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BIOSHARES

Australia's Independent Biotech Investment Resource, est.1999

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Companies covered: ACW, BB1, OPT, SNT, TLX

	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 - May '22)	-15.6%
Year 22 (May '22 - Dec '22)	-2.2%
Year 23 (CY2023)	-15.4%
Year 24 (CY2024)	40.8%
Year 25 CY2025 (current)	-0.6%
Cumulative Gain	1887%
Av. Annual gain (24 yrs)	17.6%

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Extract from Bioshares –

Actinogen Medical - Progressing its Phase IIb/III Alzheimer's Study

Actinogen Medical (ACW: $0.034) has now conducted multiple clinical studies with its lead compound Xanamem, which was recently assigned the official name *emestedastat*.

Actinogen has treated approximately 400 patients with this compound, resulting in its safety profile being well understood and appears to be acceptable as a daily, chronic treatment option for multiple diseases.

The lead indication is in Alzheimer's disease, with a 220-patient Phase IIb/III study underway. The second indication is in depression, although progression of that clinical development has been paused at this point to focus on the lead program, with the company not meeting the primary endpoint in that study.

Interim Analysis

Actinogen expects the first 100 patients in its current Alzheimer's disease study to be enrolled and to have commenced treatment by mid-year, with around 40 patients currently receiving treatment as of the end of January this year.

An interim (futility) analysis is expected to occur towards the end of this year based on blinded data from the first 100 patients who have received treatment for 24 weeks.

The 220 patients to be enrolled in the study will be treated for 36 weeks, with either a daily oral dose (10mg) of Xanamem or a placebo, with patients divided equally between the control and active arms.

Final Results

There are 25 sites recruiting patients with mild-moderate dementia due to Alzheimer's disease. Of these, 15 are in Australia and 10 are in the US. Actinogen's CEO Steven Gourlay said that the US sites are very active, with the first patient treated in the US in December last year, and the first Australian patient treated in April last year.

Final results are expected in the second half of next year from all patients treated in the study for the 36-week period. These results were previously expected in the first half of next year, indicating a six-month delay in trial progress.

Gourlay said that because the study is recruiting patients with more advanced stages of disease than the patients receiving beta-amyloid targeting drugs, there is less competition for those patients. *(Note: The Actinogen study is targeting patients with an MMSE score of between 18-26, with 30 considered normal. By comparison, Eisai is conducting a combination study with its beta-amyloid targeting drug Leqembi with a tau inhibitor in patients with an MMSE of 22 or higher, meaning those patients are less advanced.)*

Continued over

Patent Protection

The Composition-of-Matter patents around Xanamem expire from 2031, with up to five years extension possible. There is also a 10-year data exclusivity period in Europe from when a therapy first reaches market, and five years exclusivity in the US and Australia. The company has additional patents around Manufacturing (less strong) and Use patents for other indications, including for depression and for improving cognition in healthy subjects.

Previous Phase II Trial Results

Actinogen completed a Phase II study in 2019 in 185 patients with mild-moderate Alzheimer's disease. That study explored the same dose of 10mg daily of Xanamem versus placebo. It was two years for the study to reach its primary endpoint, conducted also at 25 sites. However, there were two main differences with the current study underway.

The first was that the earlier study treated patients for just 12 weeks. The current study is treating patients for 36 weeks, with a futility analysis at 24 weeks as indicated above.

The second significant difference is explained as follows. The previous study largely enrolled all patients within the set cognitive range, noting there were multiple other entry criteria as well. However in the current study, only patients with elevated plasma pTau181 protein levels are included.

In the past five years, research has shown that high levels of pTau181 are associated with the progression of Alzheimer's disease in patients with Mild Cognitive Impairment. This compares to people who develop non-Alzheimer's dementia and generally do not have elevated levels of this biomarker.

In Actinogen's first Phase II study (reported in May 2019), 10mg per day of Xanamem did not show any cognitive improvement compared to the control. However, further analysis of stored plasma samples from 72 patients was conducted.

Focusing on the 34 patients with high pTau181 levels (above the mean), it revealed a 0.6-point mean improvement on the CDR-SB scale over 12 weeks, compared to placebo.

This benefit is greater than the 0.45-point improvement seen with Leqembi (Eisai/Biogen) over 18 months, and slightly less than the 0.7-point improvement from donanemab (Eli Lilly), also over 18 months. Gourlay acknowledges that the patient population in this analysis is low.

In the current study, all patients being recruited have elevated pTau181 levels, which the company expects will deliver a contrasting, positive result to the previous Phase II study reported in 2019.

Other Trials Completed - Phase II Depression Study

In August last year Actinogen reported results from a Phase II study in 165 patients with depression. The primary endpoint was not met, prompting a 59% decline in the company's share price on the day of the results being announced.

On the primary endpoint – which Gourlay admits now was the wrong endpoint to use – there was no benefit over placebo, measured via changes in an attention composite assessment. There was an unexpectedly large placebo effect, with that group improving by 0.4 points and the treatment arm increasing by 0.3 points. The treatment duration was 6 weeks.

