7 June 2022 Sydney, Australia

# Nyrada Corporate Presentation

Nyrada Inc (ASX: NYR) is pleased to provide shareholders and the market generally with the attached presentation that will be used by Nyrada CEO, James Bonnar, during meetings with North American investors in June.

The presentation provides a summary of the progress of the Company's two lead drug development programs as they advance towards Phase I first-in-human studies.

Mr Bonnar is also attending the 12th Annual Traumatic Brain Injury Conference in Washington DC on 6-7 June, and the BIO International Convention in San Diego between 13-16 June.

-ENDS-

**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.

www.nyrada.com

*Authorised by Mr. John Moore, Non-Executive Chairman, on behalf of the Board.*

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**Forward-Looking Statements**

This announcement may contain forward-looking statements. You can identify these statements by the fact they use words such as “aim”, “anticipate”, “assume”, “believe”, “continue”, “could”, “estimate”, “expect”, “intend”, “may”, “plan”, “predict”, “project”, “plan”, “should”, “target”, “will” or “would” or the negative of such terms or other similar expressions. Forward-looking statements are based on estimates, projections, and assumptions made by Nyrada about circumstances and events that have not yet taken place. Although Nyrada believes the forward-looking statements to be reasonable, they are not certain. Forward-looking statements involve known and unknown risks, uncertainties, and other factors that are in some cases beyond the Company’s control (including but not limited to the COVID-19 pandemic) that could cause the actual results, performance, or achievements to differ materially from those expressed or implied by the forward-looking statement.

Improving Lives Through Innovation

# Corporate Presentation

James Bonnar - CEO

June 2022

**ASX: NYR**

Authorised by Mr. John Moore, Non-Executive Chairman, on behalf of the Board.

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# Portfolio of Novel High Value Small Molecule Drugs

| | Indication | Aim | Target Market (US) | Status |
|---|---|---|---|---|
| **Cardiovascular**<br>NYX-PCSK9i<br>Oral PCSK9 inhibitor | Cholesterol lowering | Best-in-class small molecule drug to disrupt and broaden the class in CV management | **>18m** Patients[1] | Phase I Study: late CY2022 |
| **Neurology**<br>NYR-BI02<br>TRPC 3/6/7 blocker | Brain Injury | First-in-class treatment to prevent secondary brain injury following moderate-severe TBI, concussion, or stroke | **>3m** Patients / year[2] | Phase I Study: 2H CY2022 |

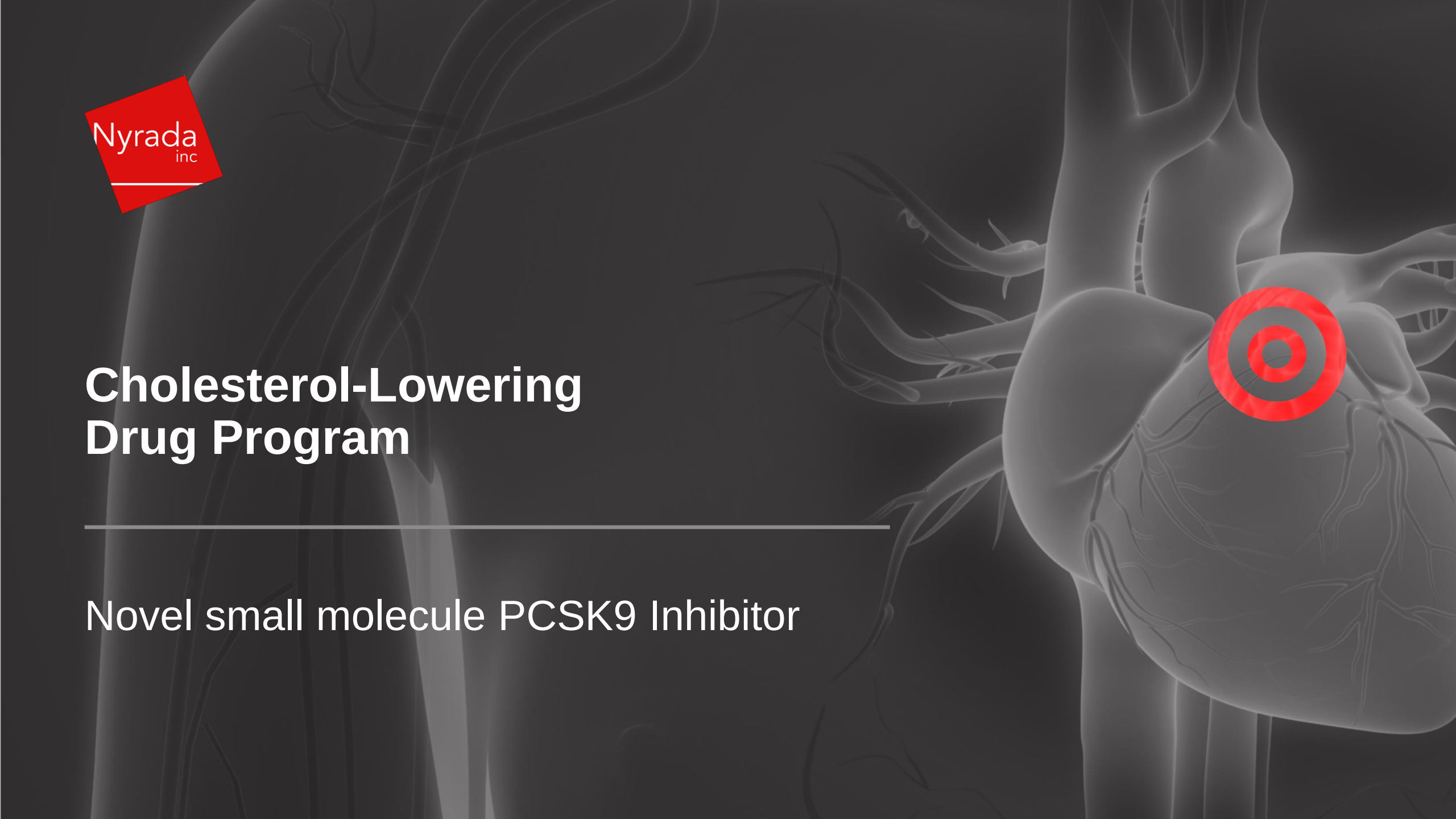
# Commercially Focused Business Model

| | |
|---|---|
| **Focus Area** | • **Novel small molecule treatments** for **serious and life-threatening diseases** where there is **unmet clinical need** and **large market share potential** |
| **Development Objective** | • Advance optimized drug candidates towards a **key value inflection point** of **confirming clinical safety and efficacy** |
| **Growth Strategy** | • **Build value** in lead drug assets by generating **clinical data** that **differentiates Nyrada's molecules as best-in-class** |

