Potent, Specific, and Durable Liver Editing of *PCSK9* in Preclinical Studies of the CRISPR Base Editing Medicine VERVE-101

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Speaker Disclosure

Taiji Mizoguchi is an employee and equity holder of Verve Therapeutics.

Investigational Product

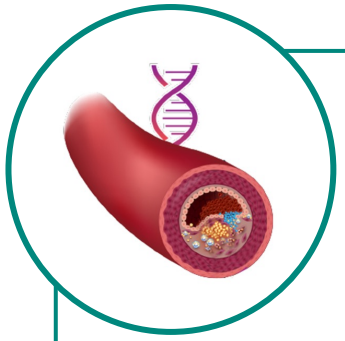
VERVE-101 is an investigational agent that is not approved for commercial use in any jurisdiction.

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 potential advantages and therapeutic potential of the Company’s programs, including VERVE-101. 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 Company’s ability to timely submit and receive approvals of regulatory applications for its product candidates; advance its product candidates in clinical trials; initiate, enroll and complete its ongoing and future 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, VERVE-102 and VERVE-201; 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 and in other filings that the Company makes with the Securities and Exchange Commission in the future. 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.

verve™ THERAPEUTICS

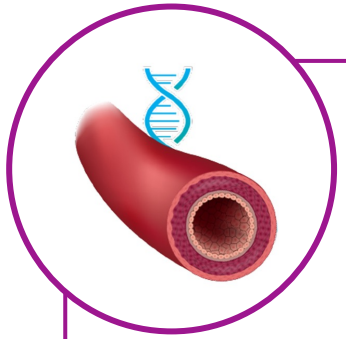
What causes ASCVD and what's a solution?



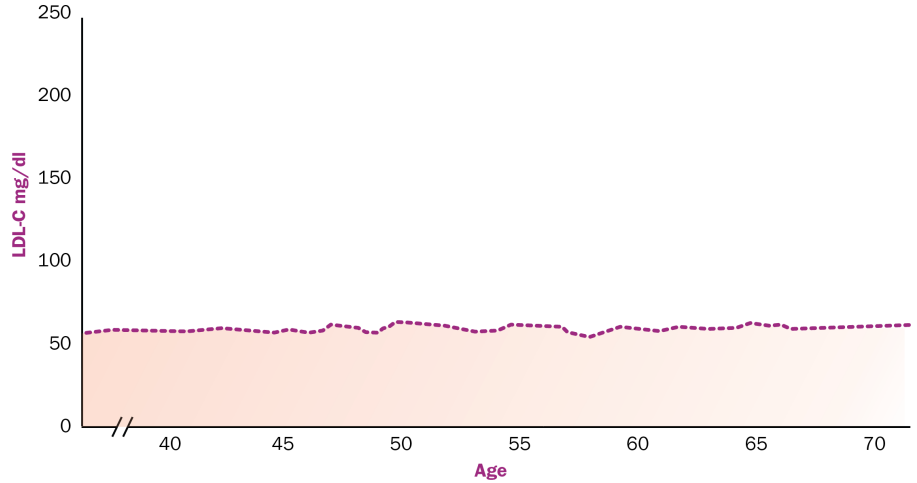
High cumulative life-long exposure to blood cholesterol clogs heart arteries

Cholesterol carried in 3 lipoproteins:

Cholesterol | Triglycerides | *Apolipoprotein B* | *Apolipoprotein(a)*



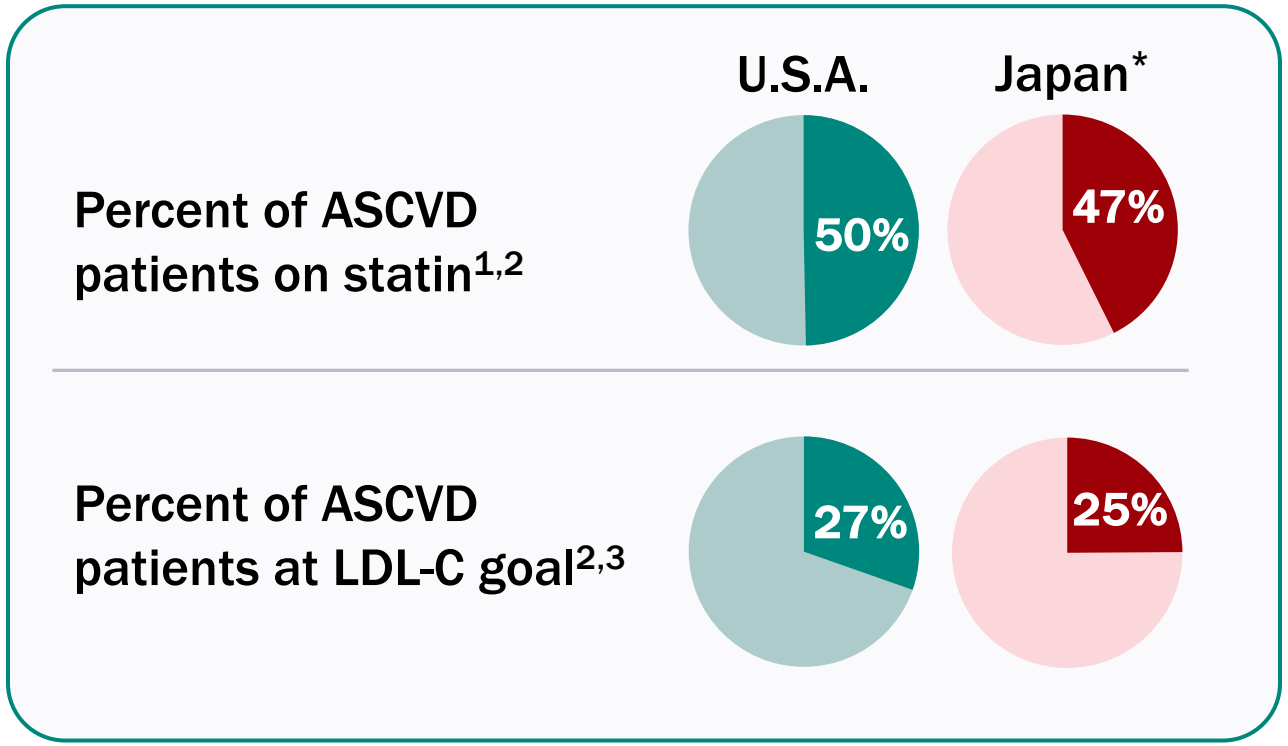
Solution: keep blood cholesterol as low as possible for as long as possible



ASCVD, atherosclerotic cardiovascular disease; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; TRL, triglyceride-rich lipoprotein

Current chronic care model to lower LDL-C seems broken: most patients do not achieve their LDL-C goal

ASCVD



PCSK9 utilization in high risk ASCVD in Japan*

*secondary prevention in high-risk ASCVD patients

1. Nelson AJ et al., J Am Coll Card. 2022;79(18):1802–13; 2. Mitani H et al. J Atheroscler Thromb. 2023; 30(11):1622-1634; 3. Gu J et al., Am J Prev Cardiol. 2022;10:100336.

Human genetics provides a potential solution: inactivate *PCSK9* to permanently reduce LDL-C

Naturally occurring loss-of-function variants in *PCSK9* result in:

- Lifelong LDL-C lowering
- Protection against CV events
- No apparent deleterious effects[1,2,3]

Pharmacologic validation of target

1. Zhao Z, et al. Am J Hum Genet. 2006;79:514-523; 2. Cohen JC, et al. N Eng J Med. 2006;354:1264-1272; 3. Rao AS, et al. Circ Genom Prec Med. 2018;11(7):e002162.
CV, cardiovascular; PCSK9, proprotein convertase subtilisin/kexin type 9

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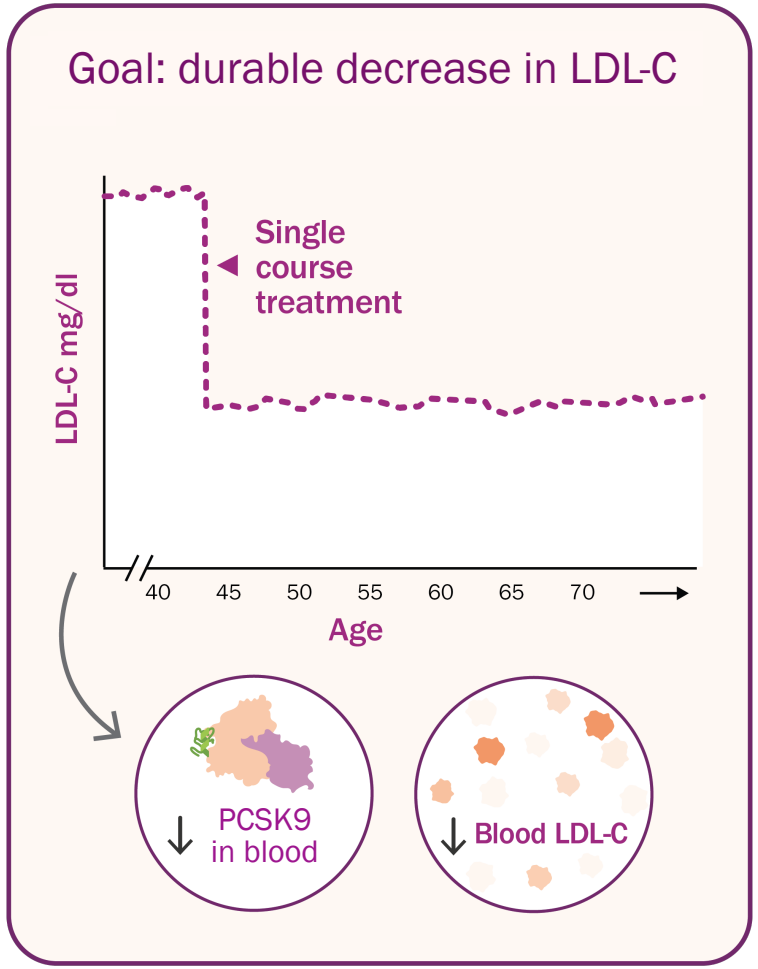


Can we develop a single-course treatment that mimics natural *PCSK9* variants which protect against ASCVD?

