Nyrada's NYX-PCSK9i with Statin Achieves 65% Cholesterol Reduction in Preclinical Study

- Encouraging efficacy from second preclinical study of NYX-PCSK9i shows:
  - Reduced total cholesterol by two-thirds (65%) when given in combination with the statin Lipitor® (atorvastatin, Pfizer), the best-selling drug of all time
  - Reduced total cholesterol by almost half (46%) when given as a monotherapy
  - Achieved an equivalent reduction in total cholesterol to the injectable PCSK9 monoclonal antibody, Praluent® (alirocumab, Sanofi/Regeneron) in a comparable study
- NYX-PCSK9i selected as the preferred compound for safety pharmacology and toxicology studies to commence in 2H 2021, with a Phase I first-in-human study anticipated to commence mid-2022
- Follow up exploratory analysis to be reported in July 2021

Sydney, 29 June 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 announces encouraging efficacy results from its *in vivo* study of NYX-PCSK9i in a specialised mouse model, called APOE*3-Leiden.CETP. The results support the selection of NYX-PCSK9i as the preferred compound for preclinical studies at an internationally recognised Contract Research Organisation, ahead of a Phase 1 first-in-human study.

Results from an *in vivo* efficacy study in a specialised mouse model showed NYX-PCSK9i reduced total cholesterol by 46% as a monotherapy, and 65% when dosed in combination with the statin drug Lipitor over the study period. This compares to the reduction achieved using Lipitor alone of 27% (see *Figure 1* and *Table 1* below). Since it was approved in 1997, Lipitor has been the best-selling drug worldwide generating lifetime sales of US$164 billion.[1] It was also the most prescribed drug in Australia in 2020.[2]

In this study, a dose of 50mg/kg was administered and evaluated over 35 days (5 weeks) with no adverse effects identified. Pleasingly, NYX-PCSK9i was well-tolerated with no significant changes in food intake, body weight, or liver function observed.

Nyrada CEO, Mr. James Bonnar commented: "NYX-PCSK9i has shown very encouraging results in this recent cholesterol-lowering study, building our confidence it is the best drug candidate to take into human trials. To our knowledge, this is the first preclinical study showing a cholesterol-reducing effect from an oral PCSK9 inhibitor drug when dosed in combination with a statin, making it exciting new territory to pioneer. It has the potential to provide a convenient and cost-competitive oral therapy for the 70% of patients at risk of cardiovascular disease who struggle to reach their target LDL cholesterol level despite taking a statin, such as Lipitor."

[1] Total Worldwide Lipitor® Sales
[2] Australian Prescriber: Top 10 drugs 2019/20

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Figure 1. *Total Cholesterol Reduction to NYX-PCSK9i and Lipitor in APOE*3-Leiden.CETP Mouse Model*

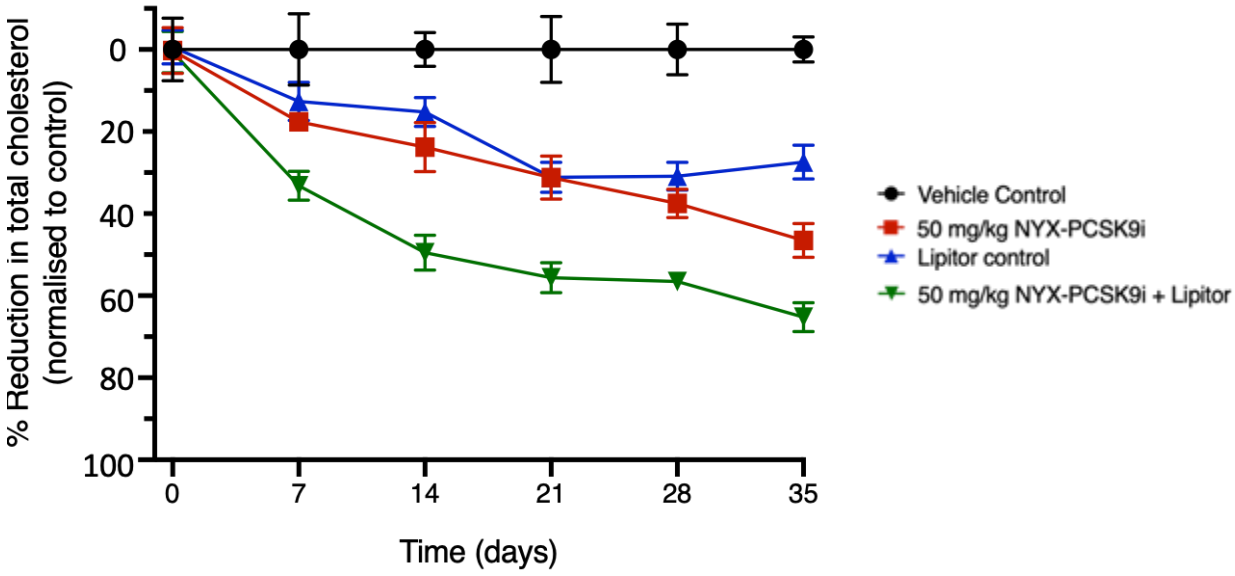

Table 1. *Percentage change in total cholesterol when compared to vehicle control. There were 8 mice in each experimental group. P-values are shown in brackets, with significant p-values in bold.*

