Cholesterol-Lowering Program Delivers Two New Potent Drug Candidates

- Medicinal chemistry work revealed two additional, more potent candidates (NYX-PCSK9i-211 and NYX-PCSK9i-212) with improved drug-like characteristics compared to NYX-PCSK9i
- An *in vivo* efficacy study in a specialised mouse model has commenced, evaluating NYX-PCSK9i in combination with a statin, and the two new drug candidates
- Study results will enable selection of the optimal candidate to go into safety and pharmacology studies at an internationally recognised CRO, before a Phase I first-in-human study
- *In vivo* study results are expected in mid-June

Sydney, 05 May 2021: Nyrada Inc (ASX: NYR) ("Nyrada" or "the Company") a preclinical stage, drug development company specialising in novel small molecule drugs to treat cardiovascular and neurological diseases today provided an update on the progress of its Cholesterol-Lowering Program.

Building on a previous *in vivo* preclinical study that showed NYX-PCSK9i reduced total cholesterol by 57% without adverse side effects, Nyrada has now commenced a new *in vivo* efficacy study in the same specialised transgenic mouse model (APOE*3-Leiden.CETP) to evaluate NYX-PCSK9i in combination with a statin ("high cholesterol mouse study"). This study aims to determine if NYX-PCSK9i enhances the efficacy of a statin drug when co-administered.

In addition, Nyrada announces recent medicinal chemistry work has revealed two promising drug candidates (NYX-PCSK9i-211 and NYX-PCSK9i-212) with *in vitro* testing confirming they have improved potency and bioavailability (absorption) compared to NYX-PCSK9i. These new candidates may be less prone to interactions with drugs prescribed to patients with high cholesterol.

Consequently, the new *in vivo* high cholesterol mouse study has been expanded to evaluate the efficacy of these new drug candidates. Results from this study are expected to be reported in mid-June and will enable Nyrada to select the optimum drug candidate to take forward into preclinical safety and toxicology testing, which is expected to start shortly after completion of the *in vivo* high cholesterol mouse study.

Nyrada has also selected a preferred, internationally recognised Contract Research Organisation (CRO) to oversee the preclinical safety and toxicology studies that are necessary before human clinical trials can commence. These studies aim to confirm cardiac, central nervous system, and respiratory safety and measure toxicological effects in two animal species, a requirement before starting clinical trials in humans. The design and structure of the studies have been agreed with the CRO.

Commencement of the preclinical safety and toxicology studies is dependent on having sufficient amounts of the clinical candidate available. Nyrada is optimising the route of synthesis for these compounds as it scales up from gram to kilogram quantities, which are required for these studies. The Company will provide an update on the expected commencement and duration of the Phase I clinical trial once the high cholesterol mouse study and scale-up manufacturing are complete.

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Nyrada CEO, Mr. James Bonnar commented, "Nyrada has built a strong portfolio of novel compounds that strengthen our intellectual property and create licensing opportunities for the Program. We are confident that scale-up manufacturing combined with the improved potency and drug-likeness of the new compounds, compared to the positive results of NYX-PCSK9i, ensures we will enter Phase I clinical trials with the optimal drug candidate."

Drug Candidate Comparison

The table below shows the progress made in developing the compounds and the strength of their performance against key parameters compared to NYX-PCSK9i.

Parameter	NYX-PCSK9i	NYX-PCSK9i-211 *(comparison to NYX-PCSK9i)*	NYX-PCSK9i-212 *(comparison to NYX-PCSK9i)*
PCSK9 binding[1]	●	● *(x3)*	● *(x2)*
LDLR protection[2]	●	●	●
Oral bioavailability[3]	●	●	● *(x2)*
Drug exposure[4]	●	● *(x3)*	● *(x12)*
Plasma half-life[5]	●	●	● *(x2)*
CYP inhibition[6]	●	●	●

1 **PCSK9 binding** is the degree of affinity the drug has on the therapeutic target, in this case, the protein PCSK9. It is determined *in vitro* and is a measure of drug potency. The two new candidates show improved potency compared with NYX-PCSK9i.

