Initial data for Alterity Therapeutics Phase 1 clinical trial released at American Academy of Neurology Annual Meeting

MELBOURNE, AUSTRALIA AND SAN FRANCISCO, USA – Monday 6th May, 2019. Alterity Therapeutics Limited (ASX: ATH, NASDAQ: ATHE) (“Alterity” or “the Company”) is today releasing interim clinical data of its Phase 1 clinical trial program for its investigative drug PBT434 at the American Academy of Neurology Annual Meeting in Philadelphia, USA.

The Platform Presentation titled: A First in Human Study of PBT434, a Novel Small Molecule Inhibitor of α-Synuclein Aggregation is being delivered by David Stamler, MD, Chief Medical Officer & Senior VP Clinical Development. The American Academy of Neurology Annual Meeting is one of the largest gatherings of clinicians and researchers focusing on neurology in the world.

The study is expected to complete mid-2019, however Alterity has been invited to present interim data from the initial four single dose cohorts and the initial three multiple dose cohorts. The data being released indicate that PBT434 was well tolerated with adverse event rates comparable to placebo and dose dependent systemic exposure following oral administration.

Importantly, the results indicate that PBT434 not only crosses the blood brain barrier in humans, confirming previous observations in animal studies, but that clinically tested doses achieve concentrations in the brain that exceed those associated with efficacy in animal models of disease.

No serious adverse events were reported and no subject discontinued dosing with PBT434 due to adverse events.

Dr David Stamler said: “The notable finding from this study is that PBT434 penetrates into the human brain and achieves concentrations that are potentially clinically relevant at doses that were well tolerated in healthy volunteers. We are very encouraged by these results which represent an important step in the advancement of PBT434. We look forward to providing final data at a medical conference later this year.”

PBT434 is an oral small molecule drug candidate with potential for treating synucleinopathies such as Parkinson’s Disease and Multiple System Atrophy, a rare and rapidly progressive neurological disorder that affects adults.

The Phase 1 Clinical Trial for PBT434 commenced in 2018 in Australia, recruiting healthy adult and older adult (≥ 65) volunteers with the primary goals of assessing the safety and tolerability of PBT434 after single and multiple oral dose administration. Secondary goals include evaluating pharmacokinetic measures that will allow Alterity understand how PBT434 is absorbed and metabolised by the body.

PBT434 is the first of a new generation of small molecules designed to block the accumulation and aggregation of α-synuclein. α-synuclein is of great interest because aggregated forms of the protein are considered a pathological hallmark of Parkinsonian conditions and are a recognised therapeutic target by neuroscientists and clinicians.
About Alterity Therapeutics Limited
Alterity’s lead candidate, PBT434, is the first of a new generation of small molecules designed to inhibit the aggregation of pathological proteins implicated in neurodegeneration. PBT434 has been shown to reduce abnormal accumulation of α-synuclein and tau proteins in animal models of disease by restoring normal iron balance in the brain. In this way, it has excellent potential to treat various forms of atypical Parkinsonism such as Multiple System Atrophy (MSA) and Progressive Supranuclear Palsy (PSP).

For further information please visit the Company’s web site at www.alteritytherapeutics.com

Forward Looking Statements
This press release contains “forward-looking statements” within the meaning of section 27A of the Securities Act of 1933 and section 21E of the Securities Exchange Act of 1934. The Company has tried to identify such forward-looking statements by use of such words as “expects,” “intends,” “hopes,” “anticipates,” “believes,” “could,” “may,” “evidences” and “estimates,” and other similar expressions, but these words are not the exclusive means of identifying such statements.

Important factors that could cause actual results to differ materially from those indicated by such forward-looking statements are described in the sections titled “Risk Factors” in the Company’s filings with the SEC, including its most recent Annual Report on Form 20-F as well as reports on Form 6-K, including, but not limited to the following: statements relating to the Company’s drug development program, including, but not limited to the initiation, progress and outcomes of clinical trials of the Company’s drug development program, including, but not limited to, PBT434, and any other statements that are not historical facts. Such statements involve risks and uncertainties, including, but not limited to, those risks and uncertainties relating to the difficulties or delays in financing, development, testing, regulatory approval, production and marketing of the Company’s drug components, including, but not limited to, PBT434, the ability of the Company to procure additional future sources of financing, unexpected adverse side effects or inadequate therapeutic efficacy of the Company’s drug compounds, including, but not limited to, PBT434, that could slow or prevent products coming to market, the uncertainty of patent protection for the Company’s intellectual property or trade secrets, including, but not limited to, the intellectual property relating to PBT434.

Any forward-looking statement made by us in this press release is based only on information currently available to us and speaks only as of the date on which it is made. We undertake no obligation to publicly updated any forward-looking statement, whether written or oral, that may be made from time to time, whether as a result of new information, future developments or otherwise.
A First in Human Study of PBT434, a Novel Small Molecule Inhibitor of α-Synuclein Aggregation

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¹Alterity Therapeutics, ²Certara Strategic Consulting

American Academy of Neurology – S4.001

Sunday, May 5, 2019
Disclosures

- 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 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
Increased Brain Iron in Areas of Pathology in Synucleinopathy

Parkinson’s disease

Multiple System Atrophy

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 Reduces Alpha-synuclein and Lowers Glial Cell Inclusions
Transgenic Mouse Model (PLP)-α-SYN of MSA

↓ α-Synuclein

Oligomeric

Aggregated

↓ Glial Cell Inclusions

Pontine Nucleus

SNpc

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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)

- 50 mg
- 100 mg bid
- 300 mg

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

- 100 mg bid
- 200 mg bid
- 250 mg bid
- 600 mg
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</td>
<td>Median</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(CV%)</td>
<td>(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>
**CSF Pharmacokinetics**

*Human: Free plasma vs. CSF*

PBT434 200 and 250 mg BID

$r^2 = 0.72$

*Mouse: Free Plasma vs. CSF*

PBT434 30 mg/kg

$r^2 = 0.93$

- 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>Single Ascending Doses</th>
<th>Placebo (N=8)</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>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥ 1 AE</td>
<td>3 (38%)</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>
</tr>
<tr>
<td>Patients with Serious AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multiple Ascending Doses</th>
<th>Placebo (N=6)</th>
<th>100 mg BID (N=8)</th>
<th>200 mg BID (N=8)</th>
<th>250 mg BID (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥ 1 AE</td>
<td>5 (83%)</td>
<td>3 (38%)</td>
<td>6 (75%)</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Patients with AEs leading to Withdrawal</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>
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</table>

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