Alterity Therapeutics

(NASDAQ:ATHE, ASX:ATH)

David Stamler, MD
CEO

January 2024

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

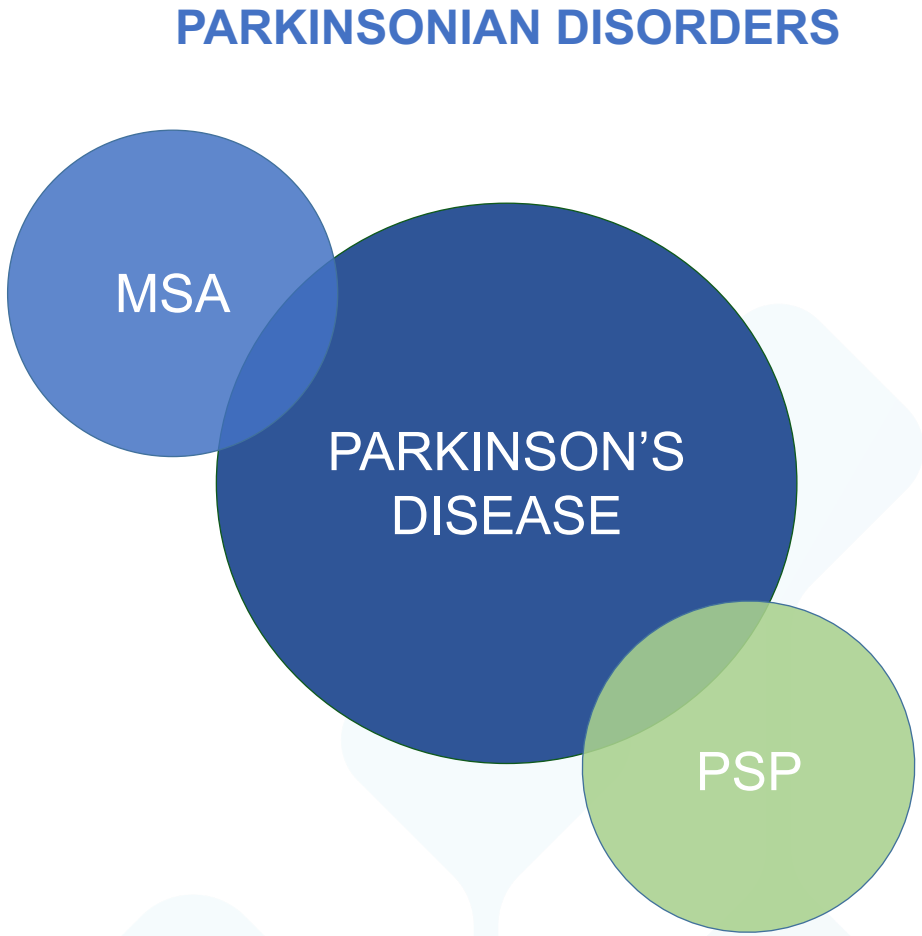
Auspex/Teva | Nextwave | Astex | Intermune | Impax Labs

- 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)
  - MSA is a rare disease without approved therapy
  - Orphan Drug designation in US and EU

Parkinson's disease and MSA have similar underlying pathology



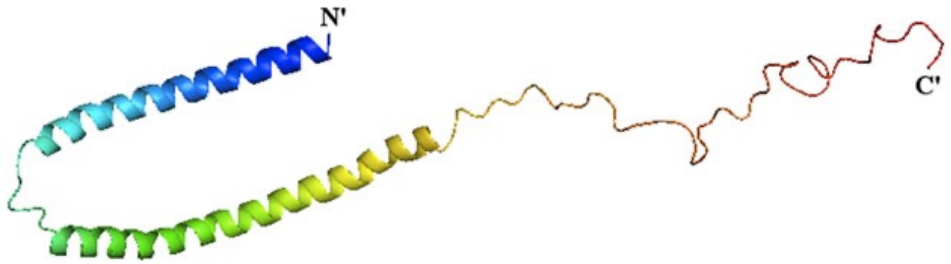
Promising Portfolio in Neurodegenerative Diseases

