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

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• Authors are employees or paid consultants of Alterity Therapeutics
Therapeutic Strategy

- Disrupting the underlying disease process of synucleinopathies
  - Parkinson’s disease
  - Atypical parkinsonism

- Inhibit accumulation and aggregation of intracellular \( \alpha \)-synuclein

- Target “labile” iron which is increased in disease

- Oral agent, crosses BBB

- Initial disease target: Multiple system atrophy (MSA)
  - Orphan disease (prevalence of \( \sim 5 \) per 100,000)
  - No therapy approved for treatment of MSA
  - Characterized by Parkinsonism, autonomic instability and/or cerebellar impairments
  - Pathological hallmark: accumulation of \( \alpha \)-synuclein within oligodendroglia and neuron loss in multiple brain regions

Lee and Trojanowski, 2006

Halliday 2015, based on Brain 2015: 138; 2293–2309
Increased Brain Iron in Areas of Pathology in Synucleinopathy

**Parkinson’s disease**

- Substantia nigra (T): n = 7, Patients; n = 9, Controls
- Substantia nigra (pc): n = 8, Patients; n = 3, Controls
- Cerebellum: n = 13, Patients; n = 24, Controls

**Multiple System Atrophy**

- Cerebral cortex: n = 8, Patients; n = 11, Controls
- Caudate nucleus: n = 8, Patients; n = 10, Controls
- Putamen (M): n = 8, Patients; n = 10, Controls
- Putamen (L): n = 8, Patients; n = 8, Controls
- Globus pallidus (M): n = 8, Patients; n = 9, Controls
- Globus pallidus (L): n = 8, Patients; n = 11, Controls
- Substantia nigra (T): n = 6, Patients; n = 9, Controls
- Cerebellum: n = 8, Patients; n = 12, Controls

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

*Dexter et al. Brain.1991;114
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

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

PBT434 blocks Aggregation of α-synuclein in vitro

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

PBT434 inhibits Lipid peroxidation in vivo

PBT434 Reduces Alpha-synuclein and Lowers Glial Cell Inclusions

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

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

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

PK parameters after 8 days BID dosing

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

**Human: Free plasma vs. CSF**

PBT434 200 and 250 mg BID

**Mouse: Free Plasma vs. CSF**

PBT434 30 mg/kg

**PBT434 in CSF 1.5-2 hrs post-dose**

- 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

<table>
<thead>
<tr>
<th></th>
<th>Single Ascending Doses</th>
<th></th>
<th>50 mg (N=6)</th>
<th>100 mg (N=6)</th>
<th>300 mg (N=6)</th>
<th>600 mg (N=6)</th>
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<tbody>
<tr>
<td></td>
<td>Placebo (N=8)</td>
<td></td>
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<tr>
<td>Patients with ≥ 1 AE</td>
<td>3 (38%)</td>
<td></td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Patients with AEs leading to Withdrawal</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patients with Serious AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
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<th>Placebo (N=6)</th>
<th>100 mg BID (N=8)</th>
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<th>250 mg BID (N=8)</th>
</tr>
</thead>
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<tr>
<td>Patients with ≥ 1 AE</td>
<td>5 (83%)</td>
<td>3 (38%)</td>
<td>6 (75%)</td>
<td>4 (50%)</td>
<td></td>
</tr>
<tr>
<td>Patients with AEs leading to Withdrawal</td>
<td>0</td>
<td>0</td>
<td>0</td>
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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