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In this edition...
In 2011, QRxPharma's pain drug MoxDuo IR was denied approval by the FDA. Now a revised pathway has been set with an Advisory Committee to help in the decision making. While positive, the company is not out of the woods just yet. Mesoblast has released positive interim results from its Phase II trial of Neofuse in patients needing lumber fusion, showing its stem cells are as good as bone grafts, with an added advantage in lessening blood loss. Bioshares Research Principal, Mark Pachacz, puts his experience of using Somnomed's sleep apnea management devices on the record. This is a personal story which it is hoped will give investors insights into sleep disorders and into a particular device based approach to treating such disorders.
Companies Covered: MSB, QRX, Road Testing the Somnodent G2

	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)	-5.9%
Cumulative Gain	**225%**
Av. annual gain (11 yrs)	**17.8%**

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

QRxPharma – FDA to Hold Advisory Committee Meeting for MoxDuo IR

QRxPharma (QRX: $0.945) has had a very strong run in its share price over January, reaching a high of $1.25. The company has announced that it has established a path forward with the FDA for its pain therapy new drug application for the immediate release (IR) version of its pain drug MoxDuo. This follows the company's receipt of a Complete Response Letter from the FDA in August 2011.

What was supposed to be a very straightforward drug commercialisation process has now become complicated. QRxPharma combined two existing opioid drugs, morphine and oxycodone, and showed there were additional benefits (in crude terms that one plus one equals three not two). This is because the two drugs act at different opioid receptors and the combination therapy delivers a synergistic pain treatment outcome.

Under the FDA's combination rule, in combining two drugs, the company was not required to show better pain control or safety, just that the combination of the two drugs was no worse that taking either of the drugs morphine or oxycodone alone.

QRxPharma has now supplied the FDA with additional data from Study 022, which appears to be the sticking point with the FDA. The FDA has since responded that it has no safety issues around any of the studies that were part of the company's original New Drug Application (NDA), which we understand did not include data from Study 022.

FDA to Hold Advisory Committee Meeting

What the FDA has now requested is that, following a resubmission of the company's new drug application (NDA), the FDA will hold an Advisory Committee meeting comprising of a panel of experts in the field, to help assess the company's NDA. The FDA has also asked the company to provide a more extensive analysis of Study 022 in its NDA re-submission.

QrxPharma expects to complete its re-submission by the end of March. The FDA will then give its decision within six months after the re-filing.

Precedent Being Set

One of the reasons the approval process has become complicated for QRxPharma is because the company is setting a precedent, whereby the combination rule is being applied for the first time to two drugs within the same drug class.

QRxPharma is also caught in what has become a political issue, where safer and more abuse-resistant drugs are being demanded in the US. QRxPharma argues that its combina-

Cont'd on page 5

In a break with our standard approach to analysis on biotech investing, below readers will find discussion and comment by Mark Pachacz, a co-founder of Bioshares (and now Research Principal, following some recent role changes), on his experience with Somnomed's dental appliances, products designed to aid in the treatment of sleep apnea and snoring. It is a very personal story but one we believe offers some real and useful insights into the Somnodent devices and the prospects for the product and the company and hence investors.

Road Testing the Somnodent G2

by Mark Pachacz, Research Principal, Bioshares

After a group holiday in March 2012, I was one of two culprits singled out for keeping the group awake during the night. The issue was my excessive snoring. I was told that it was not just my snoring, but there were also concerns that I may not last out the holiday because I seemed to stop breathing fairly regularly as well.

This didn't really surprise me as they were not the first to draw attention to my poor sleeping. My wife has often drawn attention to my sleeping issue, although a little less politely over the years with a forceful nudge with the elbow during the night and an order to roll onto my side, which sometimes works and sometimes doesn't.

