



Alterity Therapeutics

(NASDAQ:ATHE, ASX:ATH)

June 2021

David Stamler, MD
CEO

Forward Looking Statements



This presentation may contain some statements that may be considered “Forward-Looking Statements”, within the meaning of the US Securities Laws. Thus, any forward-looking statement relating to financial projections or other statements relating to the Company’s plans, objectives, expectations or intentions involve risks and uncertainties that may cause actual results to differ materially. For a discussion of such risks and uncertainties as they relate to us, please refer to our 2020 Form 20-F, filed with US Securities and Exchange Commission, in particular Item 3, Section D, titled “Risk Factors.”

Our Purpose



We exist to create an alternate future for people living with neurodegenerative diseases. An alternate, healthier life.

We're here to disrupt the trajectory for people with these diseases.

Recent Progress



.....▶ Oral presentation demonstrating the neuroprotective effect of ATH434 in animal model of MSA



7th International Congress for MSA

.....▶ Cardiovascular data which strengthens the safety profile of ATH434



.....▶ Michael J. Fox Foundation grant for ~US\$500K for Parkinson's disease



.....▶ Allowance of US patent for next generation compounds for neurodegenerative diseases



.....▶ \$35M Placement to international and Australian institutions and sophisticated investors



.....▶ Potential application of PBT2 for antibiotic resistance in superbugs



.....▶ Commence enrolling Multiple System Atrophy patients in bioMUSE Study

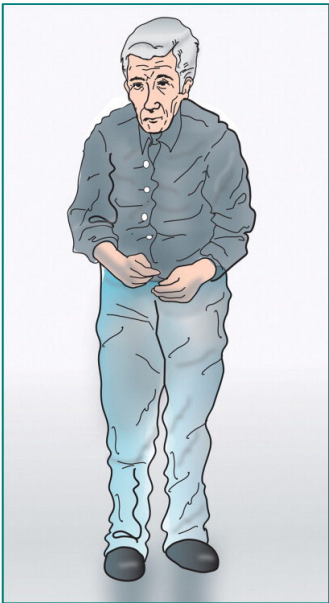


.....▶ ATH434 reduces α -synuclein pathology, preserves neurons, and improves motor performance



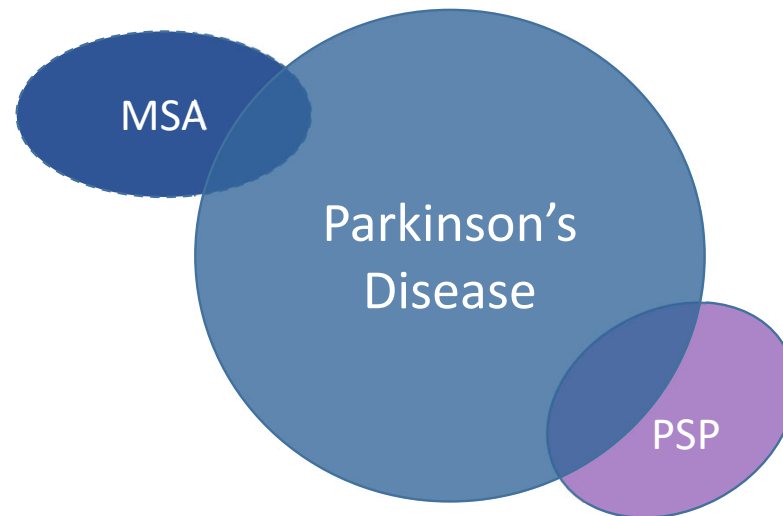
.....▶ US FDA provides development pathway for ATH434

Parkinsonian Disorders – A Significant Unmet Need



Lees et al. Lancet 2009

- Parkinsonism is a syndrome of motor symptoms that includes slowness of movement, stiffness and tremor
 - Major source of disability



- Atypical forms of Parkinsonism include Multiple system atrophy (MSA) and Progressive supranuclear palsy (PSP)
 - Atypical variants have prominent non-motor symptoms and limited response to available treatment
 - Lead indication is MSA
 - Orphan disease
 - Rapidly progressive
 - No approved treatment

Leadership of 3 FDA Approvals in Neurology



David Stamler, M.D.

- 3 FDA Approvals in Neurology
 - Led FDA Advisory Committee and approval of Xenazine® in Huntington's disease in 2008
 - Led clinical development and approval of Austedo® in Huntington's disease and Tardive dyskinesia, both approved in 2017
- Former Chief Medical Officer, Auspex Pharmaceuticals and VP, Clinical Development & Therapeutic Head, Movement Disorders, Teva Pharmaceuticals
- Part of **Teva's US\$3.5 billion acquisition of Auspex** in 2015
- Development leadership from **Auspex** joined Alterity in 2017



FDA Advisory Committee Votes Unanimously to Recommend Approval of Tetrabenazine for Chorea Associated With Huntington Disease

Dec 7, 2007



XENAZINE® (Tetrabenazine) Approved by FDA for Patients with Chorea Associated with Huntington's Disease