1. Zhao Z, et al. Am J Hum Genet. 2006;79:514-523; 2. Cohen JC, et al. N Eng J Med. 2006;354:1264-1272; 3. Rao AS, et al. Circ Genom Prec Med. 2018;11(7):e002162.
CV, cardiovascular; PCSK9, proprotein convertase subtilisin/kexin type 9

VERVE-101 is an investigational adenine base editing medicine delivered to hepatocytes by a lipid nanoparticle to inactivate *PCSK9*

DRUG SUBSTANCES

RNA components encode base editor and a guide targeting *PCSK9* gene

- mRNA for adenine base editor (ABE)
- gRNA localizes editor to *PCSK9* gene

+

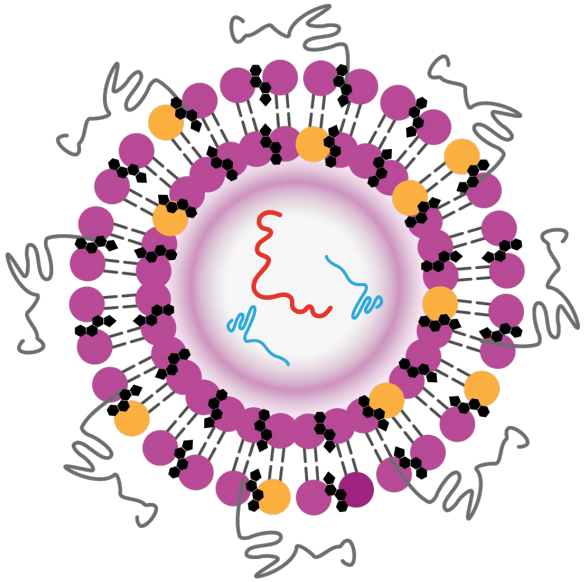
DELIVERY VEHICLE

Lipid nanoparticle (LNP) for delivery to liver cell includes 4 components

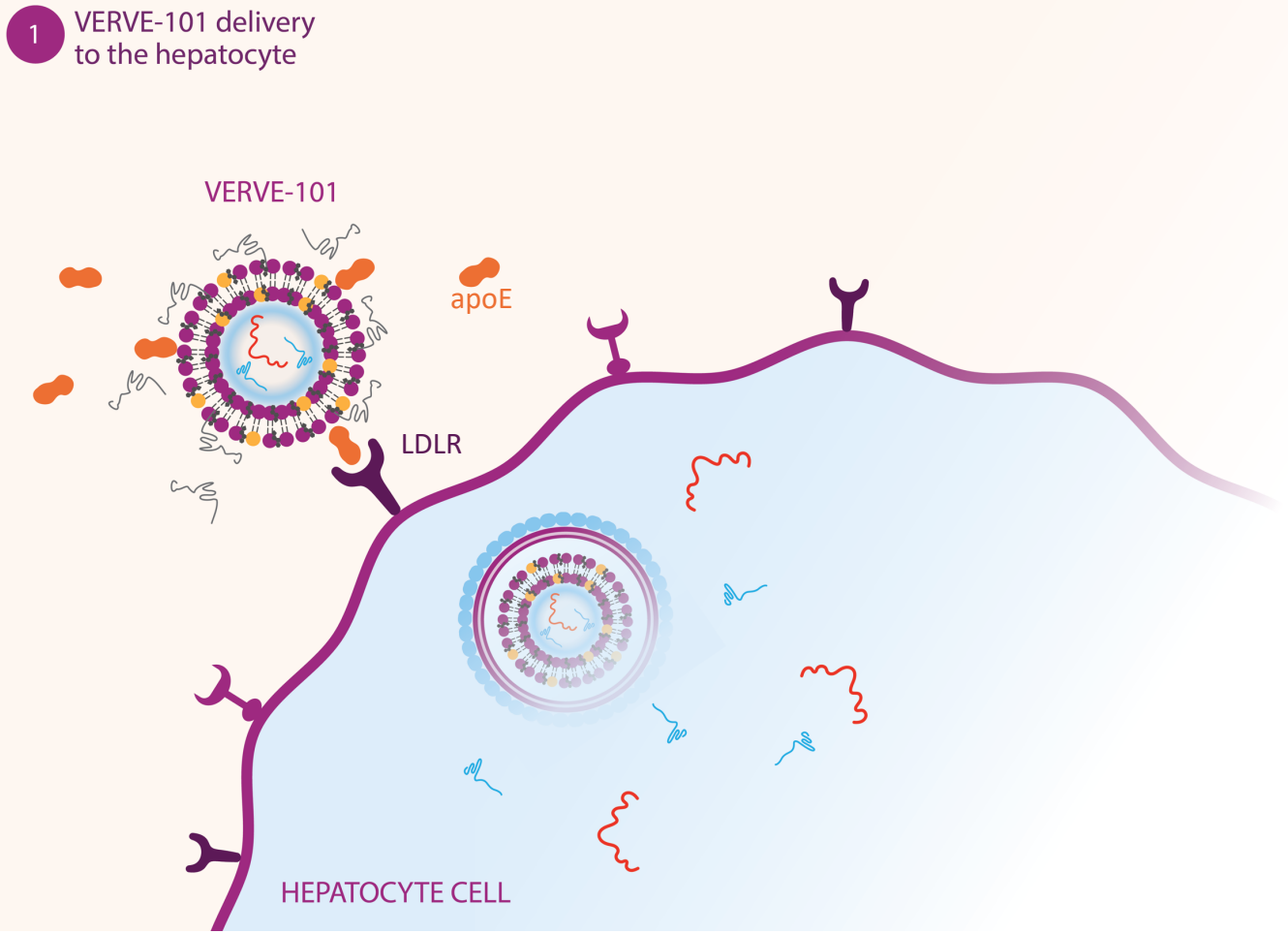
- Ionizable amino lipid
- DSPC
- Cholesterol
- PEG

=

VERVE-101

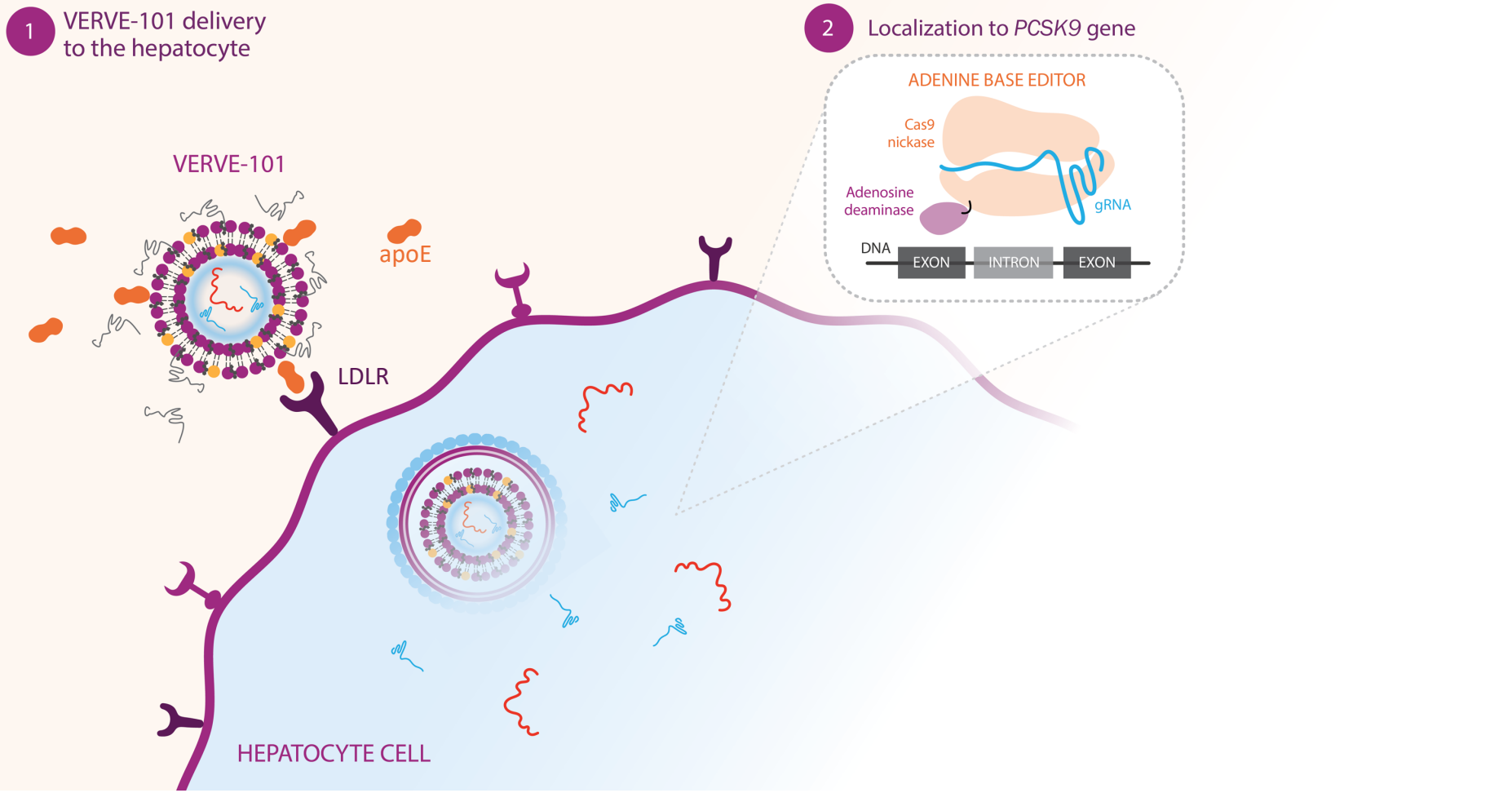


The VERVE-101 LNP enters hepatocytes by LDLR-mediated endocytosis



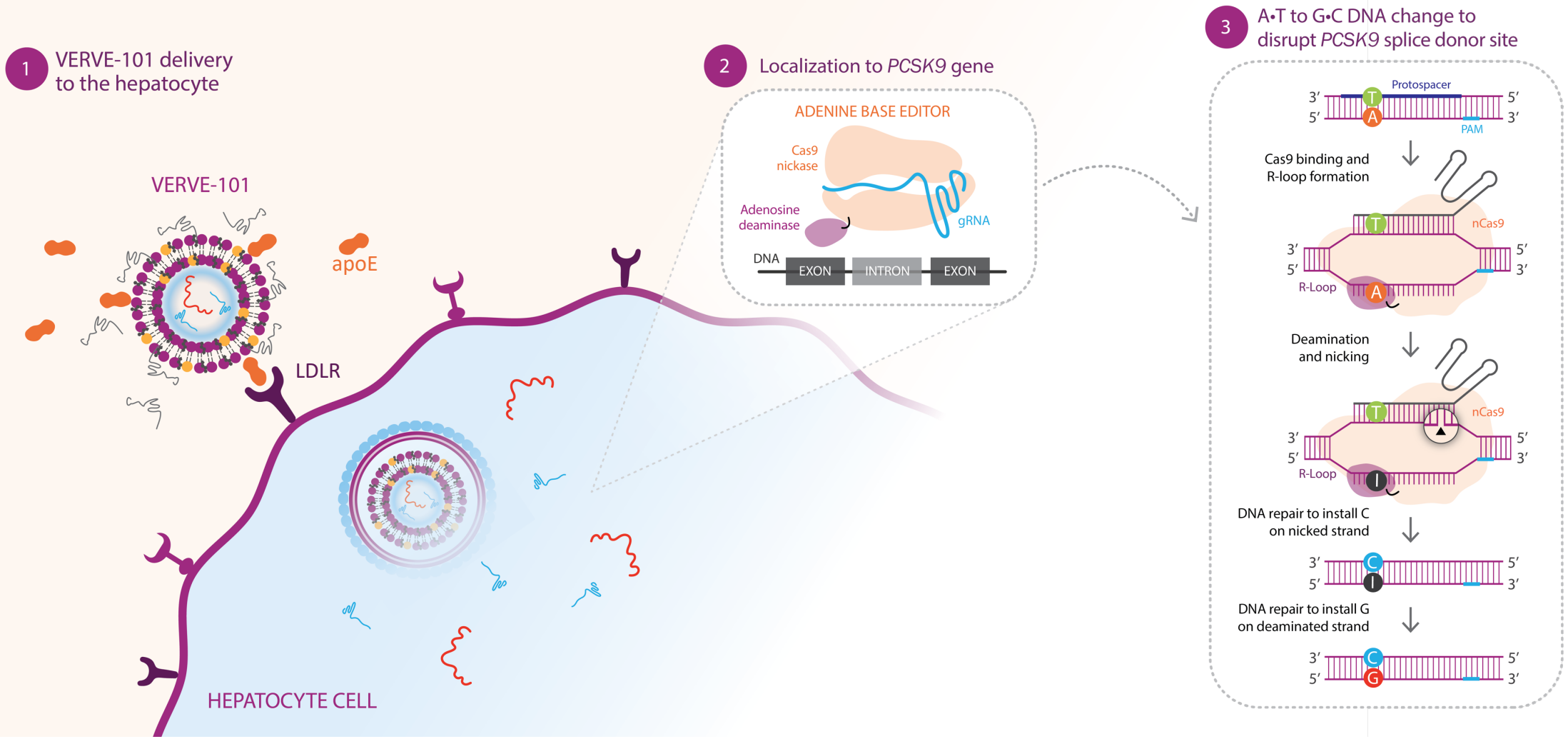
Lipid nanoparticle
Ionizable amino lipid
DSPC
LDL receptor (LDLR)
apoE
mRNA
gRNA
PEG Lipid
Cholesterol

