MND Research Network Newsletter Spring 2022

I am excited to bring you this edition of our newsletter, which highlights some of the great work happening by our MND Research Network members. A team of researchers travelled to the Australian and New Zealand MND symposium in April. Congratulations to those who represented the New Zealand MND community and presented their research. Some of the attendees have shared their experiences and take-home learnings from this first collaborative symposium. You can read more on pages 2-5.

Dr Emma Scotter gave an interesting talk on the topic "Motor Neurone Disease, who develops it, why, and what we are doing about it?" This was hosted by the Neurological Foundation of New Zealand. A copy of the recording is available here.

There have been some interesting developments with clinical trials for Biogen's Tofersen study, Triumeq Lighthouse II study, Wave Life Sciences FOCUS-C9 study, and Amylyx Pharmaceuticals AMX0035 study. These are discussed in more detail from page 6.

MND Global Awareness Day was on the 21st of June. Many events were held throughout the country including the "Ice bucket challenge" and "Cuppa tea for MND". If you are still interested in organising a fundraising activity or donating it is not too late. You can contact MND New Zealand or click here for more information.

If you know anyone interested in MND research, please encourage them to connect with us via Twitter, Facebook, or the MND Research Network website. We regularly post MND research-related updates on our social media pages and website. If you have any questions or would like the Network to feature a particular topic etc. please don't hesitate to email us.

I want to take this opportunity to thank you for your support in the movement to profile and grow MND research in New Zealand. I am returning to Ireland this year and therefore resigning from my position as manager of the MND Network and curator of the MND Registry in November. I have thoroughly enjoyed my time in this dual role over the past two years. I am inspired by those who are investing their time and expertise in progressing our knowledge of MND and striving for a better future for people living with MND in New Zealand.

Noho ora mai
Dympna Mulroy
NZ MND Research Network Manager

Australian and New Zealand MND Symposium

The first Australian and New Zealand MND Research Symposium took place in Brisbane on Thursday 28th and Friday 29th April 2022 with an MND Connect - Research Live session on Saturday 30th April. The meeting was jointly hosted by MND Research Australia and FightMND. There were approx. 220 in-person registrants and another 40 online attendees.

The opening session had a strong focus on collaborative research programs with overviews of the MND Collective, the MiNDAUS Partnership, the MND NZ Research Strategy, the MNDSA Clinical Pathway and Referral Network and the SALSA genetics database. Scientific sessions then followed, focussed on the causes of MND, the role of TDP-43, treatment, development and biomarkers, clinical research and improving care. A "Rapid-Fire Research" session was on day 2 where presenters had 5 minutes to summarise their research findings. This format provided a very stimulating fast-moving journey through the cutting-edge research being undertaken in Australia and New Zealand.

A small but strong cohort of New Zealand researchers attended in person and participated in many aspects of the event including chairing sessions, presenting their research, and networking with Australian counterparts to identify ways for collaboration between the two countries. Promising links were forged to work more closely in the future.

I spoke to Dr Claire Reilly, Dr Emma Scotter, Maize Cao, Miran Mrkela and Kyrah Thumbadoo about their experience attending the symposium and they kindly shared their thoughts below.

Dr Claire Reilly is the Community and Research Advisor for MND New Zealand and is currently involved in the Costs associated with MND study, the upcoming Lighthouse II trial, and is also an advisor on the MND Registry Steering Committee. In addition to a wealth of research knowledge, Claire brings a unique experience to the team as she lives with MND. Claire presented on the first day giving an overview of the New Zealand MND Research Strategy.

Dr Emma Scotter is the head of the MND Research Lab based at the School of Biological Sciences, University of Auckland. Emma leads the MND Research Network, is an advisor on the MND Registry Steering Committee, and PI for the New Zealand MND genetics study. Dr Scotter presented in the rapid-fire talks on the Genetics of MND in New Zealand.

Maize Cao is completing a PhD entitled "Identifying TDP-43 loss-of-function markers in MND". TDP-43 is the most important protein that is implicated in MND. Maize's study is examining this in relation to loss of function in the disease. Her most recent publication can be viewed here. Maize presented a poster at the symposium.

Miran Mrkela is completing a PhD entitled "Characterising the Genetic Heterogeneity of Motor Neuron Disease in New Zealand". Miran's research is focused on understanding the genetics which underpin the development of Motor Neuron Disease in New Zealand. This is part of the genetic study under Dr Emma Scotter. Miran presented a poster at the symposium.

