Alterity Therapeutics

Initiation of Coverage

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An undiscovered gem

Alterity (ATH.AX), formerly Prana Biotechnology (PBT.AX), is trialling ATH434 (PBT434) in Parkinsonian diseases, a group of neurodegenerative disorders associated with aggregation of alpha-synuclein (α-syn), a cell protein. ATH434 is in clinical trial for its first target, Multiple System Atrophy (MSA).
MST valuation presents upside to ATH's current trading value. Newsflow over short-medium term is likely to create investor interest.

MSA offers strategic advantages

Management's decision to target MSA first is sound. It is a rare, fatal disease. ATH has received orphan drug status for MSA conferring 7 and 10 years of market exclusivity in US and EU respectively. There is no approved treatment for MSA, creating an unmet need. Regulatory bodies are keen to assist new therapies. MSA progresses quickly offering clinical trial efficiencies.

ATH434 addresses the 'primary' cause

ATH434 promises a different approach. It is targeting the disease at an early stage, acting to prevent the 'trigger' of the aggregation of α-syn. The approach contrasts to many other drugs in development, which target 'downstream' disease manifestations, such as inflammation or reduction of the aggregation after it has formed.

Proof to date supports efficacy and safety

ATH434's Phase I trial data support the drug's safety and pharmacokinetic profile. In terms of efficacy, preclinical studies showed a reduction in the pathological markers of MSA and a related disease, Parkinson's Disease (PD). They also suggest a neuroprotective function, potentially halting the fatal disease's progression.

Management is a key asset

Both ATH CEO, Geoffrey Kempler and Senior Vice President/Chief Medical Officer, David Stamler bring extensive experience in drug development, particularly in neurology. Dr Stamler has led 3 FDA approvals in neurological disorders. We believe his expertise opens the opportunity to fully leverage ATH434's potential and is unique in the Australian biotech sector.

Valuation: A$82.8m on risk adj. DCF

MST valuation of $82.8m, $0.076ps is based on a risk adjusted DCF and is supported by comparison to ASX listed drug development companies, Immutep (IMU.AX) of A$98m, Immugene (IMM.AX) of A$195m and Kazia Therapeutics (KZA.AX) of A$53m. The valuation is subject to the usual risks and sensitivities of new drug development.

Alterity Therapeutics, formerly Prana Biotechnology (PBT.AX) is an ASX listed biotechnology company that is targeting a group of neurological diseases known as α- synucleinopathies. It is planning a Phase 2 trial for ATH434 in the treatment of MSA.

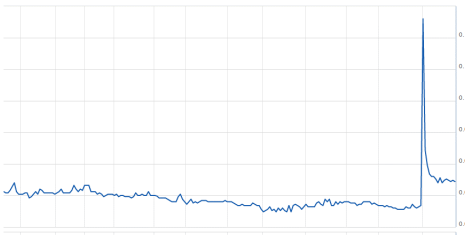
Stock	ASX: ATH
Price	A$0.036
Market cap	A$39.06m

Company data	
Net cash (31/03/20)	A$10.4m
Shares on issue	1.09bn
Options and Rights Outstanding	25.3m
Code ASX	ATH.AX
Primary exchange	ASX

Next steps

H2CY21 IND submission to FDA
H2CY21 Commence Phase 2 trial
H2CY22 Results Phase 2 trial
CY23 Commence Phase 3 Trial
H2CY25 Results Phase 3 Trial
CY26 Potential Market Entry

ATH.AX Share price performance 12 months



Investment Thesis

The investment thesis for ATH is threefold:

Management

ATH's management offers indepth experience in drug development, particularly in neurological disease. It brings a number of advantages. Many biotechs license their R&D after positive Phase 2 trials. Licensing at this stage reduces development risk but is also likely to limit reward. It also bears the risk of loss of control, with big pharma companies constantly re-prioritising their drug portfolios.

For ATH, there is logic continue the development. The primary driver is the experience of Senior Vice President, Dr Stamler. He has led three successful FDA approvals for neurological conditions. It would be difficult to find someone who can offer more regulatory/commercial experience in the area as well as the intimate knowledge of ATH434 in MSA. Secondly, the cost and length of the Phase 3 trial would be relatively moderate due to the nature of the disease.

Valuation

Valuation of ATH by both a risk adjusted DCF and comparison to ASX peers shows considerable upside to its current value. We believe that with the expected increasing newsflow of ATH434's progress, investors will have the opportunity to better understand the ATH proposition and recognise the value opportunity.

Attractive targets

In drug development, neurological conditions usually carry higher risk and this must be recognised in consideration of investment in ATH as well. There is also considerable upside.

- MSA is a rare disease. ATH has received Orphan Drug status for the key markets, US and EU, providing market protection from generic competition for 7 and 10 years respectively and expedited review.
- MSA is a rapidly progressing disease, reducing the length and hence expense of the clinical trial program. The more frequent newsflow is likely to create investor interest.
- MSA is a fatal disease. There is no approved treatment, creating an open market opportunity.

Expected Forthcoming Milestones

- H2CY21 IND submission to FDA
- H2CY21 Commence Phase 2 trial
- H2CY22 Results Phase 2 trial
- CY23 Commence Phase 3 Trial
- H2CY25 Results Phase 3 Trial
- CY26 Market Entry

Compromised α-syn → nerve cell dysfunction and death

ATH (formerly Prana Biotechnology, PBT.AX) was founded on the concept of interrupting the protein misfolding that underlies a number of neurological disorders. ATH is targeting the neurodegenerative disorders that arise from the misfolding and aggregation of the protein, α-syn, referred to as synucleinopathies.

