



# Alterity Annual General Meeting

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# Clinical Target – Parkinsonian Disorders

## Significant unmet medical need



- Parkinsonian disorders include Parkinson disease and atypical forms such as Multiple system atrophy (MSA) and Dementia with Lewy Bodies
  - Atypical forms have ancillary symptoms and a limited response to available treatments
- Parkinsonism is a syndrome of motor symptoms that include slowness of movement, stiffness and tremor
- First therapeutic target for PBT434 – Multiple System Atrophy (MSA), a devastating and rapidly progressive neurological disease with no approved treatments
- Alterity is targeting these neurodegenerative diseases which share a unifying feature –  $\alpha$ -synuclein aggregation and increased iron in areas of pathology

## Orphan Designation PBT434 for the treatment of MSA



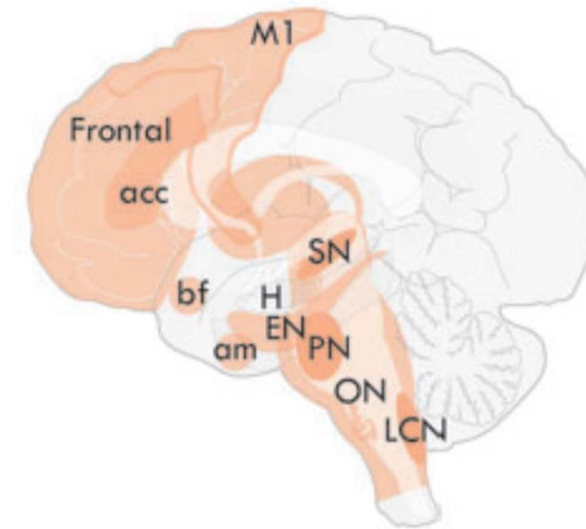
- In January 2019, US Food and Drug Administration (FDA) granted Orphan Drug Designation for PBT434
  - 7 years of market exclusivity for use of PBT434 in the treatment of MSA
  - Development incentives of the Orphan Drug Act 1983, including tax credits for qualified clinical testing
- In November 2019, we received positive opinion from the Committee for Orphan Medicinal Products of the European Medicines Agency (EMA) for PBT434
  - Anticipate a decision on Orphan Designation from the European Commission in the near term

# Multiple System Atrophy

## A form of atypical parkinsonism



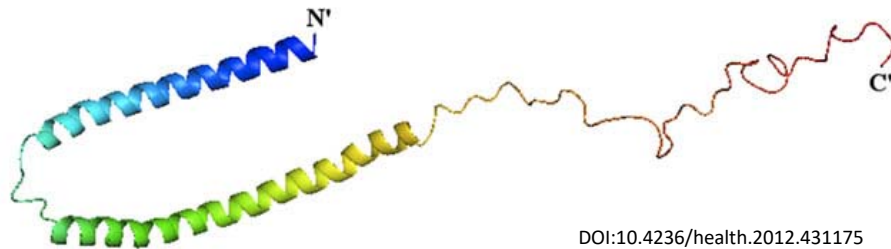
- Orphan disease
- No drug approved for treatment of MSA
- Characterized by Parkinsonism (motor symptoms), difficulty maintaining blood pressure and/or problems with gait, balance and coordinating movements
- Hallmark of MSA: accumulation of  $\alpha$ -synuclein and neuron loss in multiple brain regions