New Zealand cohort attending the symposium. L:R – Maize Cao, Kyrah Thumbadoo, Miran Mrkela, Dr Molly Swanson, Dr Emma Scotter, Dr Alan Stanley and Dr Claire Reilly (front row).

Kyrah Thumbadoo is doing a PhD under Dr Emma Scotter on "The Role of X-inactivation in the Phenotypic Expression of the X-linked Motor Neuron Disease gene *UBQLN2*". Kyrah presented a poster at the symposium.

What did you enjoy about the symposium?

Claire - The face-to-face (kanohi ki te kanohi) interactions! Teleconferences are a useful tool but it's so nice to finally exchange knowledge and ideas in person.

Emma - A wonderful chance to sure up existing collaborations and forge new relationships.

Maize - I agree with Claire, I think it was so nice being able to meet peers and have discussions with them.

Miran - I agree that the greatest part of the symposium was the face-to-face collaboration. There is something to be said for instant meetings over zoom BUT I don't think they can replace that spontaneous face-to-face discussion.

Kyrah – The symposium was very well organised, with many different sessions, and lots of opportunities to interact and discuss research with those of different interests and focuses. I especially liked that the symposium was hybrid, with some presentations, as well as Q+A, seamlessly delivered virtually.

What presentation impressed you the most and why?

Claire - I really enjoyed the talk by Mel Syron who spoke about her father's MND journey as an Aboriginal man and the difficulties he experienced. It's a reminder of how we still have much to learn about how we approach pwMND from different backgrounds and cultures.

Emma - I was very impressed by the work Fazel Shabanpoor is doing to improve the efficacy of antisense therapies for genetic MND.

Maize - I enjoyed listening to the project presented by Prof Danny Hatters on how the *C9orf72* mutation in MND produces small proteins that stall ribosomes (which are important for the production of new proteins). I thought the assays they did were very elegantly designed and clearly described. But I also thought Mel Syron's talk was heartfelt and thought-provoking. It was certainly a reminder of why we carry out the work we do.

Miran - Mel Syron's had a very memorable and personal talk regarding her father's experience. I'm sure this is only one story among many around the world in similar situations. From a scientific perspective, I enjoyed Dr. Benjamin Trist's talk on SOD1 maturation/dysfunction where he demonstrated that there is consistent SOD1 protein mislocalization in individuals who do not possess a mutation in the *SOD1* gene (the first gene linked to the development of ALS) and that it is likely that multiple biochemical pathways converge to this protein aggregation. It was exciting to see a study leverage x-ray fluorescence microscopy to create elemental maps!

Kyrah - As a student researching protein functionality and aggregation, I was especially interested in Dr. Benjamin Trist's presentation on SOD1 dysfunction, and Dr. Marco Morsch's talk on TDP-43 protein modifications and subsequent condensate formation, together highlighting the importance of intracellular protein quality control and its role in MND. Professor Samar Auon's discussion on the experience of caregivers and families of patients with MND was also a salient reminder of the overarching impact of MND.

Were there any ideas or knowledge shared that could be considered in New Zealand?

Claire - I certainly think there are opportunities for collaboration, and we have made some valuable connections with our Australian colleagues. I was particularly interested in seeing how the Australian Registry is evolving into more of a patient-focused care platform (MiNDAUS) and it will be interesting to see how this develops.

Emma- The collaborative networking and administrative support that underpins Australian MND research gives much food for thought for us in New Zealand.

Maize - Several collaborations have been initiated between our New Zealand group with various Australian groups. Watch this space!

Miran - We have already seen a strengthening in the collaborations that exist between our group and others in Australia. It was also amazing to see 'Sporadic ALS in Australia' (SALSA) announce the start of a data browsing portal for their cohort which will undoubtedly be a great tool moving forwards!

Kyrah – Mel Syron's recount of her father's experience with MND from an indigenous experience served as a good reminder that the cause and experiences of MND are heterogeneous and this means that patient care needs to be personalised to ensure maximum treatment outcomes. Steps that we can take as allies, particularly in New Zealand, is to advocate for our indigenous peoples.

After attending this symposium are you hopeful for the future of MND research?

Claire- I think the last few years have brought a lot of hope to people with MND and whānau, particularly with our new understanding of the causes of MND and the emergence of genetic therapies and new disease-modifying drugs. It was particularly encouraging to see the large number of early career researchers who are interested in MND and not just in the aetiology but also in the provision of care.

