Safety and Durability of VERVE-101

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Disclosure

I am an employee of Verve Therapeutics

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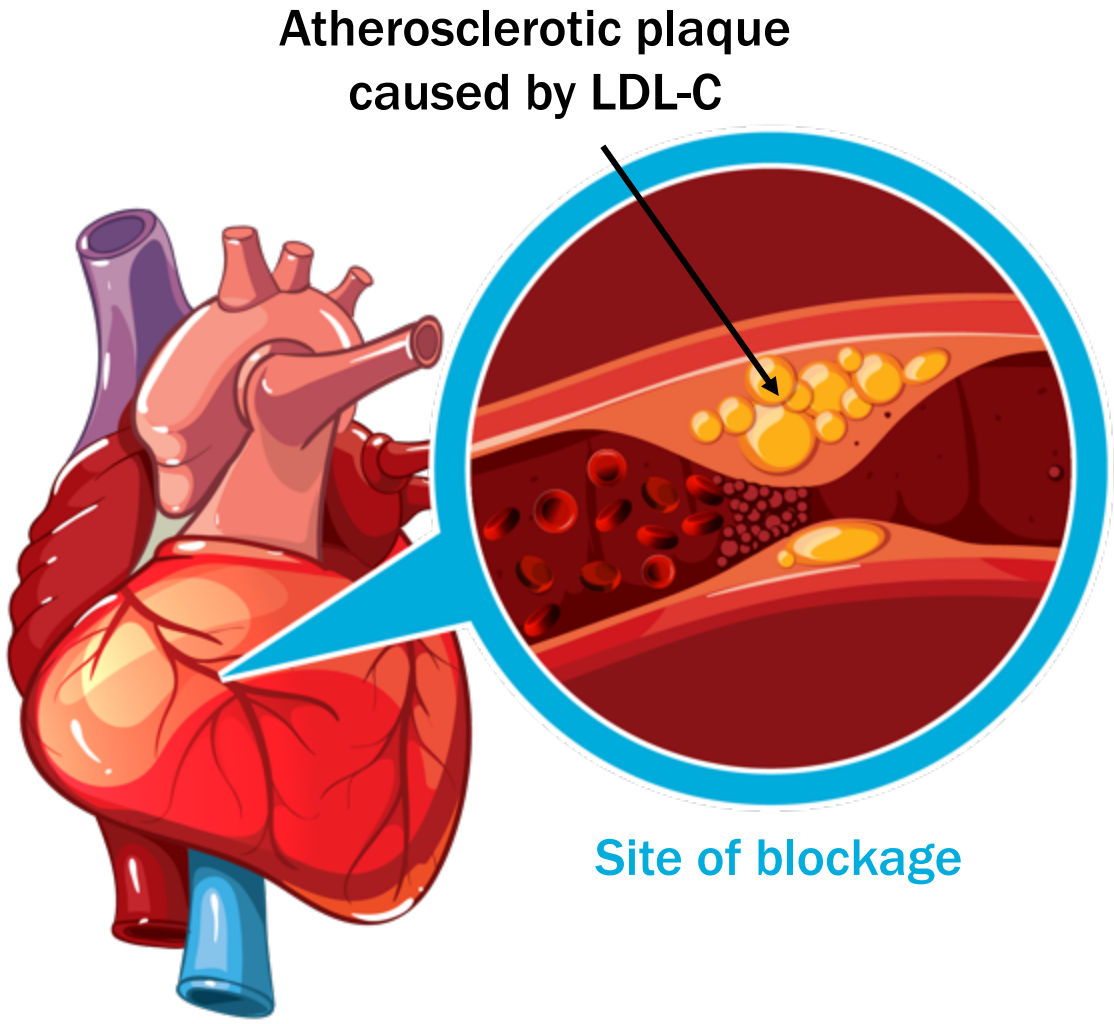
Atherosclerotic cardiovascular disease (ASCVD): blood low-density lipoprotein cholesterol (LDL-C) clogging heart arteries

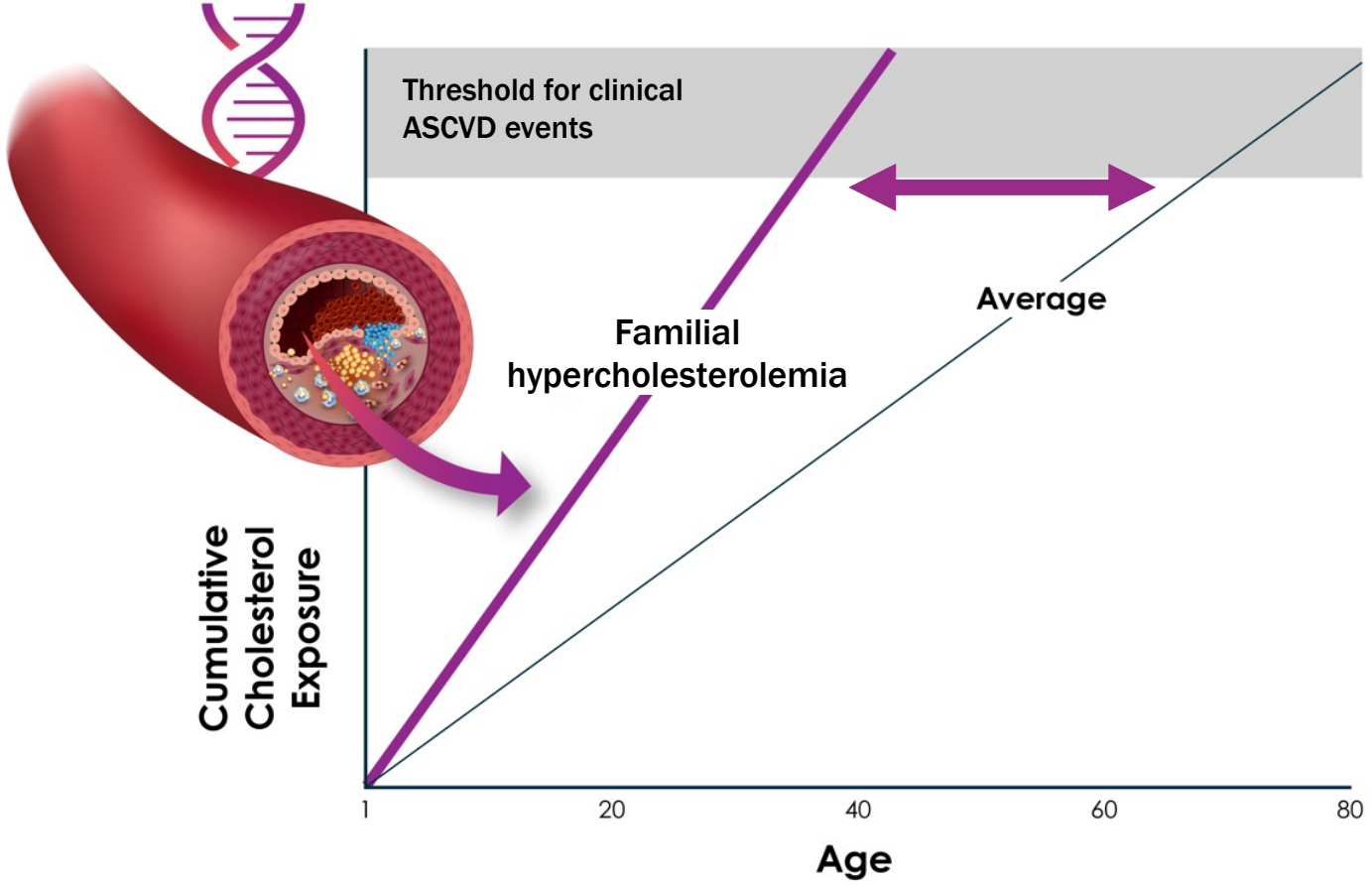
#1 cause of death worldwide

100s of millions of patients worldwide

31M with genetic form of ASCVD: familial hypercholesterolemia

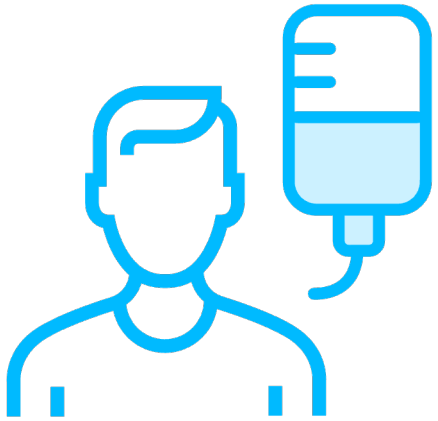


High cumulative life-long exposure to blood LDL-C established as a root cause of ASCVD

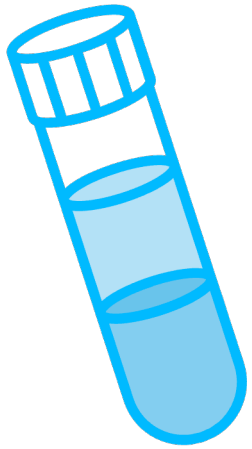


Adapted from Horton et al. J Lipid Res., 2009

Imagine if…



there was a single-course treatment that…



… durably and safely lowered blood LDL cholesterol.

Such a medicine would have potential to treat and ultimately prevent ASCVD

Developing a pipeline of single-course gene editing medicines to treat patients with atherosclerotic cardiovascular disease (ASCVD)

PROGRAM	INITIAL INDICATION	DEVELOPMENT STATUS			
		Research/ Lead optimization	IND-Enabling	Clinical	Development Milestones
Low-density lipoprotein cholesterol (LDL-C)					
VERVE-101 ABE-PCSK9	Heterozygous familial hypercholesterolemia				• IND Submission (2022) • Phase 1 Initiation (2022)
LDL-C and triglyceride-rich lipoprotein (TRL)					
ANGPTL3	Familial hypercholesterolemia				• Candidate selection (2022) • Begin IND-enabling studies (2022)

Today: two streams of new data

ABE-PCSK9

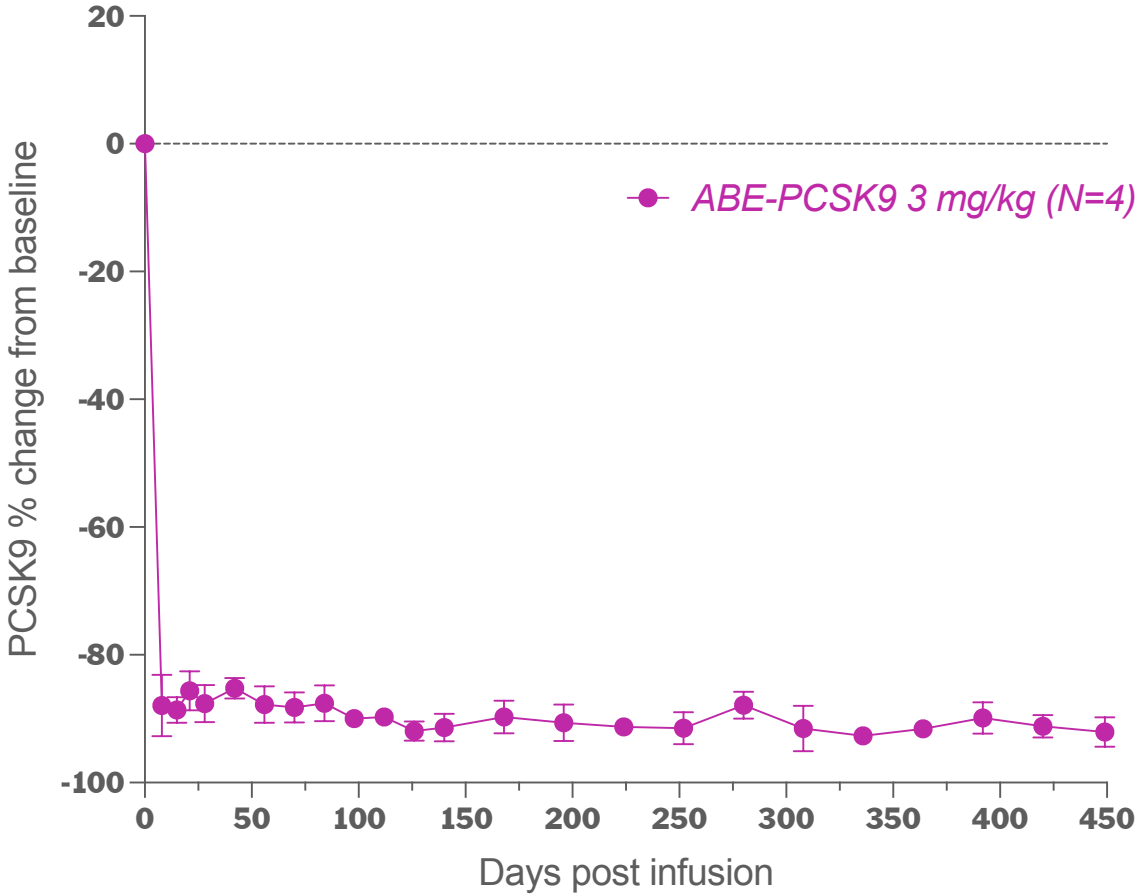
Precursor **ABE-PCSK9** formulation
15-month data

VERVE-101

New studies with
VERVE-101 drug product

Durability of PCSK9 and LDL-C reductions from ABE-PCSK9 editing extends out to 15 months in NHPs dosed with precursor formulation

