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In this edition...

Pharmaxis has at last been given the green light by the European drug regulator to market Bronchitol as a treatment for cystic fibrosis. The company has also revealed its pricing for Bronchitol, which will range from €7,300 - €9,125 per year.

Dr Mark Currie, the Chief Scientific Officer from Bionomics' BNC210 partner, Ironwood Pharmaceuticals, met Australian investors last week. Ironwood's positioning of BNC210 as a top line project is a very positive sign for Bionomics investors.

Virotherapy company Viralytics reports that its Phase II trial of CAVATAK in melanoma patients is proceeding well. We provide an update on the company and the progress in using viruses as a cancer treatment.

The Editors

Companies Covered: BNO, PXS,VLA

	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 now commenced	-19.2%
Cumulative Gain	**240%**
Av. annual gain (10 yrs)	**21.4%**

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Bioshares

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

Pharmaxis – Bronchitol Ready to Go!

After a dream run for the most part for Pharmaxis (PXS: $1.30) in commercializing Bronchitol for the treatment of cystic fibrosis, the last year has been an agonizing roller-coaster ride in getting the product approved in Europe. This week Pharmaxis finally gained marketing approval in Europe for patients aged 18 years and over with CF.

It will take up to one month to finalise labeling and to get its official coding details. After that the company will be able to start marketing and selling its pharmaceutical into 29 countries that make up the European Union.

Pharmaxis will start selling into Germany first where take up by CF centres should be more rapid and there is no need negotiate prior pricing and reimbursement. The company expects most CF clinics in Germany will have placed some orders by mid year.

The company will also immediately launch the product in the UK. The uptake of the product in the UK is expected to be slower with more time required to get the product on the hospital formularies. In the UK there are around 55 CF treatment centres and in Germany there are around 110. Pharmaxis already has sales and marketing teams in place in both the UK and Germany. Many of the UK sites were used in the company's Phase III trials.

For the first time the company has revealed details about pricing of Bronchitol. The drug will sell for between 20-25 Euros per day (ex-factory price). That translates to between 7,300 - 9,125 Euros per year per patient (AUD9,300 - AUD11,600). This is in line with our estimates for what the company has secured for pricing with the Australian Government, around $10,000 a year per patient.

In the UK, the company is working with a government drug advisory group, NICE, which provides recommendations of price effectiveness of new therapies. A positive review from NICE helps get the product onto hospital formularies and effects a quicker uptake of the therapy. NICE has yet to review any CF drugs.

The UK and Germany make up 40% of the CF market in Europe. Those two countries alone represent an addressable market, by our estimates, of between $75-$95 million a year based on only the over 18 patient population. The overall addressable market size in Europe for the over 18 population is between $190-$240 million a year.

Pharmaxis will look to start a trial in patients under 18 years of age later this year. This trial may be a short trial and only run for six weeks.

Cont'd over

The key factor now for Pharmaxis will be market penetration rates. The product will be officially launched at the CF conference in Dublin in the first week of June.

US Pathway

In this quarter the company expects to file Bronchitol for US approval. It's expected that an FDA advisory meeting to assess Bronchitol will be convened towards the end of this year with an evaluation decision from the FDA expected in early 2013 (10 months from filing its NDA).

Bronchiectasis

Pharmaxis is conducting a second Phase III trial with the same drug in the treatment of bronchiectasis, which is a broad degenerative condition of the lungs. The trial has finished recruitment and half of the patients have completed treatment. Completion of the trial is expected at the end of this year. Results are expected in early 2013.

ASM8 – An Unexpected Result

This week the company released results from a Phase II trial with its antisense drug candidate, ASM8, for the treatment of asthma. The trial delivered an unexpected result.

ASM8 was found to reduce restriction in the airways by 44% (when patients were challenged with an allergen to induce an asthma episode). The problem was that patients in the control group also experienced a similar result when receiving saline. This was due to the crossover nature of the study, where patients crossed over from control to active or from active to control.

The company believes it is likely due to a longer lasting effect of ASM8. The effect was noticed when patients crossed over from active to placebo, but not when patients received the placebo first. The drug was taken for 14 days, and there was a four-to-six week break between the crossover. That there was such a lasting effect came as a surprise.

In the sputum, the drug was shown to be completely cleared in 24 hours. However antisense drugs are absorbed by tissue in the body and can have a long acting effect. ASM8 is designed to turn down the synthesis of proteins associated with inflammation.

