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

Companies covered: CGS, VHL

	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 - May '14)	26.6%
Year 14 (May '14 - current)	7.7%
Cumulative Gain	**385%**
Av. Annual gain (14 yrs)	**16.6%**

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A Turnaround Year for Cogstate on the Way

There are two aspects to the Cogstate (CGS: $0.24) investment proposition. The first is the bigger picture, the demographic time bomb which chairman Martyn Myer made reference to at this year's AGM from the aging population and the increasing level of dementia in the community that comes with that. Cogstate is positioning itself to play a key role in all aspects of the cognitive assessment, from drug trials of emerging drug candidates for Alzheimer's disease, to primary care testing of cognition and even at home testing through mobile phone apps.

The second aspect is a shorter term picture. With revenue being flat over the last three years with increasing costs, the company now is generating record levels of contracts which should be further supported by sales from new product launches, specifically, its Precision Recruitment service.

Short Term Stock Drivers

Over the last three years, revenue from the company's clinical trials business has been constant, at around $12 million a year. The level of new contracts signed (each contract can run for between one to three years) has been falling from $14 million in 2012 to $9 million in 2014. But with increasing costs, as a result of investments in new product development and new product offerings, this resulted in a net loss of $3.9 million in FY2014.

Over the last 12 months Cogstate has been investing in its rater training service offering, which sees the company coordinating the more standard pencil and paper type tests used in Alzheimer's disease drug trials. Late last year Cogstate also decided to build a product that will allow pharmaceutical companies better screen for patients being enrolled into Alzheimer's disease trials, which it calls Precision Recruitment.

These new product offerings failed to generate any significant revenue in FY2014 but will make a meaningful impact on the current year and beyond. In June Cogstate signed its first Precision Recruitment contract worth $1.8 million. In August the company signed a rater training contract worth $7.3 million. And then in September Cogstate was awarded its second Precision Recruitment contract. This second Precision Recruitment contract may be the most profitable contract, as Cogstate will be paid a success fee for each patient it screens who is successfully enrolled into the trial with confirmed early stage Alzheimer's disease. The first contract includes only a small success fee in addition to the announced contract value.

The overall result is that in the first four months of this financial year, Cogstate has signed $11.3 million worth of contracts with a further $4.8 million of contracts that have been awarded but need to be finalised. That will bring the total to $16.1 million of contracts signed this financial year.

Cont'd over

From a revenue perspective, Cogstate expects to generate revenue of $9.6 million from current contracts in this financial year, plus $2.4 million from contracts that have been awarded but not signed, bringing the total to $12 million. Cogstate also expects to receive revenue in the second half of this financial year from its second Precision Recruitment contracts.

The second contract, which is success based aside from a small upfront fee that has already been paid, has the potential to deliver a high revenue stream with a high margin. That contract is for a 1,500 patient Phase III Alzheimer's study with Cogstate to help recruit patients in countries representing 40% of total recruitment. All online recruitment will be streamed through Cogstate in those countries although there will also be recruitment through other channels in those countries.

Cogstate is bidding on more contracts for Precision Recruitment, including another Phase III Alzheimer's disease trial. There should also be more revenue generated from its ordinary course of business over the remaining eight months of this year. From the company's AGM last year to 30 June this year, the company signed $7.8 million of new contracts which realised revenue of $3.8 million last year. The company has also made the point that it has a higher level of proposals in place now than it did 12 months ago.

The company is expecting to make a loss in the first half of this year, which appears will be around $2.5 million. From the above, we estimate Cogstate revenue this year will be between $17- $20 million. Cogstate should deliver a breakeven result or slightly better, but noting that there are increased non-recurring costs in this financial year from the Axon Sports business, the sale of Axon Sports, and software development costs for Precision Recruitment.

Restructure to Help Top and Bottom Line

A significant cost for Cogstate has been funding the Axon Sports business. The sports training part of this business has been costing the company around $1.5 million a year. The company this week announced it had signed a letter of intent to sell the business by the end of the year. There will be no upfront payment although Cogstate will receive a percentage of future revenue for five years.

Cogstate has also appointed an experienced CRO manager Lammert Albers to run the clinical trials sales team in the US, who will start next month. Lammert will report directly to the CEO. His task will be to get more out of the existing market for the Cogstate products, including the rater training and the Cogstate cognition test. With the rater training unit within Cogstate (which includes around 15 staff) now reaching a critical mass, future contracts should deliver greater margins for that work. This appointment and the revamping of the sales team is an important change for the company.

