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

Companies covered: **ANP, PXS**

This Special Edition of *Bioshares* provides analysis of Antisense Therapuetics, which has released the final results of its Phase IIa study of ATL1102 in Duchenne's Muscular Dystrophy, and Pharmaxis, which announced that Boehringer Ingelheim will discontinue the development of BI 1467335 (formerly PXS 4728A) in the indication of NASH, but is continuing with its development in diabetic retinopathy.

Extract from Bioshares –

Pharmaxis – Boehringer Ingelheim Discontinues NASH Program; Continues in Diabetic Retinopathy

Pharmaxis (PXS: $0.155) announced today that Boehringer Ingelheim will discontinue the development of BI 1467335 in the indication of NASH (non-alcoholic steatohepatitis) or fatty liver disease.

The reason cited for the discontinuation was because of potentially drug interaction effects which were observed in a small Phase I study only recently completed by Boehringer Ingelheim.

The 10 patient study evaluated the effect of BI 1467335 on monoamine oxidase B (MOA-B) levels, an enzyme involved in dopamine metabolism. Two MOA-B inhibitors, selegiline and rasagiline, are used to treat Parkinson's disease, and the hydrazine class of MOA-B drugs are used as anti-depressants.

Boehringer has decided to discontinue development of BI 1467335 in NASH because of the possibility of side effects occurring in some of the patients taking those drugs, where the numbers of those patients would be significant.

That BI 1467335 should have an effect on monoamine oxidase B (MOA-B) levels may perhaps in hindsight not come as a surprise given that it is an amine oxidase inhibitor, specifically of amine oxidase copper-containing 3 enyzme(AOC3).

The discontinuation is disappointing because the Phase II NASH study achieved its primary endpoint of reduction in AOC3 activity, showed a dose response, and clinically relevant effect on secondary endpoints, and was well tolerated with no serious adverse events.

Pharmaxis shares fell 40% in response to the announcement.

Since Pharmaxis sold its an amine oxidase inhibitor program (PXS 4728A) to Boehringer Ingelheim in May 2015 in a deal valued at up to ~$600 million at the time, that company has completed seven Phase I studies of BI 1467335 in a total of 160 subjects, with another Phase I study in 62 subjects underway, which is evaluating how BI 1467335 effects blood pressure.

These studies in healthy volunteers are in addition to a now completed Phase II study in 114 NASH patients and a Phase II study in 100 patients with diabetic retinopathy, which has completed enrolment. In total, Boehringer Ingelheim will have enrolled 426 subjects across 10 studies, with Pharmaxis having previously completed a 48 subject single as-

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cending dose study and a 24 subject multiple ascending dose study. (See table below.)

Boehringer Ingelheim will continue with the development of BI 1467335 in diabetic retinopathy for the time being. The side effect profile of BI 1467335 may be different in this indication if a lower dose is used, relative to the doses tried in the NASH study. Further, how the drug might work in the eye is likely to be different, and the risk-benefit profile for drugs used to treat retinal diseases is different, with the risk of blindness arguably outranking liver fibrosis as a chronic condition. Diabetic retinopathy is also a condition that is managed by specialists rather than GPs (with NASH) which means greater prescription control is possible.

Diabetic retinopathy has now become the lead indication under the deal with Boehringer Ingelheim and as such qualifies for a ~$60 million milestone payment, triggered by the commencement of a Phase III study. Such a trial is not expected to start until 2022, according to Boehringer Ingelheim's latest development plan.

Since 2015, when the sale of amine oxidase inhibitor program to Boehringer Ingelheim was finalised, Pharmaxis has received a total of $83 million in upfront and milestone payments.

Discussion

The discontinuation of the development by Boehringer Ingelheim of BI 1467335 in NASH is disappointing for Pharmaxis. However, the business model chosen by the company in May 2015, from a fully integrated pharmaceutical company model to a development and partnering model, appears to have been justified through this setback.

Shareholders have not born the risks for the ongoing development of the amine oxidase inhibitor program yet have received a cumulative $83 million in payments. The transaction with Boehringer Ingelheim also illustrates differences in capabilities and resources that exist between small drug discovery firms and large pharmaceutical firms. While no exact figure can be obtained for Boehringer Ingelheim's internal spending, but given that it has enrolled more than 400 patients in clinical studies, we estimate that the company has spent between $40-$50 million on clinical studies, and millions more on long term toxicology studies and the manufacture of GMP drug product for clinical and non-clinical studies.

Pharmaxis' partnering strategy has also been validated because with Boehringer Ingelheim, it secured a deal with a company committed to developing drugs to fibrotic conditions, with the ability to make investments and take risks in this area of high unmet need.

