# Verve Therapeutics: In Vivo CRISPR Base Editing to Treat ASCVD

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## I am an employee of Verve Therapeutics.

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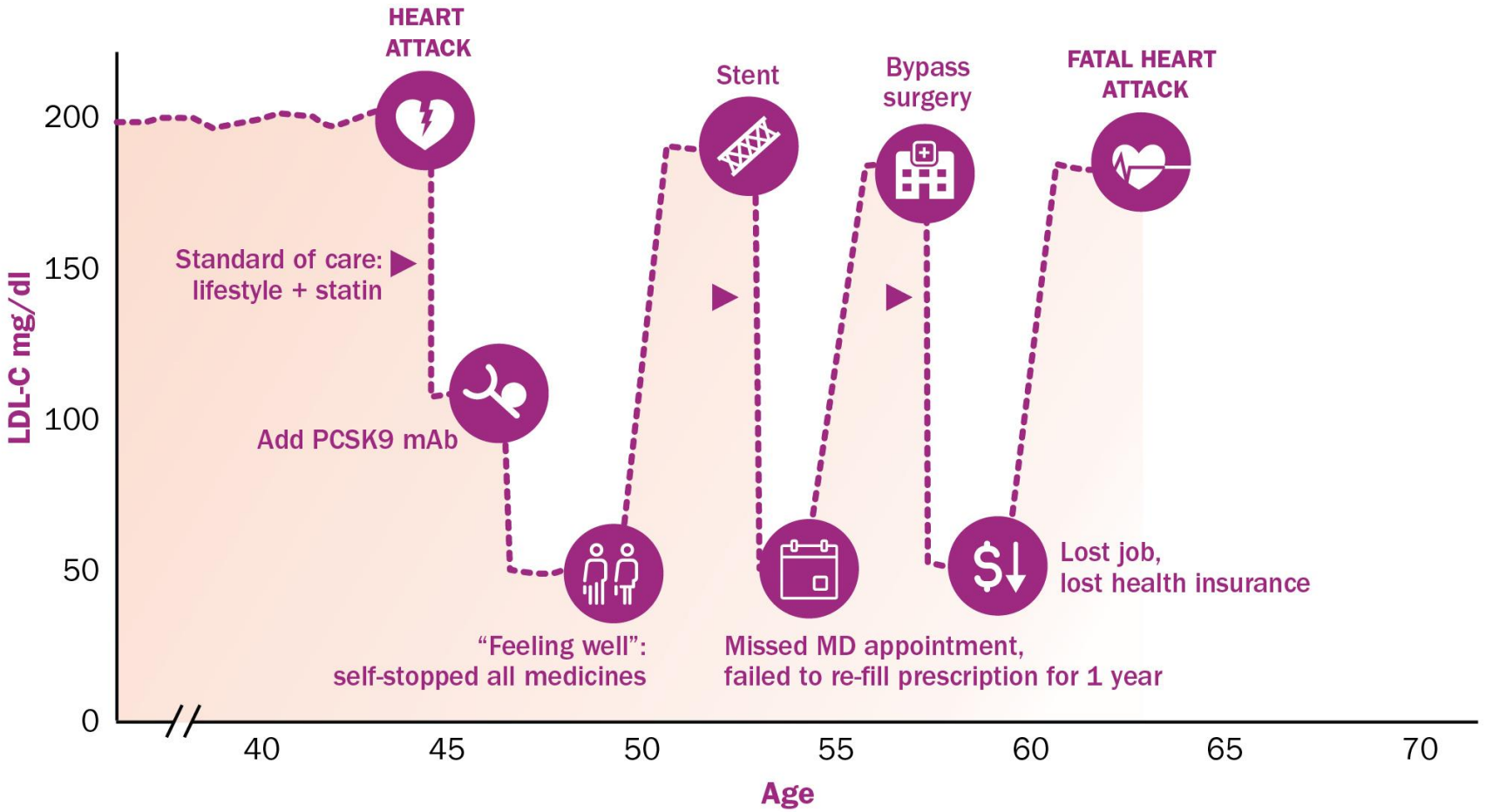
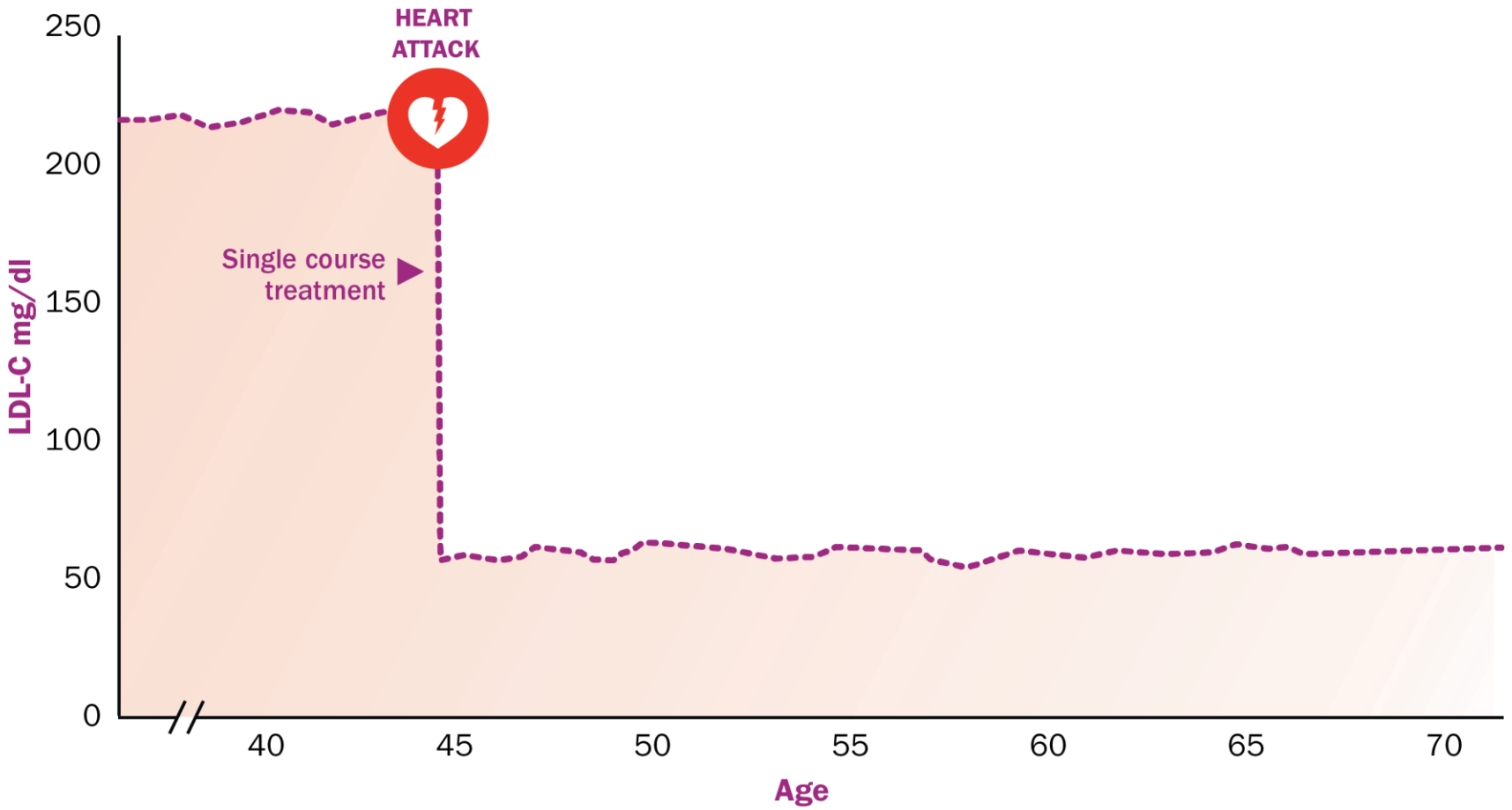
# Chronic care model results in poor control of cumulative blood LDL-C exposure



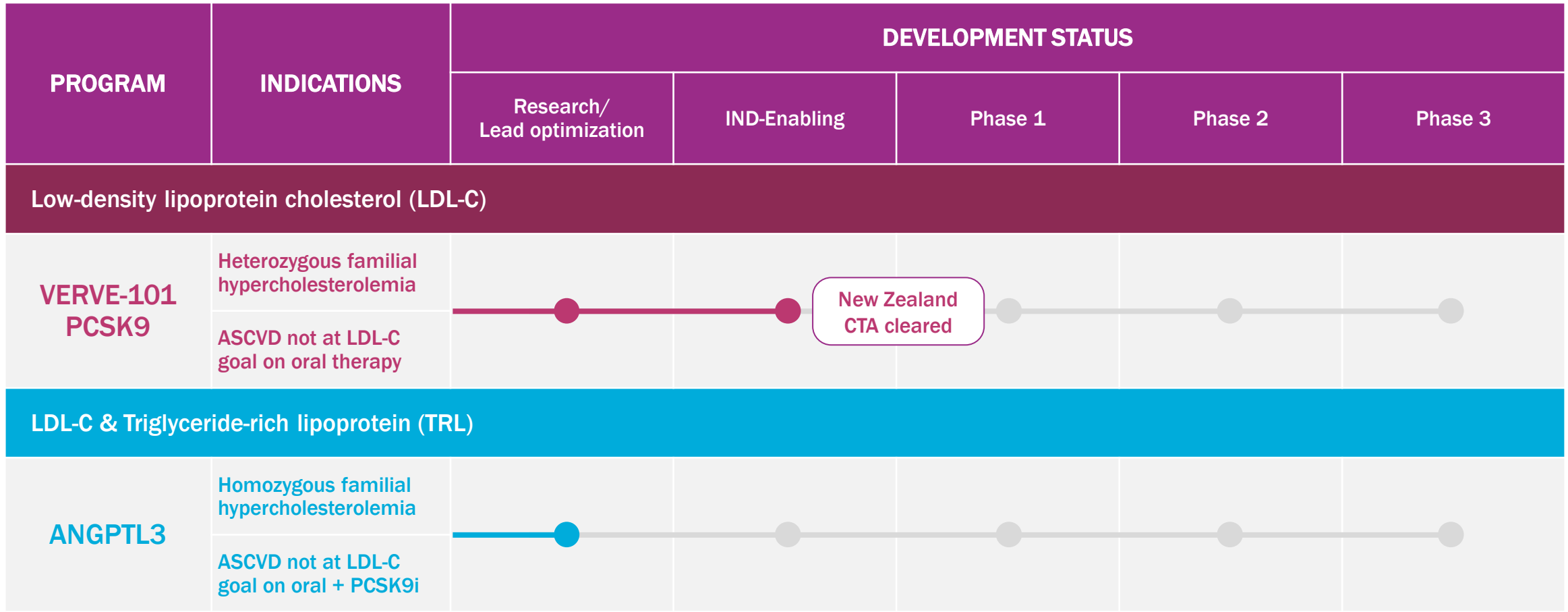

Illustrative graphic depicts the journey of a hypothetical patient with familial hypercholesterolemia who began standard-of-care treatment after suffering a heart attack at age 44