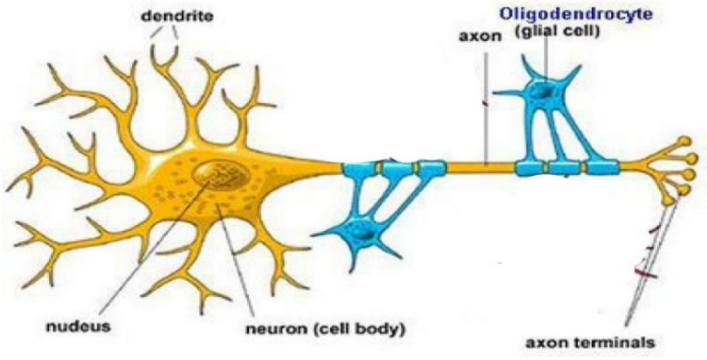
α-syn, an abundant protein in the brain, plays an integral role in nerve cell function. It is active in

- the myelination processes which 'insulate' neurons
- the release of neurotransmitters such as dopamine and serotonin.

Both are important for efficient nerve conduction. α-syn aggregation disrupts the cellular activities, leading to

- impaired myelination of the nerves
- activation of inflammatory microglia cells
- disturbance of autophagy (the cells' own disposal system)

Figure 1 –Neurones and support cells



The efficiency of the neural pathways is assisted by a system of support cells and myelin, a lipid-rich (fatty) substance that surrounds nerve cell axons. Myelin surrounds nerve cell axons to insulate them and increase the rate of nerve conduction. Myelin is formed by support of glial cells called oligodendrocytes.

Figure 2 – Pathological cascade to α-syn aggregation

Pathway to MSA

Excess Labile iron

↓

Reactive iron combines with oxygen and water

↓

H_2O_2 + reactive iron

↓

Free Radicals
•OH + HOO•

Mitochondrial dysfunction	Microglial cell activation	Aggregated proteins
Powerhouse of the cell driving the cells processes	Inflammation	α-synuclein dysfunction

Neuronal cell death

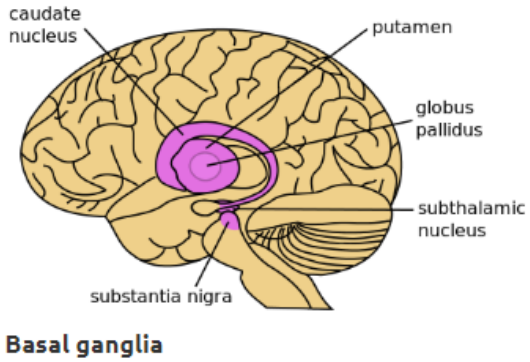
The pathology of α-syn aggregation shows excess iron as an integral factor. It is believed to trigger a cascade of downstream effects such as Reactive Oxygen Species, α-syn aggregation, cell inflammation, and mitochondrial dysfunction leading to cellular impairment and death.

Multiple Indications - first target MSA

Aggregated α-syn is found in a number of diseases, presenting ATH with multiple targets. They include Multiple System Atrophy (MSA), Parkinson's Disease (PD) and dementia with Lewy Bodies Disorders (LBD). Each disease is characterised by abnormal α-syn. The different symptoms reflect which areas of the brain are affected. They all share 'parkinsonism' symptoms; slow movement, muscle rigidity and/or tremors. The resulting abnormal gait and balance problems are also important sources of morbidity.

Figure 3 – Areas of the brain associated with synuleinopathies

Movement or motor areas of the brain are particularly associated with the Basal Ganglia (BG), a group of functionally linked brain nuclei that regulate and fine-tune voluntary and involuntary movement. The cerebellum (not highlighted) is also important in controlling balance and fluidity or smoothness of movement.



MSA affects the Basal Ganglia (BG) and/or cerebellum and intermediolateral nucleus in spinal cord.
PD mainly affects the Substantia Nigra pars compacta (SNpc).
LBD is more widespread with aggregated α-syn found in multiple areas including those associated with thinking, emotion and motor areas.

MSA is ATH's first target.

In MSA, the aggregated α-syn is found primarily in oligodendrocytes, a glial support cell, and to a lesser extent in neurons. Referred to as Glial Cytoplasmic Inclusions (GCI), these protein deposits are accompanied by axonal degeneration and microglial activation, leading to neuroinflammation, impaired cellular function and neuronal loss. Ultimately, death of the cell leads to an irreparable loss of function.

ATH434 in MSA

Clinical Trials

A Phase 1 trial in healthy subjects, at single and multiple ascending doses, demonstrated a good safety profile and tolerability. Pharmacokinetic data demonstrated that ATH434 is orally available and readily crosses the Blood Brain Barrier (BBB). There were no serious adverse events. Phase 2 clinical trials are being planned, with trials in the US, EU and Australia expected to commence from H2CY21.

Phase 1 data supports safety. There is also support of ATH434 potential efficacy through extensive preclinical data.

Preclinical data

Table 1 – Preclinical studies show ATH434 is effective in addressing the pathology of MSA and PD

Effect of ATH434 on pathological signs	ATH434
Iron reduction	√
Oxidative stress reduction	√
Ferroportin level reduction	√
SYN aggregation reduction	√
SNpc cell preservation	√
BG interconnectivity preservation	√
Movement ability preservation	√

Source: Finkelstein et al. Acta Neuropath Comm (2017) 5:53, Company reports

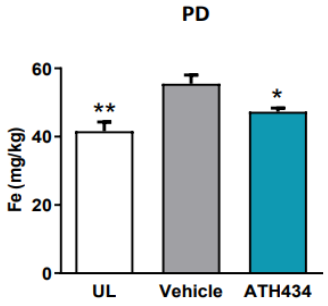
ATH434 has been the subject of number of preclinical studies, in vitro and in vivo, in both MSA and PD. As both conditions share similar underlying pathology, both are included in the discussion. The studies have shown that ATH434 addresses the hallmarks of the disease including increased cellular iron, α-syn aggregation and GCIs.

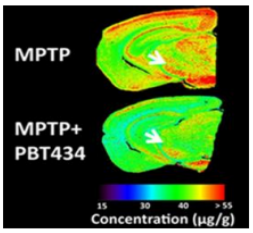
Importantly, they have also shown a reduction in the loss of neuronal cells and an improvement in motor function. The preservation of the cells may indicate that ATH434 offers more than symptomatic relief and potentially changes the inevitable progression of the disease.