After first starting research on Resmed at *Bioshares* 14 years ago, I undertook my first sleep test and was diagnosed with mild to moderate sleep apnea. My sleep physician took one look down my throat and commented that I was "born to snore"! I considered the Resmed CPAP device but decided I wasn't ready to go to sleep wearing a mask each night.

Since covering Somnomed, I had been considering trialing a Somnomed device. The main obstacle was that I would have to undergo a new sleep study before I could be prescribed a Somnomed mandibular advancement splint (the Somnomed devices work by moving the lower jaw forward, thereby helping to keep the airways open during sleep). What finally convinced me to trial the Somnomed device was input from not just one person but from a group of people who highlighted that my sleeping was unusual and very likely unhealthy, to me and them!

Obstacles to Therapy 1

One of the main obstacles in getting access to a Somnomed device in Australia is that it needs to be prescribed by a sleep specialist. The cost was not really an issue, with the full cost being $1750 (for the device and fitting by a dentist) although is probably closer to $2500 once sleep studies and specialist costs are taken into account.

However it's a convoluted process to gain access to the device. To get my first Somnomed device (the Somnodent Flex) involved the following medical visits:

1. Visit to GP for a referral to the sleep specialist
2. Meeting with the sleep specialist
3. Undergo sleep study
4. 2nd meeting with sleep specialist to discuss sleep study results
5. Visit to dentist to get mould prepared
6. 2nd visit to dentist to have device fitted
7. Undergo x-ray of jaw to monitor for any potential jaw movements down the track
8. 3rd visit to dentist to remake mould following unsuccessful first attempt
9. Follow-up visit (4th visit) to dentist to adjust device settings

So it's at least eight medical appointments if all goes well which more than anything is time consuming. (In the US, Somnomed is targeting the two million people who have already been diagnosed with sleep apnea, which would shorten this process.)

Obstacle to Therapy 2

The second obstacle to therapy is the sleep physician. After confirming that I had moderate sleep apnea, I was advised of the following choices in this order (1) Surgery (2) a CPAP device, which is considered the gold standard device (3) or an oral appliance device such as the Somnomed devices.

Surgery however has a poor chance of success. And it was definitely out of the question after talking with someone had been through surgery, found it incredibly painful and ineffective, then finding success with an oral appliance device.

I informed the physician that I did not want to wear a mask to bed and that I wanted to try an oral appliance device, specifically a Somnomed device. However I was advised to try a CPAP system by the specialist, which I was told is the gold standard. The issue with oral appliances is that the long term impact on jaw alignment is unknown I was told, and there is a lack of efficacy data. After standing my ground I received the go ahead for a Somnomed device.

Obstacle to Therapy 3

The third obstacle to therapy is getting used to the Somnodent device. The recommendations are that it takes up to four weeks to adjust to wearing the device to bed.

My experience was different. I found adjustment to the device very difficult. My experience was complicated by having a device that was very tight, too tight. Waking in the morning my teeth would be sore for 30-40 minutes, with some ongoing jaw tension for a similar period. But I was determined to get used to the device. It took around two months until I became comfortable wearing the Somnodent Flex, even though the device was still very tight, having been told by my dentist that the device should be tight.

Cont'd over

Outcomes

So why consider getting fitted with a device that will cost you around $2500, will take at least eight medical visits, take up to two months to adjust to, and leaves you with sore teeth every morning?

Firstly, the Somnomed devices if correctly fitted should not leave you with sore teeth (see G2 assessment below). Minor adjustments can be made to correct the fitting and make the device comfortable.

Secondly, if a device is fitted well, then to become comfortable wearing the device should not take two months. And once you are comfortable with wearing a mandibular advancement splint such as the Somnodent, it then becomes a normal part of your sleep.

On the price, given that a crown on your tooth costs around $1800, the device cost is very reasonable, particularly given the life changing health benefits from wearing such a device.

The overwhelming reason why using a Somnodent device is worthwhile is because of the multiple benefits that it provides to a person who lives with poor sleep without being overly obtrusive.

