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*Daily news on ASX-listed biotechnology companies*

# Dr Boreham's Crucible: Alterity Therapeutics

**By TIM BOREHAM**

**ASX code:** ATH; **Nasdaq code:** ATHE

**Share price:** 1.0 cent

**Shares on issue:** 6,656,848,719

**Market cap:** $66.6 million

**CEO:** Dr David Stamler

**Board:** Geoffrey Kempler (chair), Peter Marks, Brian Meltzer, Lawrence Gozlan

**Financials (December quarter 2024):** revenue nil, cash outflows $5.06 million, end of quarter cash $4.54 million (ahead of $40 million capital raising)

**Identifiable holders:** Bank of New York Mellon Corporation (American depository receipt holders) 34%, Kyriaco Barber Pty Ltd 1.22%, MST Financial Services 0.99%, Andrew Mark Wilmot Seton 0.83%, One Managed Funds 0.81%, Amanda Kay Lang 0.75%, Capuano Nominees (Hartman Investment Account 0.75%), Jagen Pty Ltd (Boris Liberman) 0.72%

Let's face it, when you're a drug developer it helps to have a 'celebrity sufferer' to raise awareness.

In the neurological disease sphere, Muhammed Ali flew the flag for Parkinson's disease, as does Michael J Fox.

Ronald Reagan was a high-profile Alzheimer's disease sufferer – possibly even during his presidency - while motor neuron disease became a household name through Stephen Hawking and, locally, former AFL footballer Neale Daniher.

Multiple system atrophy (MSA) is not exactly a household word - a state of affairs that Alterity is seeking to change.

The company is carrying out two ongoing phase II trials for MSA, a so-called Parkinsonian disorder characterised by similar gait problems, shuffling and tremors.

ATH-434 could also be relevant for other 'orphan' neurological diseases such as Friedreich's ataxia and the big prizes of Parkinson's disease and Alzheimer's disease.

On January 30, Alterity shares more than doubled after one of its phase II MSA studies achieved "statistical significance", with an up to 48 percent slowing of the debilitating disease in early-stage patients (see below).

This month the company followed up with a $40 million capital raising.

Of course it did.

**True to name, Alterity strives to be different**

Then known as Prana, the company was founded in 1997 by Geoffrey Kempler (its current chair) and Boris Liberman, a scion of the billionaire Melbourne Liberman family.

The technology is based on science developed in-house and with the help of boffins from Victoria's Mental Health Research Institute, the Florey Institute, the University of Melbourne and Massachusetts General Hospital.

Prana listed on the ASX in 2000 and a Nasdaq listing followed in 2002. "We wanted to single-handedly cure Alzheimer's," Mr Kempler said in 2018.

Prana at one stage was worth $800 million.

But in early 2014, Prana shares tumbled 70 percent on news that its imaging trial for Alzheimer's disease did not meet its primary endpoint of reducing amyloid beta plaques implicated in the disease.

A phase II trial for Huntington's disease using a different compound met some success - but not enough - and the company turned its gaze to multiple system atrophy.

"Rather than saying there's the disease and let's find the drug, we already had the drug so we found the disease," Mr Kempler said.

In April 2019, Prana changed its name to Alterity, which means 'the state of being different'.

**Been there, done that**

Mr Kempler bluntly reminds everyone that most drugs don't get anywhere near approval stage.

So, drug developers need to tilt the odds in their favor - and how better a way than to appoint someone who has done it all before?

Alterity's CEO since 2021, Dr David Stamler was involved in four drugs - three in neurology - that went on to be approved by the US Food and Drug Administration (FDA).

At Auspex Pharmaceuticals, Dr Stamler was responsible for the approval of Austedo, or deutetrabenazine, a treatment for the chorea associated with Huntington's disease, a neurological disorder resulting in jerky movements of the shoulders, hips and face.

Auspex was acquired by Teva Pharmaceuticals in mid-2015 for a handy $US3.5 billion.

Dr Stamler stayed at Teva for two years. Like a pharmaceutical Pied Piper, he took most of his key team with him when he joined Prana as chief medical officer in May 2017.

Mr Kempler said he "literally chased David around the world with a butterfly net" - he's figuratively speaking, presumably - to capture his services.

"Getting drugs approved is extremely difficult, so to get it done three or four times is astonishing," he says.

**What's the problem?**

With around 15,000 US sufferers, the FDA classes multiple system atrophy as an orphan disease. (In contrast, there are up-to 1.5 million Parkinson's disease patients).

"Typically, sufferers have trouble walking and have bladder and bowel problems," Dr Stamler says.

"More than half of them will need a wheelchair five years after symptoms appear."

While some drugs deal with the symptoms, there is no cure.

Alterity's lead compound ATH-434 targets the protein alpha synuclein, which is present everywhere in the body and plays a key role in neurons communicating with each other.

As with Fortescue Metals, the story is all about iron. The metal is essential to life, but excess amounts in the brain cause these proteins to clump together and they lose their ability to neuro-transmit.

"For reasons not well understood, there often is excess iron in the brain," Dr Stamler says.

“That iron imbalance causes oxidation of free radicals and creates oxidative stress, an inflammatory response and nerve death.”

