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Companies covered: **ANP, IXC**

	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)	-35.8%
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 - May '19)	-2.3%
Year 19 (May '19 - May '20)	39.5%
Year 20 (May '20 - Current)	3.9%
Cumulative Gain	1032%
Av. Annual gain (19 yrs)	17.3%

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Bioshares

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

Extract from Bioshares –

Invex Therapeutics Completes Phase II Study, Raises $26 Million

Invex Therapeutics (IXC: $1.49), which listed less than a year ago in July 2019 after raising $12 million at $0.40 per share, has successfully completed a 16 patient Phase II study of exenatide in women with idiopathic intracranial hypertension (IIH).

IIH is a debilitating condition of an unknown cause which mostly effects obese women, causing severe migraine-like headaches and vision impairment, and in the longer term, blindness in some. There is no approved drug therapy for patients with IIH. The altitude sickness drug acetazolamide (Diamox) is used off-label but has limited efficacy and is poorly tolerated.

Exenatide was developed as a treatment for type II diabetes (brand name, Byetta) and was approved in Europe in 2006 and the USA in 2005. Invex is repurposing exenatide for the treatment of IIH, and other similar conditions, and has branded its proprietary re-formulated dosage form as Presendin. Unlike the now completed Phase II trial which evaluated 10 mcg of exenatide twice a day, a future Phase III trial will evaluate Presendin as a once-a-day dose form.

Exenatide targets GLP-1 receptors, which are expressed in the choroid plexus in the brain. The proposed mechanism of action for exenatide is that it reduces cerebrospinal fluid secretion which then leads to a reduction intracranial hypertension.

Capital Raising

On May 22, Invex received commitments for $26.2 million, to be received in two tranches. The funds will support the company's planned Phase III program, and a Phase II trial of Presendin, but in the indication of IIH without papilloedema (the swelling of the optic nerve).

Phase II Trial Results

The Phase II trial met its primary endpoints, which was a reduction in intracranial pressure, from baseline to 2.5 hours (p=0.048), 24 hours (p=0.03) and 12 weeks (p=0.058) respectively. The reductions ranged from 18.1% to 20.8%, which were measured objectively using telemetric intracranial pressure sensors implanted in the brain.

The trial was 80% powered to detect a >10% change in intracranial pressure across these three endpoints. The level of significance chosen for the study was p<0.10. This is a more 'liberal' value compared to more common threshold of <0.05.

This <0.10 significance threshold was selected because of the invasive procedure required in the study, which was the implantation of the sensors for a 12-week period. If a p-value benchmark of <0.05 was chosen, the numbers of patients required to complete the study would have been much higher. The time required to complete the study would have been longer and the costs higher. Ethical considerations likely contributed to the need to balance trial numbers against the invasive nature of the trial.

Cont'd over

As Palesch notes in 'Some Common Misconception about P-values' (*Stroke*, Dec 2014), "for a certain Phase II clinical trial, where the safety and efficacy of a new treatment is still being explored, one can argue for a more liberal alpha to give the treatment a higher level of the benefit of doubt, especially when the disease or condition have only a few, if any, effective treatment options."

At the time of the company's IPO in July 2019, 10 patients had completed the trial protocol. The last patient was recruited into the trial in October 2019, completing the 12-week dosing for the trial in January 2020. The company's announcement covering the trial's results shows that 15 patients were included in the final analysis. The 16th patient was excluded from analysis because the sensor implant failed.

Secondary Endpoints

Secondary endpoints were not powered for significance. However, a significant change in monthly headaches by week 12 was observed, with a reduction of 37% (p=0.069) to 14.3 mean monthly headache days.

Another favourable result was that exenatide was shown to improve visual acuity, delivering the equivalent of a one line (of letters) improvement at week 12 (p=0.036). If not for a confounding effect of one patient in the placebo group, which showed an improvement when all others in the placebo group worsened or stayed the same, the difference between the two groups would have been even more convincing.

This visual acuity data may mean that Invex has an endpoint for its proposed Phase III trial that has a fresh relevance, even it is still a secondary endpoint. Patients who face vision loss also face complex and difficult surgical interventions, which have high relapse rates. Therefore a drug which not only halts vision loss but has the potential to improve visual acuity could, if it can be demonstrated in a robust Phase III study, provide the foundations for pricing levels for payors that could be higher, because of the additional benefits that drug could potentially deliver.

