Motor Neuron Disease Biomarkers and Pharmacodynamics Results

- Preliminary data indicate suppression of inflammation that may be responsible for MND/ALS progression
- PharmAust monepantel (MPL) tablets inhibit the mTOR signalling pathway in the blood of MND/ALS patients
- Clear correlation between reduced Peripheral Blood Mononuclear Cell (PBMC) p-RPS6KB1 (B1) and p-EIF4EBP1 (P1) protein levels with MPL treatment
- Five of seven participants have decreased B1 protein levels in PBMCs, indicating targeted mTOR pathway inhibition
- Six of seven participants have decreased P1 protein levels in PBMCs, indicating targeted mTOR pathway inhibition

4 July 2023 – Perth, Australia: PharmAust Ltd (ASX: PAA & PAAO), a clinical-stage biotechnology company, is pleased to provide an update on the pharmacodynamic data from the Phase 1/2 trial of its lead drug candidate monepantel (MPL) in Motor Neurone Disease /Amyotrophic Lateral Sclerosis (MND/ALS).

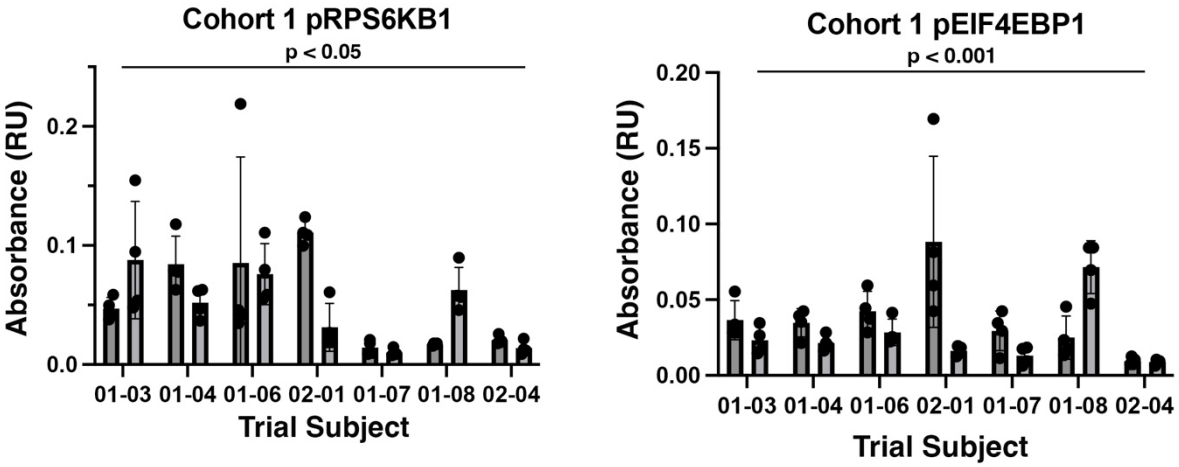
MND/ALS is believed to develop and progress due to neuronal inflammation and cell death due to production of misfolded proteins in brain tissue. Preliminary data presented here indicate suppression of inflammation that may be responsible for MND/ALS progression.

PharmAust's Executive Chairman Dr Roger Aston said, "Molecular and cellular pathways of neurodegeneration in MND are complex. However, it appears that oxidative stress, protein misfolding and aggregation may be underlying causes for the inflammation associated in neurones during MND progression."

"Here we show that in Cohort 1 of oral monepantel in treating MND there is significant suppression of inflammatory markers. In preclinical studies we have shown that monepantel crosses the blood-brain barrier. These results bode well as we analyse markers that predict MND disease progression."

PBMCs from the blood of all seven trial subjects enrolled in Cohort 1 have been collected at Calvary Healthcare Bethlehem in Melbourne and Macquarie University in Sydney, and assayed at the Florey Institute of Neuroscience and Mental Health in Melbourne. Assays are looking for changes in protein levels of the mTOR pathway markers p-RPS6KB1 (p-p70S6K) and p-EIF4EBP1 (p-4EBP1).

