A First in Human Study of PBT434, a Novel Small Molecule Inhibitor of α-Synuclein Aggregation

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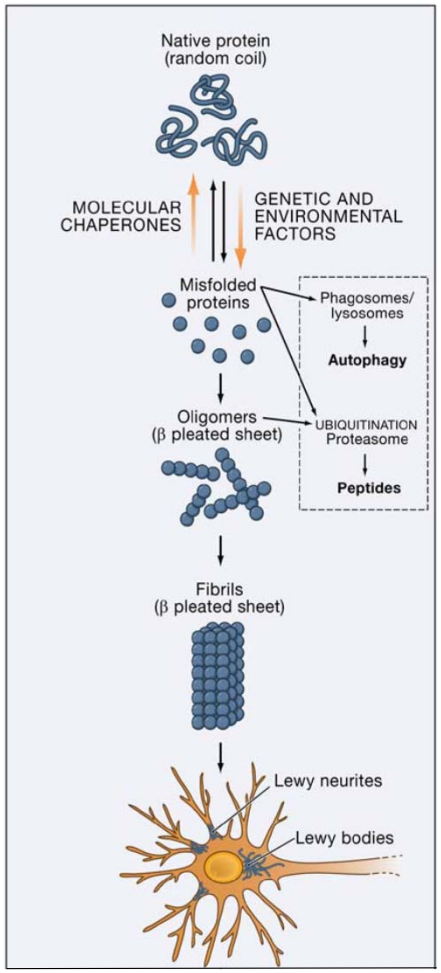
American Academy of Neurology – S4.001

Sunday, May 5, 2019

Disclosures

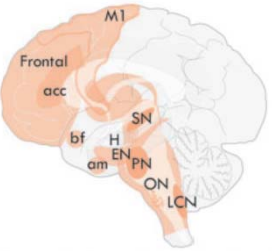
- Authors are employees or paid consultants of Alterity Therapeutics

Therapeutic Strategy



Lee and Trojanowski, 2006

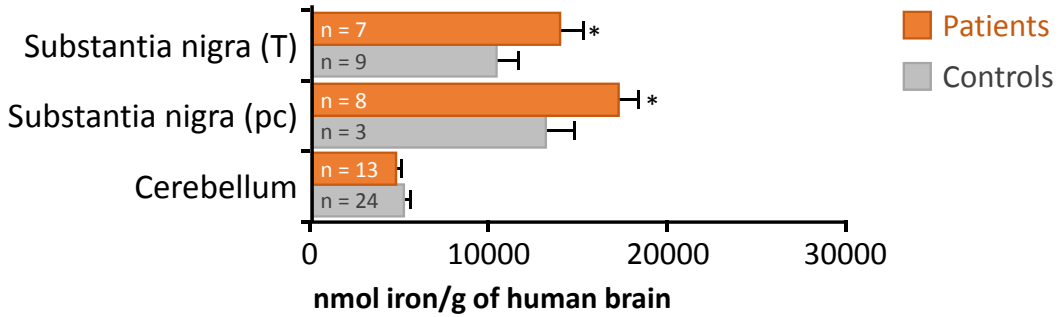
- Disrupting the underlying disease process of synucleinopathies
  - Parkinson's disease
  - Atypical parkinsonism
- Inhibit accumulation and aggregation of intracellular α-synuclein
- Target "labile" iron which is increased in disease
- Oral agent, crosses BBB
- Initial disease target: Multiple system atrophy (MSA)
  - Orphan disease (prevalence of ~5 per 100,000)
  - No therapy approved for treatment of MSA
  - Characterized by Parkinsonism, autonomic instability and/or cerebellar impairments
  - Pathological hallmark: accumulation of α-synuclein within oligodendroglia and neuron loss in multiple brain regions



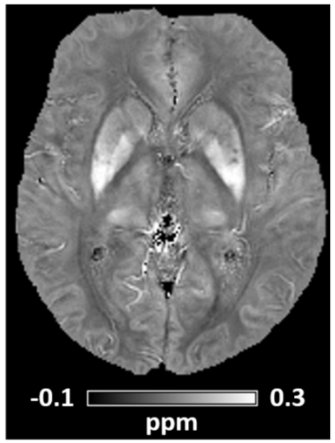
Halliday 2015, based on Brain 2015: 138; 2293–2309

