



**Alterity**  
THERAPEUTICS

# Alterity Therapeutics

(NASDAQ:ATHE, ASX:ATH)

David Stamler, MD  
CEO


March 2022





## ◆ 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 2021 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

Novel approach to **treat the underlying pathology of disease**

**Strong and highly experienced management team** with significant R&D experience including **3 drug approvals by US FDA**

ATH434 is a **novel drug candidate targeting key proteins** implicated in neurodegeneration of Parkinson's Disease and related disorders

First therapeutic target: Multiple System Atrophy (MSA), a **devastating disease with no approved treatments**

Orphan Drug designation in the U.S. and EU

Advancing to a **Phase 2 clinical trial**

Strong patent portfolio

# Recent Progress



International Parkinson and  
Movement Disorder Society



**Movement  
Disorders**



- ▶ Presentation of advanced quantitative MRI as potential novel biomarker in early MSA
- ▶ Two new US patents expand portfolio of next generation compounds for neurodegenerative diseases
- ▶ Publication demonstrating neuroprotective effect of ATH434 in animal model of MSA
- ▶ Michael J. Fox Foundation grant for ~US\$500K for Parkinson's disease



EUROPEAN MEDICINES AGENCY  
SCIENCE. MEDICINES. HEALTH.



VANDERBILT UNIVERSITY  
MEDICAL CENTER

- ▶ EMA endorses clinical strategy for Phase 2 study in early MSA patients
- ▶ US FDA provides development pathway for ATH434 in Multiple System Atrophy
- ▶ Expanding bioMUSE Natural History study in early MSA

# ◆ 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

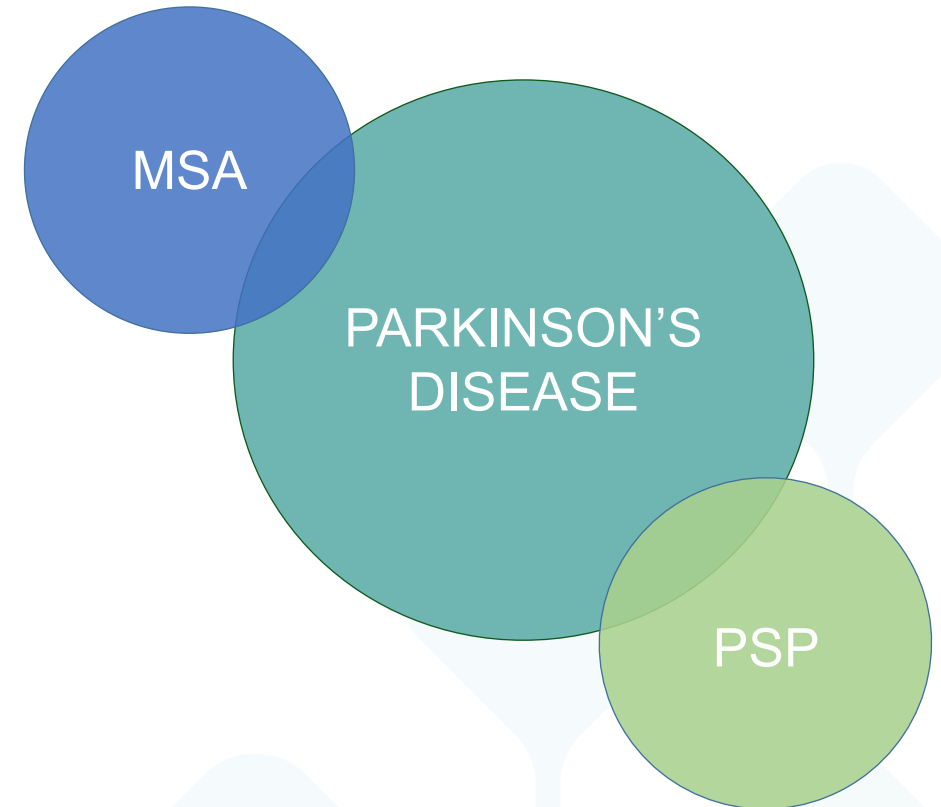
- A major source of disability

Parkinsonian disorders also include atypical forms such as Multiple system atrophy (MSA) and Progressive supranuclear palsy (PSP)



- “Atypical” as have prominent non-motor symptoms and a limited response to available treatments

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

### PARKINSONIAN DISORDERS



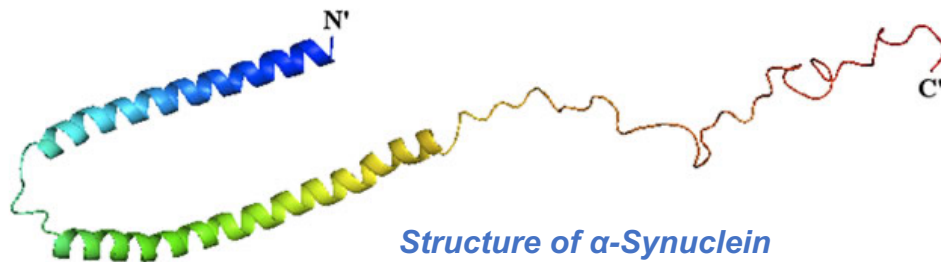
# ◆ Discovery and Development Portfolio in Neurodegenerative Diseases

Program	Indication	Current Status	Future Plans
bioMUSE Natural History Study	Multiple System Atrophy	Ongoing  Partner: 	Enrolling up to 20 patients
ATH434	Multiple System Atrophy	Phase 1 Complete	Phase 2 expected to launch Q2 2022
ATH434	Parkinson's Disease	Preclinical studies to optimize dosing  Partner: 	Proof of concept study in Parkinson's disease
Drug Discovery	Neurodegenerative diseases	Discovery ongoing	Generate new IND candidates

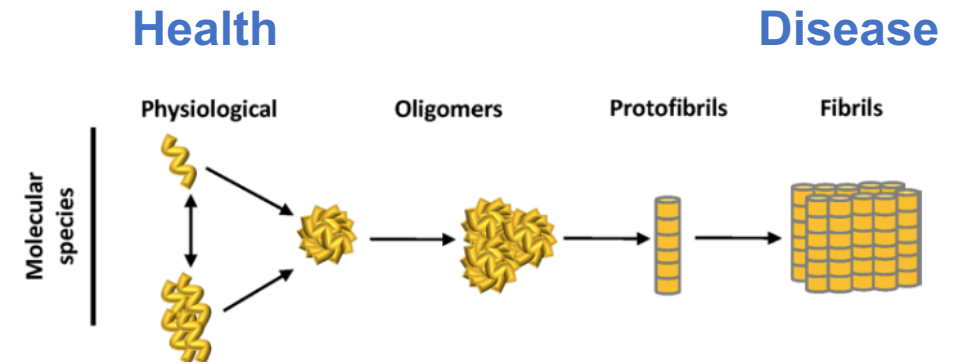


# Alterity's Approach to Treating Parkinsonian Disorders

# ◆ Alpha-Synuclein: A Major Focus for Treating Parkinsonian Disorders



- $\alpha$ -Synuclein is an intracellular protein critical for normal function of neurons
- Native, unfolded protein enables neurotransmission
- $\alpha$ -Synuclein *aggregates* in Parkinson's Disease and Multiple System Atrophy



