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

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INTRODUCTION

- PBT434 is a novel, small molecule inhibitor of α-synuclein aggregation.
- Alpha-synuclein, when aggregated in brain, is a pathological hallmark of Parkinson's disease (Lewy bodies) and Multiple System Atrophy (glial cell inclusions). Likewise, brain iron is increased in areas of pathology in these synucleinopathies.
- PBT434 is thought to act by redistributing labile iron across membranes, thereby inhibiting intracellular protein aggregation and oxidative stress. The affinity of PBT434 for iron is greater than that of α-synuclein but lower than that of iron trafficking proteins such as ferritin and transferrin.
- In transgenic murine models of Parkinson's disease and Multiple System Atrophy (MSA), PBT434 reduced α-synuclein aggregation, preserved neurons and improved motor function.[1,2] Glial cell inclusions were significantly reduced in the MSA model.
- In mice, PBT434 exposure in CSF was similar to that in free plasma and free brain.[3]

OBJECTIVES

- To assess the safety and tolerability of PBT434 after single and multiple oral dose administration
- To determine the pharmacokinetics (PK) of PBT434 after single and multiple oral dose administration in healthy adults, and after multiple oral dose administration in healthy older adults

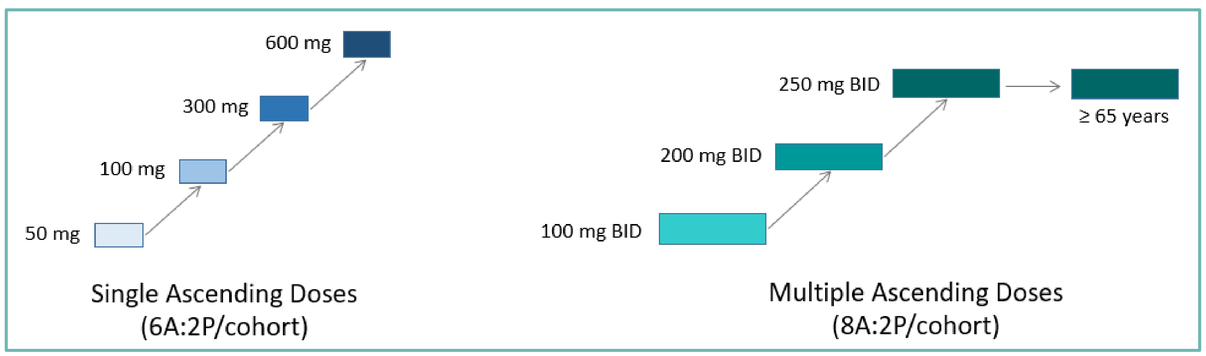

Figure 1. Study Schema

METHODS

Study Design

- Single ascending dose (SAD) phase
  - 4 dose escalation cohorts of n=8, randomized to 6 PBT434:2 placebo
  - Each cohort incorporated a sentinel dosing group (1:1)
  - 21 serial pharmacokinetic (PK) samples drawn over 72 hours post-dose
- Multiple ascending dose (MAD) phase (twice daily [BID] for 8 days)
  - 3 dose escalation cohorts of n=10, randomized to 8 PBT434:2 placebo
  - 11 serial PK samples were drawn after first dose and 17 after final dose (Day 8)
  - Steady state 12-hour urine was collected for PK
  - Cerebrospinal fluid (CSF) sampled at steady state 1.5 and 11 hrs post dosing in the 200 mg BID and 250 mg BID cohorts
  - A cohort of healthy older adults was evaluated at 250 mg BID
  - Iron homeostasis was assessed with serum iron, ferritin, transferrin and TIBC (all cohorts) and 24-hour urine for iron (250 mg BID, adults and ≥ 65) at baseline and Day 8
- Dose escalation continued to the top dose provided that 1) clinically significant adverse events did not occur and 2) predicted systemic exposures, estimated by PBT434 AUC and C_{max}, did not exceed limits based on toxicology studies.
- Progression to the next highest dose level was determined by review of safety (clinical laboratory parameters, adverse events (AEs), 12-lead ECGs), tolerability and PK data
- PBT434 (powder in capsule) was administered under fasting conditions

Key Selection Criteria

- Healthy adults age 18-55 years
- Body Mass Index ≥18 and ≤30 kg/m2
- Normal hepatic and renal function (estimated CrCl ≥ 90 mL/min)

