

# Topline Data from a Randomized, Double Blind, Placebo Controlled Phase 2 Study of ATH434 in MSA

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# Disclosures

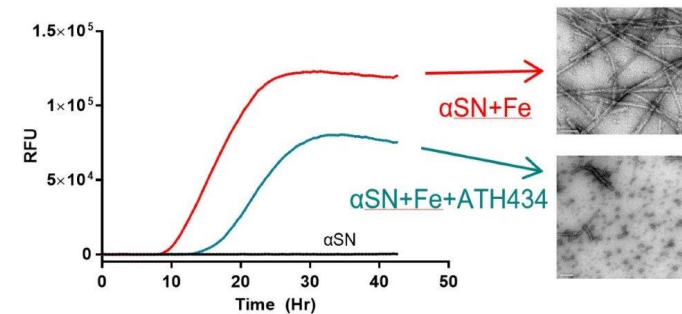
Authors are either employees of Alterity Therapeutics or received research support for their participation in the study.



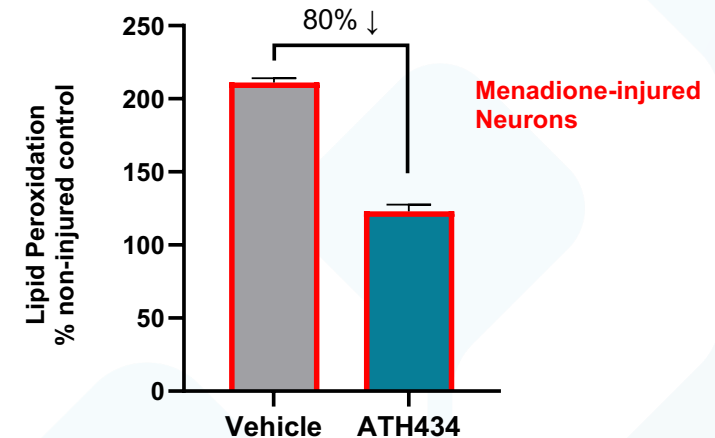
# Background

- Labile iron essential for key cellular functions
- Excess labile iron promotes
  - Alpha-synuclein aggregation
  - Oxidative injury
- MSA associated with reduced ability to control levels of labile iron
  - Iron accumulation in areas of pathology
- ATH434: Orally administered iron chaperone that redistributes excess labile iron in CNS
  - Reduces  $\alpha$ -synuclein aggregation in vitro and in vivo
  - Reduces oxidative injury by ~80%
  - Efficacy demonstrated in MSA and PD animal models

## ATH434 Reduces $\alpha$ -synuclein Aggregation



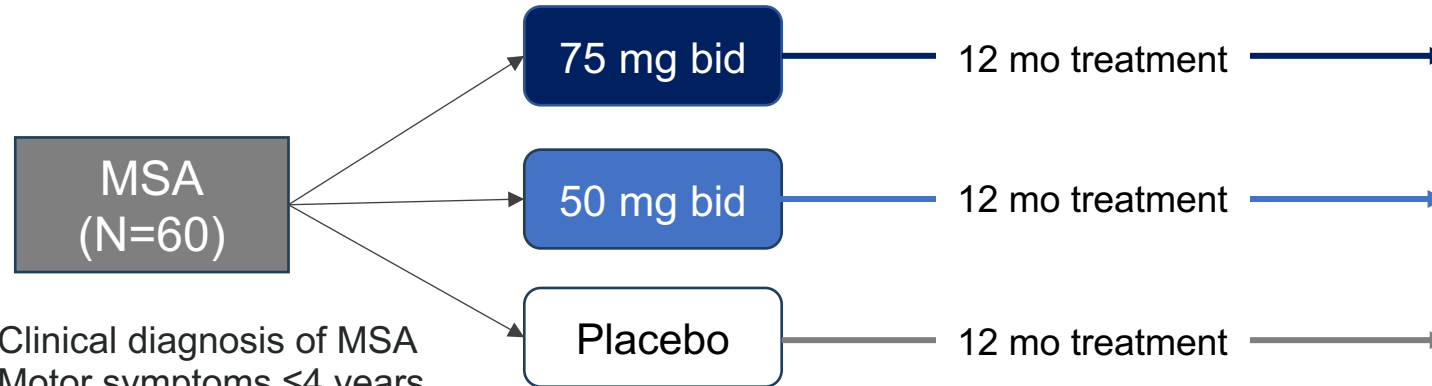
## ATH434 Reduces Oxidative Injury



# Study Objectives

- Evaluate the efficacy, biomarker response, and safety of ATH434 treatment in MSA patients

