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CEO

Webinar – bioMUSE Data Release

May 29/30, 2024

Alterity THERAPEUTICS

Forward Looking Statements

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Objectives of Today's Webinar

- Review new data from bioMUSE natural history study
- Discuss relevance of bioMUSE for ATH434-202 study
- Expert perspective on Multiple System Atrophy (MSA)
- Review timing of Phase 2 data

Promising Portfolio in Neurodegenerative Diseases

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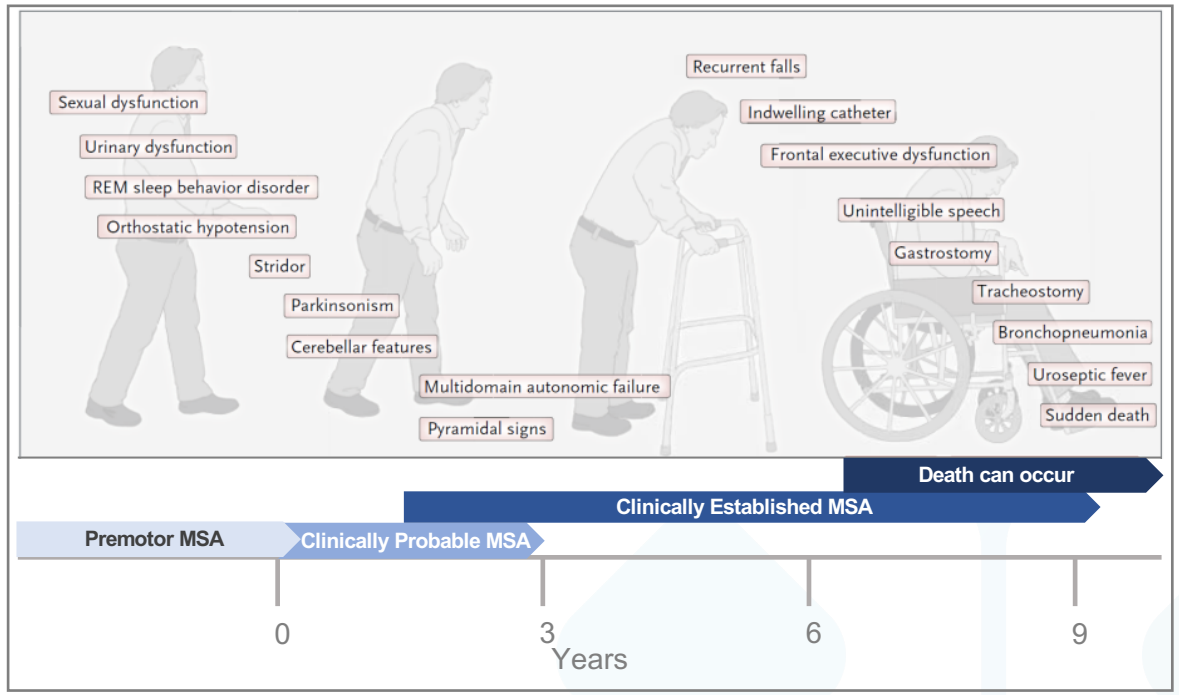
ASSET		PHASE					PARTNER
PROGRAM	**INDICATION**	**DISCOVERY**	**PRE-CLINICAL**	**NATURAL HISTORY**	**PHASE 1**	**PHASE 2**	**PARTNER / COLLABORATOR**
ATH434-201	Multiple System Atrophy *Early Stage*				*Enrollment Complete*		
ATH434-202	Multiple System Atrophy *Advanced*				*Enrollment Complete*		
ATH434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

Multiple System Atrophy (MSA): Rare, Highly Debilitating and Rapidly Progressive Neurodegenerative Disease

- Parkinsonian disorder with no approved treatment
- Orphan disease
- Disease characteristics
  - Motor: Parkinsonism, uncoordinated movements, balance problems/falls
  - Autonomic dysfunction: blood pressure maintenance, bladder control, bowel function
  - Brain atrophy in multiple regions
- Median survival 7.5 years after symptom onset

