

Date: 2 August 2019 Sydney, Australia

ASX Limited 20 Bridge Street SYDNEY NSW 2000

## NOX RELEASES INITIAL NEWSLETTER FOR NYRADA SUBSIDIARY

- Significant progress in 3 leading R&D programs
- Oral PCSK9-inhibiting drug candidate proving major first-in-class opportunity in projected multi-billion dollar hypercholesterolemia global market
- First-in-class neuroprotectant drug candidate delivering promising data suggesting potential protection in patients suffering stroke or traumatic brain injury such as sporting concussion
- Two new non-opioid drugs designed to treat nerve crush injury and pain such as sciatica without addiction about to enter animal studies

**Sydney, 2 August 2019:** Noxopharm Limited (ASX: NOX) ('Noxopharm' or the 'Company') today releases the initial Newsletter for its majority-owned U.S. subsidiary company, Nyrada Inc., providing an update on the drug development opportunities in that company.

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#### **About Noxopharm**

Noxopharm is a clinical-stage Australian drug development company with offices in Sydney and New York. The Company has a primary focus on the development of Veyonda<sup>®</sup> and is the major shareholder in Nyrada Inc, a spin-off company developing a pipeline of non-oncology drugs.

#### **About Nyrada**

Nyrada is a U.S.-registered, early-stage drug development company with three wholly-owned R&D programs in the areas of cardiovascular and neurological health. Noxopharm owns two-thirds of Nyrada and Altnia Holdings Pty Ltd one-third.

www.noxopharm.com

**Investor & Corporate Enquiries:** 

Prue Kelly
M: 0459 022 445
E: info@noxopharm.com

**Media Contact:** 

Frank de Maria Purposeful Communications T: +1 347 647 0284

E: frank.demaria@purposefulcommunications.com

**Company Secretary:** 

David Franks T: +61 2 9299 9690

E: David.Franks@automicgroup.com.au



## **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 Noxopharm about circumstances and events that have not yet taken place. Although Noxopharm 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 that could cause the actual results, performance or achievements to differ materially from those expressed or implied by the forward-looking statement. No representation, warranty or assurance (express or implied) is given or made by Noxopharm that the forward-looking statements contained in this announcement are accurate and undue reliance should not be placed upon such statements.



# From the Nyrada Team



### FROM THE CHAIRMAN

I am very excited to introduce myself as the Chairman of Nyrada and to lay out the path to creating shareholder value from our promising pipeline of drug candidates.



have had lona entrepreneurial history where the common theme has been turning small public companies with big ideas into partnerships with major enterprises that could help leverage the early stage investors capital. Sometimes this works and produces huge returns and sometimes it fails but the inspiration comes from Newton's Second Law of Motion, force = mass x acceleration. Small companies like Nyrada have great ideas that can change the world and dynamic teams devoted to showing proof of concept that large pharma cannot do efficiently. However, big pharma are excellent at funding and managing the large clinical trials that are necessary to achieve FDA approval and get our products into the market. Our number one job at Nyrada is to deploy our shareholders capital to de-risk each compound and to raise the awareness of big pharma decision makers so they will license our drugs as early as possible for optimal shareholder return.

The key ingredients to success always starts with great people and Graham has assembled a terrific management team, scientific advisory board comprised of world-renowned experts in their fields and a Board that is a tribute to the power of our possibilities. The Company's R&D programs are all in areas of huge unmet need and prolific M&A activity. We are playing in the right fields, at the right time. Our science and business are on-track.

I joined the Board of Noxopharm at a time when Nyrada was well underway. As I came to better understand the opportunity I asked Graham if I could help him with the commercial and capital needs here. I am grateful he asked me to serve as Chairman. I look forward to reporting back to you on a regular basis with good news on the company's progress.

Yours sincerely,

John Moore Chairman

## FROM THE CEO

The first half of 2019 has been a busy time for Nyrada, with excellent progress made on completing the necessary experimental groundwork across all R&D programs. The central theme of these experiments has been to gain a



better understanding of how our drugs work.

This reduces development risk and enables us to confidently utilize chemistry modelling to identify novel, more potent lead candidates with better drug-like characteristics.

To support our efforts, key vendors have now been selected and these collaborations are exceeding our expectations in terms of quality, timeliness and cost. One critical area and potential bottleneck is the synthesis of new chemical analogues to test as lead candidates and this work is being undertaken in India by Jubilant Chemsys. Earlier in the year we moved from a contract to a full-time-equivalent basis and we now have six PhD qualified chemists dedicated to Nyrada projects. This change is reaping rewards with much improved throughput and operational flexibility, and at a significantly lower cost.

Nyrada has three early stage drug programs that it owns outright, and a fourth being conducted in partnership with Noxopharm. All are aimed at addressing areas of unmet clinical need. The three programs Nyrada owns outright are:

- The PCSK9-inhibitor program is aimed at developing a cholesterol-lowering drug.
- The neuroprotectant program is aimed at a drug to protect the brain from further damage after stroke and traumatic brain injury (TBI), including concussion.
- NYX-205 is an anti-inflammatory drug being developed for the treatment of nerve tissue inflammation such as sciatica.