# ATH434-201 Study Design



- Clinical diagnosis of MSA
- Motor symptoms  $\leq 4$  years
- Elevated plasma NfL
- No severe impairment

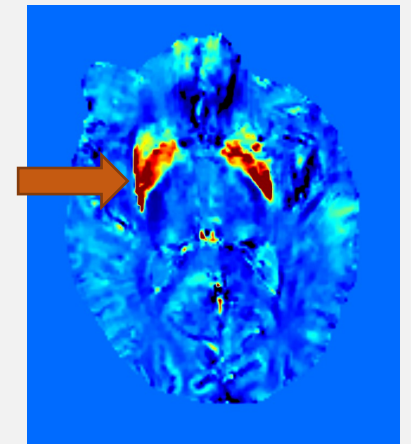
## Visit Schedule

- Clinic visits at Weeks 2, 6, 13, 21, 26, 39, 47, and 52

## Assessments for Efficacy/Target engagement

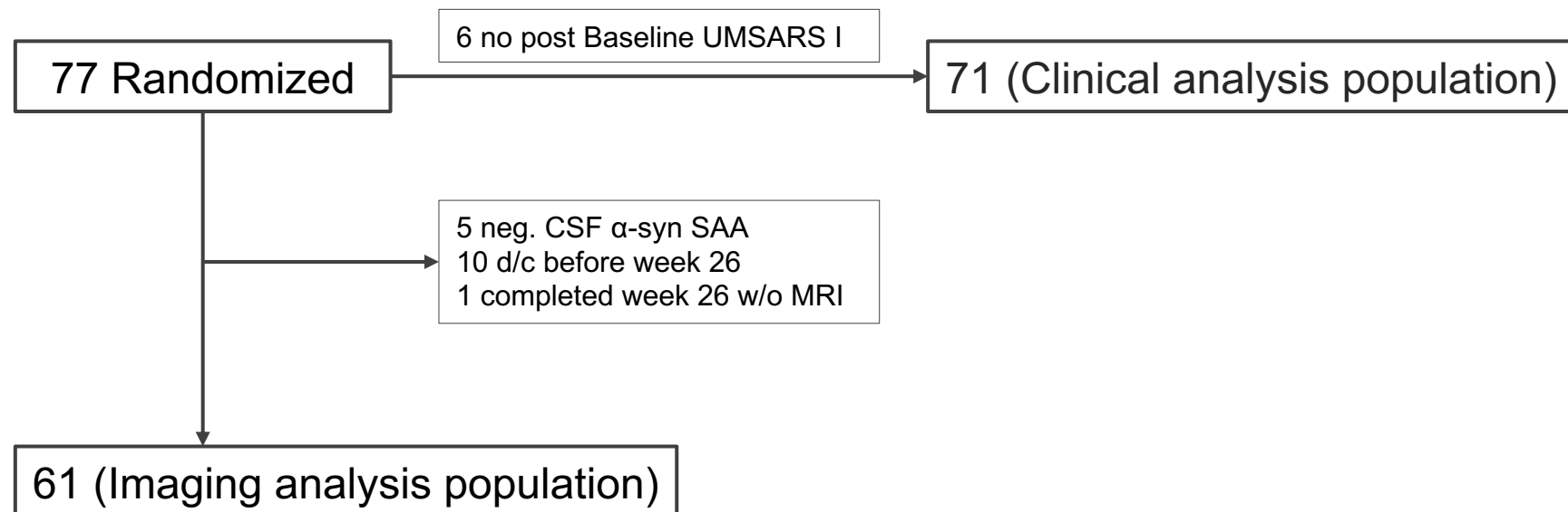
- MRI: Screening, Weeks 26 and 52
- Alpha-syn SAA (CSF): Screening, Weeks 26 and 52
- UMSARS I: Weeks 13, 26, 39 and 52
- CGI-S, OHSA, Wearables: Weeks 13, 26, 39 and 52

