responsiveness is decreased, as well as having an anti-inflammatory effect, therefore being a potential new treatment for asthma. This is the core discovery behind Invion's INV102 program.

Professor Bond made a similar discovery previously with a particular class of beta blockers with regards to the treatment of chronic heart failure, for which beta blockers were contraindicated. He brought that discovery to Dr Mitchell Glass (now Invion's Chief Medical Officer) at GlaxoSmithKline. That subset of drugs became the best drugs ever available to decreasing mortality in heart failure, according to Professor Bond. The discovery moved a $40 million selling drug in 1998 to a $1.5 billion dollar drug in 2010.

For the second time Professor Bond has sought to commercialise his work on contraindications of beta blockers through Dr Mitchell Glass, this time through Invion.

Smoking Cessation (oral INV102)

The fastest path to market for Invion is the use of an oral version of INV102 to help patients quit smoking. Coughing is exacerbated when smokers try to give up – this is one of the reasons why smokers fail to quit. The anti-inflammatory properties of INV102 in the airways may address the problem of smoker's cough.

Invion is currently enrolling patients who have chronic bronchitis, and who have previously failed to quit smoking specifically because of smoker's cough. The trial was due to start last year but was delayed because of a change in jurisdiction with the FDA for this program (to the Division of Analgesia, Anesthesia and Addictive Products) and a subsequent FDA request to change the trial protocol.

The study was started in March this year. Invion CEO Greg Collier is confident the 130 patients in the trial will be fully recruited this year. The company expects to report some interim results on secondary endpoints, such as sputum levels, this year, for the first third of the patients in the trial. The trial is evenly split between placebo and active

Cont'd over

Bioshares Model Portfolio (8 August 2014)

Company	Price (current)	Price added to portfolio	Date added
LBT Innovations	$0.120	$0.130	July 14
pSivida	$4.550	$3.800	May 14
Invion	$0.066	$0.089	February 14
Impedimed	$0.290	$0.245	December 13
Analytica	$0.033	$0.025	December 13
Imugene	$0.015	$0.022	November 13
Oncosil Medical	$0.120	$0.155	September 13
IDT Australia	$0.245	$0.260	August 13
Viralytics	$0.265	$0.300	August 13
Tissue Therapies	$0.290	$0.255	March 2013
Somnomed	$1.70	$0.94	January 2011
Cogstate	$0.285	$0.13	November 2007

Portfolio Changes – 8 August 2014

IN:

No changes

OUT:

No changes

– *Invion cont'd*

groups. The primary result will be the reduction in the number of cigarettes smoked. Invion has a granted patent around the method of treating airway diseases.

Invion expects to start a Phase III trial with this program in the first half of next year. There is also the potential to develop an inhaled version of this drug for this indication.

Asthma (oral INV102)

In March last year Invion started a Phase II trial in 60 patients with mild asthma using an oral version of INV102. That trial is officially due to be completed by mid next year although could be finished as early as this year believes Collier. The trial is fully funded by the NIH in the US. Interim results are expected in this quarter.

Researchers behind this program, including Richard Bond, who believes that "the significance of our findings (in the use of nadolol for the treatment of asthma), if confirmed in larger controlled studies, may provide a paradigm shift in the chronic management of asthma."

Lupus (with INV103, intravenous)

Invion is conducting a Phase II study in 32 patients with mild Lupus with its drug candidate INV103 (previously called alaCpn10). This program came from the merger with ASX listed CBio. Recruitment is due to be completed by October this year, although that may be extended to the end of the year if an additional cohort is added to the trial. Interim results are expected in this quarter.

IVX103 is a modified natural human protein. It is delivered intravenously. One of the issues with the development of this drug candidate previously is that a maximum tolerated dose was never established.

At the completion of this study, Invion will look to partner the program. The main reason the company is looking to partner is the high cost of manufacture of the drug candidate for a small biotech such as Invion.

INV104 (inhaled)

In October last year, Invion announced it had in-licensed a third drug candidate, called zafirlukast (INV104), from Accolade Pharma. Invion will pay Accolade 20% of any royalties that it receives from sales. Zafirlukast was originally developed by Invion's Chief Medical Officer, Dr Mitchell Glass, when he was working for ICI/Astrazeneca.

