Treatment of **Neurological Disorders**

David Stamler, MD
Chief Medical Officer and SVP,
Clinical Development

January 2019
Targeting Proteins in Neurodegeneration

**PBT2 (1st generation)**
- Mechanism of action: Zn and Cu ionophore
- Originally developed for neurological indications by targeting extracellular protein
- Evaluating non-neurological indications for further development

**PBT434 (2nd generation)**
- Targets intracellular proteins with established function: α-synuclein, tau
- Mechanism of action: Effluxes labile Fe
- Reduces α-synuclein accumulation in transgenic animal models of PD and MSA
Current Focus

**Novel Drug Candidate PBT434**
- Targets key proteins implicated in neurodegeneration of Parkinson’s disease and atypical parkinsonism
- Distinct scaffold and biological profile compared to PBT2

**Strong Research and Development**
- U.S. development team with proven track record
- Innovative discovery program
- Long standing collaborations with Harvard and Florey Institute of Neuroscience and Mental Health

**Multiple Indication Opportunity**
- PBT434 active in models of Parkinson’s disease and atypical parkinsonism including orphan diseases such as Multiple System Atrophy (MSA)

**Trading Information:**
- ASX: PBT
- Nasdaq: PRAN
- Share price: US$1.72
- Valuation: US$19M
- Cash: ~A$23M

*Approximate cash on completion of initial securities purchase agreement with Life Biosciences*

*Life Biosciences LLC Leads Strategic Investment of up to a $31.4 Million in Prana*

*January 2, 2019*
US-based development team with strong drug development experience and FDA approvals

David Stamlar, M.D.
Chief Medical Officer & Senior VP, Clinical Development

Former VP, Clinical Development and Therapeutic Head, Movement Disorders, Teva Pharmaceuticals and Chief Medical Officer, Auspex Pharmaceuticals.

Part of Teva’s US$3.5 billion acquisition of Auspex. Led development of AUSTEDO (deutetrabenazine) for treatment of Huntington disease (approved by FDA - April 2017) and tardive dyskinesia, also in 2017.

James Kerr
VP, Chemistry, Manufacturing and controls

Previously CMC leadership at Auspex/Teva. Senior member of leadership team responsible for budget management and operational direction of CMC team. Prior to Auspex, was Senior Director, CovX Operations at Pfizer WRD.

Margaret Bradbury, Ph.D.
VP, Nonclinical Development

Previously Non-Clinical leadership at Auspex/Teva. At Teva, led non-clinical development of several neuroscience programs. At Auspex Pharmaceuticals, led strategic planning and program management in Huntington Disease chorea from IND through NDA filing.

Cynthia Wong, M.P.H.
Senior Director, Clinical Operations

Previously Clinical Operations leadership at Auspex/Teva. At Auspex, led clinical trial activities for the registration study of AUSTEDO in Huntington Disease chorea. Prior to Auspex, led Phase 1-3 studies, including registration studies for marketing approval for Quillichew ER, Esbriet and Infergen.
Investment Thesis

• Alpha (α)-synuclein is an intracellular protein critical for neurotransmission
• α-synuclein accumulates and aggregates in many neurodegenerative diseases and is implicated in pathology
• PBT434 blocks α-synuclein accumulation and aggregation, preserves neurons and improves function in animal models of synucleinopathy (Parkinson’s disease, MSA)
  • PBT434 also prevents tau accumulation and improves function in animal models of tauopathy
• Link between increased brain iron and the synucleinopathies
• Phase 2 data with a related compound supports proof of concept
• Clear development path for symptomatic therapy in atypical parkinsonism
  • Current symptomatic therapy has limited benefit
• Potential path for disease modifying therapy

PBT434 is an excellent drug candidate for treating neurodegenerative diseases
PBT434: Promising Drug Profile

- Good CNS penetration based on low molecular weight and lipophilicity
  - Brain concentrations 2 to 3 fold higher than plasma
- Straightforward synthetic process with demonstrated ability to make kg amounts of GMP material
- Benign safety profile in GLP toxicology studies
  - Non-toxic dose exceeds efficacious dose by >10-fold based on allometric scaling
- Phase 1 in Healthy volunteers ongoing
Importance of α-Synuclein

• α-Synuclein is an intracellular protein, abundantly expressed in the brain
• Critical for normal function of neurons
• Soluble, in highest concentration at presynaptic nerve endings
• Key regulatory protein involved in neurotransmission
  • Enables neurotransmitter release by facilitating synaptic vesicle fusion to pre-synaptic membrane
α-Synuclein is an Important Disease Target
Strong genetic and pathological link to disease

“Collectively these data strongly suggest that alpha synuclein is a potentially important and novel target of candidate neuroprotective therapies. Several different therapeutic strategies designed to clear or prevent the formation of toxic forms of α-synuclein are currently being investigated in the laboratory, and clinical trials have already begun.”

