Disrupting the care of cardiovascular disease with single-course gene editing medicines

ASGCT, May 17, 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

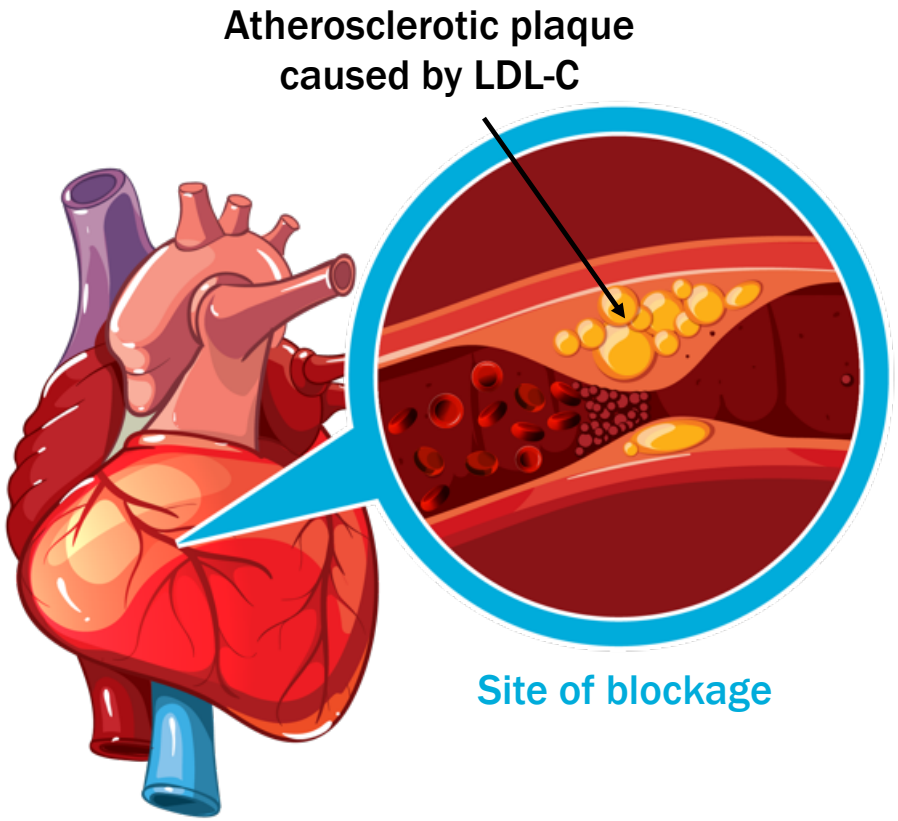
#1 cause of death worldwide

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)



Solution to ASCVD revealed by human genetics and pharmacology: get LDL-C as low as possible for as long as possible

ESC European Society of Cardiology

European Heart Journal (2022) **43**, 249–250
https://doi.org/10.1093/eurheartj/ehab532

Braunwald's Corner

How to live to 100 before developing clinical coronary artery disease: a suggestion

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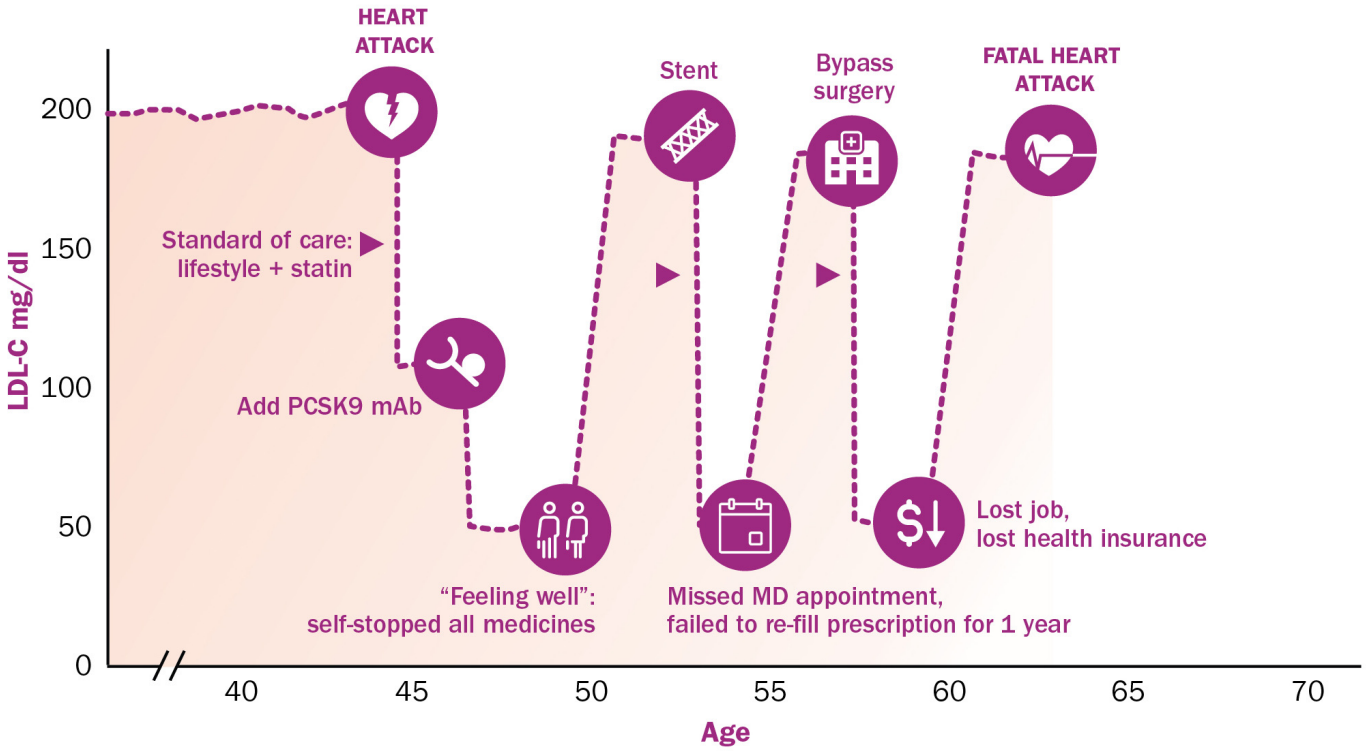
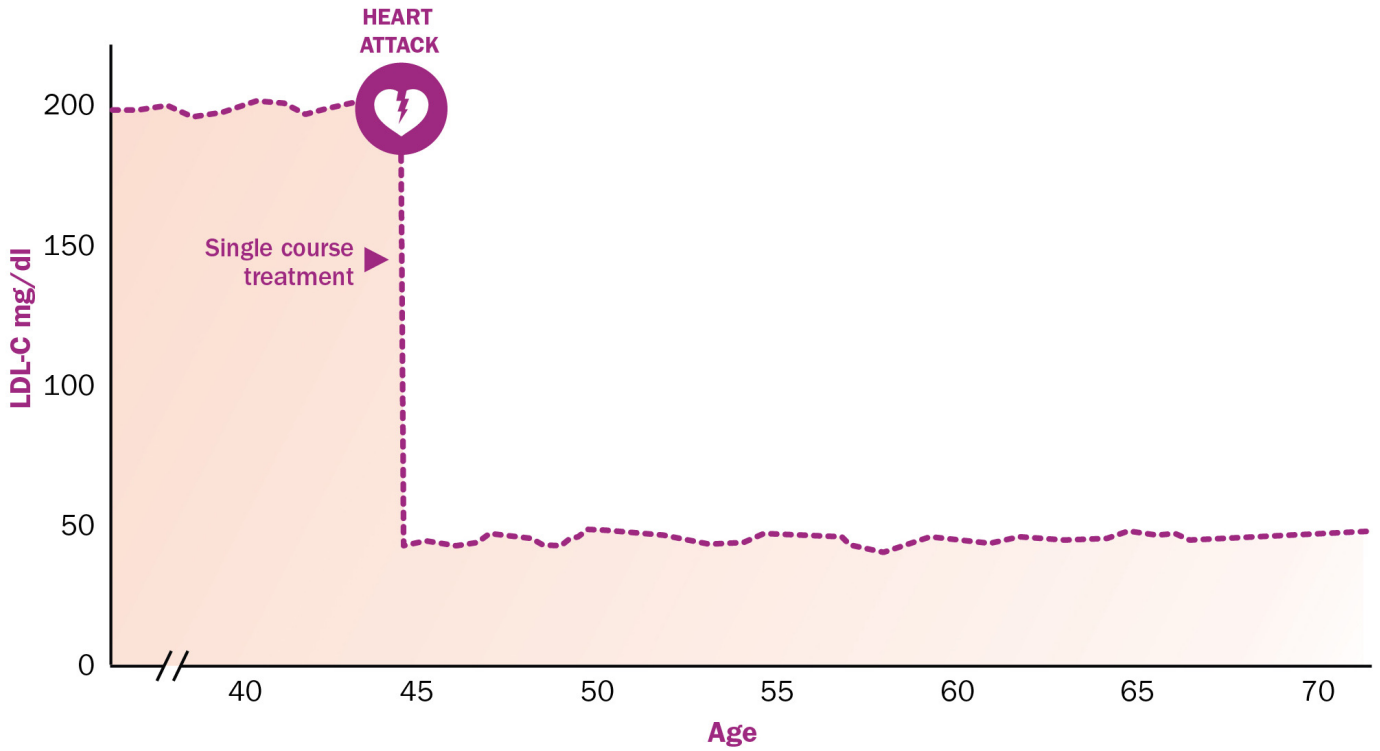
Unmet need: current chronic care model for ASCVD results in poor control of cumulative blood LDL-C exposure