Blood PCSK9 protein



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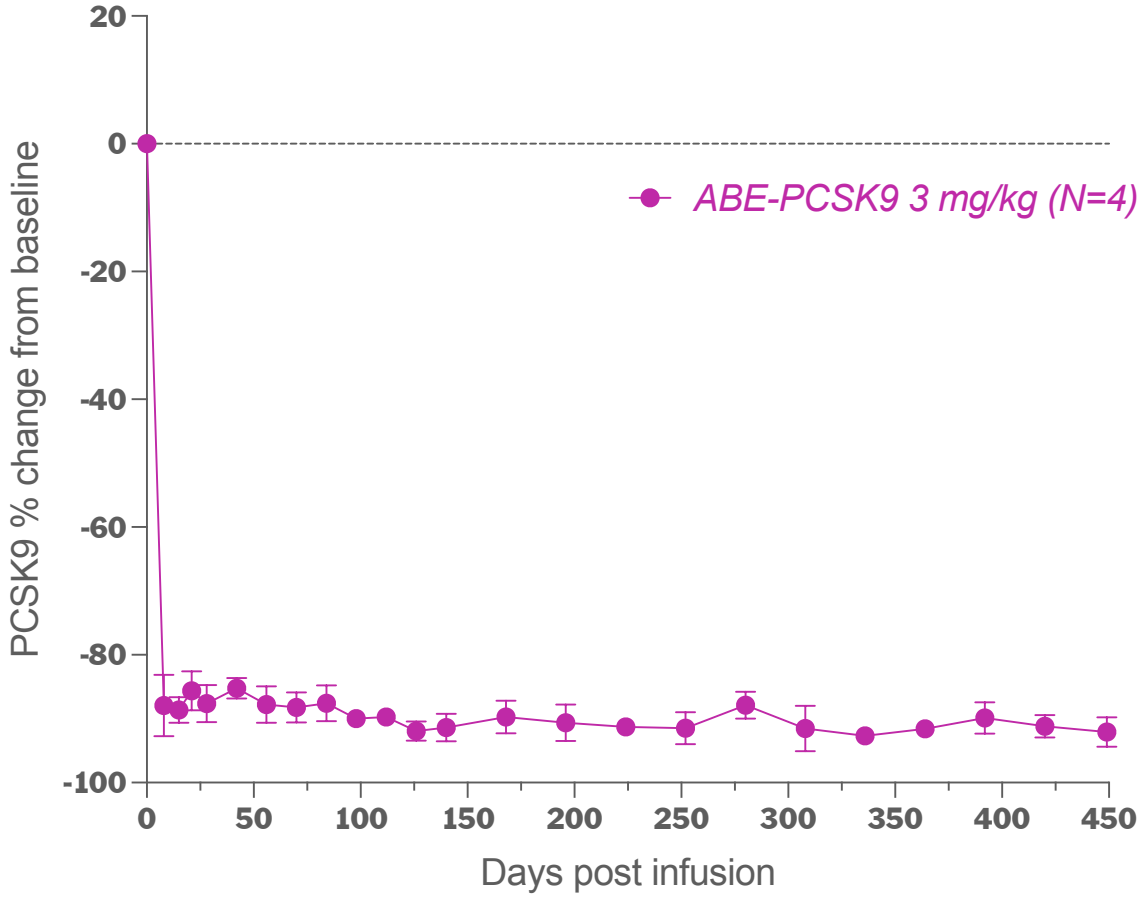
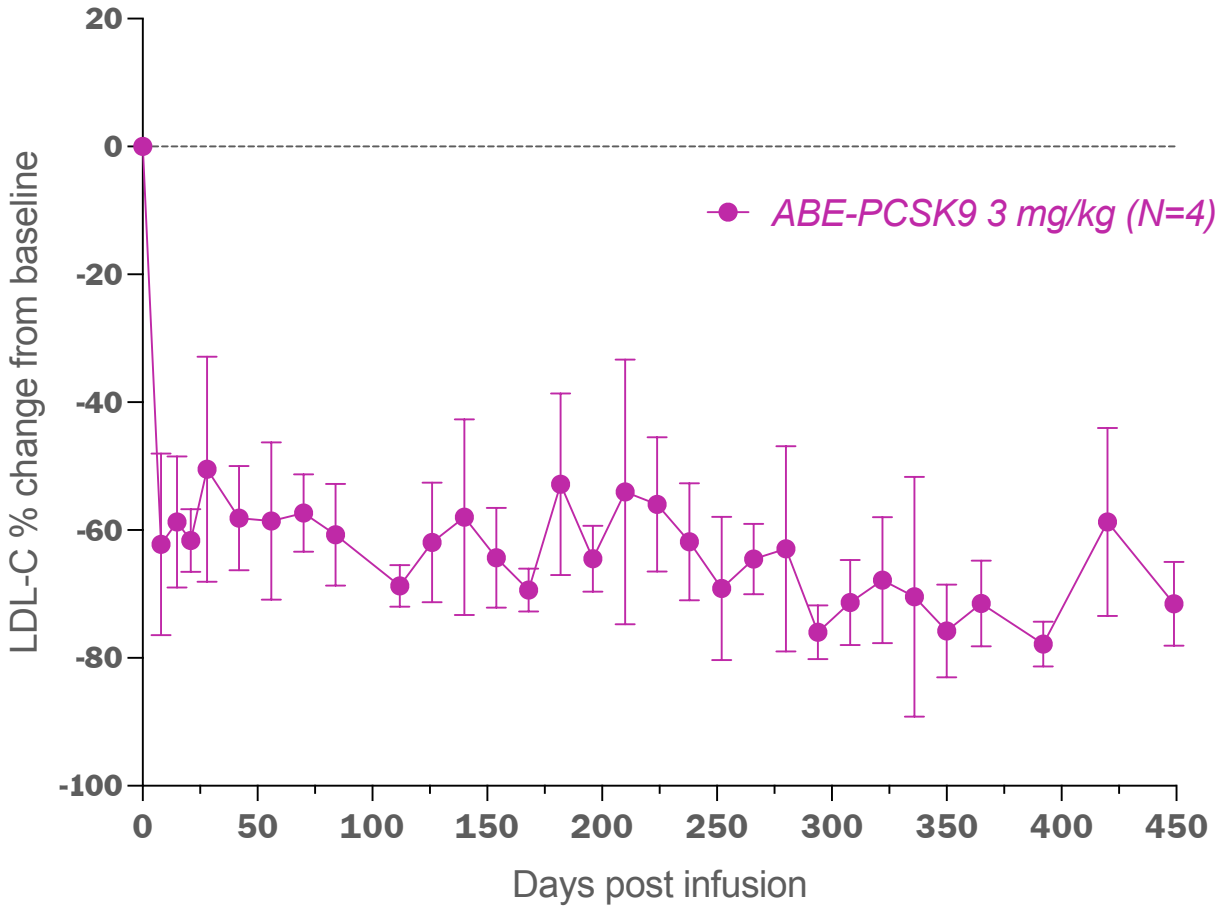


Blood LDL-C



Today: two streams of new data

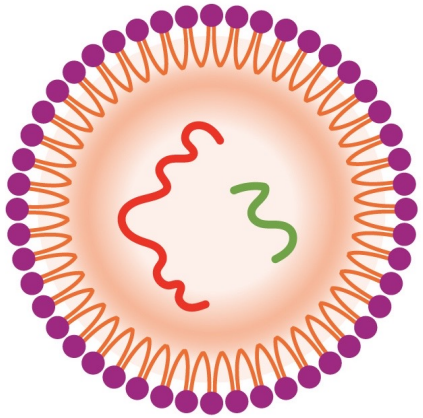
ABE-PCSK9

Precursor ABE-PCSK9 formulation
15-month data

VERVE-101

New studies with VERVE-101 drug product

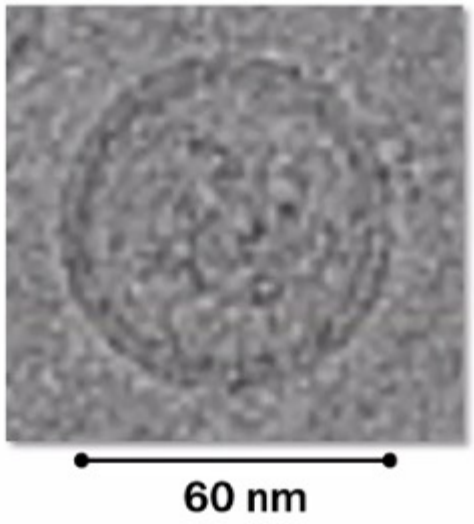
VERVE-101: an optimized adenine base editor (ABE) mRNA + guide RNA (gRNA) packaged in a lipid nanoparticle (LNP)



mRNA

gRNA

Lipid nanoparticle (LNP)



- Base editing induces single base pair change from A-to-G in PCSK9 & designed to turn off the PCSK9 gene
- Avoids double-stranded DNA breaks caused by Cas9, gRNA targeting PCSK9 with high precision
- VERVE-101 is formulated with an optimized ABE mRNA sequence and process, and an LNP that targets the liver with high efficiency and specificity

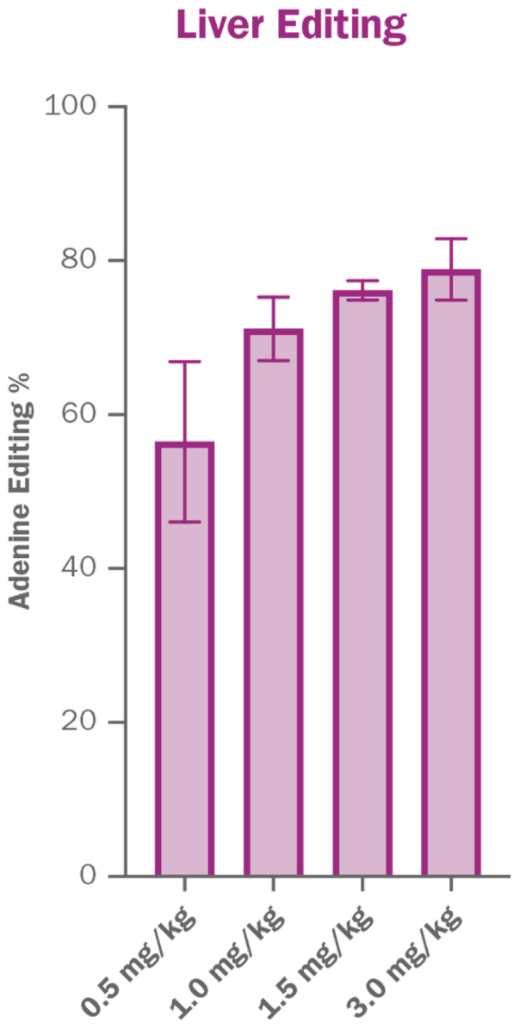
LNP licensed from Acuitas Therapeutics
Exclusive access to base editing through Beam Therapeutics

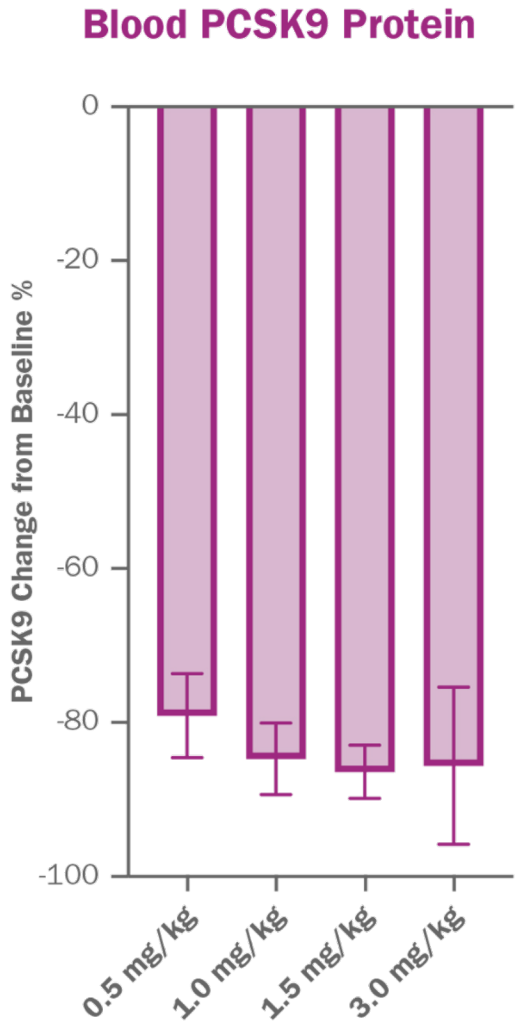
An extensive IND-enabling program for VERVE-101 is underway and on track for completion in 2022

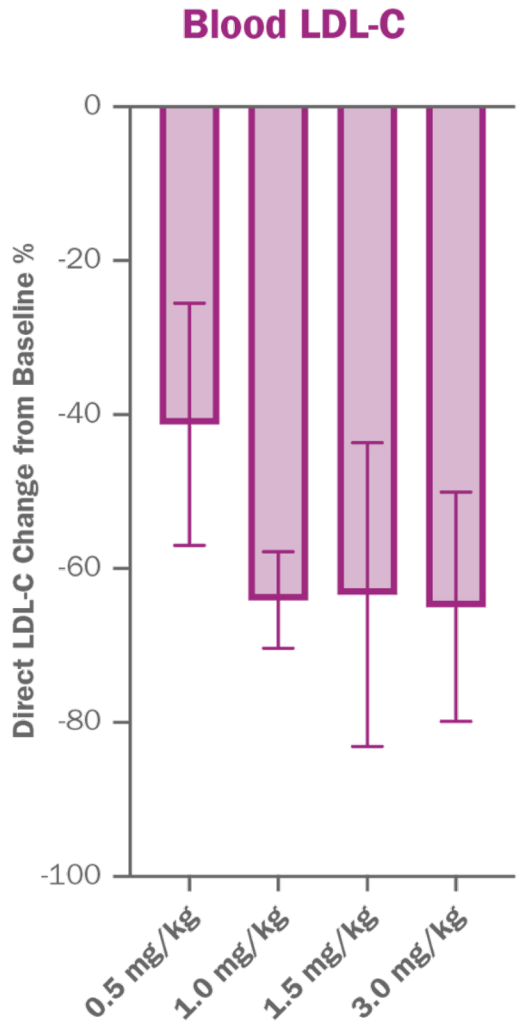
- GLP toxicology study in heterozygous FH mouse disease model
- Durability study in NHP using VERVE-101 drug product
- Studies to demonstrate the absence of germline editing
- Durability following partial hepatectomy in mouse
- Off-target evaluations to >1000 candidate sites & in multiple cell types
- Additional off-target methodologies including whole genome sequencing, RNA-seq, & evaluation for structural variants

