Alterity Therapeutics Presents ATH434-201 Phase 2 Clinical Trial Results at European MSA Symposium

MELBOURNE, AUSTRALIA AND SAN FRANCISCO, USA – 28 April 2025: Alterity Therapeutics (ASX: ATH, NASDAQ: ATHE) ("Alterity" or "the Company"), a biotechnology company dedicated to developing disease modifying treatments for neurodegenerative diseases, today announced that David Stamler, M.D., Chief Executive Officer presented the ATH434-201 Phase 2 clinical trial results at the annual MSA Research Symposium hosted by University College London, Institute of Neurology in partnership with the MSA Trust of the U.K.

"We were honoured to be selected to present the recent data from our double-blind Phase 2 trial," said, Dr. Stamler. "The Symposium brought together prominent clinicians and researchers from both Europe and the US along with industry scientists, all of whom are focused on increasing their understanding of MSA and advancing new therapies for this aggressive disorder. The strong clinical efficacy data and novel mechanism of ATH434 was well received by this esteemed group of clinicians and academics, as we collectively seek solutions to improve the lives of individuals living with MSA."

Presentation: A Randomized, Double Blind, Placebo Controlled Study of ATH434 in MSA

The oral presentation included data from Alterity's ATH434-201 Phase 2 clinical trial. The clinical analysis included 71 patients who had at least one post-baseline assessment of the key clinical endpoint, the modified UMSARS[1] I activities of daily living scale. On this endpoint, ATH434 demonstrated a clinically significant reduction in disease severity versus placebo, with a 48% relative treatment effect at the 50 mg dose (p=0.02)^ and a 30% relative treatment effect at the 75 mg dose (p=0.16) at 52 weeks. Additional efficacy assessments showed improvement consistent with the UMSARS I findings: the Clinical Global Impression of Severity Scale[2] demonstrated improvement compared to placebo at both dose levels, with difference at 50 mg achieving nominal statistical significance (p=0.0088). On the Orthostatic Hypotension Symptom Assessment (a patient reported outcome), on average placebo patients worsened by approximately 6 points over 52 weeks whereas both ATH434 treatment groups improved over the same period (p=0.08 at 50 mg, p=0.14 at 75 mg). Increased activity in the outpatient setting was observed at both dose levels as compared to placebo with wearable sensors, with clinically meaningful improvements in step count, bouts of walking, total walking time, and total standing time. ATH434 was well tolerated with similar adverse event rates compared to placebo and no serious adverse events attributed to ATH434. Regarding neuroimaging, ATH434 demonstrated target engagement by stabilizing or reducing iron at both dose levels compared to placebo in MSA affected brain regions. In addition, ATH434 demonstrated trends in reducing brain atrophy

at both dose levels compared to placebo. Overall, the study results support continued advancement of ATH434 for the treatment of MSA.

About ATH434

Alterity's lead candidate, ATH434, is an oral agent designed to inhibit the aggregation of pathological proteins implicated in neurodegeneration. ATH434 has been shown preclinically to reduce α-synuclein pathology and preserve neuronal function by restoring normal iron balance in the brain. As an iron chaperone, it has excellent potential to treat Parkinson's disease as well as various Parkinsonian disorders such as Multiple System Atrophy (MSA). ATH434 successfully completed Phase 1 studies demonstrating the agent is well tolerated and achieved brain levels comparable to efficacious levels in animal models of MSA. ATH434 recently announced positive results from the randomized, double-blind, placebo-controlled Phase 2 clinical trial in patients with early-stage MSA. A second Phase 2 open-label 2 Biomarker trial in patients with more advanced MSA is ongoing. ATH434 has been granted Orphan Drug Designation for the treatment of MSA by the U.S. FDA and the European Commission.

About ATH434-201 Phase 2 Clinical Trial

The ATH434-201 Phase 2 clinical trial is a randomized, double-blind, placebo-controlled investigation of 12 months treatment with ATH434 in patients with MSA. The study evaluated the efficacy, safety and pharmacokinetics of ATH434 as well as the effect of ATH434 on neuroimaging and protein biomarkers. Wearable sensors were employed to evaluate motor activities outside of the clinic. The study enrolled 77 adults who were randomly assigned to receive ATH434 50 mg or 75 mg twice daily or matching placebo. The topline data showed that ATH434 produced clinically and statistically significant improvement on the modified UMSARS Part I, a functional rating scale that assesses disability on activities of daily living affected in MSA. In addition to the robust efficacy demonstrated on the UMSARS Part I, trends in improved motor performance were observed on the Parkinson's Plus rating scale and overall benefit was shown on the Clinical Global Impression of Severity at the 50 mg dose. Wearable sensor data indicated that both dose levels of ATH434 led to increased activity in an outpatient setting as compared to placebo. Biomarkers were used to evaluate potential drug effect and target engagement. Both dose levels reduced iron accumulation in MSA affected brain regions and trends in preservation of brain volume were observed relative to placebo. Additional information on the Phase 2 trial can be found by ClinicalTrials.gov Identifier: NCT05109091.

About Multiple System Atrophy

Multiple System Atrophy (MSA) is a rare, neurodegenerative disease characterized by failure of the autonomic nervous system and impaired movement. The symptoms reflect the progressive loss of function and death of different types of nerve cells in the brain and spinal cord. It is a rapidly progressive disease and causes profound disability. MSA is a Parkinsonian disorder

characterized by a variable combination of slowed movement and/or rigidity, autonomic instability that affects involuntary functions such as blood pressure maintenance and bladder control, and impaired balance and/or coordination that predisposes to falls. A pathological hallmark of MSA is the accumulation of the protein α-synuclein within glia, the support cells of the central nervous system, and neuron loss in multiple brain regions. MSA affects at least 15,000 individuals in the U.S., and while some of the symptoms of MSA can be treated with medications, currently there are no drugs that are able to slow disease progression and there is no cure.[3]

About Alterity Therapeutics Limited

Alterity Therapeutics is a clinical stage biotechnology company dedicated to creating an alternate future for people living with neurodegenerative diseases. The Company is initially focused on developing disease modifying therapies in Parkinson's disease and related disorders. Alterity recently reported positive data for its lead asset, ATH434, in a Phase 2 clinical trial in participants with Multiple System Atrophy (MSA), a rare and rapidly progressive Parkinsonian disorder. ATH434 is also being evaluated in a Phase 2 clinical trial in advanced MSA. In addition, Alterity has a broad drug discovery platform generating patentable chemical compounds to treat the underlying pathology of neurological diseases. The Company is based in Melbourne, Australia, and San Francisco, California, USA. For further information please visit the Company's website at www.alteritytherapeutics.com.