# Single-course treatment for ASCVD could address key unmet need: getting LDL-C as low as possible for as long as possible

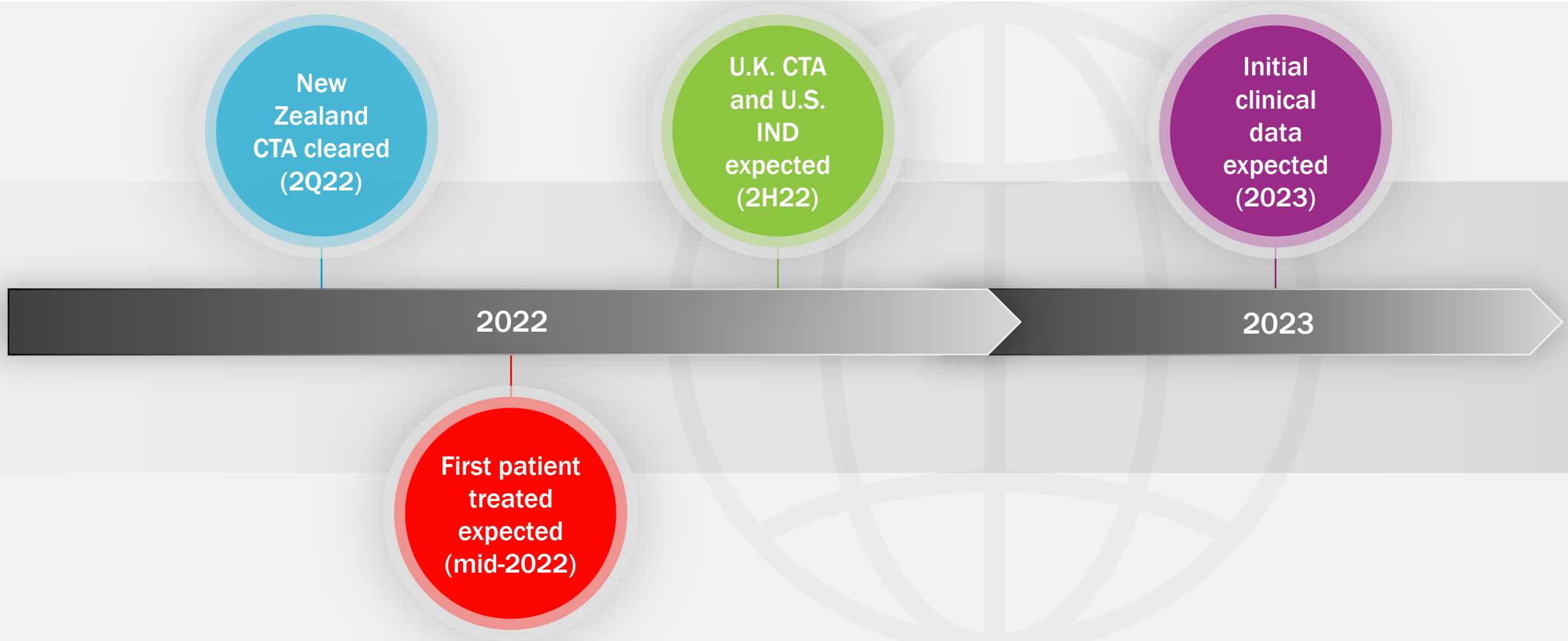



Illustrative graphic depicts the journey of a hypothetical patient with familial hypercholesterolemia who was treated with a single-course treatment after suffering a heart attack at age 44

# Advancing a pipeline of single-course *in vivo* gene editing programs to safely and durably lower LDL-C and treat ASCVD



# Global regulatory strategy: VERVE-101



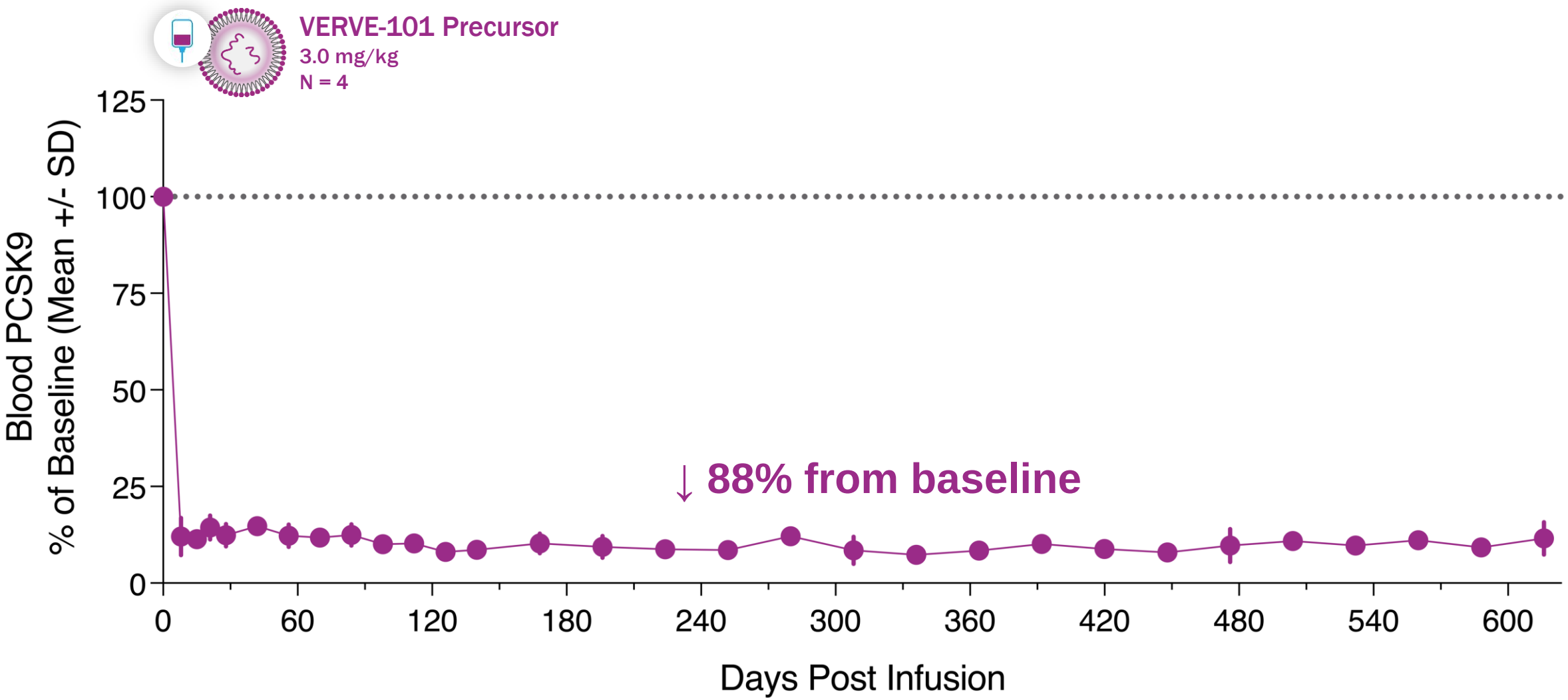
# Today sharing three new data streams

Updated durability and safety data in non-human primates for VERVE-101 precursor out to 616 days and VERVE-101 out to 1 year following infusion

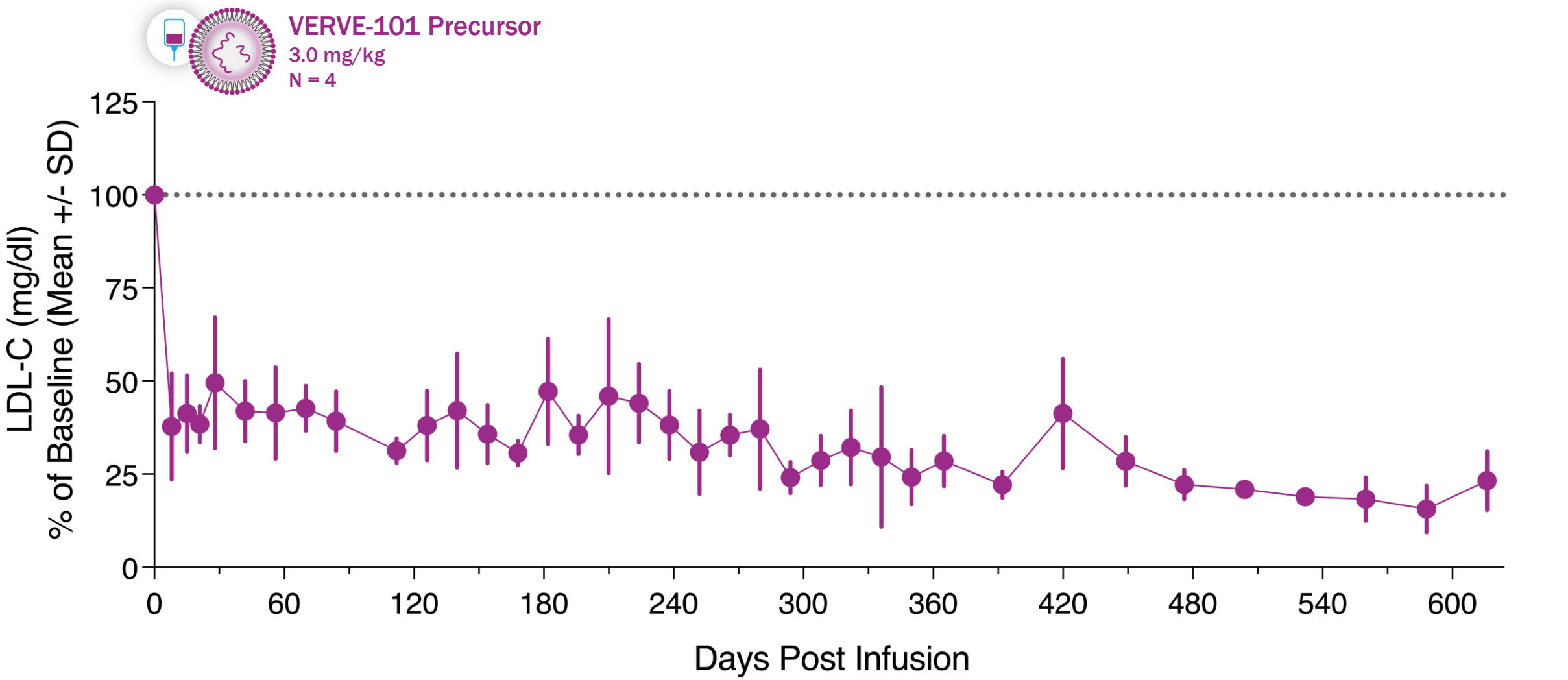
New data from VERVE-101mu GLP toxicology study in mouse heterozygous FH disease model