Increased Brain Iron in Areas of Pathology in Synucleinopathy

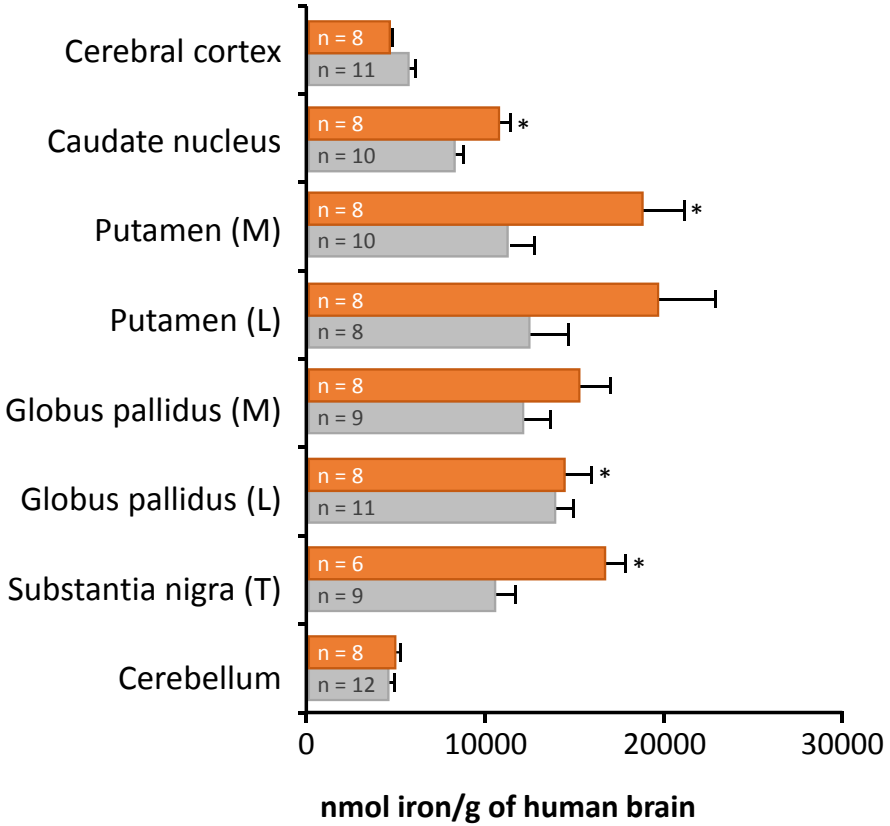
Parkinson's disease



Quantitative Susceptibility Mapping (MRI) to non-invasively quantify brain iron in PD patient