Aug 15, 2008

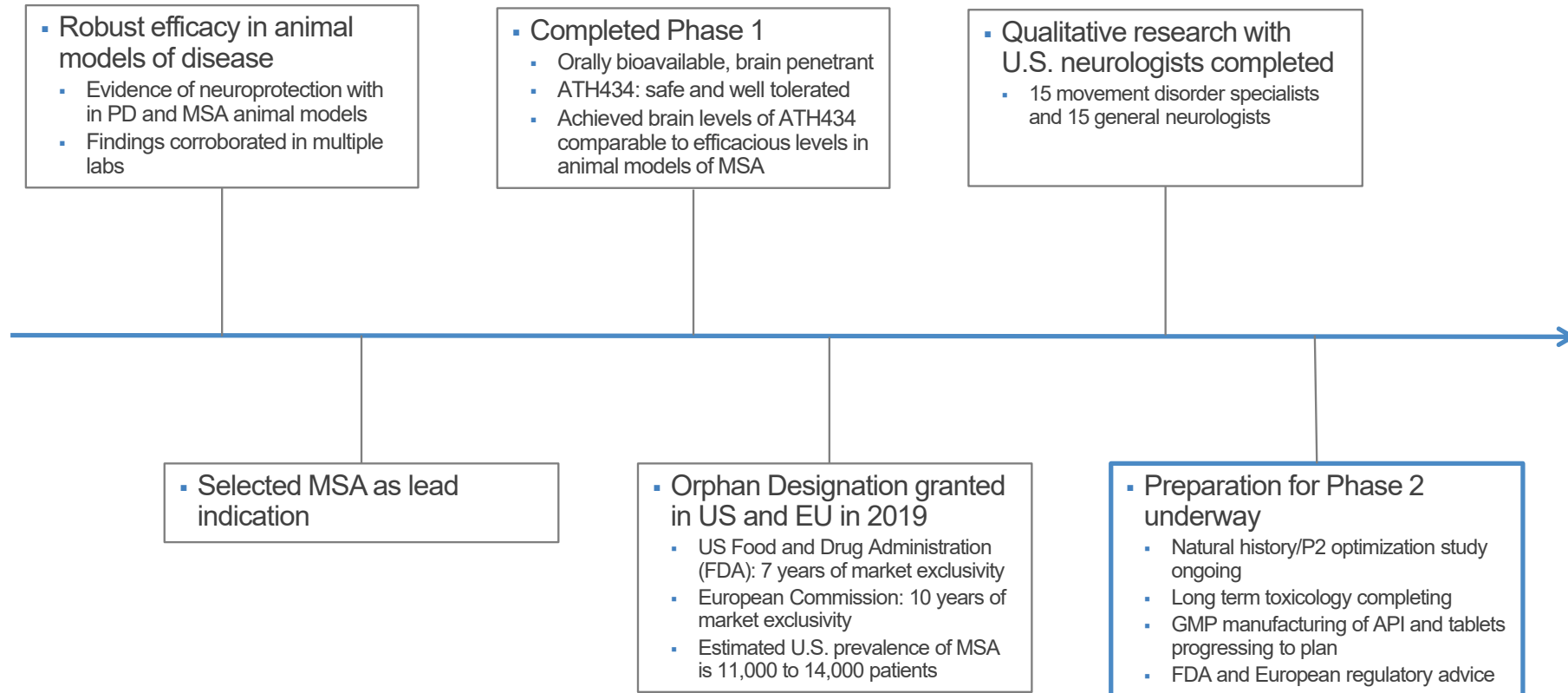


FDA approves Teva's Austedo® for Tardive Dyskinesia

Aug 31, 2017

Teva's Austedo is now the first and only therapy approved in the US to treat both tardive dyskinesia and chorea associated with Huntington's disease

Excellent Progress with Lead Drug Candidate ATH434



Commercial Opportunity – Multiple System Atrophy Independent Analysis

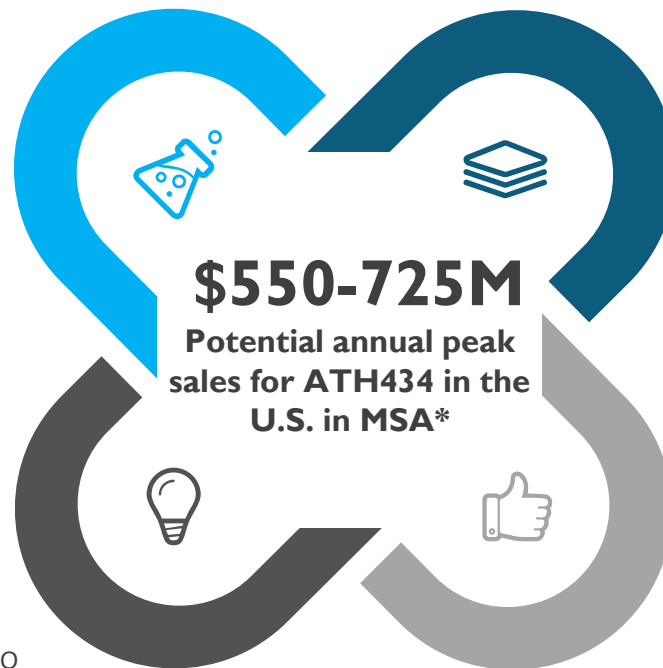


SUBSTANTIAL UNMET NEED

Severely debilitating, fatal illnesses with no current treatments are ripe for new entrants targeting what may be the actual cause of the disease.

UNIQUE MOA

Inhibition of protein accumulation and aggregation is a novel mechanism of action that may ultimately prove in clinical practice to impact more than motor symptoms.



STRONG INTENT TO PRESCRIBE

Motivated by efficacy in treating the underlying disease and not just the symptoms, clinicians intend to offer ATH434 to most of their patients with MSA.

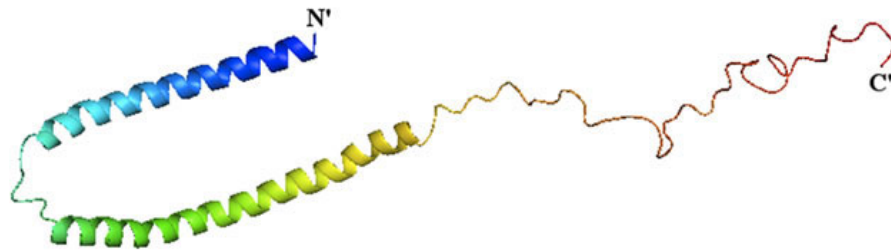
EASE OF USE

Given similar efficacy, clinicians will likely prefer ATH434's once or twice daily oral administration vs. the monthly IV infusions or injections required for alpha-synuclein antibodies that come to market.

