ISSN 1443-850X

Companies covered: **CGS, IMU, RNO, 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)	-35.8%
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 - May '15)	23.0%
Year 15 (May '15 - May '16)	33.0%
Year 16 (May '16 - May '17)	16.8%
Year 17 (May '17 - May '18)	-7.1%
Year 18 (May '18 - May '19)	-2.3%
Year 19 (May '19 - Current)	73.2%
Cumulative Gain	1252%
Av. Annual gain (19 yrs)	19.0%

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Bioshares

11 November 2019
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Delivering independent investment research to investors on Australian biotech, pharma and healthcare companies

Imugene's Expanding Oncology Pipeline

By the end of next year, Imugene (IMU: $0.033) expects to have four clinical studies underway involving four distinct programs from its expanding group of cancer immuno-therapy technologies.

Trial 1: HER-Vaxx

The first program, with HER-Vaxx, completed a Phase I study in 14 patients with gastric cancer who were Her2 positive. This therapeutic intervention mimics the antibody drug Herceptin, which attaches to Her2 receptors on the surface of breast and gastric cancer cells. Of the 14 patients, an overall response was achieved in six patients (43%) including one complete response, and disease was controlled in 10 patients (71%). This trial took 13 months to fully recruit after the first treatment.

In the Phase II study, the first of 68 planned patients was recruited in March this year. Recruitment is expected to be completed by the end of next year. The highest dose (50ug) trialed in the Phase I study has been selected as the dose for the Phase II study. Imugene director and cancer researcher Axel Hoos said last week that the most important outcome from the Phase I study is that it was shown that the vaccine is functioning as designed, prompting the patients to generate their own Her2 antibodies. There were no safety or side effect issues with the therapy, and the optimal dose was elucidated for the Phase II study.

With the Her2 target validated with the monoclonal antibody drug Herceptin, the company is focused on validating a novel approach, which is to vaccinate patients, so that they can produce their own antibodies against Her2. Antibody production was held out to 260 days following a booster therapy in the first trial.

In practice, there may be benefits in combining both Herceptin with the HER-Vaxx, with the treatment response expected to vary. Hoos said that next year (at the end of the Phase II study) the company will have enough data to talk to pharmaceutical companies (to potentially secure a licensing deal).

Trial 2: PD1-Vaxx

In June last year, Imugene licensed a synergistic B-cell vaccine technology from the Ohio State University Wexner Medical Center and the Mayo Clinic, which had been developed by Professor Pravin Kaumaya. With that transaction came a more advanced checkpoint inhibitor B-cell vaccine to inhibit PD-1. That trial, with PD1-Vaxx, is expected to move into Phase I trials next year with the vaccine already manufactured.

The trial will recruit patients who have relapsed from PD-1 antibody drug therapy. Like HER-Vaxx, PD1-Vaxx will stimulate the (internal) production of PD-1 antibodies instead of a patient needing to receive an injection of monoclonal PD-1 antibodies. PD1-Vaxx is expected to bring into action multiple parts of the immune system, and as such, a different outcome can be expected to drug therapy. PD1-Vaxx could potentially be used as an initial treatment for cancer and also as a maintenance therapy. Hoos said that he believes that safety will be workable with this vaccine.

Continued over

Trial 3: Vaxinia

Pending shareholder approval this month of the acquisition of Vaxinia Pty Ltd, Imugene intends to start a Phase I study next year with a newly developed oncolytic virus (chimeric vaccinia poxvirus) by Professor Yuman Fong and his team at the City of Hope.

The virus candidate CF33 has been named Vaxinia. This trial will seek to recruit patients with different solid tumours. The virus will be delivered through IV or directly into the tumour.

Trial 4: CheckVacc

The fourth trial to run next year will be with CheckVacc, which combines CF33 with PD-L1 inhibition, and also hNIS (a reporter gene for Human Sodium Iodide Symporter, to enable imaging).

A Phase I study is expected to start next year in patients with metastatic, triple negative, breast cancer (TNBC). This follows the approval in March this year of the checkpoint inhibitor from Roche, Tecentriq, for the treatment of TNBC.