References:

[1] UMSARS: Unified Multiple System Atrophy Rating Scale

^ All p-values are uncorrected

[2] Clinical Global Impression of Severity: a clinician assessment of the total picture of the subject including the impact of the illness on function and level of distress

[3] Multiple System Atrophy | National Institute of Neurological Disorders and Stroke (nih.gov)

Authorisation & Additional information

This announcement was authorized by David Stamler, CEO of Alterity Therapeutics Limited.

Investor and Media Contacts:

Australia
Millie Macdonald
Head of Investor Relations and Business Development
mmacdonald@alteritytherapeutics.com
+61 468 304 742

Ana Luiza Harrop
we-aualteritytherapeutics@we-worldwide.com
+61 452 510 255

U.S.
Remy Bernarda
remy.bernarda@iradvisory.com
+1 (415) 203-6386

Forward Looking Statements

This press release contains "forward-looking statements" within the meaning of section 27A of the Securities Act of 1933 and section 21E of the Securities Exchange Act of 1934. The Company has tried to identify such forward-looking statements by use of such words as "expects," "intends," "hopes," "anticipates," "believes," "could," "may," "evidences" and "estimates," and other similar expressions, but these words are not the exclusive means of identifying such statements.

Important factors that could cause actual results to differ materially from those indicated by such forward-looking statements are described in the sections titled "Risk Factors" in the Company's filings with the SEC, including its most recent Annual Report on Form 20-F as well as reports on Form 6-K, including, but not limited to the following: statements relating to the Company's drug development program, including, but not limited to the initiation, progress and outcomes of clinical trials of the Company's drug development program, including, but not limited to, ATH434, and any other statements that are not historical facts. Such statements involve risks and uncertainties, including, but not limited to, those risks and uncertainties relating to the difficulties or delays in financing, development, testing, regulatory approval, production and marketing of the Company's drug components, including, but not limited to, ATH434, the ability of the Company to procure additional future sources of financing, unexpected adverse side effects or inadequate therapeutic efficacy of the Company's drug compounds, including, but not limited to, ATH434, that could slow or prevent products coming to market, the uncertainty of obtaining patent protection for the Company's intellectual property or trade secrets, the uncertainty of successfully enforcing the Company's patent rights and the uncertainty of the Company freedom to operate.

Any forward-looking statement made by us in this press release is based only on information currently available to us and speaks only as of the date on which it is made. We undertake no obligation to publicly update any forward-looking statement, whether written or oral, that may be made from time to time, whether as a result of new information, future developments or otherwise.

A Randomized, Double Blind, Placebo Controlled Phase 2 Study of ATH434 in Multiple System Atrophy

David Stamler[1], Cynthia Wong[1], Paula Trujillo[2], Margaret Bradbury[1], Christine Lucas[1] and Daniel Claassen[2]

[1] Alterity Therapeutics, Newark, CA, USA

[2] Department of Neurology, Vanderbilt University Medical Center, Nashville, TN, USA

MSA Trust Symposium – London (UCL)

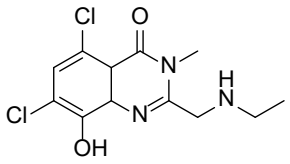
25 April 2025

Disclosures

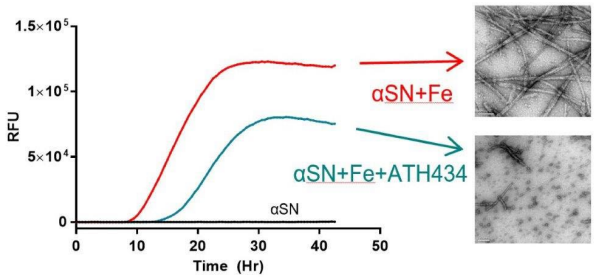
The authors are either employees of Alterity Therapeutics or received research support for their participation in the study.

Study Rationale

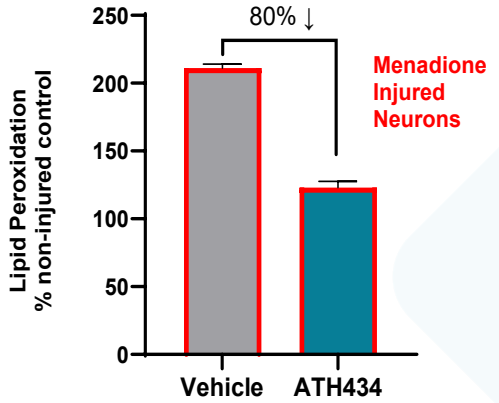
- Labile iron essential for key cellular functions
- Iron accumulation occurs in MSA affected brain areas (putamen, pallidum, s. nigra)
  - Indicative of impaired iron trafficking
- Excess labile iron promotes
  - Alpha-synuclein aggregation
  - Oxidative injury
- ATH434: Iron chaperone that redistributes excess labile iron in CNS
  - Oral agent (twice-daily)
  - Reduces α-synuclein aggregation in vitro/in vivo
  - Reduces oxidative injury by ~80%
  - Efficacy in MSA and PD animal models



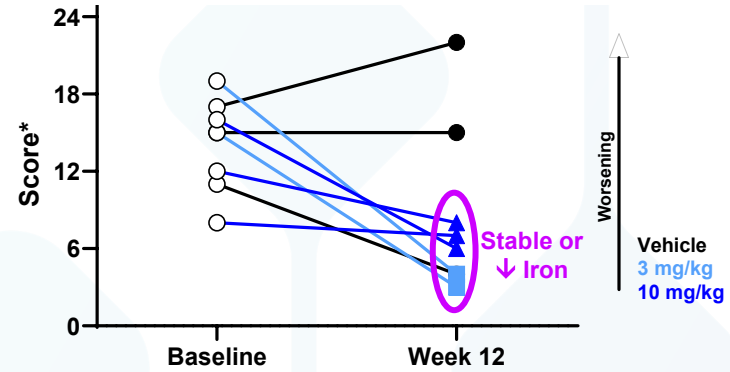
ATH434 Reduces α-syn Aggregation



ATH434 Reduces Oxidative Injury



ATH434 Efficacy in Primate PD model



* Parkinson Behavior Rating Scale Subgroup 1 (0– 32)

