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Companies covered: **ACR, CUV, IMU, NEU, PXS, 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)	-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 - May '21)	86.8%
Year 21 (May '21 - Current)	1.6%
Cumulative Gain	1968%
Av. Annual gain (20 yrs)	20.7%

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Extract from Bioshares –

Neuren - Phase III Enrolment in Rett Syndrome Complete with Readout on Track for Q4

Neuren Pharmaceuticals (NEU: $1.82) has a major inflection point in Q4 this year from the readout of its Phase III study in Rett Syndrome. The study, conducted by Neuren's licensee Acadia Pharmaceuticals was announced as completing enrolment last week.

Patients are treated for 12 weeks with the Neuren drug candidate, trofinetide. In total 184 patients have been recruited across 21 locations in the US. It includes two arms, one being those receiving trofinetide and the other receiving a placebo.

The age group of patients in the study are girls from 5 - 20. This month Acadia also started a trial in 10 younger children, aged two to five, with that trial due to be completed in 2023.

If the Phase III trial is successful and the product is launched in the US, Neuren stands to receive $111 million over the next two years (plus double-digit royalties), which includes proceeds from the sale of a Rare Pediatric Disease Priority Review Voucher. These vouchers sell for around US$100 million and Neuren stands to receive one third of that sale amount. The voucher is an incentive from the FDA to tackle certain rare pediatric diseases. The voucher allows a company to receive a faster review from the FDA for a future drug application, which can be very valuable in terms of an earlier product launch. The voucher can be sold to other companies.

Neuren CEO Jon Pilcher believes that with the trial being conducted only at US sites that a more consistent result may be achieved from the study. The trial is fully powered to deliver statistical significance.

Neuren appears to have selected a good and committed partner for this program. Acadia is forecasting US$500 million in peak sales and has invested around US$100 million into the program. One of the reasons Acadia appears to be a good choice in partner is that this program has high importance for Acadia as well, with one product on the market. That product is a drug called Nuplazid for the treatment of psychosis in patients with Parkinson's disease. Product sales were US$442 million last year. In Acadia's annual report last year, trofinetide is mentioned 56 times.

For Acadia it's also a move away from psychiatric diseases and into rare diseases and it has recently hired a new head of rare diseases drug development.

Continued over

Phase II Trial Results - Recap

In the Phase II study which involved just 27 children in the highest dose (200mg/kg), the endpoints were RSBQ (a caregiver rating) and CGI-I (a clinician rating). These are both the same primary endpoints in the Phase III study which is comparing that same dose against placebo.

On those two measures in the Phase II trial, the result was statistically significant (p=0.042 and p=0.029 respectively). The mean improvement in RSBQ was 16% in the high dose treatment arm compared to 6% in the placebo arm. For CGI-I, 22% of patients receiving the drug therapy showed a much-improved result compared to just 4% on placebo. Of interest, the result appeared to be diverging (difference between placebo and treatment arm) at the end of the six-week treatment and the Phase III study is treating patients for twice as long (12 weeks).

One change in the Phase III study is that the lighter kids will receive a higher dose per weight. This is because they underperformed in the Phase II study, after receiving a lower dose because of their lower weight (patients are dosed according to their weight). The drug is delivered in the form of a solution, 30-60 mls, twice a day.

Other Phase II Studies for New Indications

To help spread the risk for the company, Neuren will be starting three Phase II studies in other indications this half year with its next drug candidate, NNZ-2591. They are in Phelan-McDermid syndrome, Pitt Hopkins syndrome and Angelman syndrome (in Australia). These studies will continue regardless of whether the Phase III results with trofinetide are successful or not.

A fourth Phase II study with NNZ-2591 in Prada-Willi syndrome is also being planned. Obesity is a common characteristic in patients with this syndrome. In a mouse model of the disease, obesity was removed and insulin levels returned to normal.

Summary

Neuren is capitalised at $214 million with $18 million in cash at the end of June. The Phase III trial of trofinetide in Rett syndrome has a good chance of success given the statistically significant result in the smaller Phase II study and that the same endpoints are being used in the Phase III trial.

If the study is clearly positive, Acadia should be in a position to file the drug for approval with the FDA. Neuren will then look to commercialise the drug into other markets including Japan, China and Europe.

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 of 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

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