ISSN 1443-850X

In this edition...
Reva Medical is moving its bioresorbable ReZolve stent into a pivotal, CE Mark trial. Why investors need to follow this stock is because of commercial advances being made by the market pioneer for resorbable stents, Abbott Laboratories. This is a big company doing the heavy lifting, providing spill-over benefits to a small company such as Reva. The other stock examined this week is Circadian Technologies. What makes it of interest is that might, in the not too distant future, be able to 'do an Acrux', in other words fund and complete a registration trial for a relatively small sum of money. The disease in question is breast-cancer related lymphodema, a condition for which no drug treatments exist, but Circadian's VGX-100 antibody might deliver treatment benefits.
Companies Covered: ACL, CIR, RVA, TIS

	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)	-1.6%
Cumulative Gain	**240%**
Av. annual gain (11 yrs)	**17.8%**

Bioshares is published by Blake Industry & Market Analysis Pty Ltd.

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Individual Subscriptions (48 issues/year)
$400 (Inc.GST)
Edition Number 496 (22 March 2013)

Bioshares

22 March 2013
Edition 496

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

Reva's ReZolve Stent to Ride the Abbott Absorb Wave

Reva Medical (RVA: $0.52) is set to begin a pivotal trial of its ReZolve2 bioresorbable stent, the data from which will support an application for CE Mark for access to European markets. The company has now completed several key phases of a feasibility study, based on data from 22 subjects.

Stents are thin tubes which are implanted in blocked (occluded) blood vessels in order to maintain blood flow and restore structural integrity to the blood vessel.

The market is dominated by metal stents, which fall into two categories: bare metal and drug eluting. Thousands of implants occur globally each year, generating a market value close to US$5 billion. Bioresorbable stents,technically termed scaffolds, are designed to gradually erode over several months so that they have dissipated entirely at (for example), six months, in time for blood vessels to heal and revert to a healthy state.

Bioresorbable stents, by the fact of their dissipation and ultimate disappearance, are much less likely to have a long term impact, as metal stents do, on the normal dynamics of blood flow. Metal stents, it is argued by researchers such as Dr Ian Merideth at Monash University, create a problem called sheer stress. The permanent surfaces of metal stents improperly influence the flow of blood and other cells, and in so doing perpetuate inflammation of the artery at the site of the implanted stent.

Pilot Study Results [The RESTORE Trial]

The company was pleased with a low rate of adverse events at the six month point in the pilot trial, which was the primary endpoint for the trial. Two major adverse coronary events (MACE) were reported. However, only one of these was determined as a total lesion restenosis, which required re-stenting with a metal stent. The other MACE was classified as such because the stent was implanted in the wrong blood vessel.

Other endpoints for the study include late lumen loss (LLL) at 12 months (as measured by angiography) and MACEs at 60 months. The 12 month trial data is expected to be presented on an interim basis at the EuroPCR conference in May 2013 and on a complete basis at the Transcatheter Cardiovascular Therapeutics (TCT) conference in October 2013.

Late lumen loss refers to reduction in diameter of blood vessels. A cohort of patients which have been subjected to angiographic assessment all show late lumen loss to be in an acceptable range.

The pilot study was (not surprisingly) a learning experience for the company. The ReZolve stent is bigger, or bulkier, than other stents in use. This fact has caused the company to train interventional cardiologists to proceed more carefully and slowly as they implant the

Cont'd over

stent. Ultimately, Reva would train cardiologists to ensure that any ReZolve stent was implanted by a qualified physician.

CE Mark Trial [The RESTORE II Trial]

Reva's CE Mark trial of an improved version of its stent, the ReZolve2, will involve the recruitment of 125 patients across 25-30 sites in Australia, New Zealand, Brazil, Poland and Slovenia. The trial is expected to start soon.

Trial endpoints (at 6, 9 and 12 months) will include safety as measured by MACEs (<10%) as well as measures of LLL (<10%).

Reva hopes to complete enrolment by 2013 Q3 with trial data to emerge after 2014 Q3.

Abbott's Absorb Bioresorbable Stent

Reva Medical stands to gain considerably from technical and commercial advances Abbott Laboratories has made with its Absorb bioresorbable stent.

