Corporate Presentation

Alterity THERAPEUTICS

July 2025

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 2024 Form 20-F, filed with US Securities and Exchange Commission, in particular Item 3, Section D, titled “Risk Factors.”

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Alterity is a late clinical stage biopharmaceutical company dedicated to developing treatments for individuals living with neurodegenerative diseases

- Alterity means the state of being different
- Our goal is to slow the course of disease
- We strive to create an alternate future and improve patient quality of life

Investment highlights

Positive Phase 2 data in multiple system atrophy (MSA), a Parkinsonian disorder

Demonstrated robust efficacy on functional endpoint endorsed by FDA/EMA

Large market potential in neurodegenerative diseases

Fast Track & Orphan Drug Designations for ATH434 in MSA, which has no approved treatment

Oral administration preferred over competition

Patient friendly administration

Highly experienced leadership team in movement disorders

Three FDA approvals in neurology

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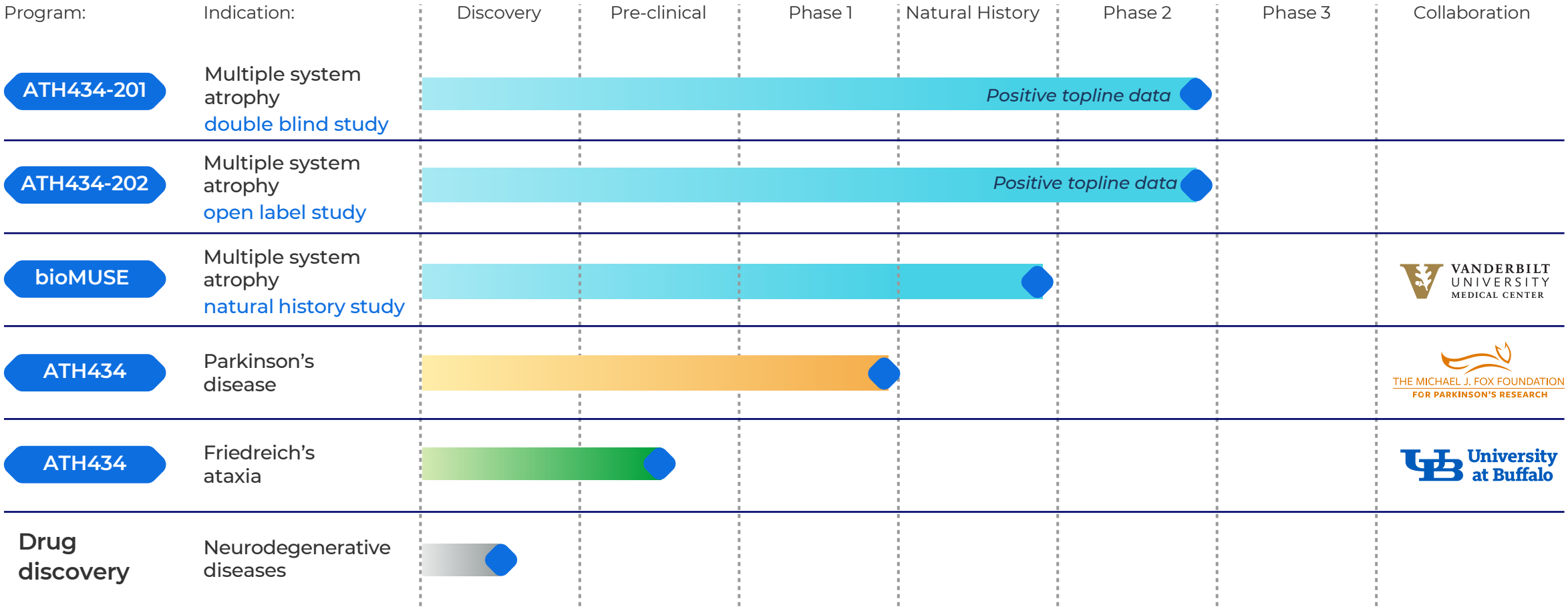
Promising portfolio in neurodegenerative diseases



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Targeting the pathology in Parkinsonian disorders

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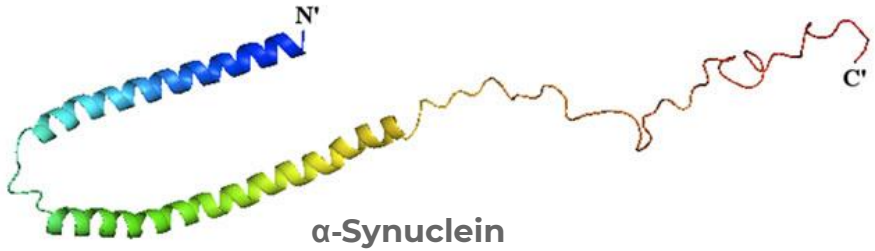
Alpha-synuclein and iron balance are important for normal CNS function

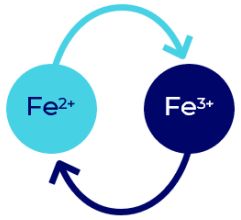
α-Synuclein protein

- Present in all neurons
- Regulates neurotransmitter release
- Facilitates neuronal communication

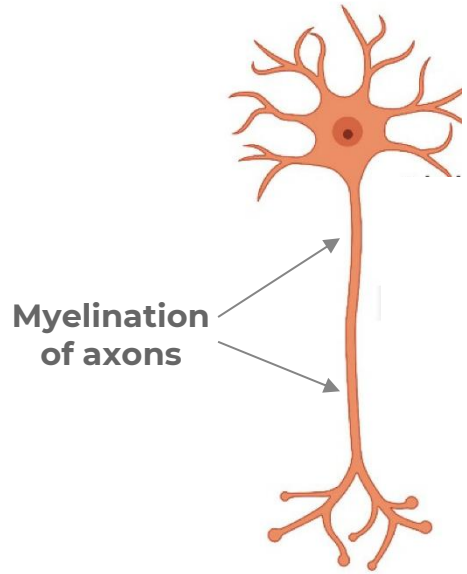


Two forms of iron required for cellular function

- Energy production and activity of many enzymes
- Neurotransmitter synthesis (e.g., dopamine)
- Myelin synthesis



Fe^{2+} Reactive
Fe^{3+} Stable



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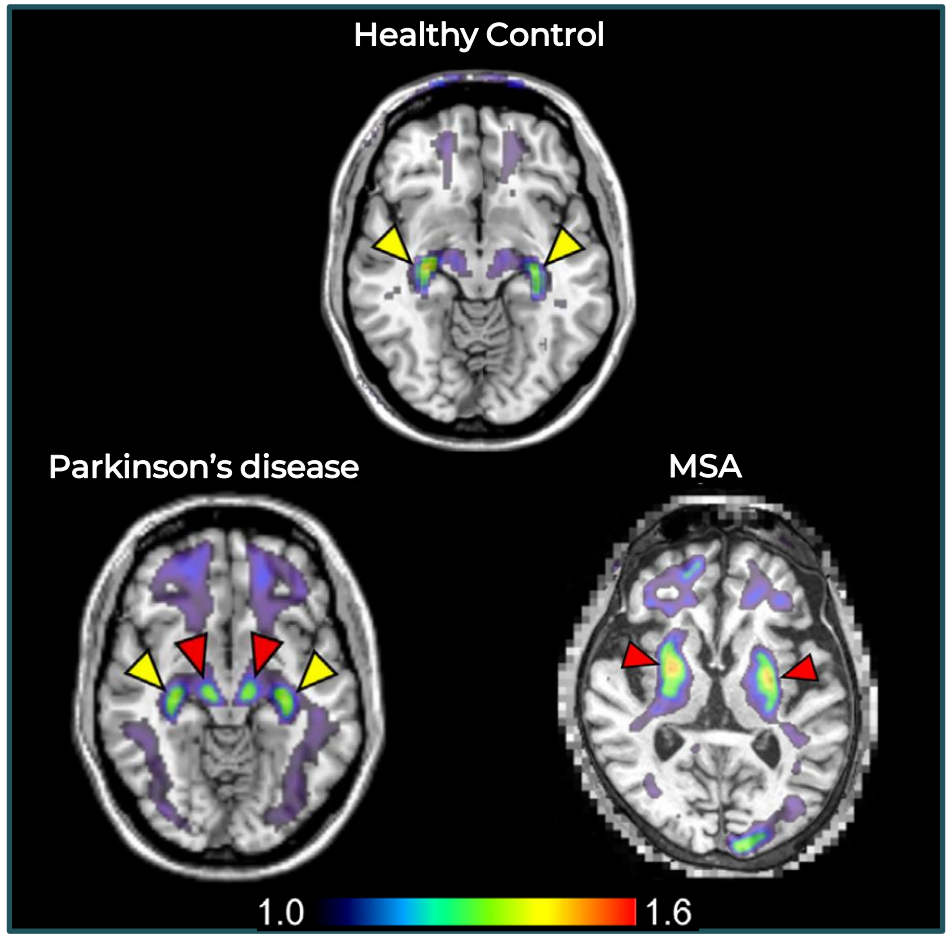
Sources: Ritchie et al, 2012; DOI:10.4236/health.2012.431175; Cronin et al, 2019, doi.org/10.3389/fmolb.2019.00116 (adapted)

