OLE Study update reveals impressive Survival Data

Highlights:

- **Compared to matched controls from the PRO-ACT Historical Database, treatment with monepantel results in a significantly (χ^2=9.39, p=0.0022) longer survival of patients with MND/ALS**
- **Treatment with monepantel significantly reduces the risk of death by 91% (HR=0.087, p=0.0154) compared to PRO-ACT matched controls**
- **Updated analysis of the rate of decline in ALSFRS-R to include the compassionate use program continued to show monepantel reduces the rate of disease progression**
- **Enrolment on to the Open Label Extension Study is now complete with 10 of the 12 patients from the Phase 1 MEND Study rolling over**
- **There were 4 patients that either had no change or had a slight improvement in ALSFRS-R score while taking monepantel under compassionate use**

5 June 2024 – Melbourne Australia: PharmAust Limited (ASX: PAA & PAAOA) ("PharmAust" or "the Company"), a clinical-stage biotechnology company, is pleased to announce that enrolment on to the Open-Label Extension (OLE) study is now complete. Updated data analysis conducted by Berry Consultants shows a statistically significant survival benefit for monepantel (MPL) compared to untreated matched-controls from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database for patients with Motor Neurone Disease (MND)/Amyotrophic Lateral Sclerosis (ALS). Treatment with MPL significantly reduced the risk of death by 91% when compared to PRO-ACT matched controls.

PharmAust Managing Director Dr Michael Thurn commented:
"I'm very pleased that we have completed enrolment in the OLE study as this is a significant milestone for PharmAust. The updated survival analysis conducted by Berry Consultants is extremely encouraging, as is the updated efficacy analysis that indicates MPL continued to slow the rate of disease progression in patients with MND/ALS. These results provide an exciting backdrop ahead of the anticipated commencement of the pivotal adaptive Phase 2/3 STRIKE study in H2 2024."

About OLE Study

The OLE study will investigate the long-term safety, tolerability, and efficacy of MPL in patients with (MND)/ALS who previously completed the Phase 1 MEND Study. Eligible patients will receive a daily dose of 10 mg/kg body weight of MPL for an additional 12 months.

Enrolment has now been completed. Ten (10) of the 12 patients who completed the Phase 1 MEND study have been successfully enrolled on to the study. Of the two (2) patients that did not enrol on to the OLE Study, one sadly deceased (reported previously) while on the compassionate use program and the other patient recently did not meet the study's inclusion criteria due to elevated liver enzymes. The raised liver enzymes were not caused by treatment with MPL.

The OLE study involves two (2) sites in Australia, Calvary Health Care Bethlehem, led by Associate Professor Susan Mathers and Macquarie University, led by Professor Dominic Rowe. The study has been registered on ClinicalTrials.gov (*https://clinicaltrials.gov/study/NCT06177431*).

Survival Analysis

Statistical consultant specialists and PharmAust partner Berry Consultants quantified the effect of MPL on the survival of patients to 24 May 2024 treated with MPL for varying durations, ranging from 11.3 to 19.7 months (median of 16.4 months), compared to historical control data from the PRO-ACT database[1]. Using disease onset location, pre-baseline ALS Functional Rating Score-Revised (FRS-R) slope, baseline ALSFRS-R score, and time since disease onset, Berry Consultants matched PRO-ACT controls to each MPL treatment patient.

To increase the robustness of the analysis Berry Consultants constructed two (2) possible comparison datasets, "Assumed" or "Confirmed" death from the PRO-ACT database. The "Assumed" dataset is defined as patients with a missing death status that are still alive, while the "Confirmed" dataset only uses data where the death status is known. Berry Consultants also varied the imputation method used to take into account patients where the time of death was missing as follows: "Drop" means the analysis excludes missing times of death for confirmed dead patients; and "Last Visit" uses the last visit time as the time of death.

The calculated Kaplan-Meier curves below in Figure 1 illustrates the differences in estimated survival probability depending on the analysis dataset used. Berry Consultants concluded that the survival patterns between MPL treatment and PRO-ACT control groups differ significantly for each dataset tested (See Table 1), even using the most conservative analysis dataset (χ^2 = 9.39, p = 0.0022). In the "Assumed" survival dataset, by dropping the missing times of death in the PRO-ACT control group leads to a higher estimated survival probability. Similarly, using the Cox proportional hazards model, Berry Consultants estimated a hazard ratio of 0.087 (95% CI: (0.012, 0.627), p = 0.0154) indicating that treatment with MPL reduces the risk of death by 91%.

