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Bioshares

14 March 2014
Edition 543

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

Companies covered: PVA, SRX

	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)	59.9%
Cumulative Gain	**470%**
Av. annual gain (13 yrs)	**19.9%**

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RA Capital Builds Position In pSiVida With US$7M Investment

Boston-based specialist life science investor RA Capital Management has made a US$7 million investment in pSivida (PVA: $4.85). The placement was made at US$4.07 per share, or approximately $4.54 per share. RA Capital has added to 1.7 million shares to its existing holding of 1.2 million shares. This would give RA Capital a 5.9% stake on completion of the placement. Other significant shareholders in pSivida are North Run Capital with 7.5% and Allan Gray with 8.5% (post the RA Capital placement). On completion of the raise, pSivida will have approximately 29 million shares outstanding and 5.3 million options and warrants.

A stated objective of the investment is to support the development of Tethadur, pSivida's silicon-based biodegradable drug delivery technology. The funds will also be used to support the clinical development of pSivida's uveitis product, Medidur, which is a product equivalent to Iluvien, which was licensed to Alimera Sciences and is available in the UK and Germany, where it is approved for the treatment of vision impairment associated with chronic diabetic macular edema where other therapies are ineffective.

RA Capital recently participated in Benitec Biopharma's $31.5 million capital raising, of which the first stage of $15.7 million has been completed. RA Captital has invested $7.5 million into Benitec, which amounted to a 7% stake at the time of the announcement.

In July 2013, pSivida raised US$10.8 million and in December 2013 entered into an at-the-market (ATM) program through which it can raise up to US$19.2 million. We estimate it has raised US$1.5 million through its ATM facility to date.

Commentary

The investment by RA Capital is worth taking note of for several reasons. The firm has at least 25 active investments across a diverse set of listed life science opportunities, which are valued at current market prices at close to US$875 million. Its most significant holding, currently worth US$120 million, is in Sangamo Biosciences, whose share price is up 150% from a year ago. RA Capital holds an 8.3% stake in Sangamo.

Cont'd over

Furthermore, according to pSiVida, RA Capital approached pSiVida, with pSiVida not currently actively seeking funding. However, in pSivida's view, the offer was too good to knock back.

According to pSivida, RA Capital's interest is in its Tethudur biosilicon technology. Although there are several other assets at play within the pSivida investment proposition, including the prospect of a US$25 million payment from Alimera when Iluvien receives FDA approval, Tethadur's promise is that it can deliver large molecules such as antibodies and proteins, as well as peptides into the eye for controlled release for the treatment of back of the eye diseases.

Currently, the highly successful protein/antibody group of drugs, which comprise Avastin, Lucentis and Elyea, for treating back of the eye diseases, must be injected. Elyea must be injected monthly for the first three months then every two months. Lucentis (a fragment of Avastin, the VEGF-A antibody) must be injected once a month. pSivida's Iluvien is designed to release its active drug, fluocinolone acetonide, for up to three years, so interest in a technology that can deliver antibodies and proteins in a controlled manner over a long period should be of interest to all players in the eye drugs market.

Medidur Phase III Trials

Medidur is technically equivalent to Iluvien but is being developed independently by pSivida for the treatment of the treatment of posterior uveitis. This condition qualifies as an orphan drug disease because less than 200,000 people suffer from the problem.

It delivers a lower dose the active drug than that delivered by Retisert, which was pSivida's second drug to receive FDA approval but for the treatment of posterior uveitis. Retisert is currently partnered with Bausch and Lomb. Medidur is arguably superior to Retisert because it is delivered by injection, whereas Retisert is surgically implanted following incision.

pSivida has initiated one Phase III posterior uveitis study of Medidur in 120 patients and has plans for a similar study, with enrolment across both trials to total 300 patients. The endpoint of the trial will be recurrence of posterior uveitis at 12 months. Posterior uveitis is an inflammatory condition of the back or the eye which can cause sudden or gradual loss of vision.

The regulatory pathway for Medidur should be reasonably clear and possibly less onerous than for Iluvien, with pSivida in a position to take advantage lessons learned from Iluvien's passage through the FDA and the EMA. In particular, the side effects pertaining to intra-ocular pressure are better understand as an area of concern for the FDA and the EMA.