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



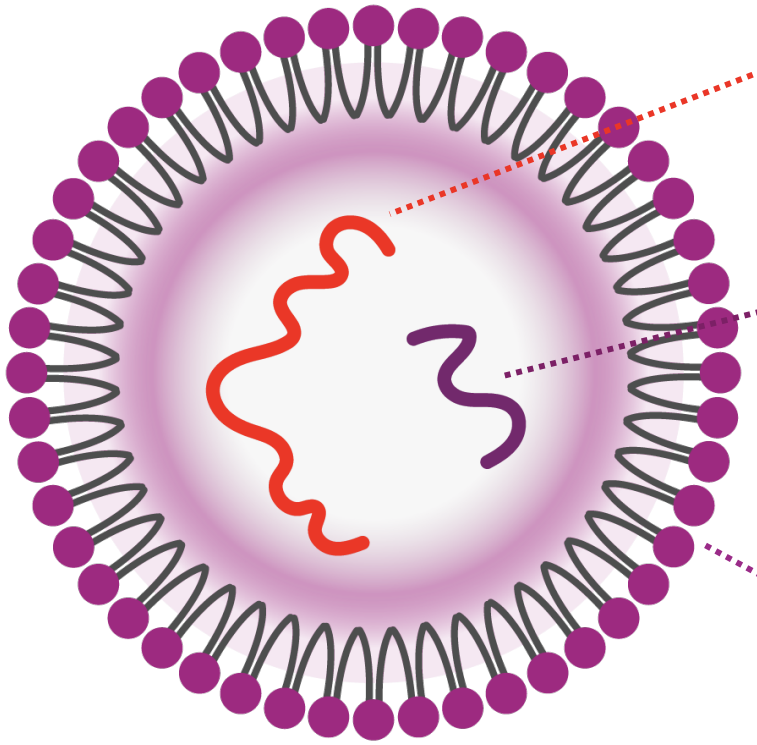
Illustrative graphic depicts the journey of a hypothetical patient with familial hypercholesterolemia who began standard-of-care treatment after suffering a heart attack at age 44

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

PROGRAM	INDICATIONS	DEVELOPMENT STATUS				
		Research/ Lead optimization	IND-Enabling	Phase 1	Phase 2	Phase 3
Low-density lipoprotein cholesterol (LDL-C)						
VERVE-101 PCSK9	Heterozygous familial hypercholesterolemia					
	ASCVD not at LDL-C goal on oral therapy					
LDL-C & Triglyceride-rich lipoprotein (TRL)						
ANGPTL3	Homozygous familial hypercholesterolemia					
	ASCVD not at LDL-C goal on oral + PCSK9i					

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

VERVE-101's three components have been designed to maximize on-target and minimize the risk of off-target editing



Adenine base editor

- Single base pair change without double stranded breaks
- delivered as an mRNA

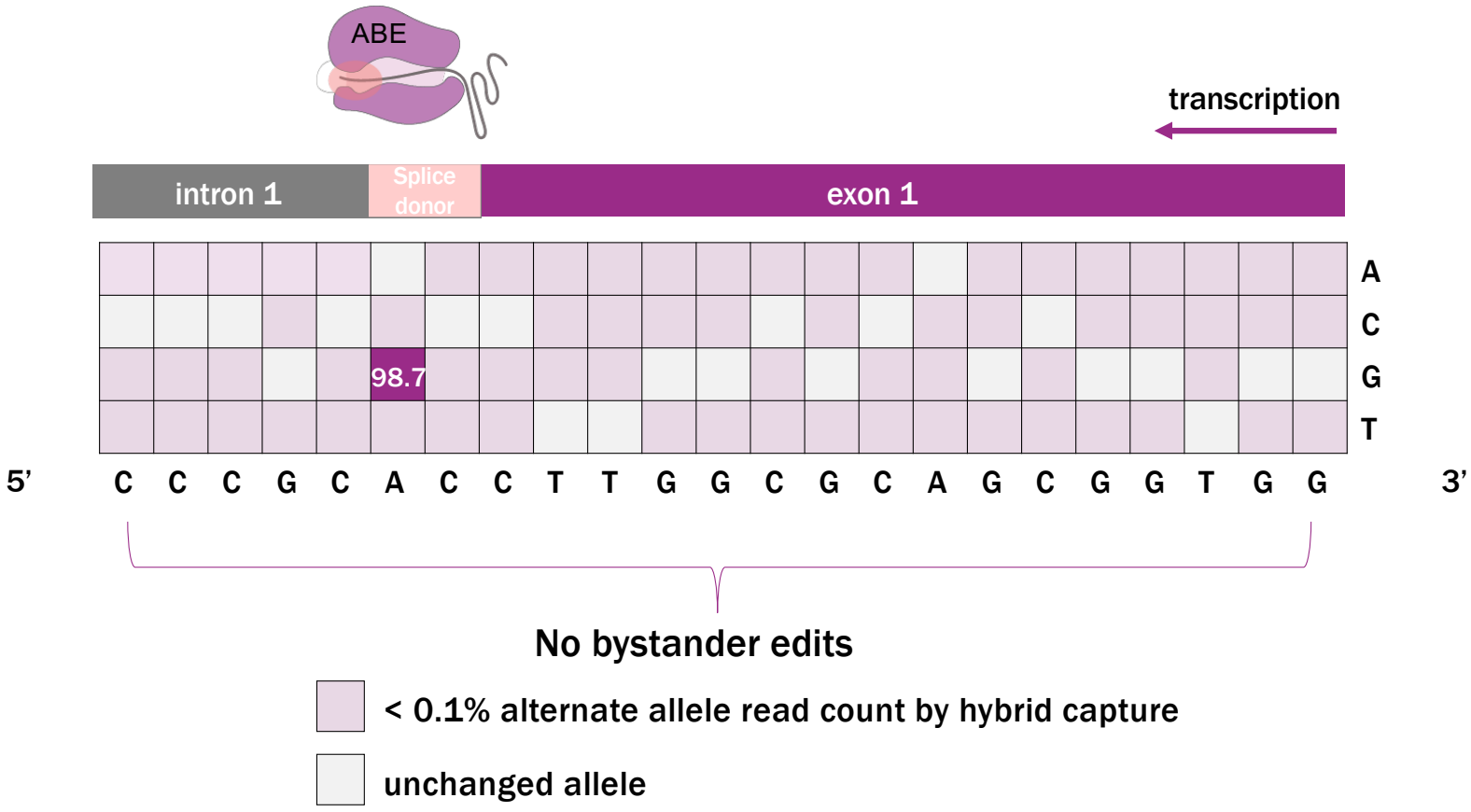
Unique PCSK9 gRNA

- No 0, 1, or 2 mismatch sites in genome
- Conserved site across human population