The last year has seen increased costs around the development of the Precision Recruitment product. The main task here has been to move the Cogstate cognition test from a clinic-based test to an at-home test. This will allow patients to be screened at home for cognition for inclusion in Alzheimer's disease trials. This product offers Cogstate very good margins, if it can correctly work out which subjects seeking to enrol into trials actually have early stage disease. Within only 12 months from concept to product, Cogstate has secured two major contracts for this product, one worth at least $1.8 million (with some performance based fees) and the second being for a 1,500 person Alzheimer's disease study which is largely success fee driven.

Longer-term Stock Drivers

Cogstate is continuing to position itself at the forefront of cognition testing, particularly in the area of Alzheimer's disease. Its test is part of a long term Alzheimer's disease study in Australia. And in March this year its test was selected to be included in a long term Alzheimer's disease prevention study. In this study, 1,000 people with no signs of Alzheimer's disease but with high levels of amyloid in the brain will be prophylactically treated with Eli Lilly's drug candidate solanezumab.

The company continues to commercialise its Cognigram product, which is sold in Canada (now without Merck as a commercial partner) to allow GPs to test for early stage Alzheimer's disease. Cogstate's involvement in clinical studies in Alzheimer's disease drugs and its involvement in longitudinal studies has allowed it to develop the Cognigram product. Commercialisation of the Cognigram product has no doubt helped the company secure Precision Recruitment contracts.

The company has indicated that it has interest from pharmaceutical groups in commercializing the Cognigram test in the US. The interest stems from the direction of Alzheimer's disease drug research, which is focusing on treatments for early stage disease. When a disease changing drug does make it to market for Alzheimer's disease, there will need to be a test available that can accurately test patients for early stage disease on a larger scale that does not require brain imaging.

Cogstate is progressing plans to have its test approved for use by the FDA as a medical device.

Another future application for the company is to have its test available on smart phones, for mobile assessment of a person's cognitive health. It has been the development of the at home testing capability of the test for the Precision Recruitment product that reduces the development cost and time to bring such a product to market.

Summary

The surge in contracts signed in this financial year by Cogstate and the record level of contracted future revenue ($18 million plus $7.8 million in contracts awarded but not signed) will support strong sales for the company for the next two to three years. Revenue from Precision Recruitment provides considerable, high-margin upside for the company. A revamped sales team in the US is very timely. Longer-term blue sky exists from success in Cognigram in major markets as well as the potential for a mobile assessment product through smart phones. And the divestment of the Axon Sports business will reduce costs by $1.5 million a year.

Cont'd on page 5

Viralytics and the Next Wave of Cancer Immunotherapies

Cancer therapy, led by melanoma treatment, has been shaken up by the emergence of two groups of immunotherapies, being in the main monoclonal antibodies that target CTLA-4 and 'checkpoint targets' PD-1 and PD-L1.

CTLA-4 is shortened from cytotoxic T-lymphocycte antigen 4, PD-1 stands for programmed death 1 and PD-L1 stands for programmed death ligand 1.

The relevance of these new therapeutics for Viralytics' (VLA: $0.29) novel oncolytic virotherapy, CAVATAK, is the potential for even better treatment outcomes to take place when CAVATAK is combined with one of these promising new approaches. Already there are many combination trials underway of these new therapeutics, to see not only if additive benefits are possible, but if multiplicative benefits are achievable.

Selected CTLA-4, PD1, PD-L1 Monoclonal Antibody Drugs in Development

Company	Drug	Target	Status
Bristol Myers Squibb	Yervoy (ipilumumab)	CTLA-4	**USA approved 2011** for melanoma; in multiple combination trials
Bristol Myers Squibb	Opdivo (nivolumab)	PD-1	**Japan approved July 2014** for unresectable melanoma; in multiple combination trials; EU MAA validated; PDUFA March 30, 2015
Merck	Keytruda (pembrolizumab) (MK3475)	PD-1	**US approved Sept 5** for secondary treatment after yervoy failure
Pfizer	Tremelimumab	CTLA-4	Various combination Phase I and II trials; Phase III lung cancer
Roche	MPDL3280A (RG7446)	PD-L1	Combination trials: Phase I - lung cancer, melanoma; Phase II - renal cancer, melanoma. Has a **Breakthrough Therapy** designation for bladder cancer
Curetech	Pidilizumab (CT-011)	PD-1	Various combination Phase II trials
AstraZeneca	MEDI14736	PD-L1	Phase II

Sources

Adapted and abridged from Immuno-Oncology Combinations: A Review of Clinical Experience and Future Prospects Antonia SJ, et al; Clin Canc Res 23-10-2014

Company announcements

Performance to Date of these New Drugs

This new generation of cancer treatments dates from the approval of Yervoy (ipulimumab) (Bristol-Myers Squibb), a CTLA-4 inhibitor, in 2011.Yervoy was approved for the treatment of unresectable or metastatic melanoma however has a label which includes a Black Box warning for the risk of fatal immune-mediated adverse reactions, with warnings applying for immune-related enterocolitis, hepatitis, dermatitis, neuropathy and endocrinopathy.