Assays show that MPL correctly targets these mTOR pathway markers in the blood, with five of seven participants having decreased p-RPS6KB1 levels and six of seven participants having decreased p-EIF4EBP1 protein levels. See Figure below.



Figures: p-RPS6KB1 and p-EIF4EBP1 levels in PBMCs from subjects in Cohort 1 at Day 0 (D0, left bar) and D29 (right bar). For pRPS6KB1, 01-04, 01-06, 02-01, 01-07 and 02-04 are reduced, overall reduction is significant at $p < 0.05$, two way ANOVA with Sidak multiple comparison post-test). For pEIF4EBP1 01-03, 01-04, 01-06, 02-01, 01-07 and 02-04 are reduced, overall reduction is significant at $p < 0.001$, two way ANOVA with Sidak multiple comparison post-test). Levels are expressed as absorbance in relative units (RU).

Significant leap forward in our understanding

The demonstration of decreased p-RPS6KB1 and p-EIF4EBP1 levels is significant as it shows MPL correctly targets the mTOR pathway in the blood of people with MND/ALS. With the correct dose, misfolded/mutant/aggregated proteins in the motor neurons may be processed with minimal localised inflammation, thereby slowing or stopping the progression of motor neuron loss that causes the disease.

PharmAust has shown in preclinical studies that MPL crosses the blood-brain barrier, so it may directly affect the central nervous system.

p-RPS6KB1 and p-EIF4EBP1 are the phosphorylated forms (p-) of proteins interpreting mTOR signalling and providing internal cellular cues to induce autophagy, commonly known to eliminate mutant cancer cells. PharmAust has already demonstrated that as an anticancer agent, MPL inhibits these mTOR signalling pathways in people with cancer, in dogs with cancer and preclinical studies involving mice and cancer cell lines, all while showing no or minimal effect upon non-cancerous cells.

In addition to assisting the elimination of mutant cancer cells, and in accordance with published literature, PharmAust proposes that inhibition of mTOR signalling and the activation of autophagy assists in eliminating mutant, misfolded and or excessive proteins associated with the damage of motor neurons causal to MND/ALS [1].

It is not yet known why one subject in Cohort 1 did not have decreased blood p-RPS6KB1 and p-EIF4EBP1 protein levels. Initial analysis indicates it may be associated with an individual's metabolic activity and/or tablet administration compliance issues. These possibilities will be explored with the ongoing analysis of the Cohort 2 data so that we can better interpret these results.

The Board authorises this announcement.

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About PharmAust Limited:

PharmAust Limited is listed on the Australian Securities Exchange (PAA) and the Frankfurt Stock Exchange (ECQ). PAA is a clinical-stage company developing therapeutics for both humans and animals. The company specialises in repurposing marketed drugs lowering the risks and costs of development. These efforts are supported by PAA's subsidiary, Epichem, a highly successful contract medicinal chemistry company that generated $3.4 million in sales of goods & services in FY 2022.

PAA's lead drug candidate is monepantel (MPL), a novel, a potent and safe inhibitor of the mTOR pathway – a pathway having key influences in cancer growth and neurodegenerative diseases. MPL has been evaluated in Phase 1 clinical trials in humans and Phase 2 clinical trials in dogs. MPL treatment was well-tolerated in humans, demonstrating preliminary evidence of anticancer activity. MPL showed objective anticancer activity in dogs. PAA is uniquely positioned to commercialise MPL for treating human and veterinary cancers and neurodegenerative diseases as it advances a reformulated version of this drug through Phase 1 and 2 clinical trials.

[1]References available at:
doi:10.3389/fnmol.2017.00263; doi:10.1016/j.jmb.2019.12.035; doi.org/10.3390/cells11081272; doi:10.3109/17482968.2012.721231B; doi:10.1007/s00401-019-01998-x; doi:10.1016/j.stemcr.2017.12.018; doi:10.1186/s13041-017-0300-4; doi:10.1242/bio.201410066; doi:10.1093/hmg/ddu580
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