VERVE-101 is potent at doses as low as 0.5 mg/kg in NHPs

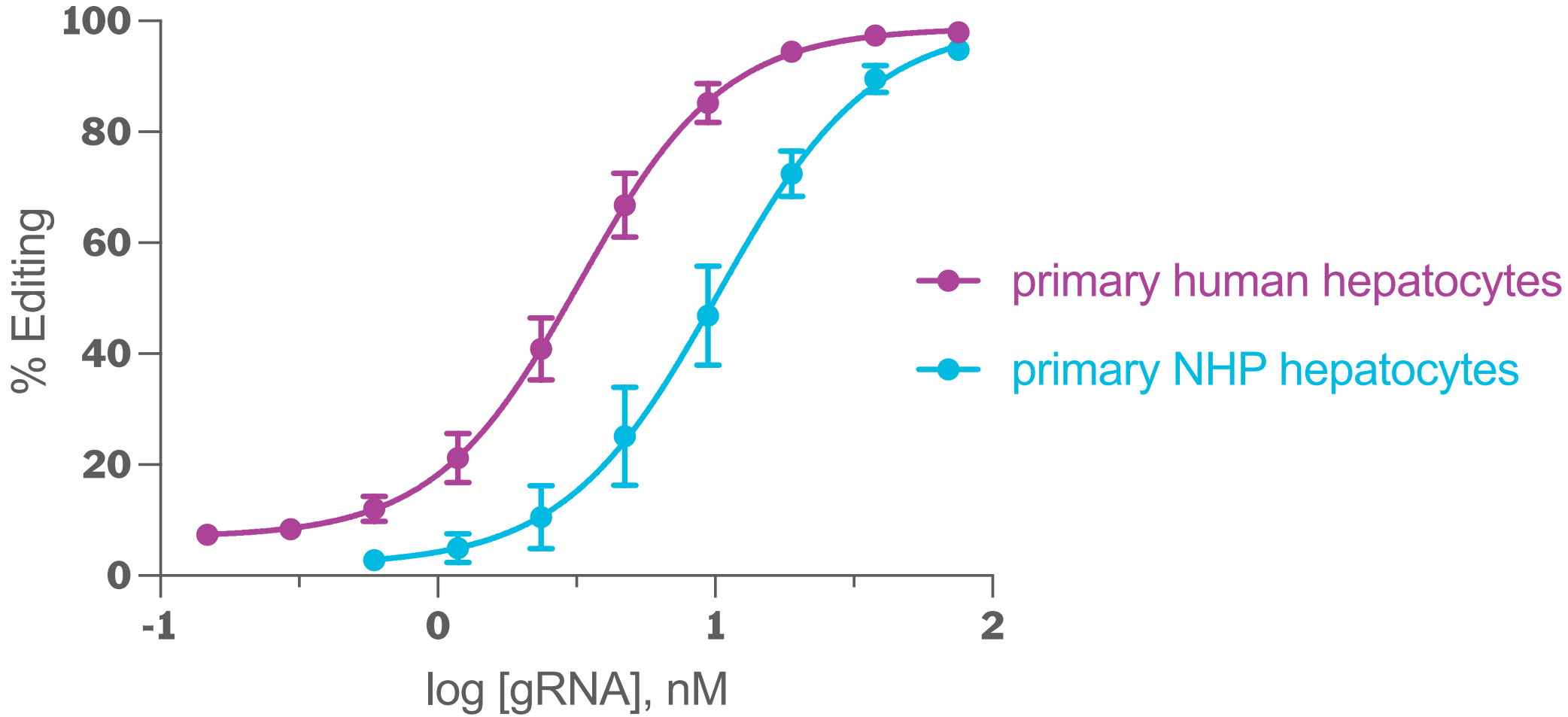
N=3 per dose group



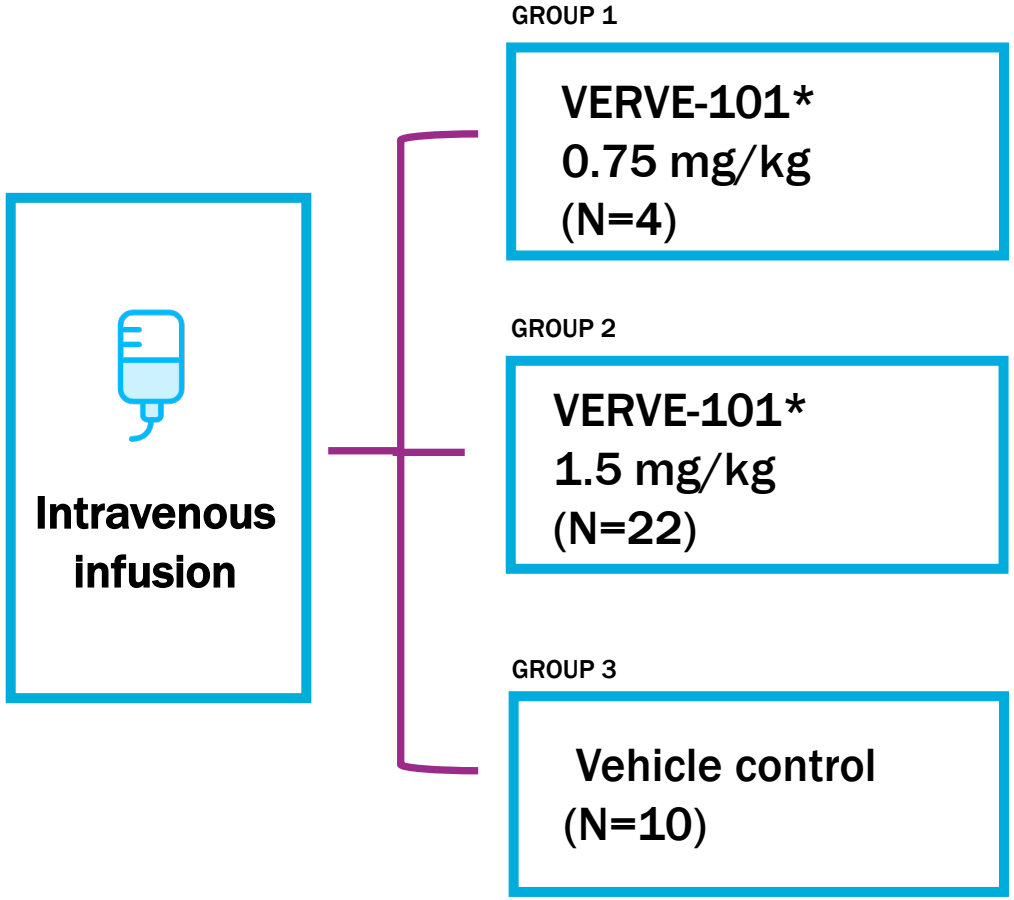




VERVE-101 appears to be more potent in human primary liver cells than it is in NHP liver cells



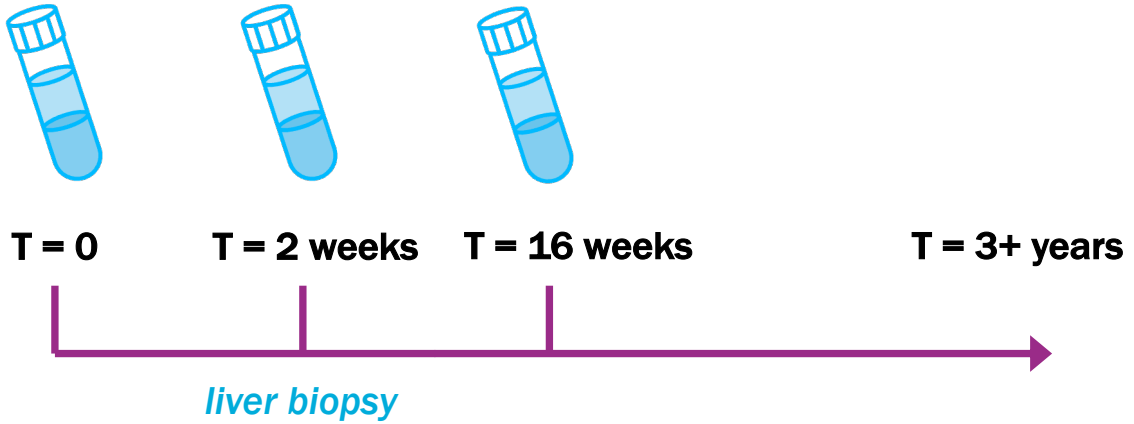
New long-term NHP study (n=36) with VERVE-101 drug product



*LNP in collaboration with Acuitas Therapeutics

Primary endpoints

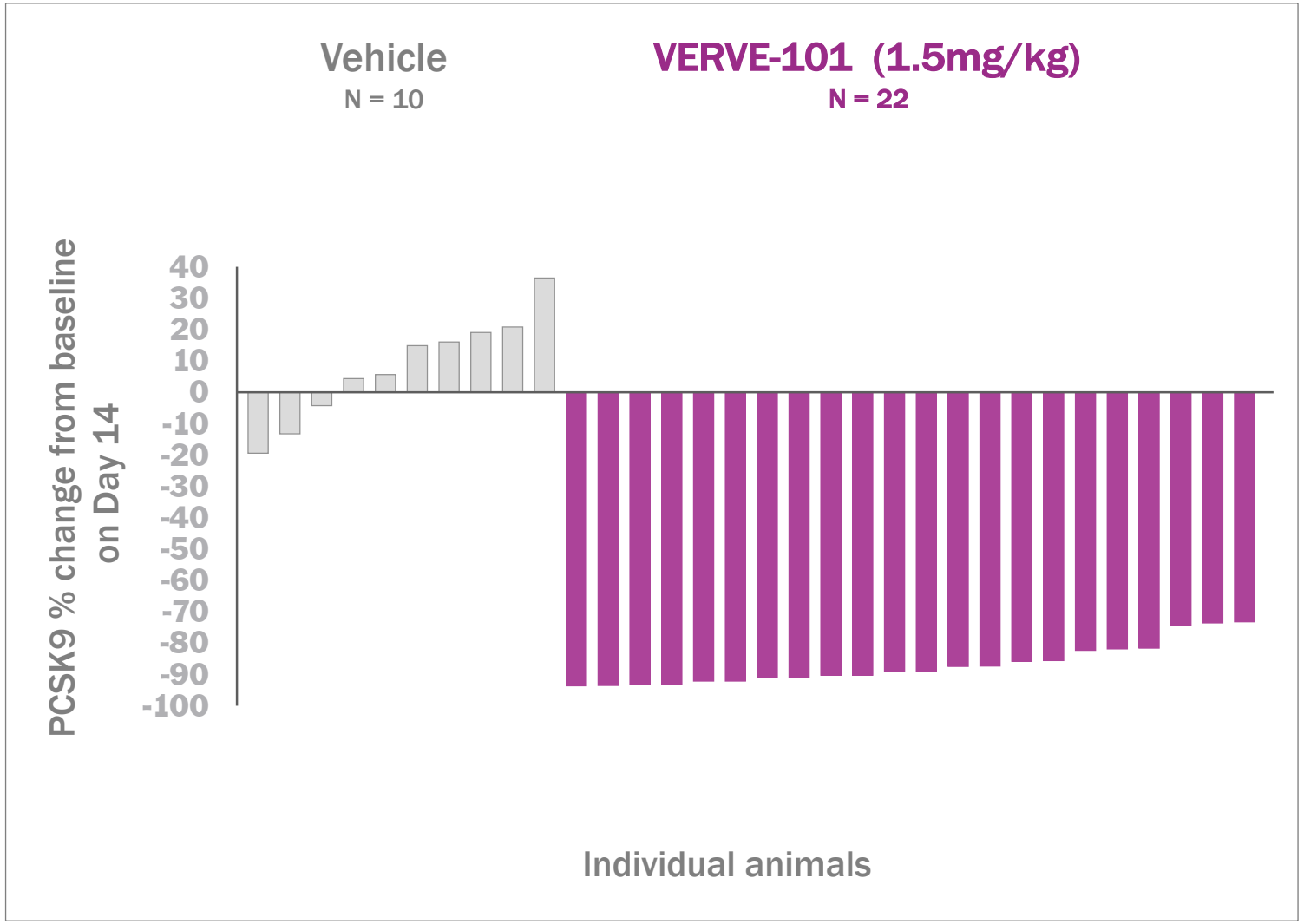
1. Whole liver DNA editing
2. Blood PCSK9 levels
3. Blood LDL-C levels



Safety endpoints

1. Liver function testing
2. Glucose homeostasis
3. Cytokines/ADAs

Robust pharmacodynamic effect of VERVE-101 observed at Day 14

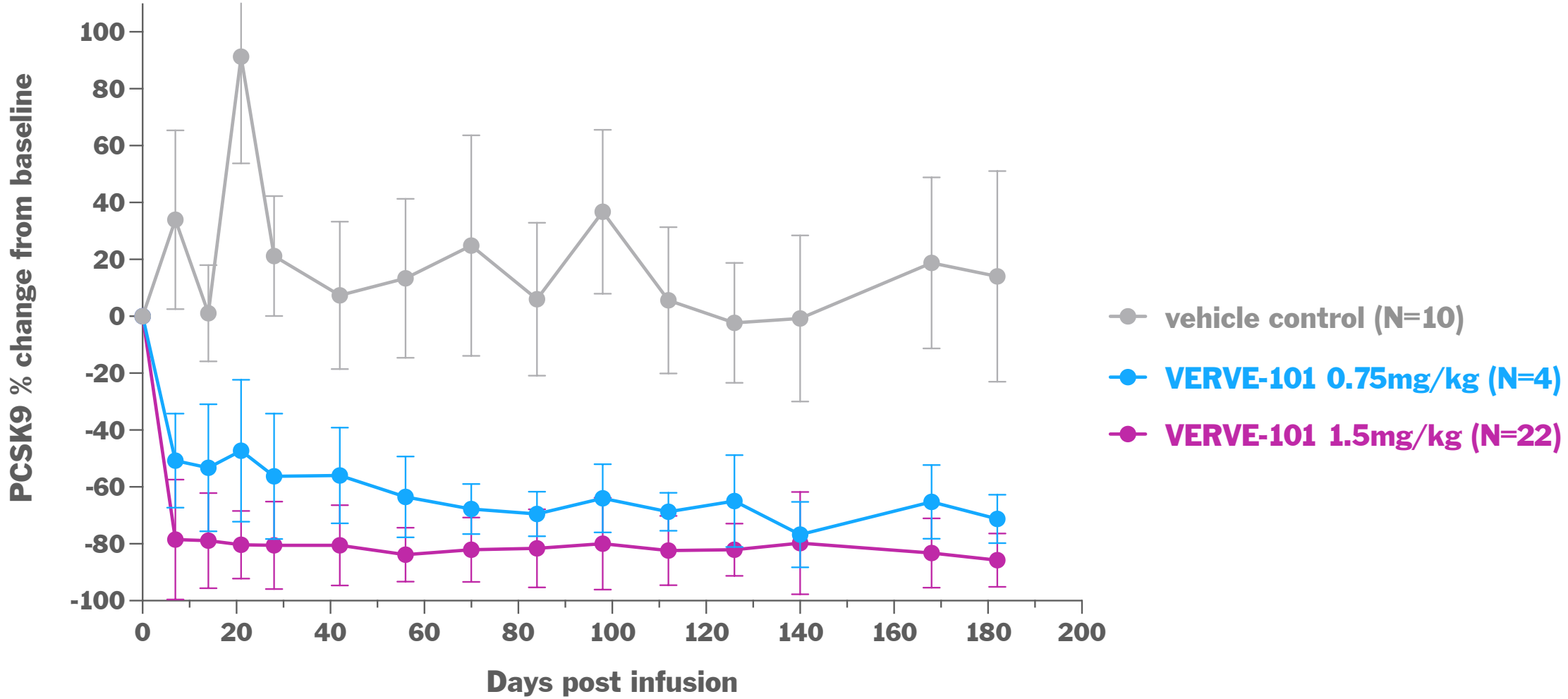


Each purple bar represents one of the 22 NHPs administered VERVE-101 at 1.5 mg/kg

