



**Alterity**  
THERAPEUTICS

# Alterity Therapeutics

(NASDAQ:ATHE, ASX:ATH)


David Stamler, MD  
CEO

November 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 2023 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 parkinsonian disorder with no approved treatment
  - Orphan Drug designation for MSA in the US and EU
  - Phase 2 program ongoing
    - Randomized, double blind study in early-stage MSA
    - Biomarker trial in more advanced MSA
- 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



# ◆ Promising Portfolio in Neurodegenerative Diseases



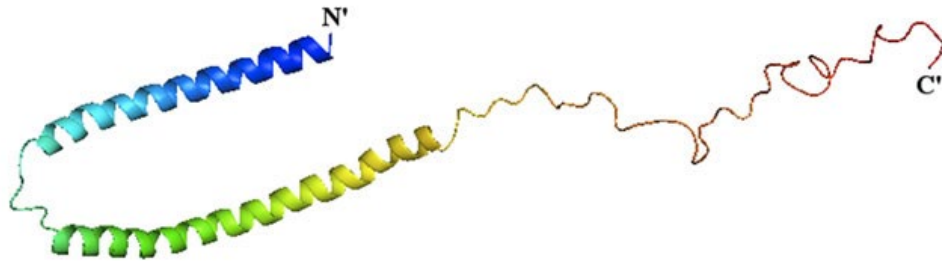
ASSET		PHASE					PARTNER
PROGRAM	INDICATION	DISCOVERY	PRE-CLINICAL	NATURAL HISTORY	PHASE 1	PHASE 2	PARTNER / COLLABORATOR
ATH434-201	Multiple System Atrophy <i>Early Stage</i>						
ATH434-202	Multiple System Atrophy <i>Advanced</i>						
bioMUSE	Multiple System Atrophy <i>Natural History Study</i>						VANDERBILT UNIVERSITY MEDICAL CENTER
ATH434	Parkinson's Disease						THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH
Drug Discovery	Neurodegenerative Diseases						



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# The Role of Alpha-Synuclein and Iron in Parkinsonian Disorders

