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

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Disclosures

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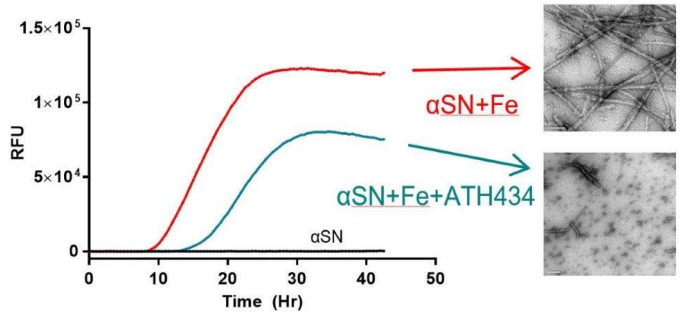
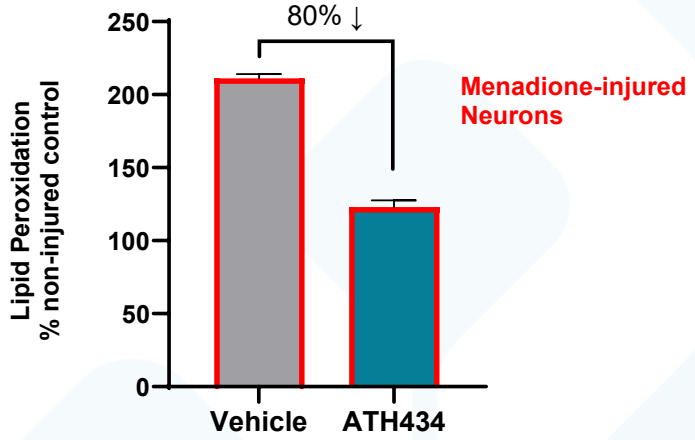
Background

- 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 α-synuclein aggregation in vitro and in vivo
  - Reduces oxidative injury by ~80%
  - Efficacy demonstrated in MSA and PD animal models

ATH434 Reduces α-synuclein Aggregation



ATH434 Reduces Oxidative Injury

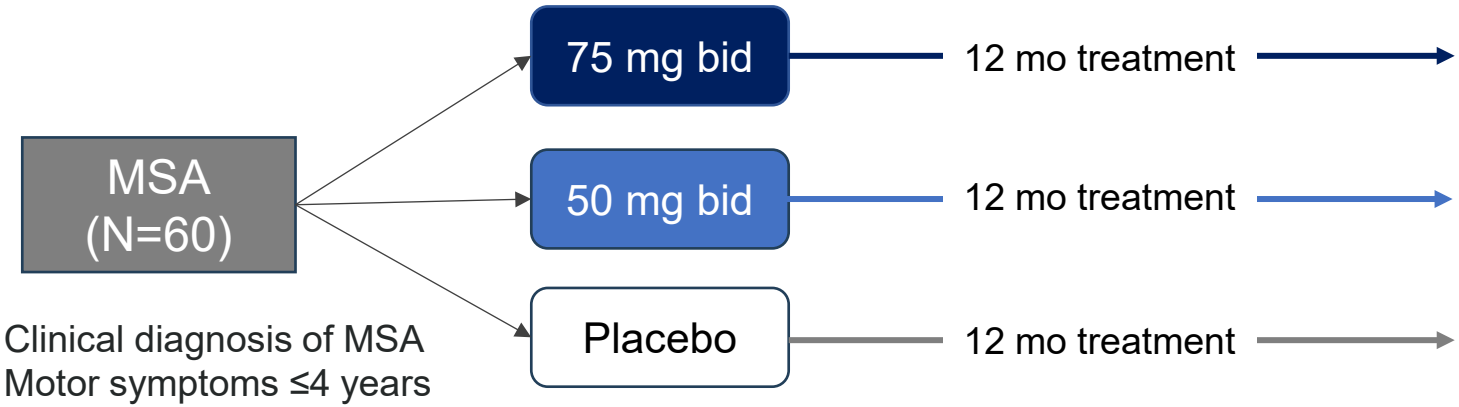


Sources: Finkelstein, et al. Acta Neuropath Comm. 2017; Bailey et al. Society for Neuroscience 2023

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 ≤4 years
- Elevated plasma NfL
- No severe impairment

