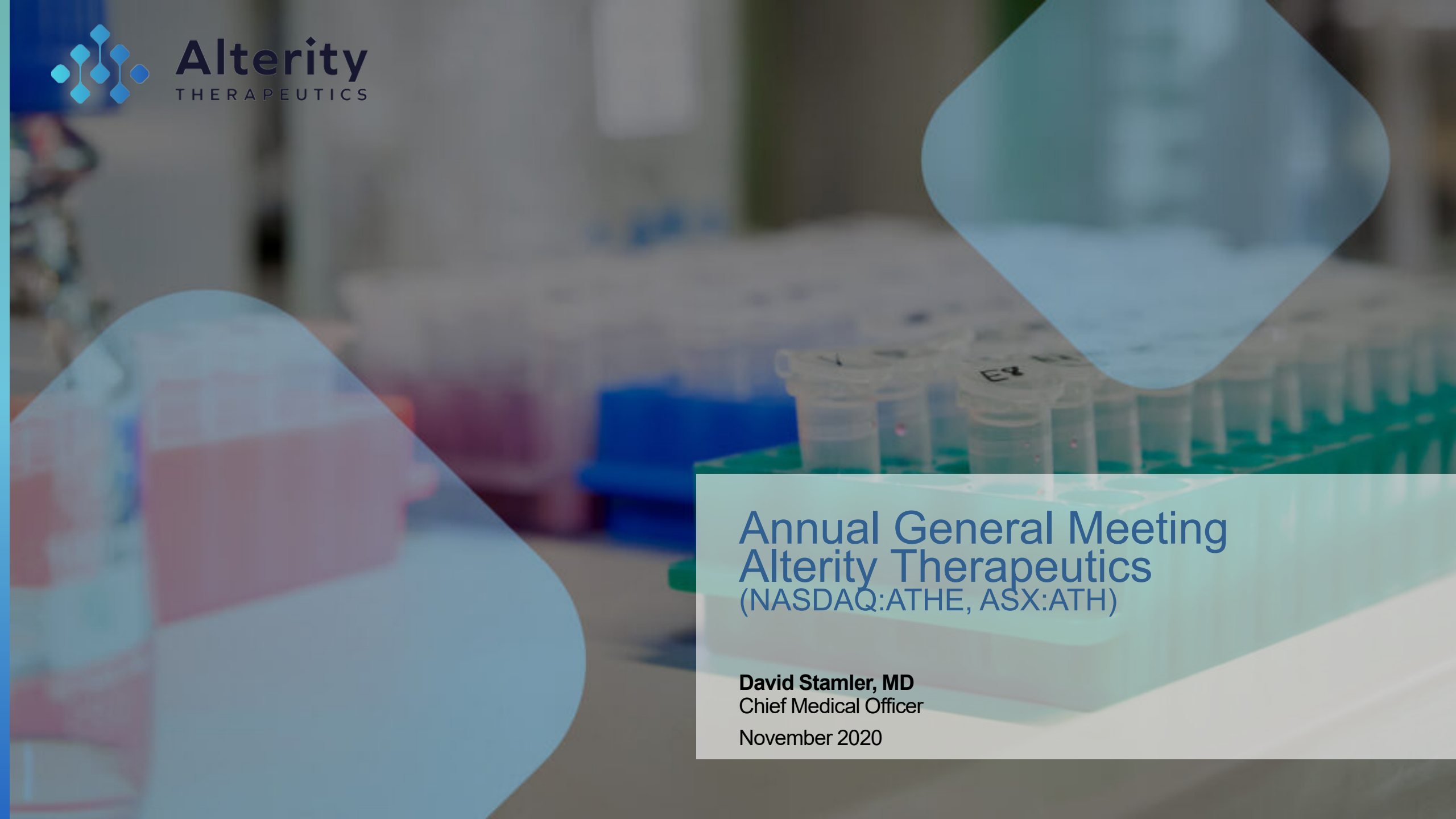


Annual General Meeting
Alterity Therapeutics
(NASDAQ:ATHE, ASX:ATH)

David Stamler, MD
Chief Medical Officer

November 2020

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.