Enhanced potency of proprietary GalNAc-modified LNPs to deliver gene editing therapies to wild-type NHPs

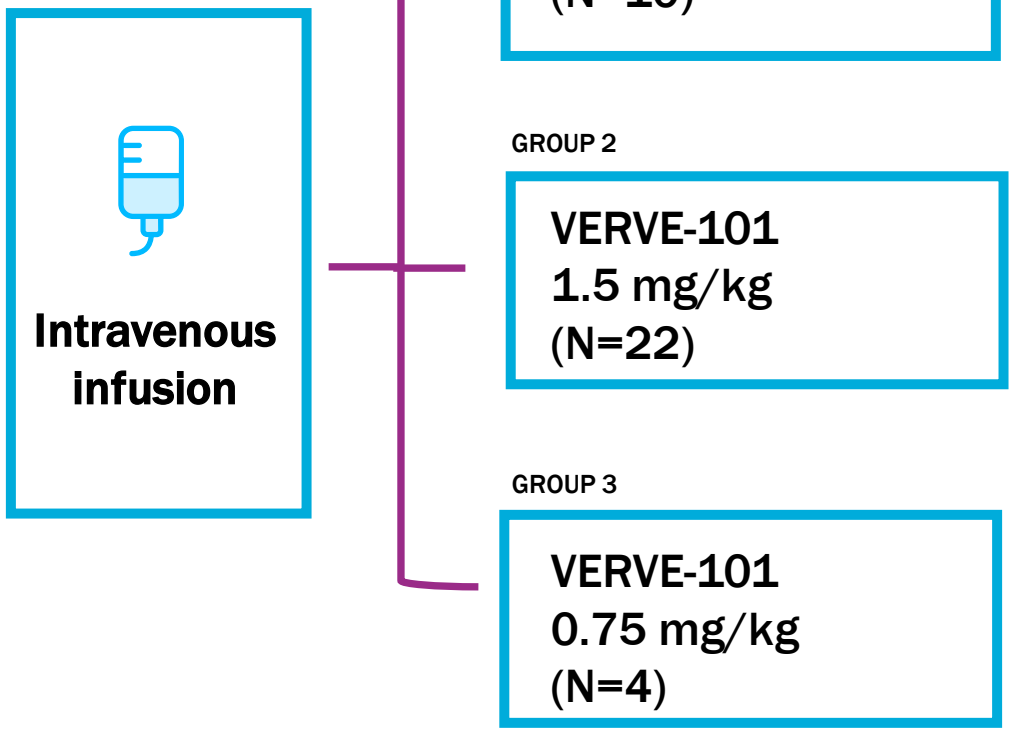
# VERVE-101 precursor given to non-human primates: 616 days following infusion, durable 88% reduction in blood PCSK9



