Alterity Therapeutics

(NASDAQ:ATHE, ASX:ATH)

David Stamler, MD
CEO

May 2023

Forward Looking Statements

This presentation may contain some statements that may be considered “Forward-Looking Statements”, within the meaning of the US Securities Laws. Thus, any forward-looking statement relating to financial projections or other statements relating to the Company’s plans, objectives, expectations or intentions involve risks and uncertainties that may cause actual results to differ materially. For a discussion of such risks and uncertainties as they relate to us, please refer to our 2022 Form 20-F, filed with US Securities and Exchange Commission, in particular Item 3, Section D, titled “Risk Factors.”

Alterity is dedicated to creating an alternate future for people living with neurodegenerative diseases.

Alterity means **the state of being different**

Our goal is to **modify the course of disease**

We’re here to **disrupt the trajectory** of illness and improve quality of life

Investment Highlights

- Developing disease modifying therapies
- ATH434: Novel drug candidate targeting proteins implicated in neurodegeneration of Parkinson's disease and related disorders
  - First indication: Multiple System Atrophy (MSA), a devastating disease with no approved treatment
  - Orphan Drug designation for MSA in the US and EU
  - Phase 2 clinical trial enrolling globally in three regions: U.S., Europe, Australia/NZ
- Strong patent portfolio
- Significant R&D experience including 3 neurology drug approvals by FDA

Experienced Leadership Team with Multiple FDA Approvals in Neurology

David Stamler, M.D.

Chief Executive Officer

Auspex/Teva | Abbott | Prestwick Xenoport | Fujisawa

- **3 FDA Approvals in Neurology**
- Former CMO, Auspex
- VP, Clinical Development & Therapeutic Head, Movement Disorders, Teva Pharmaceuticals
- Part of Teva's US$3.5 billion acquisition of Auspex in 2015
- Led development of AUSTEDO® (deutetrabenazine) for treatment of Huntington disease and Tardive dyskinesia, both approved in 2017

Kathryn Andrews, CPA

Chief Financial Officer

Antisense Therapeutics | Rio Tinto | Consultant

- Extensive experience advising private and public CFOs, mainly in the biotechnology sector
- Prior CFO and Company Secretary of Antisense Therapeutics Limited
- 15+ years in finance and accounting roles at Rio Tinto Limited and BP Australia Limited

Margaret Bradbury, Ph.D.

VP, Nonclinical Development

Auspex/Teva | Neurocrine | Merck

- Auspex - led strategic planning and program management in Huntington Disease chorea from IND through NDA filing
- Teva - led non-clinical development of several neuroscience programs

Cynthia Wong, M.P.H.

Senior Director, Clinical Operations

Auspex/Teva | Nextwave | Astex | Intermune | Impax Labs

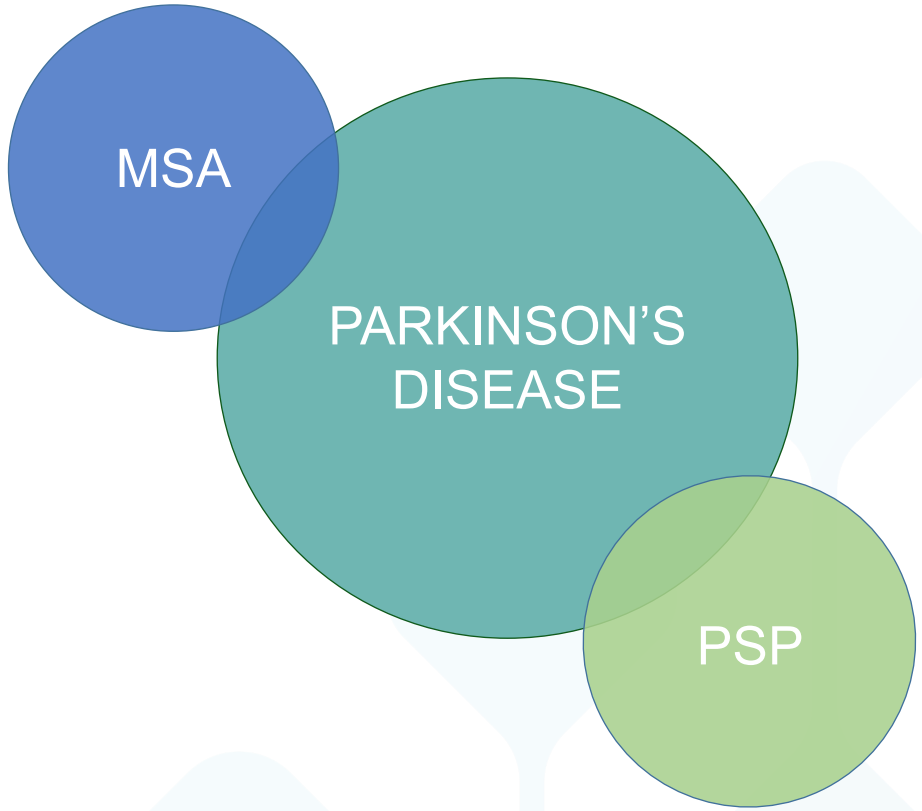
- Clinical Operations leadership at Auspex/Teva.
- Led clinical trial activities for the registration study of AUSTEDO® in Huntington Disease chorea.
- Prior, led Phase 1-3 studies, including registration studies for marketing approval for Quillichew ER, Esbriet and Infergen.

Parkinsonian Disorders: A Significant Unmet Need

- Parkinsonism is a syndrome of motor symptoms that includes slowed movement, stiffness and tremor
  - Parkinson's disease most common cause
  - Major source of disability
- Parkinsonian disorders include Multiple system atrophy (MSA) and Progressive supranuclear palsy (PSP)
  - Prominent non-motor symptoms
  - Limited response to available treatments