Year in Review

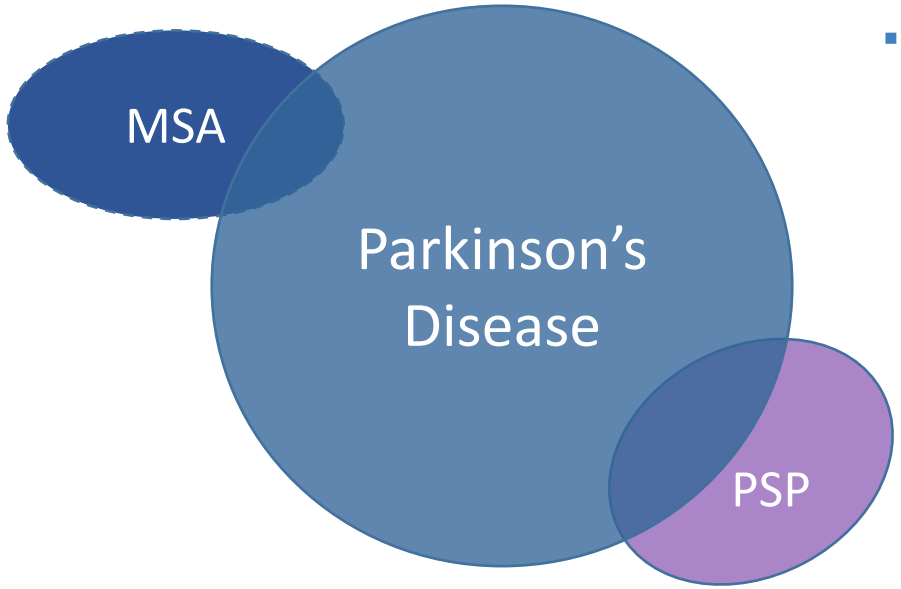
Alterity THERAPEUTICS

- Allowance of US patent for next generation compounds to treat neurodegenerative diseases
- Raises $35M in placement to international and Australian institutions and sophisticated investors
- Commences 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
- ATH434 crosses blood brain barrier in humans; clinically tested doses achieved concentrations in the brain
- European Commission approves Orphan Designation
- ATH434 clinical data presented at the 2019 MDS Congress
-
Completion of Phase 1 Clinical Trial

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



- Parkinsonian disorders also include atypical variants such as Multiple system atrophy (MSA) and Progressive supranuclear palsy (PSP)
  - Atypical forms have prominent non-motor symptoms and a limited response to available treatments
  - Lead indication is MSA, a highly debilitating disease with no approved treatments

Leadership of 3 FDA Approvals in Neurology

David Stamler, M.D.
Chief Medical Officer

- 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** (Nonclinical, CMC and Clinical operations) joined Alterity in 2017

BioSpace

FDA Advisory Committee Votes Unanimously to Recommend Approval of Tetrabenazine for Chorea Associated With Huntington Disease
Dec 7, 2007

FierceBiotech

XENAZINE® (Tetrabenazine) Approved by FDA for Patients with Chorea Associated with Huntington's Disease
Aug 15, 2008

PharmaTimes online

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

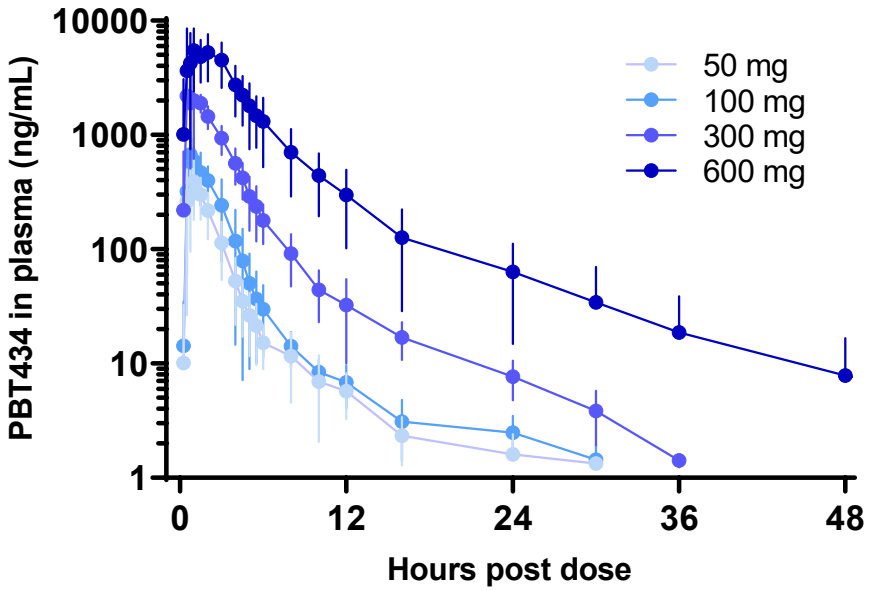
- Robust efficacy in animal models of disease
  - Evidence of neuroprotection with ATH434 treatment
  - Findings corroborated in multiple labs
- Completed Phase 1
  - Orally bioavailable, brain penetrant
  - ATH434: safe and well tolerated
  - Achieved brain levels of ATH434 comparable to efficacious levels in animal models of MSA
- Qualitative research with U.S. neurologists completed
  - 15 movement disorder specialists and 15 general neurologists

- Selected MSA as lead indication
- Orphan Designation granted in US and EU in 2019
  - US Food and Drug Administration (FDA): 7 years of market exclusivity
  - European Commission: 10 years of market exclusivity
  - Estimated U.S. prevalence of MSA is 11,000 to 14,000 patients
- Preparation for Phase 2 underway
  - Natural history/P2 optimization study commenced
  - Long term toxicology ongoing
  - GMP manufacturing of API and tablets progressing to plan
  - FDA meeting to set development path