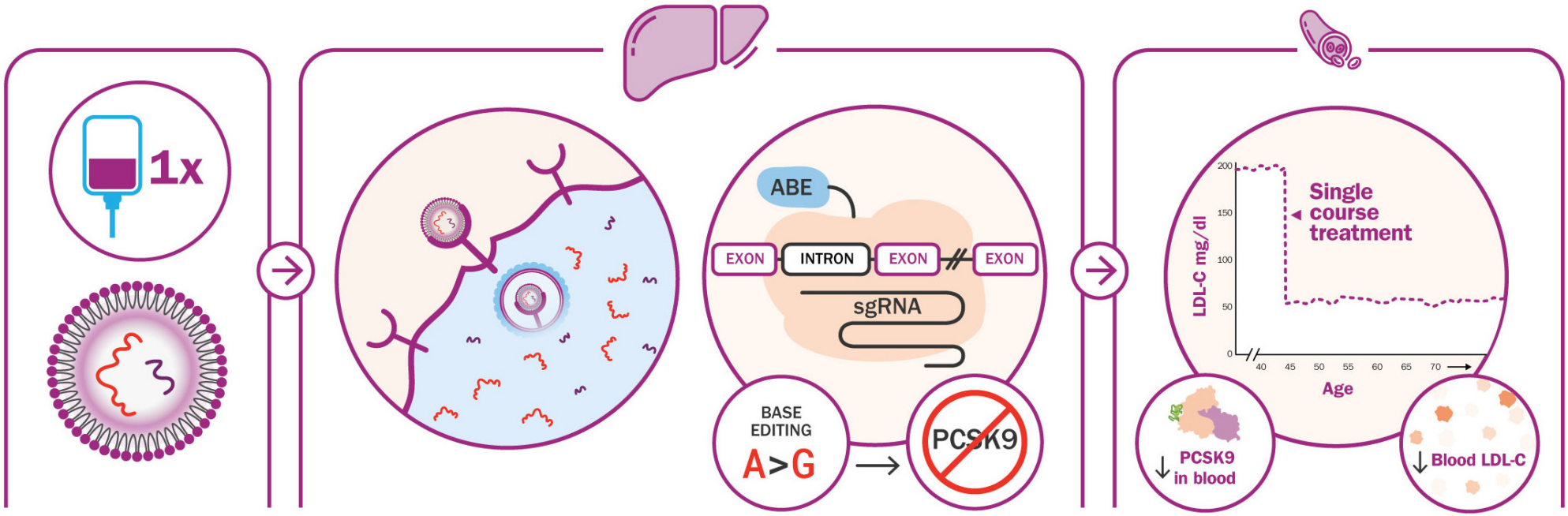
Non-viral LNP delivery

- Delivery predominantly to liver
- Transient exposure < 7 days

Base editing of the PCSK9 on-target site allows for a precise single base pair change without bystander edits

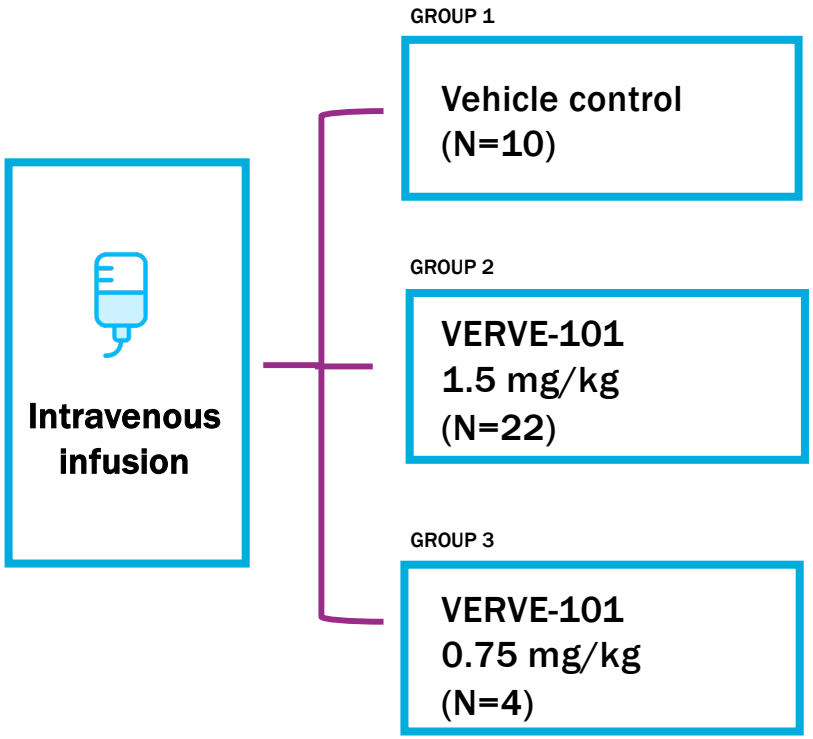


Goal: single course gene editing medicines to durably lower LDL-C and treat ASCVD



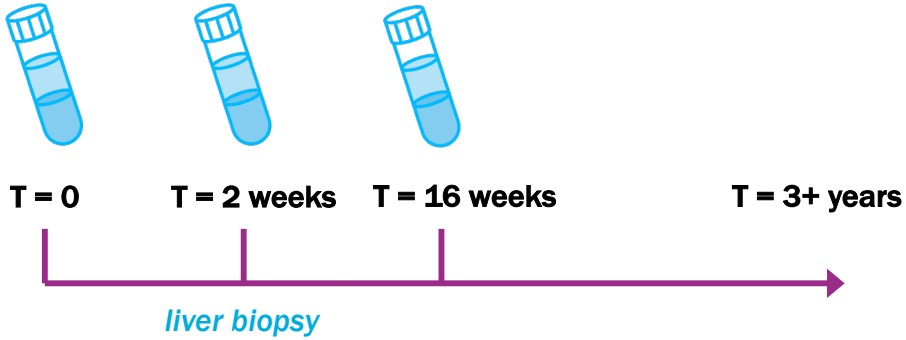
mRNA gRNA

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



Primary endpoints

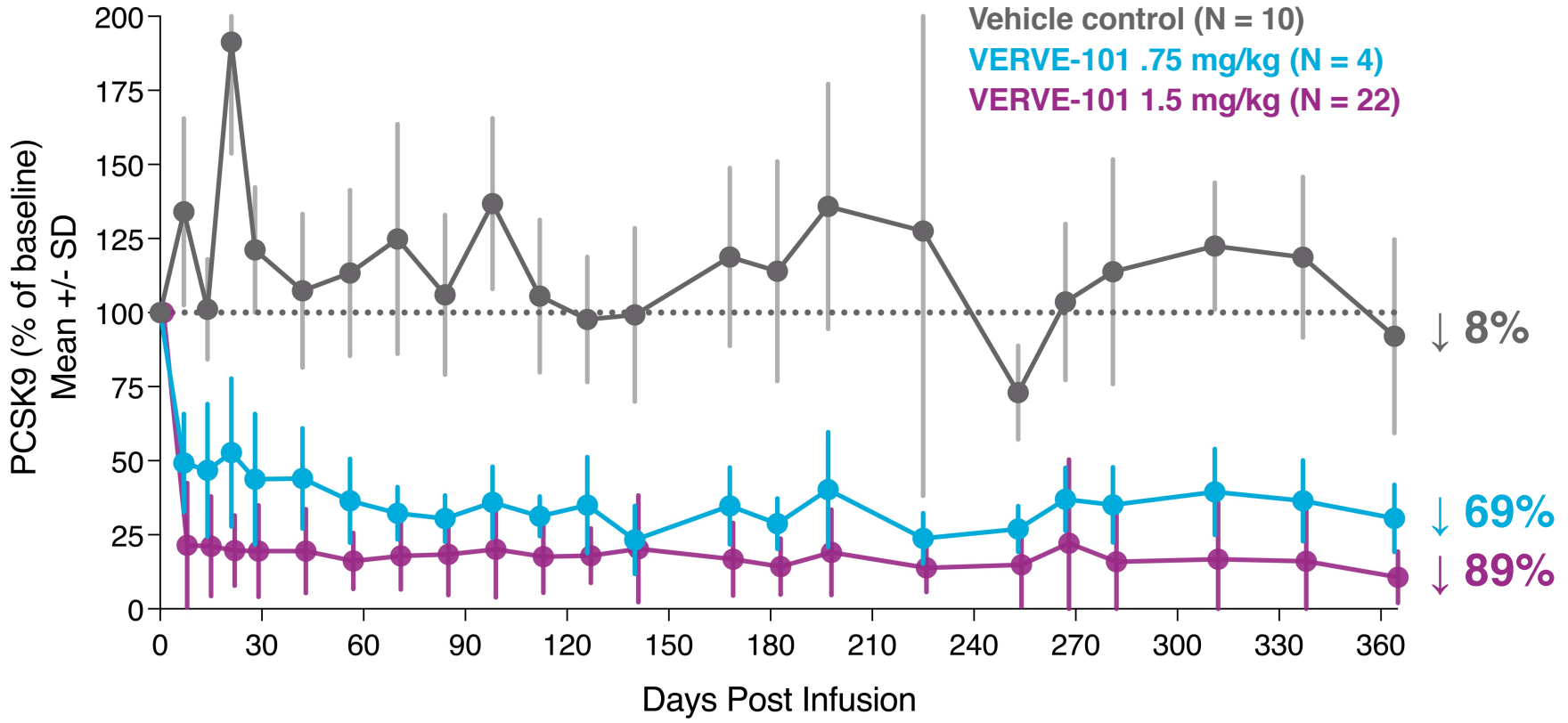
1. Whole liver DNA editing
2. Blood PCSK9 levels
3. Blood LDL-C levels