## Our Strategy

- Inhibit oligomerization and aggregation of intracellular  $\alpha$ -Synuclein
- Target misfolding  $\alpha$ -synuclein by redistributing excess iron in areas of pathology
- Address underlying pathology of disease

# ◆ Iron is Critical in the Pathogenesis of Parkinsonian Disorders

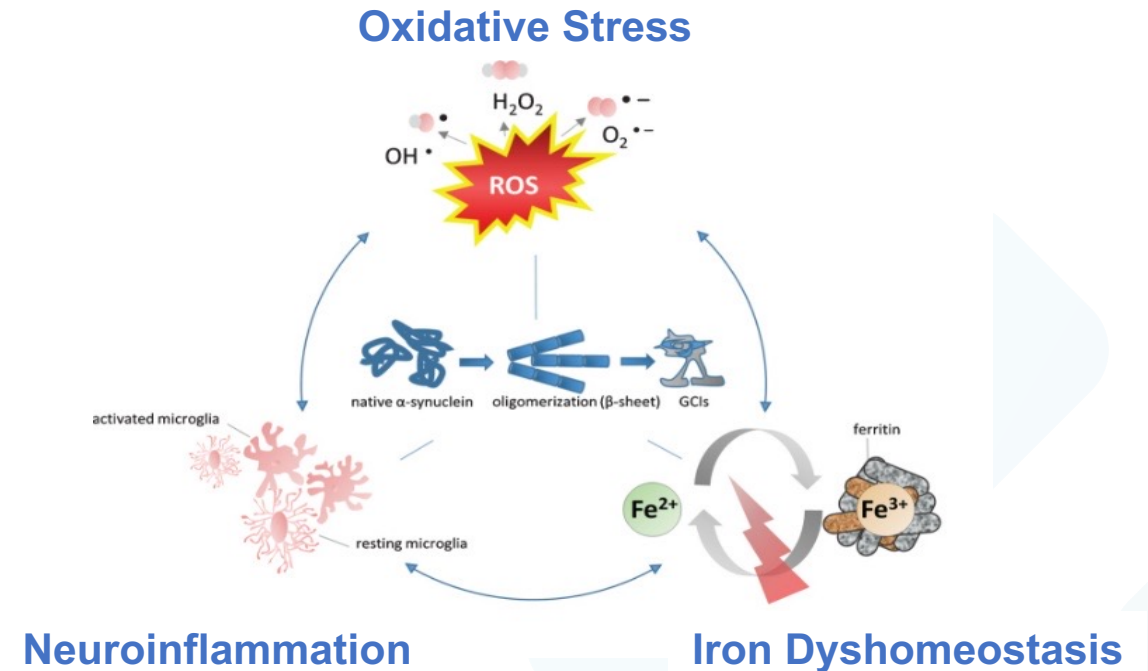
## **$\alpha$ -Synuclein and iron are strong contributors to the pathogenesis of MSA**

Prominent pathology in Oligodendroglial cells (ODG)

- ODGs are vital support cells for neurons
- Cells with highest iron content in the CNS
- Demonstrate prominent  $\alpha$ -synuclein pathology
- Hallmark of MSA: accumulation of  $\alpha$ -synuclein within ODGs and neuron loss in multiple brain regions

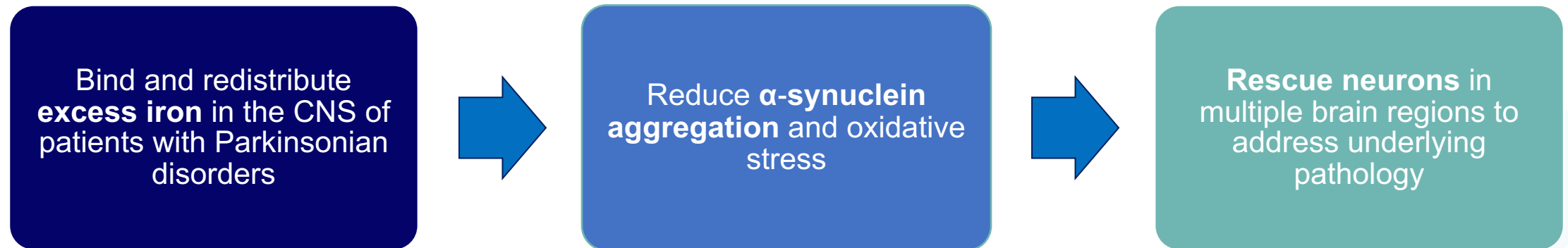
Adverse impact of increased labile iron

- Promotes  $\alpha$ -synuclein aggregation
- Root cause of oxidative stress which damages intracellular structures and leads to neuroinflammation





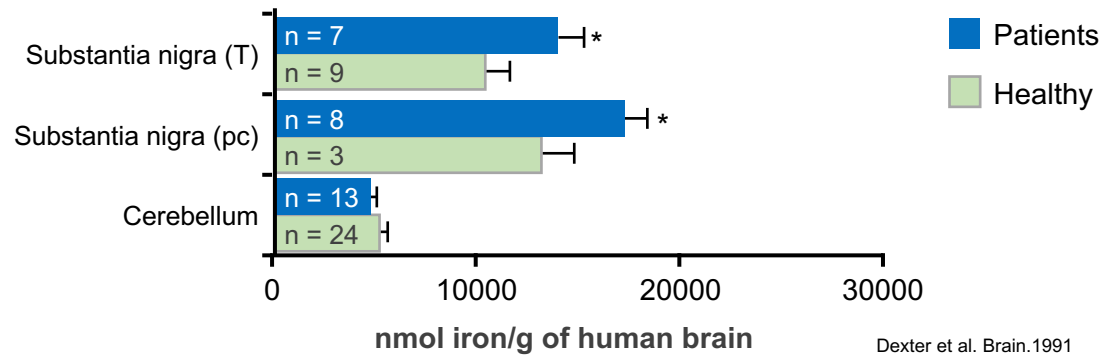
## ◆ Our Approach: Dual Mode of Action to Address the Underlying Pathology of Disease