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

The Relevance of Iron in the Pathogenesis of Multiple System Atrophy: A Viewpoint

Christine Kaindlstorfer[a], Kurt A. Jellinger[b], Sabine Eschlböck[a], Nadia Stefanova[a], Günter Weiss[c] and Gregor K. Wenning[a,*]

- Histopathology data
- MRI data

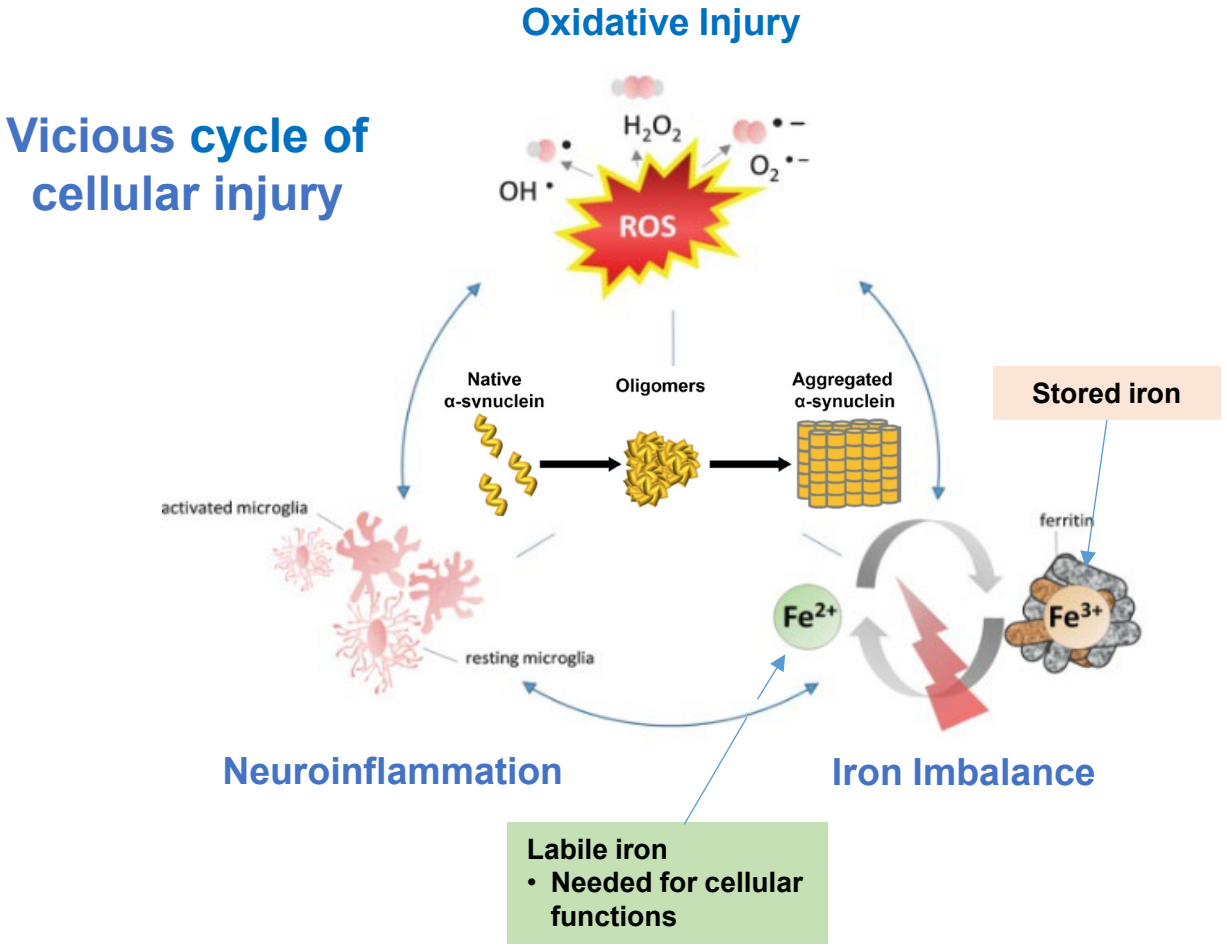
The Irony of Iron: The Element with Diverse Influence on Neurodegenerative Diseases

Seojin Lee [1,2] and Gabor G. Kovacs [1,2,3,*]

The close association of iron accumulation with distinct α-synuclein-pathology-related anatomical regions of the two disease subtypes supports the critical involvement of pathological iron in disease progression…

doi 10.3233/JAD-170601 (2018)
doi.org/10.3390/ijms25084269 (2024)

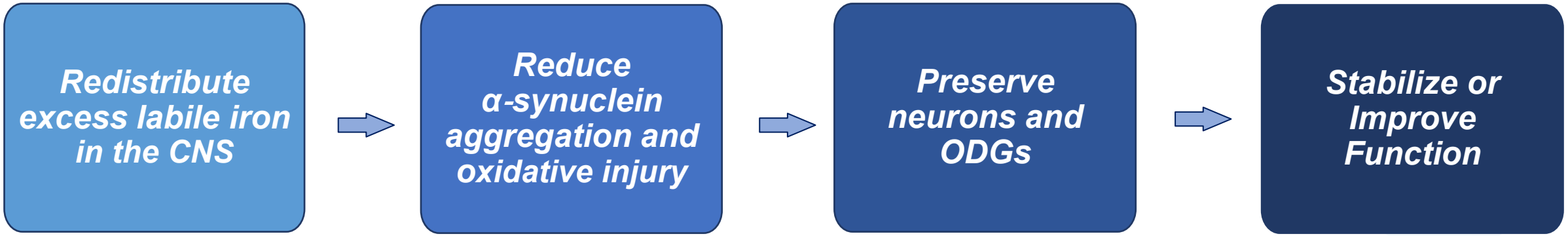
Excess Labile Iron and Misfolding α-Synuclein are Important Drivers of MSA Pathology