This trial showed that some patients were not responding to an allergen challenge for weeks after receiving ASM8. This is potentially very good for patients, however for the company it makes developing the drug more challenging.

Pharmaxis is now taking a further look into the breakdown of the results. Positively, no safety issues were noticed with the drug candidate. The next trial is unlikely to involve a crossover design.

Summary

Pharmaxis has many key milestones approaching. These include:

- Launch of Bronchitol in Germany and UK (this quarter)
- Filing Bronchitol for US approval (this quarter)
- PBS listing in Australia (this quarter)
- Launch in other European countries (2H 2012)
- FDA Advisory Panel review for Bronchitol (Q4 2012)
- Completion of bronchiectasis Phase III trial (Q4 2012)
- FDA decision on Bronchitol for CF (Q1 2013)
- Phase III bronchiectasis results (Q1 2013)

Pharmaxis is capitalised at $398 million. It had $91 million in cash at the end of March.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

Bionomics Update

Bionomics' (BNO: 46 cents) partner for BNC210, **Ironwood Pharmaceuticals**, is about to move through a major transformation. Its lead drug candidate, linaclotide, is due to be reviewed by the FDA in June. Linaclotide has been developed for the treatment of irritable bowel syndrome and chronic constipation.

The market for this drug candidate has been estimated by some US analysts at US$2 billion a year. Ironwood has a market capitalization of US$1.35 billion with US$164 million in cash.

Ironwood has developed considerable expertise in the use of patient reported outcomes as endpoints in clinical studies. Its four Phase III trials used 66 endpoints, all of these reported by the patient. Each of these endpoints delivered a positive result. The results look so good that the FDA is not convening an expert advisory panel meeting to help assess linaclotide.

The outcome of linaclotide is now important for Bionomics. If the drug gets knocked back by the FDA, then it could put pressure on resources and investment Ironwood is making in the Bionomics drug candidate, now called IW-2143.

This week *Bioshares* met with Ironwood's Chief Scientific Officer, Mark Currie. Two important questions answered at the meeting were (1) why was Ironwood attracted to IW-2143 (BNC210) and (2) where does the program sit in Ironwood's pipeline?

The key attraction to Ironwood in IW-2143 was the quality of the animal data Bionomics had generated in its preclinical studies. The stimulation of neurite growth with antidepressant activity in a rat model got Currie very excited and Currie has considerable experience in this area. As a scientist, Currie had previously tried to find an anxiolytic without the sedation effects but couldn't. "All of us want it (an anxiolytic without sedation)", said Currie. The lack of sedation in IW-2143 seems to be carrying over into clinical studies said Currie.

There appears to be some debate about the CCK panic induced model Bionomics has used in its Phase Ib trial. However the animal data has been very consistent.

What is promising in this field is that the animal models are very predictive of outcomes in people. All drugs in this class on the market, including the SSRIs (selective serotonin reuptake inhibitors), have shown activity in these animal models.

Cont'd on page 4

Viralytics & Oncolytic Virus Therapy Update

Viralytics (VLA: 34.5 cents) continues to make progress with its Phase II trial of CAVATAK, an oncolytic virus therapy that harnesses the wild type coxsackievirus strain A21 as a tumour destroying agent when injected directly into the tumour at a very large dose.

The Phase II trial is being conducted in a number centres in the US. Viralytics' Chief Scientific Officer, Dr Darren Shaffren, reports the trial is proceeding very well with the company pleased with progress.

The Phase II trial is recruiting 63 patients with Stage III or Stage IV melanoma and no circulating antibodies to coxsackievirus strain A21. Patients will receive intra-tumoural injections of doses of up to $3x10^8$ TCID50 of virus.

The primary endpoint will be immune related progression free survival at six months (see edition #440 of Bioshares), with secondary endpoints being the durable response rate at six months and progression free survival at six months.

CAVATAK has several quite separate mechanisms of action. Its primary action follows when a very large dose of cocksackievirus is injected into a tumour, overwhelming the tumour environment and through replication in tumour cells causing the cells to lyse (burst open). Oncolytic viruses reproduce preferentially in cancer cells.

A second stage of response is a cytotoxic T-cell response which also leads to cell death. Cytoxic T-cells are typically engaged when pathogens infect cells.