# ◆ Alpha-Synuclein: Critical for Normal Neuron Function

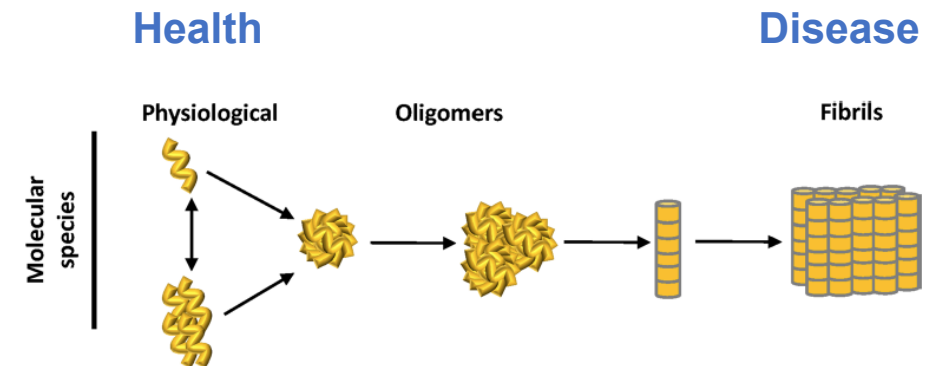


## α-Synuclein

- 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

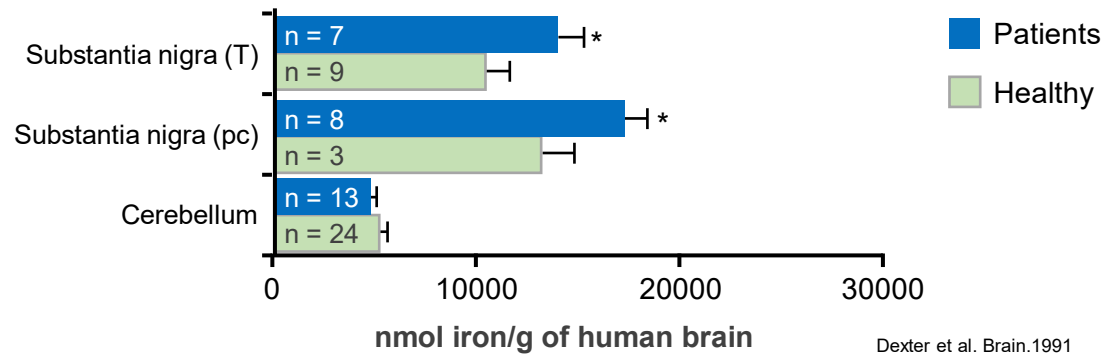
## Our Strategy

- 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

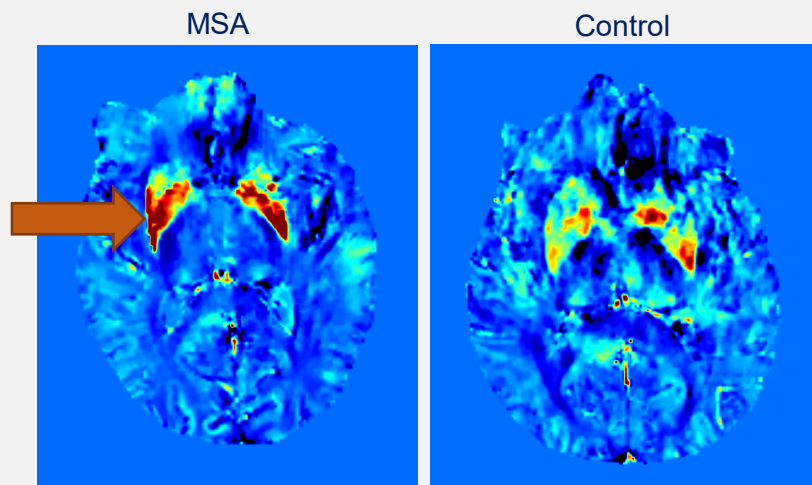


# ◆ Increased Brain Iron in Synuclein-related Diseases

## Parkinson's disease

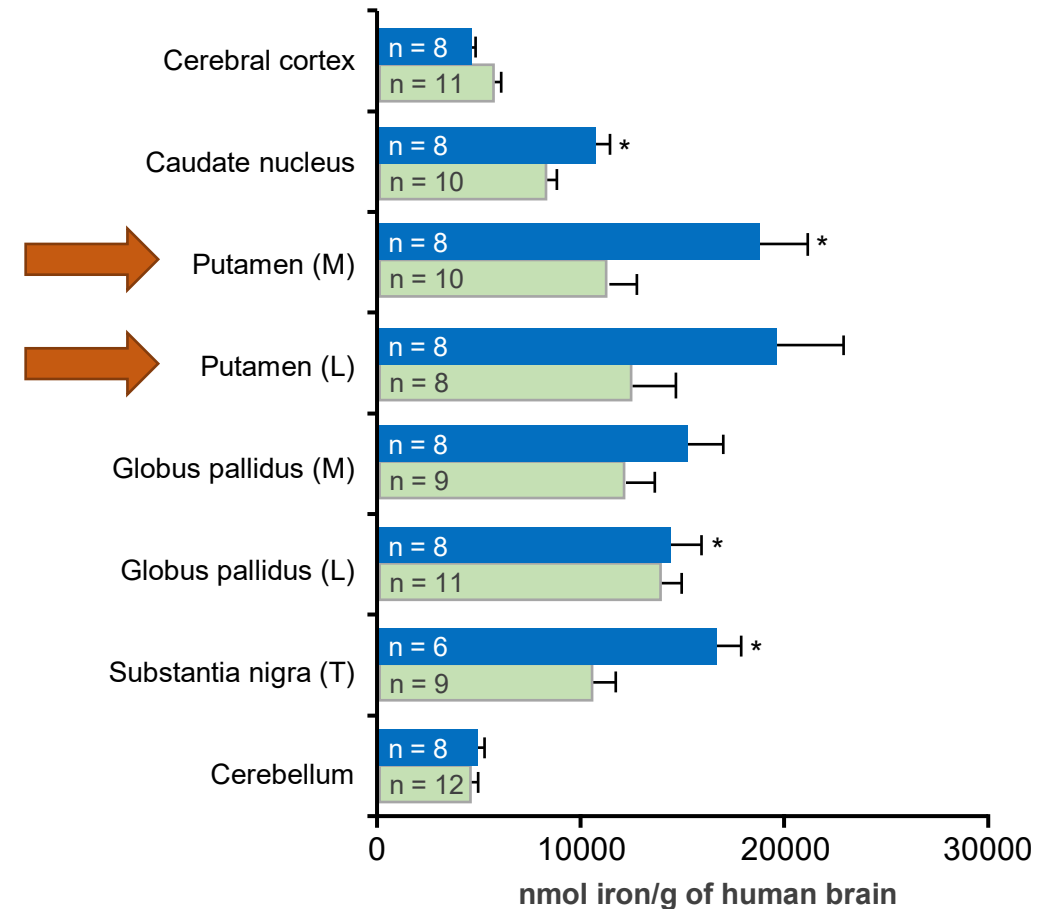


## Advanced Quantitative MRI to measure brain iron



Courtesy of P. Trujillo, D. Claassen

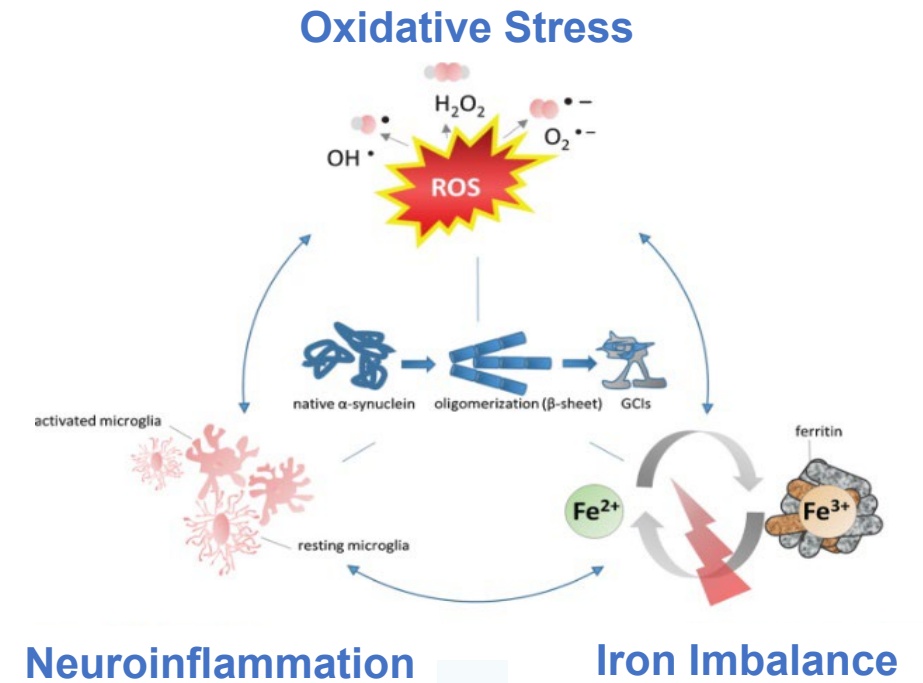
## Multiple System Atrophy



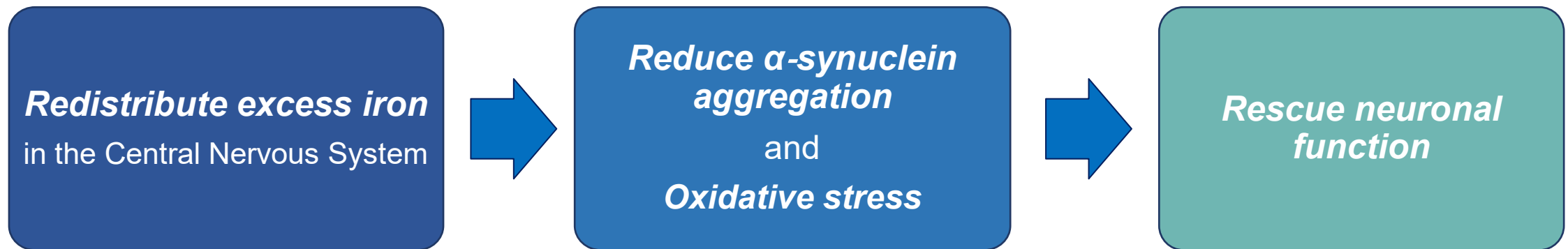