The adenine base editor is translated from the mRNA and binds with the gRNA to target *PCSK9*



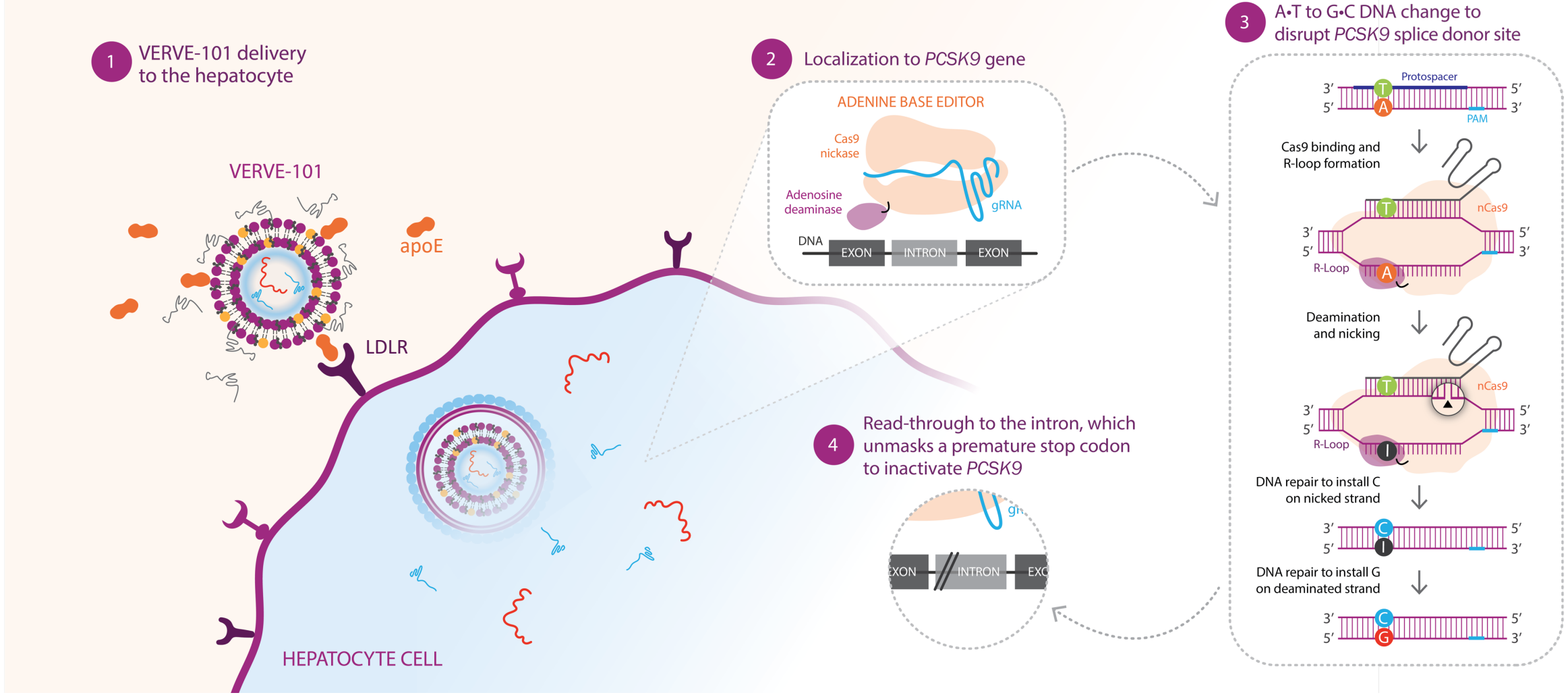
Lipid nanoparticle
Ionizable amino lipid
DSPC
LDL receptor (LDLR)
apoE
mRNA
gRNA
PEG Lipid
Cholesterol

The base editor makes a single precise A-to-G change in the *PCSK9* gene



Lipid nanoparticle | Ionizable amino lipid | DSPC | LDL receptor (LDLR) | apoE | mRNA | gRNA | PEG Lipid | Cholesterol

The A-to-G change introduces a premature stop codon in the *PCSK9* transcript and inactivates the gene



Lipid nanoparticle · Ionizable amino lipid · DSPC · LDL receptor (LDLR) · apoE · mRNA · gRNA · PEG Lipid · Cholesterol

Four key questions for *in vivo* genome editing with VERVE-101

Potency: what degree of liver *PCSK9* editing can be achieved?

Durability: what evidence supports the potential for a permanent effect?

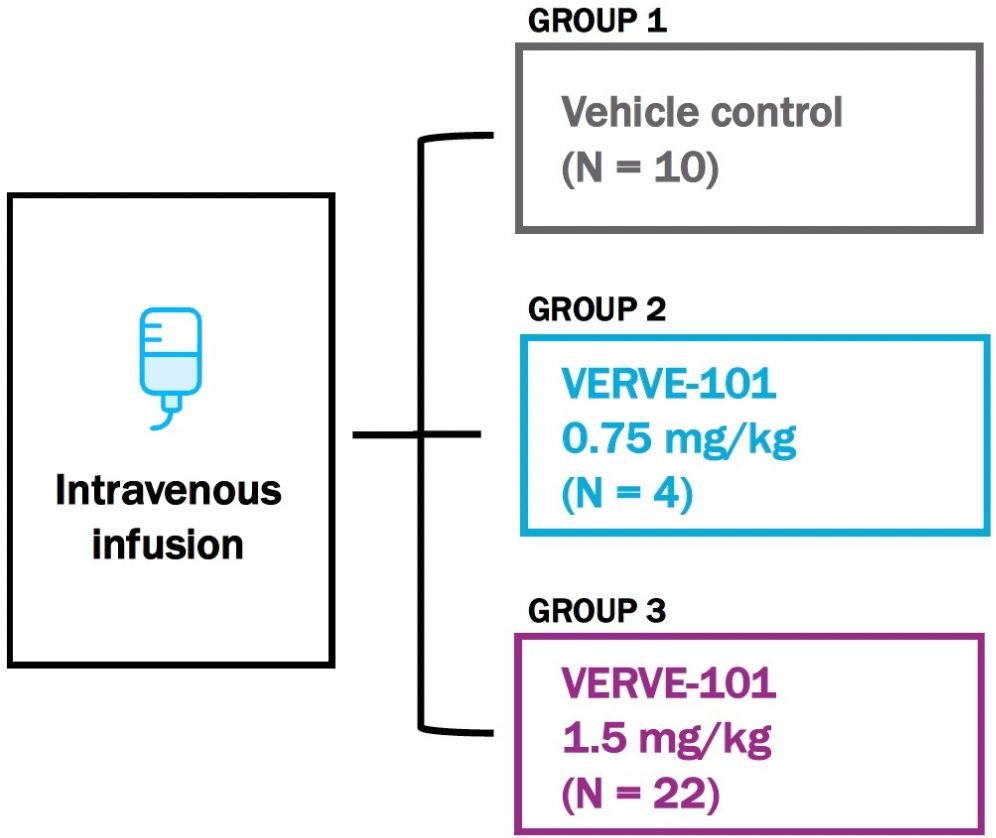
Biodistribution: is there editing outside the liver?

Off-target: does VERVE-101 edit other places in the genome?

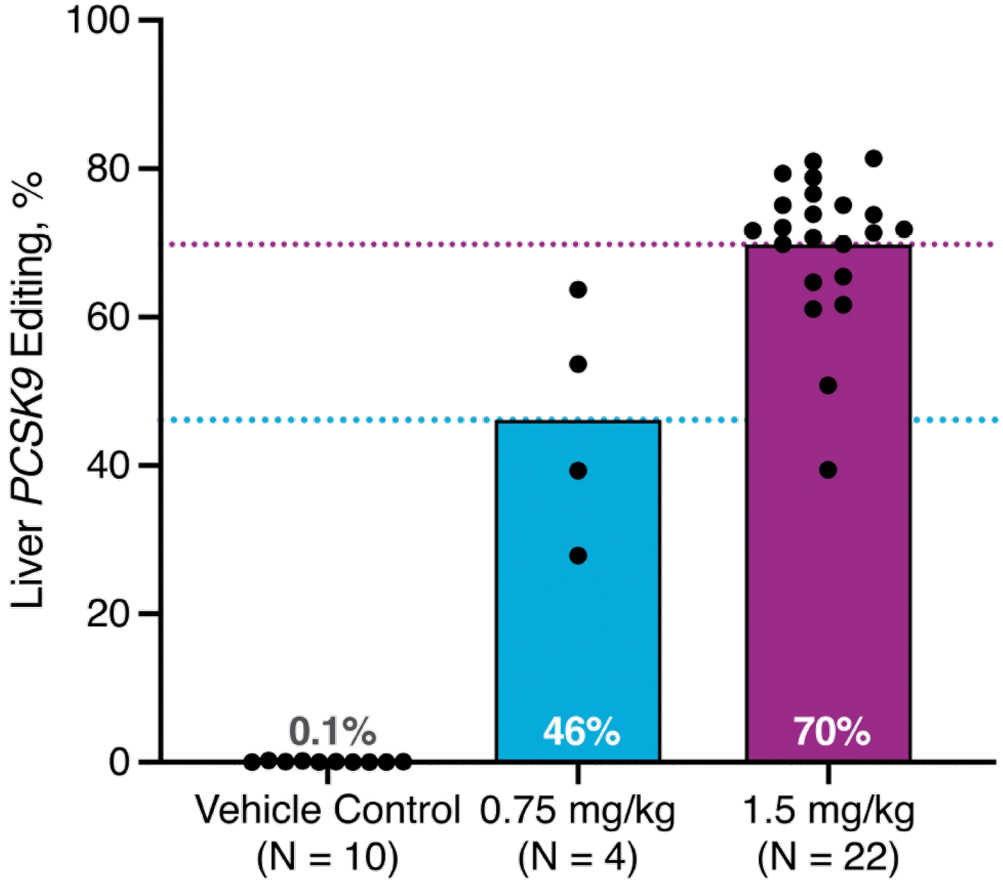
12

In non-human primates, a single infusion of 1.5 mg/kg VERVE-101 led to mean liver *PCSK9* editing of 70%

