Positive Interim Study Results from Open Label Extension Study in ALS

Highlights:

- **4 months of treatment with monepantel (MPL) at the recommended Phase 2/3 dose of 10 mg/kg daily continues to be well-tolerated, slowed disease progression and improves survival**
- **Compared to untreated matched controls from the PRO-ACT Historical Database, Amyotrophic Lateral Sclerosis (ALS) patients treated with MPL had:**
  - **Significantly increased survival (χ^2=12.82, p=0.00034)**
  - **Significantly reduced risk of death by 80.3% (HR=0.197, p=0.0059)**
  - **Reduced the rate of ALS functional decline by 43.2%**
- **56% (5 out of 9 patients) showed no functional decline**
- **Some patients have now entered their 23rd month of continuous treatment with MPL**
- **FightMND grant application update**

26 August 2024 – Melbourne Australia: PharmAust Limited (ASX: PAA & PAAOA) ("PharmAust" or "the Company"), a clinical-stage biotechnology company, is pleased to provide a 4-month progress update on the ongoing 12-month Open-Label Extension (OLE) study in patients with Amyotrophic Lateral Sclerosis (ALS). The OLE study evaluates 10 of the original 12 patients who participated in the completed Phase 1 MEND study. Treatment with monepantel (MPL) at 10 mg/kg daily continues to be well-tolerated, slowed disease progression and improved survival. This is the recommended dose for the Phase 2/3 study of MPL in the HEALEY ALS Platform Trial expected to commence enrolment next quarter (Q4 CY 2024).

PharmAust Managing Director Dr Michael Thurn commented:
"These results are extremely encouraging and continues to emphasise the excellent long-term safety profile and potential of MPL to increase the life expectancy of this very vulnerable patient population. After just 4 months in the OLE study, the rate of decline in ALSFRS-R was 0.41 points/month with daily treatment of MPL. Studies have shown that rates of decline in ALSFRS-R scores between -0.25 to -0.45 points/month translate to a median survival of 3.7 years.[1] The results also provide us with confidence on dose selection for the HEALEY ALS Platform Trial."

"In October, we will reach the 2-year anniversary since the first patients started treatment with MPL. We have made incredible progress over this period, including engaging with the US Food and Drug Administration regarding the development pathway for MPL via a Pre-Investigational New Drug meeting, being granted Orphan Drug Designation from the US FDA and more recently, monepantel being selected for inclusion in the prestigious HEALEY ALS Platform Trial at Massachusetts General Hospital, the largest teaching hospital of Harvard Medical School. We're very excited about the path ahead and the potential to help more patients."

About OLE Study
The OLE study investigates the long-term safety, tolerability, and efficacy of MPL in patients with ALS who previously completed the Phase 1 MEND Study. Eligible patients receive a daily dose of 10 mg/kg body weight of MPL for 12 months. The OLE study is taking place at two clinical 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*).

As reported previously, 10 of the 12 patients that completed the Phase 1 MEND study last year were successfully enrolled on to the OLE study. Of the 2 patients that did not enrol on to the OLE study, one patient passed away due to disease progression while on the compassionate use program, and the second patient did not meet the study's inclusion criteria due to elevated liver enzymes and has since died due to progression of their ALS.

Sadly, a third patient has now passed away after commencing on the OLE study. This patient died from complications associated with pneumonia that was unrelated to treatment with MPL. Nine (9) of the original 12 patients that commenced the Phase 1 MEND Study remain on the OLE study and continue to receive treatment with MPL.

Updated Survival Analysis

PharmAust's statistical partners Berry Consultants have a provided an updated survival probability analysis to quantify the survival benefit of treatment with MPL compared to untreated matched controls from the PRO-ACT historical control database[1]. As at the 24 August 2024, patients have been treated with MPL for varying durations, ranging from 11.3 to 22.7 months (median of 18.5 months) and at varying dose levels (2 to 10 mg/kg/day). Using disease onset location, pre-baseline ALSFRS-R slope, baseline ALSFRS-R score, and time since disease onset, Berry Consultants matched untreated PRO-ACT controls to each MPL treatment patient.