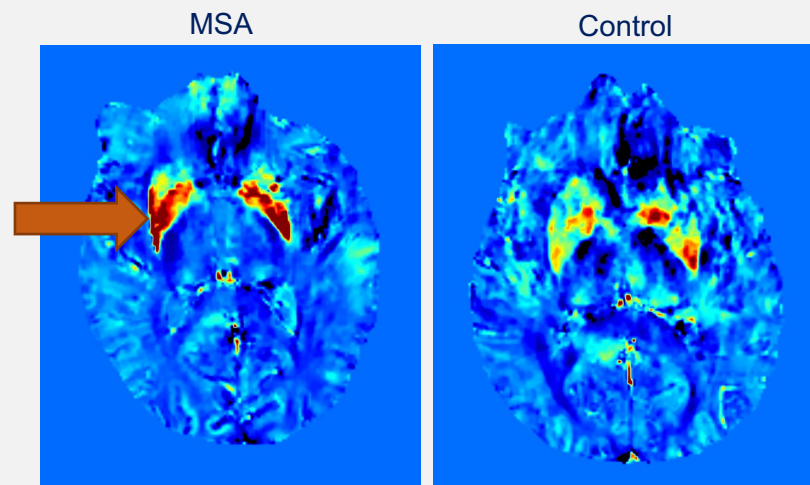
Targeting protein misfolding aggregation by binding and redistributing iron

# ◆ Increased Brain Iron in Synuclein-related Diseases

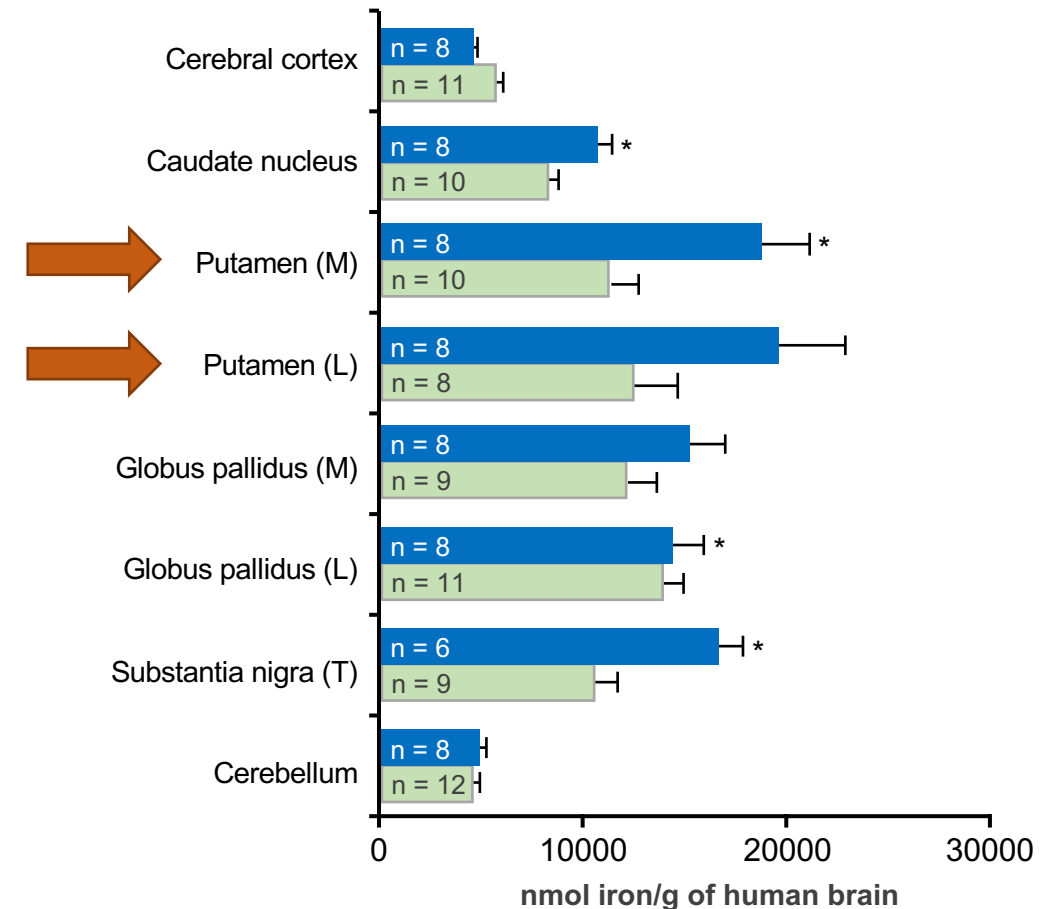
## Parkinson's disease



## Advanced Quantitative MRI to measure brain iron

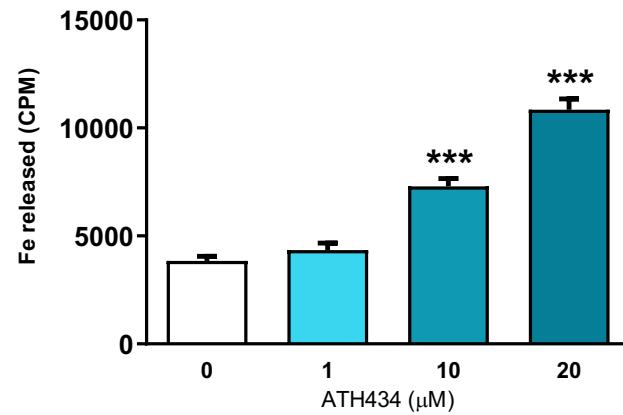


## Multiple System Atrophy



# ◆ Pharmacologic Actions of ATH434

## ATH434 redistributes excess iron



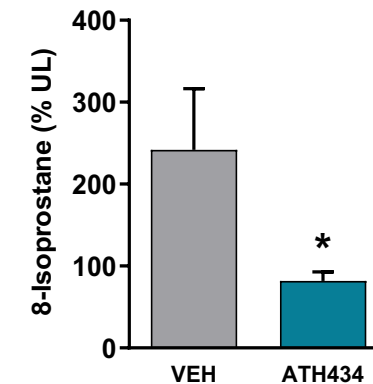
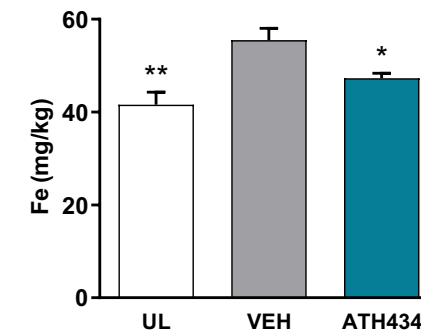
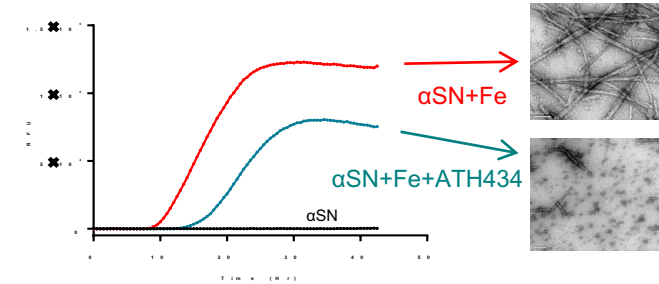
Ligand	Kd for Fe <sup>3+</sup>
α-Synuclein	10 <sup>-5</sup>
ATH434	10 <sup>-10</sup>
Ferritin	10 <sup>-22</sup>
Transferrin	10 <sup>-23</sup>
Iron trafficking proteins > <b>ATH434</b> > α-synuclein	