# ◆ Iron: Critical in Disease Pathogenesis

## $\alpha$ -Synuclein and iron are strong contributors to the pathology of MSA

- Adverse impact of excess loosely bound iron
  - Promotes  $\alpha$ -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)



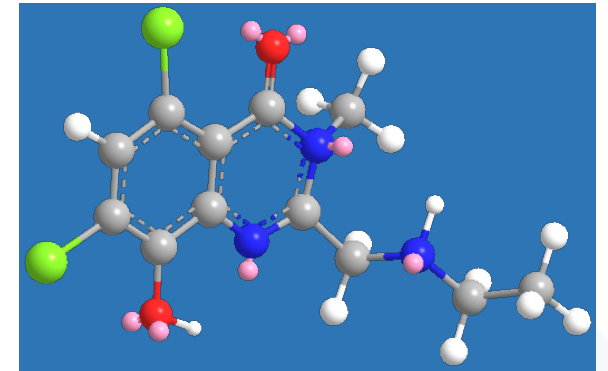
## ◆ Approach: Address Underlying Pathology of Disease



***Potential Disease Modifying Therapy for MSA***

## ◆ ATH434: Disease Modifying Drug Candidate

- Small molecule drug candidate that reduces  $\alpha$ -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
- Potential to treat various Parkinsonian disorders
- Orphan Drug Designation in the US and EU for treatment of MSA
- Development pathway endorsed by FDA and EMA