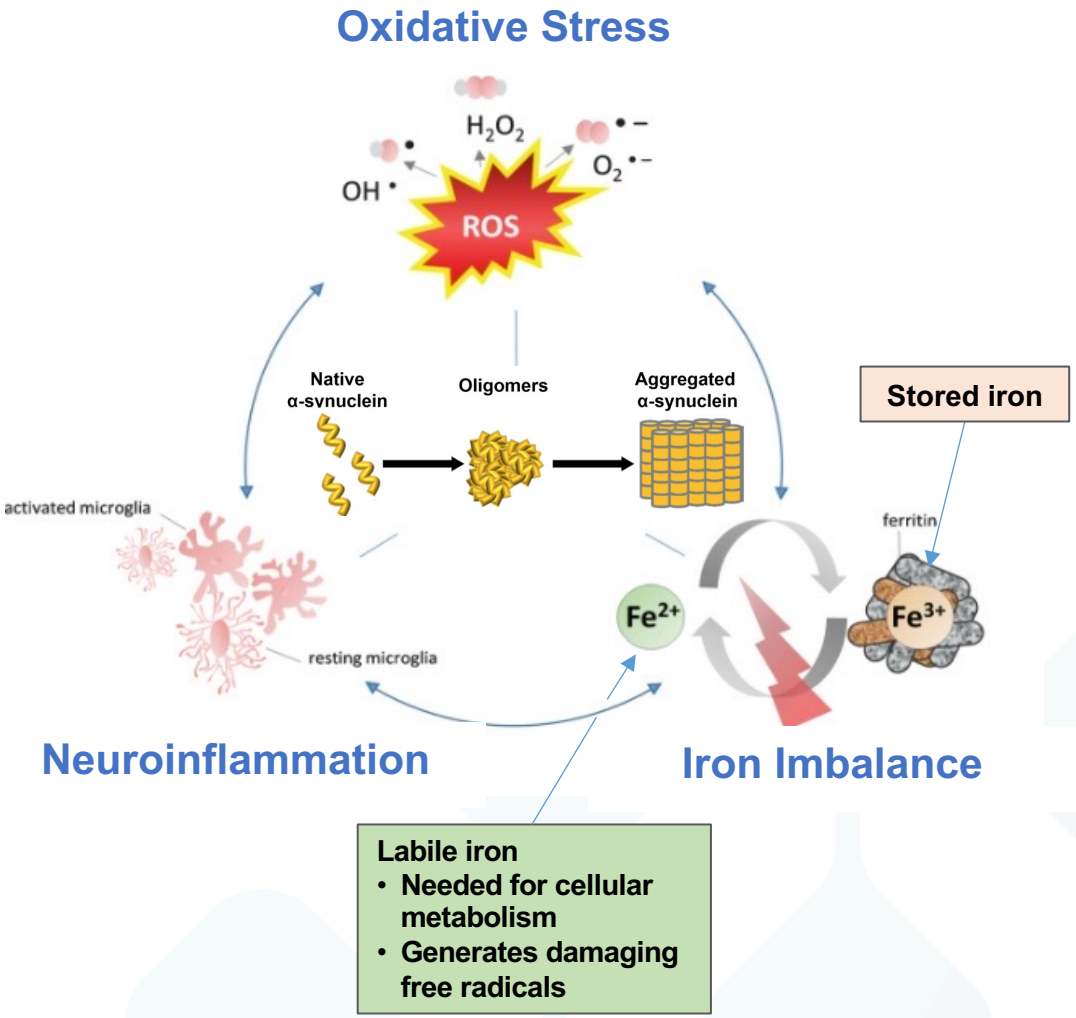


Sources: Fanciulli, Wenning. NEJM 2015 | Wenning, et al. Mov Disorders 2022 | Coon, et al. Brain 2015 | Claassen,et al. Mov Disorders 2021

Iron is Critical in Disease Pathogenesis

Iron and α-Synuclein are important contributors to MSA pathology

- Adverse impact of excess labile iron
  - Leads to *α-synuclein aggregation* → neuronal dysfunction
  - Oxidative stress with intracellular damage
  - Cell death
- Hallmark of MSA pathology
  - α-synuclein aggregates in neurons and glial (support) cells
  - Neuron and glial cells loss
  - Atrophy in multiple brain regions



Sources: Kaindlstorfer, J. Alzheimers Dis. 2018; Bengoa-Vergniory N, Acta Neuropathol. 2017

