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In this edition...
Mesoblast is the King of Timing. In September 2012, Sanofi handed back it licence to ex-USA (but not Japan) rights for Prochymal to Osiris, after US$130 million has been paid to Osiris (through Genzyme which did the original deal). A mere eight months later Mesoblast signed a Letter of Intent with Osiris and has taken on Prochymal (excluding Japan for GVHD) plus other assets on very attractive terms.
Calzada's wound and burn treatment technology is showing promise with positive results from two trials now available.
QRxPharma is ready to head back to the FDA with an updated NDA which will hopefully result in its combination opoid MoxDuo IR obtaining recognition for a superior safety profile.
Companies covered: CZD, MSB, QRX

	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)	58.3%
Cumulative Gain	**464%**
Av. annual gain (13 yrs)	**19.8%**

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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.

Mesoblast Acquires Osiris' ceMSC Assets

Mesoblast (MSB: $5.74) has acquired the culture-expanded mesenchymal stem cell (ceMSC) assets of Osiris Therapeutics (Nasdaq - OSIR). Mesoblast is developing a related class of stem cell, the mesenchymal precursor stem cell (MPC), to treat diseases of inflammation and immunity, orthopedic diseases of the spine, cardiovascular diseases and oncology diseases associated with bone marrow transplants.

The deal delivers Osiris' late stage ceMSC product Prochymal to Mesoblast, which has received conditional approval for the treatment of children's acute Graft versus Host disease (GVHD) in New Zealand and Canada and has been available in the US (from 2008) under an expanded access scheme for the treatment of GVHD in children and adults. Prochymal is also in Phase III trials in Crohn's disease.

The deal secures a point of entry into Japan through JCR Pharmaceutical Corporation. Japan has recently flagged that it will look at accelerating market access for regenerative medicines, potentially permitting approvals after the completion of Phase II trials.

Mesoblast also obtains clinical data from the treatment of more than 1,500 patients treated with Osiris' MSCs and adds 35 patent families to its estate of 26 patent families.
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Deal Terms – US$50 million plus US$50 million plus Royalties

Mesoblast will pay Osiris US$35 million front, split US$20 million in cash and $15 million in stock on the close of the transaction, followed by US$15 million in six months time. Osiris stands to receive a further US$50 million if US or European regulatory milestones are met, which could be paid in stock or cash. Osiris is also entitled to receive royalties on product sales ranging from low single digits to a 10% cap on sales in excess of US$750 million.

Included in the upfront payment was a US$1.5 million payment which accompanied the Letter of Intent which was entered into in May 2013.

Investors can note that the ex-US (but not Japan) rights to Prochymal had been previously licensed to Genyzme, which was subsequently acquired by Sanofi, were returned in September 2012. Osiris had received payments of US$130 million under the deal. This makes the time between the return of the rights to Mesoblast's Letter of Intent a period of eight months.

Osiris to Develop Biosurgery Business

Osiris will use the funds obtained from the transaction to further its biosurgey business, in particular for the development of Grafix, Ovation and Cartiform. Osiris recently published interim results of a trial with Grafix, a three dimensional matrix which includes MSCs and growth factors, in diabetic patients with chronic foot ulcers. The interim results were based on 97 patients out of 131 patients who had completed the trial. The results were compelling and statistically significant, with 62.0% of patients achieving

Cont'd over

complete wound closure at week 12 compared to 21.3% of patients in the standard of care group. It took 42 days for complete closure to take place in the treatment group versus 70 days in the standard of care group. It took six treatments to achieve closure in the Grafix group versus 12 treatments in the standard of care group. Osiris claimed that the relative improvement (of 191%) was the largest ever reported for a diabetic foot ulcer study.

What these data provide is a compelling logic for Osiris to focus on the biosurgery and wound healing opportunities, and the cash from the MSC deal with Mesoblast allows it to address those opportunities.

Prior to the deal announcement, Osiris held cash of US$1.6 million and investments available for sale of US$25.6 million. Post deal and on a proforma basis (at June 30), Osiris now holds $82 million in cash and investments for sale.

Prochymal Crohn's Phase III Trials to Finish Year End

Mesoblast will now take on responsibility for the completion of various Prochymal clinical programs. Of interest are several Phase III trials nearing completion in patients with Crohns disease (an inflammatory bowel condition).