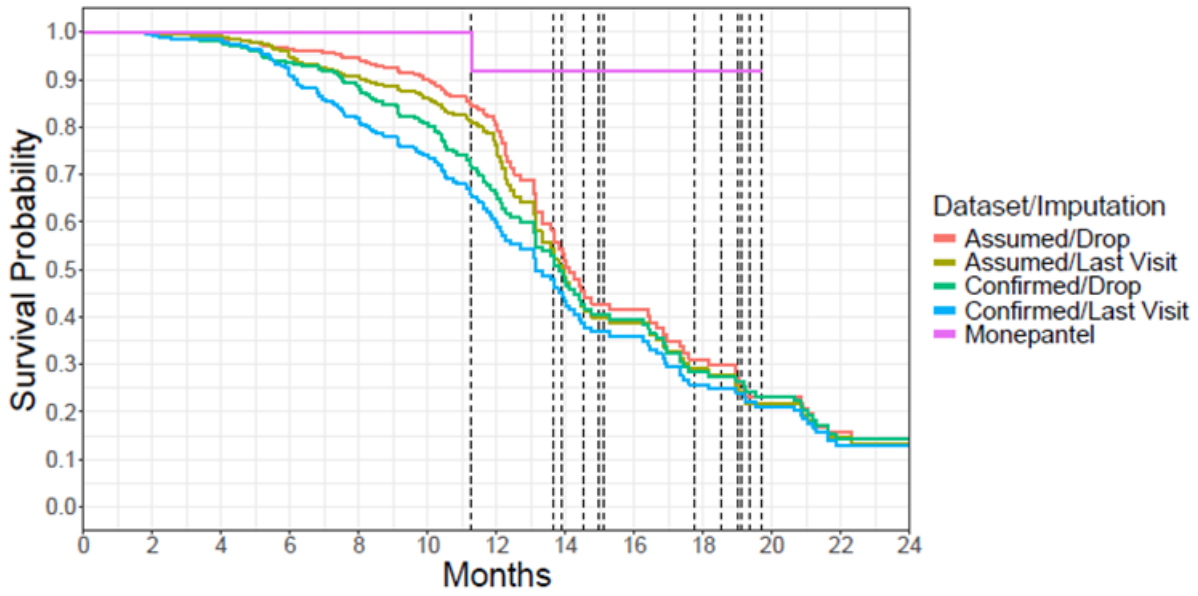

Figure 1: Calculated Kaplan-Meier curves for each of the matched-control PRO-ACT datasets described in Table 1 as well as the MPL treatment group. Vertical dashed lines represent the exposure time for all patients.

Table 1: Estimated Survival Probability by Analysis Dataset

Analysis Method		Log-Rank Test		Cox Proportional Hazards Model		
Dataset	**Death Time Imputation**	**χ^2**	**p-value**	**Hazard Ratio**	**95% CI**	**p-value**
Assumed Survival	**Leave out**	**9.39**	**0.0022**	**0.087**	**(0.012,0.627)**	**0.0154**
	Last Visit	**10.19**	**0.0014**	**0.081**	**(0.011,0.585)**	**0.0127**
Assumed Survival	**Leave out**	**10.22**	**0.0014**	**0.081**	**(0.011,0.585)**	**0.0126**
	Last Visit	**11.37**	**0.0001**	**0.074**	**(0.010,0.534)**	**0.0097**

Efficacy Analysis of Rate of Decline by ALSFRS-R

Berry Consultants also updated the analysis of the rate of decline in ALSFRS-R scores from the Phase 1 MEND study to incorporate baseline ALSFRS-R scores for the patients that rolled over on to the OLE Study. Using the same matching procedure as used for the survival analysis, the change in slope for the MPL treatment, relative to matched controls from the PRO-ACT database, was 0.40 ALSFRS-R points/month, giving an estimated rate of decline of -0.81 ALSFRSR points/month. This corresponds to a slope ratio of 0.66 or 34% slowing in ALSFRS-R decline. For Cohort 1 and Cohort 2 when analysed separately, disease progression was slowed by 23% and 44%, respectively.