Stronger binding (indicated by a green arrow pointing down from α-Synuclein to Transferrin)

Reduces  
α-synuclein  
aggregation

Blocks increase  
in brain iron

Inhibits oxidative  
stress in vivo

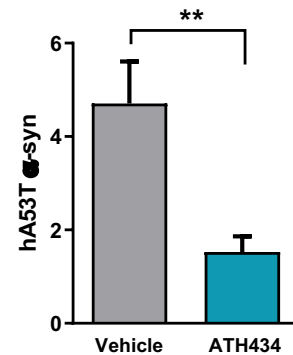




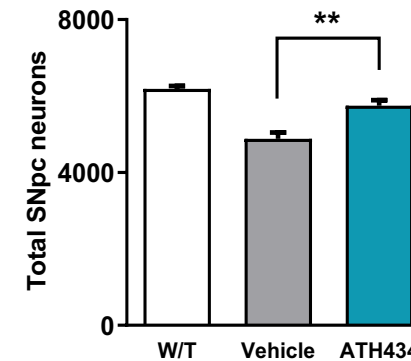
# ◆ ATH434 Reduces Alpha-Synuclein-related Neuropathology in Parkinson's Disease Animal Models

## *hA53T* Mouse

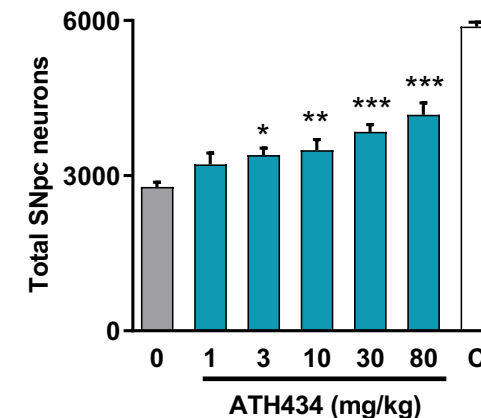
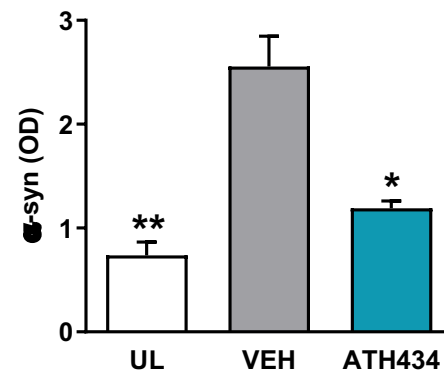
↓  $\alpha$ -Synuclein



Preserves Neurons



## MPTP Mouse

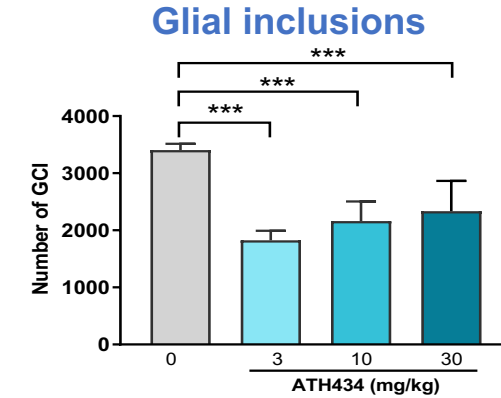
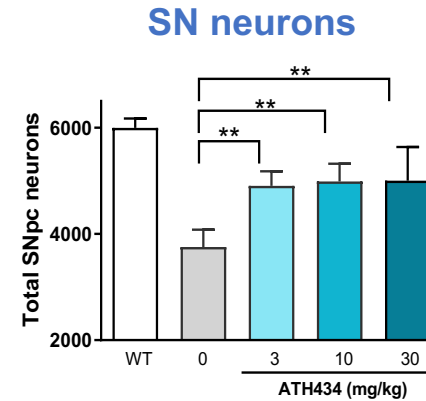
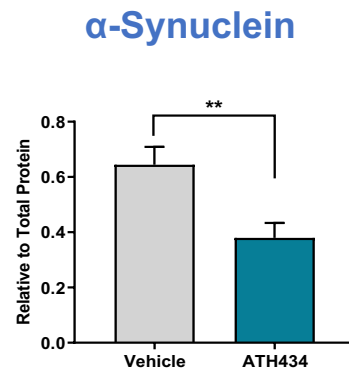


Finkelstein, et al. Acta Neuropath Comm. 2017  
 TG: transgenic, W/T: wild type, UL: unlesioned, C: control

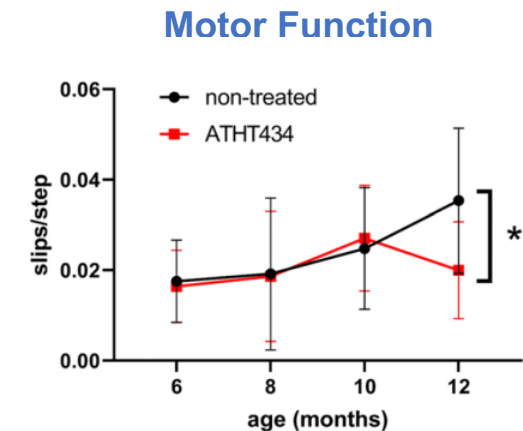
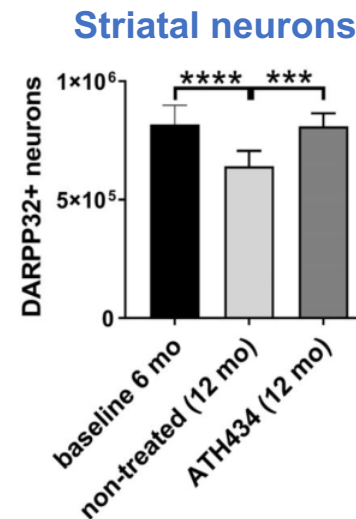
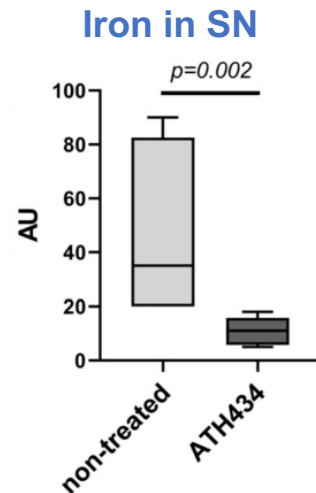
\* P < 0.05, \*\* P < 0.01, \*\*\* P < 0.001

