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In this edition...
Invion is a stock with a "Watch This Space!!!" sticker pasted over it. Its lead drug candidate INV102 is a re-purposed beta blocker that has been used to treat more than 8 million people. So its safety profile is well understood. But where the stock gets interesting is because its CMO, Dr Mitchell Glass, uncovered a fascinating treatment possibility in the area of smoking cessation. Help smokers with a high motivation to give up by defeating the dreaded smokers cough, then you have might have a very valuable drug on your hands.
Readers with a liking for trend analyis may appreciate our tabulation of cash flow figures for Somnomed and Nanosonics on page 5. Its all about finding the sweet spot for getting set in a stock.
Companies Covered: IVX, NAN, PVA, 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)	-9.0%
Cumulative Gain	**214%**
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.

Invion – Three Phase II Shots at Goal

The basic concept behind one of Invion's (IVX: 5.5 cents) drug candidates is as follows: You take an existing drug that has been used by millions of patients. It is contraindicated for a particular sub-group of patients, such as those with asthma, because it causes broncho-constriction. But then you find that if you titrate those patients with asthma, but starting with a very small dose and gradually increasing that dose, then you may actually have a treatment for the underlying asthma condition. Does that sound far-fetched?

Well that is exactly what happened with this class of drugs for a completely separate indication. The class of drugs in both cases are beta blockers. Beta blockers are used to relax the heart muscles and arteries in people with hypertension, angina, heart arrhythmias and people who have experienced a heart attack– essentially anyone who has excessive stress placed on their cardiac and vascular systems. But beta blockers were contraindicated for those patients with congestive heart failure (CHF), because the last thing one would think to prescribe is a drug to relax the heart muscle when the muscle is weak in function already.

However, Mitchell Glass (Invion's Chief Medical Officer and EVP of R&D) and his team at SmithKline Beecham (now GlaxoSmithKline) found that if you titrated patients with congestive heart failure with initially a small dose of the beta blocker Carvedilol, then mortality could be reduced in people with all classes of CHF. That breakthrough moved Carvedilol from $40 million of sales in 1998 to peak sales of $1.5 billion in 2010.

Experienced Executives and Board

Mitchell Glass is a highly experienced drug developer. He has brought 50 drugs into clinical trials and was successful in gaining five new drug approvals with the FDA. When he found out what Invion was doing with its beta blocker, using a similar strategy to treat airway diseases, he sought involvement with Invion.

Invion has a strong board and management team. Its CEO, Dr William Garner, was formerly with Hoffmann LaRoche and then worked as a venture capitalist in New York. James Campbell (formerly at Chemgenex Pharmaceuticals) is currently an executive director. Other directors include Brett Heading. And former Chemgenex founder and CEO Greg Collier is involved but only as an investor in the company.

Smoking Cessation Trial – INV102

Invion has three Phase II trials either underway or due to commence shortly. Invion will shortly start a Phase II trial with the beta blocker nadolol, called INV102. This trial will recruit 120 patients who are trying to give up smoking.

This application of INV102 was actually brought to the company by Mitchell Glass. One of the issues with giving up smoking for the older, long-term smokers is the smoker's cough that is experienced for the first two weeks of cessation. There are chemicals in cigarettes which stop these bronchospasms, which is one of the reasons only about 30% of people who try actually stop smoking.

Cont'd on page 3

Registration for the 9th **Bioshares Biotech Summit** is now open.

Visit our website for full details: http://www.bioshares.com.au/queenstown2013.htm

We wish to welcome Canaccord Genuity for the first time as a Sponsor of the Summit, joining Nexia Australia for the second year in a row and the fifth year in a row, Piper Alderman.

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– Invion cont'd

It is thought that treatment with INV102, both before cessation of smoking and after, for a treatment period of 10-12 weeks, will deliver an improvement in success rates over placebo. It is believed that INV102 will restore the epithelium in the airways and help restore mucous clearance function. To emphasise the effect, the trial will only be enrolling people who have previously failed to stop smoking because of the excessive coughing experienced in the process. A successful outcome will be if the company can move the success rate from 30% to 40%-50%.

The trial is due to finish by the end of this year or in early 2014. The trial will cost around $2 million. To get the drug to the point of filing for approval will cost around $10 million. The company is seeking to partner the program before that point.

