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Companies covered: CZD, POH, RVA, 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 - May '13)	3.1%
Year 13 (May '13 - Current)	60.9%
Cumulative Gain	**473%**
Av. annual gain (13 yrs)	**20.0%**

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Blake Industry & Market Analysis Pty Ltd
ACN 085 334 292
PO Box 193
Richmond Vic 3121
AFS Licence
No. 258032

Enquiries for *Bioshares*
Ph: (03) 9326 5382
Fax: (03) 9329 3350
Email: info@bioshares.com.au

David Blake - Editor
Ph: (03) 9326 5382
Email: blake@bioshares.com.au
Mark Pachacz - Research Principal
Ph: 0403 850 425
Email: pachacz@bioshares.com.au

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Bioshares

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

Calzada Receives FDA Approval for First Wound Healing Product

Calzada (CZD: $0.115) reached a major milestone this week with clearance received from the FDA to sell its first product into the US wound healing market. That product is the NovoPore dressing that will be used in Topical Negative Pressure (TNP) dressings, a market that is work in excess of $400 million.

Calzada's product was tested against the market leading product and gold standard, Granufoam from KCI. In an 18 patient trial, it was found that Calzada's NovoPore achieved less fragmentation into the wound and was easier to remove with less bleeding. Calzada's product also has the advantage of being biodegradable, so removing all fragments is less important that with other products. NovoPore is made from biodegradable polyurethane.

The next step in commercialising the product is to partner it with one of the existing marketers of the TNP products. There are around five major players in this field and Calzada is in discussion with most of them according to Laurent Fossaert, CEO of Polynovo Biomaterials, a fully owned subsidiary of Calzada. Calzada will seek to retain manufacturing control of the product, which is made at the company's facility in Melbourne.

In 2012 Calzada appointed David McQuillan to the board. McQuillan was formerly Senior VP of Research at KCI. Fossaert said McQuillan provides good insight on the market for this product, specifically what the market is looking for in terms of innovation, and the pressure points in the market.

In our view, a realistic timeframe for investors to look for, for the completion of a partnering deal, would be by the end of 2014.

Fossaert said the approval is a big tick in the box for the company, being important for getting the next products on the market using the same technology, and important also for potential partners. The approval lowers the risk of the entire technology platform, which can now be leveraged to bring other products to market believes Fossaert.

Cont'd over

Second product – Treatment of Donor Site Wounds

In February this year, three plastic surgeons at the Royal Adelaide Hospital were granted commercial access to the Calzada technology for the treatment of full thickness donor site wounds. This is the same hospital where the 10 patient clinical trial was completed last year with successful results. Calzada can charge for supply of the product. However, an important benefit for the company is that it will collect more data from the product's use. The name of the product for this application is NovoSorb BTM.

In that trial, it was shown that the NovoSorb BTM product could be effectively used as a dermal scaffold, in full thickness burns, with a skin graft completing the treatment once the wound was stabilised with the NovoSorb product. This was found to achieve a substantially better appearance than using a skin graft alone which results in the normal skin contraction which is obvious with full thickness wounds such as serious burns.

Burns Trials

At the end of last year, Calzada started recruitment in its burns trial in Adelaide (at the Royal Adelaide Hospital). This is a difficult trial to conduct, with the patients having serious trauma injury to 20%-50% of their body with third degree burns (where the wound extends all the way to the dermis). Similar to the donor site trial above, the NovoSorb BTM product will be used to immediately close the wound and to fill the wound site with the biodegradable polymer material. Once the patient has been stabilised, skin grafts will be taken to complete the wound treatment.

The aim of this trial is to achieve an improvement in final wound appearance with less contraction (scarring), to see how well this polymer product can be integrated into the wound, and how easily the NovoSorb BTM product can be delaminated. (The NovoSorb BTM includes a temporary epidermal seal that must be removed just before the skin graft is applied.) It was for this application for wound healing that the technology was originally developed.

A second burns trial is expected to start later this year (second half likely) in France. The size of that trial is unknown. The work of plastic surgeon John Greenwood, who is driving the clinical adoption of this product, has attracted interest from France, with one of the aims being to gain an independent assessment of use of the NovoSorb BTM.

Board Strengthened

Last month Calzada announced the appointment of David Williams to the board. Williams is a welcomed addition. He is currently Chairman of Medical Developments International (ASX: MVP) and also of the board of IDT Australia (IDT) and has an investment banking background. In November last year Chairman David Franklyn stepped down and was replaced by Dr Roger Aston.

Summary

Calzada is capitalised at $48 million. It had $5.3 million in cash at the end of December. The company is making solid progress with its technology, with its application in several areas being pioneered by Adelaide plastic surgeon John Greenwood.

After the surprise retirement of David Franklyn from the board last year, the new board appointment of David Williams is a noteworthy event and which may flag other corporate developments ahead.

Milestones to monitor will be progress in the current burns trial, filing the NovoPore product for approval in Europe, and a commercial distribution agreement for NovoPore in the US.

