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Companies covered: CIR, IPD, OSP

	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)	9.1%
Cumulative Gain	**391%**
Av. Annual gain (14 yrs)	**16.7%**

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Bioshares

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

Extract from Bioshares –

Circadian's Blockade Goal for Wet AMD with OPT-302

Circadian Technologies (CIR: $0.16) has embarked on a business plan which places its eye diseases drug candidate, OPT-302, front and centre, and shifts its cancer antibody VGX-100 into a second line position. This change of direction follows the completion of Phase I studies of VGX-100, (from January 2012 to November 2013) and a change in management at the firm, with Megan Baldwin, the former head of Circadian's eye program subsidiary Opthea, taking on the position of CEO and MD of the Circadian group.

Circadian is part way through the completion of a $17 million capital raising, with the funds sought for the development of OPT-302. This capital raising includes a $14 million placement, part of which ($12.8 million) must be approved at the company's AGM on November 18, 2014. A $3.4 million rights issue was underwritten by Bell Potter Securities, which also managed the placement. On completion of the capital raising, the company will hold an estimated $22 million in cash.

OPT-302 – A Soluble Receptor Protein That Acts Like A Sponge

OPT-302 is a soluble receptor protein i.e. a soluble version of the Vascular Endothelial Growth Factor (VEGF) receptor R3. It works as a trap molecule, or sponge, for the circulating growth factors (cytokines) VEGF-C and VEGF-D.

The role of these cytokines and receptors is to promote and aid the growth of blood vessels. In certain disease states, it is desirable to shut down excessive or faulty blood vessel growth (neo-vascularisation) and control leaky blood vessels. One of the defining features of Wet Age Related Macular Degeneration (AMD) are leaky blood vessels.

Elyea and Lucentis Driving Interest in OPT-302

The market for drugs to treat ophthalmic conditions is large and growing. Aging populations in the US, Europe and elsewhere are drivers for growth in conditions such as Wet AMD. Growth in the numbers of people with diabetes is the basis for growth in the prevalence of diabetic macular edema (DME).

Several biologic drugs, including Lucentis and Elyea, have been approved in the US and Europe to treat Wet AMD and DME. Lucentis was first approved in 2006 and Elyea was approved in 2011.

Avastin, the monoclonal antibody drug from which Lucentis is derived, is used off label (i.e. not formally approved) to treat these conditions.

Lucentis is an antibody fragment which blocks VEGF A from binding to its receptor. Lucentis is dosed monthly.

Cont'd over

Elyea is a recombinant fusion protein, which combines elements of the receptors VEGF R1 and VEGF R2, linked to an FC domain. This fusion protein serves as a decoy for VEGF 1.

Elyea has been one of the most successful biologic drugs from a launch perspective because it recorded US$840 million in net sales in the USA in the first full year after its launch late in 2011, followed by US$1.4 billion in 2013 and US$1.2 billion for the first nine months of 2104.

One of the reasons for Elyea's rapid market uptake is that while it is dosed monthly for the first three months, subsequent doses are administered every two months. Fusion proteins such as Elyea have a longer half-life if they are engineered to include Fc domains. The less frequent dosing equates to an annual cost of US$16,000 compared to $24,000 for Lucentis.

Global sales of Elyea exceeded sales of Lucentis for the first time in 2014 Q3 (US$722 million versus US$614 million.)

Net sales of Elyea in countries outside of the USA, which are managed by partner Bayer Healthcare, totalled US$472 million for 2013 and US$742 million for the first nine months of 2014.

Competive Position and Opportunity for OPT-302

An issue with Lucentis and Elyea is while they deliver high levels of efficacy in the short term, over the longer term about 50% of patients do not achieve a signicant gain in vision, only one-third of patients recover driving vision and one-sixth progress to registered blindness, according to Circadian.

Circadian has established that very high levels of VEGF C are associated with Wet AMD.

Circadian has produced data from animal model studies which suggest that a combination of OPT-302 with Elyea is capable of delivering a stronger blockade of all the vascular endothelial growth factors, together rather than separately. Lucentis blocks VEGF A, Elyea blocks VEGF A (and PIGF), whereas OPT-302 targets VEGF C (and VEGF D).

There are relatively few other companies developing biologics to treat Wet AMD and related conditions. (refer to table on page 4).

One prominent competitor is Opthotech, which is capitalised at US$1.35 billion. Opthotech's drug, Fovista, is being trialled in various combinations with Avastin, Elyea and Lucentis, given that it is not active as a single agent.

Development Plans – Combination Studies

Circadian intends to commence a Phase Ib/IIa of OPT-302 midway through 2015.

The Phase Ib trial will evaluate OPT-302 in combination with Lucentis in a three-cohort dose ascending study. The final cohort will include an additional OPT-302 monotherapy arm.

Each cohort will be assessed at 4 weeks for dose limiting toxicities, followed by a 12 week follow up period.