The conceptual force behind the development of oncolytic virotherapies is that the therapy should be well tolerated because of the application of relatively benign viruses, the injection of large doses of virus should capable of destroying tumours and also stimulating a second round immune response to specific tumours and to cancer that has spread to other areas.

Amgen's Oncolytic Virus Therapy Program

Amgen acquired **Biovex**, the developer of OncoVEX in January 2011 for a payment of US$425 million upfront and up to US$575 million in contingent payments. This has been the strongest commercial endorsement of oncolytic virotherapy to date.

Now also named talimogene laherparepvec, this candidate therapy is being progressed through a Phase III trial in 430 patients conducted at 83 sites. The trial is expected to be completed by June 2012 and the results made available by the fourth quarter of 2012.

These trial results are the next in line of Amgen's Phase III program outcomes that are expected to be become available. They will be of significance to Viralytics.

OncoVEX is a herpes simplex-1 virus (HSV-1) that has been engineered to express granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF is an immune system stimulating compound.

Relevance of OncoVEX to Viralytics

The OncoVEX program is of considerable relevance to Viralytics. This particular virotherapy is the technology sub-sector's lead program and the potential exists, if it is successful in the current Phase III trial, to spark interest in other company's programs, such as those of Viralytics, Jennerex or Oncolytics Biotech (see below).

The OncoVEX program is somewhat similar to the Viralytics program in that it being conducted in patients with Stage III and Stage IV melanoma. The virus is also delivered as an intra-tumoural injection.

However, unlike Viralytics single arm trial Phase II, Amgen's Phase III trial is a randomised, controlled trial with the control arm using GM-CSF as a comparator. GM-SCF can be used as a control arm intervention, because it is approved for the treatment of cancer, albeit one specific form of leukemia.

In a 50 patient Phase II study, OncoVEX was shown to deliver a complete response (CR) in 10 patients, including a 100% durable response in those 10 patients and the majority maintaining that durable response out to 48 months. Eighty per cent of patients in the trial were categorized with Stage IV melanoma. Another four patients showed a partial response, with three of those maintaining a durable response out to 26 months.

The primary endpoint for the Amgen trial is a statistically significant improvement in the durable response rate.

The Phase III clinical design for OncoVEX that the FDA agreed to is not likely to be an option for CAVATAK. This is because two other products, ipilimumab and vemurafenib, have now been approved for the treatment of melanoma and would now most likely have to be included in any Phase III trials. Secondly, the durable response rate endpoint is not likely to be accepted as a primary endpoint with endpoints based on progression free survival being given more importance.

However, the durability of response rate will be an endpoint worth monitoring in the Viralytics Phase II trial, even though it is a secondary endpoint. If a rate of response similar to the rate durable response rate reported by Biovex (now Amgen) in its Phase II study is recorded, then inferences on the success of a Phase III trial for CAVATAK could be made based on the Phase III trial of OncoVEX, since the data from that trial will be have been public for at least 12 months by the time the results of the Phase II CAVATAK trial are available.

Jennerex and Oncolytics Biotech

Another company developing an oncolytic virotherapy is Jennerex, a privately held US firm, which recently appointed the current Chairman and former CEO of Dendreon, Dr Mitchell Gold, to the board. Dendreon markets the immunotherapy Provenge (sipuleucel-T), an immune-therapy/vaccine which continues to generate scientific discussion and criticism following its approval by the FDA in April, 2010.

Cont'd over

– Viralytics cont'd

Jennerex's oncolytic therapy approach utilizes an engineered vacinnia virus (as opposed to Viralytics' suite of wild type coxsackievirus strains). The virus is engineered to express the GM-CSF, similar to Amgen's OncoVEX, as well as the deletion of the thymidine kinase (i.e. is not expressed).

Jennerex has completed a Phase II trial of its lead product JX-594 in liver cancer and is being progressed further in a 120 patient Phase IIb trial in advanced liver cancer in patients who have failed treatment with sorafenib (Nexavar).

Jennerex recently published the results of studies into the more detailed molecular mechanism of action of JX-594, showing that the virus selectively replicates in cancer cells because it is activated by EGFR/Ras pathway signaling and cellular thymidine kinase levels, which are traits common to many types of cancers. The finding is important, at least from Jennerex's perspective, because it explains the selectivity of the virus to cancer cells, leaving healthy cells unaffected.

Another oncolytic virotherapy in development is REOLYSIN (wild-type respiratory enteric orphan virus) by Canadian firm **Oncolytics Biotech**. This company is looking to generate a systemic response from intravenous administration. It aims to overcome the presence of neutralizing antibodies by administering very large doses of virus (5 trillion particles per day).

