A Phase 1 Study of PBT434, a Novel Small Molecule Inhibitor of α-Synuclein Aggregation, in Adult and Older Adult Volunteers

David Stamler[1], Margaret Bradbury[1], Cynthia Wong[1] and Elliot Offman[2]

[1]Alterity Therapeutics, [2]Certara Strategic Consulting

American Academy of Neurology

Oral Presentation

May 18, 2020

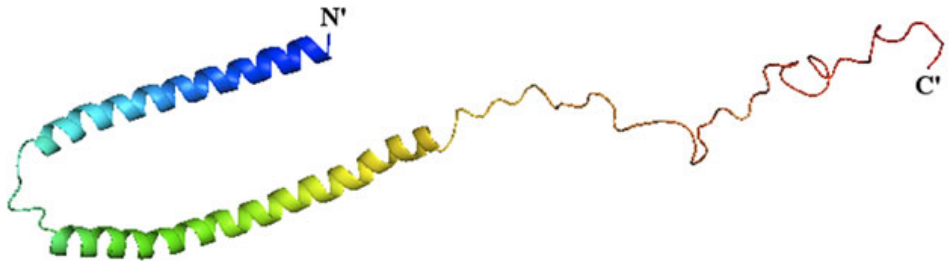
Abstract 4871

Disclosures

The authors are employees or paid consultants of Alterity Therapeutics

Alpha-Synuclein is a Major Focus of Treating Parkinsonian Disorders

Target

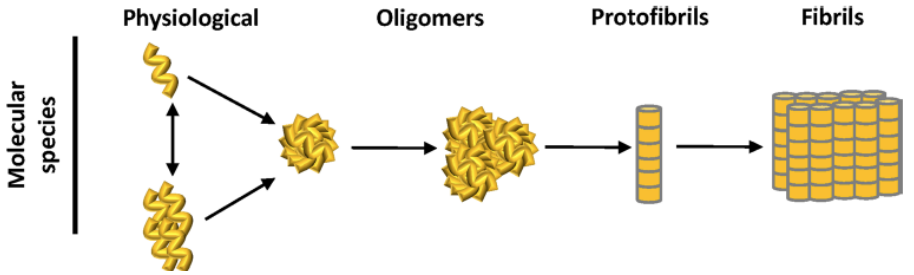


Ritchie et al, 2012; DOI:10.4236/health.2012.431175

- α-synuclein is an intracellular protein, abundantly expressed in nerve terminals
- Critical for normal function of neurons
- Native, unfolded protein facilitates neurotransmission

➢ α-Synuclein *aggregates* in conditions such as PD and Multiple System Atrophy (MSA)

Strategy

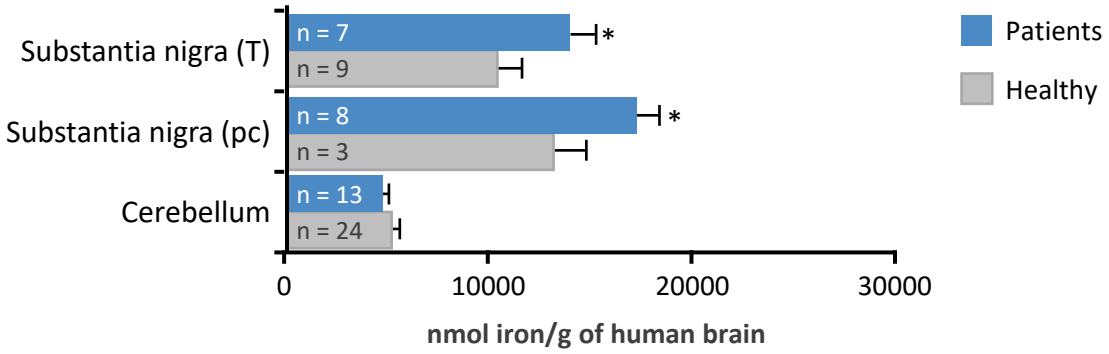


Bengoa-Vergniory et al, 2017.DOI 10.1007/s00401-017-1755-1

- Inhibit intracellular accumulation and aggregation of α-synuclein
- Oral agent for ease of use
- Lead indication: MSA
  - No approved therapy
  - Pathological hallmark: Glial cell inclusions and neuron loss in multiple brain regions