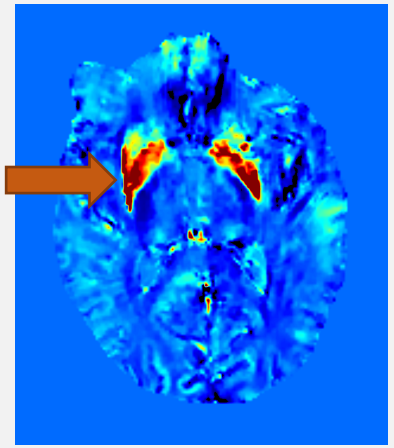
Visit Schedule

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

Assessments for Efficacy/Target engagement

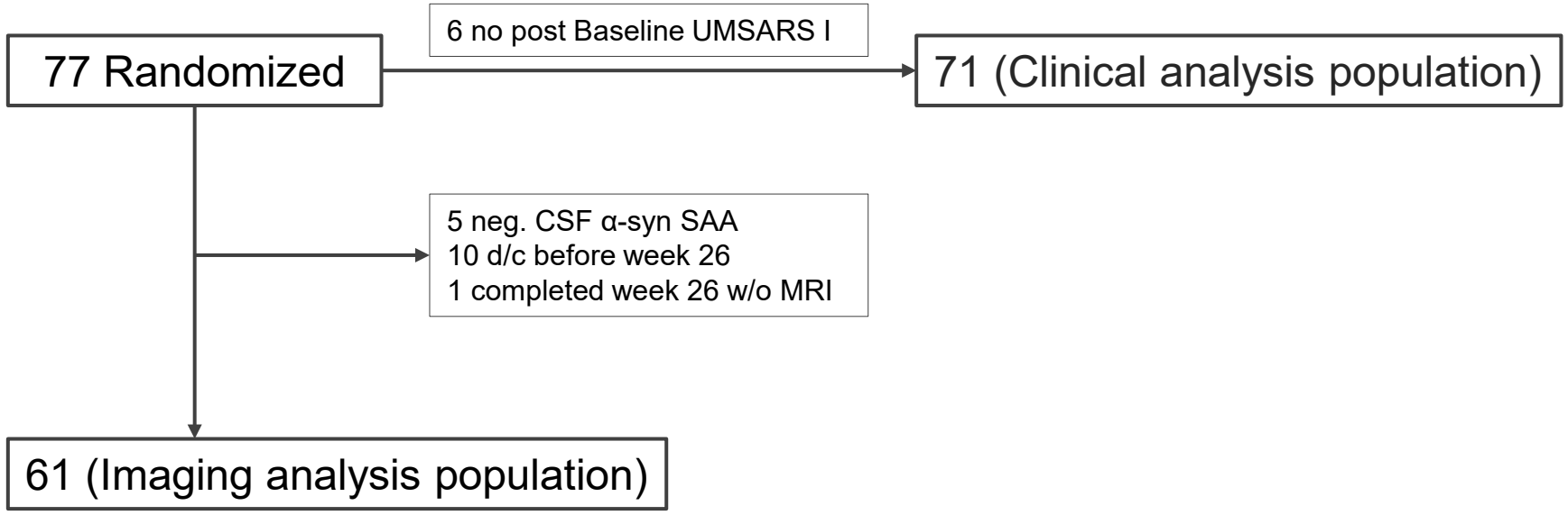
- MRI: Screening, Weeks 26 and 52
- Alpha-syn SAA (CSF): Screening, Weeks 26 and 52
- UMSARS I: Weeks 13, 26, 39 and 52
- CGI-S, OHSA, Wearables: Weeks 13, 26, 39 and 52

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)