Outcome 1

My experience has been that the Somnodent device is incredibly effective in stopping snoring. I have gone from being a heavy snorer to a non-snorer on most nights. When I don't wear the device and my partner alerts me to my snoring, I simply put the device in and my snoring stops immediately.

Outcome 2

The second major outcome is a noticeable change in energy levels. I would previously wake feeling physically tired, unable to function properly until my first coffee had taken effect. Each summer I start early morning training for a swimming event in February. This summer I have noticed that waking up in the morning to exercise is distinctly easier than in previous years. Hopefully this translates to a better time in this year's 'Pier to Perignon' swim event!

Outcome 3

The effect on cognition from better sleep is an interesting although subtle change. Whilst I experienced no noticeable change on concentration or memory, there appears to be a clear improvement in the efficiency of coordinating multiple tasks during the day.

I've also found that wearing the device facilitates more efficient sleep which allows better functioning on less sleep (great if you have an early morning business meeting interstate the next day or if you have a late night out).

Outcome 4

Perhaps the most profound impact has been on my heart function. I have always had an irregular heart beat. Two years ago I checked myself into the local hospital and was diagnosed with atrial fibrillation, although told the condition was not serious at this stage. Since wearing the Somnodent device, my heart rhythm has remarkably become perfectly normal, not skipping one beat. Perhaps it's not that remarkable that when the strain as a result of poor sleep is taken off the heart that the heart function starts to improve.

After wearing the device for nine months, there has been no negative impact on the jaw alignment or on teeth as a result of wearing the device.

Somnodent G2 Review

Somnomed has had three iterations of its devices. The first was the Somnodent Classic, followed by the Somnodent Flex, and the third being the Somnodent G2. The company also sells a Somnosnore product, which only comes in a fixed position, although sales of these are low. The Somnodent G2 has recently been released into major markets. The company continues to sell all three versions of the Somnodent devices.

Following discussion with Somnomed management about my experiences with the Somnnodent Flex, I was offered to trial the Somnodent G2 device, which I very quickly accepted.

The Somnodent devices consist of two separate solid mouth guards that fit over the teeth. The lower guard has a fin on either side pointing up, which stops the lower guard from sliding backwards past a certain point, with the fins resting against a protruding part of the top guard.

The G2 is a little different to the Somnodent Flex. The Somnodent Flex has a metal screw mechanism within the device to adjust the position of the lower jaw. The G2 has no metal parts, with the positioning of the lower mouth guard varied by interchangeable plastic parts. The G2 is also 20% smaller than the Somnodent Flex.

Assessment

Whilst a 20% reduction in device size may not seem significant, it makes a marked, immediate difference to the comfort of the device. This is a major improvement to the device. Compliance is an issue with all sleep treatment devices. For years Resmed has worked on improving the comfort of its masks for its CPAP devices. The smaller size of the G2 also makes it easier to close the mouth.

The mechanisms for adjusting the bottom jaw position work well for both the Flex and the G2. The G2 system should have a lower cost of manufacture being all plastic parts. The numbering and lettering system with the interchangeable plastic parts on the G2 do make it easier to record the settings of the device. The only down side is that plastic fittings protrude slightly more on the G2 than the Flex although the difference is marginally noticeable only. The top plastic fitting could also be more rounded, although it can be easily filed down.

The other noticeable difference is that the G2 does not allow any lateral movement, as the fins are completely vertical. On the Flex the fins are angled just slightly to allow some lateral movement. The consequence is that there is less movement possible with the G2, which takes the user a little time to adjust to after using the Flex.

Cont'd on page 5

Mesoblast Releases Interim Data from Phase II Lumbar Spinal Fusion Trial

Mesoblast (MSB: $5.93) has released interim data from a Phase II trial (SF003) of its mesenchymal precursor stem cell (MPC) product, termed Neofuse, in patients requiring lumbar spinal fusion.