Pathology Driver	*Effect*
Excess labile iron	*Alpha-synuclein aggregation*
	Free radical production
	DNA, lipid, mitochondria damage
	Cell death
Aggregating α−synuclein	*Neuron dysfunction*
	Glial cell impairment / ↓ trophic support
	Additional free radical production
	Neuron and glial cell death

Sources: Kaindlstorfer, J. Alzheimers Dis. 2018; Bengoa-Vergniory N, Acta Neuropathol. 2017

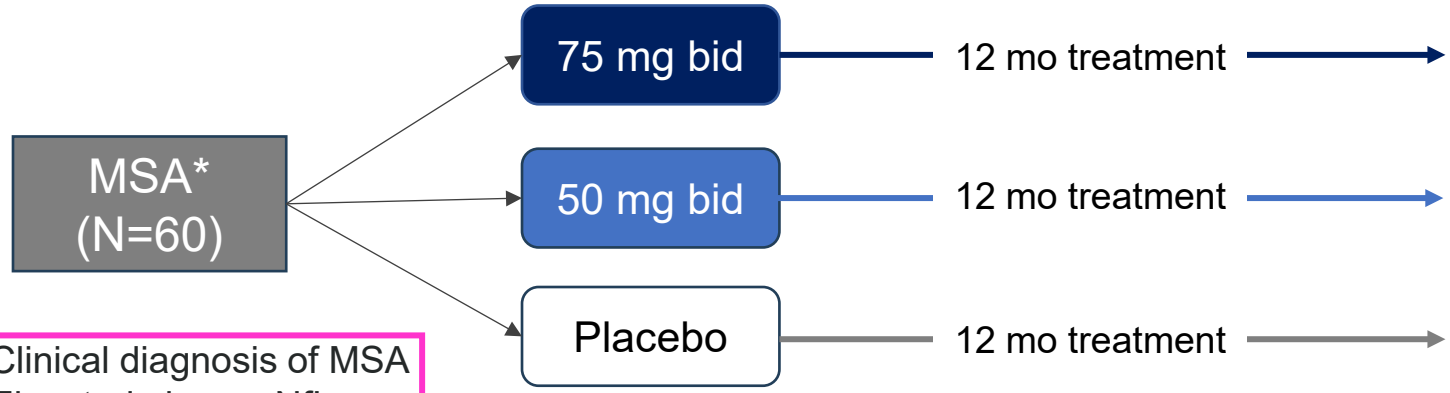
Development Approach: Address Underlying Pathology



Study Objectives

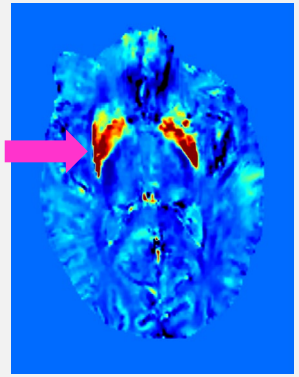
- Evaluate the efficacy, biomarker response, and safety of ATH434 treatment in MSA patients

ATH434-201 Study Design



- Clinical diagnosis of MSA
- Elevated plasma NfL
- MRI evidence of ↑ Iron
- Motor symptoms ≤4 years
- No severe impairment

Quantitative MRI



MSA patient

Target engagement/efficacy assessments

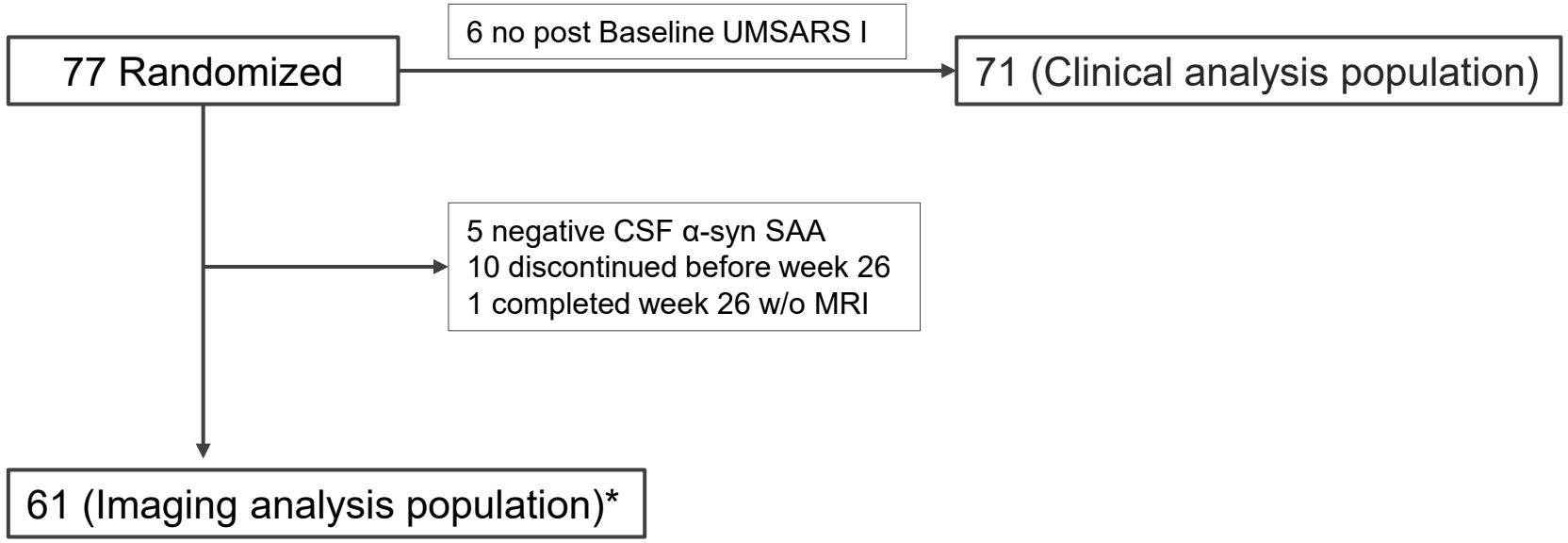
- MRI: Screening, Weeks 26 and 52
- UMSARS I: Weeks 13, 26, 39 and 52
- CGI-S, OHSA, Wearables: Weeks 13, 26, 39 and 52