## Quantitative MRI to measure iron levels



MSA patient

# 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)

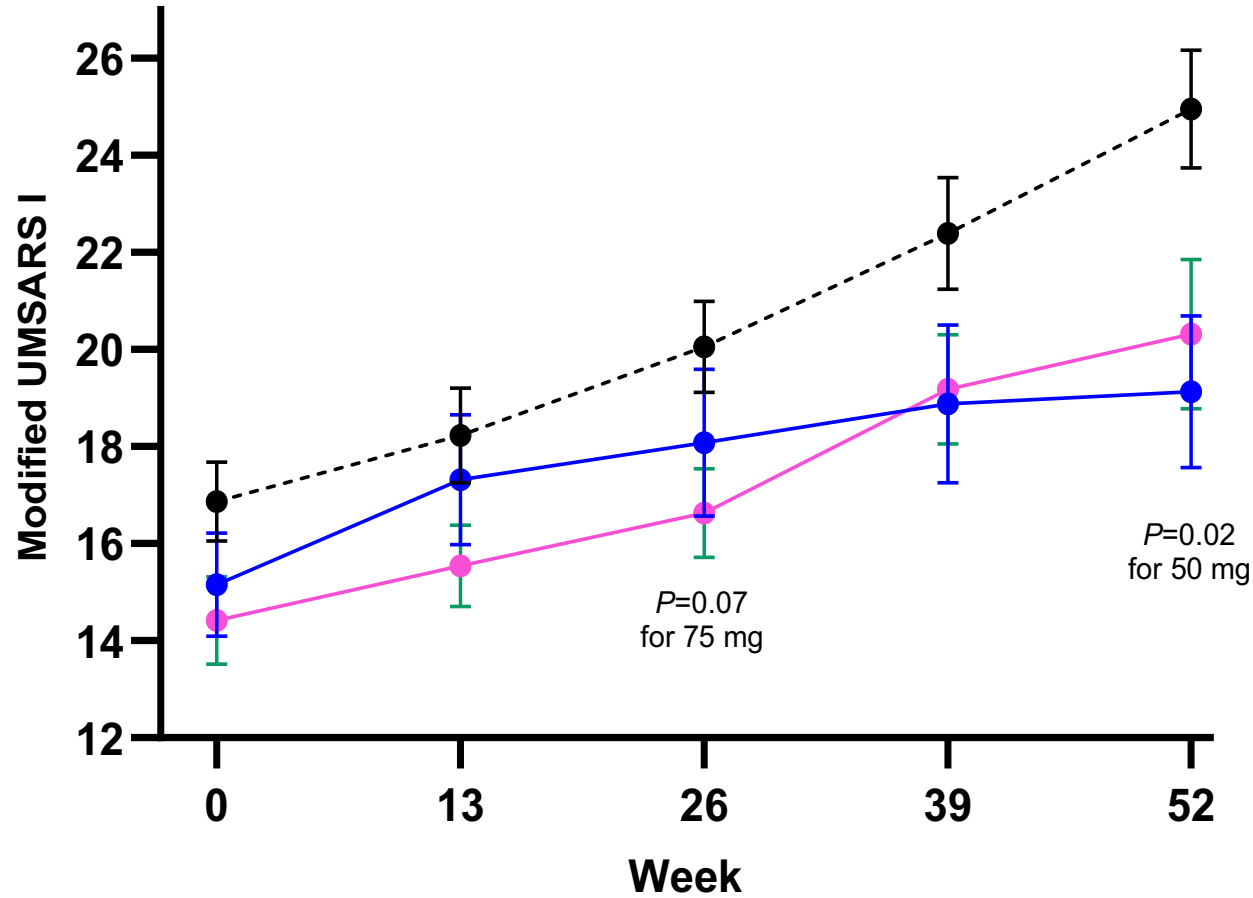
\* All patients in Imaging and Clinical analysis populations were randomized and treated

# Baseline Characteristics

Parameter	Placebo (n = 19)	50mg BID (n = 21)	75mg BID (n = 21)	Overall (n = 61)
Age (y)	61.5 (7.0)	62.9 (6.3)	64.0 (6.3)	62.8 (6.5)
Gender (% male)	63.2%	57.1%	57.1%	59.0%
Race (% white)	94.7%	81.0%	95.2%	90.2%
Modified UMSARS I	16.8 (4.2)	15.4 (4.6)	14.4 (4.7)	15.5 (4.5)
NNIPPS Motor score	57.9 (15.2)	48.6 (16.0)	49.1 (17.7)	51.7 (16.6)
NfL (plasma), pg/mL	35.4 (12.0)	31.7 (8.9)	32.4 (9.6)	33.1 (10.1)
Duration of motor symptoms (y)	2.6 (0.9)	2.6 (0.9)	2.4 (0.9)	2.5 (0.9)
Radiographic phenotype (% SND)	68.4%	52.4%	66.7%	62.3%
Severe nOH at Baseline	5.3%	4.8%	28.6%	13.1%