# ◆ **ATH434 Reduces $\alpha$ -Synuclein-related Neuropathology and Improves Motor Function in Animal Model of MSA**

## **Exp. #1**



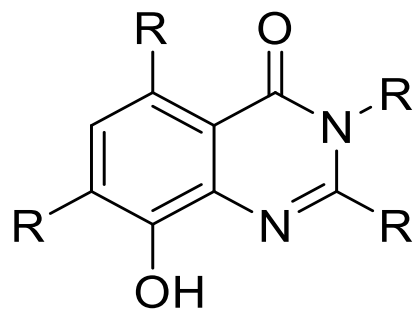
## **Exp. #2**



# ATH434: Clinical Development Program



## ◆ ATH434: Potential Use Across Multiple Indications



**ATH434**

- **Small molecule** designed to cross the blood brain barrier and inhibit  $\alpha$ -synuclein aggregation
- Potential to treat various Parkinsonian disorders
- **Orphan Drug Designation granted** by FDA and EU for the treatment of Multiple System Atrophy
  - First indication: Treatment of MSA
- Development pathway endorsed by FDA and EMA
- **Oral agent for ease of use**

# ◆ Multiple System Atrophy (MSA) is a Rare, Neurodegenerative Disorder

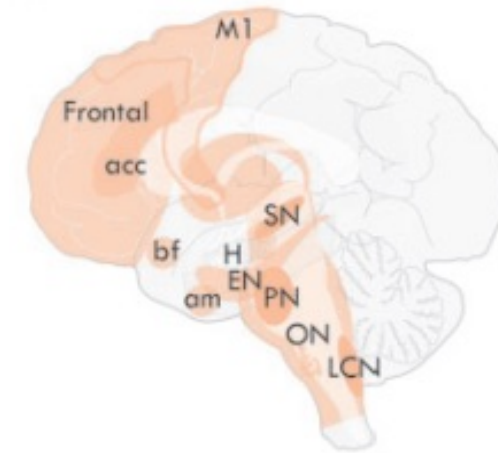
Characterized by Parkinsonism, autonomic instability and/or cerebellar impairments

Affects the body's involuntary (autonomic) functions, including blood pressure, bladder control and bowel function

Current treatments only address symptoms of MSA

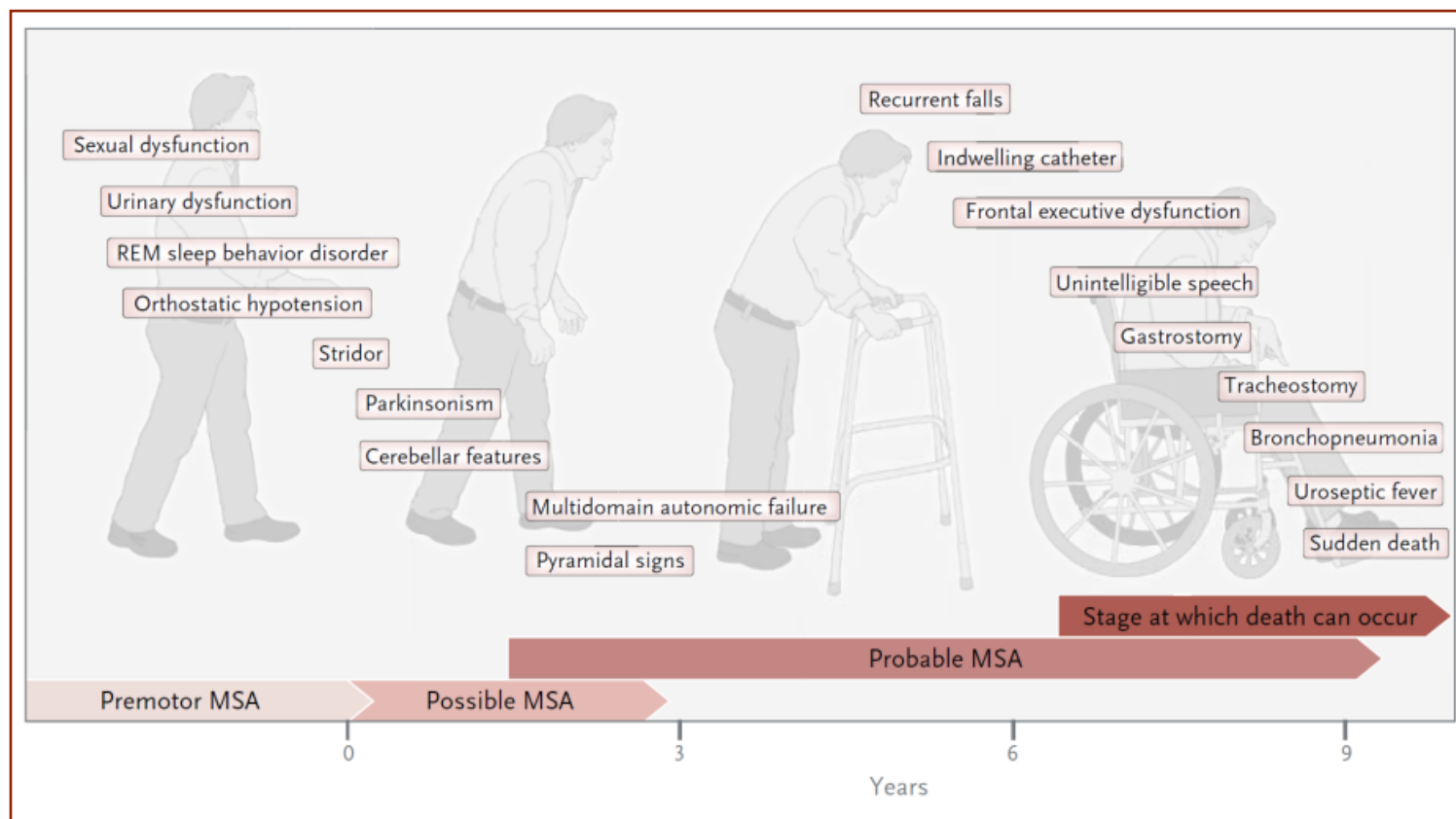
Development strategy

- Target early stage MSA patients
- Explore the effect of ATH434 treatment on biomarkers and preliminary effects on clinical measures