# VERVE-101 precursor given to non-human primates: 616 days following infusion, durable >60% reduction in LDL-C

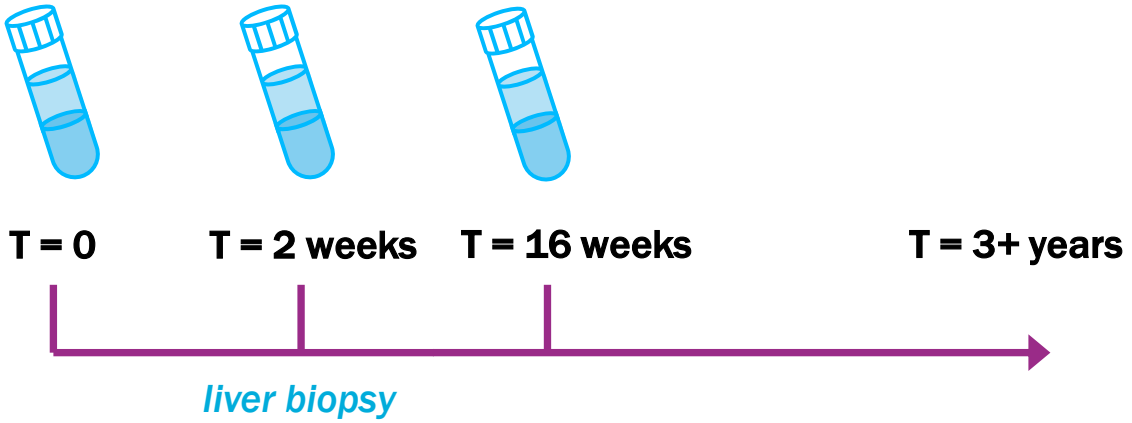


# VERVE-101 has been potent, durable, and well tolerated in NHPs




## Primary endpoints

1. Whole liver DNA editing
2. Blood PCSK9 levels
3. Blood LDL-C levels

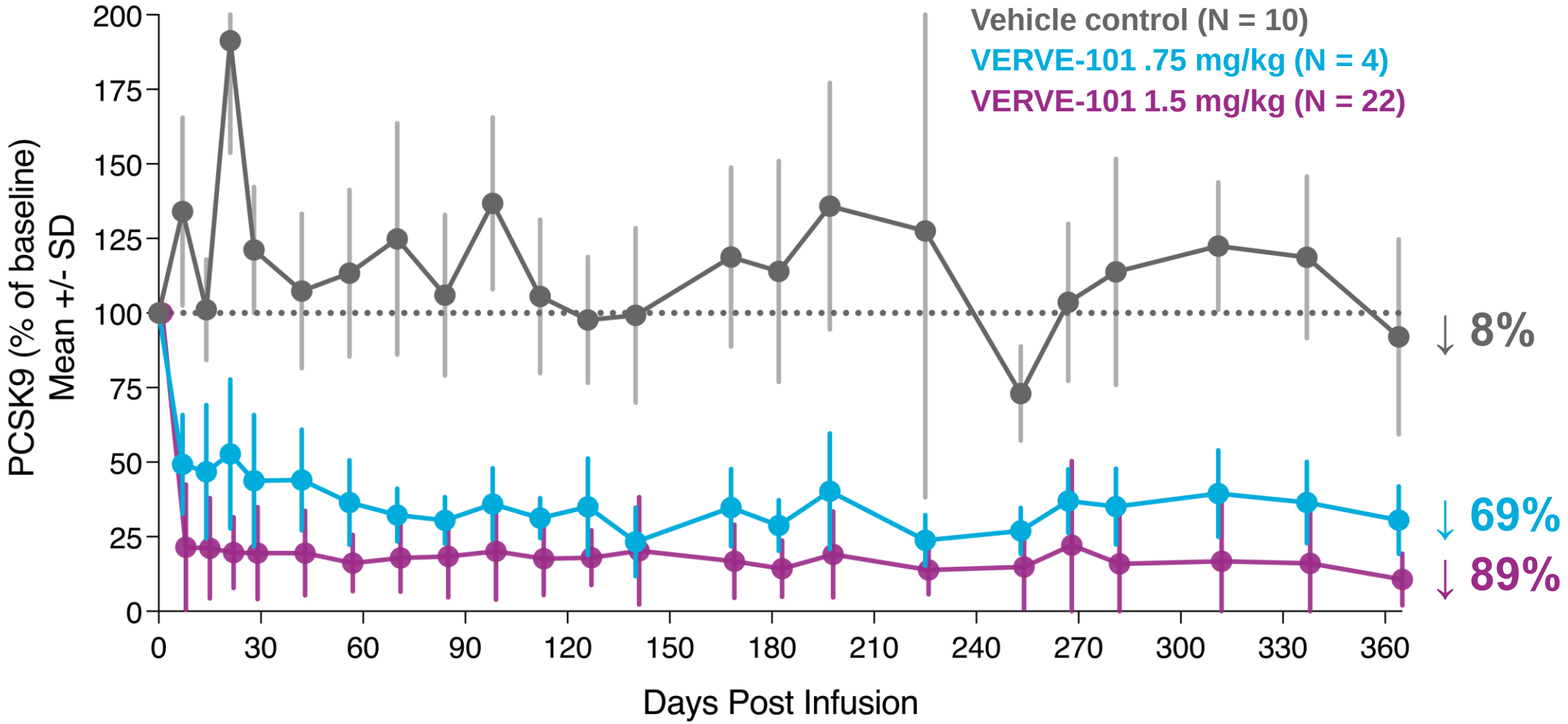



## Safety endpoints

1. Liver function testing
2. Glucose homeostasis

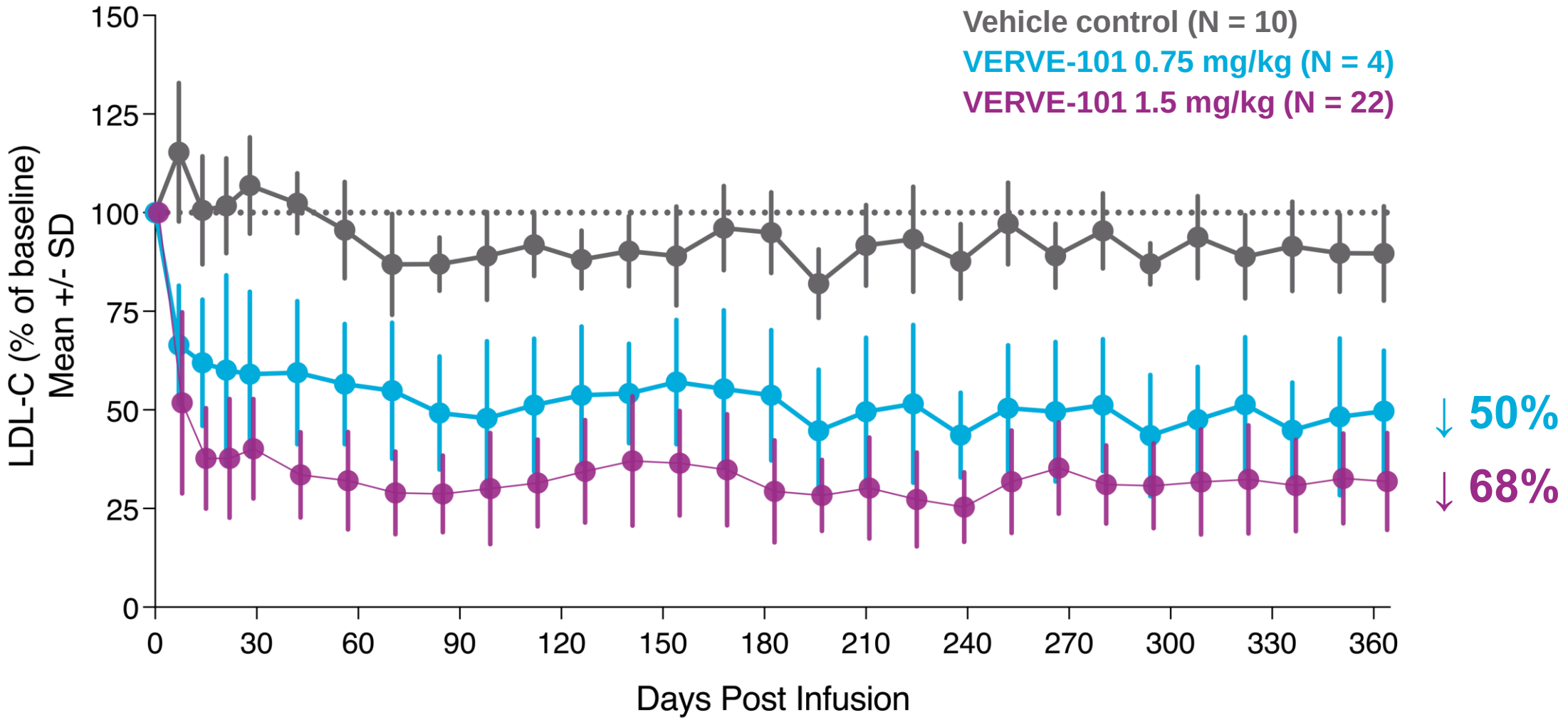
# VERVE-101: one-time intravenous infusion in non-human primates

## 89% blood PCSK9 reduction one year after therapy



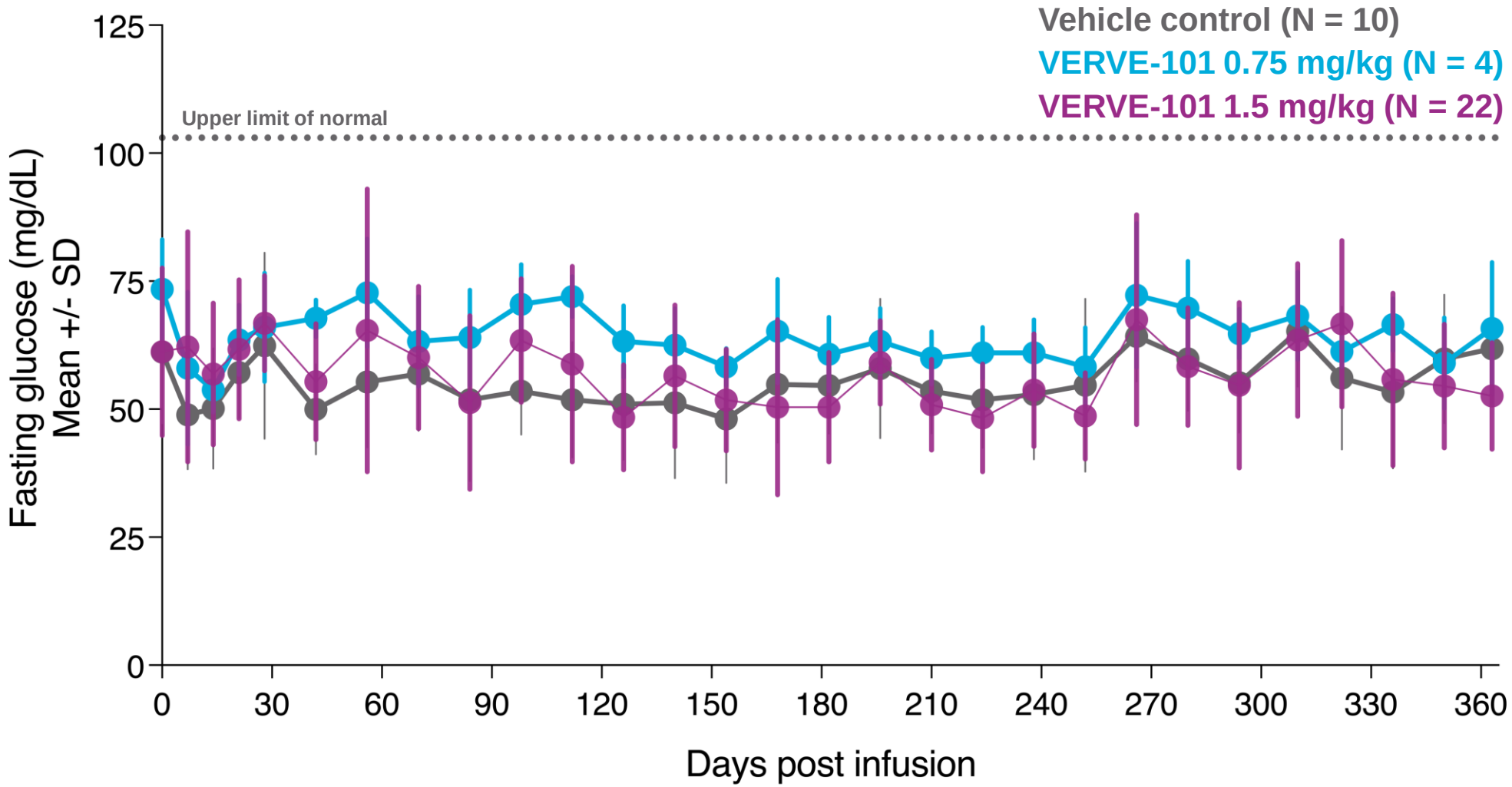
# VERVE-101: one-time intravenous infusion in non-human primates

