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In this edition...
Somnomed has completed a restructuring program in the US which should see sales growth return in that region. Of greater interest for readers are the results of a study done in Sydney (the global home of sleep medicine!) which compared the Somnodent oral device to Resmed's CPAP device, in a cross-over trial. CPAP therapy was better at reducing sleep apnea events but patients preferred the Somnodent device and achieved greater compliance. The data support the argument that the global sleep apnea market is in need of and will welcome a range of effective treatments.
After Prana Biotech, Bionomics is another company which is likely to benefit from the FDA's new guidance for developing drugs to treat Alzheimer's Disease.
Companies Covered: BNO, OBJ, 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 - May '13)	3.1%
Year 13 (May '13 - Current)	2.9%
Cumulative Gain	**266%**
Av. annual gain (12 yrs)	**16.6%**

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Somnomed – US Market Back on Track as Somnodent Shows Similar Health Outcome to CPAP Gold Standard

Terms
AHI = Apnea Hypopnea Index, or numbers of apneas per hour
MAD = Mandibular Advancement Splints (includes devices as those made by Somnomed) which advances the jaw to prevent airway closure during sleep.
Somnodent = One of the MADs sold by Somnomed
MATRx = Titration system used by Somnomed to select the settings for the Somnodent devices
DentiTrac = Tracking chip that can be incorporated into the Somnomed device to monitor compliance
CPAP = Continuous positive airway pressure; the CPAP device invented by Resmed, the gold standard in the treatment of obstructive sleep apnea
Apnea = Closure of airway during sleep

Somnomed (SOM: $0.92) announced this week that its transition issues in the US have been largely resolved and that its US business has turned the corner. Moreover, a paper published in April comparing Somnomed's Somnodent device with the gold standard CPAP system also delivers some favourable results for Somnomed. These two events set a positive short and medium term outlook for this stock.

In April this year, Somnomed announced that US sales were lagging because of restructuring changes that were taking place in its US business. Changing market conditions in the US, presumably new competition from Resmed which entered the market last year, meant the company needed to restructure its dental sales team and to introduce a medical sales team that would be marketing the Somnomed devices to sleep physicians.

By our calculations, sales in the March quarter in the US were lower than the December quarter. This was in contrast to the other side of the Atlantic, where European unit sales increased by 35% over the previous corresponding quarter, with the three European

acquisitions completed in 2012 delivering on increased unit volumes.

The company has made significant staff additions to its US management team, including the recent addition of a Chief Medical Officer, a new (US territory) President, a new VP of Dental, a new VP of Managed Care and a new VP of Sales and Marketing.

The company will provide detailed information on sales volumes for the June quarter next month. Our expectations are that the turnaround in the US will have a small impact on June quarter unit sales with a more pronounced impact in the September quarter.

Conference Presentations

At two conferences held in Baltimore this week, one for dentists (between 600-800 delegates) and one a medical sleep conference for doctors (around 5,000 delegates), Somnomed made a number of presentations. Its new CMO addressed over 100 sleep physicians. The company held an awards dinner for 150 dentists, with awards given to the leading Somnodent-fitting dentists. The inventor of the MATRx titration system that is used to titrate settings for the Somnomed devices gave a presentation.

The CEO of Braebon, which developed the DentiTrac system, also presented. Somnomed is a global distributor for this product. The DentiTrac system can be incorporated into the Somnomed devices to monitor compliance. FDA approval for this system has just been received.

The relevance of the above is that Somnomed is now positioned to compete with the CPAP systems, which it has not been able to do so previously on a level playing field.

Somnomed now has a medical sales team and a CMO that can help educate physicians about its Somnomed products. It has a way to set the right position (titration) of its Somnodent oral splints. It also has a tracking system that can allow it to monitor compliance, the same as the CPAP systems, which some groups such as insurers and trucking bodies, require. This last point is a big factor (in ensuring payment) according to Somnomed CFO Neil Verdal-Austin.

Somnomed is seeking to compete across a number of markets, and tiers within markets, in the sleep medicine product area. It has also just received approval for a mid-priced product, called the Somnodent Herbst. The Herbst is a generic style oral splint device. Somnomed has added its own flex material to the device to make it more comfortable.

Head-to-head Clinical Trial With CPAP

In April the results of a clinical study were published, which compared Resmed's CPAP (continuous positive airway pressure) with Somnomed's mandibular advancement splint. Whilst there have been other trials comparing the two systems, what was important about this trial was that it was a reasonable size, involving 126 patients, and that it was very well structured.

