Exploratory Analysis of NYX-PCSK9i *In Vivo* Study Shows Additional Positive Results

- New data shows NYX-PCSK9i significantly increased plasma PCSK9 levels supporting the mechanism of action of Nyrada's compound
- Additionally, NYX-PCSK9i treatment significantly increased the number of receptors responsible for removing cholesterol from the bloodstream
- Further analysis also revealed Nyrada's compound enhances cholesterol clearance from the body
- These additional results validate the superior performance of NYX-PCSK9i, building on results reported in December 2020, January, and June 2021
- Safety pharmacology and toxicology studies of NYX-PCSK9i in H2 2021, with a Phase I first-in-human study anticipated to commence mid-2022

Sydney, 13 August 2021: Nyrada Inc (ASX: NYR) is pleased to report exploratory analysis results from its *in vivo* cholesterol efficacy study, first announced on 29 June 2021.

In this 35-day study, NYX-PCSK9i was dosed at 50mg/kg as a monotherapy and in combination with the statin drug Lipitor® (atorvastatin, Pfizer), with no adverse effects identified. The study used a mouse model genetically modified to mimic human-like characteristics concerning cholesterol metabolism and cardiovascular health (*APOE*3-Leiden.CETP* mouse model).

Commenting on the results, Nyrada CEO James Bonnar said, "Further analysis has provided a greater understanding of how an oral PSCK9 inhibitor works *in vivo.* New data from this study affirms that NYX-PCSK9i's mechanism of action is through blocking LDL receptor degradation caused by PCSK9.

"We're very pleased with these results and our progress to date and look forward to the upcoming results from the safety pharmacology and toxicology studies, which are required prior to our Phase I studies commencing in mid-2022," Mr Bonnar added.

As previously announced in June, NYX-PCSK9i reduced total cholesterol by 46% as a monotherapy, and 65% when dosed in combination with Lipitor®, while Lipitor® alone reduced cholesterol by 27%. Today's results also build on *in vivo* studies reported in December 2020 and January 2021, which compared NYX-PCSK9i to historical *in vivo* trials of the statin Lipitor®, and injectable PCSK9 monoclonal antibody, Praluent® (Sanofi/Regeneron), in the magnitude of total cholesterol reduction.

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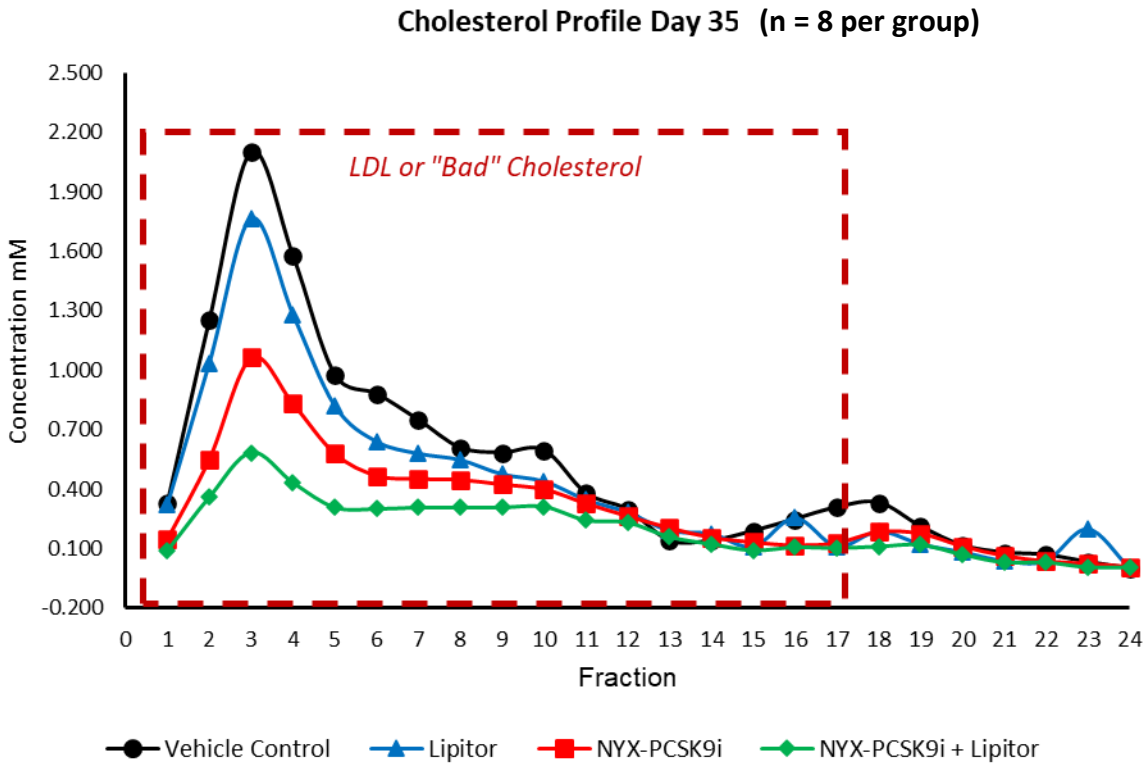
Efficacy Results from Exploratory Analysis from *In Vivo* Cholesterol Study

