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In this edition...
Mesoblast is a company that fascinates investors not only because it is developing a next generation medical technology but also because it is executing from a plan that pays meticulous attention to manufacturing, financial structuring and clinical trial design. It is a company that cannot be ignored.
Acrux shares took a hit following full year results disappointing expectations of market share growth for Axiron in the US. The stock has become very attractive buying but the market share growth is still the key determinant of value in the stock.
The FDA is a conservative beast when it comes to issues of safety. So the provision of more data from QRxPharma's MoxDuo IR Study 22 may be yet prove to be what is necessary to get MoxDuo IR across the approval line, possibly in mid-2013.
Companies Covered: ACR, MSB, MVP, 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 - current)	-20.7%
Cumulative Gain	**174%**
Av. annual gain (11 yrs)	**17.8%**

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Bioshares

24 August 2012
Edition 469

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

Mesoblast Powers Ahead With Clinical Programs

Mesoblast provided an update to the market this week. The company continues to build data from human applications of its mesenchymal precursor stem cell (MPC) technology. Although the specific efficacy data is important from each application, what is gaining importance is the safety profile of the use of these stem cells. As that data around the safety builds from use of the technology in clinical trials, and there have been no cell-related adverse events, the value of this technology also increases.

At the briefing, CEO Silviu Itescu said that safety from the Phase III heart failure trial which is due to commence in coming weeks "will be generally applicable to every other indication". In this manner, data from each trial in some way will support the development of the technology for other uses.

Moving the technology into a systemic therapy for Type 2 diabetes through a Phase II study is important to not only that application, but the safety data from that trial will also support moving the trial in a systemic therapy for rheumatoid arthritis said Itescu.

Phase III Trial in Congestive Heart Failure

The much awaited start of the Phase III trial in congestive heart failure by Mesoblast's partner, **Teva Pharmaceutical Industries**, is expected to start in coming 'weeks'. Discussions with European and US regulators and key opinion leaders has been conducted jointly by Mesoblast and Teva. Regulatory approval in the US and Europe will be timed to occur simultaneously. Most of the planning for this trial has already occurred. The trial sites have been identified, principal investigators have been identified as have data safety monitoring boards. Supply of the product is available for the trial as are the catheters to deliver the cells. However, what is yet to be made known is the number of patients to be recruited for the trial and its duration.

Teva and Mesoblast are finalising the trial protocol with the FDA. One of the key points to finalise is when the right time will be to receive some interim results, and how this might be achieved with no statistical penalties to the overall trial.

There will be a raft of key milestones approaching for the company from clinical trial activity and results. Other forthcoming major events are summarised below.

Spinal Fusion trials – Phase II Trial Results

Results from the company's Phase II spinal fusion trial are expected. Data from the lumbar fusion trial are due to be released by year's end. And data from the cervical spinal fusion trial is about six months behind the lumbar spinal fusion trial, so is expected around mid 2013.

Type II Diabetes – Phase II Trial

The Phase II trial in Type II diabetes is now underway. There will be three cohorts of 20 patients each in the trial. Some patients in each cohort will receive a placebo. Recruitment

Cont'd over

into the first cohort is expected to be finished in less than three weeks. Recruitment of the second, and possible third cohort, is expected to be completed by year's end. (The trial design is very similar to the company's very successful Phase II study in congestive heart failure.) It is currently recruiting at 12 sites in the US. The trial is primarily a safety study, employing seven safety measures not linked to diabetes, however it will also be looking at hypoglycaemic events. Presumably also the characteristics of blood glucose levels will also be measured.

Rheumatoid Arthritis – Phase II Trial to Commence

Once safety data emerges from systemic use of the Mesoblast stem cells in Type 2 diabetes, the company will look to start a Phase II trial in patients with rheumatoid arthritis. This is a very large market worth in excess of $10 billion a year.

Start of Phase II Study in Patients with Diabetic Complications

A Phase II study in patients with kidney, heart and liver complications is also expected to commence in coming months, once again presumably once sufficient safety data from the Phase II diabetes trial underway is available.