Spinal fusion is method to treat patients whose spinal discs have degenerated beyond repair and fusion with an adjacent vertebra is a means to eliminate major chronic pain.

The most common procedure currently applied is to generate fusion with a bone graft. However, bone grafts are painful, with the risk of infection and blood loss being compounding issues.

The Phase II trial enrolled 24 patients and is designed to follow patients for 36 months. Eight patients received 25 million MPCs, another eight received 75 million MPCs and the control group was treated with bone autograft.

Interim results at 12 months showed that fusion was achieved in 85.7% of the 25 million MPC group, 62.5% in the 75 million MPC group and in 75% of the standard of care group.

Neofuse has been shown to be comparable to bone autograft as a method to effect spinal fusion, to deliver similar decreases in pain and also substantially produce less blood loss during the surgical procedure.

The results are welcome news for Mesoblast primarily because they give a positive safety signal for Neofuse and secondly because there is now some early evidence of the potential competitive advantage of the product in conditions in which treatment options are limited.

Mesoblast has now fully recruited the 100 patients in its back pain trial (DR001) and expects to release results in mid-2013.

Mesoblast' bone franchise is an unpartnered program and recent postive as well and prospective results will pave the way for a partnering event potentially later in 2013.

Mesoblast is capitalised at $1.7 billion.

Bioshares recommendation: **Speculative Hold Class A**

Current and Completed Trials of Neofuse

Mesoblast Trial ID [NCT ID]	Phase	Disease or Medical Condition	Trial Start	Trial End	Indication	Duration of Study	Blinding Status	Total Planned Patient Enrolment	Study Endpoints	Secondary Endpoints
MSB-SF003 [NCT00996073]	Phase II	Degenerative disc disease (DDD), Degenerative spondylolisthesis, Spinal stenosis	2009 Q3	2014 Q3	Subjects with a diagnosis of DDD in 1 or 2 adjacent vertebral levels between L1 and S1.	36 months	Single Blind	24	Safety of NeoFuse plus carrier	Fusion success with NeoFuse plus carrier
MSB-DR001 [NCT01290367]	Phase II	DDD	2011 Q3	2015 Q3	Subjects with chronic discogenic lumbar back pain	36 months	Double Blind	100	Safety of MPCs plus carrier	To evaluate the change of treated lumbar intervertebral discs using MRI at 6 months post injection of MPCs. To evaluate the effectiveness of MPCs in reducing chronic lumbar back pain
NeoFuse / MSF0106 [NCT00549913]	Phase Ib/IIa	DDD, Degenerative spondylolisthesis, Spinal stenosis	2007 Q4	2012 Q4	Degenerative disc disease, Degenerative spondylolisthesis, Spinal stenosis	36 months	Prospective, single center, randomized, open-label controlled trial.	40	Safety of NeoFuse combined with MasterGraft Resorbable Ceramic Granules as a carrier	To evaluate overall fusion success of the use of NeoFuse plus carrier. To provide preliminary data to support dose selection
Note: Three year follow up was completed for this study (MSF0106) in 2012										
NeoFuse / MSB-CF001 [NTC01106417]	Phase II	Cervical DDD, Degenerative spondylolisthesis, Spinal stenosis	2010 Q2	2014 Q2	Subjects Undergoing Multi-Level Anterior Cervical Discectomy and Fusion With Anterior Cervical Plate Fixation	24 months	Single Blind	12	Safety of NeoFuse (time frame 2 yrs)	Fusion success with NeoFuse (time frame 1 yr)
NeoFuse / MSB-CF002 [NCT01097486]	Phase II	Cervical DDD, Degenerative Spondylolisthesis, Spinal stenosis	2010 Q2	2014 Q2	Subjects Undergoing Multi-Level Anterior Cervical Discectomy and Fusion With Anterior Cervical Plate Fixation	24 months	Single Blind	24	Safety of NeoFuse (time frame 2 yrs)	Fusion success with NeoFuse (time frame 1 yr)