Summary

pSivida is emerging again as a stock of interest for investors, with the focus moving towards the company's capabilities in the biosilicon area. The company has the potential to become a takeover target in the medium to long term, with positive progress in its Tethudur program a factor set to motivate potential acquirers.

pSivida is capitalised at $133 million and holds an estimated US $19 million in cash following the placement by RA Capital.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

RA Capital Management

SEC Registered Shareholdings at December 31, 2013 (Active)

Investments (Companies)	Code	Technology, Product or Disease Focus	Market Value (US$ M)	Shares Held	Market Cap. (US$ M)	Approx. stake (%)
Sangamo Biosciences	SGMO	Gene regulation and modification	$120.4	5,227,272	$1,450	8%
Therapeuticsmd Inc	TXMD	Women's healthcare	$89.3	11,660,108	$1,110	8%
Achillion Pharmaceuticals	ACHN	Infectious diseases (HCV)	$77.0	23,366,007	$320	24%
Prothena Corp	PRTA	Diseases caused by protein misfolding or cell adhesion	$63.8	1,641,167	$852	7%
Ophthotech Corp	OPHT	Developing Fovista and Zimura for eye diseases	$59.3	1,600,455	$1,230	5%
Novavax Inc	NVAX	Recombinant protein nanoparticle vaccines	$58.1	10,811,888	$1,120	5%
Biocryst Pharmaceuticals	BCRX	Small mol drug development; various diseases	$48.3	4,347,456	$660	7%
Arrowhead Research	ARWR	RNAi-based therapeutics	$47.2	2,049,220	$914	5%
Xencor Inc	XNCR	Antibodies: cancer/allergy/ autoimmune diseases	$37.9	2,725,000	$409	9%
Sunesis Pharmaceuticals	SNSS	Small mol drug development - cancer	$34.1	4,869,261	$421	8%
Dynavax Technologies	DVAX	Infectious diseases; vaccines and TLR inhibitors	$32.5	17,883,954	$478	7%
Acadia Pharmaceuticals	ACAD	Small mol drug development - neurodegen. & CNS	$31.4	1,169,898	$2,460	1%
Derma Sciences	DSCI	Wound care	$26.3	1,994,876	$331	8%
Tesaro Inc	TSRO	Oncology (therapeutics and supportive care)	$25.7	700,000	$1,200	2%
PTC Therapeutics	PTCT	Small mol drug development - post-transcript. diseases	$23.3	752,438	$932	3%
Dyax Corp	DYAX	Hereditary angioedema (HAE) and PKM angioedemas	$15.0	1,619,697	$1,160	1%
Mirati Therapeutics	MRTX	Small mol drug development - cancer	$14.2	656,767	$287	5%
Bluebird Bio	BLUE	Gene therapy	$12.8	467,418	$662	2%
Enzo Biochem	ENZ	Integrated diagnostics & LS services	$9.6	2,268,653	$180	5%
Ocera Therapeutics*	OCRX	Acute and chronic liver disease	$8.8	661,696	$214	4%
Macrogenics Inc	MGNX	Antibodies: cancer/ autoimmune diseases	$7.0	199,398	$948	1%
Psivida Corp	PSDV	Drug delivery (eye diseases)	$5.2	1,187,608	$120	4%
MEI Pharma**	MEIP	Oncology (histone deacetylase inhibitor)	$4.4	408,333	$233	2%
Chelsea Therapeutics	CHTP	Small mol drug development - hypotension	$3.9	666,667	$460	1%
Market Value of Investments (excl BLT and most recent PVA placement)			**$855.6**		**Ave. Stake**	**6%**

* Formerly Renovia ** Formerly Marshall Edwards, the Novogen spin-out

Source: Nasdaq, Yahoo Finance, Companies

Sirtex Medical – Expert Panel Presentations on Sir-Spheres Coverage

Last month, Sirtex Medical (SRX: $15.78) held an expert panel discussion on its Sir-Spheres treatment for liver cancer. The speakers were Sirtex's CMO, Dr David Cade, Professor Valerie Vigraine from France, who is the Principal Investigator of the SARAH study, and Associate Professor Peter Gibbs, who has been an early adopter of the treatment and Principal Investigator of SIRFLOX study.