Figure 4 –Hallmarks of MSA and PD reduced by ATH434 (PBT434)

1. Reduced labile iron

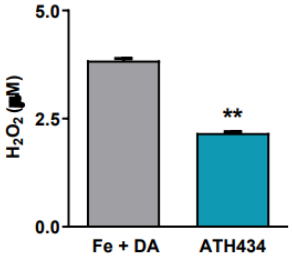
Brain scans from mice with induced PD (MPTP) showed lower iron levels in SNpc of ATH434 (PBT434) treated mice versus untreated ones.

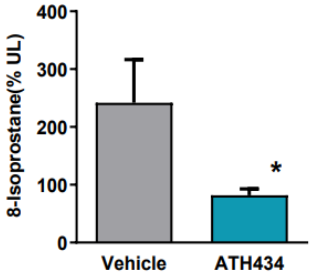




2. Reduced oxidative stress

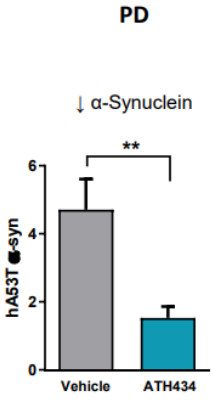
Markers of reactive oxidative stress indicators were lower in the ATH434 treated mice versus untreated.

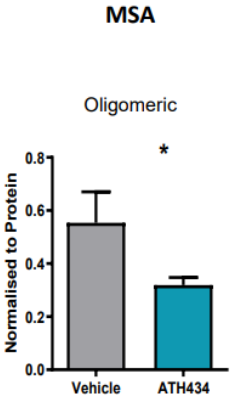


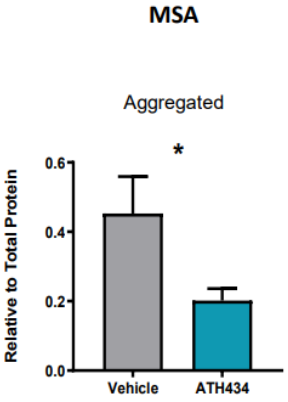


3. Reduced aggregated and abnormal *α-syn*

Levels of oligomeric and aggregated A-SYN were reduced in mice models of MSA and PD.

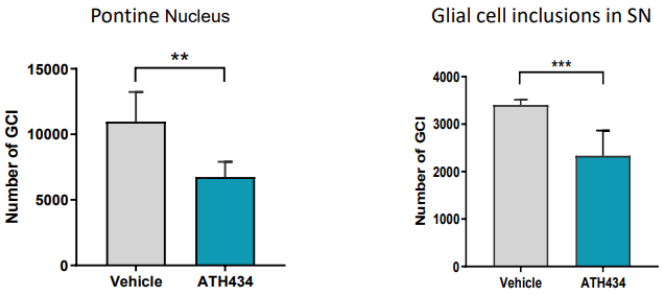






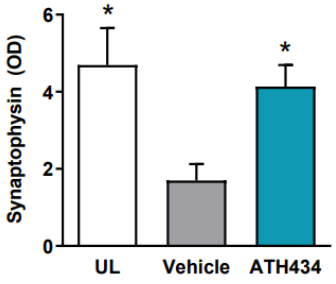
4. Reduced glial cell inclusions

A hallmark of MSA is glial cell inclusions, with aggregations of αsyn found in oligodendrocytes. Treatment with ATH434 reduced the number of inclusions in the in the basal ganglia of MSA mice models.



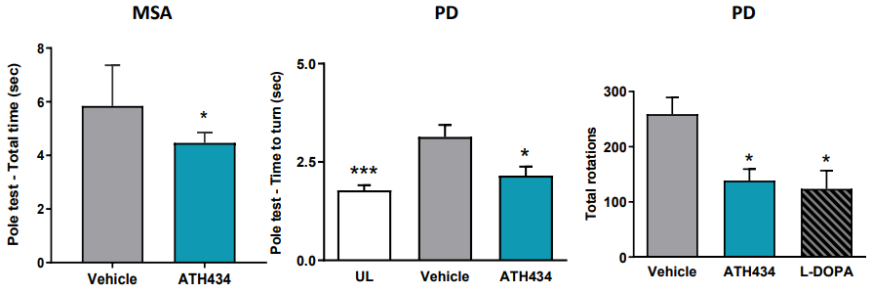
5. Maintained synapses

A measure of synapse function is the number of synaptophysin, a marker of synaptic terminals. ATH434 models retained a higher number compared to those untreated (Vehicle).



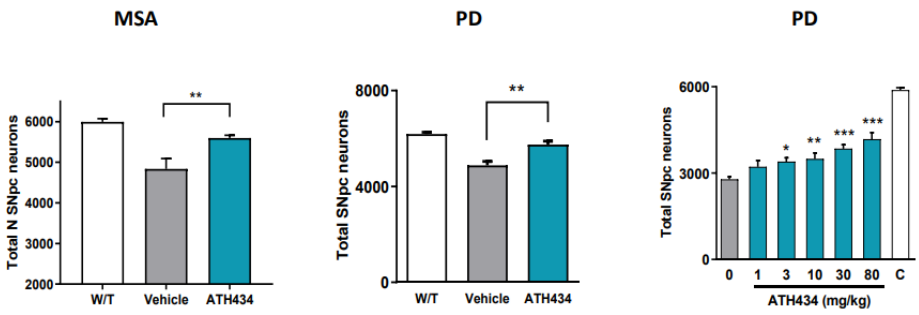
6. Preserved motor function

A number of tests have been designed to measure BG function. In both MSA and PD mice models, ATH434 treated mice showed a superior performance.



7. Preserved neurons

Studies in a number of animal models supported ATH434's potential to be 'neuroprotective' by reduced neuron cell death. They also showed preservation of the nigrostriatal pathway and inter-neurone connections between the SNpc and BG, important in movement.