Safety assessments

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

* Claassen et al. A Multimodal Approach for Diagnosis of Early MSA. *Mov. Disord,* Vol. 38, Suppl. 1, 2023

Populations and Key Endpoints



Protocol Endpoint	Change 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)	Modified UMSARS Part I	Clinical	≥ 1 post-baseline UMSARS I (13 weeks)

* Modified ITT population in protocol

^ All patients were randomized and rec'd ≥1 dose study drug

Baseline Characteristics (mITT)

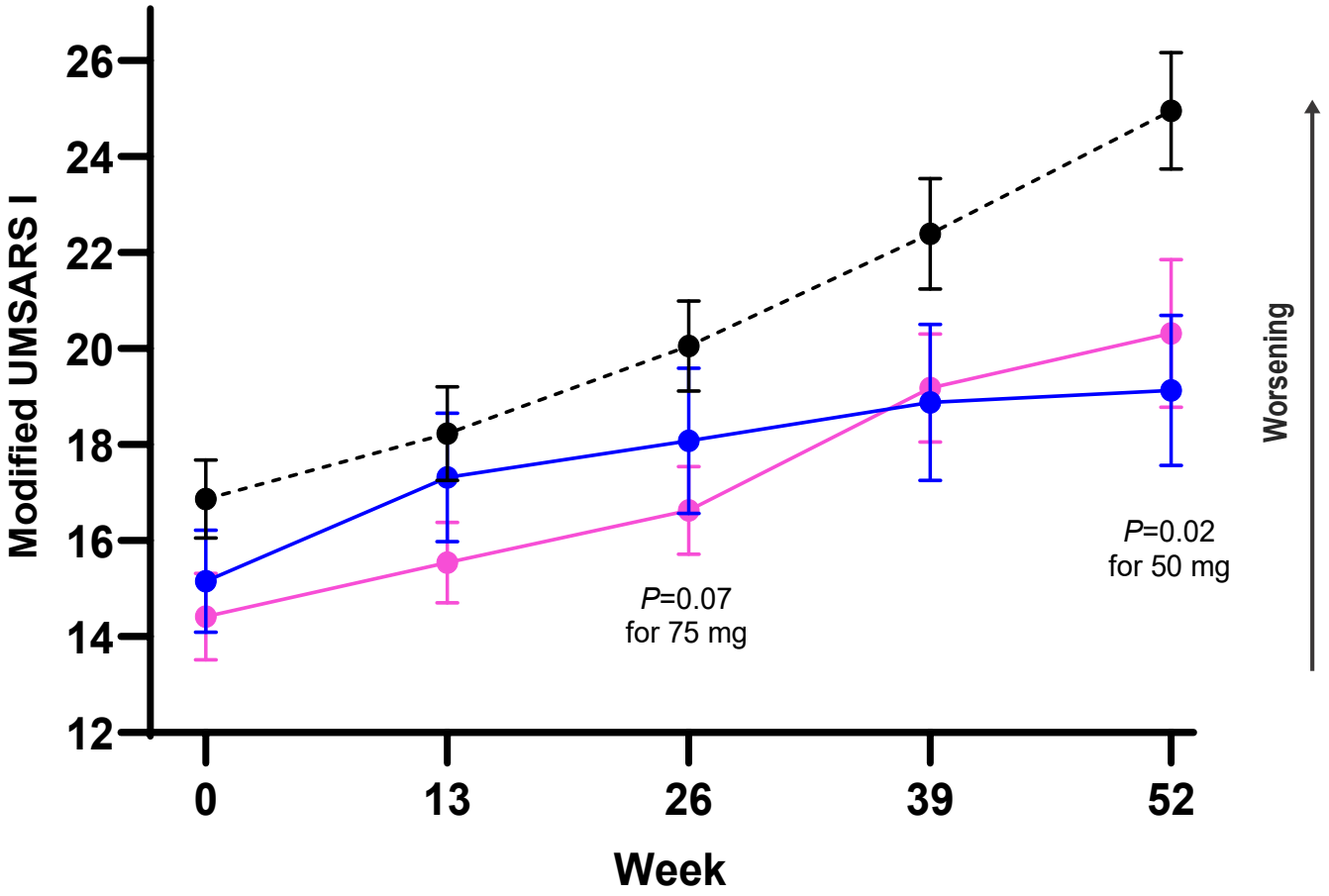
Parameter	Placebo (n = 19)	50mg BID (n = 21)	75mg BID (n = 21)
Age (yr)	61.5 (7.0)	62.9 (6.3)	64.0 (6.3)
Gender (% male)	63.2%	57.1%	57.1%
Modified UMSARS I[1]	16.8 (4.2)	15.4 (4.6)	14.4 (4.7)
Motor score of NNIPPS[2]	57.9 (15.2)	48.6 (16.0)	49.1 (17.7)
NfL (plasma), pg/mL	35.4 (12.0)	31.7 (8.9)	32.4 (9.6)
OH Symptom Assessment	13.5 (9.8)	13.8 (13.2)	15.0 (12.2)
Duration of motor symptoms (yr)	2.6 (0.9)	2.6 (0.9)	2.4 (0.9)
Radiographic phenotype (% SND)	68.4%	52.4%	66.7%
Severe OH at Baseline	5.3%	4.8%	33%

Mean (SD)

[1] Exclusion of sexual function item

[2] Payan et al. Validation of the Natural History and Neuroprotection in Parkinson Plus Syndromes Scale. PlosOne 2011