The trial design was such that each patient was assessed with both the CPAP and the Somnodent splint. Importantly, there was a four to six week acclimatisation period on each device before each patient was assessed; each patient had a two week wash out period in the middle of the trial, and acclimatised for another four to six weeks on the alternate system.

It should be also be noted that the trial involved a good cross section of patients, with 18% having mild sleep apnea (Apnea Hypopnea Index = 13), 50% having moderate sleep apnea (AHI=32) and 32% having severe sleep apnea (AHI=42).

The trial was conducted over three years at one clinical site in Sydney. It was funded by an Australian Government grant. Somnomed and ResMed donated their respective devices for use in the trial. Somnomed contributed $60,000 of funding to the trial. One aspect that could have been improved in the trial design was that it could have been a multi-centre trial.

Trial Results

AHI

The key measure in this trial is by how much the devices reduce the number of apneas each patient experiences during the night (AHI). The average baseline AHI for the patient population was 25.6. The CPAP device reduced this value to 4.5 apneas per hour, compared to 11.1 apneas with the Somnodent. While it's an excellent result with the CPAP, it's still a very good result with the Somnomed device.

Patient preference

Of the trial group, 51% indicated they preferred the Somnodent device, 23% preferred the CPAP, 21% liked both the same, and 5% preferred neither.

Compliance

There was a slightly higher compliance with the Somnodent (6.5 hours per night) compared to 5.2 hours per night with the CPAP system. The compliance was subjectively measured by the patients.

For the CPAP device, objective compliance was also measured in some patients (by the device) which showed patients wore the device for more than they thought at 5.1 hours compared to an actual figure of 4.7 hours. (Somnomed will now be able to measure compliance in future trials and in practise using the DentiTrac system which has just received FDA approval.)

Suitability

The CPAP system was able to be used for all patients. However, 20% of patients screened were deemed not suitable for the Somnodent device, presumably because of poor jaw alignment.

Cognitive function

The trial also included a driver simulator performance test on participants, presumably to measure changes in cognitive function. Both the CPAP and the Somnodent device showed equal improvements on this measure.

Comments

This is a very important study for Somnomed. In a well designed study, it shows that the Somnodent device has a substantial im-

pact on sleep apnea (reducing apneas by 56.6%), even though the CPAP performs better (82.4% reduction). These results are based on an intent to treat basis, so includes those patients who did not complete the study properly. This means the AHI values for both devices are likely even lower.

One issue historically with CPAP systems is their poor compliance. Taking the difference in compliance in this study between the two devices into account (the Somnodent device was worn for 1.3 hours longer or 25% longer), the more favourable compliance with the Somnodent system suggests a similar treatment outcome according to the paper. The authors of the paper challenge the practise that MAD treatment (mandibular advancement splints such as the Somnodent) is only recommended for those with mild to moderate obstructive sleep apnea or those who had failed CPAP therapy.

One comment on this issue made by the authors of the report was that what is strongly needed is a temporary, inexpensive device to work out on which patients the MAD devices will be effective, before a permanent device is constructed.

According to Verdal-Austin, Somnomed already has this capability with its MATRx titration system. This system is installed already in 40 sleep centres in the US, where patients can come in and be tested for suitability and for correct device settings during a sleep test. The MATRx system involves a plate placed into the mouth than can adjust the position of the jaw as the patient sleeps.

CPAP Compliance

The CPAP system remains the gold standard for the treatment of sleep apnea. The CPAP system achieved a complete response in around 75% of patients and a substantial response (more than 50% reduction in apneas of 50%) in around 90% of patients. The problem is that many people do not want to go to bed wearing a mask connected to a ventilator. Around two million people in the US have been diagnosed with sleep apnea but are not taking treatment.

Somnodent Performance

The latest study shows that the Somnodent mouth splint is also very effective in reducing sleep apneas. In this trial, 40% of patients on the Somnomed device achieved a complete response (to less than 5 apneas per hour) and around 66% (estimated from chart) achieving more than a 50% reduction in apneas. So in two out of three patients the Somnodent device has a pronounced effect. Verdal-Austin said that the company has seen cases where a person with over 80 apneas per hour has improved to less than 10 apneas per hour using a Somnomed device.

Arguably sleep therapy is not just about removing apneas altogether. It is about improving sleep in a way that is achievable in practise. That means compliance is just as important as efficacy.

Assuming that 20% of people are not suitable for a MAD system such as the Somnodent, and with the device delivering a pronounced positive effect on reducing sleep apneas in two thirds of patients, then around 53% of people with sleep apnea can be quite effectively treatment with a Somnodent device. This translates to around one million people in the US alone who are already diagnosed but not treated in the US for obstructive sleep apnea.

