ATH434-201 Phase 2 Topline Results

January 30, 2025

Alterity THERAPEUTICS

Forward Looking Statements

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Achieved Our Target Measures for Success

- Favorable Safety Profile / No Drug Related Serious Adverse Events
- Strong Clinical Results with Statistical Significance Reached on UMSARS I Rating Scale
- Drug Effect on Biomarker Endpoint with Reduction in Iron Content

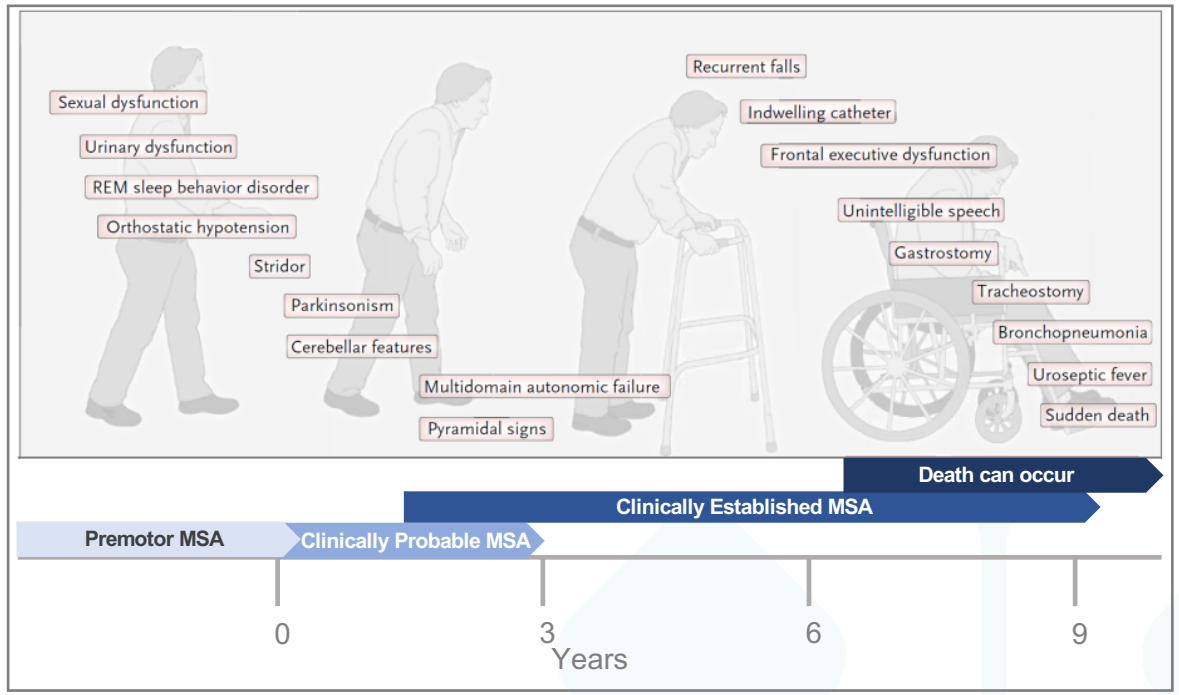
Positive ATH434 Phase 2 Trial Results

- Exceptionally strong clinical results overall
- Robust efficacy on UMSARS I rating scale
- Evidence of clinical benefit on several secondary endpoints
- Reduced or stable brain iron concentrations on MRI
- Maintained brain volume compared to placebo

ATH434 Clinical Development Program in Multiple System Atrophy

Multiple System Atrophy (MSA): Rare, Rapidly Progressive and Highly Debilitating Neurodegenerative Disease

- Parkinsonian disorder with no approved treatment
- Orphan disease: up to 50,000 patients in U.S.
- Disease characteristics
  - Motor: Parkinsonism, uncoordinated movements, balance problems and falls
  - Autonomic dysfunction: blood pressure maintenance, bladder control, bowel function
  - Brain atrophy and α-synuclein accumulation in multiple regions
- Over 50% require wheelchair in 5 years
- Median survival 7.5 years after symptom onset