Nyrada inc

# Cholesterol-Lowering Drug Program

Novel small molecule PCSK9 Inhibitor



# Cholesterol-Lowering Market

## Population, Problem, Opportunity

**62.6 million**
Americans have high cholesterol[1]

**56 million**
between ages 40 and 75
treatment eligible

**27.4 million**
taking a statin[1]

**18.4 million**
Unable to achieve
LDL-C target despite taking a statin[1]

**1 in 5 patients**
statin intolerant[3]

### Global Cholesterol Drugs Market

- USD 18.8 billion in 2021 (USD 14.7 billion statin drugs)[4]
- Est. sales revenue USD 30 billion by 2027 (**CAGR 8%**)[5]

### Drivers of Market Growth

- Increasing rate of high cholesterol in patients
- Awareness of the benefits of cholesterol lowering drugs
- New treatment options entering the market

# Current PCSK9 Injectable Drugs

## Expensive and Inconvenient



- ✓ Effective when combined with statin treatment
- ✗ Expensive US$5,800 to US$6,500 per year
- ✗ Inconvenient for patient / poor compliance
- ✗ Expensive to manufacture
- ✗ Insurer / patient co-pay reluctance

**Competitive advantages**
of a small molecule PCSK9 inhibitor

- **Patient convenience**: once per day oral treatment
- **Lower manufacturing cost**
- Dose form **can be combined with a statin** (single pill)

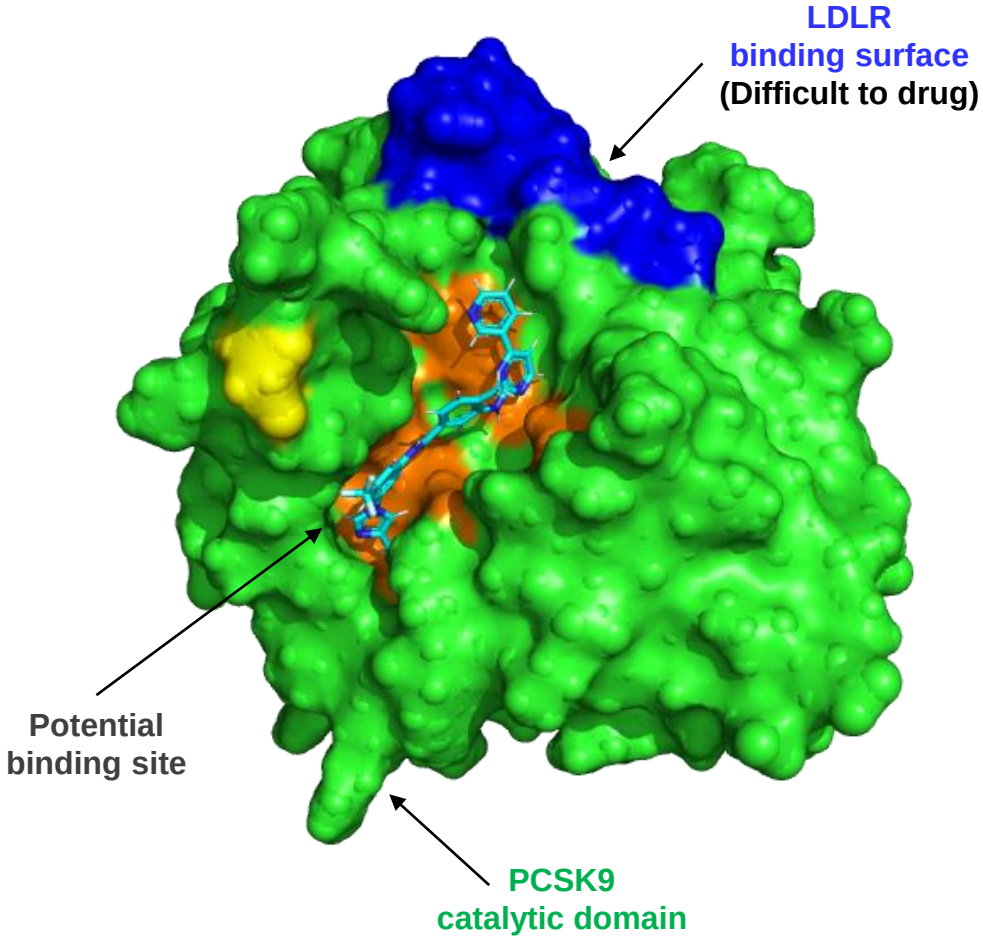
# Development of Drug Candidate NYX-PCSK9i
## Discovery to Clinical Lead

### Target Product Profile

- Small molecule suitable for once per day oral dosing
- Sufficiently potent in lowering LDL-C
- Safety / toxicology profile consistent with chronic dosing
- PCSK9 validated CVD target

### Development Overview

- Novel accessible binding site was identified
- *In silico* screen of 1,100 FDA-approved drugs and nilotinib (TASIGNA® Bcr-Abl inhibitor) emerged as a hit
- Over 400 analogs modeled, synthesized and tested for PCSK9 binding affinity (ELISA)
- NYX-PSK9i emerged as lead candidate with nanomolar PCSK9 binding affinity, oral bioavailability, and drug-like ADME-PK and physiochemical properties




