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Companies covered: **ACR, NEU, PXS, Planet Innovation**

	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)	84.2%
Cumulative Gain	1906%
Av. Annual gain (20 yrs)	20.6%

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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 –

Neuren Pharmaceuticals - Phase III Trial Results Due 2H 2021

Neuren Pharmaceuticals (NEU: $1.38) will be passing through a major inflection point towards the end of this year, with the readout from a Phase III study with its drug candidate trofinetide being conducted by Acadia Pharmaceuticals.

It's also another company that Karst Peak has taken a substantial holding in. In March last year it acquired a 12% stake in Neuren in an off-market sale from Neuren's then largest shareholder Lang Walker.

Trofinotide is a synthetic analogue of a part of IGF-1, glypromate, that has been designed with improved pharmaceutical properties. This is to provide extended half-life in the body, an ability to cross the blood-brain-barrier, and as a compound that has orally-delivered bioavailability, so it can be taken as a tablet rather than injection. Trofinetide has been shown in animal studies to correct poor synaptic signalling in the brain required for basic daily function such as communication, cognition and memory, and in guiding social behaviour.

A Phase II study with trofinetide in 82 girls with Rett Syndrome was completed in 2017 with the results published in the journal Neurology in 2019. Rett Syndrome is a genetic disorder that results in poor synaptic signalling in the brain (as a result of the underdevelopment of dendrites).

Recap of Phase II Results

In that Phase II study the children were treated with either a placebo or trofinetide for six weeks. At the highest dose a statistically significant and clinically meaningful outcome in three measures was achieved. The mean improvement in RSBQ (a caregiver assessment) was 16% compared to 6% for placebo (p=0.042). On the CGI-I score (a clinician assessment) those on the highest dose achieved a mean score of 3.0 which was better than the mean placebo value of 3.5 (p=0.029). Almost a quarter of patients (22%) achieved a much improved score (of 2.0) compared to just 4% in the placebo arm.

On the score of RTT-DSC also measured by clinicians, the high dose group's symptoms improved by 15% compared to a 5.5% mean improvement in the placebo arm (p=0.025). At lower doses (50mg and 100mg) there was no consistent difference to placebo. On the two other assessments, MBA and Top 3 Caregiver Concerns, there was a slightly better result than placebo but it was not statistically significant.

Neuren CEO Jon Pilcher said that clinicians involved with the program believe the results are clinically meaningful.

Continued over

Deal with Acadia Pharmaceuticals & Phase III Trial Design

In 2018 Neuren licensed the North American rights to trofinetide for the treatment of Rett Syndrome (and other indications) to Acadia Pharmaceuticals. The deal included a US$10 million upfront payment, future milestones worth US$455 million and a double-digit royalty from product sales.

Acadia is now conducting a Phase III study with trofinetide in Rett syndrome in 184 females. Two changes from the Phase II trial are: (1) the patients will be treated for twice as long (12 weeks); and (2) the dose will be dependent on patient weight. Importantly the two primary endpoints will be CGI-I and RSBQ, which are measures where statistical significance was achieved in the Phase II trial.

All data from the Phase III study can be used by Neuren to file the compound for approval in other territories outside of North America.

Patients in the Phase III study are being offered to continue treatment with trofenitide after the trial on a compassionate-use basis.

Market Size

There are an estimated 10,000 people living with Rett Syndrome in the US. Assuming a $100,000 a year selling price for an orphan drug such as trofinetide, it represents an addressable market in the US alone of around $1 billion a year.

Second Drug Candidate - NNZ2591

Neuren has a second drug candidate in development, NNZ-2591, which is a variation of trofinetide. NNZ2591 is a chemically modified form of a metabolite of gylpromate, called cGP (cyclic glycine proline).

NNZ2591 is only a dipeptide (not a tripeptide like trofinetide). It is easier to manufacture, has almost double the bioavailability of trofinetide and as such should only require half of the dose. It is manufactured in Europe by a third party and is delivered to patients in liquid form, similar to trofinetide.

Prior to the Phase III trial results in Rett Syndrome, Neuren intends to start three Phase II studies this year in three genetic, neurological disorders. These are in Phelan-McDermid syndrome, Angelman syndrome and Pitt Hopkins syndrome. Using knockout mice, the company has been able to assess the potential efficacy of NNZ2591 in these disorders.

Summary

Neuren finished last year with $24 million in cash. Additional funds may be received from milestone payments from Acadia, with the next milestone likely around filing trofenitide for approval or receipt of marketing approval in the US or Canada.

Acadia has been granted Rare Pediatric Disease designation from the FDA for trofenitide for the Rett syndrome indication. If trofenitide is approved, Acadia may be eligible to receive a Priority Review Voucher. The appeal of the voucher is that it can be applied to another drug approval review by the FDA, shortening the review process by four months. These vouchers can be sold, with the market value around US$100 million. (See Rhythm Pharmaceuticals' deal in January this year.) Neuren is entitled to one third of any proceeds from sale of a Priority Review Voucher by Acadia.

Neuren Pharmaceuticals is capitalised at $155 million.

Forthcoming Milestones

- Start of Phase II study in Phelan-McDermid syndrome
- Start of Phase II study in Angelman syndrome
- Start of Phase II study in Pitt Hopkins syndrome
- Results from Phase III study in Rett syndrome
- License rights to Europe for trofenitide
- License rights to Asia for trofenitide

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

Sell

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