Study of 36 Non-human Primates

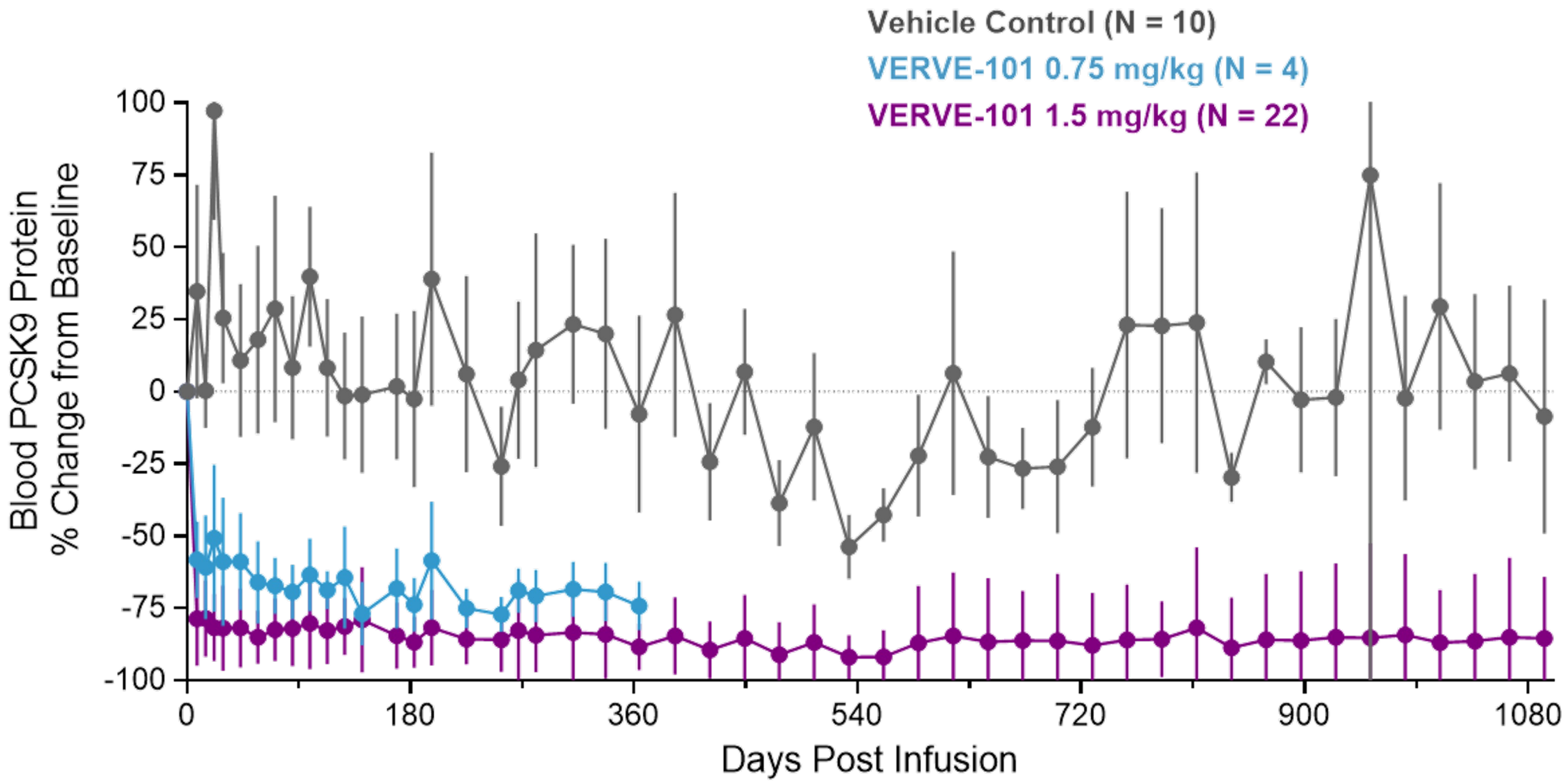


Efficient Liver PCSK9 editing



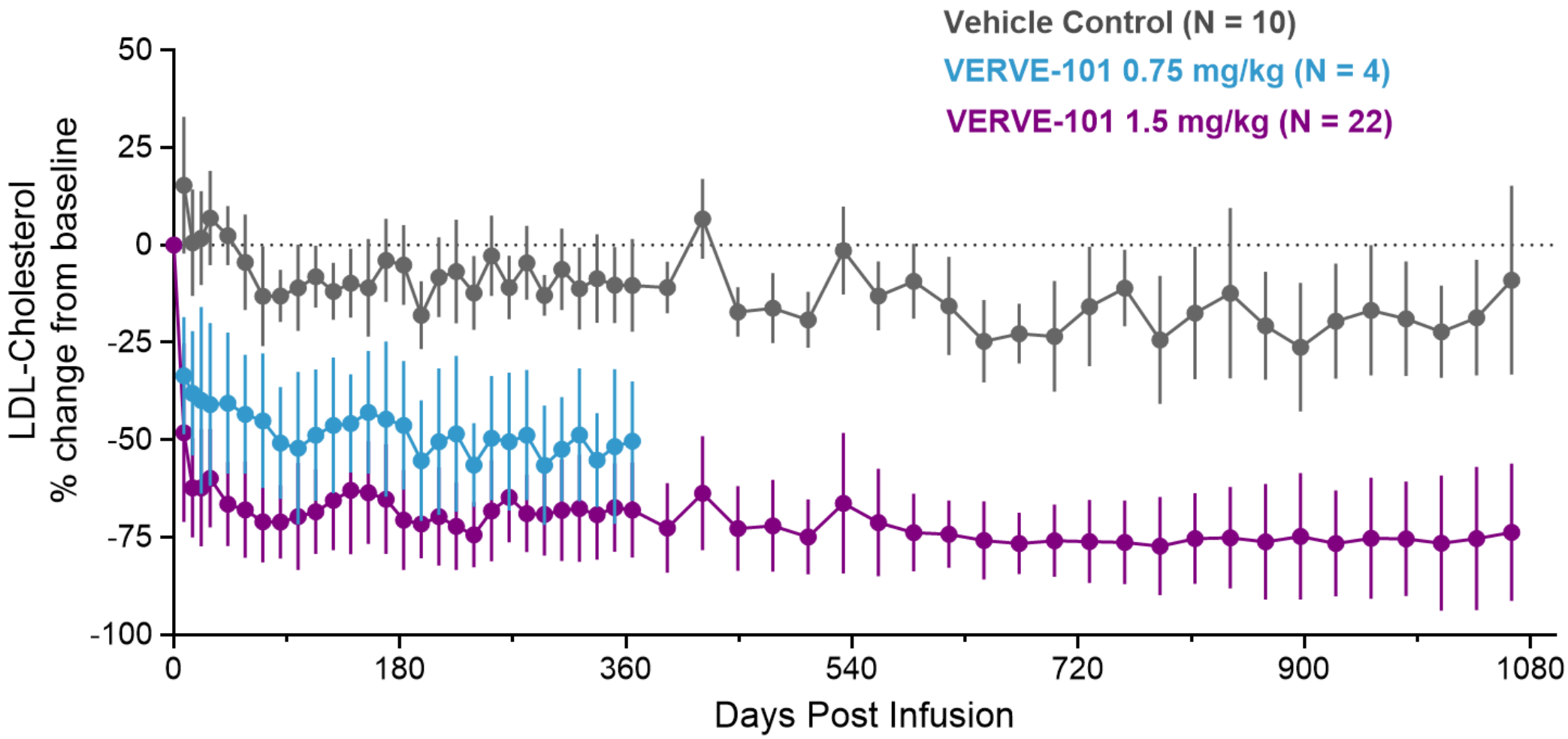
Lee R, et al. Circulation. 2023;147(3):242-53

In NHPs, a single infusion of VERVE-101 led to blood PCSK9 reductions up to 85%, durable to ~3 years and ongoing



NHP, non-human primate
Data represents mean +/- SD for cohorts which included N=10 in control and N=22 in VERVE-101 at the earliest time points and N=7 and N=16, respectively, at the last time point
Reductions are time-weighted average change from baseline

In NHPs, a single infusion of VERVE-101 led to blood LDL-C reductions up to 68%, durable to ~3 years and ongoing



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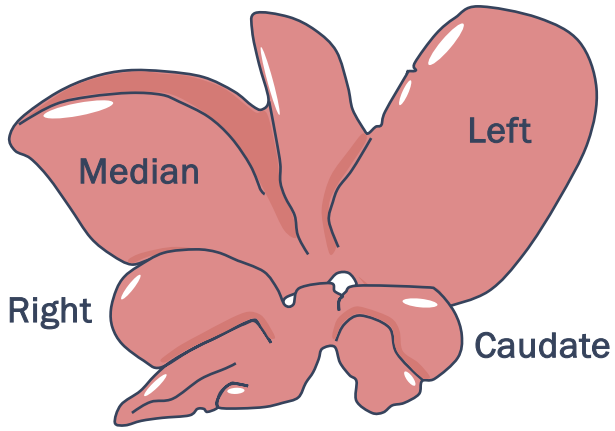
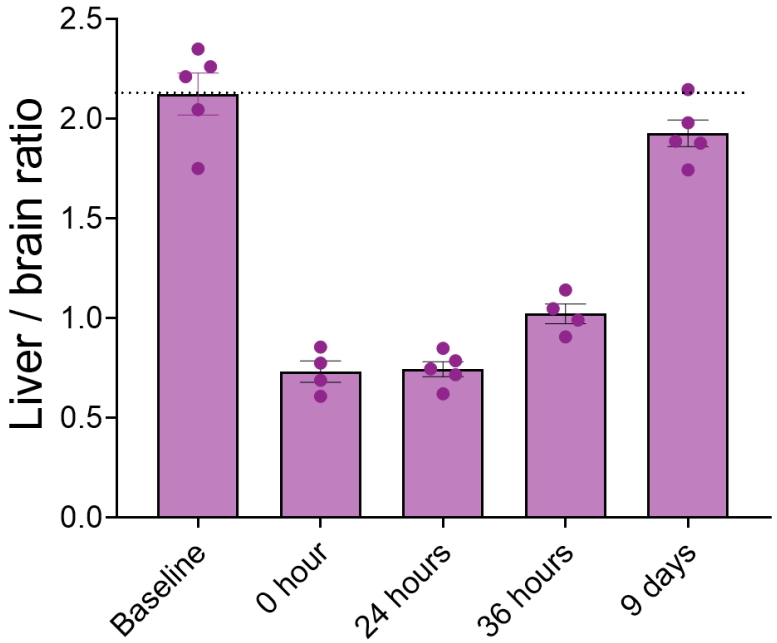
Reductions are time-weighted average change from baseline