Alterity THERAPEUTICS

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

The Role of Alpha-Synuclein and Iron in Parkinsonian Disorders

Alpha-Synuclein: Critical for Normal Neuron Function

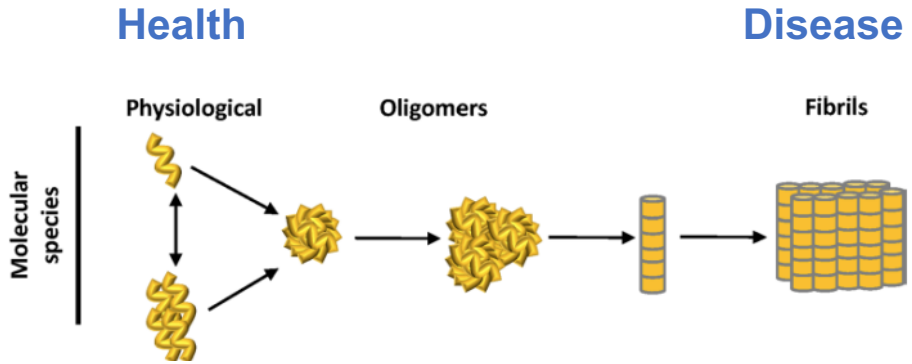


Our Strategy

- 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

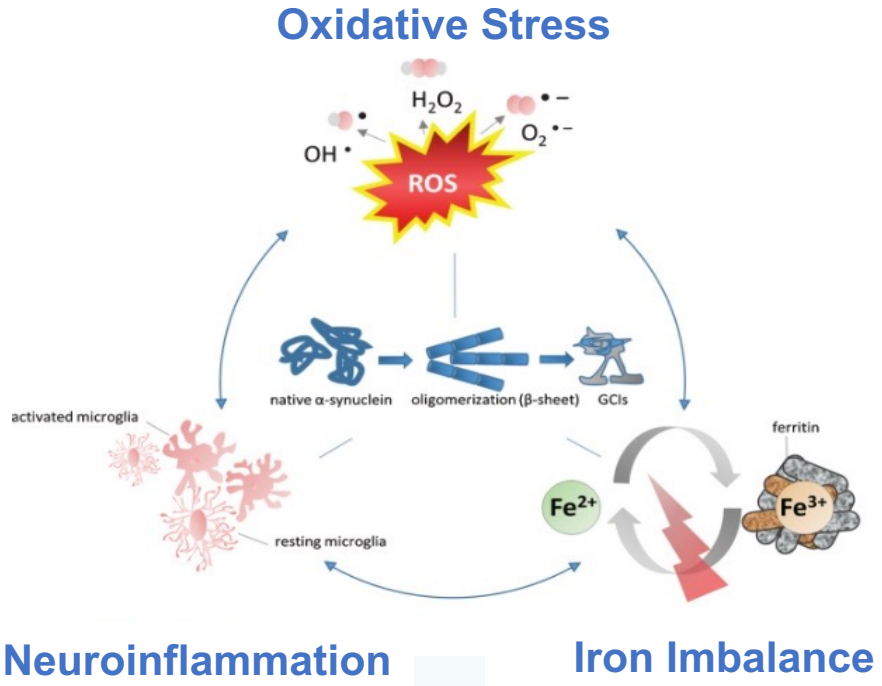


Sources: Ritchie et al, 2012; DOI:10.4236/health.2012.431175; Bengoa-Vergniory et al, 2017.DOI 10.1007/s00401-017-1755-1

Iron: Critical in Disease Pathogenesis

α-Synuclein and iron are strong contributors to the pathology of MSA

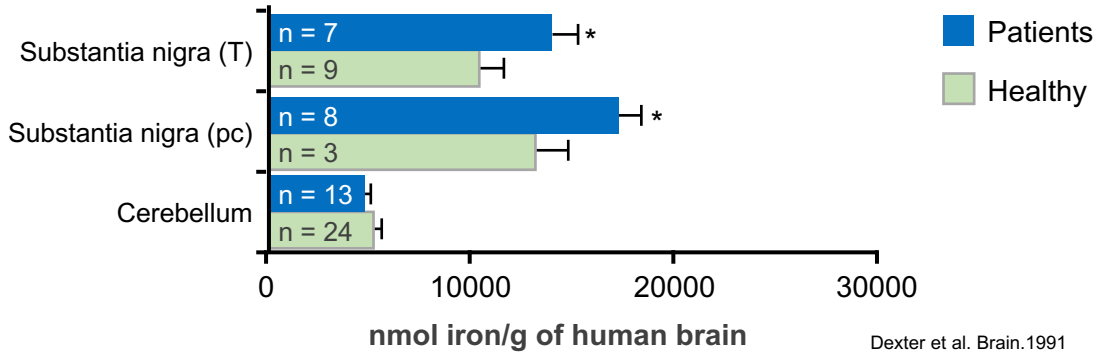
- Adverse impact of excess loosely bound iron
  - Promotes α-synuclein aggregation
  - Root cause of oxidative stress which damages intracellular structures and leads to neuroinflammation
- Hallmark of MSA pathology
  - Neuron loss in multiple brain regions



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

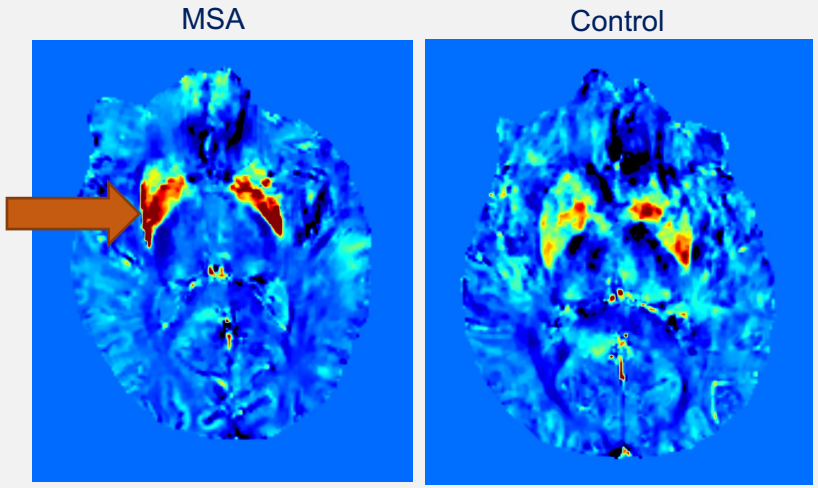
Increased Brain Iron in Synuclein-related Diseases

