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NOX PROVIDES UPDATE TO NYRADA NOTE-HOLDERS

- **Major opportunities with 3 first-in-class drug candidates across major community unmet needs**
- **Neuroprotectant program delivers first-in-class inhibitor of the biochemical process of secondary brain damage following stroke and traumatic brain injury**
- **Key proof-of-concept milestones achieved in PCSK9-inhibitor and neuropathic pain programs**
- **Company considering listing opportunity.**

Sydney, 6 March 2019: Noxopharm (ASX: NOX) today releases to the market a letter sent to shareholders and Convertible Note holders in its majority-owned U.S. subsidiary, Nyrada Inc ('Nyrada').

The letter notes the significant progress made in Nyrada's 3 R&D programs over the last 12 months, with each program making considerable strides towards clinical studies.

Neuroprotectant drug program. The aim of this program is a drug that prevents the secondary form of brain damage that follows stroke and traumatic brain injury and which is a major contributor to long-term disability. In an important development, Nyrada has achieved the first known comprehensive inhibition of the mechanisms involved in this secondary form of brain death. A lead candidate compound is currently undergoing pre-clinical work-up for what we hope will be a first-in-human study in 2020.

PCSK9 inhibition program. The aim of this program is an oral drug to combine with statin drugs to achieve LDL cholesterel levels that are considered to put patients at low risk of heart attack and stroke. Key proof-of-concept data has been obtained in an animal model, opening the way for a pre-clinical program.

Neuropathic pain program. The aim of this program is an anti-inflammatory/analgesic drug that will have the capacity to enter peripheral nerves to block pain such as that associated with peripheral neuropathies and chronic lower back pain. The Nyrada drug has achieved first-in-class access to peripheral nerves in animals, clearing the way for pre-clinical work-up for a first-in-human study, again we hope to have underway in 2020.

The future for Nyrada

The Board of Nyrada currently is considering the feasibility of a listing of Nyrada. One strategy under consideration is the feasibility of listing on the ASX as a foreign entity using CHESS Depositary Interests (CDIs).

The implementation of the possible listing of Nyrada is subject to, amongst other things, the market and the granting of the necessary approvals by ASIC and ASX. There is no assurance that approval or permission will be obtained from ASIC or ASX for the possible listing of Nyrada.

About Nyrada

Nyrada Inc is a preclinical-stage drug development company with offices in New York and Sydney. Currently it is focused on three R&D programs in the areas of neuroprotection, cholesterolemia, and neuropathic pain. 66.7% of the total issued share capital of Nyrada currently is owned by Noxopharm Ltd; Altnia Holdings Pty Ltd owns 33.3%.

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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 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.

6 March 2019

Dear Nyrada Noteholder

With the maturity date of the Convertible Notes on 14 June 2019 in mind, I wanted to provide an update on the progress of Nyrada Inc. (**Nyrada** or the **Company**) and share with you the Board's strategic thinking about the Company's future.

My summary is that you have an interest in a company that is confident in its ability to attract considerable attention, especially overseas, and confident in its potential to become a significant player in the biotech world.

The progress made by the Nyrada scientific team this past 12 months, in collaboration with NOX scientists, has exceeded my expectations and created opportunities that we were unaware of 12 months ago.

Without Nyrada, I believe that none of this would have happened. Further, it has allowed NOX to concentrate on the opportunity presented by Veyonda.

I will start with a review of the progress Nyrada has made in the last 12 months.

Neuroprotection program

Stroke and traumatic brain injury (TBI), which incorporates concussion and chronic traumatic encephalopathy (CTE), is a leading cause of death and disability in industrialized societies. The aim of the neuroprotection program is to develop a drug that will protect the brain from a form of secondary damage known as *glutamate-associated excitotoxicity*, or GAE). GAE follows any event that kills brain cells (e.g. stroke, TBI, severe epileptic seizures, etc).

The primary damage cannot be changed or repaired. But for 1-2 weeks following the primary damage, a wave of death of brain cells spreads out in a ripple effect, eventually causing an area of brain death up to 6-7x the size of the original injury. It is a strange phenomenon, and one that is difficult to rationalise for an organ as vital as the brain. But it is a very real phenomenon.

For people who survive a stroke or serious head injury, this secondary damage is the major contributor to long-lasting cognitive and physical disability.

At this time, the Company is not aware of anyone who has been able to offer any effective way of stopping this wave of secondary damage.