Emma- I feel very hopeful. There is incredible infrastructure and funding behind MND research in Australia and it shows in the numbers of attendees and the quality of the research. To see Australia join Europe, the UK, Ireland, USA and Canada as an 'MND research superpower' is heartening and reflects increasing global awareness and resources.

Maize - I think there is a lot of talent in the field of MND research, and there have been several advancements in unlocking the genetics and molecular mechanisms of MND in the last few years. We were able to hear from scientists and clinicians who could communicate their ideas very well, so I believe the future of MND research is in capable hands.

Miran - I think that science at its core is a collaborative effort and that ultimately any big ideas and breakthroughs will be those born out of this collaborative spirit. So, it was especially heartening to see people leave the conference with new and exciting collaborations!

Kyrah – The most exciting takeaway I had from the symposium was the shared enthusiasm of all the researchers and presenters. This enthusiasm is the underlying driver of our work and seeing this from all researchers at all levels of their scientific career served to further encourage and re-energise research and collaboration.

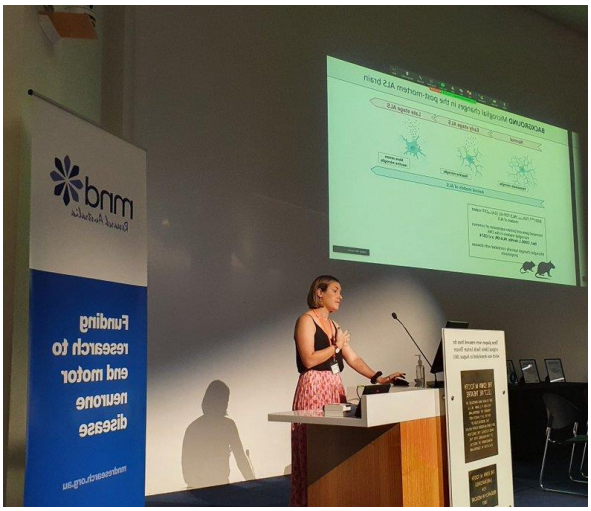
What was your take-home message from the symposium?

Claire and **Maize** - It's going to take a global collaborative effort to end this devastating illness, and everyone has a part to play and that also includes the people living with the disease. We need to make sure that people with living experience of MND can have their say in the future of research.

Emma - I agree with Claire and Maize and am increasingly seeing the value of great organisation to maximise the value of people's time and effort.

Miran - In a similar vein to what Claire said, scientific collaboration will be the path forward to important discoveries for MND.

Kyrah – Progress toward understanding the mechanisms of disease has been made and this will only continue as collaborative efforts between New Zealand and Australia further strengthen.



National MND Research News

FOCUS-C9 Wave Life Sciences, for patients with *C9orf72*-associated MND or FTD

Wave Life Sciences Ltd is a genetic medicines company committed to delivering life-changing treatments for people battling devastating diseases. They have developed an investigation drug WVE-004, and it is specifically designed for MND caused by a mutation in the *C9orf72* gene or *C9orf72*-associated frontotemporal dementia (FTD).

What does the drug do?

WVE-004 uses an approach known as 'antisense', where the drug directly interferes with the faulty instructions for making a protein. The *C9orf72* gene contains multiple sets of RNA instructions. RNA is a molecule in the cells of living things which passes instructions for protein production from the cell nucleus (where the cell's DNA is arranged into chromosomes) to the outer part of the cell where those proteins are made. In some forms of MND, errors in the *C9orf72* gene cause the RNA instructions to be faulty and this leads to the production of abnormal proteins that form toxic clumps inside cells. WVE-004 is designed to reduce the production of these toxic proteins.

Phase 1b/2a - FOCUS-C9

The Phase 1b/2a study known as FOCUS-C9 aims to evaluate the safety and tolerability of WVE-004 in people with MND or FTD with a documented mutation in the *C9orf72* gene. This study started recruitment overseas last year and is continuing to recruit across Europe, Canada, Australia and now New Zealand. In this study, participants with FTD or MND are given either the active WVE-004 medication or placebo, administered into the fluid that surrounds the spinal cord and brain via an injection near the bottom of the back (intrathecal injection) – like a lumbar puncture, which takes fluid out, but putting fluid in. The principal investigators for New Zealand are Professor Tim Anderson in Christchurch and Dr Julian Bauer in Auckland. They are recruiting participants from anywhere in New Zealand.

In April 2022, WAVE Life Science released preliminary data reporting that the drug had shown a marked decrease in levels of one of the abnormal proteins described above (called poly(GP)) in the fluid surrounding the spinal cord and brain.