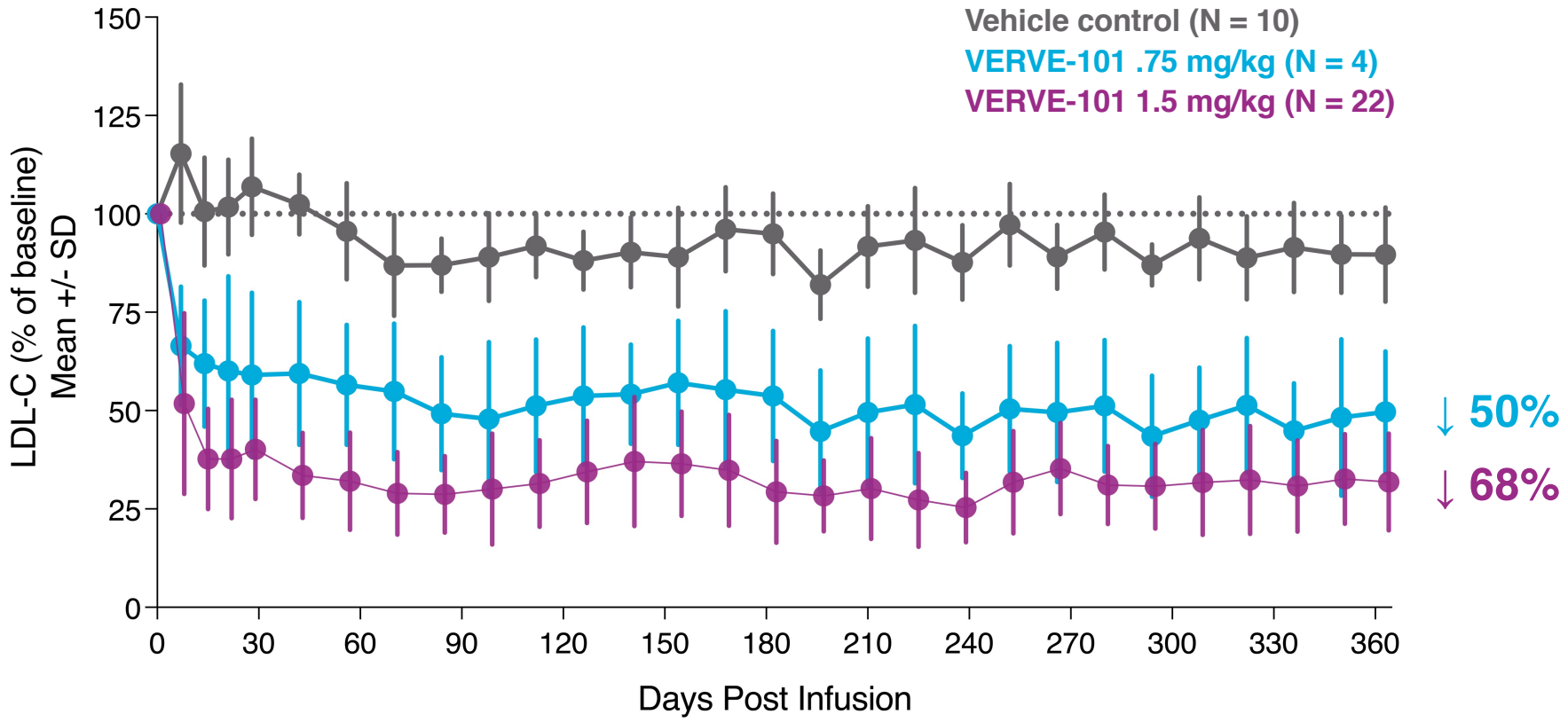
Safety endpoints

1. Liver function testing
2. Glucose homeostasis

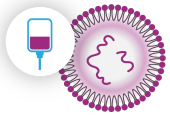
Blood PCSK9 level: 89% reduction observed at one year after one-time intravenous infusion of VERVE-101 in non-human primates (NHPs)



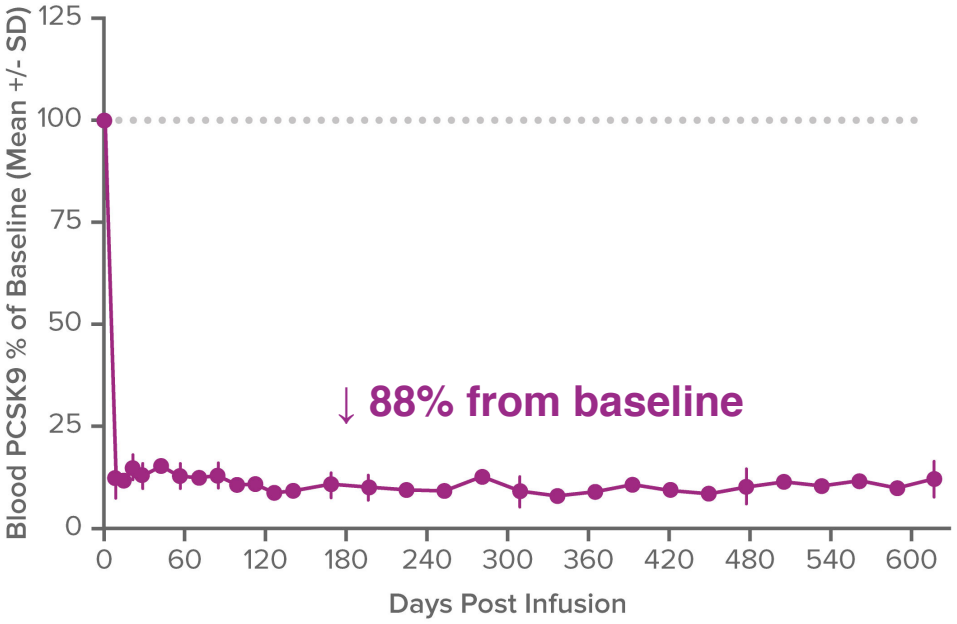
Blood LDL-C level: 68% reduction observed at one year after one-time intravenous infusion of VERVE-101 in NHPs

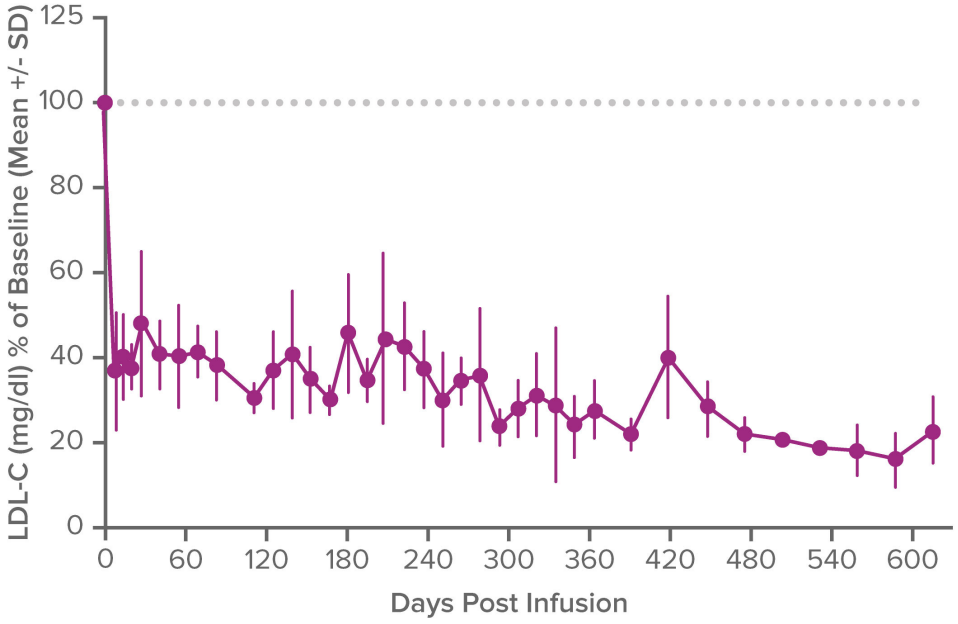


Even longer durability of PCSK9 and LDL-C reductions with precursor formulation, now out to 20 months in NHPs