Parkinson's disease



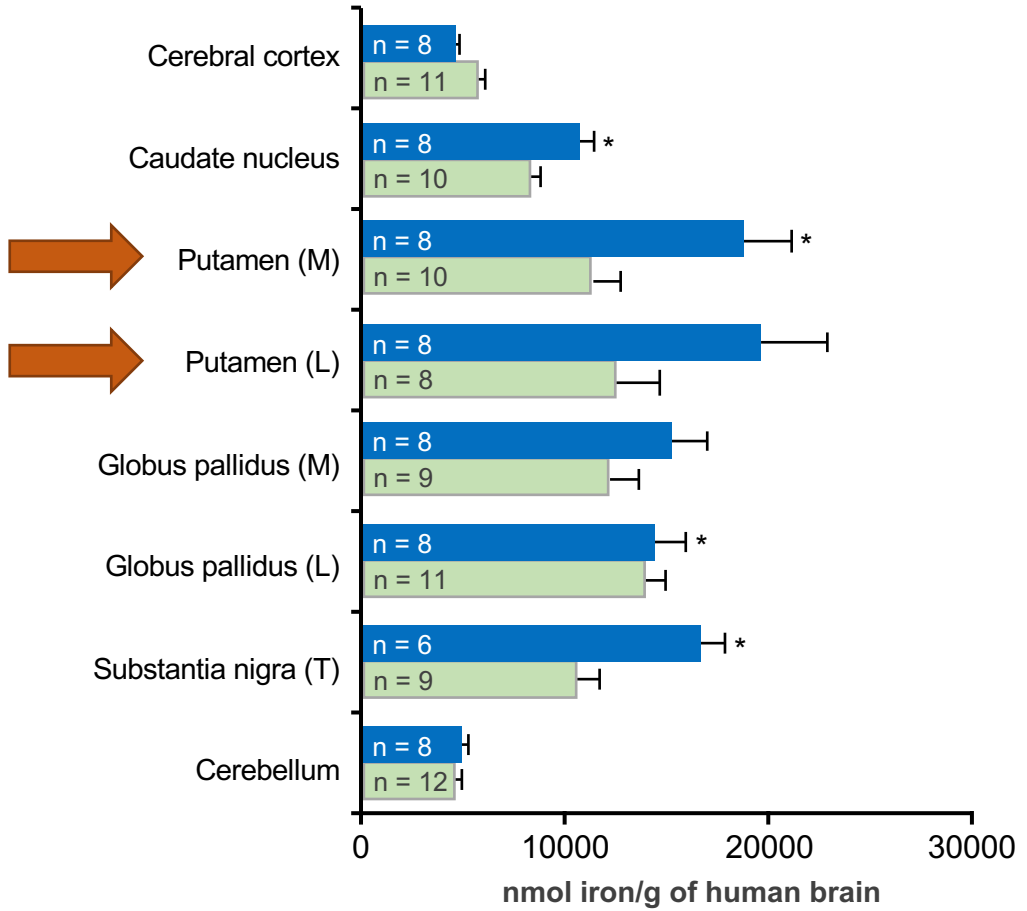
Dexter et al. Brain.1991

Advanced Quantitative MRI to measure brain iron

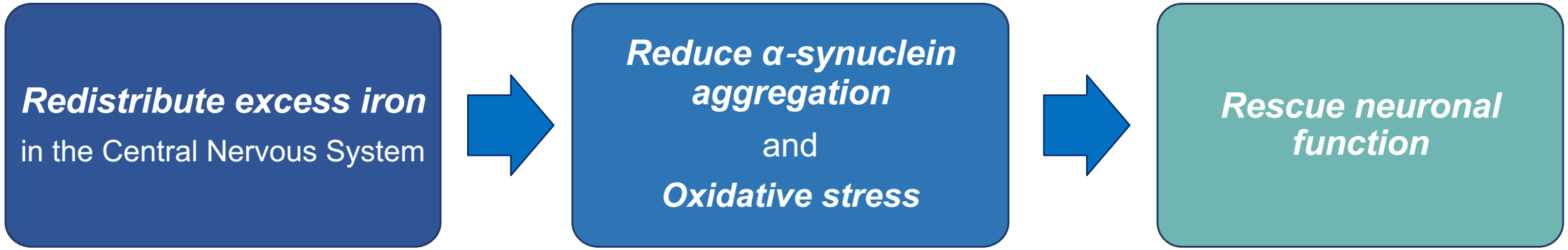


Courtesy of P. Trujillo, D. Claassen

Multiple System Atrophy



Approach: Address Underlying Pathology of Disease

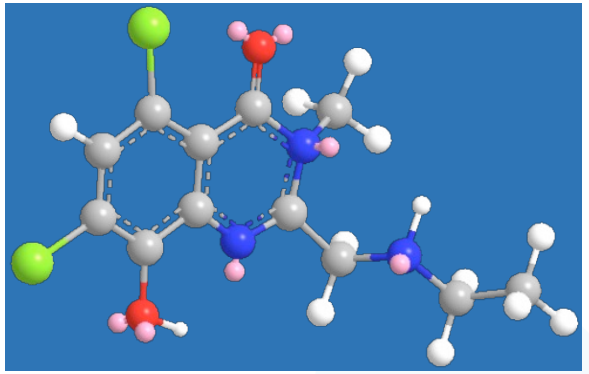


Potential Disease Modifying Therapy for MSA

ATH434: Disease Modifying Drug Candidate

ATH434: Potential Use in Multiple Indications

- Small molecule drug candidate 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
- 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