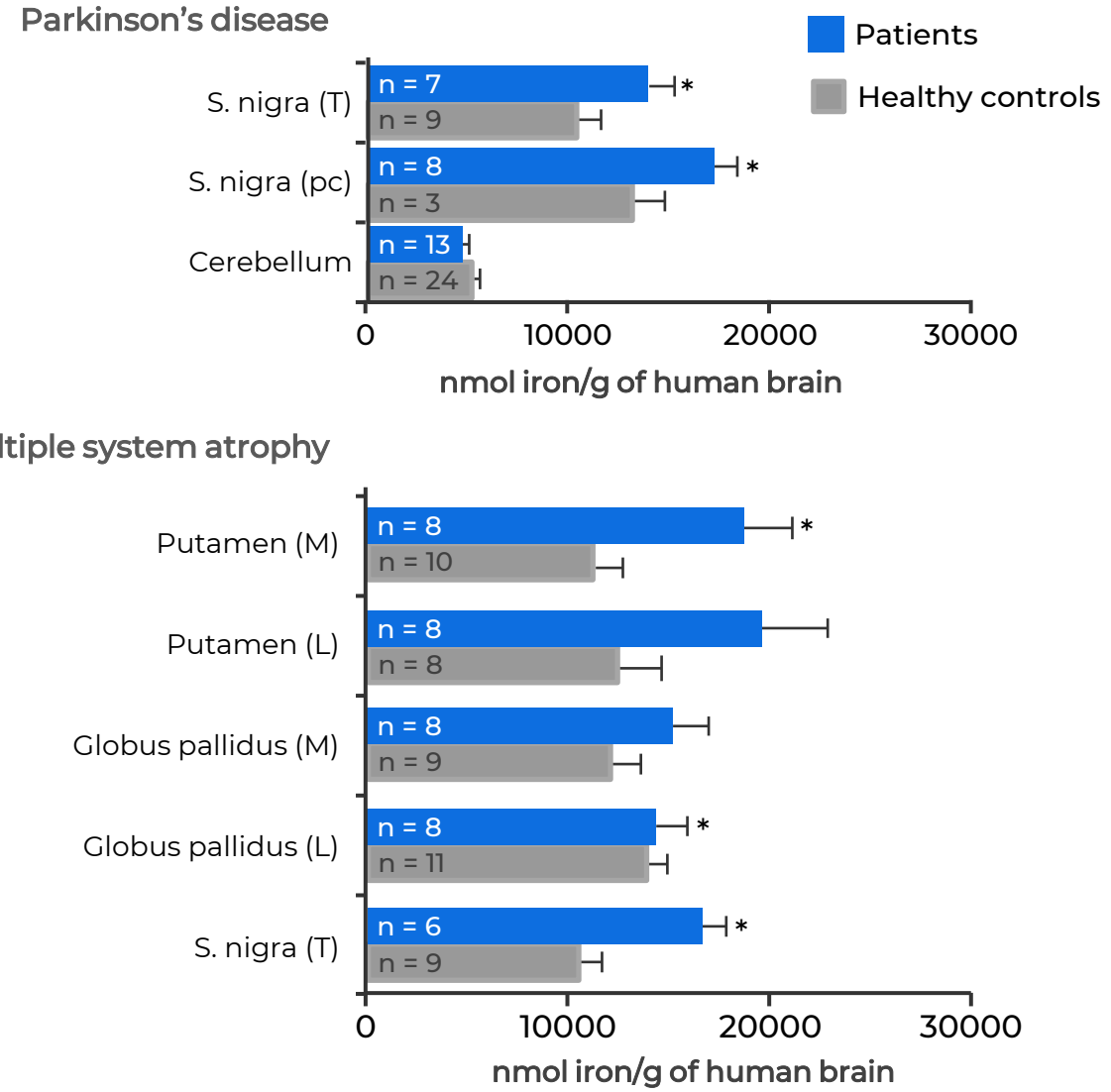
Pathology of Parkinsonian disorders

α-synuclein Aggregation



PET imaging of α-synuclein pathology (18F-C05-05)

Increased Brain Iron



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Endo et al., Neuron 2024; Dexter et al. Brain.1991

Role of iron and α-synuclein in disease pathogenesis

The Relevance of Iron in the Pathogenesis of Multiple System Atrophy: A Viewpoint

Christine Kaindlstorfer [1], Kurt A Jellinger [2], Sabine Eschlböck [1], Nadia Stefanova [1], Günter Weiss [3], Gregor K Wenning [1]

Iron converts native α-SYN into a β-sheet conformation and promotes its aggregation *either directly or via increasing levels of oxidative stress.*

The disturbance of its [iron] homeostasis leads to abnormal iron deposition in the brain and causes neurotoxicity via generation of free radicals and oxidative stress.

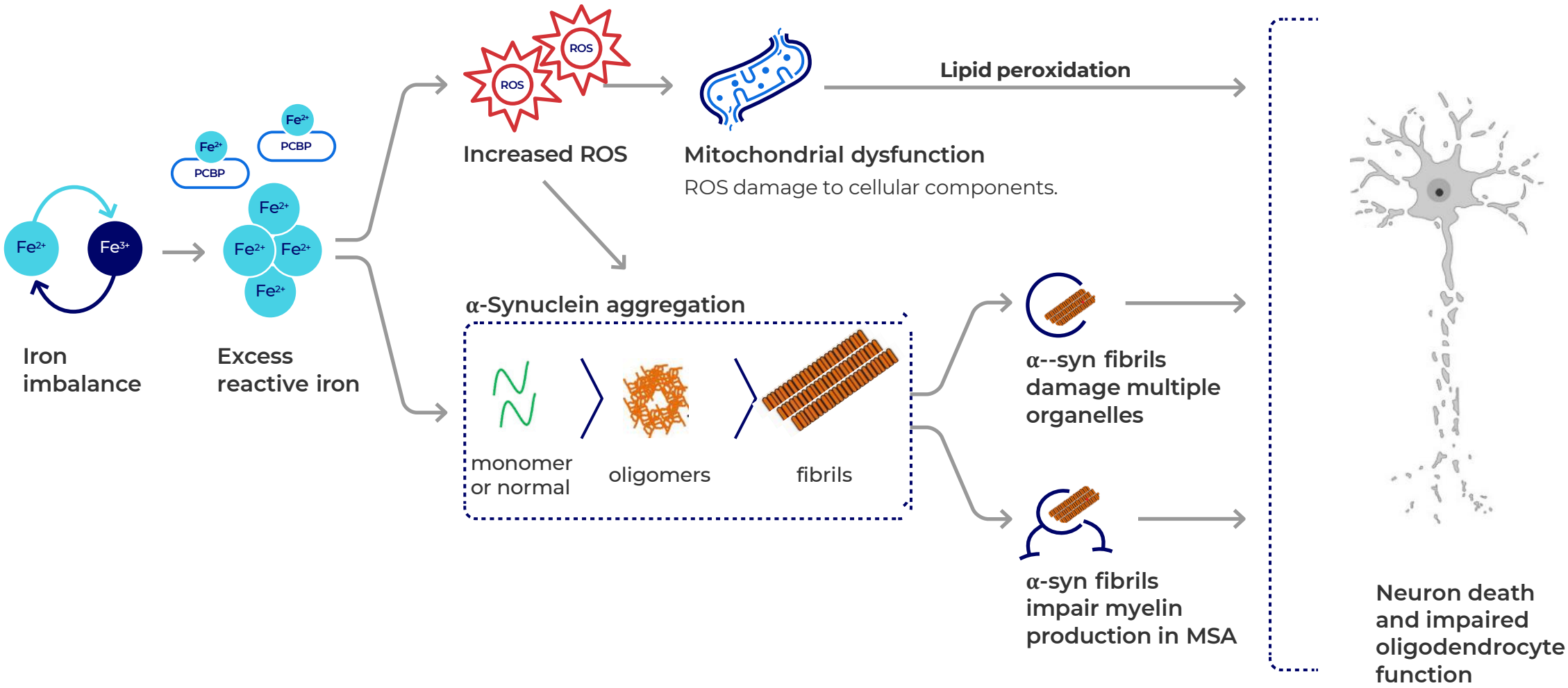
The Irony of Iron: The Element with Diverse Influence on Neurodegenerative Diseases