Accumulated Evidence of ATH434 Efficacy

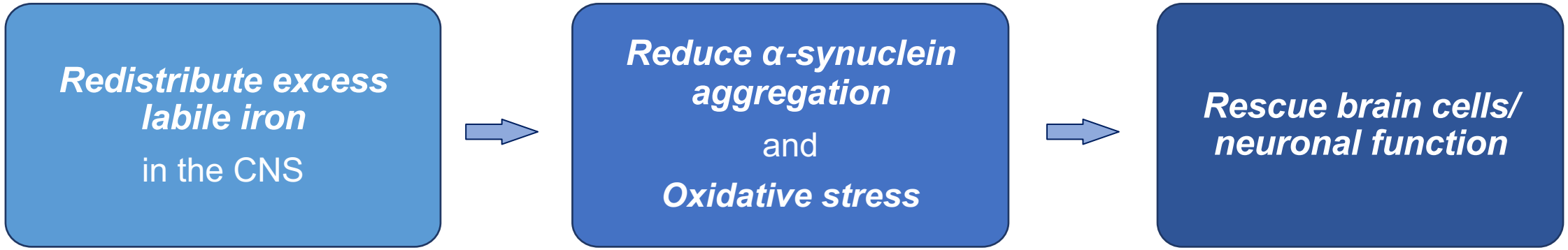
Target Disease	Model	Midbrain* Iron	α-Synuclein	Preserve Neurons/ Function	Clinical Observations
Parkinson's disease	Mouse MPTP	↓	↓	↑	Improved motor performance
Parkinson's disease	Mouse A53T	↓	↓	↑	Improved motor performance
Parkinson's disease	Mouse tau knockout	↓	↓	↑	Improved motor performance
MSA	PLP-α-syn	↓	↓	↑	Improved motor performance
MSA	PLP-α-syn	↓	↓	↑	Improved motor performance
Parkinson's disease	Monkey MPTP	↓	n/a	↑	Improved motor performance

* includes s. nigra

ATH434 consistently improved motor performance across diverse animal models of disease by redistributing iron and preserving neurons

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, Am Acad. Neurol 2024

Approach: Address Underlying Pathology of Disease



Potential Disease Modifying Therapy for MSA

Multiple System Atrophy Clinical Development Program

Clinical Studies in MSA

Study	bioMUSE – Natural History	ATH434-201 – Phase 2	ATH434-202 – Phase 2
Design	Observational	Randomized, double-blind	Single arm, open-label
Objectives	Characterize early-stage MSA	Efficacy and safety of ATH434	Efficacy and safety of ATH434
Population	Early-stage MSA	Early-stage MSA	Advanced MSA
Sample Size	N = 21	N = 77	N = 10
Observation/Treatment	12 months	12 months treatment	12 months treatment
Brain MRI Biomarkers	Iron, volume, glial pathology	Same as bioMUSE	Same as bioMUSE
Fluid Biomarkers	NFL, Aggregated α-synuclein	Same as bioMUSE	Same as bioMUSE
Other Biomarkers	Wearable movement sensors	Same as bioMUSE	–
Clinical Measures	Motor exam, autonomic function, activities of daily living, global measures	Same as bioMUSE	Same as bioMUSE

BioMUSE Natural History Study
Learnings to Date

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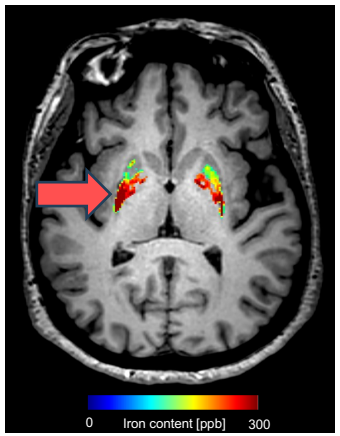
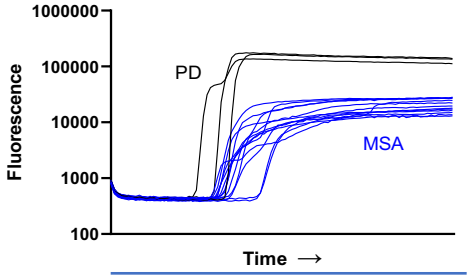
Optimize Patient Selection

Advanced MRI methods



Identify "iron signature" of early MSA

α-synuclein in CSF

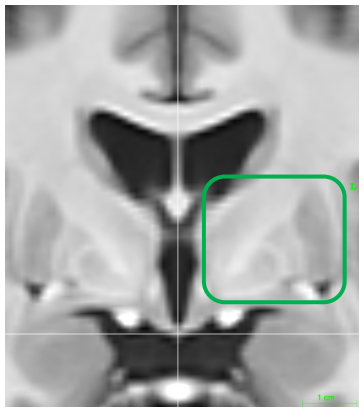


Differentiate MSA from PD

Revised selection criteria in ATH434-201 and ATH434-202 protocols to exclude PD patients