The leading Phase III trial is recruiting 270 patients with moderate to severe treatment refactory Crohn's disease. This study (Protocol 603) is comparing two doses of Prochymal (600 million cells and 1200 million cells) in patients who have failed or are intolerant to steroids and at least one immunosuppressant and one biologic drug, with a placebo. The endpoint is the number of patients who achieve remission after 28 days. A subsidiary trial (Protocol 610) is evaluating the duration of the benefit out to six months of Prochymal in 97 patients who achieved remission after 28 days.

A futility analysis was conducted part way (at 207 patients) through the Protocol 603 trial to determine which of the two doses was the more effective. The dosing of the more effective dose has continued blinded.

Another Phase III trial (Protocol 611) is a single arm safety study in 120 patients which is evaluating the dosing of Prochymal (200 million cells) out at 42-45 days, 84-87 days and 126-129 days after the initial infusion.

Protocols 603 and 611 are due for completion in December 2013 and it is this near term program completion which has been of strategic interest to Mesoblast.

Prochymal GVHD Next Steps

Mesoblast will continue the commercialization activities underway with Prochymal for GVHD. It will seek FDA approval for GVHD patients with gut or liver complications, the sub-set of patients which received a clear benefit in a Phase III trial.

Prochymal for GVHD has been granted Fast Track and Orphan Drug status by FDA and Orphan Drug status by the EMA.

Contrasting Osiris' MSCs and Mesoblast's MPCs

Although Osiris' MSCs and Mesoblast's MPCs are closely related stem cells, differences occur in how they are extracted, purified, expanded, formulated and dosed.

Osiris harvests MSCs from the bone marrow of healthy adult donors and claims it can produce up to 10,000 treatments from a single donation. A unit of Prochymal contains 100 x 10^6 viable MSCs. The product is dosed at 2×10^6 MSCs per kilogram, so a 75kg GVHD patient would for example require 1.5 units for a single treatment course (375 million cells), which realistically speaking would be two bags because unused unfrozen product would have to be thrown away. A course of treatment requires infusions 8 times over four weeks, resulting in 16 treatments. In rough terms, a single donor could yield 600 to 700 treatment courses for GVHD. Note that in the Osiris Phase III Crohn's disease trial, the dosing is for 600 million cells from four infusions over two weeks or 1,200 million cells from four infusions over two weeks.

Mesoblast also selects MPCs from healthy donors. It uses antibodies (immunochemistry) to extract specific MPCs, differentiated by a cell marker termed Stro1 ^{bright}, from source material and then expands these cells using proprietary methods.

To contrast the dosing of Mesoblast MPCs with Osiris' MSCs, Mesoblast has scheduled 12.5 million (low) and 25 million cell (high) doses in its heart attack track trial and in the company's Phase II heart failure trial, three doses of 25, 75 and 150 million cells were evaluated, with the highest dose proving to be the most effective. In other words, Mesoblast has been administering much lower doses of its cells compared to Osiris' dosing regimes. However, the dosing and frequency of dosing of stem cells remain a source of major unknowns for Mesoblast and other stem cell therapy companies and clinics in general.

Mesoblast CEO Silviu Itescu intends to hold discussions with payors and hospitals in the US to get a better understanding of diagnosic-related payments and how the pharmaco-economic benefits around mortality and hospitalisation outcomes can lead to pricing structures for stem-cell based therapies.

Commentary

The acquisition of Osiris' ceMSC assets has many benefits for Mesoblast. First, it gives the company intellectual property dominance of the mesenchymal and mesenchymal precursor stem cell space. Potential may exist for Mesoblast to apply some of its proprietary MPC preparation methods to MSCs. The acquisition might also enable Mesoblast to more freely pursue development of MPCs for GVHD, since the company has a patent covering the indication and data to suggest the superiority of MPCs over MSCs for treating GVHD. (see WO 2012/000064)

Second, the company now has a product that is much closer to market launch, or rather achieving full market access, than any other in the Mesoblast pipeline, and in two different indications.

Cont'd over

One goal Mesoblast CEO Silviu Itescu has in mind is to use the market access underway and on the near term horizon with Prochymal to build Mesoblast's knowledge of sales of stem cell products. This is an important clue for investors seeking to understand Mesoblast's long term outlook which is one where the company has involvement with all aspects of the development and sale of cell therapy products.