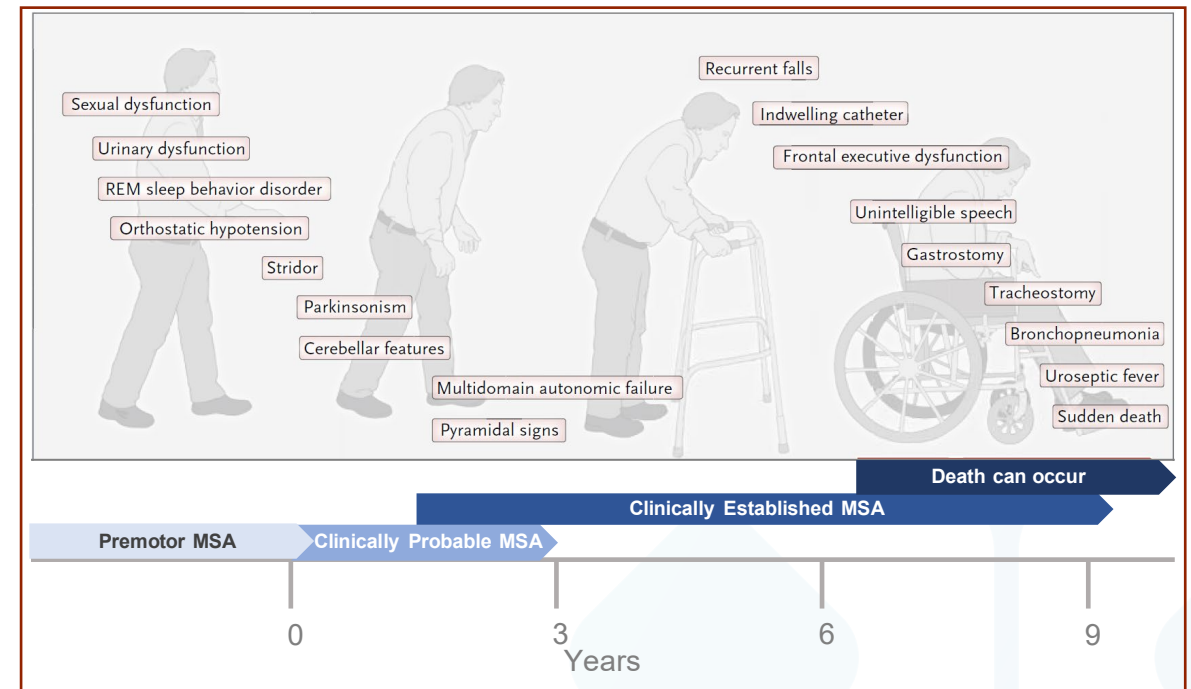


**ATH434**

# Multiple System Atrophy Clinical Development Program

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

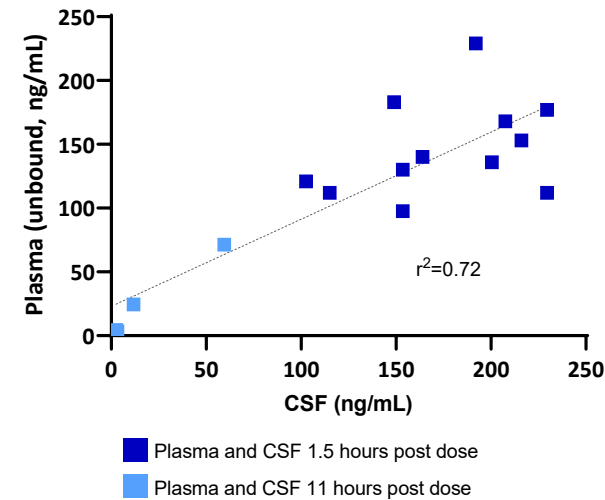
- Clinical impairments include
  - Motor: Parkinsonism, uncoordinated movements, balance problems/falls
  - Autonomic dysfunction: Reduced ability to maintain blood pressure, control bladder and bowel function
- 60% require use of wheelchair within 5 years
- Median survival 7.5 years after symptom onset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



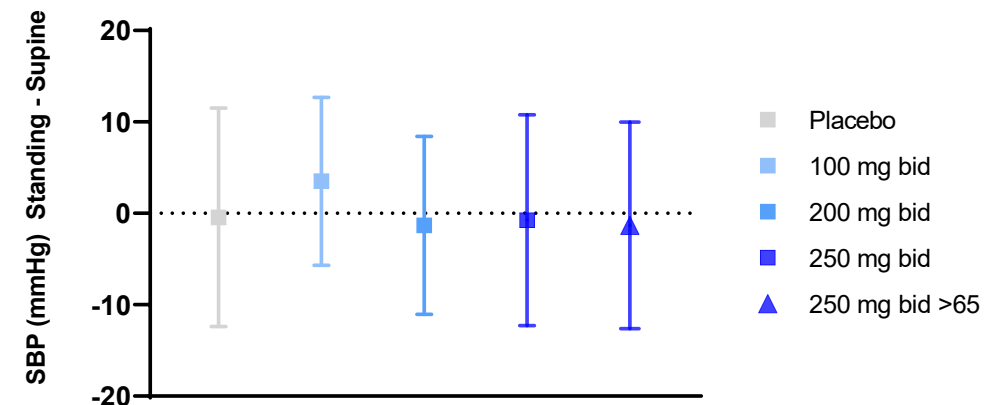
# ◆ Completed Phase 1 with Favorable Safety Profile

- Achieved drug concentrations associated with efficacy in animal models
- Adverse Events (AEs)
  - No SAEs or AEs leading to withdrawal
  - All AEs were mild to moderate in severity with headache as the most common
- No significant findings observed in vital signs, clinical labs or 12-lead ECGs
- Favorable cardiovascular safety profile

ATH434 Levels at Steady-State



No effect on BP with Standing



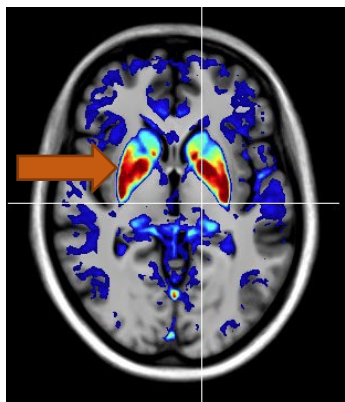
## ◆ bioMUSE: Natural History Study in MSA