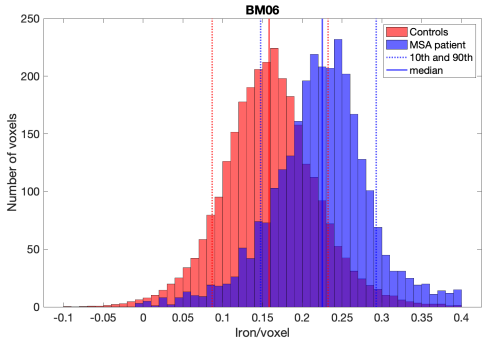
Precision Endpoint Assessment

New MRI Template



Improve precision of structural MRI

Iron distribution in MSA

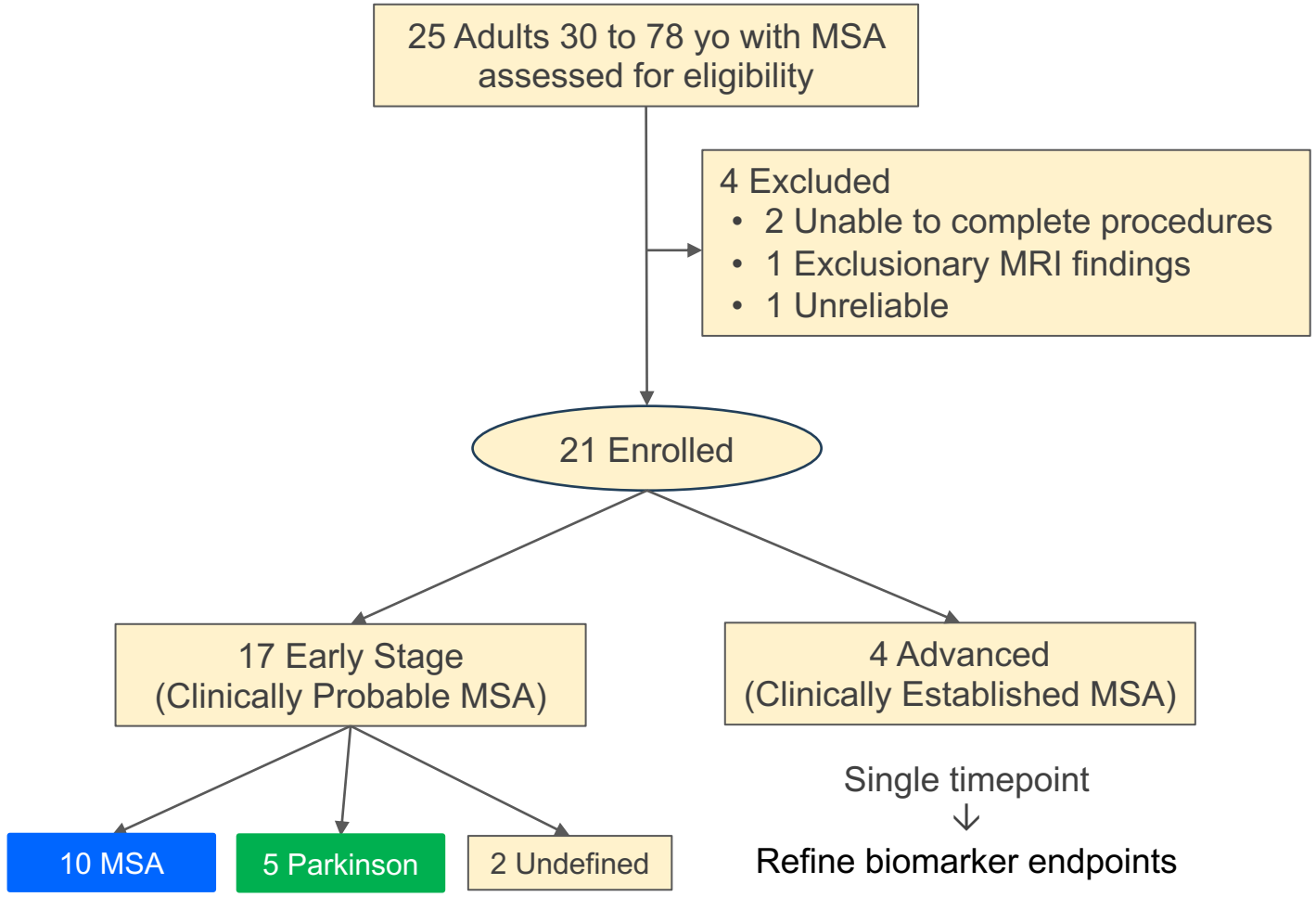


Novel strategies for measuring brain iron in individual regions

State of the art methods enabled precise measurements of iron and brain volume with MRI