It also follows preclinical work conducted by Professor Fong's team which showed that at low doses of only 10^3 PFU (plaque forming units) and 10^4 PFU, TNBC tumours were shrunk in a mouse model. According to Professor Fong, the last generation of onco-lytic viruses (such as T-Vec) require doses to be as high as 10^6 or 10^7 to be effective oncolytic agents.

Checkpoint inhibitors have become the biggest breakthrough in cancer treatment in over 30 years. The leading checkpoint inhibi-tor, Keytruda from Merck, is currently generating sales of over US$12 billion a year, following initial approval in 2014. The drug is currently approved for the treatment of 15 different cancers, and there are currently seven different PD1 or PDL1 inhibitors on the market.

Summary

Imugene continues to build its asset base of high quality, and cutting edge immunotherapy approaches to treating cancers.

With checkpoint inhibitors having firmly inserted themselves as a first-line therapy for the treatment of an increasing number of can-cer types, the demand at this point is to provide more effective and more sustained treatment benefits that may be possible from B-cell vaccines or the next generation of more potent oncolytic viruses.

Imugene is capitalised at $119 million. It had $17.8 million in cash at the end of September (including an R&D rebate received last month).

Bioshares recommendation: **Speculative Buy Class A**.

Investor Briefing Notes

At an investor briefing last week, the inventor of Imugene's CF33 technology, Professor Yuman Fong, said that viruses tend to be drawn to and infect particular parts of the body. The hepatitis virus infects the liver. Viral meningitis occurs only in the brain or spinal cord. However, oncolytic viruses infect predominantly cancer cells.

Fong said that evolutionary techniques were used to combine multiple smallpox viruses (six) to naturally produce 100 different poxviruses. These viruses were tested for activity against the National Cancer Institute's standard 60 different tumour cell lines (NCI-60) with CF33 selected due to its very high cancer killing ability against these tumours.

Professor Fong said that CF33 was more effective by orders of magnitude (2 to 5) compared to other leading oncolytic viruses including T-Vec from Amgen (approved) and GL-ONC1 from Genelus (in Phase II trials). With over 1,000 times less virus required for activity against tumours than competing oncolytic viruses, it offers the potential for a high therapeutic window, and a lower immune response against the virus which could extend activity in the body.

In September last year, Boehringer Ingelheim acquired a private Austrian oncolytic virus company, ViraTherapeutics, in a deal worth €210 million. ViraTherapeutics is still in preclinical development. It has developed a modified 'Vesicular Stomatis Virus'.

According to Professor Fong, the acquisition provided Boehringer with new intellectual property, enabling it to enter the oncolytic virus space.

Professor Fong said that CF33 is a novel construct and as such, opens up new IP to operate in, with patent applications covering composition-of-matter and use patents out to late 2037.

There are around 40 oncolytic viruses in clinical studies with most of that work having commenced in the late 1990s. However, there are two issues with many of these programs. Firstly, the patents for these oncolytic viruses are expiring, according to Professor Fong, and secondly, earlier viruses were attenuated in order to weaken them so as to limit potential safety issues.

However, with knowledge having increased considerably around the use of oncolytic viruses, more potent viruses are being developed. Another common approach is the introduction of other payloads into the virus to improve therapeutic outcomes, which is the direction of the company's CheckVacc vaccine.

CF33 is a DNA virus, which makes it more amendable to manipulation and insertion of other genetic material, compared to Viralytics' coxsackievirus which was an RNA virus.

Somnomed — US Turnaround in Place; Reimbursement Begins in Germany

Somnomed's (SOM: $2.88) business continues to track well. Sales for Q1 FY2019 were $14.6 million, which represents an 11% growth over the previous corresponding period (PCP). The net operational cash flow for the quarter was -$1.6 million.

In North America, sales increased by 9% in constant currency over the PCP, and importantly through its direct channels, where the company has had issues for the last two years, sales increased by 15% in constant currency. This is also a very good result as its largest customer in the US, S3 (in Texas), ceased operations at the end of last year.

In Europe, which has been the strongest performing region in recent years, sales were up only by 5% in constant currency.

Two of the its largest markets, The Netherlands and Denmark, continue to be hampered by short term issues. In The Netherlands, the number of dentists approved to fit Somnomed's type of oral splints has been halved, which has caused supply issues. That issue is being resolved and growth is returning to both regions now.

