FIGHT MND.


Dr Susan Mathers

Lead Investigator.
**DR SUSAN MATHERS**

Clinical Trial.
**ORAL MONEPANTEL - PHASE 1**

### Where do you work?

I am a neurologist at Monash Health, Adjunct Senior Lecturer, School of Clinical Sciences, Monash University and Clinical Director of Neurology at Calvary Health Care Bethlehem, Melbourne.

### Can you give us a summary of your clinical experience and research background?

My clinical and research interests focus on the management of progressive neurological diseases, clinical trials and models of care. At Calvary Health Care Bethlehem I lead a multidisciplinary, state-wide services for people with a progressive neurological disease living in Victoria and bordering states. Over a thousand patients attend this service, including 350 people with Motor Neurone Disease.

### Why did you begin searching for a treatment that prevents MND?

Curing MND is the ultimate goal for people with MND, their families, clinicians and researchers, alike.

### What is your favourite aspect of your research?

Being able to offer involvement with research and clinical trials at the same time as delivering care to people living with MND.

### How was Monepantel identified as a potential treatment for MND?

I was approached by Dr Richard Mollard from PharmAust and other members of the research community to develop a clinical trial of Monepantel for people with MND. Monepantel inhibits the mTOR pathway in cells, increasing the recycling and removal of excessive or misprocessed proteins. Abnormal protein aggregates in neurones in MND and other neuro-degenerative conditions are believed to disrupt cellular functions and contribute to cell toxicity and cell death.

### What excites you about Monepantel?

Monepantel is already an approved, oral drug used around the world in the treatment of animals. It has been shown to be safe in a small phase 1 trial in humans with cancer. This allows a more rapid drug development pathway for people with MND.

### How will this funding impact the potential for Monepantel?

This funding enables the safety and tolerability of Monepantel to be tested in people with MND over the next 12-18 months. We will also be looking out for signs that Monepantel may slow the progression of MND. This data, in conjunction with concurrent preclinical studies will determine whether Monepantel should go on to be tested in larger phase 2 studies.

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Dr Richard Mollard

## Lead Investigator.
## DR RICHARD MOLLARD
## Clinical Trial.
## ORAL MONEPANTEL - PHASE 1

**Where do you work?**

I work for PharmAust Ltd as Chief Scientific Officer. PharmAust is an ASX listed company and the parent of two wholly-owned subsidiaries: Pitney Pharmaceuticals Pty Ltd and Epichem Pty Ltd. I am also Chief Executive Officer of Pitney Pharmaceuticals Pty Ltd.

**Can you summarise your clinical and pharmaceutical industry experience?**

I have been involved in the pharmaceutical industry for over 20 years and clinical research for over 10 years. My pharmaceutical industry experience commenced in France with the IGBMC in conjunction with Bristol Myers Squibb. I then worked with the University of Michigan in the US in conjunction with Eli Lilly & Co. After completing an MBA at Melbourne Business School, I consulted and worked for pharmaceutical and clinical research companies in Australia and throughout South East Asia. I have worked on small molecule design and cellular therapeutic development, drug screening, clinical business diligence, pharma company corporate strategy, and Phase I and II trials in humans and pet dogs.

**What got you interested in MND research?**

I become interested in MND research while studying the potential therapeutic applications of PharmAust's lead anti-cancer drug monepantel. Monepantel is a registered veterinary livestock product and during drug screening programs for alternative indications that may be relevant to humans, PharmAust found that monepantel has off target mTOR pathway inhibitory activity. This activity is very specific to cancer cells, with normal healthy cells being relatively unaffected even at high concentrations. Molecules that inhibit mTOR signalling are known to also clear aggregate or mis-processed proteins that can lead to neurological diseases that involve proteinopathies. So for me, this property of monepantel made its potential application as a therapeutic for MND very interesting. PharmAust had already shown in its preclinical programs that monepantel could activate molecular pathways relevant to its development as an MND therapeutic.

**Monepantel recently achieved a successful anti-cancer outcome, how did you recognise its potential for benefiting people living with MND?**

That is correct, recently, PharmAust formally demonstrated that monepantel has anti-cancer properties. Monepantel is a very safe drug and is already registered in over 30 jurisdictions around the world for veterinary use. In livestock, monepantel is recognised to act on a subclass of nicotinic acetylcholine receptors that are not found in humans. So this is a very specific mechanism of action that is not relevant to humans, because we do not have these receptors. PharmAust made a surprise finding, however, that monepantel can target an alternative receptor class that is actually found in humans and these

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relate to a pathway called the mTOR pathway. By using monepantel, PharmAust looks to target the cellular machinery to assist it in dealing with disease. With cancer, inhibiting mTOR with monepantel means that the body can shut down abnormally high protein synthesis, specifically in cancer cells, to stop these cancer pathways from functioning. With MND, it is recognised that protein synthesis is not operating properly, with aggregate protein building up inside neural cells to impede normal function. Inhibiting the mTOR pathway in MND aims to clear aggregate proteins in affected neural cells, thus permitting the neural cells to function normally again.

**What will this funding enable you and PharmAust to achieve?**

This funding is a fantastic opportunity for PharmAust as it assists to accelerate its new monepantel tablet into Phase I trials for MND. Previously PharmAust had used the veterinary liquid formula in a Phase I trial in cancer patients. Despite good outcomes, this liquid had a poor palatability so PharmAust discontinued its use. PharmAust then developed tablets that do not have this palatability problem, while still delivering a significant amount of drug to the body. With this funding PhamAust will make tablets specifically for this trial, provide patients with care during the trial and also employ an outsourced trial management team to assist with independent trial oversight.

## The Clinical Trial

Monepantel is a well-known veterinary drug approved to treat parasites in animals. It has demonstrated a high safety profile in anti-cancer clinical trials in people and is being re-purposed in the fight against MND. Monepantel works by stopping the activity of a cellular pathway called mTOR that regulates the metabolism, growth and survival of the cell. Drugs that inhibit the mTOR pathway have been shown to help clear away proteins/molecules that clump together and accumulate within cells and can cause damage and death of these cells. Pre-clinical studies have shown that monepantel can slow disease progression in MND models by clearing harmful materials in a motor neuron that stick together and make them unwell. This study aims to advance monepantel as a potential therapeutic for MND.

## OBJECTIVES

This Phase 1 trial aims to:

- Test the safety and tolerability of oral monepantel tablets in 8 Australian MND patients across 2 clinical sites at Calvary Health Care Bethlehem in Melbourne, and Macquarie University in Sydney.
- Find the most appropriate dose of monepantel to treat MND in people.
- Explore if monepantel shows signs of efficacy to support the design of a larger Phase 2 clinical trial.

## OUTCOMES

- The results of the Phase 1 study will be analysed in the first half of 2022 to determine whether they support advancing monepantel to a larger Phase 2 MND trial.