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Bioshares

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

Companies covered: Summit Coverage - BLT, CYP, OSL, SPL, OCC, Polynoma

	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 -)	6.5%
Cumulative Gain	**380%**
Av. Annual gain (14 yrs)	**16.6%**

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The 10th Bioshares Biotech Summit Cell Therapies Session

Speakers from three companies, Cynata, Mesoblast and Orthocell (which is soon to list under the ticker OCC) presented in the Cell Therapies Session at the 10th Bioshares Biotech Summit, which was held in Queenstown, New Zealand over Friday July 18 and Saturday 19 July. Summaries of the Cynata and Orthocell presentations follow.

Cynata's Cymerus Technology

Cynata is a developing a stem cell technology which it has termed Cymerus. CEO Ross Macdonald summarised the history of the company. The technology comes from the University of Wisconsin. The inventors of the technology are Igor Slutkin and James Thompson, a key figure in stem cell research. The owner of the IP is the Wisconsin Alumni Research Foundation, which gives it name to the blood thinner, warfarin.

Macdonald said that the commercial interest in cell therapies has been driven by extraordinary results in treating a range of different diseases and treating damaged tissues, including spinal cord conditions, AMD and ocular conditions, chronic wounds, heart failure, heart attack, graft-versus-host disease and many others. And the modulation of the immune system by stem cells is now also being found to be particularly useful. There are 280 clinical studies around the world using mesenchymal stem cells (MSCs), he said.

One major event that has shaken up the stem cell world was the Japanese Ministry of Health's announcement last year to the speed up the registration process for stem cell therapeutics, allowing therapies to go to market at the end of Phase II. "To have thought that such a major change would have come out of such a conservative body would have been unthinkable a few years ago!" exclaimed Macdonald.

The Japanese are leading the way in bringing stem cell therapy products to market because they see the profound benefits of stem cells therapies alongside a lack of adverse events. The driver is the aging population in Japan and the devastating effect that issue will have on the Japanese economy, with other countries such as the US also facing similar aging population problems.

Macdonald queried why there was not more action in the area, given the degree of medical and investment interest in cell therapies. His answer was that there is a critical roadblock to the commercialisation of stem cell-based therapeutics.

The first problem is the limited expansion capacity of the cells themselves and the ability to manufacture enough product. A second problem is that of donor-to-donor heterogeneity, which is challenging from a regulatory point of view.

Another problem relates to purification of MSCs from natural sources. "It is very difficult to achieve purification at 100%," said Macdonald.

Cont'd over

Macdonald said that one of the greatest concerns expressed by commentators is how companies will deal with the issue of batch differences, because of reliance on either different donors or different processes for cell therapy products.

Cynata's Cymerus technology facilitates the commercial scale manufacture of consistent and reproducible stem cell based products. "Quite simply, it's better, cheaper and faster," he stated.

Dosages and Expansion Capacity Potential

A typical dose of MSCs ranges from 70 million to 140 million cells, administered IV. To get to this dose, about 10-20,000 MSCs are first isolated from an invasive donation, typically from bone marrow. To produce the necessary number of cells for 10 doses requires about 16 population doublings and to get to 10,000 doses, 26 population doublings are needed.

However, MSCs are known to enter senescence after a number of population doublings, which means they don't work any more

If it becomes a question of getting more donors then the problem of batch-to-batch consistency arises.

The challenge is confirming to regulators that a batch manufactured today is the same as tomorrow. While this is easy with small molecule drugs, it is a challenge with cell based therapies, where potency is a question.

Macdonald said that concerns have emerged about data in clinical studies where some studies have been successful and some not. The reason for this, according to analysis by some commentators, was that in some GVHD trials in Europe, where only a small number of expansions were used, the trials were successful. In contrast, trials failed in the US where many more population expansions were made.

The expansion question remains unanswered, Macdonald said. However, with bioreactor technology that should go away but there is still along way to go.

The Cymerus technology involves accessing a single donor one time, then manufacturing induced pluripotent stem cells (iPSCs) from that donor. iPSCs are for all intents and purposes embryonic stem cells (ESCs) which have been shown to have very similar properties to ESCs, in particular the capacity for infinite self renewal. This is an important feature when it comes to scale and manufacturing.