First, with more than 1,000 Absorb stents having been implanted, no thrombosis events have been reported, which is a very positive achievement for an interventional cardiology product.

Second, the Absorb stent has obtained a European reimbursement price of €2,750, which is four times the price of its Xience metal stent stable-mate.

According to Reva CEO Bob Stockman, the success of the Absorb stent is because (it appears) that the product has the potential to stabilise target lesion failure rates at 6%-8%, in contrast to failure rates for metal stents increasing out to 12%-19% after 5 years.

Abbott's Absorb stent is not approved in the US. In January 2013, Abbott initiated a US registration directed 2,250 patient trial which is designed to demonstrate the superiority of the Absorb stent over the Xeince stent.

The Absorb stent was approved for use in Europe in January 2011 following a study in 131 patients. However the product was not launched until September 2012 while the company built manufacturing capacity and trained physicians.

Features of the ReZolve2 Stent

Reva's ReZolve2 stent has several design features which confer advantages over competitor products.

- The ReZolve2 stent is fully visible under X-ray, courtesy of the iodinated polymer from which it is made. In contrast, Abbott's Absorb stent is visible only at its end points, courtesy of two separate gold dots. The imaging advantage permits greater precision when implanting the stent.

- The slide and lock design of the Rezolve2 stent means that the artery is not able to 'push back' once the stent is in place.

- The ReZolve2 stent is also amenable to being matched to fit the anatomy of the blood vessel into which it is implanted.

- A single inflation is necessary for the implantation procedure for the Rezolve stent. In contrast, other stents may require different pressure levels to support the procedure.

Risks

The most obvious risk with Reva Medical is that it may not be able to complete the CE Mark trial according to the ambitious timelines it has set itself. If the trial is not close to full recruitment by 2013 Q3 then investors will need clarity on the situation. If the trial is less than 50% recruited it may be sign of additional technical issues with the product or issues with the design of the trial. If that is the case, it may also be a trigger for a sell-down of the stock.

Another important goal the company has set itself is to address manufacturing scale-up requirements by 2013 Q4. Announcement of success towards this goal is of equal importance to progress in the clinic. One of the current drawbacks of Reva's device is that assembly is very labour intensive and improvements to the manufacturing process improvements that can lead to capacity gains and COGS improvements are required.

A consequence of missing either of the above milestones would be that the company's cash base would suffer, no doubt necessitating a capital raising. The company currently believes it has sufficient cash to take it to CE Mark approval.

Summary

Reva's positioning , either by accident or design, of ReZolve2 as a follower to Abbott's ABSORB stent is an investment positive because it means it can take advantage of Abbott's clinical experience, market preparation activities and pricing and reimbursement achievements.

With several points of difference of the ReZolve2 stent to Abbott's Absorb stent, the opportunity also exists for Reva to introduce a product that can compete head on with the market pioneer. However, we do not see Reva ever bringing the product into the US market by itself, with the sale of the company once the product has generated commercial success in Europe the more likely outcome.

Reva's stock price is 62% off its all time high of $1.38. Investors may look to buy the stock at current levels or even accumulate a holding by buying on price weakness. Events drivers ahead include the release of pilot trial data in May and October.

Reva Medical is capitalised at $172 million and held cash assets of US$44 million at December 31, 2012.

Bioshares recommendation: **Speculative Buy Class B**

Bioshares

Circadian Technologies Turns to Lymphedema

Circadian Technologies (CIR: $0.28) was recently discussed in *Bioshares* 494. It was added to the *Bioshares* Model Portfolio at the same time for three reasons. The first is because it is trading at close to cash backing; the second is that is now a clinical stage biotech with several quality assets; and the third is that the company has identified a product opportunity for the treatment of lymphedema which has the potential for accelerated commercial development. Below we provide a more in depth analysis of Circadian Technologies.

VEGF-C and VEGF-D Pathways

Circadian has built a propriety position around the VEGF-C and VEGF-D biological pathways which are involved with blood vessel and lymphatic vessel formation. Blocking the VEGF pathway has become a very successful approach in treating cancer by blocking the formation of new blood vessels that are necessary for the continued growth of tumours. The multibillion dollar cancer drug Avastin blocks the VEGF-A pathway.

