Positive Phase 1 MEND Study Top-Line Results

Highlights:

- **Monepantel displays a superior safety, tolerability to the leading FDA approved drug Relyvrio®**
- **Preliminary efficacy data shows a 58% reduction in the rate of disease progression for Cohort 2 (High Dose) using the FDA primary efficacy endpoint, ALSFRS-R**
- **Confirmation that monepantel and its active metabolite, monepantel sulfone, are both detected in cerebrospinal fluid**
- **Optimal dose identified for the pivotal Phase 2/3 clinical study, due to commence in Q3 CY2024**
- **Click here to join a webinar with PharmAust CEO Dr Michael Thurn today at 5:30PM AEDT**: **https://us02web.zoom.us/webinar/register/WN_7pVv1wrsS66OYP5lAwY6Gw**

27 February 2024 – Perth, Australia: PharmAust Limited (ASX: PAA & PAAOA) ("PharmAust" or "the Company"), a clinical-stage biotechnology company, is pleased to announce that it has met its primary safety and tolerability endpoints with monepantel (MPL) and, importantly, demonstrated a positive signal of potential efficacy. Rates of disease progression in patients with Motor Neurone Disease (MND) / Amyotrophic Lateral Sclerosis (ALS) measured by changes in ALSFRS-R may be slowed by 58% for Cohort 2, when compared to an external control cohort (PRO-ACT database).

Study Design

The Phase 1 MEND Study was a multicentre, open label study comprising a 24-hour escalating single-dose PK study and 4-week repeated escalating dose study to establish the safety, tolerability and pharmacokinetic (PK) parameters of MPL administered orally to patients with MND/ALS. Twelve participants were enrolled in cohorts of 6 patients across 2 sites. Cohort 1 was administered 2 and 6 mg/kg/day dose levels, and Cohort 2 was administered 4 and 10 mg/kg/day dose levels. Participants continued to receive MPL treatment until they were offered dose escalation or until the end of treatment.

Safety and Tolerability Endpoints

The safety and tolerability profile of MPL included no treatment-related deaths, with all 12 patients successfully completing the study, and no dose limiting toxicities experienced. A total of 56 treatment-emergent Adverse Events (AEs) were reported. Only 3 AEs, graded mild, were considered possibly related to the study drug.

Patients have remained on daily treatment of MPL for 10 to 16 months. Upon completing the study, all participants continued receiving MPL via a special access scheme and opted to enrol on a 12-month open-label extension (OLE) study.

Exploratory Efficacy Endpoints

The study's exploratory clinical efficacy markers included the ALS Functional Rating Scale-Revised ("ALSFRS-R"), ALSSQOL-R Quality of Life Questionnaire, Edinburgh Cognitive and Behavioural ALS Screen ("ECAS") and Slow Vital Capacity ("SVC"), a measure of respiratory function.

ALSFRS-R is the accepted FDA primary efficacy measure to determine ALS disease progression. It assesses for changes in a person's physical abilities over time of 12 specific functions including speech, walking, climbing stairs, dressing/hygiene, handwriting, turning in bed, cutting food, salivation, swallowing and breathing.

There were no significant differences in ALSFRS-R scores between pre-dose and end of treatment for all 12 patients ($p=0.78$), Cohort 1 ($p=0.41$), and Cohort 2 ($p=0.88$) suggesting that treatment with monepantel over 8 – 12 months slowed the rate of disease progression.

A more thorough comparative analysis of the rate of decline in ALSFRS-R scores performed by Berry Consultants against 30 matched controls from the PRO-ACT database for ALSFRS-R decline has highlighted the potential for MPL to tackle disease burden and slow disease progression. The PRO-ACT database is the largest publicly available repository of merged ALS clinical study data. Clinical study data were pooled from 16 completed Phase 2/3 ALS/MND clinical studies and one observational study. Over 8 million de-identified longitudinally collected data points from more than 8,600 persons with ALS were standardised across studies and merged to create the PRO-ACT database. This database includes demographics, family histories, and longitudinal clinical and laboratory data. Matching is a procedure that finds treatment and control subjects with similar baseline characteristics to enable treatment effect estimation.

For all 12 patients, the estimated rate of decline was -0.74 (*p=0.08*) in ALSFRS-R points per month or a 39% slowing in ALSFRS-R decline. For Cohort 1 the estimated rate of decline was -0.83 (*p=0.40*) in ALSFRS-R points per month or a 23% slowing in ALSFRS-R decline. For Cohort 2 the estimated rate of decline was -0.60 (*p=0.11*) in ALSFRS-R points per month or a 58% slowing in ALSFRS-R decline indicating a dose response.

Using the prognostic predictor model described in Elamin *et al*., 2015, [1] depending on the current severity of the disease, a 0.48 slope change as calculated for all 12 patients could provide patients with an additional 13.5- 56.5 months in median survival. Currently approved treatments for ALS/MND provide approximately 2 – 9 months in additional life expectancy.

	Estimated Rate of Decline (points per month) *	**Slowing in ALSFRS-R Decline ***	**Additional Life Expectancy ****
Combined Cohort 1 + 2	- 0.74	39%	**13.5 – 56.5 months [1]**
Cohort 1 (Low Dose)	- 0.83	23%	
Cohort 2 (High Dose)	**- 0.60**	**58%**	
Relyvrio®	- 1.24	25%	**9 months**

* Berry Consultants analysis. ** Duration is dependent upon disease severity at baseline.

The results of the additional exploratory efficacy measures of ALSSQOL-R (*p=0.11*), ECAS (*p=0.21*), and SVC (*p=0.93*) further supported slowing in disease progression. In addition, the analysis of biomarkers provided supplemental supporting evidence that MPL slows disease progression with a large reduction in cerebrospinal fluid neurofilament light chain (NfL), which is a measure of neuronal damage, amongst consenting patients (n=3).