NYX-PCSK9i actively reduces LDL ("bad") cholesterol levels

Total cholesterol is composed of HDL ("good" cholesterol) and LDL ("bad" cholesterol). These can be separated into fractions where fractions 1-17 represent LDL (shown within the red box of *Figure 1* below).

A modest reduction in LDL levels, as represented by the area under the plotted curves, was seen with Lipitor® (—▲—) with a greater reduction shown for NYX-PCSK9i, (—■—) and the two drugs in combination (—◆—).

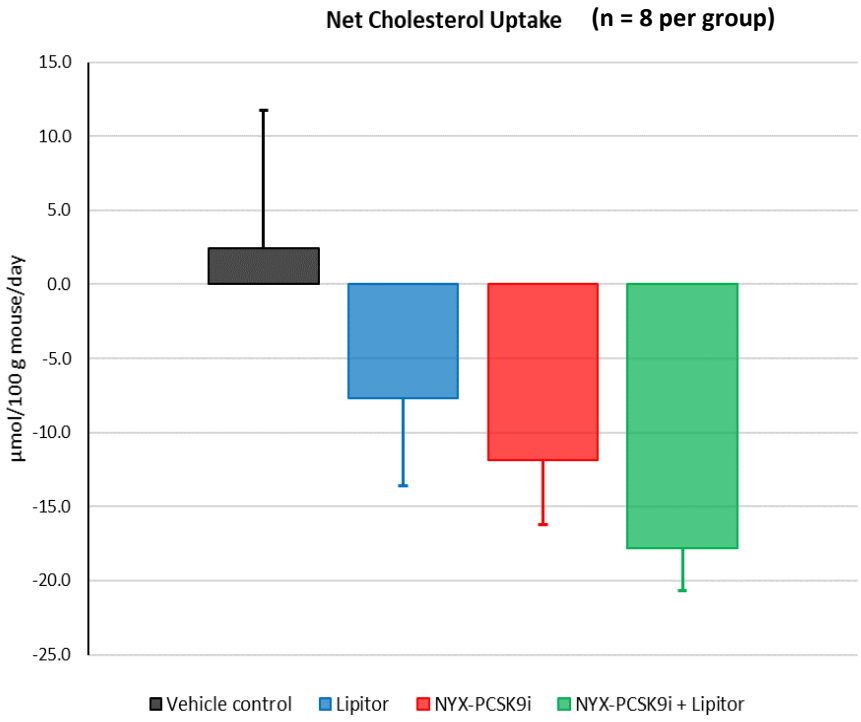
Figure 1



Cholesterol excretion facilitated by NYX-PCSK9i

Results from the study also revealed NYX-PCSK9i enabled the animals to excrete a higher volume of cholesterol than both the vehicle control and animals dosed with Lipitor® alone. An even greater level of cholesterol was expelled when Nyrada's compound was dosed in combination with Lipitor® (refer to *Figure 2* below). Net cholesterol levels were calculated by quantifying the amount of dietary cholesterol consumed, minus the amount of cholesterol excreted in all animals.

Figure 2



The control animals (■) showed a positive value which means the cholesterol consumed was greater than the cholesterol excreted.

The negative value seen with the statin treatment, Lipitor® (■) indicates the amount of cholesterol excreted was greater than consumed. The amount of cholesterol excretion was superior with NYX-PCSK9i alone (■) compared to the statin Lipitor® and an additive effect was observed when both were dosed in combination (■).

This indicates cholesterol particles from the plasma are being metabolised in the liver and excreted following treatment with NYX-PCSK9i, enabling enhanced cholesterol clearance from the body.

