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NOXOPHARM RELEASES REPORT ON KEY PROGRESS OF SUBSIDIARY NYRADA

- **Important progress reported across the Nyrada therapeutic pipeline**
- **Potential first-in-class drugs in development for multiple large underserved indications, including cardiovascular disease, stroke and peripheral neuropathy**

Sydney, 4 October 2018: Noxopharm (ASX: NOX) today releases a Report sent to the Convertible Note holders who in February 2018 provided $4 million in seed funding to Noxopharm subsidiary, Nyrada Inc. The Report provides an update on the Company's progress over the last quarter across its three non-oncology drug development programs.

Graham Kelly, Noxopharm CEO, said, "We established Nyrada twelve months ago with a mission to efficiently advance three drug development programs with significant long-term potential. Each program was promising, but certainly very early-stage. These three programs now have matured into highly valuable assets that are attracting global industry attention, particularly since they have the potential to be first-in-class therapies in areas of high unmet need. The advancement of these programs represents an important milestone for the Noxopharm Group as we transition to a drug development company with assets across a broad spectrum of underserved therapeutic indications. We look forward to numerous potentially value-creating milestones as we advance these promising drug candidates into formal clinical development."

NYX-330 is a small molecule PCSK9 inhibitor designed to augment standard-of-care statins to further lower cholesterol levels in the significant proportion of patients (70 million in the US) considered to be at high risk of cardiovascular disease. The market opportunity for NYX-330 is to become a companion drug to match the US$19 billion annual global statin market.

NYX-104 is a neuroprotectant drug designed to cross the blood-brain barrier and to protect the brain from excitotoxicity, a form of secondary damage following stroke or traumatic brain injury. NYX-104 is being developed to reduce post-stroke brain injury that currently contributes to two-thirds of recovering stroke patients who require assisted living for the remainder of their lives.

NYX-205 is an anti-inflammatory drug designed to cross the blood-nerve barrier and treat chronic inflammation, pain and loss of function in peripheral nerves of patients with peripheral neuropathy.

Approximately 20% of diabetic patients suffer from peripheral neuropathy, marking a large and growing global market opportunity.

Each program is in the preclinical 'lead optimisation' phase. First-in-human studies are on track to commence early-2020.

About Noxopharm

Noxopharm is a clinical-stage Australian drug development company with offices in Sydney and Hong Kong. The Company has a primary focus on the development of Veyonda® as a radio-sensitiser/immuno-stimulant, plus a developing pipeline of non-oncology drugs.

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NYRADA R&D UPDATE
October 2018

Page

Introduction

Since I last reported, the Company has made considerable strides, so time for an update.

In summary, the Company has made meaningful progress across its pipeline of novel drug candidates:

- We are pursuing three areas of drug development in large market opportunities.
- We remain on-track to achieve a number of potentially value-creating milestones as we advance towards clinical studies.
- I believe our ingenuity and nimbleness have given us an advantage over large pharmaceutical competitors in these therapeutic areas.

Driving our research and development efforts are four young scientists – James Bonnar (Team Leader), Benny Evison, Alexandra Suchowerska and Jasneet Parma. This is a highly qualified, productive and cohesive group of scientists who have made significant achievements in recent months, to the potential long-term benefit of patients and shareholders alike.

We remain focused on potential first-in-class drugs in the fields of:

- *Blood cholesterol-lowering*. The need to lower cholesterol levels to safer levels in people at high risk of heart attack or stroke
- *Neuro-protection*. The need to protect the brain from an uncontrolled process of self-destruction, excitotoxicity, that follows stroke or head trauma
- *Neuro-inflammation*. The need to treat chronic inflammatory conditions affecting the brain and peripheral nerves.

Each of these areas is underserved by current therapeutic options and success in any one of these programs would represent a major commercial opportunity.