Degenerative Disc Disease – Phase II Trial

Itescu said the company was rapidly enrolling patients into its Phase II study in patients with invertebral disc damage. This is a major market for the company. An effective treatment would stop patients from degenerating to a stage where they would require spinal fusion, by treating the damage earlier. The 100 patient study is expected to complete recruitment by the end of next month. Rapid recruitment of any therapy gives a very clear indication of the need for a particular product.

Financials

Mesoblast ended the year with $207 million in cash. Its loss was $47.8 million for the year. The company expects to spend between $63-$67 million this year as a guide. Mesoblast generated $10.5 million of revenue in interest alone. The company spent $36.9 million on R&D and importantly $22 million on manufacturing. Manufacturing is a key asset for the company in our view. It currently has access to an existing **Lonza** facility in Singapore to produce its stem cells for clinical studies.

Summary

What is working in Mesoblast's favour is that it is developing allogeneic stem cell products, where the same source of cells from a master donor is used for each patient. This is more similar to a pharmaceutical model than a specific, autologous cell therapy approach. The benefit of this is that regulators are more likely to embrace this approach, than the somewhat unregulated and complicated approach of autologous cell therapy products.

One issue confronting regulators at the moment is that some autologous stem cell products are completely bypassing regulators such as the FDA, with the argument that minimal manipulation of a patient's own cells lie outside of regulators' authorities. Simply re-implanting a patient's own cells with a slight manipulation of the cells falls under the medical practise it is being argued, and so is the responsibility of state medical boards in the US, not the FDA.

Mesoblast continues to build important data on the efficacy of the use of its MPC technology. It is arguably the world's leading stem cell company. The potential for value creation exists in the achievement of clinically meaningful but commercially relevant results from just some of the myriad of clinical trials underway and planned. However it is not just efficacy that will be an important result; building the safety data around this technology will also contribute substantial value to this company.

Mesoblast is capitalised at $1.77 billion.

Bioshares recommendation: **Speculative Hold Class A**

Bioshares

Medical Developments Int. Rewards Investors with 3 Cent Final Dividend

Medical Developments (MVP: $1.13) has posted a strong profit result of $2.7 million for FY2012, an increase of 55% from the previous year. Revenues of $11.3 million were 11% higher from $10.2 million in the previous year.

The company announced it would pay a fully franked final dividend of 3 cents a share. The profit result was largely driven by improvements to the company's gross margin, which improved from 64% in FY2011 to 69% for the latest year.

Medical Developments markets the Penthrox pain treatment product (used in trauma settings), asthma spacer products and other medical equipment, predominantly in Australia and New Zealand.

Commentary

Medical Developments has achieved a very positive result for the financial year ended. However, the share price has run well ahead of fair value for the stock. On a price/earnings basis, the stock is trading on a multiple of 23, well in excess of a 12-15 multiple applicable to industrial stocks with revenue growth at or above general economy wide growth. We don't expect gains in margins to be bettered in the next financial year and overall revenue is likely to grow at a similar rate for FY2012, implying a similar growth in profits of 10-11% for FY2013.

The company's European clinical trial of Penthrox has now been completed. However, it is too early to value Penthrox from an European asset point of view until pricing and reimbursement for the product is better understood.

Medical Developments is capitalised at $63 million.

Bioshares recommendation: **Sell**

Bioshares

Acrux – Watch the Battle for Market Share

Acrux (ACR: $3.33) closed the week down 18.8% from the close in the previous week following the release of the company's full year results for FY2012.

The company posted a profit of $7.4 million from revenues of $10.7 million for FY2012. In the previous year Acrux posted a profit of $57 million from revenues of $93.5 million. Revenues in FY2011 included an $87 million milestone payment from Eli Lilly.

Income from license agreements totalled $8.8 million for FY2012.

The company announced that it would pay a tax-free dividend of eight cents a share.

The company's cash balance, after accounting for its dividend payment is $16.7 million. Acrux stated that is current cash burn stands at $5 million per annum.

Axiron Royalty Payments

Acrux received US$6 million in Axiron royalty payments from its global licensee **Eli Lilly** for FY2012. Axiron is a replacement therapy for men with low levels of testosterone.