Positive Competitive Outlook for ATH434

Current Treatment for MSA

As discussed, there is no disease-modifying therapy available for MSA patients. The disease progresses with an average life expectancy of 6-9 years post diagnosis. With no treatment to target the underlying disease, therapy is limited to management of the presenting symptoms. MSA symptoms vary according to the areas of the brain that are involved. Clinically, there are two common subtypes of MSA.

- The Parkinsonian subtype (MSA-P), which predominantly involves the BG area, presents with classic 'Parkinson-type' movements: slowness, muscle rigidity, tremors, and postural instability. Patients are commonly prescribed a dopamine replacement therapy. While the standard of care in PD, dopamine is only effective in around 30% of MSA patients.
- The cerebellar subtype (MSA-C) is characterised by cerebellar ataxia with balance difficulty and loss of co-ordinated movement.

Autonomic nervous system symptoms are also commonly involved in both MSA-P and MSA-C. Management is based on presenting symptoms; drugs to increase blood pressure, intracavernosal injection of paraverine or prostaglandin E1 for impotence, laxatives for constipation, and Botox to reduce rigid muscle tone. Later-stage symptoms of swallowing difficulties and breathing complications may see the need for a feeding tube or tracheostomy.

Potential New Therapies

The unmet need for an MSA treatment and the potential wider application across other synucleinopathies have attracted research interest. The complexity of the disease process opens a number of potential therapy targets - α-syn aggregation, neuroinflammation, neuronal cell loss, autophagy disturbances and oxidative stress. Expectedly, many are targeting α-syn.

Table 2 – List of Developmental Drugs and Targets

Drug Candidate	Target	Clinical Trial
α - syn Targeted		
α - syn aggregation inhibitors		
Anle138b	*α - syn aggregation*	A phase I trial
CLR01	*α - syn aggregation*	Preclinical
ATH434	*α - syn aggregation*	A phase II trial in preparation
α - syn degradation enhancers		
Rapamycin	*α - syn clearance*	A phase II
Anti-miR-101	*α - syn clearance*	Preclinical
MPLA	*α - syn clearance*	Preclinical
TFEB	*α - syn clearance*	Preclinical
Monophosphoryl lipid A	*α - syn clearance*	
VX-765	*α - syn cleavage/aggregation*	Preclinical
Neurosin	*α - syn cleavage/aggregation*	Preclinical
α - syn immunotherapy		
AFF1(PD01A),PD03A -	*Active immunisation*	Phase I trial - good immunogenicity, safety

Drug Candidate	Target	Clinical Trial
CD5-D5	*Passive Immunisation*	Preclinical
Anti-inflammatory therapies		Preclinical
Lenalidomide	*Neuroinflammation*	
Verdiperstat	*Neuroinflammation*	A phase III planned
IVIg	*Neuroinflammation*	Pilot study showed benefit
Other therapies		
Exendin-4	*Brain insulin resistance*	Preclinical
GDNF	*Trophic support*	Preclinical
Benztropine	*Myelin*	Preclinical
Sodium phenylbutyrate	*Histone deacetylase inhibition*	Preclinical
CoQ10	*Mitochondrial dysfunction*	Phase II A

Source: L Mészáros et al International Journal of Molecular Sciences Review Apr 2020, Wassilios G. Meissner et al. Multiple System Atrophy: Recent Developments and Future Perspectives, Movement Disorders 2019

α-syn aggregation inhibitors and degradation enhancers

A number of small-molecule drugs are targeting aggregation, either by preventing it or by breaking it down. Anle138B binds with the aggregated α-syn directly. Rapamycin, in Phase 2 clinical trial, targets α-syn breakdown by accelerating autophagy, the cell's 'disposal system'. Other approaches, including antisense oligonucleotides (ASOs), are in early stage exploration.

α-syn immunotherapy

Several studies have demonstrated the therapeutic potential of anti-α-syn immunotherapy in different animal models. Two α-syn vaccines (PD03A, PD01), based on active immunisation have shown a reduction in a number of the key markers of the disease, α-syn accumulation, demyelination and neurodegeneration. Phase 1 data showed good immunogenicity, safety and tolerability in both MSA and PD. Efficacy must now be demonstrated.

Modulation of microglial inflammation

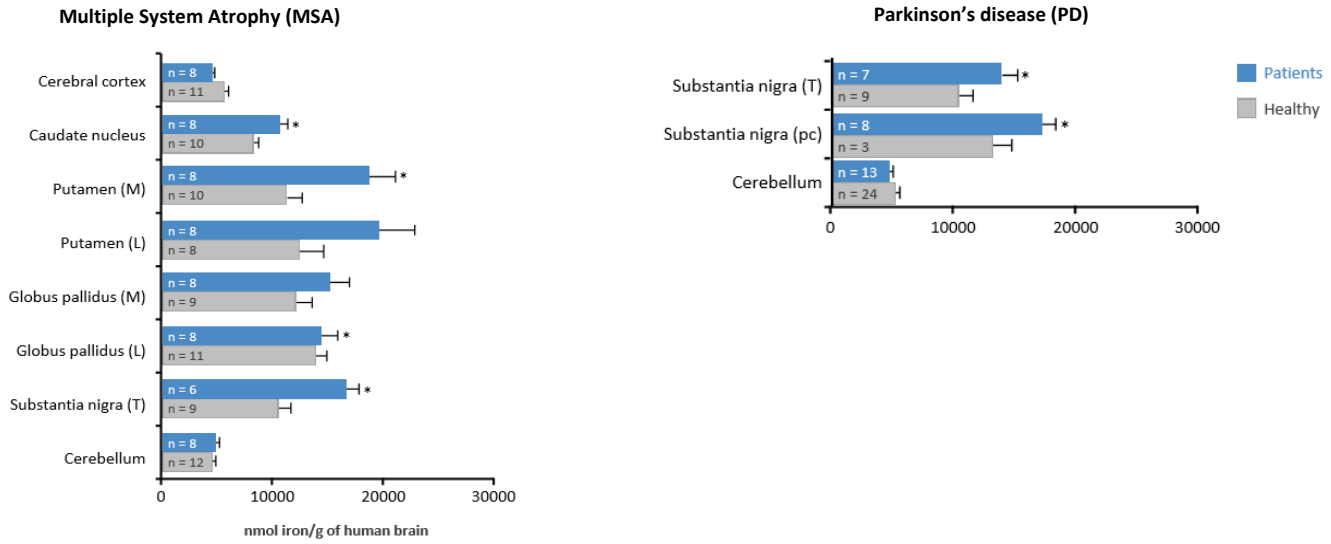
Microglial cells activation and neuroinflammation constitute important features of MSA. The dysfunctional α-syn activates microglial cells, leading to inflammation, α-syn aggregation and cell death. An anti-inflammatory drug, Verdiperstat, is in Phase 3 trials. It has received orphan drug status and Fast Track designation. Plasma-derived intravenous immunoglobulins (IVIg) are also being trialled in a single centre, open-label pilot study. Patients have reported significant improvement in a number of clinical scores.