Another strategic angle on the selling process is that Mesoblast is now more in control of discussions over pricing and reimbursement. Previously with Osiris controlling the commercialisation of Prochymal, the pricing discussions that would have taken place product would have been outside the influence of Mesoblast. Now this risk is mitigated and such pricing discussions can now be better influenced by Mesoblast. Prochymal is essentially a first in class medicine and the need to strike product prices that set reference levels for future products would no doubt been seen as having high strategic importance to Mesoblast.

Summary

Mesoblast's CEO Silviu Itescu has once again demonstrated an amazing knack for strategic decision making by securing the stem cell assets of Mesoblast's closest rival, but also structuring the deal so that Osiris can receive benefits in the long term should Prochymal become a successful product. Mesoblast can certainly be applauded for such strategic deal making.

The acquisition of advanced stage clinical programs and conditionally approved indications not only spreads the risk in Mesoblast's portfolio but should bring forward the foundational work required to build a commercial sales oriented medical products business.

The deal goes some way to imbuing value in the Mesoblast stock price, which is continuing to trade on high expectations of clinical success and progress. However, the integration of the Osiris assets into the Mesoblast portfolio is not expected to require additional funding.

Mesoblast is capitalised at $1.8 billion and held cash of $315 million as of June 30, 2013.

Bioshares recommendation: **Accumulate On Price Weakness Below $5.00**

Calzada Makes Important Steps Forward in Changing Wound and Burns Treatment Paradigms

Calzada (CZD: $0.08) has delivered two positive clinical trial results for its Novosorb technology this year.

The first was with its topical negative pressure (TNP) trial, and the second in repairing free flap donor sites. The first product provides an improved alternative over incumbent products.

The second potentially provides a more affordable and robust way to treat major wounds in the body.

A third, longer term application of the technology has the potential to provide a composite skin product that can cover 100% of the body. The technology is being championed by Adelaide plastic surgeon Professor John Greenwood.

TNP Trial Result

Last month Calzada reported a positive result in using the NovoSorb material in TNP dressing. In the 18 patient trial, it was shown that Novosorb achieved less fragmentation in the wound than existing products, and was easier to remove with less bleeding. That NovoSorb is biodegradable is also a benefit.

Calzada filed the product for approval in the US last month under a 510k pathway and if all goes well, the company expects approval in 2014 Q1. The company is currently in discussions with potential licensing partners.

Full Thickness Surgical Wounds Trial Result

This week Calzada released comprehensive results from a trial in 10 patients with full thickness surgical wounds. The trial showed that the NovoSorb product could very effectively be used as a dermal scaffold in what is called a Biodegradable Temporising Matrix (BTM). In this trial, patients had a section of full thickness skin removed from one site that was used in reconstructive surgery in another part of the body.

The standard of care is to repair the donor site by using a thin skin graft from another part of the body. However because it is repairing a deep wound, a cavity in the skin remains that is only partially filled by the skin graft (see announcement 10 October 2013, page 7, top left photo - note that these are very graphic medical photos). This means that where the harvest site for the free flap procedure is the forearm, movements of tendons in the arm are visible after the area is treated.

The free flap donor site was filled with the polyurethane biodegradable NovoSorb polymer, which was later completed using a skin graft (21-49 days later). The outcome was a well treated wound that was flush with the surrounding skin, and with only a small amount (3.2%) of wound contraction (see announcement 10 October 2013, page 7, bottom right photo).

Substantially Better Appearance with NovoSorb BTM

Skin grafts contract depending on the thickness of the graft; thinner grafts will contract more. The NovoSorb BTM can be used to make thin skin grafts look like a thick graft according to Greenwood. The more contraction of a wound also affects functionality, with mobility restricted when there has been a lot of wound contraction, limiting mobility of limbs.

In discussion with *Bioshares*, Greenwood argued the NovoSorb product will 'massively improve appearance', looking similar to the collagen-based Integra product, which Greenwood said is very good but is also very expensive and prone to infection issues.

This Calzada trial result was a major advance for the technology because it shows that the NovoSorb polymer material can fill the wound site with a robust outcome that allows skin grafts to successfully complete treatment.

A detailed report from Greenwood was provided in the company announcement and the comments are worth highlighting.

In one patient, 'the skin graft took well, leaving him with an excellent result without visible underlying tendons.'