Current therapies treat the symptoms and NOT the underlying pathology of disease

PARKINSONIAN DISORDERS

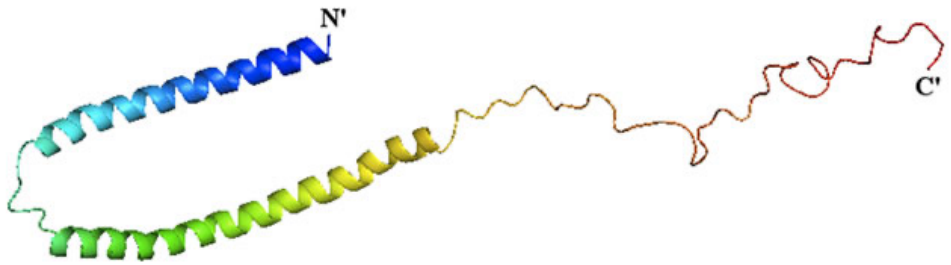


Discovery and Development Portfolio in Neurodegenerative Diseases

Program	Indication	Current Status	Future Plans
ATH434	Multiple System Atrophy	Phase 2 Ongoing	Expand enrollment globally
Natural History Study "BioMUSE"	Multiple System Atrophy	Enrollment complete Partner: Vanderbilt University Medical Center	Patient monitoring ongoing Presentations & publications
ATH434	Parkinson's Disease	Nonclinical studies to optimize dosing Partner: The Michael J. Fox Foundation for Parkinson's Research	Proof of concept study in Parkinson's disease
Drug Discovery	Neurodegenerative diseases	Discovery ongoing	Generate new IND candidates

The Role of Alpha-Synuclein and Iron in Parkinsonian Disorders

Alpha-Synuclein: Critical for Normal Neuron Function

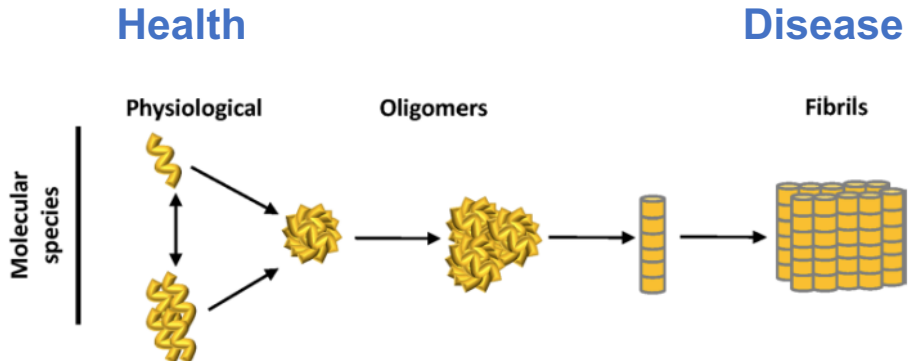


Our Strategy

- Inhibit misfolding and aggregation of intracellular α-synuclein
- Target misfolding α-synuclein by redistributing loosely bound excess iron in areas of pathology
- Address underlying pathology of disease

α-Synuclein

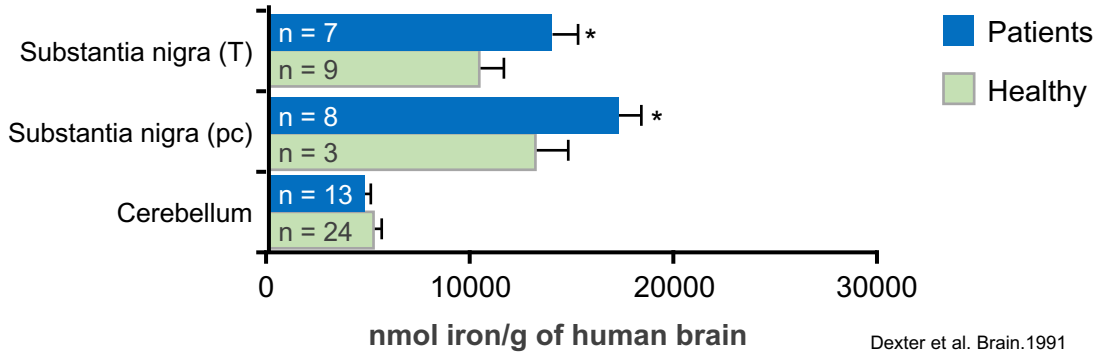
- An intracellular protein critical for normal function of neurons
- Native, unfolded protein enables neurotransmission
- α-synuclein *aggregates* in Parkinson's Disease and Multiple System Atrophy



Sources: Ritchie et al, 2012; DOI:10.4236/health.2012.431175; Bengoa-Vergniory et al, 2017.DOI 10.1007/s00401-017-1755-1

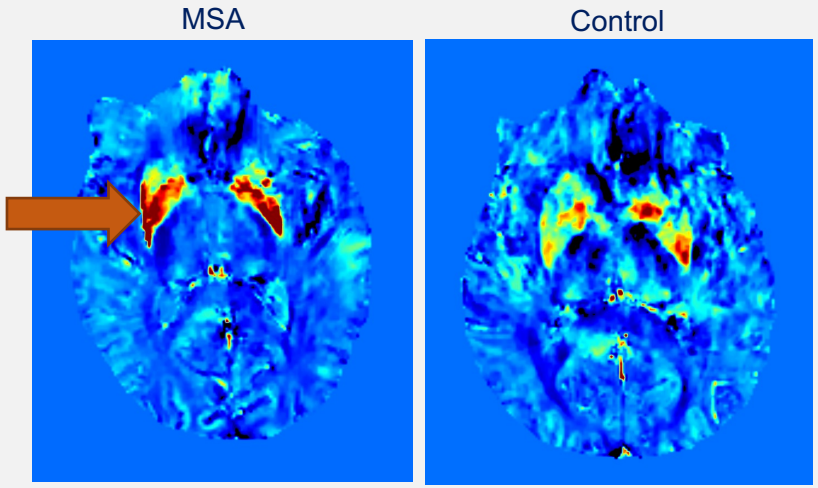
Increased Brain Iron in Synuclein-related Diseases