	% Difference in plasma cholesterol versus vehicle control (*p*-value)				
Time (days)	7	14	21	28	35
NYX-PCSK9i	-18% (0.066)	-24% **(0.002)**	-31% **(0.001)**	-37% **(<0.001)**	-46% **(<0.001)**
Lipitor	-13% (0.275)	-15% (0.077)	-31% **(0.001)**	-31% **(<0.001)**	-27% **(<0.001)**
NYX-PCSK9i + Lipitor	-33% **(<0.001)**	-49% **(<0.001)**	-56% **(<0.001)**	-57% **(<0.001)**	-65% **(<0.001)**

Comparisons with Current Treatments

Whilst the NYX-PCSK9i *in vivo* study was of shorter duration, the results compare favourably to a historical study of Praluent (alirocumab), an injectable PCSK9 monoclonal antibody. In the 2014 study by Kühnast and colleagues[3] alirocumab was shown to reduce cholesterol by 37-46% (moderate-optimal dose) in APOE*3-Leiden.CETP mice when injected weekly for 18 weeks.

In the same study, Praluent decreased cholesterol by 58% when dosed in combination with Lipitor. This compares with the 65% reduction in total cholesterol achieved dosing with NYX-PCSK9i using the same statin in this study.

[3] Kühnast S et al. J Lipid Res. 2014 Oct;55(10): 2103–2112

Prof. Gilles Lambert, Nyrada Scientific Advisory Board Member, and Professor in Cell Biology and Biochemistry at the University of La Réunion Medical School commented: "Results of this study extend those reported earlier demonstrating equivalency of NYX-PCSK9i to the PCSK9 monoclonal antibody, Praluent. This new study not only demonstrates the efficacy of NYX-PCSK9i at reducing plasma cholesterol levels, but also that the cholesterol-lowering effects of NYX-PCSK9i are additive to those of Lipitor in a mouse model known to be highly predictive of human outcomes. These very exciting observations support the advancement of NYX-PCSK9i to the next stage of development."

Additional Exploratory Arms of *In Vivo* Study

Earlier medicinal chemistry work revealed analogues NYX-PCSK9i-211 and NYX-PCSK9i-212 as two compounds more potent than NYX-PCSK9i, which led to their inclusion as additional arms of the study.

NYX-PCSK9i-211 showed a 39% reduction by 14 days (compared with a 24% reduction by NYX-PCSK9i over the same period), however the compound was not well-tolerated. Notwithstanding, NYX-PCSK9i-211 has the characteristics of a strong second-generation compound. The Company is undertaking further medicinal chemistry work in a targeted approach to improve the tolerability of the compound. Nyrada has several promising compounds in its portfolio and continues to develop these through its medicinal chemistry program that runs in tandem with its primary preclinical studies.

NYX-PCSK9-212 showed a modest reduction in total cholesterol but did not reach statistical significance.

Next Steps

Follow-up exploratory analysis of the *in vivo* study will be reported in July, detailing further study parameters. In addition, safety pharmacology and toxicology studies of NYX-PCSK9i will commence in H2 2021 in preparation for a Phase I first-in-human study, which is set to commence mid-2022.

Nyrada Uses a Specialised Transgenic Mouse Model

Nyrada selected a specialised mouse model called the APOE*3-Leiden.CETP mouse model that has been specifically generated to possess human-like characteristics concerning cholesterol metabolism and cardiovascular health. The model expresses three human genes to specifically model the human hyperlipidemia condition and is very well regarded in the cardiovascular field, having been used for over 170 drug intervention studies by the pharmaceutical industry over the last 15 years.

Importance of LDL Cholesterol to Health and the Role of PCSK9

When the body has too much LDL (bad) cholesterol, it can accumulate on artery walls, restricting blood flow which can lead to heart attack and stroke. LDL cholesterol is cleared from circulation by binding to LDL receptors (LDLR) on the surface of liver cells. PCSK9 is a naturally produced protein that plays a counter role in this regulation process. It does this by degrading the LDLR, lowering the number of receptors available to remove LDL cholesterol. This leads to increased levels of LDL cholesterol in the bloodstream. Inhibition of PCSK9 function causes a beneficial increase in LDLR on the surface of cells, improving the body's ability to clear LDL cholesterol from the bloodstream.

Glossary

In vivo	A medical test, experiment, or procedure that is done on (or in) a living organism such as a laboratory animal or human.
LDL	Low-density lipoprotein cholesterol often referred to as "bad" cholesterol.
LDLR	Low-density lipoprotein receptor. This receptor binds to particles called low-density lipoproteins (LDLs), which are the primary carriers of cholesterol in the blood.
NYX-PCSK9i	NYX-PCSK9i is the Nyrada oral small molecule PCSK9 inhibitor, developed to bind to PCSK9 with the purpose to increase LDLR levels and thus reduce LDL cholesterol. NYX-PCSK9i-211 and NYX-PCSK9i-212 are analogues of this compound.
PCSK9	Proprotein convertase subtilisin/kexin type 9 (PCSK9), an enzyme predominantly produced in the liver. PCSK9 is a key player in plasma cholesterol metabolism.
Statistical significance	Statistical significance is a measure of how likely a test result is likely to be due to chance e.g., a p-value of 0.05 means there is a 5% likelihood that the result is a false positive and a 95% likelihood that it is real. A p-value of 0.001 means there is a 0.1% likelihood that the result is a false positive and a 99.9% likelihood that the result is real. In general, the larger the study size, or the larger the effect, the lower the p-value.

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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.

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