# Verve Therapeutics

## Disrupting the Care of Cardiovascular Disease through Single-course Gene Editing Medicines

January 2022

# Forward looking statements

This presentation contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995 that involve substantial risks and uncertainties, including statements regarding the initiation, and timing, of the Company’s planned regulatory submissions, future clinical trials, its research and development plans and the potential advantages and therapeutic potential of the Company’s programs. All statements, other than statements of historical facts, contained in this presentation, including statements regarding the Company’s strategy, future operations, future financial position, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “should,” “target,” “will,” “would” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements are based on management’s current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in, or implied by, such forward-looking statements. These risks and uncertainties include, but are not limited to, risks associated with the Company’s limited operating history; the timing of and the Company’s ability to submit applications for, and obtain and maintain regulatory approvals for, its product candidates; continue to advance its product candidates in clinical trials; initiate and enroll clinical trials on the timeline expected or at all; correctly estimate the potential patient population and/or market for the Company’s product candidates; replicate in clinical trials positive results found in preclinical studies and/or earlier-stage clinical trials of VERVE-101 and its other product candidates; advance the development of its product candidates under the timelines it anticipates in current and future clinical trials; obtain, maintain or protect intellectual property rights related to its product candidates; manage expenses; and raise the substantial additional capital needed to achieve its business objectives. For a discussion of other risks and uncertainties, and other important factors, any of which could cause the Company’s actual results to differ from those contained in the forward-looking statements, see the “Risk Factors” section, as well as discussions of potential risks, uncertainties and other important factors, in the Company’s most recent filings with the Securities and Exchange Commission. In addition, the forward-looking statements included in this presentation represent the Company’s views as of the date hereof and should not be relied upon as representing the Company’s views as of any date subsequent to the date hereof. The Company anticipates that subsequent events and developments will cause the Company’s views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, the Company specifically disclaims any obligation to do so.

# Atherosclerotic cardiovascular disease (ASCVD): blood low-density lipoprotein cholesterol (LDL-C) clogging heart arteries

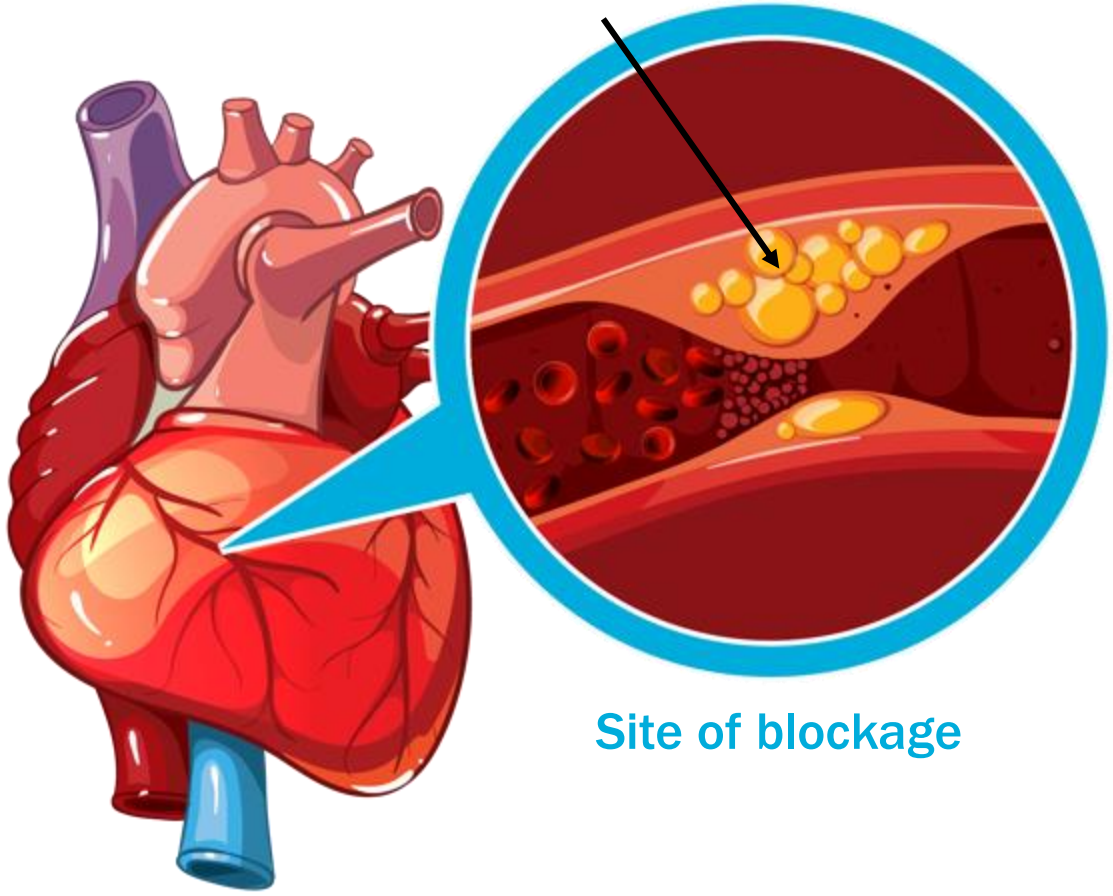
#1 cause of death worldwide

100s of millions of patients worldwide

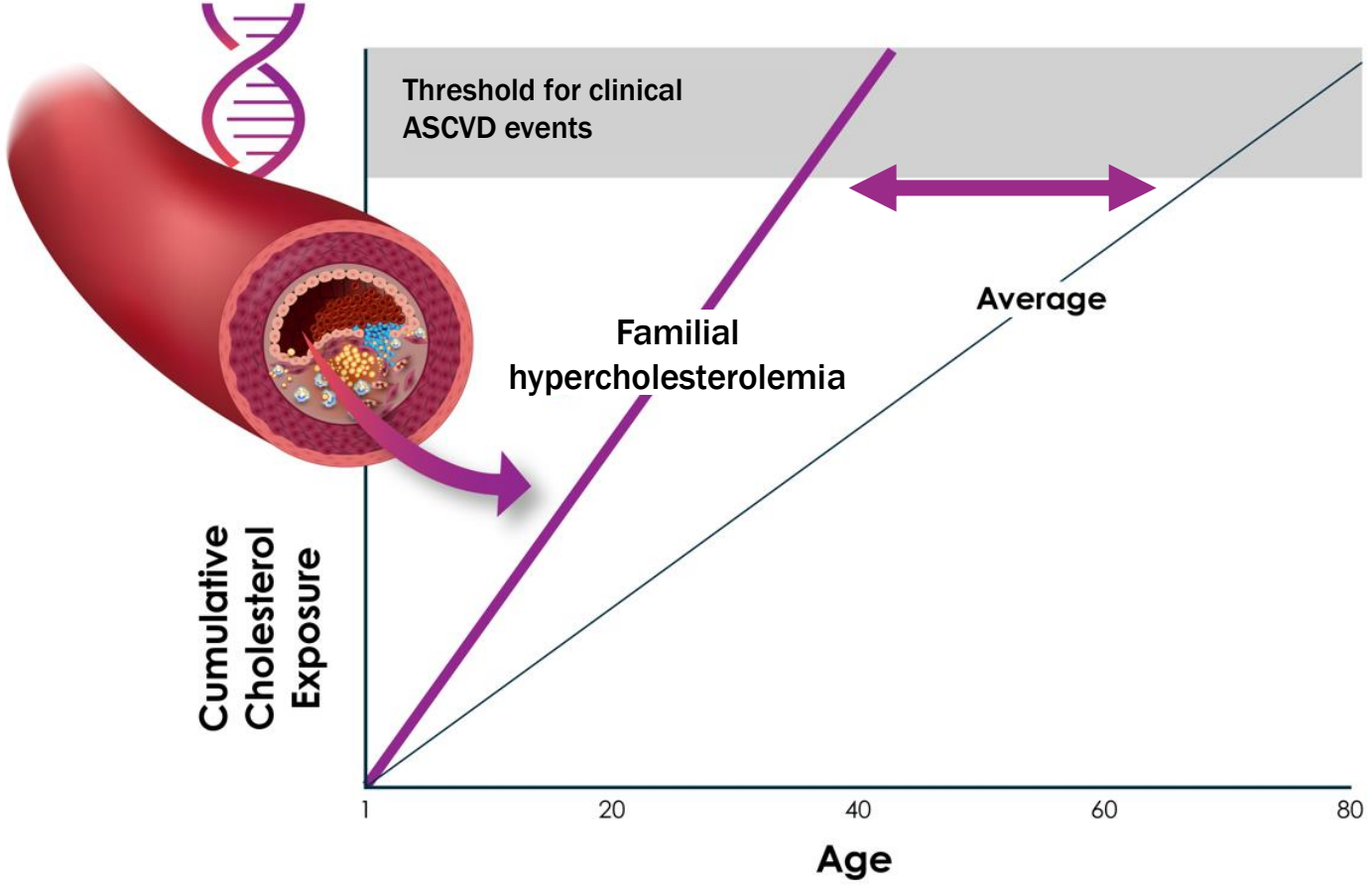
31M with genetic form of ASCVD:

familial hypercholesterolemia (FH)

- *Heterozygous FH (HeFH; 1 in 250)
- *Homozygous FH (HoFH; 1 in 250,000)

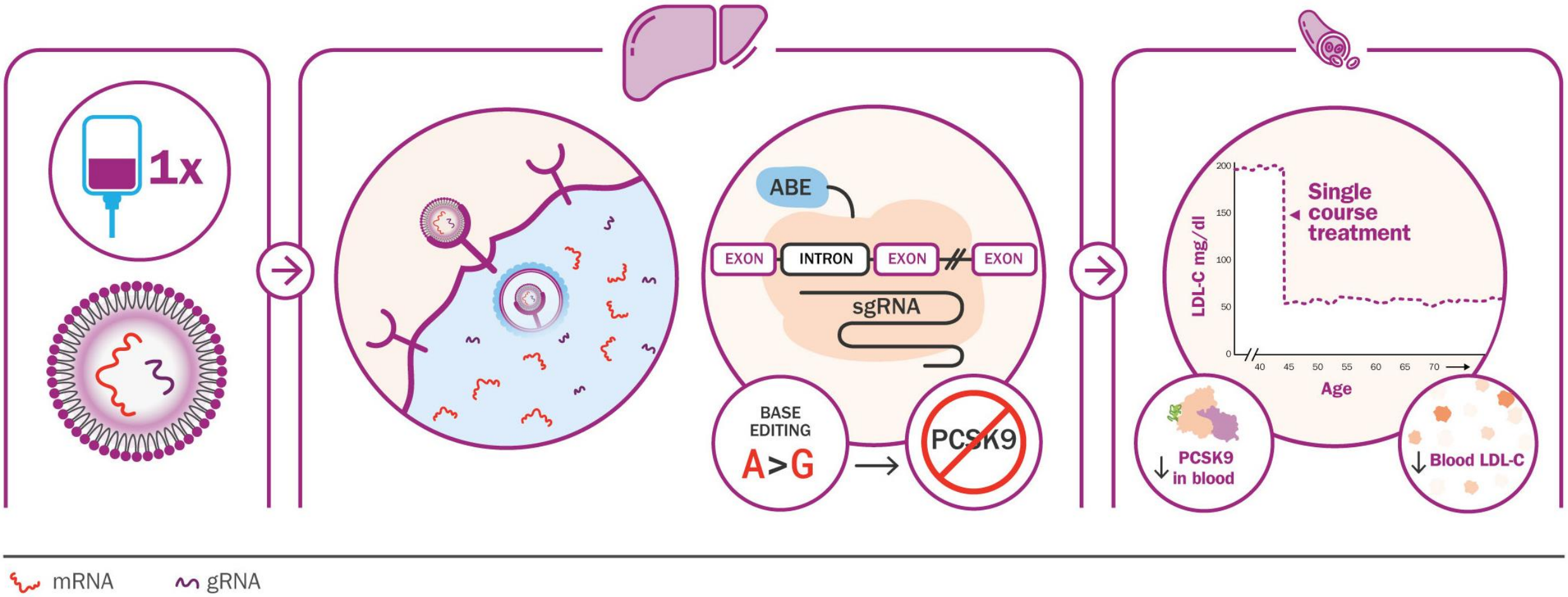


# High cumulative life-long exposure to blood LDL-C established as a root cause of ASCVD




*Adapted from Horton et al. J Lipid Res., 2009*

# Goal: single course gene editing medicines to durably lower LDL-C and treat ASCVD




mRNA gRNA

# Core capabilities to develop *in vivo* liver gene editing medicines

Internally developed novel lipid nanoparticles (LNPs)

Guide RNA design and purification

mRNA design, purification, and GMP production


Comprehensive off-target optimization

Rigorous execution of rodent and non-human primate (NHP) studies to evaluate and optimize all components for *in vivo* editing efficacy and safety endpoints aligned with regulatory expectations

# Lead programs target PCSK9 and ANGPTL3 genes

| PROGRAM | INITIAL INDICATION | DEVELOPMENT STATUS | | | |
|---|---|---|---|---|---|
| | | Research/ Lead optimization | IND-Enabling | Clinical | Upcoming Milestones |
| **Low-density lipoprotein cholesterol (LDL-C)** | | | | | |
| **VERVE-101**<br>**ABE-PCSK9** | Heterozygous familial hypercholesterolemia | → | | | • Preclinical data in NHPs (1H 2022)<br>• Regulatory submissions (2H 2022)<br>• First patient treated (2H 2022) |
| **LDL-C and triglyceride-rich lipoprotein (TRL)** | | | | | |
| **ANGPTL3** | Familial hypercholesterolemia | → | | | • Preclinical data in NHPs (1H 2022)<br>• Lead candidate selection (2H 2022)<br>• Begin IND-enabling studies (2H 2022) |