*Does not include spontaneous use in PD

Our Target is Alpha-Synuclein

A Major Focus of Treating Parkinsonian Disorders



Structure of α -synuclein

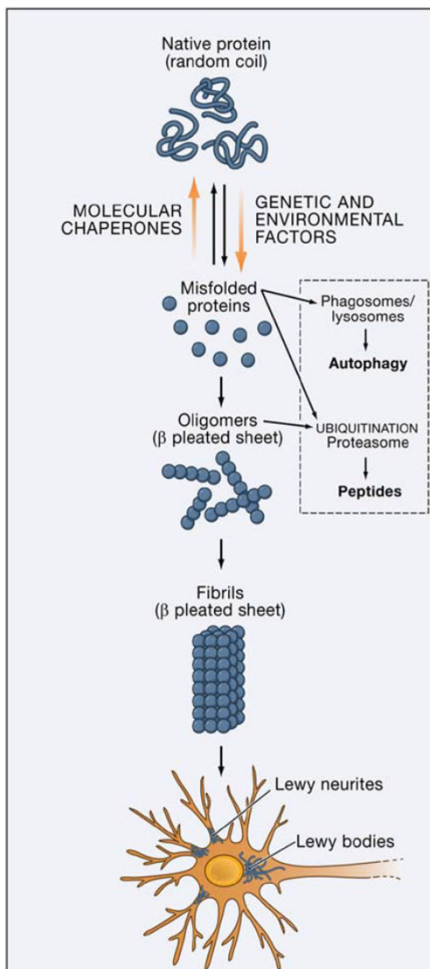
- α -synuclein is an intracellular protein, abundantly expressed in nerve terminals
- Critical for normal function of neurons
- Native, unfolded protein enables neurotransmission
- α -Synuclein *aggregates* in certain Parkinsonian conditions such as PD and MSA



"We conclude that alpha-synuclein remains one of the most compelling therapeutic targets for Parkinson's disease and related synucleinopathies, and that the multitude of approaches being tested provides hope for the future."

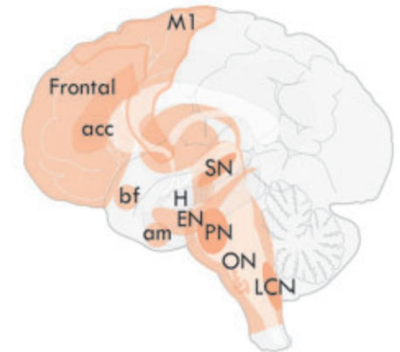
Exp. Neurol. 298,225-235, 2017.

Development Strategy Overview



Lee & Trojanowski, Neuron 2006

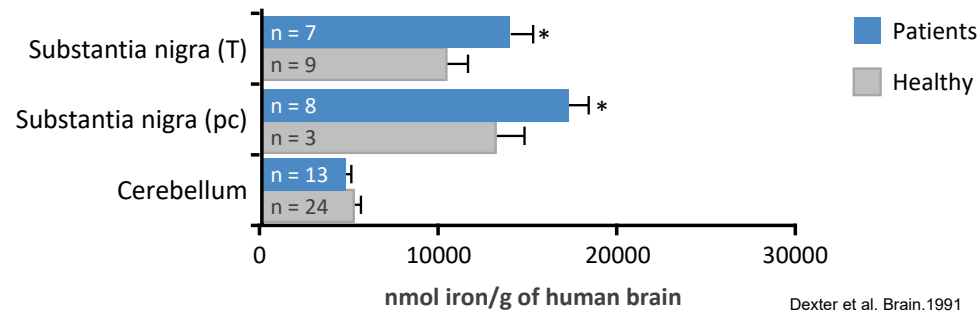
- Disrupt the underlying pathology of α -synuclein related diseases
 - Atypical parkinsonism (i.e., MSA)
 - Parkinson's disease
 - Inhibit accumulation and aggregation of intracellular α -synuclein
 - Target “labile iron” which is increased in areas of pathology
 - Oral agent for ease of use
-
- Lead indication: Multiple System Atrophy (MSA)
 - Severely debilitating, rapidly progressive
 - No approved treatment for MSA
 - Characterized by Parkinsonism, autonomic instability and/or cerebellar impairments
 - Pathological hallmark: accumulation of α -synuclein in glial cells (glial cell inclusions) and neuron loss in multiple brain regions



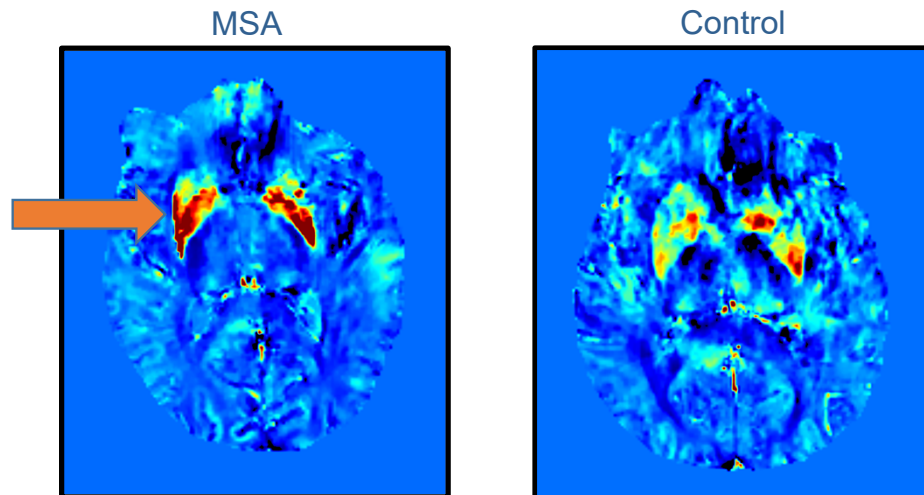
Halliday Brain 2015, based on
Cykowski et al, Brain 2015