Design	<ul style="list-style-type: none"><li>• Observational</li></ul>
Objectives	<ul style="list-style-type: none"><li>• Design and de-risk Phase 2</li><li>• Identify biomarker endpoints for treatment study</li></ul>
Population	<ul style="list-style-type: none"><li>• Early-stage MSA patients similar to Phase 2 population</li><li>• ~20 participants</li></ul>
Observation Period	<ul style="list-style-type: none"><li>• 12 months</li></ul>
Biomarkers	<ul style="list-style-type: none"><li>• MRI: Iron (QSM/R2*), glial pathology (MRS), neuromelanin, regional blood flow</li><li>• Fluid: NfL protein (CSF, plasma), Aggregating <math>\alpha</math>-synuclein (CSF), phos-<math>\alpha</math>-synuclein (skin)</li><li>• Wearable movement sensors</li></ul>
Clinical Endpoints	<ul style="list-style-type: none"><li>• Clinical: Motor exam, autonomic function, activities of daily living, global measures of severity and change (clinician, patient)</li><li>• Functional: Timed Up and Go, 2 min Walk Test</li></ul>

# ◆ bioMUSE Natural History Study

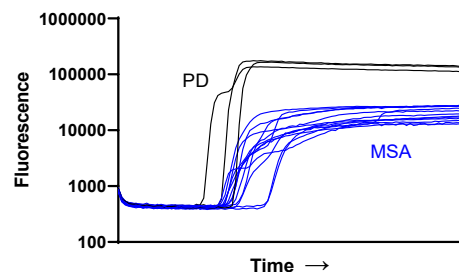
## Design and De-risk Phase 2

### Advanced MRI methods



Identify “iron signature”  
in early MSA vs. PD

### $\alpha$ -synuclein in CSF



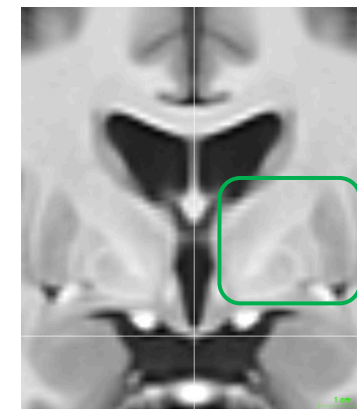
Differentiation of early  
MSA from PD

**Optimize Patient Selection**

**Assess Endpoints with Precision**

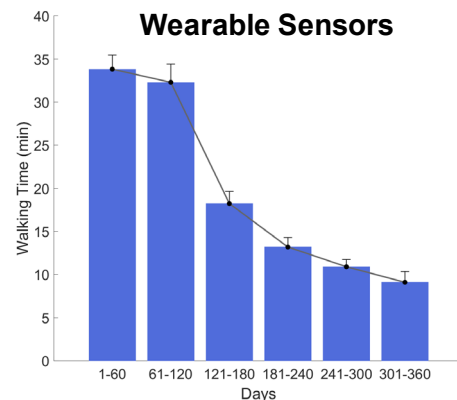
**Pilot Clinical Measures**

### New MRI Template



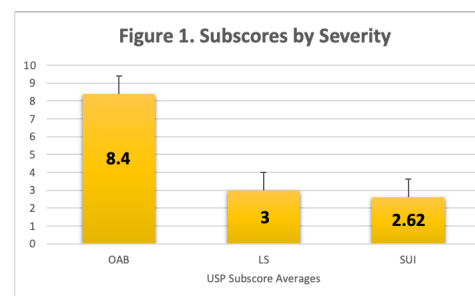
Improve precision of iron  
quantification by MRI

### Wearable Sensors



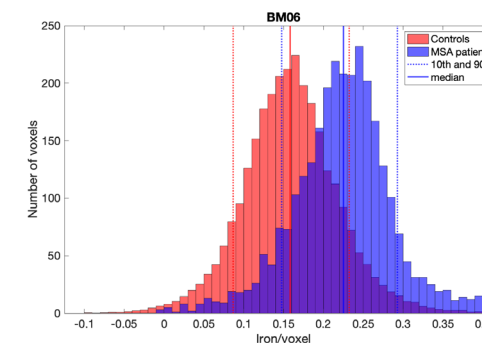
Quantitative assessment  
of motor performance