Parkinson's disease



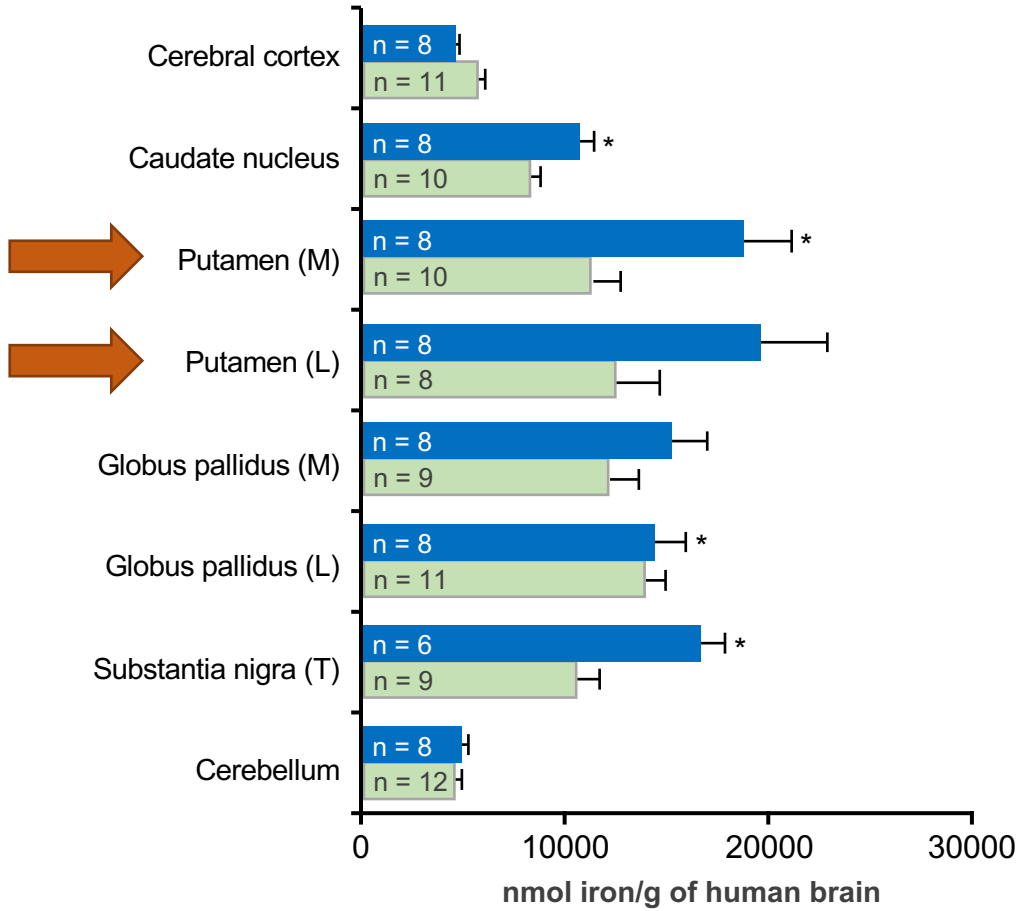
Dexter et al. Brain.1991

Advanced Quantitative MRI to measure brain iron



Courtesy of P. Trujillo, D. Claassen

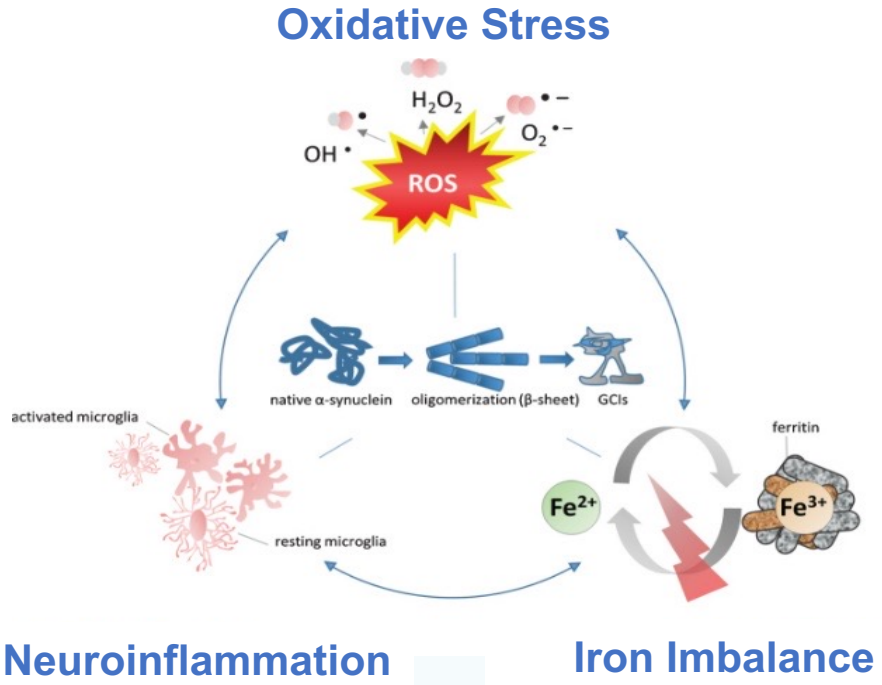
Multiple System Atrophy



Iron: Critical in Disease Pathogenesis

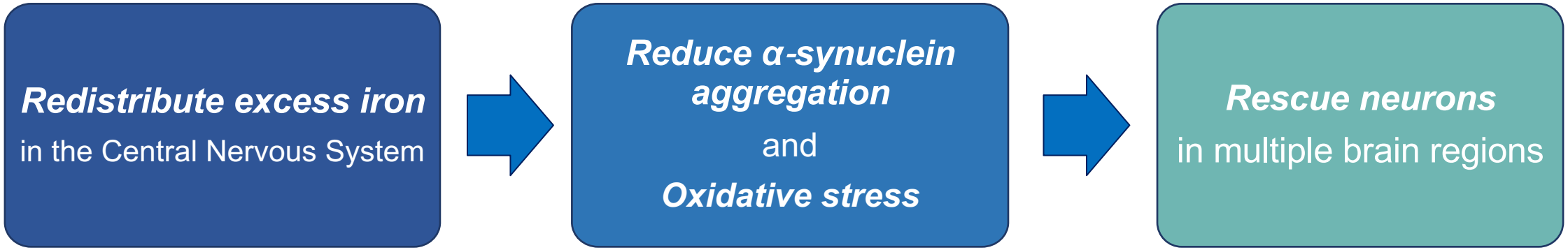
α-Synuclein and iron are strong contributors to MSA pathology

- Adverse impact of excess loosely bound iron
  - Promotes α-synuclein aggregation
  - Root cause of oxidative stress which damages intracellular structures and leads to neuroinflammation
- Hallmark of MSA pathology
  - Neuron loss in multiple brain regions
  - Glial cytoplasmic inclusions (GCI)



Sources: Kaindlstorfer, J. Alzheimers Dis. 2018; Rodgers, J Neural Transm (Vienna). 2011