Circadian is developing drugs to block the VEGF-C and VEGF-D biological pathways. The first approach is to combine its anti-VEGF-C therapy named VGX-100 with anti-VEGF-A drugs such as Avastin to gain improvements in treating cancer. Blocking not just the VEGF-A pathway but also the VEGF-C pathway should deliver a more comprehensive approach to inhibit tumour blood vessel growth. This has shown to be the case in preclinical studies.

The second application is with VGX-300 to compete with or be used in conjunction with VEGF-A inhibitor drugs such as Lucentis (a smaller form of the oncology drug Avastin) or Eylea for the treatment of eye diseases including wet Age-related Macular Degeneration (AMD).

The third, and potentially a lead application, is with VGX-100 as a single agent therapy for breast cancer-related lymphedema.

Phase Ia/Ib Cancer Study

Circadian is evaluating its lead drug candidate, VGX-100, in a Phase Ia/Ib trial in patients with late stage solid tumours. VGX-100 is a human antibody that blocks the VEGF-C pathway involved with blood and lymphatic vessel formation.

This trial started in January last year. The first part of the trial has been exploring VGX-100 on its own, with five different doses having been trialed (up to 20 mg/kg). The final dose to be tested is 30 mg/kg.

The second part of the Phase I study combines VGX-100 with Avastin, to see if there are any overlapping toxicities or an additional clinical responses from combining the two drugs. The third dose stage has been completed and there are two higher doses of VGX-100 in the combination therapy to be tested. More than 30 patients have been treated in the Phase 1 study.

The trial is expected to be completed by mid year with results anticipated to be presented at cancer conference later this year. From there, the company will look to move into a Phase II study towards early next year testing a combination therapy of VGX-100 plus Avastin in patients with recurrent glioblastoma multiforme. To complete this Phase II study with will take up to nine months and cost between $3-$4 million. The company may partner this program in the next 12 months.

Insights into Lymphedema

In June last year, Circadian was approached by medical researcher Dr George Sledge, currently the Chief of Oncology at the Stanford University Department of Medicine. Dr Sledge is a pioneer in development of new therapies for breast cancer. What drew him towards Circadian was the potential to use VEGF-C inhibitors to treat lymphedema. Circadian now has a VEGF-C inhibitor in the clinic and has a proprietary position in this area.

In recent years, the theory on the mechanisms behind why lymphedema occurs in women who undergo breast cancer surgery has been turned on its head. It's known that VEGF-C is involved in both the growth of new blood vessels and the growth of lymph vessels. So how could inhibiting lymph vessel growth using a VEGF-C blocker actually improve lymphedema?

In 2010 a new mechanism of action was proposed. When the lymphatic system is disrupted, as is the case in breast cancer surgery, the VEGF-C protein acts on blood vessels because there are less lymphatic vessels around. Essentially it works on one or the other and when the other is missing (lymph vessels) then it acts on the one that is present (blood vessels). What this does is create more capillaries which in turn increases the fluid flow to the nearby lymphatic system (in the arms) without the lymph vessels in place to return/circulate the fluid through the body, thereby resulting in/contributing to lymphedema. It has also been shown that VEGF-C is up-regulated in women with lymphedema post breast cancer surgery.

A clinical group which had met with Circadian at the 2012 meeting of the American Society of Clinical Oncology (ASCO), had previously found that using the small molecule drug pazopanib, which acts on the VEGF-C receptors VEGFR2 and VEGFR3, showed improvements in breast cancer related lymphedema. However, the effects of pazopanib were limited by toxicities with the drug. Pazopanib is a VEGFR inhibitor.

Lead Potential?

The potential use of VGX-100 for the treatment of breast cancer related lymphedema may leapfrog the cancer indications and become the lead program for the company. This indication is appealing for a number of reasons. The first is cost. A Phase II trial in lymphedema is estimated to cost around $1 million, compared to around $5 million for larger phase II studies in cancer. The company already has sufficient VGX-100 drug material for the Phase II lymphedema study, whereas more of the drug will need to be manufactured to fully complete Phase II cancer studies.