By way of example of its commitment, Boehringer Ingelheim signed a collaboration and licensing deal in July with Korean company Yuhan Corporation for that company's dual GLP-1 and FGF21 ago-

Studies of BI 1467335 (PXS-4728A)

Phase	Pts Enrolled	Pt Type	Type of Study	Completion Date	Dosing: BI 1467335 (PXS-4728A)	Dosing: Other
Pharmaxis Studies (PXS-4728A)						
Phase Ia	48	Healthy Subjects	Safety, PK, (SAD) (5 days)	April, 2015	1, 3, 6, 10, 15 or 20 mg	Placebo
Phase Ib	24	Healthy Subjects	Safety, PK, (MAD) (15 days)	Sept, 2015	3mg to 10 mg (three doses)	
Boehringer Ingelhiem Studies (BI 1467335)						
Completed						
Phase I	36	Healthy Subjects	Safety, PK, PD	July 12, 2017	Low, medium, high dose	Placebo
Phase I	18	Healthy Subjects	Oral solution versus tablet, food effect	April 4, 2017	Three different dosing conditions	Placebo
Phase I	48	Healthy Subjects	Safety, PK	December 16, 2017	Multiple rising doses	Placebo
Phase I	16	Healthy Subjects	PK, ADME	April 19, 2018	Single oral dose, dose not specified	
Phase I	12	Healthy Subjects	PK study - IV, oral	June 5, 2018	Dose not specified	
Phase I	20	Renal Insufficiency, Healthy Volunteers	PK study	August 16, 2018	Dose not specified	
Phase I	10	Healthy Subjects	MAOB study (drug-drug interaction)	November 18, 2019	High dose, low dose	
Phase Iia	114	NASH - Biopsy confirmed	Proof of clinical principle, dosing	June 14, 2019	Four doses, 12 weeks	
Recruiting; Active, not recruiting						
Phase I	62	Healthy Subjects	Tyramine sensitivity factor study (blood pressure study)	May 5, 2020	Low dose, high dose	Phenelzine sulfate, tyramine, placebo
Phase IIa	100	Diabetic Retinopathy	Proof of clinical principle	May 14, 2020	One dose, 12 weeks	Placebo

Source: clinicaltrials.gov, Pharmaxis, ANZCTR

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– PXS cont'd

nist for the treatment of NASH and related liver diseases. Yuhan received US$40 million in upfront and near-term payments and stands to receive up US$830 million in potential milestone payments plus royalties.

In July, Boehringer Ingelheim struck a deal with Bridge Biotherapeutics, also from South Korea, for the autotaxin inhibitor BB-877, to treat patients with fibrosing interstitial lung diseases, including IPF. The drug was first developed by LegoChem Biosciences. The terms of this deal were €$45 million upfront and up to €$1.1 billion in milestone payments.

Current In-house Programs and Near-term Value Drivers

BI 1467335 has been a long-term value driver for Pharmaxis, but which has now been reduced in potential value. The risk exists that Boehringer Ingelheim could also discontinue development of the drug candidate in diabetic retinopathy. A point to note is that the next potential BI 1467335 milestone uplift is more than two years away (in diabetic retinopathy).

Of more immediate interest to investors should be the signing of a deal for Pharmaxis' Phase II-ready LOXL2 program. The company said discussions with potential partners are ongoing and it has been looking at a range of deal structures, including global and regional deals.

Pharmaxis' LOXL2 inhibitors are designed to inhibit the cross linking of collagen fibres, which is a feature of the latter stage of fibrosis. The indications relevant to the LOXL2 program include NASH and liver fibrosis, IPF, and kidney and cardiac fibrosis.

The company has taken longer than originally expected to conclude a deal for the LOXL2 program. However, when a deal (or possibly the first of several deals) is struck, the stock is likely to rebound, if the terms are reasonable.

In today's conference call Pharmaxis CEO Gary Phillips said that the company had started a small Phase I study to look at the PK/PD profile its LOX2 inhibitor under fed and fasting conditions, but that deal discussions were not contingent on this data.

The company's Pan-LOX program (see *Bioshares* 816) has involved the development of a compound, PXS5505A, that targets all members of the lysyl oxidase family (LOX, LOXL1, 2,3 and 4), which opens up its application for the treatment of pancreatic cancer and myelofibrosis. A Phase Ib multiple ascending dose study is scheduled for completion in Q1 2020.

Pharmaxis will hold discussions with the FDA next year to inform the development of PXS5505A for the treatment of myelofibrosis, an Orphan Drug indication. Myelofibrosis is currently treated with the JAK inhibitors, Jakafi and Inrebic. However, these drugs are noted for causing thrombocytopenia (low platelet counts), anemia (low red blood cell counts), and neutropenia (low levels of neutrophils). PXS5505A could potentially be investigated for use in combination with these therapies.

Pharmaxis has funds to support its current programs, holding $23 million in cash at September 30, with $6.2 million received in October from an R&D tax refund. Another US$10 million is due when Chiesi Farmaceutica launches Bronchitol in the US, expected in Q3 2020. The company is capitalised at $41 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

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