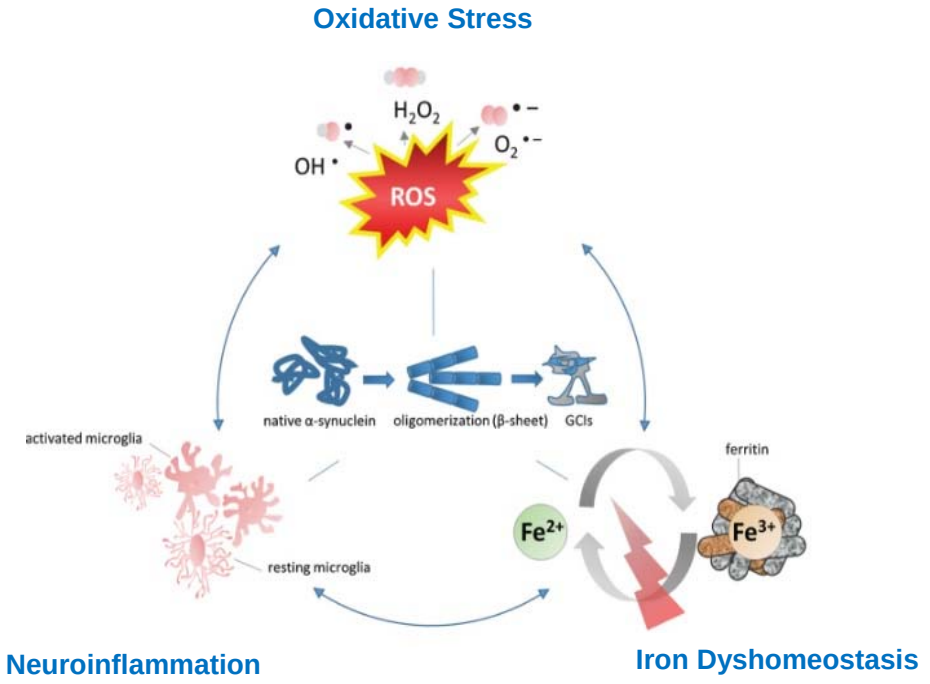
Multiple System Atrophy



Dexter et al. Brain.1991;114
Langkammer. PLoS ONE 11(9): e0162460. 2016

Role of Iron in the pathogenesis of MSA

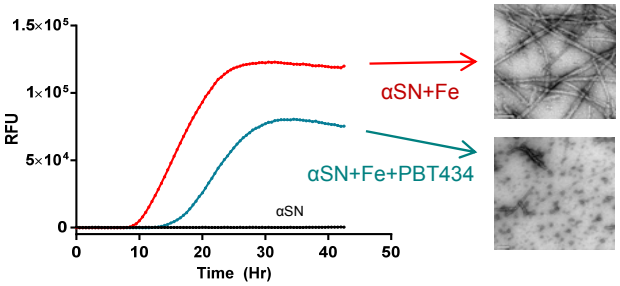
- Oligodendroglia – CNS cell population richest in iron
- Compelling evidence that “labile iron” is central in the pathogenesis of MSA
- Elevated iron in regions of α-synuclein aggregation and neurodegeneration
- Labile iron drives continuous redox cycling and neuroinflammation

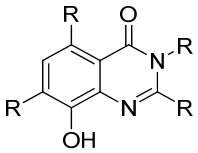


J. Alz. Disease. 2018; 61: 1253. DOI 10.3233/JAD-170601

PBT434 Inhibits α-Synuclein Aggregation and Accumulation and Reduces Oxidative Stress by Restoring Intracellular Iron Balance

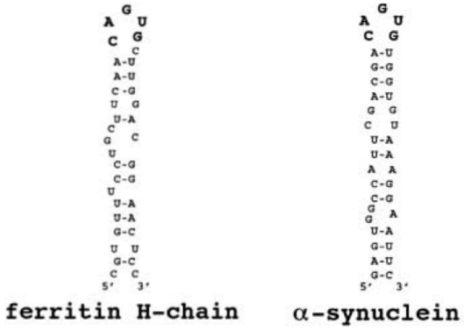
PBT434 blocks Aggregation of α-synuclein in vitro



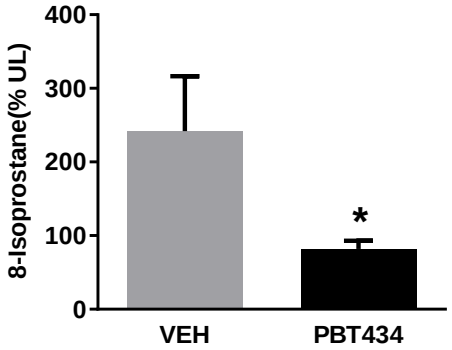


PBT434

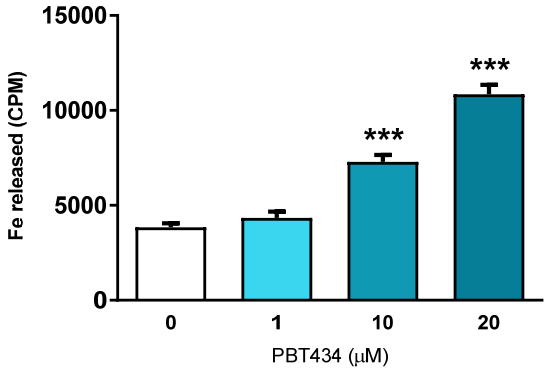
Strong homology in Iron Responsive Element of Ferritin and α-Synuclein