Partial hepatectomy in mouse is a challenge model for the durability of base editing in the liver

Partial hepatectomy (PHx)

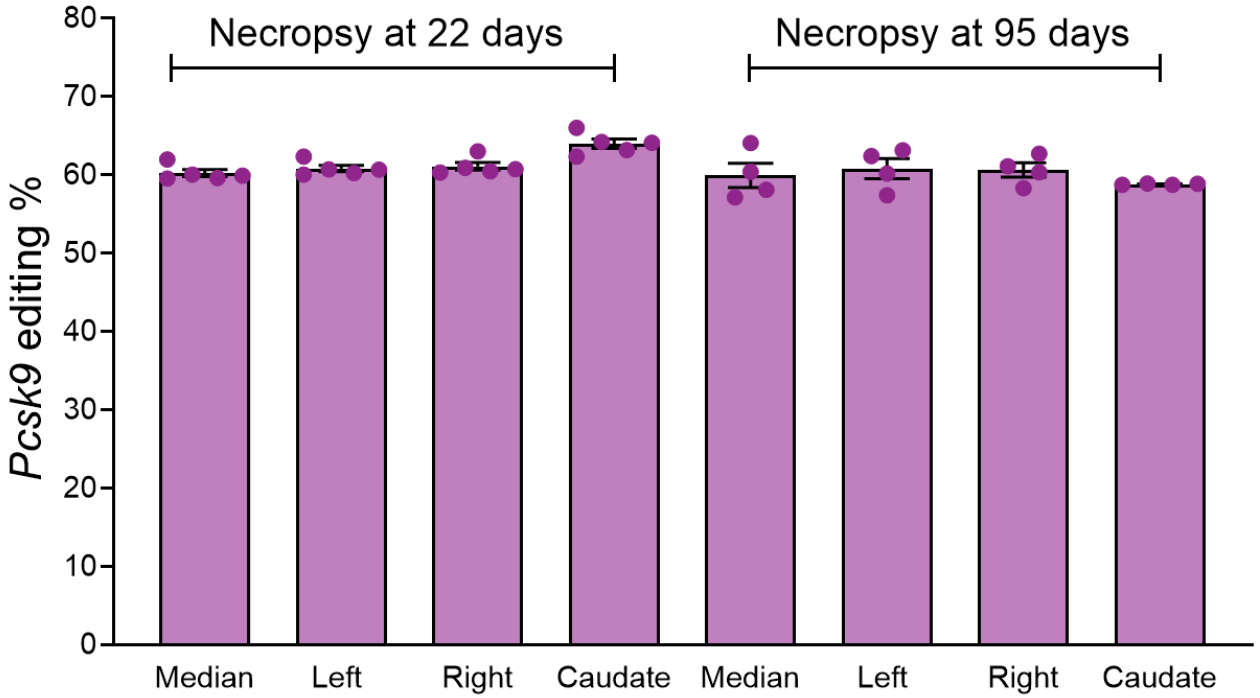




* VERVE-101mu: murine surrogate VERVE-101

VERVE-101mu induced robust editing in mice that is durable in the sham surgery group to 3 months in all liver lobes

Sham Surgery Group



All animals shown received 0.5 mg/kg VERVE-101mu

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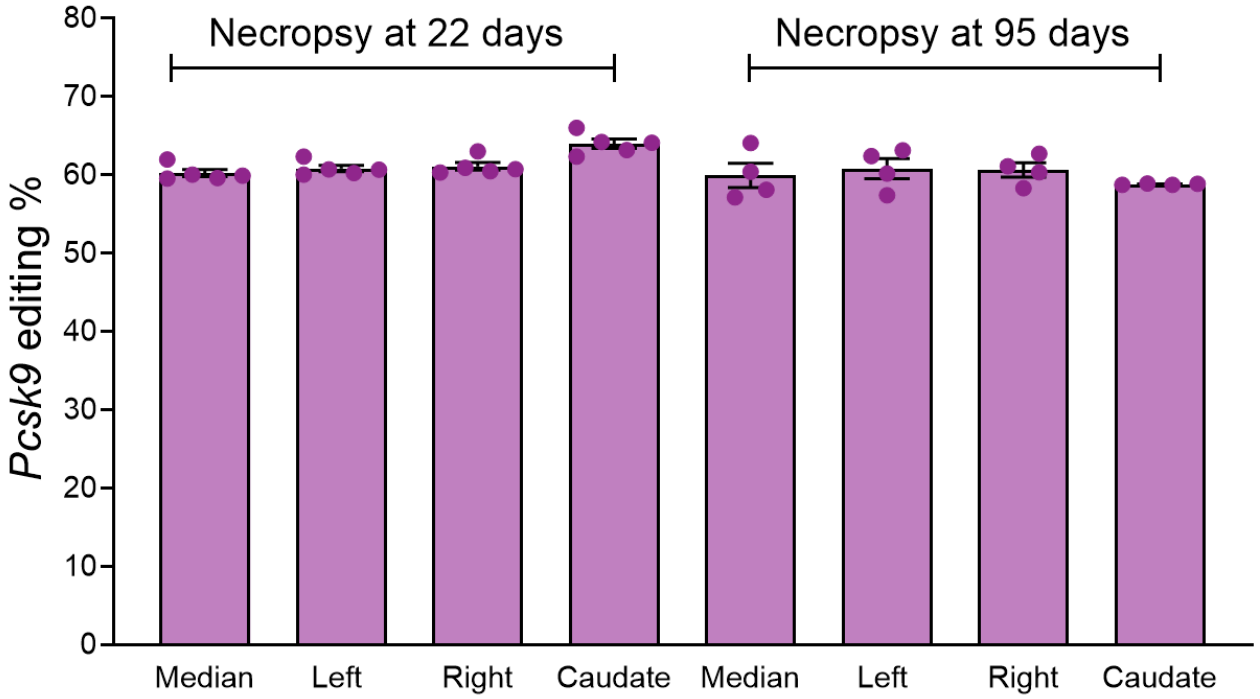
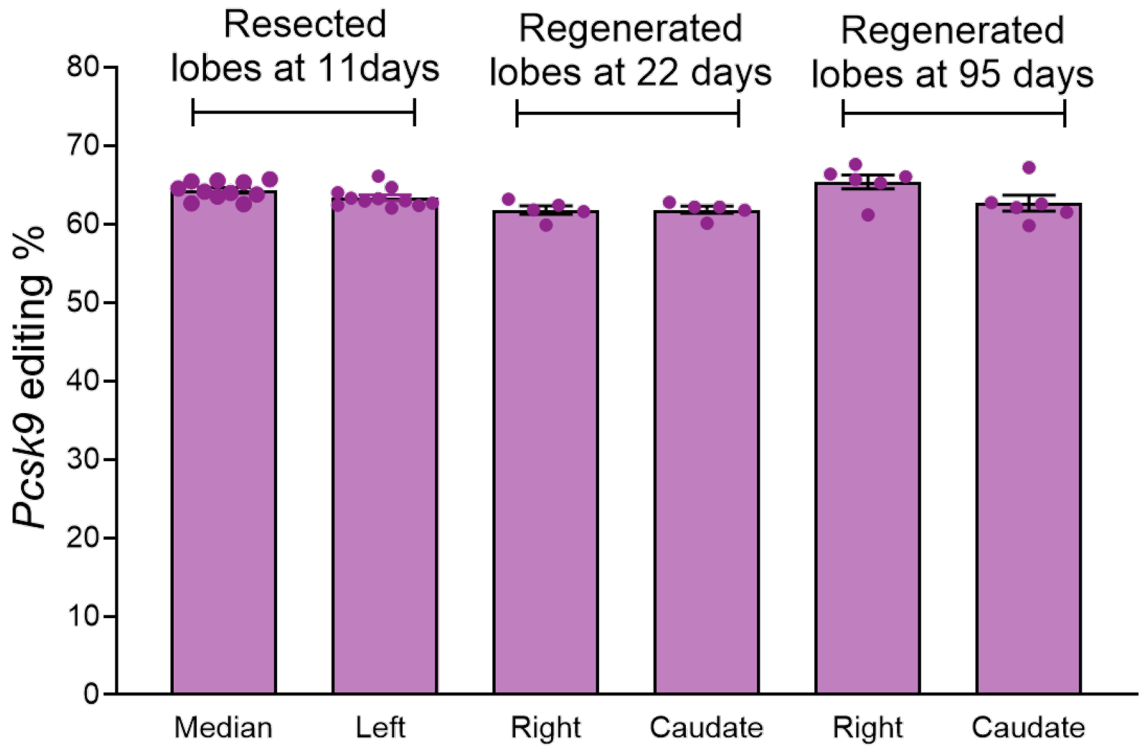
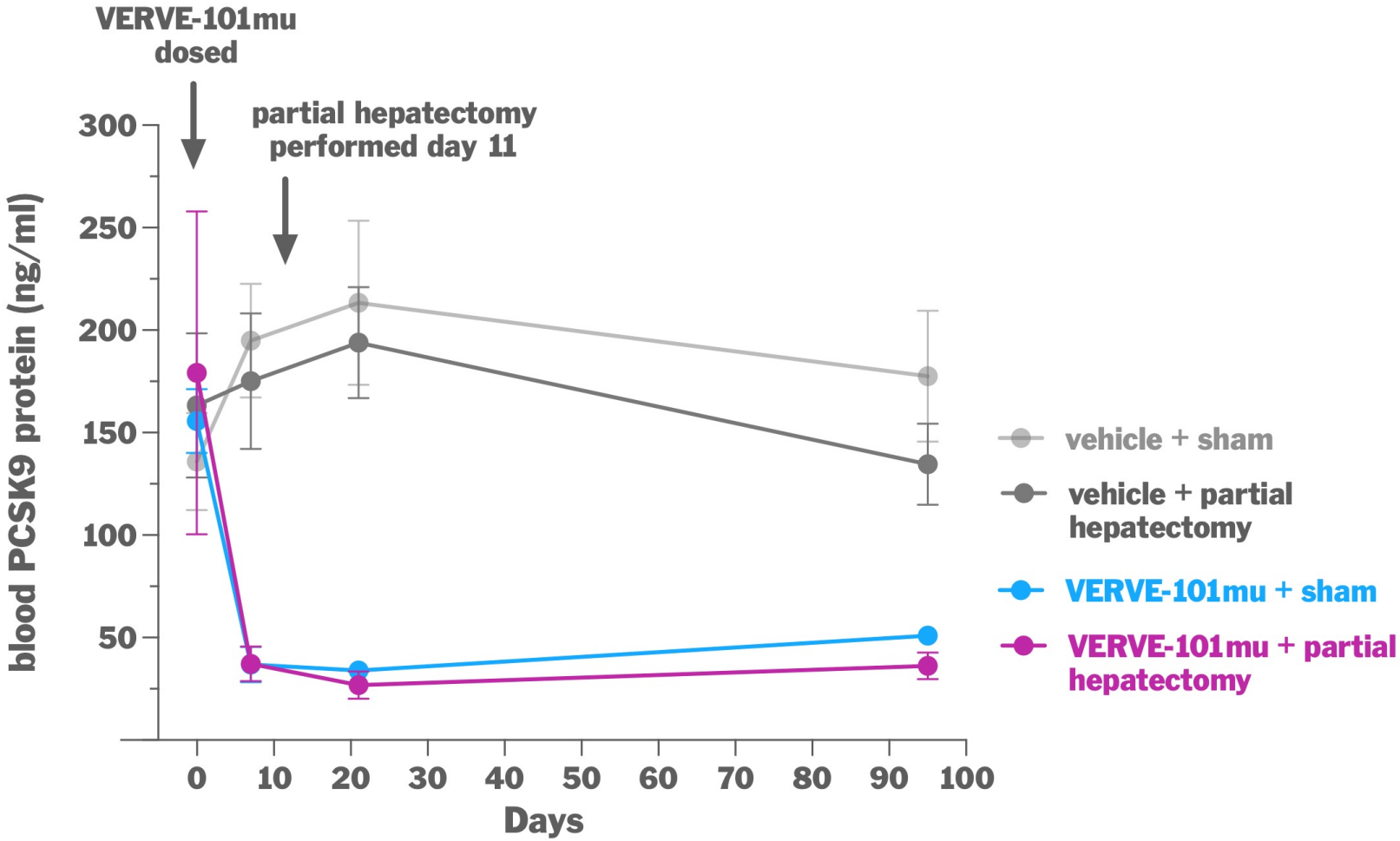