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

Participant Flow in bioMUSE



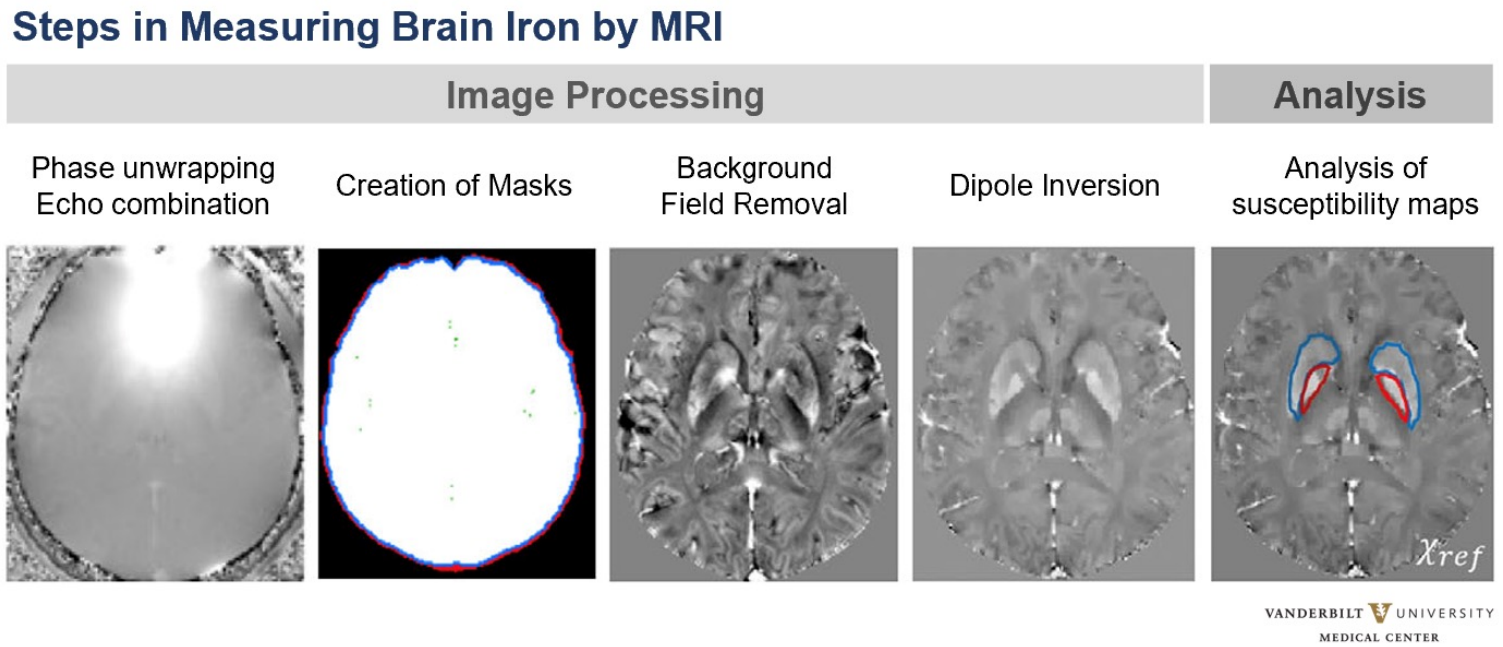
Source

BioMUSE Brain Imaging Biomarkers
Assessed in MSA Regions

Biomarker	How Assessed	Status
Iron content	MRI/QSM	12 mo data reported today
Volumes	MRI/T1w	12 mo data reported today
N-acetylaspartate/ myoinositol	MR spectroscopy	Preliminary data reported in 2023
Neuromelanin	MRI	In process