Mean (SD)

# Modified UMSARS Part I



↑  
Worsening

- Placebo (n=22)
- ATH434 50 mg BID (n=25)
- ATH434 75 mg BID (n=24)

Relative Treatment Effect* vs Placebo at 52 weeks	
50 mg bid	48%
75 mg bid	30%

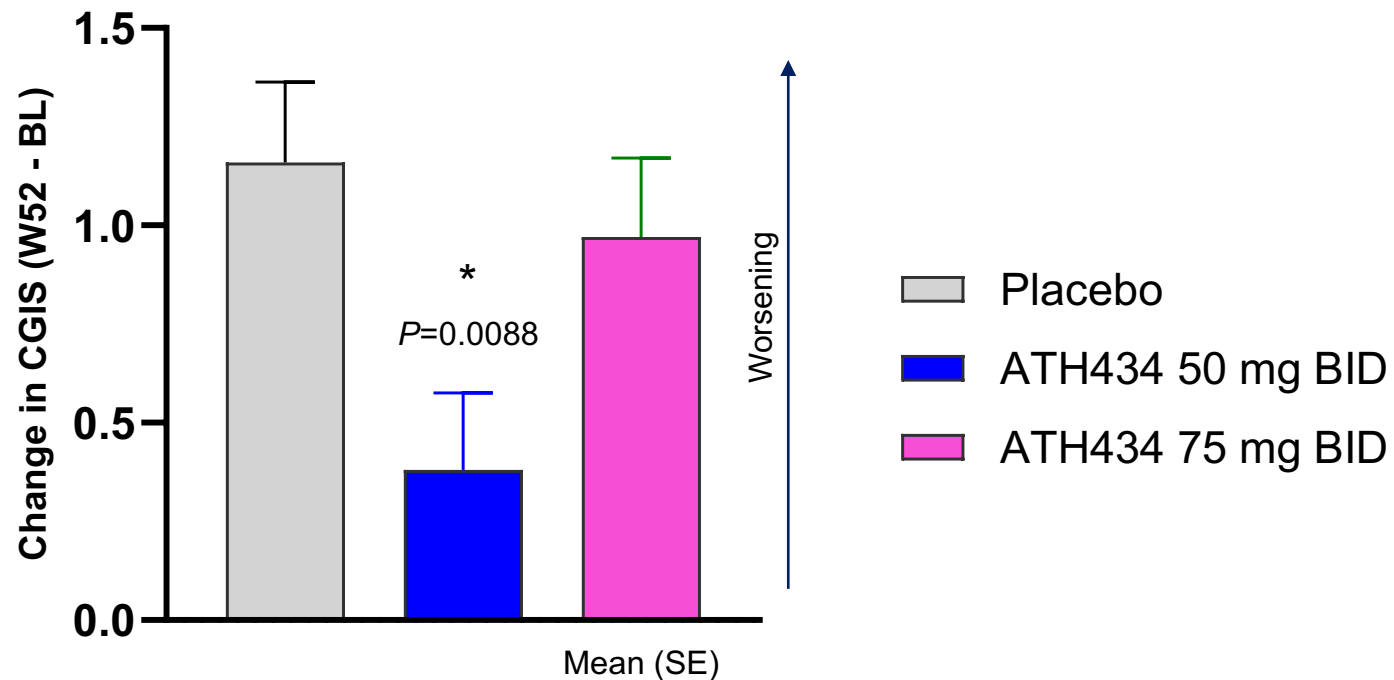
$$* \frac{\text{Change}_{\text{ATH434}} - \text{Change}_{\text{Placebo}}}{\text{Change}_{\text{Placebo}}}$$