In Germany, Somnomed has been cleared to have its products reimbursed by one of the top three insurers with a reimbursement code and price now set. That insurer covers around 15%-20% of the market. As the dental network is built in that country and as other insurers come on board, it will become an important market to Somnomed.

The single most important growth market for Somnomed remains North America, where penetration rates against CPAP remain low at 8%. At the end of last month, Somnomed signed an agreement with App-Nea LLC in the US.

App-Nea LLC, which is around one year old, facilitates interactions between sleep physicians and dentists, allowing physicians to track the status of their patients, including through follow-up sleep studies after fitting with a Somnomed device.

For Somnomed, the partnership allows Somnomed to bridge the relationship between the sleep physicians and dentists, allowing Somnomed to play an important role in that process.

Somnomed's CEO Neil Verdal-Austin said that growth in the US is coming from three areas that are currently aligning. First, the company is securing high volume, new customers. Second, it is regaining those dentists lost previously from its RSS clinic rollout which has now closed.

And importantly, its latest device, the SomnoDent AVANT, is being seen as a game changer by some major customers in the US. This device is smaller, more comfortable and more effective because of its different binding system at the front of the device which is reducing the number of sleep interruptions (apneas) each night.

Somnomed is capitalised at $181 million.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

Cogstate – Momentum Turns in Alzheimer's Disease Race

For cognitive assessment company Cogstate (CGS: $0.32), its fortunes have been tied to the successes and failures of the Alzheimer's disease drug development market, which is the overwhelming focus of the company's work. Although it has been broadening its activities into areas such as rare diseases, Alzheimer's disease trials have been the major part of its revenue base.

That includes conducting trials for biotech and pharmaceutical companies, and more recently, providing a cognitive test for use across the broader population to monitor declining cognition.

Over the last three years, there have been at least six late stage failures announced in Alzheimer's disease drug development. The impact on Cogstate's share price can be seen below, with the stock having fallen almost 90% from its high in January 2017, to its low of $0.15 in July this year.

However, with the momentum turning with a series of positive developments in the Alzheimer's disease drug development space, Cogstate's share price has bottomed and should be in a strong correction phase over the medium term.