Summary

Over the last year Somnomed has equipped itself to tackle CPAP manufacturers head on with its alternative approach sleep apnea management. It has installed a medical sales and advisory team, it now has a compliance capability for its device, patients can be titrated in a sleep lab, just like with the CPAP devices, and there is now good clinical evidence of comparable health outcomes between the two approaches to treating sleep apnea.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

Bionomics' Brighter Future for BNC375

Bionomics (BNO:$0.35) is well advanced in developing BNC375 as a drug candidate potentially applicable to the treatment of a broad range of cognitive deficit disorders, including Alzheimer's Disease, Parkinson's Disease, Attention Deficit Hyperactive Disorder and Cognitive Dysfunction in Schizophrenia and mood and anxiety disorders.

BNC375 is an alpha 7 nicotinic acetylcholine receptor (alpha 7 nAChR) modulator discovered through Bionomics' internal drug discovery program. The compound is currently being progressed through pre-clinical studies.

As discussed in last week's edition of *Bioshares*, the FDA has, with newly issued guidance for the development of Alzheimer's Disease drugs, simplified the trials process by accepting a single composite primary endpoint score in pro dromal AD, signaled a willingness to support a conditional approval process, recognized the relevance of intervention in the early stages of the disease and recognized that certain clinical studies can be designed with cognition endpoints alone, and not with cognition endpoints *and* executive function endpoints, as valid.

The FDA's guidance changes the risk-reward profile for BNC375 as it also does for Prana Biotech's PBT2.

Although later stage drug development would still be best left for larger pharmaceutical companies with greater resources to take on, the change in benefit to companies such as Bionomics is that deal terms are likely to improve and the payoff off from progressing further down the development pathway has also increased.

In other words, where a company such as Bionomics might have previously considered out-licensing BNC375 as a pre-clinical asset, it is now in a much stronger position to seek funding to extend development through to the Phase IIb proof-of-concept stage.

How BNC375 Works

BNC375 is a positive allosteric modulator of alpha 7 nAChR. This means that is *does not* act in two of the main ways in which drugs are often designed to work, which is as an antagonist or as an agonist. An antagonist sits at a receptor, blocking other chemicals (ligands) from fitting into the site. It does not stimulate a downstream biochemical response. In contrast, an agonist does fit into the receptor site and initiates a downstream biochemical response.

In the case of BNC375, positive allosteric modulation means that it works to *amplify* the effect of acetylcholine, the chemical messenger which is what normally binds to the alpha7 nicotinic acetylcholine receptor.

Acetylcholine receptors have been recognized for many years as a suitable target for the treatment of Alzheimer's and other similar diseases. Several approved drugs including donepezil, rivastigmine and galantamine work as inhibitors of acetylcholine receptors. However, these drugs do not specifically target the alpha7 nAChR. *[Note, acetylcholine receptors are divided into two classes, muscarinic and nicotinic. There are five sub-types of muscarinic receptors and 17 sub-types of nicotinic receptors.]*

The rationale for targeting the alpha 7 nAChR in Alzheimer's Disease is to do with its being part of an anti-inflammation pathway and because the beta-amyloid protein has been found to bind with this receptor. (Many drug developers have been unsuccessful in targeting the excess deposition of beta-amyloid in the brain as a point of mechanistic intervention in Alzheimer's Disease.)

The rationale from Bionomics' point of view is that BNC375 can be expected to improve the functioning of existing alpha 7 receptors, which becomes important when they lose function or are lost due to beta-amyloid build up.

Competitor Programs

There are several other 'alpha 7' programs in development. The most advanced of these is being conducted by the privately held, VC-backed En Vivo Pharmaceuticals, with its EVP-6124 molecule.

En Vivo completed a Phase II study of EVP-6124 in 2012 in patients with mild-to-moderate AD and is now planning to enter the drug into Phase III development.

Phase II results were that EVP-6124 (at 2mg) delivered statistically significant positive effects on cognition (measured by ADAS Cog) and clinical function (measured by Clinical Dementia Rating Scale Sum of Boxes). The drug was also shown to be safe and well tolerated.

En Vivo also has two other trials planned or underway in people with schizophrenia.

AbbVie (the drug development company spun out of Abbott Laboratories) is developing ABT-126 for the treatment of Alzheimer's Disease and cognitive dysfunction in schizophrenia. The ABT-126 program includes two Phase II dosing studies in patients with schizophrenia, one enrolling 430 patients and the second with 150 patients who are smokers. In the larger trial the drug will be administered over 24 weeks while in the second, over 12 weeks.

AbbVie is also conducting two Phase II studies of ABT-126 in patients with mild-to-moderate AD, with the first enrolling 350 patients and the second 420 patients. Both studies will involve 24 week dosing.

