Additional Phase 1 data suggest MPL may inhibit motor neurone disease

- Nfl plasma concentrations are correlated with motor neurone disease progression
- 11 out of 12 patients in PharmAust's Phase 1 trial dosed with MPL showed no significant change in Nfl plasma and are defined as "stable"

22 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).

As the Principal Investigator recommended, results from the Interim Analysis show that Neurofilament Light Chain (Nfl) protein concentrations in the plasma of participants in its Phase 1 clinical trial do not increase following MPL treatment. Research suggests a correlation between Nfl increases and motor neurone disease progression. Only one patient in cohorts 1, 2 and 3 showed increased Nfl; the other 11 showed no significant change in Nfl, which corresponds to stabilised MND progression.

Dr Roger Aston, Executive Chairman of PharmAust, commented:

"We are delighted with the results that 11 of 12 trial participants show no significant change in Nfl plasma concentrations and are "stable". MPL has emerged as a leading candidate with enormous potential to aid MND therapy development. It's a fantastic result for PharmAust that MPL is showing a clinical benefit."

MPL is a promising treatment for MND

According to the International Alliance of ALS/MND Associations, MND affects over 350,000 people globally and kills more than 100,000 people yearly. The disease is invariably fatal with the average life expectancy of someone with MND being around 27 months. The MND/ALS addressable market is US$3.6Bn per annum, with Riluzole already reaching ~US$1Bn annual sales.

The disease is progressive, meaning the symptoms get worse over time. MND has no cure and no effective treatment to reverse its progression. Independent studies have shown that one-third of patients die within 12 months after the first diagnosis. PharmAust notes that patients have been dosed with MPL for up to 10 months in the clinical trial with no signs of material adverse events and appear "stable".

PharmAust demonstrated in its preclinical programs that MPL has the potential to activate molecular pathways relevant to the treatment of MND. MPL could reduce the rate of degeneration and loss of motor neurons in the brainstem's anterior horns and motor nuclei. Several additional surrogate clinical endpoints are being monitored during the trial. PharmAust has developed and manufactured a bespoke MPL tablet for the trial.

With success in the clinic, PharmAust hopes that MPL could receive orphan drug designation by the TGA and FDA for motor neurone disease. Such designations come with financial and supportive benefits, and PAA is evaluating this opportunity.

FightMND, Australia's largest independent funder of MND research, is investing $881,085 in PharmAusts's Phase1/2 MND study.

Annexure A – additional scientific information

Nfl light chain is produced by neurons of both the peripheral and central nervous system [1]. Plasma concentrations are recognised to provide a readout of neuron damage [2]. For example, concentrations in the plasma are known to increase for the first year following the onset of MND/ALS symptoms and then plateau [3] (see Figure 1). If a successful intervention is commenced within the first year of diagnosis, it is not known, but may be expected that Nfl plasma concentrations will plateau at a lower rate, corresponding to a slowing down of disease progression [4, 5]. If a successful intervention is commenced after the plateau concentration has been reached, it is not known whether levels would fall or remain stable. If Nfl plasma concentrations rise following this plateau and after an experimental treatment is given, it is expected that this experimental treatment is causing harm [2].