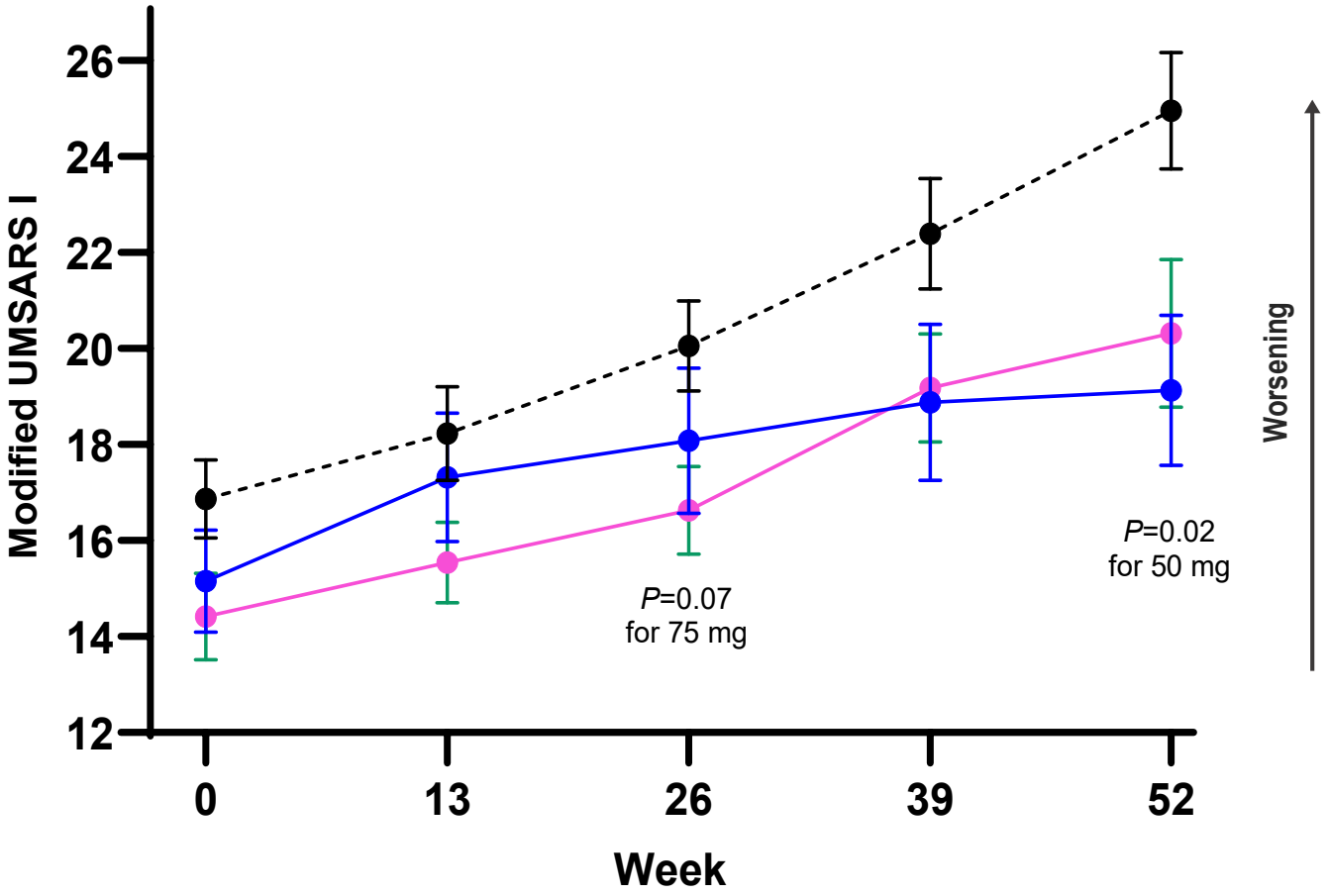
* All patients in Imaging and Clinical analysis populations were randomized and treated

Baseline Characteristics (mITT)

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



Placebo (n=22)

ATH434 50 mg BID (n=25)