PBT434 inhibits Lipid peroxidation in vivo



PBT434 Promotes Iron Efflux from M17 cells



Ligand	Kd for Fe^{3+}
α-Synuclein	10^{-5}
PBT434	10^{-10}
Ferritin	10^{-22}
Transferrin	10^{-23}
Deferiprone	10^{-36}

Stronger binding

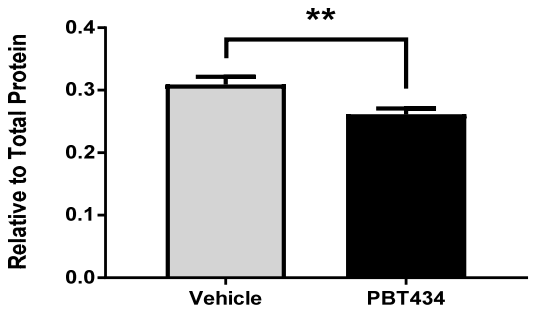
Finkelstein, et al. Acta Neuropath Comm. 2017;5(1):53
Friedlich, et al. Mol Psychiatry. 2007;12(3):222-223

PBT434 Reduces Alpha-synuclein and Lowers Glial Cell Inclusions

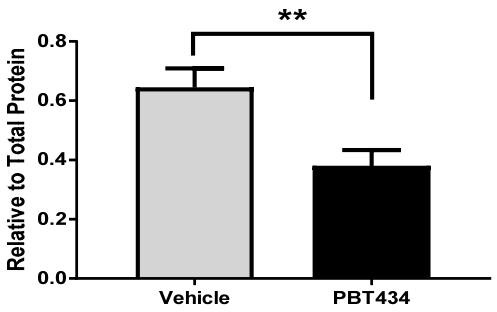
Transgenic Mouse Model (PLP)-α-SYN of MSA

↓ α-Synuclein

Oligomeric



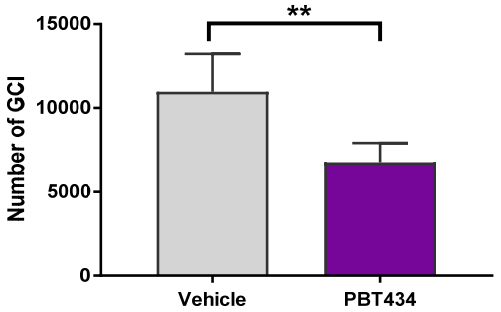
Aggregated



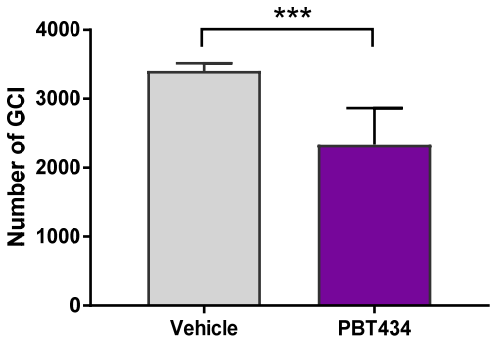
Finkelstein et al. AAN 2019 Poster no. 8-006, Session P5, Thursday May 9. Abstract 837.

