57% Reduction in Total Cholesterol from Nyrada's NYX-PCSK9i *In Vivo* Study

- Very encouraging preliminary *in vivo* efficacy results for Nyrada's oral PCSK9 inhibitor NYX-PCSK9i, showing a 57% reduction in total cholesterol
- Provides proof-of-concept in a specialised mouse model which has demonstrated high predictability of human cholesterol metabolism and cardiovascular health outcomes
- NYX-PCSK9i results compare favourably with historical *in vivo* trials of the statin, Lipitor® (Pfizer), and injectable PCSK9 monoclonal antibody, Praluent® (Sanofi/Regeneron), in the magnitude of total cholesterol reduction
- Results mark significant progress towards an effective, convenient, and cost-competitive *single-pill* treatment option for the 70% of patients unable to reach their target LDL cholesterol level despite taking a statin, replacing ongoing expensive injections
- Results confirm the dose to be carried forward into further testing of NYX-PCSK9i in combination with a statin to determine potential cholesterol-lowering enhancement

Sydney, 21 December 2020: Nyrada Inc (ASX: NYR) is pleased to report encouraging efficacy results from its cholesterol-lowering drug program which is directed at developing an oral PCSK9 inhibitor treatment for hypercholesterolemia (high cholesterol).

Preliminary data, from an *in vivo* study evaluating Nyrada's lead product candidate, NYX-PCSK9i, has shown it reduces total cholesterol, including LDL cholesterol, in the APOE*3-Leiden.CETP mouse model by 57%. Two dose levels (30 and 50 mg/kg) were administered and evaluated over 28 days, with a dose-dependent response observed (see ***Figure 1*** and ***Table 1***). No adverse effects were identified and NYX-PCSK9i was well-tolerated at both dose levels. Additional exploratory analyses will continue for secondary study measures, which Nyrada anticipates reporting in the New Year.

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

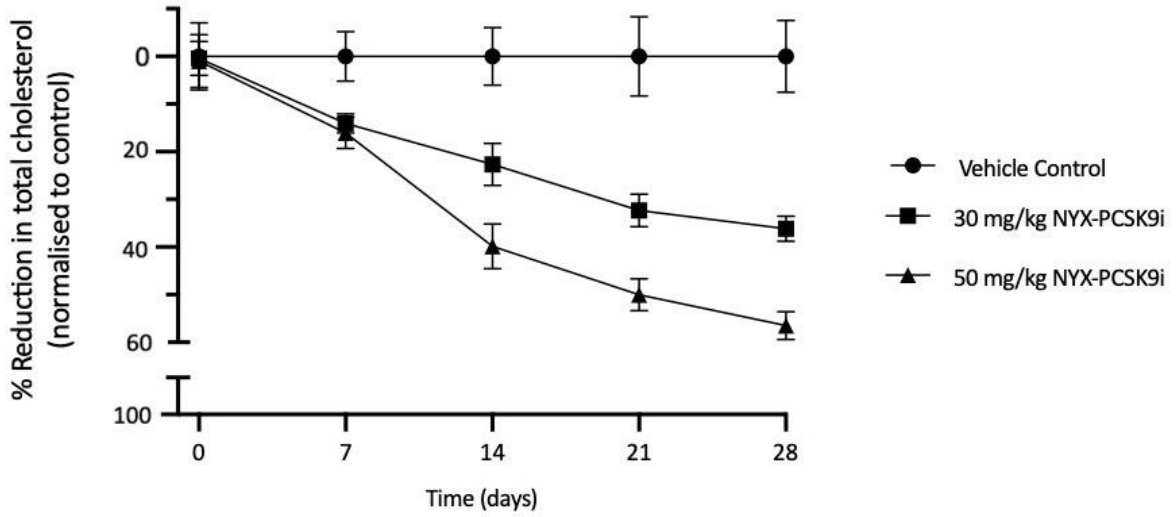

Table 1. *Percentage change in total cholesterol when compared to vehicle control. There were 8 mice in each experimental group. P-values are shown in brackets, with significant p-values in bold*

	% difference in plasma total cholesterol versus vehicle control (*p*-value)			
Time (days)	7	14	21	28
30 mg/kg NYX-PCSK9i	-14% **(0.05)**	-23% **(0.015)**	-32% **(0.002)**	-36% **(<0.001)**
50 mg/kg NYX-PCSK9i	-16% **(0.05)**	-40% **(<0.001)**	-50% **(<0.001)**	-57% **(<0.001)**

Prof. Gilles Lambert, Nyrada Scientific Advisory Board Member and Professor in Cell Biology and Biochemistry at the University of La Réunion Medical School commented: "The results from this study are extremely promising and build on the results reported in July which demonstrated equivalency of NYX-PCSK9i to the PCSK9 monoclonal antibody medications Repatha® and Praluent® in protecting low-density lipoprotein receptors (LDLR) from degradation in healthy human white blood cells. The *in vivo* study demonstrates proof-of-concept within whole-system biology and, importantly, in a mouse model known to be highly predictive of human outcomes."