Seojin Lee [1 2], Gabor G Kovacs [1 2 3]

The close association of iron accumulation with distinct α-synuclein-pathology-related anatomical regions of the two disease subtypes supports the critical involvement of pathological iron in disease progression *and further suggests the two disease subtypes as distinct pathological identities in relation to disease pathogenesis.*

doi 10.3233/JAD-170601 (2018); doi.org/10.3390/ijms25084269 (2024)

Excess reactive iron drives α-synuclein aggregation and promotes oxidative injury



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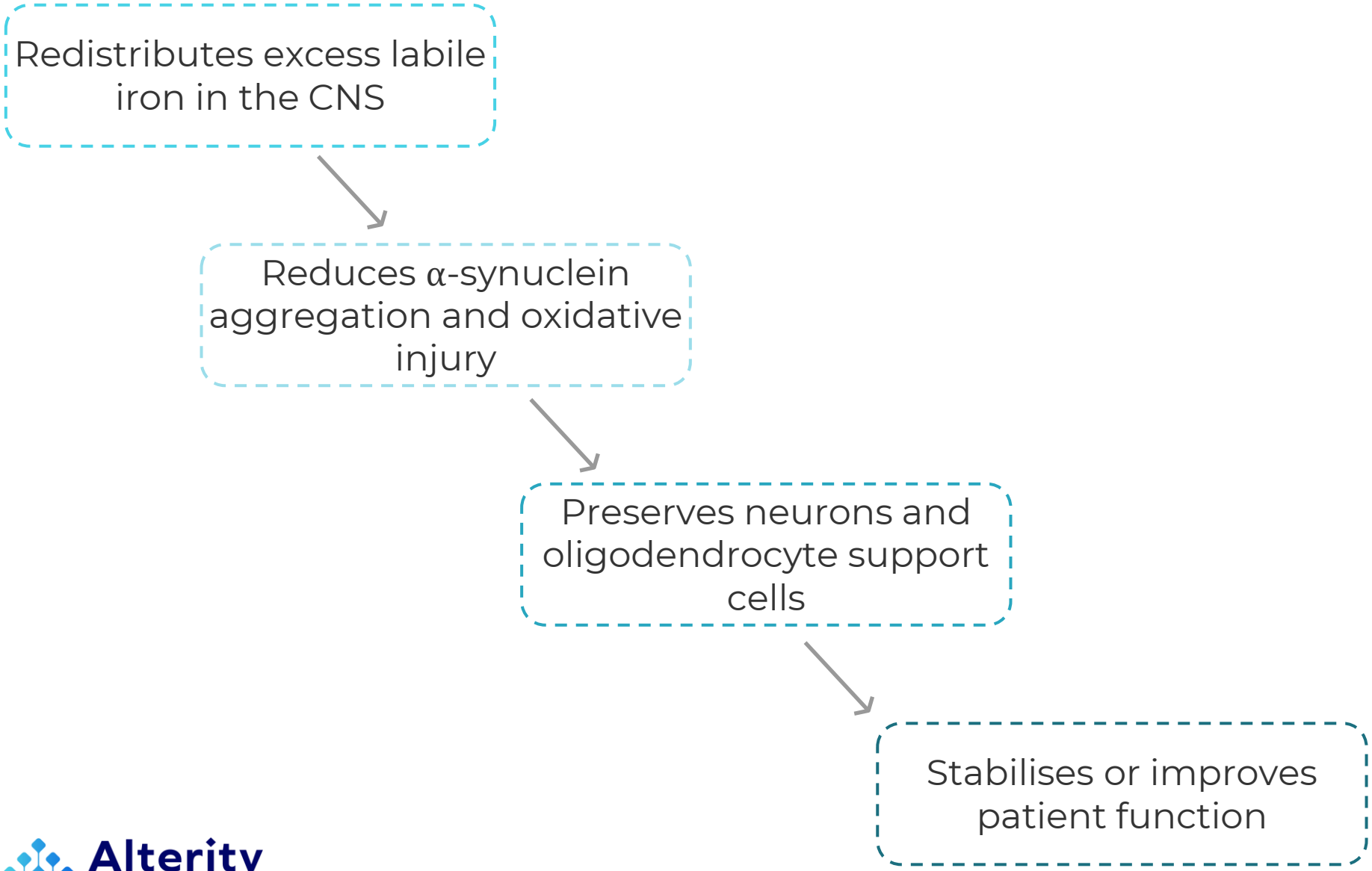
Treatment approach: Address underlying pathology



Potential Disease Modifying Therapy

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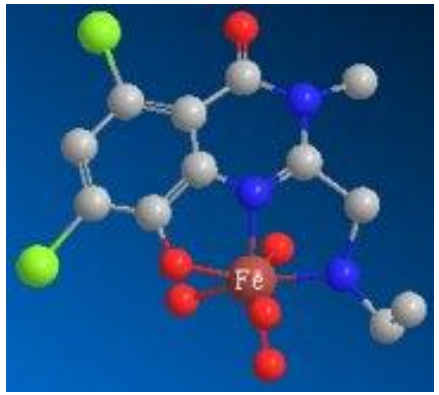
ATH434: Potential disease modifying drug candidate

Small molecule	Penetrates blood-brain barrier and acts intracellularly to address pathology
Iron chaperone	Moderate binding affinity, *redistributing* excess labile iron in CNS
Oral administration	Preferred by patients and doctors vs infusions (IV, intrathecal) or injections
Broad treatment potential	Potential to treat many neurodegenerative diseases (e.g., Parkinson's, Frederich Ataxia)
Orphan and Fast track designations	US FDA Fast Track Designation and Orphan drug designation in U.S. and EU

ATH434 binding to iron



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Accumulated evidence of ATH434 efficacy

Target disease	Model	Midbrain iron incl. s. nigra	α-Synuclein	Preserve neurons / function	Clinical observations
Parkinson's disease	Monkey MPTP	↔	n/a	↑	Improved motor performance
Parkinson's disease	Monkey MPTP	↓	↓	↑	Improved motor performance
Parkinson's disease	Mouse A53T	↓	↓	↑	Improved motor performance
Parkinson's disease	Mouse tau knockout	↓	↓	↑	Improved motor performance
MSA[1]	PLP-α-syn	↓	↓	↑	Improved motor performance
MSA[2]	PLP-α-syn	↔	↓	↑	Improved motor performance

↔ Stable

ATH434 consistently improved motor performance by reducing α-synuclein aggregation and preserving neurons