Cynata has patented the process to differentiate its iPSCs into a special mesenchymal stem cell, called the mesenchymal angioblast cell, from which 10^{22} cells can be produced.

"In essence this technology facilitates commercial manufacture. It's patent protected. We only have to see a donor one time. From that one donor comes a uniform, pharmaceutical-grade off-the-shelf MSC product which has easier manufacturing, an easier regulatory route and better clinical predictability," said Macdonald.

Orthocell – Focusing on Tendon Repair

Paul Anderson, the CEO of regenerative medicine company Orthocell, said he had been involved with the medical devices sector for over 20 years. He was fortunate to be involved with one of the first products for cell therapy for cardiac regeneration in 1999. "We took that product through registration and reimbursement and the company eventually through to a trade sale. It was during that period that we began to look for the next opportunity in a musculo-skeletal area to use both scaffolds and stem cells for the regeneration of human tissue and that led to the formation of Orthocell," he said.

Orthocell was founded in 2006 from IP that came from the University of Western Australia. The company is revenue generating and has products approved for the Australian market place, with patients also treated in Hong Kong and in New Zealand.

Orthocell has focused on musculo-skeletal applications using both stem cell and scaffold technologies. Some tissues require cells, some require scaffolds and some require both. Orthocell has developed two products, one for the regeneration of damaged tendon tissue which uses the body's own tendon progenitor stem cells (TPSCs). A paper describing these cells was first published in 2007. This an autologous and homologous approach. The company has also developed a collagen based medical device for the repair of soft tissue.

Orthocell currently sells its tendon product into the Australian/SE Asia market for $3,200 for an injection. The company has treated over 250 patients over the last two years. Orthocell's cartilage regeneration product sells into the Australian, New Zealand and SE Asian markets for $6,500 per procedure. It has treated over 300 patients with that product over the last two and a half years.

Orthocell was driven to develop its own scaffold product. Through that process the company discovered that its scaffold was not only useful for cell therapies, but also for orthopedic applications, for the augmentation of tendon repair and for general surgical, soft tissue repair and reconstruction applications.

The company believes it has two highly complementary technology platforms in the form of its TPSCs and its scaffold product.

The Scaffold Product

The scaffold is placed into the body surgically and cells from the body – endogenous cells – infiltrate into the scaffold and replace the extra-cellular matrix. An ideal scaffold is a bio-compatible and resorbable material that disappears and is replaced by natural tissue.

Orthocell's goal was to develop a scaffold that was strong and highly pliable, surgically compliant, had high purity, and the ideal porosity to promote cell growth, a point that has been lost by a lot of scaffold companies in the past, said Anderson.

The scaffold has to be natural, biocompatible, absorbable, and degrade at a controlled rate. Orthocell has developed a scaffold with all of these properties.

The scaffold can be manufactured from a thicknesses as thin as 80 microns up to 450 microns, holding 750 Newtons of strength. Anderson said the platform has provided Orthocell with a whole range of entry points into both ENT and reconstructive areas.

Orthocell is currently conducting a study using its 80 micron scaffold for the repair and regeneration of human timpanic membranes of eardrums.

However, the company originally had an orthopedic focus and it continues to be the company's focus. It is developing a scaffold for the augmentation of rotator cuff tendon and other tendons. "We have some exciting gynecological and urological applications which are entering the clinic this year," he said.

Orthocell has a number of clinical trials underway and it has regulatory submissions at final stages for CE Mark and 510k into the US and with the ARTG in Australia.

The Ortho-ATI (Tendon) Product

Ortho-ATI is an injectable cell suspension for tendon regeneration and in an intra-tendon injection. Orthocell has regulatory approval in Australia through a licence to manufacture human tissues from the TGA.

Ortho-ATI is an autologous and homologous cell product, which means cells are taken not just from the patient, but from the patient's own tendon tissue. Those cells are expanded and then put back in with an intra-tendon injection. Those cells then engraft. The cells secrete growth factors and collagen, which reforms and provides structural repair for the tendon.

How Is The Tendon Product Made and Delivered?

A tendon biospy is taken from a patient using a 14 gauge biopsy needle so the patient donor site morbidity is negligible. The cells are sent to Orthocell's facility for expansion, which takes about a month to complete. The expansion process is where the company's IP lies. "Historically, these cells have been very difficult to isolate and very difficult to expand in what we describe as a clinically commercially significant time," said Anderson.