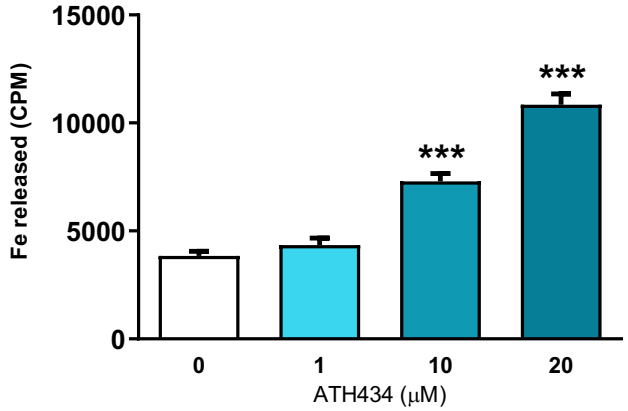


ATH434

Pharmacologic Actions of ATH434

Alterity THERAPEUTICS

Redistributes loosely bound excess iron

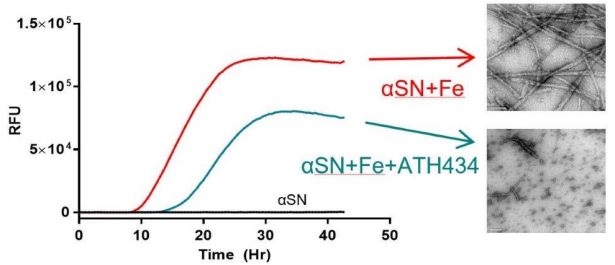


Ligand	Kd for Fe^{3+}
α-synuclein	10^{-5}
ATH434	10^{-10}
Transferrin	10^{-23}

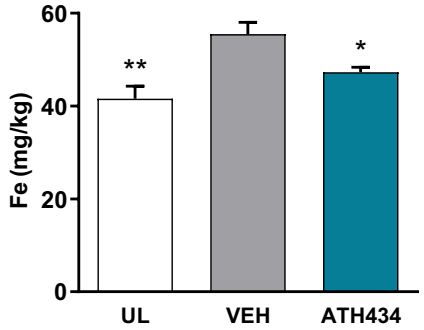
Stronger binding

ATH434 does not interfere with normal iron trafficking proteins

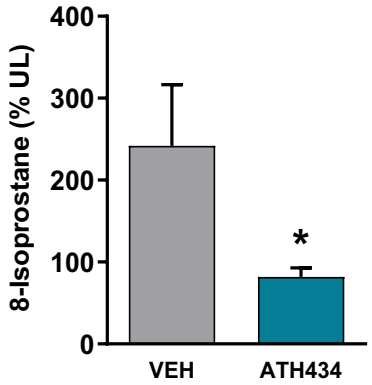
Reduces α-synuclein aggregation



Blocks increase in brain iron



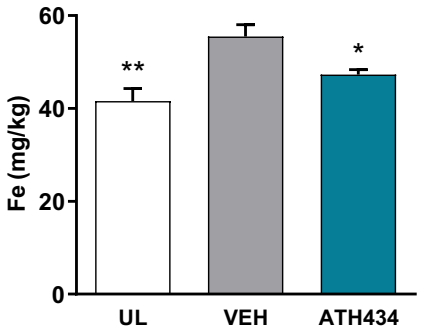
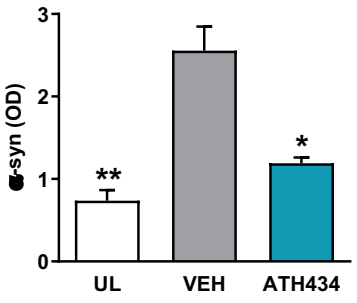
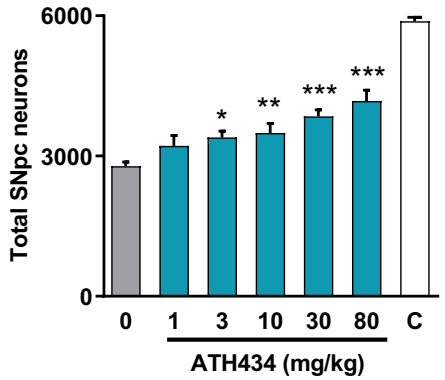
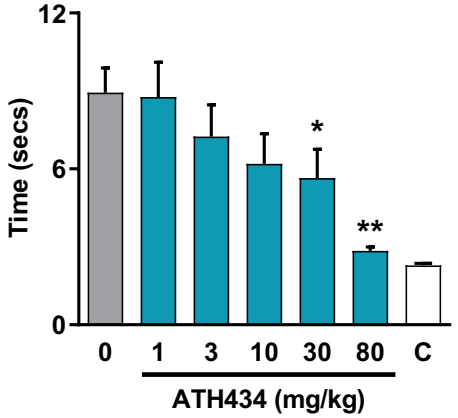
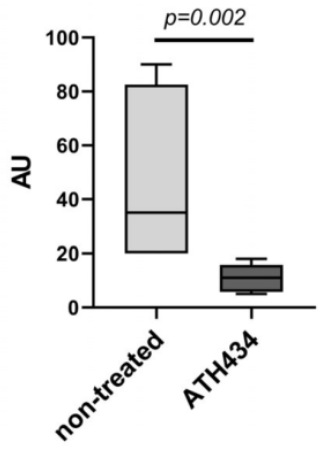
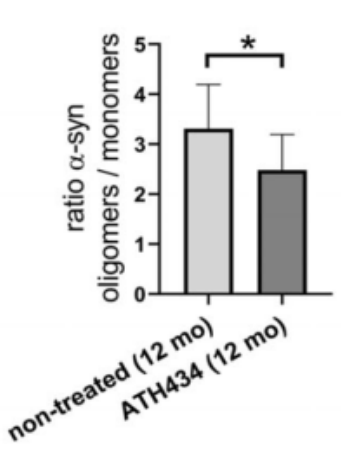
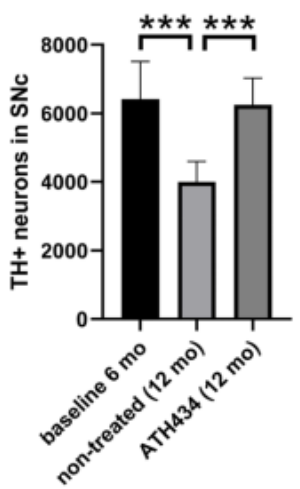
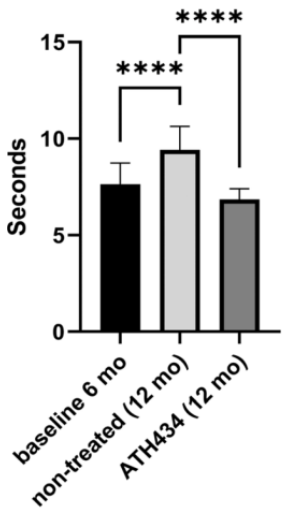
Inhibits oxidative stress in vivo



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

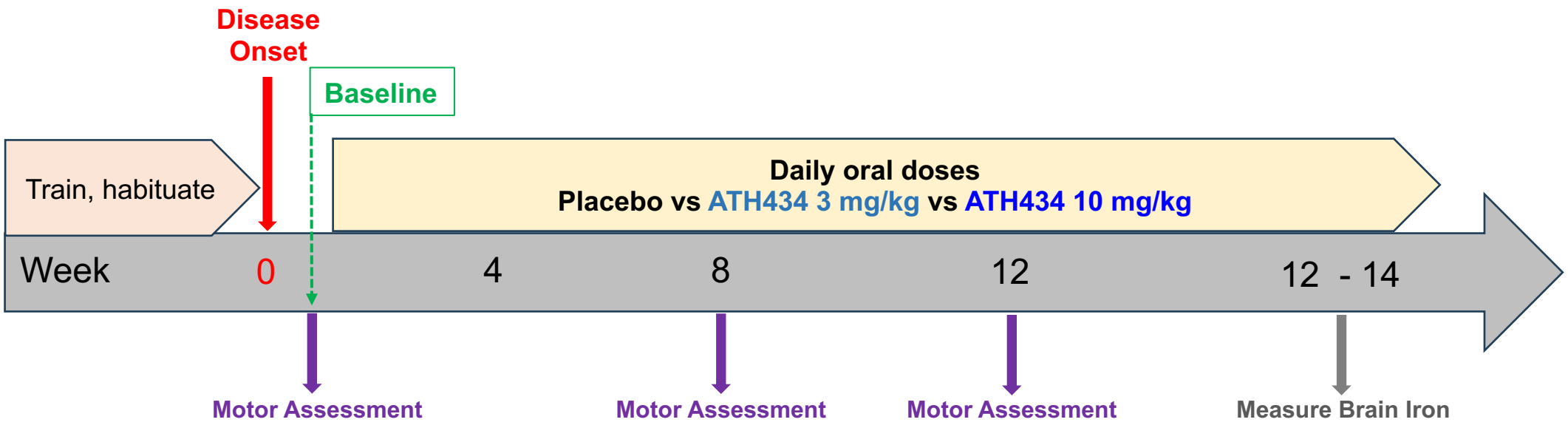
ATH434 Reduces Neuropathology and Improves Motor Function in Parkinson's Disease and MSA Animal Models

