PharmAust Completes Cohort 3 Pharmacokinetics in MND Patients

- Elevated Monepantel/Monepantel Sulphone (MPL/MPLS) levels in Cohort 3 data are in line with increasing *anti*-mTOR pathway activity in MND patients and reducing inflammation associated with neurones
- Cohort 3 blood samples have been collected to determine MPL and MPLS levels
- Treatment continues to be well tolerated even after escalation to Cohort 3 and up to 10 months of self-administration
- Cohort 3 patient 24 hour PK demonstrate MPLS plasma steady state concentrations increase proportionally to the MPL tablet dose increase from Level 1
- Longer term plasma analysis shows MPLS increases in the plasma by up to 64% in some patients
- The final group Cohort 4 has been approved to commence dosing by the trial Safety Committee

9 August 2023 – Perth, Australia: PharmAust Limited (ASX: PAA & PAAO), a clinical-stage biotechnology company, is pleased to report progress on its Phase 1 clinical trial of its lead drug candidate monepantel (MPL) in people with Motor Neurone Disease/Amyotrophic Lateral Sclerosis (MND/ALS).

PharmAust has completed an interim pharmacokinetic analysis of plasma MPL and MPLS concentrations in Cohort 3 MND patients receiving MPL at 6mg/kg. Importantly, Cohort 3 patients are the same as those escalated from Cohort 1 allowing for a direct comparison of tablet behaviour in the same people at different doses. The 24 hour intensive pharmacokinetics data demonstrate the presence of MPL and MPLS in all measured patients. MPL was more rapidly cleared from the plasma of these patients, showing some apparent faster MPLS metabolism. Average MPLS maximum levels following dosing were approximately 1.8 fold increased between Cohort 1 and 3, while calculated steady-state MPLS concentrations (Css) were 2.6 fold increased (see Figure 1).

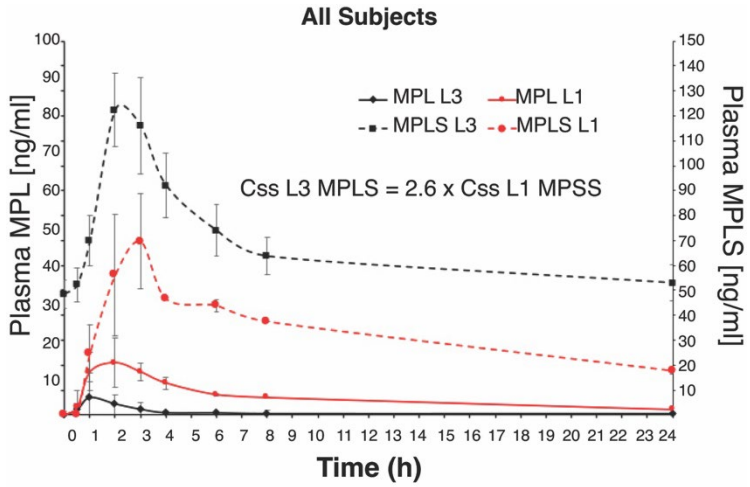

Figure 1. MND patient Level 1 and Level 3 24 h pharmacokinetics following dosing at 2 mg/kg bw (Cohort 1) and 6 mg/kg bw (Cohort 3). Some dose proportionalities in Cmax and steady state.

PharmAust's preclinical cancer data suggest MPLS displays similar anti-mTOR pathway activity to MPL, suggesting anti-mTOR pathway activity between Cohort 1 and Cohort 3 has increased. It is hypothesised that decreasing mTOR pathway activity leads to increased autophagy and the removal of misfolded or accumulated proteins associated with motor neurone death.

Over the long term and following repeat dosing, MPLS levels were increased by 13-64% for most patients. In contrast, 2 of 6 patients noted overall decreases in average MPLS plasma levels despite the increased dose.

Some compliance issues were expected in patients due to poor muscle control associated with tablet swallowing. The patients with these issues may sometimes correlate with reduced MPLS levels. It is noteworthy though that mortality for MND patients is reported to be 34% at one year from diagnosis[1]. In the current trial patients have been receiving MPL for four to 10 months, with all patients alive and free of Serious Adverse Events and keen to continue MPL treatment.

Furthermore, pharmacodynamic data of the PBMC markers p-RPS6KB1 and p-EIF4EBP1 were significantly reduced by Wilcoxon signed-rank test and ANOVA tests, respectively. Similarly the Urinary p75ECD marker was significantly reduced by Mixed Effect analysis and p75ECD urinary protein biomarker/urinary creatinine ratios were reduced in three of six trial subjects.

The combined data points to some preliminary evidence for MPL activity and enables PharmAust to commence planning a Phase 2 trial.

At a recent Safety Committee meeting on 7 August, approval was given to escalate the MPL dose to the final treatment Cohort 4 and begin Phase 2 planning. High individual variability in plasma levels of MPL within the Cohort 2 patients has meant that analysis of these patients' plasma has been postponed until further data is collected. This variability may originate from non-compliance in dosing. Given the same Cohort 2 patients will be escalated to Cohort 4, PharmAust will be able to reconcile these data soon and report in due course.

"Dr Roger Aston, Executive Chairman of PharmAust added, "Further to completing the treatment schedule for Cohort 3, we can note several encouraging outcomes: Firstly, we have a good safety profile and no serious adverse events, even after prolonged periods of dosing patients (4-10 months). Secondly, it is reassuring to see effective absorption of MPL from tablets and the metabolism of MPL into MPLS, which we believe the latter is fully active based on preclinical study data. Thirdly, it is encouraging that despite the challenges of dosing MND patients, the patients have generally adhered to the protocol and have elected to remain on treatment. So far, these outcomes are consistent with previously measured biomarkers such as p-RPS6KB1 and p-EIF4EBP1 and p75ECD. Fourthly, independent studies[1] have shown that one third of patients die within 12 months after first diagnosis, lending support to continue treatment."

Neurofilament Light Chain results due in mid August 2023

As announced on 28 July, the results of the highly specialised testing of Neurofilament Light Chain (NfL) are expected in early August. The University of Tasmania (UTAS) has confirmed the NfL assay were processed on 4 August. The pending results will be formally interpreted by a pharmacologist and biostatistician and will be announced as soon as possible.

[1] Reference: doi: 10.1186/s12883-014-0197-9.

This announcement is authorised by the Board.

Enquiries:
Dr Roger Aston
Executive Chairman
investorenquiries@pharmaust.com

P +61 (8) 9202 6814
F +61 (8) 9467 6111

About PharmAust Limited:

PharmAust Limited is listed on the Australian Securities Exchange (code: PAA) and the Frankfurt Stock Exchange (code: 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.

PAA's lead drug candidate is monepantel (MPL), a novel, 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 demonstrated objective anticancer activity in dogs. PAA is uniquely positioned to commercialise MPL for treatment of human and veterinary cancers as well as neurodegenerative disease as it advances a reformulated version of this drug through Phase 1 and 2 clinical trials.