The price of the drug may be as low as $1,000 -$2,000 per treatment, but could be argued to provide healthcare cost savings of up to $75,000, so the price may be higher. There are 600-750,000 people who have tried but have failed to give up smoking each year because of the smoker's cough, so it's still a very large market even at the bottom end of that price range.

Asthma Trial – INV102

Earlier this year Invion commenced a Phase II trial of INV102 in 60 people with asthma. As discussed above, it had been shown that acute dosing of beta blockers causes broncho-constriction, which would compound the effects of asthma. But chronic dosing, titrated from a small dose, has been shown to provide protection in the airways from constriction due to airway challenges from allergens such as dust mites and pollen.

In a Phase IIa study over nine weeks in 10 patients with mild asthma, INV102 was shown to have a positive effect on airway hyper-responsiveness, similar to that achieved by corticosteroids. However there was also a 5% reduction in lung volume in patients as well (as measured by FEV1).

This study is funded by a US$4.4 million grant from the US National Institutes of Health. Patients will be treated for four months. The trial is expected to conclude in the first half of 2015.

Lupus Trial (Systemic Lupus Erythematosus) – INV103

Invion was formed last year through the merger of Inverseon (which brought in INV102) and CBio. CBio's core asset was Xtoll, which was trialed but failed in the treatment of rheumatoid arthritis. The drug has been trialed in 255 patients in nine clinical studies.

What came from these studies however was a drop in the cytokine IL-6 in patients taking a higher dose. IL-6 plays a pivotal role in Lupus and more of an associate role in rheumatoid arthritis. This is why the company is now progressing into a Phase II trial in lupus (SLE) (see *Bioshares* 490). That compound has been renamed INV-103.

Lupus is a vascular inflammatory disease. If the inflammation of the blood vessels can be blocked by inhibiting IL-6, then INV103 may have a significant impact on this disease the company believes.

Invion is planning to submit its IND to the FDA and start the Phase II trial this quarter. Data from the trial is expected by year's end or in early 2014.

Summary

Invion appeals on a number of levels to investors. Firstly, it has three programs going through major investment inflexion points, that being Phase II clinical development. The second is the high calibre of people involved with the company, particularly Mitchell Glass. The third is that the drug nadolol has already been used in over eight million people, so its safety profile is well known, as is INV103, which has been tested in 255 patients to date.

Invion is capitalised at $21 million. It had $3.4 million in cash at the end of last year.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

pSivida's Eye Drug Due for Launch in Europe this Quarter

pSivida's (PVA: $2.05) licensee, Alimera Sciences, earlier this month re-filed the eye drug Iluvien with the FDA for approval, which makes it the third attempt. Iluvien is a depot injection that provides a three year treatment for diabetic macular edema (DME). pSivida is entitled to around a 15% royalty from sales. It is also entitled to a US$25 million payment from Alimera if the product gets FDA approval.

Alimera received approval in Europe for the treatment of DME in patients with chronic DME. While rejected twice by the FDA because of an insufficient risk/benefit ratio, Alimera is hoping that benefit swings its way by focusing on those patients who have had DME for longer, the chronic disease patients, in its revised submission.

Alimera expects to launch the product in Germany and the UK this quarter. The only remaining hold up is that the company needs MHRA (Medicine and Health products Regulatory Agency) approval in the UK as it has increased the manufacturing batch sizes. In the UK, about 80% of private insurers will reimburse the product for £5,500 per implant. NICE (National Institute of Health and Clinical Excellence) in the UK has rejected that pricing of the product in the UK. Alimera has submitted a patient access scheme for the public market in the UK and is awaiting a decision from NICE. This decision will not impede launch into the private sector. The list price in Germany will be €7,975.

Launch in France is expected in the last quarter of this year and in Spain in the first half of next year.

Psivida is capitalised at US$52 million. It had $15.7 million at the end of December. Alimera Sciences is capitalised at US$88 million. It had $49.5 million cash at the end of last year.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

Bioshares Model Portfolio (19 April 2013)

Company	Price (current)	Price added to portfolio	Date added
Circadian Technologies	$0.260	$0.270	March 2013
Tissue Therapies	$0.140	$0.255	March 2013
Allied Healthcare	$0.028	$0.026	February 2013
Psivida	$2.05	$1.550	November 2012
Benitec	$0.014	$0.016	November 2012
Nanosonics	$0.440	$0.495	June 2012
QRxPharma	$1.10	$1.66	October 2011
Somnomed	$0.91	$0.94	January 2011
Cogstate	$0.370	$0.13	November 2007
Clinuvel Pharmaceuticals	$2.00	$6.60	September 2007
Universal Biosensors	$0.60	$1.23	June 2007

Portfolio Changes – 19 April 2013

IN:
No changes.