The royalty is calculated on net sales, which is based on gross sales after deductions have been made for rebates, discounts and returns. The royalty is also structured so that royalties are smaller to begin with and increase over time to a maximum. We estimate the royalty for Axiron received for FY2012 equates to an average rate of 15%.

Since Axiron was launched in the US in 2011 Q2, Eli Lilly has been offering rebates to patients by way of a co-pay card so that the cost to the patient roughly equates to the price those patients would have paid for other similar testosterone drugs. The co-pay works to support the uptake of Axiron until the insurance companies have accepted Axiron as a reimbursable drug.

Axiron's market share in the US had risen to 12.5% in July 2012, following its launch in April 2011.

Commentary

The sell-off in Acrux shares could be attributed to a slower than expected growth rate in market share obtained by Eli Lilly for Axiron.

Another explanation for the share price fall is the impact of Acrux's reporting of a low royalty figure for the FY2012 period stemming from low sales figures for Axiron which are a consequence of co-payment deductions made by Eli Lilly to gross sales. For an initial period while US health insurers include Axiron on their formularies, Eli Lilly has been rebating patients for approximately 65% of the cost of an Axiron prescription.

Gross sales are currently running at an annualised rate of $US238 million, assuming that Axiron's market share is maintained at 12.5% and a 2012 estimated transdermal testosterone drug market in the US of US$1.9 billion. We estimate the royalty pertaining to that figure to be in the range of US$36 million at an average royalty rate of 15%.

Shares of Total Prescriptions for Transdermal (Testosterone) Products - US

	Apr-11	*Jul-12*	*Change*
Androgel 1%	*72%*	*30%*	*-42%*
Androgel 1.62%		*33%*	*33%*
Total Androgel	*72%*	*63%*	*-9%*
Testim	*20%*	*16%*	*-4%*
Axiron	***0%***	***13%***	***13%***
Androderm	*7%*	*5%*	*-2%*
Fortesta	*1%*	*3%*	*2%*

Source: Acrux

(However, this illustrative royalty, if adjusted for the cost of the co-pay or rebate, would be ~US$13 million.)

In time, the co-pay/rebate arrangements supported by Eli Lilly will be wound back (Acrux expects by Q4 2012) and royalties on Axiron sales will increase as sales increase. When combined, these two factors will have considerable impact on Axiron-derived revenues for Acrux.

Furthermore, it is worth noting that Acrux anticipates receiving several additional milestone payments from Eli Lilly, being US$25 million in FY2014 and US$50 million in FY2014. The payment for FY2014 comes into effect when US net sales of Axiron exceed US$100 million, presumably in CY2013. At current rates of growth in sales, and with the co-pay/rebate expected to not impact net sales in CY2013, it is highly likely that the milestone will be achieved.

The most important Axiron sales figure to monitor is market share. Eli Lilly needs to achieve strong growth in Axiron's market share *over the next twelve months* (mostly at the expense of **Abbott Laboratories**' Androgel, which in two formulations stood at 63% in July), if it is to cement the drug's position firmly in the top two men's transdermal products in the US.

Summary

The potential for Acrux to return substantial dividend payments to shareholders over the longer term remains high, although it is necessary to recognise that revenues are a function of Eli Lilly's ability to increase Axiron's market share in the US. Further upside exists as and when sales of Axiron begin to grow in other markets.

Acrux is capitalised at $544 million.

Bioshares recommendation: **Buy**

Bioshares

QRxPharma Meets with the FDA

QRxPharma (QRX: 70 cents) met with the FDA this week to discuss the Complete Response Letter it received in June for its new drug application for MoxDuo IR, an opioid pain combination therapy comprising of morphine and oxycodone. QRxPharma reported the meeting as being productive and is seeking to get the product re-assessed and approved by mid 2013.

Waiting on the Meeting Minutes

The next step for QRxPharma is to receive the minutes from its meeting with the FDA, which will take up to 30 days. QRxPharma will then send the FDA additional information requested. QRxPharma is aiming to refile its NDA with the FDA by the end of October, with a re-assessment from the FDA then possible by the end of April 2013.