Halliday *Brain* 2015, based on Cykowski, *Brain* 2015

# ◆ MSA is Highly Debilitating and Rapidly Progressive



**60% require wheelchair confinement within 5 years**



# ◆ Excellent Progress with Lead Drug Candidate ATH434

## Robust efficacy in animal models of disease

Evidence of neuroprotection in PD and MSA animal models

Findings corroborated in multiple labs



## Completed Phase 1

Orally bioavailable, brain penetrant

Well tolerated

Achieved brain levels comparable to efficacious levels in animal models of MSA



## Phase 2 Execution

bioMUSE Natural history study ongoing

Long term toxicology completed

Drug product (tablet) manufactured and packaged

FDA and European regulatory advice

# ◆ Phase 1 Clinical Trial Design

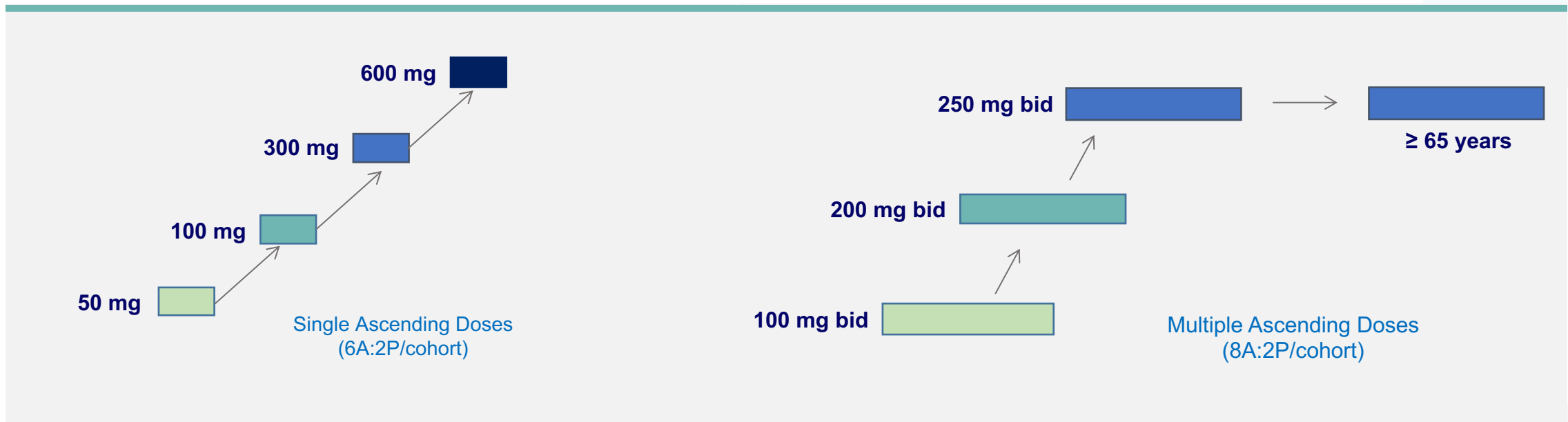
Design: Randomized, double blind, placebo-controlled, healthy adult and older adults (≥65 yo)

Objectives: Assess safety and pharmacokinetics of ATH434 after single and multiple oral doses

Plasma PK in each cohort, CSF sampled in two top multiple dose levels

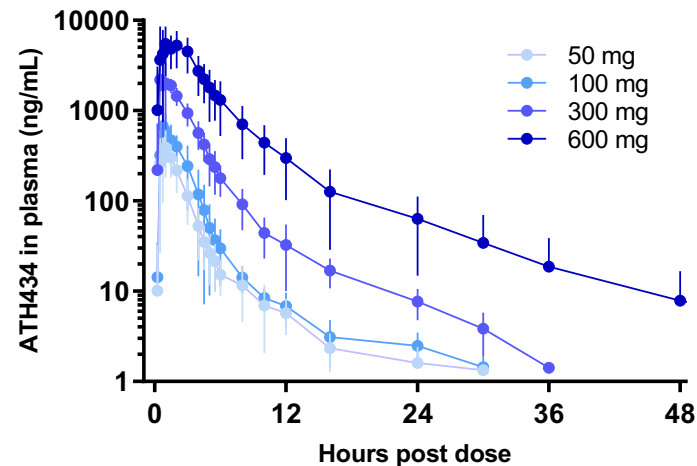
Safety: Adverse events, clinical labs, vital signs including orthostatics

Continuous 12-lead digital ECGs for QT assessment



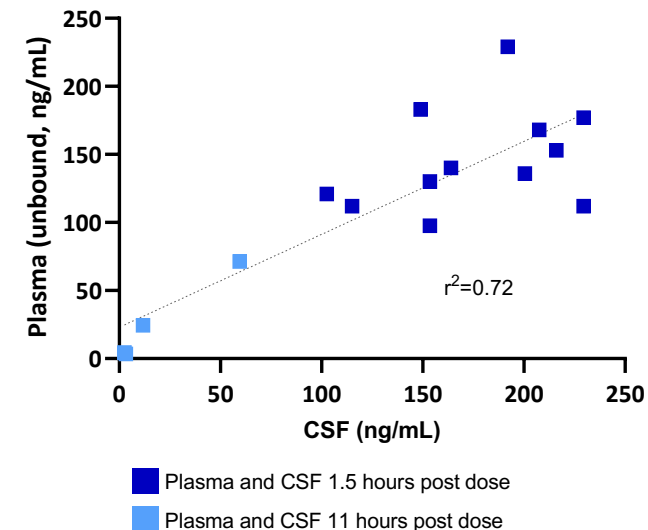
# ◆ Phase 1 Achieved Target Drug Concentrations Associated with Efficacy in Animal Models

## 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

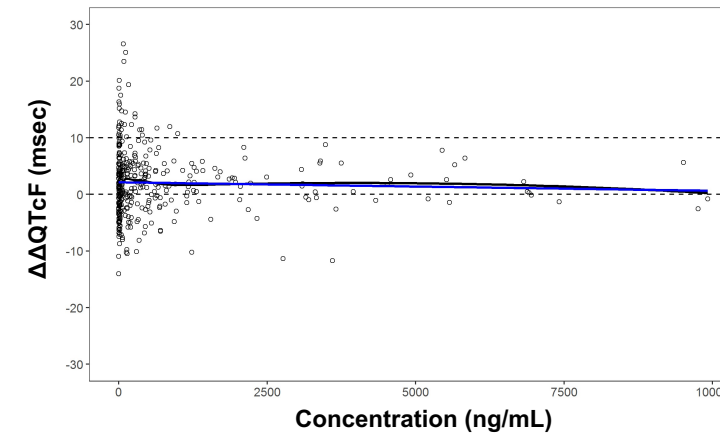


- CSF and free plasma levels strongly correlated and within 2-fold of each other
- CSF concentrations at steady state exceed those associated with efficacy in animal models of PD and MSA

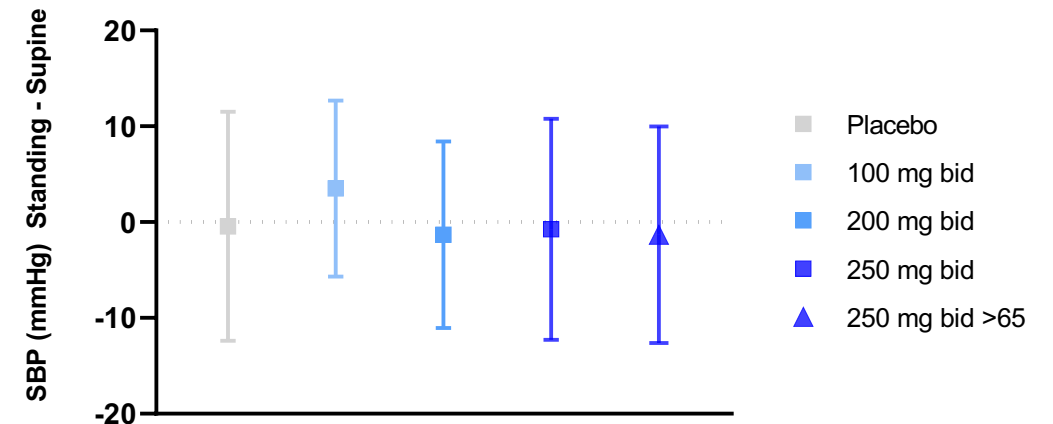
## ◆ Favorable Safety Profile

- No clinically significant AEs
- All AEs were mild to moderate in severity
- Most common AE reported in ATH434 subjects was headache
- Similar AE profile for adults and older adults ( $\geq 65$  years)
- 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