Clinical Development

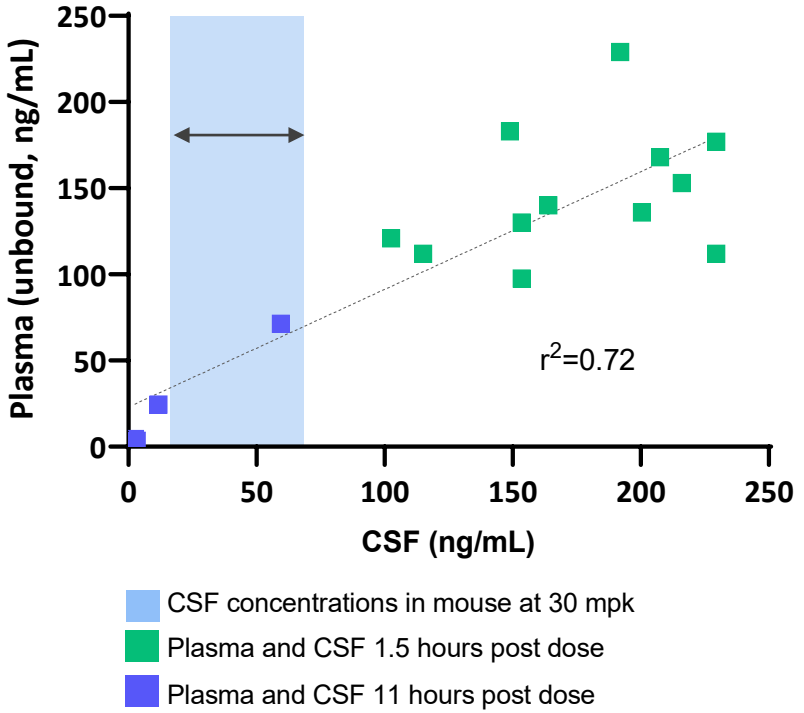
Phase 1 Completed
Clinical Pharmacokinetics of ATH434

Plasma Profile after Single Dose Administration



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

CSF Levels at Steady-State



- CSF concentrations at well-tolerated doses in subjects exceeded those associated with efficacy in animal models of PD and MSA

Stamler et al. Neurology 2019; 92 (15 Suppl.)

Adverse Event Summary

Single Ascending 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 Ascending 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 with ATH434 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 laboratory parameters or 12-lead ECGs
- No evidence of QT prolongation at projected clinical doses

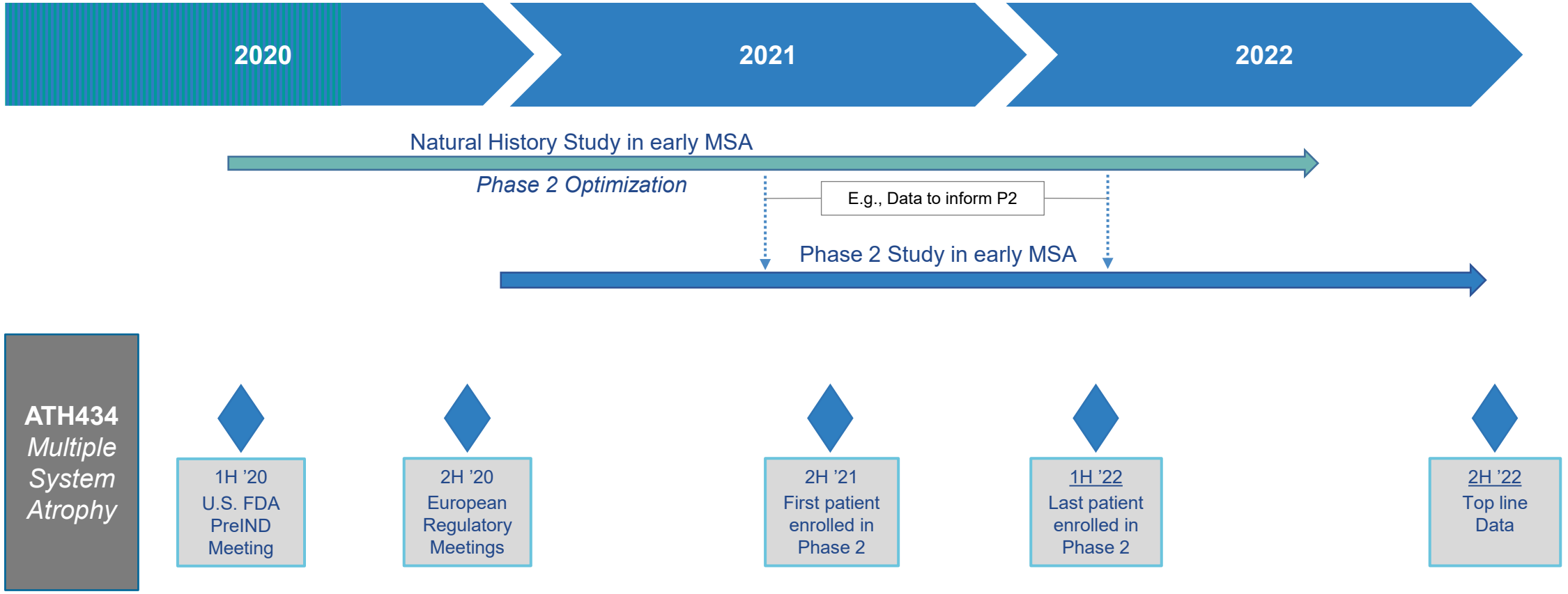
bioMUSE Natural History Study

- 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 manifestations in patients with early MSA to track disease progression
- Population: Early MSA patients similar to Phase 2 population
- Observation period: 12 months
- Initial cohort: 10
- Biomarkers
  - MRI: Iron content, neuromelanin, oxidative stress, regional blood flow/metabolism
  - Protein: neurofilament light protein (CSF, plasma), Aggregating α-synuclein (CSF), phos-α-synuclein (skin)
  - Wearable movement sensors
- Clinical Endpoints
  - Clinical: Motor exam, function/ADL inventory, global assessments of severity and change (clinician, patient)
  - Functional: Timed Up and Go, 2 min Walk Test