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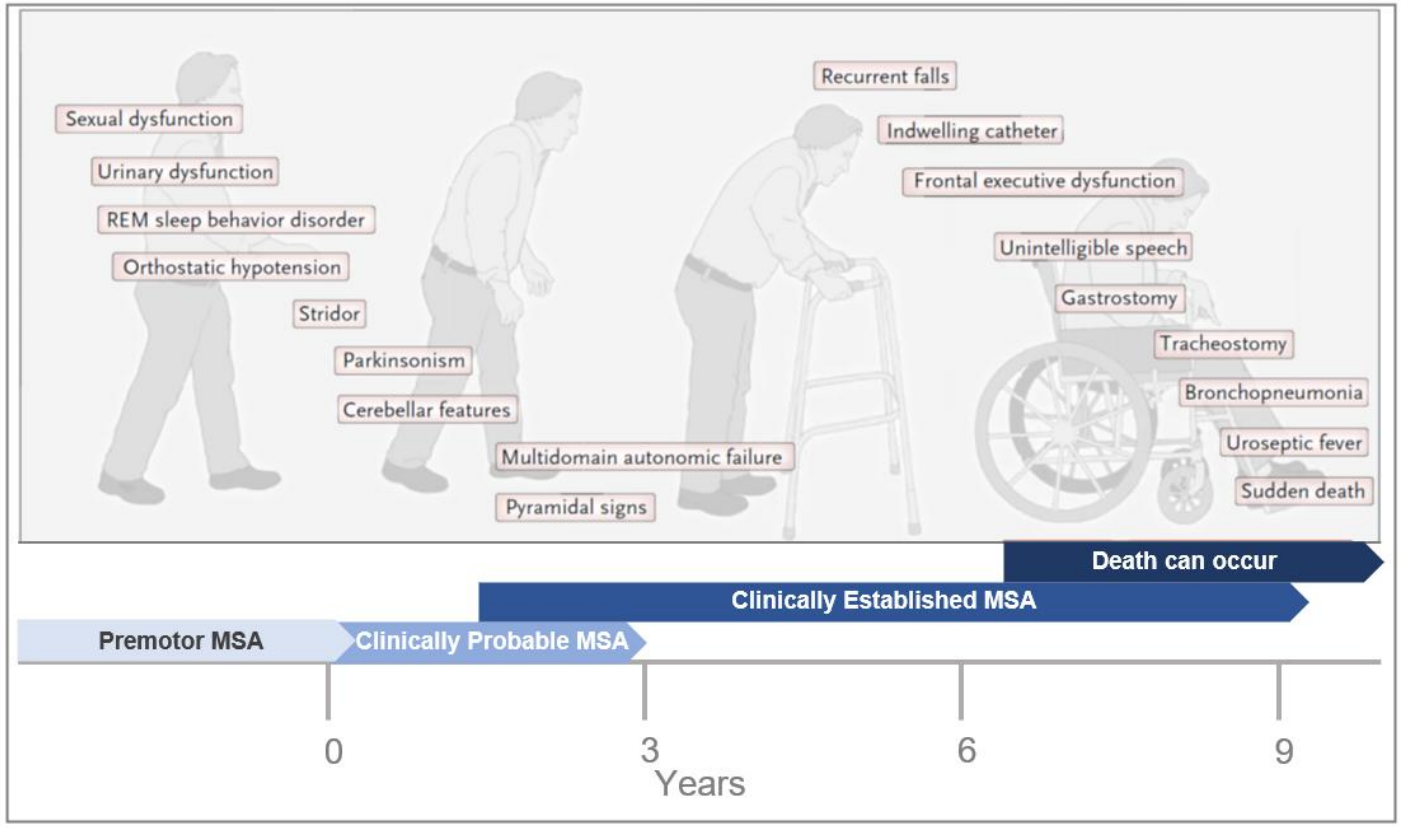
Sources: Bradbury et al, Am Acad. Neurol 2024; Finkelstein, Acta Neuropath Comm 2017; Beauchamp et al, Neurotherapeutics 2022; [1] Heras-Garvin et al, Mov Disord. 2021; [2] Finkelstein et al, J Park Dis 2022

ATH434 clinical development program in MSA

Multiple System Atrophy (MSA): Parkinsonian disorder with no approved treatment

- Highly debilitating and rapidly progressive
- Orphan disease: up to 50,000 patients in U.S.
- Disease characteristics
  - Motor: Parkinsonism, uncoordinated movements, balance problems, falls
  - Autonomic dysfunction: blood pressure maintenance, bladder control, bowel function
  - Atrophy and α-synuclein accumulation in multiple brain regions
- Over 50% require wheelchair in 5 years
- Median survival 7.5 years after symptom onset



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Sources: Fanciulli, Wenning. NEJM 2015 | Wenning, et al. Mov Disorders 2022 | Coon, et al. Brain 2015 | Multiple System Atrophy: National Institute of Neurological Disorders and Stroke (nih.gov)

Our diligent clinical development approach to achieve meaningful outcomes in MSA

Phase 1 Program

ATH434

- achieved half-life and twice daily dosing
- achieved blood levels in humans that exceeded efficacious concentrations in the animal model
- favorable safety profile
- demonstrated that the drug was well-tolerated

Natural History Study

bioMUSE

- observational study in individuals with MSA
- designed to de-risk clinical development program
- optimized patient selection for Phase 2 trials

Phase 2:

ATH434-201

Randomized double-blind placebo-controlled trial

Results: clinically meaningful efficacy on MSA rating scale, measures of orthostatic hypotension, disease severity

ATH434-202

Open label trial in advanced MSA patients

Results: showed improved neurological symptoms in more advanced patients and favorable safety

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BioMUSE natural history study informs and de-risks treatment studies

N=21 Observational

Patient criteria:

Clinically Probable MSA

Biomarkers:

- MRI: iron, volume, glial pathology
- Fluid: NfL, aggregated α-synuclein
- Digital: Wearable movement sensors

Clinical: UMSARS 1, autonomic function, motor function global measures

Treatment: 12 months

Objectives:

Optimize patient selection and endpoints for Phase 2

Biomarker observations:

- Iron content: Significant increase in iron observed at 12 months in key brain region (substantia nigra)
- Brain volume: Significant decrease in volume observed over 12 months in MSA affected regions
- Neuronal injury marker: Increase in neurofilament light chain (NfL) at 6 and 12 months

BioMUSE natural history study allowed us to optimize patient selection for our Phase 2 trials

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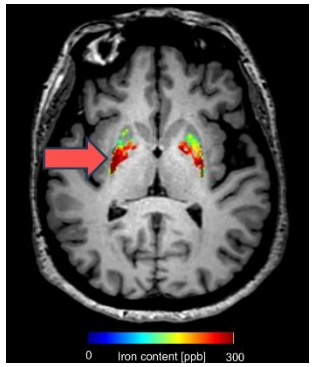
*Biomarkers of progression in Multiple System Atrophy (bioMUSE).; 1NfL: Neurofilament light chain

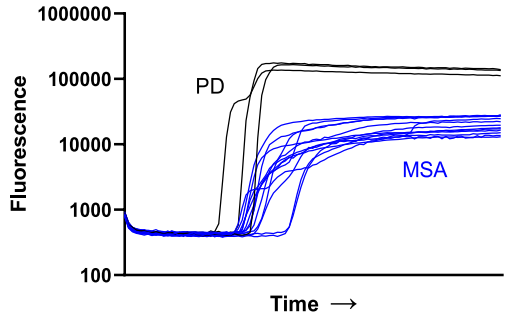
BioMUSE natural history study results

Optimized patient selection in Phase 2 trials:

Advanced MRI methods:



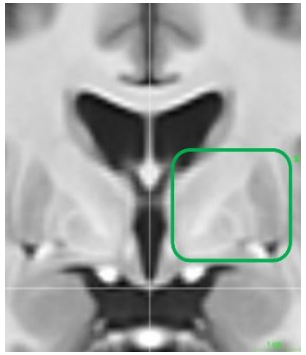
α-synuclein in CSF:



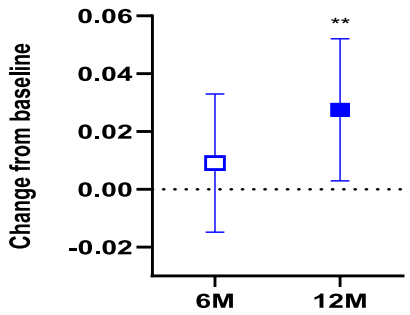
- Identified ”iron signature” of early MSA
- Differentiated MSA from Parkinson’s disease (PD)
- Revised selection criteria in ATH434-201 and ATH434-202 protocols to exclude PD patients

Precision biomarker assessment:

Structural mapping:



Iron content in substantia nigra:



- Improved precision of volume measurements
- Novel strategies for measuring brain iron in individual regions
- State of the art methods enabled precise measurements of brain iron and volume with MRI