QRxPharma CEO John Holaday said he left the meeting (with the regulator) very pleased with the discussion that took place.

Over 1,600 people have been administered MoxDuo IR. However, what the FDA is particularly interested in is safety data from the company's Study 022, which looked at oxygen desaturation levels.

The FDA is particularly interested in the incidence of serious adverse events, in particular vomiting episodes and oxygen desaturation levels on an individual patient level throughout the entire trial, which involved 375 patients.

More Studies Not Required

At this stage the FDA is not requesting that further studies be undertaken. It is requesting more complete information from Study 022 that has become available after the NDA was submitted, together with more individual patient data mentioned above.

Study 022

Of all of the studies conducted, Study 022 is the one study that produced some ambiguous results and in hindsight it is not surprising that the FDA has requested more detail from this trial. The study's primary endpoint was to look at respiratory depression as measured by oxygen desaturation. Oxygen desaturation is one of the most serious issues relating to opioid use and is what causes death from opioid overdose, including heroin overdose.

In this study changes in oxygen desaturation levels were compared between equal analgesic amounts of morphine, oxycodone, and MoxDuo IR. The result was that MoxDuo had a significantly better safety profile than oxycodone, but not over morphine. However there was a beneficial trend that showed MoxDuo was safer than morphine.

With respect to moderate-to-severe vomiting, there was significantly less in the MoxDuo arm compared to those patients taking oxycodone, although the rates were comparable between MoxDuo and morphine. The requirement to give patients anti-nausea medication in this trial may have clouded measurement of this secondary endpoint.

After this trial, QRxPharma looked in this data further, looking at the worst 10th percentile of cases in oxygen desaturation. Importantly, this showed that the risk of getting to dangerous oxygen desaturation levels was significantly greater in those taking morphine ($p<0.009$) and morphine ($p<0.002$) than MoxDuo. Potentially dangerous desaturation events occurred in 12% of those on morphine, 15% of those on oxycodone and 3% in those on MoxDuo.

That there is some ambiguity over these results, it is right and arguably the responsibility of the FDA to request more information where safety is concerned. Blood oxygen levels in the patients were monitored every two seconds for 48 hours in each of the patients. That information should give the regulator more comfort in deciding whether to approve this combination opioid product.

Summary

QRxPharma had $23 million in cash at the end of June. Holaday said the cash is enough to take the company out to the end of 2013. At this time, it is not known whether the company will need to raise further funds.

MoxDuo was very close to gaining FDA approval at the first pass and based on the information at hand, we expect the company maintains a strong likelihood of gaining approval in 2013. Our view is that the supply of additional information from Study 022 should be sufficient to gain regulatory approval for MoxDuo IR.

QRxPharma is capitalised at $101 million.

Bioshares recommendation: **Speculative Hold Class A**

Bioshares

Bioshares Model Portfolio (24 August 2012)

Company	Price (current)	Price added to portfolio	Date added
Nanosonics	$0.480	$0.495	June 2012
Osprey Medical	$0.37	$0.40	April 2012
QRxPharma	$0.70	$1.66	October 2011
Mayne Pharma Group	$0.330	$0.435	September 2011
Somnomed	$0.85	$0.94	January 2011
Phylogica	$0.026	$0.053	September 2010
Biota Holdings	$0.67	$1.09	May 2010
Tissue Therapies	$0.40	$0.21	January 2010
Bionomics	$0.29	$0.42	December 2007
Cogstate	$0.270	$0.13	November 2007
Sirtex Medical	$7.30	$3.90	October 2007
Clinuvel Pharmaceuticals	$1.57	$6.60	September 2007
Pharmaxis	$1.13	$3.15	August 2007
Universal Biosensors	$0.62	$1.23	June 2007
Alchemia	$0.520	$0.67	May 2004

Portfolio Changes – 24 August 2012

IN:
No changes

OUT:
No changes

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, Tissue Therapies, Viralytics, Phosphagenics, Immuron, Phylogica, Bluechiip, pSivida, Antisense Therapeutics, Benitec BioPharma, Allied Healthcare Group, Genetic Technologies, Calzada, Bioniche, Atcor Medical

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