Map of brain of  
MSA Patient

Halliday 2015, based on  
Brain 2015: 138; 2293–2309

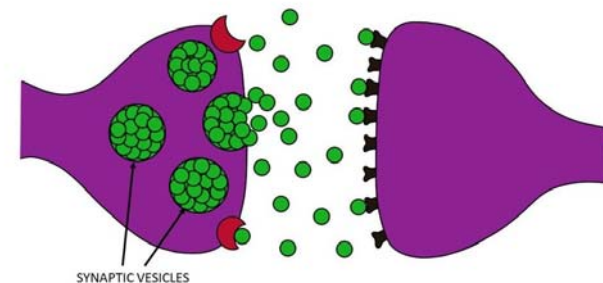
# PBT434 Targets Alpha-Synuclein



DOI:10.4236/health.2012.431175

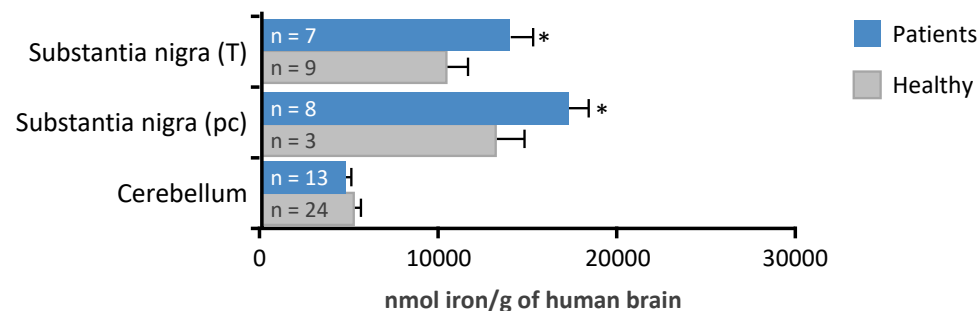


- $\alpha$ -synuclein is an established disease target
- Abundant protein in the brain
- Critical for normal function of neurons
- Key protein involved in neurotransmission
  - Enables neurotransmitter release through synaptic vesicle fusion to nerve terminal



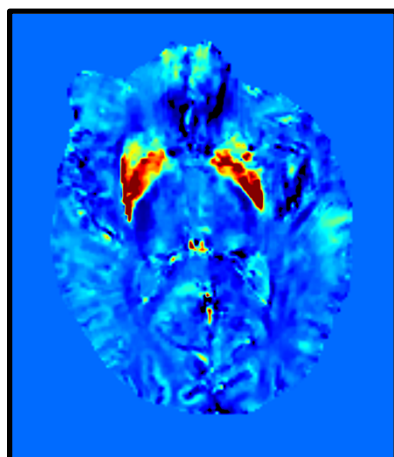
# Brain Iron Increased in Areas of Pathology