Phase 2 Study Design

- Design: Randomized, double-blind, placebo controlled
- Objectives
  - Assess target engagement and preliminary efficacy of ATH434
  - Evaluate safety and tolerability of ATH434
- Population: Early MSA patients (parkinsonian variant) with motor symptoms ≤ 3 years
- Sample size: 60
- Treatment: 6 months duration
  - ATH434 high dose
  - ATH434 low dose
  - Placebo
- Biomarkers
  - MRI: Iron content, neuromelanin, oxidative stress, regional blood flow/metabolism
  - Protein: neurofilament light protein (CSF, plasma), Aggregating α-synuclein (CSF), phos-α-synuclein (skin)
  - Wearable movement sensors
- Clinical Endpoints
  - Clinical: Motor exam, function/ADL inventory, global assessments of severity and change (clinician, patient)
  - Functional: Timed Up and Go, 2 min Walk Test
- Safety Endpoints: AEs, clinical laboratory parameters, 12-lead ECGs

Clinical Development Timeline



Commercial

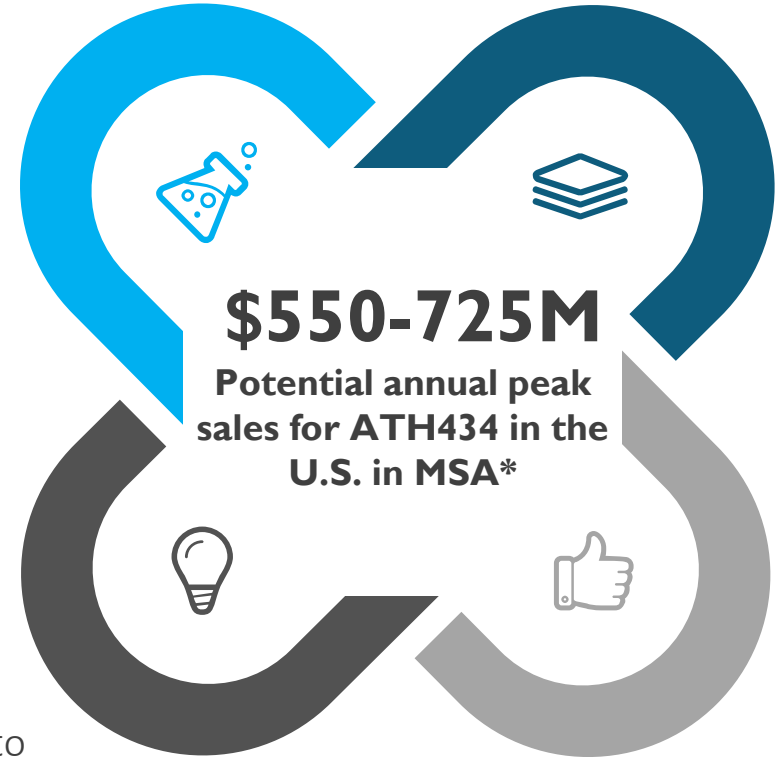
Commercial Opportunity – Multiple System Atrophy
Independent Analysis

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.

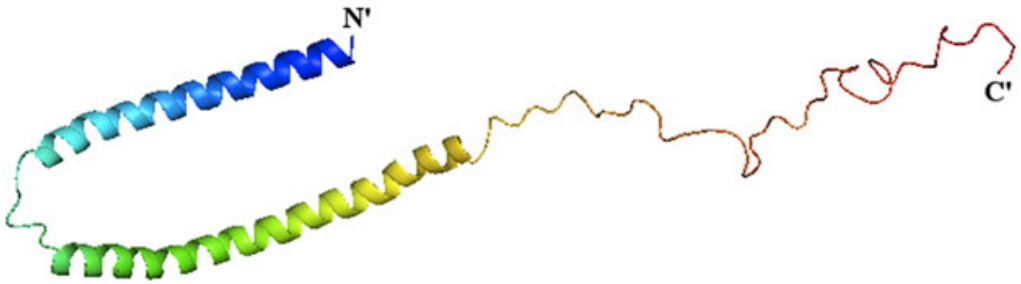
*Does not include spontaneous use in PD

Deal Landscape

	Biogen Sangamo Therapeutics	Biogen Pfizer	Alector abbvie	Takeda Denali Therapeutics	Roche prothena
Target / Therapeutic area	Neuro including AD, PD	AD & PD	AD	Neuro including AD, PD	PD
Development phase	Preclinical	Phase 1	Phase 1	Preclinical	Preclinical
Royalties (% on net sales)	High-single to low double-digit	Sub-teens to High single-digit	Undisclosed	Undisclosed	Double-digit
Upfront & equity	$125m payment + $225m in equity purchase	$75m	$205m payment + $20m in equity purchase	$150m	$45m
Milestones	Up to $2.37b $925m pre-commercial, $1.445b for sales thresholds	Up to $635m Development, commercial	Up to $986m	Up to $90m	Up to $600m Development, commercial