In pharmaceutical industry parlance, each of these programs is in the 'lead optimisation' phase. This means that we identified an active ('lead') compound and obtained enough evidence in the laboratory to believe that clinical development is warranted. 'Lead optimisation' involves seeing if we can improve upon our current findings to develop drug candidates that we believe offer a greater chance of success in the clinic. Our in-house team of scientists, together with our consultant chemists, believe that improvement can be achieved across all three programs and are currently focused on optimization efforts.

While we still have pre-clinical work to do, we are methodically advancing these compounds in the most time and cost-efficient manner.

In closing, I am extremely optimistic that we are on the path to providing novel treatment options to patients in need, and I am pleased to be able to provide this update. I hope that you take time to read and absorb what we believe is an exciting and emerging opportunity that you will be hearing a lot more about of over the coming months.

Graham Kelly
Chief Executive Officer, Noxopharm Group

NYX-330

NYX-330 is our flagship program, a small molecule PCSK9 inhibitor to help lower LDL (low density lipoprotein) cholesterol levels in people considered to be at high risk of cardiovascular disease. In the U.S., this is estimated to be as many as 70 million people, and significantly more globally.

Background

Much debate persists within the medical community over the significance of elevated LDL cholesterol levels. There is little argument that high levels clearly put you at risk of cardiovascular disease (hypertension, heart disease, stroke), while very low levels carry a much lower risk of cardiovascular disease. It is the in-between that it up for debate. But irrespective of where you stand in that debate, the medical profession on the whole believes that patients should seek to lower their blood cholesterol levels, starting with lifestyle changes (eg. better diet, lower body weight, more exercise, smoking cessation and reduced alcohol intake) before progressing to medication where necessary.

The most commonly prescribed form of cholesterol-lowering medication is a class of drug known as 'statins' (which block cholesterol production by the body) combined with ezetimibe, commercially known as Zetia (a drug that blocks re-absorption of cholesterol from the gut). Both are oral medications taken once-a-day.

This treatment regimen has limitations. First, about 50% of individuals fail to achieve cholesterol levels targeted by their physicians. Second, statins have side-effects (muscle pain and increased risk of diabetes and dementia) that prevent patients from taking statins or prevent them from taking the optimal dosage.

About 15 years ago it was discovered that a protein in blood, known as PCSK9, has a major effect on blood cholesterol levels by helping to retain LDL cholesterol within the blood. Further, that statin drugs actually led to higher levels of PCSK9 in the body, effectively reducing their cholesterol-lowering potency.

Several large clinical studies now have shown that when a statin and a PCSK9 inhibitor are given together, LDL cholesterol levels fall considerably more than with statins alone and that this leads to notably fewer incidences of heart attack and stroke.

Finding a successful PCSK9 inhibitor has become one of the global pharmaceutical industry's most taxing, and potentially rewarding, challenges, with the goal being to develop a companion drug with the potential to match or exceed the annual $19 billion of statin sales globally.

Early attempts by the industry at producing an oral therapy that inhibited PCSK9 were unsuccessful. The industry then pursued the monoclonal antibody path, with two drugs, Repatha® and Praluent®, coming to market three years ago. Both drugs require bi-weekly injections and cause side-effects (mainly injection site reactions). Further, these drugs cost upwards of US$14,000 per year, a cost that remains unsubsidised for most patients.

Not surprisingly, these negatives have resulted in a slow uptake by patients and doctors with sales last year totalling about $1 billion for both drugs combined, representing a very limited market penetration. Currently in the U.S. there is a major advertising campaign aimed at addressing this challenge: (https://www.ispot.tv/ad/wPpl/repatha-the-risk-is-real)

The pharmaceutical industry generally accepts that to achieve full market acceptance and to stand any hope of increasing sales from $1 billion to the potential $19+ billion level, means developing a product with the following attributes:

- Delivering at least a 60% decrease in LDL cholesterol levels in conjunction with a statin drug
- Being an oral preparation with once-a-day administration
- Being sufficiently well tolerated for long-term use
- Delivering a pharmacoeconomic case that is likely to support reimbursement by health authorities (eg. being placed on the PBS in Australia).