Alterity THERAPEUTICS

	↓ Iron	↓ α-Synuclein	Preserves Neurons	Improves Motor Function
Parkinson's Disease Mouse Model				
MSA Mouse Model				

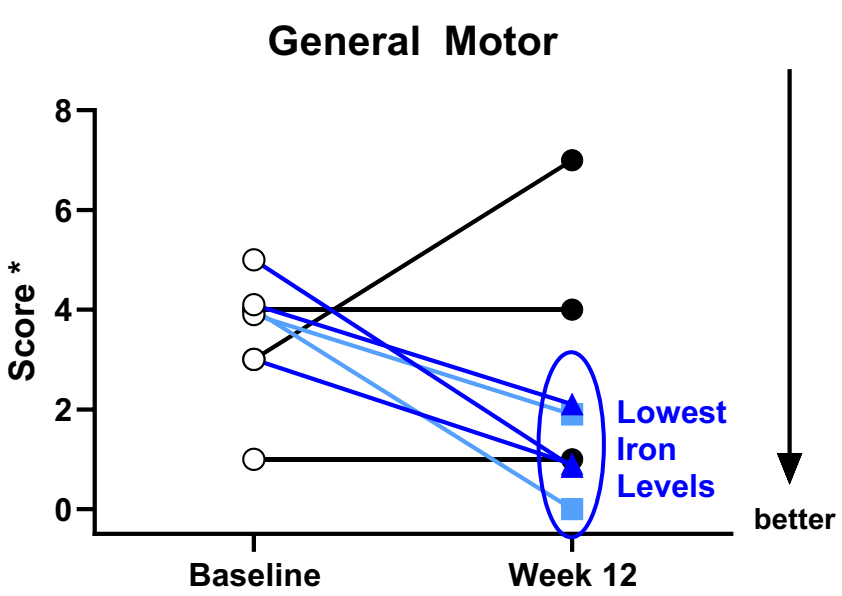
Sources: Finkelstein, et al. Acta Neuropath Comm. 2017; Heras Garvin, et al. Mov. Disord. 2021. UL: unlesioned, C: control |* P < 0.05, ** P < 0.01, *** P < 0.001, ****P < 0.0001

Monkey Parkinson's Disease Study

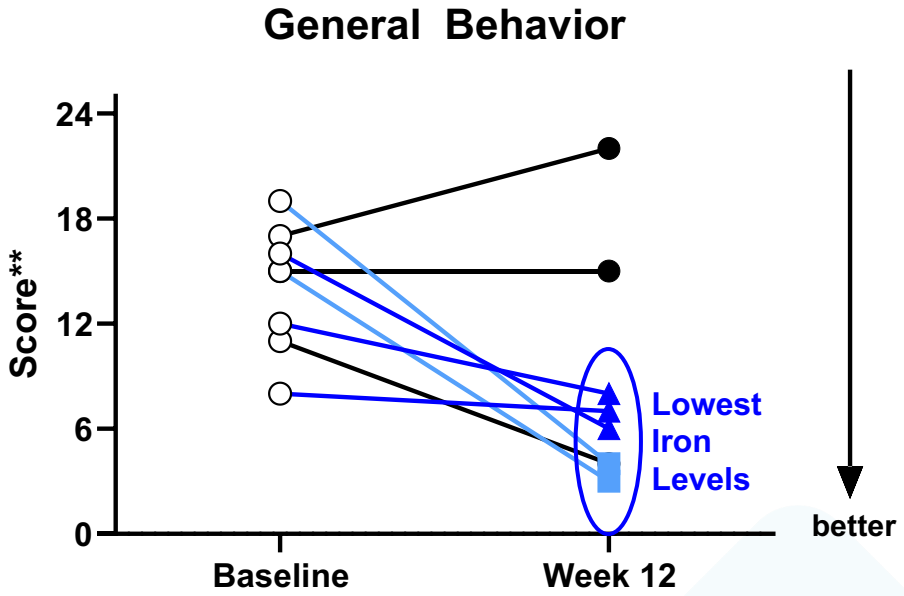


Source: Bradbury, et al, "Effects of ATH434, a Clinical-Phase Small Molecule with Moderate Affinity for Iron, in Hemiparkinsonian Macaques", Future of Parkinsons Disease, 2023

ATH434 Improved Motor and Behavior Scores
Improvement Associated with Reduced Iron



* Fine motor skills, eating, eyeblink



Placebo (veh)
3 mg/kg
10 mg/kg

** Appetite, response to food, activity, appearance, posture, balance, climbing, tremor, freezing, facial expression, defensive reactions

ATH434: All (N=5) had Improved Motor and Behavior Scores
Placebo: 2 of 3 had Stable or Worsening Scores

Primate Study Validates ATH434 Clinical Approach

- Well established model of Parkinson's, primate closer to humans
- ATH434 treatment **improved motor skills** and **general behavior/function** in monkeys with experimentally induced Parkinson's disease
- Favorable impact on Parkinson's symptoms in animals with lower brain iron *in the area of pathology*
- ATH434 also increased levels of synaptophysin, a protein marker that reflects functional connections between neurons
- Increases our overall confidence in ongoing Phase 2 trials

Accumulated Evidence of ATH434 Efficacy

Target Disease	Model	Brain Iron	α-Synuclein	Neurons/ Connectivity	Clinical Observations	Author
Parkinson's disease	Mouse MPTP	↓	↓	↑	Improved motor performance	Finkelstein
Parkinson's disease	Mouse A53T	↓	↓	↑	Improved motor performance	Finkelstein
Parkinson's disease	Mouse tau knockout	↓	↓	↑	Improved motor performance	Beauchamp
MSA	PLP-α-syn	↓	↓	↑	Improved motor performance	Heras-Garvin
MSA	PLP-α-syn	↓	↓	↑	Improved motor performance	Finkelstein
Parkinson's disease	**Monkey MPTP**	**↓**	**n/a**	**↑**	**Improved motor performance**	**Bradbury**