Mode of Action Exploratory Data Supporting PCSK9 Inhibition

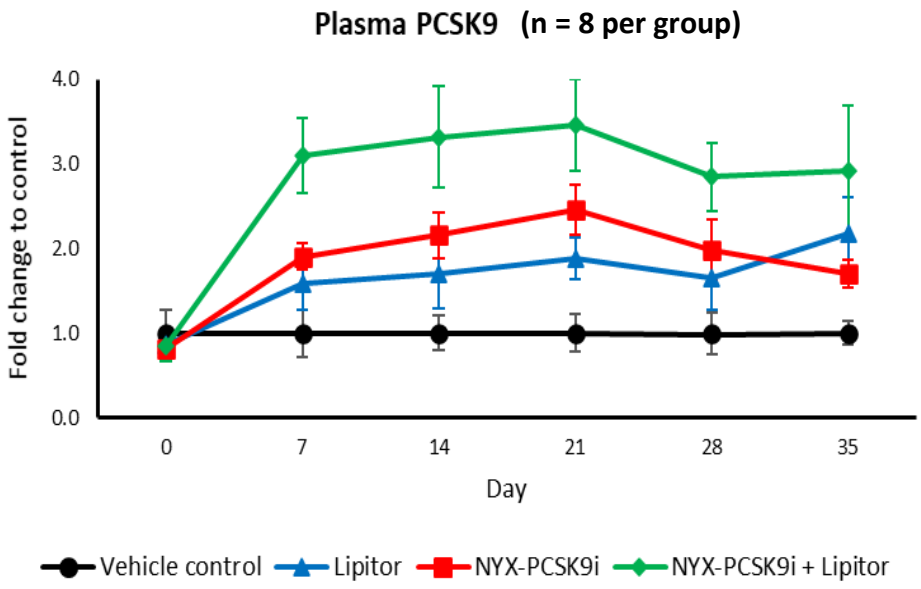
NYX-PCSK9i increases PCSK9 plasma levels

Increased PCSK9 plasma levels are found following treatment with PCSK9 inhibitors. This was what was observed with NYX-PCSK9i (—■—) treatment in the study, affirming that inhibition of PCSK9 by NYX-PCSK9i is the mechanism of action that results in the lowering of cholesterol levels in the blood.

Similarly, increased PCSK9 plasma levels following statin treatment in both humans and animals has been widely reported in published data. This is the reason why PCSK9 inhibitors work well when dosed in combination with a statin. As anticipated, Lipitor® (—▲—) showed a measurable increase in plasma PSCK9 levels.

NYX-PCSK9i significantly increased PCSK9 plasma levels ($p < 0.05$) from day 7 of the study, a trend that continued (see *Figure 3* below). Dosing NYX-PCSK9i in combination with Lipitor® led to an additive effect, showing an even greater increase in PCSK9 plasma levels (—◆—).

Figure 3

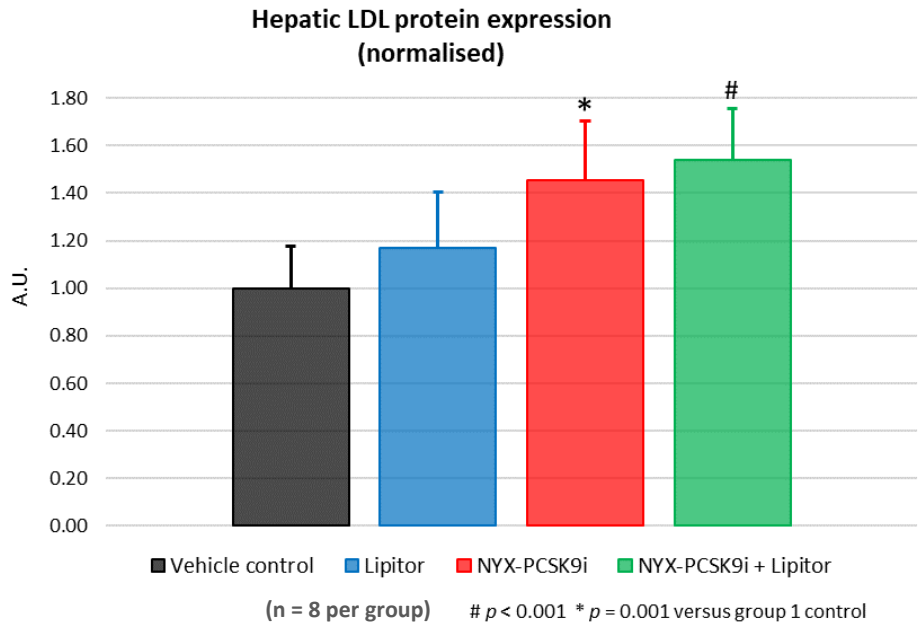


NYX-PCSK9i increases LDL receptor numbers

LDL cholesterol particles circulating in the blood are picked up by a specialised protein present on the surface of liver cells called an LDL receptor (LDLr). LDLr binds to cholesterol particles in the blood and absorbs them into the cell where they are broken down.