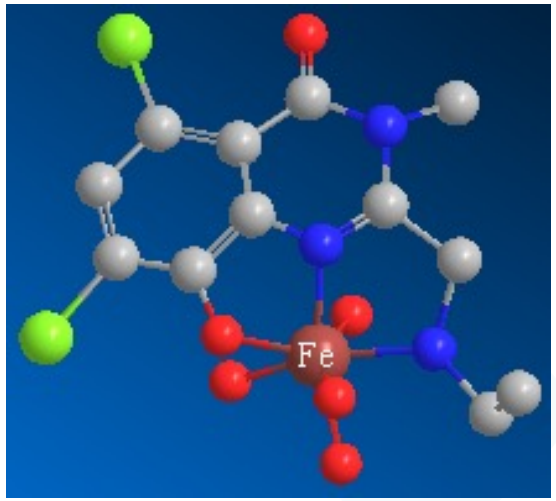


Sources: Fanciulli, Wenning. NEJM 2015 | Wenning, et al. Mov Disorders 2022 | Coon, et al. Brain 2015 | Claassen,et al. Mov Disorders 2021 | Multiple System Atrophy: National Institute of Neurological Disorders and Stroke (nih.gov)

ATH434: Potential Disease Modifying Therapy

- Small molecule drug candidate
  - Decreases pathologic protein aggregation (α-synuclein) in CNS
  - Iron chaperone: redistributes excess labile iron in CNS
- **Oral medication**
  - **Preferred over infusions and injections**
- Potential to treat iron-related neurodegenerative disease
- Orphan Drug Designation in the US and EU for MSA treatment
- Development pathway endorsed by FDA and EMA

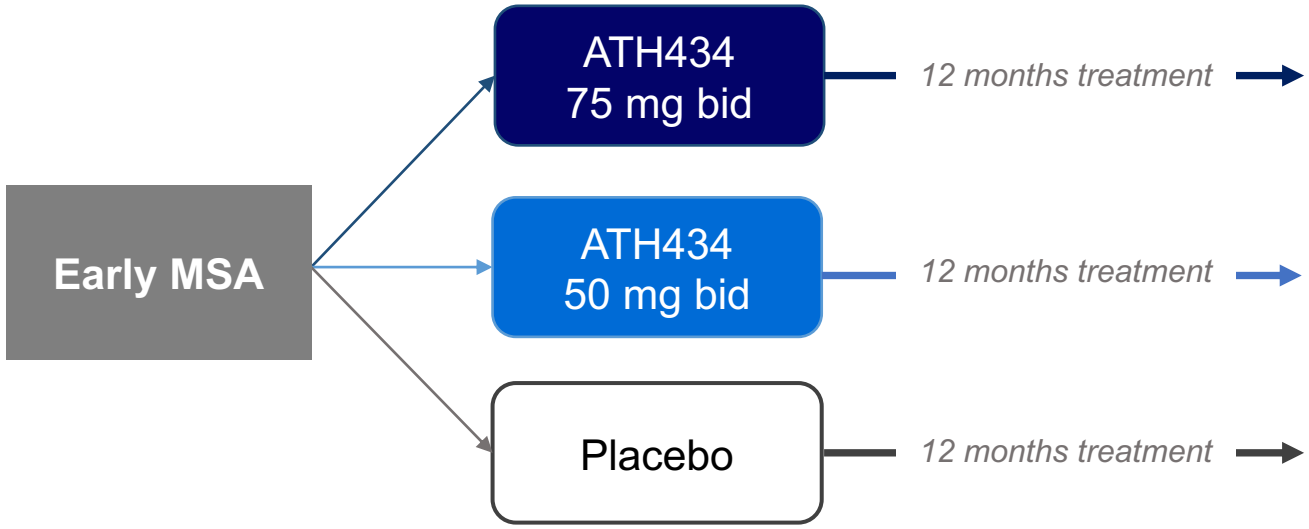
ATH434 binding to iron



ATH434-201 Trial Design in Early-Stage MSA

Study	ATH434-201 – Phase 2
Design	**Randomized, double-blind, placebo controlled**
Objectives	Efficacy, safety and pharmacokinetics of ATH434
Population	**Early-stage MSA**
Sample Size	N = 77
Treatment	12 months
Clinical Endpoints	Activities of daily living (UMSARS), global measures, motor exam, autonomic function
Brain MRI Biomarkers	Iron, volume
Fluid Biomarkers	Neurofilament light chain (NfL), Aggregated α-synuclein (baseline)
Other Biomarkers	Wearable movement sensors