The volume of the cells Orthocell manufactures, from a mesenchymal stem cell perspective, is on average 10 million cells. "From a cost effectiveness and a manufacturing perspective, our IP has enabled us to take this from a concept into a commercial reality, and most importantly to a clinical success," said Anderson.

"The real keys to doing this is to have viability, identity and potency assays which provide you with certainty around stability and quality of these cells. This is a really important part to the commercialisation of this technology and a really important part of the regulatory process," he said.

When Orthocell began looking at this technology in the area of tendon regeneration it had a choice of cell types to use. However, the company assessed the risk with each type. "We came to the view that you don't need a Maserati to drive down to the shop to buy some milk."

Orthocell selected the tenocyte progenitor cell because it was stable, autologous, homologous and the company could show identity and potency. "These cells gave us a defined pathway to market and a defined pathway to proving that it would be an effective treatment for damaged tendon tissue."

Ortho cell has completed three clinical studies and now has four and half years of data from a clinical trial in tendon repair.

In a study in elite athletes it found that the patients had significant improvements – an 87% improvement in their pain scores, a 93% improvement in their functional scores and 85% improvement in their ability to grip, using that tendon. With four and half years data, the ability to grip is now at 133%. "These patients continue to improve out to 4.5 years, which is a fantastic outcome."

"Physicians are describing the product as a disruptive technology and a disease-modifying technology. When you are talking about reimbursement and the regulatory process, they are two very key words," commented Anderson.

Orthocell recently closed its IPO round, completing an oversubscribed $8 million raising. It will list shortly under the ticker OCC.

Bioshares

Clinical Trials Session: Starpharma, Oncosil, Polynoma, Benitec

Starpharma Holdings – DEP Docetaxel Phase I Study

DEP docetaxel is the first drug delivery clinical candidate for Starpharma Holdings. Docetaxel is blockbuster chemotherapy product that has now gone generic. In 2012 the drug generated sales of US$3.2 billion.

Docetaxel has very poor solubility. Starpharma's version uses an inert polymer scaffold to which 32 docetaxel molecules are attached to the surface as well as poly ethylene glycol (PEG) compounds. Docetaxel includes a detergent, polysorbate 80, in order to make the drug more soluble. However, this brings significant toxicity, causing an anaphylactic reaction and deaths in some patients, with patients requiring steroid pretreatment to prevent this reaction. The reaction to the steroids is as much of an issue as the side effects of the cancer drug according to some of the oncologists that Starpharma has spoken with.

Starpharma's version of the drug has not only made an insoluble compound water soluble, but its increased size gives it an improved pharmacokinetic profile.

The half-life of the drug has been increased 60-fold and much higher levels – 40-fold increase – of the drug are achieved in the tumour, said Starpharma CEO Jackie Fairley. But this version of the drug is getting protection from other side effects, namely neutropenia (decrease in white blood cells), which is the dose-limiting side effect, in preclinical studies. The aspect of no neutropenia has been seen in three cancer drugs tested by Starpharma to date said Fairley.

Fairley expects to see this effect also in current clinical studies, which will be one of the aspects that will be measured in the current Phase I clinical study. Fairly said this is the only docetaxel formulation that has exhibited this effect, from its own studies and also from discussions with Sanofi, the orginator of the drug Taxotere (docetaxel).

In preclinical studies, the efficacy of Starpharma's DEP docetaxel was much greater than docetaxel, with 60% of mice showing no evidence of tumour re-growth at 90 days, compared to 100% of mice treated with the original docetaxel seeing tumour re-growth.

The larger drug size is believed to be preferentially taken up in the capillaries of the rapidly growing and larger capillaries that characterize solid tumours. The size of DEP docetaxel is too large to get into hair cells and other normal tissue, believes Fairley, but is taken up by the larger leaking blood cells in tumours. "You essentially get a size exclusion effect (and) you get a selective concentration effect in the tumour tissue, which is exactly where you want it to be."

Phase I Study

Starpharma is recruiting patients in a Phase I clinical study across three sites in Australia. Those patients are being treated with DEP docetaxel every three weeks and will not be pretreated with steroids. Up to 30 patients will be treated and it will be an open label study, allowing progressive results to be released according to Fairley.