Results to be Presented at June Conference

The trial data is expected to be submitted to a scientific publication and to be presented at the 4th European Headache Congress (June 29 - July 2, 2020).

Single Phase III Trial [due to Orphan Drug Designation]

Invex has outlined a single, Phase III trial which would recruit 200-250 patients. Since IIH is classified as an Orphan Drug indication, only one Phase III trial would be required. The trial is planned to commence in H1 2021.

The primary endpoints which are being considered for this 24-week trial (of a dose that has yet to be determined) could be either change in perimetric mean deviation (PMD) at week 24 or the number of monthly moderate-to-severe headache days. PMD is a measure of visual field loss.

One drug that has been used off-label to treat IIH, but with limited success because of negative side effects, is acetazolamide. A 165 patient Phase II/III trial of acetazolamide plus a low salt diet, which was completed in 2014, used the mean change in perimetric mean deviation as its primary endpoint [NCT01003639]. This trial reported a modest improvement in visual field function. This study has been one of three Phase III studies conducted for the indication of IIH, of which two were terminated, according to Clinicaltrials.gov.

After 24 weeks, the placebo arm would receive Presendin, with both arms continuing to receive Presendin for a following 24-week period. This design feature would satisfy ethical considerations for trial participants in the placebo arm, who would not benefit from any efficacy that might occur in the treatment arm. The extension of drug treatment to the placebo group would also expand the safety data set for Presendin.

Possible secondary endpoints could include whichever of the above is excluded as a primary endpoint in addition to visual acuity, optic nerve magnitude, a visual function questionnaire, body weight, quality-of-life and a headache impact test.

Market analysis provided by Invex Therapeutics places the annual incidence of IIH across Europe and the USA at almost 40,000 cases, of which 60% are diagnosed and of those 90% amenable to drug therapy. Invex has proposed a market with 21,500 new cases per annum, and a prevalence market of 92,500. It estimates the annual addressable market for new cases each year to be worth $387 million, using an indicative pricing of $1500 per month of drug.

The growth rate estimated by Invex for new cases is 3.4% per annum, based on growth rates in obesity prevalence in the UK.

Outlook

In our view the likelihood of an acquisition of Invex Therapeutics has increased now that the company has convincingly demonstrated clinical proof-of-concept for exenatide in IIH, has drafted a Phase III clinical study plan and set in motion development for an additional indication.

What would make Invex appealing to a pharmaceutical company are the following:

1. The safety profile of exenatide has been established with the marketed drugs Byetta (a daily dose form) and Bydureon (an extended release form). While these two drugs have limitations, it is the awareness of these limits that have the potential to reduce the development and commercial risk of Presendin. The once-a-week Bydureon has a Black Box warning label, likely reflecting the very high dose of the drug (2mg) compared to the low 10 mcg dose for Byetta administered daily. Warnings and precautions supplied for Byetta relate to reports of fatal and non-fatal haemorrhagic or necrotising pancreatitis, risks of use with sulfonylurea, and with patients with severe gastrointestinal disease and severe renal impairment.

Continued over

– Invex cont'd

2. The NPV of Presendin for IIH, assuming registration in the EU and the USA, the securing of payment for an annual course of treatment of $18,000, for an annual prevalence market of 92,000 patients growing at 3.4% per annum, an 80% penetration rate, and an Orphan Drug designation granting Presendin seven years market exclusivity in the USA and 10 years in Europe, could be upwards of $2 billion. A key assumption is that Presendin achieves very strong market penetration as well as securing premium pricing.

3. The yet to be confirmed Presendin formulation will differ to the currently approved Byetta (10 mcg twice daily) and Bydureon (2 mg weekly), by being a once a day dose. This would confer additional protection against the use of those two drugs in the indication of IIH.

The company's next milestone will be the completion of a PK study of Presendin in animals this quarter, followed by the Phase III trial design in Q3 2020.

Invex Therapeutics is capitalised at $112 million, assuming the issue of 20.15 million new shares and is now funded to complete its Phase III study and commence a Phase II study in a second indication. Invex will have a cash position of $36.6 million, including new capital as cash at hand.

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, Heramed, Imugene, Exopharm, Immutep, Neuroscientific Biopharmaceuticals, Invex Therapeutics