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In this edition...
Mesoblast has previously generated investor interest because of the potential of its MPC stem cell product to treat heart failure and because very promising clinical data in the area that secured Cephalon (now Teva) into a licensing agreement. However, interest is shifting towards Mesoblast's investigation of systemic applications of its stem cells to treat Type 2 diabetes and other inflammatory conditions. Results from a Phase II trial in 60 patients with Type 2 diabetic are expected by year end which may burst open a new arena of opportunity. A restlessness to strive to achieve high growth rates looks to be behind Somnomed's decision to restructure its management. Bioxyne is offering investors a short-term trading opportunity ahead of the release of Phase IIb results in June.
The Editors
Companies Covered: BXN, MSB, SOM

	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)	-7.2%
Cumulative Gain	**220%**
Av. annual gain (11 yrs)	**17.8%**

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Bioshares

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

Extract from Bioshares –

Multiple Value Drivers Support Interest in Mesoblast's Share Price

Mesoblast ($MSB: 6.85) is a company that has many shots on goal for its mesenchyal precursor stem cell (MPC) technology. It has mid-to-late stage programs underway or due to start in heart failure, Type 2 diabetes, spinal fusion, invertebral disc repair, the eye disease wet AMD, and in bone marrow transplantation. Its lead program is a Phase III trial that is due to be initiated soon by its partner **Teva Pharmaceutical Industries.** The company's Phase II trial in Type 2 diabetes is open for recruitment and this trial alone could deliver a major result for the company.

Phase III Congestive Heart Failure Trial

The Phase III CHF trial clinical program is now being driven by and paid for by Teva. Mesoblast has been involved in the trial design, discussions with regulators, and it will manufacture the adult cells for the trial. Teva and Mesoblast have met with both European and US regulators. The start of this trial by Teva, expected to be in Q2 2012, will be a significant event.

Only one Phase III trial involving 1,500 patients may be required to gain product approval and the timeline for product approval for CHF remains at the end of 2015.

Phase III Interim Analysis?

Depending on the significance in the results, there is the possibility of an interim analysis of results, which could reduce development time by a year. It is anticipated that the patient population intended to be treated has a 20% chance of not living beyond 12 months. If it is observed that the overall survival of patients in the trial is much higher than the expected (i.e. suggesting that the stem cell treatment may be having a pronounced effect on survival, as seen in the 60 patient Phase II trial), then an interim analysis could occur. This could happen when 1,000 patients have been recruited. However there is a risk it could compromise the data if there is a higher than expected survival rate in the control group.

Phase II Type 2 Diabetes Trial

Mesoblast's Phase II trial in patients with Type 2 diabetes is currently open for enrollment. This will be a 60 patient trial, with three different doses and a control group (similar to its very successful heart failure trial). There will be a 12 week end point in the trial. Results should be rapid with the trial expected to be completed by the end of this year.

The three doses will be escalating, with the company anticipating the highest dose to be most effective. Each dose will be monitored by a safety committee and there may be interim data emerging from the trial.

There are a number of reasons the application of MPCs in diabetes may have merit.

Cont'd over

1. Positive preclinical studies

In preclinical studies in 17 non-human primates with diabetes (the monkeys live on sugar plantation), there was over a 60% reduction in glucose levels in the higher doses over six months following a single IV dose of the Mesoblast stem cells. There was also a drop in CRP levels (a marker of inflammation). Elevated CRP levels present a major risk of heart attack in people with Type 2 diabetes.

2. Role of Osteocalcin

What works out to be of benefit for Mesoblast is the role its population of stem cells play in diabetes. The hormone osteocalcin has been reported by others to promote beta cells in the pancreas to release more insulin, while also directing fat cells to release more of the hormone adiponectin which increases insulin sensitivity. Type 2 diabetes is characterised by not enough insulin circulating in the body and the body being resistant to insulin.

Mesoblast's mesenchymal cells are the precursor to the osteoblast cell that produces the osteocalcin hormone that promotes beta cell function. Increasing the level of insulin produced in the pancreas and increasing the body's sensitivity to insulin can both be very helpful in treating Type 2 diabetes.

3. Role of Inflammation

The second fortunate feature of the Mesoblast mesenchymal precursor stem cells is that they have an anti-inflammatory action. It's the pro-inflammatory effect in diabetes, as indicated by the high CRP levels, that can have fatal outcomes for patients with diabetes.