Evison *et al*. Bioorg. Med. Chem. (2020) **28**: 115344

# Benchmarking Efficacy
## NYX-PCSK9i in Human Lymphocyte Cells

- NYX-PCSK9i shows **equivalency to Repatha® and Praluent®** in human lymphocytes
- LDLR retention **confirmed with/without a statin**, supporting NYX-PCSK9i use alone or in combination with statin

| | - Mevastatin | | + Mevastatin | |
|---|---|---|---|---|
| | **% LDLR retention** (with PCSK9 present) | **p-value** | **% LDLR retention** (with PCSK9 present) | **p-value** |
| No Drug | 51% | n/a | 64% | n/a |
| NYX-PCSK9i (1 µM) | 53% | 0.74 | 78% | 0.13 |
| NYX-PCSK9i (2 µM) | 64% | **0.01** | 77% | **0.06** |
| NYX-PCSK9i (4 µM) | 89% | **0.001** | 90% | **0.003** |
| alirocumab (Praluent®) | 78% | **0.002** | 88% | **0.04** |
| evolocumab (Repatha®) | 84% | **0.0009** | 89% | **0.0001** |

**bold =** statistically significant

# Benchmarking Efficacy

## NYX-PCSK9i +/- Lipitor® in Transgenic Mouse Hyperlipidemia Model

### Study Objective:

Determine if additive reduction in total cholesterol can be achieved with combination statin therapy

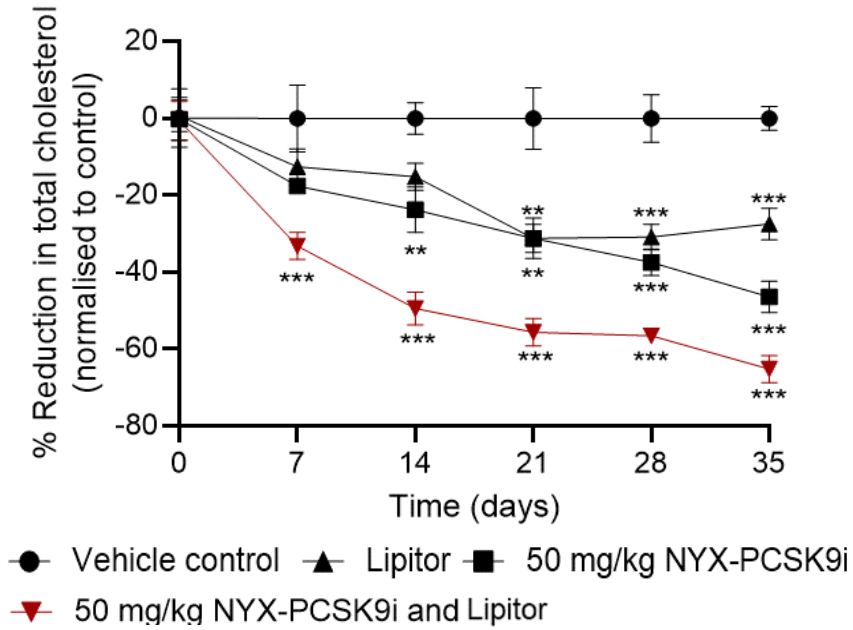
- APOE*3Leiden.CETP mouse hyperlipidemia model
- Mouse treated for 35 days (50 mg/kg BID NYX-PCSK9i)

### Results:

- **NYX-PCSK9i + Lipitor® achieves 65% total cholesterol reduction**
- **No effect on body weight, food intake, liver enzymes**

| | % Difference in plasma cholesterol versus vehicle control (p-value) | | |
|---|---|---|---|
| **Time (days)** | 7 | 14 | 35 |
| NYX-PCSK9i | -18% (0.066) | -24% **(0.002)** | -46% **(<0.001)** |
| Lipitor® | -13% (0.275) | -15% **(0.077)** | -27% **(<0.001)** |
| NYX-PCSK9i + Lipitor® | -33% **(<0.001)** | -49% **(<0.001)** | -65% **(<0.001)** |

**bold** = statistically significant



# Program Milestones and Path to the Clinic

## 2H CY2020

**DEC 2020**

NYX-PCSK9i shows 57% reduction in total cholesterol in mouse study

**JULY 2020**

NYX-PCSK9i demonstrates *ex vivo* equivalency to Repatha® and Praluent®

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## 1H CY2021

**MAY 2021**

Potent new drug candidates identified

**JAN 2021**

NYX-PCSK9i well tolerated, lowers LDL cholesterol in a dose-dependent manner[1]

**JUN 2021**

NYX-PCSK9i reduces total cholesterol by 65% when given in combination with a statin, outperforms Lipitor® (atorvastatin, Pfizer)

## 2H CY2021

**JUL 2021**

USPTO grants patent for Nyrada's PCSK9i inhibitor technology

**DEC 2021**

Charles River Laboratories appointed to conduct preclinical studies in US

**AUG 2021**

NYX-PCSK9i mechanism of action confirmed following further exploratory analysis

## UPCOMING

**CY 2022**

Preclinical studies to commence in Q3 CY2022
Phase I first-in-human clinical trial to commence late 2H CY2022

**MAY 2022**

EPO notified intention to grant patent for Nyrada's PCSK9i inhibitor technology

# Phase I Study Design

**OBJECTIVES**

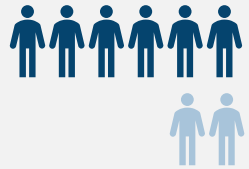
- Evaluate safety, tolerability, and pharmacokinetics of NYX-PCSK9i
- Measure changes in LDL cholesterol

**DESIGN**

- Double-blind, randomized, placebo-controlled, dose escalation study
- Single ascending oral dose (Cohorts 1-5)
- Once daily oral dose over 14-day treatment period (Cohorts 6, 7)
- Pharmacokinetic and pathology samples will be collected at selected time points over the trial period for all subjects.