# 2021 was a momentous year

## MILESTONES

### Q1

- ✓ Series B ($94M raise)
- ✓ VERVE-101 selected as lead candidate

### Q2

- ✓ IPO raised $307M

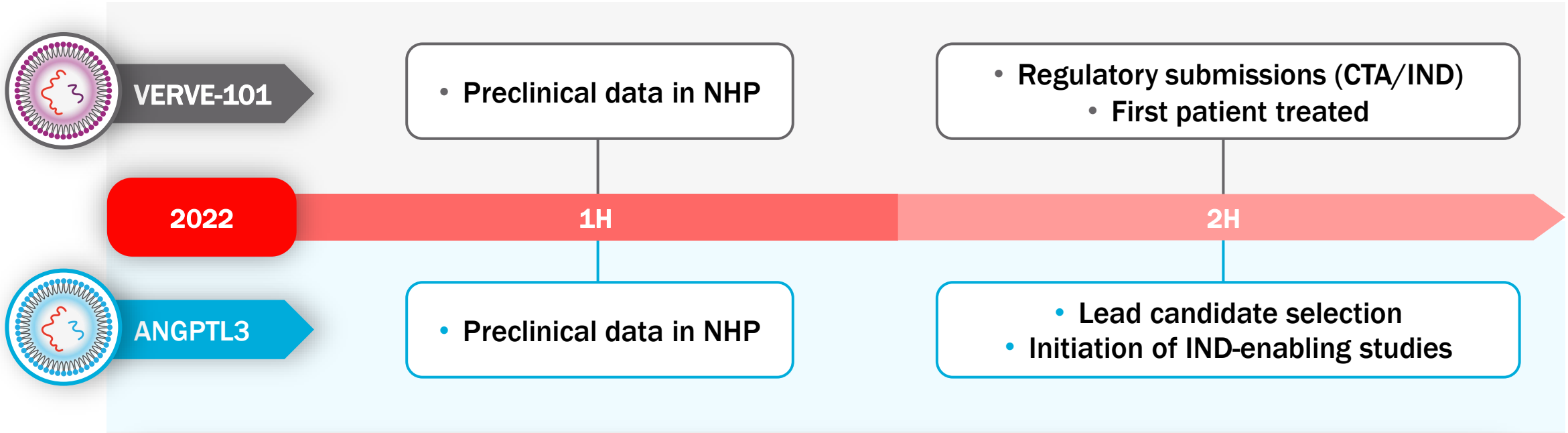
### Q3

- ✓ IND-enabling studies: VERVE-101 is potent & durable in NHPs
- ✓ Development of proprietary Gal-NAc LNP delivery system

### Q4

- ✓ Gal-NAc LNP effective in NHP model of homozygous FH
- ✓ ANGPTL3 program: >90% lower plasma ANGPTL3 protein

# 2022 milestones set the stage for a transformative year




**Ongoing activities throughout 2022 expected to drive value**

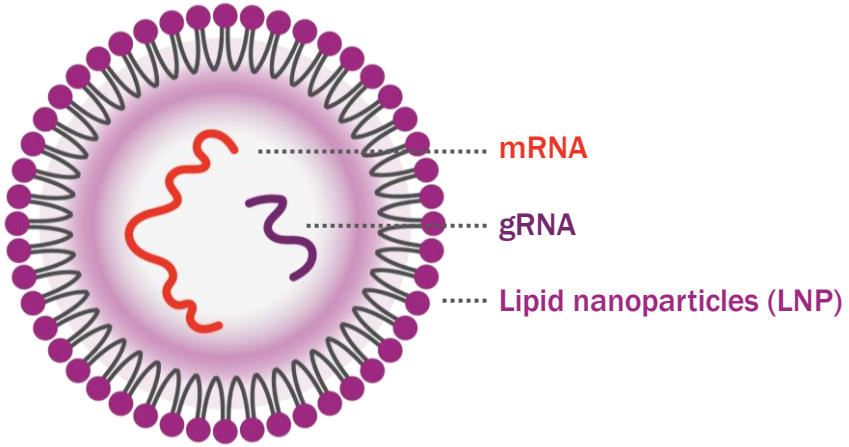
**Present and publish data** positioning Verve's leading programs and platform

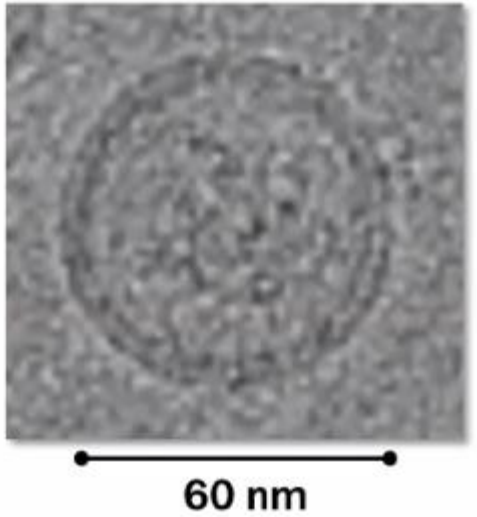
**Establish GalNAc-LNP proprietary delivery system** as a leading platform and leverage its value

**Strengthen world-class team** focused on single-course gene editing medicines for cardiovascular disease

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

# VERVE-101: an optimized adenine base editor (ABE) mRNA + gRNA packaged in a LNP; edit designed to turn off the PCSK9 gene



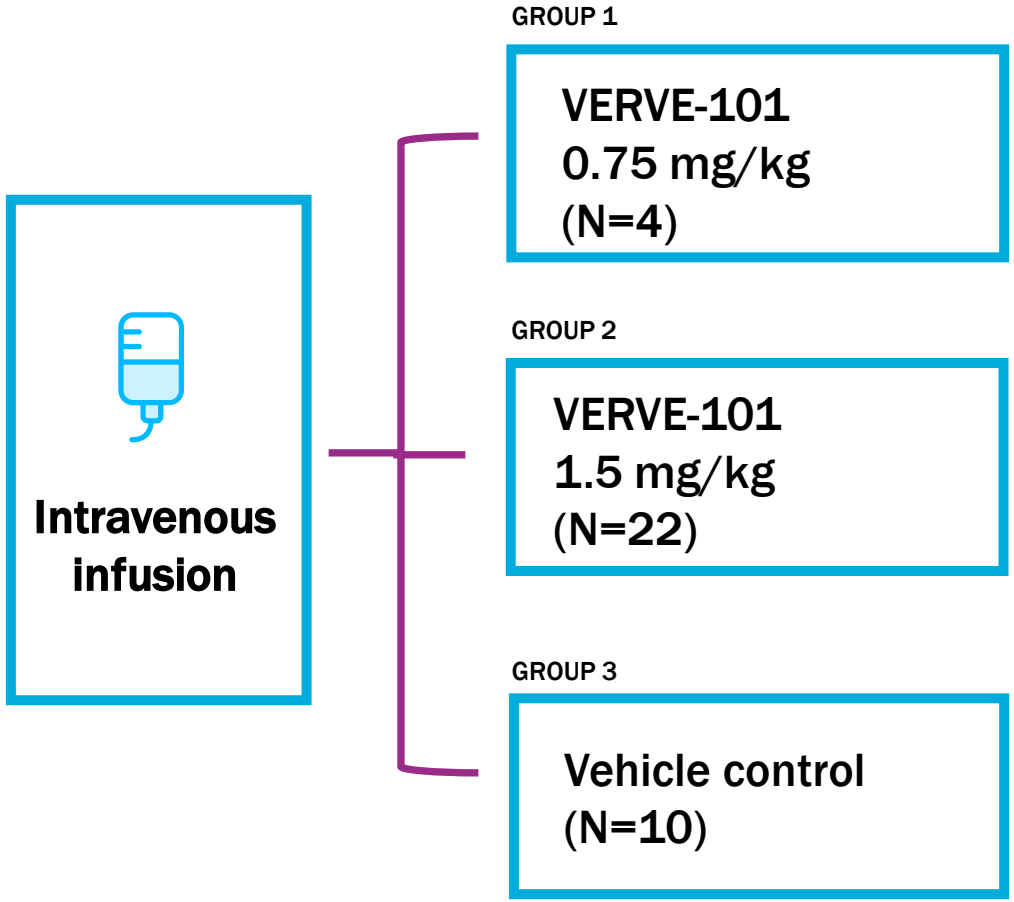

**Base editing induces single base pair change from A-to-G in PCSK9 gene**

LNP licensed from Acuitas Therapeutics
Exclusive access to base editing through Beam Therapeutics

# An extensive IND-enabling program for VERVE-101 is underway and on track for completion in 1H 2022

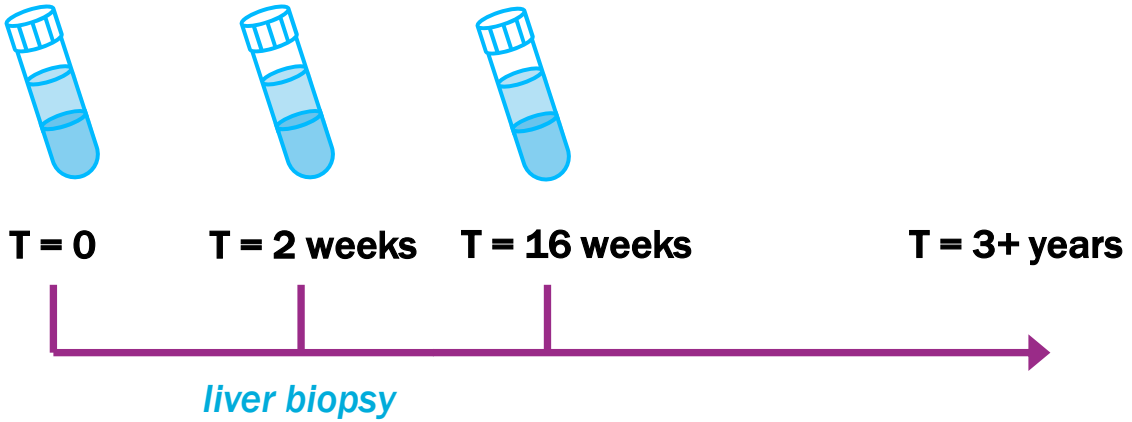
- GLP toxicology study in heterozygous FH mouse disease model
- Durability study in NHP using VERVE-101 drug product
- Studies to demonstrate the absence of germline editing
- Durability study following partial hepatectomy in mouse
- Off-target evaluations to >3000 candidate sites & in multiple cell types

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




## Primary endpoints

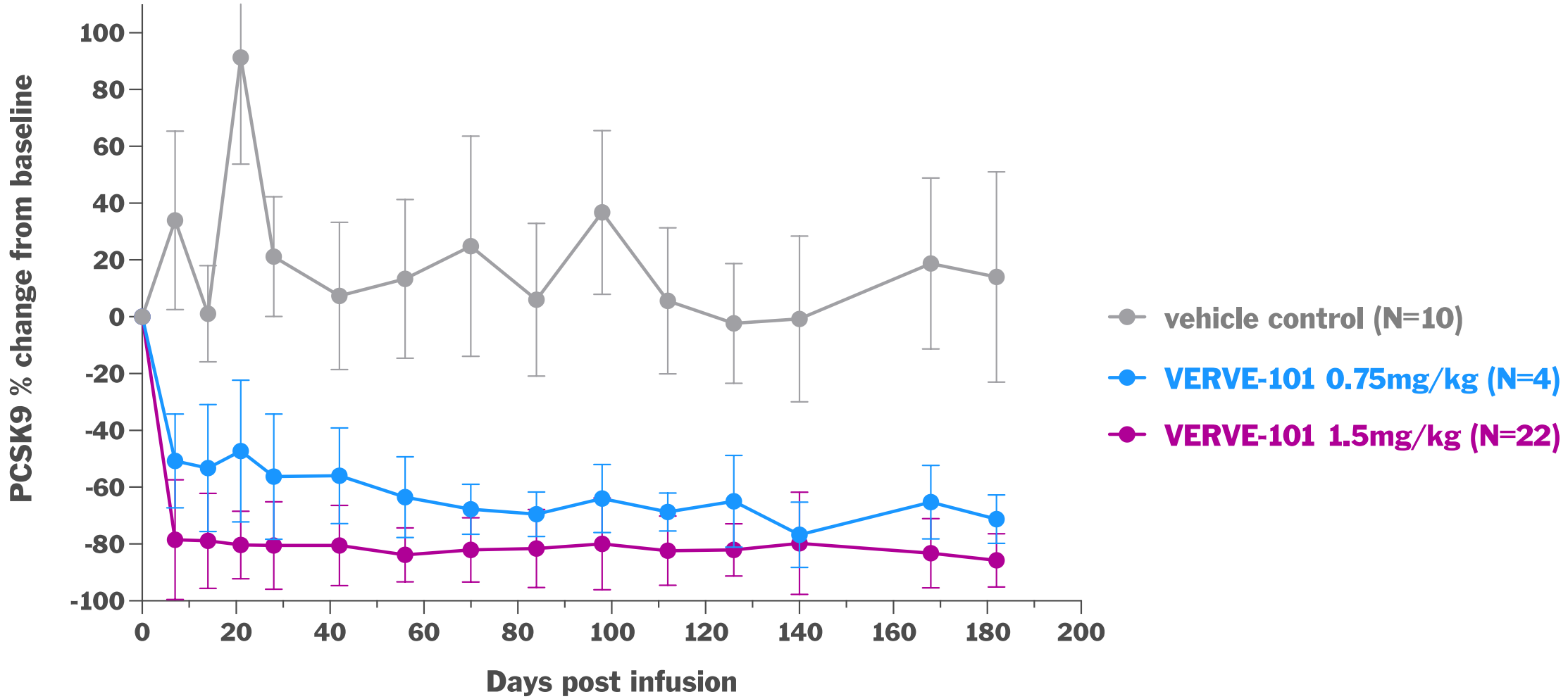
1. Whole liver DNA editing
2. Blood PCSK9 levels
3. Blood LDL-C levels