Pharmacokinetics

Concentrations of MPL sulfone, the active metabolite of MPL, increased proportionally with the higher doses of MPL. MPLS was found in the cerebrospinal fluid indicating that both MPL and MPLS have the ability to cross the blood brain barrier.

Target Engagement (mTOR Pathway)

Target engagement of the mTOR pathway (p-EIF4EBP1 and p-RPS6KB1) in the peripheral mononuclear blood cells was confirmed at all dose levels.

MEND participant, S-W, commented:
"The Monepantel phase 1 study has been a very positive experience for me with no ill effects at all. At Calvary I have been treated with the most kind, caring and considerate doctors, nursing & administration staff and I know I am receiving the best care possible. I am more than happy to participate in this trial with the knowledge that MND patients may be helped in the future."

MEND participant, L-G, commented:
"I feel that the Monepantel may have slowed my neurological deterioration. Increasing dosage from 3 per day to 4 may also have been beneficial. My dosage was increased to 6 several days ago. There appears to be no side effects with it."

Associate Professor Susan Mathers commented:
"This study has shown oral Monepantel to be safe and well tolerated by people with MND. Given the promising findings on preliminary efficacy markers, I look forward to progressing a phase 2 study as soon as possible"

PharmAust Chief Executive Officer Dr Michael Thurn commented:
"The release of the top-line Phase 1 MEND study results is an exciting milestone for PharmAust as we take a significant step towards helping people diagnosed with this rare and incurable disease. The 58% slowing in ALSFRS-R decline amongst Cohort 2 participants clearly demonstrates the potential to provide meaningful clinical benefit to people living with MND/ALS. To know that we have potentially prolonged the lives of 12 patients is extremely satisfying and humbling. We now look forward to advancing discussions with strategic partners who share our vision for monepantel. I want to thank the trial participants, their caregivers, and families, as well as the sites' principal investigators, Associate Professor Susan Mathers and Professor Dominic Rowe, and their study coordinators for their tremendous ongoing contribution to the MEND study."

PharmAust acknowledges the support of FightMND and its donors, in particular the patients, their families and friends and their support network.

About FightMND
Founded in 2014, FightMND was established in Australia with the purpose of finding effective treatments and ultimately a cure for Motor Neuron Disease (MND), also referred to as ALS or Lou Gehrig's Disease. FightMND, with its vision of a world without MND, is one of the largest independent funders of MND research in the world. Since 2014, FightMND has investment more than $98 million into MND research and care equipment to improve the lives of those fighting the disease. FightMND is determined to help facilitate the translation of the growing body of new knowledge about the disease into a cure for MND patients in Australia and abroad. For more information about FightMND, visit the website at www.fightmnd.org.au

About Berry Consultants
Berry Consultants is a statistical consulting company based in Austin, Texas USA, specialising in innovative clinical trial design, analysis, execution, and software solutions for the pharmaceutical and medical device industry. Berry Consultants employs world-renowned experts in Bayesian statistics and strives to set the standard for adaptive clinical trial design and analysis across all medical disciplines. www.berryconsultants.com

The Board authorises this announcement.

Enquiries:
Dr Michael Thurn
Chief Executive Officer
investorenquiries@pharmaust.com

Media:
Matthew Wright
NWR Communications
matt@nwrcommunications.com.au
0451 896 420

P +61 (8) 9202 6814
F +61 (8) 9467 6111
www.pharmaust.com

Investor Webinar

PharmAust CEO Dr Michael Thurn will present the Phase 1 MND Study Top-Line Results in a webinar to be held at 5:30pm AEDT Tuesday 27 February 2024. Those interested in attending the webinar are encouraged to register at the following link: https://us02web.zoom.us/webinar/register/WN_7pVv1wrsS66OYP5IAwY6Gw

About PharmAust Limited:

PharmAust Limited is listed on the Australian Securities Exchange (ASX Code: PAA). PAA is a clinical-stage biotechnology company developing therapeutics for human and animal health applications. The company is focused on repurposing monepantel (MPL) for human neurodegenerative diseases and treating cancer in dogs.

MPL is a potent and safe inhibitor of the mTOR pathway. This pathway plays a central role in cell growth and proliferation of cancer cells and degenerating neurons. The mTOR pathway regulates the cellular “cleaning process”, where toxic protein is broken down into macromolecules to be reused. This autophagic process is disrupted in most neurodegenerative diseases, including motor neurone disease (MND/ALS).

PAA’s lead MPL program is for the treatment of MND/ALS, a rare, incurable disease. The company is currently completing a Phase 1 study in patients with MND/ALS. Top-line results are expected to be announced in Q1 CY2024. PAA anticipates starting an adaptive Phase 2/3 clinical study in H2 CY 2024 that could lead to accelerated approval with the US Food and Drug Administration in 2026. PAA is preparing to start a pivotal field trial in dogs with B-Cell Lymphoma to enable product registration in the US in 2025. PAA has previously successfully completed a Phase 1 oncology clinical study of monepantel in humans and pilot studies in canine cancer.

[1] Elamin M, Bede P, Montuschi A, Pender N, Chio A, Hardiman O. Predicting prognosis in amyotrophic lateral sclerosis: a simple algorithm. J Neurol. 2015 Jun;262(6):1447-54. doi: 10.1007/s00415-015-7731-6. Epub 2015 Apr 11. PMID: 25860344; PMCID: PMC4469087.

PharmAust Investor Hub:

We encourage you to utilise our Investor Hub for any enquiries regarding this announcement or other aspects concerning PharmAust. This platform offers an opportunity to submit questions, share comments, and view video summaries of key announcements.

Access the investor hub by scanning the QR code or visiting: https://investorhub.pharmaust.com/