



Nyrada Unveils Target of its Brain Injury Program as TRPC Ion Channels & Provides Phase I Study Update

- Brain Injury Program target revealed as versatile TRPC ion channels
- NYR-BI02 is a potent blocker of three TRPC ion channel subtypes, limiting excitotoxicity
- Patent application filed to protect Nyrada's technology
- No FDA-approved drug exists to treat secondary brain injury
- Potential to pursue multiple additional diseases involving TRPC ion channels, including further neurological diseases and diseases of the kidneys, heart, lung, and muscle
- Pending manufacturing and ethics committee approval, recruitment of patients into the Phase I traumatic brain injury trial is expected to commence in 2H CY2022 in Australia

Sydney, 6 June 2022: Nyrada Inc (ASX: NYR), a preclinical stage, drug development company specialising in novel small molecule drugs to treat cardiovascular and neurological diseases, today announces the biological target for the Company's Brain Injury Program is versatile Transient Receptor Potential Canonical (TRPC) ion channels, creating the potential for future studies in a broad range of other neurological diseases along with diseases of the kidneys, heart, lung, and muscle. In addition, the Company provides an update on the planned Phase I study.

Nyrada's Drug Candidate Targets TRPC Ion Channels

Nyrada's Brain Injury Program targets a class of proteins known as the "Canonical" Transient Receptor Potential, or TRPC ion channels. These channels are present on the surface of brain cells and allow calcium to enter the cell. Following brain injury such as a stroke, accident impact or concussion, these channels are constantly activated, allowing sustained calcium entry into the cells which in turn causes cell death.

Nyrada's brain injury drug candidate NYR-BI02 is a potent blocker of three subtypes of the channel – TRPC3, TRPC6 and TRPC7. NYR-BI02 is also able to cross the blood-brain-barrier indicating it can reach the injured brain at a therapeutic level.

According to animal studies and published literature, these three TRPC channel subtypes facilitate a secondary injury pathway, leading to an undesirable larger injury following a traumatic brain injury or stroke. This larger injury is responsible for poor patient outcomes such as increased disability, along with reduced patient survival and quality of life. Presently, there are no FDA-approved small molecule blockers of TRPC 3, 6, 7 ion channels.

As part of its active intellectual property protection program, Nyrada has filed a provisional patent covering a library of molecules that block these channels. It is anticipated that the patent will have coverage firstly in Australia, followed by the UK and US.



Nyrada CEO, James Bonnar said: “We are pleased with the results of initial studies showing that our drug candidate, NYR-BI02, is a potent blocker for three of the TRPC channels, with significant potential for the treatment of those suffering an injury following traumatic brain injury (TBI) or stroke. The filing of a patent for molecules blocking these channels is a key milestone and part of Nyrada’s active IP strategy for the Brain Injury Program. The team is focused on finishing drug synthesis and finalising the TBI efficacy study design, ahead of a Phase I first-in-human trial later this year.”

Relevance of TRPC Channels to Secondary Brain Injury

When TRPC ion channels activate they allow calcium to enter the cell. While calcium is critical to cell survival, excess calcium triggers cell death pathways. Following an injury in the brain, the mechanisms that keep the calcium levels in-check fail as they rely on energy, which quickly depletes. The sustained activation of TRPC channels results in an excess build-up of calcium and cell death. By targeting these channels, Nyrada’s brain injury drug candidate is able to interrupt this process and thereby reduce secondary brain injury.

Previously, proteins such as the NMDA receptor (a receptor and ion channel found in neurons) that allow calcium and other ions into the cells have been targeted by drug developers in an attempt to reduce secondary brain injury. However, due to the critical role of these proteins in normal brain functioning, adverse events were observed when attempts were made to block them.

The TRPC 3, 6 and 7 ion channels, while involved in normal brain functioning, including embryo and neonatal brain development and motor coordination, are considered a safer target. In addition, the Nyrada molecule will undergo a rigorous CNS safety preclinical study prior to administration in healthy volunteers to confirm its safety profile.

TRPC 3, 6, 7 channels have been assessed for their contribution to brain injury in animal models. Through utilisation of transgenic mouse models, TRPC 3/6/7 ion channels have been shown to play a significant role in secondary brain injury following ischemia. Mice with genetic deletion of the TRPC 3/6/7 subtypes have smaller injury sizes and ameliorated motor deficits compared to wild-type mouse controls following middle cerebral artery occlusion.¹

Nyrada will initially test the efficacy of its NYR-BI02 molecule as a TRPC 3, 6 and 7 channel blocker in a model of traumatic brain injury via its existing collaboration with the Walter Reed Army Institute of Research (WRAIR), and explore potential avenues for non-dilutive clinical trial funding. With the initial pilot work at WRAIR and UNSW Sydney now complete, the study design for the efficacy study is being finalised. The study will initiate once the drug synthesis has finished.