Partial Hepatectomy Groups



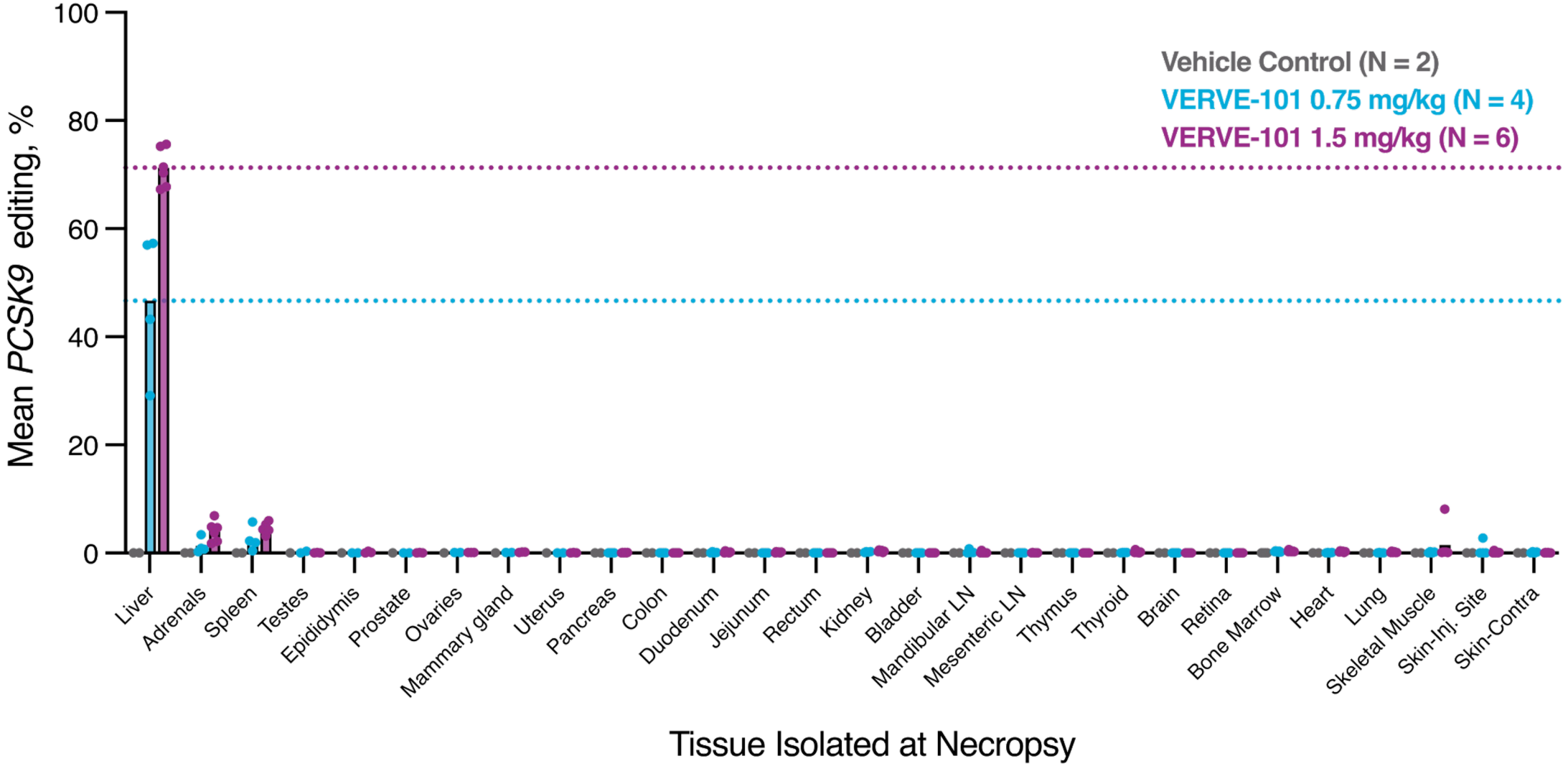
All animals shown received 0.5 mg/kg VERVE-101mu

VERVE-101mu induced sustained reductions in PCSK9 protein levels following partial hepatectomy in mice



VERVE-101mu dose: 0.5 mg/kg
Distinct animals are represented at each time point due to planned necropsies, mean +/- SD

In NHPs dosed with a single infusion of VERVE-101, on-target *PCSK9* editing occurred mostly in the liver



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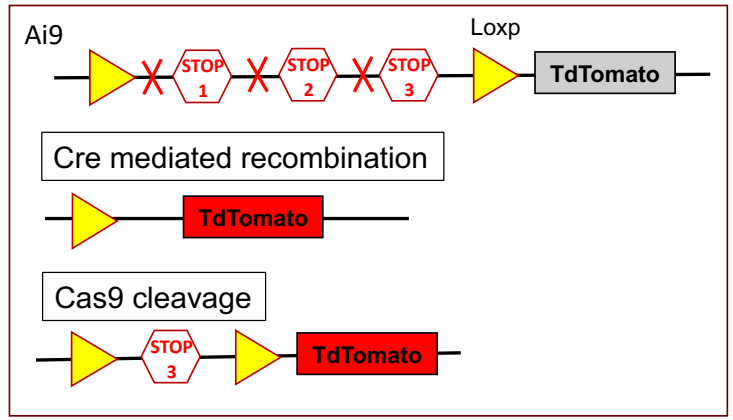
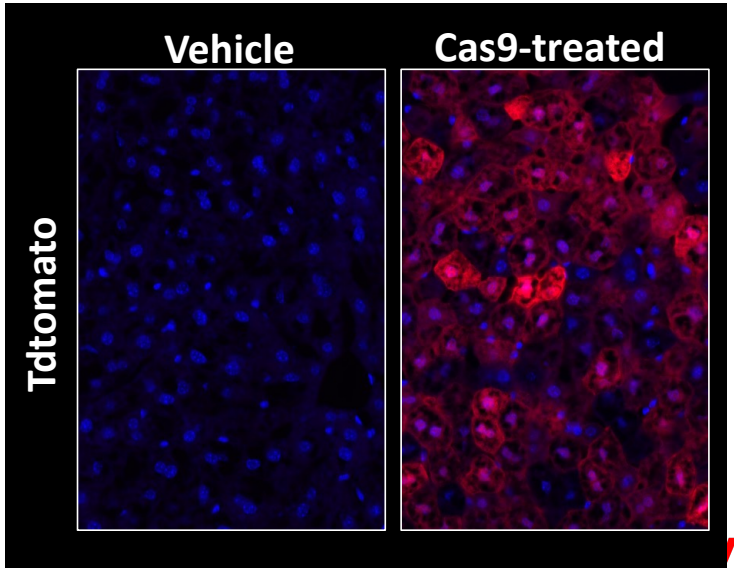
The Ai9 reporter mouse is a valuable tool for evaluating biodistribution at the cellular level

Ai9 reporter mouse

- TdTomato construct with 3 stop cassettes in the promoter
  - Cas9/gRNA LNP edits 2 of 3 STOP cassettes, allowing expression of the fluorescent protein
  - Allows for analysis of cell-specific editing in tissues
  - Chromogenic IHC techniques to detect TdTomato positive cells
- Positive control constitutively expresses TdTomato
  - Tissue can be assessed for Cas9-mediated editing