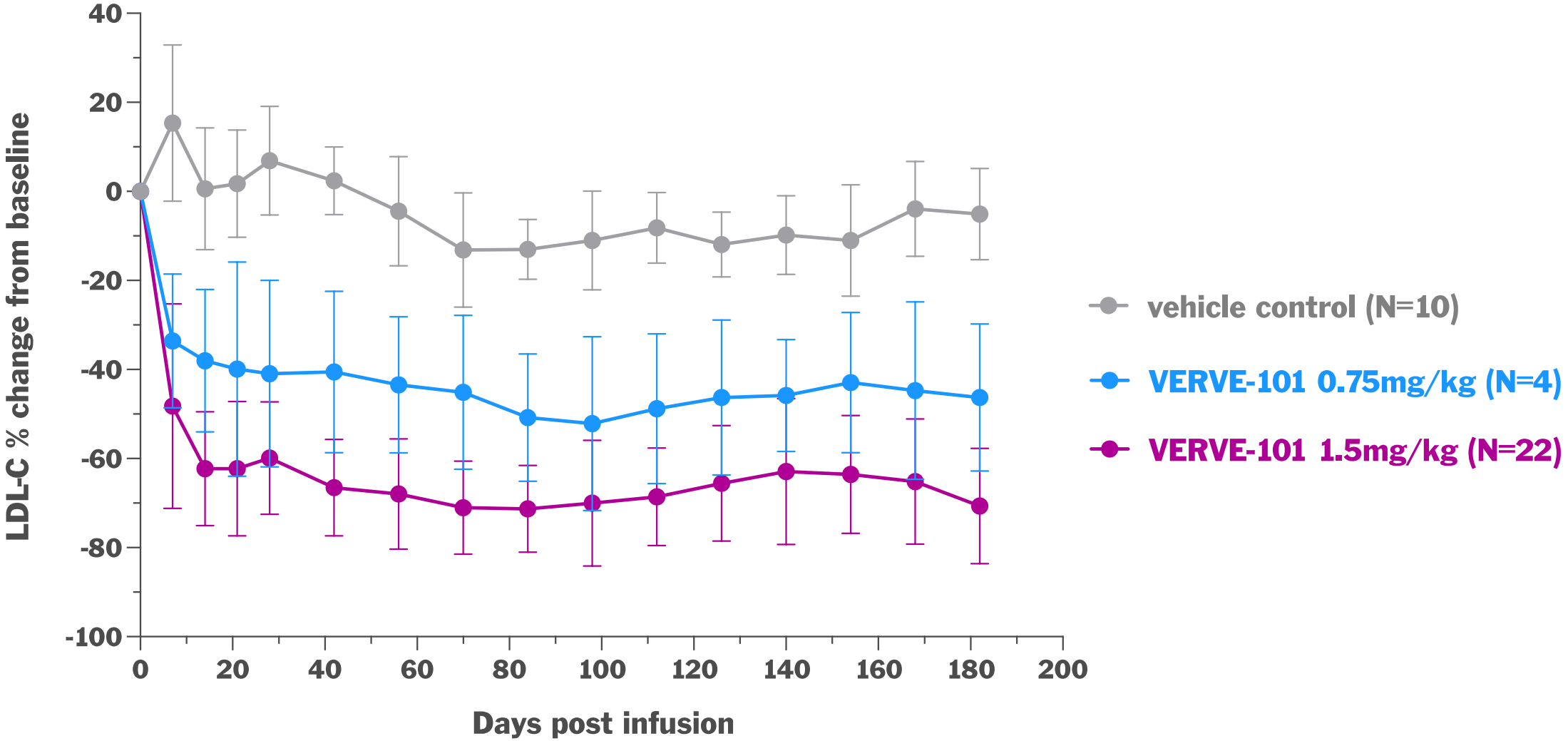

## Safety endpoints

1. Liver function testing
2. Glucose homeostasis
3. Cytokines/anti-drug antibodies

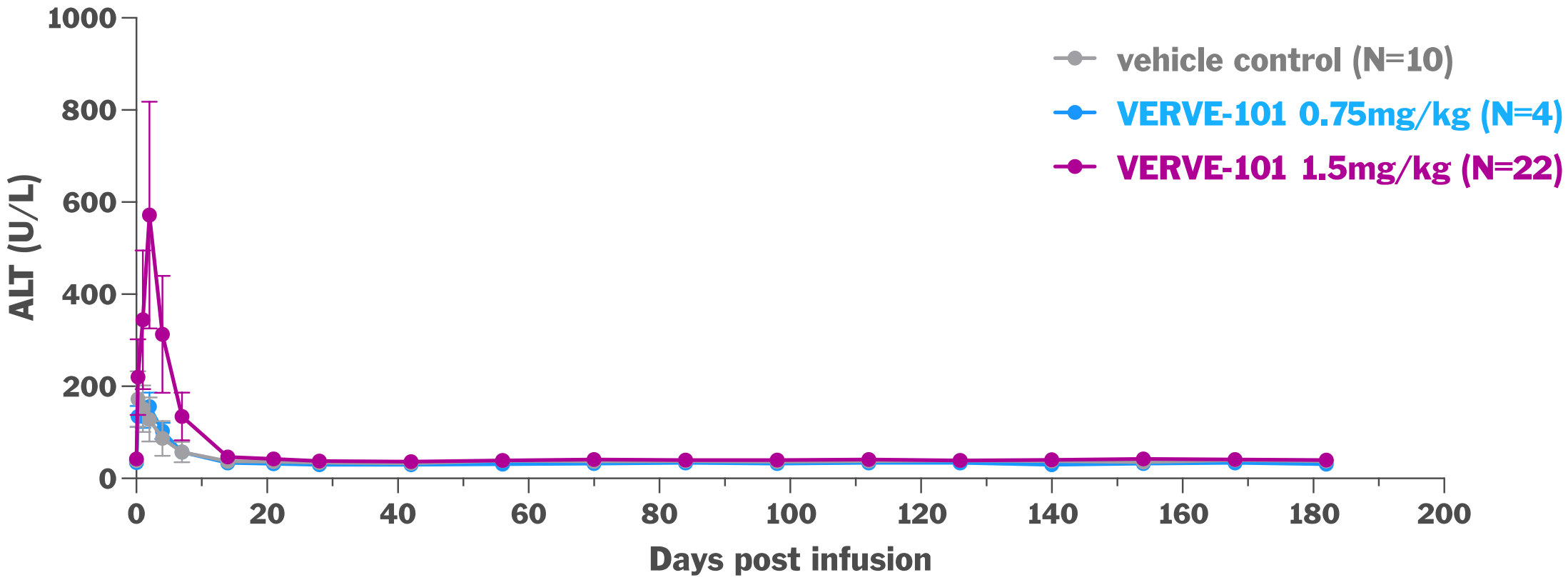
# Blood PCSK9 level: robust and durable reduction observed through six months in NHPs



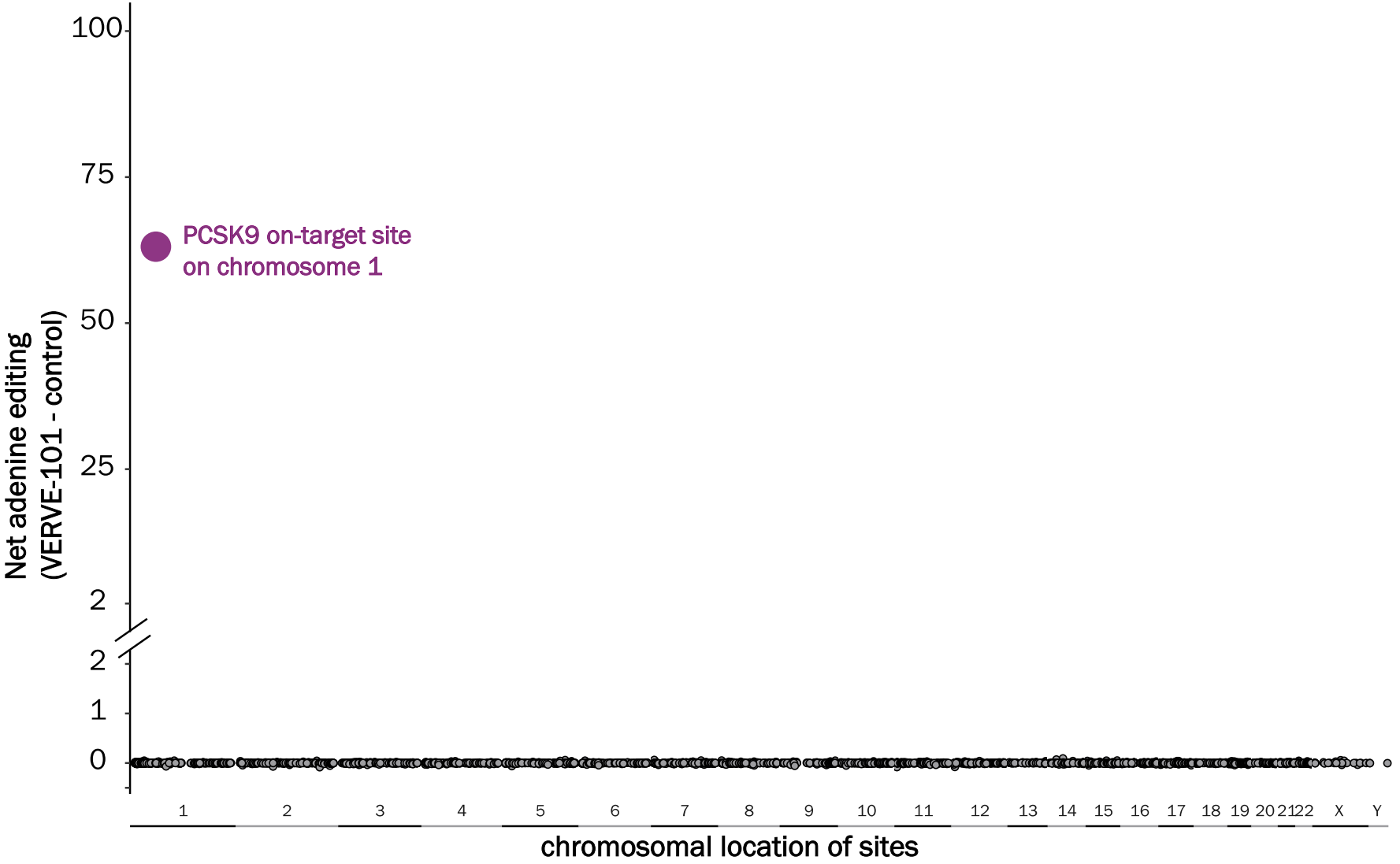
# Blood LDL-C level: durability of VERVE-101 observed through six months in NHPs



# No long-term effects observed on liver function tests following treatment of VERVE-101 in NHPs



# No observed significant off-target editing at ~3000 candidate sites in human primary liver cells treated with VERVE-101




- Manhattan style plot of ~3000 candidate sites nominated by discovery off-target assays.
- No candidate sites show statistically significant net editing.