Increased Brain Iron in Synuclein-related Diseases

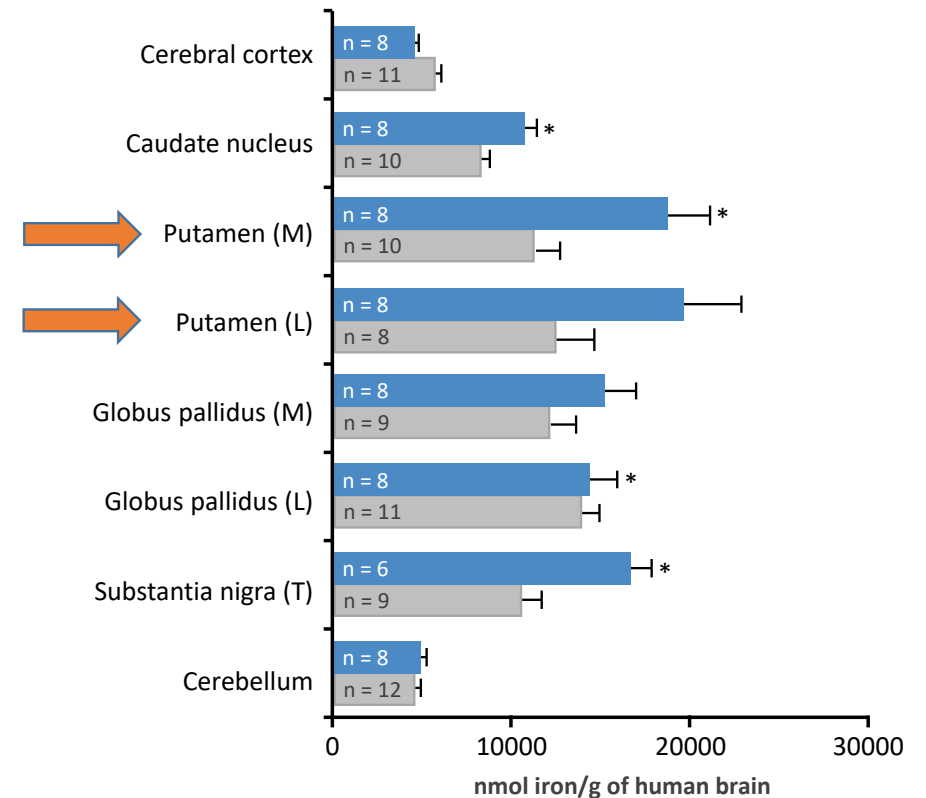
Parkinson's disease



Quantitative Susceptibility Mapping (MRI) to assess brain iron



Multiple System Atrophy

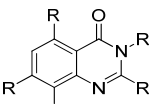


Pharmacologic Actions of ATH434

ATH434 restores intracellular iron balance

Ligand	Kd for Fe ³⁺
α-Synuclein	10 ⁻⁵
ATH434	10 ⁻¹⁰
Ferritin	10 ⁻²²
Transferrin	10 ⁻²³

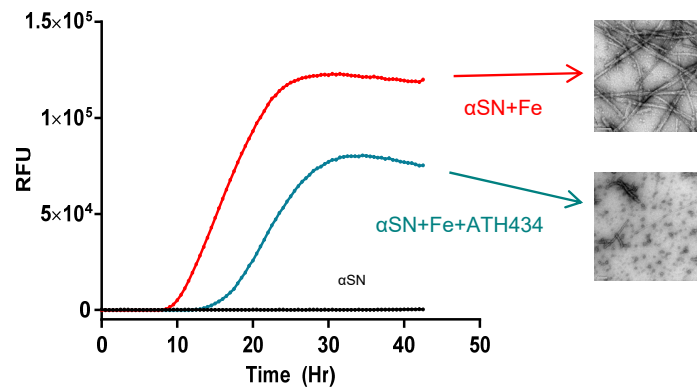
Stronger binding



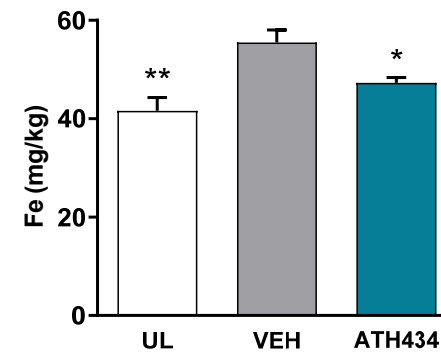
ATH434

Iron trafficking proteins > **ATH434** > α-synuclein

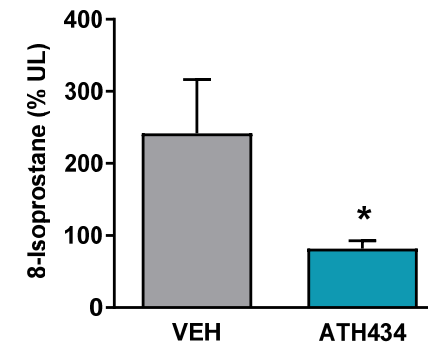
ATH434 blocks aggregation of α-synuclein



ATH434 blocks increase in brain iron



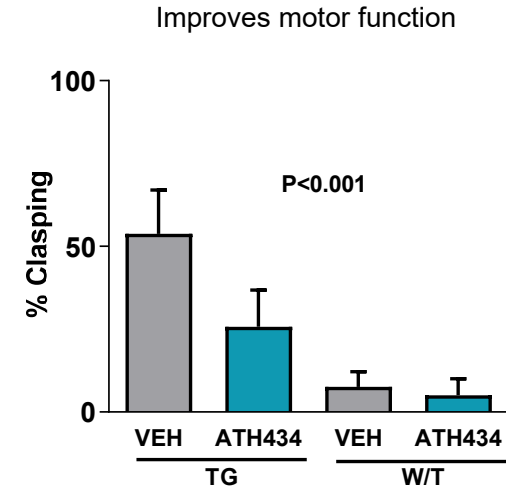
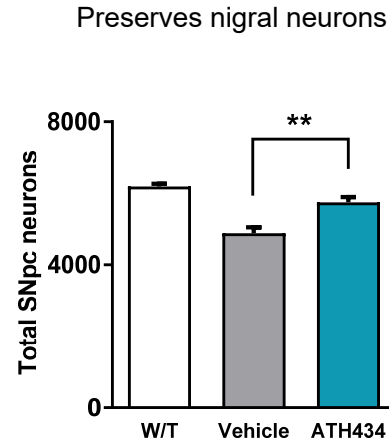
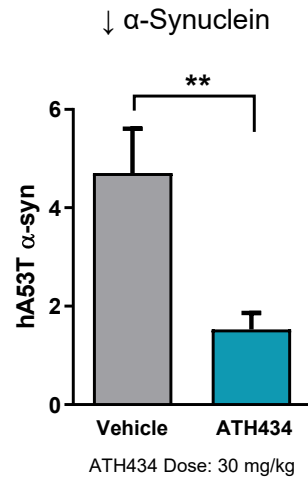
ATH434 inhibits oxidative stress