OUT:
No changes.

Tracking Operational Cash Flows at Somnomed and Nanosonics

We have prepared a table (see next page) in which quarterly net operational cash flows for Somnomed and Nanosonics are presented.

Tracking trends in net operational cash flows can assist investors looking to buy a stock ahead of its entry into profitability. Many companies become 'visible' to a wider group of investors when consistent and/or growing net profits are reported.

For companies such as Somnomed, which has grown sales on a value and volume basis, its low profits have masked its re- investment in the business from earnings that could have been otherwise used to grow NPAT.

Despite a listing that took place in 2004 and unit sales now in excess of 130,000 in total, Somnomed is still very much in an early establishment phase of marketing and selling its premium oral appliance therapies for sleep apnea, snoring and bruxism.

The breakthrough quarter for Somnomed for when it turned in a positive net operational cash result was the June quarter of FY2009. This was the year when unit sales increased by 178%. While not all subsequent quarters have been cash flow positive, the company has been profitable for the last three years.

Somnomed's growth rates have fallen off lately as market pressure in the US from low cost alternatives has appeared. The company is investing heavily in new management in the US in order to grow the business there.

Nanosonics' path to profitability may be about to emerge with that company posting its lowest net operational cash flow loss (-$0.57 million) since it listed in FY2007.

Nanosonics may run a string of low negative operational cash flows for several quarters to come. Such a trend will be helpful to investors seeking to time an entry into the stock before it posts a profit and increases in visibility to more investors.

Looking back on Somnomed's share price history it becomes evident that FY2009, the year in which Somnomed posted it first positive operational cash flow, was the best time to buy the stock, with the share price trading below 40 cents for most of the year. Strong growth in quarterly volume figures pushed Somnomed's share price the following year to the $1 mark.

Somnomed has excellent growth drivers. The market for sleep apnea therapies is very large and underserved. In the US, two million people are diagnosed with sleep apnea each year; of these 1.7 million are prescribed CPAP therapy. However, CPAP therapy has a large non-compliance rate which leaves a gap for alternatives.

Nanosonics also has excellent growth drivers based on the convenience of its Trophon unit and significant OH&S benefits to clinicians and technicians who work with ultrasound probes.

Comparisons

Nanosonics and Somnomed are both manufacturers and tracking performance based on unit sales or an installed base basis is a plus for investors. However, their markets, customers and pricing are different. Somnomed's Somnodent is, roughly speaking, a sub-$1,000 product whereas Nanosonics' Trophon EPR is a $12,000 unit (list price) that also elicits a consumables income stream.

What has been common to both are strong boards that have driven the business and which have been unafraid to change management (or boards) if performance has not been satisfactory.

On the funding front, Somnomed has been more reluctant to raise funds. Since listing, in 2004, Somnomed has conducted three funding rounds, raising a total of $20 million. Since listing in 2007, Nanosonics has also conducted three funding rounds, raising a total of $66 million.

A final point to note is that both companies may not ever need to post a series of growing profit results to generate considerable (capital) returns to investors. This is because they are both likely to become acquisition targets as and when they sustain top-line sales growth and build sizable market share for their respective products.