**PARTICIPANTS**

- 56 healthy volunteers (18 to 50 years)
- 7 cohorts (6 active: 2 placebo per cohort)



**Active arm**

**Placebo**

**LOCATION & DURATION**

- Study will be conducted at a clinical trial center in Australia
- The dosing period will vary between 1 – 14 days


*trial design subject to ethics approval

# Brain Injury Drug Program

Novel small molecule TRPC 3/6/7 blocker

# Brain Injury Market

## Population, Problem, Opportunity

Each year

**2.8 million**

Americans suffer a TBI[6]

**5.3 million**

Americans live with a post-TBI disability[7]

Each year

**800 thousand**

Americans suffer a stroke[8]

**One drug class for stroke (tPA)** suitable for >15% of patients

**TBI Treatment Market**

- USD 6.7 billion sales revenue in 2020 (US, UK, Europe, Japan)[9]
- Sales revenue **CAGR 5%** to 2030[9]

**Stroke Drug Market (tPA)**

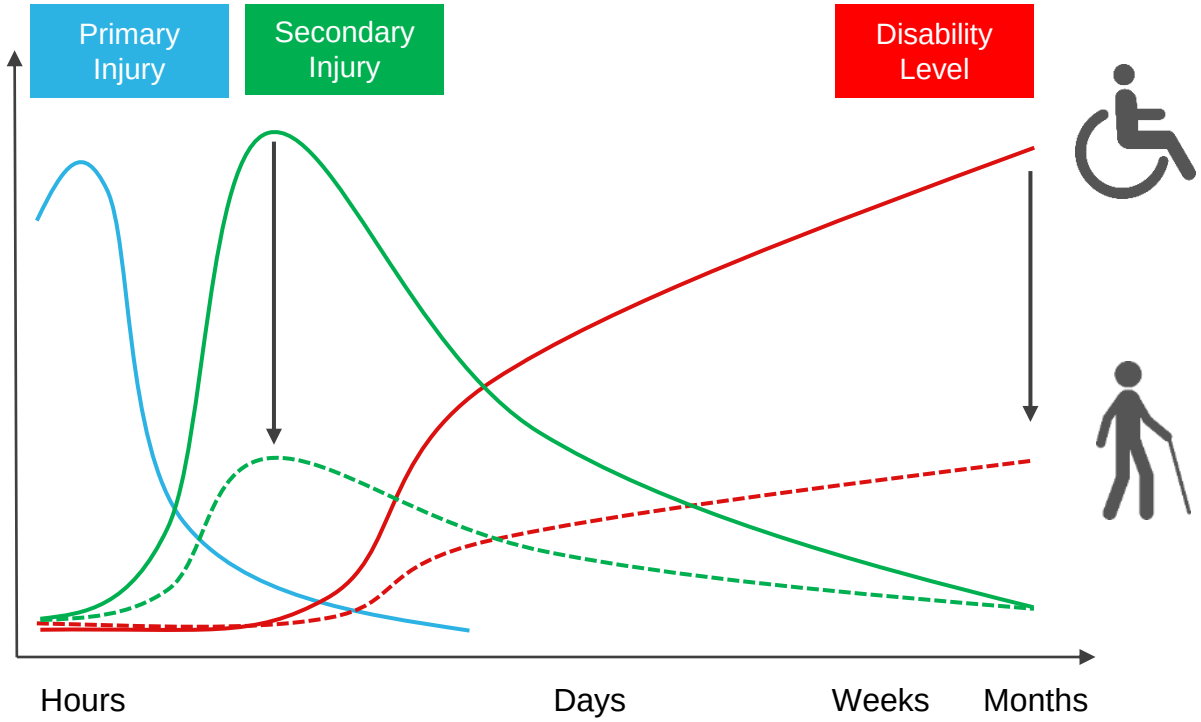
- USD 3.4 billion global revenue in 2018[10]
- Sales revenue **CAGR 7%** to 2027[10]

### Problem and Opportunity

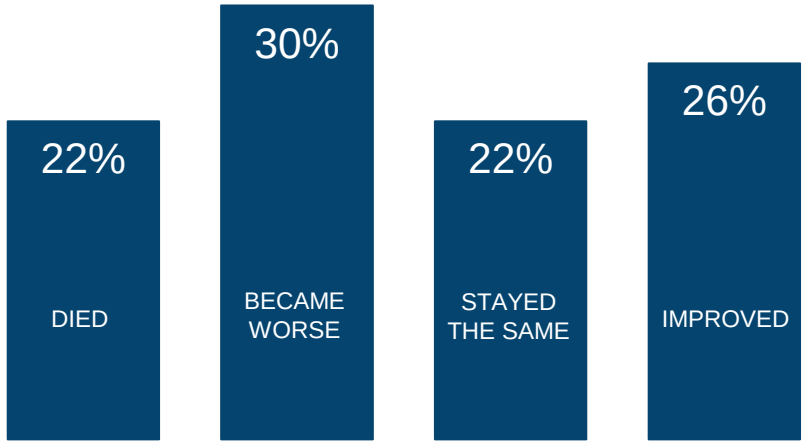
- **Unmet clinical need** with no approved drugs for TBI and limited treatment options for stroke
- **Effective treatment** will **improve patient outcomes** and **reduce high costs** associated with long-term care of brain injury survivors
- Moderate to severe TBI is an **orphan indication**

Nyrada is developing a first-in-class **neuroprotectant drug to prevent secondary injury**