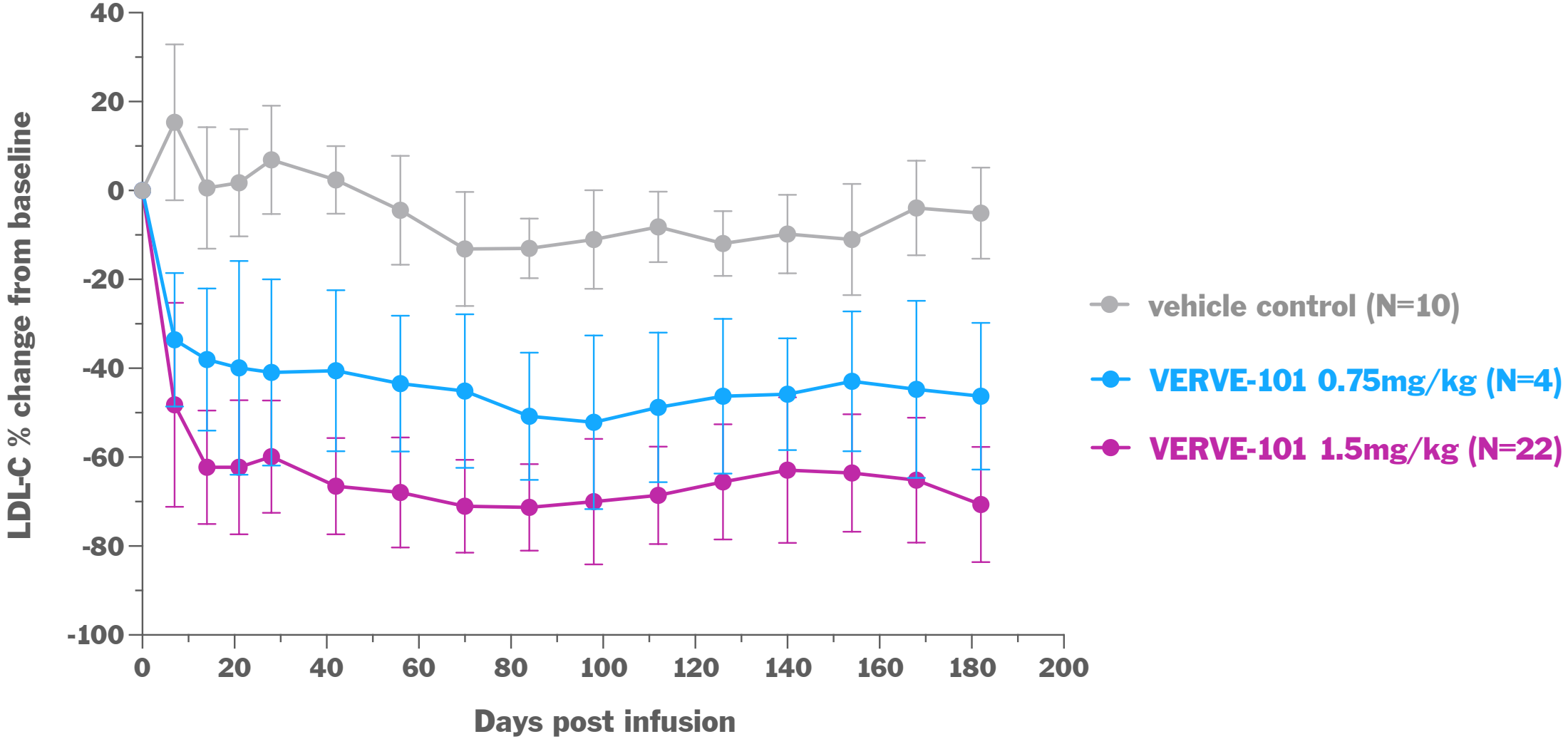
Mean PCSK9 reduction at Day 14 ~ 86%

Mean PCSK9 editing in the liver at Day 15 ~ 70%

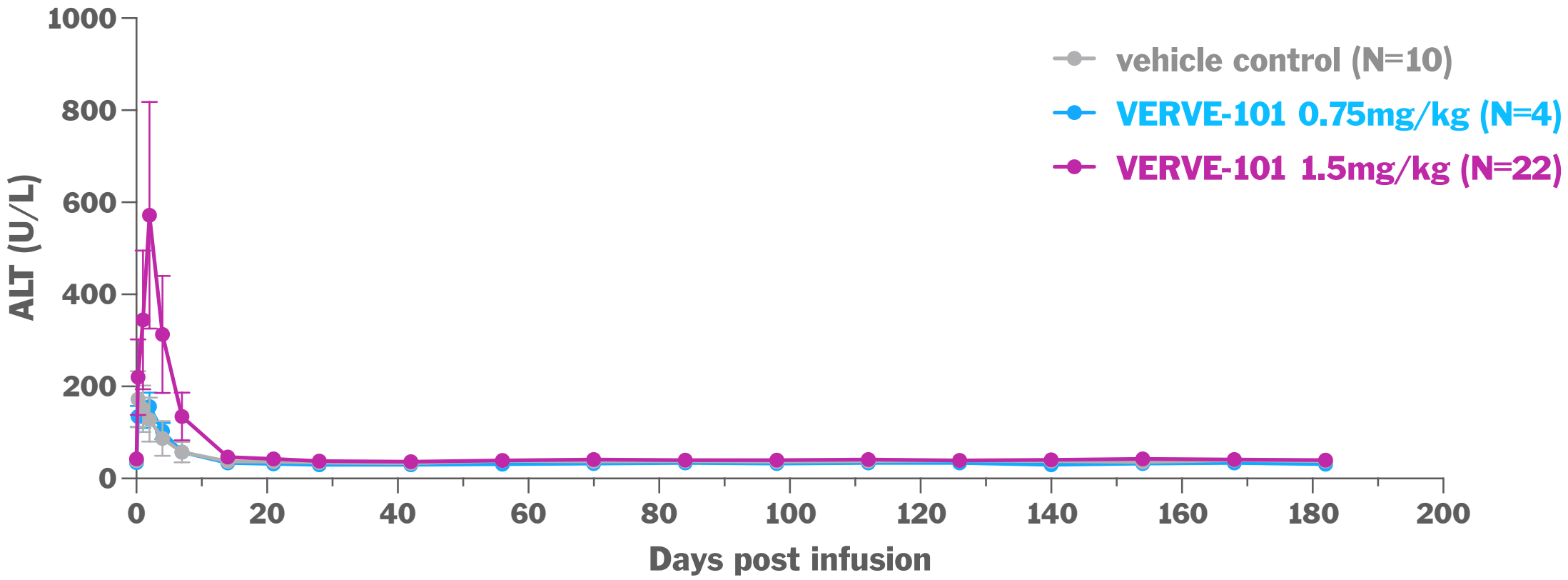
Blood PCSK9 level in new study: durability of VERVE-101 drug product to 6 months in NHP, confirms results from pilot study



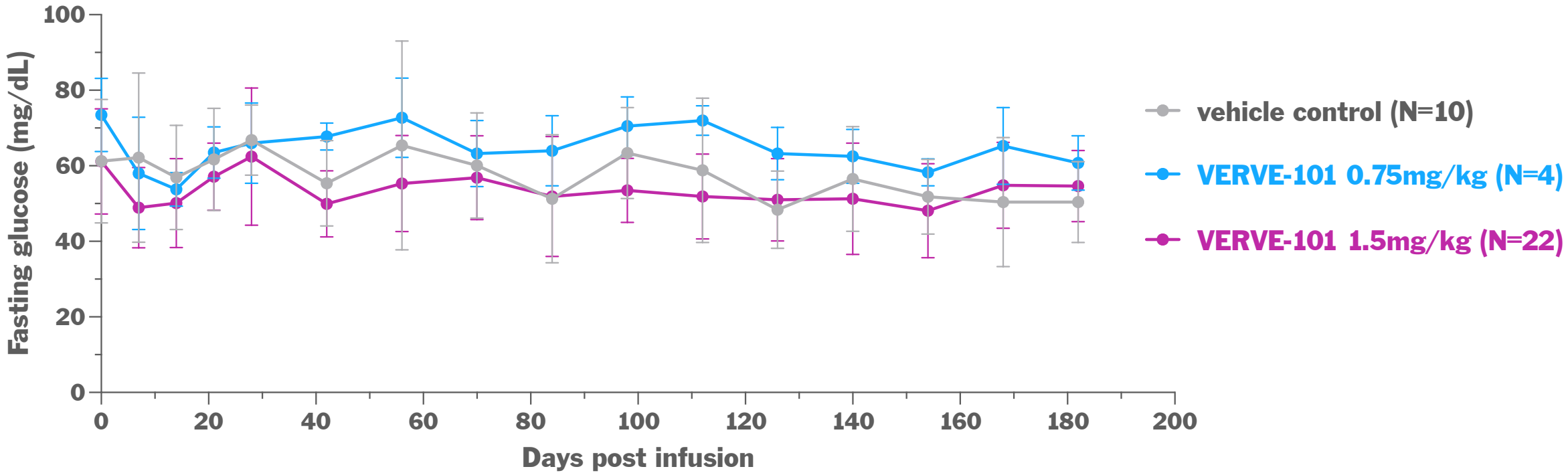
Blood LDL-C level in new study: durability of VERVE-101 drug product to 6 months in NHP, confirms results from pilot study



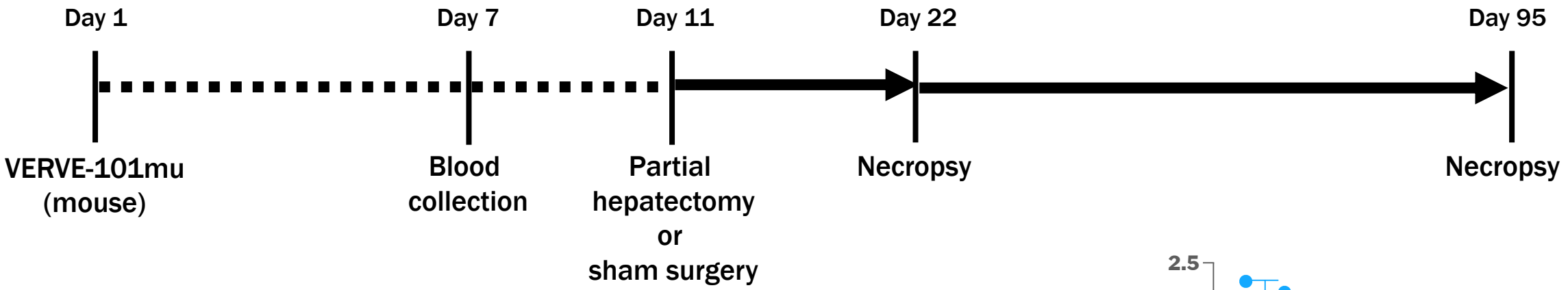
No long-term effects observed on liver function tests following VERVE-101

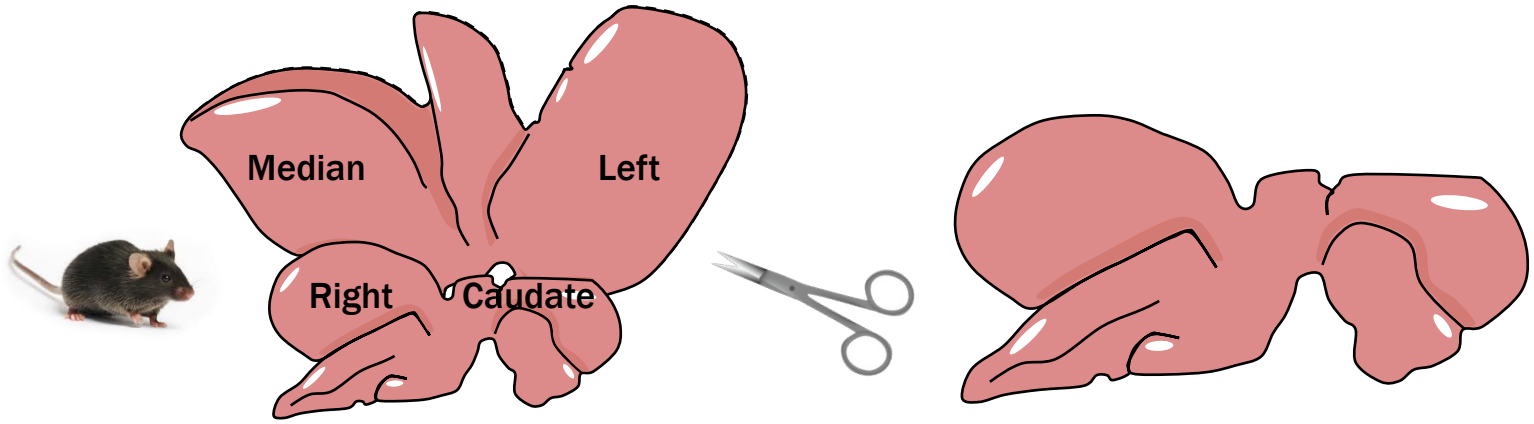


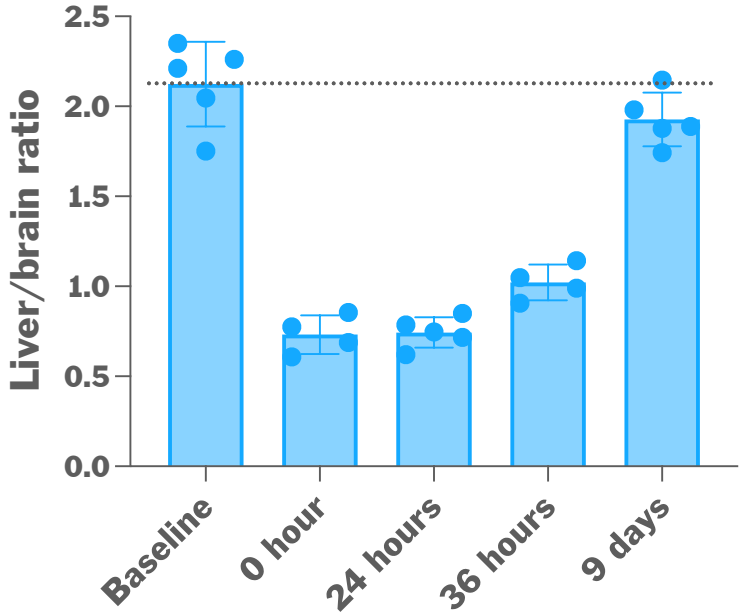
Glucose homeostasis has not been perturbed following administration of VERVE-101 in NHPs