Summary of presentation by Professor Vigraine

Professor Vigraine is the Head of Radiology at the Hospital Beaujon in Paris, which is one of the leading hospitals in Europe for the treatment of liver cancer. Her talk focussed on the treatment of primary liver cancer (HCC).

HCC largely occurs as a result of cirrhosis of the liver, with 90% of people with HCC having had cirrhosis first for around 10 years. It is the third largest cause of mortality from cancer, with 780,000 cases a year, and about the same number of people dying from the cancer as well each year.

Treatment of primary liver cancer starts with tumour resection if that is possible, then options such as liver transplantation are explored, followed by localised chemotherapy (TACE) and then finally sorafenib. The drug sorafenib has been the standard of care for the treatment of advanced HCC since 2008. The SARAH study commenced in 2012 and is a head-to-head comparison between Sir-Spheres and the approved liver cancer drug sorafenib.

The SARAH study had recruited 67% of the 400 patients in the study at the end of last year. Full recruitment is expected at the start of 2015 with results expected one year later according to Professor Vigraine. Convincing results in her view would be an improvement in overall survival (over sorafenib).

The outcome of this trial will be to see if Sir-Spheres offers a beneficial or comparable outcome, with sorafenib having some disadvantages. These include the need for continuous treatment, it is expensive, and it has side effects which include fatigue, weight loss and diarrhea.

How Sir-Spheres will be used in the future depends on the results from current studies

Professor Vigraine provided an overview of clinical studies in HCC using Sir-Spheres. Nine studies have been completed and 20 are ongoing.

There may be other potential ways that Sir-Spheres could fit into the HCC treatment landscape other than just being used in place of sorafenib which are being explored in ongoing studies or have been explored, or being used as a salvage therapy, which is its current use. Sir-Spheres could be used to bridge patients whilst waiting for a liver transplant to become available, for which the wait is currently one year in France.

Sir-Spherescould potentially be used pre-surgery, it could used in place of TACE with fewer side effects, where TACE has failed or where patients are not suitable for TACE. A longer hospital stay is required for TACE where Sir-Spheres treatment can be managed in one day or overnight.

Sir-Spherescould be used instead of sorafenib (depending on results from the SARAH and SIRveNIB (64% complete) studies), or be used in conjunction with sorafenib (depending on results from the SORAMIC (53% complete) study).

According to Professor Vigraine, robust evidence was already presented in 2011 on the survival achieved with Sir-Spheres. In 325 patients, median survival of 12.8 months was achieved. (However, comparative data is now required.)

SARAH Study

The SARAH study is 1:1 randomised study recruiting 400 patients with over 300 already recruited. In a previous study (SHARP study) it was shown that sorafenib achieved a median overall survival of 10.7 months. Sir-Spheres compares favourable with a mean 15 month overall survival from pooled studies using Sir-Spheres.

Professor Vigraine said that France is a good place to run this study with no reimbursement for Sir-Spheres at the moment, even though the therapy is approved (making recruitment easier). About 100 patients were recruited in the second half of 2013.

Why conduct the SARAH and SIRveNIB studies?

Professor Vigraine said the SARAH study with Sir-Spheres is important because at the moment sorafenib provides only a 2.8 month survival benefit and the drug has the disadvantages listed above. It is also important to conduct a similar study in Asia (SIRveNIB) because in Asia liver cancer occurs more from Hepatitis B and in the west from Hepatitis C due to excessive alcohol consumption. Professor Vigraine said that different survival benefits can be expected from those two studies as was seen with sorafenib.

Subsequent to the presentation, Bayer this month announced that in a Phase III trial, sorafenib did not meet the primary endpoint of improving recurrence-free survival in patients with primary liver cancer who had no detectable disease after resection or local ablation. This result will make it more difficult for that drug to be used for the treatment of early stage disease.