This is the lofty but achievable objective that the NYX-330 program is targeting.

Current status

On the basis of results to date, the Company believes that NYX-330 has the potential to meet the attributes cited above. There is much work yet to do, but the last four months of research and development serve to reinforce our belief that we are on the right path.

In our last report, I explained that we had a drug (NYX-330) that blocked the action of human PCSK9 in the test-tube. NYX-330 is a traditional small molecule, not a monoclonal antibody. That alone is a major breakthrough, thanks to a small team of Australian chemists who succeeded where a number of major pharmaceutical companies could not.

That said, there is a significant difference between something working in a test-tube and working in an animal, and that is the challenge we have addressed over the last several months. To summarize our findings:

☑ The drug works as intended and blocks PCSK9 activity in a recognised animal model
☑ A once daily oral regimen is achievable
☑ The drug is well tolerated in the short-term.

With those key proof-of-principle findings behind us, we have moved to the next stage of development which involves:

⊕ Modifying the structure of the drug to potentially increase potency
⊕ Gaining a better understanding of exactly how the drug is working in the body.

Current studies are expected to run through 2018 at which point we commence development of the final oral formulation and undertake the standard animal safety steps ahead of taking the drug into humans in formal Phase 1 studies, a major milestone for our Company that is on the horizon.

NYX-104

The objective of this program is to produce a drug known as a ***neuroprotectant***, or a drug that protects the brain from an unusual form of self-destruction known as *excitotoxicity*.

Currently there are no approved therapies approved to treat brain injury, a severe and life-threatening condition with a high cost to society. This is a field of research with significant medical importance and a compelling commercial opportunity.

In terms of confirming that we have a drug with the potential to work in humans, this program is at a similar stage of development as the NYX-330 program. However, the challenges in bringing a drug into the clinic for brain injury are considerably greater for lowering cholesterol. NYX-104 almost certainly will advance into the clinic after NYX-330.

Background
Damage to any tissue outside of the nervous system results in that tissue being repaired and replaced with healthy tissue. The nervous system is unique - not only does it not replace injured tissue, but it compounds the problem by considerably extending the area of original injury in a unique form of self-destruction.

This self-inflicted phenomenon is known as *excitotoxicity*, and is essentially a short-circuiting failure where damaged brain cells send out excessive chemical signals that *over-excite* connecting brain cells to the point of killing them. Following the initial injury that leaves a core area of damage, a wave of cell death emanates out from that primary zone, continuing for about 5-10 days. By the time it stops, the final area of brain death can be as much as six times the size of the original injury.

Excitotoxicity occurs with stroke, acute brain and spinal injury, concussion and severe epileptic seizures. At its most prominent, neural excitotoxicity from concussion manifests in professional boxers or NFL footballer players with severe dementia. Excitotoxicity from the concussive effect of loud noise in servicemen and servicewomen or rock musicians manifests as profound hearing loss. Excitotoxicity following stroke is thought to account for a large proportion of the two-thirds of surviving stroke victims who require assisted living for the rest of their lives.

The purpose of a neuroprotectant drug is to block this excitotoxicity process. It is not designed to address the original injury, as that tissue is irreversibly damaged and won't be replaced. A neuroprotectant will ideally prevent or diminish the secondary damage and limit the damage to the original area of injury. In the case of stroke, for example, an effective neuroprotectant drug should mean considerably less long-term paralysis and loss of function, as well as faster rehabilitation.

Currently there is no effective treatment to block the excitotoxicity process, mainly because no drug has been developed that works on the two main mechanisms involved in excitotoxicity. Some drugs

have been developed against one of those mechanisms, but not against both mechanisms, and a single-use drug is unlikely to be effective.

