Alterity Annual General Meeting

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Clinical Target – Parkinsonian Disorders
Significant unmet medical need

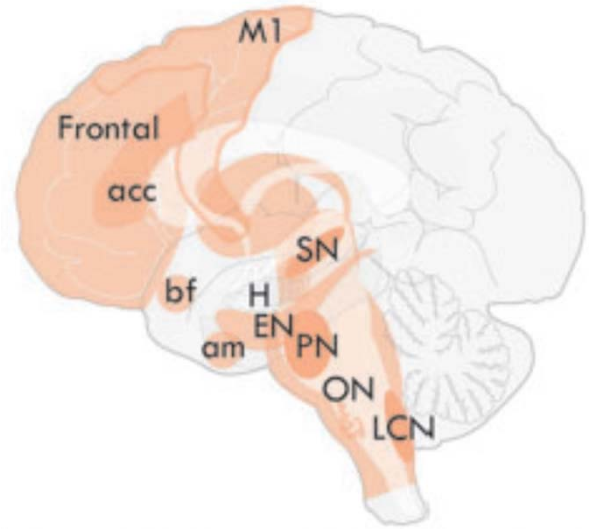
- Parkinsonian disorders include Parkinson disease and atypical forms such as Multiple system atrophy (MSA) and Dementia with Lewy Bodies
  - Atypical forms have ancillary symptoms and a limited response to available treatments
- Parkinsonism is a syndrome of motor symptoms that include slowness of movement, 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 – α-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

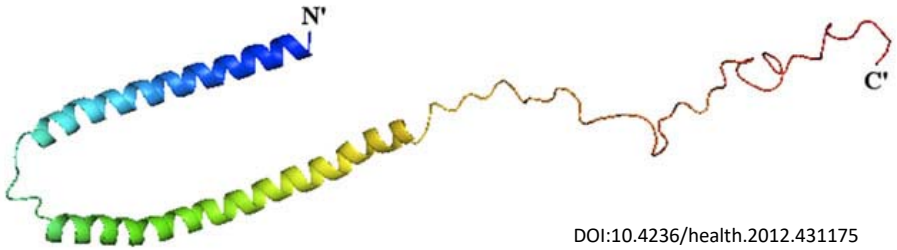
- Orphan disease
- No drug approved for treatment of MSA
- Characterized by Parkinsonism (motor symptoms), difficulty maintaining blood pressure and/or problems with gait, balance and coordinating movements
- Hallmark of MSA: accumulation of α-synuclein and neuron loss in multiple brain regions



Map of brain of MSA Patient

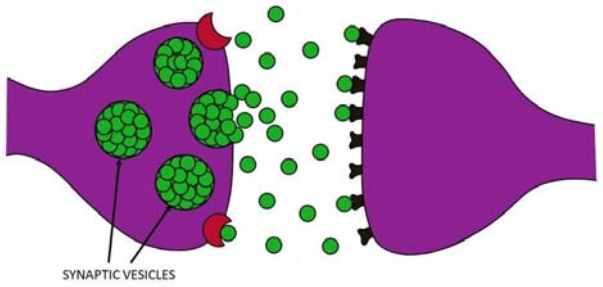
Halliday 2015, based on
Brain 2015: 138; 2293–2309