Scientific Background

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

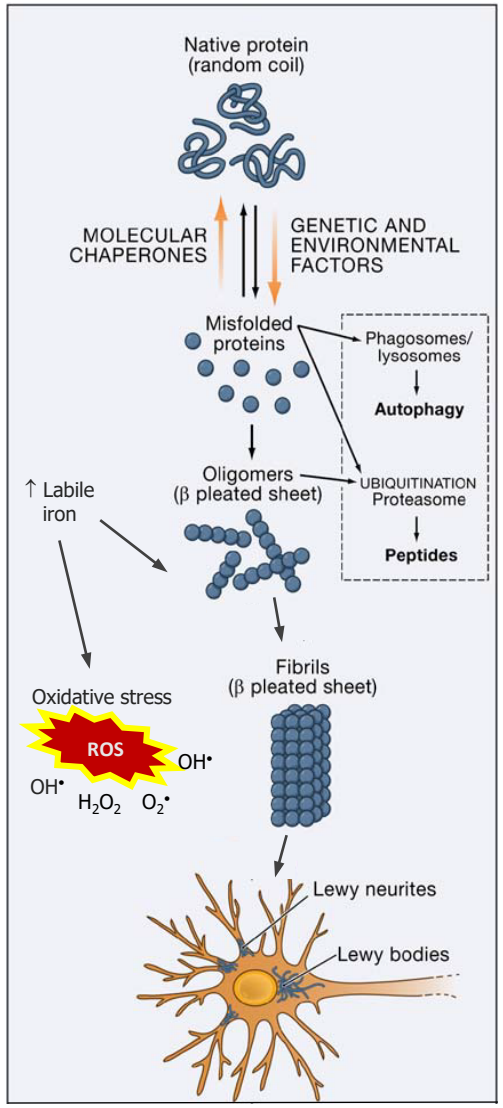
➢ α-Synuclein *aggregates* in certain Parkinsonian conditions such as PD and MSA

"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.

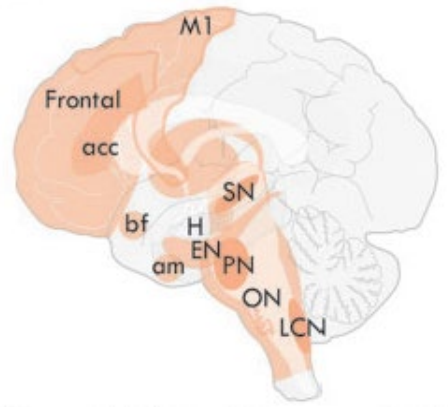
DOI:10.4236/health.2012.431175

Disease Background and Strategy Overview



Adapted from Lee & Trojanowski, Neuron 2006

- Lead indication: Multiple System Atrophy (MSA)
  - Severely debilitating and rapidly progressive disease
  - No approved therapy for treatment of MSA
  - Characterized by Parkinsonism, autonomic instability and/or cerebellar impairments
  - Pathological hallmark: accumulation of α-synuclein within oligodendroglia cells (glial cell inclusions) and neuron loss in multiple brain regions

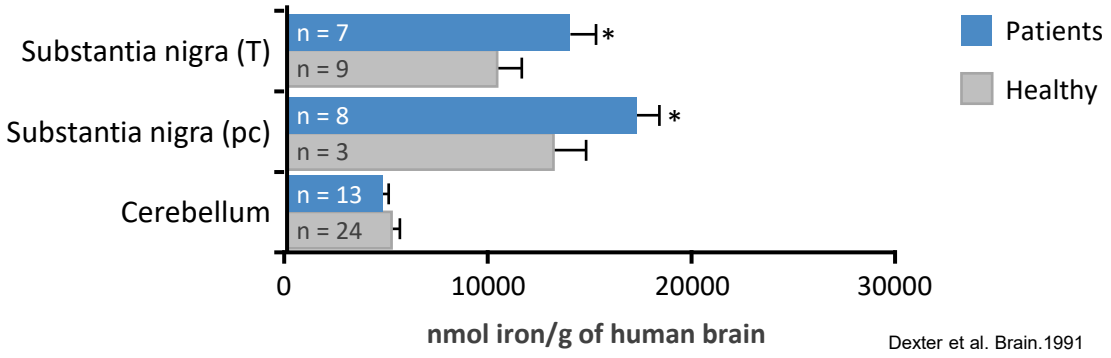


Halliday Brain 2015, based on Cykowski et al, Brain 2015

- Disrupt the underlying pathology of α-synuclein related diseases
  - MSA, a form of atypical parkinsonism
  - Parkinson's disease
- Inhibit accumulation and aggregation of intracellular α-synuclein
- Target "labile iron" which is increased in areas of pathology

