Preliminary Efficacy and Safety of ATH434 in Multiple System Atrophy

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OBJECTIVE

To assess the efficacy, safety, and tolerability of ATH434 in participants with clinically established Multiple System Atrophy (MSA).

BACKGROUND

- MSA is a rapidly progressive neurodegenerative disorder characterized by parkinsonism, cerebellar ataxia, and autonomic failure. It leads to widespread brain degeneration and iron accumulation.
- Currently, there are no approved disease-modifying treatments for MSA, and available therapies focus primarily on symptomatic relief.
- **ATH434** is a moderate-affinity iron chaperone designed to inhibit the aggregation of α-synuclein, reduce oxidative stress, and preserve neuronal function.
- Preclinical studies have demonstrated its potential to slow neurodegeneration in animal models of MSA.[1,2]
- Here, we present interim data from an open-label clinical study evaluating ATH434's safety, efficacy, and impact on neuroimaging and biomarker outcomes in MSA patients.

METHODS

Participants: 10 individuals with clinically diagnosed MSA, elevated iron in the lentiform nucleus or substantia nigra (assessed by MRI), and elevated plasma neurofilament light chain (NfL) levels.

Treatment: ATH434 75 mg, orally administered twice daily for 12 months.

Assessments:

- Clinical assessments were performed at baseline, 6 months, and 12 months, using the following scales:
  - *Unified MSA Rating Scale (UMSARS I)*[3] – evaluates motor and autonomic symptoms.
  - *Parkinson Plus Scale (PPS)*[4] – assesses severity of parkinsonism features.
  - *Patient Global Impression of Change (PGIC) and Clinical Global Impression of Change (CGIC)* scores were recorded at 6 and 12 months using a 7-point Likert scale.

Imaging and Biomarkers:

- **Iron Imaging**: 3T MRI with quantitative susceptibility mapping (QSM) to measure iron content in the substantia nigra, putamen, globus pallidus and dentate nucleus.
- **Brain Volume**: Subcortical volume measurements were obtained from T1-weighted MRI scans using a deep learning-based automatic segmentation tool.
- **Biomarkers**: Plasma and CSF levels of neurofilament light chain (NfL) were measured at baseline and every 6 months.

RESULTS

Baseline Demographic and Clinical Parameters	
No. Subjects	10
Sex (M/F)	3/7
Age (years), mean (SD)	64.5 (7.1)
Duration of motor symptoms (years), mean (SD)	3.9 (1.9)
Schwab and England ADL	59.0 (27.4)
UMSARS I score (items 1-12), mean (SD)	22.0 (5.3)
PPS total motor score, mean (SD)	57.5 (19.3)
Plasma NfL (pg/mL), mean (SD)	42.1 (13.3)

Safety Profile:

- ATH434 was well tolerated with no drug-related serious adverse events. Most adverse events were mild to moderate, showing a favorable safety profile.

Clinical Findings at 6 Months (n=10):

- 30% of participants (3/10) showed **stable or improved neurological symptoms**, based on UMSARS I and PGIC/CGIC scores (clinical responders).
- On average, ATH434-treated participants experienced a 3.2-point increase in their UMSARS-I score, compared to an expected 3.9-point increase in a similar MSA cohort over 6 months.[5]

Biomarker and Imaging Data at 6 Months:

- **Brain Iron Content**: Clinical responders showed stability in iron levels in the substantia nigra, putamen, and globus pallidus compared to non-responders with increased iron.