Zafirlukast was developed as an oral treatment for mild-moderate asthma as an oral dose. However the drug has some side effects, including suicidal thoughts. Invion plans to develop this drug as an inhaled version into the lungs, with a smaller dose (one tenth) with no systemic presence in the body.

In February this year Invion started a collaboration with 3M Drug Delivery Systems to gain access to that company's metered dose inhalation technology. Zafirlukast will be one of the drugs that will trialed with the 3M technology to develop an inhaled version for the treatment of asthma. The company is aiming to lodge an IND in the first half of next year and start a Phase I study.

INV102 (inhaled) – COPD

In the first half of next year, Invion will commence a Phase I trial with an inhaled version of INV102 for the treatment of COPD. Subsequent programs with an inhaled version of INV102 will include asthma (1H 2015) and cystic fibrosis.

Mechanism of action of INV102 now explained

In March this year, Professor Richard Bond and other researchers had a scientific paper published in *Current Opinion in Pharmacology*. That paper was titled "Ligand bias prevents class equality among beta blockers". Why this paper was important for Invion is because it explains why nadalol (INV102) works in treating asthma whilst other beta blockers do not work, including other inverse agonist beta blockers, which is the class that INV102 fits into.

Bond and his group suggested that inverse agonist beta blockers are not all the same when it comes to the potential treatment of asthma. They have shown that only nadalol (INV102) and ICI-118,551 (an old compound that is too toxic to develop) are effective in blocking the beta-arrestin mediated pathway, whilst other inverse agonist beta blockers act on the G protein-mediated pathway.

Cont'd over

Clinuvel Pharmaceuticals Rejects Takeover Bid from Retrophin

Clinuvel Pharmaceuticals (CUV: $2.19) has rejected the $95 million takeover offer for the company from US-based biotech Retrophin. However Retrophin has continued to build its stake in Clinuvel, increasing from a 4.88% a week ago to now 6.7%.

While the bid was unsolicited, opportunistic and underpriced, there are some good reasons to have Retrophin on the register. However, Clinuvel has declined the bid for two reasons.

Reason 1: Bid Too Low

The first was that Clinuvel believed the bid of $2.17 per share was too low, with Retrophin seeking to make an opportunistic bid less than three months before a decision from European regulators on Clinuvel's marketing application for Scenesse. Scenesse is depot injection that increases skin pigmentation and protects a small population from extreme sunlight effects.

Reason 2: Potential to Destabilise the Regulatory Process

Another important but less tangible reason was that a change of ownership at this point potentially destabilises the regulatory approval process in Europe, which is at a critical phase, as well as creating uncertainties for patients and physicians who have been following the development process of Scenesse, some for many years.

The CEO of Clinuvel, Philippe Wolgen, argued that if you lose the trust at this stage from any of the three stakeholders – the regulators, physicians or doctors – then you will be left with a damaged asset. "You can't afford to frustrate the process at this point," said Wolgen, "particularly for such a complicated program."

Clinuvel's management has been dealing with the same group within the European agency for nine years. "Trust is paramount in US and Europe (regulatory groups)," said Wolgen, who described the commercialisation of Scenesse as an "acrobatic process". One of the core concerns with regulatory agencies is the possibility of abuse of this drug for cosmetic purposes. What has made the progress of this program even more impressive in recent years is that before Wolgen joined the company, the therapy was being developed as a tanning product. Not only has the company needed to do a complete U-turn, but it has needed to repeatedly assure regulators that there will be no off-label cosmetic abuse of the drug.

Clinuvel has also relied on the patients to support the development of this drug candidate for some obscure orphan diseases in some cases, such as EPP (Erythropoietic Protoporphyria). Some of these patients have been invited to speak to regulators to explain the disease and the impact it has on their lives. "Patients need to be assured that (you are) not abandoning them or trespassing the boundaries," explained Wolgen. "You rely on these people. It is important not to lose that support or confidence."

According to Wolgen, the majority of shareholders spoken with also rejected the offer. However this was more on sentiment as those shareholders were not given a formal valuation.

The interest from Retrophin has been a positive for Clinuvel and its shareholders. For the first time, commercial interest in Scenesse has been achieved, which has resulted approximately in a 40% increase in the stock price. But having Retrophin on the register is important for another reason – Retrophin now has a substantial stake in the company and should there be any delays in the regulatory approval process, Retrophin would be a likely source of funding, which mitigates some of the funding risk.