ATH434-201 Phase 2 Double-Blind Design



- Key Clinical Endpoint: Change in modified UMSARS Part I (activities of daily living)
- Key Biomarker Endpoint: Change in brain iron concentration by MRI

Unified MSA Rating Scale (UMSARS) Key Clinical Outcome

- Validated rating scale developed specifically for MSA
- Part I assesses functional impairment in areas affected in MSA
  - Part I, symptom inventory of 12 items
  - Modified version of scale used in our trial excludes the sexual function domain
- Rated from 0 to 48 (higher scores worse)
- **Most important clinical endpoint to support regulatory approval for treatment of MSA**

UMSARS Part I Items

- Speech
- Swallowing
- Handwriting
- Cutting food
- Dressing
- Hygiene
- Walking
- Falling
- Orthostatic symptoms
- Urinary Function
- Bowel Function
- [Sexual Function]

Key Eligibility Criteria

Inclusion Criteria

- Clinical evidence of parkinsonism
- Evidence of autonomic impairment
- Ambulatory without assistance
- Elevated iron on brain MRI

Exclusion Criteria

- Motor symptoms for > 4 years
- Significant swallowing impairment (choking > 1x per week)
- Frequent falling (≥ 1x per week)

ATH434-201 Phase 2 Topline Results

Baseline Characteristics Consistent with Early-Stage MSA Patient Profile

Parameter	Placebo (n = 19)	50mg BID (n = 21)	75mg BID (n = 21)	Overall (n = 61)
Age (yrs)	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%
Modified UMSARS I	16.8 (4.2)	15.4 (4.6)	14.4 (4.7)	15.5 (4.5)
Parkinson Plus Scale Motor	57.9 (15.2)	48.6 (16.0)	49.1 (17.7)	51.7 (16.6)
NfL (plasma)	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)

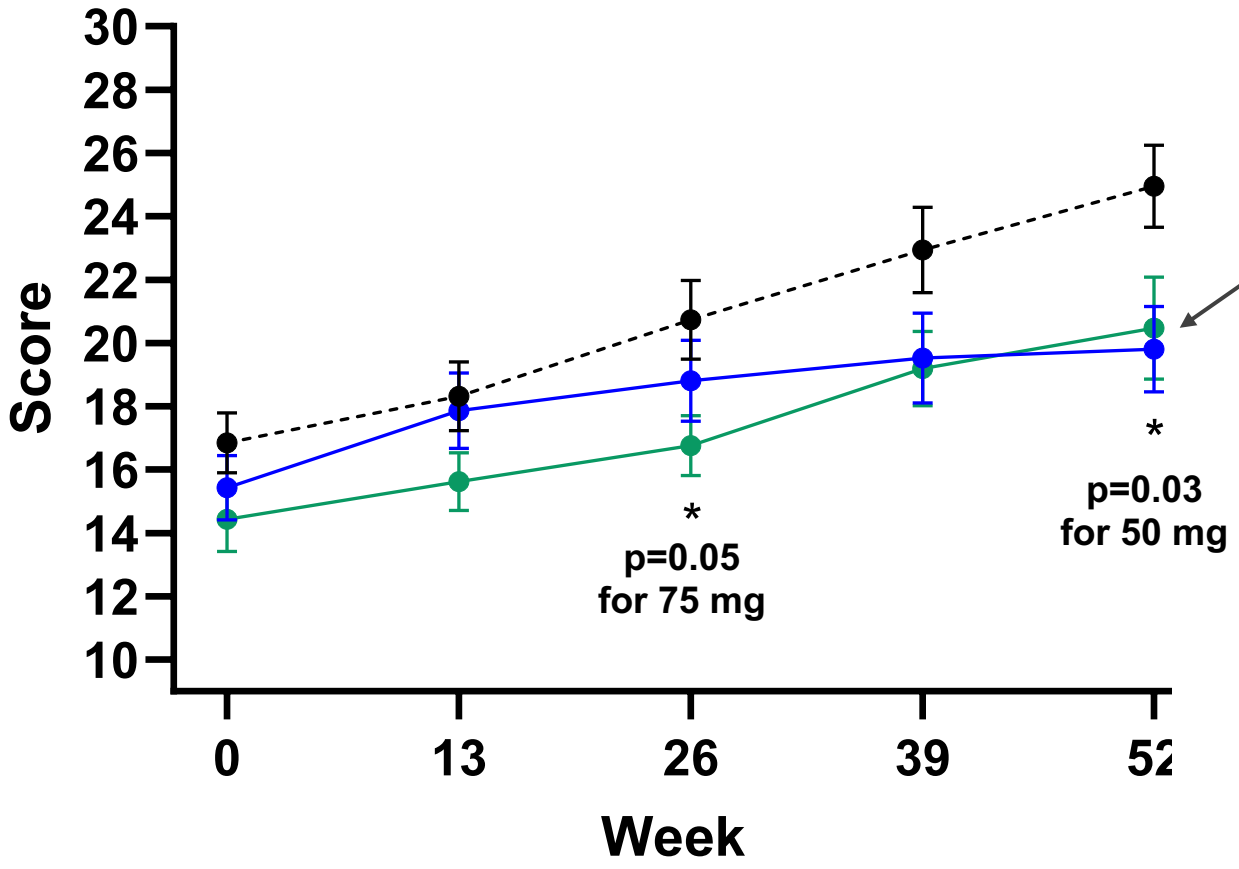
Mean (SD)