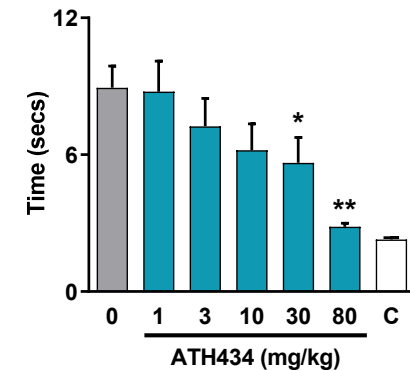
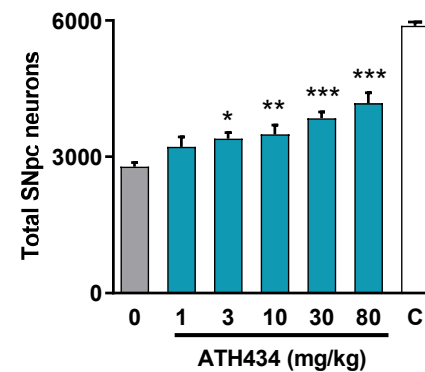
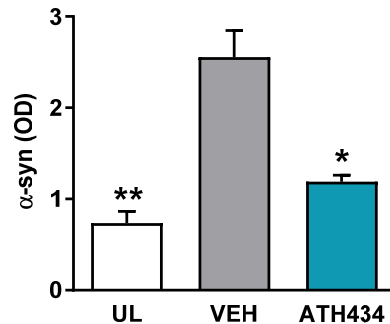
ATH434 Reduces Alpha-Synuclein-related Neuropathology and Improves Motor Function in Parkinson's Disease Animal Models



hA53T Mouse



MPTP Mouse



Finkelstein, et al. Acta Neuropath Comm. 2017
TG: transgenic, W/T: wild type, UL: unlesioned, C: control

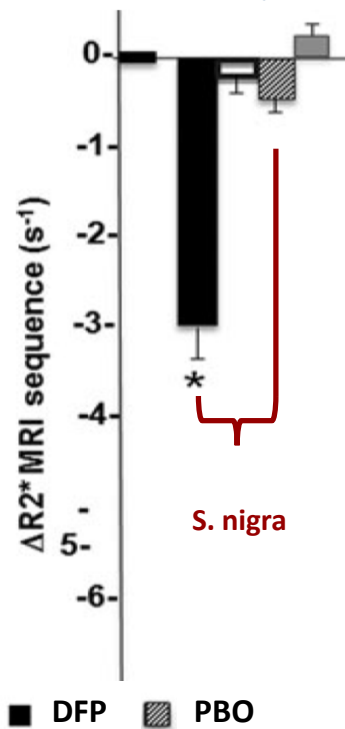
* P < 0.05, ** P < 0.01, *** P < 0.001

Strategy Supported by Proof of Concept with Iron Binding Drug

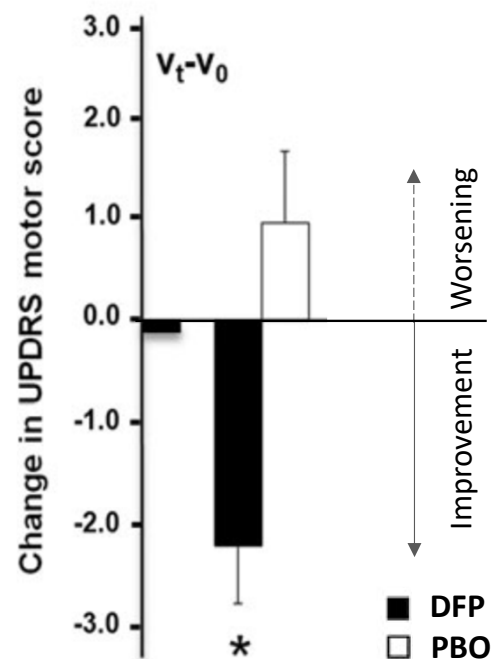
6-month placebo-controlled data from study of Deferiprone in Parkinson's disease



Brain Iron by MRI



Motor Symptom Severity



Reducing excess iron led to improved motor function

Deferiprone

- Approved for treating iron overload
- Binds iron with very high affinity
- Boxed Warning for hematological toxicity

Ligand	K _d for Fe ³⁺
α-Synuclein	10 ⁻⁵
ATH434	10 ⁻¹⁰
Ferritin	10 ⁻²²
Transferrin	10 ⁻²³
Deferiprone	10 ⁻³⁶



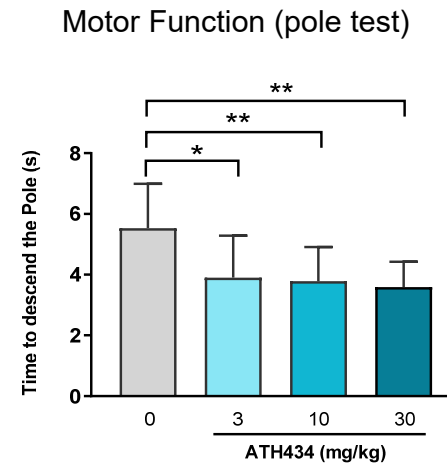
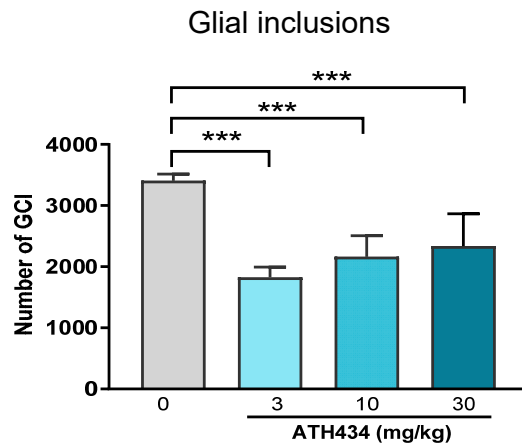
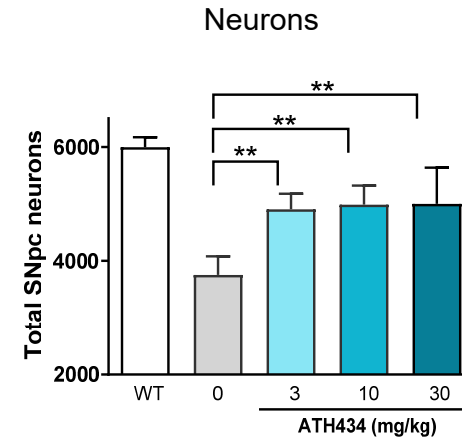
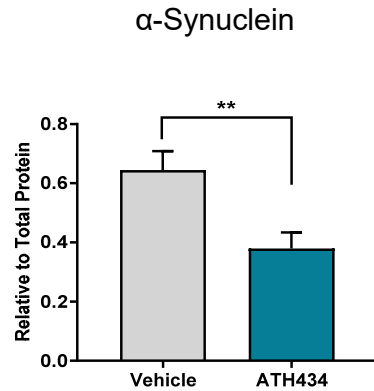
FERRIPROX® (deferiprone) tablets, for oral use
Initial U.S. Approval: 2011