PBT434 Targets Alpha-Synuclein



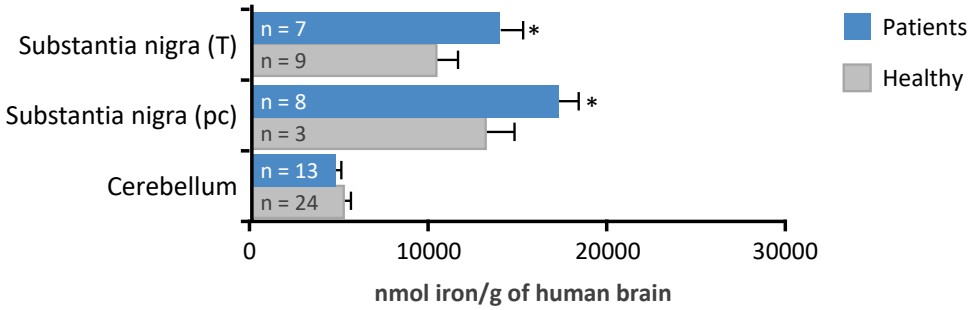
DOI:10.4236/health.2012.431175

- α-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



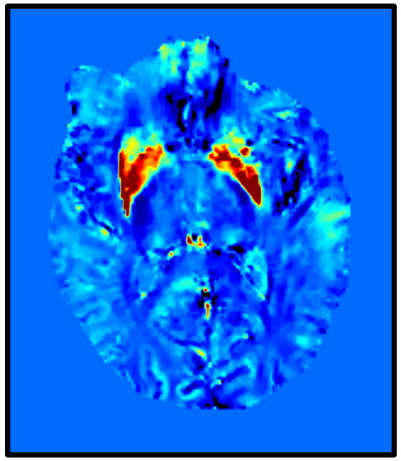
Brain Iron Increased in Areas of Pathology

