ISSN 1443-850X

Companies covered: **ALC, CGS, PXS, RAP, RNO**

	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)	-0.6%
Cumulative Gain	694%
Av. Annual gain (17 yrs)	17.1%

Bioshares is published by Blake Industry & Market Analysis Pty Ltd.

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Individual Subscriptions (48 issues/year)
$470 (Inc.GST)
Edition Number 789 (29 April 2019)

Bioshares

29 April 2019
Edition 789

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

Extract from Bioshares –

Pharmaxis Update

Pharmaxis (PXS, $0.30) held $35.1 million in cash at the end of the March quarter, 2019, compared to $42 million at the end of December. Net cash used in operating activities was $6.1 million for the quarter, up from $4 million in the previous quarter.

The higher quarterly negative net operational cash flows was due to higher R&D spending, which was $2.7 million for the March quarter, up from $1.8 million in the previous quarter.

During the quarter Pharmaxis commenced a Phase I trial of its Pan LOX inhibitor in a single ascending dose (SAD) study in 40 healthy subjects. A multiple ascending dose study will follow the SAD study, and then in 2020, the company will initiate a Phase Ic/II study in pancreatic and myelofibrosis patients.

Pharmaxis' current lead asset is a compound in development to treat Non-alcoholic Steatohepatitis (NASH) and diabetic retinopathy. Both are diseases with high unmet need. The compound, BI1467335, now owned by Boehringer Ingelheim, completed enrolment in a Phase IIa NASH study in February. Data from the 114 patient NASH study is expected to be reported in September or October. Data from the Phase IIa diabetic retinopathy trial is expected this half.

The NASH study has been evaluating four different doses of BI1467335 (once daily), over a 12 week period of administration with a four week follow-up. The trial includes a placebo arm. The primary endpoint of the trial is the activity of the amine oxidase copper-containing 3 (AOC3) protein in plasma, compared to a baseline figure, 24 hours after the drug has been dosed. The trial is focused on establishing the biological activity of the drug, to confirm a dose response of the drug, rather than the effects on liver tissue or other NASH efficacy endpoints.

BI1467335 is an amine oxidase inhibitor, blocking semicarbazide-sensitive amine oxidase, but it is also known as vascular adhesion protein. Its mechanism of action is to block leucocyte adhesion and tissue infiltration in the inflammatory processes that lead to the fibrosis that characterises NASH.

Leucocytes, otherwise known as white blood cells, are cells used by the immune system to protect against infection. However, if their signalling or recruitment function is left 'on', downstream tissue injury and scarring leading to fibrosis can occur.

Boehringer Ingelheim has completed five Phase I studies of BI1467335, with one more Phase I planned, looking at the effects on different dose levels of BI1467335 in the brain. The extent of Phase I studies initiated or planned by Boehringer Ingelheim is an example of the depth of capabilities and strength in resources that a large pharmaceutical company can bring to drug development.

Cont'd over

Pharmaxis stands to receive milestone payments as various stages are passed for BI1467335, with the next milestones of €37 million anticipated on entering a Phase III NASH study and €25 million anticipated on entering a Phase III study for diabetic retinopathy. To date Pharmaxis has received $83 million in upfront and milestone payments from Boehringer Ingelheim.

Gilead's Selonsertib Fails Two Phase III Studies

A development in the NASH field during the quarter was the failure of Gilead Science's selonsertib in a Phase III trial, followed by the more recent announcement of that drug's failure in a second Phase III trial.

In the second, 802 patient Phase III trial, only 9.3% of patients on the 18mg dose achieved an equal or better than one stage improvement in fibrosis without worsening of NASH after 48 weeks. Likewise, 12.1% on the 6mg dose achieved an equal or better than one stage improvement in fibrosis, with the placebo group achieving a 13.2% improvement.

Selonsertib was designed to block the molecule ASK-1, which is activated by oxidative stress. The failure of drug candidates at such an advanced stage serves to promote the advancement of therapies next in line, especially in the Phase II stage, as well as triggering asset transactions as larger companies look to infill their pipeline.

The most advanced drug in development for NASH is Intercept Pharmaceutical's Ocaliva, a farnesoid X receptor (FXR) agonist which affects bile acid synthesis. Bile acids accumulate in liver at the NASH disease stage. They damage liver by acting as a detergent. (see Garber, *Nature Biotechnology*, March 2019).

Data from that company's current Phase III REGENERATE study showed Ocaliva 25mg improved fibrosis scores in 23% of patients, compared to 12% on placebo (p=0.0002). However, Ocaliva increases insulin resistance, lowers high density lipoprotein (undesirable), raises low density lipoprotein (also undesirable) and causes itching. Ocaliva was approved in 2016 for treating primary biliary cholangitis.

Next in line is Genfit's elafibranor, which targets PPAR-alpha and PPAR-delta. It has an anti-inflammatory mode of action. Phase III results are expected this year.

Allergan's cenicriviroc, also in a Phase III trial, is a dual antagonist of the chemokines CCR2 and CCR5. it has a downstream anti-inflammatory mechanism of action.

Including Boehringer Ingelheim's Phase II trial, at least 47 Phase II trials are in progress or planned for 37 therapies for the treatment of NASH or non-alcoholic fatty liver disease (which precedes NASH).

Although the space may appear congested, Gilead's failure with selonsertib is a positive for newcomers, and Ocaliva's side effects may limit the drug's use. Selonsertib is also being evaluated in two Phase II combination drug trials, but the results from its Phase III trials may mean it is once again less likely to succeed.

Pharmaxis is capitalised at $118 million.

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, Antisense Therapeutics