In another patient, 'The post-graft result is a wound flush with the surrounding skin surface, robust and durable. The underlying tendons move freely and without any evidence of graft tendering - unlike similar defects that have been primarily grafted over tendons.'

In a third patient, the treatment 'took well and has left her with a robust, well-contoured result, which was superior in contour and texture to the primary split skin graft.'

Greenwood said that the company has ' learnt loads' about applying this product to wound treatment from this trial. In some cases, there was fluid build-up under the BTM from fluid running down the tendons to the wound so there needs to be a drainage hole in the seal placed on the BTM to release the fluid build-up and prevent lifting of the BTM, which occurred in some cases.

One impressive feature of the NovoSorb BTM technology is that in could easily be salvaged and repaired when required, in cases such as infection, which occurred in some patients and was successfully treated. In one case 30% of the BTM from the centre of the dressing was successfully removed to treat an underlying infection. The BTM product subsequently integrated with the rest of the wound, which was a positive and surprising outcome.

For patients who were very ill and had difficulty healing all wounds, it was found that the BTM needed to be left on the wound sealed for longer before the skin graft was applied to complete the treatment.

Overall the BTM integration in the wound was 100% successful in nine from 10 patients, with the one patient (above) needing 30% of the BTM product removed to treat (successfully) infection.

Cont'd over

Comparison with Integra

The NovoSorb BTM product is much more robust than the leading product on the market, called Integra. However Greenwood says because this is a collagen based product, if you don't get it exactly right then bacteria grows because it feeds off the collagen. With NovoSorb, because it is synthetic, bacteria can't feed off it according to Greenwood.

Calzada plans to file the NovoSorb BTM for approval in the US in Q1 2014 also under a 510k pathway as a dermal scaffold in surgical wound applications.

Burns Treatment

This technology wasn't designed for repairing free flap wounds, which it can repair quite easily says Greenwood, but for burns. The next clinical trial will be in the treatment of burn wounds. Greenwood says this is a much bigger challenge because of the size of the wounds that require treatment. Greenwood has received ethics approval to commence a clinical trial in Adelaide, which is expected to start before the end of the year.

A product for burns treatment will be used both in the first world, where the number of cases is falling because of better safety practices, and in the second and third worlds, where the number of cases is increasing.

In 2014 Q1, the company also expects to start a 10 patient burns trial in France.

Cultured Composite Skin: The Holy Grail of Burns Treatment, but a Much Longer Term Project

The urgency for the treatment of serious burn wounds is that the wound needs to be sealed to prevent infection and also water loss. Stopping the water loss also stops contraction of the wound. To treat burns wounds, a skin graft is taken from another part of the body. However for larger wound areas, finding sufficient donor sites is a problem, which is amplified where thick skin grafts need to replace deeper wounds.

A future application of this technology is the development of a cultured composite skin (CCS) product. Here a skin graft is taken and the skin cells are separated and grown in a bioreactor on the NovoSorb matrix. Greenwood said that a 10cm by 10cm graft treated in this way would be sufficient to produce enough composite skin sheets to cover the entire body within 21 days. Preclinical proof of principle studies in animal models have been achieved. The latest trial results in free flap surgery with Novosorb bring this application a step closer to a reality.

Share structure notes

Calzada owns 100% of Metabolic Pharmaceuticals and 100% of Polynovo Biomaterials. Polynovo Biomaterials owns 80% of NovoSkin and NovoWound which has licensed the rights to the NovoSorb technology in the wound management area. Professor John Greenwood, through Skin Pty Ltd owns the remaining 20% of these private companies.

Summary

Showing that the NovoSorb biodegradable material can be successfully incorporated into a wound for treatment is a major advance for Calzada. Greenwood suggested the technology is very close to entering a paradigm shift in the field of wound treatment.

With the results achieved this year, we expect this stock will start to receive increased attention from investors. And with the increasing attractiveness of the Polynovo assets, there is a strong argument that the company should focus on this technology rather than the Metabolic drug assets that have failed to deliver meaningful commercial value.