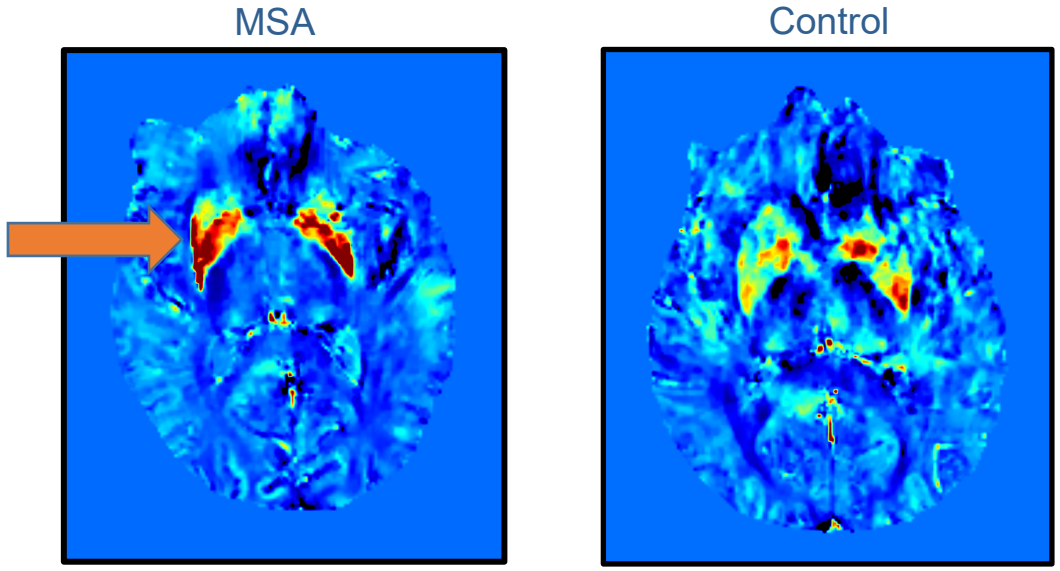
Increased Brain Iron in Synuclein-related Diseases