## ◆ ATH434 Well-Tolerated with No Serious Adverse Events

Single Doses	Placebo (N=8)	50 mg (N=6)	100 mg (N=6)	300 mg (N=6)	600 mg (N=6)
Patients with $\geq 1$ AE	3 (38%)	0	0	1 (17%)	1 (17%)
Patients with AEs leading to Withdrawal	0	0	0	0	0
Patients with Serious AEs	0	0	0	0	0

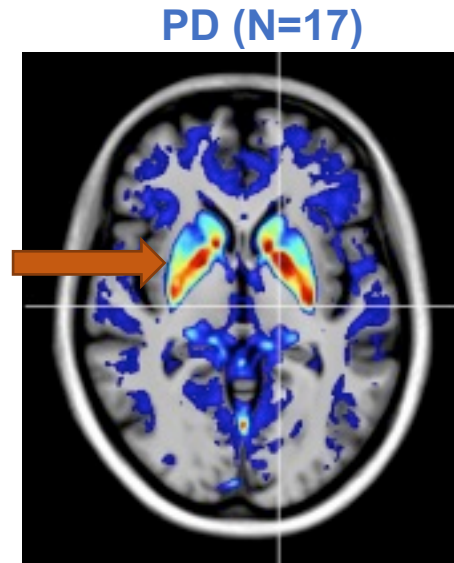
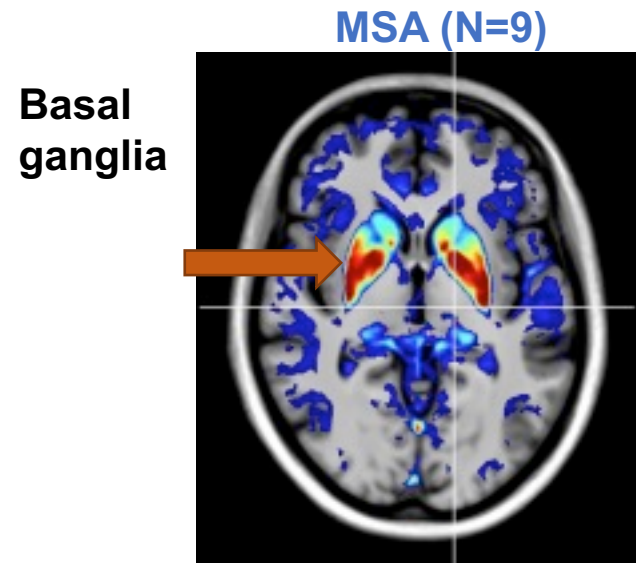
Multiple Doses	Placebo (N=8)	100 mg BID (N=8)	200 mg BID (N=8)	250 mg BID (N=8)	250 mg BID $\geq 65$ (N=8)
Patients with $\geq 1$ AE	5 (63%)	3 (38%)	6 (75%)	4 (50%)	5 (63%)
Patients with AEs leading to Withdrawal	0	0	0	0	0
Patients with Serious AEs	0	0	0	0	0



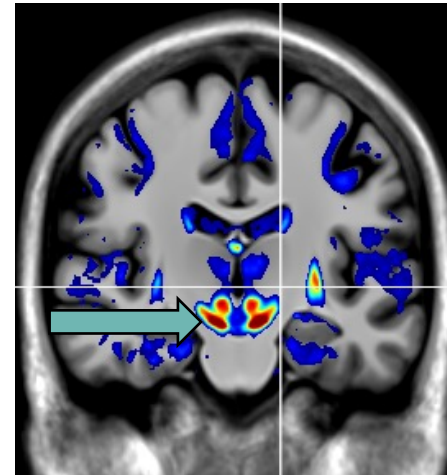
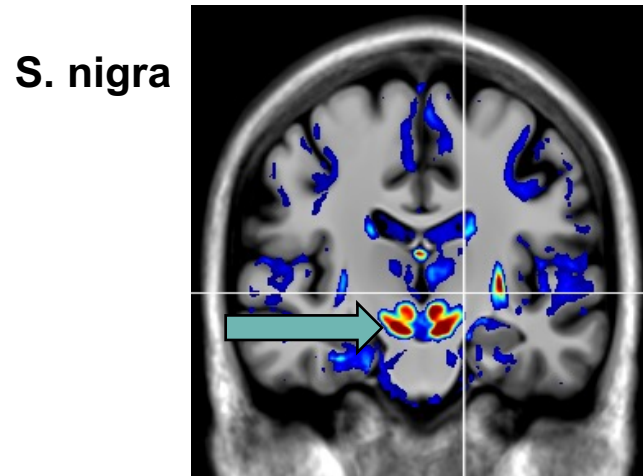
# ◆ Biomarkers of Progression in Multiple System Atrophy (bioMUSE) Natural History Study

Design	<ul style="list-style-type: none"><li>• Observational</li></ul>
Objectives	<ul style="list-style-type: none"><li>• Inform and de-risk Phase 2</li><li>• Identify biomarker endpoint(s) for treatment study</li><li>• Evaluate the change in biomarkers and clinical manifestations in early MSA</li></ul>
Population	<ul style="list-style-type: none"><li>• Early-stage MSA patients similar to Phase 2 population</li><li>• Expanding to n=20 subjects</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*), regional blood flow (ASL), neuromelanin</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 inventory, global measures of severity and change (clinician, patient)</li><li>• Functional: Timed Up and Go, 2 min Walk Test</li></ul>