Phase II Lymphedema Trial

Circadian is planning to start the Phase II lymphedema study by the end of this year. An interim analysis of safety and efficacy could be reviewed by in the first half of next year based on current

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timelines, and the trial could be completed by September next year. The trial will involve up to 20 patients and will be an open label study, which means the company will be able to monitor patient progress closely. The trial provides the opportunity to quickly deliver some proof-of-concept efficacy data in the clinic building on the safety data being acquired in the current Phase Ia/Ib cancer study.

Perhaps the most attractive feature of moving into lymphedema is that a pivotal Phase II/III study could be completed for around $7.5 -10 million, which might be sufficient to get the drug to market

If the Phase II study scheduled to start later this year is a success, Circadian could potentially raise the funds to complete the pivotal Phase II/III trial independently, not unlike the way Acrux raised $22 million to complete its Phase III Axiron study.

Ophthalmic Indications

Circadian is developing a second drug candidate, VGX-300, for the treatment of eye diseases, with the first indication being wet age-related macular degeneration (AMD). Two drugs on the market for this indication are Eylea, with annual sales of more than US$800 million and Lucentis, which generates annual sales greater than US$1.5 billion.

Eylea is a fully human soluble receptor fusion protein and Lucentis is a smaller form of the Avastin antibody approved for cancer treatment applications. Eylea binds to VEGF-A and two other members of the VEGF family, VEGF-B and Placental Growth Factor (PLGF). Eylea is administered as an injection into the eye monthly for the first three months and then every second month. Lucentis needs to be injected into the eye monthly.

Circadian CEO Robert Klupacs noted that in the pivotal registration trials of drugs inhibiting VEGF-A there was only improvement in vision in 40%-50% of patients. Anecdotal feedback from ophthamologists is that the actual number of patients in the real life clinical setting who obtain vision gain is probably only around 30% according to Klupacs.

The combination therapy with a VEGF-C and VEGF-A inhibitor, through sequential administration of VGX-300 and Eylea or Lucentis, has the potential to improve vision in a greater number of patients, improve vision in patients where current therapy does not work and may also reduce the required frequency of therapy, for instance once every four months rather than every two months currently required for Eylea. The last factor is very important given the delivery method for these drugs. Combining VGX-300 with Eylea could potentially shut down all of the VEGF pathways.

Reagents Business and CUP Test

In February this year, Circadian began the sale of research reagents i.e. VEGF-C and VEGF-D proteins, to the research community. These sales are intended to support the company's drug development programs. In addition, two months ago the company launched its Cancer of Unknown Primary (CUP) test in Australia, New Zealand, Singapore and Australia. That test is being sold by Healthscope and is designed to detect the origin of secondary cancers, so-called "Cancers of Unknown Primaries". This test will also be launched in the northern hemisphere with or without a partner. Circadian believes that revenue from the CUP test could reach $5 million in three years time, of which Circadian would receive a large royalty stream.

Circadian has launched its VEGF-D diagnostic test in the United States to detect or exclude the possibility of a rare lung disease in women known as LAM. It is currently marketed as a laboratory developed test under CLIA waiver. However, Circadian is in the process of obtaining FDA approval to enable expanded usage.

Next year the company plans to submit a marketing application for a VEGF-C diagnostic. It is known that VEGF-C levels start to increase when resistance to Avastin therapy starts to emerge in a patient. As such it could become an important companion diagnostic to justify the ongoing dosing of Avastin.

Subsidiaries Structure

Of interest is that Circadian has its programs residing in different (100% owned) subsidiaries. The cancer and lymphedema applications and assets are owned by Ceres Oncology; the ophthalmic applications are owned by Opthea; and Precision Diagnostics owns the diagnostic and reagents products business. This allows the possibility for Circadian to return to its company spin-out model, which yielded companies such as Antisense Therapeutics, Metabolic Pharmaceuticals, Axon Instruments and Optiscan Imaging, giving Circadian a range of future funding and commercialisation options.

Summary

Circadian is now firmly placed as clinical stage company with a range options in play for VGX-100. Although we believe the company will need to raise additional funding in the future, the motivation to buy the stock with the stock rests with the prospects for VGX-100 as a treatment for lymphodema.