VERVE-101 Precursor
3.0 mg/kg
N = 4





Multiple orthogonal techniques have been used to nominate ~3000 candidate off-target sites

entire human genome

identification techniques

Experimental: ABE-digenome-seq

Unbiased whole genome sequencing of liver genomic DNA treated with ABE in vitro

Experimental: ONE-Seq

library of ~30,000 barcoded sites with greatest sequence similarity to on-target site treated with ABE in vitro

Bioinformatics:

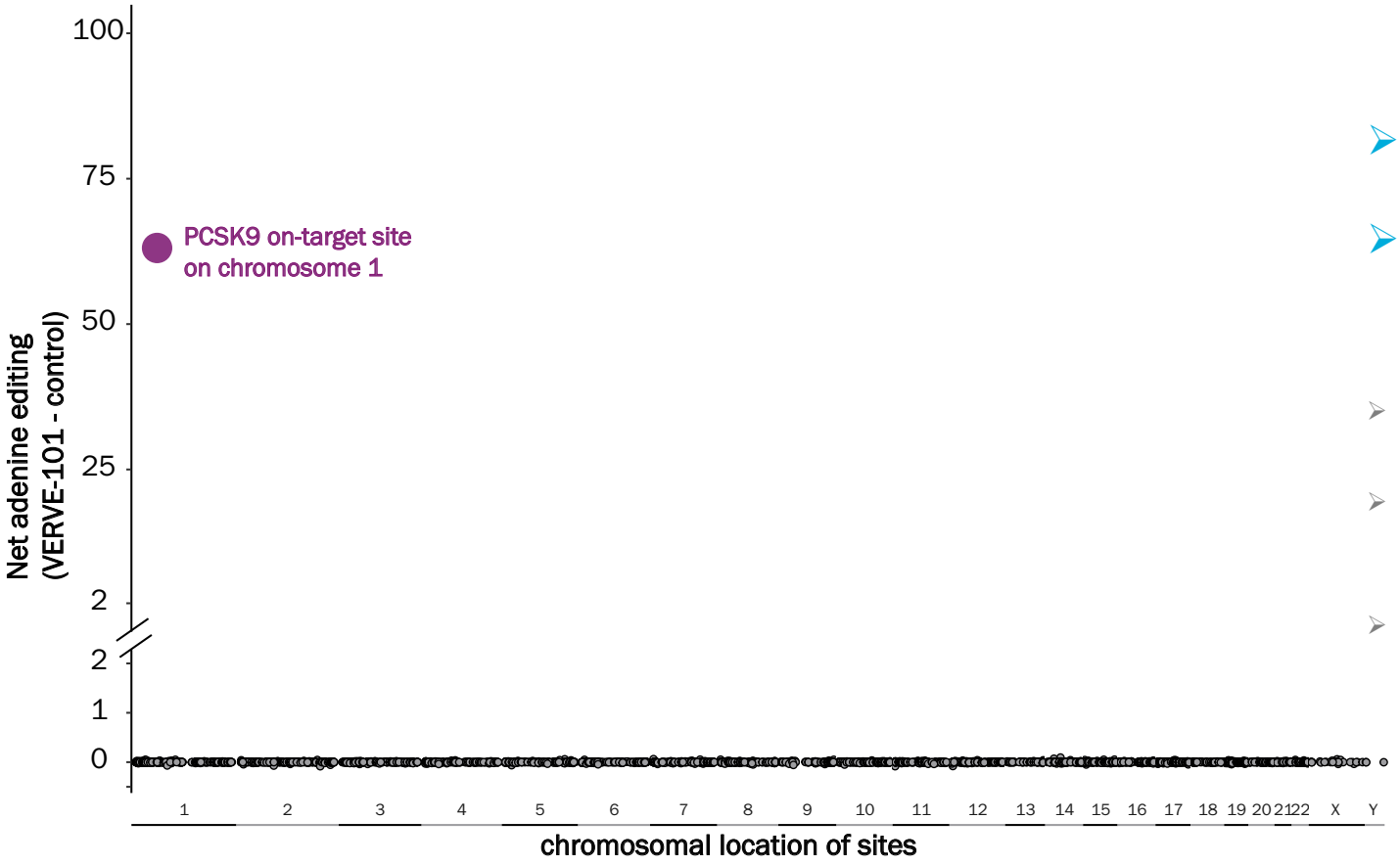
sites of greatest sequence homology

panel of candidates

3166 sites

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

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

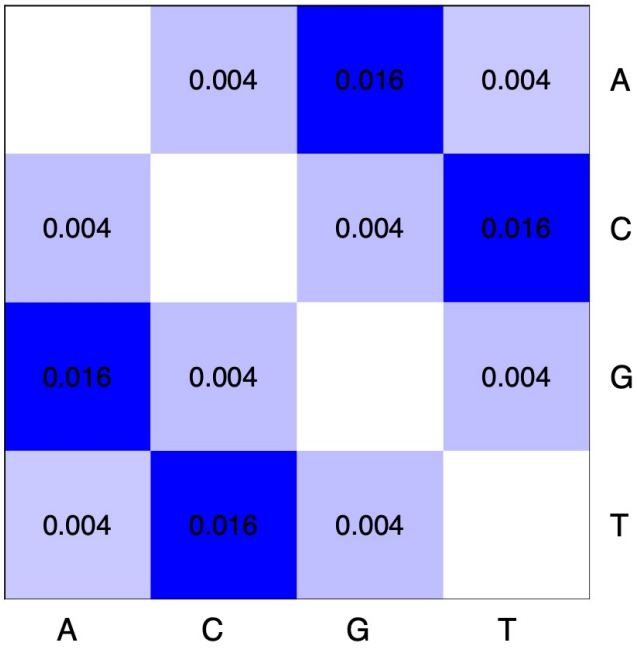


- **Manhattan style plot of ~3000 candidate sites**
- **No candidate sites show statistically significant net editing**

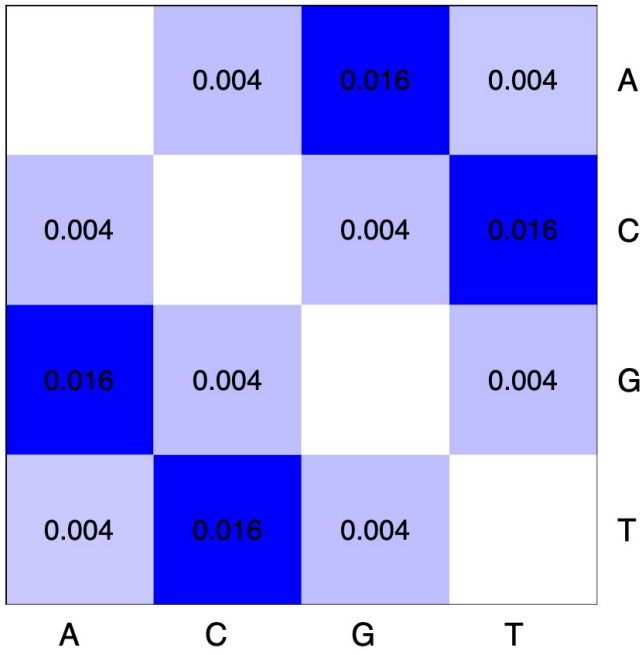
- Y axis indicates net editing (alternate allele frequency in treated primary human hepatocytes - matched untreated controls)
- Logistic regression statistical test is performed at each candidate site comparing alternate read counts in treated cells versus untreated cells
- Sites of somatic variation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

Whole genome sequencing (500X) of VERVE-101 treated huh-7 liver cells shows no increase in global adenine editing compared to untreated controls