Lighthouse II – Triumeq in MND/ALS Phase 3 clinical trial

By October of this year, a small group of New Zealanders living with Motor Neuron Disease will begin their journey as members of the first-ever international phase 3 MND clinical trial to be offered in New Zealand, across multiple locations. MND New Zealand is proud to have been able to contribute funding to secure access to Lighthouse II, an international clinical trial looking at whether human endogenous retroviruses (HERVs) play a role in MND.

Research teams in Bay of Plenty, Wellington, Christchurch, and Dunedin have elected to participate in this trial opportunity. Dr Alan Stanley, Hawkes Bay neurologist and MND New Zealand Council member will be the New Zealand Principal Investigator for this trial.

The Lighthouse II Project will investigate whether targeting HERVs with anti-retroviral therapy might slow disease progression in patients with MND/ALS. HERVs are ancient viruses that have left their genetic material in our DNA during human evolution. In some people, this old genetic material may become activated and play a role in the development of MND.

Phase 2 of the Lighthouse Trial showed that Triumeq could suppress this genetic reactivation and may slow disease progression in patients with MND. Triumeq is a drug that is used to treat patients with the human immunodeficiency virus (HIV) and is shown to be safe and well tolerated in patients with MND. The publication from phase 2a of the trial is available here.

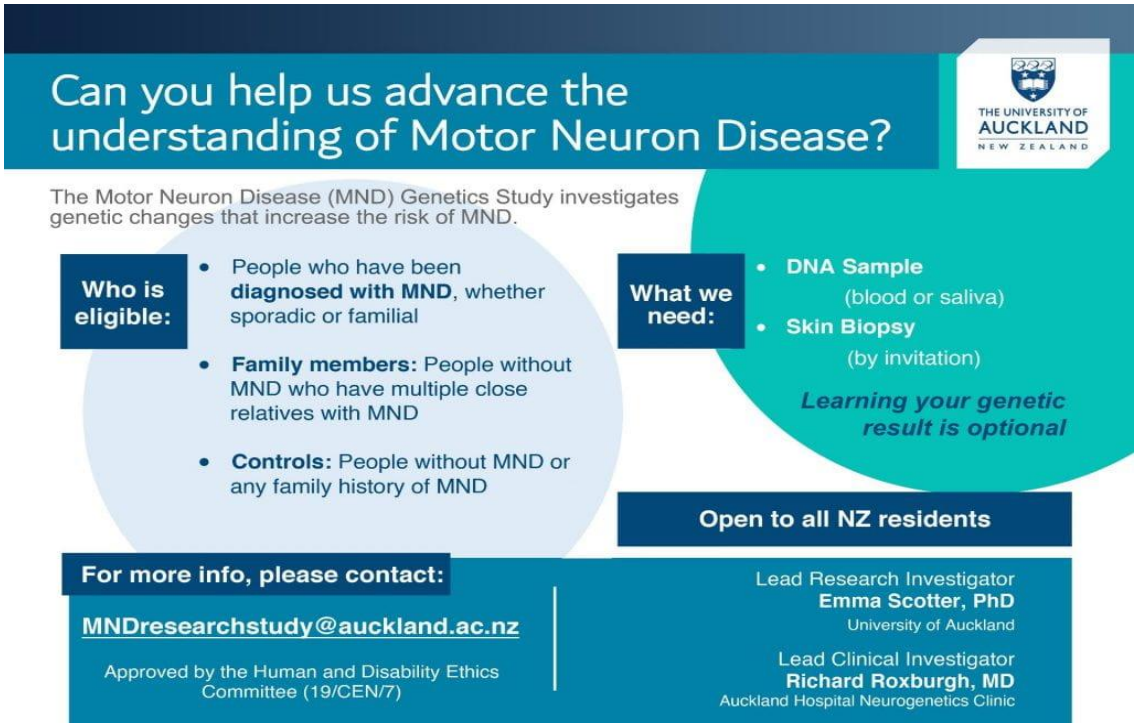
Phase 3, known as Lighthouse II, is a randomised, double-blind, placebo-controlled study. This study aims to determine if Triumeq improves survival in people with ALS/MND compared with a placebo. Lighthouse II is expecting to enrol 390 participants worldwide, who will take Triumeq for a maximum of 24 months; 20 of these participants will be MND patients from New Zealand.