# Brain Injury Trajectory, Patient Outcomes, Treatment Aims




## 5-Year Patient Outcomes following TBI[11]



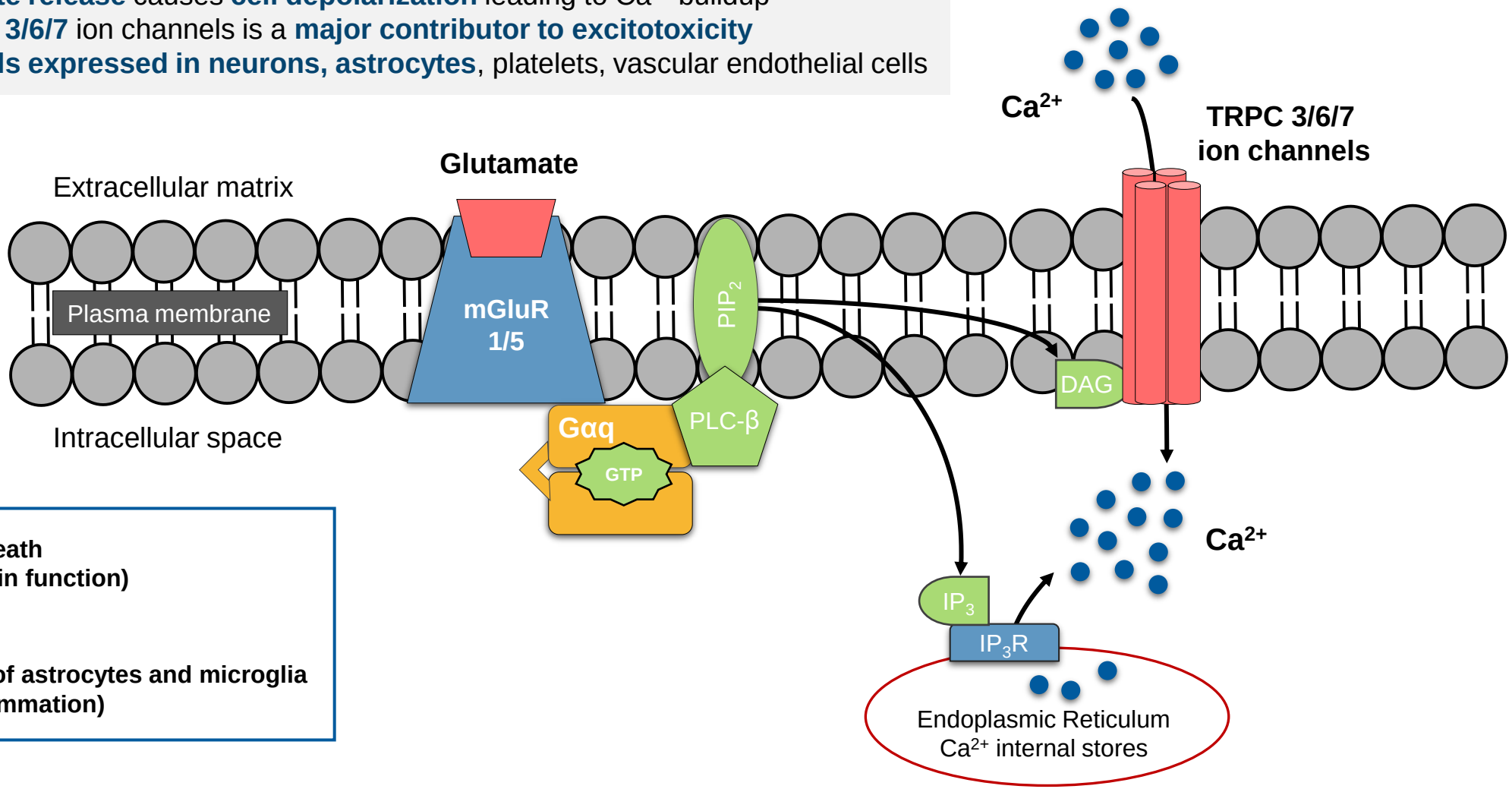

Data are US population estimates based on the TBIMS National Database. Data refer to people 16 years of age and older who received inpatient rehabilitation services for a primary diagnosis of TBI.

**Nyrada drug NYR-BI02**
An acute 3-day intravenous treatment

**Reduce secondary injury resulting from TBI or stroke**
- **Improve survivability, limit disability**
- **Improve quality of life**

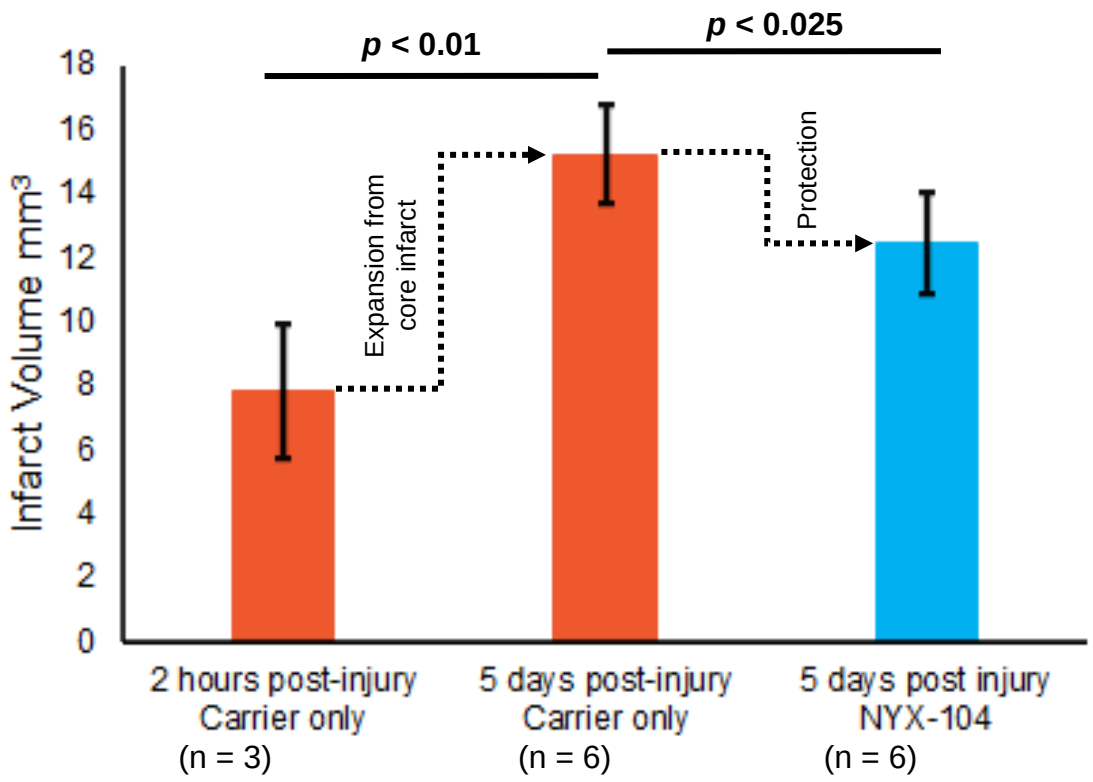
# TRPC 3/6/7 Ion Channels as a Therapeutic Target[12]