But even if a promising drug was to be developed, there would still be the challenge of getting that drug across the blood-brain barrier, a barrier that serves to exclude the vast majority of foreign chemicals from reaching the brain.

Current status
In our last report, we stated that:

⇒ NYX-104 looked to be the first drug to our knowledge that deals comprehensively in the test-tube with the two main cellular mechanisms underlying excitotoxicity
⇒ We were able to translate this *in vitro* effect into the whole animal by blocking the degree of excitotoxicity by as much as 56% in a mouse model of human stroke
⇒ A five day treatment course of NYX-104 was well tolerated in those mice

These highly encouraging results were significant in that they demonstrated we had succeeded in developing a drug that laboratory data suggested should work, which we followed up by validating that it did work in an animal model. The drug also was well-tolerated. By any measure, this represented an important breakthrough in the development of an effective neuroprotectant drug.

However, at that point we were not clear how the drug worked…we lacked a mechanism of action. Answering that question has been the focus of our studies for the past four months. I can now report that those experiments have been successful to an extent that I would call *breakthrough*. We are confident that we have identified NYX-104's mechanism of action.

We know which protein in a neuron the molecule is binding to, and more importantly, exactly where on that protein NYX-104 binds. The main benefit of this finding is that we now are able to use chemical design software to modify the NYX-104 molecule so that it binds to its target in a stronger way. Our aim is to develop a drug capable of delivering much greater than the 56% inhibitory effect we have already achieved. If we could reproduce an inhibitory effect of 56% in a stroke patient, we believe that this would translate into lives being saved and the functional consequences of a stroke being significantly reduced. So, looking to see if we can go beyond the current 56% should have a very worthwhile benefit for patients.

That work is ongoing, with a range of modified forms of NYX-104 currently being synthesised for testing. Data should be available in early 2019, and with that we will focus on advancing the drug into human testing.

The notional treatment regimen with NYX-104 in stroke patients is daily administration for 1-2 weeks following a stroke. Current treatments of stroke are aimed at restricting the size of the initial injury and these depend on removing the clot in a highly time-dependent way within a matter of hours following the stroke. NYX-104 is targeting the secondary damage and we do not expect that commencing NYX-104 will be so time-critical.

NYX-205

NYX-205 is an anti-inflammatory drug that has been designed to treat inflammation associated with various diseases affecting peripheral nerves (known as peripheral neuropathy).

Background

Peripheral neuropathy is the result of damage to peripheral nerves that often causes weakness, numbness, hypersensitivity and pain, usually in extremities such as hands and feet. Peripheral neuropathy is not a single disease but a general term for a series of disorders that result from damage to the body's peripheral nervous system.

Peripheral neuropathy occurs when nerves are damaged or destroyed and messages are no longer transmitted between the brain and spinal cord on the one hand, and muscles, skin and other parts of the body on the other.

Symptoms vary depending on whether motor, sensory, or autonomic nerves are damaged.

- **Motor nerves** control voluntary movement of muscles such as those used for walking, grasping, or talking.
- **Sensory nerves** transmit information such as the feeling of a light touch or heat or pain from a cut.
- **Autonomic nerves** control organ activities that are regulated automatically such as breathing, digesting food, and heart and gland functions.

More than 100 types of peripheral neuropathy have been identified and an estimated 20 million people in the U.S. suffer from some form of peripheral neuropathy.

The three main forms of peripheral neuropathy are diabetic, idiopathic and chemotherapy-associated.

Diabetic peripheral neuropathy is the most common form of peripheral neuropathy, with an estimated 60-70% of diabetics afflicted with the mild form and between 15-25% afflicted with a more severe form.

If not managed correctly, diabetic peripheral neuropathy is the number one cause of non-traumatic lower limb amputation in the U.S. Approximately 54,000 diabetics in the U.S. undergo amputations each year, with 75% of these amputations considered to be preventable.