He describes ATH-434 as a “chaperone” which takes the excess iron and deposits it in less harmful parts of the body.

The key is to enable the molecule to bind to the iron tightly - but not so much that it won’t let go.

But is the excess iron a symptom - or cause - of the disease?

The answer is chicken-and-egg.

“It’s probably both,” Dr Stamler says.

“I don’t think anyone knows for sure, but we do know it’s not normal for the iron to be there.”

Given it is a small molecule, ATH-434 is easily administered as a tablet. Given patients would need to take it for the rest of their lives, this is just as well.

**In the clinic (1)**

Alterity is carrying out two ongoing phase II trials for MSA, after a phase I study in healthy volunteers showed “excellent safety and concentration in spinal fluid, consistent with efficacy in animal models”.

ATH-434-201 is a 77-patient, randomized, double-blinded, placebo-controlled effort - the “gold standard” of study designs.

January’s results showed 48 percent of patients had a “slowing of clinical progression” on a 50-milligram dose at week-52, relative to placebo.

This was measured by the Unified Multiple System Atrophy Rating Scale (Umsars), which assesses the ability of patients to undergo daily activities.

The results also showed “preservation of brain volume”.

Somewhat oddly, the 75mg dose showed a 62 percent slowing at week-26, but only a 29 percent response at week-52.

Nor surprisingly, the company is pondering the discrepancy.

Nonetheless, Dr Stamler says the company is “thrilled that ATH-434 has demonstrated significant slowing of clinical progression and an excellent safety profile in this rare, rapidly progressive disease.”

**In the clinic (2)**

The second study (ATH-434-202) is an open-label exercise that enrolled 10 patients in advanced stages of the disease.

An interim six-month assessment, in July 2024, showed that three of seven patients had improved daily living function, as measured by Umsars.

The endpoint was a reduction in accepted symptoms such as problems with speech, swallowing, urinary and bowel functions and walking.

Overall, three of 10 had a “clinical response” - improved symptoms and stable iron levels in the three parts of the brain affected by multiple system atrophy. Brain volume was stable between six and 12 months.

“That was unexpected in a patient population like this, which has an inexorable decline and deterioration in symptoms,” Dr Stamler says.

Topline results are expected by July 2025.

**What’s next?**

Alterity plans to meet with the FDA to discuss the potential for fast-track approval.

Dr Stamler notes that the FDA has been willing to approve drugs on biomarker data only. Two years ago, the agency did so on this basis for Biogen’s drug Qalsody (toferson), for a genetic form of amyotrophic lateral sclerosis (ALS, a form of motor neuron disease).

“If we get clear biomarker efficacy and any [clinical] benefit, we will have a very active discussion with the FDA to accelerate approval and skip the next stage [a phase III trial],” Dr Stamler says. “It depends on the strength of the data. With an untreated disease, if you show robust efficacy the FDA will take it seriously”.

**Finances and performance**

On February 10, Alterity said it would raise $40 million by way of a two-tranche placement to advance ATH-434. The fully subscribed placement was done at 1.1 cents per share, an 8.3 percent discount. The issue includes one free option for every three shares subscribed for, at an exercise price of 2.8 cents, on or before February 26, 2027.

In February 2024, the company raised $5.25 million, in a placement and share plan at 3.8 cents and 3.5 cents per share respectively (with attached options).

At the end of December 2024, Alterity had $5.06 million in the bank. With the first tranche of the raising banked and a Federal Research and Development Tax incentive of $5.7 million due in the current quarter, Alterity is more cashed up than a sailor on shore leave.

The company burnt through just over $5 million in the December quarter. Management estimates once the trials are completed, quarterly spend will fall to between $1 million to $1.5 million. The study is costed at $US15 million and the company estimates it has spent $40 million to $50 million to get the MSA program to this point.

On average, a small molecule orphan drug in the US sells for $US200,000 a year. Given the small number of MSA patients - an estimated 15,000 in the US - management believes insurers would not deny a therapy to advanced-stage patients.

Over the last five years Alterity shares have traded as high as 6.0 cents (August 2020) and a record low of 0.2 cents in the second half of 2024. The stock hit an all-time high of $2.50 in mid-2002.

**Dr Boreham's diagnosis:**

Dr Stamler stresses the company intends ATH-434 to be a therapy, rather than a cure.

"The notion of curing a disease where you don't know the underlying process gives a sense of false hope," he says. "Cure is too high a bar … but if you can extend quality of life, that is good."

Meanwhile, Alterity is the only ASX-listed biotech working on the 'brain iron overload' theory.

"There's an urgent need to find something to slow down the progression of this disease," Dr Stamler says. "Without an effective treatment, patients won't come out of the shadows."

Dr Stamler laments Alterity's lowly share price, which is only partly attributable to the US biotech sector's difficulties.

"When we raised funds in 2021, we had a market cap that was multiples of our current valuation," he says. "We get good news and the share price goes up, but [then] people take money off the table."

At the same time, Alterity slowly is becoming de-risked as the phase II studies advance.

"It's a source of frustration, so I can only do the best I can and tell the story."

***Disclosure: Dr Boreham is not a qualified medical practitioner and does not possess a doctorate of any sort. He can only do his best and tell the story.***