- **Excessive glutamate release** causes **cell depolarization** leading to $Ca^{2+}$ buildup
- $Ca^{2+}$ entry via **TRPC 3/6/7** ion channels is a **major contributor to excitotoxicity**
- **TRPC 3/6/7 channels expressed in neurons, astrocytes**, platelets, vascular endothelial cells



# Proof of Concept
## Early Discovery Molecule shows Neuroprotection

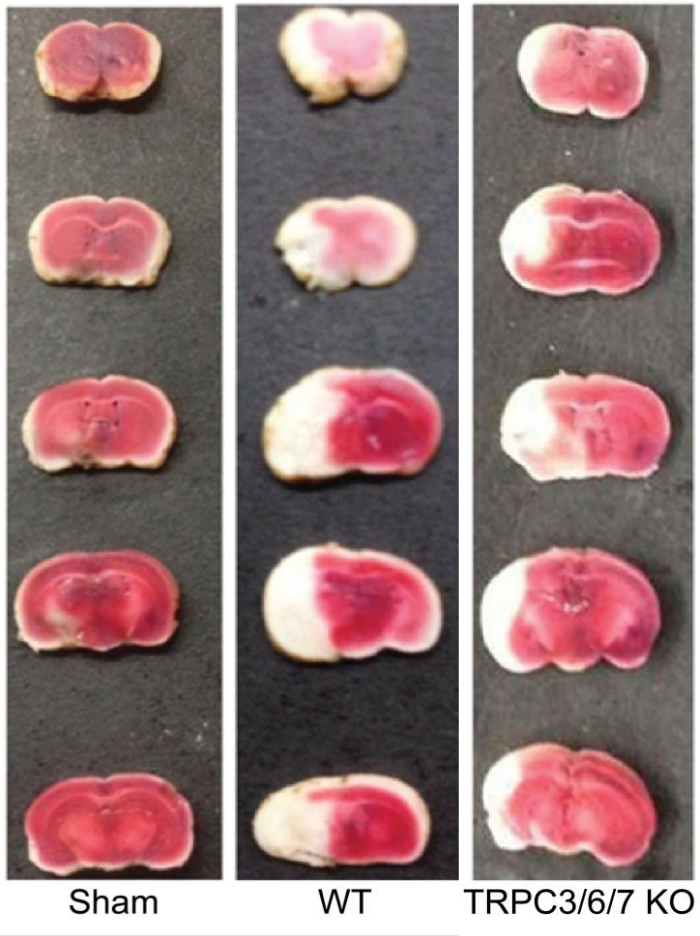
**NYX-104 shows Neuroprotection in a Photothrombotic Mouse Model**



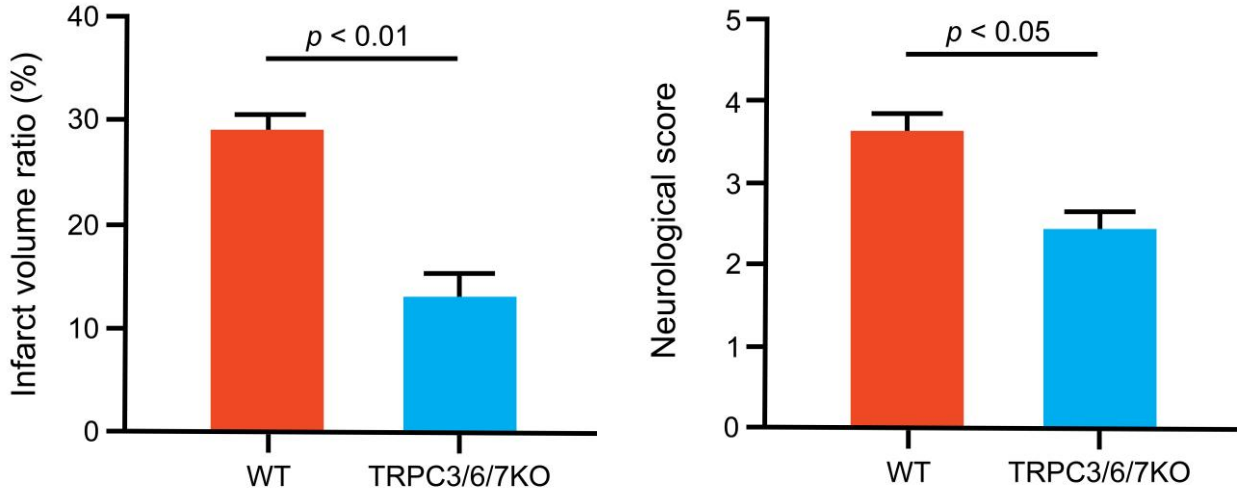

- First generation molecule **NYX-104 reduced $Ca^{2+}$ entry via the TRPC ion channel** (target upstream of TRPC channel but unknown)
- The 1st dose of NYX-104 (100 mg/kg via suppository) was given 45-mins post stroke, then once daily for 4 days
- Mice given NYX-104 had **38% protection** in the expansion of injury
- Molecule abandoned due to **poor ADME**
- New molecules designed to specifically block the TRPC 3/6/7 ion channels