ATH presents another approach

The lack of treatment to date reflects a complex and multi-level disease process. Late diagnosis may bring the added challenge of advanced disease with destruction of cells and irreversible pathology. ATH434 with potential application in the underlying pathology, the aggregation α-syn, may have an advantage as it intervenes earlier in the disease pathway, potentially preventing the multi-site dysfunction in the nerve cells.

ATH434 binds and redistributes excess labile iron. Research has demonstrated that a number of neurodegenerative diseases are associated with increased levels of iron in the brain, supporting ATH434's MOA. The excess iron leads to a cascade of downstream effects such as ROS, α-syn aggregation, cell inflammation, and mitochondrial dysfunction leading to cellular impairment and death.

Table 3 – Higher iron deposits in patients with Multiple System Atrophy and Parkinson's Disease vs. healthy subjects



Source: Dexter et al. Brain.1991

The studies demonstrate the higher iron levels in key areas of the brain associated with movement in MSA and PD patients versus healthy subjects.

Proof of principle: Deferiprone supports ATH434's MOA

A drug, Deferiprone, is being repurposed for use in another synucleinopathy, PD. It provides proof of concept for ATH434. Iron chelators reduce excess iron and have been used for over 50 years, in systemic blood diseases such as thalassemia where iron levels are too high. Chelators have a very strong affinity or binding ability with iron. Once bound, they 'transport' iron out of the cell into the bloodstream, where it can be redistributed to other cells or excreted.

Deferiprone is in a 400-patient Phase 3 trial in PD. Its two Phase 2 clinical demonstrated an effect in the disease's hallmarks with reduction of iron in the brain, including the BG, and improvement of impaired movement, with the larger study demonstrating statistically significant results.

ATH434 and Deferiprone in PD – potential competitors?

As discussed, MSA and PD share underlying pathological processes. ATH434 while being trialled in MSA is likely to target PD and similarly, Deferiprone may seek approval in MSA. There is also the potential for both to be used off label.

In order to prevent α-syn aggregation, ATH434 and deferiprone must bind more effectively with the excess labile iron than α-syn does. The iron affinities or binding capacities of deferiprone 10^{-36} and ATH434 10^{-10} compare to α-syn10^{-5}, therefore they should both 'out-compete' α-syn10^{-5}.

Table 5 – Affinity to Iron of Various Molecules

Iron affinity	Kd for Fe^{3+}
A SYN	10^{-5}
ATH434	10^{-10}
Ferritin	10^{-22}
Deferiprone	10^{-36}

Source: Company reports

However, from a safety perspective, ATH434 may have a significant advantage. Deferiprone is associated with a number of serious adverse effects which may limit its use. Its FDA approval carries a black box warning regarding neutropenia/agranulocytosis where loss of white blood cells leaves the patient vulnerable to life-threatening infections. Seven patients had to withdraw from the Phase 2 trial in PD due to adverse effects. In contrast, no serious adverse effects were reported in ATH434's Phase 1 clinical trial data in healthy volunteers. While this will need to be confirmed in larger, patient Phase 2/3 trials, ATH434 is not expected have the same serious side effects.

In addition, there is another potential risk relating to deferiprone's higher affinity to iron. Systemic diseases such as thalassemia for which deferiprone is approved, involve excess iron in the ferritin stores in peripheral or body cells. Deferiprone's high affinity of 10^{-36} is important as it must 'take' iron from ferritin 10^{-22}. In neurological conditions such as synucleinopathies, iron levels are generally normal outside the brain. Deferiprone's use in these conditions may lead to anaemia and other complications. In contrast, ATH434 is 10^{-10}, and will only target the excess labile iron as it would be ineffective against ferritin's affinity of 10^{-22}.

MSA is a strategic choice

As discussed, the underlying pathology of aggregated synuclein also occurs in PD and LBD.

ATH's preclinical research in PD and MSA showed activity in both in both diseases in animal model studies and in-vitro testing. From a strategic perspective, the selection of MSA is strategic as:

- it is rare
  With an incidence of 3.4 per 100,000, MSA represents a rare disease. As a result, ATH has received FDA orphan drug status and because it is a serious disease without an approved therapy, is eligible for priority review. In the US, orphan drug status confers 7 years of market exclusivity from generic competition. ATH434 has also been granted Orphan designation in EU which provides 10 years of market exclusivity. Rare disease drugs typically carry a premium with average prices in $100,000+ to compensate for high R&D costs in small patient populations. The smaller market makes it a more attractive target from a marketing perspective for ATH. The specialty market can be serviced by a small pharma sales force. Throughout the trial process ATH has the opportunity to learn more of the patient population and Key Opinion Leaders, in readiness for commercialisation.