- Y axis indicates net editing (alternate allele frequency in treated primary human hepatocytes - matched untreated controls)
- Logistic regression statistical test is performed at each candidate site comparing alternate read counts in treated cells versus untreated cells
- Sites of somatic variation seen in the untreated primary cells have been removed from the plot for clarity

# VERVE-101: transitioning to a clinical stage company

## Planned Clinical Trial Design

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

### Part A: Single Ascending Dose

- High Dose
- Medium Dose
- Low Dose

3-4 planned dose levels, n=3-6 per group
participant staggering, sentinels

### Expansion Cohorts

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

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

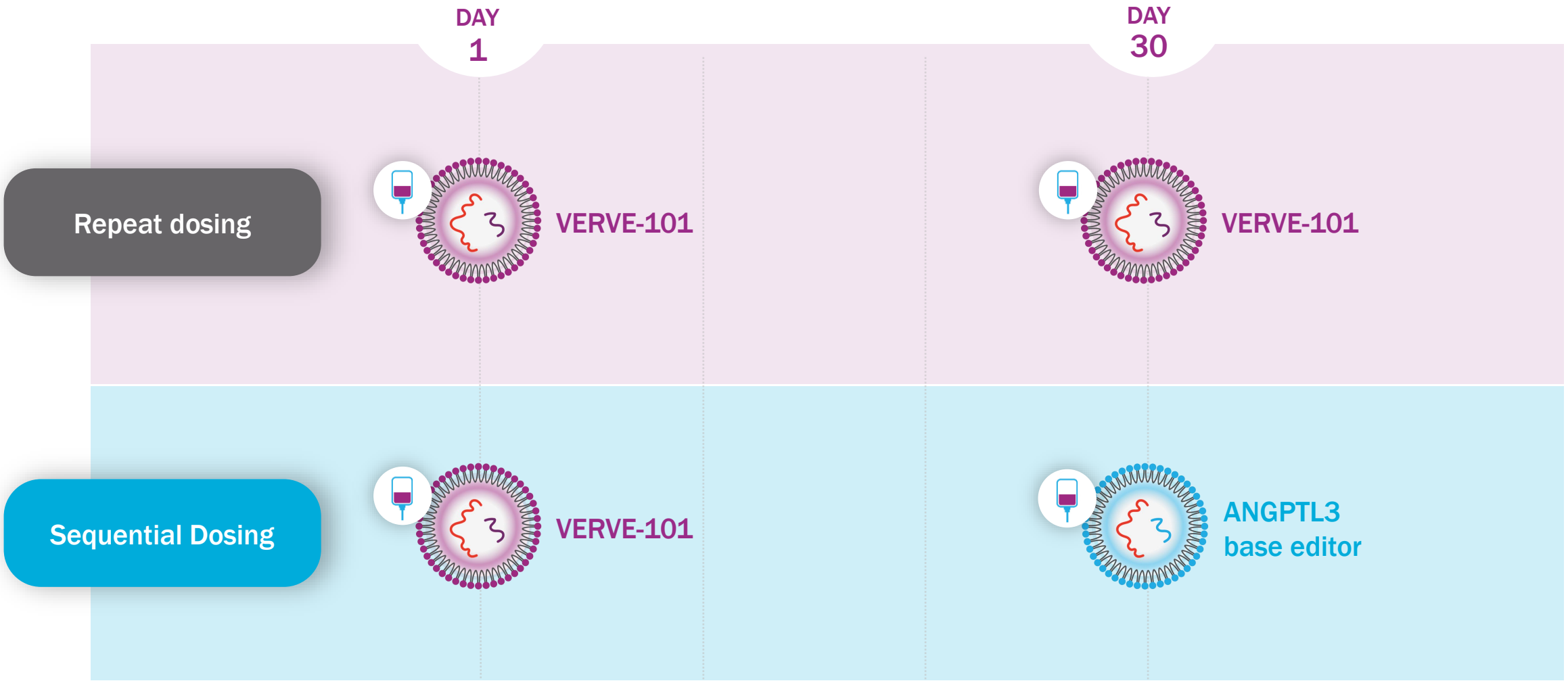
### Study Timing


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

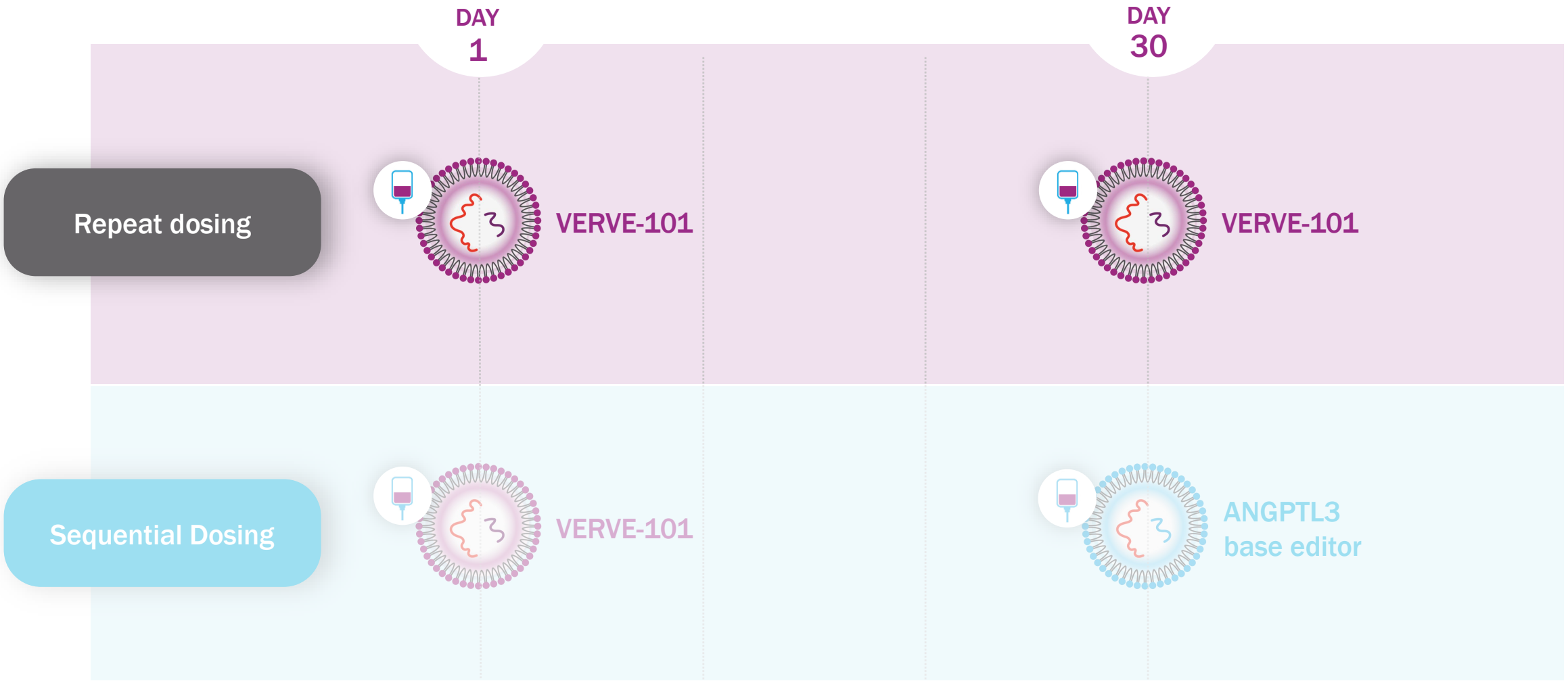
- Safety and tolerability
- Blood PCSK9 reduction
- LDL-C, ApoB reduction

# Stepwise clinical development strategy starting with HeFH and expanding to broader population with ASCVD

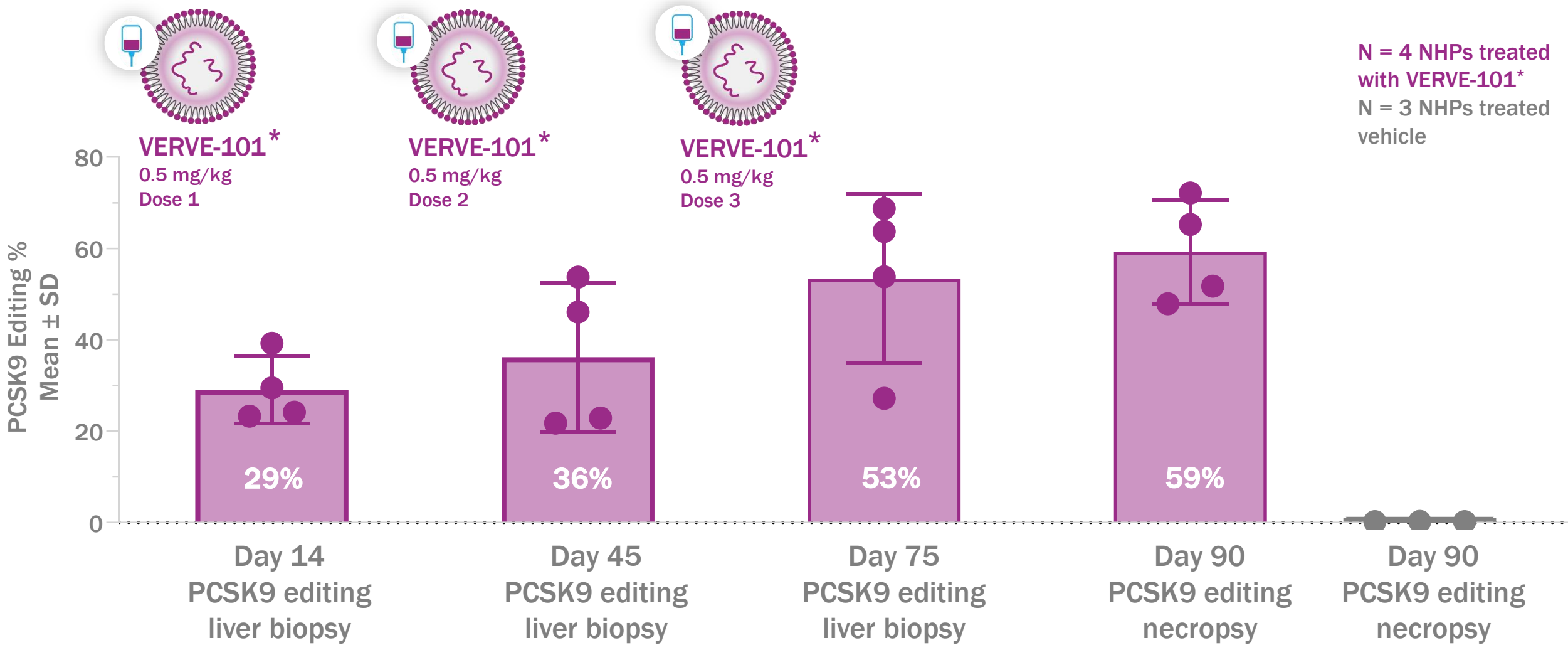
# New data in NHPs: multiple additional dosing regimens for VERVE-101 & ANGPTL3 program for the treatment of ASCVD



# If needed, can VERVE-101 be safely re-dosed?



# Repeat dosing of VERVE-101 three times, with each 0.5 mg/kg dose given a month apart in NHPs: stacking of liver editing efficacy