Modified UMSARS Part I



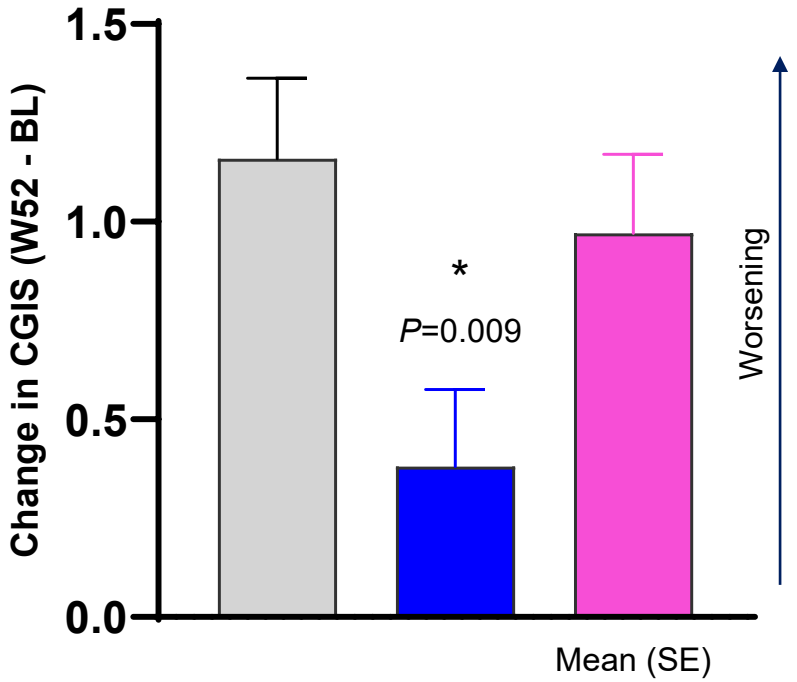
Dose	Mean difference vs. placebo	Relative treatment effect*
50 mg	- 3.8	48%
75 mg	- 2.4	30%

