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Bioshares

7 December 2021
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Delivering independent investment research to investors on Australian biotech, pharma and healthcare companies

Companies covered: NEU

	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)	5.5%
Cumulative Gain	2046%
Av. Annual gain (20 yrs)	20.7%

Positive Phase III Trial Results for Neuren Pharmaceuticals

Neuren Pharmaceuticals' (NEU: $3.25) partner, Acadia Pharmaceuticals, has released positive top-line results from its Phase III study in Rett syndrome with a drug candidate, trofinetide, licensed from Neuren. The trial reached statistical significance on both primary endpoints as well as with a secondary endpoint relating to improved communication.

Acadia plans to file the drug candidate for approval mid next year with the FDA, with rest-of-world rights remaining with Neuren. Over 2022 and 2023 Neuren expects to receive around $111 million from milestone payments and also from one third of the value of a Rare Disease Priority Review Voucher (US$50 million and US$33 million respectively). The company will be entitled to a royalty from product sales, we estimate starting at between 10%-12% and increasing to around 15% as sales increase. Peak sales for the drug of around US$500 million per annum in the US could be achievable. Total future milestone payments that Neuren is eligible to receive amount to US$455 million.

The trial conducted by Acadia was in 187 girls and young women with Rett syndrome. Rett syndrome is caused by a rare genetic mutation that causes brain development impediments in females due to a lack of synaptic function causing communication malfunction in the brain. Trofinetide's method-of-action is to supplement IGF-1 levels in the brain to help support cognitive, behavioural and motor function. (It is an orally available synthetic analogue of a section of IGF-1.)

Neuren was the first company to conduct a clinical study in Rett syndrome. Given the new therapeutic area, the FDA requested that both primary endpoints be met in the Phase III study. Statistical significance was met on the measure of Rett Syndrome Behaviour Questionnaire (RSBQ) (p=0.003) and the Clinical Global Impression of Improvement (p=0.0175). The efficacy results were unambiguously positive and consistent across all age groups irrespective of the severity of disease. On the RSBQ measure, there was improvement in all eight measures that contribute to this assessment score.

On the safety profile, trofinetide did cause mild-moderate diarrhea and mild-moderate vomiting in some patients in the study (80% compared to 19% in placebo and 27% compared to 10% on placebo respectively). However more than 95% of study participants elected to continue with treatment into the open label phase after the 12 week treatment period. There was a 17% discontinuation rate (compared to 2% for placebo) due to treatment emergent adverse events.

On a conference call this week, Neuren CEO Jon Pilcher highlighted that constipation is common and a significant chronic issue with this patient population. Diarrhea management protocol was optimised during the study.

Continued over

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Bioshares Model Portfolio (7 December 2021)

Company	Code	Price (current)	Price added to portfolio	Recommend-ation	Cap'n ($M)	Date added
Clinuvel Pharmaceuticals	CUV	$28.68	$20.31	Buy	$1,417	November 2020
Neuren Pharmaceuticals	NEU	$3.25	$3.25	Spec Buy A	$410	December 2021
Immutep	IMM	$0.47	$0.32	Spec Buy A	$396	March 2019
Cogstate	CGS	$2.35	$0.24	Accumulate	$402	April 2019
Opthea	OPT	$1.15	$0.16	Spec Buy A	$400	November 2014
Aroa Biosurgery	ARX	$1.06	$1.11	Spec Buy A	$361	November 2021
Antisense Therapeutics	ANP	$0.18	$0.22	Spec Buy A	$131	November 2021
Micro-X	MX1	$0.27	$0.38	Spec Buy A	$124	May 2017
Anteris Technologies	AVR	$8.50	$8.70	Spec Buy A	$122	December 2021
Chimeric Therapeutics	CHM	$0.26	$0.27	Spec Buy A	$87	December 2021
Patrys	PAB	$0.036	$0.013	Spec Buy B	$74	July 2020
Cynata Therapeutics	CYP	$0.50	$0.70	Spec Buy A	$72	December 2020
Dimerix	DXB	$0.23	$0.09	Spec Buy A	$57	December 2018
Pharmaxis	PXS	$0.10	$0.26	Spec Buy A	$46	December 2016
Acrux	ACR	$0.10	$0.31	Spec Buy A	$28	July 2017

Portfolio Changes

IN:
Neuren Pharmaceuti-cals has been added at $3.25

OUT:
No changes

Stocks Removed from Bioshares Portfolio in TTM

Date removed	Stock
September 2021	LBT
July 2021	1AD
June 2021	CYC

There are currently no approved therapies for Rett syndrome. Trofinetide is eligible for priority review by the FDA (up to three months faster) under the Orphan Drug Designation. Acadia management stated that there is alignment with the FDA that one Phase III study would be sufficient to file the drug for approval if there was a positive result in both primary endpoints. Acadia is currently conducting a supplementary study in girls aged two to five. That trial is progressing well according to Acadia with data from that study expected to be included in the NDA submission.

Trofinetide is protected out to 2035 under a method-of-use patent for the treatment of Rett syndrome.

Summary

Neuren Pharmaceuticals is very well placed with the potential for significant revenue streams from milestone payments, proceeds from the sale of the Rare Pediatric Disease Priority Review Voucher and royalties from product sale if trofinetide gains FDA approval. The chances of approval could be considered high given the unambiguous efficacy results, with the side of diarrhea being manageable and arguably preferred to the existing constipation effect common in people with Rett syndrome.

The positive outcome also provides additional optimism for Neuren's second drug candidate, NNZ-2591. This compound is a dipeptide (not a tripeptide like trofinetide) and is a chemically modified form of a metabolite of glypromate (cyclic glycine proline). Its bioavailability is substantially better than trofinetide, which means a lower dose can be used and likely lower side effects. It is also easier to manufacture.

Neuren is now also in a position to out-license the rest-of-world rights to trofinetide, with data from Acadia's studies available to Neuren. The company will consider single country deals, regional deals, or a full rest-of-world licensing deal.

For the year ahead the focus for Neuren is to conduct its four Phase II studies with NNZ-2591.

Neuren is capitalised at $410 million.

Bioshares recommendation: **Speculative Buy Class A**

Neuren has been added to the Bioshares Model Portfolio.

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

Corporate Subscribers: Cogstate, LBT Innovations, Opthea, ResApp Health, Pharmaxis, Dimerix, Adalta, Actinogen Medical, Patrys, Antisense Therapeutics, Imugene, Exopharm, Immutep, Invex Therapeutics, Anteris Technologies, Chimeric Therapeutics, Neuren Pharmaceuticals, Neurotech International

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