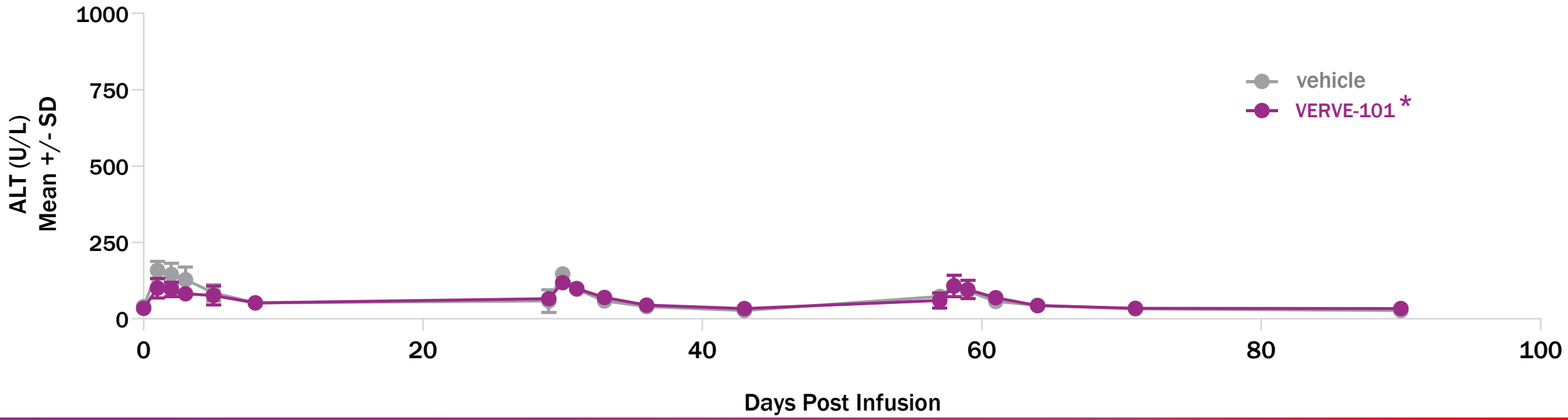

* VERVE-101 precursor

# No evidence of liver injury observed following repeat dosing in NHPs

VERVE-101 *
0.5 mg/kg
Dose 1

VERVE-101 *
0.5 mg/kg
Dose 2

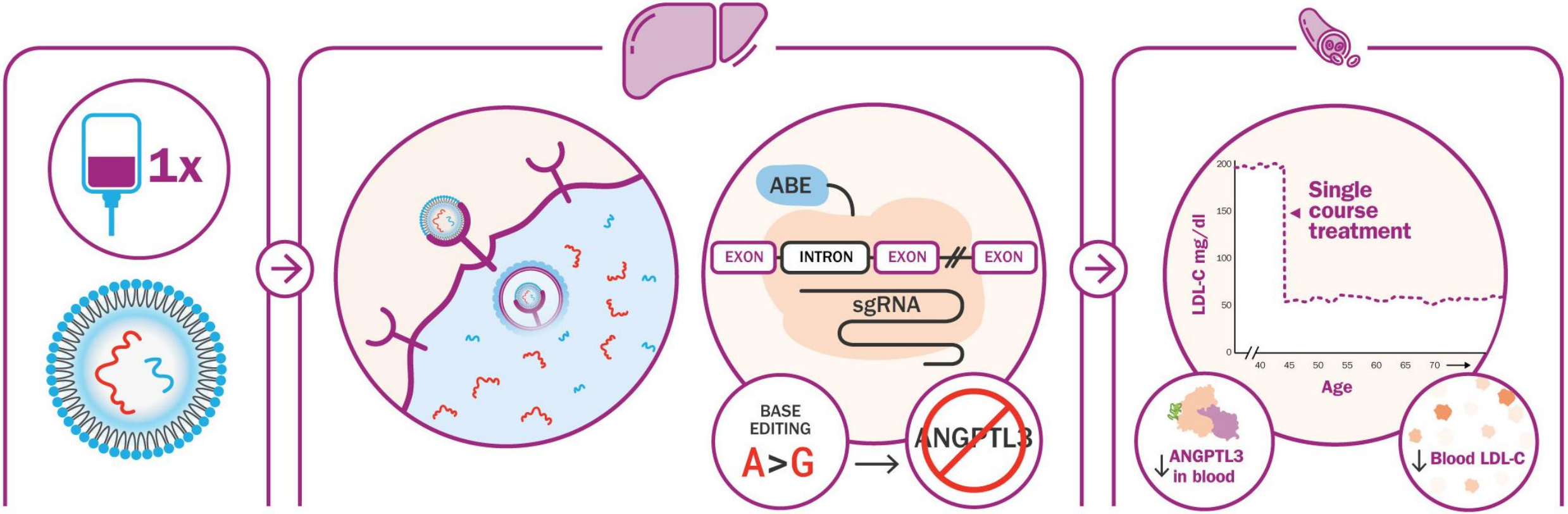
VERVE-101 *
0.5 mg/kg
Dose 3




* VERVE-101 precursor with modestly reduced potency

# Advancing ANGPTL3 program to IND-enabling studies in 2022

# Goal: ANGPTL3 program turns off gene with base editing to lower LDL-C and treat ASCVD




mRNA gRNA

# Inactivation of ANGPTL3 is a compelling target to lower LDL-C: human genetics and human pharmacology

## validated by human genetics

**Heterozygous deficiency:**
Low lipids in population
Resistant to heart attack

**Human knockout:**
Triglycerides: 19 mg/dL
LDL-C: 37 mg/dL

***Rare Gene Mutations Inspire New Heart Drugs***

**By Gina Kolata**

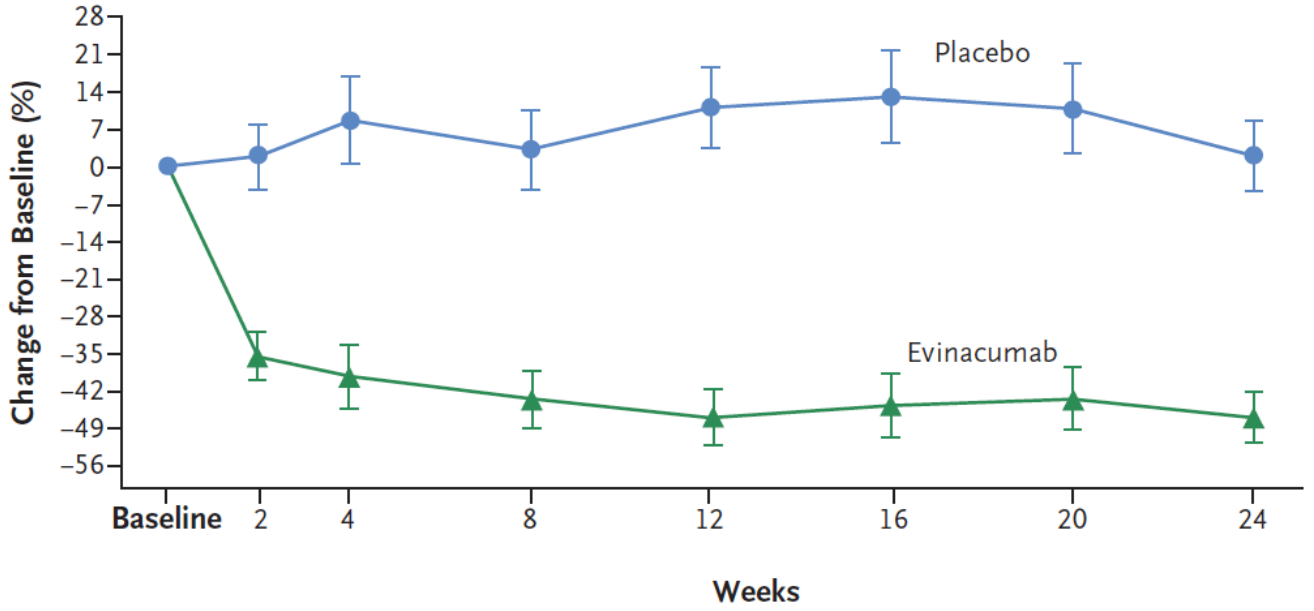
May 24, 2017

**Anna Feurer** learned she had unusually **low triglyceride levels** after having bloodwork at a corporate health fair. The discovery prompted researchers to recruit her and her family for a research study of their genetic makeup.

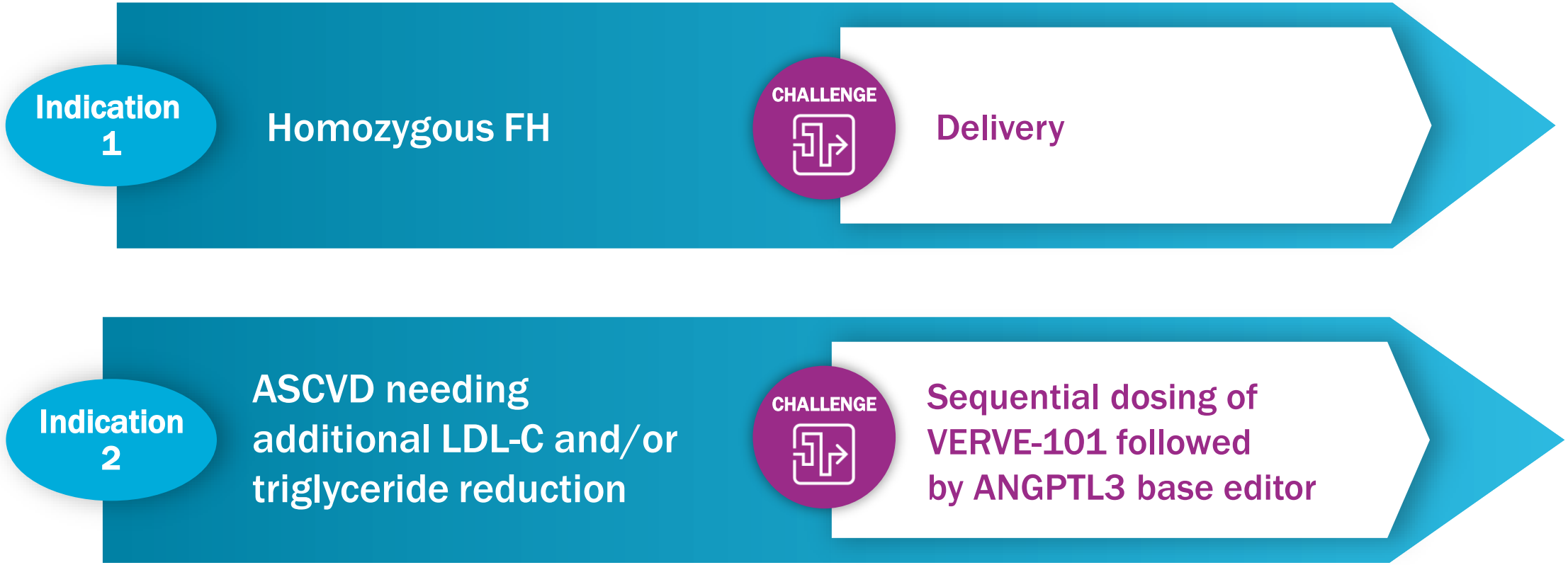
***Credit***. *Jess T. Dugan for The New York Times*

## validated by human pharmacology

- ANGPTL3 inhibition with evinacumab lowered LDL-C by about 49% in a pivotal phase 3 trial in patients with HoFH
- Evinacumab now approved for HoFH