As a result of a collaboration with the University of NSW, Nyrada believes that it has developed a drug that finally offers hope in reducing the impact of this secondary damage.

A year ago, we had identified a compound (NYX-104) from the NOX drug library as our likely drug candidate. In the laboratory, NYX-104 blocked the biochemical processes responsible for causing GAE, and it did so in a comprehensive way that, as far as we are aware, no other compound had been shown to do. More importantly, when NYX-104 was given to mice with a brain injury that mimicked human stroke, we were able to reduce the extent of secondary brain damage by 58%. It's a big leap from mouse to man, but at least we have confirmed proof of being able to block the GAE process in a mammalian brain.

We have spent the intervening 12 months looking to see if NYX-104 was the best drug we were going to get in terms of potency, or whether we could improve on it. If the 58% effect observed in an animal model was translatable to humans, it would be reasonable to expect that this would reduce post-injury disabilities to a meaningful degree, and thereby reduce time spent in rehabilitation and the number of people requiring lifelong assisted care. Nevertheless, we believed it made sense to spend a bit of time to see if we could do better.

- As a result of these efforts, we now have identified a close relative of NYX-104 known as NYX-250 that is considerably more potent and we currently are in the process of filing a patent for this new compound.
- We have made considerable progress in identifying the mechanism of action of these compounds. In so doing, we believe that we have created new and important IP that may contribute to neuroscientists' understanding of brain function and the mechanism of injury.
- We now are in a position to start the preclinical studies that we are aiming to get us into a first-in-human study in 2020.

At the same time as we are moving towards the clinic, we have started reaching out to parties with an interest in seeing the development of a neuroprotectant.

Sporting codes involving potential head injury are just one of those parties. The article below on concussion in the NFL suggests that 1 in 10 NFL players could eventually develop brain lesions associated with post-concussive secondary brain damage.

https://www.insidescience.org/news/whats-risk-chronic-traumatic-encephalopathy-nfl-players

This gives some idea of a need being increasingly acknowledged in contact sports that includes rugby, AFL, soccer and boxing. The Company is in the process of reaching out to these bodies.

Add to this the victims of stroke, plus all the cases of head trauma from motor vehicle accidents, plus the defence personnel who suffer concussive injury, and you start to understand the need for a successful neuroprotectant drug.

What is this opportunity worth? It is impossible to estimate because, as far as the Company is aware, no-one has brought a successful neuroprotectant to market. But the societal need is considerable:

- an estimated 800,000 people each year in the U.S. suffer stroke, with about 60% of surviving patients requiring life-long assisted living;
- there are approximately two million emergency room visits each year in the U.S. for TBI, with 80,000-90,000 of these suffering severe long-term disability;
- according to the US Defense and Veterans Brain Injury Center, 383,947 service members received a TBI diagnosis from 2000 until the first quarter of 2018;
- a study by the National Foundation for the Brain estimates the annual societal cost in the U.S. for TBI is $48.3 billion.

Cholesterol-lowering

Just to refresh your memory of this program, our objective is to develop a drug that will be used in conjunction with statin drugs to lower LDL cholesterol levels to what is regarded as 'low risk' levels in terms of cardiovascular disease (stroke, atherosclerosis and heart attack). Statin drugs could do that job on their own, but for the fact that the way statins work also causes levels of the blood protein, PCSK9, to rise, and PCSK9 works against statins by holding LDL-cholesterol in the blood. A case of the left hand giving, and the right hand taking.

A combination of a statin plus a PCSK9-inhibitor has been shown to allow some people to achieve target LDL cholesterol levels which generally are regarded to be desirable.

Injectable PCSK9 inhibitors came to market 4 years ago, but cost and inconvenience of fortnightly injections have proven to be significant barriers to widespread uptake.

We believe the solution is an oral drug, taken once daily that offers convenience and a potential reimbursable cost close to the cost of statins.

A year ago, we had a molecule (NYX-330) that we had shown blocked the ability of PCSK9 to bind to the LDL cholesterol receptor. This was what a PCSK9-inhibitor needed to do, so it was a good start. But we had yet to find out if it would work in the body.

A year later, we have the answer…… it does, in mice. We have obtained proof-of-concept in the standard mouse model that NYX-330 lowers LDL cholesterol levels and does so in a dose-related way.

Just like the neuroprotectant program, NYX-330 is a product of the first effort at finding a successful drug, so the sensible thing was to continue the screening process to see if we could come up with a more potent drug. That process of designing/screening/redesigning/rescreening has been going on for the last 6 months. Preliminary testing suggests that we may have been successful in uncovering a more potent molecule, and we currently are at a stage of determining whether this is our final drug candidate.