### Urinary Symptom Profile



Demonstrated utility in  
early MSA

### Iron distribution in MSA

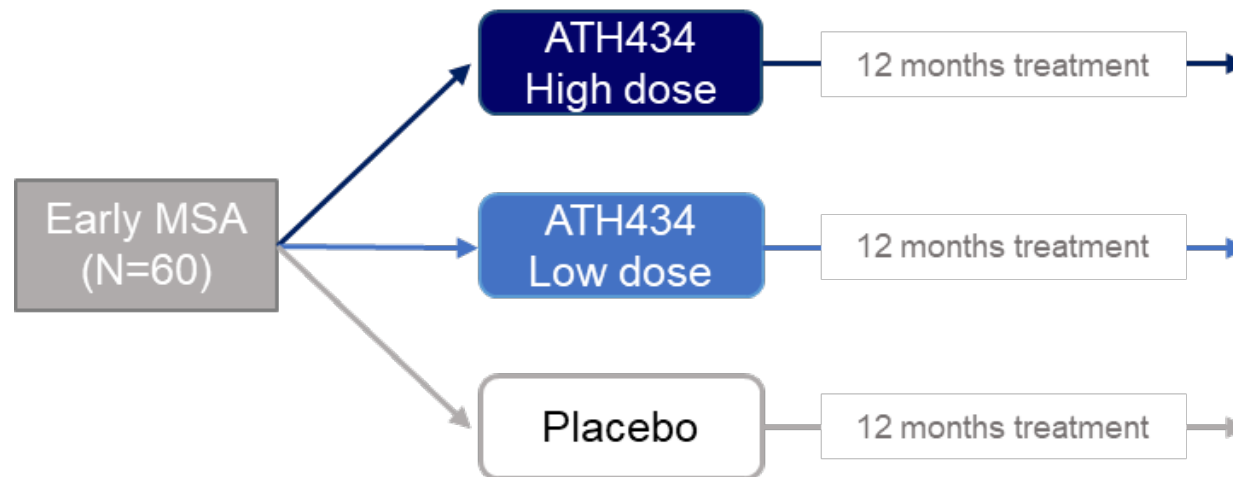


Novel strategies for measuring  
brain iron in individual regions

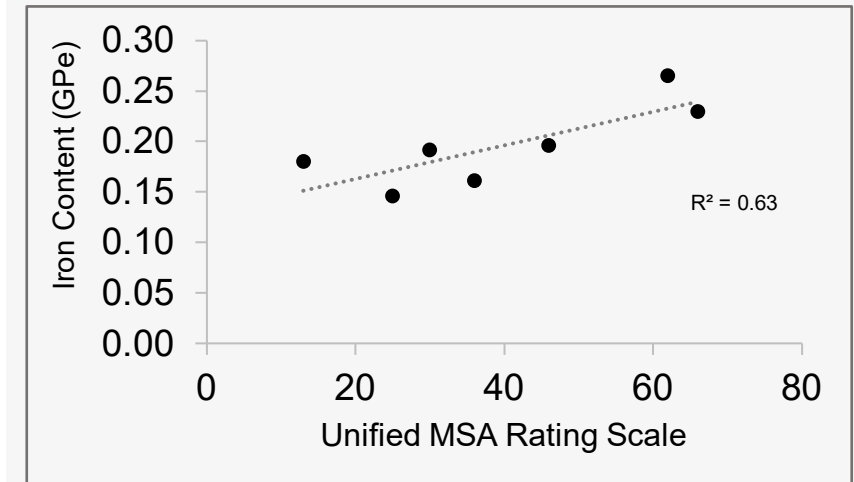
## ◆ ATH434-201: Randomized Phase 2 Clinical Trial in Early-Stage MSA

Design	<ul style="list-style-type: none"><li>• Randomized, double-blind, placebo controlled</li></ul>
Objectives	<ul style="list-style-type: none"><li>• Assess efficacy and safety of ATH434 in participants with MSA</li><li>• Assess target engagement based on imaging and fluid biomarkers</li></ul>
Population	<ul style="list-style-type: none"><li>• Early-stage MSA: ambulatory with biomarker evidence of MSA</li></ul>
Sample Size	<ul style="list-style-type: none"><li>• N=60 at up to 30 sites in ANZ, Europe and the U.S.</li></ul>
Treatment	<ul style="list-style-type: none"><li>• 12 months</li><li>• Three arms: Two dose levels of ATH434 or placebo</li></ul>
Primary Endpoint	<ul style="list-style-type: none"><li>• Change in iron content as measured by brain MRI</li></ul>
Secondary Endpoints	<ul style="list-style-type: none"><li>• Clinical: Activities of daily living inventory (UMSARS I), motor exam, autonomic function</li><li>• Additional imaging biomarkers, fluid biomarkers (aggregating <math>\alpha</math>-synuclein, NfL protein), wearable sensor measures</li></ul>