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

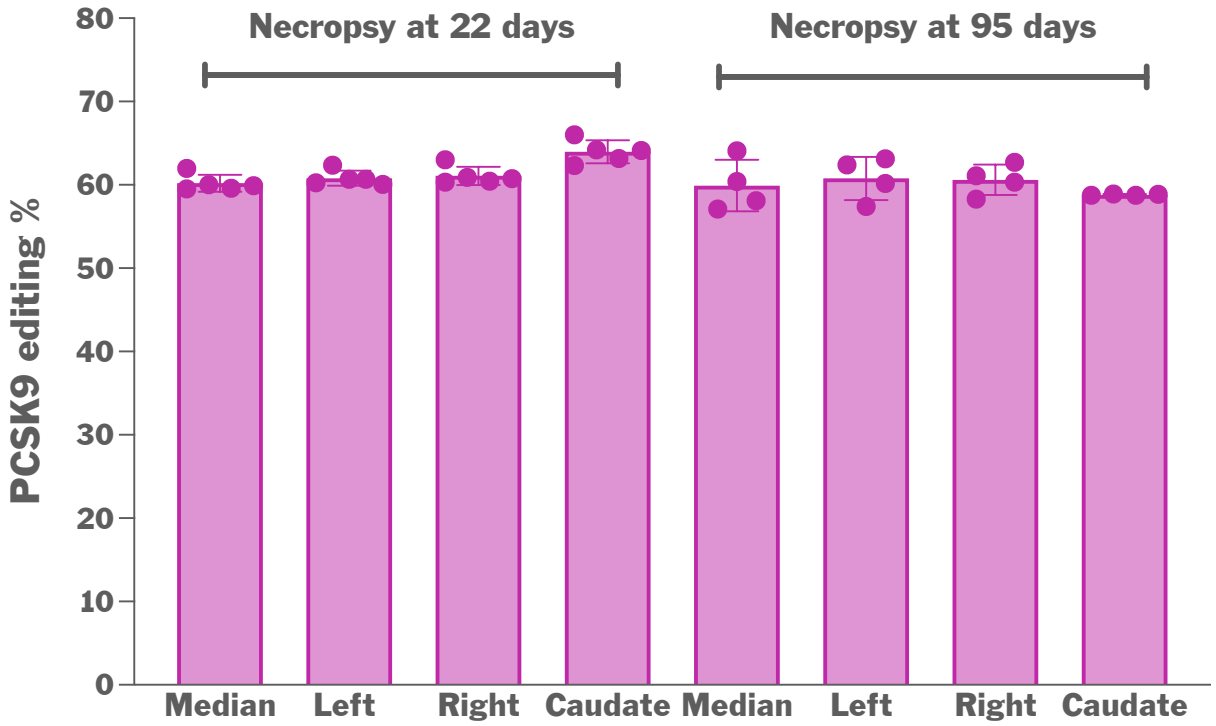






VERVE-101 (mouse version) induced robust editing in mice that is durable in the sham surgery group to 3 months in all liver lobes

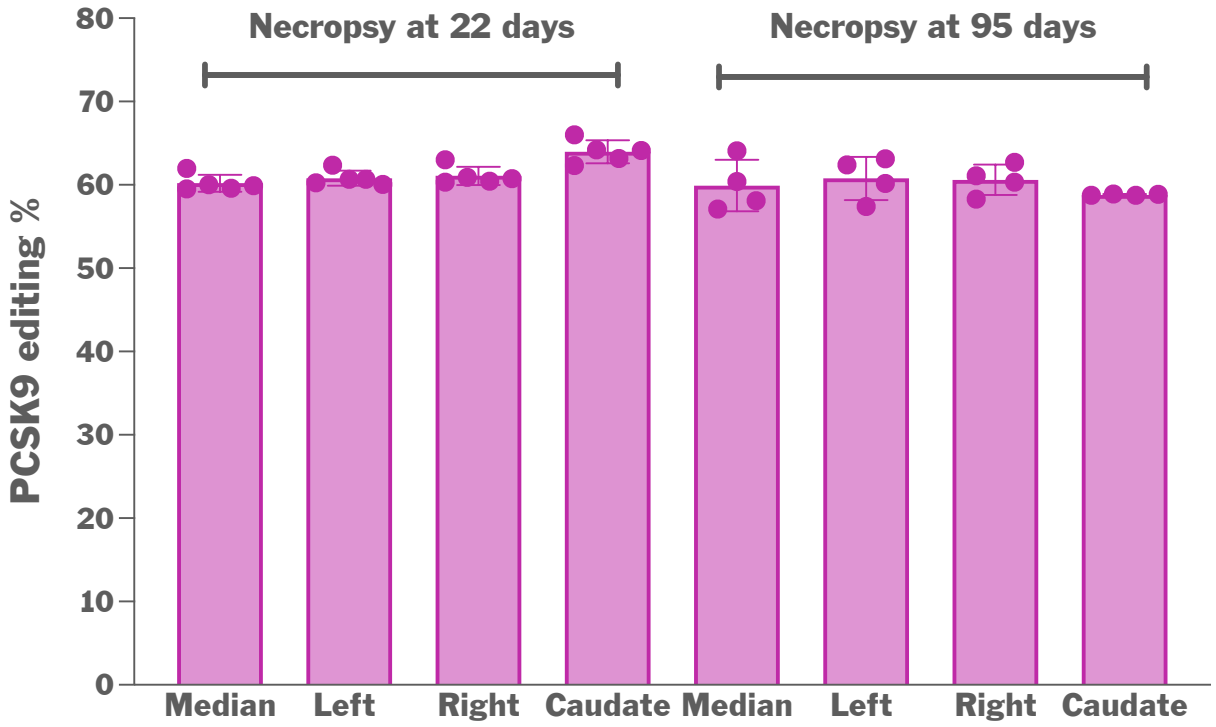
Sham Surgery Group



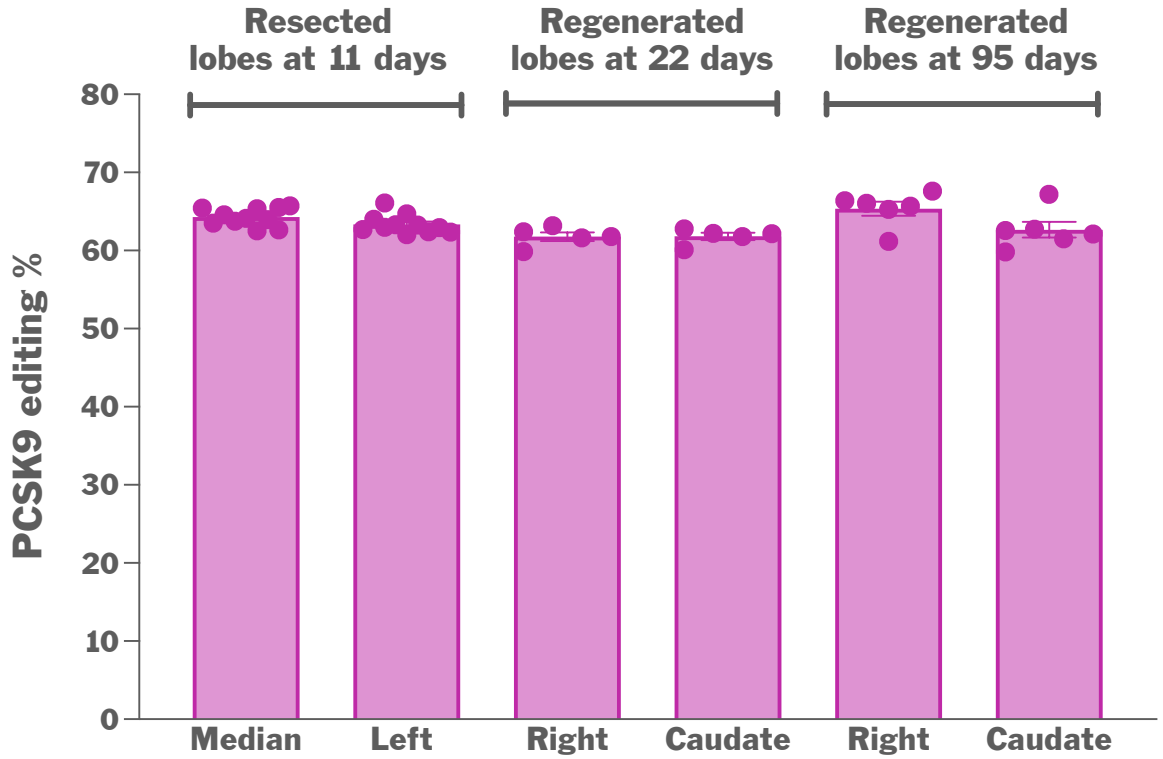
All animals shown received 0.5 mg/kg VERVE-101mu

Following partial hepatectomy in mice, base editing of PCSK9 with VERVE-101 (mouse) was sustained in regenerated liver lobes

