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

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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
- Revised MDS diagnostic criteria do not use MRI findings for defining clinically probable MSA[1]
- ATH434 is a moderate affinity iron chaperone that inhibits α-synuclein aggregation and reduces oxidative injury 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

- Clinically probable MSA based on revised MDS MSA diagnostic criteria[1]
- Increased iron content in basal ganglia on Screening MRI
- Elevated plasma neurofilament light chain (NfL) at Screening
- Ambulatory with motor symptoms ≤ 4 years duration
- Clinical features of parkinsonism, evidence of orthostatic hypotension and/or bladder dysfunction, and ataxia and/or pyramidal signs on neurological examination

Clinical assessments obtained at BL and months 3, 6, 9 and 12

- Activities of Daily Living
  - Unified MSA Rating Scale Part I (UMSARS I)
  - Schwab and England Activities of Daily Living Scale
- Motor examination: Natural History and Neuroprotection in Parkinson Plus Syndromes - Parkinson Plus Scale[2]

Biomarkers assessed at BL, 6 and 12 months

- Lumbar puncture for NfL, α-synuclein SAA
- NfL measured with ultrasensitive Simoa assay with a mean inter-assay CV of 5.6%
- Iron content by MRI using quantitative susceptibility mapping (QSM)
- Subcortical volume measurements by MRI using AssemblyNet segmentation[3]

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] Coupé, et al. AssemblyNet: A large ensemble of CNNs for 3D whole brain MRI segmentation. Neuroimage, vol. 219, p. 117026, Oct. 2020
[4] Li, et al. Age-dependent changes in brain iron deposition and volume in deep gray matter nuclei using QSM. Neuroimage. 2023.

METHODS

Increased iron deposition on MRI for regions of interest (ROI) based on:

- Age-specific thresholds for the putamen (PT), globus pallidus (GP), substantia nigra (SN), and dentate nucleus (DN) were established using data from healthy controls[4]
- Voxels above upper 95%CI for each ROI and ≥10% of voxels in ROI exceed this threshold

Decreased volumes on MRI:

- Thresholds for reduced brain volume for ROIs defined as those < 5th percentile of the age-matched normal population from the Human Connectome Project

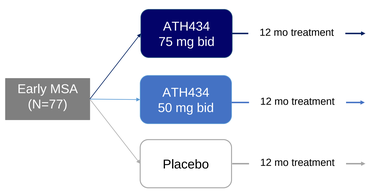

Figure 1. Study Design

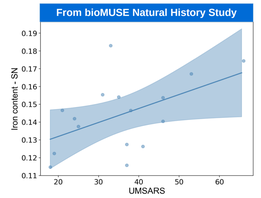

Figure 2. Correlation of SN iron and UMSARS. Correlations significant at baseline (p<0.05) and over time (p=0.004, adjusting for baseline scores, age, and sex)

RESULTS

Of 128 patients evaluated, 51 (40%) failed screening: 23 did not meet various selection criteria, 11 had advanced MSA, 6 had low NfL level, 5 did not have ↑ brain iron, 6 investigator/patient decision

Baseline Demographic and Clinical Parameters	Result
No. Subjects	77
Sex (M/F)	45/32
Age (years), mean (SD)	63 (6.4)
Duration of motor symptoms (years), mean (SD)	2.5 (0.8)
Schwab and England ADL	72.9 (17.5)
UMSARS I score (items 1-12), mean (SD)	18.7 (5.2)
PPS total motor score, mean (SD)	53.0 (17.8)
Plasma NfL (pg/mL), mean (SD)	30.8 (10.9)

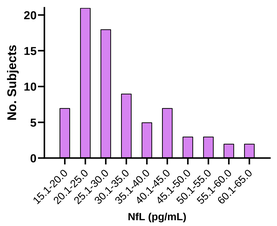

Figure 3. Distribution of baseline plasma NfL values

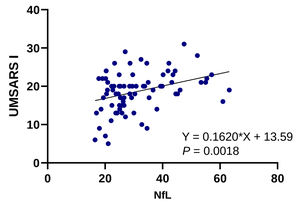

Figure 4. Correlation between plasma NfL and UMSARS I at baseline

RESULTS

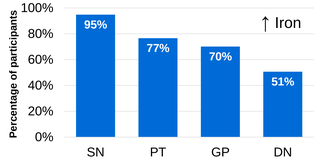

Figure 5. Patients with increased iron by ROI

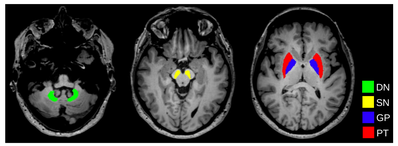

Figure 6. Iron ROIs overlaid on a T1w image to estimate iron deposition from QSM images.

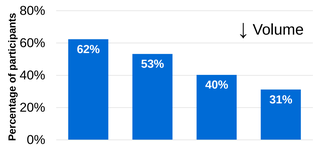

Figure 7. Patients with reduced volume by ROI
BS=Brainstem; CB=Cerebellum

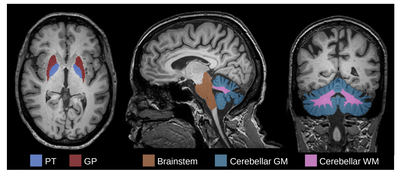

Figure 8. Volumes were obtained from ROIs segmented using AssemblyNet.

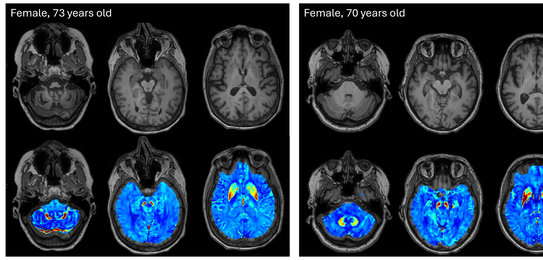

Figure 9. Radiologic phenotypes. T1w images (top) and QSM images (bottom) for participants with elevated iron in the DN and SN (left) or SN, PT, and GP (right). Brain atrophy is visible in the T1w images.

CONCLUSIONS

- In this Phase 2 study, early stage MSA patients have elevated plasma NfL levels which correlate significantly with disease severity at baseline and over time
- Iron content in the SN is consistently increased in early MSA patients and less frequently in the PT, GP and DN
- Two radiologic phenotypes of iron accumulation and atrophy (SN/PT/GP and DN/SN) were observed that correspond with neuropathological patterns of MSA (SND, OPCA)
- The accuracy of diagnosing clinically probable MSA may be increased using a multimodal approach that includes neuroimaging biomarkers (increased iron content, reduced subcortical volumes) and fluid biomarkers
- ATH434 is a potential disease modifying therapy based on its ability to redistribute excess labile iron, inhibit α-synuclein aggregation and reduce oxidative injury

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