Approach: Address Underlying Pathology of Disease

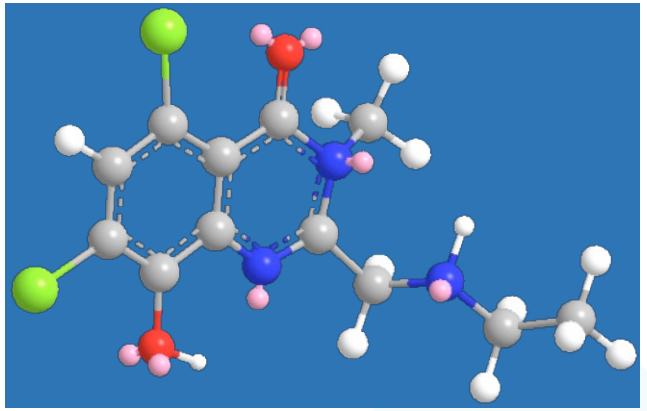


Potential Disease Modifying Therapy for MSA

ATH434: Disease Modifying Drug Candidate

ATH434: Potential Use in Multiple Indications

- Small molecule drug that reduces α-synuclein aggregation
  - Iron chaperone, redistributes loosely bound excess iron in brain
  - Oral agent (tablet) for ease of use
  - Readily absorbed, shown to reach site of action in man



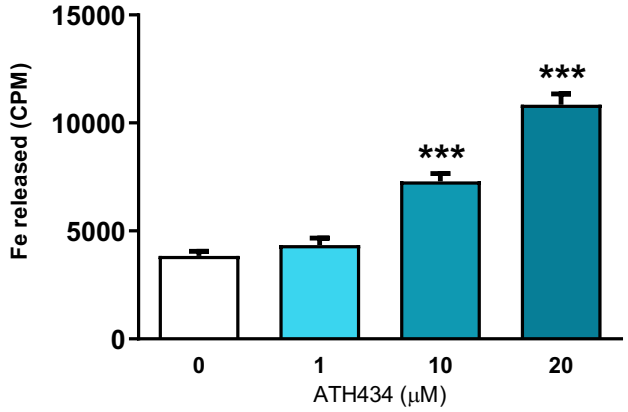
ATH434

- Potential to treat various Parkinsonian disorders
- Orphan Drug Designation in the US and EU for the treatment of MSA
- Development pathway endorsed by FDA and EMA

Pharmacologic Actions of ATH434

Alterity THERAPEUTICS

Redistributes loosely bound excess iron

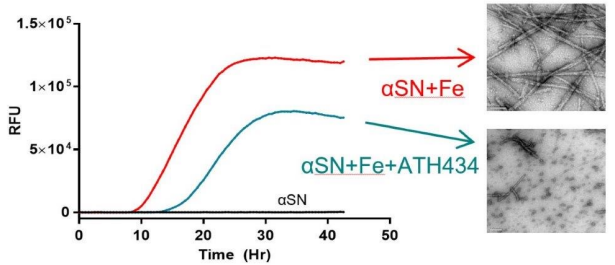


Ligand	Kd for Fe^{3+}
α-synuclein	10^{-5}
ATH434	10^{-10}
Transferrin	10^{-23}

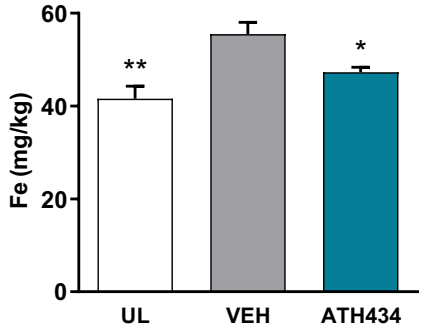
Stronger binding

ATH434 does not interfere with normal iron trafficking proteins

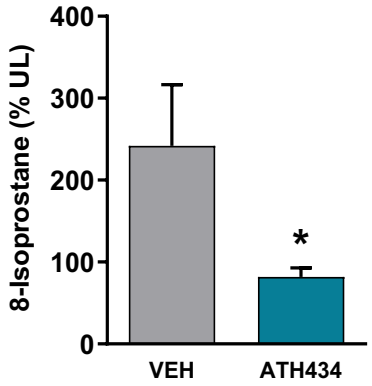
Reduces α-synuclein aggregation



Blocks increase in brain iron



Inhibits oxidative stress in vivo



Sources: Davies et al, 2011; Finkelstein, et al, 2017; Harris WR, 2002.
* P < 0.05, ** P < 0.01, *** P < 0.001

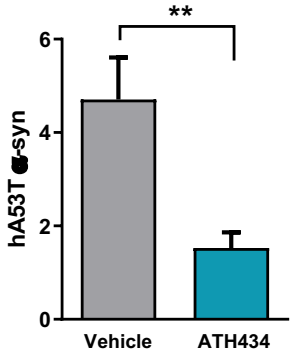
ATH434 Reduces Alpha-Synuclein-related Neuropathology in Parkinson's Disease Animal Models

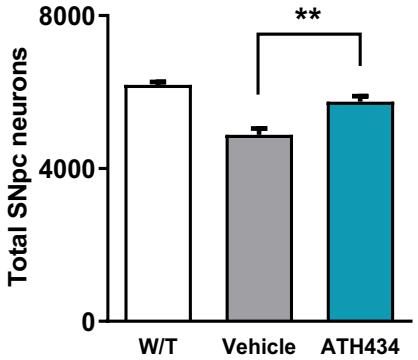
Alterity THERAPEUTICS

↓ α-Synuclein

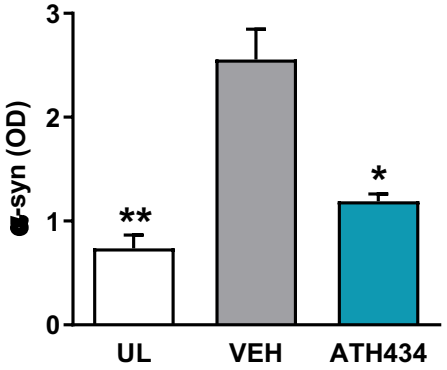
Preserves Neurons

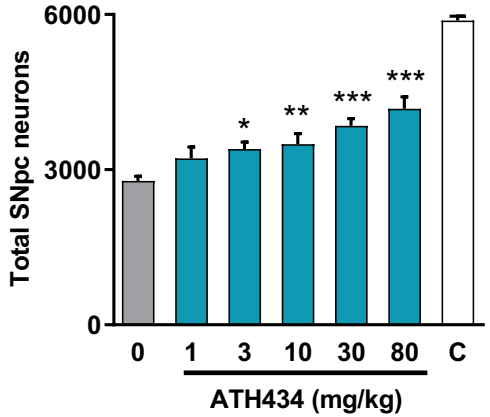
hA53T Mouse





MPTP Mouse





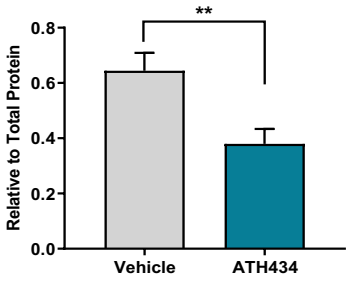
Sources: Finkelstein, et al. Acta Neuropath Comm. 2017 | TG: transgenic, W/T: wild type, UL: unlesioned, C: control |* P < 0.05, ** P < 0.01, *** P < 0.001