AstraZeneca and Takeda establish collaboration to develop and commercialise MEDI1341 for Parkinson’s disease 29 August 2017

α-Synuclein as Target for PBT434

- α-synuclein fibrillizes readily
- Factors regulating its production and conformation are relevant to disease pathogenesis and treatment
- Homeostasis of iron is disrupted in PD and atypical parkinsonism
- α-synuclein is highly conserved in vertebrates but only humans develop synucleinopathy
- Human α-synuclein mRNA contains an iron responsive element

The iron responsive element (IRE) of α-synuclein is a 5′-untranslated region of mRNA predicted to form a single RNA stem loop

The stem loop shows striking similarity to the 5′-UTRs of mRNAs encoding ferritin and ferroportin

Lee and Trojanowski, 2006

from Friedlich, Tanzi, et al. 2007
PBT434 Inhibits α-Synuclein Aggregation by Restoring Intracellular Iron Balance

PBT434 blocks the aggregation of α-synuclein in vitro

Iron efflux from cultured M17 cells

PBT434 treatment preserves ferroportin levels in vivo

PBT434 Dose: 30 mg/kg
Alpha-synuclein Pathology and PBT434 Mechanism of Action
Iron Chaperone, reducing α-synuclein accumulation, aggregation and preserving neurons

Accumulation → α-Synuclein Protein → Native, unfolded protein → Aggregation of fibrillar protein → Ineffective autophagy → ↑ Oxiative Stress → ↑ H2O2 → ↑ Fe → PBT434 exports Fe from cell → Cytoplasm Extracellular → ↑ Ferroportin → Transferrin → Normal Iron trafficking → ↑ Ferroportin

Cell Death

Dopamine

H2O2

Oxidative Stress

↑
PBT434 Lowers α-Synuclein, Prevents Neuronal Death and Improves Motor Function

*Transgenic Animal Model (hA53T) of Parkinson’s Disease*

↓ α-Synuclein aggregation

Preserves neurons in S. nigra

Foot Clasping

Treatment randomly allocated

• 4-8 months of age
• ~30 mg/kg/day (via feed)
Assessments done in blinded manner

Strategy Supported by Proof of Concept with Deferiprone
6 month placebo controlled data in Parkinson’s disease patients

Brain Iron by MRI

Motor Function – UPDRS III

Deferiprone
• Indicated for Treatment of Iron Overload
• Black Box for neutropenia and agranulocytosis
• Iron Binding Affinity Kd=10^{-36}

Reducing excess iron associated with improved motor function

PBT434 has Optimal Iron Binding Affinity for Efficacy and Safety

<table>
<thead>
<tr>
<th>Agent/Protein</th>
<th>Kd for Fe³⁺</th>
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<tbody>
<tr>
<td>α-Synuclein</td>
<td>10⁻⁵</td>
</tr>
<tr>
<td>PBT434</td>
<td>10⁻¹⁰</td>
</tr>
<tr>
<td>Ferritin</td>
<td>10⁻²²</td>
</tr>
<tr>
<td>Transferrin</td>
<td>10⁻²³</td>
</tr>
<tr>
<td>Deferiprone</td>
<td>10⁻³⁶</td>
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Davies et al. PLoS ONE. 2011; 6; 1; e15814. doi.org/10.1371/journal.pone.0015814
Kline MA and Orvig C. Clin Chem (1992); 38: 562-565
Link Between Iron and Severity of PD

The Relevance of Iron in the Pathogenesis of Parkinson’s Disease

The nigral increase in iron levels identified biochemically in the postmortem brain from parkinsonian patients appears to be confirmed and is related to the severity of the disease in the living patient as assessed by magnetic resonance imaging (MRI).53–56

Midbrain iron content in early Parkinson disease
A potential biomarker of disease status
Martin, et al. Neurology 2008;70:1411–1417

However, biochemical studies have reported increased iron content in the nigra in PD,2-4 with the changes most marked in severe disease (PD)5
Brain Iron Increased in Parkinson’s Disease Patients

And in Multiple System Atrophy Patients

Specialized MRI Technique (QSM) to Non-invasively Quantify Brain Iron (PD Patient)