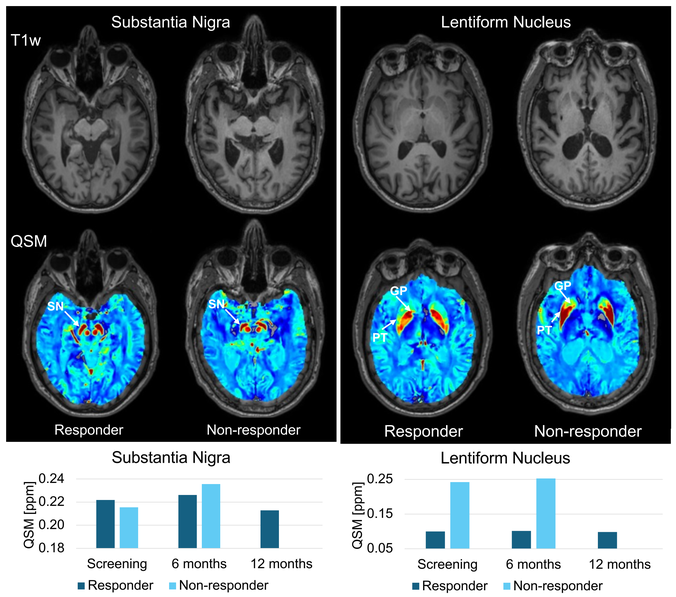

Fig. 1. T1-weighted and QSM images from a responder (62-year-old male) and a non-responder (65-year-old male), displayed at the levels of the substantia nigra (SN, left) and lentiform nucleus (putamen (PT) and globus pallidus (GP), right). Corresponding bar plots present QSM values for the SN and lentiform nucleus in the responder (dark blue) and non-responder (light blue) at screening, 6 months, and 12 months. The responder shows stable or decreasing QSM values, while the non-responder exhibits an increase over time.

RESULTS

- **Brain Volume:** At 6 months, all participants exhibited brain volume declines consistent with MSA progression. However, clinical responders maintained stable brain volumes at 12 months.

- **Neurofilament Light Chain (NfL):**
  - Clinical responders had **stable or reduced NfL** levels in CSF and plasma.
  - At 6 months, the average increases in NfL were 2.7% in CSF and 4.5% in plasma, compared to 17.9% and 19.3% in the bioMUSE natural history participants, respectively.

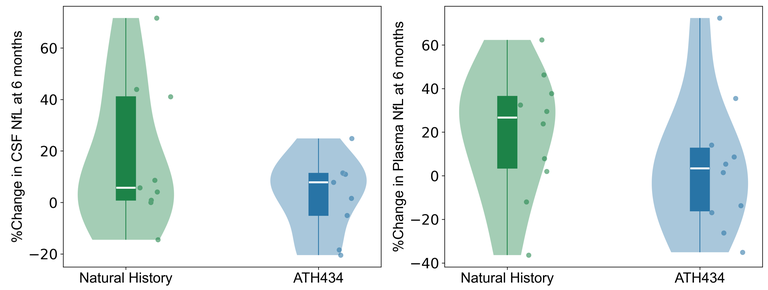

Fig. 3. Violin plots illustrating the changes in NfL at 6 months for ATH434 participants (blue) compared to natural history participants (green).

KEY FINDINGS

- The interim data suggest that ATH434 may have a disease-modifying effect in MSA, with **30% of participants showing stable or improved clinical outcomes**.
- The modest average change in UMSARS I scores over 6 months **is smaller than typically observed in untreated MSA patients**,[5] suggesting that ATH434 could have a potential to modify disease progression.
- Stabilization of iron content in key subcortical regions, combined with NfL biomarker data, indicates that **ATH434 may target neurodegeneration by modulating brain iron levels and reducing oxidative stress**.

CONCLUSIONS

- ATH434 shows promise as a disease-modifying therapy for MSA, with interim data suggesting potential stabilization of clinical symptoms, brain volume, and iron content in a subset of participants.
- Continued analysis at the 12-month time point, and further studies with larger participant cohorts and randomized controls, will be crucial in validating ATH434's efficacy.

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References
[1] Heras-Garvin, Mov Disord. 2022; [2]Finkelstein, J Parkinsons Dis. 2022; [3] Wenning, Mov Disord. 2004; [4] Payan, PLoS One. 2011; [5] Wenning, Lancet Neurol. 2013.