Increased Brain Iron in Synucleinopathies

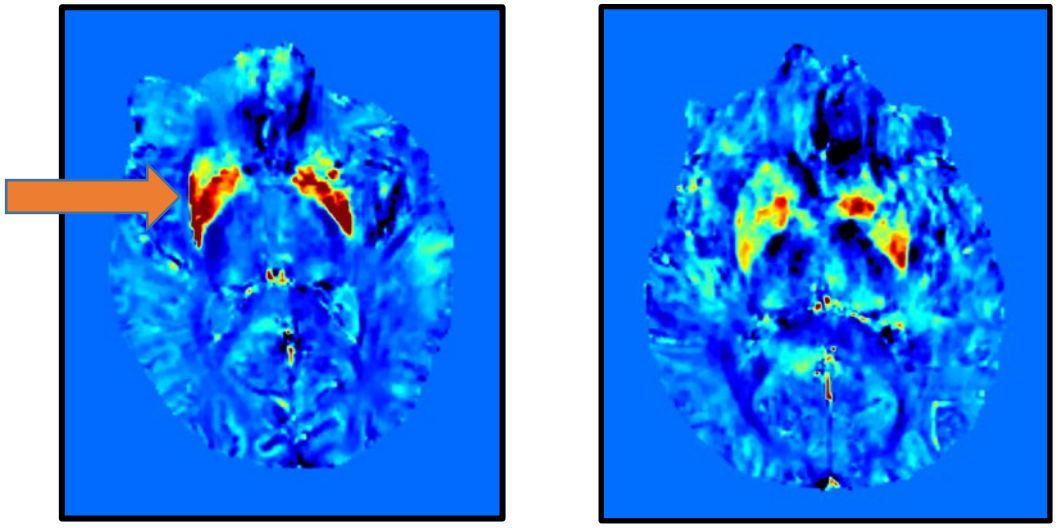
Parkinson's disease



MRI Quantitative Susceptibility Mapping of Brain Iron

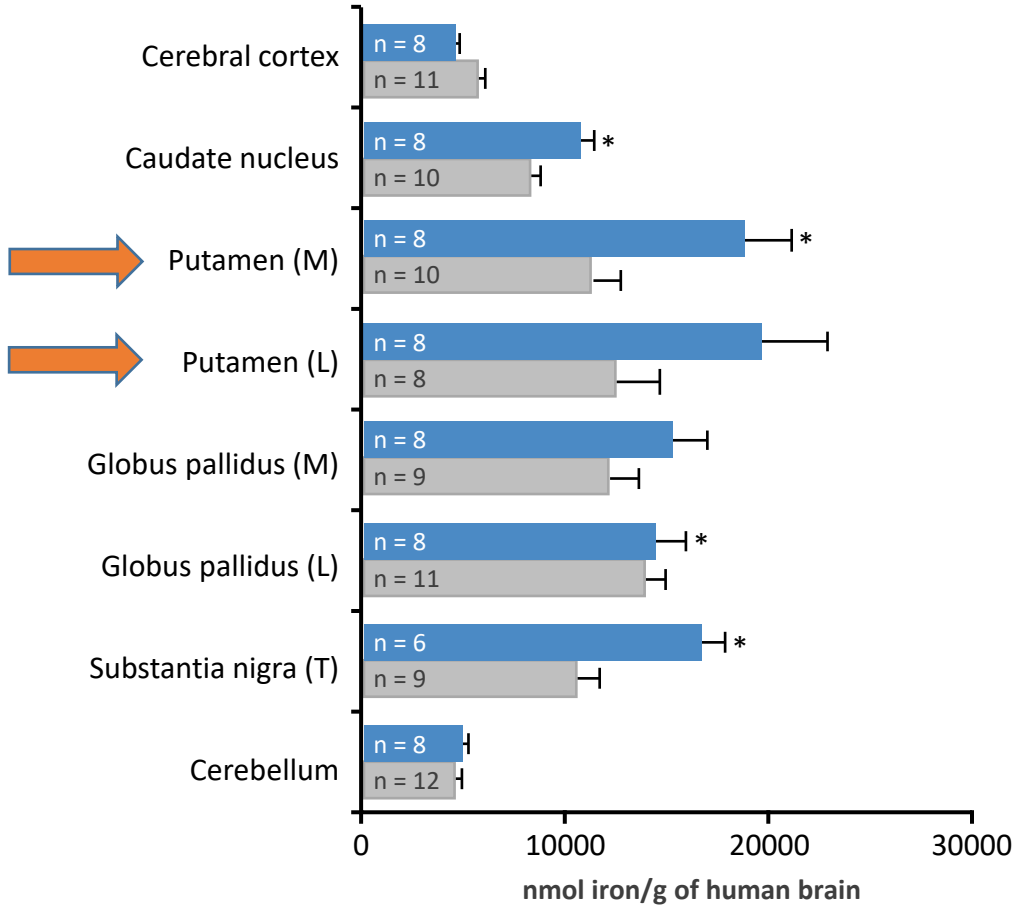
MSA patient

Healthy Control



Courtesy of P. Trujillo, D. Claassen

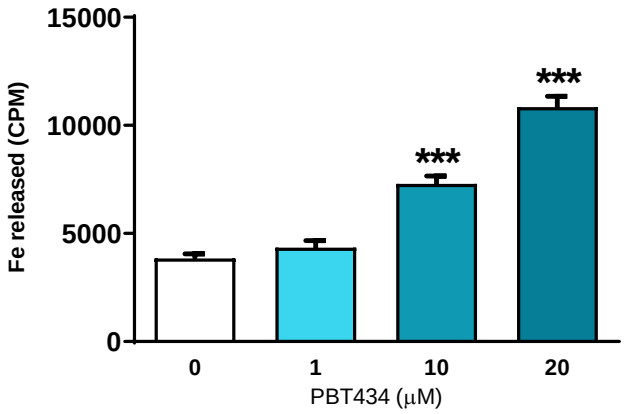