Efficacy analyses performed on the modified Intent-to-Treat (mITT) population
^NfL: Neurofilament light chain

Outstanding Clinical Outcomes

ATH434 Exceptional Results on Key Clinical Endpoint

Modified UMSARS Part I



Clinical progression v. placebo at 52 weeks
- Low dose: 48% slowing (p=0.03)
- High dose: 29% slowing (p=0.2)

Placebo (n=19)
Low Dose (n=21)
High Dose (n=21)

Both ATH434 dose levels demonstrated clinically meaningful slowing of disease progression over 12 months

Evidence of Efficacy on Other Clinical Endpoints

Clinical global impression of severity (7-point scale, lower score = improvement)
Clinician assessment of the total picture of the participant over prior 28 days

- Mean change at 50 mg: -0.81 (p=0.009)
- Mean change at 75 mg: -0.18 (p=NS)

Parkinson Plus total motor scale
Trends in improvement in both dose groups at 26 and 52 weeks

- Clinical benefit observed in multiple domains

Increased activity on wearable sensors in both groups

- ↑ step count
- ↑ bouts of walking
- ↑ total walking time
- ↑ standing time

Orthostatic Hypotension Symptom assessment (patient rated) showed trends favoring benefit in both groups (p=0.13 at 50 mg)

Positive Impact on Brain Iron & Volume

Brain Iron and Volume Assessments are Unique Aspects of the Phase 2 Trial

Brain Iron Content

- MRI is an unconventional outcome measure that was designed specifically for the ATH434-201 trial to evaluate target engagement
- Led to the primary endpoint: change in iron content as measured by brain MRI
  - Assessed MSA affected brain regions
  - We originally felt this was the best opportunity to observe a drug effect
- MRI analysis is highly technical and we will continue to explore the data

Brain Volume

- Colleagues at Vanderbilt developed the MSA Volume Index to assess brain volume changes in MSA participants

