Companies covered: **DVL, OPT, SOM, TLX**

	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 - 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 - current)	-13.1%
Cumulative Gain	594%
Av. Annual gain (17 yrs)	17.1%

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Opthea's Strategy to Build Value for OPT-302

At Opthea's (OPT: $0.56) AGM held last week, the company's CEO Dr Megan Baldwin discussed the company's progress over the last 12 months. In particular, she reviewed findings from the company's Phase Ib component of the Phase I/II trial of OPT-302 in patients with persistent Diabetic Macular Edema (DME) (sub-responders).

The Phase Ib component of the trial was directed at evaluating the safety and dosing of OPT-302 delivered in combination with aflibercept (Eylea). The safety endpoint was met, with the drug found to be safe and well tolerated. The Phase IIb component is exploring the highest dose (2mg) from the dose escalation study.

A very promising indicator of the drug's potential came from five of nine patients in the Phase Ib study. These five had both eyes treated (bilateral disease), one with OPT-302 and aflibercept, and the other with an anti-VEGF-A monotherapy, either aflibercept or ranibizumab (Lucentis).

Eyes treated with OPT-302 and aflibercept achieved a 10 letter average gain in visual acuity at week 12, compared to 2.6 for the monotherapy eye. The improvement in the treatment eye compared to the monotherapy eye is a very positive indicator of the combined benefit of OPT-302 (which inhibits VEGF-C and -D) and aflibercept (which inhibits VEGF-A,-B and PIGF) because it is a within patient comparison.

Recruitment in Phase II AMD Trial Closed 5 Months Ahead of Schedule

The company's rapid recruitment in its Phase II wet (neovascular) AMD trial exceeded expectations, contributing to a five month gain in the development timeline for OPT-302 in that indication. It is unusual for drug developers to close out recruitment early. It suggests the level of interest in the drug from ophthalmologists is both positive and high.

The OPT-302 Value Proposition

What makes OPT-302 a potentially valuable drug asset is that it is one of a small number of drugs that are being developed to treat both wet AMD and DME, to address weaknesses with current standard-of-care drugs.

Baldwin said that the DME market opportunity is expected to exceed the wet AMD opportunity, with growth in DME occurring because of the underlying growth worldwide in obesity and diabetes.

The table on following pages shows that there is a wide field of drugs in clinical development for wet AMD, but far fewer specific to DME or for both wet AMD and DME.

Why Opthea's strategy matters is that it not only aligns with the reality of the current market leaders (Lucentis, Eylea and Avastin (off label)) being used in both areas, it aligns with Novartis' brolucizumab (RTH258), which is well advanced in several Phase III studies in both wet AMD and DME.

Continued over

Brolucizumab appears to be designed (in a commercial sense) to exploit a forthcoming opportunity stemming from patent expirations for Lucentis (Roche/Genentech) and Eylea (Regeneron). These patents are expected to expire in the US in 2020, although patent extensions may see Eylea hold out to 2023.

Brolucizumab is a humanised single-chain antibody fragment which is designed to inhibit VEGF-A. It is only 26kDa in size and is smaller than Eylea (at 115 kDa) and Lucentis (48 kDa). Its smaller size means that a greater concentration per dose can be administered, benefiting duration of effect and tissue penetration, according to Hussain and Ciulla (*Review of Ophthalmology*, March 2018).

96 week data from a Phase III trial in wet AMD showed that brolucizumab is non-inferior to aflibercept and was superior in reduction of retinal fluid at 48 weeks.

Opthea's OPT-302 appears to be the next most advanced molecule in development for both indications. OPT-302 could become an appealing target to companies wanting to protect their franchises against biosimilars (there are about 18 in development) by offering a drug that addresses the shortcomings of the first-line biologics in both indications.

While Roche's faricimab is being trialled in both wet AMD and DME, the fact that two Phase III trials are underway in DME and none in wet AMD is suggestive of a bias towards DME.

SciFluor has trials of its topical integrin alpha-v-beta3 inhibitor, SF0166, underway in wet AMD and DME. However, until this candidate is evaluated against standard-of-care, its potential is somewhat limited.

Summary

Opthea has the potential to attract significant investor interest in the second half of 2019, when results from the Phase IIa component of the DME trial and the results from the Phase IIb wet AMD trial are expected to be released. The stock could perform strongly in the lead up to the release of the results and strengthen further if positive and compelling data is delivered.

Opthea is in a strong financial position, holding cash of $37 million at the end of November. Opthea recently received $13.3 million from the exercise of options (at $0.27) and an R&D tax refund of $12 million. Opthea is capitalised at $113 million.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

Select Trials of Therapies in Development to treat Wet Age Related Macular Degeneration and/or Diabetic Macular Edema

Excludes Lucentis (ranibizumab), Avastin (bevacizumab) and Eylea (aflibercept) and biosimilars thereof e.g. SB11 and MYL-1701P