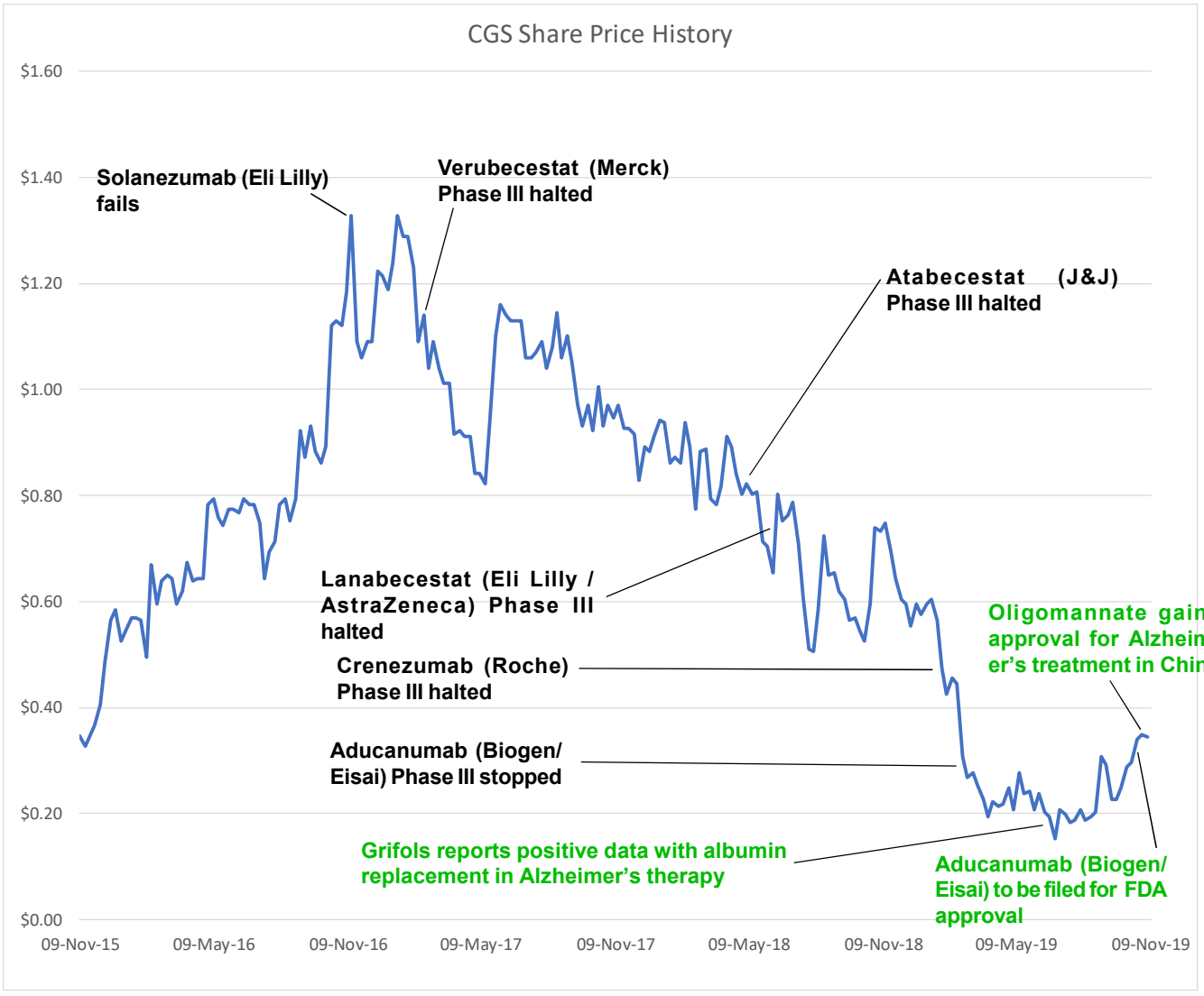
Grifols Generates Positive Results in Moderate Alzheimer's Disease

The first positive news in the field was announced at the Alzheimer's conference in July, AAIC (Alzheimer's Association International Conference), by Spanish plasma company, Grifols. The company's trial of its albumin replacement therapy achieved a statistically positive outcome (p=0.05) in a 496 patient study over 14 months.

The ADAS-Cog benefit was 3.9 points, or 61% less cognitive decline over the 14 months compared to placebo in patients with moderate disease. There was no benefit shown in patients with mild disease, however both the treatment and control arms did not decline, with the company believing that more time is required to measure benefit of treatment in patients with more mild disease.

Further results from the study are due to be reported at next month's Alzheimer's disease conference, CTAD (Clinical Trials on Alzheimer's Disease) in San Diego.

Cont'd over



Biogen/Eisai Resurrects Aducanumab and Readies for FDA Approval Filing

What has particularly taken the field by surprise is the resurrection of the Biogen/Eisai drug candidate, aducanumab. In March this year, Biogen announced that it was stopping the Phase III studies with this drug candidate after a futility analysis indicated that the trial was unlikely to yield positive results.

Aducanumab initially looked like it was not going to achieve clinical benefit. Initial patients in the study were being titrated towards higher doses to prevent brain swelling (ARIA) side effects.

It appears that not only is the compound potentially effective at the higher dose, but it may take the large part of the first year of treatment to remove plaque build-up (beta amyloid deposits) in the brain before more cognitive benefits are observed. "It took 20 years to build up that much (plaque) and in the context of an 18 month trial, you have to remove a large amount of plaque...to see an effect on clinical outcomes," believes Biogen's Executive VP of R&D, Alfred Sandrock.

It has also now been shown that titrating patients to the higher dose does in fact reduce the incidence of ARIA.

In the second of the Phase III studies (EMERGE), the primary endpoint measured by CDR-SB was met. In those patients receiving the higher dose, a statistically significant result was achieved ($p=0.01$) with a 23% reduction in clinical decline (over placebo). The lower dose group also had less decline than placebo.