Parkinson's disease

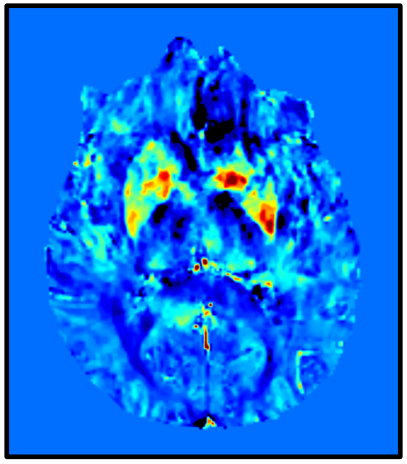


Specialized MRI to Measure Brain Iron

MSA

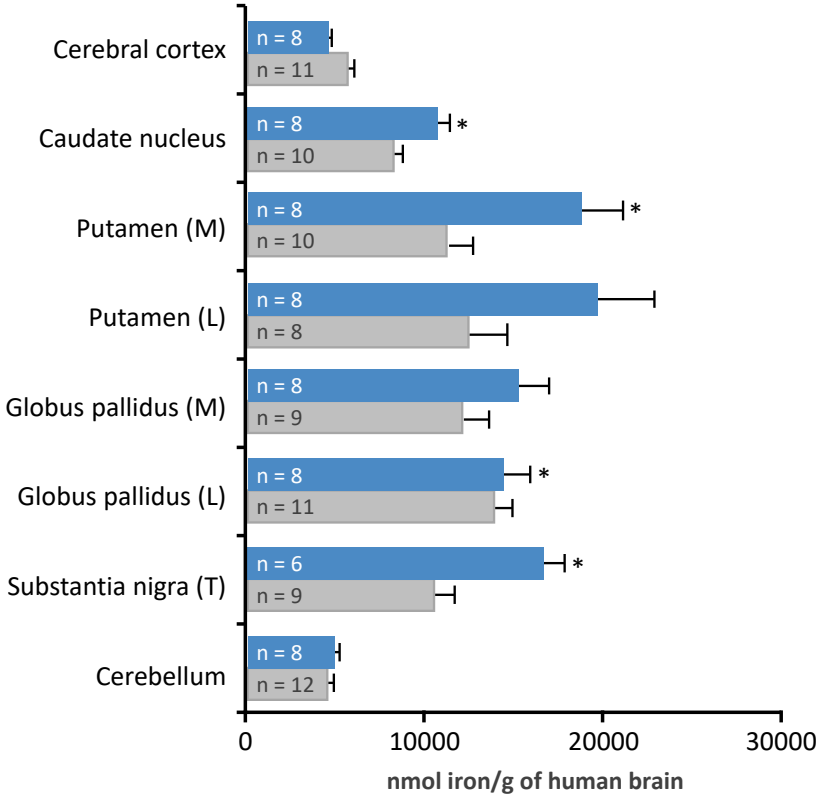


Healthy



Courtesy of P. Trujillo, D. Claassen

Multiple System Atrophy

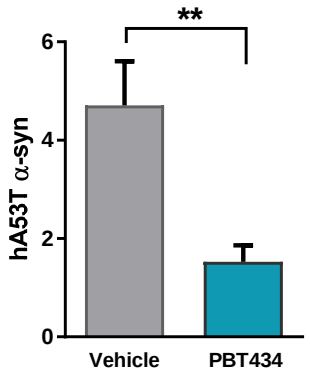


Dexter et al. Brain.1991;114

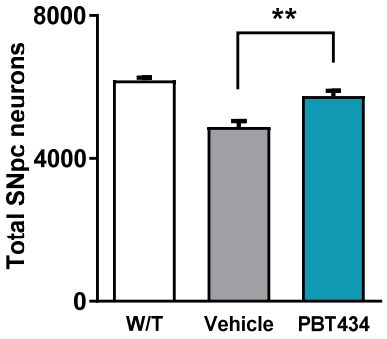
PBT434 is Efficacious in Parkinsonian Disease Animal Models

Parkinson's disease Model

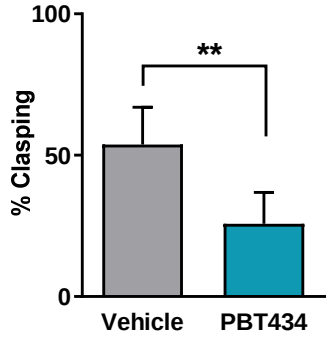
↓ α-Synuclein aggregation



Preserves nigral neurons

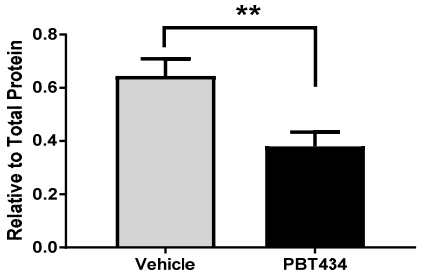


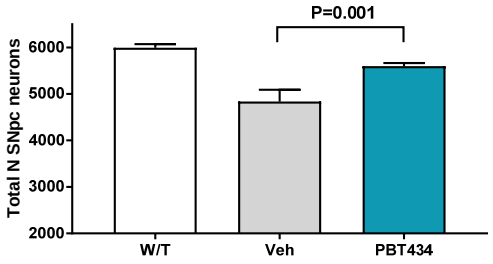
Improves motor function

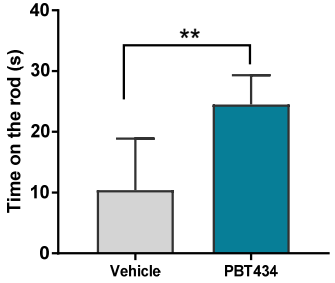


Atypical Parkinson's Model

Aggregated



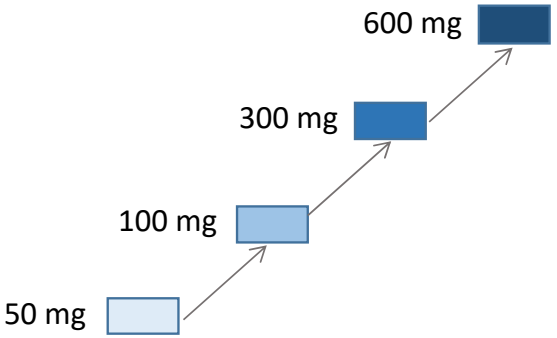




Finkelstein et al. Acta Neuropath Comm (2017) 5:53
Finkelstein et al. Movement Disorders (2018) Vol. 33, Suppl. 2