Untreated



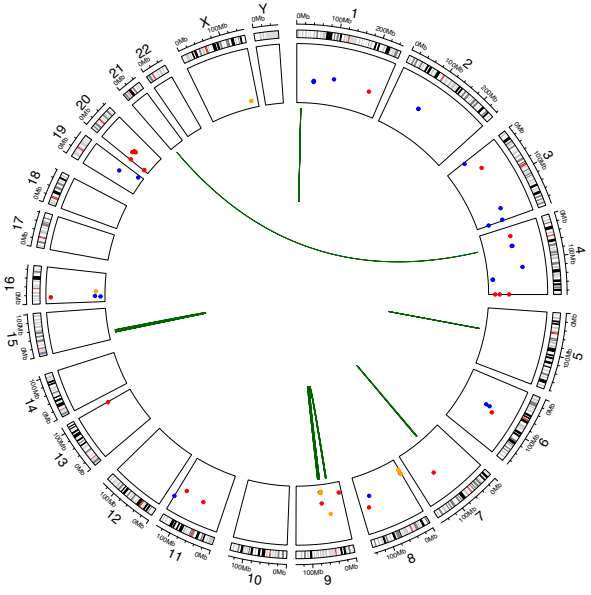
VERVE-101 treated



- Summary heat-map of 500x whole genome sequencing
- Numbers in cells of heat map reflect percentage of observed non-reference sequencing reads in comparing reference base (x-axis) to non-reference base (y-axis)

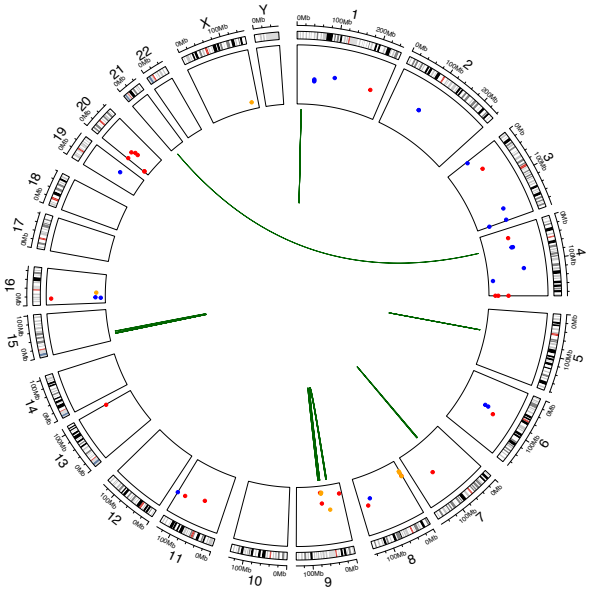
No structural variants observed from VERVE-101 treatment in primary human hepatocytes: whole genome optical mapping

Untreated



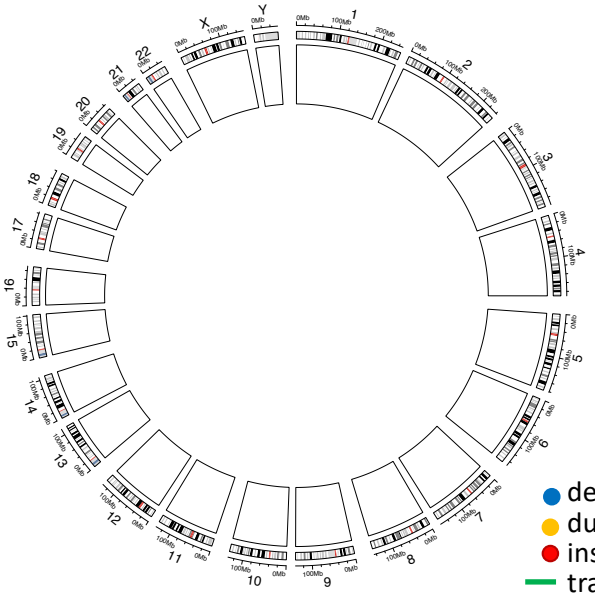
Structural variants are observed in control untreated PHH donor cells

VERVE-101 treated



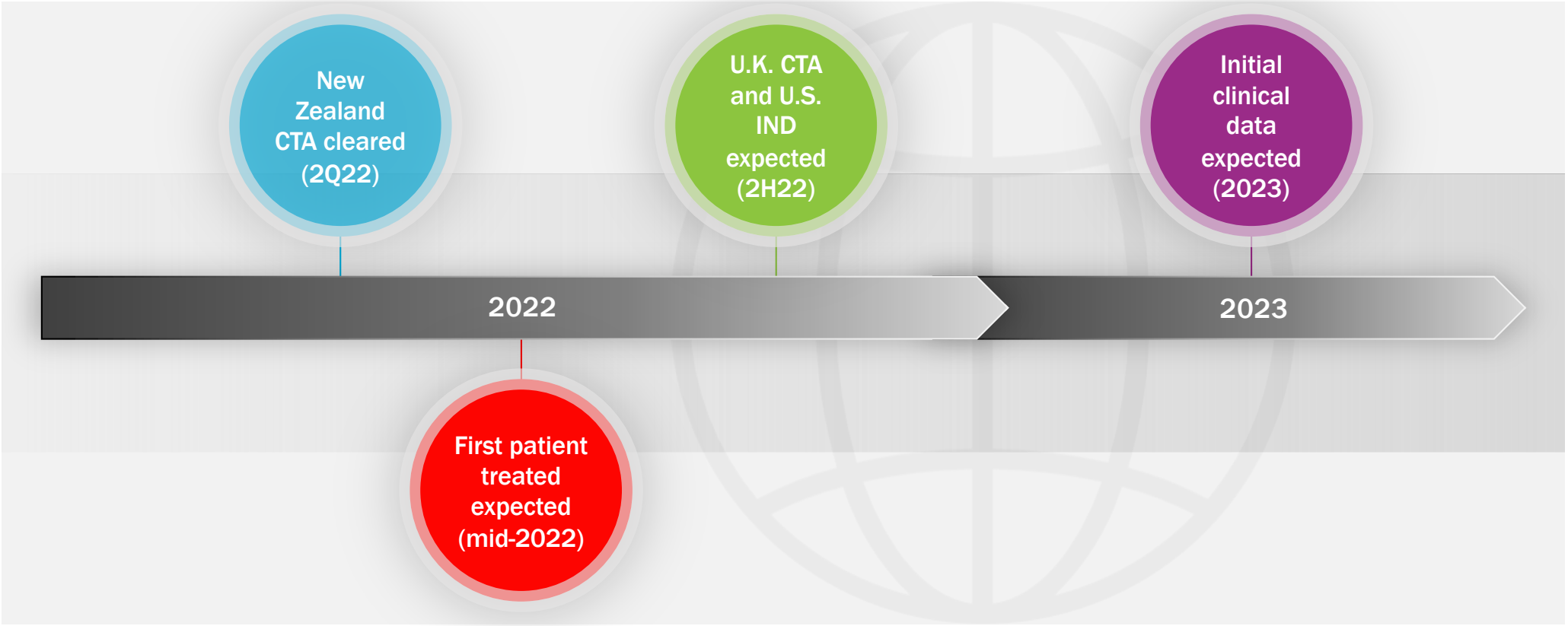
Identical structural variants are observed in the VERVE-101 treated PHH donor cells

VERVE-101 minus Untreated



No treatment-related structural variants are observed in VERVE-101 treated PHH donor cells

Clinical Trial Application (CTA) clearance for VERVE-101: a first for *in vivo* liver base editing