Older Adult Selection Criteria

- Age ≥ 65 years
- Estimated CrCl ≥ 60 mL/min
- Common supplements and concomitant medications with low risk for interaction were permitted

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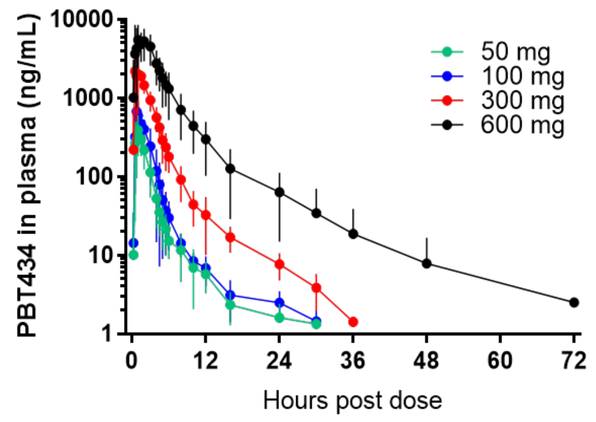

Figure 2. Plasma Profile of PBT434 after Single Dose Administration

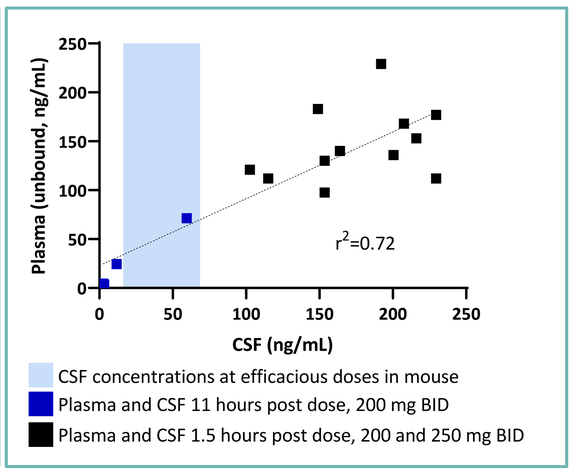

Figure 3. PBT434 Free Plasma vs. CSF at Steady-State

RESULTS

Pharmacokinetics

- PBT434 was rapidly absorbed after oral administration, with a T_{max} of 0.5 to 2 hours
- PBT434 demonstrated dose dependent pharmacokinetics over the dose range studied after single and multiple doses
- Mean elimination half-life up to 9.3 hours was observed, independent of dose
- Steady-state was achieved by approximately 7 days based on trough exposures
- Steady-state urinary excretion of unchanged PBT434 was < 2.5% of the administered dose

CSF Exposure at Steady State

- CSF concentrations of PBT434 strongly correlated (r^2=0.72) with free plasma levels across a broad concentration range
- CSF concentrations of PBT434 collected near T_{max} ranged between 102.5 and 229.5 ng/mL

Safety

- No SAEs or AEs leading to discontinuation in any subject
- All AEs were mild to moderate in severity
- 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
- No changes were observed in serum iron parameters and there was no detectable iron on 24-hour urine

Adverse Events

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 → 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 → Withdrawal	0	0	0	0	0
Patients with Serious AEs	0	0	0	0	0

CONCLUSIONS AND DISCUSSION

- PBT434 is safe and well tolerated at the doses evaluated in this first in human study
- PBT434 is rapidly absorbed after single and multiple oral doses and exhibits 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 novel, orally bioavailable, brain penetrant small molecule inhibitor of α-synuclein aggregation with the potential to treat synucleinopathies including Parkinson's disease and MSA

References

1. *Finkelstein DI, Billings JL, Adlard PA, et al. The novel compound PBT434 prevents iron mediated neurodegeneration and alpha-synuclein toxicity in multiple models of Parkinson's disease. Acta Neuropathol Commun. 2017;5(1):53.*
2. *D. Finkelstein, P. Adlard, N. Stefanova, D. Stamler. PBT434 prevents the accumulation of glial cell inclusions and insoluble alpha-synuclein in a mouse model of Multiple System Atrophy. Mov Disord, Vol. 33, Suppl. 2, 2018. Abstract 990.*
3. *Data on file*