The primary outcome from this study is to establish the maximum tolerated dose, which was 2-2.5 times higher than docetaxel in the preclinical study. This means dosage levels to patients should be higher with the Starpharma version of this drug.

The more interesting data will come from the secondary endpoints. An important aspect to monitor will be the neutropenia effect which is seen in the first seven days. With taxotere, 75% of patients experience severe neutropenia, which is a life threatening condition.

Starpharma is around 20% recruited into the Phase I study and there has been no evidence of neutropenia at all. The company has also seen no hair loss, and no evidence of gastrointestinal side effects, which are both common with Taxotere. The toxicity profile seen so far has been exceptionally benign said Fairley.

The trial is currently in the escalation phase. If this side effect profile is maintained, then it will be the first version of docetaxel to show no neutropenia effects in patients. The current dose of DEP docetaxel is close to the maximum tolerated dose of Taxotere. Generally, mild neutropenia, hair loss and gastrointestinal side effects are seen with even at low doses of Taxotere. In this trial, patients had reported feeling well even after several cycles of DEP docetaxel.

With the depth of data available on the drug Taxotere, Starpharma will be able to make detailed comparisons of its results from this single arm study compared to historical data with Taxotere.

If the drug is successful, Starpharma may also look to have it compete with Taxotere, but also in applications where Taxotere was shown not be effective but DEP docetaxel may be effective because of the higher and more targeted doses that may be administered.

Fairley said that DEP docetaxel is the first in a number of products to be trialed using the company's drug delivery platform.

SPA for Vivagel Phase III Program

Fairley also discussed the Special Protocol Assessment it has negotiated with the FDA for the company's Phase III trial with Vivagel for the prevention of recurrent bacterial vaginosis. With the SPA in place, it effectively removes the regulatory risk for this program said Fairley. The average time to be granted an SPA is around eight months. Starpharma received its SPA in an impressive 45 days.

Starpharma is due to commence two 600 patient Phase III studies in the prevention of recurrent bacterial vaginosis. Ethics approval has been received from several sites with treatment expected to start shortly.

In these trials, patients will be treated every second day for 16 weeks, with either Vivagel or a placebo (even numbers in each). If the condition returns, patients will be removed from the study as a failed result. There will be a follow-up assessment after treatment stops but that will not form part of the primary endpoint.

Cont'd over

Around 100 trial sites have been selected, with some of those sites having 100-150 patients with the condition. These is currently no drug available for the prevention of recurrence of bacterial vaginosis.

Oncosil Medical – Pivotal 150 Patient Study To Commence

One of the differences between Oncosil Medical's radiation treatment for solid tumours and Sirtex Medical's Sir-Sphere's treatment is that Oncosil's therapy attacks the tumour from the inside of the tumour, where Sir-Sphere's attack the tumour from the outside of the tumour, explained Oncosil CEO Neil Frazer. (The Oncosil product is injected directly into pancreatic tumours; Sir-Spheres are delivered into the liver through a catheter placed into the hepatic artery.)

The Oncosil therapy is delivered under a general anesthetic, a procedure which takes around 30 minutes. The radio-therapy dose lasts for three months. The chances of systemic effects are avoided because the therapy is injected into the tumour with sticky microparticles. The therapy is localised such that it does not move further into the pancreas either, which could cause diabetic effects.

In a 17 patient trial with the therapy, 82% disease control was achieved with a 35% reduction in pain levels. The treatment gave the patients around four months on average before the therapy started to progress again and more than 10 months overall survival compared to around six months historical average. Radiation therapy will never cure pancreatic cancer, but it will prolong life and improve quality of life said Frazer.

The Oncosil therapy is classified as a device. As such, it takes around five years to get to market compared to 10 years for a drug. Only a pilot study (which has been completed) and a pivotal study (due to commence) are required for a device.

Oncosil announced it had received ethics approval in Australia to commence its global pivotal study. The ethics committee reviewed not only the trial protocol but also the quality of the science said Frazer. The company now has the go ahead to start recruiting in multiple public hospitals in Australia.

Frazer wants Oncosil to become the standard of care for pancreatic cancer. He believes the company can capture 20% of the European market. Frazer said the therapy would not compete with existing therapies, as it will be used in conjunction with existing chemotherapy.

In the pivotal study, of the 150 patients, 100 will receive the Oncosil therapy and 50 will receive the standard-of-care alone. The trial will use only the one implant of Oncosil.