- it is rapidly progressive in comparison to other Parkinsonian disorders
  The average survival of MSA patients is significantly shorter than in PD. MSA patients survive 6-9 years post diagnosis, while PD patients survive 15–20 years, commonly dying from other causes. The rapid progression of MSA reduces the time to detect the efficacy measure differences between drug and placebo cohorts, thereby requiring fewer patients.

- it is needed
  MSA is a fatal condition with no approved treatments. It has a profound impact on quality of life represents an unmet medical need. Regulators are highly motivated to work with sponsors developing drugs for diseases such as MSA.

- it is the first step in a well-planned commercialisation strategy
  The selection of MSA as the first target indication reflects a commercialisation strategy that not only leverages the characteristics of MSA, but allows the company to optimise its assets IP portfolio to seek other indications.

Commercialisation and Intellectual Property

As discussed, the choice of MSA is strategic from the nature of the disease. It is also part of a corporate strategy to develop its IP portfolio to facilitate entry into other markets.

IP Development Strategy

ATH434 was transferred to ATH from Prana Biotechnology's portfolio. The passage of time has seen the drug's key patents expire. Its IP strategy is aimed to provide market protection in both MSA and PD and potentially other related disorders.

In selecting MSA the first indication, ATH will be able to use Orphan Drug designation to provide market protection. PD with a higher prevalence does not qualify. Instead, while MSA trials progress, ATH has an active program, developing 2nd generation compounds that also bind to and redistribute iron. As 'new' compounds, management will develop a suite of new IP to afford market protection and advance the '2nd generation' compounds into clinic for the treatment of PD.
The strategy also bears logic from a pricing perspective. Orphan drugs usually command a high premium to compensate for high R&D costs across a small patient population. In PD a more competitive pricing model would be needed. With 'two' drugs ATH does not have to cannibalise its MSA market pricing to be competitive in PD.

ATH's Clinical trial program for MSA

Phase 2

ATH is planning its Phase 2 trial following a successful Phase 1 safety trial. Before commencing trials in the US, an Investigational New Drug (IND) application is required from the FDA. ATH management has had a pre IND meeting with the FDA to discuss Phase 2 trial requirements including proposed patient population, safety monitoring plan.

The primary endpoint is still under development and the FDA has agreed to collaborate with ATH on this activity. ATH plans to undertake a natural history study, referred to as bioMUSE, or biomarkers of Progression in Multiple System Atrophy. It will enrol early stage MSA patients and track change in clinical parameters and biomarkers for up to one year. In parallel, Alterity is also pursuing a regulatory pathway to European and Australian markets.

The Phase 2 trial is expected to start enrolling patients in H2CY21 with results data released in H2CY22. A long term toxicology program is underway.

Phase 3 and beyond?

On positive Phase 2 results the company may decide to license ATH434 for its Phase 3 trial and commercialisation. It also has the option to continue its development. The decision to license a candidate drug or continue its development must weigh up risk versus reward.

Commonly, a biotechnology company with its first product in development, will progress to Phase 2 trial, and on positive results license the compound for further development and commercialisation. After a positive Phase 2 result, with evidence of efficacy, licensing agreements will capture some value without the cost, risk and required expertise to conduct the Phase 3 trial.

The decision to continue development provides the opportunity to maximise value. However, failure bears the risk of the cost of undertaking the larger Phase 3 trial and loss of upfront milestone payments.

We believe the licensing option is less likely. Dr Stamler, the Senior Vice President and Chief Medical Officer (CMO) has led three successful New Drug Approvals (NDA) applications in neurological diseases. He has in depth experience in clinical trial development, regulatory authority requirements and marketing/sales/distribution. It would seem difficult to find someone more qualified to undertake ATH's development. Licensing also bears the risk of surrendering control of the drug. There are many tales of woe where a licensed drug loses priority in the licensing company's portfolio and no longer actively marketed.

From a market perspective, MSA lends itself to the model as well. It is a rare disease, affecting around 12,000 patients in the US. Patients are usually managed by a limited number of tertiary specialist neurologists who have an interest in these diseases. It opens the opportunity for a small specialty pharmaceutical sales force to cover the MSA market.

Management

ATH's two key persons, Mr Geoffrey Kempler and Dr David Stamler, MD, bring extensive experience in drug development.

Mr Kempler is the founder, Chairman of the Board of Directors since 1997 and CEO since 2005. He offers in depth 'hands on' experience through the development of PBT2 through early and clinical development. He has a long association with the Australian and US equity markets.

Dr. Stamler has more than 20 years of central nervous system development experience and a deep understanding of the regulatory environment. As discussed, he has led three successful NDAs to approval in the US. While at Prestwick Pharmaceuticals, he undertook a successful prosecution of the New Drug Application, including leading Advisory Committee activities, at the FDA, which led to the approval of Xenazine (tetrabenazine).

Dr. Stamler worked at Auspex Pharmaceuticals and then at Teva Pharmaceuticals (NYSE TEVA), following Teva's US$3.5 billion acquisition of Auspex. Dr. Stamler led the development of Auspex's a novel drug Austedo (deutetrabenazine) for the treatment of Huntington's disease and later for Tardive Dyskinesia. It was approved by the FDA in both conditions.

Board

Mr. Geoffrey Kempler Chairman and CEO
Mr Kempler has served as Chairman of our Board of Directors since November 1997, between November 1997 and August 2004 he served as our Chief Executive Officer, and in June 2005 he again assumed the position of Chief Executive Officer. Mr Kempler is one of the founders of the Group. Mr Kempler is a qualified psychologist. Mr Kempler, who has extensive experience in investment and business development, has been responsible for the implementation of the strategic plan and the commercialisation of our technology.