## Parkinson's disease

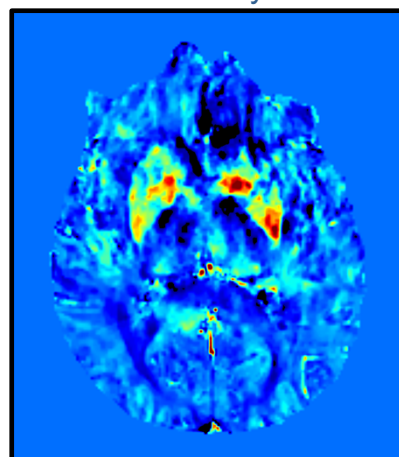


## Specialized MRI to Measure Brain Iron

MSA

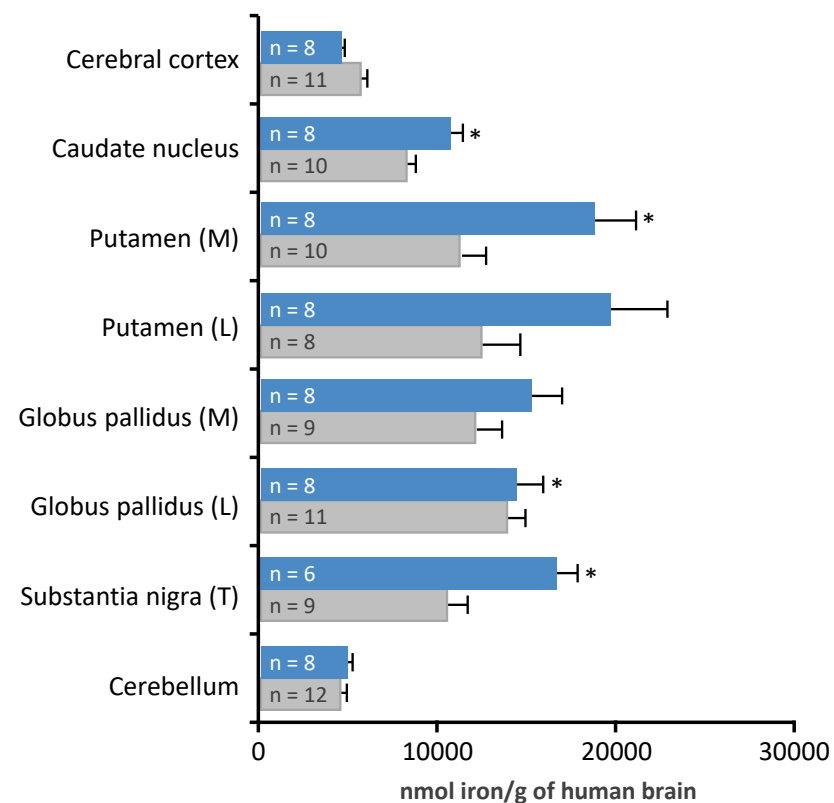


Healthy



Courtesy of P. Trujillo, D. Claassen

## Multiple System Atrophy



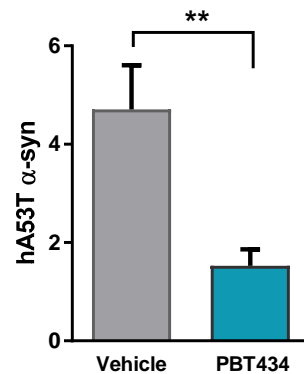
Dexter et al. Brain.1991;114

# PBT434 is Efficacious in Parkinsonian Disease Animal Models

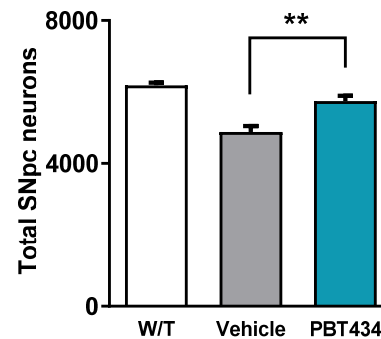


## Parkinson's disease Model

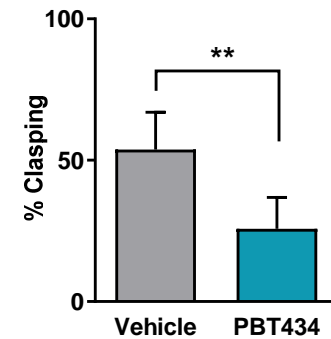
↓  $\alpha$ -Synuclein aggregation



Preserves nigral neurons

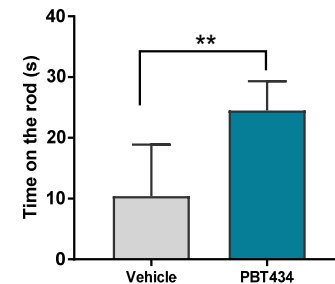
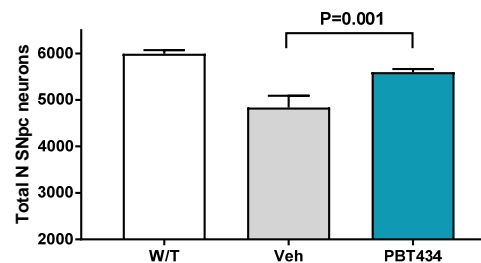
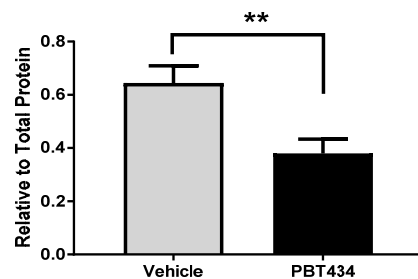