We are excited to present a new corporate look in the form of a redesigned and upgraded website. Up until the time of the listing, we are required to keep the website fairly basic. Post-listing there will be a 'news section' where we will post regular updates.

Yours sincerely,

James Bonnar CEO

# PCSK9 inhibitor Program



### AIM

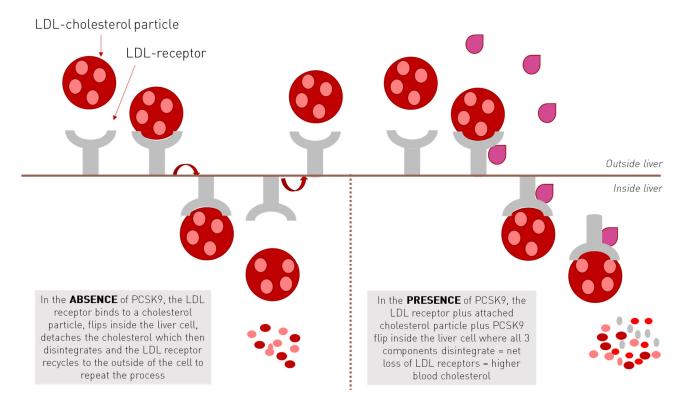
This program is the Company's lead program and is also the most advanced, with lead-optimisation well underway.

The aim is clear and concise – to develop an oral drug that can be used in conjunction with standard statin drugs to achieve better lowering of cholesterol levels. Statins are still one of the largest-selling drug sectors in the world with 2018 annual sales of US\$19 billion. However, in about 50% of patients, they don't work as well as patients and doctors would like them to. Additionally, there is another 10-15% of patients who suffer side-effects to the extent of having to reduce their statin dosage or stop altogether.

The answer has proven to lie in blocking the action of the blood protein, PCSK9, an important player in the way the body regulates its cholesterol levels. Blocking PCSK9 has been shown to make statins more effective by dropping blood cholesterol levels by an additional 40-60%.



Figure 1. Diagram of liver cell showing effect of PCSK9 on the recycling of the LDL-cholesterol receptor



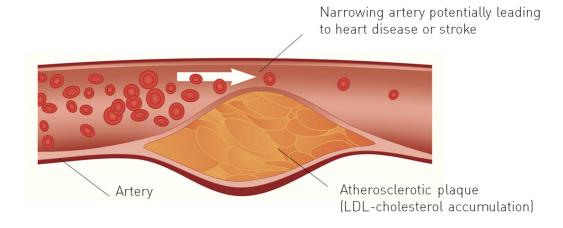
Two injectable PCSK9 inhibitors currently are on the market, with more expected to come over the next few years, all driven by the goal of developing a new class of drug capable of matching the US\$19 billion statin market.

Nyrada believes that the largest market opportunity lies not in expensive, injectable drugs, but in an oral

drug, offering the convenience of a daily tablet at an affordable price. No oral drug has yet come to market, putting Nyrada in what it believes to be a prominent and potentially leading position.

The Company's aim is to have an oral PCSK9 inhibitor in a first-in-human study in 2 years.

Figure 2. Effect of excess LDL-cholesterol on the artery wall. The build-up of LDL-cholesterol in arteries results in the formation of atherosclerotic plaques. These plaques restrict the flow of blood through arteries, which can result in blood occlusion and ultimately a heart attack.



### **PROGRESS**

NYX-330 has been identified as a potential drug candidate and remains our working lead candidate, having provided proof-of-principle evidence in the test-tube and in animals as blocking PCSK9 function. NYX-330 belongs to a class of chemicals that the Company is confident is novel and belong to it and can be protected by patents.

In the meantime, we are looking to see if we can get a more potent compound based on the same chemistry, with recent tests showing this has been achieved. We anticipate that the final drug candidate will be finalised within the next 6 months. The lead candidate then will be subject to a mandatory battery of regulatory pre-clinical safety and toxicology studies. Once all regulatory studies have been completed, the Company's PCSK9 inhibitor will enter human trials, predicted to be within the next two years.

To help elevate the Company's profile in the PCSK9 drug development field, Nyrada has put together a scientific paper of its successful research and development results and is in the process of submitting the paper to a well-respected, peer-reviewed journal. The paper is anticipated to be published towards the end of 2019.



# Neuroprotection Program



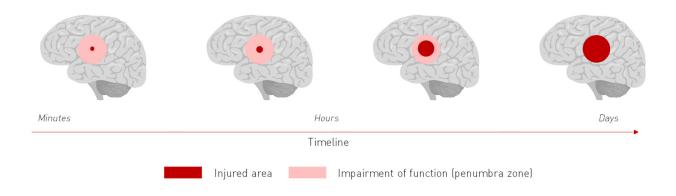
#### AIM

The company is developing a drug to be given to an individual quickly after suffering acute brain damage from a stroke or traumatic brain injury (TBI) such as severe concussion, with the goal of limiting the degree of damage and thereby the extent of long-term disability. Stroke or TBI causes an initial area of brain death that is unrecoverable. But spreading out from that core area of death is a secondary wave of death, fuelled by chemicals coming from dead brain cells causing a build-up of

toxic levels of calcium ions (Figure 3). Nyrada, in collaboration with a team of researchers at UNSW, Sydney, have identified a family of compounds able to stop this calcium toxicity.