On the secondary endpoint of MMSE, at the higher dose in the second study, a 15% lower decline (over placebo) was achieved ($p=0.06$) and using ADAS-Cog13, a 27% reduction was achieved ($p=0.01$).

In the first Phase III study (ENGAGE) which started slightly earlier, fewer patients received the higher dose within the first 12 months and produced no overall treatment effect.

Sandrock said that these results "…represent an inflection point in neuroscience drug development…by demonstrating the removal of aggregated forms of beta amyloid can result in improved clinical outcomes." Sandrock believes the results also have positive implications for other internal programs, including BAN2401 (also partnered with Eisai), its tau programs, its alpha-synuclein antibody for Parkinson's disease, and its antisense programs for ALS.

Prior to gaining approval, Biogen now aims to make the therapy available to patients involved in its Phase I, II and III studies with aducanumab. More details on the ENGAGE and EMERGE Phase III studies will be presented at CTAD next month.

China NMPA Grants Conditional Approval for Microbiome Treatment for Alzheimer's

Last week, the National Medical Products Administration in China granted conditional approval for a novel Alzheimer's disease treatment from **Shanghai Green Valley Pharmaceuticals**. That compound, Oligomannate, rebalances the gut microbiome to reduce neuro-inflammation which is believed to be implicated in disease progression.

In a nine month Phase III study, coordinated by Signant Health and IQVIA, an ADAS-Cog12 benefit of 2.54 points was achieved, a result that was highly statistically significant ($p<0.0001$). A multicentre Phase III study is expected to start early next year with the compound in the US, Europe and Asia. Shanghai Green Valley Pharmaceuticals was formed in 1997 and employs around 1,500 people.

Pre-clinical research on the compound was published in *Cell Research* in September last year (Wang *et al*). In an analysis piece on the research in the same edition written by several researchers, including David Holtzman who sits on the SAB for Genentech, the researchers noted that the immune system plays an important role in the pathogenesis of Alzheimer's disease, including both innate and adaptive immunity in the CNS. "Wang et al elegantly demonstrate that a gut microbiota imbalance facilitates peripheral immune cells to infiltrate the brain, resulting in enhanced microglial activation that contributes to cognitive impairment and beta amyloid burden in mouse models of beta amyloid amyloidosis."

Oligomannate, which is marine algae-derived oligosaccharide "decreases beta-amyloid related pathologies by reconditioning the gut, providing further evidence that gut-targeted interventions may serve as novel strategies to tackle Alzheimer's disease", according to Holtzman and the other reviewers.

In a mouse model of beta amyloid amyloidosis, it was found that the ratio of Firmicutes to Bacteroidetes in the gut increased significantly at seven months compared to the wild type (control) mice. As the degradation in synaptic function and the gut dysbiosis progressed, pro-inflammatory types of microglia increased in the transgenic mice as they aged. The hypothesis is that gut dysbiosis promotes infiltration of immune cells into the CNS which contributes to beta amyloid pathogenesis through excessive neuroinflammation.

Implications for Cogstate

For Cogstate, one implication is that advancing knowledge and positive progress in drug development for what has to date been an intractable disease, will likely see a big lift in activity in drug development over the next three years. If Biogen/Eisai's aducanumab reaches the market, companies such as these will need a triaging tool to help establish which patients with cognitive decline may have early Alzheimer's disease, which will require a PET scan for confirmation prior to drug treatment, and which people are simply slowing down and occasionally forget where they have placed their car keys.

We note that Cogstate already has a licensing deal with Eisai to use its cognitive test within the broader population in Japan.

Cogstate is capitalised at $53 million.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

Bioshares Model Portfolio (11 November 2019)