# Proof of Concept
## Knockout Model shows Neuroprotection

### TTC Staining




### Functional Improvement following Brain Injury in TRPC 3/6/7 KO Mice[13]

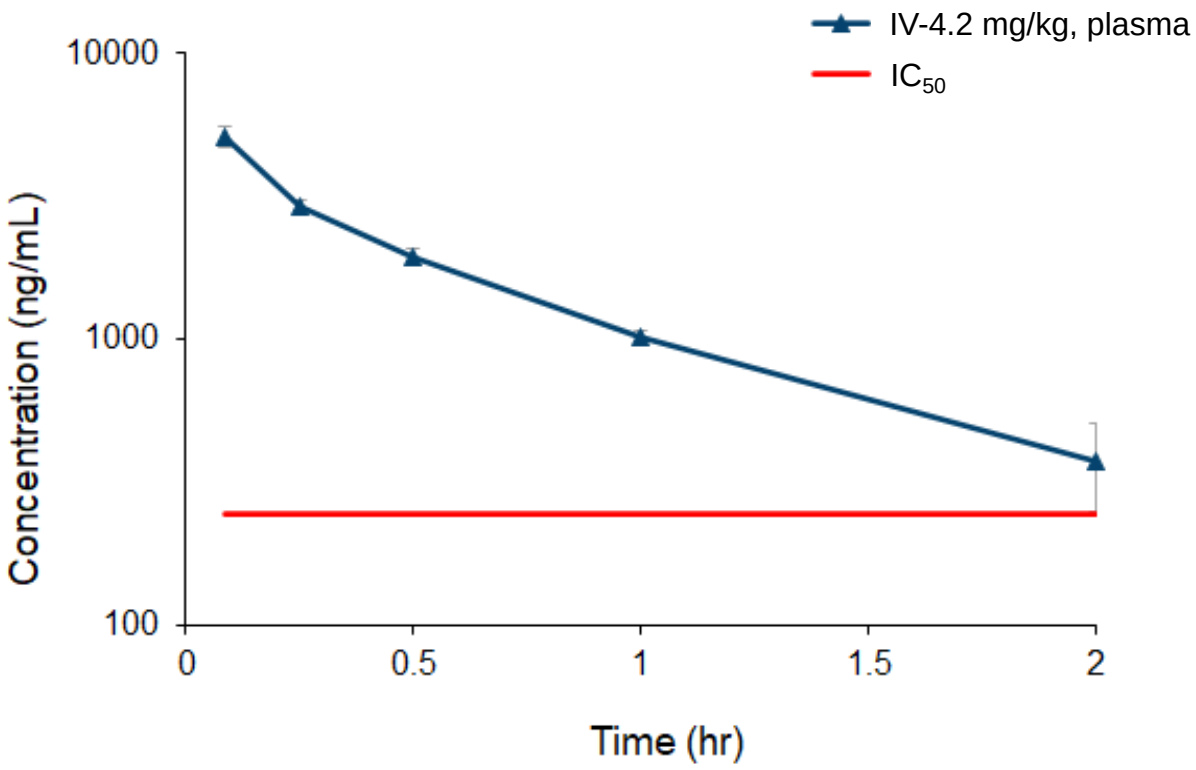



Adapted from Chen et al. Mol. Neurobiol. 2017

- TRPC 3/6/7 KO mice have significantly **smaller lesion sizes** compared to WT
- TRPC 3/6/7 KO mice have significantly **better neurological score** compared to WT
- Nyrada molecule **NYR-BI02 blocks TRPC3/6/7 channels** ($IC_{50}$ = 0.6 µM)
- **NYR-BI02 will be tested in models of TBI (WRAIR) and stroke Q3 2022**

# Nyrada's Brain Injury Drug NYR-BI02
## ADME-PK Profile

**Mean Plasma Concentration-Time Profile of NYR-BI02 in Mice**




NYR-BI02 **advanced to efficacy studies** in collaboration with WRAIR.

- **Nanomolar potent** TRPC 3/6/7 blocker
- Intact **blood-brain barrier penetration** (>50%)
- ADME-PK **compatible with continuous infusion dosing** (preferred dosing method for moderate to severe TBI and stroke)

Exploratory study shows NYR-BI02 **could be taken orally** (preferred dosing method for concussion)

# Program Milestones and Path to the Clinic

## 2H CY2020

### JUL 2020

- Nyrada Brain Injury Data published at the premier US Military Health conference, US Military Health System Research Symposium
- Drug candidates successfully delivered by continuous intravenous infusion, maintaining effective therapeutic levels in the brain, with no adverse effects observed
- Pilot study evaluating the intranasal route of delivery for drug candidates

## CY2021

### FEB 2021

- Collaboration secured with WRAIR and UNSW Sydney

### JUN 2021

- New, more potent analog of Nyrada's brain injury candidate identified (NYR-BI01)
- Pilot work to optimise PBBI model, drug formulation and delivery, and MRI scanning, (WRAIR & UNSW Sydney)

WRAIR Walter Reed Army Institute of Research Soldier Health • World Health

UNSW SYDNEY

## CY2022

### MAR 2022

- NYR-BI02 selected for Phase I study

### MAY 2022

- Provisional patent application filed

### UPCOMING

- Brain injury drug candidate testing in preclinical model of stroke in Q3 CY2022
- Complete PBBI efficacy study
- Phase I first-in-human study anticipated to commence second half of CY2022
- Study will support Phase II development in Moderate-severe TBI and stroke (acute IV dosing)

# Phase I Study Design

**OBJECTIVES** To assess the safety, tolerability, and pharmacokinetics of NYR-BI02

**DESIGN**

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

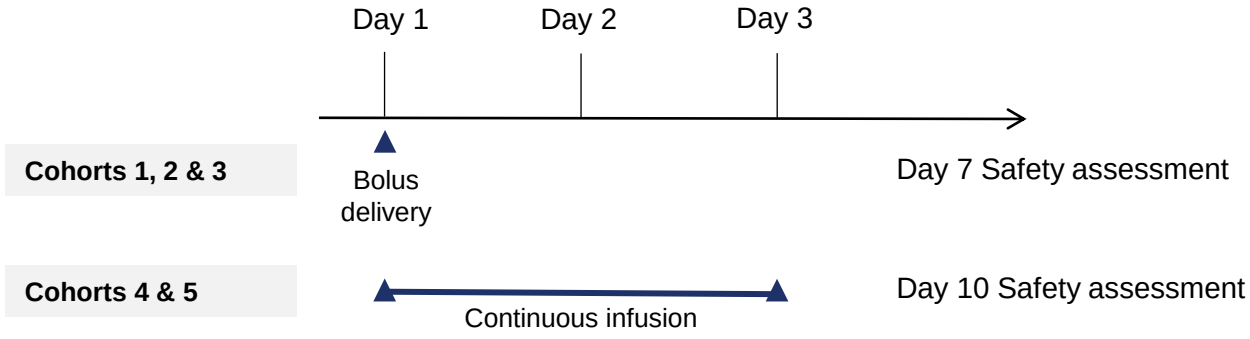
**PARTICIPANTS**

- 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) |

**LOCATION & DURATION**

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




*trial design subject to ethics approval

# Corporate Snapshot

ASX:NYR

# Corporate Snapshot

| Key Metrics | |
|---|---|
| Market capitalisation (as at 06 June 2022) | **A$23.4M (US$16.9M)** |
| Share price (as at 06 June 2022) | **A$0.15 (US$0.11)** |
| CDIs free float | **156,008,700** |
| Cash at bank 31 March 2022:<br>• Adequate funding for Phase I studies | **A$11.3M (US$8.1M)** |
| ASX listing | **January 16, 2020** |