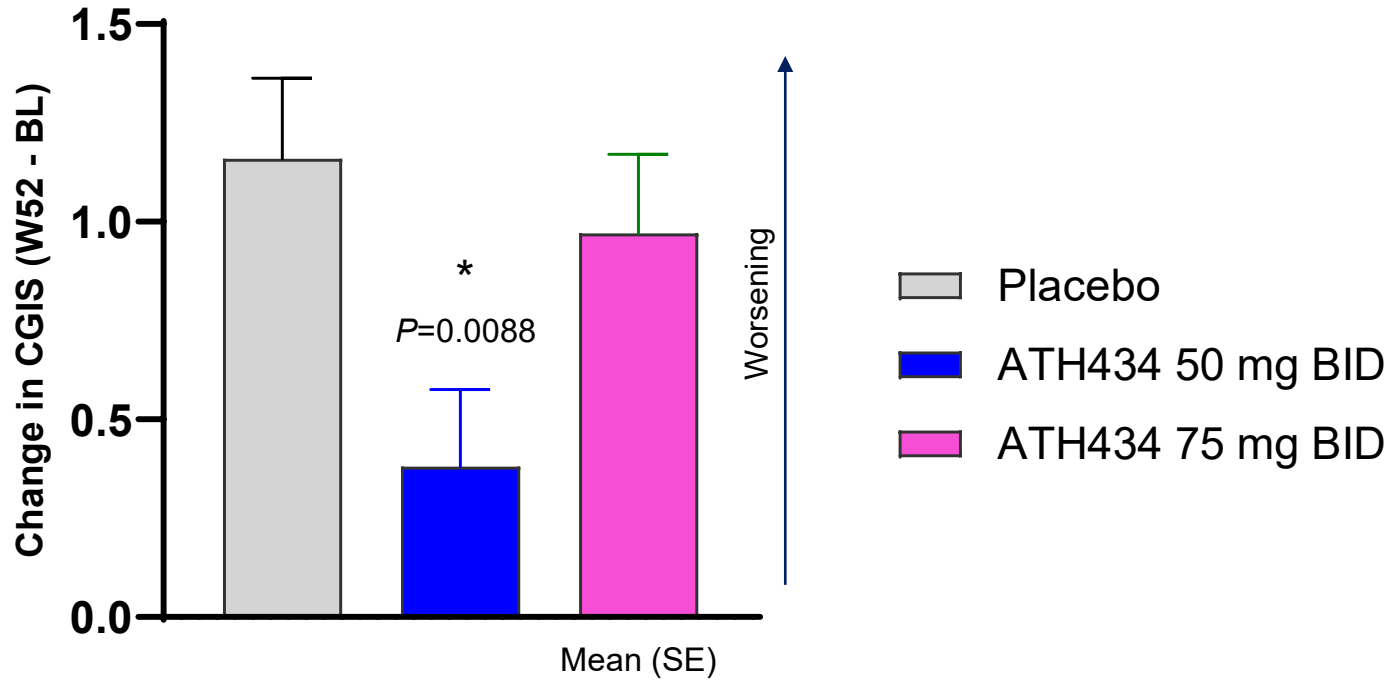
ATH434 75 mg BID (n=24)

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

$$* \frac{Change_{ATH434} - Change_{Placebo}}{Change_{Placebo}}$$

Clinical Analysis Population

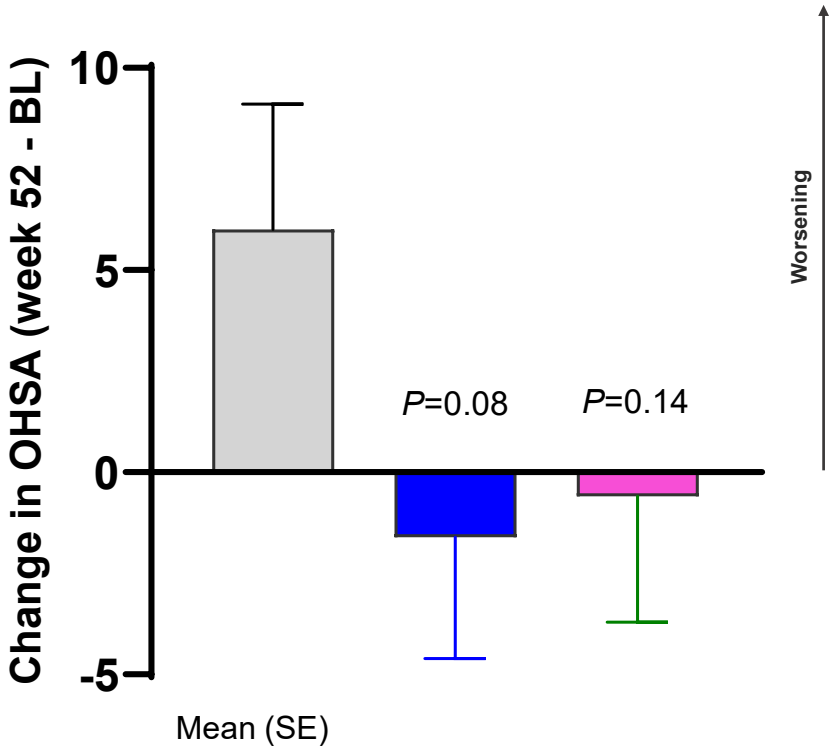
Clinical Global Impression of Severity
Change from Baseline to Week 52



- 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.