Improves motor function



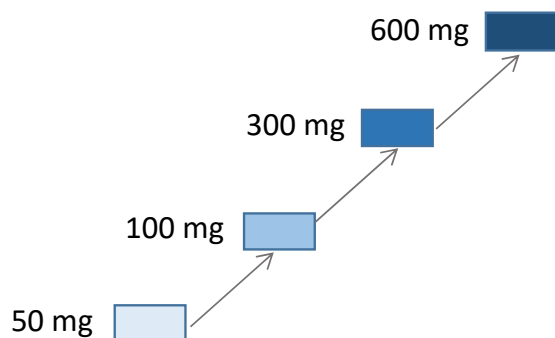
## Atypical Parkinson's Model

Aggregated

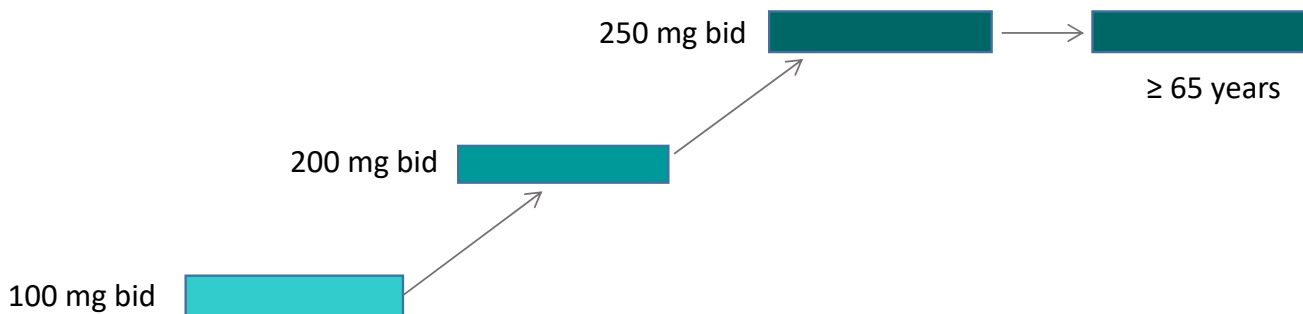


# Phase 1 Design

- Population: Healthy adult and older adult ( $\geq 65$  yo) volunteers



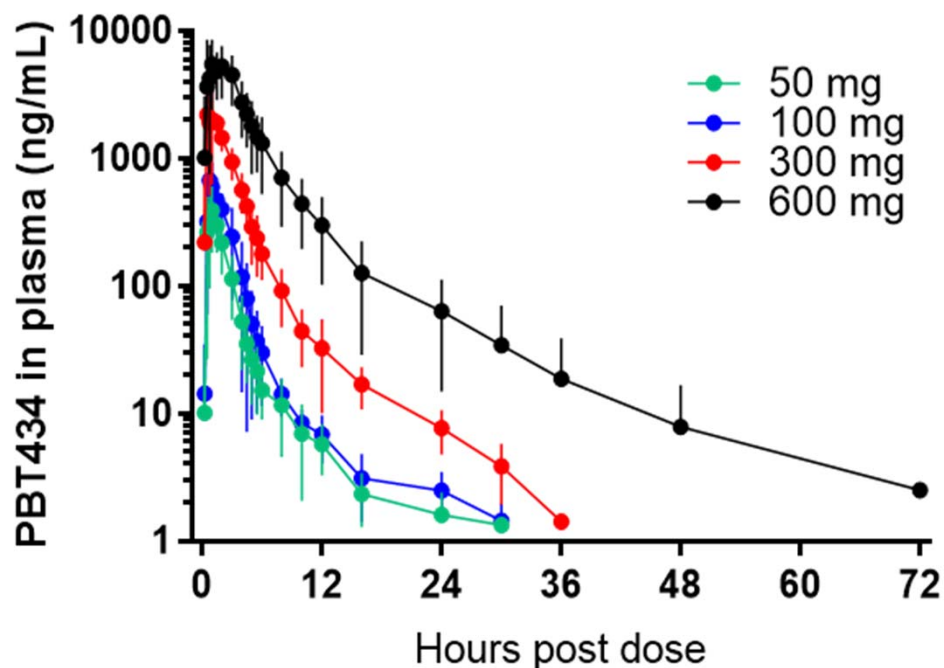
Single Ascending Doses  
(6A:2P/cohort)