↓ Glial Cell Inclusions

Pontine Nucleus



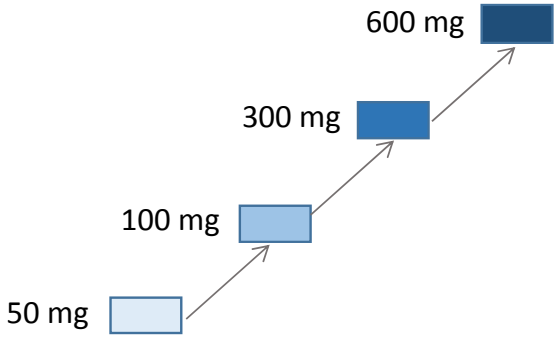
SNpc



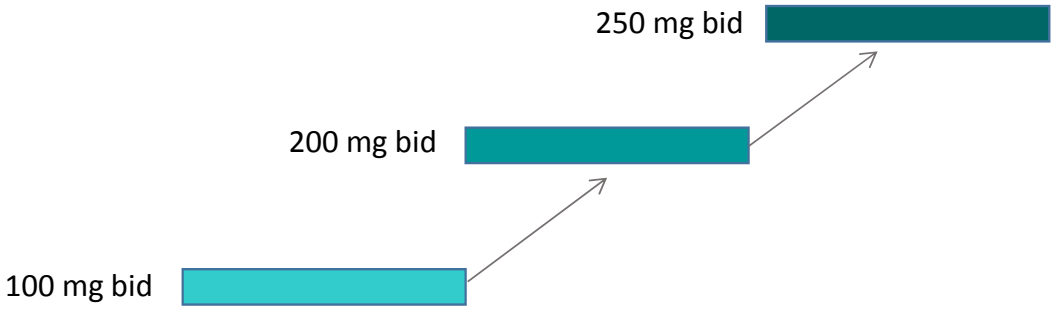
Treatment: 30 mg/kg/day or Vehicle for 4 months
Data presented are for animals at 16 mo age

Phase 1 Design

- Randomized, double blind, placebo controlled
- Population: Healthy adult and older adult (≥65) volunteers (older adult data pending)
- Objective: Assess safety, tolerability and PK of PBT434 after single and multiple oral doses for 8 days
- Pharmacokinetics: Plasma and CSF
  - Plasma sampled through 72 hours post-dosing
  - CSF sampled at steady state 1.5 and 11 hrs post dosing in two top multiple dose levels
- Safety: Adverse events, clinical laboratory parameters, 12-lead ECGs



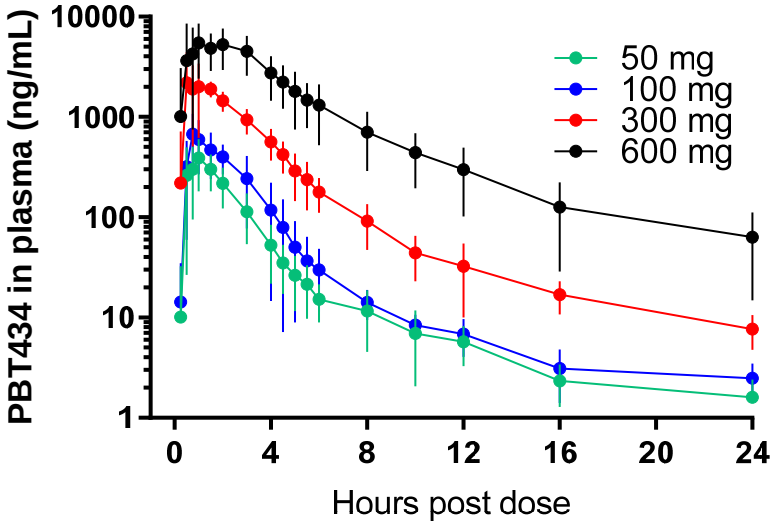
Single Ascending Doses
(6A:2P/cohort)