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

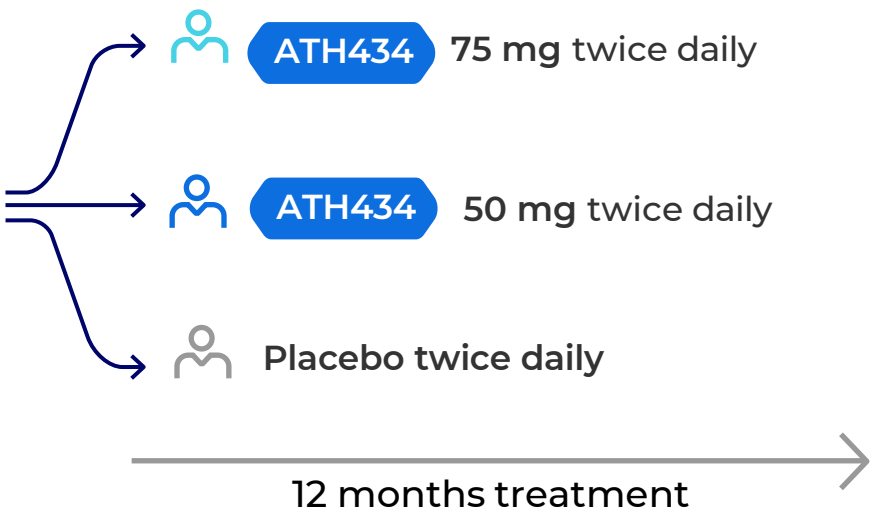
ATH434-201 randomized, double-blind, placebo-controlled trial

Patient criteria:

N=77

- Clinical diagnosis of MSA
- Motor symptoms ≤4 years
- No severe impairment
- Elevated brain iron on MRI
- Elevated plasma NfL

Study design:



Endpoints:

Key clinical endpoint:
modified UMSARS Part 1

Key biomarker endpoint:
brain iron content by MRI

Additional secondary endpoints:
CGI-S, OHSA, Wearable Sensors, Safety

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MRI - Magnetic Resonance Imaging; **UMSARS -** Unified MSA Rating Scale (UMSARS) Scale– measures activities of daily living
CGI-S - Clinical Global Impression-Severity scale; **OHSA** - Orthostatic Hypotension Symptom Assessment

Importance of the Unified MSA Rating Scale Part I (UMSARS I)

UMSARS Part I Items:

- Speech
- Swallowing
- Handwriting
- Cutting food
- Dressing
- Hygiene
- Walking
- Falling
- Orthostatic symptoms
- Urinary function
- Bowel function
- Sexual function*

Rated from 0 to 48
higher scores worse

Validated rating scale to assess MSA disease severity

Rates functional impairment in domains affected in MSA

UMSARS is the FDA endorsed clinical endpoint to support approval for the treatment of MSA

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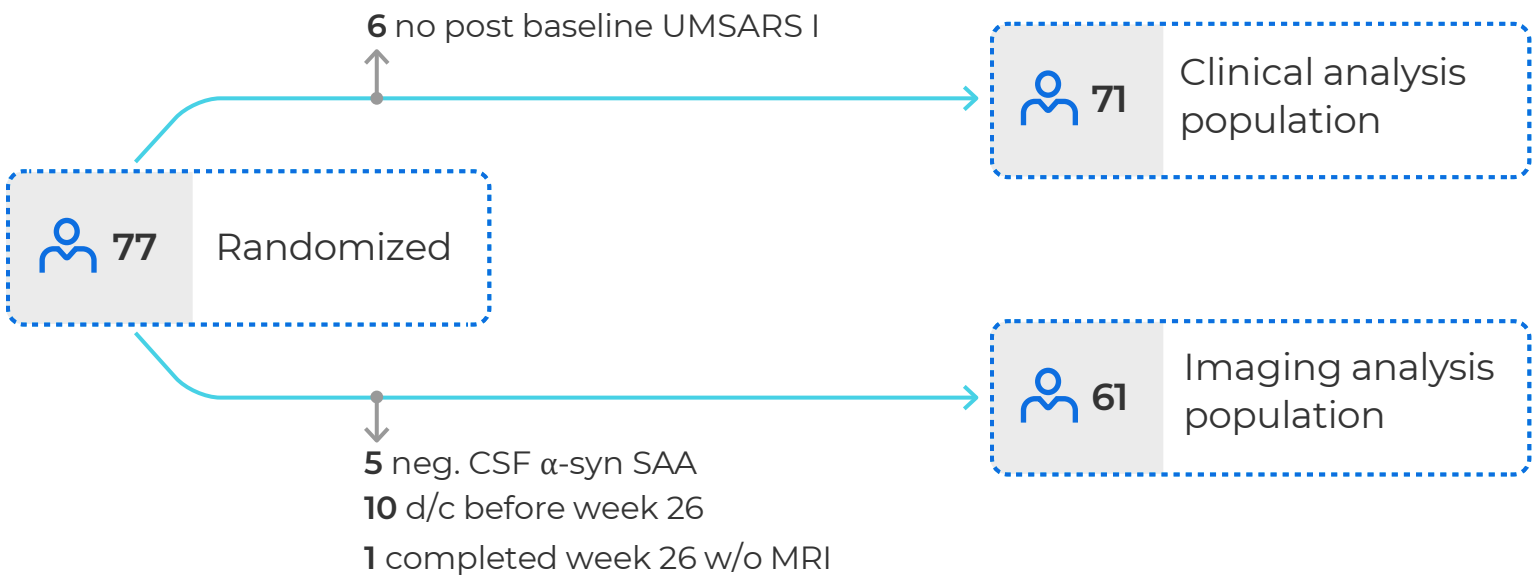
* Modified version of UMSARS I excludes sexual function item

Populations and key endpoints



Endpoint:	Change from BL to week 52:	Population:	Criteria*
Primary (Biomarker)	Iron content in s. nigra by MRI	Imaging	≥ 1 post-baseline MRI (26 weeks) (+) aggregating α-synuclein SAA
Key secondary (Clinical)	Change in Modified UMSARS Part I	Clinical	≥ 1 post-baseline UMSARS I (13 weeks)

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* All patients in Imaging and Clinical analysis populations were randomized and treated

Baseline characteristics

	Placebo N=22	ATH434-201 50 mg twice daily N=25	ATH434-201 75 mg twice daily N=24
Age (y)	61.3 (6.6)	63.1 (6.1)	63.9 (6.7)
Gender (% male)	63.6%	52.0%	62.5%
Duration of motor symptoms (y)	2.5 (0.8)	2.6 (0.8)	2.3 (0.9)
Modified UMSARS I1	16.9 (3.9)	15.2 (5.4)	14.4 (4.4)
Motor score of Parkinson plus scale[1]	57.6 (14.2)	47.8 (18.4)	48.9 (16.8)
Plasma NfL (pg/mL)	34.9 (12.5)	31.1 (9.1)	32.3 (9.0)
CSF aggregating α-syn SAA (+)	91%	92%	96%
OH symptom assessment	13.5 (9.8)	13.8 (13.2)	15.0 (12.2)
Clinical phenotype: MSA-P (%)	59.1%	60.0%	70.8%
Severe orthostatic hypertension	4.5%	4.0%	29.2% ↑