A significant increase in the number of LDLr was observed following treatment using NYX-PCSK9i alone and in combination with Lipitor® (see *Figure 4*) which confirms the mechanism of action of Nyrada's compound. The greater the number of LDLr, the better the body can process and thereby reduce LDL cholesterol levels.

Figure 4

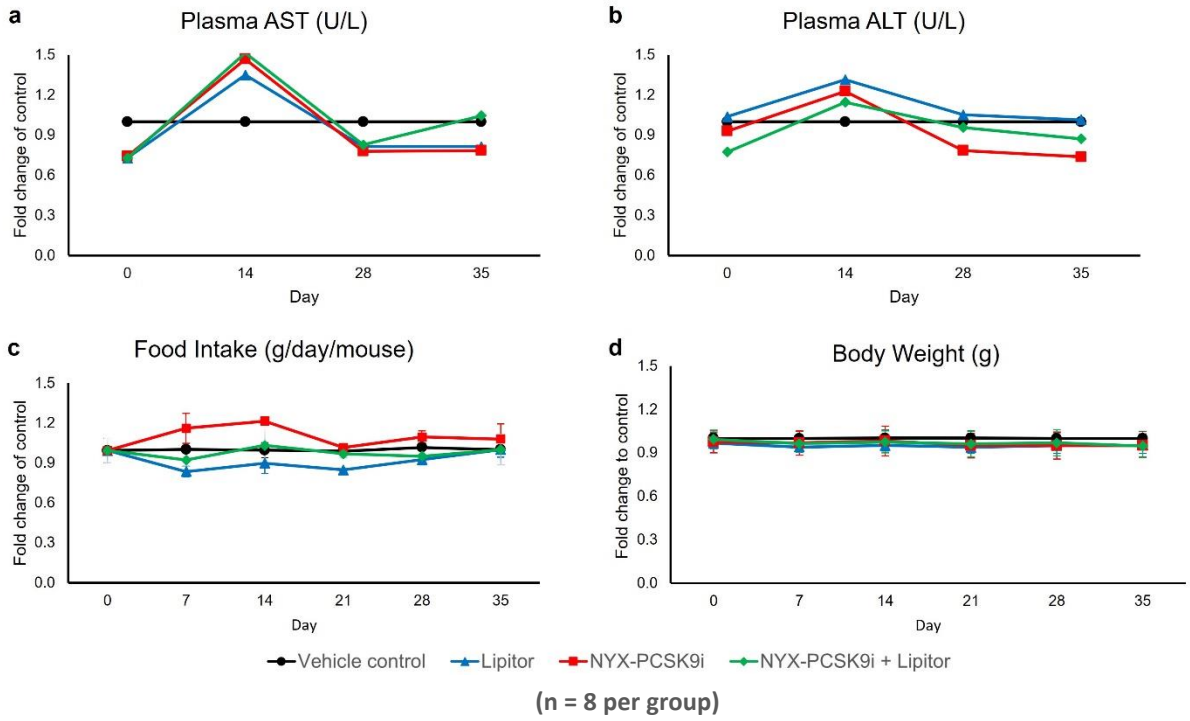


NYX-PCSK9i Safety Profile Information

Plasma levels of key liver enzymes AST and ALT were measured as markers of liver health. A significant increase in ALT and AST is indicative of liver toxicity. No elevation in AST or ALT levels was observed (see *Figures 5a* and *5b* respectively), consistent with normal liver function.

Food intake (*Figure 5c*) and body weight (*Figure 5d*) were also measured as markers of overall health and appetite in animals. Treated and untreated animals had similar levels of food intake and body weight remained consistent throughout the 35-day study.

Figure 5



(n = 8 per group)

Next Steps

Work is well underway to commence safety pharmacology and toxicology studies of NYX-PCSK9i in the second half of 2021, in preparation for a Phase I first-in-human study, which is planned to commence in mid-2022. Nyrada will provide updates to the market as data becomes available from these studies.

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.
Fold change of control	Change compared to the vehicle-treated control group.
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.

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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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