Overall survival will be the primary endpoint. Secondary endpoints will be progression-free survival, quality of life and reduction in pain. The company expects to recruit 12 patients a month with an interim readout (progression-free survival) six months after the first 30 patients have been treated (in around nine months time).

It is expected to take around three years to get FDA approval under the PMA process said Frazer. Frazer also said that keeping the money coming into the company will also increase investor confidence in Oncosil Medical.

Polynoma – A 1,000 Patient Phase III Trial – Melanoma Vaccine

John Chiplin returned to the Bioshares Biotech Summit as CEO of US-based Polynoma. Chiplin was formerly CEO of Australian biotech Arana Therapeutics. His new venture Polynoma is seeking to list either in Australia or the US in coming months.

Chiplin said that 20 years ago commentators said treating cancer with vaccines couldn't be done. Now 'treating the patient who treats the cancer' has become mainstream therapy.

Polynoma is due to commence a large Phase III study in over 1,000 patients with what Chiplin believes will become the future of melanoma cancer vaccine therapy. Polynoma has a Special Protocol Assessment with the FDA, which means the FDA has agreed on the trial structure and endpoints.

This pivotal study will be an adaptive Phase III trial, which is becoming more common. It involves a lead-in trial in 150 patients, where the biological activity and immune response as well as safety will be assessed in two doses and compared against a placebo arm over 10 weeks.

This part of the trial started in 2012. However recruitment was slow because they were recruiting through oncologists. When they moved to dermatologists, who remove the tumours, recruitment accelerated very quickly, recruiting 150 patients in a year. Results are expected in the current quarter. The company is seeking to list on the back of this data.

The company will also be monitoring for Recurrence-Free Survival (RFS) over the next three years.

The pivotal phase of the study in 960 patients is expected to start recruiting in October, including in Australia. The endpoint for that study will be RFS at 362 events or overall survival at 472 events. There will also be an interim analysis when tumour recurrence is seen in 40% of the patients.

Patients will be dosed 15 times over two years using a prime-boost approach (11 in the first year and four in the second year).

Chiplin is pleased with the trial structure which includes an SPA with the FDA, and interim readout, and the trial is well powered with an expected 37.5% improvement over the placebo arm.

The one problem with the commercialisation plans for the company was its capital markets strategy said Chiplin. Investors will need to invest for 3.8 years until the final readout from the pivotal study. Polynoma had to work out how to then retrofit a capital markets strategy with what Chiplin believes is a very solid FDA approval strategy.

Cont'd over

– Polynoma cont'd

There are three parts to this strategy. The first is that the Part B section of the trial in 960 patients will have the same treatment design as the Part A lead-in phase in 150 patients. This will allow results in PFS and overall survival to emerge from the lead-in study in 2015, 2016 and 2017. While the lead-in study is not powered for significance, it will provide a hint of whether the treatment is efficacious for the company and its investors according to Chiplin.

The second part of the strategy is to conduct a smaller combination study with some 'checkpoint inhibitor' compounds that take the brakes off the immune system. These may be complementary to Polynoma's vaccine therapy. This smaller study will begin next year and data should come out in 2016. Polynoma will look to combine its therapy with either PD-1 antibody drugs or Ipilimumab (a CTLA-4 drug).

The third aspect in generating early data will be to access interim data. The FDA was receptive to the idea accessing interim data given the long-term nature of the study. The FDA agreed to a 40% interim analysis of the pivotal study data.

Interim results are expected in late 2016 and final results in later 2018. The company expects to file its BLA with the FDA for product approval at the end of 2018.

Chiplin said that much of the funding for Polynoma has come from one investor from Hong Kong, who has contributed $65 million to see the program through. That investor would prefer to see the company listed in Australia, as long as there is not a significant valuation disparity between the US. Although the US market is very hot at the moment, stated Chiplin, it's uncertain for how long that will continue to be the case.

Benitec Biopharma – Phase I HCV Trial

There was early excitement in the RNAi field, with Merck acquiring Sirna for around US$1 billion and Alnylam signing a US$1 billion deal with Merck. However, this enthusiasm waned when difficulties arose in getting the RNAi compounds into cells and being effective said Benitec Biopharma CEO Peter French.