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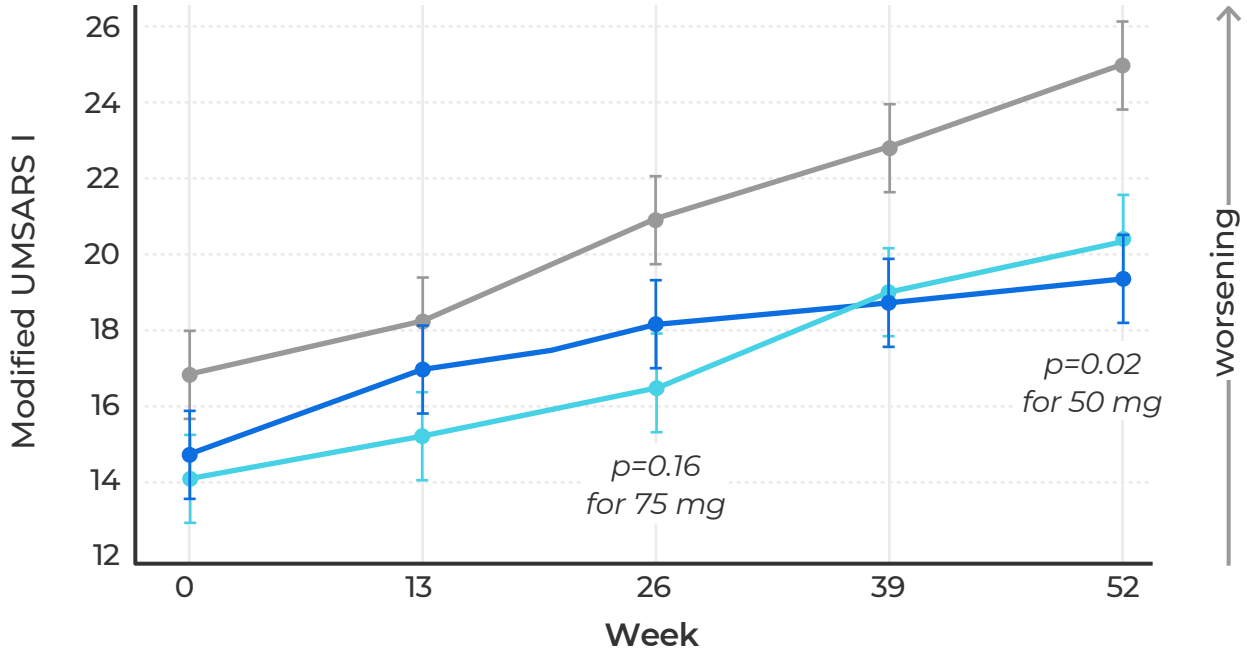
Clinical analysis population

[1] Payan et al. PlosOne 2011

Severe OH is a predictor of rapid disease progression

Achieved clinically significant efficacy on modified UMSARS Part I

change from baseline to week 52



	Difference vs. placebo LS mean (SE)	Relative treatment effect
Placebo N=22		
ATH434-201 50 mg N=25	**- 3.8 (1.6)**	**48%**
ATH434-201 75 mg N=24	**- 2.4 (1.7)**	**30%**

Relative Treatment Effect

$$\frac{\text{Change}_{\text{ATH434}} - \text{Change}_{\text{Placebo}}}{\text{Change}_{\text{Placebo}}}$$

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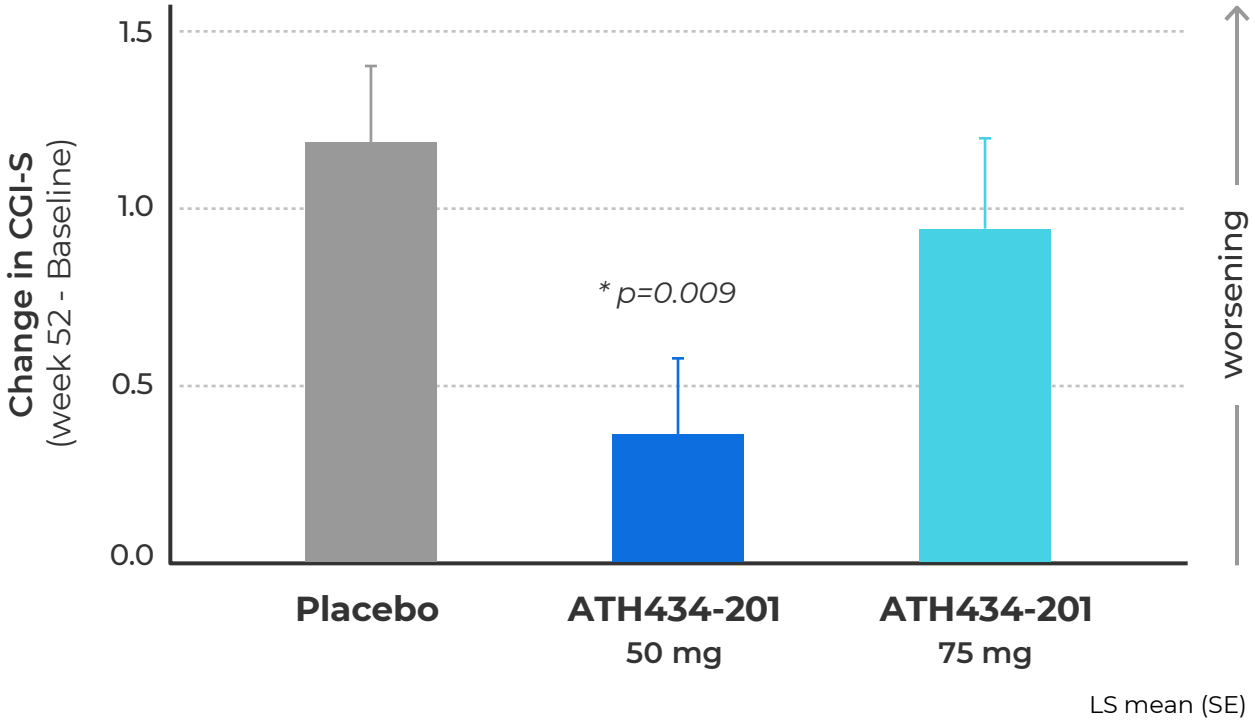
Clinical Analysis Population

Efficacy on Clinical Global Impression of Severity (CGI-S) scale

change from baseline to week 52



- CGI-S is a single-item questionnaire that uses a 7-point Likert Scale ranging from 1 to 7 where a **higher score indicates a worse outcome**
- Assesses total picture of participant over the prior 28 days:
  - illness severity, impact of illness on function, level of distress and any other aspects of impairment

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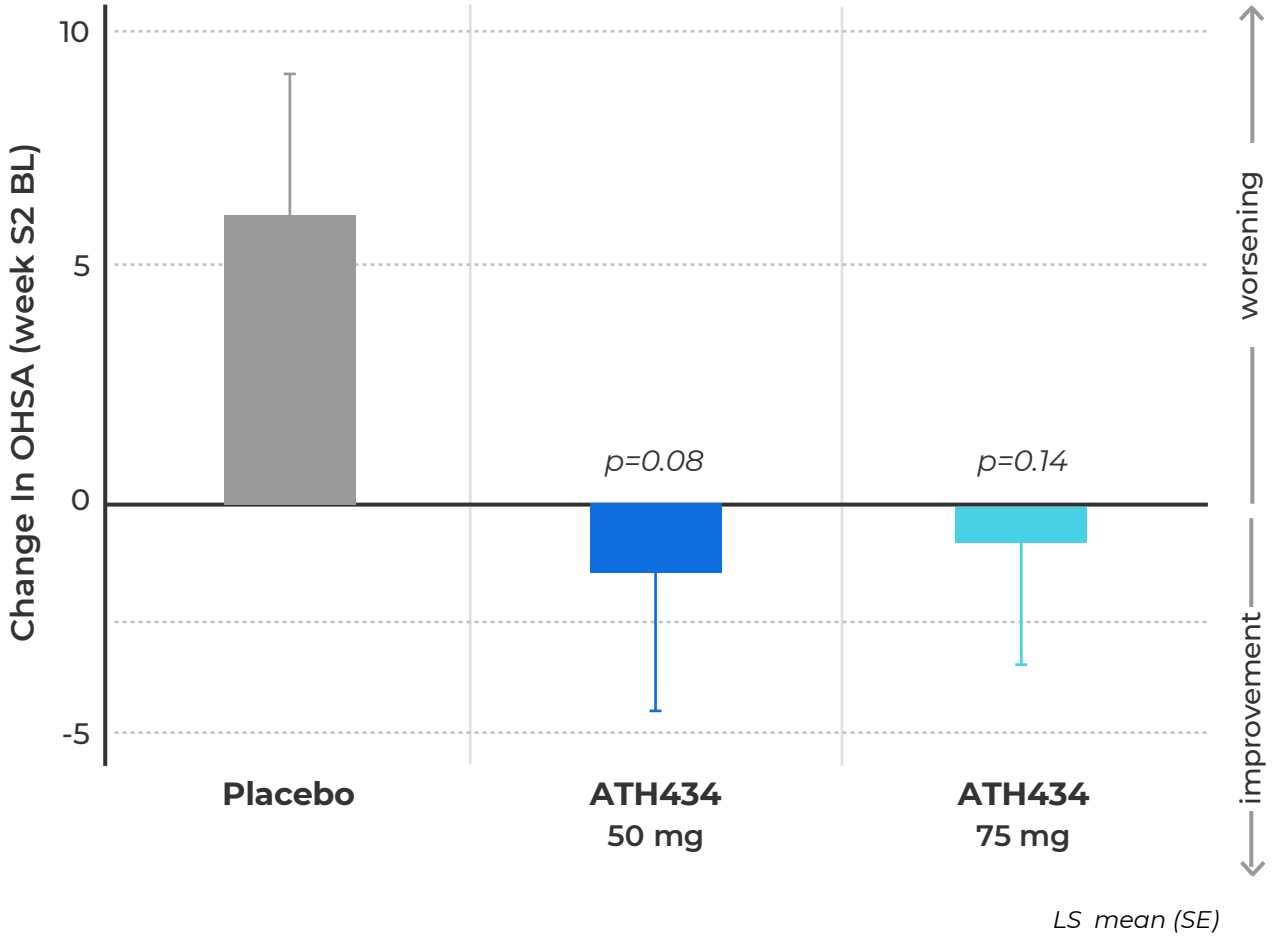
Clinical Analysis Population

