21 April 2020 **Sydney, Australia**

Approval to be sought for COVID-19 Clinical Study in U.S.

Highlights:

- **NOX to seek approval from U.S. FDA for clinical study of Veyonda® in COVID-19 patients**
- **Objective to block progression of patients with early-stage disease into multi-organ failure and likely death**
- **Rationale based on inhibition of STING signaling**

Sydney, 21 April 2020: Noxopharm (NOX:ASX) previously (1 April 2020) announced a discovery by the Hudson Institute of Medical Research (Hudson Institute) about a novel mode of action of idronoxil, the active ingredient in Veyonda®. Noxopharm now is able to reveal that this mode of action involves inhibition of the STING signalling pathway, a discovery that leads the Company and the Hudson Institute to believe that Veyonda® holds potential to block the hyper-inflammation stemming from the infection and which is believed responsible for deaths in patients with COVID-19 infection.[1]

The current announcement provides the market with an update on the action currently being taken by the Company to act on that discovery.

Graham Kelly PhD, Noxopharm CEO, said, "With the emerging possibility that an abnormally high STING response is a factor in COVID-19 death, having an inhibitor of STING signaling ready to be tested in COVID-19 patients is both a considerable responsibility and opportunity. Proving the value of Veyonda® to COVID-19 patients is both a humanitarian and regulatory approval opportunity that we cannot overlook."

"The need to prevent the phenomena of cytokine storm and septic shock in COVID-19 patients looks likely to remain for some considerable time, and may even remain a long-term need should development of an effective vaccine prove challenging."

For Noxopharm, Veyonda® is first and foremost an oncology drug, with end-stage prostate cancer remaining its primary focus. Any clinical studies in non-oncology patients will require non-dilutive funding, something that the Company believes in the current environment should be achievable once it receives the go-ahead to conduct a clinical study.

Regulatory strategy
Noxopharm currently is moving to obtain guidance from the FDA on the appropriate regulatory approval pathway to pursue in the U.S. in relation to COVID-19 patients. The Company also is pursuing the option of testing Veyonda® in patients suffering septic shock from a range of infective agents other than the SARS-CoV-2 virus.

Noxopharm has been developing an oral dosage formulation of idronoxil for some time and the Company originally considered using an oral dosage form in non-oncology patients. However, under advice, the Company will proceed instead with Veyonda®, given that product's current Investigational New Drug (IND) status in the U.S., on top of the considerable clinical experience and data amassed with this dosage form. The provisional patent lodged in relation to use in septic shock patients covers broad drug dosage forms including oral and suppository.

Rationale
The rationale is to use Veyonda® to block a process known as STING signaling, which in some COVID-19 patients is thought to contribute to lethal self-destruction of major organs.

STING (Stimulator of Interferon Genes) is part of a primitive defence mechanism that detects the presence of invading pathogenic organisms such as viruses or bacteria. In addition, STING plays important roles in the clearance of damaged cells and tissues. Both responses involve the production of proteins known as cytokines whose task it is to coordinate the subsequent immune and tissue repair (inflammatory) responses.

STING engagement in the early stages of infections can contribute positively to the body's immune response to some pathogens. However, STING engagement becomes a negative and self-destructive force if the infection persists and progresses to the point of causing extensive tissue damage.[2] Under those conditions, the STING pathway contributes to the so-called 'cytokine storm', along with the production of blood clotting factors, all promoting further organ damage and forming the basis of the condition known as septic shock.[2]

In COVID-19 patients, a trigger for this 'cytokine storm' or septic shock is mounting tissue damage associated with poor oxygen levels (hypoxia) stemming from poor lung function,[3] with this tissue damage believed responsible for triggering a toxic STING response.[4] High levels of cytokines and clotting factors are proving to be a predictor of mortality in COVID-19 patients.[3]

The Hudson Institute, in studies led by Dr Michael Gantier, discovered that idronoxil, the active ingredient in Veyonda®, blocks the STING signalling pathway associated with cellular damage of the kind caused by hypoxia.

Dr Michael Gantier, head of the Nucleic Acids and Innate Immunity laboratory, said, "We have shown that idronoxil is a very potent inhibitor of STING signaling in cell-based assays using STING agonists, and also in the context of cellular damage caused by a chemotherapy agent. The inhibitory activities measured were measured in the sub-micromolar range, on par with other inhibitors recently reported.[5]

Competitive landscape

To address the 'cytokine storm' phenomenon, clinical trials are in progress in COVID-19 patients with drugs that block the function of individual cytokines such as IL-6 and TNF-alpha. Those studies will show whether blocking individual cytokines out of the large number involved in a 'cytokine storm' will have any meaningful effect.

Noxopharm believes that a more rational approach is an upstream approach to block the 'cytokine storm' process at its roots by inhibiting the STING pathway, offering the potential of blocking the production of a broad range of cytokines and holding the promise of halting the rapid deterioration of COVID-19 patients once they develop poor lung function.

The infancy in understanding the critical role of STING in inflammation and septic shock has meant that clinical studies of STING inhibitors have yet to get underway. Noxopharm is in the position of having a clinic-ready drug candidate to test the potential value of blocking STING signaling in COVID-19 patients.

Veyonda® also has the advantage of having addressed the issue of safety by proving to be well-tolerated in patients with advanced cancers and poor quality of life.

About COVID-19 deaths

The danger with COVID-19 infection lies in its progression from a mild disease into an overwhelming and fulminant condition characterised by respiratory failure, multi-organ failure (heart and kidney failure), clotting problems and septic shock. Treatment at that end-stage is limited to supportive treatment including antibiotics and the use of ventilators. To date there is no approved treatment for COVID-19 related disease and the death rate continues to be very high in these patients.

Cytokines are proteins secreted by immune cells and which trigger inflammation and tissue repair. These include interleukins (IL-6, IL-8, IL-1β, tumour necrosis factor (TNF) and interferon beta (IFNβ). Cytokine levels in blood rise in response to COVID-19 infection but undergo extreme rise in a small proportion of patients in what is known as 'cytokine storm', with this extreme rise being highly predictive of death.[3]

About Idronoxil and cancer

Idronoxil is a small molecule with multiple anti-cancer mechanisms. Inhibition of the sphingosine-1-phosphate (S1P) and STING signalling pathways are thought to be the two principal factors, both playing key roles in regulating the immunological and inflammatory responses in tumours.

S1P is a key master driver of pro-survival mechanisms in all cells and is over-expressed in most tumour cells.[6] Idronoxil inhibits S1P production via inhibition of the ENOX2-sphingosine kinase axis.

The STING signalling pathway can directly contribute to cancer development and metastasis by initiating pro-tumorigenic inflammation.[7-10]

About Noxopharm

Noxopharm is a clinical-stage Australian oncology drug development company with offices in Sydney and New York. The Company has a primary focus on the development of Veyonda® and is the major shareholder in the non-oncology drug development company, Nyrada Inc. (ASX:NYR).

www.noxopharm.com

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Graham Kelly, CEO and Chairman of Noxopharm, has approved the release of this document to the market.

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