Clinical Analysis Population



# Clinical Global Impression of Severity

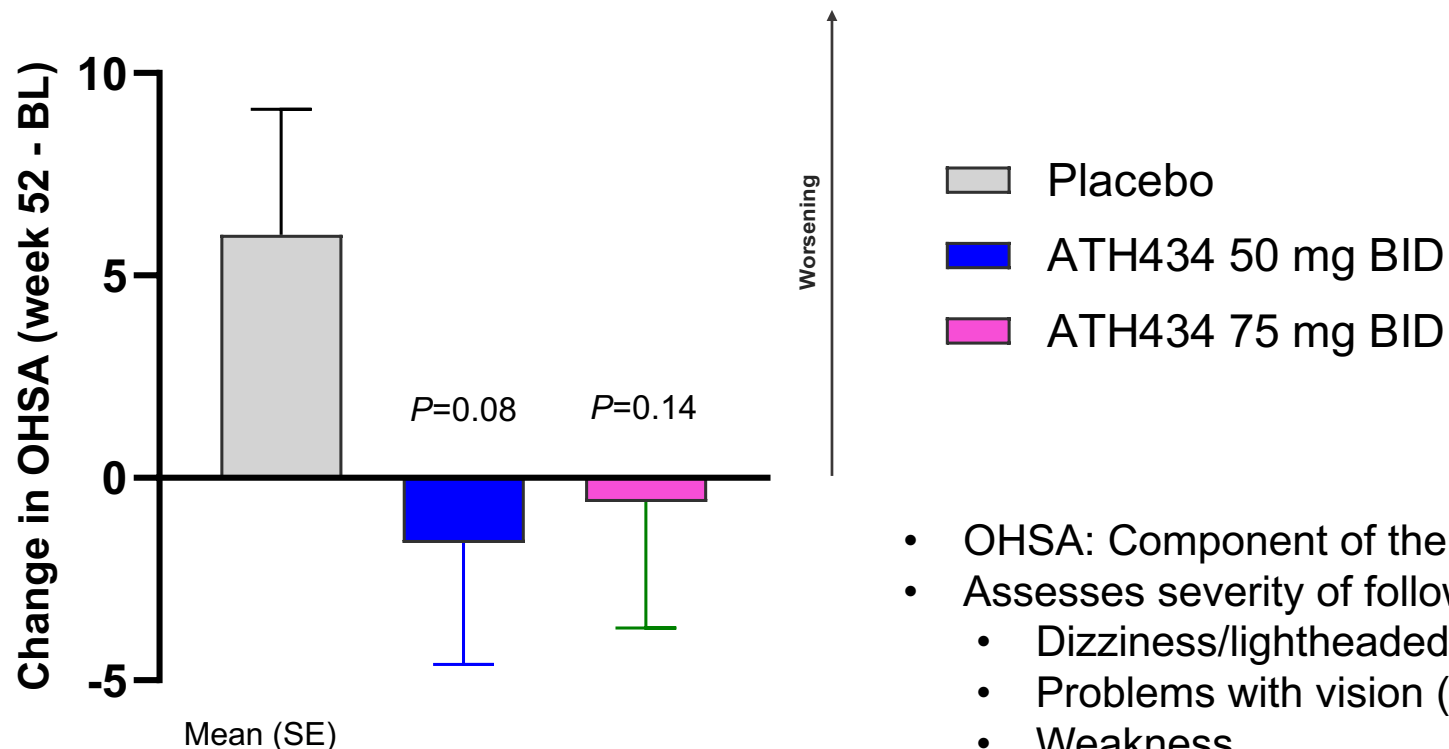
## Change from Baseline to Week 52



- 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 subject over the prior 28 days: illness severity, impact of illness on function, level of distress and any other aspects of impairment.