Other Clinical Milestones Ahead

Disc Repair

Mesoblast expects to complete its Phase II disc repair trial by the end of this year. If this is positive, Mesoblast could move into a Phase III trial, in 500-600 patients, running the trial on its own. This application is preferable over the spinal fusion use (see below) as there is no existing competition. An effective disc repair product could also reduce the need for spinal fusion procedures.

Spinal Fusion

Mesoblast is completing two Phase II spinal fusion trials. They are both fully recruited and are waiting on reaching six month endpoints. Results from these trials should also be available towards the end of this year. The spinal fusion market is more competitive with an existing product, Infuse from Medtronic, on the market. However this product has safety concerns and sales are declining.

Key Teva Advisor Joins Mesoblast board

Although it was only a one page announcement by Mesoblast, the appointment of Dr Ben-Zion Weiner to the board of Mesoblast is an important move. Dr Weiner replaced Kevin Buchi, who was formerly CFO and then CEO of Cephalon which was acquired by Teva. Buchi has now left Teva.

Dr Weiner was formerly head of R&D at Teva and is now a special advisor to the CEO of Teva. His placement on the Mesoblast board indicates Teva wants to stay very close to developments at Mesoblast.

There have been questions by some of the commitment of Teva to the Mesoblast programs following the acquisition of Cephalon. Mesoblast CEO Silviu Itescu said Teva is very committed to the Mesoblast partnership and believes it will not sell its 19.9% stake in Mesoblast.

Teva, which was built around a generics businesses, is in the process of transforming into a branded (drug development) pharmaceutical company. In January it appointed a new CEO, Jeremy Levin, who was formerly a senior executive at Bristol Myers-Squibb, which is not a generics business. Mesoblast's technology has the potential to help transform Teva into a drug discovery and development company.

We understand that what were **Arana Therapeutics'** drug discovery assets and acquired by Cephalon, were being considered for a spin out from Teva. However that option has been removed with the focus now from Teva to build its branded drug business.

Learning from the Osiris Experience

Overnight US stem cell company **Osiris** received approval from the Canadian drug regulator for its stem cell therapy Prochymal for the treatment graft-versus-host disease.

Graft-versus-host disease occurs when a patient receives a bone marrow transplant but the match is not quite exact, resulting in the transplanted immune cells in the bone marrow attacking the patient's organs. First line therapy is the use of steroids to dampen the immune system.

In 2009 Osiris failed in two pivotal late stage trials in graft-versus-host disease. The therapy is believed to be more effective in more severe cases of the disease. The Canadian regulator has approved the therapy for children who have failed steroid treatment.

Osiris is also trying to commercialise its treatment for Crohn's disease, type 1 diabetes and heart failure although has also had some setbacks here as well.

The Mesoblast technology differs from the Osisris stem cells in that its population of cells is much more concentrated. Mesoblast has learnt from Osiris' mistakes in commercializing its own stem cell technology. Osiris started with a systemic, broader acting therapy (graft-versus-host disease, Crohn's disease) and has then pursued more targeted therapies.

Mesoblast has proven first that its technology works in specific, targeted therapies such as heart failure and bone fractures. Having achieved its proof-of-concept here, it will now expand into less targeted or directed, intravenous formulations for disorders such as diabetes.

Osiris was once the commercial leader in the stem cell space with a market value of over $1 billion. It is now capitalised at only US$182 million and Mesoblast has become the global leader in the stem cell space with a market value of $2 billion.

Cont'd over

– Mesoblast cont'd

Developments such as the approval of Osiris' allogeneic stem cell product in Canada, pharmaceutical group **Baxter** commencing a Phase III study in January in 450 patients with chronic myocardial ischemia using its autologous stem cell therapy (see *Bioshares* 446), and the widespread progress at Mesoblast indicates the commercial development of stem cell therapy is gaining momentum.

Summary

There are many significant milestones ahead for Mesoblast. These are summarised below. The outcome from the company's Phase II trial in diabetes could be a major event for the company. Not only does it have the potential to open up an extremely large market opportunity for the company in Type 2 diabetes, but it will support other systemic therapy applications including rheumatoid arthritis (caused by inflammation), which is over a $10 billion a year market as measured by existing product sales.

Mesoblast is capitalised at $1.95 billion. It had $226 million cash at the end of March.

Forthcoming Mesoblast Milestones

- Dosing of first patient in Phase II Type 2 diabetes trial (60 patients) – imminent
- Start of Phase III heart failure trial by Teva – Q2 2012
- Results from disc repair trial – end 2012
- Results from two spinal fusion trials – end 2012
- Interim Phase II diabetes data – end 2012

Bioshares recommendation: **Speculative Buy Class A**

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