RNAi is susceptible to nucleases in the blood stream and doesn't cross the cell wall. But then Tekmira Pharmaceuticals invented SNALPs (stable nucleic acid lipid particles) to coat RNAi particles which provided some systemic delivery protection and allowed these compounds to enter cells.

Alnylam used SNALPs with its RNAi technology to deliver positive results two years ago in a Phase II trial in TTR cardiac amyloidosis, an orphan disease. That resulted in a rapid rise in Alnylam's share price and today it is capitalized at US$4.1 billion.

Benitec has just started a Phase I trial with its ddRNAi therpy in patients with Hepatitis C (HCV). This therapy provides the potential for a single shot cure of the disease. The trial is being conducted at two sites in the US, with the first now dosing patients and the second site having just recently come on-line according to French.

French said this has been a challenging program from a regulatory perspective because it is essentially a gene therapy treatment. Once the therapy is in the cells, it can't be withdrawn. So doses will start low and gradually increase.

Six weeks ago the first patient was treated, and safety results from this patient are expected to be announced shortly. French said he is confident about the outcome of this trial because of the extent of preclinical studies that have been carried out. Pfizer was working on this program and spent an estimated $10-$20 million on the project believes French.

Hepatitis C – A Very Big Market

HCV is a very big market opportunity. In 2011, Vertex Pharmaceuticals released its new hepatitis C drug Incivek, which was the fastest drug to reach US$1 billion of sales. This was blown away by Gilead's Sovaldi recently, which generated US$2.3 billion of sales in the first quarter. "There's some big money for HCV treatment," said French.

French believes a single shot treatment for HCV would be a game changer in the treatment of this disease. This will also support the development of other programs within Benitec, including the hepatitis B program, with that therapy to be delivery using the same vector, with the same design targeting the virus at three mRNA sites.

Comparative Valuations

French looked at some comparator companies with respect to market value. Arrowhead has a Phase I study in hepatitis B and is capitalized at US$700 million; Dicerna is at a preclinical stage and is valued at US$350 million; and Benitec is now capitalised at $120 million and is at a Phase I stage of development said French.

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Bioshares Model Portfolio (25 July 2014)

Company	Price (current)	Price added to portfolio	Date added
LBT Innovations	$0.130	$0.130	Jul 14
pSivida	$4.650	$3.800	May 14
Invion	$0.059	$0.089	February 14
Impedimed	$0.270	$0.245	December 13
Analytica	$0.036	$0.025	December 13
Imugene	$0.016	$0.022	November 13
Oncosil Medical	$0.145	$0.155	September 13
IDT Australia	$0.270	$0.260	August 13
Viralytics	$0.280	$0.300	August 13
Tissue Therapies	$0.255	$0.255	March 2013
Somnomed	$1.76	$0.94	January 2011
Cogstate	$0.250	$0.13	November 2007

Portfolio Changes – 25 July 2014

IN:

No changes

OUT:

No changes

Calzada's Wound Dressing Product Receives CE Mark

Calzada's (CZD: $0.11) wound dressing product Novopore has received CE Mark certification. Polynovo, the Calzada subsidiary developing the topical negative pressure product, can now market the product in Europe and other countries which accept CE Marking.

Novopore was granted a 510(k) clearance from the US FDA in March.

The next commercialisation step for this product is for Polynovo to find a distribution and marketing partner.

Management Changes

Calzada announed on July 15 that is seeking to appoint a Managing Director who will be responsible for the Corporate and Polynovo business. It will also expand its commercial, clinical, regulatory, quality and manufacturing capabilities.

Two directors of Calzada, David McQuillan and Philip Powell, will serve as joint acting Managing Director until a permanent MD is appointed.

The goal of the changes is to put more depth and focus into the management of the company.

Company chairman David Williams indicated that the company will look to both speed up and expand the clinical development opportunities for Polynovo's Novosorb BTM product by making use of a range of external funding sources, but supplemented by some of Calzada's funds. The company could potentially have 10 trials underway in the short-to-medium term.

The commercial driver for initiating these trials is to get more data, which is necessary for partnering, and sales and marketing. An equally important goal of an expanded clinical program will be to build the number of Key Opinion Leaders who support Polynovo's products.

Calzada is capitalised at $46 million and retained cash of $5.3 million at December 31, 2013.

Bioshares recommendation: **Speculative Buy Class B**

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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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