To be eligible for this trial, participants must be on the NZ MND Registry, reside in one of the four site locations – Bay of Plenty, Wellington, Christchurch, Dunedin, and meet the inclusion criteria set by the trial.

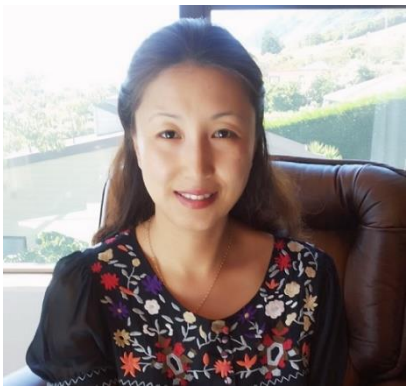
More information about the Lighthouse trial including a list of FAQs can be found on our website.

Genetic Screening in Motor Neuron Disease

The University of Auckland and Auckland City Hospital teams are still recruiting for their nationwide MND Genetics Study. The purpose of this study is to understand the genetic causes of MND in New Zealanders. If you know individuals with MND please inform them of this study.

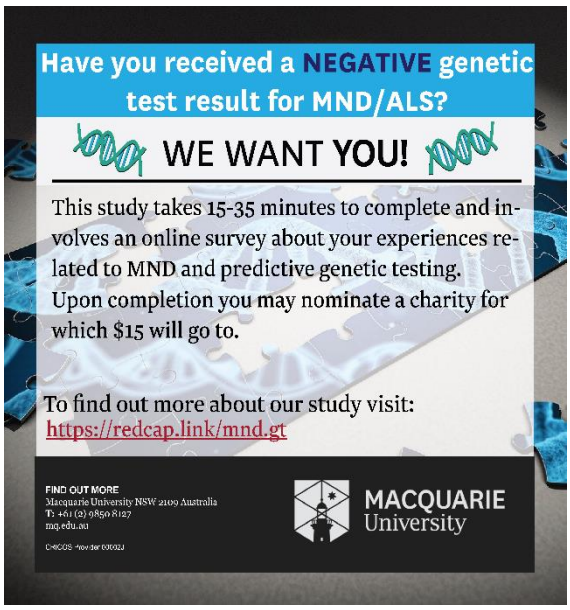


Environmental risks associated with MND



New Zealand MND researcher Grace Chen recently published two papers from her population-based control MND study. Grace is a research officer at the Research Centre for Hauora and Health, Massey University. Grace and the team are investigating associations between occupational and environmental exposures and MND. They have examined associations between motor neurone disease and occupational exposures to; electric shocks, low-frequency magnetic fields, pesticides, or other chemicals. Their most recent paper assesses whether sports, physical trauma and emotional trauma are associated with motor neurone disease. Grace's scientific papers can be viewed here.

Predictive Genetic Testing for Motor Neurone Disease



Researchers at Macquarie University, Sydney are seeking participants for their study that aims to understand the psychological impacts of familial MND and predictive genetic testing. They also wish to investigate what factors influence an individual's decision to receive or not receive predictive genetic testing for MND.

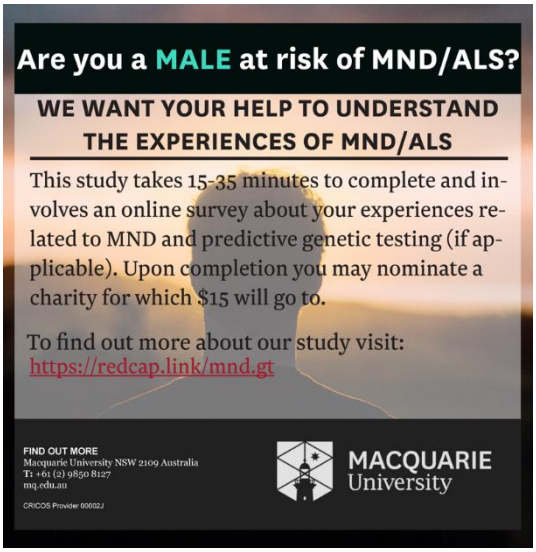
Eligible participants who consent to participate in the survey will answer a series of questionnaires on REDCap including questions on their general wellbeing, their family functioning and the psychological impact of their experiences related to familial MND.

Individuals must have a confirmed family history of MND (regardless of whether they have received a positive/negative/have not had testing). They are still looking for participants for the following categories:

- **Males** (regardless of if they have received a **negative/positive** or have not received a genetic test result)
- **Female / Other Genders** (ONLY if they have received a **negative** genetic test result)

The researchers would appreciate you sharing this advert with anyone who may be eligible for this study as they are struggling to recruit to the two categories outlined above.