Bioshares Model Portfolio (18 January 2013)

Company	Price (current)	Price added to portfolio	Date added
Psivida	$1.30	$1.550	November 2012
Benitec	$0.015	$0.016	November 2012
Nanosonics	$0.520	$0.495	June 2012
Osprey Medical	$0.58	$0.40	April 2012
QRxPharma	$0.95	$1.66	October 2011
Somnomed	$1.05	$0.94	January 2011
Cogstate	$0.325	$0.13	November 2007
Clinuvel Pharmaceuticals	$2.25	$6.60	September 2007
Pharmaxis	$1.24	$3.15	August 2007
Universal Biosensors	$0.85	$1.23	June 2007
Alchemia	$0.345	$0.67	May 2004

Portfolio Changes – 18 January 2013

IN:
No changes

OUT:
No changes

– QRxPharma cont'd from page 1

tion therapy is safer because it does not contain paracetamol like the drug Vicodin (excessive paracetamol use can lead to liver failure) and the company has shown that its drug causes less respiratory depression (in Study 022).

The market for pain drugs is very large, being worth billions of dollars a year because pain drugs are widely prescribed. The flip side to that is that in getting a pain therapeutic approved, regulators will be more cautious when assessing these drugs. Hence the reassessment of MoxDuo by the FDA and the request now that a specialist panel review the medical data.

That the FDA has requested more extensive analysis on Study 022 in the company's re-submission, suggests that this study, which looked at changes in oxygen saturation levels in the blood, is an area of keen interest by the FDA. QRxPharma has previously stated that in this study, the more severe drops in oxygen levels in the blood came from the groups that were not taking the MoxDuo combination therapy. The FDA has not requested further trials be conducted.

QRxPharma will wait until the FDA Advisory Committee is held before it commits to its Phase II controlled release study. The company has sufficient funds to the end of 2013. If it gets the green light from the FDA, the company expects to launch the drug, through its partner Actavis Group, either later in the third quarter or in the fourth quarter of this year. QRxPharma will also be filing for regulatory approval this year in Australia, Canada and Europe.

Summary

QRxPharma now has clarity for progressing MoxDuo IR in terms of a pathway and timing. However, the addition of a new hurdle in the form of a review panel introduces another regulatory risk factor for the drug. It is not a fait accompli that the drug will be endorsed and approved according to the pathway and timelines now set before investors.

QRxPharma is capitalised at $135 million.

Bioshares recommendation: **Speculative Hold Class A**

– Road Testing the SomnodentG2 cont'd

Overall View

It took around two weeks to become completely comfortable with wearing the G2 after using the Somnodent Flex device. The improvement in size and comfort is significant. And the better fitting has resulted in no soreness in the teeth or jaw.

How the Somnomed Systems Could be Improved

With the Somnodent G2 having reached a level where comfort and function is excellent, future improvements in the Somnodent systems could come not from changes in the device, but perhaps in focusing on delivering consistency of fitting, which could be achieved by regular and continued education of fitting dentists. Fitted well, the Somnodent G2 is very comfortable and should take less time to adjust to wearing during than earlier versions. This should translate into better compliance.

Summary

Sleep is a crucial part of our lives. Getting good sleep should become a health priority. There are a raft of health issues now recognised as attributable to poor sleep and the strain that poor sleep places on our bodies. This includes heart disease, stroke, diabetes and high blood pressure. Preventative healthcare should become a priority for health management authorities around the world.

As Resmed founder Peter Farrell correctly puts it, governments focus on providing a 'sickcare' system not a healthcare system. Sleep therapy products such as those produced by Somnomed allow people with poor sleep to live longer, more functional and healthier lives. Sleep medicine is one of the biggest preventative medicines out there.

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A complimentary device and fitting of the Somnodent G2 was provided by Somnomed.

The author owns shares in Somnomed.

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

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