## 68% LDL-C reduction one year after therapy

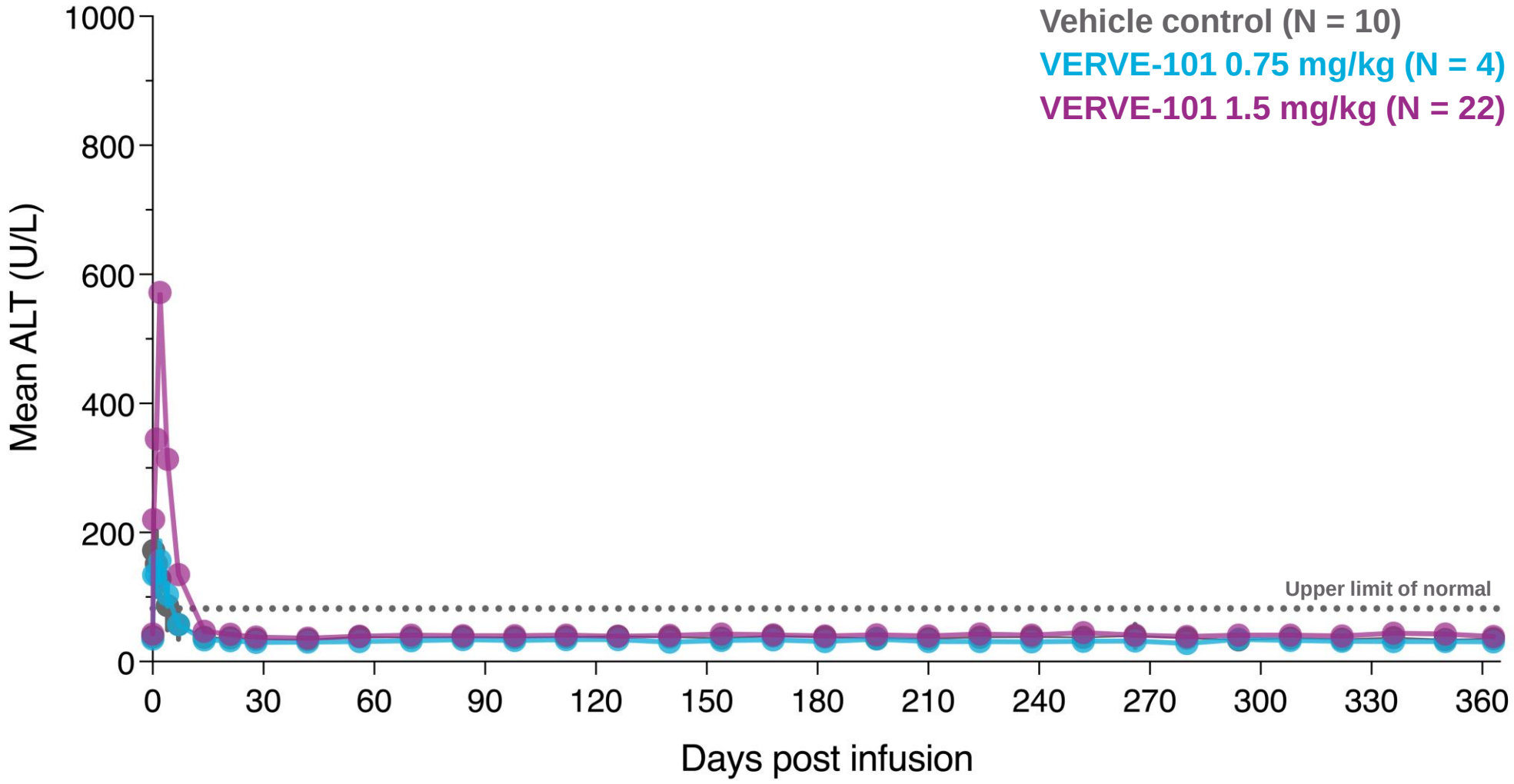


# VERVE-101: one-time intravenous infusion in non-human primates

## No impact on fasting glucose

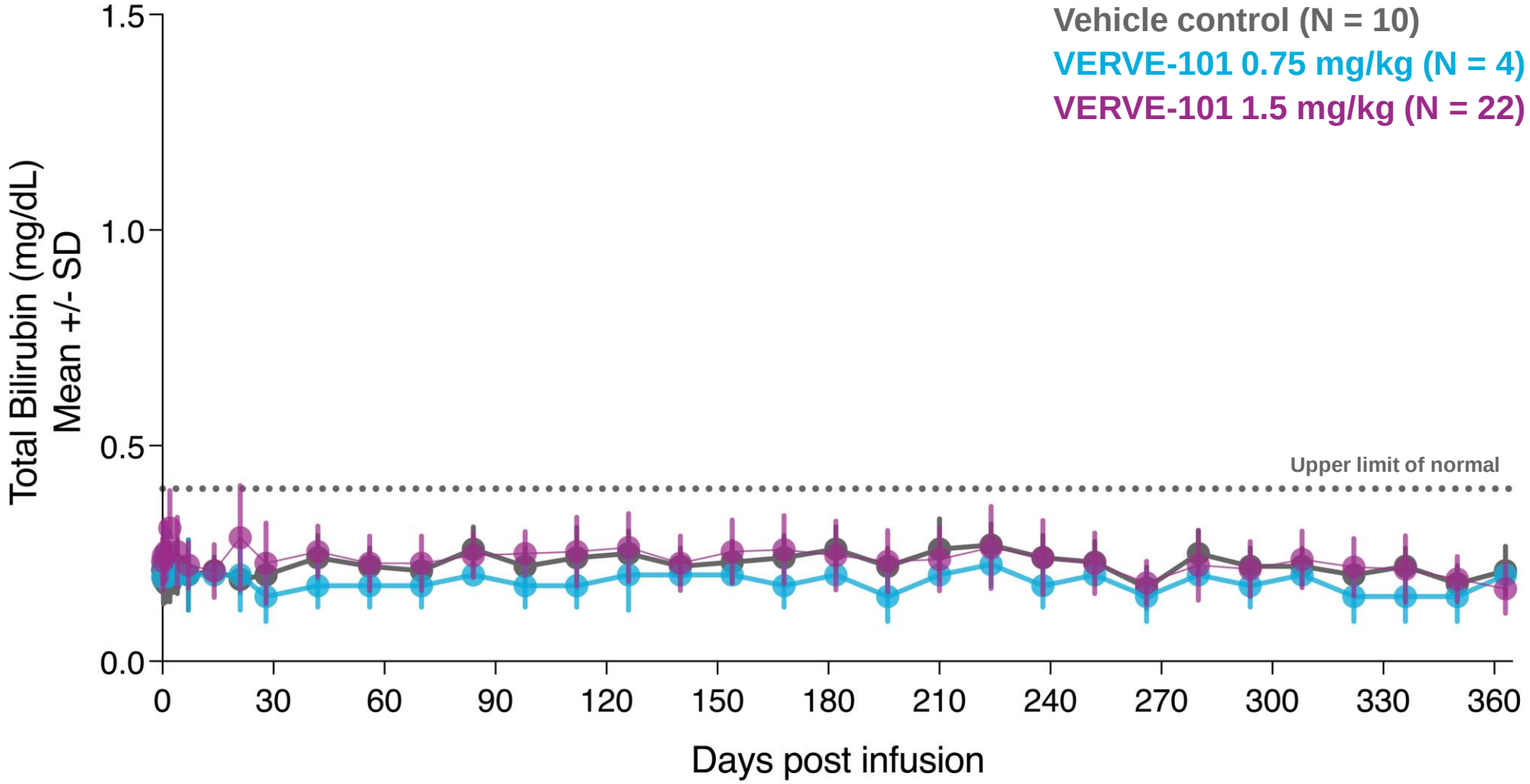


# VERVE-101: one-time intravenous infusion in non-human primates
## Transient impact on alanine aminotransferase (ALT)



# VERVE-101: one-time intravenous infusion in non-human primates

## No impact on total bilirubin



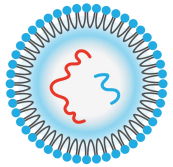
# VERVE-101mu GLP toxicity study in wild-type and HeFH mouse models

## Supports efficacy and safety

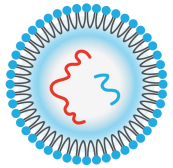
# 6-month GLP toxicity study of VERVE-101 mouse surrogate
# 528 mice: wild-type or *Ldlr*$^{+/-}$ (HeFH model)

## 100-fold dose range from 0.05 to 5 mg/kg

VERVE-101mu intravenous infusion



Wild-type mice
- Vehicle Control (N = 66)
- 0.05 mg/kg (N = 66)
- 0.5 mg/kg (N = 66)
- 5.0 mg/kg (N = 66)

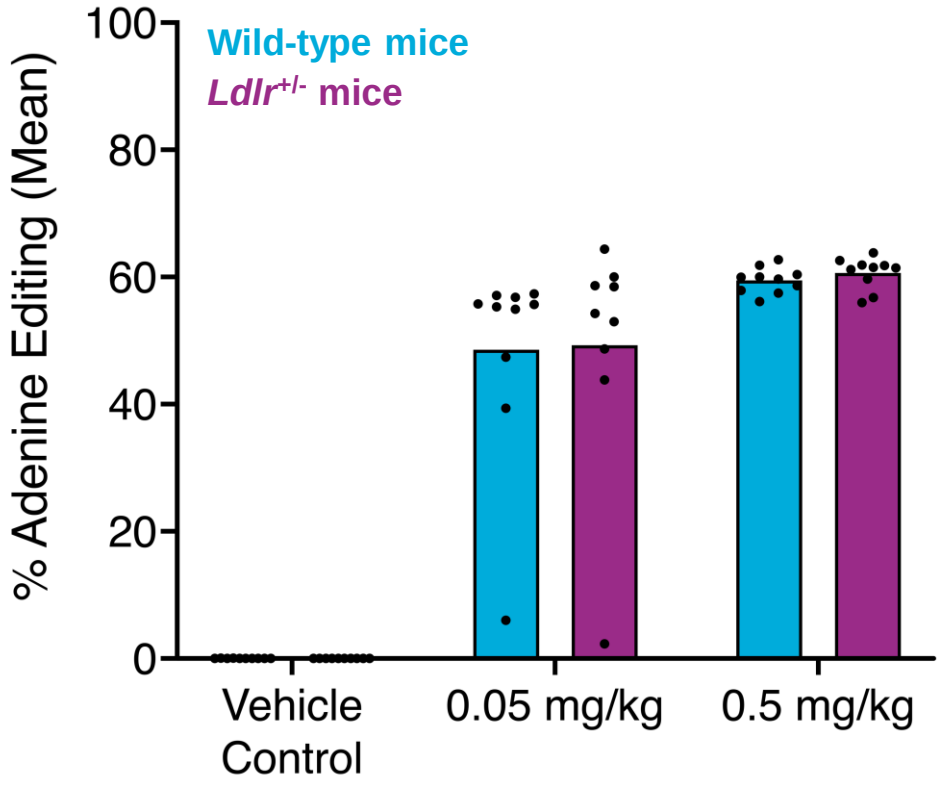


*Ldlr*$^{+/-}$ Mice (HeFH model)
- Vehicle Control (N = 66)
- 0.05 mg/kg (N = 66)
- 0.5 mg/kg (N = 66)
- 5.0 mg/kg (N = 66)

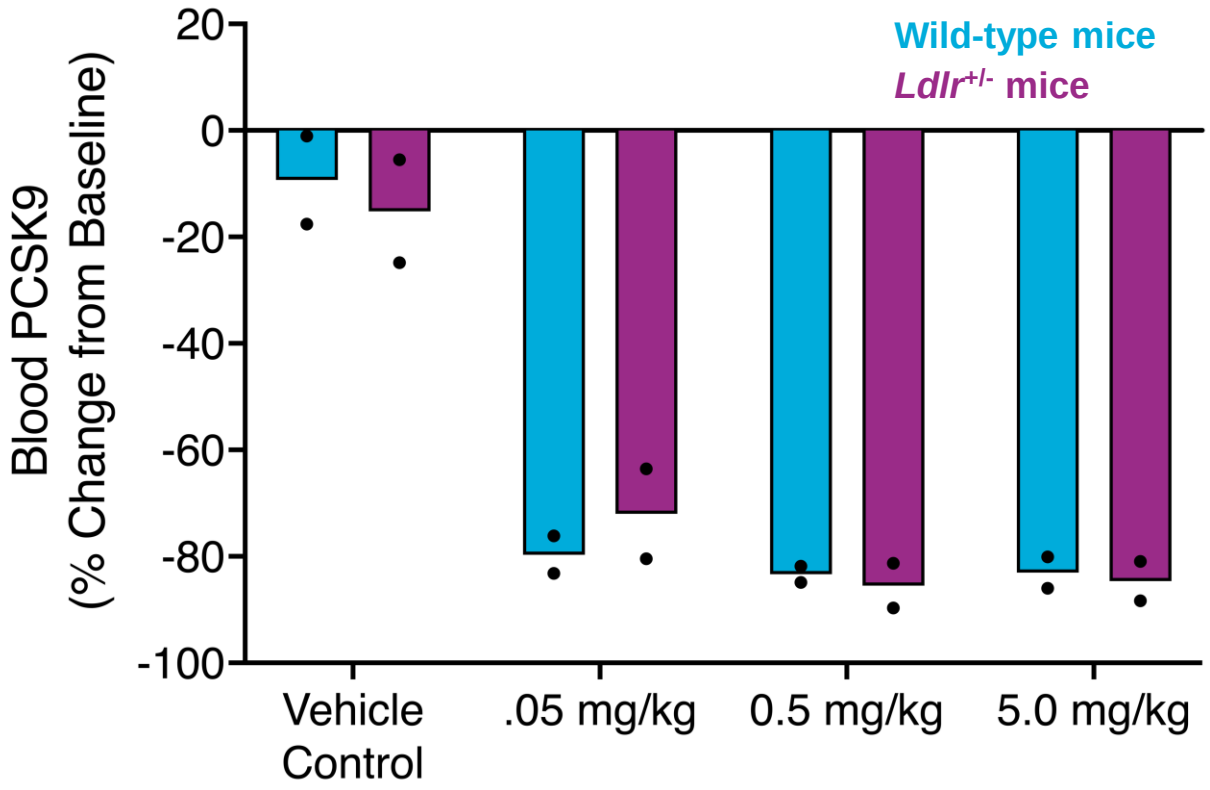
**Key endpoints:**
- PCSK9 protein and liver editing
- Clinical pathology
- Histopathology