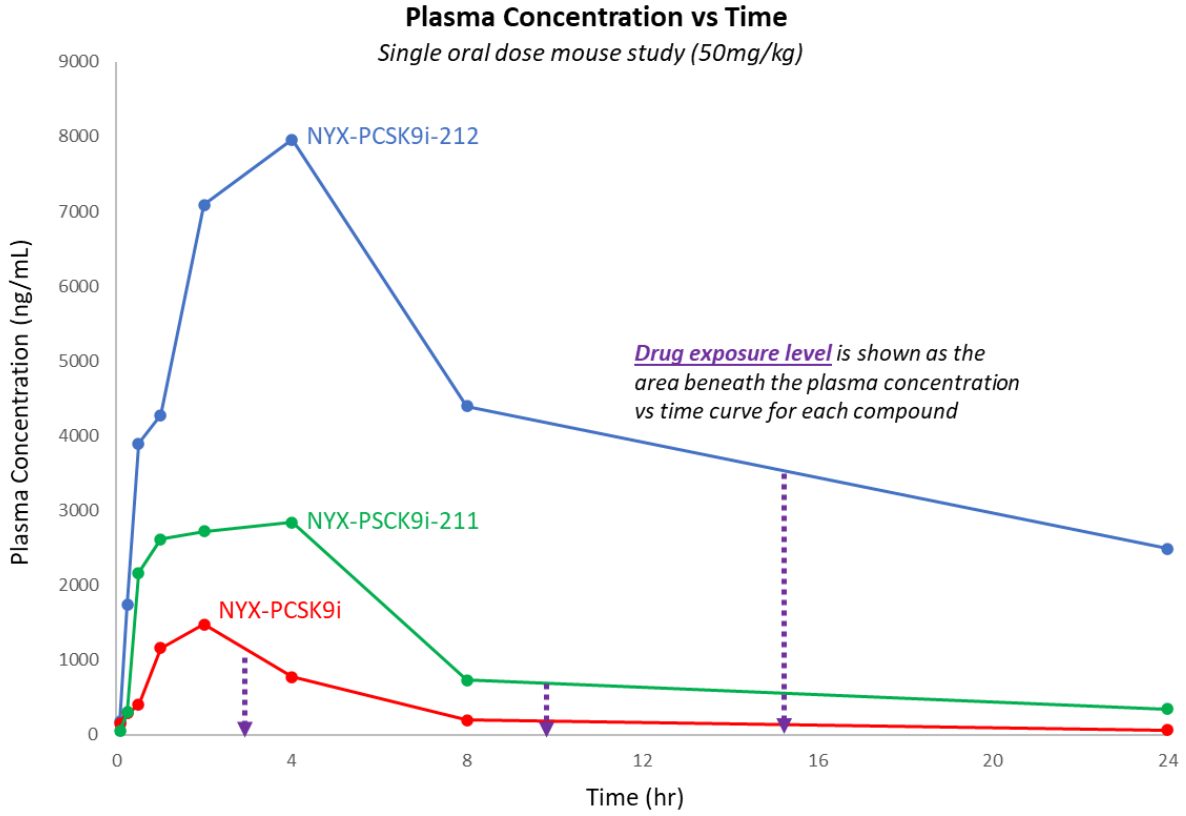
2 **LDLR protection** refers to the degree to which drugs protect LDL receptors (LDLR) from degradation due to the action of PCSK9. This is determined in a cell-based assay using human lymphocytes (white blood cells). It is a good predictor of the therapeutic effect of drugs *in vivo*. All three candidates offer excellent protection of LDLR from degradation and in a dose-dependent manner.

3 **Oral bioavailability** is the ratio of drug detected in plasma following oral and intravenous dosing. Drugs with good oral bioavailability can be administered at lower doses in smaller pills. Nyrada's two new candidates show improved absorption and bioavailability following oral administration, compared with NYX-PCSK9i.

4 **Drug exposure** is the area under the plasma concentration versus time curve (see graph on page 3). Higher drug exposure is desired as it can enable lower therapeutic doses.

5 **Plasma half-life** is the time it takes to reach a 50% reduction in plasma drug concentration. A longer half-life is necessary for once-per-day dosing in humans.

6 **CYP inhibition** refers to the main way in which drugs are metabolised in the liver. Drugs that are metabolised by Cytochrome P450 (CYP) enzymes in the liver are more likely to exhibit undesirable interactions with other drugs. Amber indicates moderate metabolism by CYP P450 enzymes and green indicates mild or no significant metabolism.



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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

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