# Orthostatic Hypotension Symptom Assessment (OHSA)

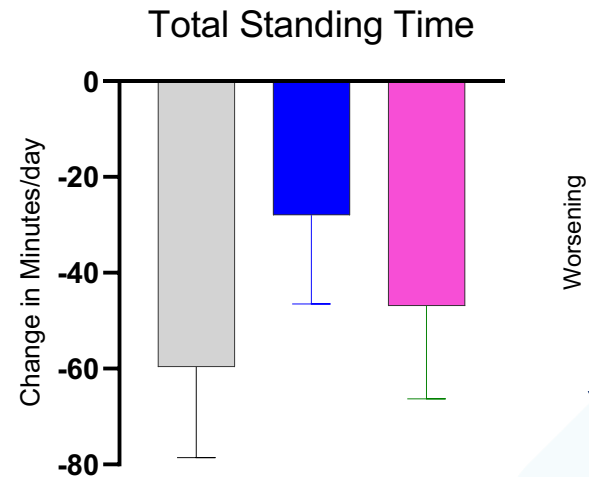
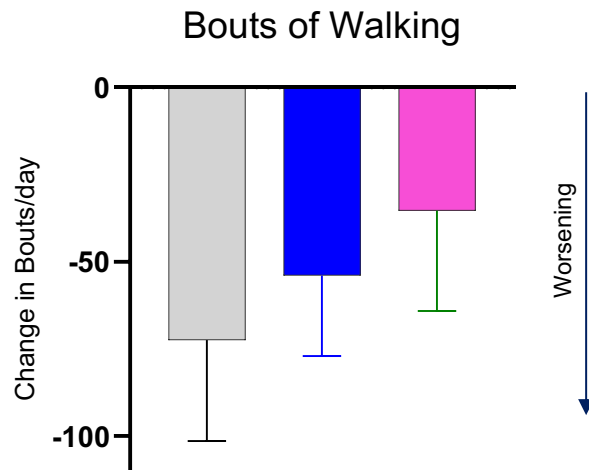
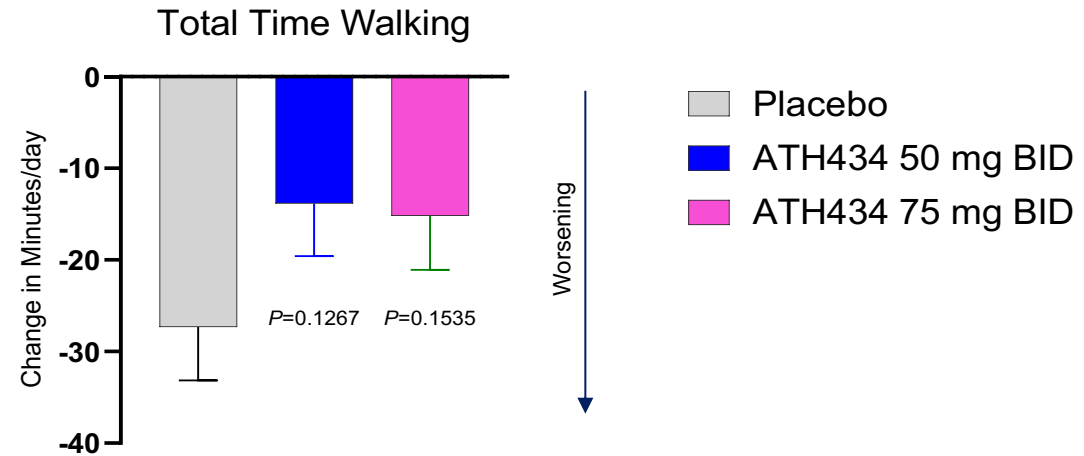
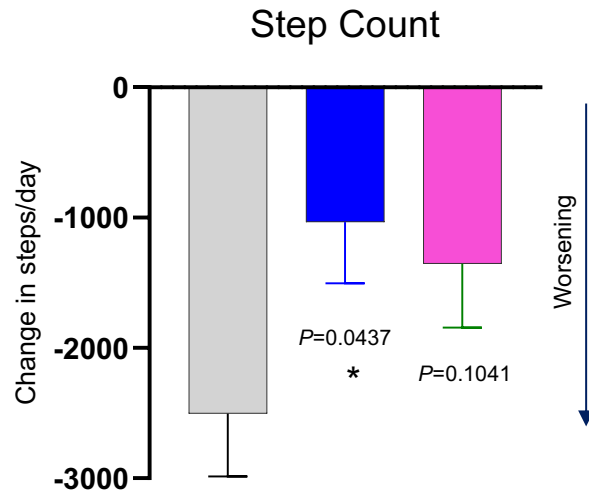
## Change from Baseline to Week 52



- OHSA: Component of the Orthostatic Hypotension Questionnaire
- Assesses severity of following
  - Dizziness/lightheadedness/feeling faint/feeling like blacking out
  - Problems with vision (blurry, seeing spots, tunnel vision)
  - Weakness
  - Fatigue
  - Concentration
  - Head and neck discomfort

# Wearable Sensors: Activity in Outpatient Setting

## Change from Baseline to Week 52



Legend:

- Placebo
- ATH434 50 mg BID
- ATH434 75 mg BID

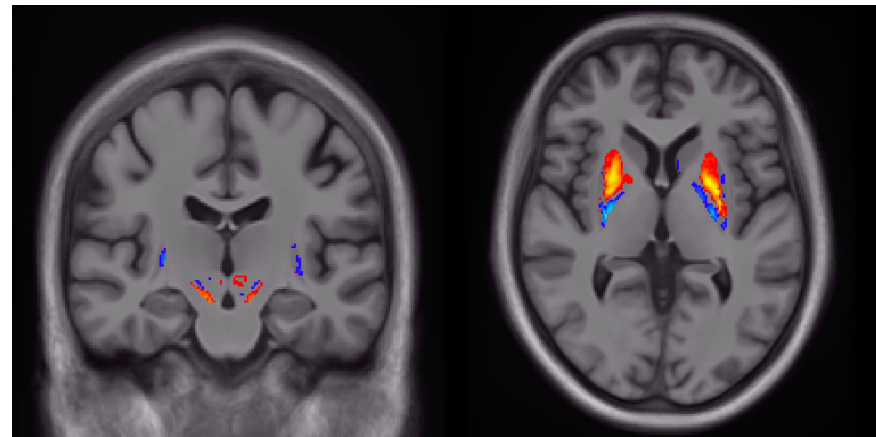
Clinical Analysis Population

Mean (SE)