Sham Surgery Group

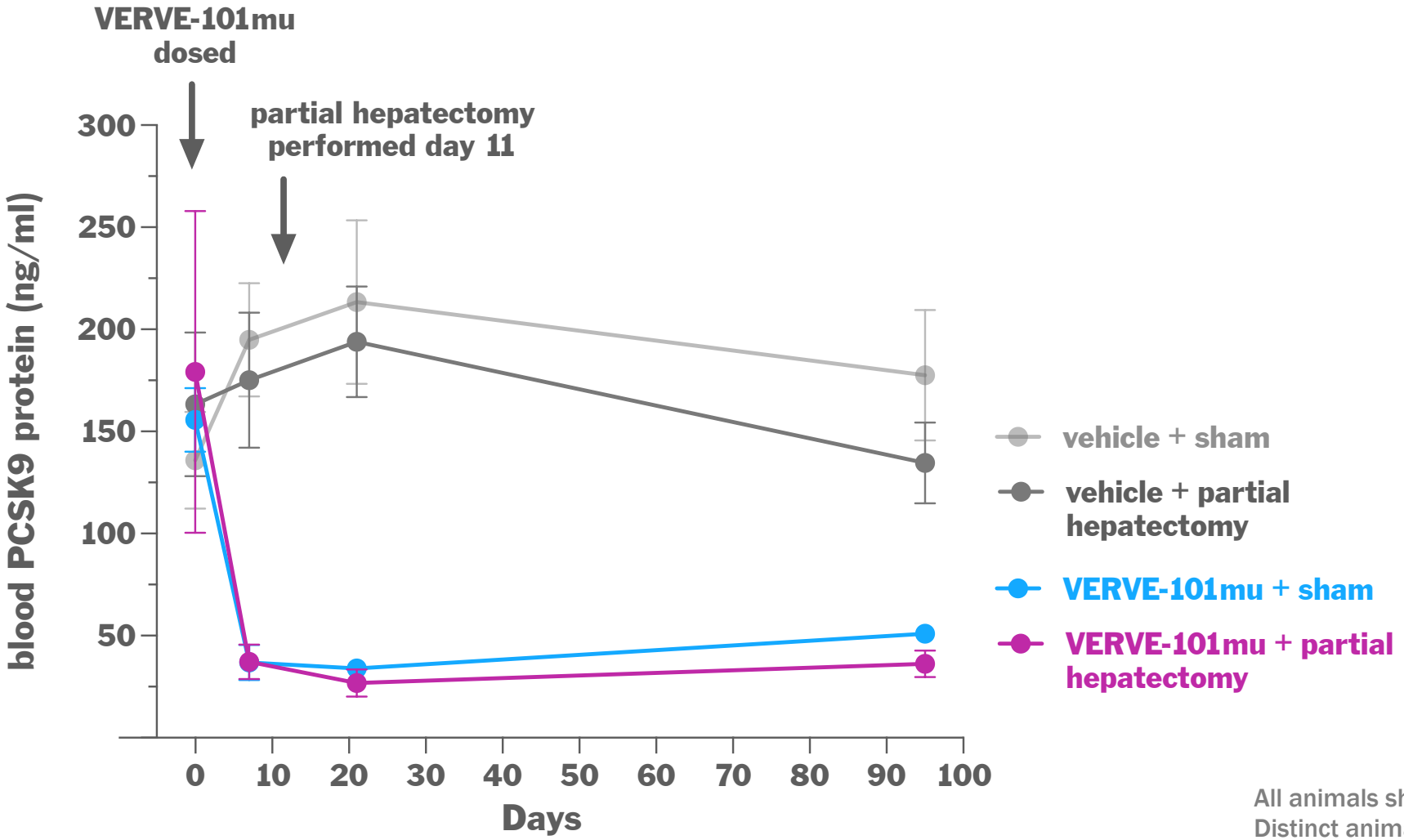


Partial Hepatectomy Groups



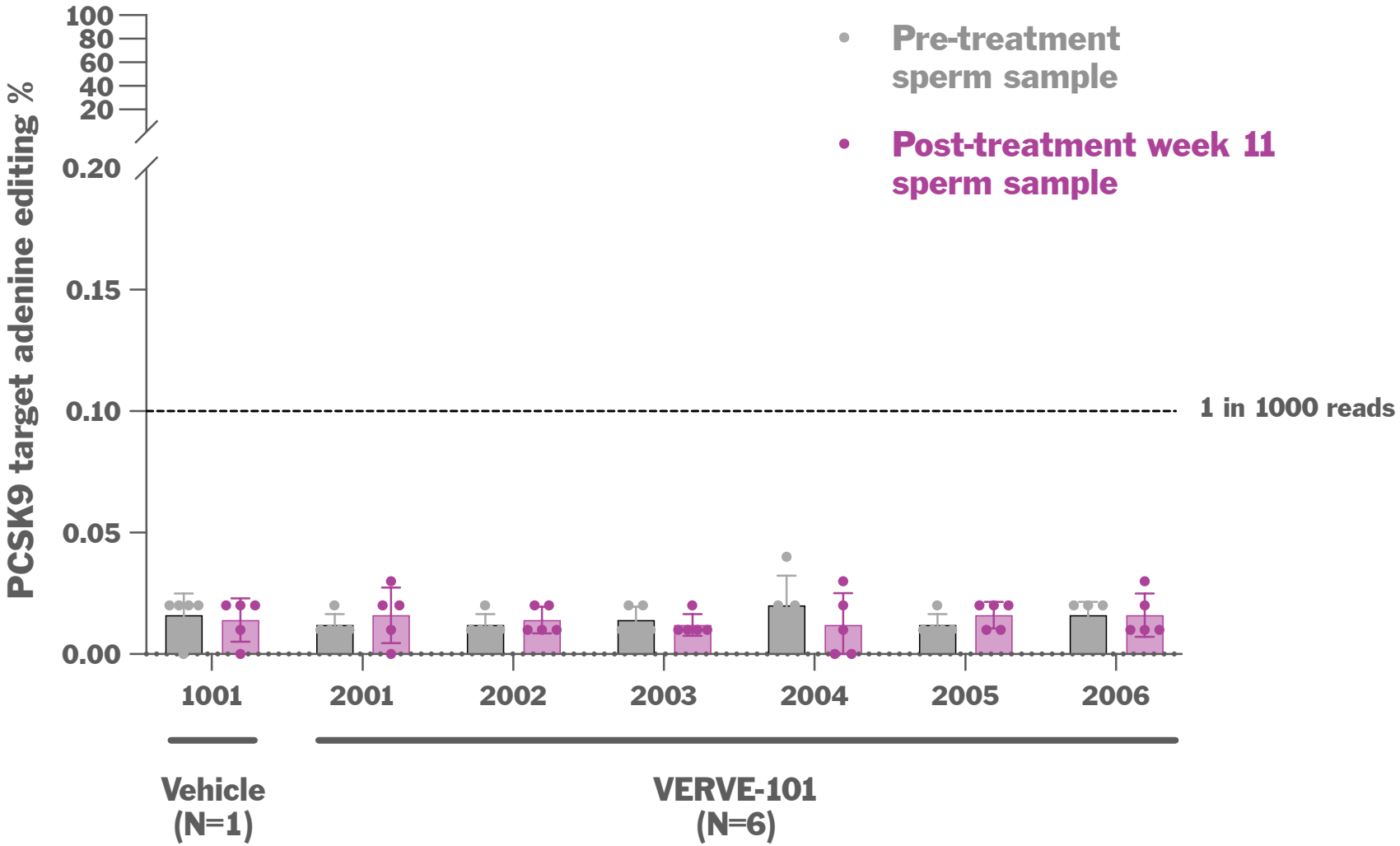
All animals shown received 0.5 mg/kg VERVE-101mu

VERVE-101 (mouse) induced sustained reductions in PCSK9 protein levels following partial hepatectomy in mice



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

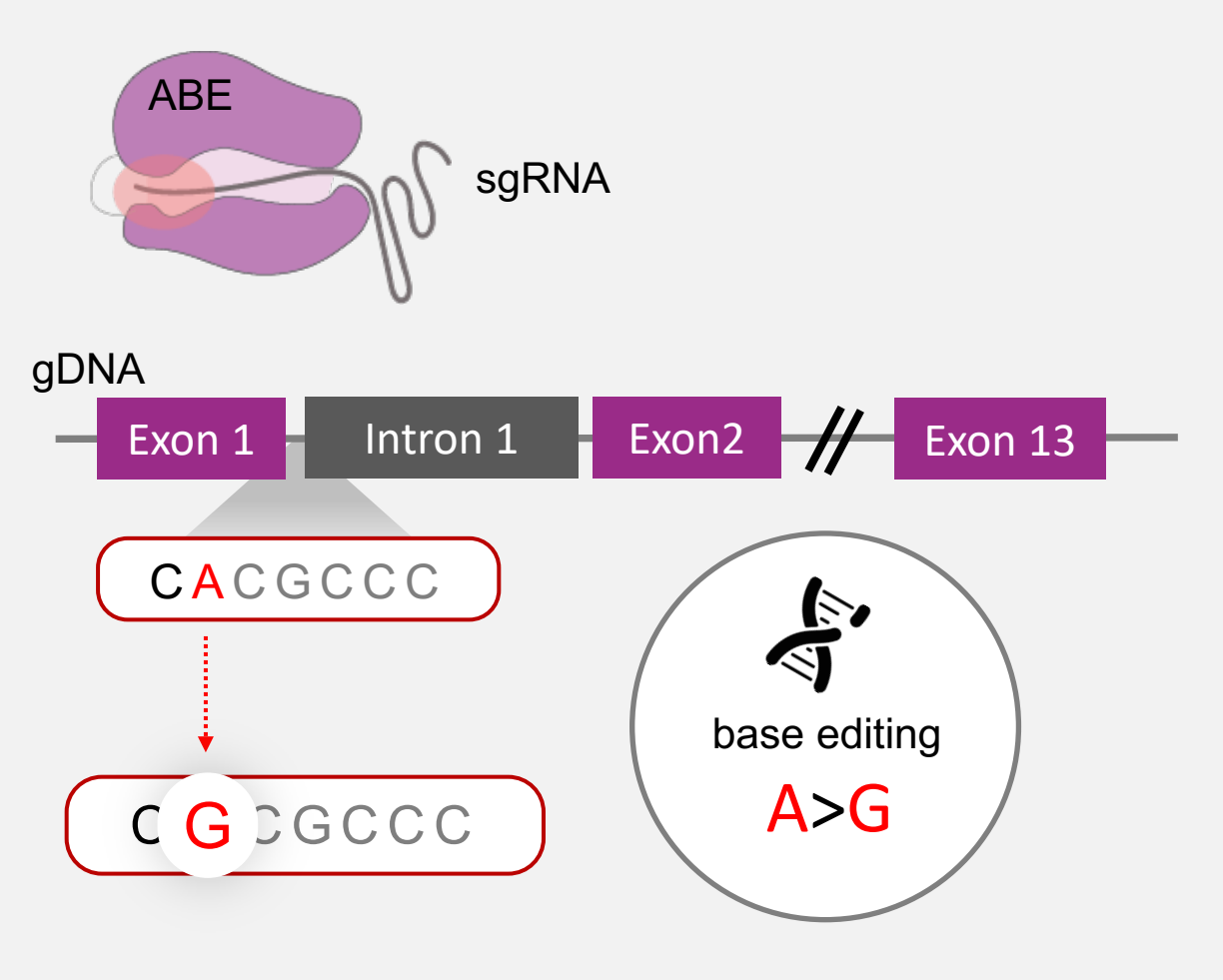
No evidence of editing of sperm in sexually mature male NHPs



- Pre-treatment sperm sample
- **Post-treatment week 11 sperm sample**

N=6 animals received a saturating dose of 1.5 mg/kg VERVE-101
Sperm samples were collected from N=1 control animal and N=6 treated animals prior to dosing and 11 weeks (>1 full cycle of spermatogenesis) after dosing

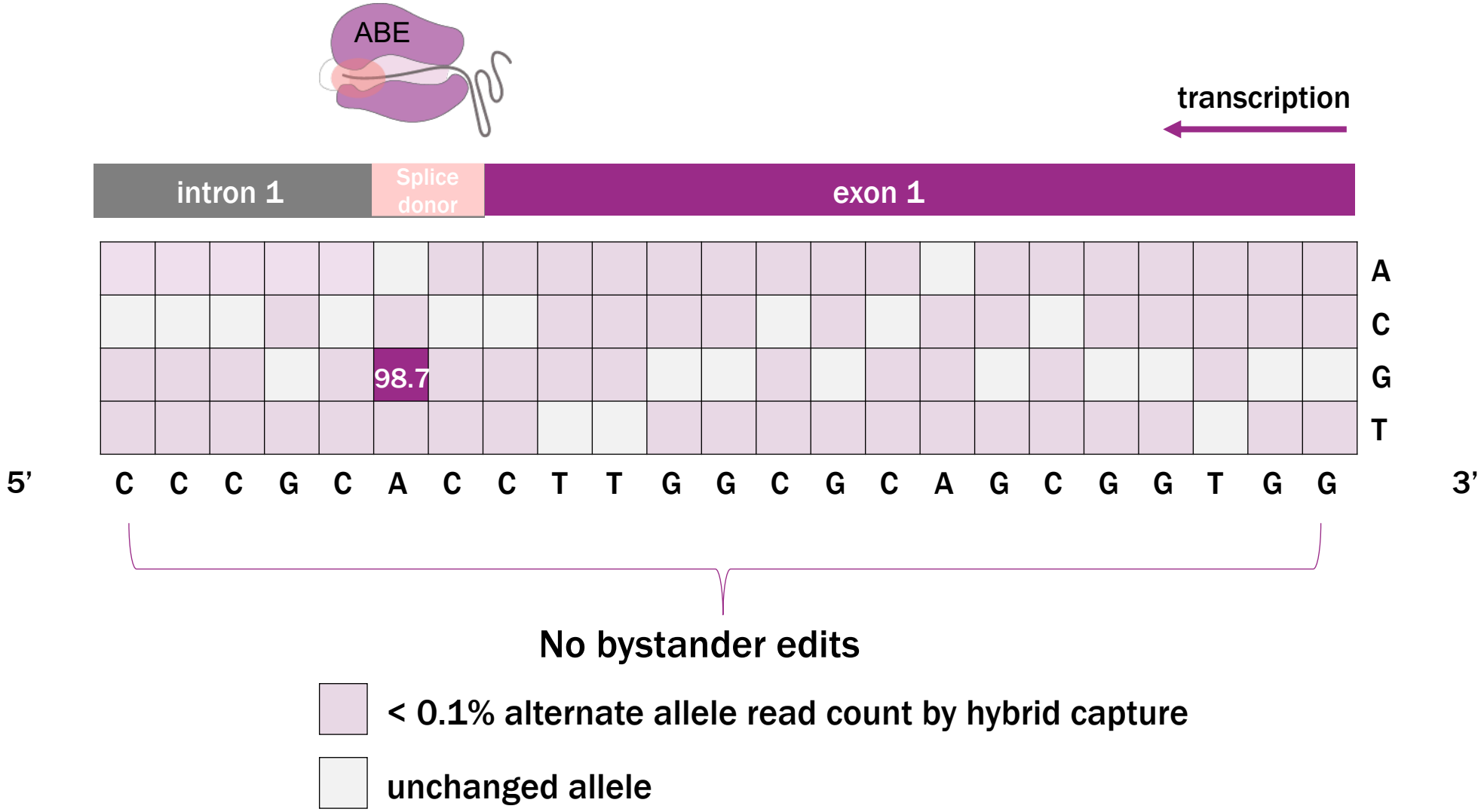
VERVE-101 is designed to precisely disrupt PCSK9 protein expression with a single base pair change



Why this site in PCSK9?

1. Location early in the PCSK9 gene
2. Site that is homologous between humans and non-human primates to aid the nonclinical development
3. Absence of significant genetic variation at the site in humans. 99.97% of individuals have two PCSK9 alleles that perfectly match the protospacer/PAM sequence
4. Demonstrated high efficiency in cellular models (eg, primary human and monkey hepatocytes)
5. Editing site followed by a downstream stop codon to result in protein truncation and nonsense mediated decay of the resulting mRNA
6. Orthogonality of the target sequence from the rest of the human genome to enhance the probability of minimal off-target editing

Base editing at this PCSK9 target site allows for precise single base pair changes without bystander edits



Comprehensive off-target assessment in hundreds to thousands of candidate off-target sites in multiple tissues

Experimental

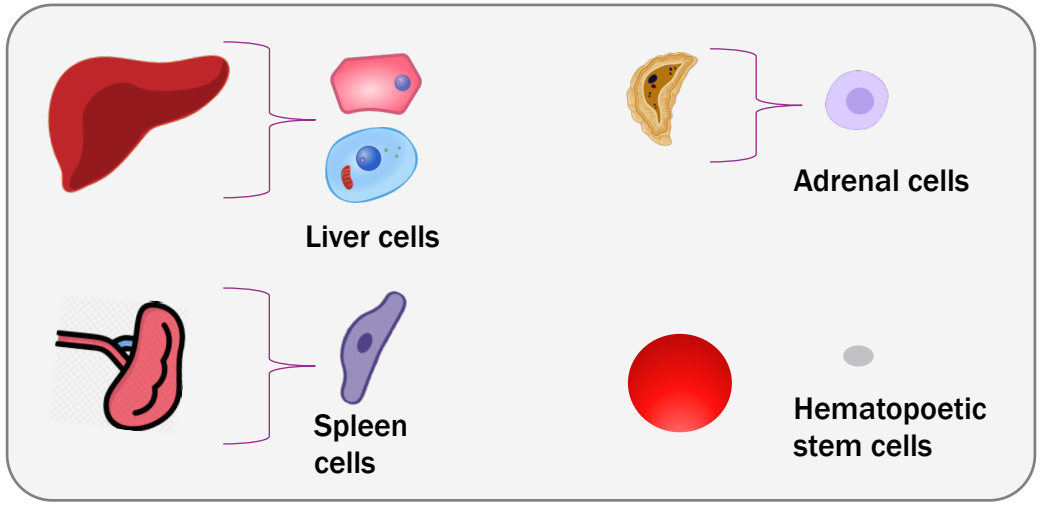
One-Seq — Synthetic library of 30K sequences treated with ABE in vitro

ABE-digenome — De-chromatinized DNA from liver cells treated with ABE in vitro

Bioinformatic

In silico — sites with high homology to gRNA sequence

- Identify 100s to 1000s of candidate sites
- Identify the cell types with the greatest exposure to VERVE-101 in vivo (biodistribution)
- Treat representative cell types at high conc. of VERVE-101, isolate genomic DNA