There is no guarantee that this drug will succeed, but if it does we see a substantial global market if statin therapy could be made more effective and safer (a combination with a PSCK9-inhibitor should allow the statin dosage to be reduced).

Neuropathic pain program

This is our NYX-205 drug. NYX-205 is an experimental anti-inflammatory drug that has selective actions on inflammation, rather than the more comprehensive action of commonly used anti-inflammatories. NYX-205 blocks certain parts of the inflammatory process, but spares others. The parts it spares are the one you want to spare if you need to take an anti-inflammatory on a long-term basis – such as avoiding gastric ulceration and heart toxicity associated with certain anti-inflammatories.

We thought we could use the NOX LIPROSE drug delivery technology to get NYX-205 to cross the blood-nerve barrier and to enter peripheral nerves. If we could, then that opened up the opportunity to use NYX-205 to treat inflammation and pain in nerves in different parts of the body. That barrier has proven effective at keeping all drugs from reaching nerves at levels likely to relieve chronic pain, so being able to get NYX-205 across that barrier was both an enormous challenge and opportunity.

A year ago, we had the drug, but no evidence that it would cross the blood-nerve barrier.

A year later we have the evidence that it does cross the blood-nerve barrier. By using the NOX LIPROSE drug delivery technology, we have been able to show that NYX-205 crosses into the peripheral nerves (sciatic nerve) of rats at levels we believe will be therapeutic. That now has cleared to way to conduct rat studies designed to test its ability to block pain in peripheral nerve damage.

Again, we believe this is a great opportunity for Nyrada and will meet a substantial societal need. Neuropathic pain is a large community problem that only increases with greater longevity. Chronic lower back pain is a classic example, where pain relief generally is not well managed with standard anti-inflammatories, many of which like aspirin, ibuprofen and acetaminophen are associated with unwanted side-effects, and like opioids which carry the risk of addiction.

The Nyrada team

James Bonnar is leading the scientific team and recently was appointed CEO of Nyrada, reporting to me as Group CEO.
The team is:

- Dr Benny Evison PhD, Chief Scientific Officer
- Dr Alexandra Suchowerska PhD, Research Scientist
- Dr Jasneet Parma PhD, Research Scientist

The Scientific Advisory Board is:

- Professor Gary Housley PhD (*SAB Chairman*), Chair of Physiology and Director, Translational Neuroscience Facility, School of Medical Sciences, University of NSW, Australia
- Professor Junichi Nabekura PhD, Professor of Physiology and Neuroscience, and Director of the National Institute of Physiological Sciences, Japan
- Emeritus Professor David Burke, AO, MD, DSc, FRACP, FAA, FTSE (Previously) Bushell Professor of Neurology, The University of Sydney
- Professor Gilles Lambert PhD. Professor in Cell Biology and Biochemistry, University of La Reunion, France
- Dr Jim Palmer PhD. Consultant chemist.

The future for Nyrada

The Company has indicated from the start that it hoped to achieve a listing at some point, the aim being to provide Noteholders with the chance to convert their Convertible Notes to Nyrada shares and to provide an exit opportunity.

We went a considerable way down the listing path in 2018, but with the second half of 2018 turning out not to be a happy time for IPOs, particularly in the U.S., the Board decided it was in the best interest of Noteholders to delay a listing, focus on the science and to review the market's appetite for IPOs in early-2019.

The IPO market, while not fully recovered, is better than it was, and given the Board's confidence in the Nyrada science, the Board is currently considering the feasibility of a listing of Nyrada. If Nyrada was to proceed with a listing, it would prefer (if it can) to achieve this prior to the Convertible Notes' maturity date. We will, however, only go down that path if we think it is a feasible option for Nyrada.

One strategy which the Board is considering is the feasibility of listing Nyrada on the ASX as a foreign entity using CHESS Depositary Interests (CDIs).

Noteholders should be aware that the implementation of the possible listing of the Company is subject to, amongst other things, the market and the granting of the necessary approvals by ASIC and ASX. There is no assurance that approval or permission will be obtained from ASIC or ASX for the possible listing of Nyrada.

We have a busy 4 months ahead of us as we put this plan into operation. I will keep you updated as we move through the process.

Yours sincerely

Graham Kelly
Noxopharm Group CEO