ATH434 Reduces α-Synuclein-related Neuropathology and Improves Motor Function in MSA Animal Model

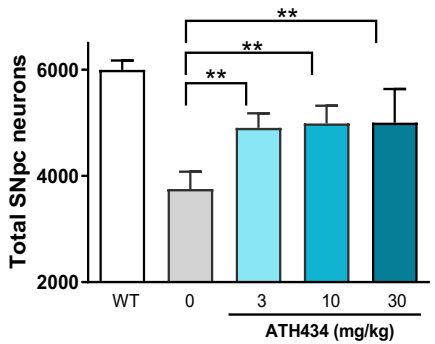
Alterity THERAPEUTICS

Exp. #1

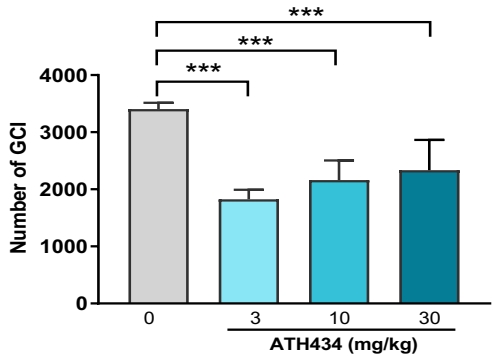
α-Synuclein



SN neurons

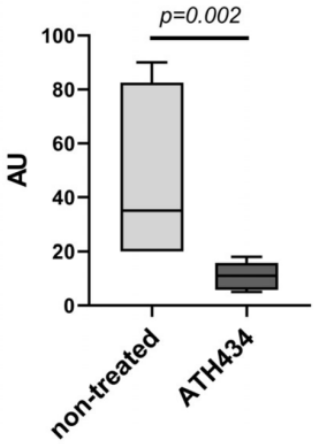


Glial inclusions

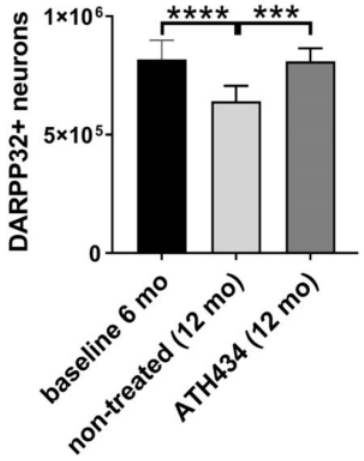


Exp. #2

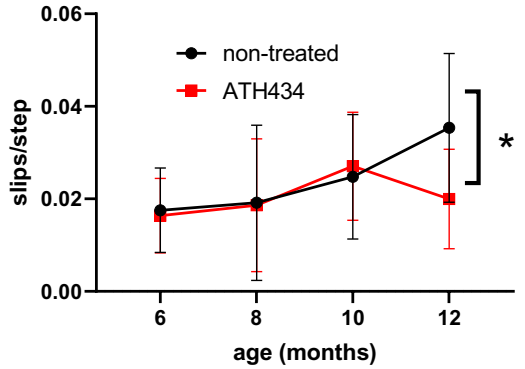
Iron in SN



Striatal neurons



Motor Function

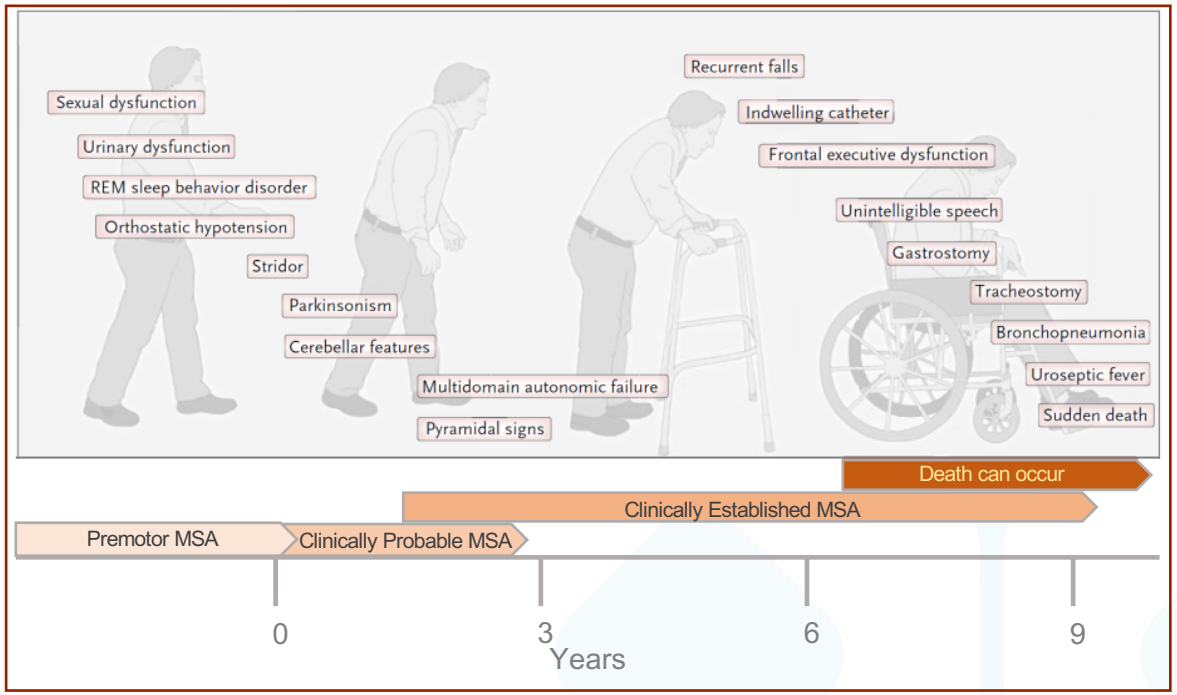


Sources: Finkelstein, et al. J. Parkinson's Disease 2022 | Heras-Garvin, et al. Mov. Disorders 2021
* P < 0.05, ** P < 0.01, *** P < 0.001