The company will need to take a far more professional approach to future capital raisings than that adopted with a raising in June 2012 which raised a modest $1 million.

Circadian is capitalised at $13.6 million. It retained $12.2 million in cash at the end of 2012.

Bioshares recommendation: **Speculative Buy Class B**

Bioshares

Bioshares Model Portfolio (22 March 2013)

Company	Price (current)	Price added to portfolio	Date added
Circadian Technologies	$0.280	$0.270	March 2013
Tissue Therapies	$0.160	$0.255	March 2013
Allied Healthcare	$0.031	$0.026	February 2013
Psivida	$2.00	$1.550	November 2012
Benitec	$0.012	$0.016	November 2012
Nanosonics	$0.475	$0.495	June 2012
QRxPharma	$1.12	$1.66	October 2011
Somnomed	$1.10	$0.94	January 2011
Cogstate	$0.405	$0.13	November 2007
Clinuvel Pharmaceuticals	$2.45	$6.60	September 2007
Universal Biosensors	$0.75	$1.23	June 2007

Portfolio Changes – 22 March 2013

IN:
No changes.

OUT:
No changes.

Tissue Therapies Receives Regulatory Setback

Tissue Therapies (TIS:$0.18) has received a confounding response from the group the company is using to progress its marketing application of its VitroGro product in Europe. Previously the company had been told that its product would be assessed as a device by the Notified Body it is using, called the British Standards Institute (BSI).

The BSI made a submission to the EMA which was passed onto the Medical Devices Group meeting. At that meeting the vote was that the therapy should be regulated as a medicine not a device.

Tissue Therapies says the information provided by the BSI to the EMA was poor, as assessed by an independent expert.

In what appears to be a highly convoluted process, Tissue Therapies has the UK Medicines and Healthcare products Regulatory Agency on its side (MHRA) which believes VitroGro should still be treated as a device.

If the product is treated as a device, then it should get onto the market in 210 days from device certification. If the company has to go down the medicines path, then more trials will be required and the earliest approval will be in late 2015.

The good news for Tissue Therapies is that it can now bypass the BSI, which it couldn't do before. While the Medical Devices Group has voted, there has not been a final decision from the EMA. The MHRA will now take a new briefing document to the EMA.

If the EMA decides to treat VitroGro as a medicine, then the company can appeal, although historically appeals have not had high success rates.

Tissue Therapies is working with two regulatory consultants, one who previously worked with the EMA and the other with the MHRA. The ex-EMA consultant is an expert in recombinant proteins. Both believe the therapy should be treated as a device.

CEO Steven Mercer said there a multiple precedents where animal matrix protein products have been treated as a device. Its product forms a matrix on the wound. It should even be a safer option because it is produced recombinantly.

Regulatory risk continues to be a major issue for many Australian biotechs. The risk profile of Tissue Therapies has been increased following the decision from the Medical Devices group. If it can not convince the EMA to see its product as a device then it will need to raise more cash and product launch will be delayed by two years. However with the MHRA on its side, there's a chance that device certification may yet be achieved. But trying to assign a level of probability to a regulatory decision, as we are seeing, is very difficult.

Bioshares recommendation: **Speculative Hold Class B**

Bioshares

Alchemia's Volatile Future?

Alchemia (ACL: $0.35) has announced the addition of Nathan Drona and Dr Susan Kelly to its board. Drona was a director of Avexa from April 2008 to July 2010, including a period as Chairman. Dr Kelly served on the board of Audeo Oncology

The move spells more uncertainty and volatility with this stock because of the potential for conflict between major shareholders to increase, between those interested in fondaparinux revenues and others interested in HA-Irinotecan.

The appointments follow the resignation of CEO Pete Smith in January and the appointment soon after of CFO Charlie Walker as his replacement in February. The likelihood of other board changes is very high.

The appointment of an internal candidate in a rapid time frame to the CEO position can be read as evidence of a lack of succession planning, weak evidence of instability at the executive level and potentially evidence of a board inattentive to the long term viability of the company and one that is also biased towards the interest of some shareholders at the expense of others (usually many small shareholders).

Alchemia recently raised $10 million through a placement and is seeking to raise $2 million through an SPP.

Bioshares recommendation: **Sell**

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