Calculated Kaplan-Meier curves displayed below in Figure 1 illustrates the differences in estimated survival probability across 4 different analysis datasets from least (over estimates survival) to most conservative (under estimates survival). Regardless of the dataset used to analyse for a difference in the survival pattern, treatment with MPL prolonged the survival when compared to untreated matched controls from the PRO-ACT database. The extension in life expectancy was highly statistically significant for each dataset tested (See Table 1). For the most conservative analysis dataset the χ^2 test statistic was 12.82 with a p value of 0.00034. Under the companion analysis, the Cox proportional hazards model, the estimated hazard ratio was 0.197 (95% CI: (0.062, 0.627), p = 0.0059) indicating that treatment with MPL significantly reduced the risk of death by 80.3%.

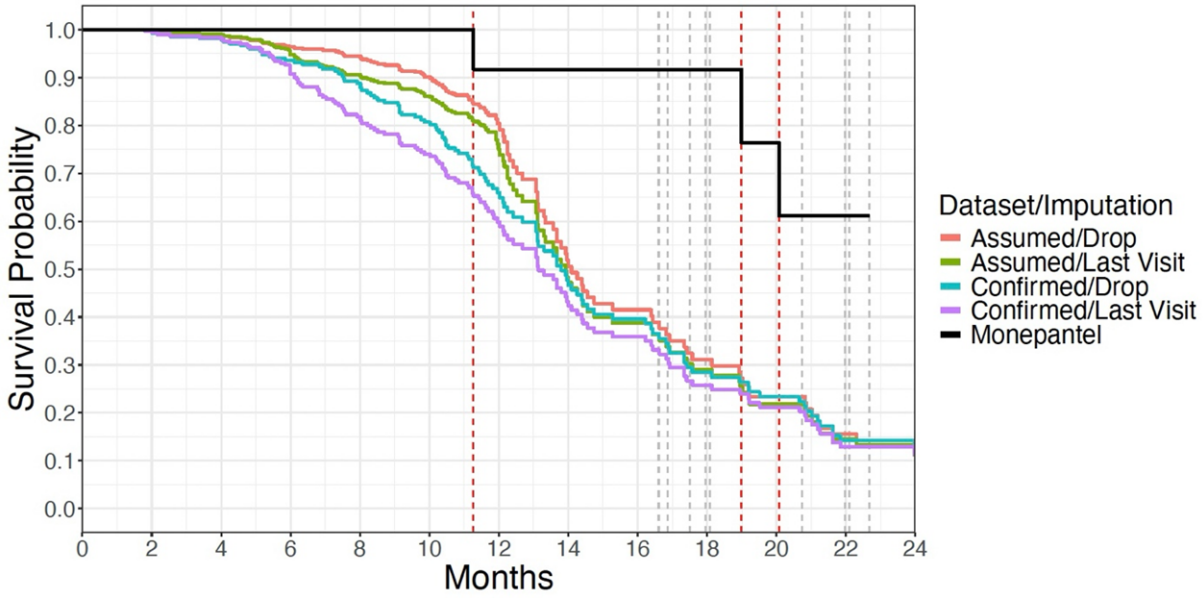

Figure 1: Calculated Kaplan-Meier curves for each of the untreated matched-control PRO-ACT datasets described in Table 1 as well as the MPL treatment group. Here "Assumed" Dataset assumes that missing death status indicates living status, while "Confirmed" only uses data with non-missing death status. The imputation method "Drop" means that it excludes missing times of death for confirmed dead subjects, while "Last Visit" uses the last visit time as the time of death. 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	**Leave out**	**12.82**	**0.00034**	**0.197**	**(0.062,0.627)**	**0.0059**
Assumed	**Last Visit**	**14.07**	**0.00018**	**0.187**	**(0.059,0.593)**	**0.0044**
Confirmed	**Leave out**	**14.52**	**0.00014**	**0.186**	**(0.059,0.586)**	**0.0041**
Confirmed	**Last Visit**	**16.35**	**0.00005**	**0.173**	**(0.055,0.546)**	**0.0028**

ALSFRS-R Scores after 4-months in OLE Study

Disease progression in the OLE study is being tracked by assessing each patient's ALSFRS-R score bimonthly. Figure 3 below shows the mean rate of decline and each individual patient's ALSFRS-R score at Baseline, Month 2 and at the Month 4 visit. The mean rate of decline over the 4 months for the 9 patients treated daily with 10 mg/kg of MPL was 0.41 ALSFRS-R points/month. The mean rate of decline relative to their untreated matched controls from the PRO-ACT database, was estimated to be 0.71 ALSFRS-R points/month by Berry Consultants. This corresponds to a slope ratio of 0.58 or a 42% slowing in ALSFRS-R decline in just over 4 months. Furthermore, 5 (56%) out of 9 patients treated with MPL showed no decline in motor function over the 4 months from Baseline.