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

~40 patients with HeFH

LDLR mutation, ASCVD, LDL>100, on oral SOC

Part A: Single Ascending Dose

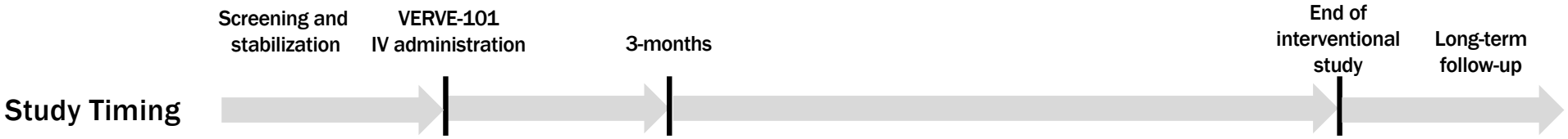
- High dose
- Int. dose
- Low dose
- Starting dose

n=3-6 per group
participant staggering, sentinels

Expansion Cohorts

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

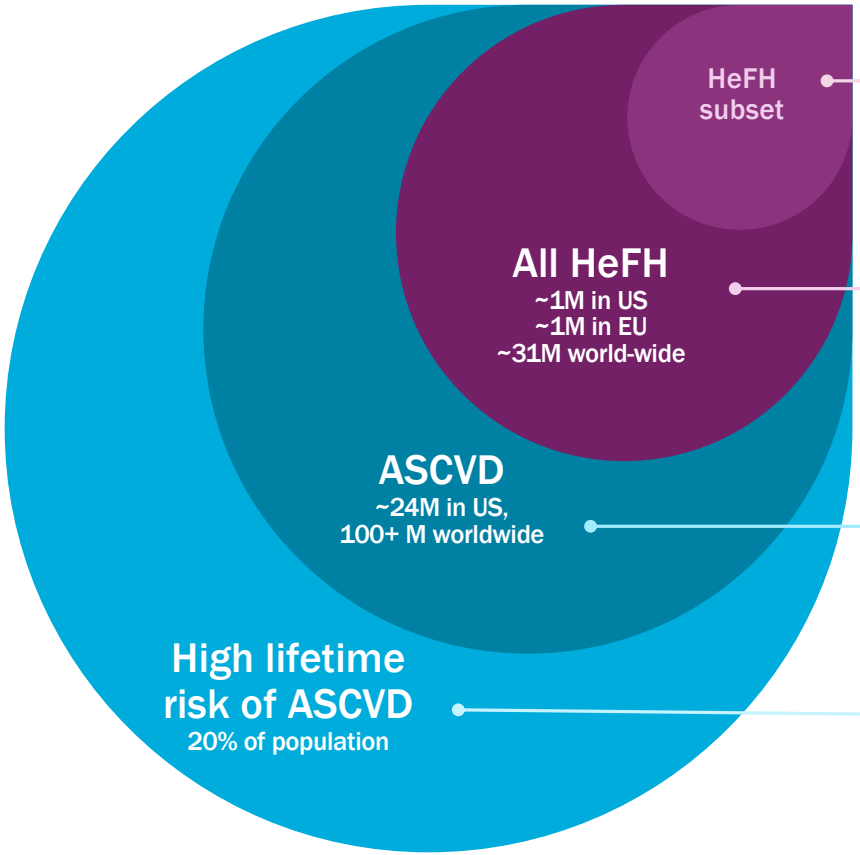
Part C: Second dose offered to participants in part A who received lower dose than part B



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

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

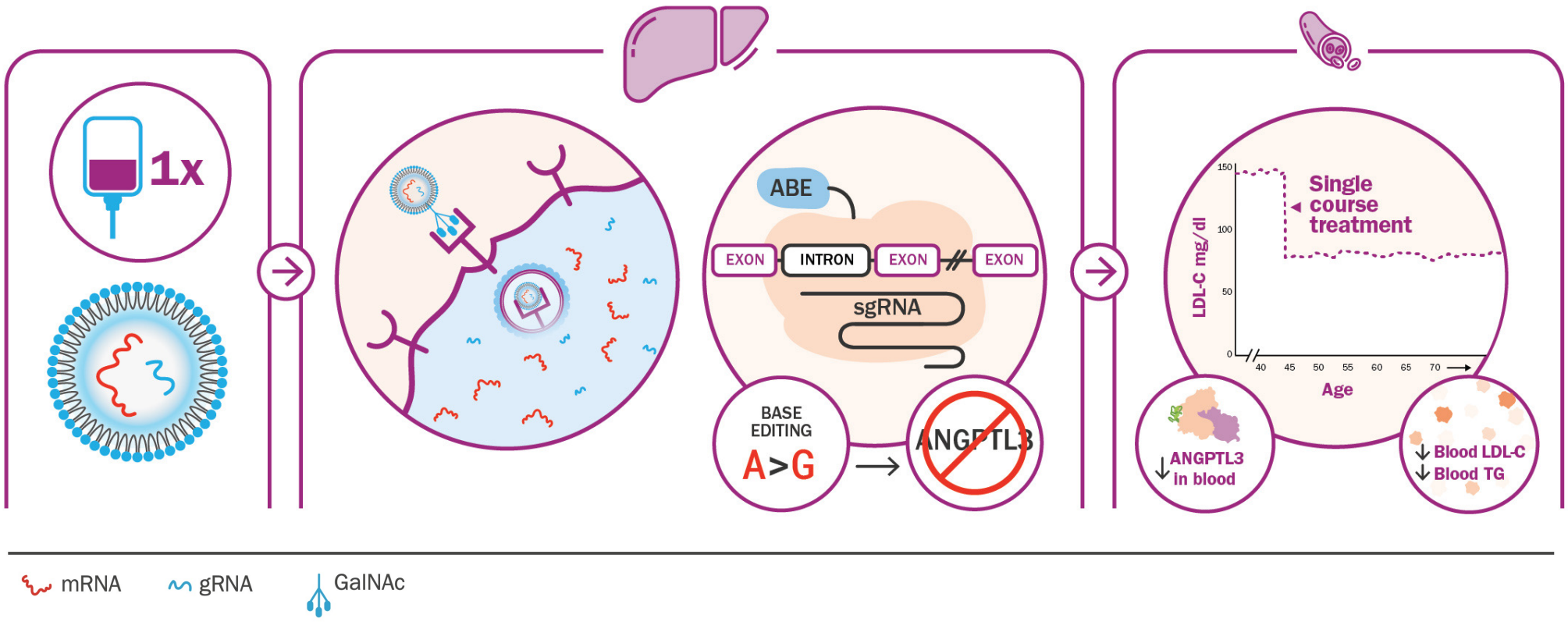
Stepwise clinical development strategy starting with FH and expanding to broader population with ASCVD



- Phase 1b proof-of-concept in high-risk HeFH
- Phase 2 in all HeFH
- Pivotal Phase 3 in all HeFH, approval based on LDL-C endpoint at 24 weeks
- Pivotal Phase 3 in ASCVD, approval based on LDL-C endpoint at 24 weeks
- Post-approval studies including CVOT in ASCVD

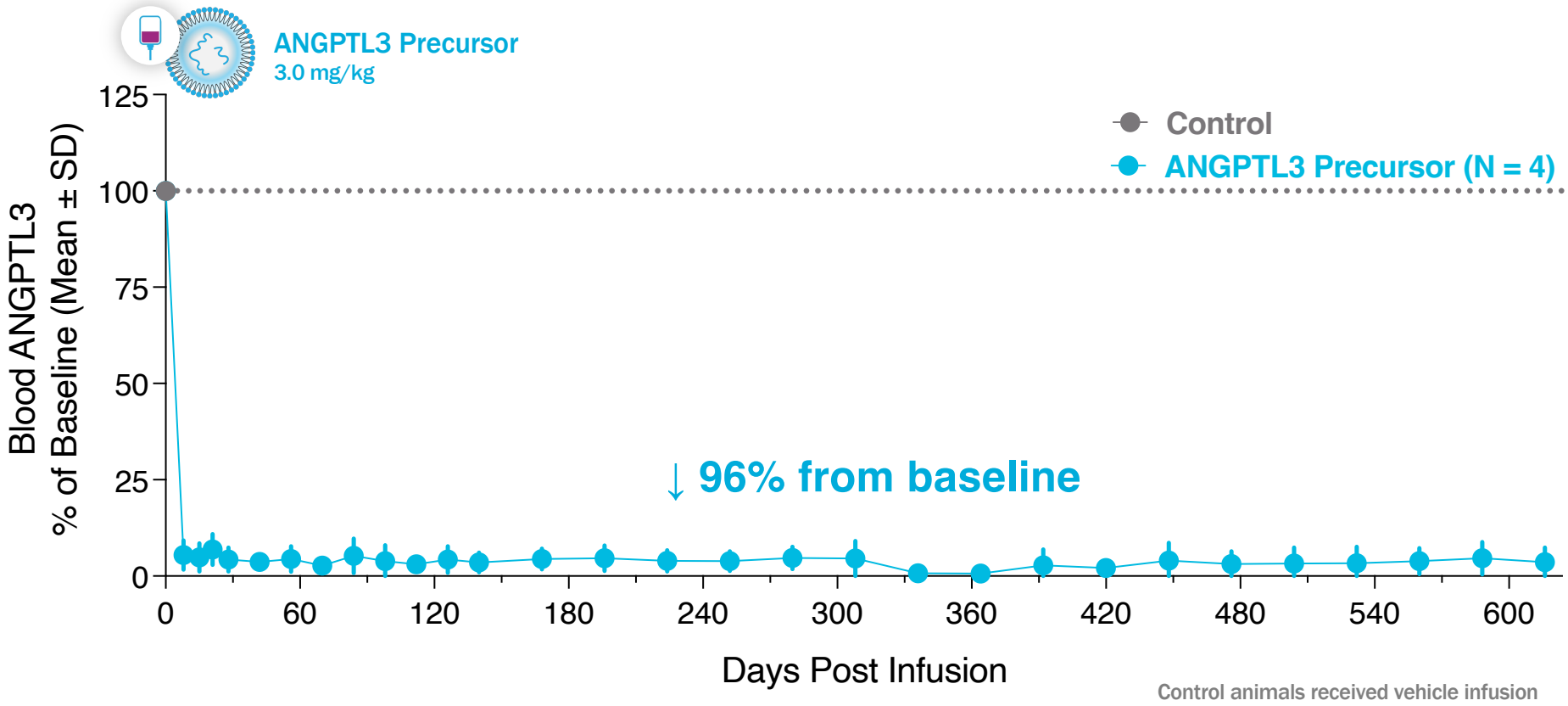
Advancing ANGPTL3 program to IND-enabling studies in 2022

