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In this edition...
The testing of drugs and devices in humans, as opposed to mice, pigs and sheep, is where the cis-polyisoprene (rubber) hits the road for new products. It's a numbers game where recruiting patients on time means that you can also (probably) meet the budget for the job. That appears to be the case for Starpharma which has completed recruitment for two Phase III trials of Vivagel for the treatment of bacterial vaginosis. In stark contrast, cancer immunotherapy company Prima Biomed's enrollment for its Phase III trial of CVac has had a very slow start, and interim data from a Phase II trial is only providing weak evidence of benefit, if any. Interim data from Viralytics' CAVATAK Phase II trial is positive as are the results from Calzada's first two patients treated with its Novosorb BTM product.
Companies Covered: CZD, PRR, SPL, 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 (May '11 - May '12)	-18.0%
Year 12 (May '12 - current)	-12.5%
Cumulative Gain	**202%**
Av. annual gain (11 yrs)	**17.8%**

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

Clinical Trial Updates for Starpharma, Prima Biomed and Viralytics

Starpharma Completes Recruitment for Two Phase III Trials

Starpharma (SPL: $1.485) announced that it completed recruitment for both of the Phase III trials it is conducting of Vivagel as a treatment for bacterial vaginosis. Results of the trial are expected to be made available in December. Vivagel is gel with anti-viral properties, which also has the potential to be used as a topical microbicide against HIV, HPV and genital herpes.

The primary endpoint of the trials are the number of women with 'Clinical Cure at the Test of Cure visit' as evaluated between days 21 to 30. A clinical cure is defined by resolution of the Amsel criteria which define bacterial vaginosis. The criteria include homogeneous vaginal discharge, amine odour when potassium hydroxide solution is added to vaginal secretions, presence of clue cells (greater than 20%) on microscopy and a vaginal pH greater than 4.5. (see www.medicalcriteria.com/criteria/gin_vaginosis.htm)

The identical trials commenced in March 2012 and have been completed on schedule. Both trials enrolled 250 patients each from more than 30 sites globally. The trials have been conducted under a Special Protocol Agreement with the US FDA.

Starpharma is capitalised at $420 million and held cash of $43 million at June 30, 2012.

Bioshares recommendation: **Lighten**

Prima Biomed Reports Interim Phase II Results

Prima Biomed (PRR: $0.0115) recently released interim results from a 63 patient Phase II trial of CVac, an immunotherapy or vaccine that is being evaluated as a potential therapy for ovarian cancer patients.

The therapy is personalised in that immune cells from a patient (dendritic cells) are harvested from a patient and are pulsed or presented to a recombinant human fusion protein (mucin 1-glutathione S-transferase coupled to oxidized polymannose). The immune cells are injected back into the patient with the hypothesis being that the primed immune cells will deploy further the machinery of the immune system to destroy cancer cells which over express mucin 1.

Prima reported that the Phase II trial interim progression free survival data showed a 'favourable trend towards patients receiving CVac staying in remission longer than those in the observational standard of care (OSC) group.'

The median progression free survival for patients randomised to CVac was 365 days and 321 days for the OSC group, based on the data pooled from two subgroups, being groups of patients being in either their first or in their second remission. No measures of statistical significance were reported.

Cont'd over

The pooling of the interim data is somewhat problematic because median PFS was obtained for CVac patients in the first remission group but not patients on OSC. The median PFS was obtained for OCS patients in the second remission group but had not been reached for CVac patients.

The data is inconclusive at this stage and the trial cannot be properly assessed until it is completed and analysed by 2013 Q4.

Phase III Trial – The CANVAS Study (CAN-004)

Prima Biomed is also conducting a much larger 1,000 patient Phase III study of CVac in patients with epithelial ovarian cancer.

When the first patient was enrolled in this trial in February 2012, the company stated that it expected to complete enrolment in two years or less. However, the company reported that by September 24, 2012, only 16 patients had been randomized into the trial and that nine sites across Australia and the US were actively enrolling, from a total of 97 selected sites. The enrolment rate for the period from February to September stood at ~2 patients per month.

The rate of recruitment in the CANVAS study is now a major cause for concern for investors. To meet its enrolment target of 1,000 patients by 2014 Q1, it would have to enrol 58 patients a month. By way of example, an enrolment rate of 20 per month would not see the trial meet its enrolment target until November 2016.

The clinical development of CVac is further complicated by the immunotherapy process itself which requires a collection step at a qualified centre and a processing step to take place in a specialised cell therapy facility. Prima is coordinating activities at 50 cell collection centres and at three cell therapy manufacturing facilities.

The longer the Phase III trial takes to complete then the greater the impact on Prima's working capital requirements.

Prima Biomed is capitalised at $122 million and retained cash resources of $33 million at September 30, 2012.