WARNING: AGRANULOCYTOSIS/NEUTROPENIA

See full prescribing information for complete boxed warning.

- Ferriprox can cause agranulocytosis that can lead to serious infections and death. Neutropenia may precede the development of agranulocytosis. (5.1)
- Measure the absolute neutrophil count (ANC) before starting Ferriprox and monitor the ANC weekly on therapy. (5.1)
- Interrupt Ferriprox if infection develops and monitor the ANC more frequently. (5.1)
- Advise patients taking Ferriprox to report immediately any symptoms indicative of infection. (5.1)

ATH434 Reduces Alpha-Synuclein-related Neuropathology and Improves Motor Function in Animal Model of MSA



Finkelstein, et al. Neurology 2019; 92 (15 Suppl.)
Transgenic Mouse Model of MSA (PLP-αSyn)

* P < 0.05, ** P < 0.01, *** P < 0.001

4 months treatment with ATH434 or vehicle
Pathology data shown for S. nigra

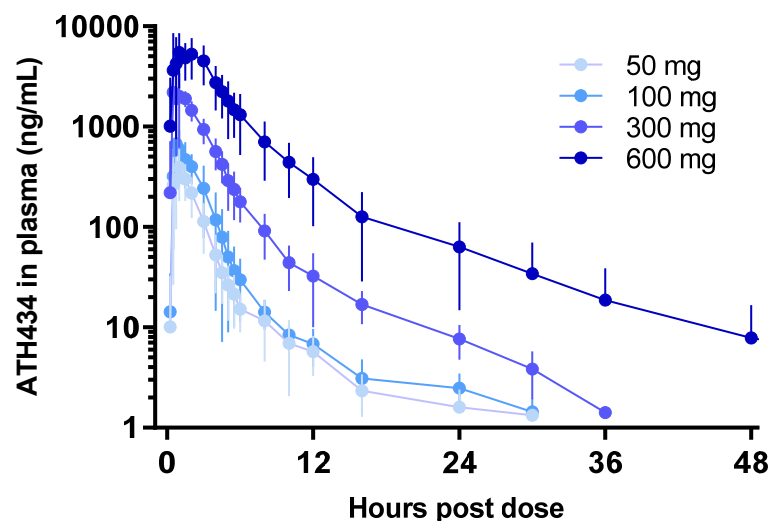
Clinical Development

Phase 1 Completed

Clinical Pharmacokinetics of ATH434

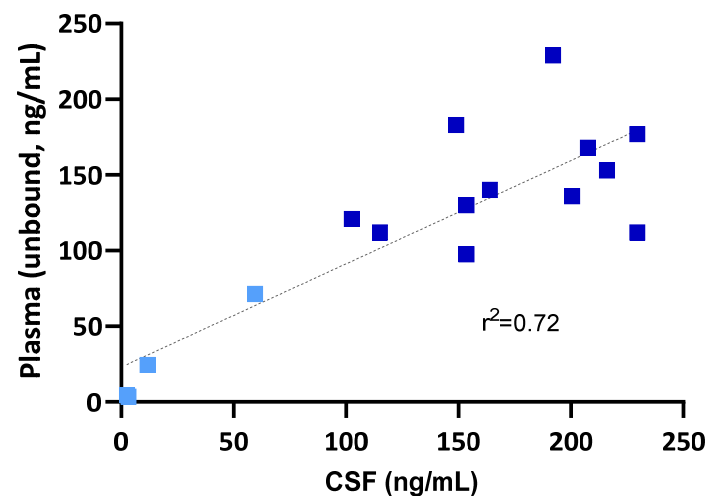


Plasma Profile after Single Dose Administration



- Rapid absorption after oral administration
- Dose dependent pharmacokinetics
 - Single doses up to 600 mg
 - Multiple doses up to 250 mg bid
- Mean elimination half-life up to 9.3 hrs

Plasma and CSF Levels at Steady-State



- Plasma and CSF 1.5 hours post dose
- Plasma and CSF 11 hours post dose
- CSF and free plasma levels strongly correlated across a broad concentration range
- CSF concentrations at steady state exceed those associated with efficacy in animal models of PD and MSA

Adverse Event Summary



Single Doses	Placebo (N=8)	50 mg (N=6)	100 mg (N=6)	300 mg (N=6)	600 mg (N=6)
Patients with ≥ 1 AE	3 (38%)	0	0	1 (17%)	1 (17%)
Patients with AEs leading to Withdrawal	0	0	0	0	0
Patients with Serious AEs	0	0	0	0	0

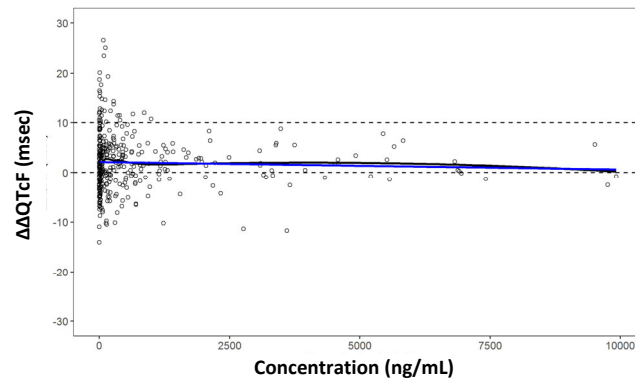
Multiple Doses	Placebo (N=8)	100 mg BID (N=8)	200 mg BID (N=8)	250 mg BID (N=8)	250 mg BID ≥ 65 (N=8)
Patients with ≥ 1 AE	5 (63%)	3 (38%)	6 (75%)	4 (50%)	5 (63%)
Patients with AEs leading to Withdrawal	0	0	0	0	0
Patients with Serious AEs	0	0	0	0	0

