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Companies covered: **LBT, MGZ, PXS**

	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)	-18.5%
Cumulative Gain	551%
Av. Annual gain (17 yrs)	17.1%

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Bioshares

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Extract from Bioshares –

Pharmaxis Investor Briefing Summary

Last month Pharmaxis (PXS:$0.265) held an investor briefing which included presentations from the company's management, R&D team, directors and also from representatives from the company's partner, Boehringer Ingelheim (BI).

The company's CEO, Gary Phillips, summed up the business model for Pharmaxis. It has drug discovery expertise, it uses CROs to run its clinical studies, and then seeks to partner out those assets (once successful clinical data has been achieved).

In the last five years the company has developed six lead compounds with three now in clinical development, including the compound sold to Boehringer Ingelheim in 2015. Its next program to enter the clinic is expected to be a pan LOX compound next year.

One of the company's directors, Dr Kathleen Metters, discussed the big picture setting of how biotech companies are a necessary source of future products for Big Pharma.

Metters said that the healthcare sector has never been healthier. However, large pharmaceutical companies have become victims of their own success. They have downsized internal R&D and are now aggressively looking for opportunities to fill their pipelines. Metters should know. When at Merck, she ran basic research for the company with 3,000 staff reporting to her.

Metters said that Pharmaxis has all of the attributes to make it a compelling partner for the large pharmaceutical companies. The company has an incredibly positive culture and is working in an area that is an extremely scientifically challenging domain. Data from two clinical programs is expected in 2019 and early 2020 from Boehringer's trials in NASH and diabetic retinopathy.

Update on BI Programs

Thomas Jensen and Dr Petra Moroni-Zentgraf from Boehringer provided an update on the clinical programs underway with the compound acquired from Pharmaxis. Boehringer spends €3.1 billion a year on R&D, with €1.5 billion spent on external collaborations.

The Phase IIa NASH study is seeking to recruit 108 patients in Europe and the US. It is exploring four different doses with the compound, BI1467335, delivered daily for 12 weeks in oral form. The trial is expected to be completed in May next year, with the sample size reduced by 27% due to better than expected baseline data.

Jensen said that the company would need to see a good signal from this study to argue the case to progress the program into Phase IIb testing. The current study is not taking liver biopsies.

The key outcomes of efficacy will be changes in liver enzymes. Jensen said that Boehringer is a company that likes to do blood tests.

Continued over

The primary outcome is changes in AOC3, which is the enzyme that Pharmaxis has shown was inhibited in Phase I studies. Secondary measures include changes in ALT and AST liver enzymes.

APhase IIb study is in planning. The difference with the Phase IIb study is that it will be larger, treat patients for longer, and the patients will have confirmed disease through a biopsy.

Jensen said that BI1467335 could become an essential anti-inflammatory compound for the treatment of NASH. Between 1.5% - 6.45% of the general population may develop NASH, with 30% of the population having excess fat in their livers (NAFLD).

There are currently no approved therapies for NASH. Current management approaches include improved diet (low sugar and saturated fat), increased physical exercise, and reduced alcohol consumption.

Diabetic Retinopathy

A Phase IIa diabetic retinopathy study started in January this year. It is seeking to enrol around 100 patients. However, completion of the study has been extended by eight months to January 2020 due to slower than expected recruitment. Additional sites have been added for this trial. A Phase IIb trial is in planning. Around 5% of people with type 2 diabetes develop blindness over 10 years due to this disease.

Diabetic retinopathy is caused by high glucose levels in the blood which leads to vascular disruptions. This damages permeability which reduces oxygen levels and initiates inflammatory responses and new capillary formation.

The most recently approved treatment for diabetic retinopathy is an anti-VEGF compound, Lucentis, approved in April last year in the US.

LOXL2 Program

Dr Wolfgang Jarolimek, Head of Drug Discovery for Pharmaxis, said that inflammation and fibrosis was the key to many diseases. The LOXL2 enzyme plays a major role in fibrosis of organs, with the stiff tissue causing mechanical damage to the organ.

The LOXL2 program is almost ready for partnering, with the final data from three month toxicology in two different species nearly complete.