However, on the secondary endpoint measure of symptoms of depression (MADRS), there was a 1.5 point benefit in the Xanamem arm over placebo at the end of the six-week period. This increased to a 2.7 point benefit four weeks after treatment stopped, potentially due to the partial removal of the placebo effect.

The impact was more pronounced in patients with lower levels of depression (MADRS score less than 26), showing a 3.7-point improvement with Xanamem compared to placebo.

Additionally, patients not taking antidepressants experienced a greater benefit, with a 4.3 point improvement over placebo. However, a clinically meaningful result is typically considered a minimum of a 6 point improvement on the MADRS scale.

Learnings to Date

Over the 10 years of the clinical development of Xanamem, there have been significant learnings around the compound, which works by lowering cortisol levels in the body.

Firstly, the company has conducted PET imaging scans that shows sufficient target inhibition in the brain can be achieved at between 5-10mg/day oral dose of Xanamem. Previous studies had been conducted using a 20mg/day dose. Inhibiting the target (11beta-HSD1) subsequently blocks the production of the stress hormone cortisol.

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Clinical Results with Xanamem

Stage	Reported	Indication	Endpoints met	Endpoints not met	Period of study	Number of subjects
Phase II	2019	Mild Alzheimer's disease	0.6 point benefit on cognition (CDR-SB) in patients with high pTau181 levels	No benefit over placebo in cognition overall	12 weeks	185 (34 with high pTau181)
Phase Ib	2022	Healthy older volunteers	Enhances attention, psychomotor function and working memory	No dose response, with lower dose showing better outcome. No effect in non-attention (IDSSTS)	6 weeks	107
Phase II	2024	Depression (MDD)	1.5, 3.7, 4.3 point benefit in MADRS depression scale in all pts, pts with more mild depression, and pts not on antidepressants respectively.	No benefit over placebo in cognition, with high placebo effect	6 weeks	165
Phase IIb/III	Ongoing	Mild Alzheimer's disease, with high pTau181	Study underway	Study underway	36 weeks	220

The safety profile of the compound appears benign and has been well characterized from long term preclinical studies, and has been validated by dosing around 400 patients and volunteers.

Studies in healthy, older volunteers have shown Xanamem to have a positive impact over six weeks on working memory, visual attention and psychomotor function, at both 5mg/day and 10mg/day.

From the company's Alzheimer's disease studies, it has been shown that 10mg/day is an effective dose (half-life of 10-14 hours), and that slowing down of cognitive decline can be achieved in patients with high levels of the protein pTau181.

In the indication of depression, it has been shown that the compound Xanamem has a positive impact on symptoms, with the effect greater in patients with less severe depression, and in those not taking antidepressants.

Application of Learnings

In Actinogen's Phase IIb/III study, the company is investigating the effect of its compound it a larger patient population, and for a longer treatment period which will help identify the treatment effect. It is also selecting patients with high levels of pTau181 which is an indicator of Alzheimer's induced dementia.

Capital Raisings

Actinogen finished last year with $22.9 million in cash. It raised $20 million in 2024 at $0.025 and $0.03 a share in two separate raisings, as well as receiving a $9 million R&D tax rebate. The company's cash outflow from operations in FY24 was $17 million.

Gourlay also participated in the last funding rounds for Actinogen, bringing his total investment in Actinogen up to $2 million.

Summary

Actinogen has spent over a decade in building the clinical data and knowledge around its drug candidate Xanamem. The safety profile has been well characterized with no safety or tolerability concerns.

Developing therapies to treat CNS conditions is challenging. Nonetheless, the potential reward in developing a therapy that can assist with slowing cognitive decline in Alzheimer's disease is very high.

Gourlay said that many of the steps required for development success have been passed: long- and short-term toxicology studies have been completed, with an outstanding safety profile; manufacturing has been de-risked; the drug blocks the target in the brain, crossing the blood-brain-barrier, the company knows the correct dose to use; and its biomarker studies show why the last trial in Alzheimer's disease was not successful. Gourlay also believes there is a low regulatory bar, given the limited available treatment options.

Of particular interest in the current study will be not just the short term efficacy, but whether a prolonged benefit occurs, indicating disease modification.

A positive outcome from Actinogen's Phase IIb/III study will provide the company with the opportunity to secure a lucrative licensing deal, which may be regional or for global rights. Any licensing transaction will likely occur at the end of the current Alzheimer's disease study, at the end of next year.

Actinogen Medical is capitalized at $107 million.

Bioshares recommendation: **Speculative Buy Class B**

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, Syntara Dimerix, Patrys, Imugene, Chimeric Therapeutics, Neuren Pharmaceuticals, Aroa Biosurgery, Anteris Technologies, Immuron, Clinuvel Pharmaceuticals, Botanix Pharmaceuticals, Island Pharmaceuticals, Clever Culture Systems, Actinogen Medical