

ATH434 Demonstrates Disease-Modifying Signal in Multiple System Atrophy Using the MuSyCA Composite Scale

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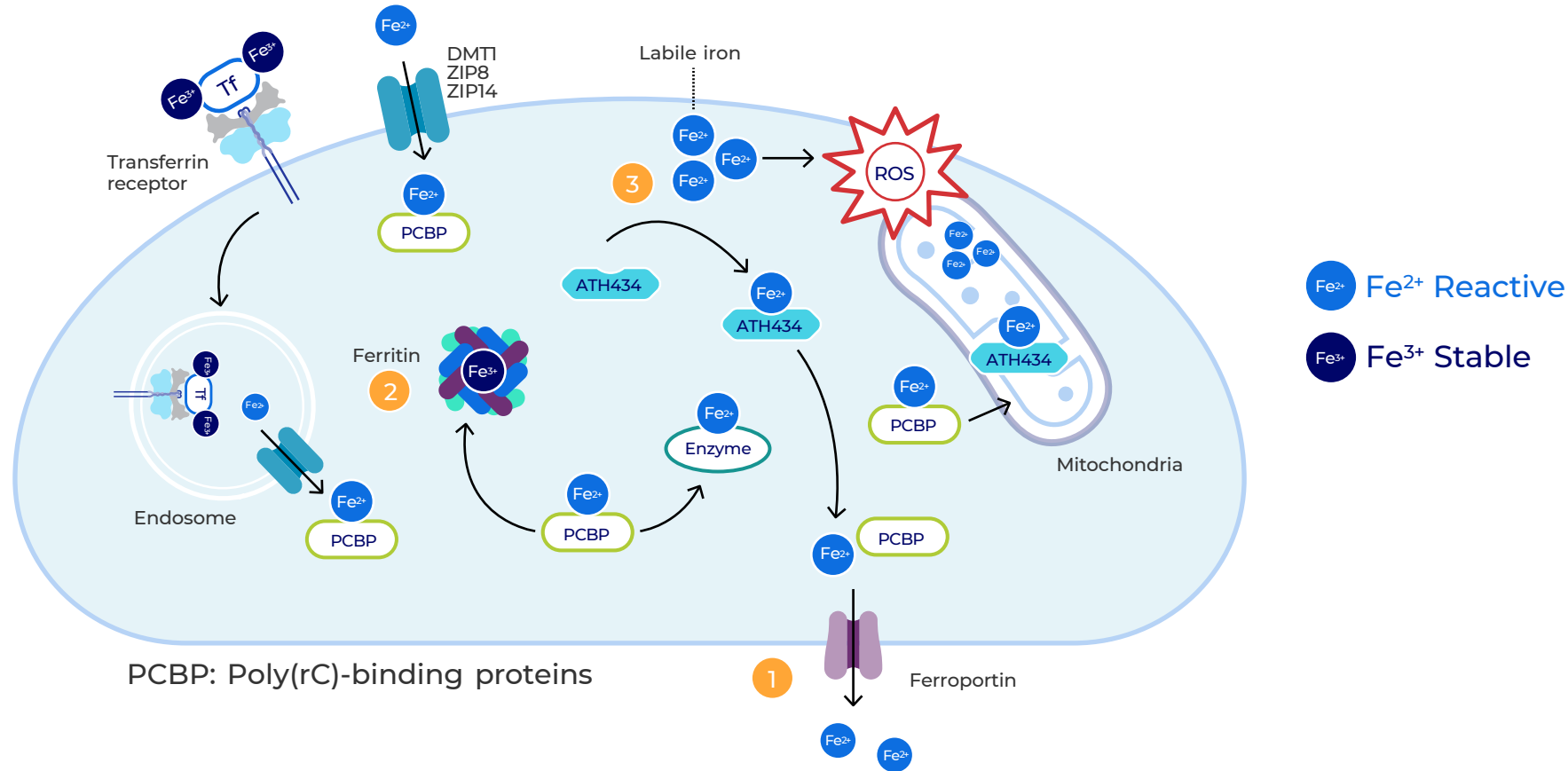
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ATH434 mechanism of action: Iron chaperone

ATH434 chaperones excess labile (reactive) iron to reduce neuronal injury



Chaperone mechanisms:

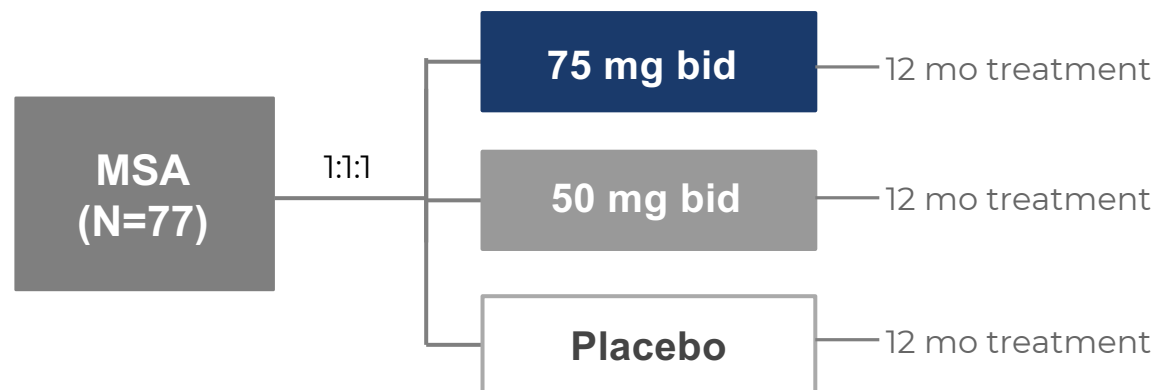
- 1 Efflux iron from cell (ferroportin)
- 2 Increase iron storage (ferritin)
- 3 Buffering Fe^{2+} in labile iron pool

- Labile iron essential for key cellular functions
- Iron accumulation occurs in MSA affected brain areas
 - Indicative of impaired iron trafficking
- Excess labile iron drives pathology in CNS
 - α -synuclein aggregation
 - Oxidative injury
- ATH434: Iron chaperone that redistributes excess labile iron



Sources: Finkelstein, et al. Acta Neuropath Comm. 2017; Bailey et al. Society for Neurosci 2023; Pall et al, Metallomics 2024

ATH434-201 Study Design



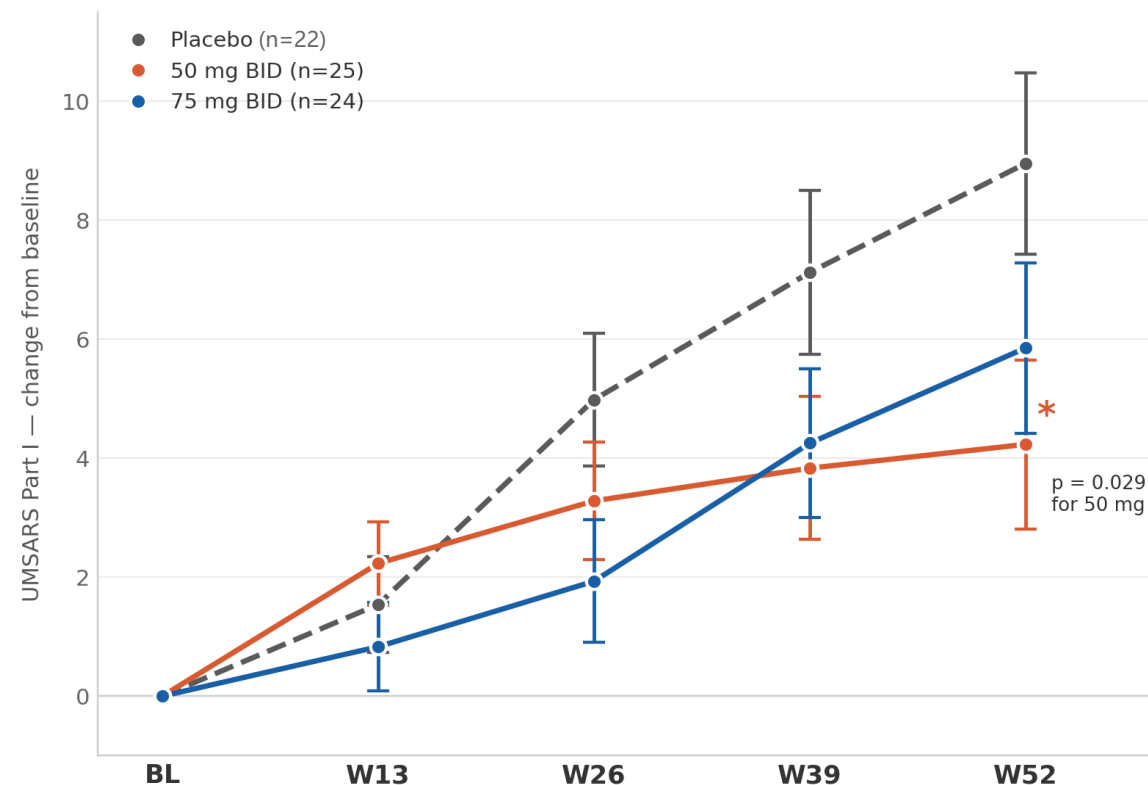
- Clinical diagnosis of MSA
- Motor symptoms ≤ 4 years
- Elevated plasma NfL
- MRI evidence of $\uparrow$ Iron (QSM)