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

Pharmacokinetic Results

Plasma PK Profile after Single Doses



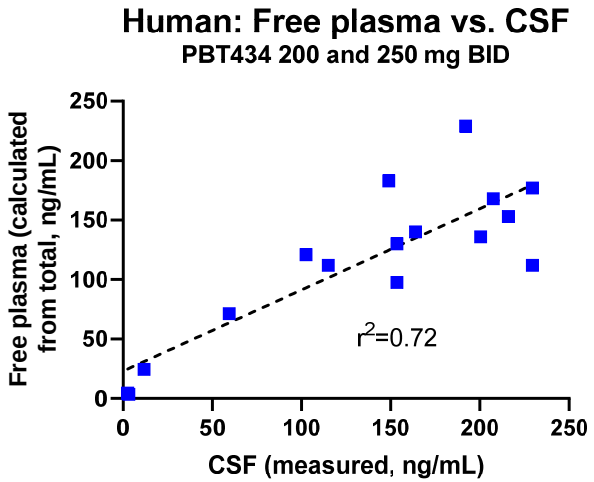
PK parameters after 8 days BID dosing

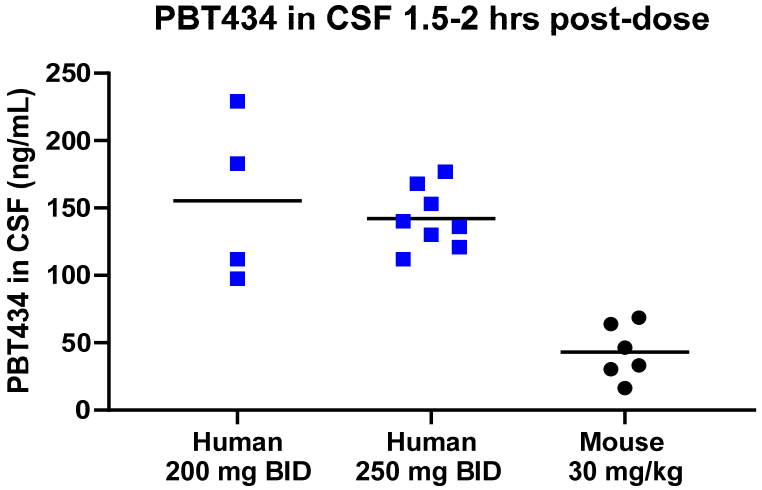
Regimen	AUCtau (ng*h/mL)	Cmax (ng/mL)	Tmax (hr)
	Arithmetic mean (CV%)		Median (Min-Max)
100 mg BID	2,561 (50.7)	961.3 (49.6)	1.25 (0.75-2)
200 mg BID	12,330 (46.4)	3,199 (39.2)	1.25 (0.5-2)
250 mg BID	13,000 (15.8)	3,329 (37.3)	1.13 (0.5-2)

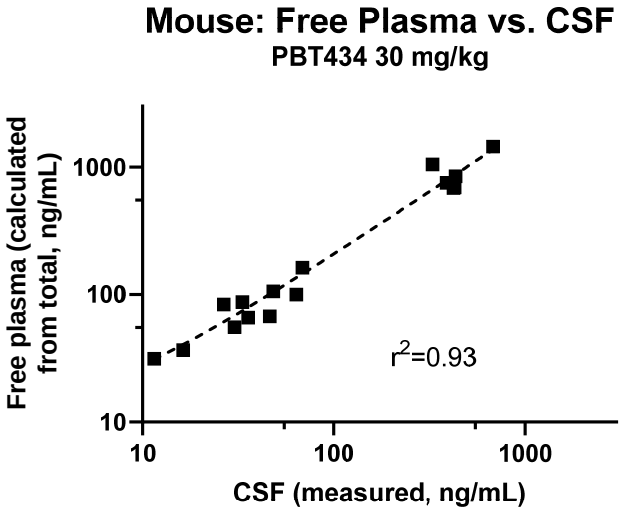
Systemic Pharmacokinetics

- PBT434 was rapidly and extensively absorbed after oral administration
- PBT434 demonstrated dose dependent pharmacokinetics after single and multiple doses
- Mean elimination half-life up to 9.3 hrs

CSF Pharmacokinetics







- Plasma concentrations of PBT434 in plasma strongly correlate with CSF levels in both humans and mouse
- PBT434 at 200 to 250 mg bid achieve CSF levels greater than in mice dosed at 30 mg/kg/day – a dose level associated with robust efficacy in an MSA mouse model

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	1
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=6)	100 mg BID (N=8)	200 mg BID (N=8)	250 mg BID (N=8)
Patients with ≥ 1 AE	5 (83%)	3 (38%)	6 (75%)	4 (50%)
Patients with AEs leading to Withdrawal	0	0	0	0
Patients with Serious AEs	0	0	0	0

PBT434 was well tolerated with similar rates of AEs compared to placebo
No serious AEs or AEs leading to withdrawal

Safety

- All AEs with PBT434 were mild to moderate in severity
- Most common AEs reported in PBT434 subjects was headache
- No clinically significant findings observed in vital signs, clinical laboratory parameters or 12-lead ECGs

Summary

- PBT434 is an orally bioavailable, brain penetrant small molecule inhibitor of α-synuclein aggregation
- Single and multiple dose administration of PBT434 was well tolerated with an AE profile comparable to placebo
- PBT434 demonstrated dose dependent pharmacokinetics after single and multiple doses in healthy volunteers
- At 200 to 250 mg BID, PBT434 achieved CSF concentrations exceeding those associated with robust efficacy in an animal model of MSA