Efficacy on Orthostatic Hypotension Symptom Assessment (OHSA)

change from baseline to week 52



LS mean (SE)

OHSA: component of the orthostatic hypotension questionnaire
Assesses severity of six symptoms:

- dizziness/lightheadedness/feeling faint/feeling like blacking out
- problems with vision
  (blurry, seeing spots, tunnel vision)
- weakness
- fatigue
- concentration
- head and neck discomfort

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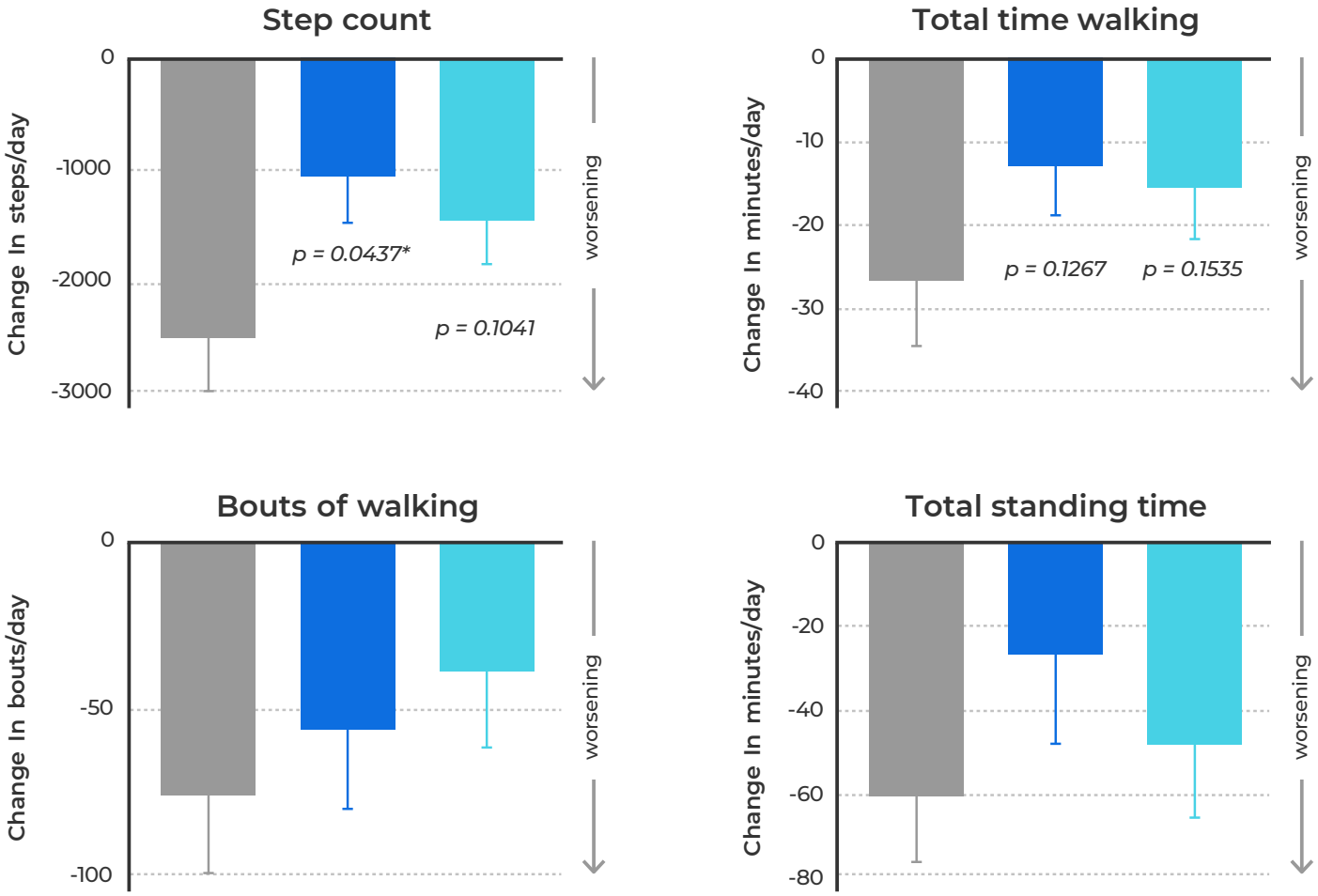
Clinical Analysis Population

Kaufmann, et al. Clin Auton Res 2012..

ATH434 preserved activity in outpatient setting
change from baseline to week 52

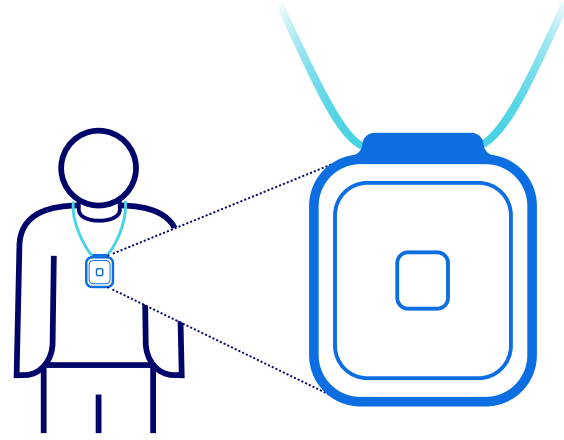


Placebo

ATH434-201
50 mg

ATH434-201
75 mg

Pendant
for wearable sensor



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Clinical Analysis Population

Adverse Events

N (%) of subjects [1]	Placebo twice daily N=26	ATH434-201 50 mg N=25	ATH434-201 75 mg N=26
Any Adverse Event (AE)	24 (92.3%)	21 (84.0%)	25 (96.2%)
UTI	14 (53.8%)	10 (40.0%)	7 (26.9%)
Fall	8 (30.8%)	7 (28.0%)	8 (30.8%)
Covid-19	1 (3.8%)	6 (24.0%)	4 (15.4%)
Fatigue	2 (7.7%)	1 (4.0%)	5 (19.2%)
Back pain	1 (3.8%)	3 (12.0%)	2 (7.7%)
Severe AEs [2]	8 (30.8%)	3 (12.0%)	6 (23.1%)
Serious AEs [2]	10 (38.5%)	5 (20.0%)	7 (26.9%)

- Similar rates of AEs in ATH434 and placebo participants
- No treatment associated effects on hemoglobin or iron parameters

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1 - Reporting one or more event
2 - None related to Study Drug