Mr. Brian Meltzer Independent Non-Executive Director
Subsequent to several years as Chief Economist of ICI Australia (now Orica), Mr Meltzer spent 25 years in investment banking. His breadth of expertise includes major property transactions, corporate advisory, corporate finance, management buyouts, venture capital and large scale syndications. He has held a number of Board and Board Advisory roles for private companies in the human resources, health, aged care, software, entertainment and finance sectors, including Director of a federal government licensed Innovation Investment Fund and co-founder of OSA Group, a provider of mental health services to corporates. Mr Meltzer is also a Director of the Australia-Israel Chamber of Commerce, Chairman of Independence Australia and Chairman of a privately owned corporate health business.

Mr. Peter Marks Independent Non-Executive Director
For the period November 21, 2006 to October 20, 2011, Mr. Marks has also served as Executive Chairman of iSonea Ltd, formerly KarmelSonix Ltd, a medical devices company listed on the ASX that was focused on developing and commercializing a range of devices in the respiratory and medicine space. For over 13 years until the end of August 2014, Mr. Marks was a Director of Peregrine Corporate Ltd, an Australian-based investment bank. Mr. Marks was until late 2016, a Director of Armadale Capital Plc (formerly Watermark Global Plc), an AIM listed investment company, focused on natural resources projects based principally in Africa with its current major investments being a gold exploration company in DRC and a coal briquetting operation in South Africa.

Mr. Lawrence Gozlan Non-Executive Director

Mr. Gozlan, a leading biotechnology investor and advisor, is the Chief Investment Officer and Founder of Scientia Capital, a specialised global investment fund focused exclusively in life sciences. Scientia Capital was founded to provide high level expertise and to manage investments for high net worth individuals, family offices and institutional investors wanting exposure to the biotechnology industry.

Dr. David Sinclair Non-Executive Director

Dr. Sinclair is the co-founder and chairman of Life Biosciences LLC. He is also a tenured professor in the Department of Genetics at Harvard Medical School, a co-director of the Paul F. Glenn Center for the Biology of Aging Research, and serves on the non-profit boards of the American Federation for Aging Research and the Sanford Lorraine Cross Award. Dr. Sinclair is regarded as one of the world's leading researchers on aging and age-associated diseases, with key contributions to understanding why we age and how to slow and even reverse the process. He has co-founded multiple biotechnology and genomics companies working on aging, neurological, metabolic, infectious and rare diseases.

Mr. Tristan Edwards Non-Executive Director

Mr Edwards is the co-founder and President of Life Biosciences LLC. Tristan has extensive global financial capital markets, regulatory compliance, and fiduciary oversight experience, following a 16-year investment career spanning leading financial organizations across Australia, London, HK and Singapore. His professional background has been in senior investment roles at leading financial groups such as Goldman Sachs, Brevan Howard, Trafalgar Capital and Mosaic Asset Management. He started his career as an analyst with the Australian Commonwealth Department of Finance. Tristan has a degree in Commerce from the University of Tasmania, and held the CFA, CMT and CPA designations.

Valuation, Risks and Sensitivities

We value ATH at $82.8m. It is based on a risk adjusted DCF for the indication of MSA only. No value has been ascribed to other potential clinical applications. As a drug in development, assumptions have been made regarding the probability of its approval to enter the US and EU markets, costs associated with its further development and its likely commercial performance. The valuation is supported by comparison to other drug development ASX listed companies; Immutep (IMU.AX) of ¬A$98m, Immugene (IMM.AX) of A$195m and Kazia Therapeutics (KZA.AX) of A$53m.

The assumptions bring sensitivities and risk. Commercial performance, market size, pricing, patient usage, timing of regulatory approval and reimbursement are based on market averages. They present upside and downside risk in the valuation assumptions. Delays from slow patient recruitment, particularly in the COVID 19, and other events may impact the financial forecasts and may lead to additional funding requirements.

Key Valuation Assumptions	
ATH434 Price	US$150K
Probability of Approval post Phase 1 trial	14%
Phase 2 Clinical trial result	H2CY22
Phase 3 Clinical trial result	H2CY25
US Market Entry	CY2026

Key DCF valuation metrics

Licensing versus Ownership Retention

The MST valuation assumes that management will continue to develop ATH434 if the Phase 2 trial results are positive. The assumption is based on the characteristics of the MSA market and the expertise and experience of the Senior Vice President, Dr David Stamler. As discussed, the company may decide to license the drug after Phase 2 trials. ATH434 may fail the Phase 2 trial, and not progress to Phase 3.

Probability of approval

Review of the data shows that the probability of a drug's approval varies according to the type of disease, disease prevalence, and the type of drug molecule. The probability of a neurological drug being approved from Phase 1 is around 14%.

Timing

ATH has announced that it will commence Phase 2 trial in H2CY21. We expect the Phase 3 trial will follow in CY23 with data release at the end of CY25. A successful Phase 3 trial may see market entry in 2026.

Markets

ATH has announced it will seek regulatory approval in US, EU and Australia. Potential patient population for ATH has been determined by application of the prevalence of 1:20,000 – 1:50,0000 of MSA in the US and EU populations. As data emerges regarding efficacy these assumptions will be reviewed.

Competition

MSA is a fatal condition with no approved treatment, however there is strong interest with a multiple candidate drugs in development. ATH presents a different MOA to most of the drugs being investigated. Thereby opening the opportunity for combination therapy.

Its MOA has some overlap with Deferiprone in Phase 3 trial for PD. If Deferiprone is approved, it may be used off label in MSA. However, we believe that the significant adverse effects associated with this drug are likely to limit its uptake. ATH434's Phase 1 trial to examine safety showed no significant side effects.