# ANGPTL3 program: two indications, two challenges



# ANGPTL3 program: two indications, two challenges

**Indication 1**

Homozygous FH

CHALLENGE

Delivery

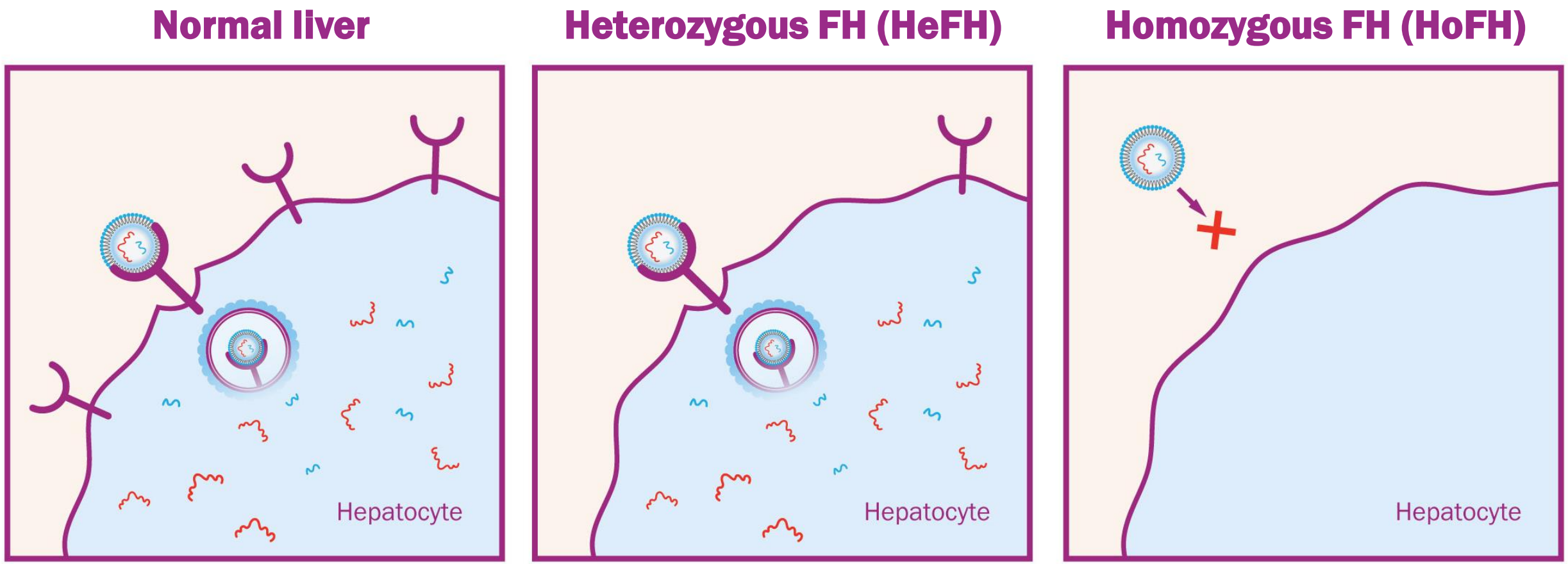
**Indication 2**

ASCVD needing additional LDL-C and/or triglyceride reduction

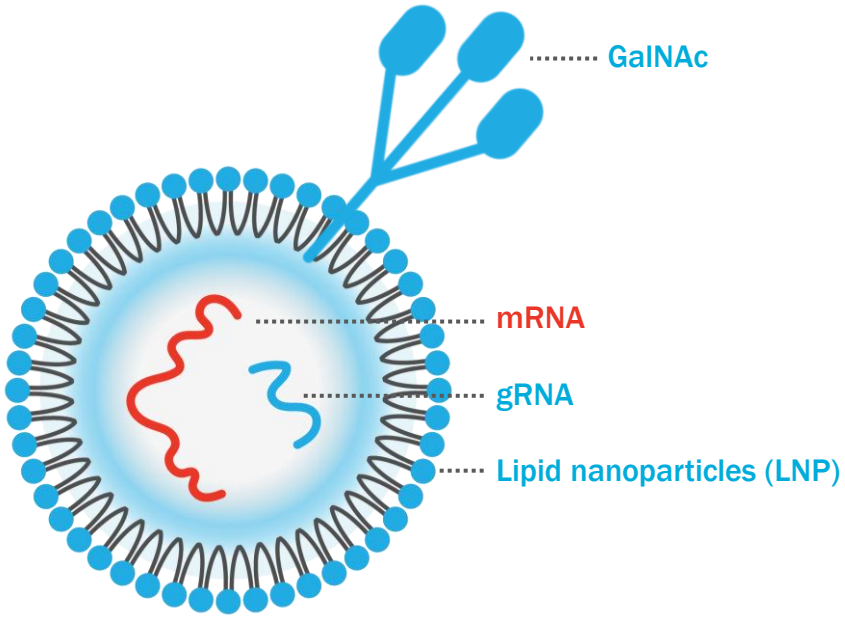
CHALLENGE

Sequential dosing of VERVE-101 followed by ANGPTL3 base editor

# Delivery challenge: HoFH patients completely lack LDL receptor; in this setting, standard LNPs don't work

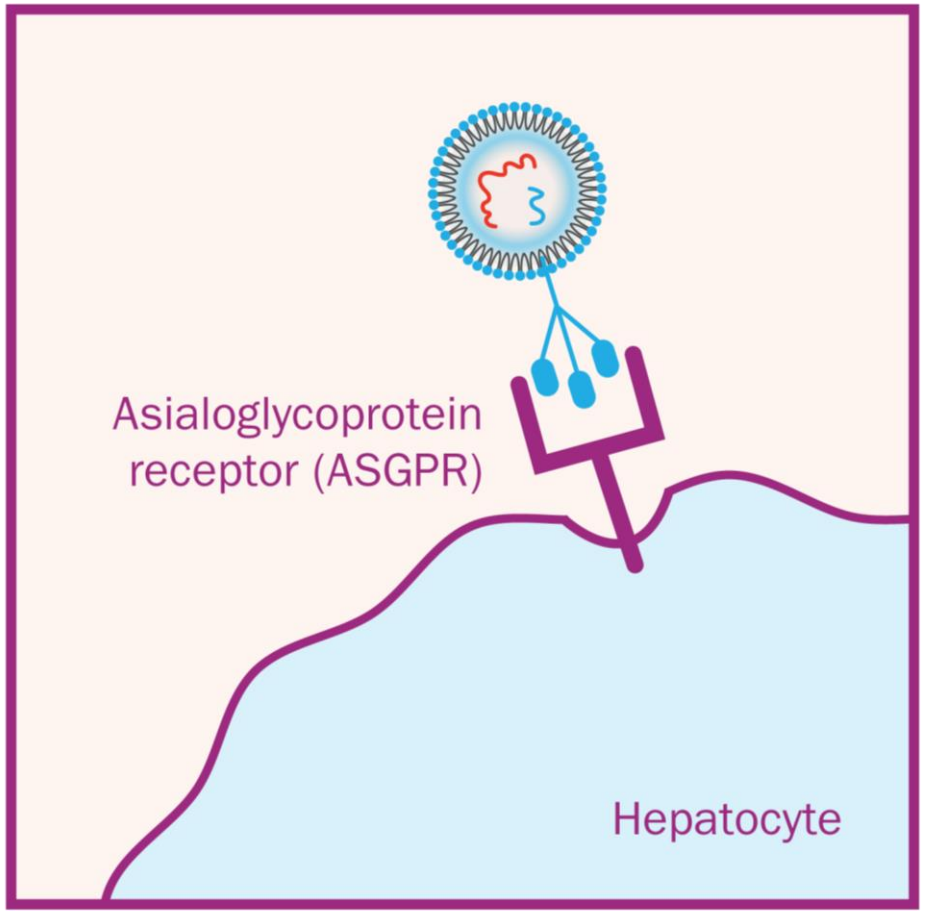


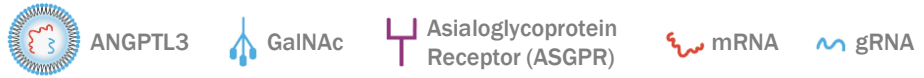
# Our solution: addition of proprietary GalNAc targeting ligand to LNP allows delivery through ASGPR




United States Patent
Rajeev et al.

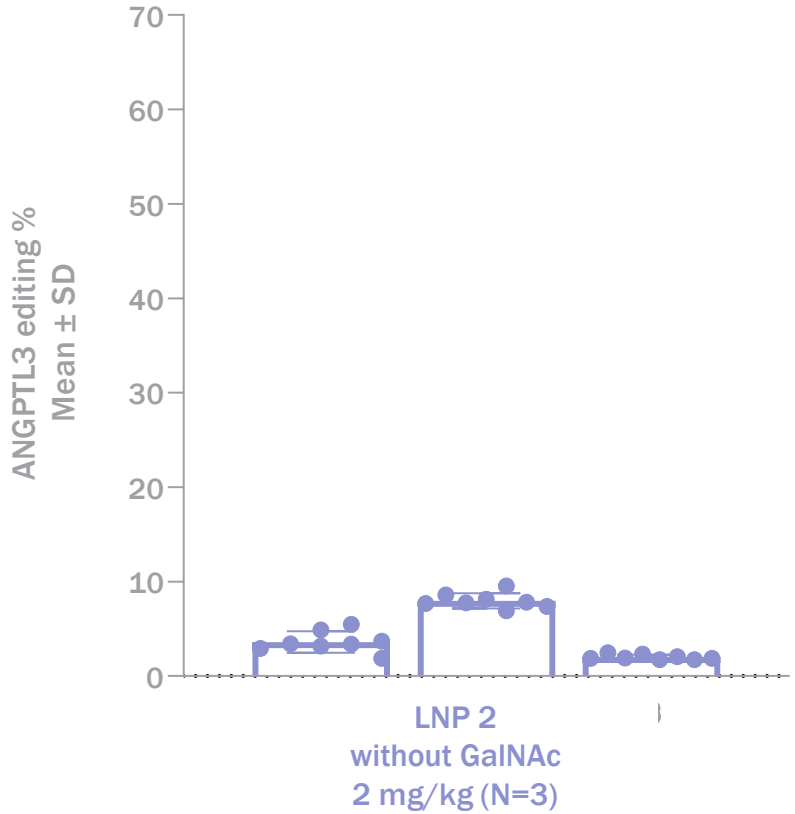
Patent No.: US 11,207,416 B2
Date of Patent: Dec. 28, 2021