Clinical Analysis Population

Orthostatic Hypotension Symptom Assessment (OHSA)
Change from Baseline to Week 52



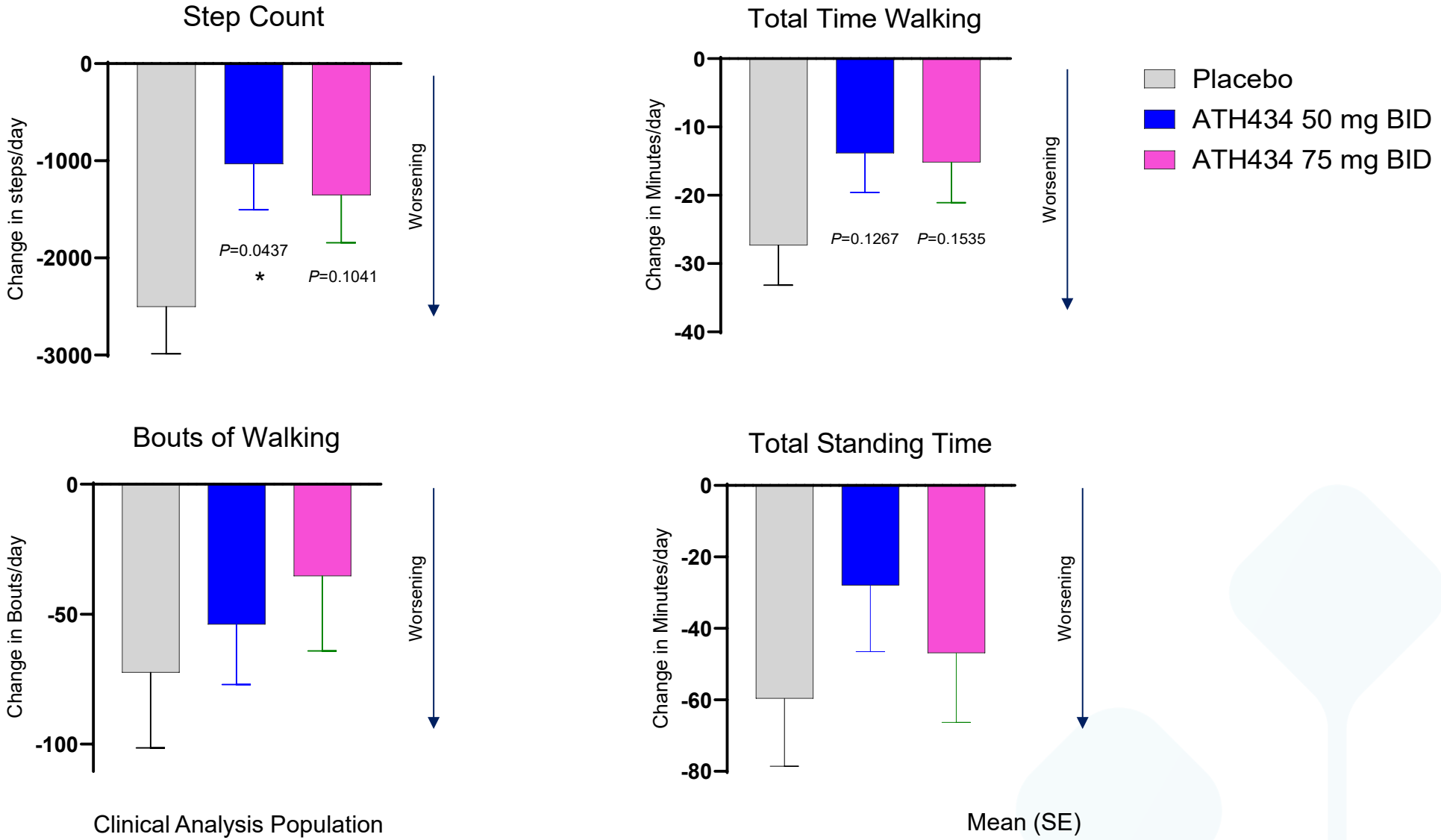
- Placebo
- ATH434 50 mg BID
- ATH434 75 mg BID