Parkinson's disease



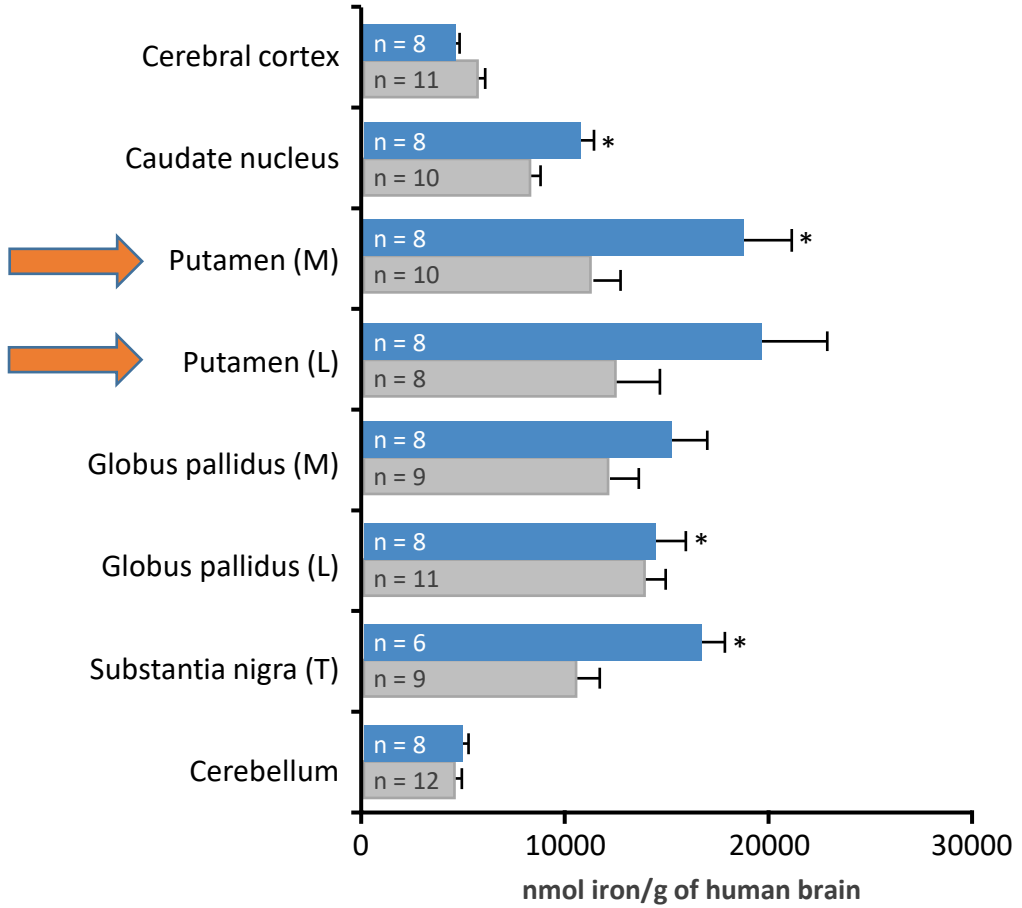
Dexter et al. Brain.1991

Quantitative Susceptibility Mapping (MRI) to assess brain iron

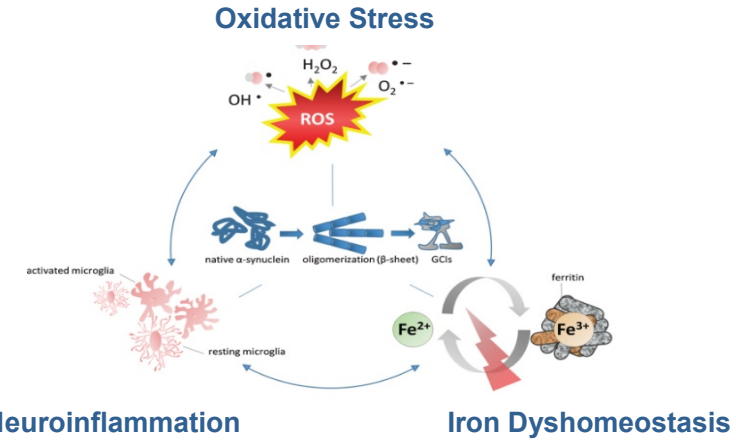


Courtesy of P. Trujillo, D. Claassen

Multiple System Atrophy

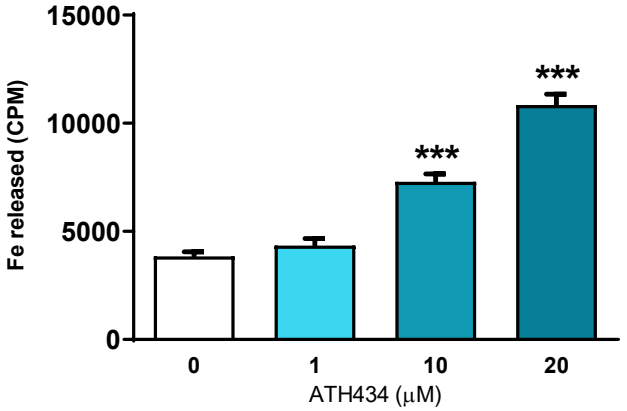


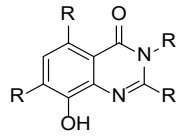
Iron is Critical in the Pathogenesis of MSA



- Abundant evidence that labile iron is central in the pathogenesis of MSA
- Adverse impact of increased labile iron
  - α-synuclein aggregation
  - α-synuclein accumulation
  - *root cause* of oxidative stress which promotes free radical production and neuroinflammation

ATH434 restores intracellular iron balance





ATH434

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

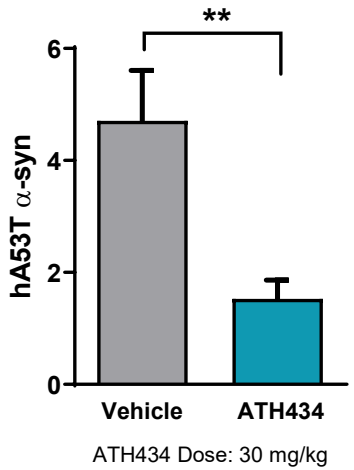
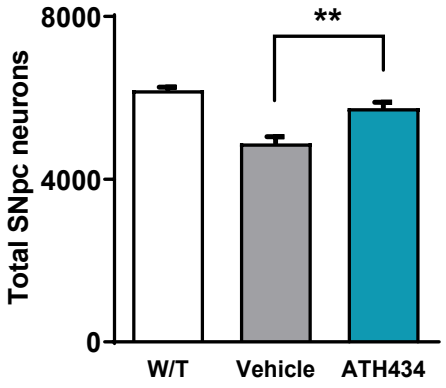
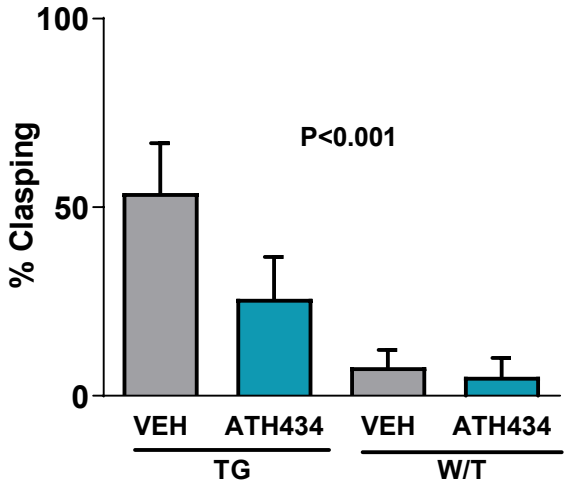
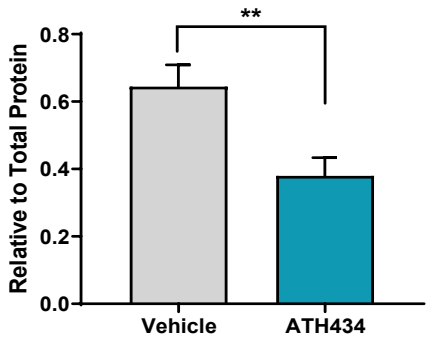
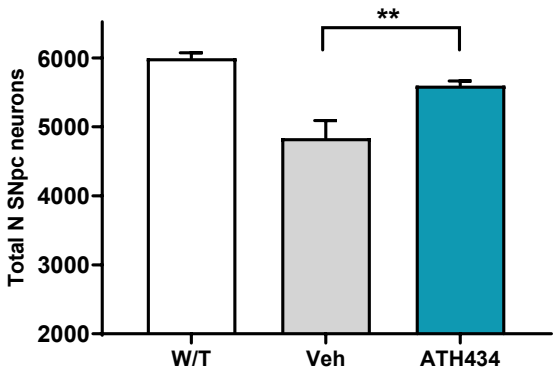
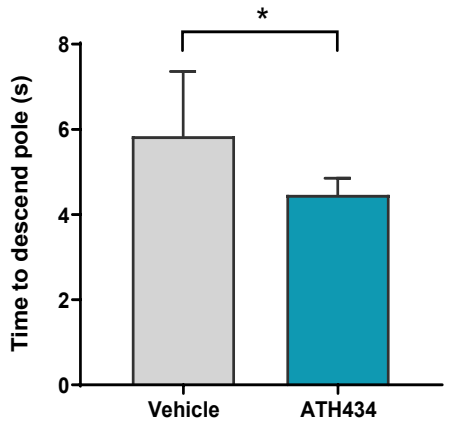
Stronger binding