James Bonnar, Nyrada CEO commented: "These very encouraging results advance the possibility for an effective, convenient, and cost-competitive *oral* PCSK9 inhibitor cholesterol-lowering treatment, either as a monotherapy for those who are statin-intolerant or combined with a generic statin in a *single pill*. This would benefit the 70% of patients at risk of cardiovascular disease who struggle to reach their target LDL cholesterol level despite taking a statin[1]. Currently, the best option for these patients is ongoing adjunct treatment on top of a statin with expensive and inconvenient injectable drugs such as Repatha® and Praluent®, or Leqvio® (inclisiran, Novartis) the injectable siRNA inhibitor recently approved in Europe."

"The lipid management medicine market is substantial and growing, with statins Crestor® and Lipitor® the number 1 and 2 most prescribed drugs in Australia. Combined global sales of Repatha® or Praluent® exceeded US$900 million in FY2019. We look forward to updating the market with further results as we advance the program towards the first human study in late 2021."

Comparison with Current Treatments

The results from the NYX-PCSK9i *in vivo* study indicate that, under similar testing conditions, NYX-PCSK9i is comparable with FDA approved cholesterol-lowering drugs from two classes: a statin, Lipitor® (atorvastatin, Pfizer), and the monoclonal antibody, Praluent® (alirocumab, Sanofi/Regeneron). Given that NYX-PCSK9i has been shown in this study to be effective and orally bioavailable, it is positioned to provide a substantial advancement over injectable drugs such as monoclonal antibody PCSK9 inhibitors Repatha® (evolocumab, Amgen) and Praluent®, which are prohibitively expensive (A$5,800 – A$8,700 per year) and inconvenient for patients, requiring dosing by injection every two to four weeks for life.

[1] Wong ND *et al.* Prevalence of the American College of Cardiology/American Heart Association statin eligibility groups, statin use, and low-density lipoprotein cholesterol control in US adults using the National Health and Nutrition Examination Survey 2011–2012. *J Clin Lipidol*. 2016;10(5): 1109–1118

In 2013, a study by Berbée and colleagues[2] evaluated the total cholesterol response to a moderate dose of atorvastatin (Lipitor®) in the APOE*3-Leiden.CETP mouse model and showed a 22% reduction in total cholesterol when administered over 18 weeks. In 2020, a study by Härdtner and colleagues[3] evaluated the total cholesterol response to an optimal dose of Lipitor® in the APOE*3-Leiden.CETP mouse model and showed a 50% reduction in cholesterol when administered for 20-weeks.

Similarly, the NYX-PCSK9i *in vivo* study results are comparable to a study of alirocumab (Praluent®), a PCSK9 monoclonal antibody. In the 2014 study by Kühnast and colleagues[4], alirocumab was shown to reduce cholesterol by 37-46% (moderate-optimal dose) in APOE*3-Leiden.CETP mice when injected weekly for 18 weeks.

The APOE*3-Leiden.CETP mouse model has historically been shown to be a highly predictive model of the cholesterol-lowering effect in human clinical studies.

The *in vivo* results announced today follow previously announced encouraging efficacy data from an earlier study of NYX-PCSK9i in healthy human white blood cells (lymphocytes) (ASX Announcement 6 July 2020). The study found NYX-PCSK9i to be effective in increasing the surface expression of LDL receptors which are necessary to lower cholesterol in patients. NYX-PCSK9i also demonstrated equivalency with the two approved monoclonal PCSK9 antibody drugs Repatha® and Praluent®.

Next Steps

Nyrada anticipates reporting full study outcomes in Q1 of 2021 once all study parameters have been analysed and the final report issued. In the meantime, the Company has initiated larger-scale production of NYX-PCSK9i, ahead of preclinical regulatory studies to commence in Q1 2021.

Nyrada will continue to evaluate the efficacy of NYX-PCSK9i in reducing cholesterol in a further *in vivo* study utilising the same APOE*3-Leiden.CETP mouse model. The study will investigate a high dose of NYX-PCSK9i, with and without a statin, to explore the maximal effect as a monotherapy and the potential enhancement effect when dosed in combination. The study is expected to commence in Q1 2021 and take 6-8 weeks.

Nyrada has filed a provisional composition of matter patent for PCSK9 inhibitor NYX-PCSK9i and related compounds.

Nyrada Uses a Specialised Transgenic Mouse Model

Nyrada selected a specialised mouse model called the APOE*3-Leiden.CETP mouse model which 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 hyperlipidaemia 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.

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[2] Berbée JFP *et al.* Resveratrol protects against atherosclerosis but does not add to the antiatherogenic effect of atorvastatin in *APOE*3-Leiden.CETP* mice. *J Nutr Biochem.* 2013;24(8): 1423-1430

[3] Härdtner C *et al.* Inhibition of macrophage proliferation dominates plaque regression in response to cholesterol lowering. *Basic Res Cardiol.* 2020 Dec;115:78

[4] Kühnast S *et al.* Alirocumab inhibits atherosclerosis, improves the plaque morphology, and enhances the effects of a statin. *J Lipid Res.* 2014 Oct;55(10): 2103–2112

Why is LDL Important to Health and what is 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.
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.

General

Nyrada has a solid cash position having A$5.2 million in the bank on 30 September 2020. Also, the Company is actively pursuing a variety of non-dilutive funding and collaboration opportunities for the development of its drug candidates. The Company also confirms that its operations and supply chains currently remain unaffected by the COVID-19 pandemic.

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.

-ENDS-

Authorised by Mr. John Moore, Non-Executive Chairman, on behalf of the Board

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Forward-looking Statements

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