Multiple System Atrophy Clinical Development Program

Multiple System Atrophy (MSA) is a Rare, Highly Debilitating and Rapidly Progressive Neurodegenerative Disorder

- Clinical impairments include
  - Motor: Parkinsonism, uncoordinated movements, balance problems/falls
  - Autonomic dysfunction: Reduced ability to maintain blood pressure, control bladder and bowel function
- 60% require use of wheelchair within 5 years
- Median survival 7.5 years after symptom onset
- Excess brain iron correlates with disease severity



Phase 2: Targeting early-stage patients

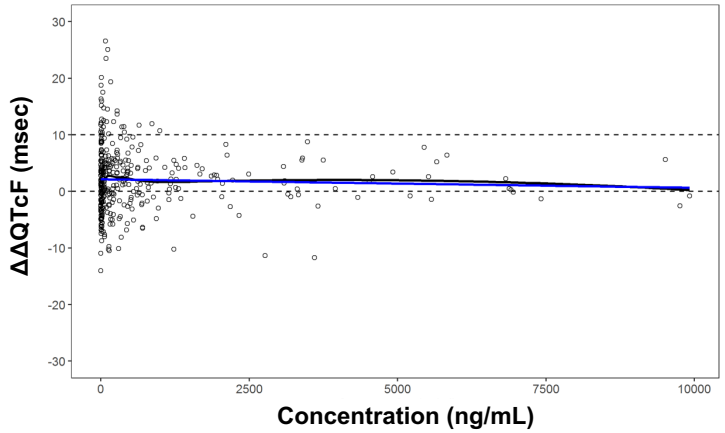
Sources: Fanciulli, Wenning. NEJM 2015 | Wenning, et al. Mov Disorders 2022 | Coon, et al. Brain 2015 | Claassen,et al. Mov Disorders 2021

Phase 1: ATH434 Well-Tolerated with No Serious Adverse Events

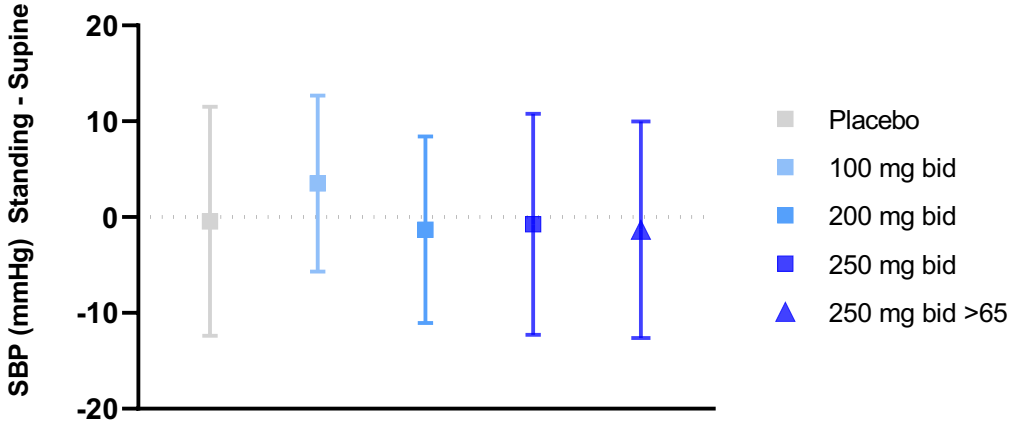
- No SAEs or AEs leading to withdrawal
- All AEs were mild to moderate in severity
- Most common AE reported was headache
- Similar AE profile for adults and older adults

- No significant findings observed in vital signs, clinical labs or 12-lead ECGs
- Favorable cardiovascular safety profile

No evidence of QT prolongation



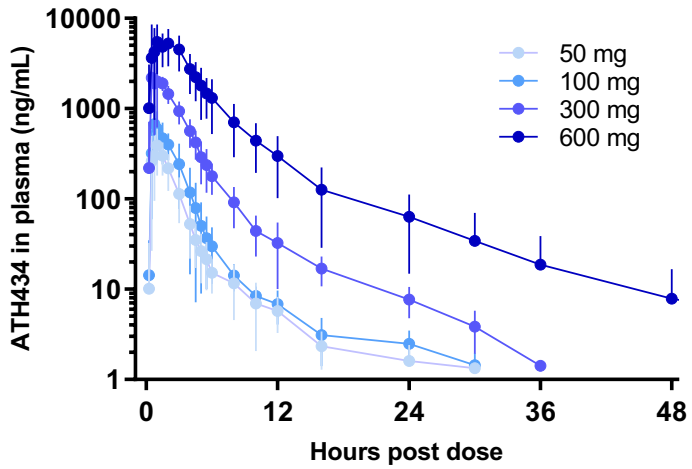
No effect on BP with Standing



Source: Phase 1 clinical trial; Alterity data on file

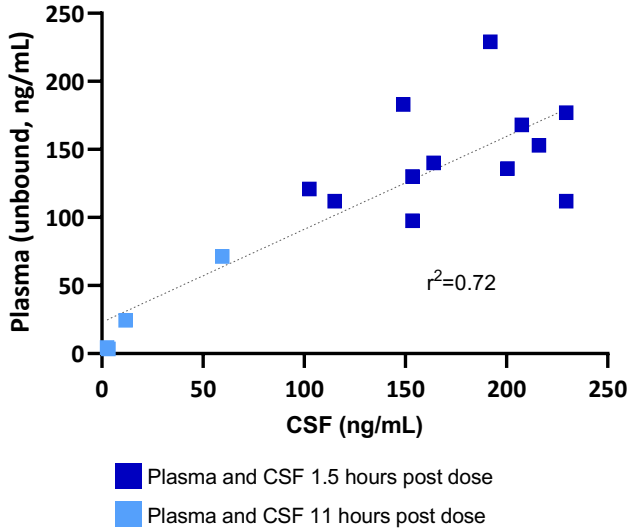
Phase 1: Achieved Drug Concentrations Associated with Efficacy in Animal Models

Plasma Profile after Single Dose Administration



- Rapid absorption after oral administration
- Dose dependent pharmacokinetics
  - Single doses up to 600 mg
  - Multiple doses up to 250 mg bid
- Mean elimination half-life up to 9.3 hrs