Multiple System Atrophy



Dexter et al. Brain.1991

Actions of PBT434

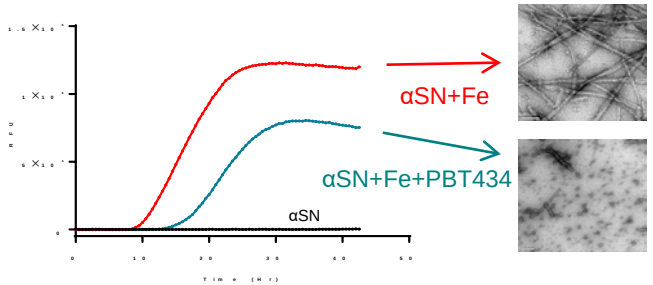
PBT434 redistributes labile iron



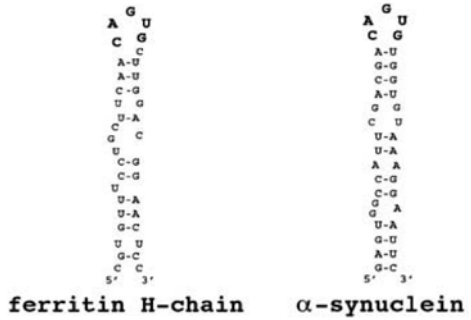
Ligand	Kd for Fe^{3+}
α-Synuclein	10^{-5}
PBT434	10^{-10}
Ferritin	10^{-22}
Transferrin	10^{-23}