Bioshares recommendation: **Speculative Hold Class B**

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– Invion cont'd

Summary

Invion has plans to build a therapeutic product franchise in the respiratory health area. It is repositioning two approved drugs for the treatment of mild-moderate asthma (zafirlukast or INV104) and moderate-severe asthma (nadolol or INV102). Its speed to market strategy will see its smoking cessation program move into a Phase III trial next year pending successful Phase II studies. Inhaled versions of its compounds will see the company move into at least four clinical trials in the first half of next year.

Invion's Chief Medical Officer, Dr Mitchell Glass, said the company will have a lot of data out for its three drugs in the next 12 months and that the company "will have an extraordinary story to tell around these drugs in 18 months."

Invion is capitalised at $36 million. The company had $4.0 million cash at the end of June.

Bioshares recommendation: **Spectulative Buy Class A**

Milestones to Monitor

- Interim Phase II asthma results (Q3 2014)
- Interim results from Phase II lupus trial (Q3 2014)
- Interim Phase II smoking cessation study results, secondary endpoints (2H 2014)
- Final results from smoking cessation (1H 2015)
- Final results from Phase II lupus trial (2015)
- Start Phase III trial in smoking cessation (1H 2015)
- Start Phase I trial in mild-moderate asthma with zafirlukast (1H 2015)
- Start Phase I trial in COPD with inhaled INV102 (1H 2015)
- Start Phase I trial in asthma with inhaled INV102 (1H 2015)

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Five Stock Wrap

Company	Alchemia	**Code**	ACL	**CMP**	$0.56	**Cap'n ($M)**	$180.0	**Cash ($M) 30/6**	$11.1	**SI**	**6.1**

- ACL generates revenues from the generic anticoagulant, fondaparinux, under a profit share agreement with Dr Reddys
- Fondaparinux held a 32% volume market share in the March quarter; market was experiencing volume and pricing pressure
- The average of net sales of fondaparinux for the most recent six quarters was US$10M, of which ACL has averaged a 27% profit share
- Pivotal Phase III trial of HA-irinotecan is expected to report in September 2014. Endpoint is progression free survival
- The trial has enrolled 415 pts (76 sites, **5.5pt/site**) with 2nd and 3rd line metastatic colorectal cancer, comparing FOLFORI to FOLF(HA)iri
- Original plan was to enroll 390 pts at 55 sites (**7pt/site**), with PFS endpoint (or disease progression from 350 pts) expected Q3 2013
- Endpoint goal is at least 6 weeks improvement in PFS [benchmarks - Avastin delivered 10.5 weeks, Erbitux 6.5 weeks]
- The challenge for HA-irinotecan will be willingness by hospital pharmacies to substitute it for a very cheap existing drug
- Institutional investor Hunter Hall has built a 9.02% stake in ACL

Comment: In-licensing of new compounds in March does not indicate ACL's confidence of a strong trial result

Bioshares recommendation: **Sell** | Timing -

Company	Avita Medical	**Code**	AVH	**CMP**	$0.115	**Cap'n ($M)**	$37.4	**Cash ($M) 30/6**	$3.6	**SI**	**0.5**

- Avita Medical markets ReCell, a 'spray on skin' product and two respiratory products, Breath-A-Tech and Funhaler
- Revenues for FY2014 were $3.3M, across all sources
- ReCell sales in the June quarter were impacted by restructuring of UK operations and issues at the UK's National Health Service
- Company said it will increase investment in its respiratory products to improve cash flow while building ReCell sales
- AVH's chronic wounds trial has enrolled 28 out of 65 patients, with full enrollment expected in Q1 CY2015
- FDA granted an humanitarian IDE for ReCell in a number of cases; is still in discussion about modifying its US burns trial
- Investigator-led study showed ReCell was superior to medical needling in treating hypo-pigmented scars
- UK reimbursement process for ReCell was stalled when a NICE meeting was post-poned

Comment: Although a $1.4M tax refund is expected, AVH's cash position is a cause for concern, flagging a need for a capital injection