Company	Code	Price (current)	Price added to portfolio	Recommend-ation	Cap'n ($M)	Date added
Opthea	OPT	$3.010	$0.160	Take Some Profits	$753	November 2014
Volpara Health Technologies	VHT	$1.910	$0.375	Spec Hold A	$416	June 2017
Telix Pharmaceuticals	TLX	$1.800	$0.910	Spec Hold A	$456	May 2019
Somnomed	SOM	$2.880	$0.94	Spec Buy A	$181	January 2011
Immutep	IMM	$0.275	$0.320	Spec Buy A	$107	March 2019
Cyclopharm	CYC	$1.210	$1.35	Spec Buy A	$83	September 2019
Pharmaxis	PXS	$0.210	$0.260	Spec Buy A	$83	December 2016
Cogstate	CGS	$0.320	$0.24	Spec Buy A	$52	April 2019
Micro-X	MX1	$0.250	$0.38	Spec Buy A	$41	May 2017
Acrux	ACR	$0.220	$0.31	Spec Buy A	$37	July 2017
Rhinomed	RNO	$0.220	$0.24	Spec Hold B	$37	Jun-19
Dimerix	DXB	$0.117	$0.09	Spec Buy B	$19	December 2018

Stocks Removed from Bioshares Portfolio in TTM

Date removed	Stock
September 2019	1AD, ALC, BCT
June 2019	CUV
March 2019	CGS, CYP, MGZ
February 2019	RNO
November 2018	FTT
October 2018	BNO

Portfolio Changes – November 11, 2019

IN:
No changes

OUT:
No changes

Note: Immutep (IMM) has had a 10:1 share consolidation.

Rhinomed September Quarter Results

Rhinomed (RNO: $0.22) reported a relatively flat result for the September quarter, 2019. Revenue for the period was $0.84 million, similar to that in the previous quarter ($0.83 million) although 15% higher than the previous corresponding period.

The number of units shipped in the period was 67,072, which was similar to the previous two periods (69,092 and 71,554) and up slightly from the PCP (62,000 units).

Investment in advertising and marketing for the quarter was $0.62 million, compared to $1.0 million and $0.63 million for the previous two quarters. This month the company plans to start a national radio advertising program for its products in the US, where its products are in over 9,000 stores.

The company ended the quarter with $5.9 million in cash, following a $6.0 million capital raising conducted in September which saw eight institutional investors participate in the raise. It was conducted at $0.22 a share. The company's net cash burn for the quarter was $1.25 million. In the company's quarterly report, it was stated that its key objective is to reach a sustainable cash flow position.

During the quarter, the company's third product, Pronto Sleep, was launched in 1,000 Walgreens stores although revenue from this product have yet to be recognised. In time for the northern hemisphere winter, a Pronto Clear product is expected to be launched, which includes a nasal decongestant.

Five new products are expected to be launched in 2020. One will use the Pronto design to deliver medicinal cannabis for a variety of conditions. This product will be sold in the US through its partner Columbia Care. Rhinomed also plans to release four cannabidiol (CBD) products for the treatment of nausea, allergies, and to help with sleep and anxiety, with a further four CBD-based products to be launched in 2021.

CBD is an extract from cannabis that does not include THC and has been shown to have medical benefits for children with epilepsy. THC provides the psychoactive effects associated with cannabis. Rhinomed believes it can increase bioavailability to between 30%-40% through its nasal delivery compared to 3%-4% through oral delivery.

Elixinol Global, which listed on the ASX in January 2018 (raising $20 million), specialises in selling CBD products in the US. The company has at least 10 different CBD products in its range, including capsules, oils, water soluble powders and skin care products. In H1 CY2019, Elixinol generated sales of $17.5 million, which was up 17% on the PCP, with its CBD products contributing to 87% of sales last year. Elixinol has a market capitalisation of $189 million, having raised $50 million in June this year to expand its US CBD operations and $40 million in September last year.

Summary

Rhinomed's weekly store sales have been largely constant over the last 12 months, at around $60 per store. Its products are currently stocked in around 13,000 stores in Australia, the UK and the US. Its growth strategy is to expand its product offering through new product development, such as the range of Pronto products, and simultaneously expand its store presence, particularly in the US. Although its new product development is progressing , including with plans to accelerate over the next two years, its growth in store penetration has slowed. Currently around 30% of sales are through Amazon.

Rhinomed is capitalised at $37 million.

Bioshares recommendation: **Speculative Hold Class B**

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 Some 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, LBT Innovations, Opthea, ResApp Health, Pharmaxis, Dimerix, Adalta, Actinogen Medical, Patrys, Cyclopharm, Emvision, Antisense Therapeutics, Heramed, Imugene, Exopharm, Immutep, Neuroscientific Biopharmaceuticals

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