Oncolytics Biotech is overseeing five Phase II and one Phase III trial. This company is capitalised at US$297 million with current cash resources of US$35 million, implying a technology valuation of US$262 million. This market valuation is a healthy sign of the interest in an emerging therapeutic approach, at least from a North American market perspective.

Other Developments

Several other developments that have occurred over the last six months to note with Viralytics include the exiting of La Jolla Cove Investors from the register, which had provided the company with US$6 million in convertible note funding, and the addition of Dr Leonard Post to the board.

The exit of La Jolla Cove investors means that a significant seller of stock is no longer on the register.

The appointment of Dr Leonard Post to the board is a very welcome addition. Dr Post is a virologist by training but had a significant role in developing the drug Nexavar while at Onyx Pharmaceuticals. He was founder of LEAD Therapeutics and currently serves as Chief Scientific Officer for BioMarin Pharmaceuticals. He also was head of discovery research at Parke Davis and was director of infectious diseases research at The Upjohn Company. More recently he was a director at Biovex, and it his experience from that company that may be of much value to Viralytics. Dr Post is also an advisor to Brisbane-based CM Capital.

Summary

With progress of Viralytics' Phase II trial reported to be going well, investors should also be factoring in the potential for newsflow and valuation trends from other oncolytic virotherapy companies to support their involvement with this stock, in particular the year end announcement of Amgen's Phase III results for OncoVEX.

Viralytics is capitalised at $26 million and retained cash of $8 million at December 31, 2011.

Bioshares recommendation: **Speculative Buy Class B**

Bioshares

– Bionomics cont'd

Ironwood plans to conduct a Phase 1b trial and then move on to a Phase IIa study. Currie stressed that his company would not be talking much about this program until the Phase IIa study has been completed.

IW-2143 has considerable importance for Ironwood. It is the third most important program for Ironwood, following on from linaclotide, and IW-9179, which is a second generation linaclotide program. The company has put significant resources behind this program, with over 40 people working on the compound's development. The Phase IIa study is likely to involve less than 120 patients.

Ironwood's experience in using patient reported outcomes will also be valuable in clinical trial design for IW-2143.

Currie said that Big Pharma moved away from this development space, but it's a great area for companies such as Ironwood and Bionomics to be in.

BNC105

Bionomics is on track to enrol its target of 134 patients for its renal cancer study with BNC105 by the end of 2012. Its Phase II ovarian cancer study is now commencing.

Alzheimer's Disease

The company expects to have a lead drug candidate for its latest program in Alzheimer's disease ready for preparations for clinical studies in third quarter of this year.

Summary

Ironwood Pharmaceuticals appears to be an excellent partner for Bionomics for the commercialisation of IW-2143. The program has obtained a high priority within Ironwood's pipeline. Ironwood appears committed to invest in and support the program with over 40 staff working on this program at the current stage of development. It represents an important second area of focus for Ironwood and because it is a smaller and aggressive biotech, development progress can be expected to be managed as rapidly as is possible. However a clean regulatory pass through the FDA for its lead compound linaclotide is a relevant consideration for investors in both companies.

At the end of March Bionomics had $17.9 million in cash. Bionomics is capitalised at $159 million.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

Bioshares Model Portfolio (20 April 2012)

Company	Price (current)	Price added to portfolio	Date added
QRxPharma	$1.80	$1.66	October 2011
Mayne Pharma Group	$0.280	$0.435	September 2011
Acrux	$3.95	$3.37	June 2011
Somnomed	$0.87	$0.94	January 2011
Phylogica	$0.049	$0.053	September 2010
Biota Holdings	$0.95	$1.09	May 2010
Tissue Therapies	$0.45	$0.21	January 2010
Atcor Medical	$0.08	$0.10	October 2008
Bionomics	$0.46	$0.42	December 2007
Cogstate	$0.25	$0.13	November 2007
Sirtex Medical	$6.16	$3.90	October 2007
Clinuvel Pharmaceuticals	$1.67	$6.60	September 2007
Pharmaxis	$1.30	$3.15	August 2007
Universal Biosensors	$0.80	$1.23	June 2007
Alchemia	$0.510	$0.67	May 2004

Portfolio Changes – 20 April 2012

IN:
No changes

OUT:
No changes

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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