Pharmaxis has developed two LOXL2 lead candidates, which it refers to as C1 and C2. Both compounds have a half-life of 22 hours. With daily oral administration, there is a constant level of the drug in the blood stream after seven days of treatment, with more than 85% of inhibition of the target enzyme. (After only one dose, more than 80% inhibition of LOXL2 was achieved in just 24 hours.) The two compounds completed Phase I assessment in 108 healthy volunteers.

A major difference between this drug candidate and the failed Gilead program in LOXL2 inhibition (in three clinical studies including two in NASH) is that Gilead never knew whether its drug candidate was inhibiting the target, unlike Pharmaxis which developed a proprietary assay for this purpose.

Jarolimek said that when seeking to transact a Phase I asset, there is a lot of attention paid to preclinical data by potential partners.

The company looked at over 500 compounds over six years in selecting its C1 and C2 leads, with many challenges around ensuring the right pharmacokinetic profile could be achieved.

The leads have been assessed in five different types of animal tissue (including liver, kidney, heart and lung) and *in vitro* studies with human lung tissue with 10 different collaborators around the world.

The compounds have also been evaluated in several preclinical safety models, to ensure there are no adverse effects on cardiac function, breathing and no cognitive impairment.

The aim for this program is potentially to move into between three to five different diseases. C1 and C2 are protected on separate patents (which provides the option for more than one licensing deal), with patent protection out to at least 2036. Both compounds inhibit both LOXL2 and LOXL3, with the later implicated in pulmonary fibrosis.

Best in Class?

Phillips said that with the company being very well funded (with $46.7 million in cash) its does not need to rush into a commercial deal, with the emphasis being to find the right partner.

On the topic of competition, Pharmakea, which was founded in 2012 with seed funding from Celgene and US$44 million in collaborative funding, has a LOXL2 program that completed Phase I studies last year. However, its compound blocks only LOXL2 and is rapidly cleared from the body with low target engagement. Pharmaxis believes its LOXL2 inhibitor is the best-in-class.

And while there are many programs in clinical development for the treatment of NASH, an anti-fibrotic approach is the least common.

Pan LOX Program – Pancreatic Cancer

In Q1 2019, Pharmaxis expects to move its pan LOX program into the clinic for the treatment of pancreatic cancer, which is a highly fibrotic cancer, and as such, is highly resistant to drug treatment. The first Phase I study will be in healthy volunteers with the next study, in patients, expected to start in Q4 2019.

The pan LOX inhibitor inhibits all five LOX enzymes (LOX, LOX1, LOX2, LOX3 and LOX4).

With pancreatic cancer, as the tumour grows, fibrotic tissue builds around it. This has two negative impacts. The first is that it stops chemotherapy drugs from entering the tumour.

The fibrotic networks also facilitate the spread of the cancer to other organs, according to Dr Thomas Cox from the Cancer Division at the Garvan Institute of Medical Research, which is working with Pharmaxis in assessing the pan LOX inhibitors.

Continued over

The Garvan Institute in Sydney is co-located with The Kinghorn Cancer Centre, which is running over 200 clinical trials, and provides a translational medical research facility. There are more than 250 researchers and clinicians at this one facility providing bench-to-bedside development of novel medical therapeutics.

One of the aims of Pharmaxis' pan LOX program is to inhibit the growth of fibrotic networks growing around the tumour; chemotherapeutic agents in fact help build fibrotic tissue around the tumour, according to Cox.

Around 3,200 people develop pancreatic cancer each year in Australia, with less than 20% of patients alive after one year. The five year survival rate is between 7% - 8%, which has not changed in the last 25 years.

In pancreatic cancer, all of the LOX family of enzymes are elevated said Cox. Targeting just one of these enzymes has been previously shown to obtain a clinical benefit in conjunction with chemotherapy. Cox said that the Pharmaxis inhibitor has shown promise as a more robust approach to improving treatment with chemotherapy in preclinical studies.

Phillips said that Pharmaxis intends to retain the pan LOX program in-house and to take it into Phase II studies. The plan for Pharmaxis is to build an 'unencumbered pipeline'.

Pharmaxis is capitalised at $104 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, Cyclopharm, Adalta, Medibio, Pharmaust, Actinogen Medical, Patrys