ATH434 Reduced Iron Accumulation Compared to Placebo

Brain Iron by MRI

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

Compared to placebo

↓ Reduced Iron content,

↔ No observable difference

^ *P* = 0.025, uncorrected

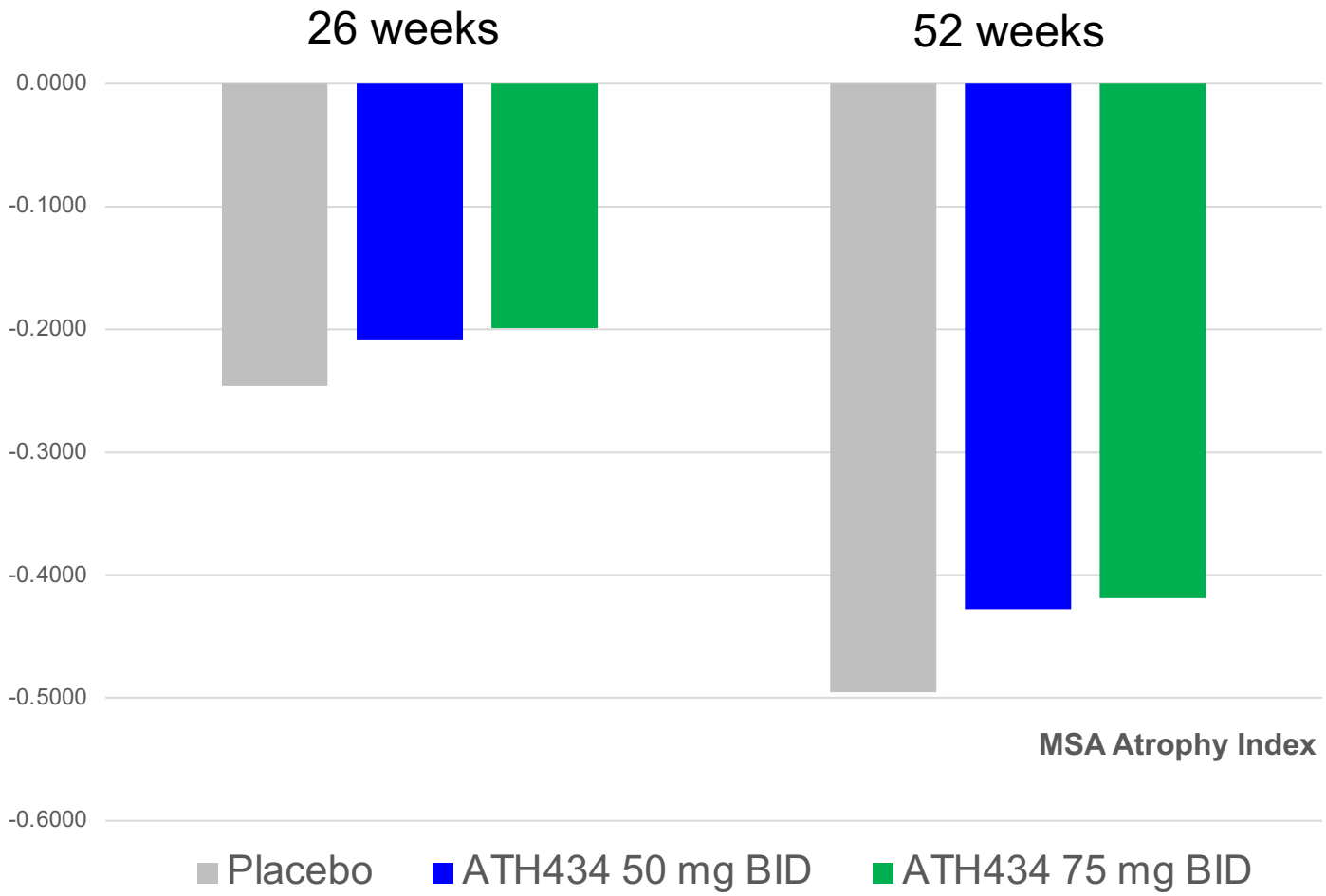
* *P* = 0.08, uncorrected

Clear Trends Showing ATH434 is Reducing or Stabilizing Iron Content in MSA Brain Regions

- Achieved objective of demonstrating target engagement of iron in the brain
- Preliminary analysis is positive with reductions in iron content in key brain regions affected by MSA
- **Significant reduction in iron content the putamen (p=0.025) at Week 26 and trend of iron reduction in pallidum (p=0.08) at Week 52 for the 50 mg dose**
- **Stable iron content in other MSA affected brain regions**

ATH434 Demonstrated Trends in Reduced Brain Atrophy

Change from Baseline in Brain Volume



Source

Well-Tolerated Safety Profile with No Serious Adverse Events (SAEs) Related to Study Drug

Safety population: enrolled participants who received at least one dose of treatment

- 50 mg dose (n=26)
- 75 mg dose (n=25)
- Placebo (n=26)

Safety Results:

- ATH434 was well-tolerated with similar adverse event (AE) rates in ATH434 treatment groups and placebo
- Most AEs were mild to moderate in severity
- No serious adverse events (SAEs) related to ATH434 were reported
- Discontinuations for AEs were similar in the placebo (n=3) and 75 mg dose (n=5) groups and lowest at 50 mg (n=0). None of the AEs leading to discontinuation were related to treatment.

Summary

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