Bioshares recommendation: **Sell**

Viralytics Sparks Interest with Interim Phase II News

Viralytics (VLA: $0.42) is conducting a Phase II trial of its CAVATAK therapy in 63 patients with melanoma. The therapy that involves the administration of large quantities of cocksackievirus type 16. The virus has generally benign effects in humans.

The mode of action is two-fold. The virus binds to a receptor (ICAM-1) that is found on the surface of many cancer cells. Saturation of the cells, due to the large dose, invokes an implosive or destructive cascade inside the cells. A secondary immune effect takes place as pieces of tumour cells or debris become recognized and then targeted by the immune system. This second arm of the response takes much longer to develop.

One of the attractions of this therapeutic approach is that side effects are less relative to many chemical therapy approaches, with no nausea or diarrhea observed and at worst symptoms associated with the common cold appearing. In particular it aims to harness the immune system rather than disrupt or degrade the immune system.

Viralytics reported that 13 of 63 patients have been dosed with CAVATAK in its unblinded, non-randomised Phase II trial. Three patients demonstrated immune-related progression free survival (irPFS) and two of these have moved into an extension study. The extension study is open to patients who have completed dosing and have demonstrated stable disease for six months.

Of interest is that the progress update shows that for patients who had passed the six month irPFS point, three out of eight patients demonstrated irPFS, which is an encouraging number.

An immediate challenge for Viralytics is to improve the rate at which it enrols patients in the trial. The company will add more sites to the current five sites it is using. Viralytics believes that because clinical momentum has now gained hold in the trial, it may end up turning away sites that want to be involved in the trial.

Investment Appeal

There is a simple, unequivocal investment appeal to Viralytics. The goal of the board is to effect a sale of the company should the Phase II trial yield convincing data, which may occur before the trial is completed. What is likely to capture the interest of potential acquirers is the durability of the response.

Sustaining progression free survival in patients with melanoma well beyond six months, both on a time basis and an a response rate, could be sufficient for a larger company to acquire the Viralytics. Metastatic melanoma survival rates remain poor despite the relatively recent approval of two new drugs, ipulimumab (brand name: Yervoy) and vemurafenib (for BRAF V600 positive patients).

The current benchmark for treating Stage III or IV metastatic melanoma has been set by ipulimumab which generated a median survival rate of 10 months versus 6.4 months for a gp100 peptide vaccine comparator in a 676 patient Phase III trial. In another trial in 502 patients, ipulimumab with dacarbazine generated a median survival rate of 11.2 months against 9.2 months for dacarbazine alone. However, the deleterious side effect profile and high cost of ipulimumab means that the demand for effective, safe and cheaper approaches remains strong.

Summary

Although Viralytics is one of a handful of pioneers of a new approach to cancer therapy, that being the use of viruses to destroy tumours, the company has the benefit of riding in the wake of Amgen, which following the acquisition of Biovex in 2011 for an upfront payment of US$425 million, could benefit further if Amgen's Phase III trial of its virotherapy delivers positive results in the first half of 2013.

Viralytics is capitalised at $32 million and retained cash resources of $4.5 million at September 30, 2012

Bioshares recommendation: **Speculative Buy Class B**

Calzada – First Human Implants Successful

Calzada (CZD: 5.1 cents) has successfully used its wound repair product in treating full thickness wounds in two patients requiring flap donor site treatment. The treatment, called the Novosorb Biodegradable Temporizing Matrix (BTM), is a biodegradable polyurethane polymer.

Early Clinical Results Positive

The results from the treatment of the first two patients in the Novosorb BTM trial are important because proof-of-concept in man has now been achieved. Animal studies have shown the implanted polymer wound dressing works well, but in-human studies have now confirmed its positive features. There was no discomfort from the polymer implant and the wounds have been effectively sealed with a final skin graft treatment.

A free flap application was used because it is a scheduled procedure. In such cases, the skin is taken from one part of the body and is used to replace skin or tissue structures in other areas of the body.

Advantage 1 – Avoids Immediate Skin Graft

The Novosorb BTM has a number of functions. Firstly it allows the wound to be sealed, reducing the chances of infection in a major burn wound. It also importantly stops water loss from the wound.

The alternative is to immediately give the patient a skin graft from another area of the body. However, in the case of major burns, patients first need to be stabilised, skin grafts then need to be taken once the patient is stabilised, and for large wounds there may be insufficient body areas to deliver a graft. Often there is an additional delay, of more than 10 days, to allow the donor site to regrow to allow a second and third graft to be taken. In the meantime the wound is open to infection and water loss occurs.

Novosorb BTM has been designed to offer immediate wound closure, and to be followed by a skin graft at a later stage, once the patient has been stabilised.