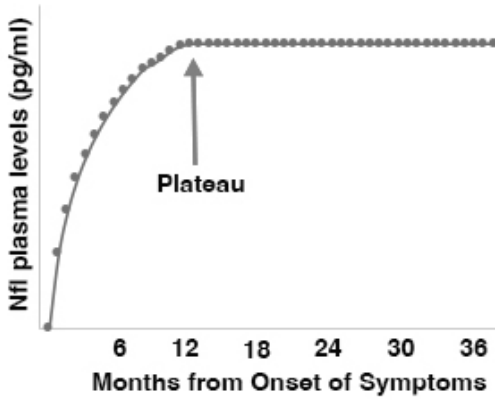
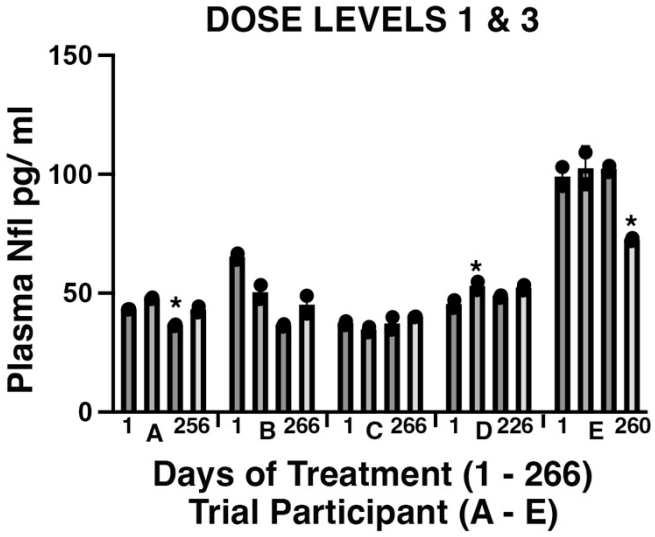


Figure 1. A plateau in Nfl protein plasma levels is recognised to occur at approximately 12 months following onset of MND/ALS symptoms.

Analysis of all available plasma samples from participants in dose Level 1 and Level 3 show that Nfl plasma levels have overall plateaued (five participants; Figure 2; One Way ANOVA, no change). An exception may be participant "E", whose Nfl plasma levels significantly reduced at the last measured time point (between days 231 and 267 of treatment); the meaning of this reduction requires further follow up (Two Way ANOVA with Tukey's multiple comparison post-test, $p < 0.05$). For example, Participant "A" 's levels are significantly reduced only at one point between approximately days 29 and 227 of continual treatment with no other changes found between any other time points ($p < 0.05$). Furthermore, Participant "C" 's levels are significantly increased between Days 1 and 29 of treatment, with no other changes found at any other time point. All participants commenced MPL treatment more than one year after the onset of symptoms (NB, for Participant B, diagnosis is understood to be more than 50 days after onset of symptoms). According to the literature, therefore, MPL is not doing any harm to trial participants and continued assessment is warranted.



Participant	Time of D1 MPL after Diagnosis (days)	Duration MPL Treatment (days)	Total time since Diagnosis (days)
A	377	256	633
B	323	266	589
C	480	226	706
D	668	266	934
E	432	260	692

Figure 2. The concentration of Nfl protein in the plasma of participants and their MPL treatment time and time since diagnosis. Specific concentrations reflect the assay used. Considering duration from diagnosis to the first day of MPL treatment (D1), it can be seen that generally levels have plateaued and have not changed since MPL treatment.

References Cited
1. Davies, J.C., et al., *Limited value of serum neurofilament light chain in diagnosing amyotrophic lateral sclerosis.* Brain Commun, 2023. **5**(3): p. fcad163.
2. Benatar, M., J. Wuu, and M.R. Turner, *Neurofilament light chain in drug development for amyotrophic lateral sclerosis: a critical appraisal.* Brain, 2023. **146**(7): p. 2711-2716.
3. Thompson, A.G., et al., *Multicentre appraisal of amyotrophic lateral sclerosis biofluid biomarkers shows primacy of blood neurofilament light chain.* Brain Commun, 2022. **4**(1): p. fcac029.
4. Verde, F., et al., *Neurofilament light chain in serum for the diagnosis of amyotrophic lateral sclerosis.* J Neurol Neurosurg Psychiatry, 2019. **90**(2): p. 157-164.
5. McCluskey, G., et al., *Serum Neurofilaments in Motor Neuron Disease and Their Utility in Differentiating ALS, PMA and PLS.* Life (Basel), 2023. **13**(6).

The Board also provides an update on two other matters:
Firstly, PharmAust met last week with representatives of Thermaquatica and both parties agreed that the Sub-License Agrement between the parties relating to OHD dated 18 March 2021 automatically terminated on the day that Epichem entered voluntary liquidation without any notice needing to be given.
Secondly, PharmAust is making arrangements to ship its tablets stored at Epichem to an alternative secure location.

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
www.pharmaust.com

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.