MRI Methods to Measure Brain Iron

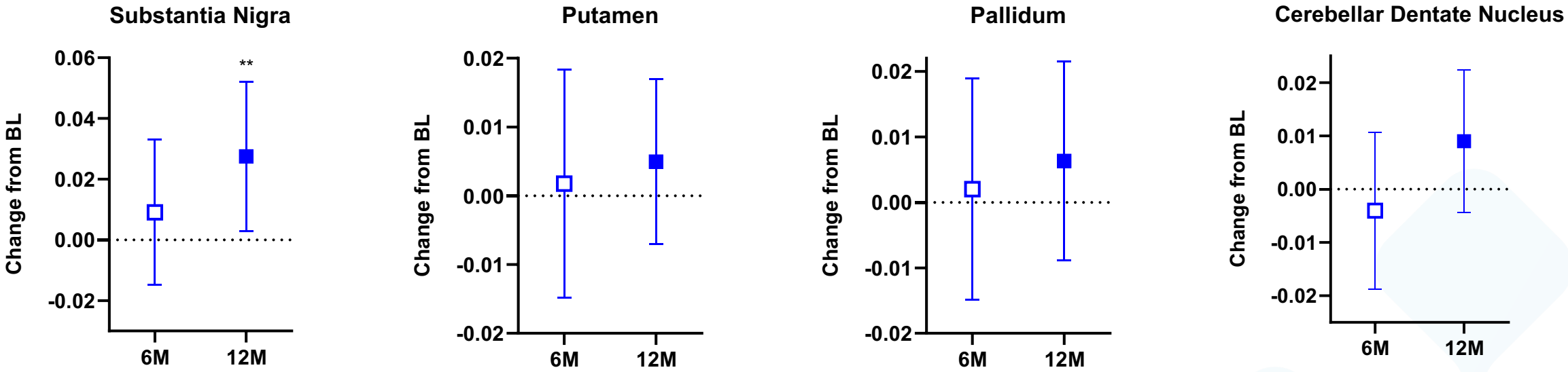
- Based on routine (e.g., structure/volume) and specialized MRI techniques
- Bioengineer evaluated MRI processing algorithms to optimize measurement[1,2]
- Method selected which is reproducible and minimizes artifacts between MRIs



We have established standardized methods to analyze brain iron in bioMUSE and will apply same methods in the Phase 2 studies

[1] Marques. QSM reconstruction challenge 2.0. *Magn Reson Med*. 2021
[2] QSM consensus Committee. Recommended implementation of QSM. *Magn Reson Med*. 2024

BioMUSE: Change in Iron Content by MRI
Brain Regions affected in MSA



Statistically significant increase in iron over 12 months in the substantia nigra

** $p < 0.01$

Optimizing MRI Methods to Measure Brain Volumes

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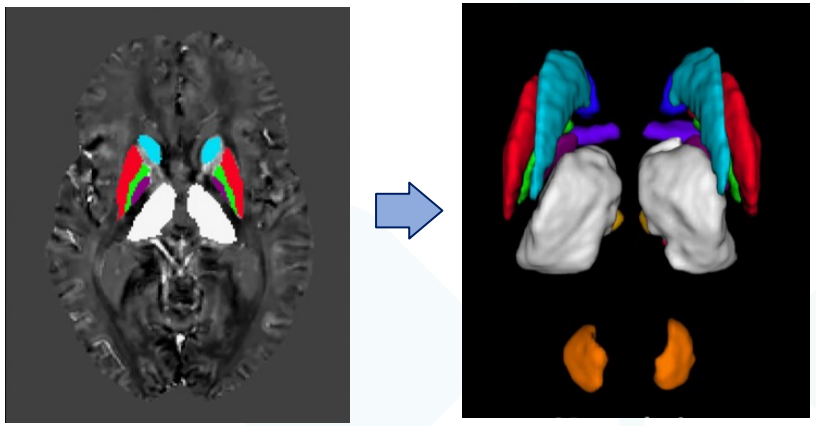
- Multiple System Atrophy = atrophy (shrinking) of brain structures
- Routine MRI are analyzed in 2 dimensions (2D)
- We are interested in measuring brain volume (in 3D)
- Needed a new method to measure volumes in MSA affected areas

Method Development

- Neuroradiologist manually traced 2D images for each bioMUSE subject
  - 2D MRI → 3D rendering → measure volume
  - Human time: 10 hours per MRI
- Bioengineer employed Machine Learning/AI to teach computer to do the same
  - Computer time: 5 minutes per MRI