Yervoy has been a breakthrough medicine for treating metastatic melanoma, generating 10 months median overall survival alone, compared to 10 months in combination with gp100 and 6 months for gp100 alone.

Opdivo, a PD-1 inhibitor, was approved earlier this year in Japan, with a US PDUFA date scheduled for March 2015. Bristol-Myers Squibb, the sponsor of Opdivo, recently released interim results from its CheckMate 037, 370 patient, Phase III trial, which is evaluating Opdivo against an investigator's choice of chemotherapy (ICC) in patients previously treated with Yervoy. Drugs used in the ICC arm were dacarbazine or carboplatin. Co-primary endpoints are overall response rate and overall survival.

The objective response rate in the Opdivo arm (in the first 120 of the 268 patients) was 32% versus 11% in the ICC arm (in the first 47 of the 102 patients) in patients with at least six months of follow up, with 95% of responses in the Opdivo arm still ongoing.

A Phase I study with Opdivo, published in the *New England Journal of Medicine* in June 2012, reported response rates of 18% for non-small cell lung cancer, 28% for melanoma patients and 27% for renal cell cancer. The surprise from this and a related study was the observation of the response rates in cancers other than melanoma, which had been characterized to date as a strongly immunological cancer. The implications for the PD-1 (and similar) classes of drugs is that they may have wide application.

A combination study of Opdivo and Yervoy, with 53 patients treated concurrently in patients with advanced melanoma, demonstrated a one year survival rate of 82%, and roughly 70% surviving to more than 30 months. Data for the trial led by Dr Jedd Wolchok was first published in the *New England Journal of Medicine* (July 2013), with this more recent survival date communicated to the authors of Immuno-Oncology Combinations: A Review of Clinical Experience and Future Prospects (Antonia SJ, et al; *Clin Canc Res* 23-10-2014).

Merck's PD-1 drug Keytruda demonstrated a 69% one year survival rate in advanced melanoma patients and an estimated 18 months survival rate of 62%. Curetech's PD-1 drug candidate pidilizumab demonstrated an 84% survival rate at 18 months in 72 patients with large B-cell lymphoma following autologous stem cell transplantation.

Implications for Viralytics' CAVATAK Therapy

The investigation of Viralytics' oncolytic virotherapy Cavatak in combination with a PD-1 inhibitor could result in an efficacious as well as more tolerable regime for treating various cancers.

Already, the data from Viralytics' single arm Phase II study in melanoma patients has shown a one year survival rate of 73% (from 33 out of 45 subjects) and an overall response rate of 28% (from 16 out of 57 patients). Most importantly, no grade 3 or 4 drug related adverse events have been reported. In contrast, the percentage of grade 3 or grade 4 drug related adverse events reported in the Wolchok study mentioned above (with Opdivo and Yervoy)

Cont'd over

was 72%. Toxicity is a considerable issue for immune-modulating therapies, as is even more clearly shown by Yervoy's Black Box label.

Viralytics is exploring additional studies in melanoma patients where CAVATAK is administered in combination with checkpoint inhibitors such as Opdivo, or Yervoy, or even with another class of small molecule drugs that have a similar immune-modulatory function (the BRAF/MEK inhibitors).

Recent Combination Drug Animal Studies

Animal studies conducted by Viralytics showed that CAVATAK, administered intra-lesionally and combined with an anti-PD1 drug, resulted in 75% (of animal subjects) being tumour free after 45 days, in contrast to 0% with CAVATAK alone and 0% of anti-PD1 alone being tumour free at 45 days.

While animal data should always be treated with circumspection, it is interesting to note that the combination of CAVATAK and an anti-CTLA-4 antibody achieved an estimated 45% survival out to ~78 days. However, a 100% survival effect persisted much longer in the combination group than any other treatment group in the study (to ~51 days); 100% survival persisted to ~43 days for CAVATAK alone and ~37 days for anti-CTLA-4 alone.

These data would appear to be supportive of clinical studies in human subjects in which CAVATAK is combined with anti-PD1 or anti CTLA-4 therapies.

Outlook

Viralytics' goal is to produce a package of data for CAVATAK which can build the case for a strong partnering outcome. Hence, the availability of interim results from its intravenous study (STORM) in 2015, along with survival data from the CALM study in Q1 2015 should set Viralytics up for a period of share price re-calibration in the first half 2015.