# ◆ ATH434-201 Phase 2 Design and Primary Endpoint



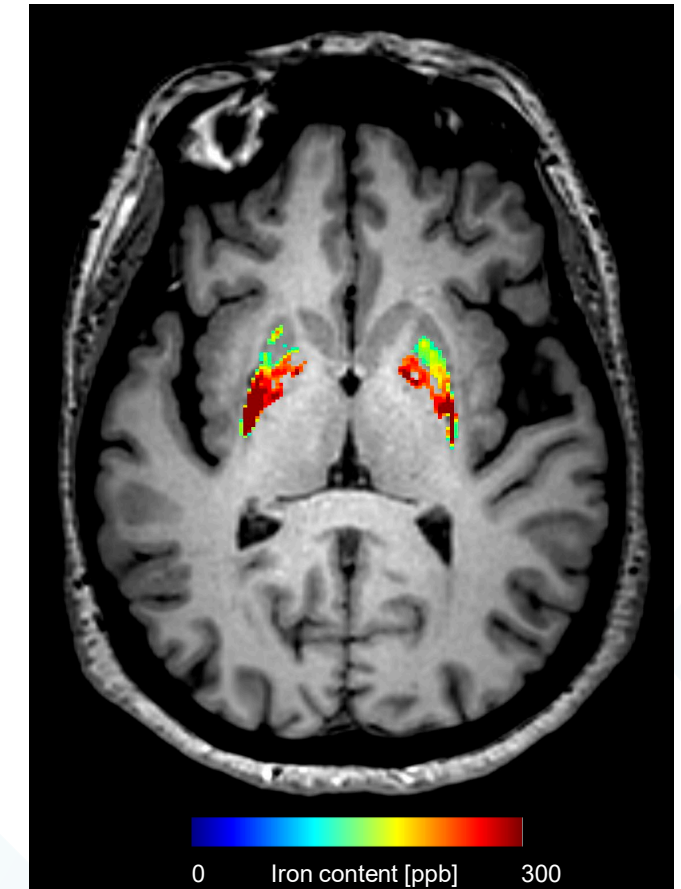
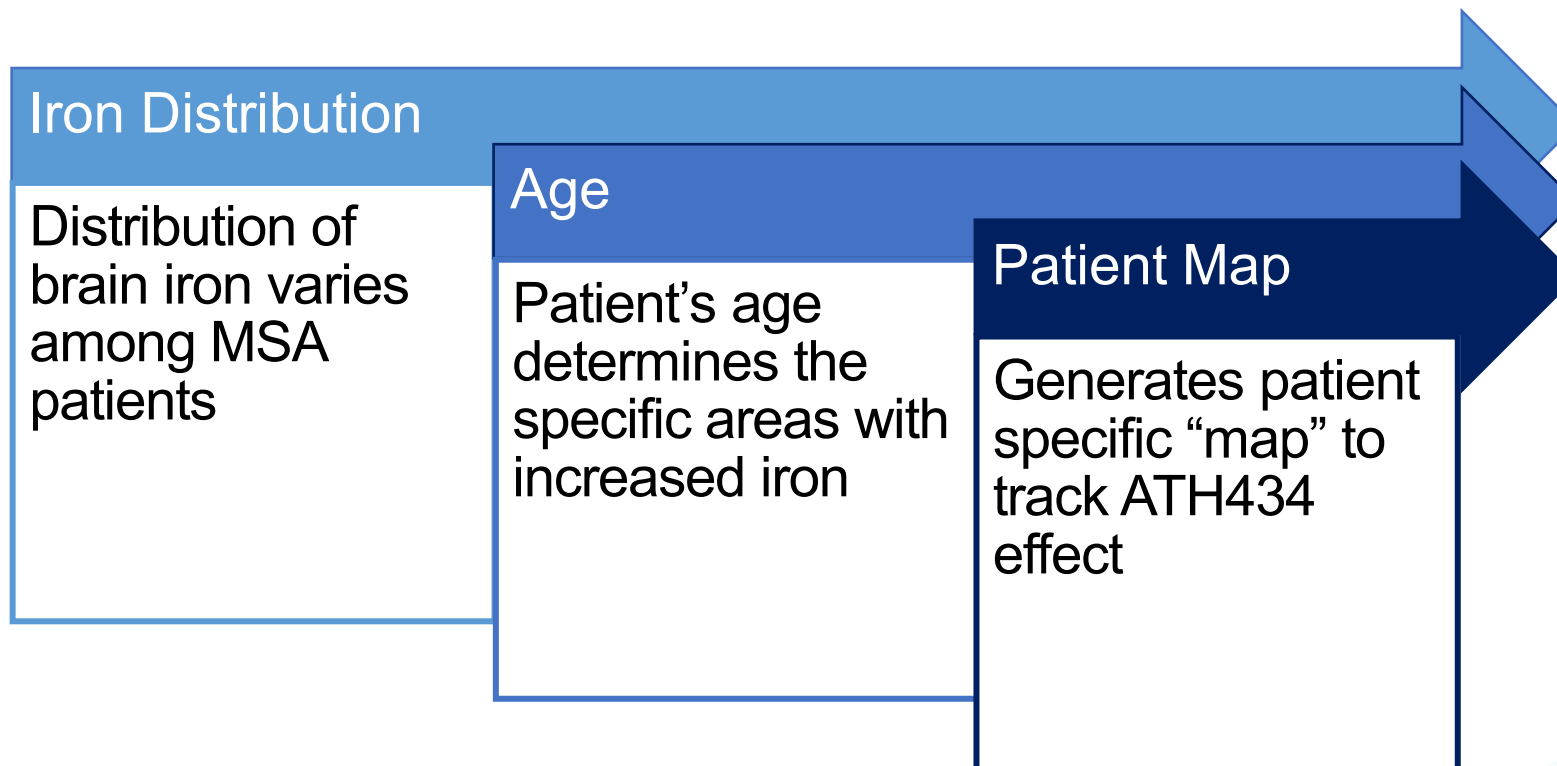
Primary Endpoint:  
Change in Brain Iron on MRI