# No observed difference in PCSK9 editing or protein reduction between wild-type and HeFH mouse models with VERVE-101mu

## Liver PCSK9 editing




## Blood PCSK9




* Outliers at 0.05 mg/kg dose being investigated

# VERVE-101: on track to treat first FH patient mid-2022

# VERVE-101: on track for clinical trial initiation in mid-2022

**~40 patients with HeFH**
LDLR mutation, ASCVD, LDL>100, not on PCSK9 Tx

## Part A: Single Ascending Dose

- High dose
- Int. dose
- Low dose
- Starting dose

n=3-6 per group
participant staggering, sentinels

## Expansion Cohorts

**Part B:** 12–20 additional participants get one selected dose

**Part C:** Second dose offered to participants in part A who received lower dose than part B


Periodic interim analyses of 3-month data expected to enable early readouts of:

- Safety and tolerability
- Blood PCSK9 reduction
- LDL-C, ApoB reduction

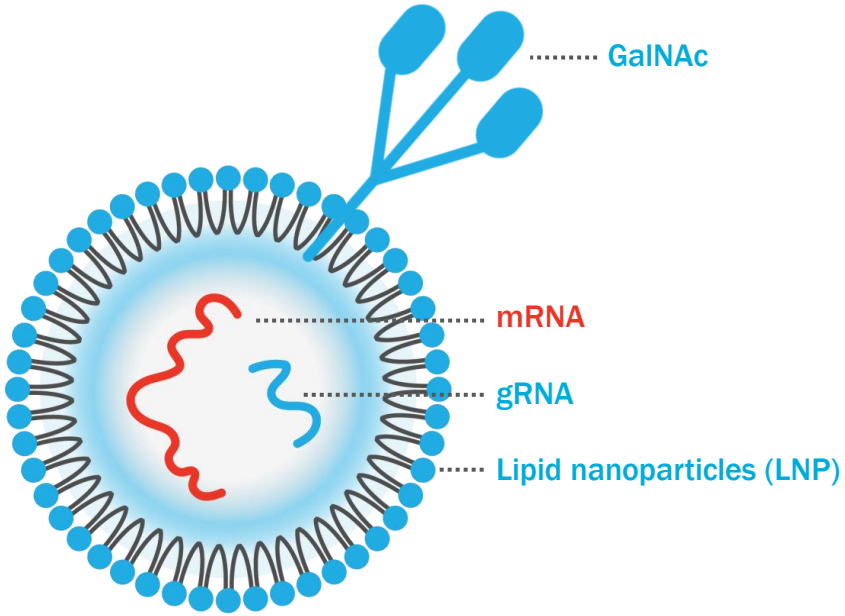
# VERVE-101 Summary: on track for clinical trial initiation in mid-2022

- **Significant unmet need** in achieving target LDL-C for patients with HeFH and ASCVD
- **Precise A-to-G edit** inactivates liver PCSK9 with a single intravenous infusion
- **Durable and potent effect** – LDL-C ↓ by 68% in non-human primates 1 year after dosing
- **Well-tolerated in mice** GLP toxicity study, across a 100-fold dosing range
- **CTA submission cleared** in New Zealand with additional global filings in process

# Innovation in delivery of *in vivo* gene-editing products

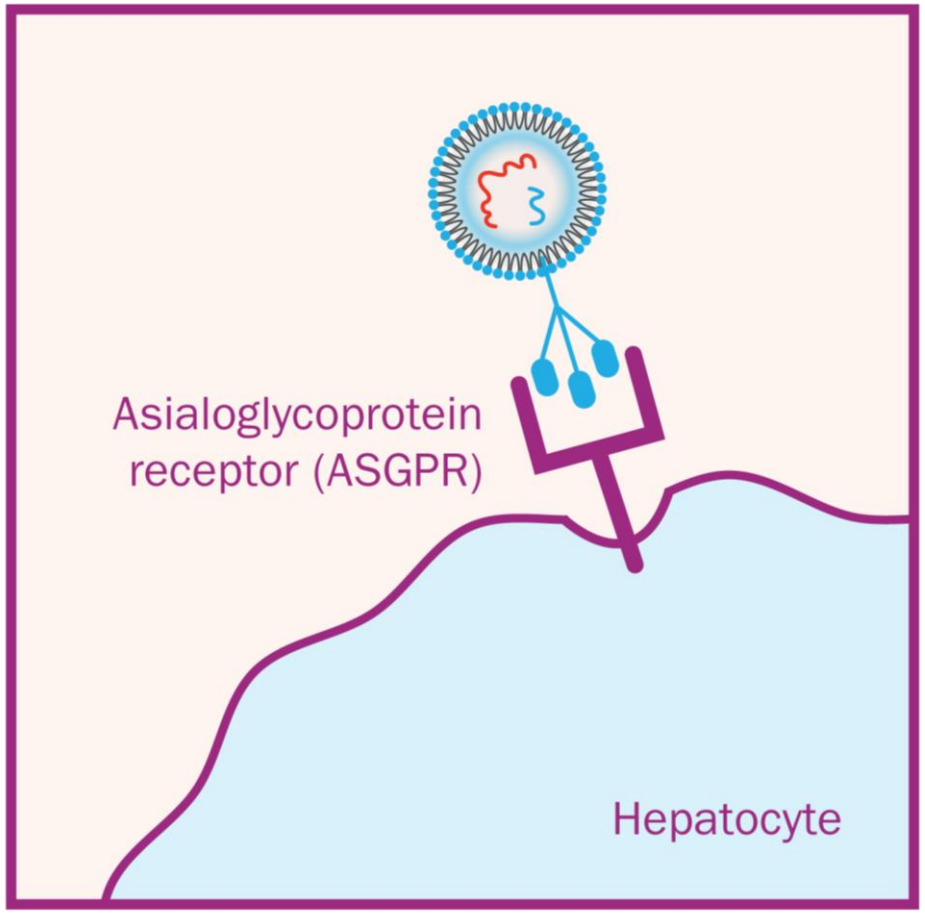
## standard LNPs have limited uptake in HoFH models

# Verve solution: addition of proprietary GalNAc targeting ligand to LNP allows delivery through ASGPR



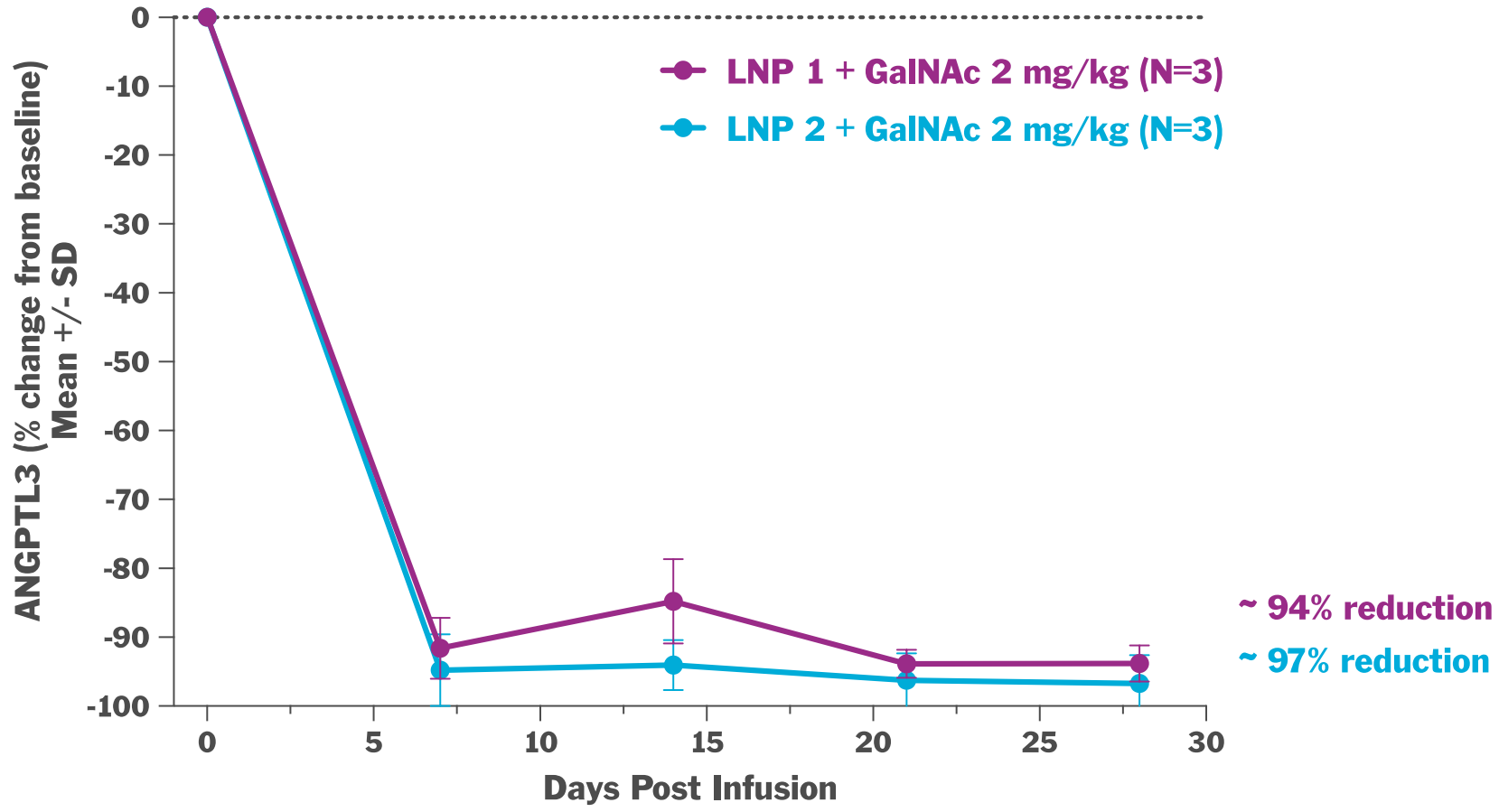

United States Patent
Rajeev et al.