In addition, Nyrada will test the efficacy of the molecule in a model of ischemic stroke with results anticipated in Q3 CY2022.

¹ X. Chen et al., 2017



Potential to Pursue Multiple Additional Diseases Involving TRPC Ion Channels

TRPC 3, 6 and 7 ion channels are involved in other neurological diseases including epilepsy, neuropathic pain and neuro-oncology. These channels are also involved in diseases related to the kidneys, heart, lung, and muscle.

While Nyrada is focussing on moderate-severe TBI as the primary indication and stroke as the secondary indication, the Company’s preclinical and clinical safety studies can support potential Investigational New Drug (INDs) applications with the FDA for both these indications. Pursuing any other indications will require additional preclinical and clinical studies using an oral route of administration.

Brain Injury Program Phase I Study

Objectives: To assess the safety, tolerability, and pharmacokinetics of NYR-BI02


Design:

- Randomised double-blind placebo-controlled design
- 5 cohorts; 8 participants in each cohort; 6:2 active and placebo treatments
- 3 cohorts will be single ascending doses
- 2 cohorts will be given continuous infusion doses


Participants:

- Male and female healthy volunteers
- 18-50 years age

Cohort number	Dose administered
1	Low dose single bolus
2	Medium dose single bolus
3	High dose
4	Low dose continuous infusion (72 hrs)
5	High dose continuous infusion (72 hrs)



Active arm



Placebo

Location & Duration:

- Study will be conducted at a clinical trial centre in Australia
- The study duration will vary between 1 – 4 days

The trial participants will be split into 5 groups of 8, with 6 receiving the drug and 2 receiving a placebo. Cohorts 1 and 2 will be given a bolus single ascending dose, while cohorts 3, 4 and 5 will be given bolus and continuous infusion in ascending doses for 72 hours via intravenous infusion.

Blood samples will be drawn several times throughout the study period and analysed for drug levels. Participants will be monitored for clinical signs throughout the study duration.



Pending scale-up manufacturing of the drug and ethics committee approval of the trial protocol, recruitment and dosing of the first participant is expected to commence in 2H CY2022. The Phase I study will be run in Australia.

Other Updates

Preclinical Stroke Model Study and TBI Efficacy Study

The covid-related lockdowns in Shanghai, China have delayed the start of the preclinical stroke model study and scale-up manufacture of the Company's lead brain injury drug candidate, NYR-BI02 as CRO staff have been unable to access laboratory work sites. As Shanghai is starting to re-open, it is anticipated the results of the preclinical stroke model study will be available in Q3 CY2022.

The TBI Efficacy Study will commence as soon as the drug manufacture process is complete.

-ENDS-



About the Walter Reed Army Institute of Research (WRAIR)

The Brain Trauma Neuroprotection (BTN) Branch is part of the Center for Military Psychiatry and Neuroscience at WRAIR. The primary mission of the BTN program is to develop ground-breaking solutions to mitigate the effects of TBI at the point of injury to reduce morbidity and mortality. Providing field-based options for diagnostics, preventive strategies, and treatments are critical to Soldiers. Since 1893, the Walter Reed Army Institute of Research (WRAIR) has been a leader in solving the most significant threats to Soldier readiness and lethality such as disease and battle injury. WRAIR's broad research capabilities at its Washington, D.C., area and expeditionary laboratories function in concert to afford Soldiers the best medical protection and support possible before, during, and after deployment by addressing both longstanding and emerging threats. Though WRAIR's research is focused on Soldier health, its products have important civilian applications, saving countless lives around the world.

About the Translational Neuroscience Facility, UNSW

The Translational Neuroscience Facility (TNF) is a core neuroscience research platform in the Faculty of Medicine & Health at UNSW. The TNF broadly supports neuroscience research and advanced translational research training directed towards treatment of neurological disorders.

About Nyrada Inc

Nyrada is a preclinical stage, drug discovery and development company, specialising in novel small molecule drugs to treat cardiovascular and neurological diseases. The Company has two main programs, each targeting market sectors of significant size and considerable unmet clinical need. These are a cholesterol-lowering drug and a drug to treat brain injury, specifically traumatic brain injury and stroke. Nyrada Inc. ARBN 625 401 818 is a company incorporated in the state of Delaware, US, and the liability of its stockholders is limited.

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