# ◆ bioMUSE Interim Results: Increased Brain Iron in MSA and PD



*MSA patients have higher iron in basal ganglia*

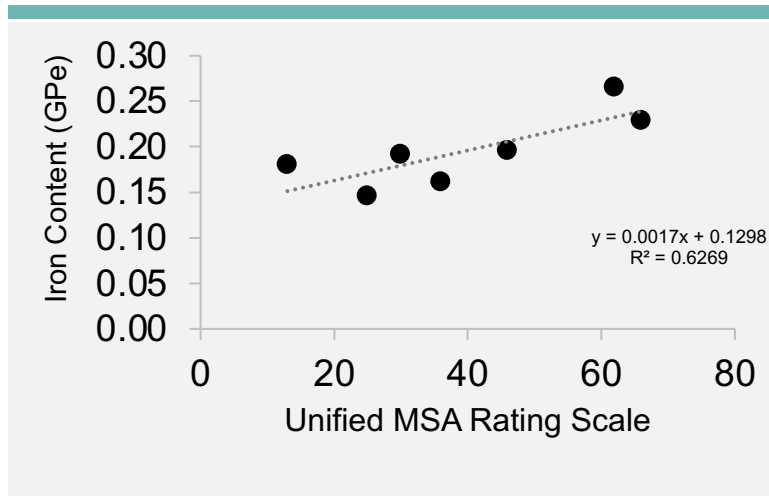


*MSA and PD patients have increased iron in s. nigra*

Iron Content by Region of Interest	
ROI	MSA vs PD <sup>†</sup>
PT	0.03*
GPe	0.04*
GPI	0.18
SN	0.94

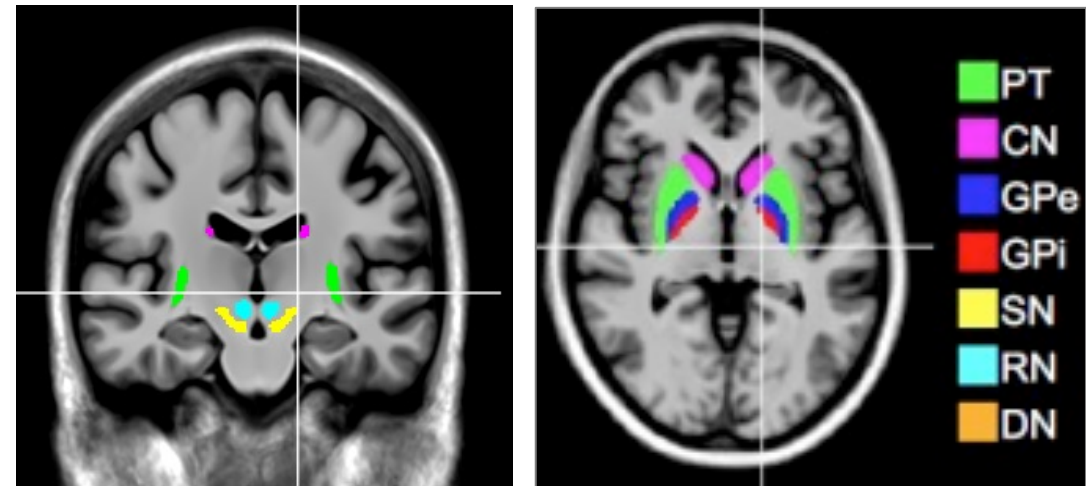
<sup>†</sup> P-value

## ◆ Phase 2 Primary Endpoint: Change in Brain Iron by MRI



**Brain iron correlates with disease severity in MSA**

BioMUSE images registered with PD25 MNI template



**Goal: Develop New MSA template from bioMUSE to improve precision of iron quantification in Phase 2**

# ◆ ATH434 Phase 2 Clinical Trial Early-Stage MSA Patients

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 subjects with MSA</li><li>• Assess target engagement based on imaging and fluid biomarkers of disease severity</li><li>• Evaluate the pharmacokinetics of ATH434 in target population</li></ul>
Population	<ul style="list-style-type: none"><li>• Early-stage patients with clinical diagnosis of MSA who are ambulatory, not severely impaired, and do not have long standing motor symptoms</li></ul>
Sample Size	<ul style="list-style-type: none"><li>• N=60 at ~30 sites in Australia, New Zealand, Europe and the U.S.</li></ul>
Treatment	<ul style="list-style-type: none"><li>• 12-months treatment</li><li>• Three groups: 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>• Additional imaging biomarkers and fluid biomarkers (aggregating <math>\alpha</math>-synuclein, NfL protein)</li><li>• Clinical measures of motor function, autonomic function, activities of daily living</li></ul>

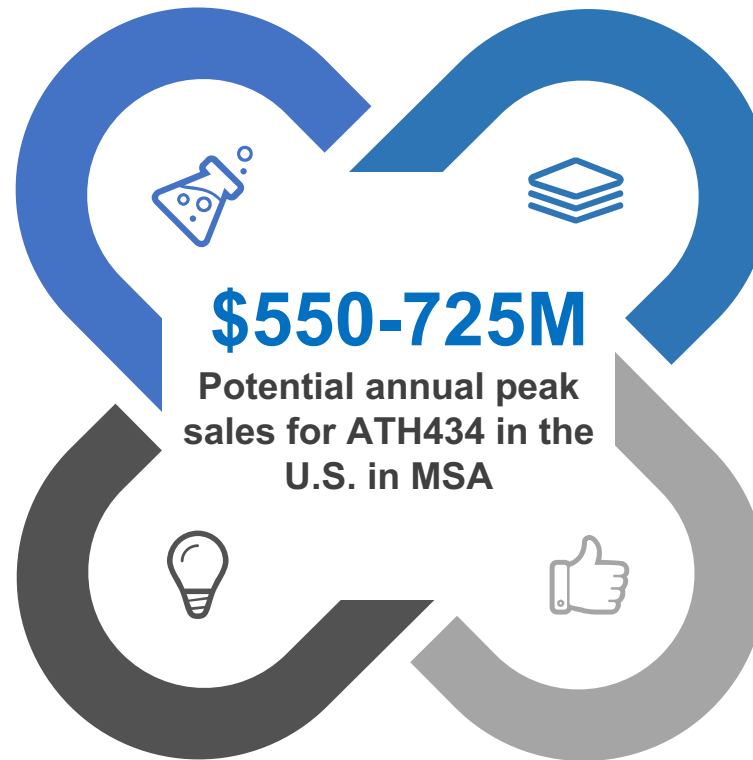
# ◆ Significant Commercial Opportunity in Treating Multiple System Atrophy

## Substantial Unmet Need

Severely debilitating illnesses with no current treatments are ripe for new entrants targeting what may be the actual cause 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
- ✓ Development team with proven track record and multiple FDA approvals
- ✓ Lead drug candidate ATH434 Progressing to Phase 2
  - Completed Phase 1 demonstrating well-tolerated safety profile and delivery of drug to site of action
  - Recent publications validating mechanism of action targeting  $\alpha$ -synuclein
- ✓ Drug discovery team generating patentable compounds as next generation therapies
- ✓ Strong balance sheet with 37M AUD as of 31 Dec '21

### Milestones

- Q1 2022: Submit ATH434 European Clinical Trial Application (CTA)
- Q2 2022: Launch ATH434 Phase 2 Clinical Trial in New Zealand
- 2H 2022: Launch ATH434 Phase 2 in Europe
- 2H 2022: Submit ATH434 U.S. IND
- 2H 2022: Launch ATH434 Phase 2 in U.S.
- Q3 2022: Present bioMUSE Natural History biomarker data



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