Plasma and CSF Levels at Steady-State



- CSF and free plasma levels strongly correlated and within 2-fold of each other
- CSF concentrations at steady state exceed those associated with efficacy in animal models of PD and MSA

Source: Stamler et al. Neurology 2019; 92 (15 Suppl.)

bioMUSE: Biomarkers of Progression in MSA Natural History Study

Design	• Observational
Objectives	• Design and de-risk Phase 2 • Identify biomarker endpoints for treatment study
Population	• Early-stage MSA patients similar to Phase 2 population • ~20 participants
Observation Period	• 12 months
Biomarkers	• MRI: Iron (QSM/R2*), glial pathology (MRS), neuromelanin, regional blood flow • Fluid: NfL protein (CSF, plasma), Aggregating α-synuclein (CSF), phos-α-synuclein (skin) • Wearable movement sensors
Clinical Endpoints	• Clinical: Motor exam, autonomic function, activities of daily living, global measures of severity and change (clinician, patient) • Functional: Timed Up and Go, 2 min Walk Test

bioMUSE Natural History Study Design and De-risk Phase 2

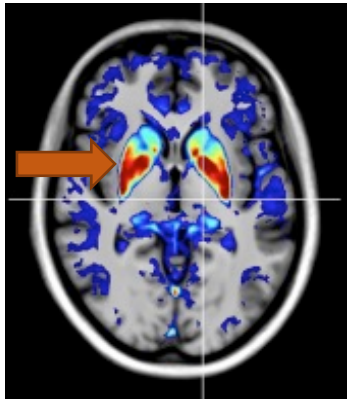
Alterity THERAPEUTICS

Optimize Patient Selection

Assess Endpoints with Precision

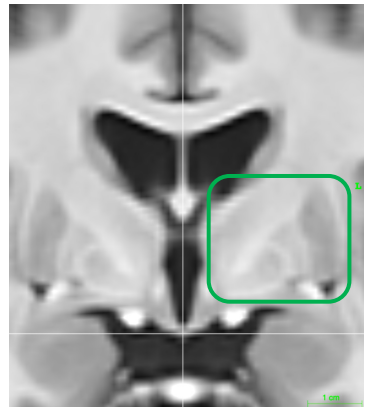
Pilot Clinical Measures

Advanced MRI methods



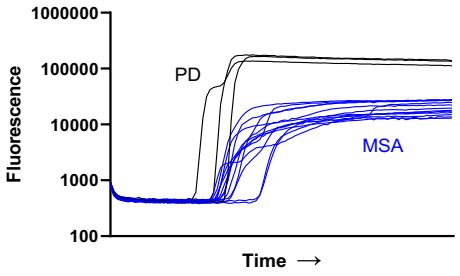
Identify "iron signature" in early MSA vs. PD

New MRI Template



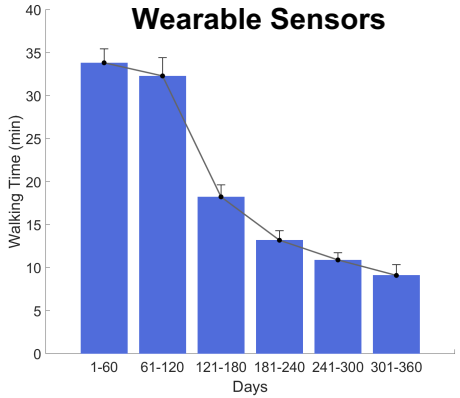
Improve precision of iron quantification by MRI

α-synuclein in CSF



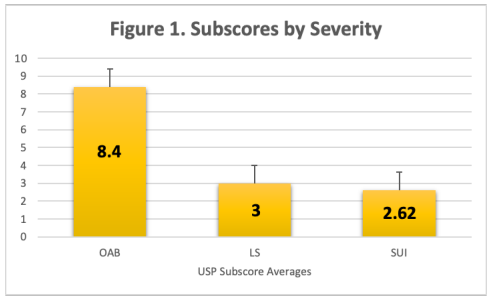
Differentiation of early MSA from PD

Wearable Sensors



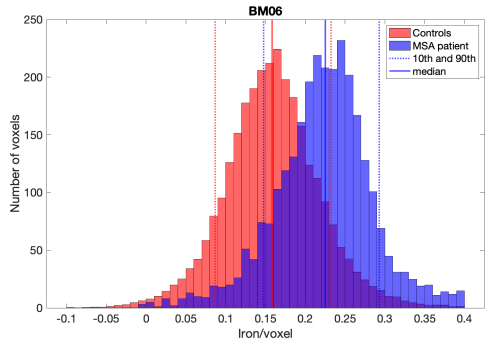
Quantitative assessment of motor performance

Urinary Symptom Profile



Demonstrated utility in early MSA

Iron distribution in MSA



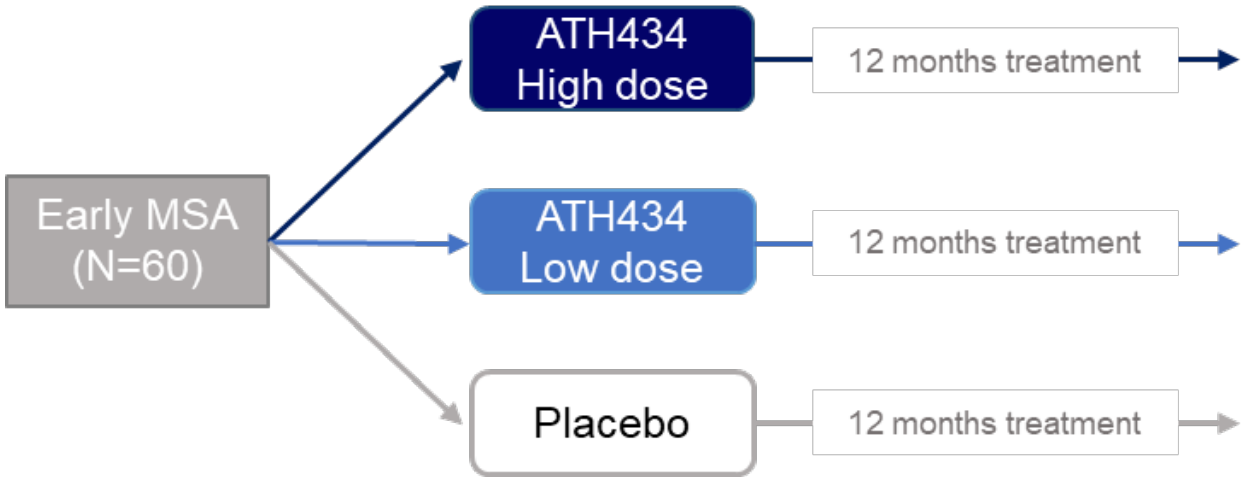
Novel strategies for measuring brain iron in individual regions

Sources: Presentations/Posters on file, including Claassen et al, MDS Conference 2021 and 2022.