Advantage 2 – Less Skin Graft

The second advantage from having a polymer implant is that the thickness of the skin graft required is much lower, with the skin graft only the final layer placed on top of the Novosorb BTM implant

This reduces the demand on skin grafts from other areas of the body. In the two patients treated in this trial, the Novosorb BTM product was 5-6mm in depth.

Advantage 3 – Less Wound Contraction

The third advantage in using a polymer to immediately close the wound is that it results in less contraction in the wound and therefore less disfiguration of the skin. The body naturally tries to close a wound if it is not sealed, thereby contracting the skin.

Also if there is not sufficient skin depth in the skin graft, the treated wound is lower than the surrounding skin and this adds to the contraction in the skin. In the first two patients treated, the wounds were full thickness and the final treated wound area was level with the surrounding skin, achieving a visually appealing result (see announcement 15 October 2012 for images). Contraction of the skin can also restrict the mobility in the limbs.

BARDA Contract Submission

The technology from Calzada's subsidiary Polynovo is being championed by burn surgeon Dr John Greenwood in Adelaide. Dr Greenwood was the only non-US burn surgeon invited to advise the US government on its disaster planning response to a potential major catastrophe in the US.

This is an important point because Novoskin, which is 80% owned by Calazada and 20% by Dr Greenwood, was invited to submit a proposal for a US BARDA contract to develop a product for the treatment of mass burn casualties. Calzada expects a decision on its application for a $16.9 million contract with BARDA to be decided in the next six months. The Novosorb BTM could potentially be stockpiled by BARDA for use in event of a major catastrophe. Novosorb BTM can be mass produced and can be readily stored for emergency use.

Advantage 4 – Robust and Easy to Use

The fourth advantage with Novosorb BTM is that it is robust and easy to use, compared to the Integra product in the market which is more delicate. Calzada also believes its technology is more reliable than Integra, with reliability being a very important issue. Integra has several limitations, one of those being its very high cost.

The appeal of Novosorb BTM in a mass casualty situation (see BARDA Contract Submission) is that it is durable, easy to use, reliable, much less expensive to produce that Integra (Integra is made from bovine collagen and shark chondrocyte), and can be mass produced and stored.

Additional Patient Recruitment

Novoskin (the joint venture between John Greenwood and Calzada's subsidiary Polynovo) will continue to enrol more patients into this trial and on the back of the positive results to date, it may look to expand the trial into burn wounds, looking to recruit around a further 10 patients in the next 12 months.

Next Product – Composite Cultured Skin

A major advance in wound treatment is using the Novosorb technology to create a complete bilayer skin product that would potentially replace the need for a skin graft. The company has already developed proof-of-concept in an animal study that it can develop a bilayer skin product.

This involves producing two layers of skin, where the skin is grown up in a bioreactor from a small biopsy. The process takes 21 days. It forms a dermal structure from fibroblast cells and a second layer using epidermis cells. The cells are held in place using the Novosorb biodegradable polymer scaffold, allowing vascularisation to occur to provide nutrients to the cells.

Cont'd over

Bioshares Model Portfolio (26 October 2012)

Company	Price (current)	Price added to portfolio	Date added
Nanosonics	$0.500	$0.495	June 2012
Osprey Medical	$0.32	$0.40	April 2012
QRxPharma	$0.73	$1.66	October 2011
Somnomed	$0.92	$0.94	January 2011
Phylogica	$0.023	$0.053	September 2010
Tissue Therapies	$0.47	$0.21	January 2010
Cogstate	$0.365	$0.13	November 2007
Sirtex Medical	$10.60	$3.90	October 2007
Clinuvel Pharmaceuticals	$1.60	$6.60	September 2007
Pharmaxis	$1.32	$3.15	August 2007
Universal Biosensors	$0.90	$1.23	June 2007
Alchemia	$0.550	$0.67	May 2004

Portfolio Changes – 26 October 2012

IN:
No changes

OUT:
Biota has been removed following the vote by shareholders to delist the company from the ASX.

– *Calzada cont'd*

In the two patients treated to date with the Novosorb BTM scaffold, tissue ingrowth into the scaffold and vascularisation was observed.

Summary

Calzada's wound therapy technology appeals on a number of levels. It has now achieved early proof-of-concept evidence in two patients showing that it works as designed, potentially offering a much needed wound healing therapy. And it has a burns surgeon to champion its use and coordinate clinical assessment.

Calzada is capitalised at $18 million. It had $4.8 million in cash at the end of June.

Bioshares recommendation: **Speculative Buy Class B**

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, Biota Holdings, Impedimed, QRxPharma, LBT Innovations, Mesoblast, Tissue Therapies, Viralytics, Phosphagenics, Immuron, Phylogica, Bluechiip, pSivida, Antisense Therapeutics, Benitec BioPharma, Allied Healthcare Group, Genetic Technologies, Calzada, Bioniche, Atcor Medical, Invion

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