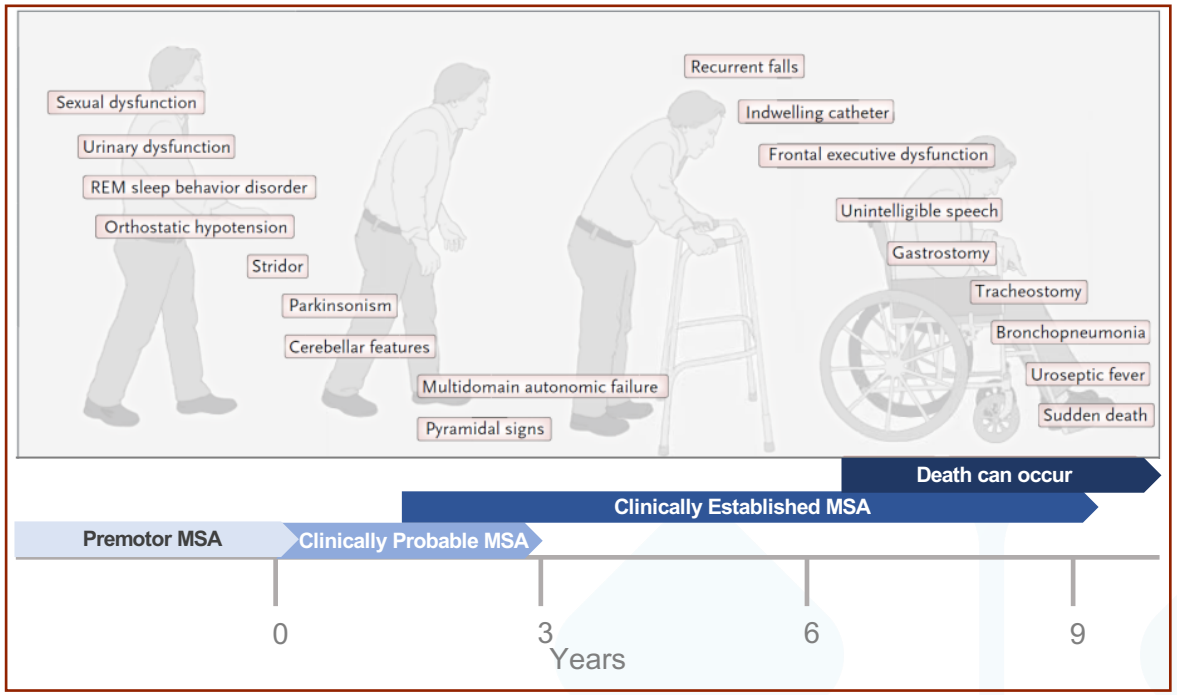
ATH434 consistently **improved motor performance** across diverse animal models of disease with reduced brain iron and α-synuclein

Source: Finkelstein, Acta Neuropath Comm 2017; Beauchamp et al, Neurotherapeutics 2022; Heras-Garvin et al, Mov Disord. 2021; Finkelstein et al, J Park Dis 2022; Bradbury et al, Future of PD, 2023

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

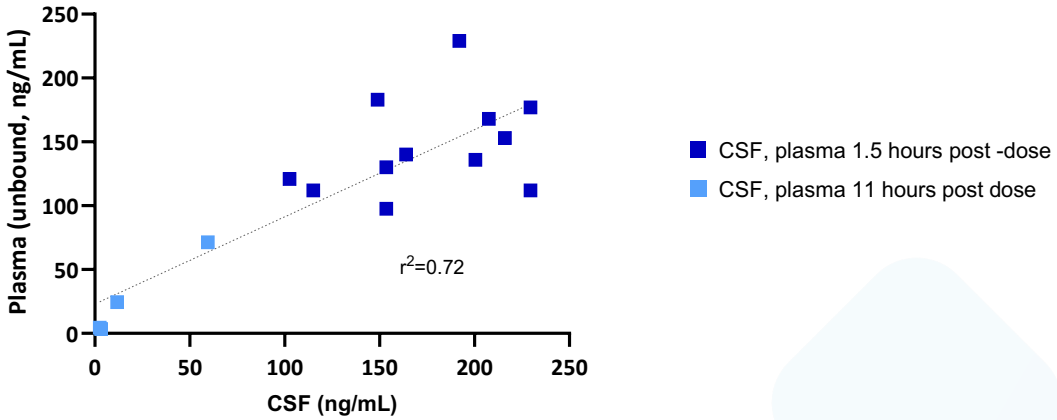


Sources: Fanciulli, Wenning. NEJM 2015 | Wenning, et al. Mov Disorders 2022 | Coon, et al. Brain 2015 | Claassen,et al. Mov Disorders 2021

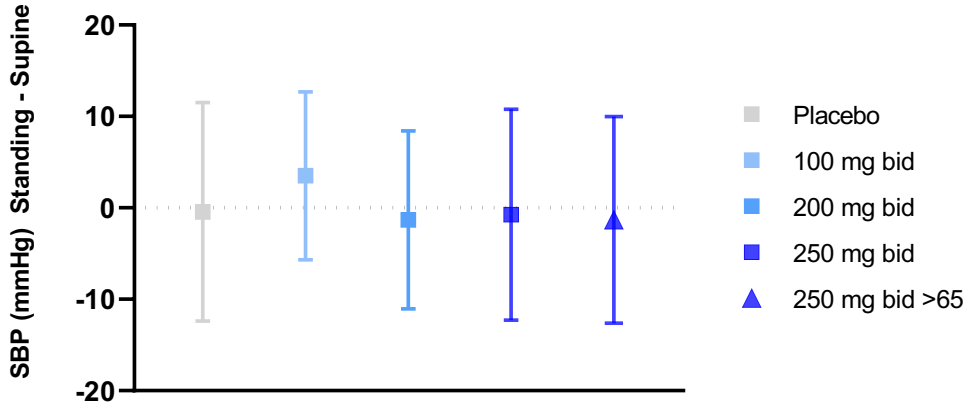
Completed Phase 1 with Favorable Safety Profile