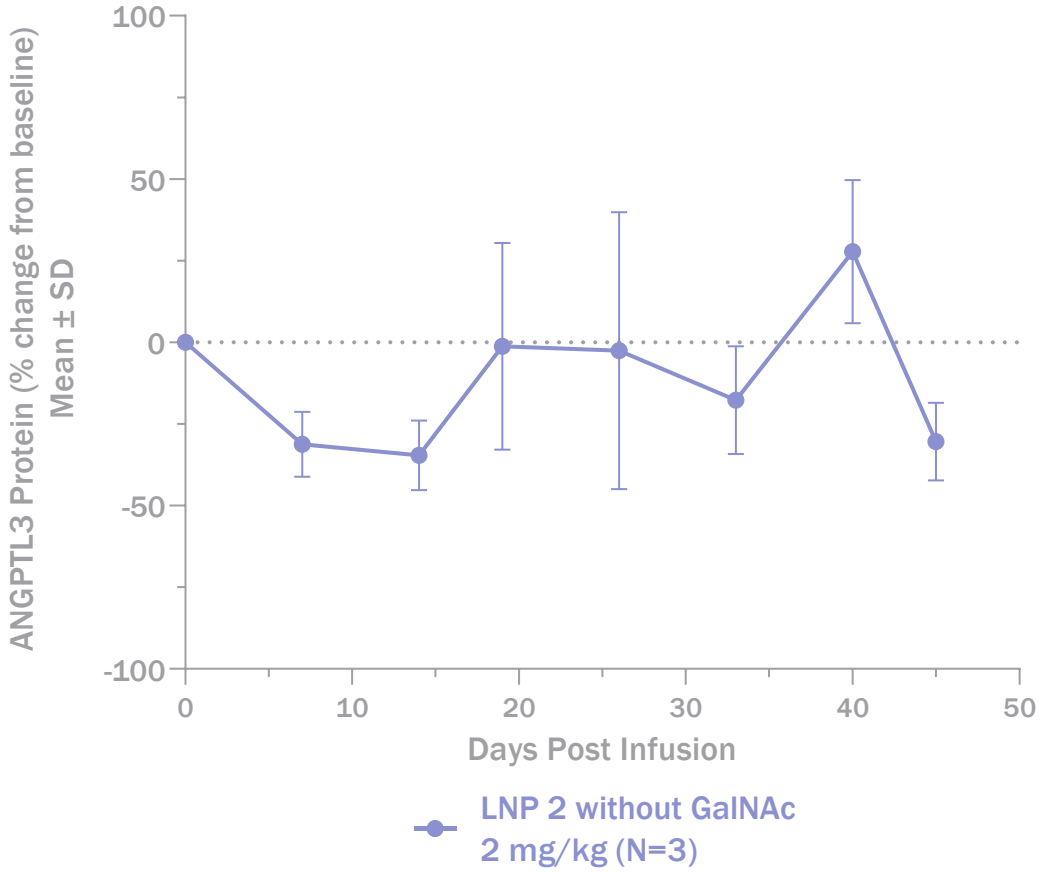


# Standard LNPs (without GalNAc) do not achieve effective ANGPTL3 base editing in the liver of NHP model of HoFH

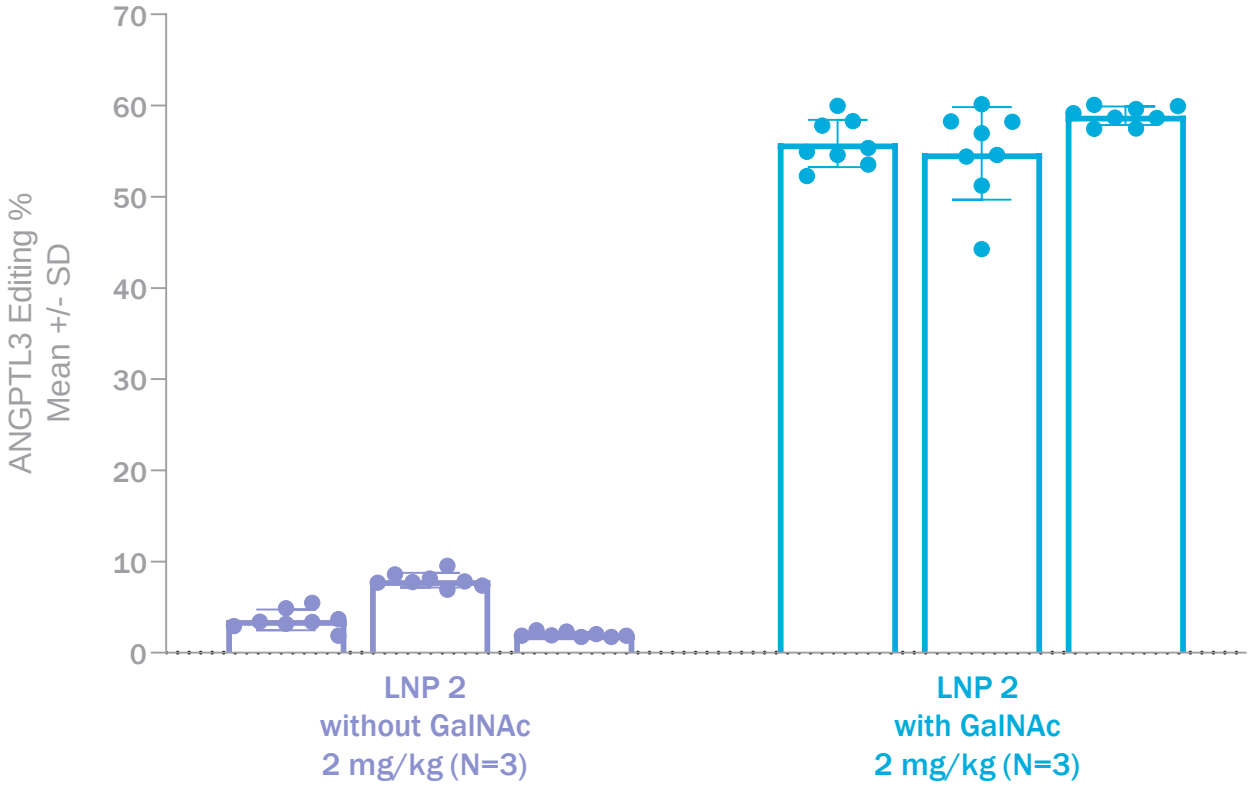
## Standard LNP in HoFH NHP model

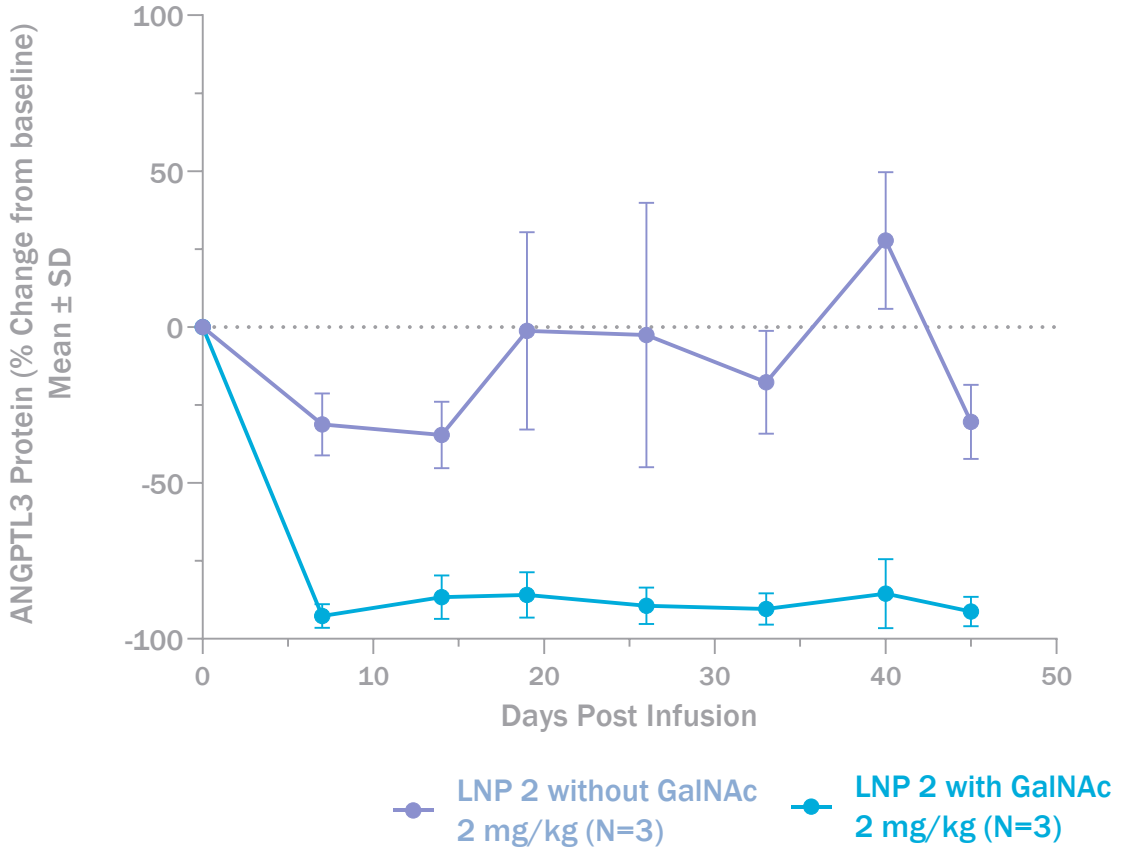


# Our GalNAc-LNP enabled effective ANGPTL3 base editing in the liver of NHP model of HoFH

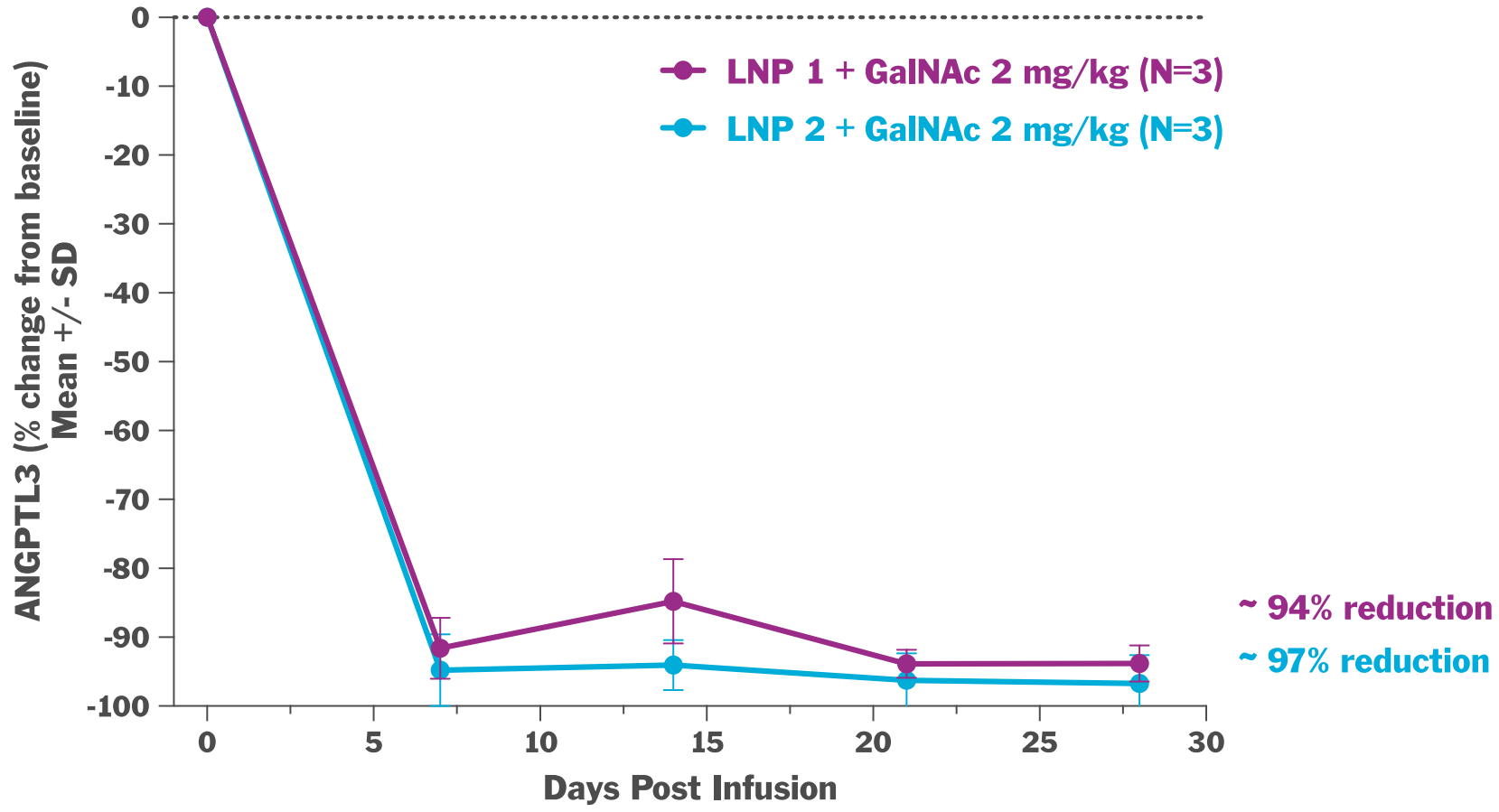
## GalNAc-targeting bypassed LDLR and enabled liver editing



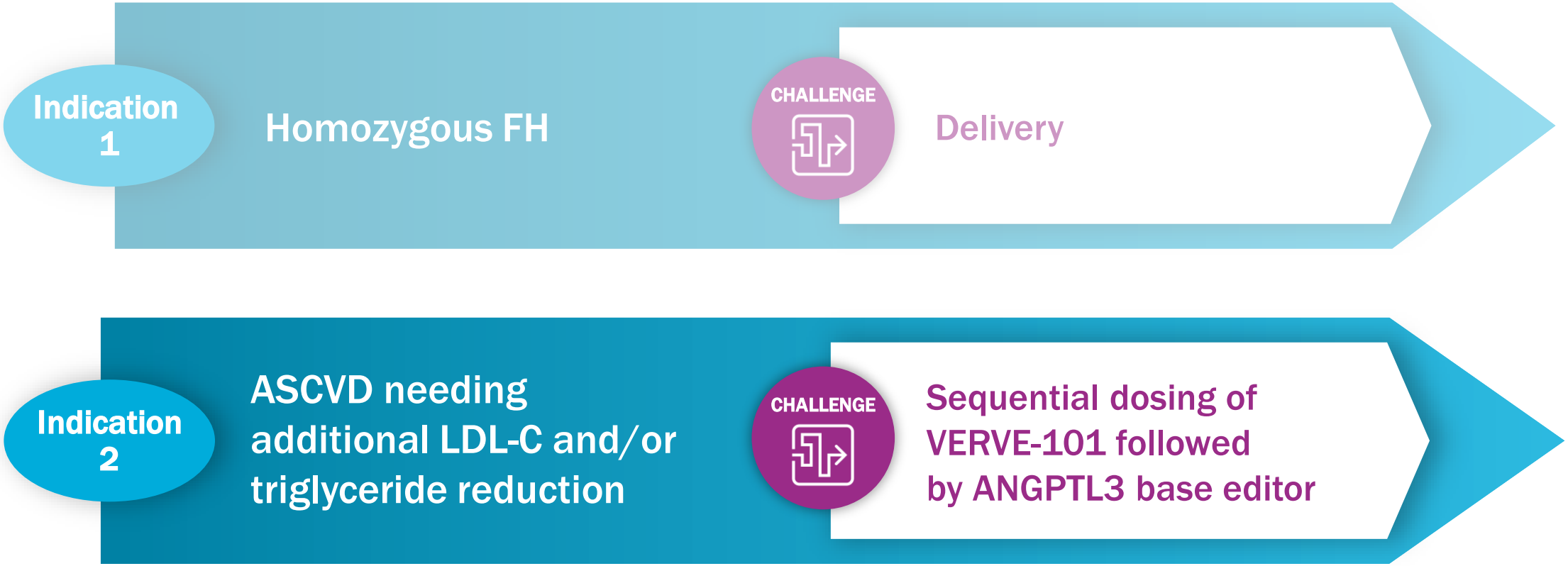



# Base editing of ANGPTL3 via GalNAc-LNPs reduced blood ANGPTL3 by 94% - 97% in NHP model of HoFH

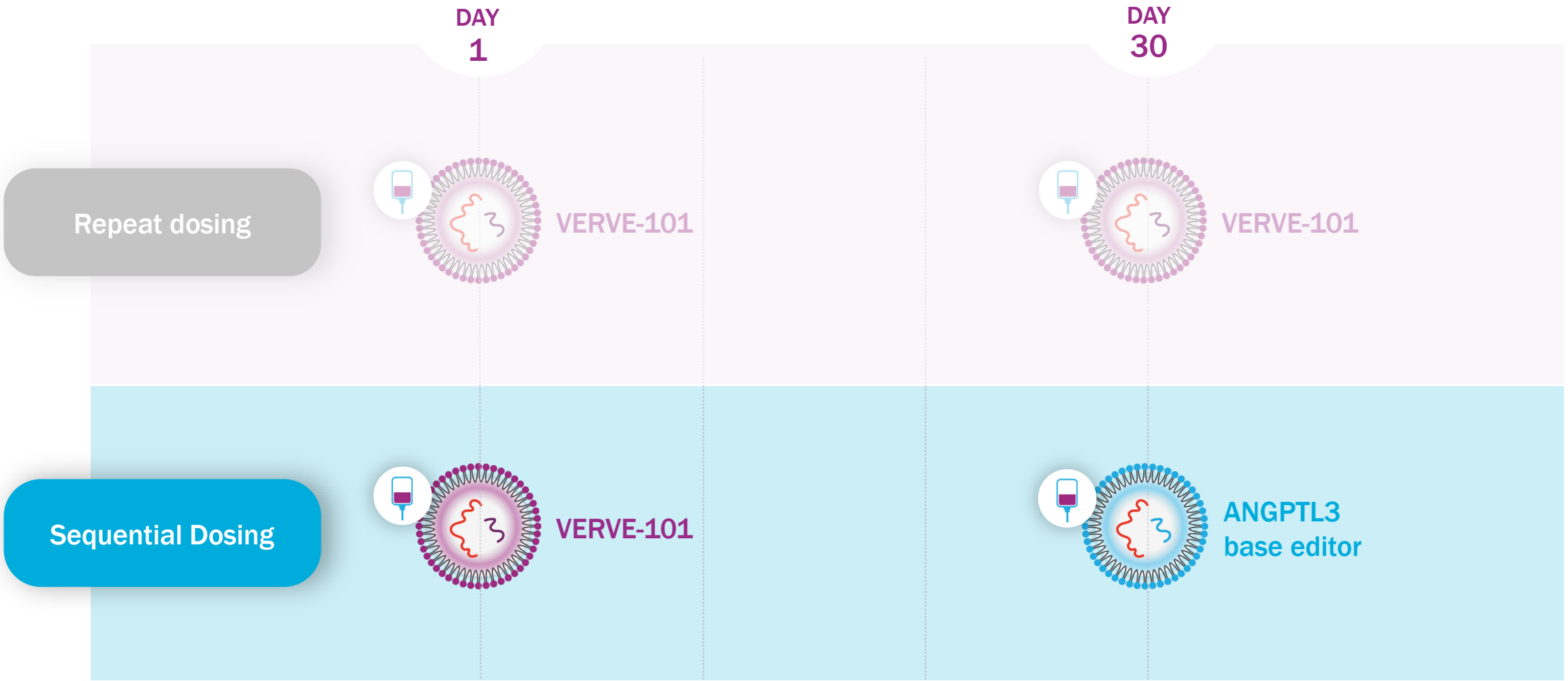
GalNAc LNPs (encapsulating ABE-ANGPTL3 base editing payload) dosed to HoFH NHPs that already have stable disruption of LDLR protein and markedly elevated LDL-C



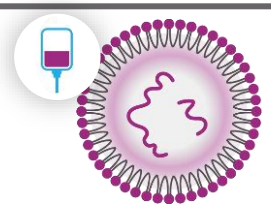
# ANGPTL3 program: two indications, two challenges



# Can ANGPTL3 base editor be sequentially dosed after VERVE-101 to target two independent CV risk pathways?



# Sequential dosing of VERVE-101

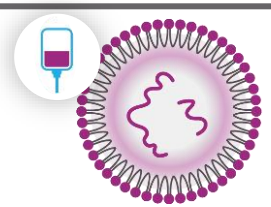


VERVE-101
1.0 mg/kg

| | | Biopsy Day 15 PCSK9 editing |
|---|---|---|
| Treatment | NHP 1 | 70% |
| | NHP 2 | 67% |
| | NHP 3 | 79% |
| | NHP 4 | 69%* |
| | average | 71 ± 5% |
| Control | NHP 1 | 0.1% |
| | NHP 2 | 0.3% |
| | NHP 3 | 0.2% |

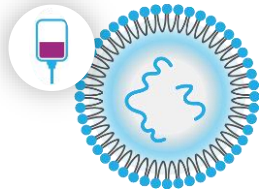
* biopsy error, initial biopsy 16%, repeat 69%

# Sequential dosing of VERVE-101, followed by dosing with an ANGPTL3 base editor on day 30 in NHPs



VERVE-101
1.0 mg/kg

Biopsy
Day 15
PCSK9 editing



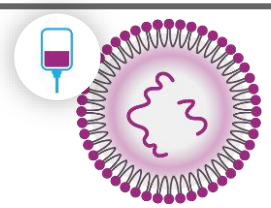
ANGPTL3
1.0 mg/kg

Biopsy
Day 45
ANGPTL3 editing

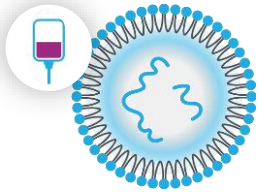
| | | | |
|---|---|---|---|
| Treatment | NHP 1 | 70% | 59% |
| | NHP 2 | 67% | 50% |
| | NHP 3 | 79% | 54% |
| | NHP 4 | 69%* | 44% |
| | average | 71 ± 5% | 52 ± 6% |
| Control | NHP 1 | 0.1% | 0.2% |
| | NHP 2 | 0.3% | 0.2% |
| | NHP 3 | 0.2% | 0.2% |