Dexter. Brain.1991;114
Multiple System Atrophy
A form of Atypical Parkinsonism

• Rapidly progressive neurodegenerative disorder leading to severe disability and impairment in quality of life
• Sporadic, typically presents in 50s to 60s
• Orphan Indication: Prevalence ~5 per 100,000 in the U.S.
• Characterized by a variable combination of
  • Parkinsonism, which responds poorly to levodopa
  • Cerebellar impairments: impaired gait and speaking
  • Autonomic failure: Orthostatic hypotension, bladder dysfunction, erectile dysfunction, constipation
• MSA patients have neuron loss in multiple brain regions
• The hallmark of MSA is the accumulation of α-synuclein within neurons and glial support cells

Halliday 2015, based on Brain 2015: 138; 2293–2309
PBT434 reduces Alpha-synuclein and Lowers Glial Cell Inclusions

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

↓ α-Synuclein

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<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>PBT434</th>
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<tbody>
<tr>
<td><strong>Oligomeric</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ratio to Ponscau</td>
<td>0.35</td>
<td>0.30</td>
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<tr>
<td><strong>Aggregated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative to Total Protein</td>
<td>0.60</td>
<td>0.55</td>
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Treatement: Randomly allocated, 4 months, ~30 mg/kg/day or Vehicle (Veh)
Data presented are for animals at 16 mo age
PBT434 Preserves Neurons and Improves Motor Function

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

Treatment: Randomly allocated, 4 months, ~30 mg/kg/day or Vehicle

S. Nigra Neurons at 16 months

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<tr>
<th></th>
<th>W/T</th>
<th>Veh</th>
<th>PBT434</th>
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<tr>
<td>Total N SNpc neurons</td>
<td>6000</td>
<td>4000</td>
<td>6000</td>
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P=0.001

Pole Test after 4 months treatment
30 mg/kg at 16 months

Rotarod after 4 months treatment
30 mg/kg/day at 20 months

Time to descend the pole (s)

Vehicle

PBT434

Time on the rod (s)

Vehicle

PBT434

**
Brain Iron is also Increased in **Tauopathies**
Progressive Supranuclear Palsy (PSP)
A form of Atypical Parkinsonism

Brain Iron increased compared to Healthy controls

PBT434 in an Animal Model of Acute Oxidative Stress

MPTP mouse model
- MPTP is a potent inhibitor of complex 1 of the mitochondrial electron transport chain
- Significant neuron loss in SNpc and motor impairment

- Rapid and sustained elevation of iron in the SNpc
- Causes acute elevation in ROS and oxidative damage
- PBT434 or vehicle treatment† started 1 day after toxin administration

For α-synuclein, lipid peroxidation: PBT434 dose 30 mg/kg/d
†Treatment randomly allocated, assessors blinded
*P<0.05, **P<0.01, ***P<0.001

PBT434 preserves neurons, improves motor function and reduces α-Synuclein accumulation and oxidative stress in the MPTP mouse
Development Milestones

• Phase 1 Completion 1H ‘19
• Initiate LT toxicology 1H ‘19
• Initiate Phase 2 planning study 1H ‘19
• Initial Patient study start 2020
Preliminary Market Assessment (U.S. only)

**Substantial Unmet Need**
- Severely debilitating, fatal illnesses with no current treatments are ripe for new entrants targeting what may be the actual cause of the disease, even if only motor symptom endpoints

**Non-Competitive Landscape**
- PBT434 likely to be used in combination with symptomatic treatments and alpha-synuclein antibodies given it works differently and targets different aspects of MSA and PSP

**Unique MOA**
- Inhibition of iron-mediated protein accumulation and aggregation is a novel mechanism of action that may ultimately prove in clinical practice to impact more than motor symptoms

**Ease of Use**
- Given similar efficacy, clinicians will likely prefer PBT434’s once or twice daily oral administration vs. the monthly IV infusions or injections required for any alpha-synuclein or tau antibodies that come to market

*Additional market research required to validate preliminary opportunity assessment.
Summary

• PBT434 is an excellent drug candidate to prevent alpha-synuclein aggregation and reduce oxidative stress by targeting intracellular reactive iron

• Brain iron pathologically increased in Parkinson’s disease and atypical parkinsonism

• PBT434 has demonstrated efficacy in various animal models of neurodegeneration and has been shown to prevent acute oxidative damage *in vivo*

• Multiple indication opportunity, with potential for treating PD and atypical parkinsonism such as Multiple System Atrophy, an orphan disease

• Significant commercial opportunity given limited treatment options which target underlying cause of disease