- Achieved drug concentrations associated with efficacy in animal models
- Favorable safety profile
  - All Adverse Events (AEs) were mild to moderate in severity
  - No SAEs or AEs leading to withdrawal
- 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



Source: Phase 1 clinical trial; Alterity data on file

bioMUSE: Natural History Study in MSA

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

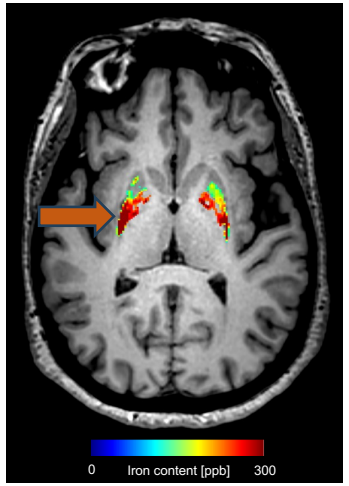
Alterity THERAPEUTICS

Optimize Patient Selection

Assess Endpoints with Precision

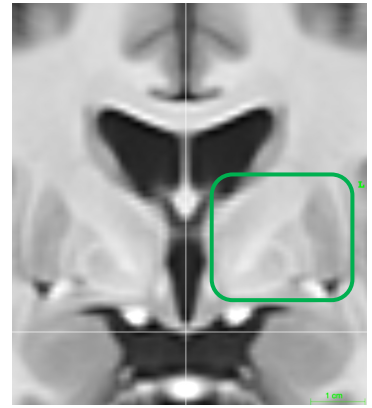
Pilot Clinical Measures

Advanced MRI methods



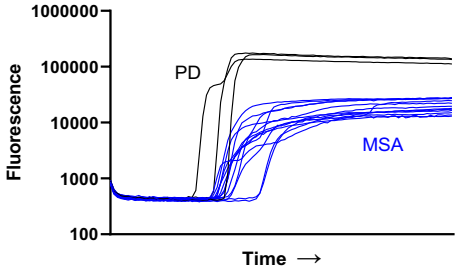
Identify "iron signature" in early MSA vs. PD

New MRI Template



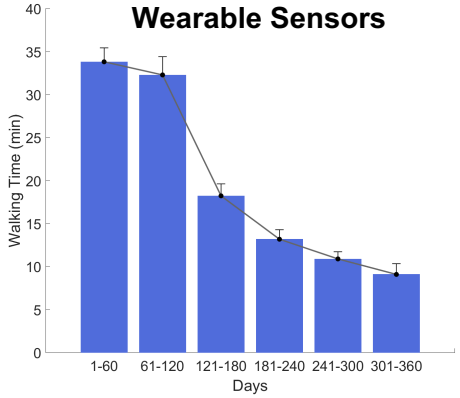
Improve precision of iron quantification by MRI

α-synuclein in CSF



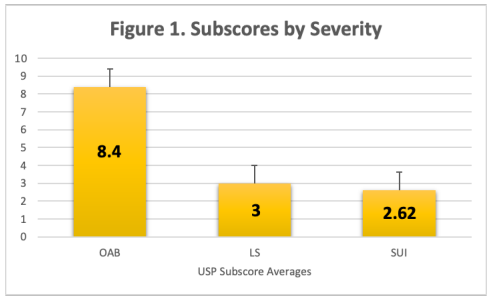
Differentiation of early MSA from PD

Wearable Sensors



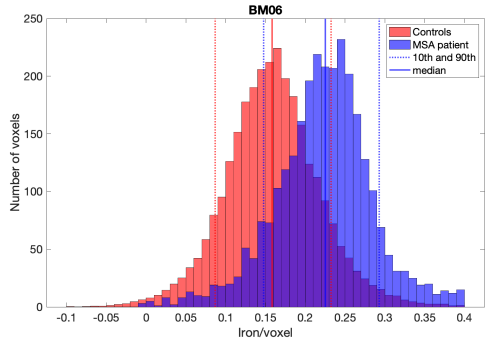
Quantitative assessment of motor performance

Urinary Symptom Profile



Demonstrated utility in early MSA

Iron distribution in MSA



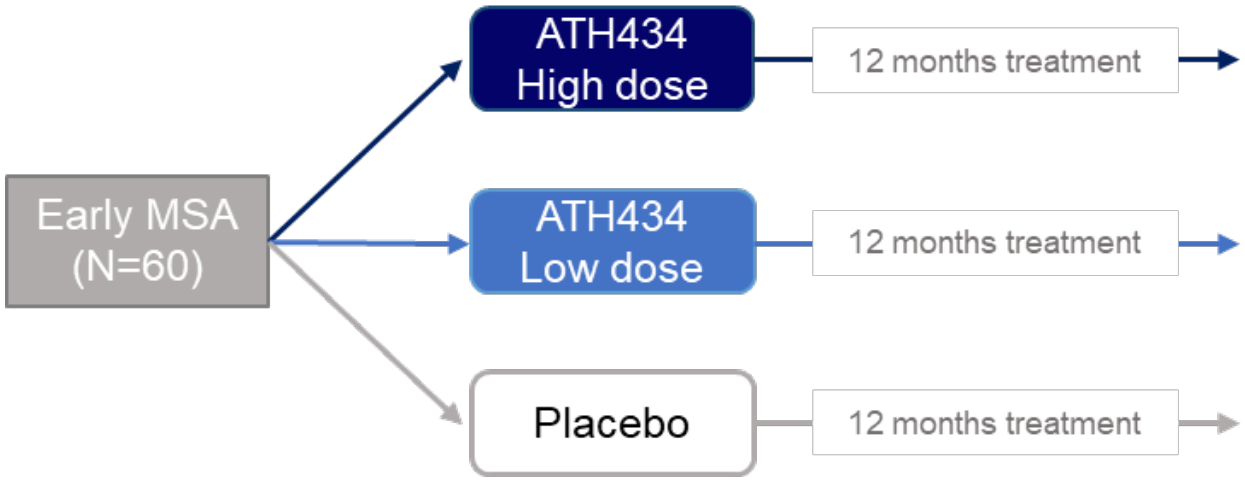
Novel strategies for measuring brain iron in individual regions