* biopsy error, initial biopsy 16%, repeat 69%

# On necropsy at day 90, high efficiency liver editing of both PCSK9 (69%) and ANGPTL3 (62%) genes



VERVE-101
1.0 mg/kg

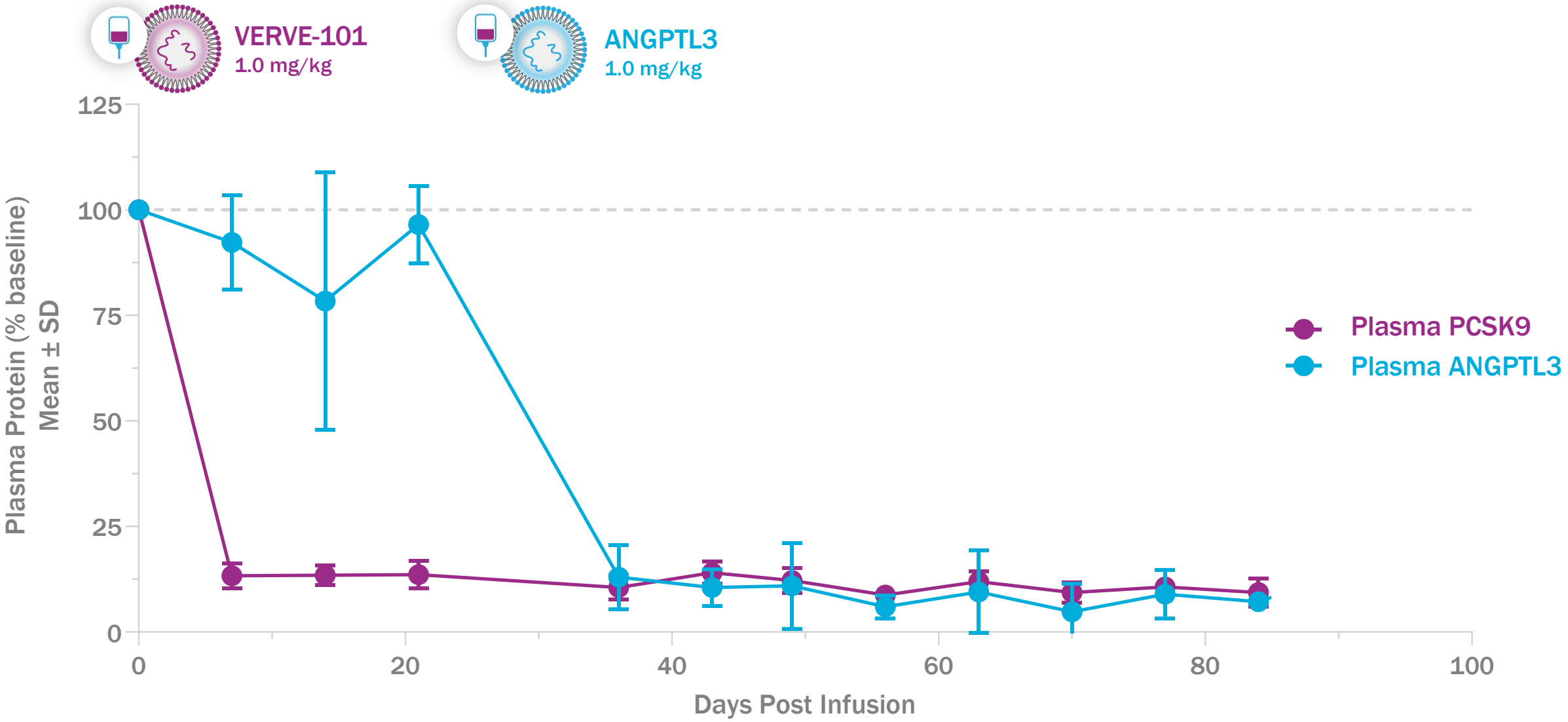


ANGPTL3
1.0 mg/kg

| | Biopsy Day 15 PCSK9 editing | Biopsy Day 45 ANGPTL3 editing | Necropsy Day 90 |
|---|---|---|---|
| Treatment | | | |
| NHP 1 | 70% | 59% | 68% PCSK9<br>63% ANGPTL3 |
| NHP 2 | 67% | 50% | 69% PCSK9<br>62% ANGPTL3 |
| NHP 3 | 79% | 54% | 70% PCSK9<br>62% ANGPTL3 |
| NHP 4 | 69%* | 44% | 70% PCSK9<br>63% ANGPTL3 |
| average | 71 ± 5% | 52 ± 6% | 69 ± 1% PCSK9<br>63 ± 1% ANGPTL3 |
| Control | | | |
| NHP 1 | 0.1% | 0.2% | 0.1% PCSK9<br>0.1% ANGPTL3 |
| NHP 2 | 0.3% | 0.2% | 0.1% PCSK9<br>0.2% ANGPTL3 |
| NHP 3 | 0.2% | 0.2% | 0.1% PCSK9<br>0.2% ANGPTL3 |

* biopsy error, initial biopsy 16%, repeat 69%

# Sequential dosing in NHPs: >90% reduction of plasma PCSK9 protein followed by >90% reduction observed of plasma ANGPTL3 protein



# Building a world-class team to nimbly solve problems

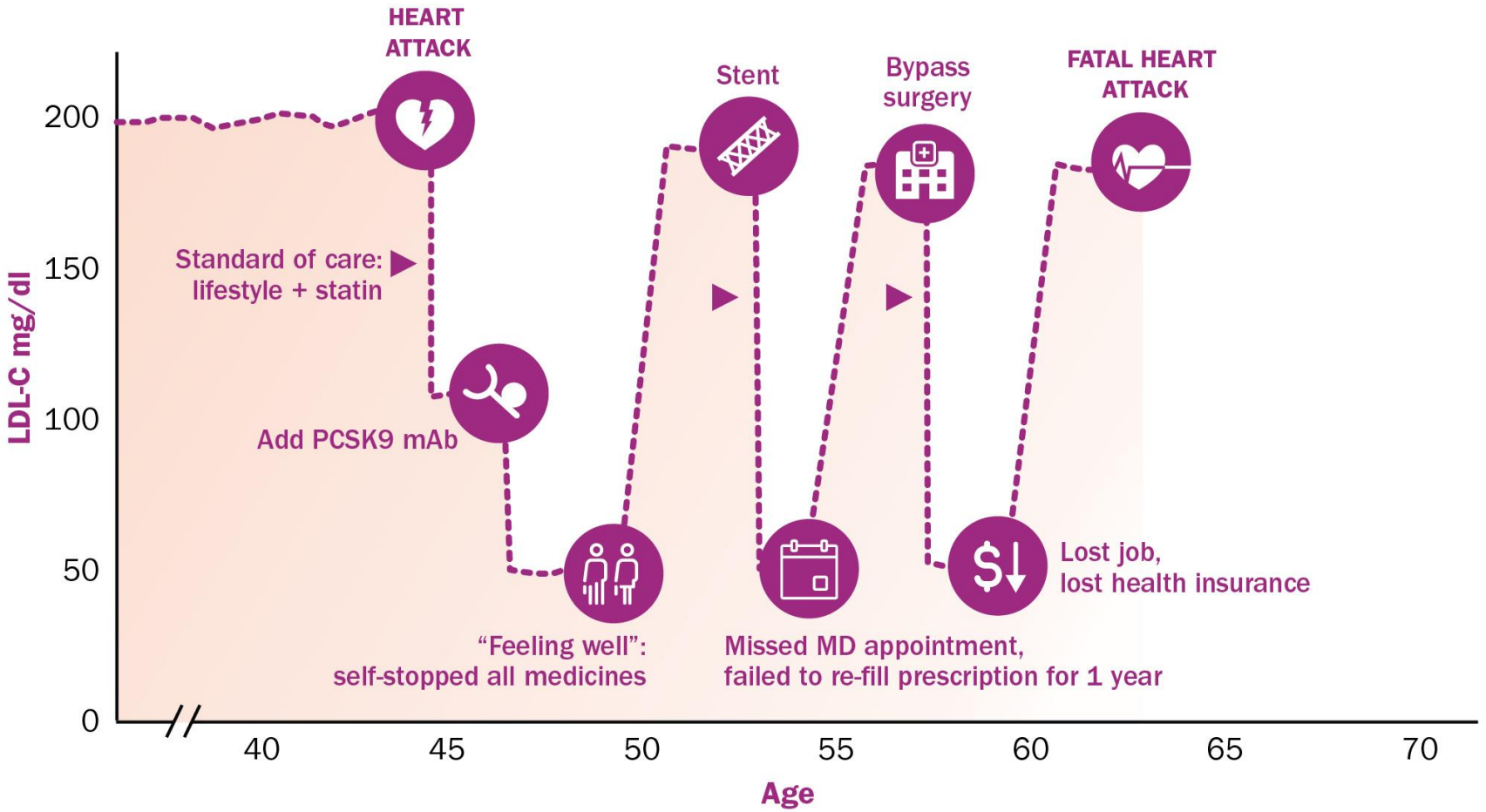
The Boston Globe
TOP PLACES TO WORK 2021
MASSACHUSETTS

BOSTON BUSINESS JOURNAL
BPtW
2021 BEST PLACES TO WORK

BOSTON BUSINESS JOURNAL
BPtW
2020 BEST PLACES TO WORK

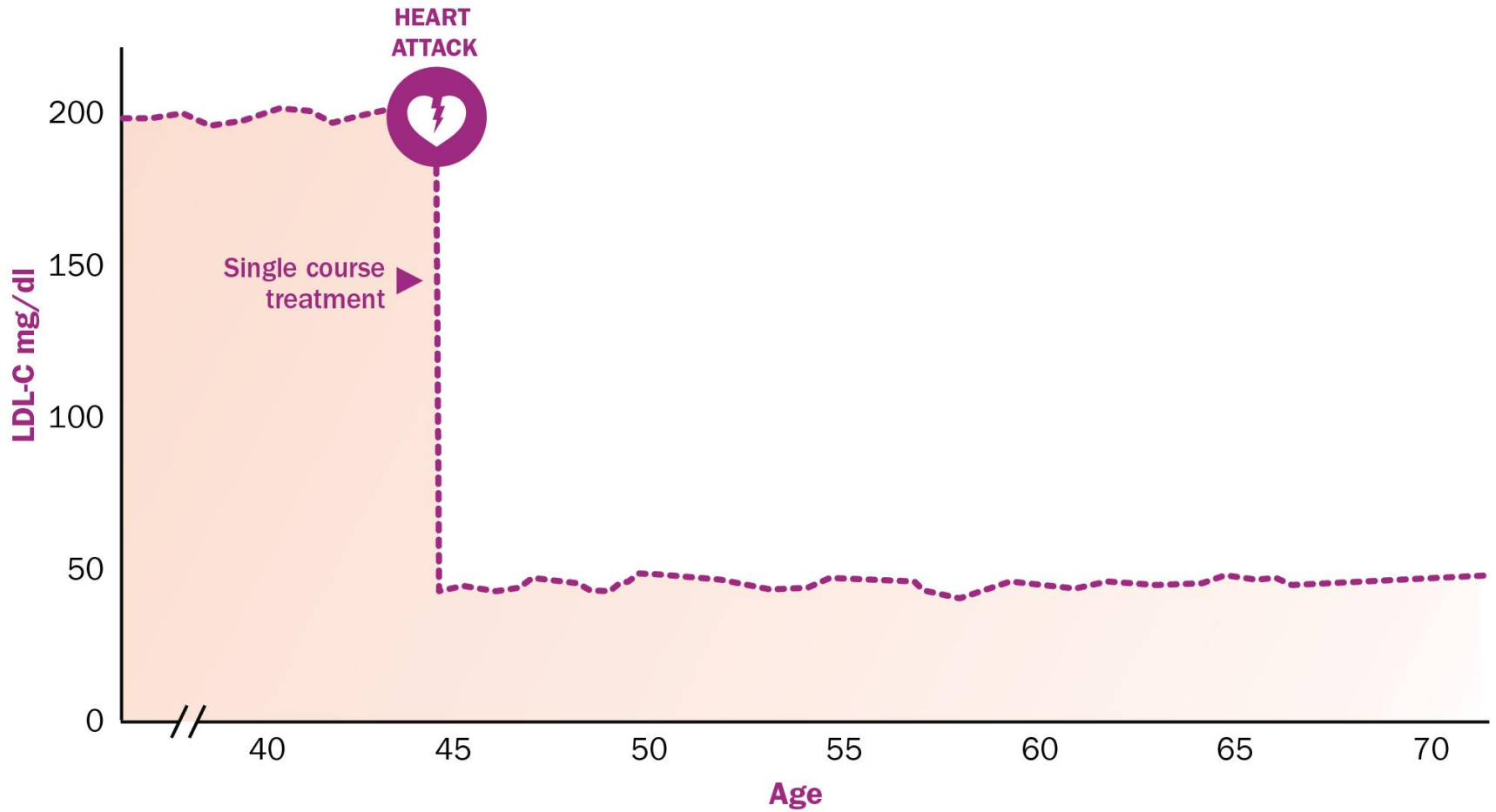
# Why a single-course treatment when there is a standard of care for cholesterol lowering?

# 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 began standard-of-care treatment after suffering a heart attack at age 44

# 2022 will be a transformative year

## Mission: to transform the care of cardiovascular disease with single-course gene editing medicines