ATH434 was well tolerated with similar rates of AEs compared to placebo
No serious AEs or AEs leading to withdrawal

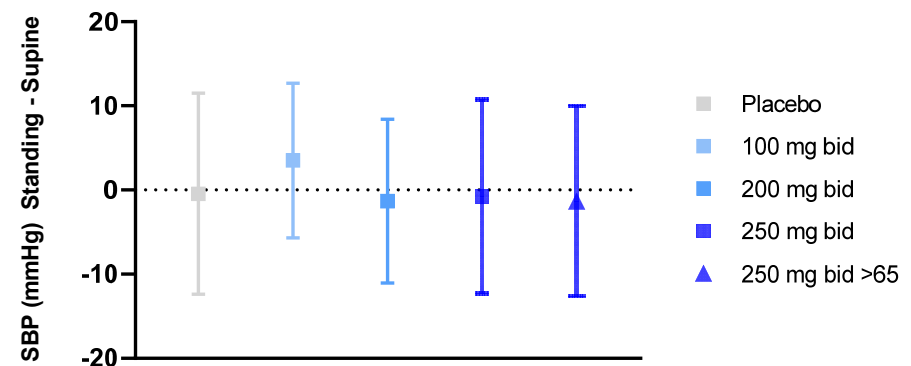
Excellent Safety Profile

- No clinically significant AEs
- All AEs were mild to moderate in severity
- Most common AEs reported in ATH434 subjects was headache
- Similar AE profile for adults and older adults (≥ 65 years)
- No significant findings observed in vital signs, clinical labs or 12-lead ECGs
- Favorable cardiovascular safety

No evidence of QT prolongation



No effect on BP with Standing



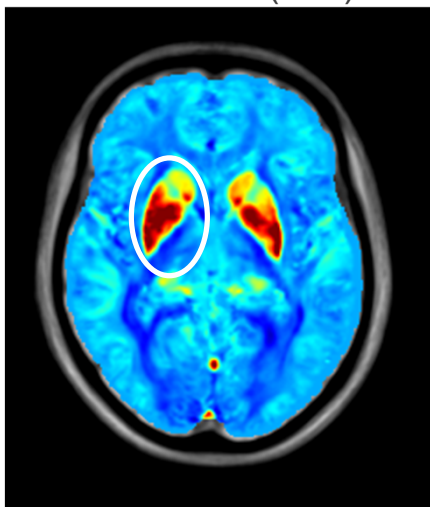
bioMUSE Natural History Study



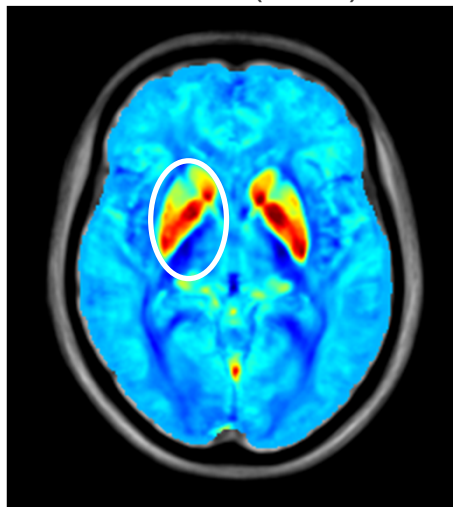
- Design: Observational (no treatment)
- Objective: De-risk Phase 2 study
 - Identify biomarker(s) suitable for endpoint in treatment study
 - Evaluate the change in biomarkers and clinical scales in patients with early MSA to track disease progression
- Population: Early MSA patients similar to Phase 2 population
- Observation period: 12 months
- Sample size: 10
- Biomarkers
 - MRI: Iron content, regional blood flow/metabolism, neuromelanin, oxidative stress
 - Protein: neurofilament light protein (CSF, plasma), Aggregating α -synuclein (CSF), phos- α -synuclein (skin)
 - Wearable movement sensors
- Clinical Endpoints
 - Clinical: Motor exam, UMSARS (function/ADL inventory), global assessments of severity and change (clinician, patient)
 - Functional: Timed Up and Go

bioMUSE – Preliminary Brain Iron Data

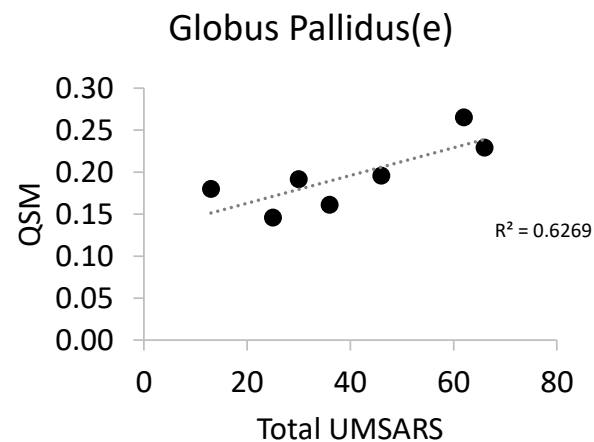
QSM MSA (n=7)



QSM PD (n=17)



- Preliminary MRI QSM data shows increased iron in bioMUSE patients
- Higher iron content than Parkinson's disease in Globus pallidus and Putamen