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

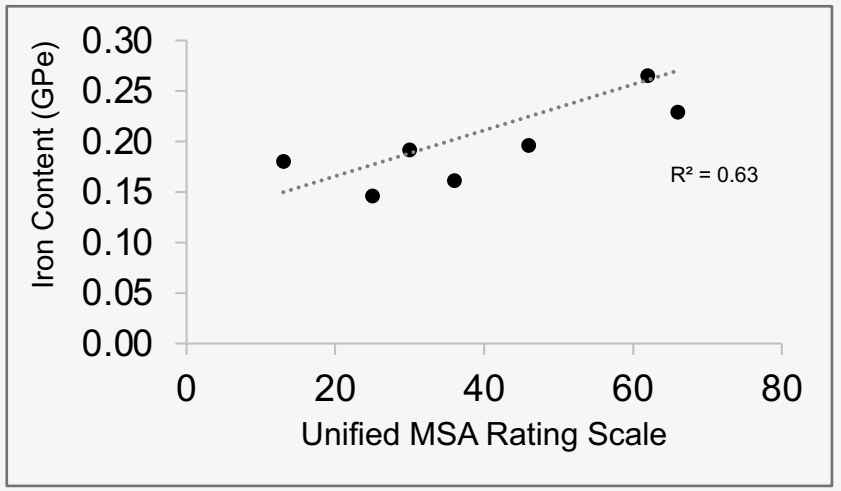
ATH434-201: Randomized Phase 2 Clinical Trial in Early-Stage MSA

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=77 at ~25 sites in U.S., Europe and ANZ
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

ATH434-201 Phase 2 Design and Primary Endpoint



Primary Endpoint:
Change in Brain Iron on MRI



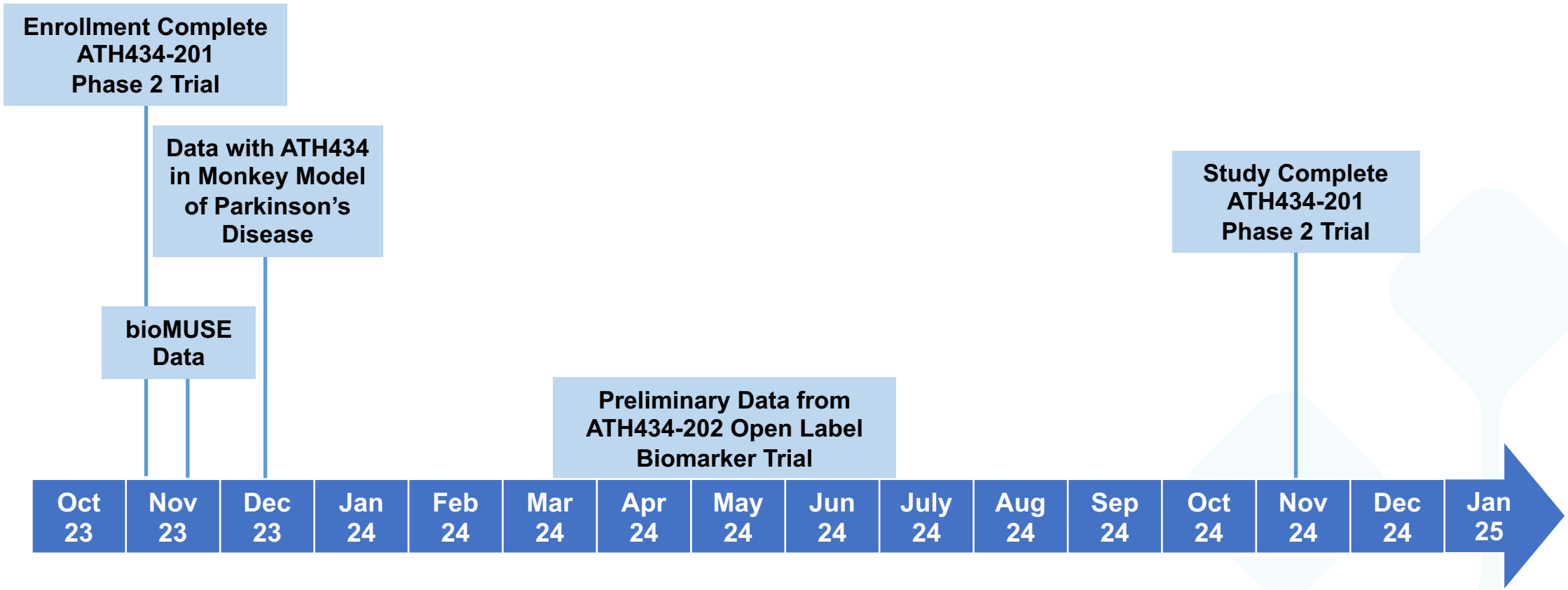
BioMUSE Natural History Study Demonstrates
Brain iron correlates with disease severity in MSA

Source: Claassen, et al. Mov Disorders 2021

ATH434-202: Phase 2 Biomarker Trial in MSA

Design	• Single arm, open-label
Objectives	• Assess target engagement based on imaging and fluid biomarkers • Assess efficacy and safety of ATH434 in participants with MSA
Population	• Clinically Established (advanced) MSA with biomarker evidence of disease
Sample Size	• N=15
Treatment	• 12 months
Primary Endpoint	• Change in iron content as measured by brain MRI *(same as in Study ATH434-201)*
Secondary Endpoints	• Clinical: Activities of daily living inventory (UMSARS I), motor exam, autonomic function • Additional imaging biomarkers, fluid biomarkers (aggregating α-synuclein, NfL protein)

Key Development Milestones



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, updated 2023

Alterity: Poised for Progress

- Targeting Orphan disease with no approved treatments
- Two Phase 2 clinical trials ongoing
  - Global double-blind trial enrollment completed
  - 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 $16.7M AUD as of 30 Sept 2023
  - A$4.8M Placement (Nov/Dec 2023)
  - Up to A$2M Stock Purchase Plan (Jan 2024)

Upcoming Catalysts

ATH434-201 Phase 2 Double-Blind Trial

- ✓ Nov 2023: Enrollment Complete
- Nov 2024: Study Complete
- Jan 2025: Topline Data

ATH434-202 Phase 2 Biomarker Trial

- H1 2024: Preliminary 6-mo Data
- H2 2024: Preliminary 12-mo Data

MSA Natural History Study

- H1 2024: Present new biomarker data


Alterity
THERAPEUTICS