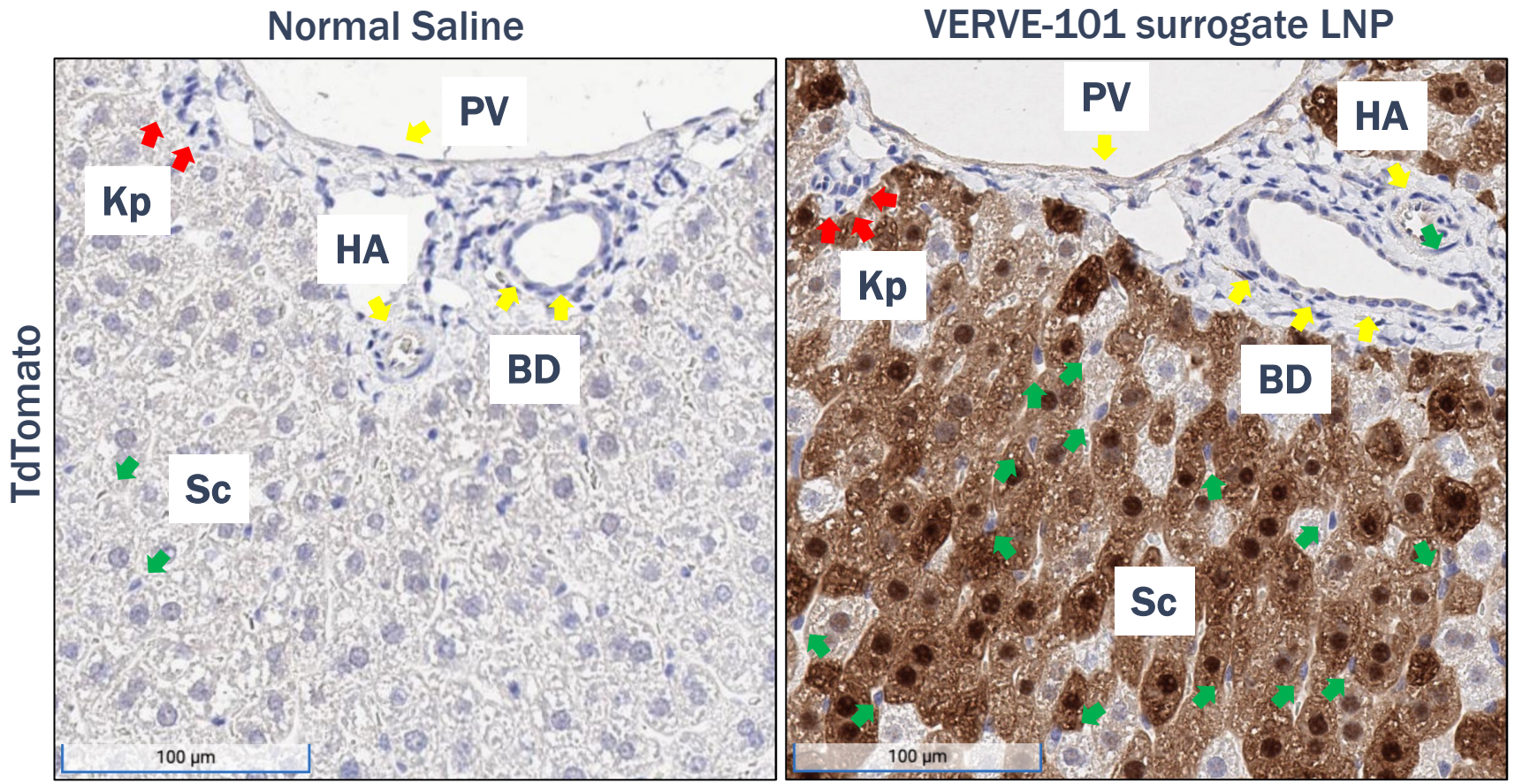
VERVE-101 surrogate LNP

- The same LNP formulation as VERVE-101
- Guide RNA targeting STOP cassette and SpCas9 mRNA

IHC, immunohistochemistry

VERVE-101 surrogate LNP shows high specificity for hepatocytes in the liver

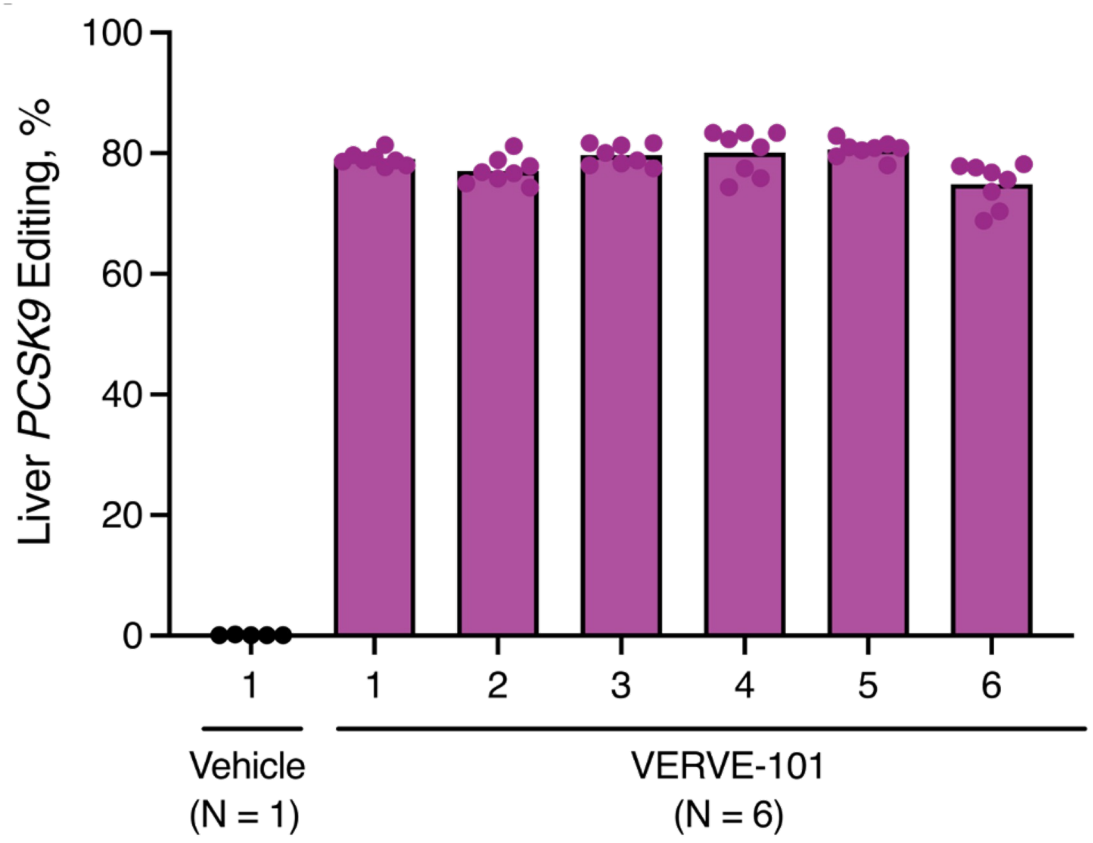
Ai9 mice treated with VERVE-101 surrogate LNP at saturating dose (0.5 mg/kg) or normal saline



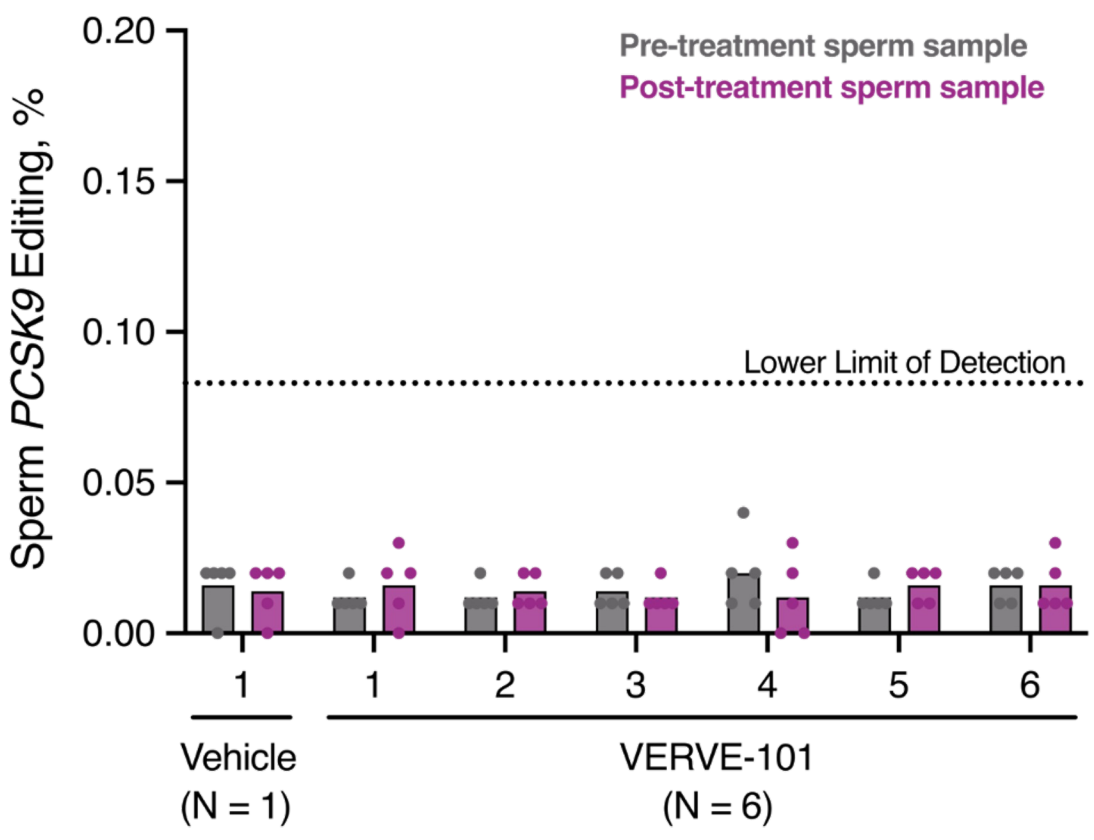
PV: Portal vein **HA**: Hepatic artery **BD**: Bile duct **Kp**: Kupffer cell **Sc**: Sinusoidal endothelial cell

In sexually mature male NHPs treated with VERVE-101, no evidence of *PCSK9* editing in sperm

6 NHPs treated with VERVE-101
Mean liver *PCSK9* editing 79%



Sequencing of sperm noted no detectable *PCSK9* editing



NHP, non-human primate

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F1 progeny study of VERVE-101mu treated female mice

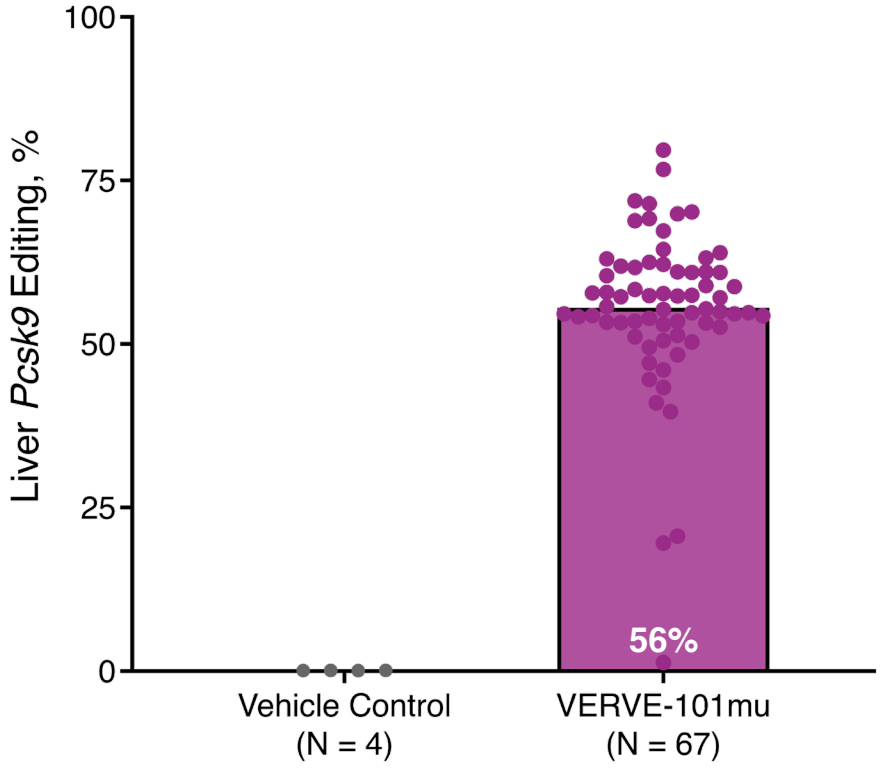
Problem

Not technically feasible to reliably dissect oocytes from ovarian tissue to assess for germline editing

Solution

Assess editing in offspring of 90 female mice treated with 0.1 mg/kg VERVE-101mu saturating dose

Liver *PCSK9* editing confirmed in VERVE-101mu treated female dams



Data from 67 out of 90 treated females who became pregnant.