Cont'd over

Net Sales - Elyea

Period	USA ($US M) (Regeneron)	PCP % change	RoW ($US M) (Bayer Healthcare)	PCP % change	Comments
2011 Q4	$25				Commenced Sales Wet AMD
2011 CY	**$25**				
2012 Q1	$124				
2012 Q2	$194				
2012 Q3	$244				Commenced Sales ME post CRVO
2012 Q4	$276	1013%	$19		
2012 CY	**$838**	**n.a.**	**$19**		Bayer Healthcare commenced sales
2013 Q1	$314	154%	$62		
2013 Q2	$330	70%	$102		
2013 Q3	$363	49%	$125		
2013 Q4	$402	46%	$184	868%	
2013 CY	**$1,409**	68%	**$472**	**n.a.**	
2014 Q1	$359	14%	$218	252%	
2014 Q2	$415	26%	$247	142%	
2014 Q3	$445	23%	$277	122%	Received FDA approval for DME
2014 Q4					
2014 CY YTD	**$1,219**		**$742**		

The primary endpoint will be the evaluation of ocular and systemic safety. Secondary endpoints will explore changes in visual acuity, central retinal thickness and choroidal neovascularisation thickness, the extent of antibody formation and also gather pharmacokinetic data.

The design of the Phase IIa section of the trial would see OPT-302 evaluated head to head against Lucentis in Wet AMD patients, with a primary analysis conducted at 16 weeks, and applying the same endpoints of the Phase I trial.

Aspects of these trials could change, with Elyea potentially being substituted for Lucentis.

Patents and IP

Circadian holds composition of matter patents covering soluble VEGF receptor 3, which have been granted in Europe, Japan, Canada and Australia and which expire in 2022. The US filing for this patent has been allowed in the USA, and if granted in 2015 will offer an expiry date in 2026.

Circadian also has a granted US patent covering the use of a soluble VEGF receptor 3 capable of binding VEGF-C to inhibit blood vessels in mammals giving diseases characterised by expression of VEGF receptor 3 in blood vessels. This patent expires in 2023.

The company (or a licensee) can gain additional data and market exclusivity in various jurisdictsions, for example, in the US where 12 years data exclusivity applies to biologics and 8 years in Europe.

In short, Circadian appears to hold a reasonably comfortable intellectual property position of OPT-302, in terms of patent life and market exclusivity and in terms of use.

Summary

There are several very positive features of Circadian's plan to place its focus on developing a therapy for ophthalmic conditions such as Wet AMD and DME.

The first is that the indications are large and growing and relatively uncontested, compared to many fractional cancer indications. This lends significant clarity to defining the market opportunity for OPT-302 which is also likely to make the licensing process for the drug easier and potentially result in attractive terms being written in Circadian's favour, if Phase II data meets expectations.

The second is that the time to obtaining clinical data is relatively short with clinical endpoints that are clear and accepted and Phase III studies of OPT-302 may require no more than twelve months data. The duration of assessment for novel therapies to treat eye conditions has been eased in recent times, falling from 24 months for Lucentis, to twelve months for Elyea.

Circadian is capitalised at $24 million and will hold an estimated $23 million in cash, both of which assume completion of the capital raising.

Bioshares recommendation: **Speculative Buy Class A**

Milestones to Monitor

– 2014 Q4/2015 Q1 - Complete GLP toxicology studies in rats and monkeys
– 2015 H1 - File IND submission (FDA), commence Phase I trial
– 2016 Q1 - Complete Phase I study

Bioshares

Selected Wet AMD Biologics - Approved and In Development

Company	Drug	Format	Target	Status	Indications
Regeneron/Bayer Healthcare	Elyea (aflibercept)	**Soluble decoy receptor** [recombinant fusion protein of portions of VEGFR1 and VEGFR2, fused to Fc portion of human IgG1]	VEGF-A and PIGF	Approved US 2011, EU 2012	Wet AMD, DME, macular edema following choroidal neovascularization
Novartis/Genentech	Lucentis (ranimizumab)	humanized mAb fragment	VEGF-A	Approved US 2006, EU 2007	Wet AMD, DME, macular edema following RVO, choroidal neovascularization secondary to pathologic myopia, and other eye indications
Genentech	Avastin (bevacizumab) (off-label)	humanized mAb	VEGF-A	Used to treat wet AMD, DME, and macular edema following RVO	Wet AMD, DME, and macular edema following RVO
Chengdu Kanghong Pharmaceutical Group	Conbercept	decoy receptor protein[fusing VEGF receptor 1 and VEGF receptor 2 extracellular domains with the Fc region of IgG]	VEGF-A, VEGF-B, PIGF	Approved - China - wet AMD but in development for other indications	Wet AMD
Ophthotech Corporation	Fovista	Aptamer	PDGF-B	Phase III (in combination with Avastin or Eylea)	Wet AMD
Novartis	ESBA1008	Single chain antibody fragment	VEGF-A	Phase II	Wet AMD
Allergan/Molecular Partners	Anti-VEGF-A-DARPin	designed ankyrin repeat proteins	VEGF-A	Phase II	Wet AMD and related conditions
Genentech	R06867461	Bi-specific antibody		Phase II	Wet AMD
Genentech	Lucentis Sustained Delivery System		VEGF-A	Phase I	Wet AMD and related conditions
Regeneron/Bayer Healthcare	REGN2176-3	Elyea formulated with mAb to PDGFR-beta	VEGF-A PDGFR-beta	Phase I	Wet AMD
Circadian Technologies	OPT-302	**soluble** VEGF receptor 3	VEGF C, VEGF D	Pre-clinical	Wet AMD and related conditions

Adapted from Regeneron 10K 2013

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