- 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

Clinical Analysis Population

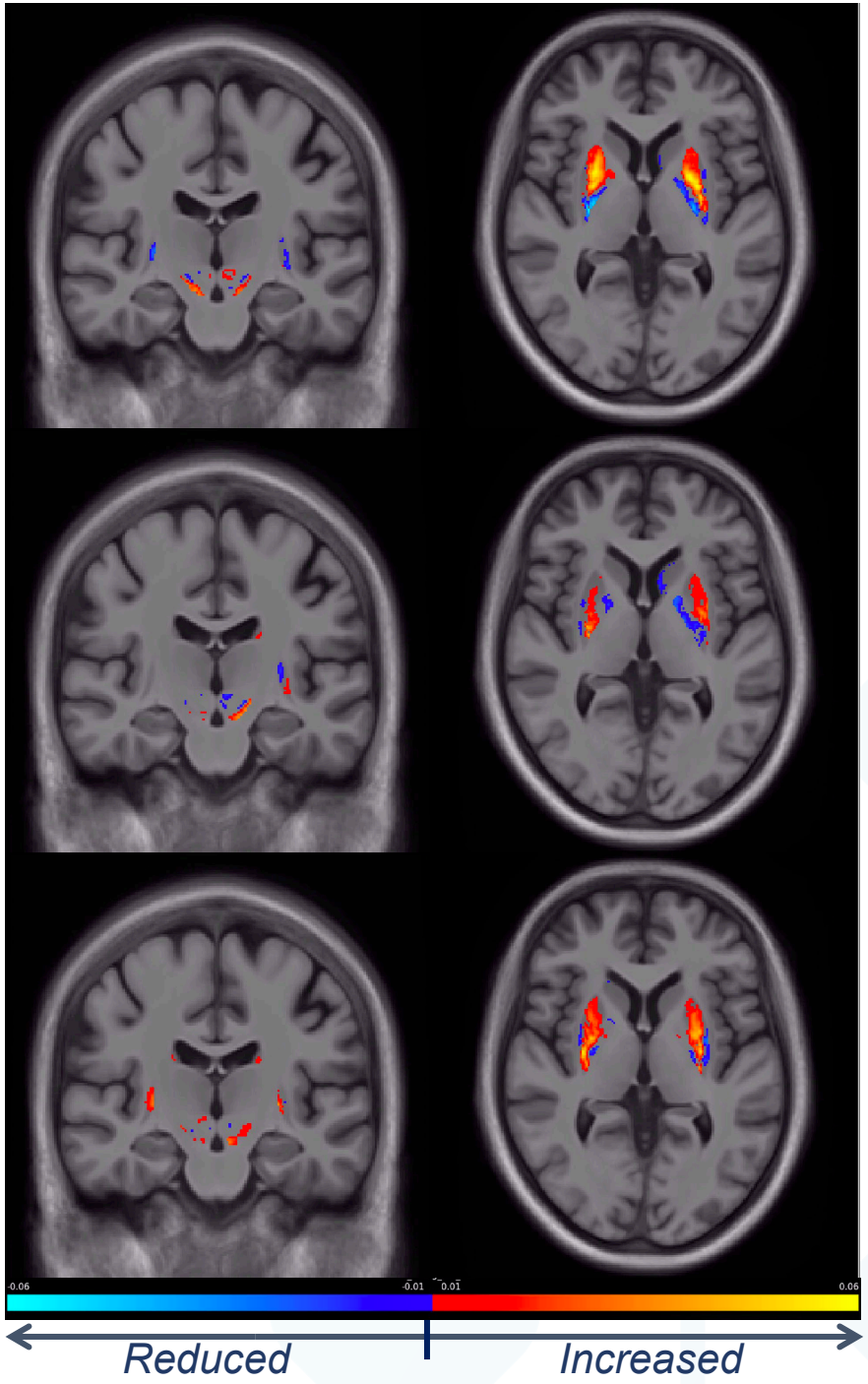
Kaufmann, et al. Clin Auton Res 2012

Wearable Sensors: Activity in Outpatient Setting
Change from Baseline to Week 52



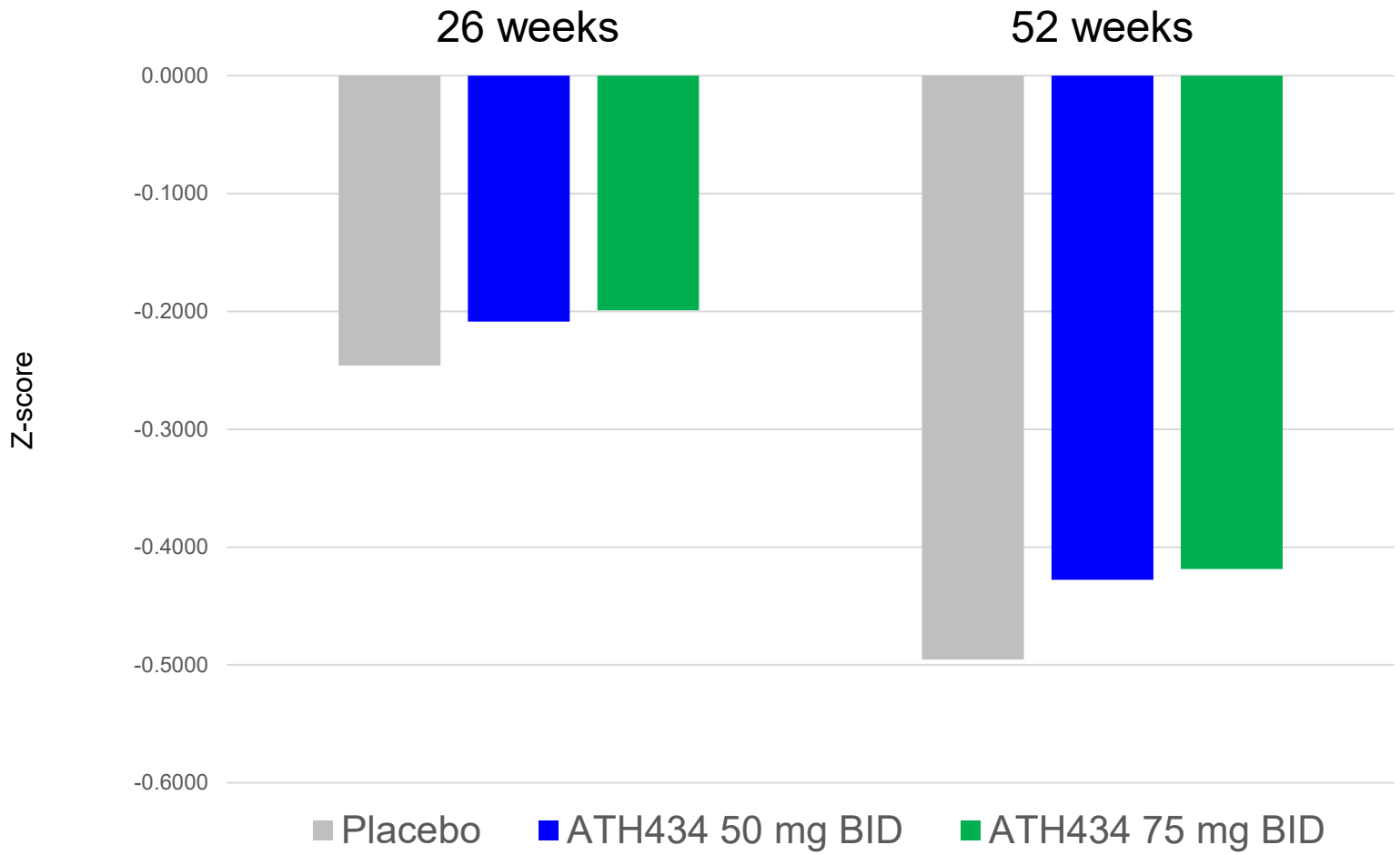
Group Change in Iron Content
(Week 52 − Baseline)

- 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



ATH434 Demonstrated Trends in Reduced Brain Atrophy

Change from Baseline in Brain Volume – MSA Atrophy Index^



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

Summary of Adverse Events

Number (%) of Subjects[1]	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[2]	10 (38.5%)	5 (20.0%)	7 (26.9%)

[1] Reporting one or more event
[2] None related to Study Drug

Most frequent Adverse Events

- 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

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