# Management Team with Proven Industry Experience

**James Bonnar - CEO**

- Business executive with 25 years experience in healthcare companies in the UK, China, New Zealand, and Australia
- Experience in drug manufacture, preclinical development, clinical operations, regulatory affairs, and quality assurance
- Biotech experience spanning various therapeutic areas including cardiometabolic disease, neurodevelopment disorders, and brain injury

**Cameron Jones - CFO**

- Finance executive with experience as CFO and Company Secretary of ASX Listed and VC investee healthcare companies
- Supported several healthcare companies through IPOs, capital raisings and M&A transactions
- Managing Director of Bio101, financial services firm
- Chartered Accountant, Member of the Governance Institute of Australia and Registered Tax Agent

**Dr Benny Evison - CSO**

- More than 20 years experience in the discovery and development of small molecule inhibitors as therapies for various cancers, cardiovascular diseases and neurodegenerative diseases
- Obtained a PhD at La Trobe University (Melbourne, Australia) in biochemistry and molecular biology, and a postdoctoral fellowship in chemical biology at St Jude Children's Research Hospital, (Memphis TN)

**Supported by specialist advisers:**

- **Prof Gilles Lambert**
  Cholesterol-lowering program
- **Prof Gary Housley**
  Brain injury program
- **Dr Jim Palmer**
  Medicinal Chemist
- **Dr Phillip Coghlan**
  Medicinal Chemist
- **Dr Zoran Rankovic**
  Medicinal Chemist
- **Dr John Mao**
  Toxicologist

# International High Caliber Board

- Nyrada operates under the direction of a board of international caliber
- Strong track record in finding and realizing the value of biotech companies
- Experience in dealmaking, US/AU capital markets, and relevant therapeutic area experience

**John Moore**
**Non-Executive Chairman**

**Dr Ian Dixon**
**Non-Executive Director**

**Peter Marks**
**Non-Executive Director**

**Marcus Frampton**
**Non-Executive Director**

**Dr Rüdiger Weseloh**
**Non-Executive Director**

**Christopher Cox**
**Non-Executive Director**

# Summary

## Best-in-class small molecule PCSK9 inhibitor

- Oral, once per day dosing, patient convenience
- Manufacturing and cost advantages over biologics and peptides
- Can be administered with a statin to achieve additive therapeutic effect (monotherapy or combination)

## First-in-class treatment to prevent secondary brain injury

- TBI and stroke
- Novel biological target – TRPC 3/6/7 ion channels
- Collaboration with WRAIR and UNSW - opportunity to pursue non-dilutive funding

## Strong cash position

- A$11.3M as at 31 March 2022
- Adequate funding for Phase I studies

# References


1 Wong ND et al. Prevalence of the American College of Cardiology/American Heart Association statin eligibility groups, statin use, and low-density lipoprotein cholesterol control in US. J Clin Lipidology. 2016

2 Brain Injury Alliance (Connecticut): http://www.biact.org/understanding-brain-injury/brain-injury-facts-statistics and US Centers for Disease Control and Prevention: https://www.cdc.gov/stroke/facts.htm

3 Management of Statin Intolerance in 2018: Still More Questions Than Answers, Toth PP, Patti AM, Giglio RV, Nikolic D, Castellino G, Rizzo M, Banach M. Am J Cardiovasc Drugs. 2018 Jun;18(3):157-173

4 Cholesterol Lowering Drug Market Research Report by Disease Type, Class of Drug, Distribution Channels, Region - Global Forecast to 2027 - Cumulative Impact of COVID-19, April 2022 and Global Statin Market – Industry Trends and Forecast to 2029, Data Bridge Market Research

5 Cholesterol Lowering Drug Market Research Report by Disease Type, Class of Drug, Distribution Channels, Region - Global Forecast to 2027 - Cumulative Impact of COVID-19, April 2022

6 Brain Injury Alliance (Connecticut): http://www.biact.org/understanding-brain-injury/brain-injury-facts-statistics

7 Report to Congress: Traumatic Brain Injury in the United States | Concussion | Traumatic Brain Injury | CDC Injury Center

8 US Centers for Disease Control and Prevention: https://www.cdc.gov/stroke/facts.htm

9 Global Traumatic Brain Injury Market to 2030 - Insight, Epidemiology and Forecast by ResearchAndMarkets.com

10 Stroke Treatment Market Insight and Trends 2027 - TMR (transparencymarketresearch.com)

11 'Moderate to Severe Traumatic is a Lifelong Condition', CDC publication available at: https://www.cdc.gov/traumaticbraininjury/pdf/moderate_to_severe_tbi_lifelong-a.pdf

12 Jeon J, Bu F, Sun G, Tian J,Ting S, Li J,Aronowski J, Birnbaumer L, Freichel M, and Zhu MX (2020). Contribution of TRPC Channels in Neuronal Excitotoxicity Associated With Neurodegenerative Disease and Ischemic Stroke. Front Cell Dev Biol. doi: 10.3389/fcell.2020.618663

13 Chen X, Lu M, He X, Ma L, Birnbaumer L, and Liao, Y. (2017). TRPC3/6/7 knockdown protects the brain from cerebral ischemia injury via astrocyte apoptosis inhibition and effects on NF-small ka, CyrillicB translocation. Mol. Neurobiol. 54, 7555–7566. doi: 10.1007/s12035-016-0227-2

Nyrada inc

| Brain Injury Solution Animation | Cholesterol-Lowering Animation |
| --- | --- |