Targacept is conducting a 456 patient Phase IIb study of TC-5619 for cognitive dysfunction in people with schizophrenia.

The molecule being developed by En Vivo Pharmaceuticals is a partial agonist whereas the molecules being developed by AbbVie and Targacept are full agonists of the alpha 7 receptor.

A likely problem for the full agonist group of molecules is that they will incur cardiovascular and gastro-intestinal toxicities because of the potential for their mode of action to generate excess calcium influx (into cells) through the receptor's ion channel structure.

Where BNC375 may deliver a competitive advantage is that is has, according to the company, a wider therapeutic index (window). In

Bioshares Model Portfolio (7 June 2013)

Company	Price (current)	Price added to portfolio	Date added
Atcor Medical	$0.070	$0.082	May 2013
Circadian Technologies	$0.300	$0.270	March 2013
Tissue Therapies	$0.140	$0.255	March 2013
Allied Healthcare	$0.054	$0.026	February 2013
Psivida	$3.62	$1.550	November 2012
Benitec	$0.015	$0.016	November 2012
Nanosonics	$0.605	$0.495	June 2012
QRxPharma	$1.20	$1.66	October 2011
Somnomed	$0.92	$0.94	January 2011
Cogstate	$0.330	$0.13	November 2007
Clinuvel Pharmaceuticals	$1.85	$6.60	September 2007
Universal Biosensors	$0.65	$1.23	June 2007

Portfolio Changes – 14 June 2013

IN:
No changes

OUT:
No changes

– *Bionomics cont'd*

other words, this means it is likely to be a much safer or better tolerated drug. The drug appears to be effective at low nanomolar doses and matches the company's target product profile criteria for once a day dosing.

BNC375 has begun to take shape as a valuable, competitive asset for Bionomics. GMP manufacture and IND enabling studies are expected to be completed this half. However, much more value creation would take place in the clinic where both safety and efficacy are studied. There is now a clear option for Bionomics to consider making a greater investment in this molecule.

Cash and Funding Resources

Bionomics currently holds $24 million in cash, a position which was boosted by a rights issue which raised $16.4 million in April.

We expect the company's R&D spend for FY2013 to be in the order of $15 million. Additional future income for the company could come from the partnering of the company's Kv1.3 multiple sclerosis program, R&D tax refunds and milestone payments from the IW-2143 program with Ironwood Pharmaceuticals (with $5 million of $13 million received to date).

A challenge for the company will be to balance its commitments between its emerging cancer antibody program with its CNS programs, particularly BNC375.

Summary

Bionomics is in a relatively well funded position at present. However, the risk-reward profile of its various cancer drug assets are high-low, whereas its CNS assets (an area of expertise and source of competitive advantage) have shifted to the opposite: low-high. This state of affairs is not reflected in the share price. Investors would be better placed to wait until the stock is priced to properly reflect the risk-reward contribution that each sub asset makes to the stock price.

Bionomics is capitalised at $143 million.

Bioshares recommendation: **Sell**

OBJ Fundraising

Perth-based OBJ (OBJ: $0.011) recently completed a rights issue, which raised $0.7 million and an options issue which raised $81,000. The company has appointed Baker Young Stockbrokers to manage the placement of a shortfall of 188 million shares.

The purpose of the capital raising is for OBJ to further development of several of its own products. OBJ is commercialising a novel drug (or active ingredient) delivery technology that uses magnetic fields and microarrays.

OBJ's technology can be applied to alter the rate and depth of penetration of molecules across the skin. A potential advantage of the technology is that chemical penetration enhancers aren't used and which together with the core technology, can reduce the amount of active chemical required for a desired drug or cosmetic outcome, hence lowering the cost profile of a product.

The company has a number of collaborations in progress, including with GlaxoSmithKline for oral health and pharmaceuticals, with Proctor & Gamble for consumer products and with Coty Inc in the cosmetics area.

The company's internal program is focused on a pain patch product and a musculoskeletal product, the Bodyguard patch. The Bodyguard patch's purpose is to enhance the synovial fluid in joints. This fluid contains chondroitan sulphate, hyaluronic acid and glucosamine among others. The market for glucosamine supplements is well established and the Bodyguard product would compete in this market. However, OBJ intends to conduct trials to generate claims data and to develop and control manufacturing, ultimately leaving branding in the hands of sales partners.

Summary

While OBJ has an product development execution challenge in front, its desire to capture more value for investors is positive. The company is capitalised at $13.5 million and March 31, 2013 it retained cash of $2.7 million.

Bioshares recommendation: **Speculative Buy Class C**

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