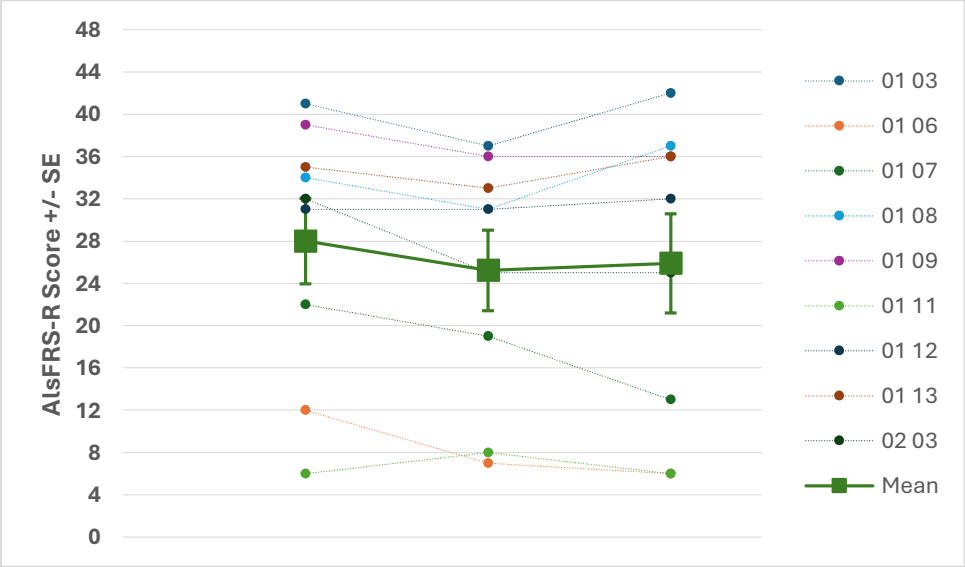

Figure 2: OLE Study ALSFRS-R Progress Scores

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 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.

FightMND Grant Application Unsuccessful

PharmAust also advises its application submitted in March 2024 for FightMND grant funding to help cover the costs of its planned Phase 2 study was unsuccessful. FightMND has played a vital role in the early clinical development of MPL, fully funding the successful Phase 1 MEND study. However, since the grant application was made MPL has secured selection for inclusion in the HEALEY ALS Platform Trial for the treatment of ALS (as announced on 15 July 2024). As the HEALEY ALS Platform Trial does not allow for study sites in Australia, PharmAust's application was no longer eligible for funding. Inclusion in the HEALEY ALS Platform Trial has substantial financial and operational advantages for PharmAust, providing the Company with the most cost efficient and safest, accelerated pathway to bring MPL to all patients.

About HEALEY ALS Platform Trial

The HEALEY ALS Platform Trial is an innovative Phase 2/3 platform trial structure conducted out of the Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital in the US. It allows for multiple investigational treatments to be tested simultaneously using a shared master protocol. The platform trial model, successfully utilized in oncology, aims to expedite the study of multiple therapies, allowing investigators to test more potential therapies, increase patient access, reduce costs, and shorten development timelines. With over 70 trial sites across the United States, the platform aims to enrol 160-240 participants per regimen, offering an optimised 3:1 active drug to placebo ratio. Drug candidates that enter the platform trial are chosen by a group of expert ALS scientists and members of the Healey & AMG Center Science Advisory Committee.

For more information about the HEALEY ALS Platform Trial, please visit their website.

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 announced positive top-line results for its Phase 1 MEND study in patients with ALS in February this year. MPL was recently selected for inclusion in the HEALEY ALS Platform Trial and anticipates commencing enrolment in Q4 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.[3]

[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.

[2] 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.

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

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