Evaluate for presence of actual off-target editing

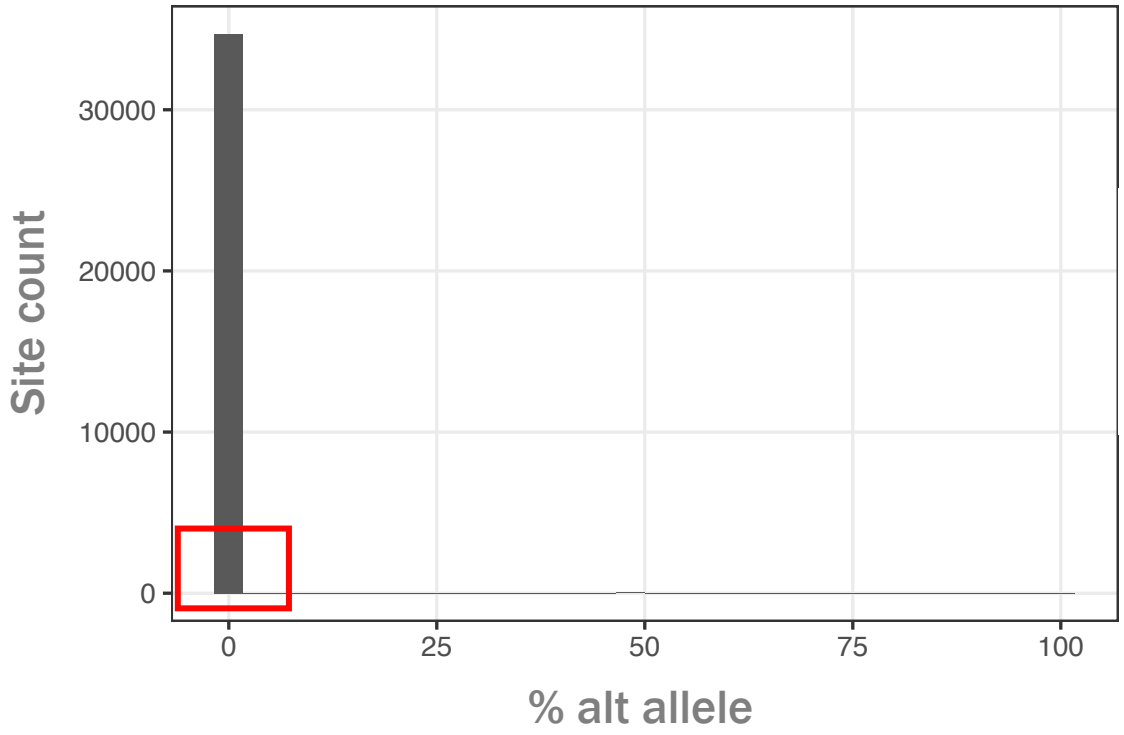
Edited and unedited control cells

Isolated genomic DNA

Hybrid capture panels with low background

Highly-sensitive hybrid capture off-target validation assay

Analysis: NGS quantification of all alleles different from the reference genome
Control samples: untreated control primary human hepatocytes (**4 lots, two replicates each**)
Sites: ~35,000 data points from from 244 potential sites
Background: >99% of panel members have alt allele < 0.1 %



Highly-sensitive hybrid capture off-target validation assay

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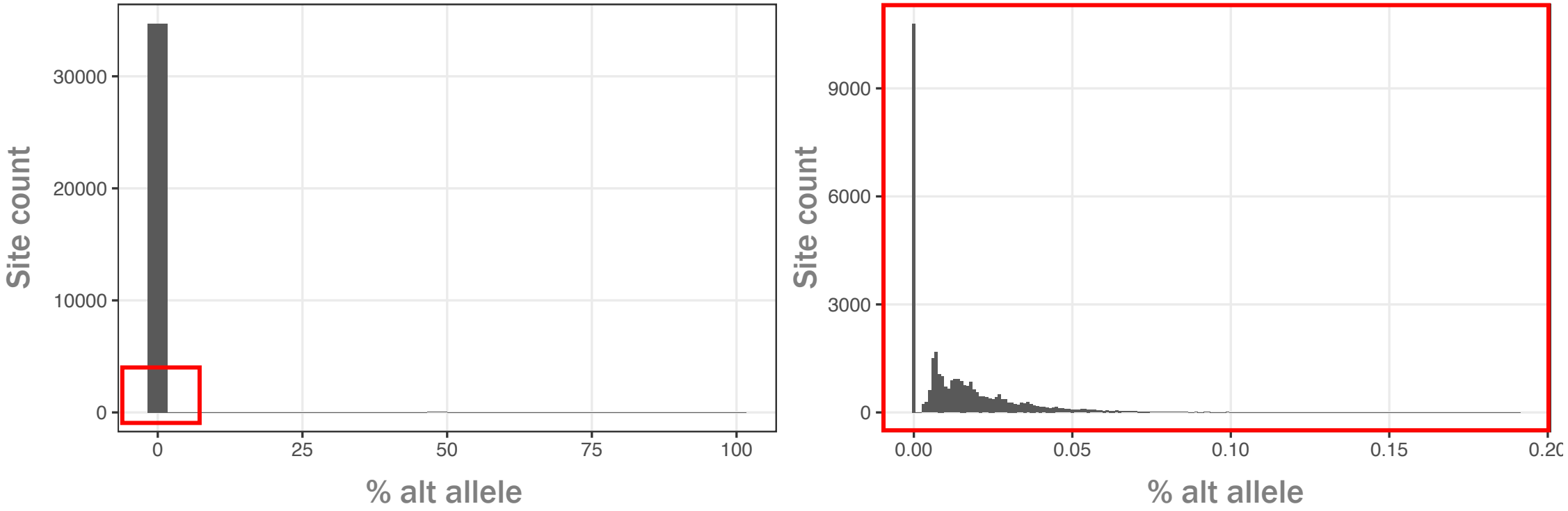
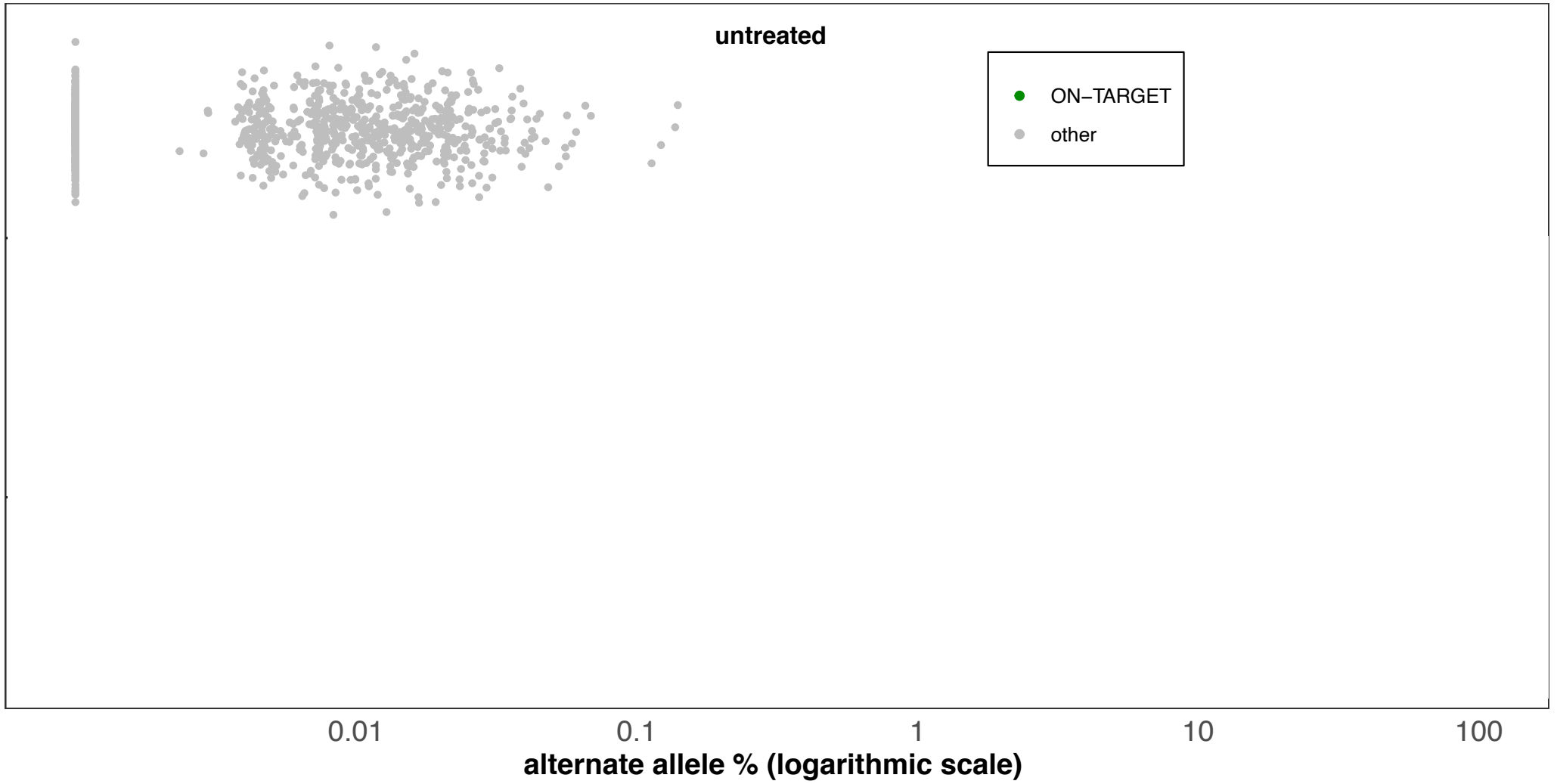
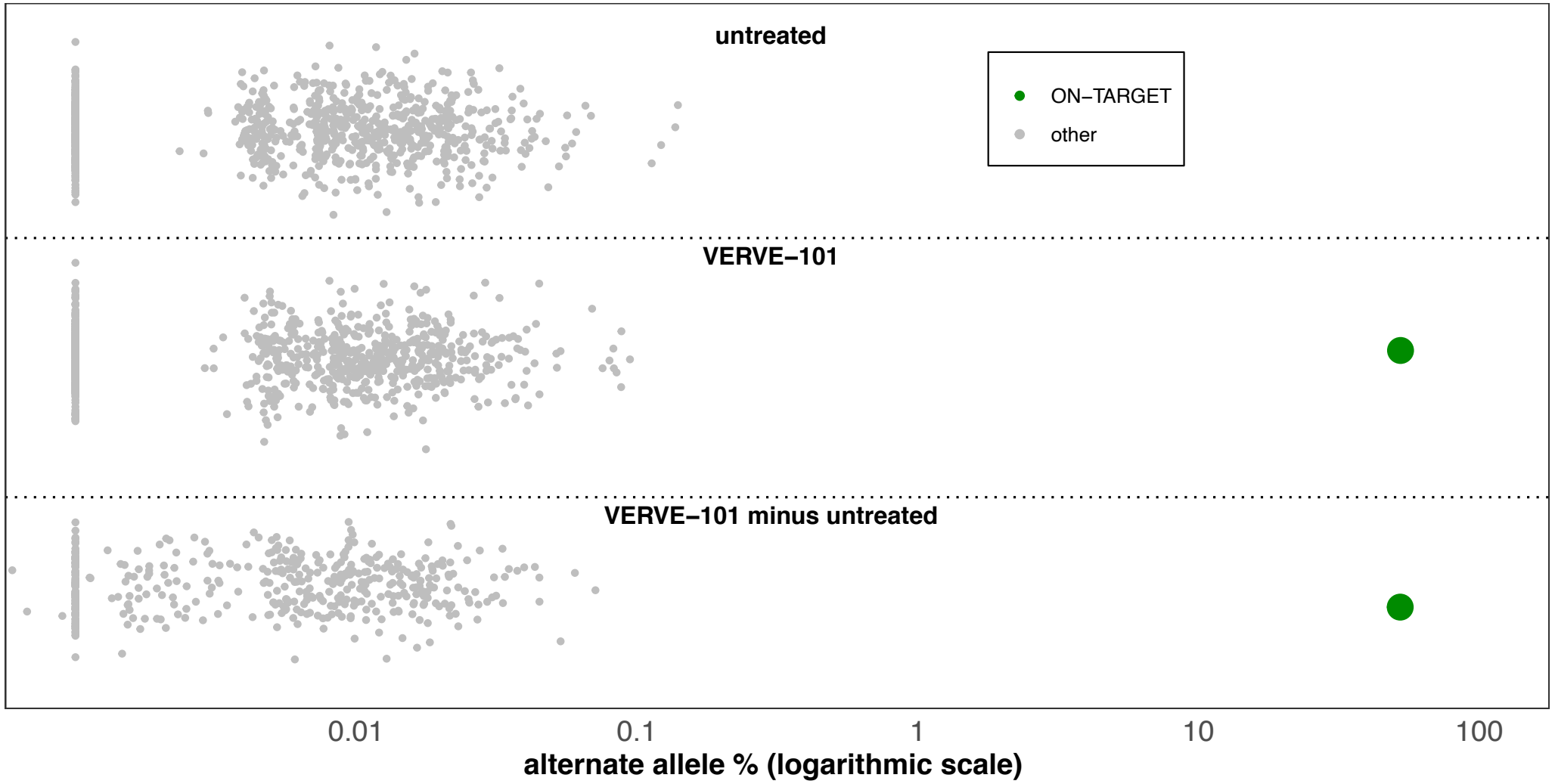