Patent No.: US 11,207,416 B2
Date of Patent: Dec. 28, 2021



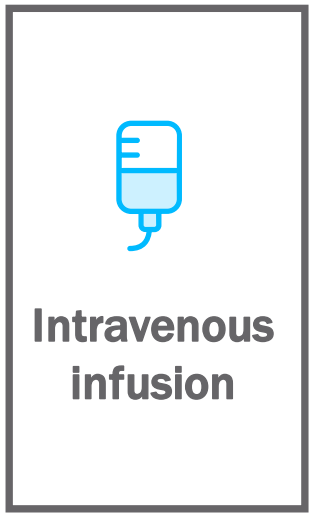
# Base editing of ANGPTL3 via GalNAc-LNPs reduced blood ANGPTL3 by 94% - 97% in NHP model of HoFH

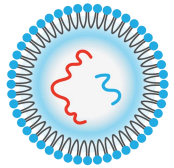
GalNAc LNPs (encapsulating ABE-ANGPTL3 base editing payload) dosed to HoFH NHPs that have stable disruption of liver LDLR protein and markedly elevated LDL-C



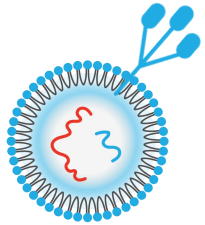
# How do GalNAc-LNPs perform in wild-type NHP?

## Dose ranging study of ANGPTL3 precursor in NHP



**Standard LNP**
- 0.75 mg/kg (N = 3)
- 1.5 mg/kg (N = 3)
- 3.0 mg/kg (N = 3)

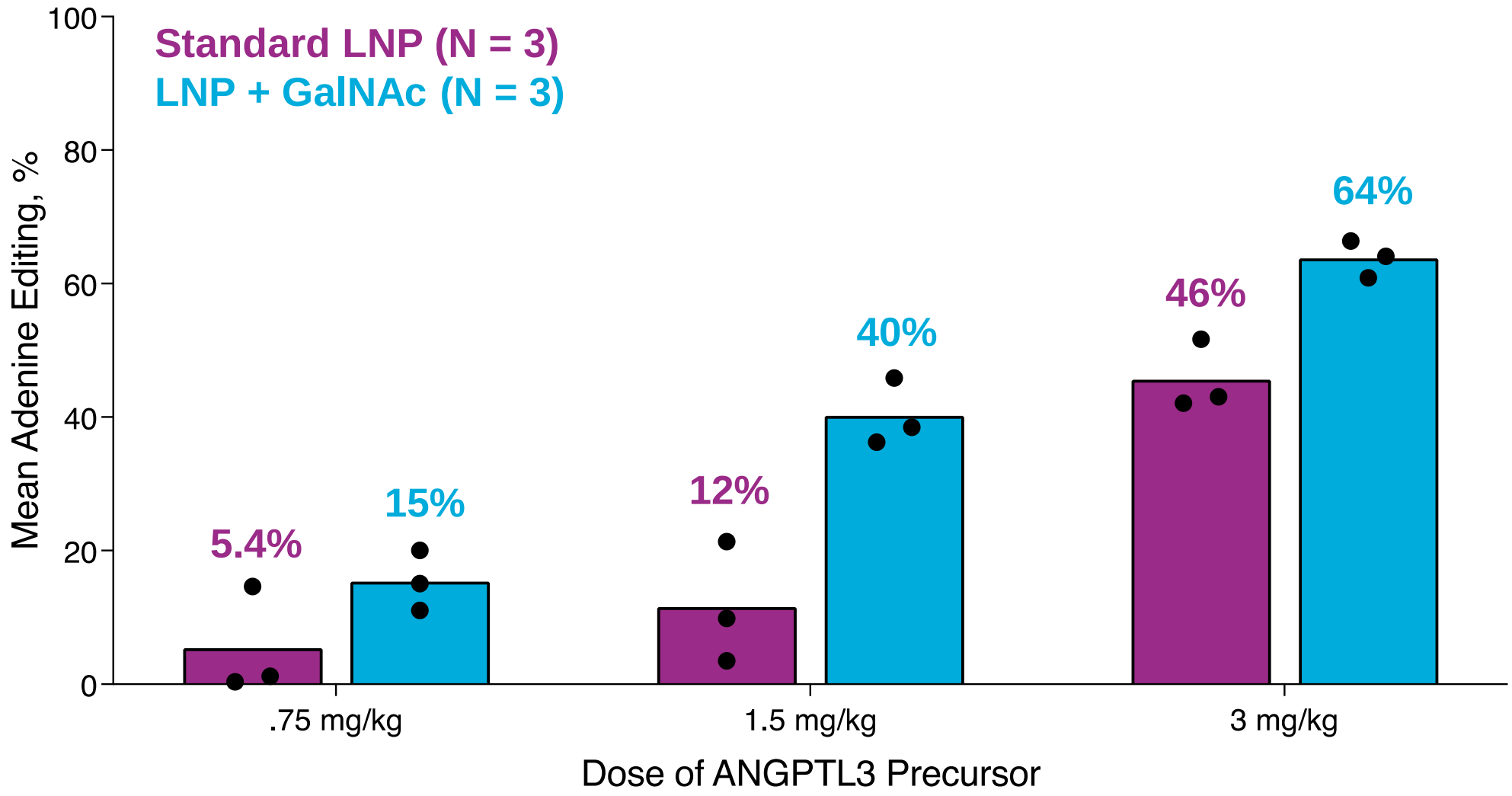


**LNP + GalNAc**
- 0.75 mg/kg (N = 3)
- 1.5 mg/kg (N = 3)
- 3.0 mg/kg (N = 3)

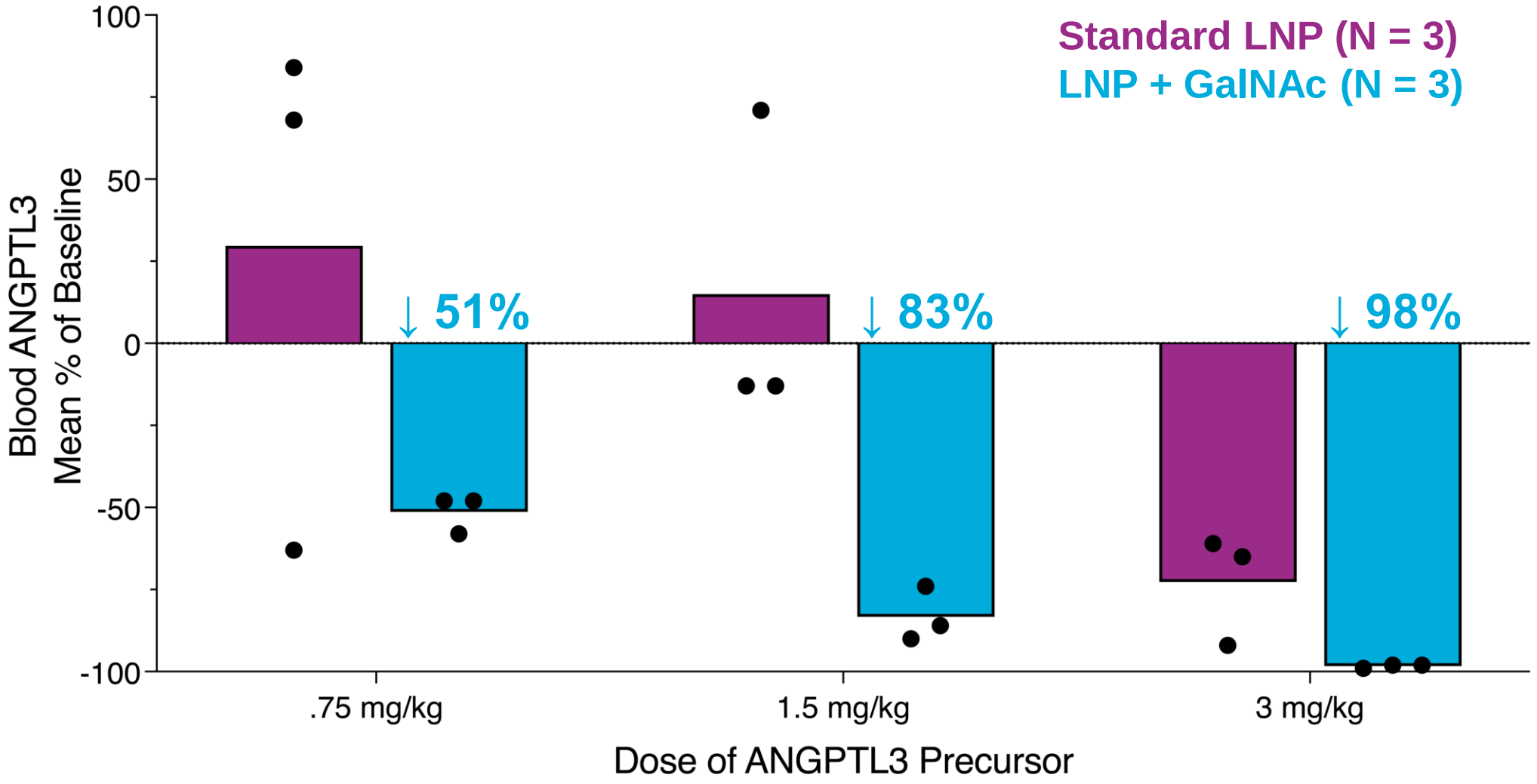
LNPs are identical other than the addition of GalNAc-lipid

**Key endpoints at Day 15 necropsy**
- Liver ANGPTL3 editing
- Blood ANGPTL3 protein level
- Biodistribution

# In wild-type NHPs, GalNAc-LNP leads to increased ANGPTL3 editing potency compared with standard LNP



# In wild-type NHPs, GalNAc-LNP shows up to 98% reduction in blood ANGPTL3, reflecting improved consistency versus standard LNP