Bioshares recommendation: **Speculative Buy Class B**

Bioshares

Bioshares Model Portfolio (10 October 2013)

Company	Price (current)	Price added to portfolio	Date added
Oncosil Medical	$0.130	$0.155	September 13
Calzada	$0.080	$0.073	September 13
Invion	$0.077	$0.060	August 13
IDT Australia	$0.360	$0.260	August 13
Viralytics	$0.365	$0.300	August 13
Circadian Technologies	$0.280	$0.270	March 2013
Tissue Therapies	$0.290	$0.255	March 2013
Benitec Biopharma	$0.415	$0.40	November 2012
Somnomed	$1.20	$0.94	January 2011
Cogstate	$0.475	$0.13	November 2007
Universal Biosensors	$0.62	$1.23	June 2007

Portfolio Changes – 10 October 2013

IN:
No changes.

OUT:
No changes.

QRxPharma Now Set To Re-file its NDA

QRxPharma (QRX: $0.69) had a positive meeting with the FDA regarding its new drug application (NDA) for is combination opioid treatment MoxDuo IR. QRxPharma expects to submit its NDA next month, which should see a decision from the regulator six months later.

In the company statement, QRxPharma indicated that the FDA stated that the safety and efficacy of MoxDuo was not in question, and that an FDA Advisory Committee would assess the respiratory safety advantages of MoxDuo IR, over morphine and oxycodone taken individually.

In June last year, QRxPharma was not successful in getting its drug approved because the FDA wanted additional information, specifically a more complete data set relating to oxygen desaturation levels in Study 022. QRxPharma refiled its NDA with the FDA in February this year with that additional data. However in June, the company discovered some timing inaccuracies in 17% of the 375 patients as a result of adjustments to day light saving time at one site. QRxPharma was unsuccessful in resubmitting the corrected (and audited) data set within the timeframe (to allow the FDA to give its decision within six months after filing) and as such delivered the company its second Complete Response Letter (which means the new drug application is not approved).

QRxPharma is now very confident it has resolved data integrity issues with the data assessed by two different groups.

QRxPharma is using the 505(b)(2) pathway to get its combination drug to market. The company said there have been no deaths linked to the combination therapy and no toxicology issues.

Oxygen Desaturation Benefits – Previous data

In an investor presentation from March this year, the company highlighted the benefit of MoxDuo with respect to oxygen saturation levels in the blood over morphine and oxycodone. The chances of having a serious desaturation of oxygen levels in the blood (to less than 80%) was clearly lower for MoxDuo than for Oxycodone at all times, and similar to morphine for the first 17 hours. After that time, risk of a serious fall in blood oxygen saturation levels for morphine exceeded that for MoxDuo.

In older patients (great than 60 years of age) the respiratory safety benefit was even more pronounced. Only 2% of those taking MoxDuo experienced serious oxygen desaturation events (to less than 70% Sp02) compared with 14.9% in those taking morphine and 17.4% in those taking oxycodone.

In those less than 60 years of age, 6.5% of those patients who received MoxDuo experienced oxygen saturation levels falling below 70%. For those receiving morphine, the result was about the same, and for those receiving oxycodone, almost twice as many patients experienced Sp02 drops below 70%.

Summary

QRxPharma's Study 022 was one of the last completed. The full data from this trial was submitted after the original NDA was filed. Changes in oxygen saturation levels were not a specific endpoint. However, because the information became available, the FDA requested to see the full data set because of its importance.

On the data available, MoxDuo does offer considerable safety advantages with respect to blood oxygen levels, which the company says still holds up following the correction of the data set discussed above. The question in *Bioshares* view is whether the FDA may like to see more data (trials) around this aspect, however neither the regulator nor the company have suggested that more trials will be required.

It has become increasingly difficult to predict regulatory outcomes in recent years. However, QRxPharma's positive meeting with the FDA is a step in the right direction.

QRxPharma is capitalised at $97 million. It had $12 million in cash at the end of June. The company has indicated that it may look to improve its funding position prior to FDA review.

Bioshares recommendation: **Speculative Hold Class B**

Bioshares

Correction - Bioshares 523

In the table 'Selected Clinical Trial Developments -2013 Q3', the reference to Bone Medical should be replaced by Progen Pharmaceuticals.

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: Starpharma Holdings, Cogstate, Bionomics, Impedimed, QRxPharma, LBT Innovations, Mesoblast, Tissue Therapies, Viralytics, Phylogica, pSivida, Antisense Therapeutics, Benitec BioPharma, Allied Healthcare Group, Calzada, Atcor Medical, Invion, Circadian Technologies

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