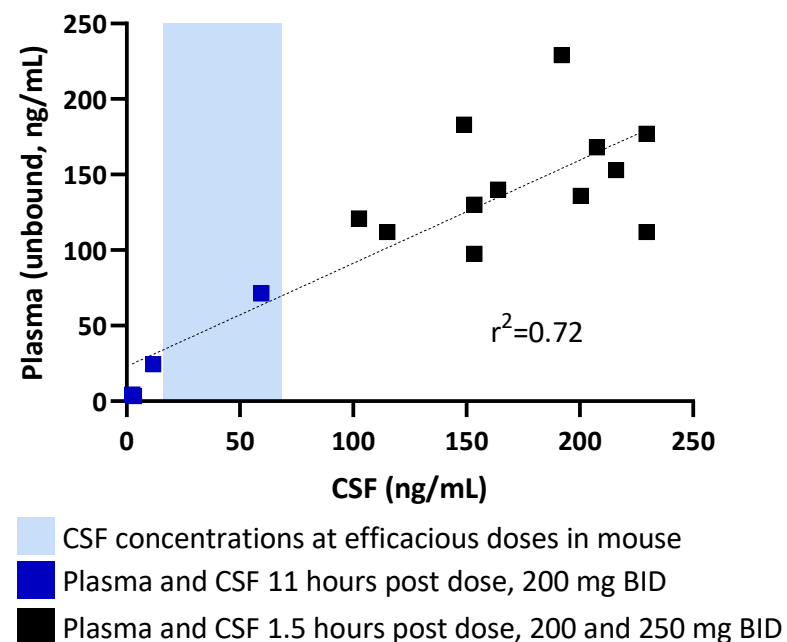
Multiple Ascending Doses  
(8A:2P/cohort)

# Plasma and Spinal Fluid Concentrations of PBT434

Plasma after Single Doses



Spinal Fluid at Steady-State



## Takeaways

- PBT434 demonstrated dose dependent pharmacokinetics with a mean elimination half-life up to 9.3 hrs
- CSF concentrations of PBT434 at doses  $\geq 200$  mg BID were greater than those associated with robust efficacy in animal models of PD and MSA**

## Safety of PBT434



- All adverse events (AEs) were mild to moderate in severity
- No serious AEs or AEs leading to discontinuation in any subject
- Headache was the most common AE in subjects receiving 8 days PBT434
- The AE profile was similar for adult and  $\geq 65$  year-old volunteers
- No clinically significant findings were observed in vital signs, clinical laboratory parameters or 12-lead ECGs

# Summary



- ✓ Targeting Orphan disease with no approved treatments
  - Potential peak sales of US\$750 million (U.S. only)
- ✓ Development team with proven track record at FDA
- ✓ Lead drug candidate passed Phase 1
  - PBT434 was well tolerated with an AE profile comparable to placebo
  - PBT434 achieved CSF concentrations exceeding those associated with robust efficacy in MSA animal model of MSA
- ✓ Phase 2 planning ongoing
  - Preparing for FDA interaction
  - Phase 2 optimization study to start in near term
- ✓ Strong pipeline potential