Phase 1 Design

- Population: Healthy adult and older adult (≥65 yo) volunteers

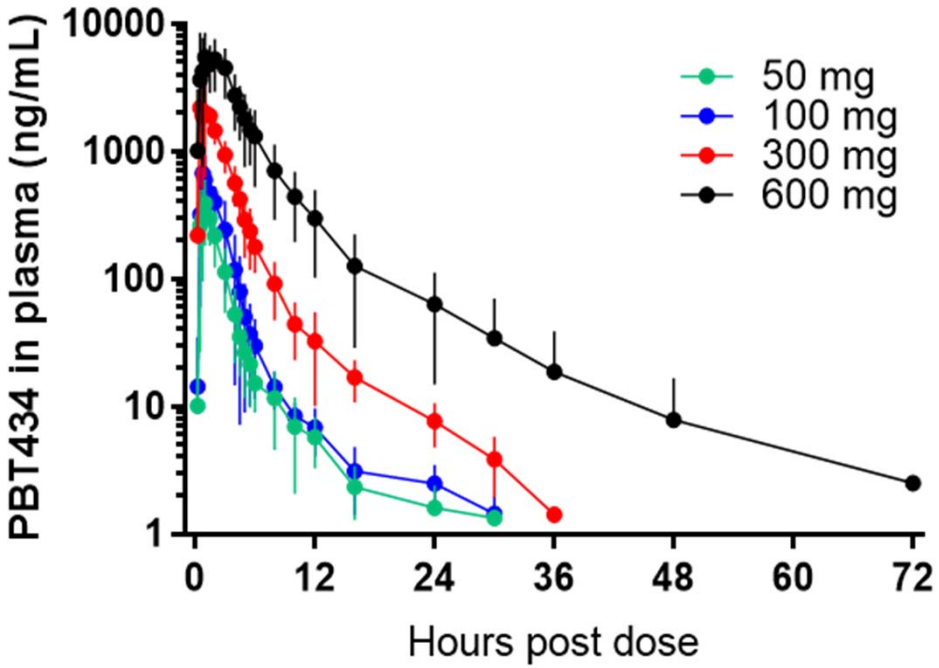


Single Ascending Doses
(6A:2P/cohort)

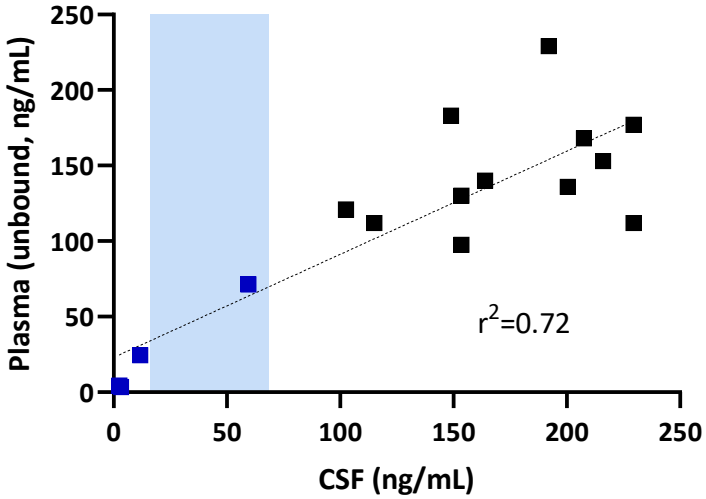
Multiple Ascending Doses
(8A:2P/cohort)

Plasma and Spinal Fluid Concentrations of PBT434

Plasma after Single Doses



Spinal Fluid at Steady-State



CSF concentrations at efficacious doses in mouse

Plasma and CSF 11 hours post dose, 200 mg BID

Plasma and CSF 1.5 hours post dose, 200 and 250 mg BID

Takeaways

- PBT434 demonstrated dose dependent pharmacokinetics with a mean elimination half-life up to 9.3 hrs
- **CSF concentrations of PBT434 at doses ≥ 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 ≥ 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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THERAPEUTICS