Bioshares recommendation: **Speculative Buy Class B**

Bioshares

Viralytics Starts Phase I/II Storm Study With Intravenous Cavatak

Viralytics (VLA: $0.315) this week announced it had started a 30 patient Phase I/II study (called STORM) in the UK with its investigational cancer therapy, Cavatak. This comes on the back of a $27 million capital raising recently which has transformed the company.

Viralytics previously had a largely retail shareholder base. Following the capital raise, the company is now 45% owned by institutional investors, including some 'big name' biotech investors from the US according to CEO Malcolm McColl.

Phase II CALM trial results

Viralytics has completed enrolment in a Phase II study (CALM) with Cavatak, which uses a virus to attack cancer cells. The virus used is Coxsackievirus A21, which is an unaltered form of the common cold. There is a theory that spontaneous remission in some cancer patients has potentially been due to infection of the common cold.

The results from the Phase II study have been very impressive, matching those achieved by Amgen with its oncolytic virotherapy, which was acquired through a US$1 billion deal.

The latest data shows that 35% of patients reached the six month immune related progression-free survival at 6 months. And 60% of patients were alive at 12 months. This is a very good result, given most patients with Stage III/IV melanoma are not expected to live out a year.

This week the company also announced that these results will be formally presented at the American Association for Cancer Research next month by the Principal Investigator of the trial, Dr Robert Andtbacka. What is new is that the company indicated that Dr Andtbacka will focus on the activity in non-injected metastatic tumours, something the company has talked little about.

The way the trial was conducted was that tumours were directly injected with the virus. That causes lysis, which destroys that tumour. However, the therapy is meant to work by attacking distant tumours as well, by initiating an immune response against other non-injected tumours. If this therapy is to be of commercial relevance, then it will need to show strong activity against distant tumours.

Phase I/II STORM Study

The STORM study just started is important for two reasons. The first is because the company will look at four different solid tumours: late stage melanoma, prostate, lung and metastatic bladder cancer. The first part of the trial will look at Cavatak alone, and see which types of tumours the virus is attracted to most.

The second relevant part is that this study will involve an intravenous delivery of Cavatak, rather than being injected directly into a tumour. Once the preferred type of tumour is select, the second part of the trial will focus on patients with that type of tumour and combine that treatment with the preferred chemotherapy regime.

An effect on efficacy is expected in the second phase of this trial. If this trial is successful, with results expected from early 2015 to 2016, then it has the potential to expand the market opportunity for this product.

Phase II Randomised Study

In the second half of this year, Viralytics will start a randomized study with Cavatak in patients with advanced melanoma. The difference between this study and the CALM study is that this trial will include a control arm to objectively assess the benefit of this treatment. It is expected to take around three years to complete.

Summary

Viralytics is now capitalised at only $57 million but holds $27.5 million in cash following completion of the capital raising, which this week received shareholder approval.

Cancer immunotherapy is a hot area of drug development which supports the recent interest behind Viralytics. Healthcare investment bank Leerink Swann believes that a half of all cancer therapies over the next decade may involve immunotherapy. And the editors of *Science* magazine chose cancer immunotherapy as 'The Breakthrough of the Year' in 2013.

Viralytics is following the path of Amgen with is T-Vec virotherapy approach. Potentially both therapies could be used sequentially in the treatment of melanoma and other solid cancers.

Important milestones ahead for Viralytics are:

- Presentation of CALM study at AACR (April) with results on distant tumours important
- Top line results from CALM study (Q3 2014)
- Start of randomized Phase II study (2h 2014)
- Survival data from CALM study (Q1 2015)
- Initial data from STORM study (Q1 2015)

Bioshares recommendation: **Speculative Buy Class B**

Bioshares

Reva Medical Sets Its Sights On A Third Generation Product

Reva Medical (RVA: $0.40) recently provided an update to investors on the progress it is making with the development of its Rezolve2 bioresorbable coronary scaffold. The product is designed to take the place of metal stents, which are used widely in the treatment of diseased arteries. The product is made of polymer materials which dissolve in the body, arguably contributing positively to cardiovascular health because certain stress factors that metal stents place on blood flow are eliminated progressively over time.

The company achieved enrolment in its CE Mark trial of the Rezolve2 product of 112 patients in December, across 29 sites in Australia, Germany, Brazil and New Zealand. Although it was envisaged that 120 patients would be enrolled in the trial, Reva believes that it now has sufficient numbers to eventually support its CE Mark application. The company expects to file this application before the end of 2014 or early in 2015. However, that submission is dependent on all patients completing follow up evaluations.

The primary endpoints for the trial are the number of major cardiac events at six and 12 months and measures of late lumen loss at nine months.

The company presented one month data from the trial for 65 patients at the Transcatheter Therapeutics Conference held in late on October 2013 and will provide more data at the European Percutaneous Cardiovascular Interventions conference in May 2014.

