A Phase 2 study of ATH434, a Novel Inhibitor of α-synuclein Aggregation, for the Treatment of Multiple System Atrophy

David Stamler[1], Cynthia Wong[1], Paula Trujillo[2], Margaret Bradbury[1],Christine Lucas[1] and Daniel O. Claassen[2]
[1] Alterity Therapeutics, Newark, CA [2] Vanderbilt University Medical Center, Nashville, TN

OBJECTIVE

- Describe baseline fluid biomarker, neuroimaging and clinical data of an early MSA population enrolled in a Phase 2 double-blind trial

INTRODUCTION

- MSA is a rapidly progressive neurodegenerative disorder without approved therapy
- MSA is characterized pathologically by aggregated α-synuclein, glial cytoplasmic inclusions and neurodegeneration in midbrain, basal ganglia, cerebellum, and brainstem
- Increased brain iron has been demonstrated in the basal ganglia of MSA patients
- The revised MDS diagnostic criteria use MRI findings for defining clinically established but not clinically probable MSA[1]
- ATH434 is a moderate affinity iron chaperone which inhibits α-synuclein aggregation and reduces oxidative stress by redistributing excess labile iron for cellular export or sequestration
- ATH434-201 is a randomized, double-blind, placebo-controlled Phase 2 study in ambulatory MSA patients.

METHODS

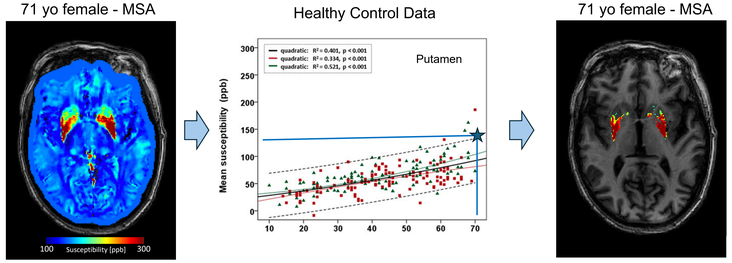
- Participants were diagnosed with clinically probable MSA based on the revised MDS MSA diagnostic criteria[1]
- Participants were ambulatory with duration of motor symptoms ≤ 4 years
- Participants had biomarker evidence of MSA on MRI and in plasma
- Participants had clinical features of parkinsonism, evidence of orthostatic hypotension and/or bladder dysfunction, and ataxia and/or pyramidal signs on neurological examination
- Clinical assessments were obtained at BL and months 3, 6, 9 and 12
  - Activities of Daily Living:
    - Unified MSA Rating Scale (UMSARS I) – Historical Review
    - Schwab and England Activities of Daily Living Scale
  - Motor examination: Natural History and Neuroprotection in Parkinson Plus Syndromes - Parkinson Plus Scale[2] (PPS)
- 3T MRI was performed at BL, 3 and 6 months and iron content was measured using quantitative susceptibility mapping (QSM) methods
- Plasma neurofilament light chain (NfL) was measured with an ultrasensitive Simoa assay with a mean inter-assay CV of 5.6%

References
[1] Wenning, et al. The MDS Criteria for the Diagnosis of Multiple System Atrophy. Mov. Disord. 2022. doi: 10.1002/mds.2900
[2] Payan, et al. Disease severity and progression in PSP and MSA: Validation of the NNIPPS-Parkinson Plus Scale. PLoS One. 2011;6(8):e22293.
[3] Li, et al. Age-dependent changes in brain iron deposition and volume in deep gray matter nuclei using QSM. Neuroimage. 2023. doi:10.1016/j.neuroimage.2023.119923.

METHODS

Determining Increased Iron on MRI for Regions of Interest (ROI)

- Age-specific thresholds for PT, GP, SN, and DN were based on healthy control data[3]
- Voxels > upper bound of 95% CI were identified using subject age for specific ROI
- Elevated iron defined as ≥ 10% of the voxels within an ROI above threshold for subject
- Number of voxels in cluster >100



QSM Image **Voxels with ↑ Iron**

RESULTS

Of 109 patients evaluated, 44 (40%) failed screening: 26 did not meet selection criteria, 6 had NfL levels below cutoff, 5 did not have elevated brain iron, 7 investigator/patient decision

Baseline Demographic and Clinical Parameters	Result
No. Subjects	65
Sex (M/F)	40/25
Age (years), mean (SD)	63 (6.4)
Duration of motor symptoms (years), mean (SD)	2.7(0.8)
Schwab and England ADL	72.8 (17.1)
UMSARS I score (items 1-10), mean (SD)	14.2 (4.5)
PPS motor score, mean (SD)	53.1 (17.8)
Plasma NfL (pg/mL), mean (SD)	30.3 (10.4)

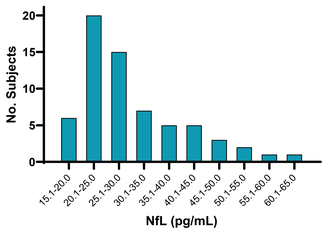


Figure 1. Distribution of baseline plasma NfL values

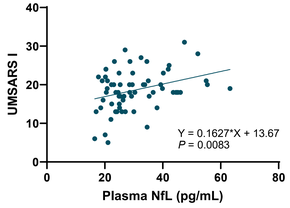


Figure 2. Correlation between plasma NfL and UMSARS I at baseline

RESULTS

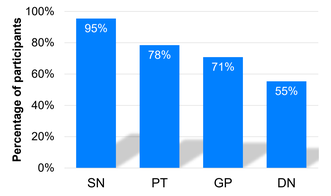


Figure 3. Patients with increased iron by ROI

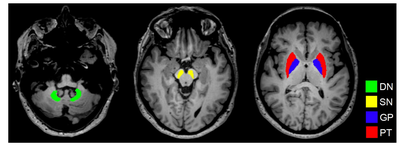


Figure 4. Overlay of ROIs on T1w image

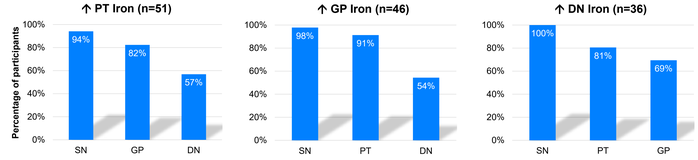


Figure 5. Concomitant increases in iron by ROI

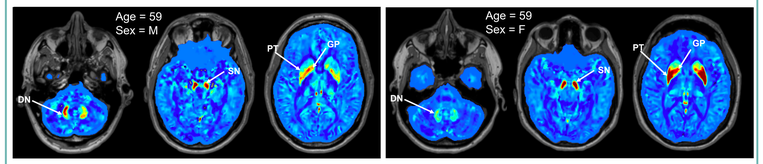


Figure 6. QSM images for participants with elevated iron in DN and SN (left) or SN, PT and GP (right)

CONCLUSIONS

- In this Phase 2 study, MSA patients with < 4 years of motor symptoms have elevated plasma NfL levels at baseline which correlate significantly with disease severity
- Patients with clinically probable MSA have increased iron in multiple subcortical regions, with elevations most frequently observed in the SN > PT > GP
- Two distinct patterns of iron accumulation (DN/SN and SN/PT/GP) were observed, with elevated SN iron in nearly all patients
- The specificity of diagnosing clinically probable MSA may be increased with biomarkers such as elevated iron on MRI/QSM or elevated plasma NfL
- ATH434 is a potential disease modifying therapy based on its ability to redistribute excess labile iron, inhibit α-synuclein aggregation and reduce oxidative stress

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