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

Clinical Analysis Population

Clinical Global Impression of Severity

Change from Baseline to Week 52



Placebo

ATH434 50 mg BID

ATH434 75 mg BID

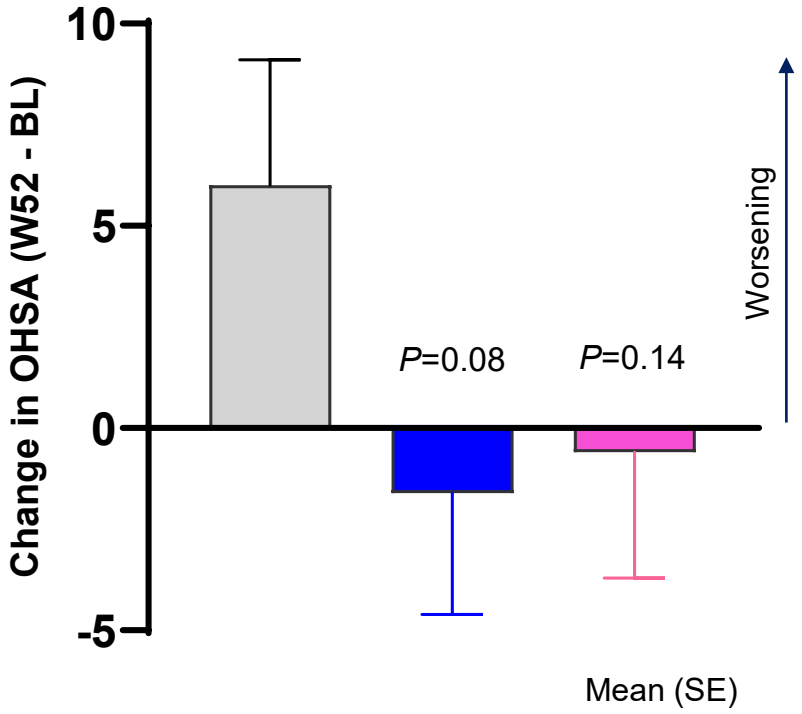
7-point Likert scale

- Higher score = worse outcome
- Total picture of patient over 28 days

Clinical Analysis Population

Orthostatic Hypotension Symptom Assessment

Change from Baseline to Week 52



Placebo

ATH434 50 mg BID

ATH434 75 mg BID

Clinical Analysis Population

Patient reported outcome

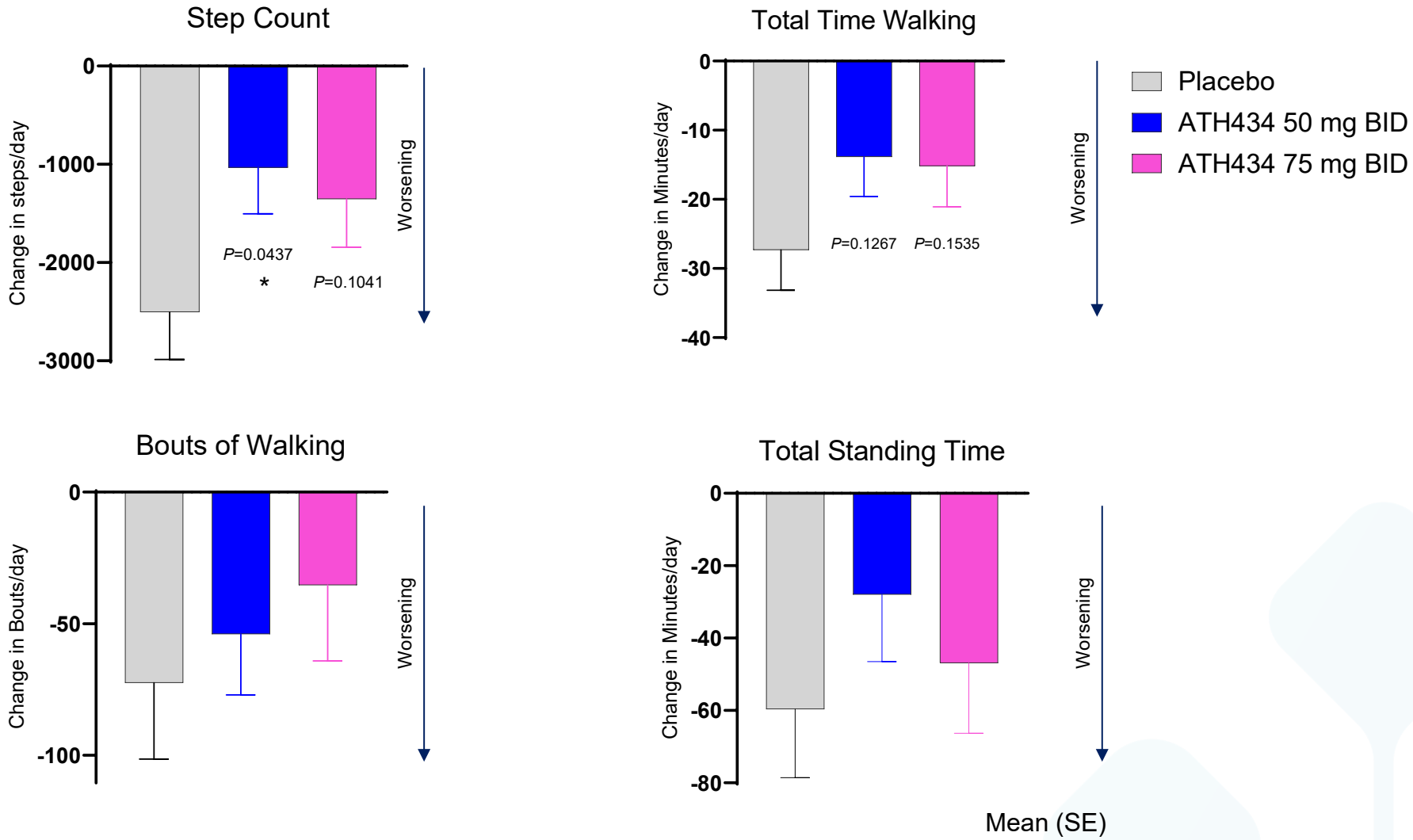
Assesses severity of 6 items

- Dizziness/lightheadedness/feeling faint/like blacking out
- Problems with vision (blurry, seeing spots, tunnel vision)
- Weakness
- Fatigue
- Concentration
- Head and neck discomfort

Kaufmann, et al. Orthostatic Hypotension Questionnaire (OHQ): validation of a novel scale. Clin Auton Res 2012

Wearable Sensors: Activity in Outpatient Setting

Change from Baseline to Week 52



Clinical Analysis Population

Summary of Adverse Events

Number (%) of Subjects	Placebo BID (n=26)	50mg BID (n=25)	75mg BID (n=26)
Any Adverse Event (AE)[1]	24 (92.3%)	21 (84.0%)	25 (96.2%)
UTI	14 (53.8%)	10 (40.0%)	7 (26.9%)
Fall	8 (30.8%)	7 (28.0%)	8 (30.8%)
Covid-19	1 (3.8%)	6 (24.0%)	4 (15.4%)
Fatigue	2 (7.7%)	1 (4.0%)	5 (19.2%)
Back pain	1 (3.8%)	3 (12.0%)	2 (7.7%)
AE by Severity[1]			
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[1, 2]	10 (38.5%)	5 (20.0%)	7 (26.9%)

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

Change in Iron Content by MRI (QSM)

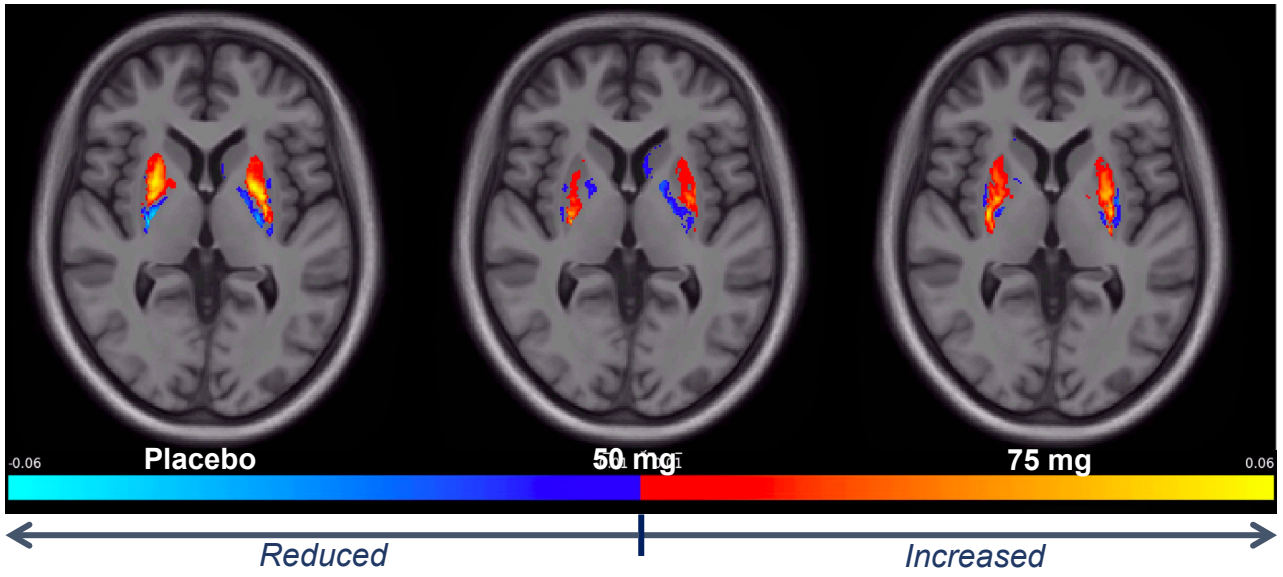
Alterity THERAPEUTICS

By-subject analysis of iron content

Region	50 mg BID		75 mg BID	
	Week 26	Week 52	Week 26	Week 52
S. nigra	↔	↓	↔	↔
Putamen	↓^	↓	↔	↔
Pallidum	↓	↓*	↓	↓

Compared to placebo: ↓ Iron content, ↔ No observable difference, ^ *P* = 0.025, * *P* = 0.08

Group change in iron content (week 52 − baseline)