Key Clinical Endpoint

- 11-item[†] UMSARS I: BL, Wk 13, 26, 39 and 52

[†]Excluding sexual function item

11-item UMSARS I



Dose	LS Mean Difference vs. Placebo	Relative Treatment Effect*
50 mg	-4.7	53%
75 mg	-3.1	35%

* $(\text{Change}_{\text{ath434}} - \text{Change}_{\text{placebo}}) / \text{Change}_{\text{placebo}} \cdot \text{mITT} \cdot \text{MMRM} \cdot \text{CSF NfL-adjusted}$

Background: Limitations of UMSARS & Need for MuSyCA

MSA is rapidly progressive with no approved disease-modifying therapy · Current outcome measures have key limitations for clinical trials

UMSARS: Unified MSA Rating Scale

Limitations of UMSARS Part I + II in Clinical Trials

- Floor and ceiling effects
 - Item redundancy
 - Limited responsiveness
 - No integration of biomarkers
-
- FDA focus on endpoints: How patients feel, function, or survive

MuSyCA: MSA COMBINED OUTCOME ASSESSMENT

MuSyCA is a multimodal scale including 11 items from UMSARS I and II relevant to disease progression

UMSARS I: Functional assessment

6 UMSARS-I items : swallowing, handwriting, utensils, dressing, hygiene, walking

UMSARS II: Neurological Exam

5 UMSARS-II items: speech, leg agility, arising from chair, body sway, gait

MuSyCA range: 0–44 · Development supported by NIH U01NS122419 ·
Validation ongoing through 2027

Baseline Characteristics

ATH434-201 · Clinical Analysis Population

	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 I	16.9 (3.9)	15.2 (5.4)	14.4 (4.4)
MuSyCA baseline	17.9 (4.98)	15.8 (6.66)	14.9 (5.51)
Motor score, Parkinson Plus Scale	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 hypotension	4.5%	4.0%	29.2%

Values are mean (SD) unless otherwise noted. OH = orthostatic hypotension; SAA = seed aggregation assay; NfL = neurofilament light chain.

Results: Change in MuSyCA over 52 weeks

Change from baseline in MuSyCA score · ANCOVA analysis · Weeks 26 and 52

MuSyCA CHANGE FROM BASELINE — ANCOVA		
	Week 26	Week 52
Placebo (n=22) LSM Change from BL (SE)	+6.1 (1.21)	+9.7 (1.38)
ATH434 50mg (n=25) Treatment effect vs PBO LSM Difference (SE)	-2.2 (1.57) p=0.166	-4.0 (1.82) p=0.034
ATH434 75mg (n=24) Treatment effect vs PBO LSM Difference (SE)	-2.7 (1.64) p=0.099	-1.9 (1.94) p=0.322

KEY FINDINGS

41%

reduction in functional decline
ATH434 50mg vs placebo at Week 52

p=0.034

Statistically significant treatment
effect at Week 52 for 50mg dose

+9.7 pts

Placebo progression confirms MuSyCA
sensitivity to detect disease change

SE = standard error · BL = baseline · ANCOVA adjusted for baseline MuSyCA score and CSF NfL

Conclusions

1 MuSyCA demonstrated robust sensitivity to disease progression

Placebo participants progressed approximately +10 MuSyCA points over 52 weeks, confirming the scale captures clinically meaningful change

2 ATH434 slows functional decline on MuSyCA

Treatment effect of -2 to -4 points at Week 52. Slowing functional decline in this rapidly progressive disorder. Comparable efficacy to that observed on 11-item UMSARS I, the functional measure endorsed by FDA and EMA

3 MuSyCA represents a new concept for outcomes in MSA

Assessment that combines patient-reported function, clinical assessment. Future efforts may incorporate other quantitative biomarkers (NfL and imaging), and objective performance tests — provides a comprehensive platform for disease-modification claims.

4 Results support ATH434 as a potential disease-modifying therapy for MSA

The significant Week 52 signal provides a compelling rationale for Phase 3 evaluation (ATH434-301)

Kaufmann H, Palma JA, Millar Verneti P, et al. for the MuSyCA Working Group · Clin Auton Res 2026 · DOI: 10.1007/s10286-026-01192-6