2D image | 3D rendering

Allows measurement of brain volumes with precision in all Phase 2 participants

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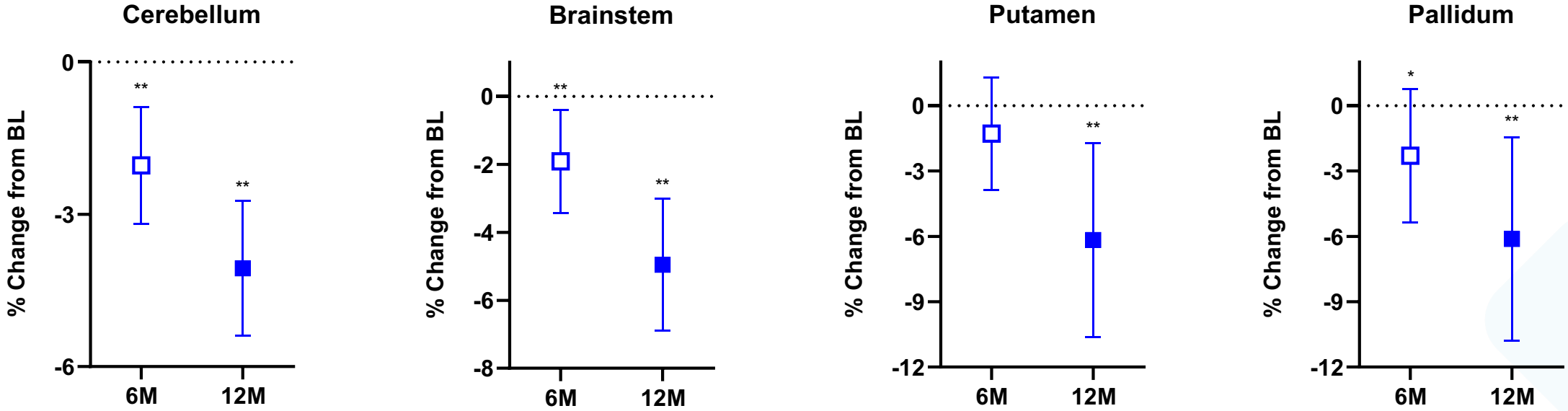
BioMUSE: Change in Brain Volume by MRI
Brain Regions affected in MSA

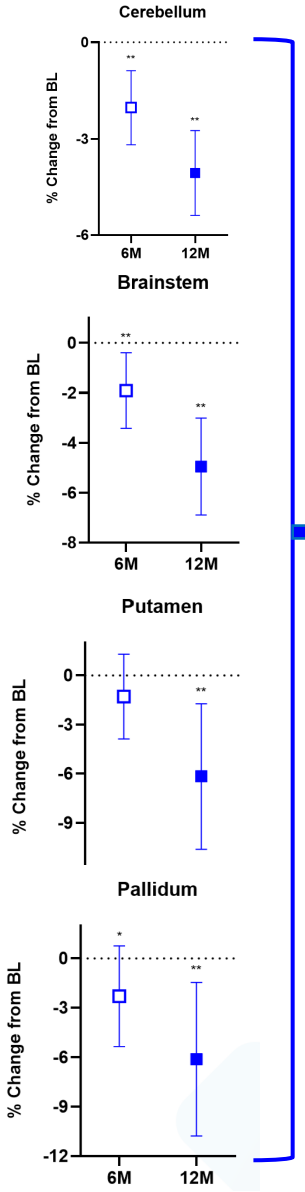


Statistically significant decreases in brain volume observed in all regions at 12 months and in 3 of 4 regions at 6 months