Bioshares recommendation: **Sell** | Timing -

Company	Medical Developments Int.	**Code**	MVP	**CMP**	$1.070	**Cap'n ($M)**	$61.8	**Cash ($M) 31/12**	$1.0	**PE***	**72.5**

- MVP markets a range of medical products, notably its Penthrox short term pain relief product, popularly known as the Green Whistle
- Share price surged to a twelve month high of $1.72 (08/13), likely based on expectations of market opportunities for Penthrox in Europe
- Company advised in May that full year sales were likely to be around $9.3 million (FY2013 - $11.7M)
- Reasons for softer result relate to a cancelled contract from GSK, a merger of two trading partners, an order deferral in New Zealand
- MVP submitted marketing authorisation application to the UK's MHRA in November 2013
- MVP submitted answers to first round of questions from the MHRA in January 2014
- Company advised in May the it expected the MHRA review to be completed in about six months (i.e. around Nov/Dec 2014)
- Long standing director of 10 years, Maurice van Rin, recently resigned from the board to pursue travel and other opportunities

Comment: Regulatory passage for Penthrox is an outstanding risk for MVP; delays are not uncommon

Bioshares recommendation: **Sell** | Timing - Revisit post-MHRA approval

Company	Osprey Medical	**Code**	OSP	**CMP**	$0.600	**Cap'n ($M)**	$73.9	**Cash ($M) 30/6**	$17.1	**SI**	**1.8**

- OSP's current lead program is the AVERT system, a device which enables the controlled infusion of dye, as used in heart procedures
- The 2nd generation AVERT system was cleared (approved) by the FDA in June
- OSP has a 700 pt trial across 45 sites (ave **15.5 pt/site**) underway, to support a claim of "reduction of contrast induced nephropathy"
- First pt enrolled Jan 2014; reported enrollment rate average of 0.8 pts/site/ month (through July), so now expanding number of sites to 65
- Our estimate is that at 0.8 pts/month across 25 sites over 7 months that 140 pts had been enrolled (through July)
- Intends to expand AVERT into the setting of peripheral artery disease treatment; 25 pts treated so far in Texas
- Dye exposure can occur on at least three occasions in PAD treatment and management
- OSP is also conducting a 20 pt trial of its diabetic limb recovery system, 14/25 pts enrolled, full enrollment expected Q4 2014
- Company is conducting 'ongoing R&D efforts to enrich' its pipeline

Comment: The signals emanating from OSP's AVERT trial suggest that the trial will take longer than planned to complete or exceed budget

Bioshares recommendation: **Sell** | Timing -

Company	Pharmaust	**Code**	PAA	**CMP**	$0.012	**Cap'n ($M)**	$17.3	**Cash ($M) 30/6**	$2.30	**SI**	**1.5**

- Pharmaust includes a drug chemistry services business, Epichem, and a drug development business Pitney Pharmaceuticals
- PAA has commenced an open label Phase I trial of its oral anti-cancer compound, PPL-1, at Royal Adelaide Hospital
- PPL-1 is the Pharmaust identifier for the veterinary ant-parasite treatment, monopantel
- The primary endpoints of the trial concern safety, tolerability, dose limiting toxicities and to explore the maximum tolerated dose
- Three doses will be evaluated, commencing with 5mg /kg, then 25mg/kg, and finally 62.5 mg/kg, over 28 days of daily dosing
- The trial will enroll 12-15 subjects, recruited from a broad pool of cancer types, who have failed standard of care treatment
- PAA is also working on a veterinary anti-cancer PPL-1 product, initiating a trial in dogs in February
- PPL-1's safety profile is well established through its use as a sheep drench, but its anti-cancer MOA is still being characterised
- Epichem earned revenues of $1.8 million in FY2014

Comment: The attraction of PAA's Phase I study is that results should appear within a short time frame (we estimate 6-12 months)

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

Notes: PE - Price/Equity ratio (annualised NPAT) ; SI - Survival Index (refer to Bioshares 562 for explanation)*

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: Cogstate, Bionomics, Impedimed, QRxPharma, LBT Innovations, Tissue Therapies, Viralytics, Phylogica, pSivida, Antisense Therapeutics, Benitec BioPharma, Admedus, Calzada, Invion, Circadian Technologies, Imugene, Analytica

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