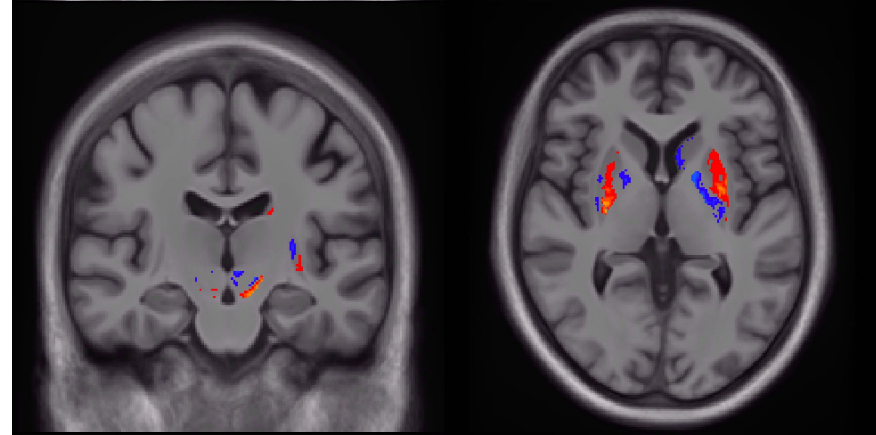
# Group Change in Iron Content (Week 52 – Baseline)

- No statistically significant changes to iron levels in predefined ROI (s. nigra)
- Evidence for reduced iron in globus pallidus
- Iron increases in key regions over time in placebo > ATH434