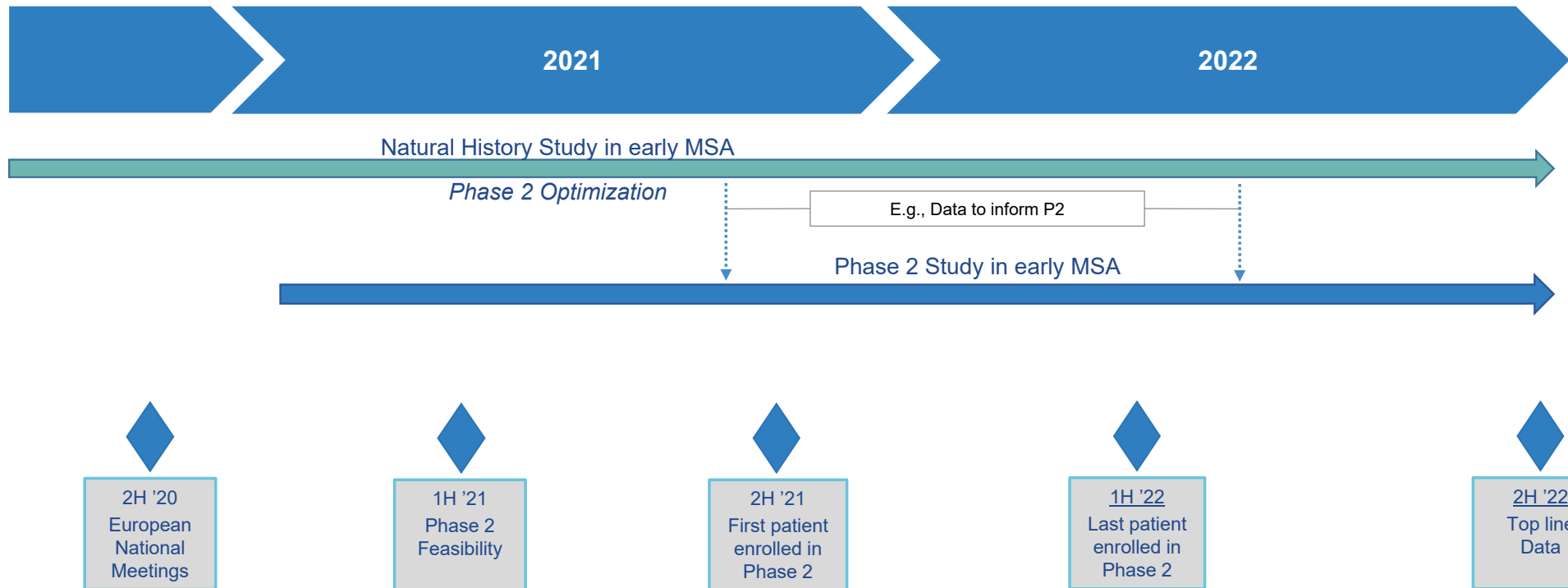


Phase 2 Design

- Design: Randomized, double-blind, placebo controlled
- Objectives:
 - Assess efficacy, safety and tolerability of ATH434 in subjects with MSA
 - Assess target engagement based on imaging and fluid biomarkers of disease progression
 - Evaluate the pharmacokinetics of ATH434 in target population
- Population: Early MSA patients
 - Parkinsonism, motor symptom onset < 3 years, ambulatory (assistance ok)
 - No severe impairment on speech, swallowing, walking, falls
- Sample size: 60
- Sites: ~25
- Treatment: 6 months
 - ATH434 high dose BID
 - ATH434 low dose BID
 - Placebo
- Efficacy Endpoints
 - MRI: Iron by QSM/R2*, neuromelanin, regional blood flow/cerebral metabolism, oxidative stress
 - Fluid/tissue biomarkers: Neurofilament light protein (CSF, plasma), Aggregating α -synuclein (CSF), phos- α -synuclein (skin)
 - Wearable movement sensors
 - Clinical: Motor exam, UMSARS (function/ADL inventory), levodopa dose equivalents, global assessments of severity and change
 - Functional: Timed Up and Go
- Safety Endpoints: AE reporting, clinical laboratory parameters, 12-lead ECGs

Clinical Development Timeline

ATH434 in Multiple System Atrophy



Competitive Landscape



AGENT (COMPANY)	INDICATION	MOA TARGET	DEVELOPMENT PHASE/ ESTIMATED COMPLETION	MEASURES/ENDPOINT	FORMULATION
RG7935/PRX002 (Roche/Prothena)	Parkinson's Disease	Alpha-synuclein Antibody	Phase 2 / Apr '20	52 wk change UPDRS	IV Infusion every 4wks
MEDI1341 (AZ/Takeda)	Parkinson's Disease	Alpha-synuclein Antibody	Phase 1 / Jan '21	Safety/Tolerability	IV infusion
Affitope® PD01A (AFFiRiS)	Parkinson's Disease	Alpha-synuclein Vaccine	Phase 2 start 2H'20	Not disclosed	Injection every 4 wks
UCB0599 (Neuropore/UCB)	Parkinson's Disease	Alpha-synuclein misfolding	Phase1b / Sep '20	Safety/Tolerability	Oral
BHV-3241/ Formerly AZD-3241 (Biohaven)	MSA	Myeloperoxidase (MPO) inhibitor	Phase 3 / Dec '21	48 wk change - UMSARS	Oral
Anle138b (MODAG)	MSA	Alpha-synuclein misfolding	Phase 1 completed	Safety/Tolerability	Oral
BIIB101 (Biogen)	MSA	SNCA ASO	Phase 1 started	Safety/Tolerability	Intrathecal
ATH434 (Alterity)	MSA	Alpha-synuclein misfolding and oxidative stress	Phase 1 completed	Safety/Tolerability	Oral

Sources: ClinicalTrials.gov; FDA Orange Book; Pharmaceutical Company Websites

Investment Summary



- ✓ Targeting Orphan disease with no approved treatments
 - ATH434 has potential U.S. peak sales up to US\$ 725 million
- ✓ Development team with proven track record at FDA
- ✓ Lead drug candidate ATH434
 - Completed Phase 1 with excellent safety profile
 - Achieved CSF concentrations associated with robust efficacy in MSA animal model
 - Novel mechanism targets α -synuclein aggregation and root cause of oxidative stress
- ✓ Phase 2 program
 - Ongoing Natural History study to de-risk P2 study
 - Enrollment to start 2H '21
- ✓ Strong pipeline potential with new patent family supporting next generation therapies