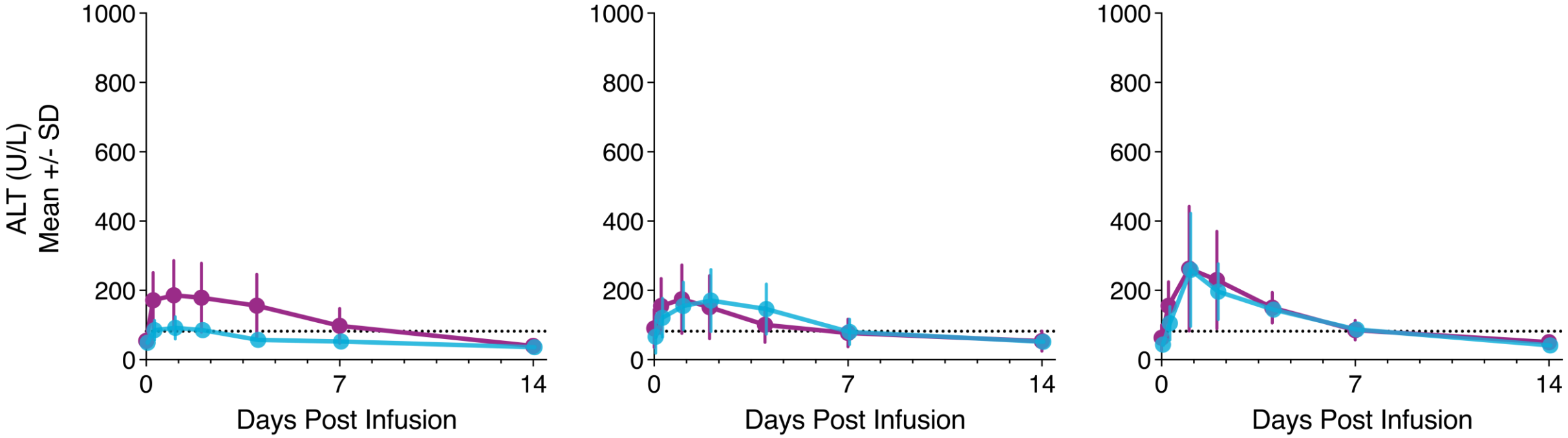


# Addition of GalNAc to LNP did not alter safety profile
## Transient impact on alanine aminotransferase

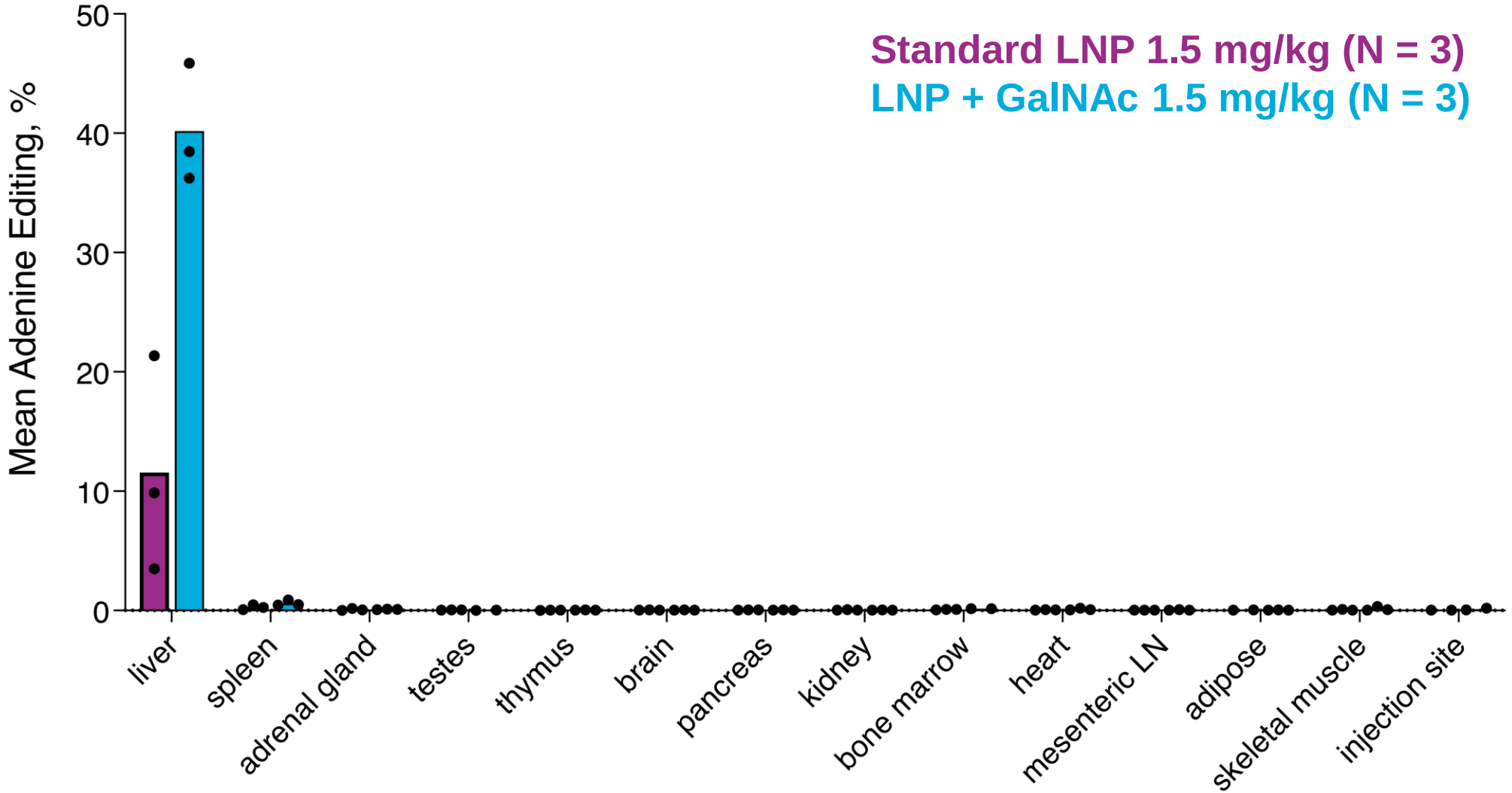
**Standard LNP 0.75 mg/kg (N = 3)**
**LNP + GalNAc 0.75 mg/kg (N = 3)**

**1.5 mg/kg (N = 3)**
**1.5 mg/kg (N = 3)**

**3.0 mg/kg (N = 3)**
**3.0 mg/kg (N = 3)**



# Specific delivery to the liver with LNP + GalNAc



# Proprietary GalNAc-LNPs are a potentially best-in-class technology to deliver genetic medicines to the liver

**DESIGNED TO**

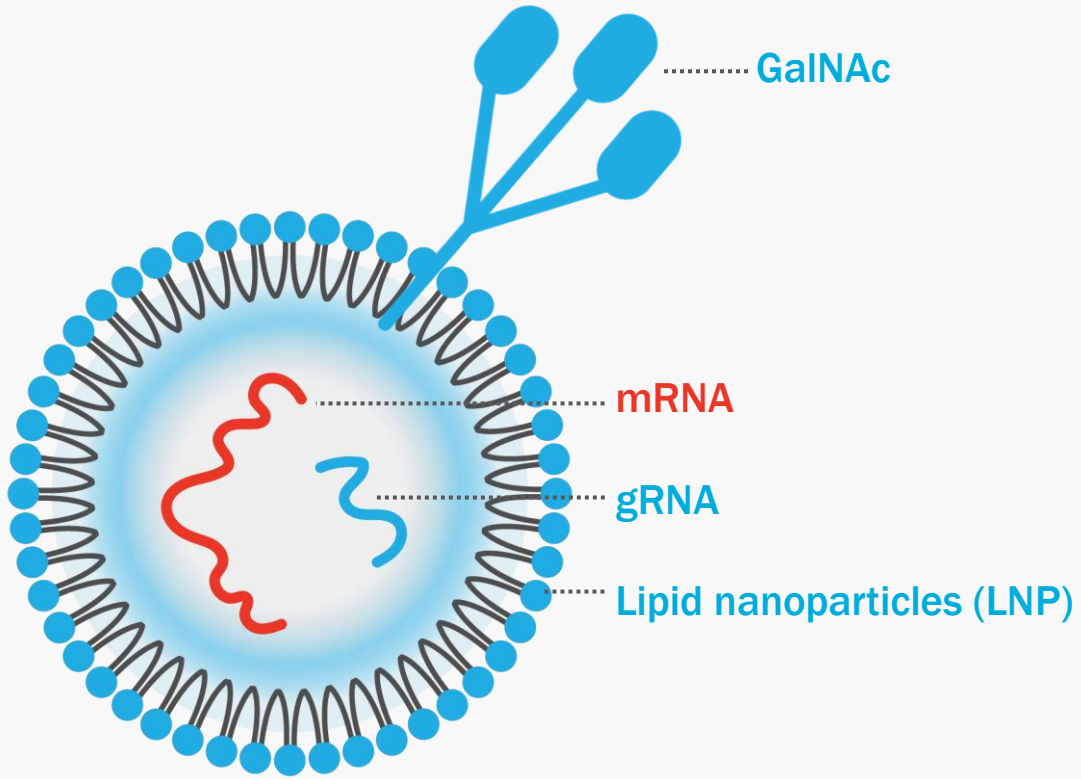
bypass LDLR for HoFH patient population

**OBSERVED TO BE**

Potent in wild-type NHPs

Consistent

Liver-specific ASGPR uptake



# Conclusion #1: VERVE-101 first-in-human dosing on track for mid-2022
# Conclusion #2: Growing proprietary tool kit for therapeutic delivery

VERVE-101 reduced blood PCSK9 up to 89% and LDL-C up to 68% in non-human primates one year following infusion

Mouse surrogate of VERVE-101 achieves efficient editing of *Pcsk9* and is well-tolerated in both wild-type and HeFH mouse models

Proprietary Verve LNPs enable delivery of ANGPTL3 precursor in HoFH NHP model, with new evidence of enhanced potency in wild-type NHPs as well

Verve is on track to deliver on key milestones of first-in-human dosing of VERVE-101 and announcement of ANGPTL3 drug candidate in 2022