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

## ◆ Patient Specific “Map” to Evaluate Primary Endpoint with Precision

*ATH434 targets increased iron in patient-specific Region of Interest*



## ◆ ATH434-202: Phase 2 Biomarker Trial in MSA

Design	<ul style="list-style-type: none"><li>• Single arm, open-label</li></ul>
Objectives	<ul style="list-style-type: none"><li>• Assess target engagement based on imaging and fluid biomarkers</li><li>• Assess efficacy and safety of ATH434 in participants with MSA</li></ul>
Population	<ul style="list-style-type: none"><li>• Clinically Established (advanced) MSA with biomarker evidence of disease</li></ul>
Sample Size	<ul style="list-style-type: none"><li>• N=15</li></ul>
Treatment	<ul style="list-style-type: none"><li>• 12 months</li></ul>
Primary Endpoint	<ul style="list-style-type: none"><li>• Change in iron content as measured by brain MRI</li></ul>
Secondary Endpoints	<ul style="list-style-type: none"><li>• Clinical: Activities of daily living inventory (UMSARS I), motor exam, autonomic function</li><li>• Additional imaging biomarkers, fluid biomarkers (aggregating <math>\alpha</math>-synuclein, NfL protein)</li></ul>

# ◆ 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

## ◆ Alterity: Poised for Progress

- Targeting Orphan disease with no approved treatments
- Two Phase 2 clinical trials ongoing
  - Double-blind trial enrolling globally
  - Biomarker trial enrolling in U.S.
- bioMUSE Natural History Study de-risking Phase 2
- Development team with multiple FDA approvals
- Drug discovery generating patentable compounds as next generation therapies
- Cash balance of \$16.7 M AUD as of 30 Sept 2023
  - \$4.8M AUD Placement plus SPP announced in November 2023

### Clinical Milestones

#### ATH434-201 Phase 2 Double-Blind Trial

- ✓ Q1 2023: First Patients Dosed in U.S. and Europe
- ✓ Q2 2023: First Patient Dosed in Australia
- ✓ Q3 2023: DMC recommends continuing trial as planned
- ✓ October 2023: Closed Screening
- ✓ November 2023: Complete Enrollment
- Q4 2024: Study Complete

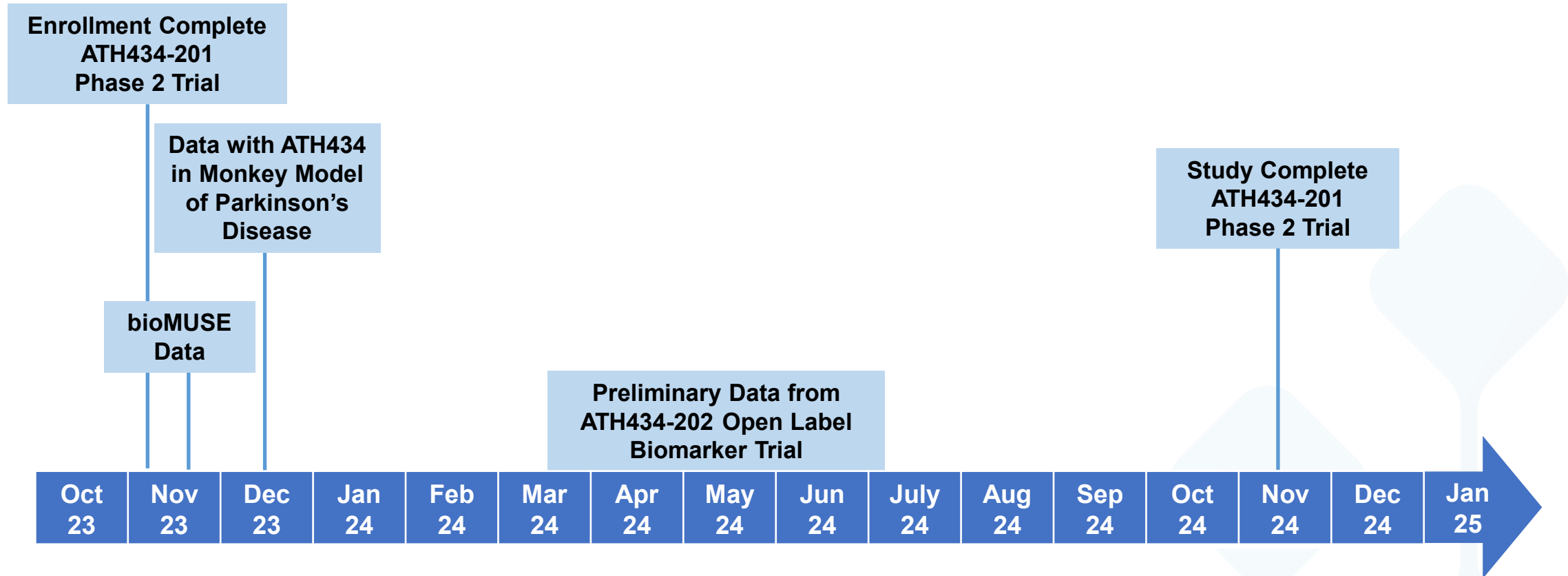
#### ATH434-202 Phase 2 Biomarker Trial

- ✓ Q2 2023: Initiate Trial
- H1 2024: Preliminary Data

#### MSA Natural History Study

- ✓ Q2 2023: Diagnostic Precision Data
- Q4 2023: Present new biomarker data

# ◆ Key Milestones





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