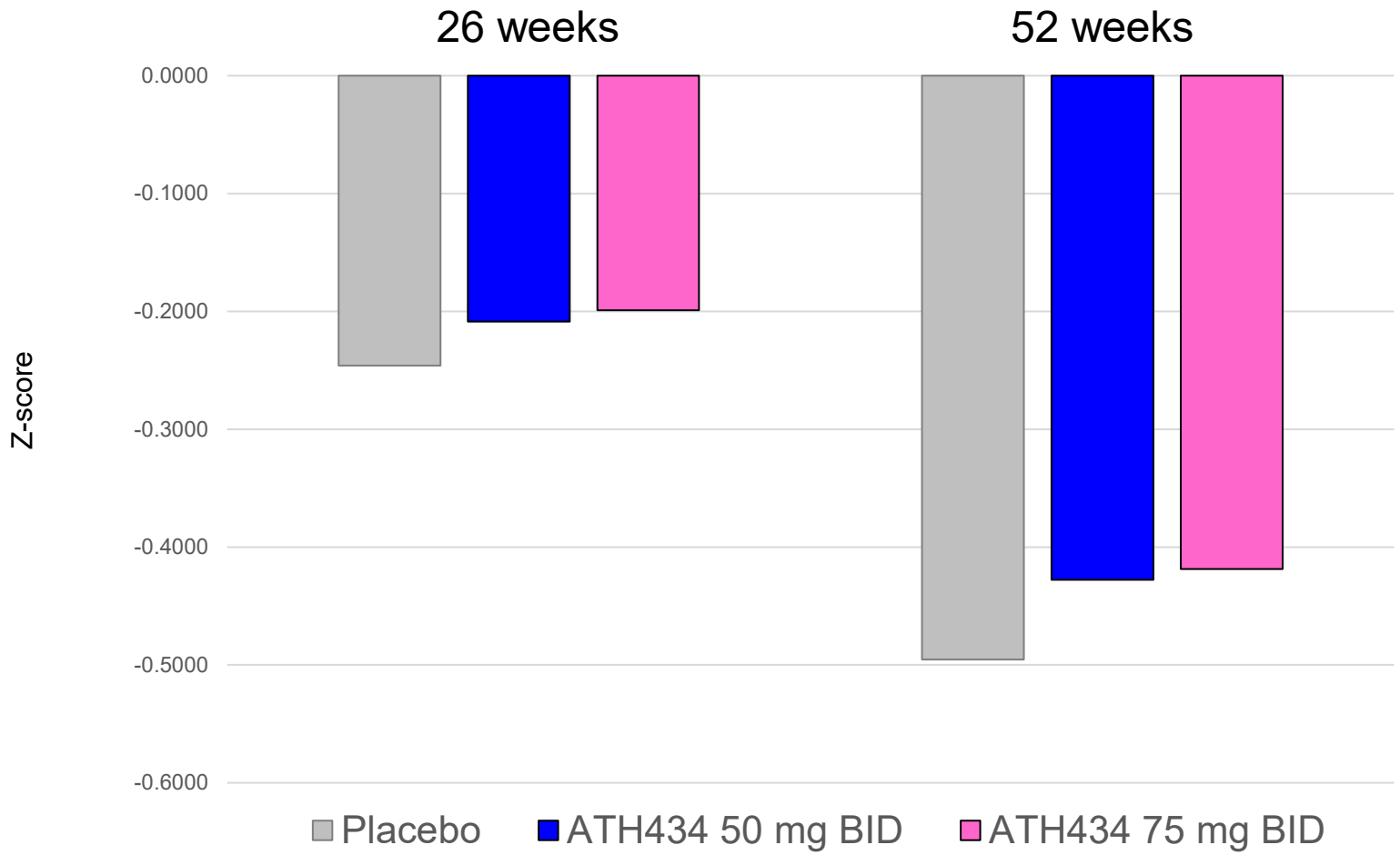
By-subject analysis
- Evidence for reduced/stabilized iron content in Pallidum > Putamen
- Reductions in iron in s. nigra at 50 mg dose but not 75 mg (primary endpoint)

Group-wise analysis
- Iron increases in key regions over time in placebo > ATH434
- Evidence for ↓ iron accumulation in globus pallidus

Imaging Analysis Population

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 vs. healthy age-matched population

Summary and Conclusions

- ATH434 showed clinically significant efficacy in modifying disease progression
  - UMSARS I plus important secondary clinical outcomes
- Baseline differences in disease severity and pathology likely explain different response in 50 mg and 75 mg treatment groups
- ATH434 demonstrated target engagement by reducing iron accumulation in MSA affected brain regions
- ATH434 well tolerated with similar AE rates as placebo and no serious AEs attributed to study drug
- Alpha-synuclein SAA requires continued refinement in MSA
- Results support further exploration of the role of excess labile iron in neurodegeneration

Acknowledgements

The authors would like to thank the study participants, their care partners, and the clinical site staff for their contributions to the study.

Country	Investigator	Study Coordinator	Institution
France	Wassilios Meissner	Sandrine Villars	Groupe Hospitalier Pellegrin, Bordeaux
	Jean-Christophe Corvol	Carine Lefort	Hôpital Universitaire Pitié Salpêtrière, Paris
	Olivier Rascol	Nadera Ainaoui	Hôpital Pierre-Paul Riquet, Toulouse
	Alexandre Eusebio	Manel Nouira	Hôpital de la Timone, Marseille
Italy	Maria Teresa Pellecchia	Dominga Valentino	Azienda Ospedaliera Universitaria San Giovanni di Dio Ruggi d'Aragona, Salerno
	Roberto Ceravolo	Valentina Giordano	Azienda Ospedaliero-Universitaria Pisana, Pisa
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	Alessio Di Fonzo	Diego Scalabrini	Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan
UK	Viorica Chelban	Samuel Barnett	University College London Hospitals NHS Foundation Trust, London
	Christopher Kobylecki	Kathryn Slevin	Northern Care Alliance NHS Foundation Trust, Manchester
	David Ledingham	Caroline Brunton	Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne
	Victoria Marshall	Catriona McNeill	NHS Greater Glasgow and Clyde, Glasgow
US	Amy Brown	Carol Wallace	Vanderbilt University Medical Center, Tennessee
	Kevin Klos	Shannon Klos	Movement Disorder Clinic of Oklahoma
	Sheng-Han Kuo	Haidyn Emmerich	Columbia University Irving Medical Center, New York
	Deborah Hall	Savannah Melan	Rush University Medical Center, Illinois
	Katherine Longardner	Michael Skipworth	University of California San Diego, California
	Jee Bang	Kori Ribb	Johns Hopkins University Neurology Research Office, Maryland
Australia	Kelly Bertram	Charmaine Catipon	The Alfred, Melbourne
	Victor Fung	Sarah Bray	Westmead Hospital, Westmead
	Stephen Tisch	Fatima Abdi	Saint Vincent's Hospital Sydney, Darlinghurst
New Zealand	Tim Anderson	Laura Paermentier	New Zealand Brain Research Institute, Christchurch
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Thank You