Bioshares recommendation: **NAN - Speculative Buy Class A ; SOM - Buy**

Bioshares

Tracking Operational Cash Flows at Somnomed and Nanosonics

	Somnomed (SOM: $0.91)		**Nanosonics (NAN: $0.45)**	
		FY2005		
	Narrative	NOCF ($M)	Narrative	NOCF ($M)
Q1	IPO -$12 M	-$0.96		
Q2		-$0.80		
Q3		-$0.69		
Q4		-$0.97		
	FY Profit/Loss ($M)	**-$3.27**		
	End of Year Cash $M)	$6.64		
		FY2006		
Q1		-$0.89		
Q2		-$0.88		
Q3		-$0.99		
Q4		-$1.09		
	FY Profit/Loss ($M)	**-$4.19**		
	End of Year Cash $M)	$2.31		
		FY2007		
Q1		-$1.18		
Q2	Rights Issue (u/w) $3.5 M	-$0.44		
Q3		-$0.47		
Q4	**Full Year Unit Sales : 3,503**	-$0.34	Q4 IPO - $27 M	-$1.1
	FY Profit/Loss ($M)	**-$3.27**	*FY Profit/Loss ($M)*	**-$5.7**
	End of Year Cash $M)	$3.21	*End of Year Cash $M)*	$31.9
		FY2008		
Q1	Appoints Barschow CEO; acquires 50% in Flex jv	-$0.89	Q1	-$2.7
Q2	Placement $3M and SPP $1.87	-$0.32	Q2 CEO Marshall steps down	-$0.6
Q3	FDA clears Flex material	-$0.61	Q3	-$1.8
Q4	**Full Year Unit Sales : 7,033; 101% pcp**	-$0.36	Q4 Trophon gains CE Mark	-$2.0
	FY Profit/Loss ($M)	**-$2.73**	*FY Profit/Loss ($M)*	**-$7.1**
	End of Year Cash $M)	$5.43	*End of Year Cash $M)*	$24.2
		FY2009		
Q1		-$0.44	Q1 TGA approves Trophon	-$1.8
Q2		-$0.52	Q2 First sales orders received from Europe, Australia	-$2.3
Q3		-$0.43	Q3	-$2.9
Q4	**Full Year Unit Sales : 12,544; 178% pcp**	$0.08	Q4 Trophon launched in EU	-$2.2
	FY Profit/Loss ($M)	**-$1.82**	*FY Profit/Loss ($M)*	**-$8.8**
	End of Year Cash $M)	$4.01	*End of Year Cash $M)*	$13.9
		FY2010		
Q1		-$0.16	Q1	-$1.8
Q2		-$0.09	Q2 Placement - $12 M	-$2.1
Q3		-$0.15	Q3 SPP - $3.6 M	-$2.1
Q4	**Full Year Unit Sales : 19,543; 56% pcp**	$0.87	Q4	-$1.8
	FY Profit/Loss ($M)	**$0.79**	*FY Profit/Loss ($M)*	**-$8.2**
	End of Year Cash $M)	$4.30	*End of Year Cash $M)*	$21.1
		FY2011		
Q1		-$0.77	Q1	-$2.1
Q2		$0.23	Q2	-$2.5
Q3	US Medicare reimburses oral appliance therapy	-$0.02	Q3 FDA clears Trophon	-$2.5
Q4	**Full Year Unit Sales : 25,119; 29% pcp**	$0.35	Q4 Signs on GE Healthcare; CEO Radford steps down	-$2.0
	FY Profit/Loss ($M)	**$0.74**	*FY Profit/Loss ($M)*	**-$11.2**
	End of Year Cash $M)	$3.95	*End of Year Cash $M)*	$12.4
		FY2012		
Q1	New board appointments: Ausburn and Scherini	-$0.35	Q1	-$2.1
Q2		-$0.37	Q2	-$0.7
Q3	Acquired Dutch distributor; FDA clears MATRX	$0.26	Q3	-$1.5
Q4	CEO Barschow steps down; FDA clears G2 model	$0.53	Q4 Placement - $15.5 M; Con Note - $7.5 M; SPP - $0.38 M	-$0.6
	Full Year Unit Sales : 30,864; 23% pcp		**FY Sales : $12.3 M; 447% pcp; inc. manufact. capacity 50%**	
	FY Profit/Loss ($M)	**$0.70**	*FY Profit/Loss ($M)*	**-$4.7**
	End of Year Cash $M)	$3.54	*End of Year Cash $M)*	$29.3
		FY2013		
Q1		$0.12	Q1	-$1.83
Q2	Acquired MAS Nordic and Orthosom (France)	-$0.01	Q2	-$1.85
Q3	Appoints Chief Medical Offficer; expands US management	-$0.58	Q3	-$0.57
	Q3 Year to Date Sales : 33,952			
	Total Funding to Date (inc. IPO) ($M)	$20	*Total Funding to Date (inc. IPO & Con Note) ($M)*	$66
	Number of Funding Events	3	*Number of Funding Events*	3
	Capitalisation ($M)	$39	*Capitalisation ($M)*	$118

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, Biota Holdings, 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