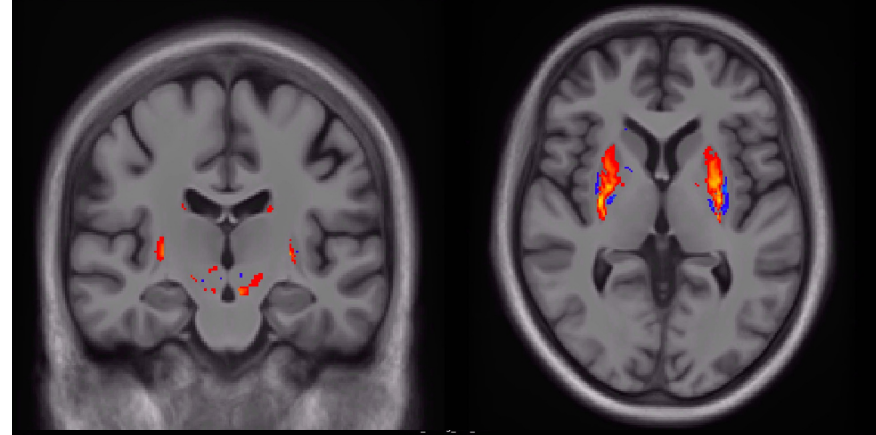
Placebo



50 mg bid

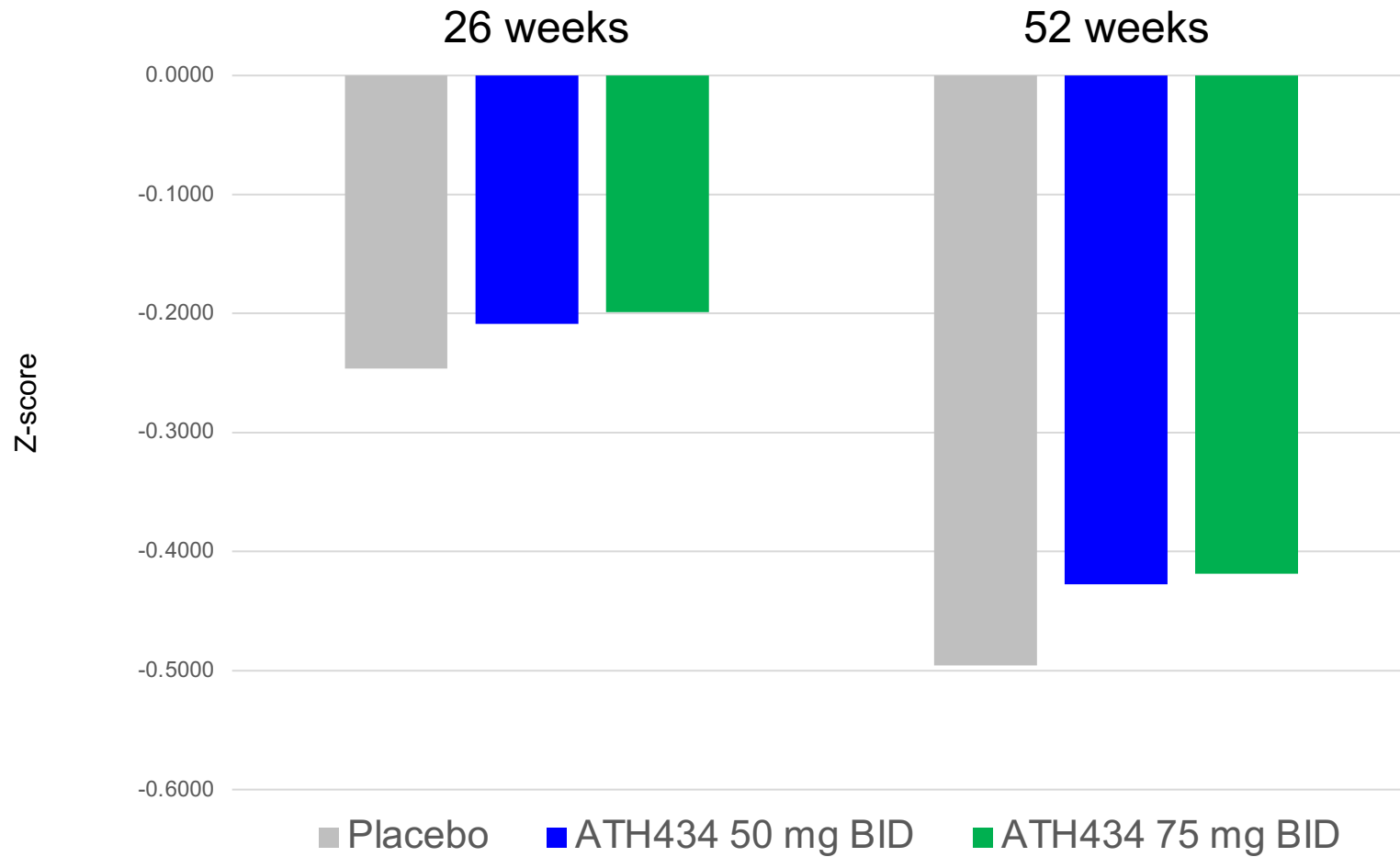


75 mg bid



# ATH434 Demonstrated Trends in Reduced Brain Atrophy

Change from Baseline in Brain Volume – MSA Atrophy Index<sup>^</sup>



<sup>^</sup> Composite z-score of the putamen, globus pallidus, cerebellum and brainstem regions vs. healthy age-matched population

# Summary of Adverse Events

Number (%) of Subjects <sup>1</sup>	Placebo BID (n=26)	50mg BID (n=25)	75mg BID (n=26)
Any Adverse Event (AE)	24 (92.3%)	21 (84.0%)	25 (96.2%)
AE by Severity			
Mild	10 (38.5%)	10 (40.0%)	8 (30.8%)
Moderate	6 (23.1%)	8 (32.0%)	11 (42.3%)
Severe	8 (30.8%)	3 (12.0%)	6 (23.1%)
Serious AEs <sup>2</sup>	10 (38.5%)	5 (20.0%)	7 (26.9%)

<sup>1</sup> Reporting one or more event

<sup>2</sup> None related to Study Drug

## Most frequent AEs

- UTI, fall, Covid-19, fatigue, back pain
- Similar rates across groups

# Conclusions

- ATH434 demonstrates clinically significant efficacy in modifying disease progression
  - UMSARS I and several additional clinical outcomes
- Study results support continued advancement of ATH434 for the treatment of MSA
- Baseline differences in pathology and disease severity may explain different response in ATH434 treatment groups
  - Analysis ongoing
- Imaging outcomes indicate heterogeneous localization of pathology
- ATH434 reduces iron signal in MSA affected brain regions
- Alpha-synuclein SAA requires continued refinement in MSA
- Results support further exploration of the role of excess labile iron in neurodegeneration

# Acknowledgements

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