The goal is a drug that could be given to a stroke patient or someone suffering TBI from any cause, starting within about 12 hours of the injury and continuing for about 4-5 days.

Figure 3. The effect of time on the extent of death of brain cells following a stroke



### **PROGRESS**

The Company's working drug candidate is NYX-104. NYX-104 blocks the build-up of calcium ions through a specific signalling pathway. Following on from a positive outcome with NYX-104 in a mouse model of stroke where the degree of brain damage was reduced by half, Nyrada believes that targeting this pathway could be an effective strategy in the treatment of stroke and TBI.

The Company has now identified a key protein in this pathway that it believes NYX-104 is inhibiting, a discovery of significant commercial value, allowing it to design new compounds that are more potent versions of NYX-104. The Company has submitted provisional patents on composition of matter for these compounds.

Important discussions with various stakeholders in the area of TBI continue to assist in the development of the program. Lead optimisation will continue for the next 6-12 months, followed by testing in a range of stroke and TBI animal models to assess efficacy.



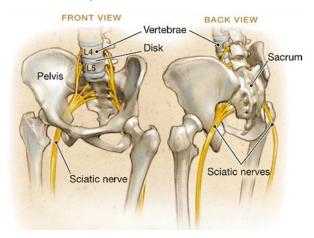
# Peripheral Neuropathic Pain Program



#### AIM

The aim is a drug to treat the inflammation and pain associated with crushed nerve injury.

Figure 4. Anatomy of the human pelvis and spine. The sciatic nerve is the largest nerve in the body and runs from the base of the spine to the base of the foot. (Artist: Cassio Lynm)

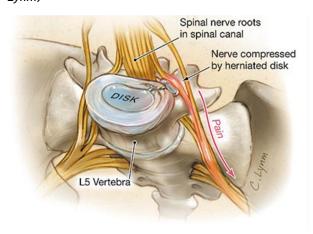


Neuropathic pain arising in the lower back and radiating into the buttock, hip and down one leg to the foot is called sciatica. An estimated 200,000-400,000 Australians are thought to be affected by sciatica each year, whilst in America, the incidence is estimated at about 1 in 10 adults. The most common cause of sciatica is a spinal disk herniation, or a bulging disk, leading to compression of individual nerves in the lower back. Currently, there are no drugs proven to work in the treatment of sciatica. Forms of treatment, such as aspirin and ibuprofen have their own side effects including increased risk of peptic ulcer disease, acute renal failure, stroke and myocardial infarction. Given the evolving opioid crisis, particularly in the U.S., strong opioids are now recommended as the last choice in case of insufficient response and/or side effects to first-line or second line medications. A key aim of this program is a non-addictive drug.

The global neuropathic pain market is expected to reach US\$8.1 billion by 2023.

Figure 5: The herniation of spinal cord discs can place pressure on surrounding tissue, including nerves.

Compressed nerves can be very painful with pain radiating down the length of the nerve (Artist: Cassio Lynm)



### **PROGRESS**

NYX-205 is an anti-inflammatory compound that has a mechanism of action that potentially spares the body from many of the side-effects associated with aspirin and ibuprofen, and the addiction associated with opioids. Even more importantly, it has been shown in an animal study to have the ability to cross the blood-nerve barrier and enter peripheral nerves.

Recently, the Company has identified another compound that it believes also could be efficacious in the treatment of neuropathic pain. Both this newly identified compound and NYX-205 are now set to go head-to-head in an animal model of sciatica.

Nyrada has engaged with the global research organisation Shanghai ChemPartners to conduct a pre-clinical study on the efficacy of both compounds in the treatment of sciatic nerve-associated pain. One well-established animal model of sciatica is called the Chronic Constriction Injury (CCI) model. Shanghai ChemPartner will test both compounds in the CCI model to determine what the likely success of either compound in the treatment of neuropathic pain would be. The readout from this study is anticipated in the second half of 2019 and will determine which compound is taken further into pre-clinical testing.

## IRAK4- Autoimmune Disease Program



### AIM

Autoimmunity occurs when the body's immune cells start attacking the body's own healthy cells. The aim of this program is an anti-inflammatory drug capable of blocking signalling pathways known to be important in the development of a range of autoimmune diseases including psoriasis. Those particular signalling pathways involve key regulating proteins known as IRAK4 and TPL2.

## **PROGRESS**

Although the program is in its early stages, much progress has been made in the first half of 2019. An IRAK4-inhibitor has been identified and the precise binding mechanism of action determined by X-ray crystallography. This has allowed for more precise molecular modelling, which has resulted in the development of more potent drug analogues. Compound optimisation is anticipated to continue over the next 18 months, with the running of in vivo efficacy studies planned for 2020. The intellectual property in the drug assets the subject of this program is licensed by Nyrada from Noxopharm Ltd. Nyrada has an option to acquire all or part of this intellectual property at fair market value.

At this stage, the primary autoimmune clinical indication being sought is psoriasis.