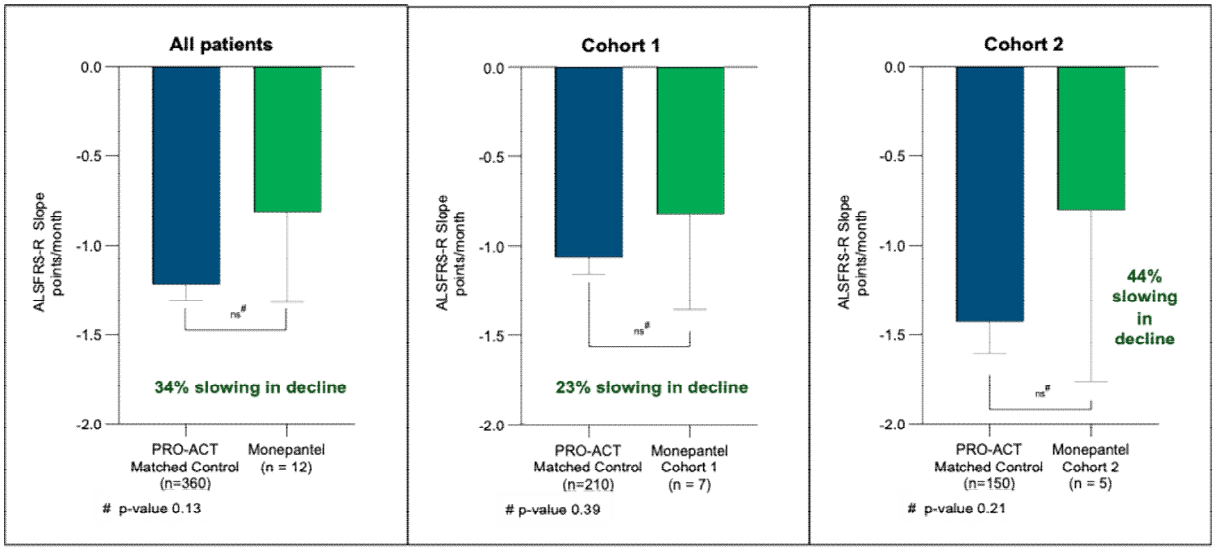

Figure 2: Rate of Decline by ALSFRS-R

ALSFRS-R Scores during Compassionate Use

To understand how patients tracked with their ALSFRS-R scores while taking part in the compassionate-use program the ALSFRS-R scores at the end of the Phase 1 MEND Study were compared to their baseline ALSFRS-R scores upon enrolment in the OLE Study. The mean rate of decline was -0.80 ALSFRS-R points/month for the 10 patients. This compares well to the rates of decline estimated in the Phase 1 MEND Study. There were 4 patients that either had no change or their ALSFRS-R score was slightly improved over this period.

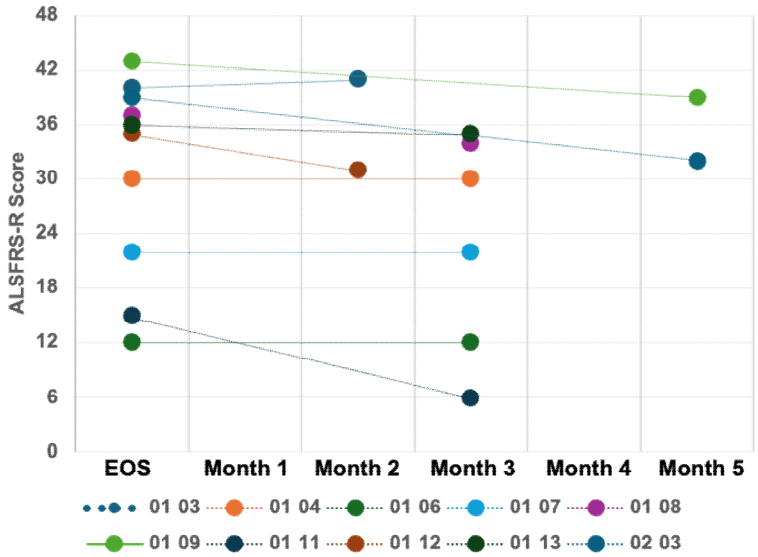

Figure 3: ALSFRS-R Scores during Compassionate-Use Program

About the PRO-ACT Database
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.

This announcement is authorised for release by the Board of Directors of PharmAust Limited.

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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 neurodegenerative diseases. The company is focused on repurposing monepantel (MPL) for amyotrophic lateral sclerosis (ALS). ALS is the most common form of motor neurone disease (MND) and affects both upper and lower motor neurons.

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

The company recently announced positive top-line results for its Phase 1 MEND study in patients with ALS. PAA is in the planning stages for a registration adaptive Phase 2/3 STRIKE clinical study and anticipates commencing enrolment in H2 CY 2024. This single pivotal study could potentially lead to accelerated approval with the US Food and Drug Administration for monepantel for the treatment of ALS in 2026.

In 2024, the Neurodegenerative Disease Market size is estimated to be worth USD 55.12 billion, with a forecast growth (CAGR) of 7.14% the market size is expected to reach USD 77.82 billion by 2029.[2]

[1] Atassi N, Berry J, Shui A, Zach N, Sherman A, Sinani E, Walker J, Katsovskiy I, Schoenfeld D, Cudkowicz M, Leitner M. The PRO-ACT database: design, initial analyses, and predictive features. Neurology. 2014 Nov 4;83(19):1719-25. doi: 10.1212/WNL.0000000000000951. Epub 2014 Oct 8. PMID: 25298304; PMCID: PMC4239834.

[2] https://www.mordorintelligence.com/industry-reports/neurodegenerative-disease-market

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