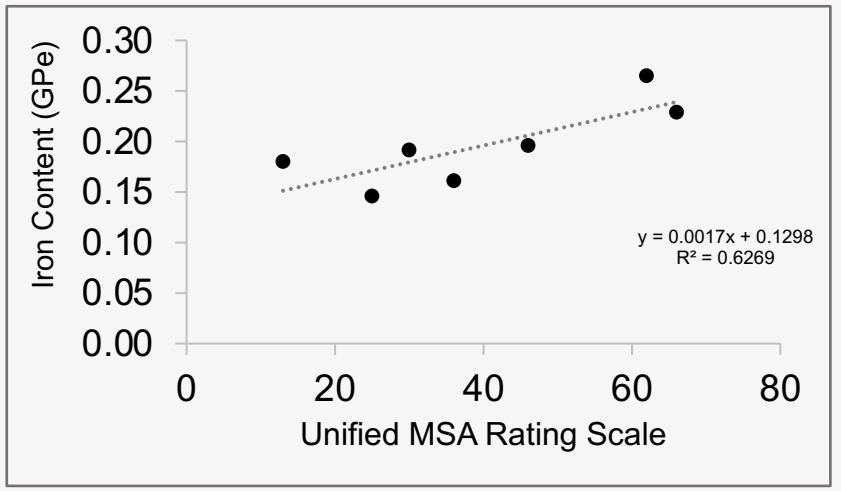
Phase 2 Clinical Trial in Early-Stage MSA Patients

Design	• Randomized, double-blind, placebo controlled
Objectives	• Assess efficacy and safety of ATH434 in participants with MSA • Assess target engagement based on imaging and fluid biomarkers
Population	• Early-stage MSA: ambulatory with biomarker evidence of MSA
Sample Size	• N=60 at up to 30 sites in ANZ, Europe and the U.S.
Treatment	• 12 months • Three arms: Two dose levels of ATH434 or placebo
Primary Endpoint	• Change in iron content as measured by brain MRI
Secondary Endpoints	• Clinical: Activities of daily living inventory (UMSARS I), motor exam, autonomic function • Additional imaging biomarkers, fluid biomarkers (aggregating α-synuclein, NfL protein), wearable sensor measures

Phase 2 Design and Primary Endpoint



Primary Endpoint:
Change in Brain Iron on MRI



BioMUSE Natural History Study Demonstrates
Brain iron correlates with disease severity in MSA

Source: Claassen, et al. Mov Disorders 2021

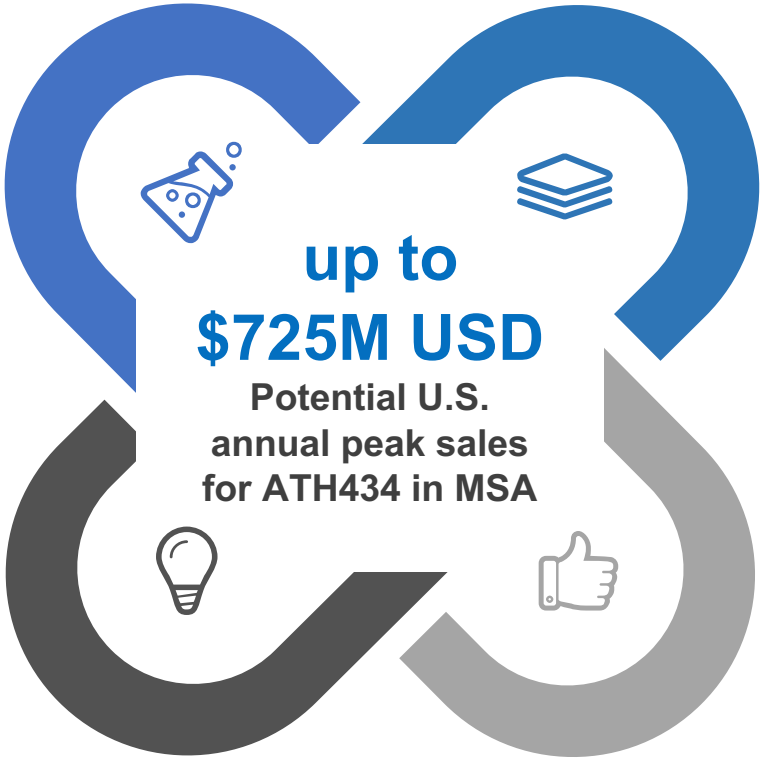
Significant Commercial Opportunity in Treating Multiple System Atrophy

Substantial Unmet Need

Severely debilitating illnesses with no current treatments are ripe for new entrants targeting underlying pathology of the disease.

Unique MOA

Inhibition of protein aggregation is a novel mechanism of action that may prove to impact more than motor symptoms.



Strong Intent to Prescribe

Motivated by efficacy of treating the underlying disease and not just the symptoms, clinicians intend to offer ATH434 to most of their patients with MSA.

Ease of Use

Twice daily oral administration of ATH434 preferred by physicians

Source: Survey of U.S. neurologists

Alterity: Poised for Progress

- ATH434 Phase 2 trial enrolling globally
- Targeting Orphan disease with no approved treatments
- bioMUSE Natural History Study de-risking Phase 2
- Development team with proven track record and multiple FDA approvals
- Drug discovery generating patentable compounds as next generation therapies
- Cash balance of 21.9 M AUD as of 31 March 2023

Milestones

- ✓ 2H 2022: FPI in ATH434 Phase 2
- ✓ Q1 2023: Launch ATH434 Phase 2 in U.S.
- ✓ Q1 2023: Phase 2 FPI in Europe
- ✓ Q1 2023: Phase 2 FPI in U.S.
- ✓ Q2 2023: Present updated bioMUSE wearable sensor data
- ✓ Q2 2023: Phase 2 FPI in Australia
- Q3 2023: Complete enrollment in Phase 2


Alterity
THERAPEUTICS