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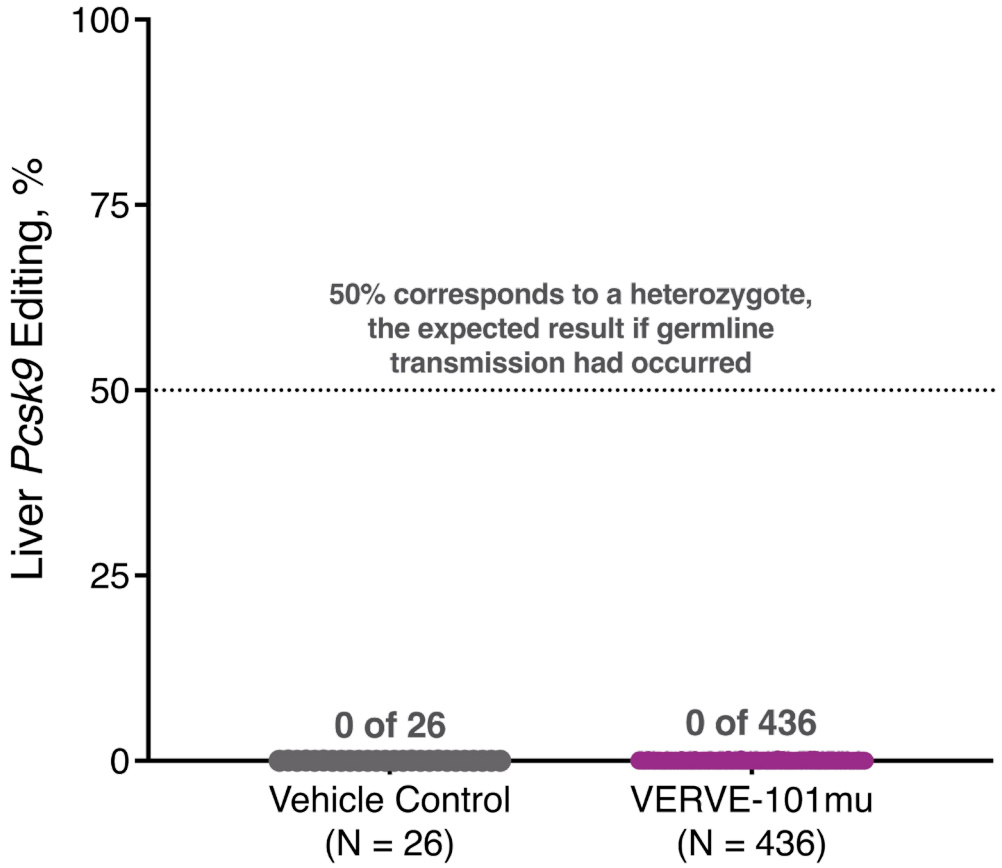
F1 progeny study of VERVE-101mu treated female mice shows no evidence for germline transmission of the *PCSK9* edit

436 offspring of treated females
No detectable transmission



0 of 436 translates into upper bound of the 95% CI of 0.8%.

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Multiple orthogonal methods used to nominate candidate sites for off-target editing screen

candidate site nomination methods

Experimental: ABE-digenome-seq[1,2]

Genome-wide analysis of DNA from human liver cells exposed to base editor

Experimental: ONE-Seq[3]

Editing of synthetic library of tens of thousands of DNA sequences with high homology to target site

Bioinformatics:

In silico assessment of human genome

panel of candidates

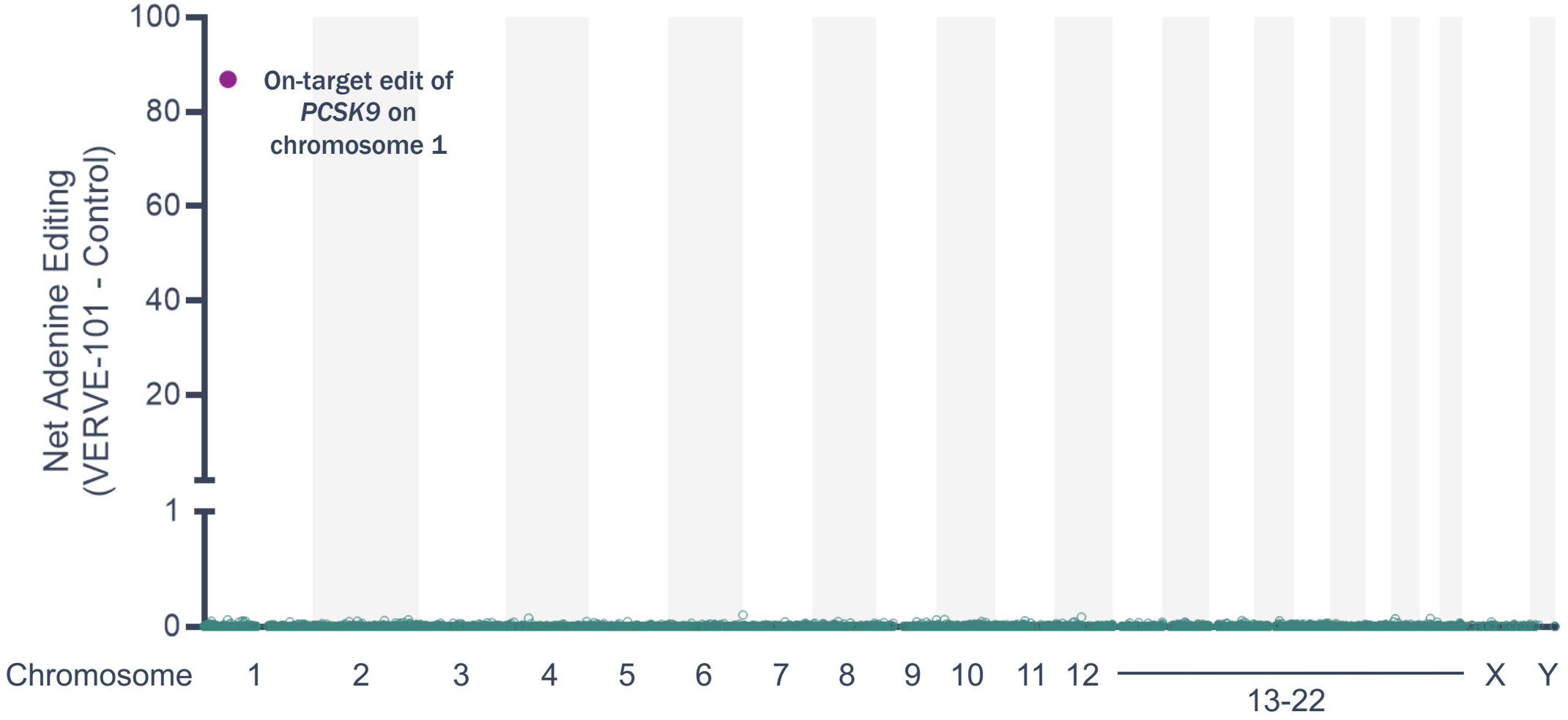
~6000 sites

across the genome with experimental or bioinformatic similarity to the on-target site

1. Kim et al. Nature Biotechnology 2019;37(4):430-435. 2. Liang et al. Nature Communications 2019;10(1):67; 3. Petri et al. bioRxiv 2021;2021.04.05.438458.

No off-target editing with VERVE-101 in primary human hepatocytes

Manhattan style plot of net adenine editing in analysis of ~6000 candidate sites in PHH



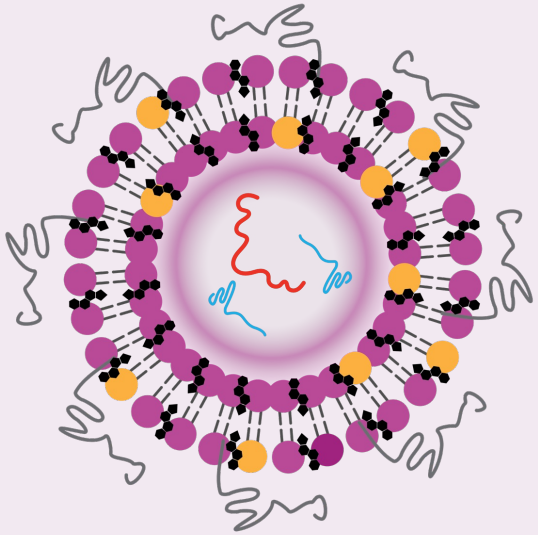
Y axis indicates net editing (alternate allele frequency in treated primary liver cells – matched untreated controls); PHH, primary human hepatocytes

Potent, specific, and durable *PCSK9* editing of animal models with VERVE-101

- Mean 85% reduction in blood PCSK9 protein and 68% reduction in LDL-C in NHPs treated with 1.5 mg/kg of VERVE-101, durable to ~3 years and ongoing
- Mouse partial hepatectomy model shows *PCSK9* inactivation is durable in hepatocyte daughter cells
- *PCSK9* editing is highly specific to hepatocytes with no evidence for germline transmission
- No off-target editing observed in primary human hepatocytes

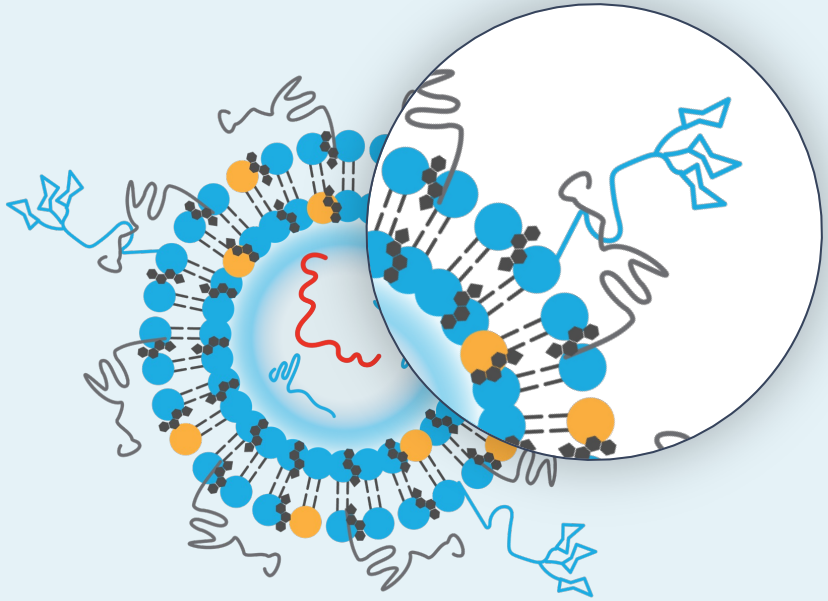
Verve has two *in vivo* CRISPR base editing product candidates that target *PCSK9* with an identical ABE and gRNA but different LNP delivery systems

VERVE-101



First-in-human program

VERVE-102



Dosing ongoing

- Different ionizable lipids
- VERVE-101 enters hepatocytes through the LDL receptor (LDLR)
- VERVE-102 has an added GalNAc targeting ligand – enabling entry by LDLR or asialoglycoprotein receptor

ABE, adenine base editor; gRNA, guide RNA; LNP, lipid nanoparticle