PBT434 affinity for iron > α-synuclein but < key iron trafficking proteins

Blocks α-synuclein aggregation

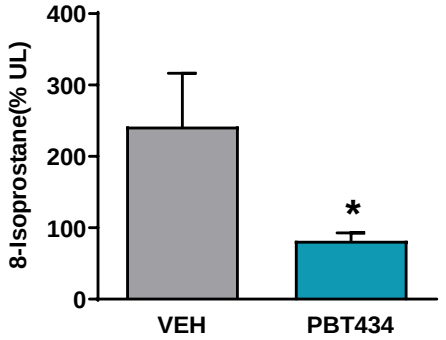


Reduces iron-mediatated ↑ α-synuclein synthesis



Iron responsive element in mRNA

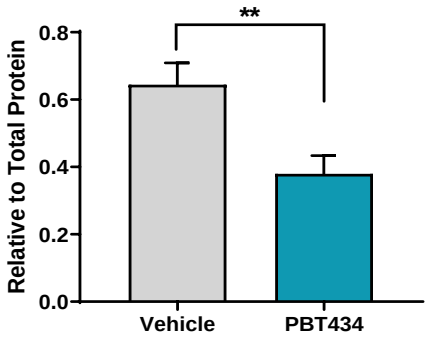
Inhibits oxidative stress



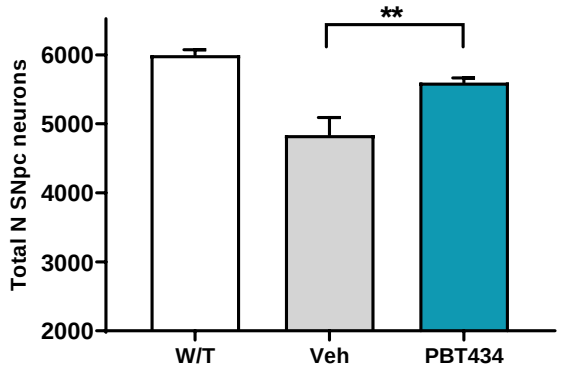
Finkelstein, et al. Acta Neuropath Comm. 2017; Friedlich, et al. Mol Psychiatry. 2007; * P < 0.05, ** P < 0.01, *** P < 0.001

PBT434 Reduces α-Synuclein-related Neuropathology and Improves Motor Function in Animal Model of MSA

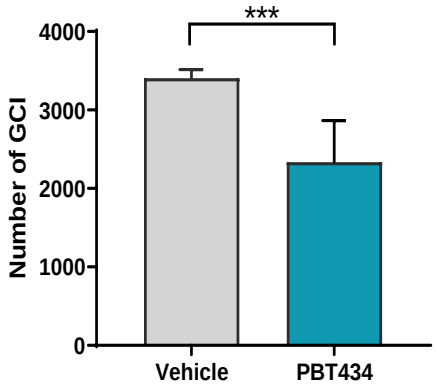
α-Synuclein



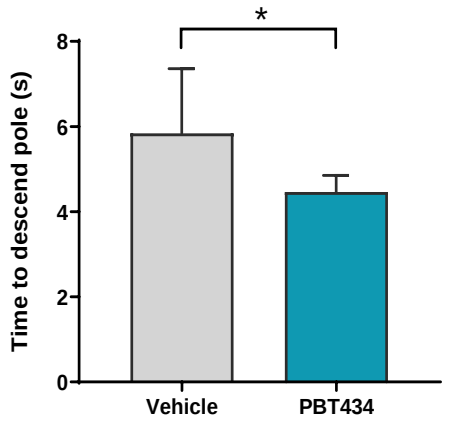
Neurons



Glial cell inclusions



Motor Function (pole test)



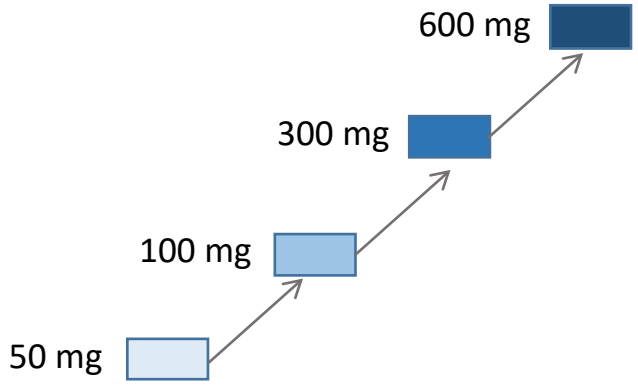
Finkelstein et al. Mov. Disorders. 2018
Transgenic Mouse Model of MSA (PLP-αSyn)

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

Treatment: 30 mg/kg/d or vehicle for 4 months
Pathology data shown for S. nigra

Study Design

- Randomized, double blind, placebo controlled
- Population: Healthy adult and older adult (≥65 yo) volunteers
- Objective: Assess safety, tolerability and PK of PBT434 after single and multiple oral doses
- 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