How the CTLA-4 and PD-4 Inhibitors Work: Taking the Foot off the Brake

Tumours grow and spread because they develop various means to evade surveillance and response by the body's immune system. Tumours can express, or shed, a protein called PD-L1 which can cause T-cells to halt their surveillance for cancer cells.

When the PD-L1 (the ligand, or circulating protein) binds to PD1 receptors on T-cells, which are a key component of the body's active immune response, the immune response is suppressed. By stopping PD-L1 from binding by blocking the PD1 binding site, or 'soaking up' the circulating PD-L1, then T-cells can remain active.

Yervoy (ipulimumab) acts in a similar way with its blocking of CTLA-4 binding to cell receptors CD80/86.

PD-1 and CTLA-4 are negative regulators of the immune system, which means they act as brakes on the immune system. So by releasing the brakes, the immune system can get back to the job of attacking cancer cells and tumours.

An even stronger partnering outcome might be achieved once clinical data emerges from some of the possible combination therapy trials which may take place.

Viralytics retained cash of $23.8 million at September 30, 2014. Viralytics is capitalised at $54 million.

Bioshares recommendation: **Speculative Buy Class B**

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Selected Recent Clinical R&D Deals for Immunotherapy Programs

Date	Company	Partner	Subject	Terms
October 23, 2014	Curetech	Medivation	World wide rights to pidilizumab - a PD1 inhibitor	US$5 M upfront; US$85 M in MSPs; tiered royalties from 4%-11%; includes manufacturing and supply agreement

Selected Recent Pre-clinical R&D Deals for Immunotherapy Programs

Date	Company	Partner	Subject	Terms
October 20, 2014	NewLink Genetics	Genentech (Roche)	NLG919, an IDO pathway inhibitor	US$150 M upfront; > US$1 B in MSPs; escalating double digit royalties; retains co-promotion rights
March 17, 2014	Five Prime	Bristol Myers Squibb	Discovery and development of therapies for two undisclosed immune checkpoint pathyway inhibitors	US$20 M upfront; research funding US$9.5 M; US$21 M for 5% of stock; up to US$300 M in MSPs; tiered mid single digit to low double digit royalties
March 13 ,2014	Anaptys	Tesaro	Development of mabs targeting TIM-3, LAG-3 and PD-1 (all checkpoint receptors)	US$17 M upfront: US$18 M for development milestones; US$90 M for certain US and ex US reg submissions; tiered single digit royalties
Feb 12, 2014	Aurigene (India)	Pierre Fabry (France)	World-wide rights to AUNP-12	Undisclosed upfront payments and milestone payments

Bioshares Model Portfolio (24 Oct 2014)

Company	Price (current)	Price added to portfolio	Date added
Actinogen	$0.038	$0.050	September 14
LBT Innovations	$0.115	$0.130	July 14
pSivida	$4.520	$3.800	May 14
Invion	$0.060	$0.089	February 14
Impedimed	$0.475	$0.245	December 13
Analytica	$0.032	$0.025	December 13
Oncosil Medical	$0.115	$0.155	September 13
IDT Australia	$0.205	$0.260	August 13
Viralytics	$0.290	$0.300	August 13
Tissue Therapies	$0.315	$0.255	March 2013
Somnomed	$2.52	$0.94	January 2011
Cogstate	$0.240	$0.13	November 2007

Please note that CGS was dropped from the above table in Bioshares 573 as a result of a cut and paste error

Portfolio Changes – 24 October 2014

IN:

No changes

OUT:

We have removed BLT, (placing a Speculative Hold Class A) pending improvements in clinical trial recruitment rates and IMU, (placing a Speculative Hold Class B), pending improved progress towards clinical trial initiation.

– Cogstate cont'd

Cogstate has made considerable investments in new products over the last two years. It has proven to be able to deliver rapid product development over this time with the Cognigram test, Precision Recruitment and its generic rater training offering.

It is placing itself in a central position in what chairman Martyn Myer referred to as a virtuous loop, which sees the company involved in the testing of new drugs for Alzheimer's disease (and other diseases) as well providing cognition assessment in the primary care market.

It is very timely to consider this stock, which is at an important turnaround point.

Cogstate had $5.4 million at the end of September and is capitalized at $24 million.

Bioshares recommendation: **Speculative Buy Class A**

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: Cogstate, Bionomics, Impedimed, QRxPharma, LBT Innovations, Tissue Therapies, Viralytics, Phylogica, pSivida, Benitec BioPharma, Admedus, Calzada, Invion, Imugene, Analytica, Circadian Technologies, Reproductive Health Science

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