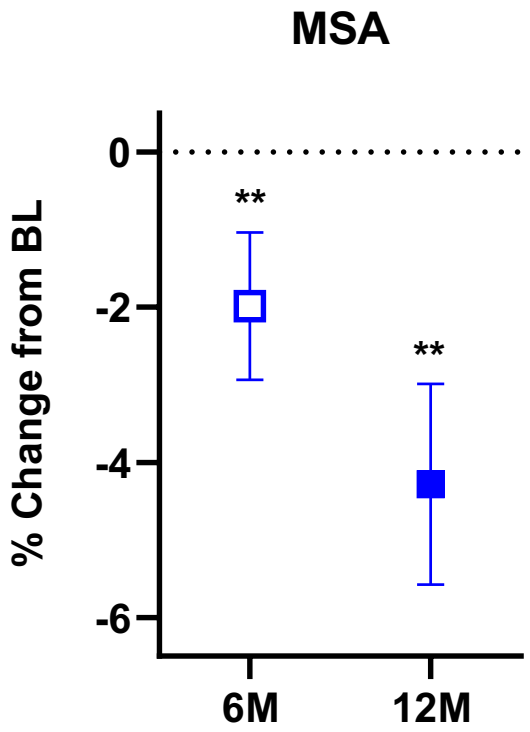
* $p < 0.05$
** $p < 0.01$

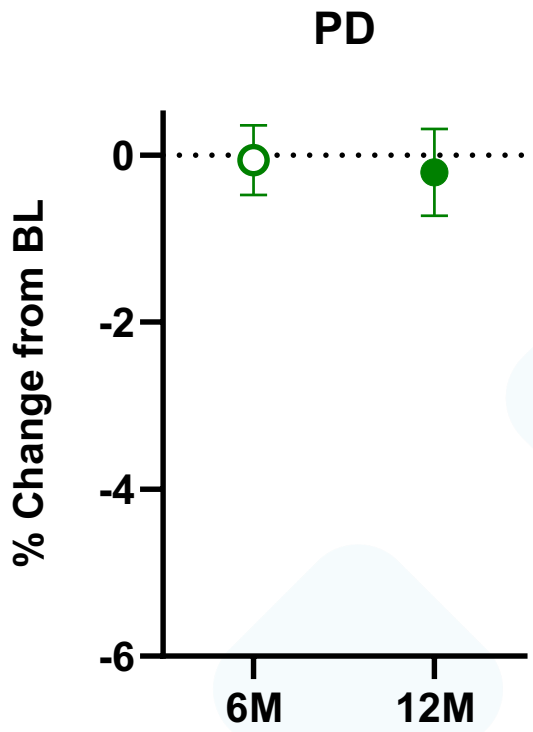
BioMUSE: Change in Brain Volume by MRI

Brain Atrophy in MSA



Combine volume of these 4 regions affected in MSA





New Imaging Biomarker
MSA Volume Index

BioMUSE Summary

- Observational Study in MSA
- Goals: improve patient selection and choose endpoints for Phase 2
- Iron content: **Significant increase in iron** observed at 12 months in one brain region (s. nigra)
- Brain volume: **Significant decrease in volume** observed over 12 months in all four MSA regions
  - ❖ Novel Imaging Biomarker: **MSA Volume Index**

Implications of bioMUSE Data on ATH434-202 Study

Endpoint Selection in Treatment Trials

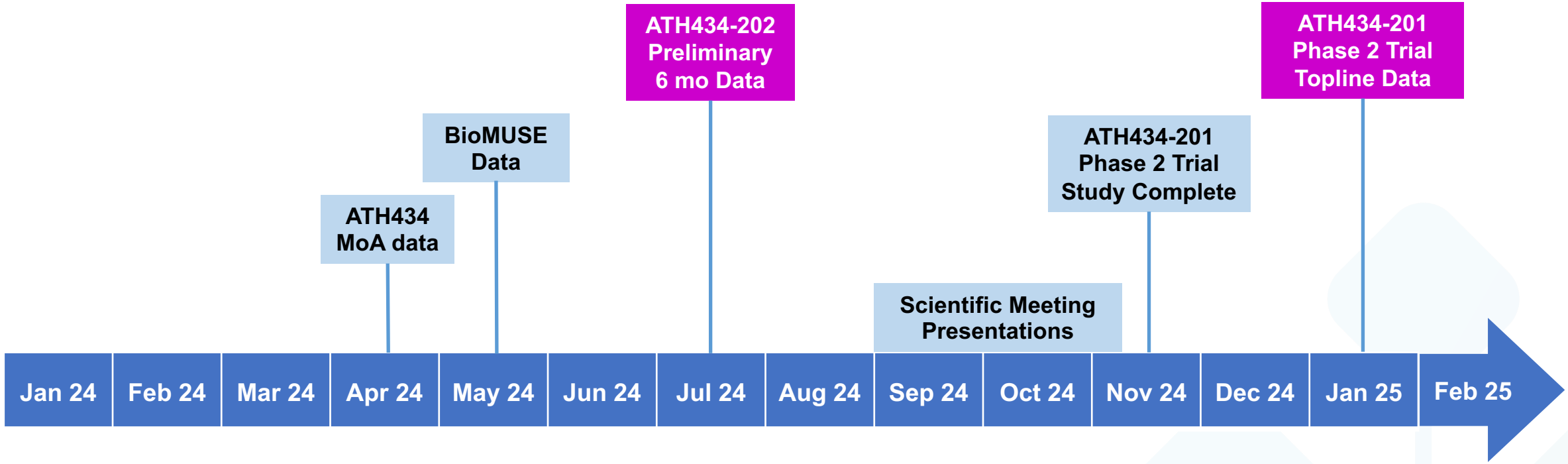
Biomarker Endpoint Selection		
Relevant to underlying disease	Tracks with disease progression	Preclinical indication of drug effect

We target endpoints with the largest change over the planned study period to more readily demonstrate a drug effect

ATH434-202 Key Study Endpoints

Primary Endpoint	**Change in *MSA Volume Index* by MRI at 12 months** • Based on the significant decrease in volume in relevant brain regions in MSA
Secondary Endpoint	**Change in *Iron content* in the substantia nigra by MRI at 12 months** • Based on the significant increase in iron in relevant brain region in MSA

Key Milestones



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Principal Investigator of bioMUSE

Coordinating Investigator of the ATH434-201 Clinical Trial

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