To find out more about this study visit www.redcap.link/mnd.gt



International MND Research News

Tofersen (BIIB067) Biogen; Adults with symptomatic SOD1

In the previous newsletter, we spoke about Tofersen, an experimental antisense oligonucleotide (ASO) designed to reduce SOD1 protein in people with MND caused by *SOD1* gene mutations. In October 2021, VALOR, a six-month phase 3 randomized study, did not meet the primary endpoint of change from baseline to week 28 in the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R). However, reduced disease progression across multiple secondary endpoints e.g. respiratory function was observed.

In June, Biogen, the pharmaceutical company behind Tofersen, announced new 12-month data that shows earlier initiation of Tofersen (compared to delayed initiation) slowed declines in clinical function, respiratory function, muscle strength, and quality of life.

More recently on July 26, Biogen announced that it is seeking approval of Tofersen under the FDA's accelerated approval pathway, based on the use of neurofilament as a surrogate biomarker. Decision expected 25 Jan 2023. Results from their phase 1 up to the most recent phase 3 VALOR and open-label extension studies are included.

Edaravone

Edaravone is an antioxidant drug that protects nerve cells by mopping up free radicals in the body. Our cells become less efficient dealing with free radicals as we age. When neurons are damaged, as happens in neurodegenerative diseases, then more free radicals are produced, and the body becomes less effective at eliminating them.

This drug was approved by the U.S. FDA in 2017 but required intravenous administration. However, on 12th May 2022, the U.S. FDA granted approval for oral edaravone (RADICAVA ORS) for the treatment of ALS/MND. The long-term safety and tolerability of RADICAVA ORS up to 96 weeks are currently being evaluated in an ongoing phase 3 study. This drug has not been approved for use in Europe or New Zealand. Trials are ongoing to evaluate the long-term safety and tolerability of oral edaravone in subjects with MND over 24 and 48 weeks. As more data emerges, and if Europe approves its use, then it may be one for Medsafe to consider in New Zealand. Click here to read more about this drug.

Albrioza (AMX0035); Amylyx Pharmaceuticals

Albrioza, also known as AMX0035, has been approved by Health Canada subject to conditions, including being dependent on the safety and efficacy data from the ongoing Amylyx Pharma phase 3 PHOENIX trial. The regulatory decision was based on data from the CENTAUR Phase 2 clinical trial (NCT03127514) and its extension study (NCT03488524), which showed that Albrioza significantly slowed MND patients' functional decline and reduced their risk of death.

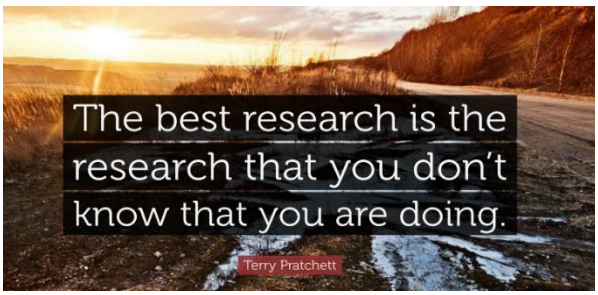
AMX0035 is an oral fixed-dose combination therapy that may reduce neuronal cell death as a stand-alone therapy or when added to existing treatments. It is the first investigational therapy to demonstrate statistically significant benefit on this pre-specified primary outcome in people with MND since edaravone.

Canada is the first country to approve ALBRIOZA as a treatment for ALS. Similar approval applications are being reviewed by health authorities in Europe and the United States, with a U.S. decision expected by the 29th of September. As Amylyx Pharma continue negotiations with the Canadian authorities so eligible Canadians living with MND can have access to AMX0035 as quickly and efficiently as possible, it is hoped more countries will follow Canada's lead. Amylyx anticipates top-line results from the PHOENIX trial in 2024. Click here to read more. Answers to frequently asked questions about ALBRIOZA is available here.

Conferences

Many conferences are hybrid or online again this year. This makes global events more accessible to everyone. Click here to see a list of upcoming MND conferences/seminars. Recorded past events are also available to view on our website.

We want to hear from you!



We are starting to look towards 2023 identifying goals and outcomes for the MND Network. If there is anything you would like us to focus on e.g., specific topics in MND, or you would like to share any work you are doing in the MND space, please let us know. We would love to hear your ideas on how we can continue to grow and expand the New Zealand MND Research Network.