Neuroimaging Endpoints

Change in Iron Content by MRI

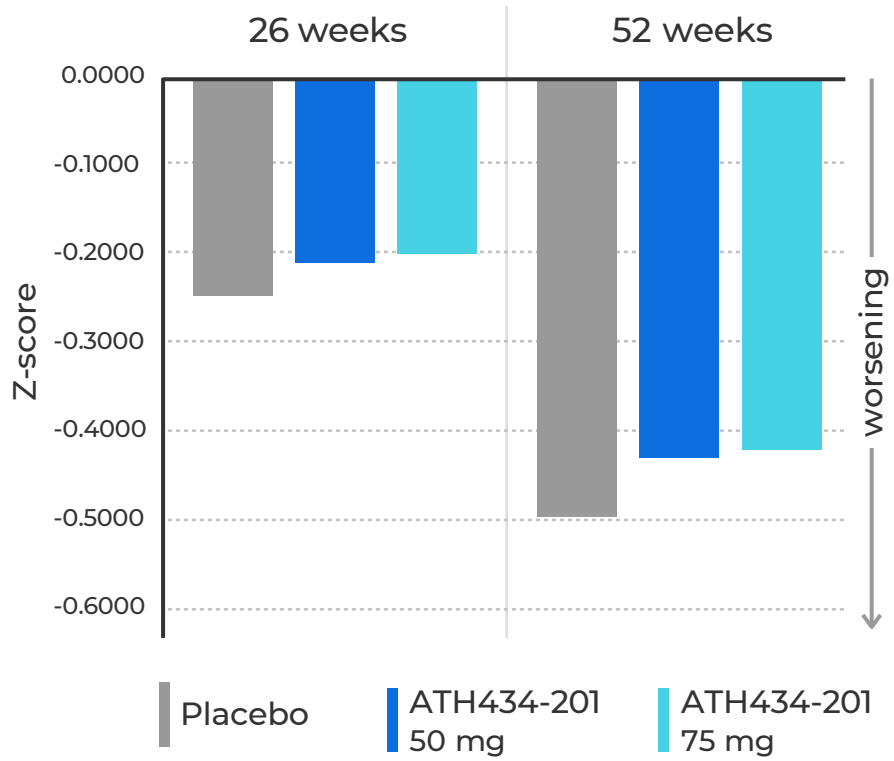
Region	50 mg Week 26	50 mg Week 52	75 mg Week 26	75 mg Week 52
Pallidum	↓	↓	↓	↓
Putamen	↓^	↓	↔	↔
S. nigra	↔	↓	↔	↔

*Compared to placebo: ↓ Iron content, ↔ No observable difference, ^p = 0.025, *p = 0.08*

Evidence of target engagement

- Reduced/stabilized iron content in Pallidum (GP) > Putamen
- Reduced iron content in s. nigra at 50 mg dose but not 75 mg (primary endpoint)

Change in Brain Volume*



- ATH434 demonstrated target engagement on MRI
- ATH434 showed trends in preserving brain volume

* MSA Atrophy Index: composite z-score of putamen, GP, cerebellum and brainstem vs. healthy age-matched population

ATH434-201 trial conclusions

- **ATH434 demonstrated clinically significant efficacy in modifying disease progression in MSA**
  Both 50 and 75 mg efficacious on UMSARS I and important secondary endpoints
- **Demonstrated target engagement with reduced iron accumulation in MSA affected brain regions**
- Baseline differences in disease severity likely explain lower-than-expected response at 75 mg
- Showed trends in preserving brain volume in MSA affected areas
- No safety signals and was well-tolerated
- Results strongly support continued advancement of ATH434 for the treatment of MSA

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ATH434-202 - study design

Design	Single arm, open-label
Objectives	Efficacy and safety of ATH434
Population	Advanced MSA (n=10)
Treatment	ATH434 75 mg BID x 12 months
Brain MRI Biomarkers	Iron, volume
Fluid Biomarkers	NfL, Aggregated α-synuclein
Clinical Measures	UMSARS I, clinical/patient global impressions of change

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ATH434 202 - Baseline characteristics

Comparison to 75 mg group in double-blind study

Parameter	**ATH434-202 | 75 mg BID (N=10)**	ATH434-201 | 75mg BID (N=24)
Age (yr)	**64.5 (7.5)**	63.9 (6.7)
Gender (% male)	**30.0%**	62.5%
Duration of motor symptoms (yr)	**3.9 (1.8)**	2.3 (0.9)
Modified UMSARS I[1]	**19.2 (5.3)**	14.4 (4.4)
Motor score of Parkinson Plus Scale[2]	**57.5 (20.4)**	48.9 (16.8)
Plasma NfL (pg/mL)	**42.1 (14.1)**	32.3 (9.0)
CSF aggregating α-syn SAA (+)	**100%**	96%
OH Symptom Assessment	**16.7 (14.8)**	15.0 (12.2)
Severe Orthostatic Hypotension	**40.0%**	29.2%

[1] Excluding sexual function item
[2] Payan et al. PlosOne 2011

Mean (SD)

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ATH434-202 - Key efficacy data at 75 mg

Comparison to double blind study at 12 mo

Parameter	**ATH434-202 | 75 mg BID (N=10)**	ATH434-201 | 75mg BID (N=24)
Modified UMSARS I	**3.5 (4.7)**	5.6 (5.6)
Clinical global impression of change (%stable)	**30%**	21%
Patient global impression of change (%stable)	**30%**	26.4%
Change in brain volume[1]	**-0.44 (0.14)**	-0.42 (0.29)

Mean (SD)

- **Reduced iron accumulation** in the pallidum and putamen, versus placebo in Study 201, **provide evidence of target engagement** and support the clinical efficacy of ATH434
- The **pattern of iron accumulation** in the substantia nigra was **comparable** to that observed in the 75 mg dose group in Study 201

The 75 mg dose demonstrated comparable efficacy to that observed in the double-blind study

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[1] MSA affected areas by MSA-atrophy index. Trujillo, P. et al Annals of Clin and Trans Neuro, 2025

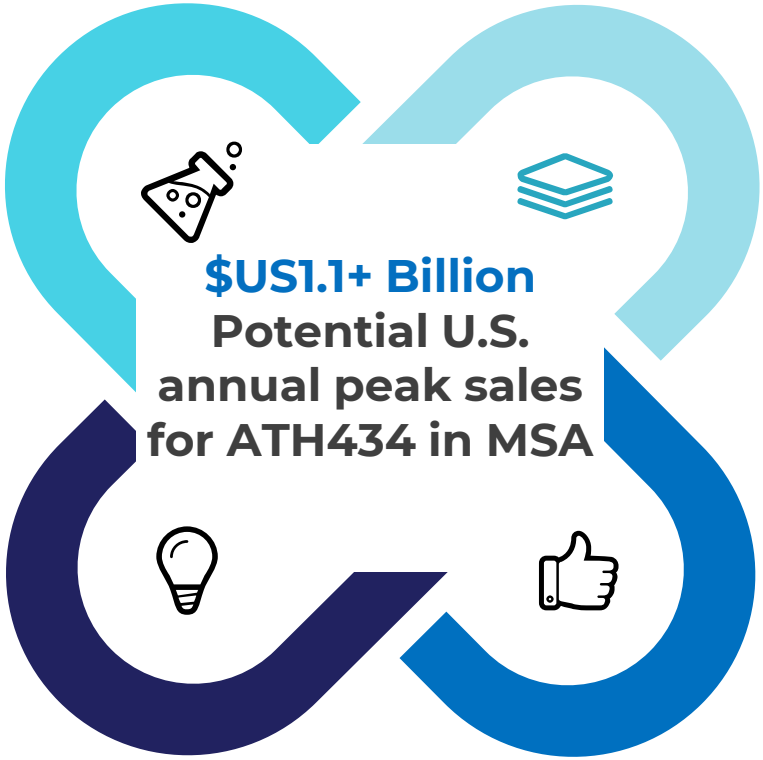
Significant commercial opportunity in MSA

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

Creating strong momentum in 2025

1. Robust efficacy in Phase 2 double-blind trial
2. Open label trial and Natural History study support ATH434 clinical development
3. Lead indication MSA is an Orphan Disease with no approved treatment
4. Highly experienced development team with multiple FDA approvals in neurology
5. **Strong cash balance:** A **$40.7M** as of 30 June

Multiple Meaningful Catalysts

- ATH434-201 Positive Topline Data
- ATH434-202 Positive Topline Data
- FDA Fast Track designation in MSA
- Data presentations at AAN and MSA Congress

Data presentations at MDS, AAS, ANA	Q4 25
FDA End-of-Phase 2 Meeting	Q4 25

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THANK YOU

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