Financial Summary

Alterity Therapeutics (ATH)

Year ending 30 June A$

STATEMENT OF PROFIT OR LOSS	2018A	2019A	2020E	2021E	2022E
Interest income	201,174	108,538	111,724	130,966	130,511
Other income	3,125,775	4,951,167	4,800,000	2,838,375	3,090,675
Expenses					
Intellectual property expenses	-224,580	-322,097	-300,000	-300,000	-300,000
General and administration expenses	-4,341,058	-4,308,352	-4,300,000	-4,500,000	-4,500,000
R&D expenses	-6,698,016	-12,983,185	-6,525,000	-7,105,000	-8,555,000
Other operating expenses	-58,172	-132,965	-130,000	-130,000	-130,000
Other gains/losses	-270,860	349,064	0	0	0
Loss for the year	**-8,265,737**	**-12,337,830**	**-6,343,276**	**-9,065,659**	**-10,263,814**
Total comprehensive loss for the year	**-8,265,737**	**-12,337,830**	**-6,343,276**	**-9,065,659**	**-10,263,814**

STATEMENT OF FINANCIAL POSITION	2018A	2019A	2020E	2021E	2022E
Current Assets					
Cash and cash equivalents	15,235,556	14,399,904	8,056,628	18,621,935	8,488,632
Trade and other receivables	3,152,410	4,829,497	4,808,352	4,808,352	4,808,352
Other current assets	266,625	631,769	631,769	631,769	631,769
Total Current Assets	**18,654,591**	**19,861,170**	**13,496,749**	**24,062,056**	**13,928,753**
Non-Current Assets					
Property, plant and equipment	71,422	48,748	48,748	48,748	48,748
Total Non-current Assets	**71,422**	**48,748**	**48,748**	**48,748**	**48,748**
Total Assets	**18,726,013**	**19,909,918**	**13,545,497**	**24,110,804**	**13,977,501**
Current Liabilities					
Trade and other payables	2,055,247	2,718,174	2,700,000	2,700,000	2,700,000
Provisions	588,693	601,995	600,000	600,000	600,000
Total current liabilities	**2,643,940**	**3,320,169**	**3,300,000**	**3,300,000**	**3,300,000**
Non-current Liabilities					
Provisons	916	34,976	34,000	34,000	34,000
Total non-current Liabilities	**916**	**34,976**	**34,000**	**34,000**	**34,000**
Total Liabilities	**2,644,856**	**3,355,145**	**3,334,000**	**3,334,000**	**3,334,000**
Net Assets	**16,081,157**	**16,554,773**	**10,211,497**	**20,776,804**	**10,643,501**
Equity					
Contributed equity	143,910,328	156,632,636	156,632,636	176,132,636	176,132,636
Reserves	1,753,954	1,158,975	1,158,975	1,158,975	1,158,975
Accumulated losses	-129,583,125	-141,236,838	-147,580,114	-156,514,807	-166,648,110
Total Equity	**16,081,157**	**16,554,773**	**10,211,497**	**20,776,804**	**10,643,501**

STATEMENT OF CASH FLOWS	2018A	2019A	2020E	2021E	2022E
Cash flows from operating activities					
Payments to suppliers and employees	-9,466,459	-17,325,579	-11,255,000	-11,904,034	-13,354,489
R&D tax refund	3,022,673	3,251,672	4,800,000	2,838,375	3,090,675
Interest received	198,598	119,089	111,724	130,966	130,511
Net cash outflow from operating activities	**-6,245,188**	**-13,954,818**	**-6,343,276**	**-8,934,693**	**-10,133,303**
Cash flows from investing activities					
Withdrawal of rental deposit	43,988				
Payments for property, plant and equipment	-62,405	-7,022			
Net cash outflow from investing activities	**-18,417**	**-7,022**			
Cash flows from financing activities					
Proceeds from share issues and other equity securities		13,084,629		20,000,000	
Transaction costs relating to issue of equity	-107,678	-362,320		-500,000	
Net cash inflow from financing activities	**-107,678**	**12,722,309**		**19,500,000**	
Net increase/decrease in cash and cash equivalents	**-6,371,283**	**-1,239,531**	**-6,343,276**	**10,565,307**	**-10,133,303**
Cash at the beginning of period	**21,884,957**	**15,513,674**	**14,399,904**	**8,056,628**	**18,621,935**
Cash at the end of period	**15,513,674**	**14,399,904**	**8,056,628**	**18,621,935**	**8,488,632**

Shareholder Register

20 Largest Shareholders of Ordinary Shares	Number of Ordinary Shares	% of Issued Share Capital
HSBC CUSTODY NOMINEES (AUSTRALIA) LIMITED	413,392,841	47.58%
LIFE BIOSCIENCES LLC	269,905,533	31.07%
JAGEN PTY LTD	15,567,983	1.79%
BAYWICK PROPRIETARY LIMITED <THE RETAIL DISCRETIONARY A/C>	14,165,000	1.63%
MARQUETTE HOLDINGS PTY LIMITED	7,692,308	0.89%
J P MORGAN NOMINEES AUSTRALIA PTY LIMITED	6,143,499	0.71%
DONATELLO NIZZI	4,678,362	0.54%
MS JIA LU	4,309,879	0.50%
SCHWA PTY LTD <MAINLAND PROPERTY A/C>	4,000,000	0.46%
MR JAMES V BABCOCK	3,980,263	0.46%
THE ENTRUST GROUP INC <ROBERT DAVIDOW IRA A/C>	3,598,740	0.41%
CITOS SUPER PTY LTD <CITOS PTY LTD SF A/C>	3,085,499	0.36%
NRB DEVELOPMENTS PTY LTD	2,970,000	0.34%
MS CHAO LEI	2,520,422	0.29%
HSBC CUSTODY NOMINEES (AUSTRALIA) LIMITED - A/C 2	2,421,246	0.28%
STONY RISES PTY LTD <BOYLE FAMILY A/C>	2,035,000	0.23%
MOUBRAY PTY LTD <ROBERT HALLAS SF A/C> A/C>	2,000,000	0.23%
MR DAVID JOHN SOUTHON FAMILY A/C>	2,000,000	0.23%
ROBERT & ARDIS JAMES FOUNDATION/C	1,826,024	0.21%
MRS KATE ELIZABETH SCHROETER	1,724,993	0.20%
Total	**768,017,592**	**88.41%**

The register is tightly held with a limited free float. In April 2019, US based Life Biosciences LLC made an investment of US$7.5m.

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