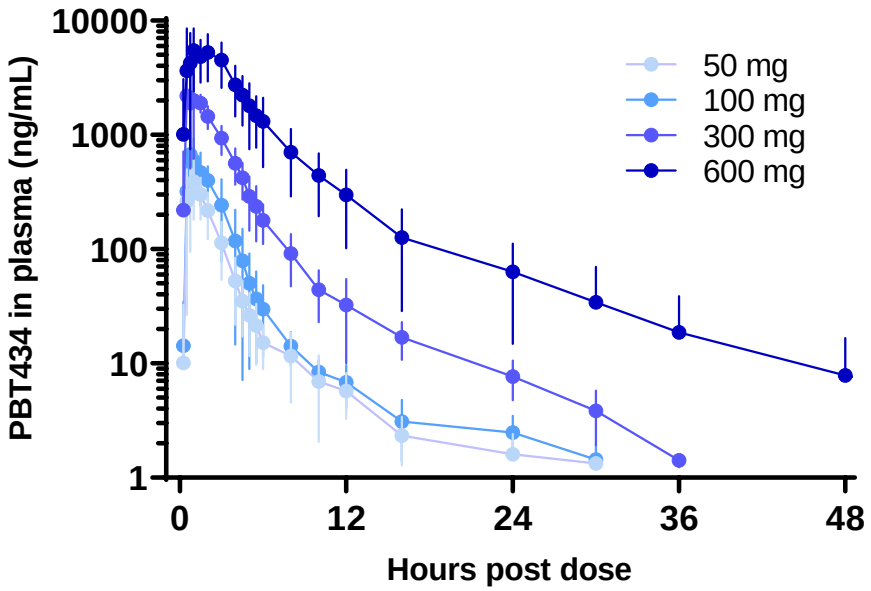


Single Ascending Doses
(6A:2P/cohort)

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

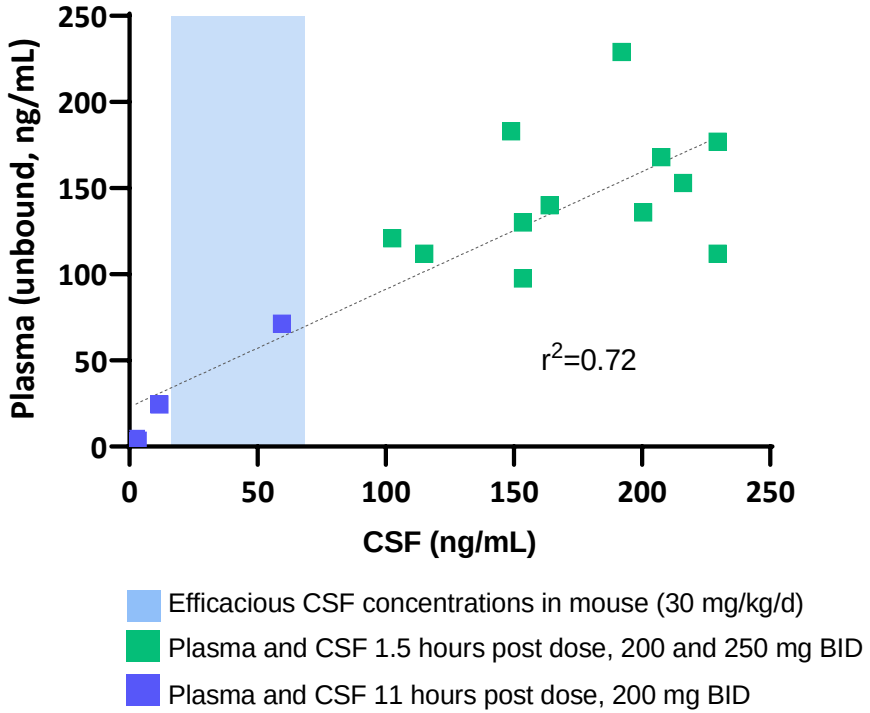
Clinical Pharmacokinetics of PBT434

Plasma Profile after Single Dose Administration



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

CSF Levels vs Plasma Levels at Steady-State



- Plasma concentrations strongly correlated with CSF levels
- CSF concentrations at doses ≥ 200 mg BID exceeded those associated with efficacy in animal models of PD and MSA

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)**
Subjects with ≥ 1 AE	3 (38%)	0	0	1 (17%)	1 (17%)
Subjects with AEs leading to Withdrawal	0	0	0	0	0
Subjects 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)**
Subjects with ≥ 1 AE	5 (63%)	3 (38%)	6 (75%)	4 (50%)	5 (63%)
Subjects with AEs leading to Withdrawal	0	0	0	0	0
Subjects with Serious AEs	0	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 Profile

- All AEs with PBT434 were mild to moderate in severity
- No serious AEs or AEs leading to withdrawal
- Most common AEs reported in PBT434 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 for QT prolongation at projected clinical doses

Summary

- PBT434 is an orally bioavailable, brain penetrant small molecule inhibitor of α-synuclein aggregation
- Single and multiple dose administration of PBT434
  - Well tolerated with an AE profile comparable to placebo
  - Similar safety profile for adults and older adults
  - Dose dependent pharmacokinetics
- CSF concentrations of PBT434 at doses ≥ 200 mg BID were greater than those associated with efficacy in animal models of PD and MSA

- PBT434 is a drug candidate with potential to treat synucleinopathies