Third Generation Product

CEO Bob Stockman said that as the Rezolve2 clinical program has neared completion, and the company has been able to focus on the next generation of bioresorbable scaffold. The company has used an improved polymer to construct the scaffold, which it believes can result in a reduced profile (i.e. is thinner) which should improve the deliverability of the scaffold. These improvements would be added to several of the scaffold's existing key features, including radiopacity (the product is more easily imaged as compared to rival products because it is tagged with iodine) and single step inflation.

Reva has commenced pre-clinical testing of its next generation bioresorbable scaffold, with clinical trials planned to commence this year. According to Stockman, the trial will be 'a CE Mark study not unlike the current Rezolve2 trial.'

Reva emphasised that its strategy is to continue to improve its products over time, and to have a sequence of products in development. The company is also working on reducing manufacturing costs because of the constant pressures on healthcare budgets which in turn impact on the pricing of medical devices.

Relationship With Boston Scientific

Stockman elaborated on the company's relationship with Boston Scientific, which has an option to negotiate a sales and distribution agreement with Reva Medical. Boston Scientific is a medical device company which markets, among many products, the ION, PROMUS and TAXUS range of drug eluting metal stents.

Under the option agreement, Reva Medical has an obligation to provide data from 200 patients, after which Boston Scientific can elect to proceed towards a distribution agreement. Stockman said that even without marketing approval in place, matters such as minimum (volumes) and marketing efforts would need to be agreed upon. Currently a transfer price has been established, with Reva obligated to manufacture product for Boston Scientific. Decisions about which markets to sell into and at what price are at Boston Scientific's discretion. Stockman also said that Reva Medical is entitled to a 50% royalty on distribution.

Funding

Reva Medical held cash of US$20 million as of December 31, 2013 and employed 84 people. The *Bioshares* Survival Index measure for Reva Medical (based on its December 31, 2013 cash position) was 0.9, meaning that it had less than a year's cash at hand to fund operational activities. While the company's spending on its Rezolve2 trial is expected to taper off, spending on the next generation product would be expected to increase as and when it enters a clinical program.

Stockman said that the company does intend to raise capital and that it had 'spent considerable efforts interacting with financing sources over the past several months.'

The company listed on the ASX in 2010, raising $85 million at the time.

Comments

Reva's share price of $0.40 is approximately 40% below its high of $0.65 reached in 2013. More recently it achieved an all time low of $0.33. The weak share price is indicative of several things, first of which is that the company has probably struggled to gain traction with its fundraising endeavours. The company's conference call has shed some light on why this might be the case, with much emphasis being placed on yet a third version of its bioresorbable stent, for which a CE Mark clinical trial must be completed and more importantly funded.

Reva Medical has also (as far we can tell) not yet obtained data from 200 patients for its scaffolds, either the first generation Rezolve product or the second generation Rezolve 2 product, which would be needed to trigger discussions with Boston Scientific. The future cash needs of Reva Medical could also include funding to support marketing, post CE Mark, which could be used to build numbers to the 200 patient mark, up from an estimated 172 at present.

The need to develop an improved scaffold, for which it has been emphasised will be thinner and have improved deliverability, suggests that the current product is possibly not that attractive to interventional cardiologists from a use point of view.

Investors will be better placed to consider this stock once it has resolved its funding issues and more clarity emerges with respect to the clinical development of its third generation scaffold.

Bioshares recommendation: **Sell**

Bioshares Model Portfolio (7 March 2014)

Company	Price (current)	Price added to portfolio	Date added
Invion	$0.076	$0.089	February 14
QRxPharma	$0.850	$0.620	December 13
Impedimed	$0.225	$0.245	December 13
Analytica	$0.025	$0.025	December 13
Imugene	$0.014	$0.022	November 13
Oncosil Medical	$0.135	$0.155	September 13
IDT Australia	$0.370	$0.260	August 13
Viralytics	$0.315	$0.300	August 13
Tissue Therapies	$0.370	$0.255	March 2013
Somnomed	$1.63	$0.94	January 2011
Cogstate	$0.340	$0.13	November 2007
Universal Biosensors	$0.37	$1.23	June 2007

Portfolio Changes – 7 March 2014

IN:
No changes

Recommendations:

OUT:

No changes

Recommendations:

Phosphagenics Board Changes

Changes to the Phosphagenics (POH:$0.10) board have finally been made, following the accounting irregularities which were discovered last year and announced in July. Several staff including the then CEO Dr Esra Ogru were implicated in the misappropriation of $5.7 million that took place over five years.

Directors Stuart James, Dr Sandra Webb, Don Clarke and Jonathan Addison retired from the board. New appointees to the board were Lawrence Gozlan, Nathan Drona and Dr Geert Cauwenbergh.

However, complete board refreshment, a move recommended by *Bioshares* in previous editions, has not taken place as Harry Rosen continues as a director of the company in an executive capacity.

Phosphagenics held cash of $8.8 million as at December 31, 2013.

Bioshares recommendation: **Avoid**

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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