The SARAH and SIRveNIB trials involve 800 patients. The results from these trials have the capacity to change the way in which advanced primary liver cancer is treated according to Professor Vigraine. The results will either confirm or refute the survival benefit of Sir-Spheres and the trials will also provide information of procedure costs and quality of life.

Summary of Presentation by Assoc. Professor Gibbs

Peter Gibbs treated his first patient with Sir-Spheres in 2002. That patient, a university professor, is still alive today. A less successful outcome occurred with the second patient he treated, due to side effects. 'The skill level in delivering Sir-Spheres is absolutely critical,' said Gibbs. If the spheres are not contained to the liver, the stomach ulcers that can occur are devastating according to Gibbs. 'It is a real learning curve'. Gibbs has now treated over 100 patients.

– Cont'd over

Bioshares Model Portfolio (14 March 2014)

Company	Price (current)	Price added to portfolio	Date added
Invion	$0.078	$0.089	February 14
QRxPharma	$0.870	$0.620	December 13
Impedimed	$0.240	$0.245	December 13
Analytica	$0.026	$0.025	December 13
Imugene	$0.012	$0.022	November 13
Oncosil Medical	$0.125	$0.155	September 13
IDT Australia	$0.300	$0.260	August 13
Viralytics	$0.360	$0.300	August 13
Tissue Therapies	$0.370	$0.255	March 2013
Somnomed	$1.69	$0.94	January 2011
Cogstate	$0.350	$0.13	November 2007
Universal Biosensors	$0.35	$1.23	June 2007

Portfolio Changes – 14 March 2014

IN:
No changes

Recommendations:

OUT:

No changes

Recommendations:

– Sirtext Medical cont'd

In Melbourne at present there is only one Interventional Radiologist who delivers the therapy, however the system will become more streamlined in the future according to Gibbs.

Results from previous clinical studies with Sir-Spheres for mCRC
There have been six previous clinical studies with Sir-spheres in patients with liver cancer than has spread from the colon. All have achieved a positive outcome. However, those studies have all been small, involving 38 patients each on average.

In the first randomised study with Sir-Spheres, comparing with Sir-Spheres plus chemotherapy in a first line treatment, it was found that Sir-Spheres delivered a 6.2 month improvement in time to disease progression. At three years, 17% of patients who received Sir-Spheres were alive, compared to only 6% of patients in the chemotherapy arm. That trial involved 70 patients. These results led to the approval of Sir-Spheres in Europe and the US.

In the second study comparing Sir-Spheres similarly with chemotherapy in 21 patients, an impressive 16.6 month benefit in survival was achieved with Sir-Spheres. This study was also in a first line treatment setting.

In the third randomised study of Sir-Spheres versus Sir-Spheres plus chemotherapy in 44 patients, only a 3.4 month improvement in survival was achieved. However in this trial, patients were on last line therapy.

For Gibbs to prescribe a new therapy, like other oncologists, they need data to support the use. However, patients also consult 'Dr Google' and request Sir-Sphere treatment in some cases. This data also needs to compare treatments such as Sir-Spheres with the current chemotherapy options, not what was used 10 years ago, which is no longer relevant.

What will it take to convince oncologists to use Sir-Spheres more widely?
Normally a 6-8 week improvement in disease control (progression free survival) and a survival benefit is what's required to convince oncologists to prescribe a new therapy over existing therapies. In the case of Sir-Spheres, it's more likely to be more than three months improvement in progression free survival (given the invasiveness of the therapy) to warrant first line use. If a benefit of 4-5 months was achieved in the studies underway then it would be very hard to ignore this therapy said Gibbs.

The gold standard in liver cancer treatment is to improve overall survival. If a survival benefit could be achieved in the SIRFLOX study (comparing Sir-Spheres plus chemotherapy and Avastin against chemo and Avastin) then use of Sir-Spheres for first-line use could be mandated.

Similarly if a benefit is seen increasing the rate of liver resection, then it could increase the use of Sir-Spheres in patients who are borderline in warranting liver resection stated Gibbs.

The SIRFLOX study completed recruitment in March last year. Results are anticipated to be presented in May/June 2015.

Sirtex Medical is capitalised at $885 million.

Bioshares recommendation: **Take Profits**

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

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