Company / Therapy	wet AMD				DME				
	Phase	Treatment	Other Arms	Num. Pts	NCT Number	Phase	Treatment	Other Arms	Num. Pts	NCT Number
Adverum Biotechnologies										
ADVM-022 (AAV.7m8-aflibercept) (gene therapy)										
	Phase I	3 dose levels	none	18	NCT03748784					
Allergan										
abicar pegol (monoDARPIN - blocks all isoforms of VEGF-A)										
	Phase III	abicipar pegol	ranibizumab plus sham	946	NCT02462486					
	Phase III	abicipar pegol	ranibizumab plus sham	939	NCT02462928					
AnewPharma (China) (Tyrogenex-US)										
CM082 (derivative of sunitinib) (PGDF & VEGF-A inhibitor) (oral)										
	Phase II	CM082 Tablet	none	64	NCT03710863					
	Phase I	CM082 Tablet	none	38	NCT02452385					
Apellis Pharmaceuticals										
APL-2 (complement C3 inhibitor) (cylic peptide)										
	Phase I/II	APL-2	none	17	NCT03465709					
Adverum Biotechnologies										
ADVM-022 (AAV.7m8-aflibercept) (gene therapy)										
	Phase I*	DS-7080a	ranibizumab/ plus combination	56	NCT02530918	(Trial enrolled across both AMD and DME patients)				NCT02530918
Feramda										
AS101 (tellurium)										
	Phase I/II	AS101	placebo	40	NCT03216538					
Huabo Biopharm (China)										
HB002.1M (Fc fusion protein containing domain 2 and flanking sequence of VEGF receptor-1)										
	Phase I	HB002.1M	none	30	NCT03387566					
Jiangsu T-Mab Biopharma (China) (Lic'd from Apexigen)										
TK001 (sevacuzimab) (anti VEGF mab)										
	Phase I	TK001 (3 doses)	none	36	NCT03021785					
	Phase I	TK001 (5 doses)	none	27	NCT03021785					
KalVista Pharmaceuticals										
KVD001 (Plasma Kallikrein Inhibitor)										
						Phase II	KVD001 Injection	sham	123	NCT03466099
Novartis										
brolucizumab (RTH258) (VEGF-A single chain antibody)										
	Phase III	brolucizumab	aflibercept	151	NCT03386474	Phase III	brolucizumab	aflibercept	356	NCT03481660
	Phase III*	brolucizumab	aflibercept	500	NCT03710564	Phase III	brolucizumab	aflibercept	534	NCT03481634
	Phase II	brolucizumab	none	51	NCT02507388					
LKA651 (Erythropoietin inhibitor)										
	Phase I*	LKA651	sham	28	NCT02867735	(Trial enrolled across both AMD and DME patients)				NCT02867735
Opthea										
OPT302 (VEGF-C/D Trap)										
	Phase II	OPT302 plus ranibizumab	ranibizumab plus sham	366	NCT03345082	Phase I/II	OPT302 plus aflibercept	aflibercept / sham	117	NCT03397264
Oxford Biomedica										
RetinoStat (lentiviral vector expressing endostatin and angiostatin)										
	Phase I*	Retinostat	none	21	NCT01301443					
PanOptica										
PAN-90806 Ophthalmic Suspension (VEGFR2 inhibitor)										
	Phase I/II	PAN-90806 3 doses	none	60	NCT03479372					

Select Trials of Therapies in Development to treat Wet Age Related Macular Degeneration and/or Diabetic Macular Edema

Excludes Lucentis (ranibizumab), Avastin (bevacizumab) and Eylea (aflibercept) and biosimilars thereof e.g. SB11 and MYL-1701P

Company / Therapy	wet AMD				DME				
	Phase	Treatment	Other Arms	Num. Pts	NCT Number	Phase	Treatment	Other Arms	Num. Pts	NCT Number
Pfizer										
PF-05206388 (Human Embryonic Stem Cell Derived Retinal Pigment Epithelium (Rpe) Living Tissue Equivalent										
	Phase I	PF-05206388	none	10	NCT01691261/ NCT03102138					
Regenxbio										
RGX-314 (AAV gene therapy vector carrying a coding sequence for a fragment of an anti-VEGF protein)										
	Phase I	RGX-314 (4 doses)	none	24	NCT03066258					
Ribomic (Japan/USA)										
RBM-007 (aptamer technology) (targets FGF2)										
	Phase I/II	RBM-007 (dose escalation)	none	9	NCT03633084					
Roche										
faricimab (RO6867461; RG7716) (bi-specific mab binding Ang2 and VEGF-A)										
	Phase II	faricimab	ranibizumab	76	NCT03038880	Phase III	faricimab	aflibercept, sham	900	NCT03622593
						Phase III	faricimab	aflibercept, sham	900	NCT03622580
Santen (Lic'd from Tracon)										
DE122 (Endoglin antibody)										
	Phase II	DE-122 (low dose and high dose)/ ranibizumab	ranibizumab	56	NCT03211234					
SciFluor										
SF0166 (integrin αvβ3 inhibitor)										
	Phase I/II*	SF0166 (topical - eye drops) (low dose)	SF0166 (topical - eye drops) (high dose)	44	NCT02914639	Phase I/II*	SF0166 (topical - eye drops) (low dose)	SF0166 (topical - eye drops) (high dose)	44	NCT02914613
Universidad Nacional Autonoma de Mexico										
levosulpiride (dopamine D2 dopamine D2 receptor blocker)										
						Phase II	levosulpiride	lactose pill, ranibizumab	120	NCT03161652
Wills Eye										
dorzolamide-timolol (commonly available glaucoma eye drops)										
	Phase II/III	dorzolamide-timolol	placebo	50	NCT03034772					
Xiaodong Sun (China)										
Conbercept (KH902) (fusion protein composed of extracellular components of VEGFR-1 and VEGFR-2, plus Fc portion of IgG1)										
	Phase III	Conbercept (2 doses)	aflibercept	1140	NCT03577899					
	Phase III	Conbercept (2 doses)	aflibercept	1140	NCT03630952					
YD Global Life Science (Korea)										
YD312 (imatinib mesylate) (oral)										
						Phase II	YD312 (3 doses)	placebo	100.00	NCT03635814

*completed

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, Cyclopharm, Adalta, Medibio, Pharmaust, Actinogen Medical, Patrys