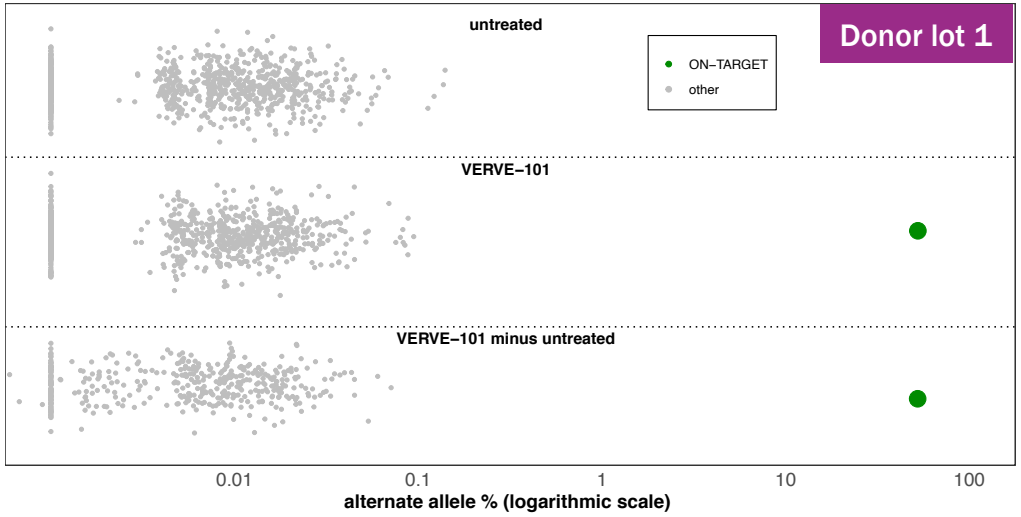
Control (untreated) primary hepatocytes

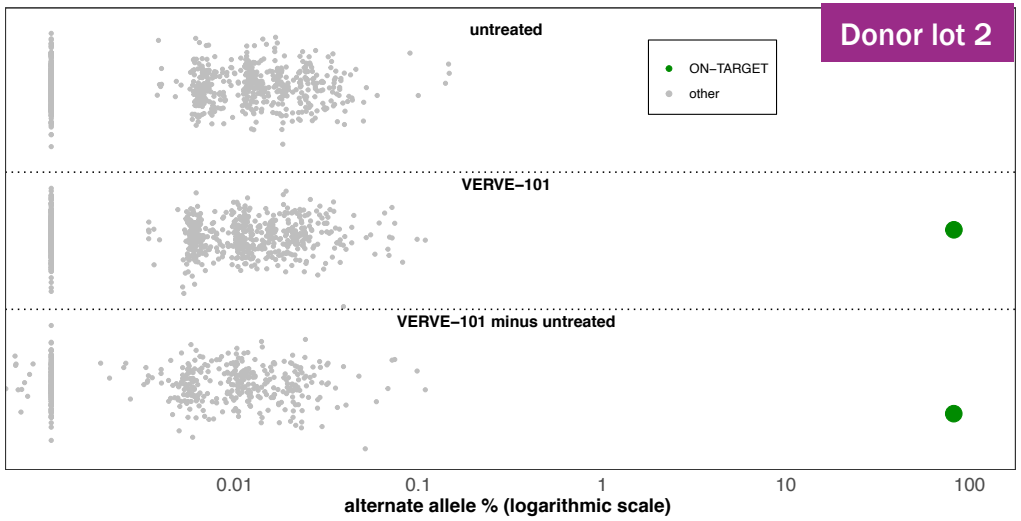


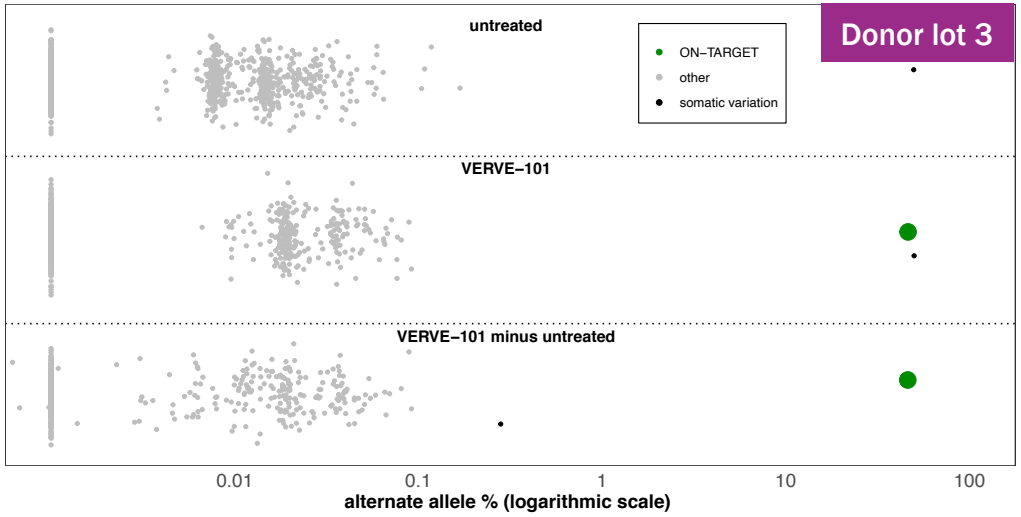
No significant off-target editing observed in primary human hepatocytes among top 244 candidate sites

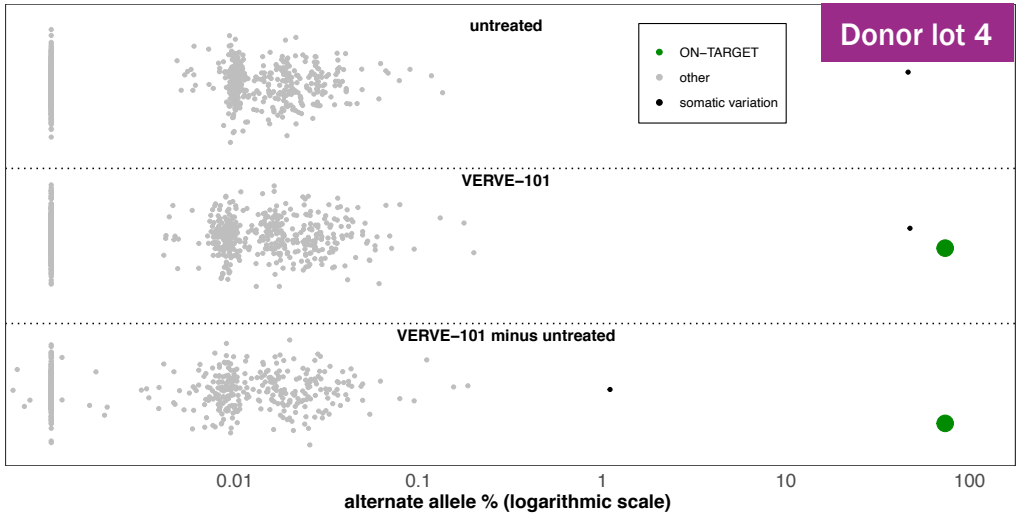


Results replicated across multiple lots of primary human hepatocytes from different donors



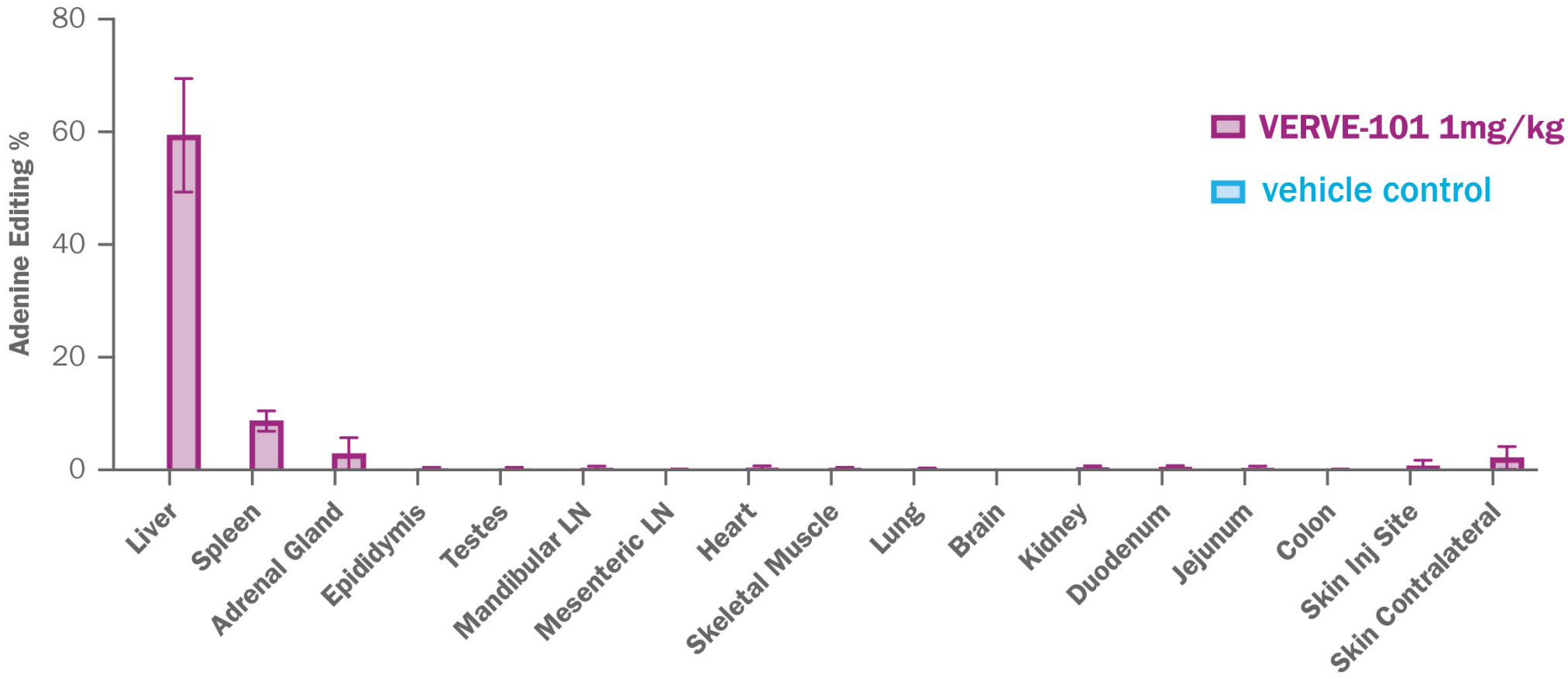




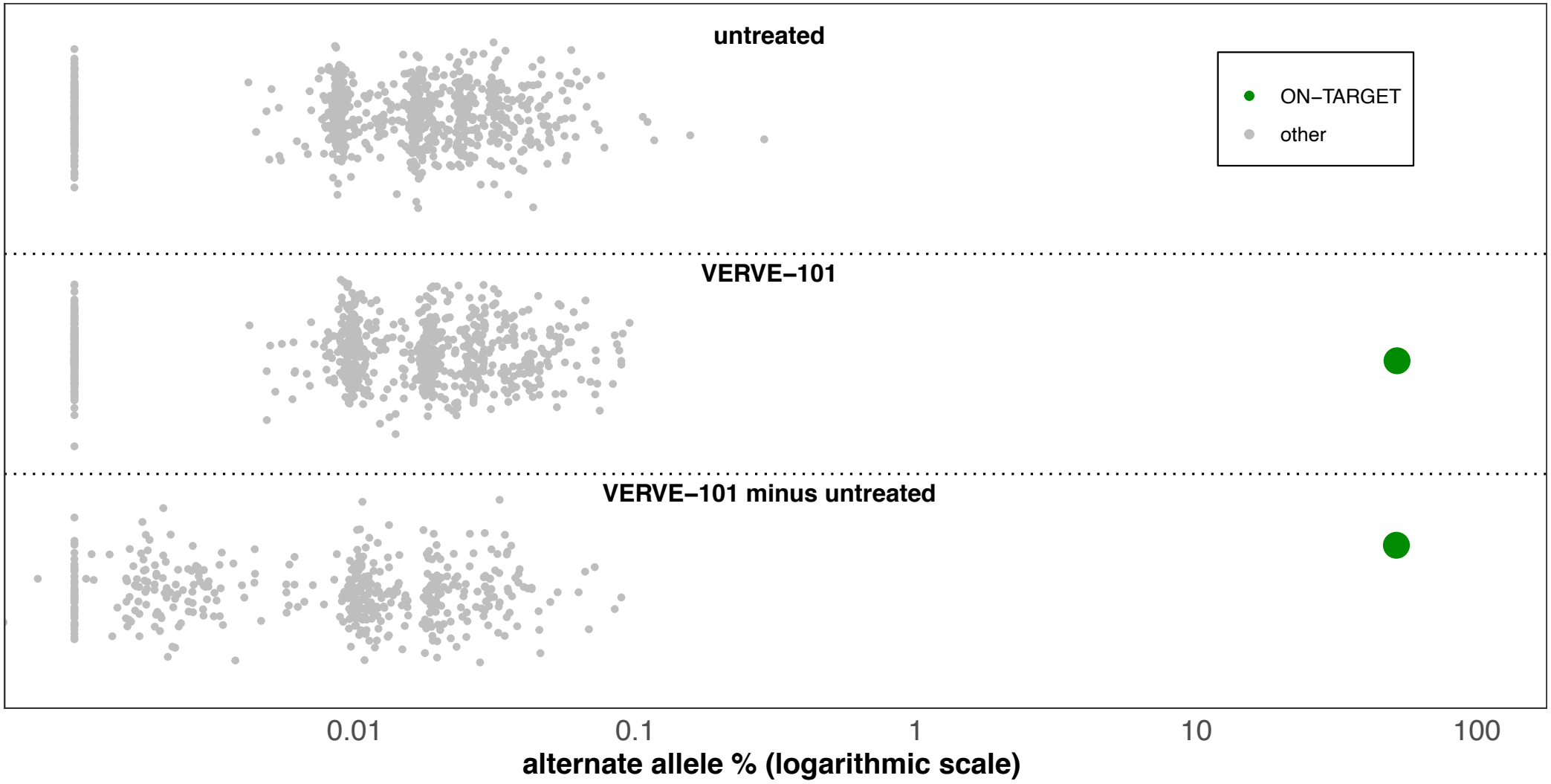


SNPs or other somatic mutations are present and detected in two lots of primary human hepatocytes at one site each and are denoted as black dots in control and treated samples

VERVE-101 observed to predominantly distribute to the liver, as assessed by editing across a range of NHP tissues at necropsy



Off-target evaluation in primary spleen cells replicates these results – no off-target editing observed in top 244 candidate sites



VERVE-101 IND-enabling studies to date support durability and safety of base editing PCSK9 in mice and NHP

Precursor ABE-PCSK9	• **15-month data of the PCSK9 reduction and LDL-C reduction of ABE-PCSK9 editing with precursor formulation**
New studies with VERVE-101 clinical candidate	• **High potency and consistency in a large (N=36) confirmatory study with optimized VERVE-101 drug product** • **Durability to 6 months in confirmatory study** • **VERVE-101 generally well tolerated** – No evidence of any long-term liver enzyme effects – No evidence of any impact to glucose homeostasis • **Durability in challenge mouse partial hepatectomy model out to 3 months** • **Expanded off-target analysis of VERVE-101 without evidence of significant edits** – to 244 potential sites – using highly sensitive hybrid capture technique with very low background – evaluation in multiple tissues including both liver and spleen – using multiple primary human hepatocyte lots

VERVE-101 IND-enabling studies support a potential 2022 IND submission and Phase 1 clinical trial

Thank you to our world-class team of problem solvers

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2020 BEST PLACES TO WORK

ENDPOINTS 11
Biopharma's Most Promising Startups in 2020

verve™ THERAPEUTICS

Disrupting ASCVD care from chronic management to single-course gene editing medicines

Pioneering a pipeline of single-course gene editing medicines to treat ASCVD

In-licensed technologies including multiple lipid nanoparticles (LNPs) and exclusive access to base editing for certain cardiovascular targets

Lead candidate, VERVE-101, demonstrates high potency *in vivo* liver editing & good tolerability in non-human primates; plan for IND submission in 2022

Stepwise development strategy with initial focus on patients with genetic ASCVD - familial hypercholesterolemia (FH) - followed by expansion to patients with established ASCVD

Well capitalized following $306.7 million IPO in June 2021