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Companies covered: **IMM, OPT, Large Cap Results Review**

	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)	-12.1%
Cumulative Gain	603%
Av. Annual gain (17 yrs)	17.1%

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Bioshares

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

Major Inflection Points for Opthea in 2019 as Case for Positive Results Build

Opthea (OPT: $0.76) has passed the second safety milestone of its 366 patient, Phase IIb wet AMD study. It includes 209 patients who have completed six month treatment and the remaining patients who have been treated for less time. There is one more blinded safety analysis before the results are due to be reported in Q4 this year.

At an investor meeting recently, CEO Megan Baldwin said that it is important to ensure that the company's drug candidate, OPT-302 which is injected into the eye, is manufactured in a clean process and that patients need to tolerate any potential inflammation in the eye from the treatment, which involves combining it with the eye drug Lucentis (in wet AMD).

Passing this second blinded safety hurdle should be considered another valuable step in the commercialisation process for OPT-302, ensuring what appears to be a good and tolerable safety profile so far.

Opthea is running two Phase II studies concurrently, one in wet AMD and one in diabetic macular edema (DME). However a difference between the two trials is that the Phase IIb wet AMD trial is assessing the combination treatment in naïve patients and the DME study is trialing a combination treatment in patients who have previously had a poor outcome from a monotherapy with one of the VEGF-A inhibitors (Lucentis or Eylea).

Baldwin said that one of the reasons for structuring the trials in this way was that it would provide the company with data across two indications looking at naïve and sub-optimal responders. In wet AMD, treating naïve patients will also position the therapy as a first line treatment.

Another consideration is that both studies are considering different VEGF-A inhibitors; Lucentis in the AMD study and Eylea in the DME trial. These two drugs generated sales of US$9 billion in 2017 according to Baldwin, which accounted for only 40% of the market, with 60% treated with Avastin off label (Lucentis and Avastin are the same drug, but one is approved for the treatment of eye diseases and the second for the treatment of solid tumours).

Baldwin believes that the company's share price has surged in recent weeks because of the anticipation of data release nearing closer this year (from its AMD study in Q4 and the DME results due in 2H this year). She believes the valuation of the business will far exceed the current price if the company hits its endpoints in its current studies.

Recap of Results Presented Last Year

The reason for the growing confidence in Opthea's position is the consistent data that has been emerging from the current and previous studies and the rapid progress that has been achieved in trial recruitment.

Continued over

In the company's 366 patient study in wet AMD in naïve patients, the company has seen accelerated recruitment, with full recruitment occurring four months ahead of schedule. This highlights the need for improved therapies in this indication as well as the growing confidence and interest in OPT-302 based on data achieved to date, both safety and efficacy data from the Phase IIa study. Around 50% of patients with wet AMD (and two thirds with DME) do not achieve an improvement in vision from the VEGF-A inhibitors.

In its Phase IIa study in wet AMD in 38 patients treated with OPT-302 and Lucentis, the naïve treated patients (those who did not have previous VEGF-A therapy) gained a mean 10.8 letter improvement in vision. For those treated previously with VEGF-A drugs, a mean 4.9 letter improvement was achieved.

With respect to fluid build up in the EYE, CST (central subfield thickness) levels fell by 119uM in the naïve patients and by 54uM in the prior VEGF-A treated patients. This reduction in fluid build up has encouraged the company to investigate a treatment for DME which is characterised by excess fluid in the eye (macula).

DME Phase Ib Lead-in Trial Results

In DME, prior to starting the 108 patient Phase IIa study which is currently underway (in those who have responded poorly to VEGF-A drugs), Opthea conducted a Phase Ib safety study (in nine patients) to see if combining Eylea with OPT-302 would produce any complications (previous studies have combined OPT-302 with Lucentis). The combination was found to have a good safety profile, with only side effects from the injection which were resolved, but importantly no clinically significant increases in eye pressure (IOP).

The trial also looked at efficacy in these nine patients. It found a dose dependent response in vision (measured as increased letters on the chart that could be read) at 0.3mg, 1.0mg and 2.0mg doses, giving an improvement of 3.0 letters, 5.7 letters and 14.3 letters respectively. The average improvement was 7.7 letters. Baldwin believes that an improvement of just 3 - 5 letters is clinically meaningful, with just a small improvement in visual acuity translating in a large increase in quality-of-life for patients. These patients had all been receiving prior treatment with a VEGF-A inhibitor.

Changes in swelling (fluid) of the macula was also measured in these nine patients. From a mean starting point of 434uM, a 71uM reduction (16%) in CST was achieved.

Bilateral Comparison in 5 Patients – Interesting Data

In five of the nine patients, combination treatment was given to only one eye and compared to the outcome of the other eye which received only VEGF-A treatment. The mean gain in the combination treatment arm (across all three doses of OPT-302) was 10 letters compared to just a mean 2.6 letter improvement in the VEGF-A only treated eyes.

With respect to CST, there was an 18% reduction (80uM) with the combination therapy compared to only a 1.5% drop (6uM) in the VEGF-A only treated eyes.

The current Phase IIa trial in DME with OPT-302 (plus Eylea) is assessing the highest dose of OPT-302 used in the lead in study (2mg), with two thirds treated with the combination therapy and one third with VEGF-A only (Eylea).

Summary

Opthea continues to deliver consistent results for its novel ophthalmic therapy. It is consistent with respect to mechanism of action as well, where shutting down two other passages for new (unwanted) blood vessel formation, VEGF-C and VEGF-D, as well as the current VEGF-A pathway that is well serviced by current therapies, Lucentis and Eylea, is delivering improvements in vision and reductions in excess fluid in the eye.

We expect *strong interest to build in this* stock this year in anticipation of positive results from two major studies in wet AMD and DME later this year.

Opthea is capitalised at $190 million with $40 million in cash at the end of last year.

Bioshares recommendation: **Speculative Buy Class A**

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 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