Idiopathic peripheral neuropathy has no specific cause and occurs typically in middle-aged and elderly individuals. Possible causes include exposure to toxins, smoking, hereditary factors, vitamin deficiency and alcohol abuse. It is estimated that 23% of all neuropathy patients are diagnosed with idiopathic neuropathy.

Chemotherapy-induced peripheral neuropathy occurs in 30-40% of all cancer patients receiving chemotherapy. Chemotherapy is most damaging on the nervous system due to the fact the nerve cells more sensitive to toxic agents than are other cells. This painful condition can persist for months after chemotherapy stops.

At this time, there are no known effective treatments for peripheral neuropathy of any type. Medications such as analgesics and anti-inflammatories are used to control pain, but these provide only temporary relief. Neuropathic pain can seriously affect emotional well-being and overall quality of life. Many chronic neuropathies worsen over time, becoming painful and potentially debilitating.

Current status

As of the last report, we had shown that NYX-205 readily crossed into the peripheral nerves of rats. This was a significant and fundamental discovery because the exclusion barrier that prevents foreign chemicals from gaining access to the brain is the same one that blocks most drugs from passing from the blood into peripheral nerves. And accounts for why commonly available anti-inflammatories and pain-killers have little or no effect on peripheral neuropathy.

Since then, the NYX-205 program has tracked a similar path to NYX-104. At one level we wanted to understand the mechanism of action of NYX-205 as an anti-inflammatory. At another level we wanted to see whether this was the best and most active form of the drug that we could develop in order to maximise the chances of success in the clinic.

As with the NYX-104 program, our team has been successful in identifying the actual protein target and the actual binding site. This is yet another key breakthrough that has led to computational modelling currently being used to design a new family of NYX-104 derivatives that we are confident will lead to more potent anti-inflammatory compounds.

As with the NYX-104 program, these data should be available in early 2019, and we plan to spend 2019 focused on advancing the final drug into humans.

At this stage we intend to develop NYX-104 as a treatment of neuro-inflammation. And while neuro-inflammation is a contributor to a wide variety of neurodegenerative and autoimmune conditions affecting the brain, our current intention is to bring NYX-104 (or its derivative) into the clinic for diabetic peripheral neuropathy, a major and growing community need.

Logistics

Nyrada continues to function as a subsidiary of Noxopharm, created for the specific purpose of housing the Noxopharm Group's non-oncology drug programs.

The scientific team is based in the Noxopharm Sydney offices, drawing on the resources of Noxopharm (chemistry, drug design, drug manufacture, legal/financial support).

The Nyrada Scientific Advisory Board (SAB) provides a vital consultancy role. Chaired by Professor Gary Housley (Director of the Translational Neuroscience Facility, UNSW Sydney), the SAB has been constituted to provide specific advice across all three programs:

- Professor Housley and Professor Junichi Nabekura (Vice Director of the National Institute for Physiological Sciences in Okazaki, Japan, and a global expert in brain response to injury) are overseeing the neuroprotectant drug program;
- Professor Gilles Lambert (Professor in Cell Biology and Biochemistry at the University of La Réunion Medical School, France, and a principal investigator) is one of the pioneers in the discovery of PCSK9 and is playing a direct project management role in the PCSK9 program;
- Professor David Burke (Professor of Medicine, University of Sydney, a neurologist and world authority on nerve conduction) has recently joined the Board to provide guidance on the neuroinflammation program.
- Dr Jim Palmer, an Australian-based consultant synthetic chemist with extensive international experience and track-record in successful drug design.

Timetable

Our projected timetable is for all three programs to advance from 'lead optimisation' to 'lead confirmation' by the end of February 2019. That means having identified each of the three final drug candidates that will be taken through into the clinic, as well as having identified how each drug candidate is working.

We then will move each drug candidate through a standard pre-clinical testing program that typically takes 9-12 months as we advance these experimental drugs into first-in-human studies.