ATH434 binds iron more tightly than α-synuclein but less than key iron trafficking proteins

Kaindlstorfer, et al. J. Alzheimers Dis. 2018
Rodgers, et al. J Neural Transm (Vienna). 2011

ATH434 Reduces Alpha-Synuclein-related Neuropathology
Preserves Neurons and Improves Function in PD and MSA Animal Models

Alterity THERAPEUTICS

	↓ α-Synuclein	Preserves nigral neurons	Improves motor function
Parkinson's disease model			
MSA model			

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

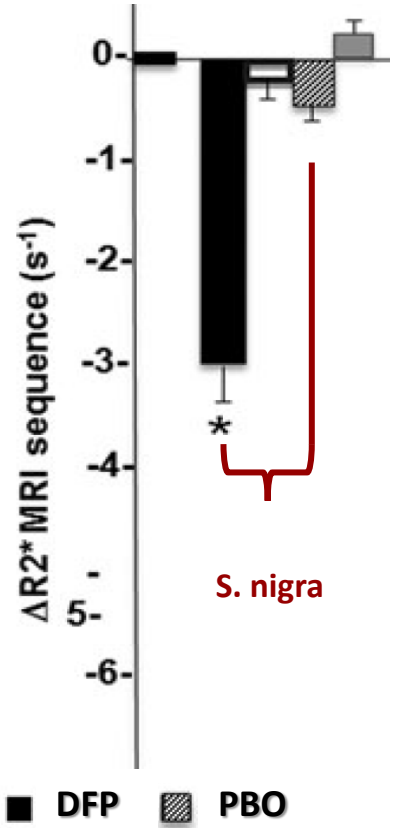
* P < 0.05, ** P < 0.01, *** P < 0.001

Strategy Supported by Proof of Concept in Parkinson's

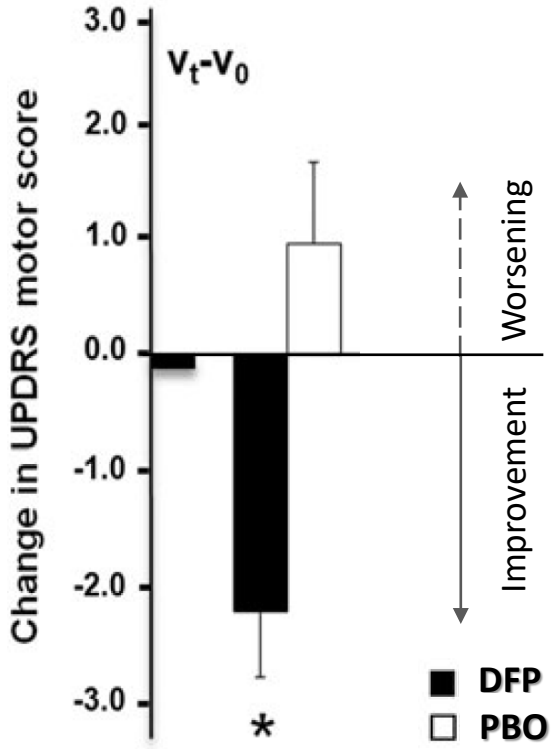
6 month placebo-controlled data from study of Deferiprone – a drug for treating iron overload

Alterity THERAPEUTICS

Brain Iron by MRI



Motor Symptom Severity



Reducing excess iron led to improved motor function

Deferiprone

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

Ligand	Kd for Fe^{3+}
α-Synuclein	10^{-5}
ATH434	10^{-10}
Ferritin	10^{-22}
Transferrin	10^{-23}
Deferiprone	10^{-36}

Stronger binding

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)**

Adapted from Devos. Antiox. and Redox Signaling. 2014

Competitive Landscape

AGENT (COMPANY)	INDICATION	MOA TARGET	DEVELOPMENT PHASE/ ESTIMATED COMPLETION	MEASURES/ENDPOINT	FORMULATION
BIIB054 (Biogen)	Parkinson's Disease	Alpha-synuclein Antibody	Phase 2 / 2H '20	Safety, PK and PD	IV Infusion every 4wks
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 started mid '19	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
  - Commenced natural history study to inform Phase 2 study
  - 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 data 2H ‘22
- ✓ Strong pipeline potential with new patent family supporting next generation therapies
- ✓ Strong balance sheet

Alterity
THERAPEUTICS