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



mRNA gRNA GalNAc

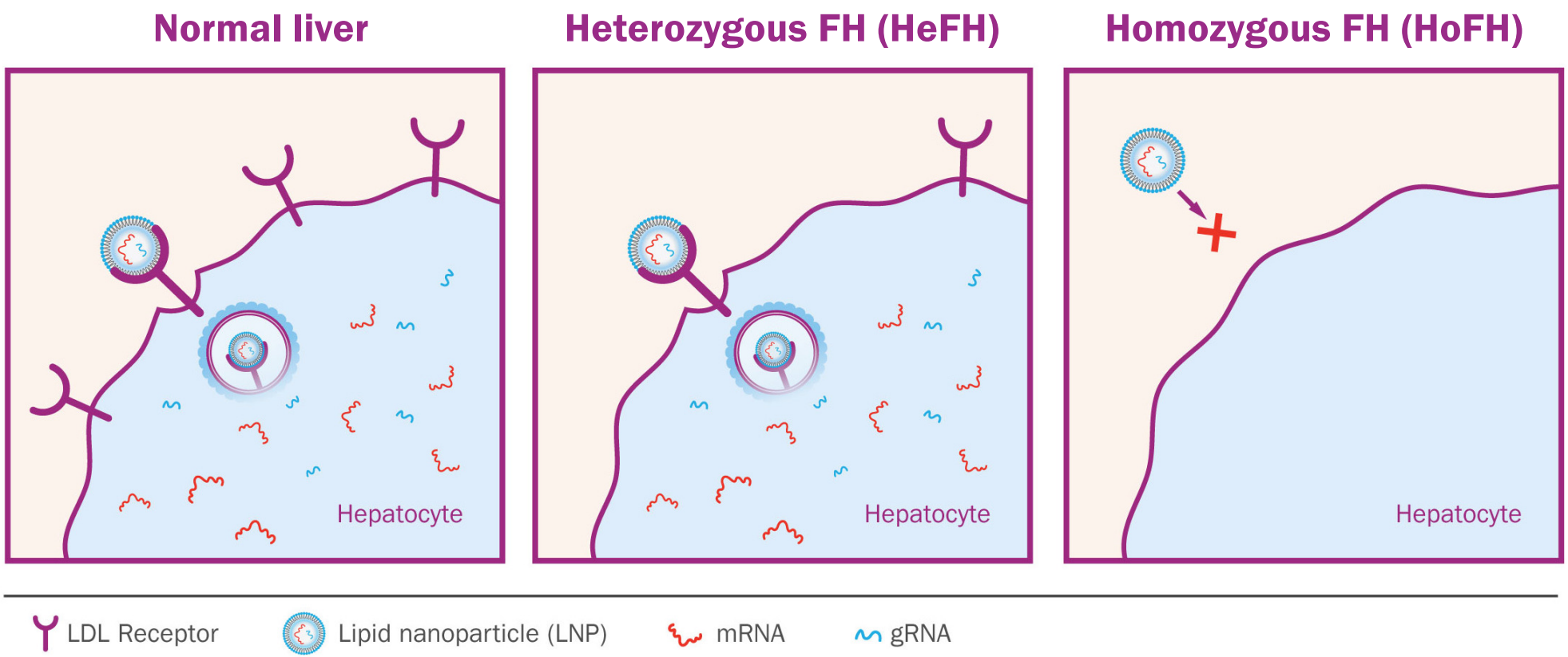
Verve ANGPTL3 precursor administered to NHPs: 616 days following infusion, durable >90% reduction in blood ANGPTL3



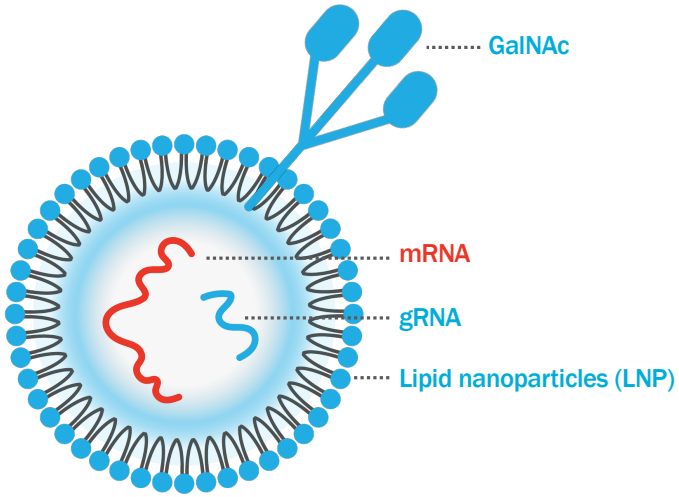
Control animals received vehicle infusion

Novel GalNAc-LNP delivery technology platform

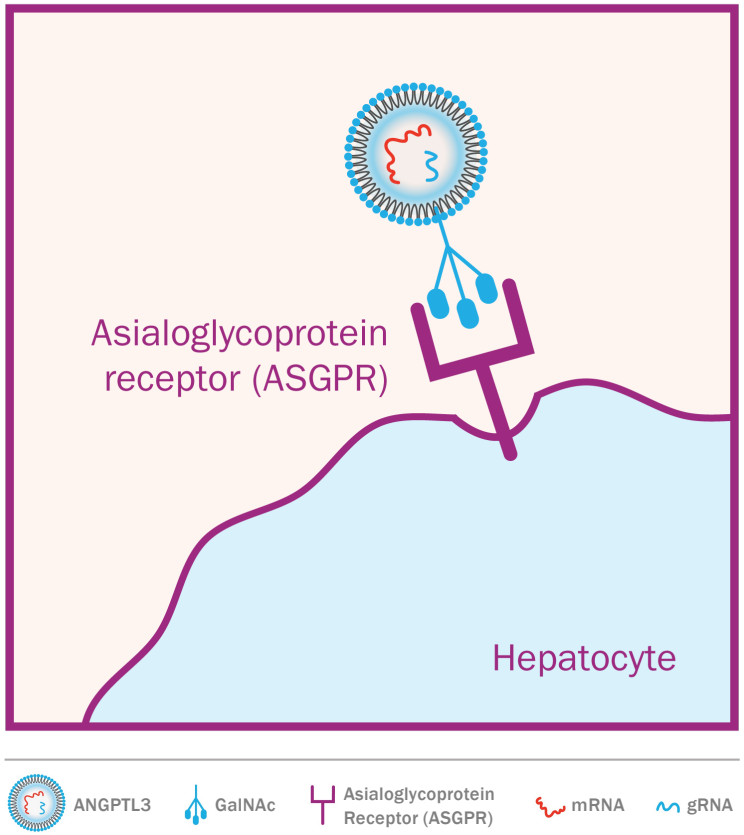
Delivery challenge: HoFH patients completely lack LDL receptor; in this setting, standard LNPs don't work



Proprietary GalNAc-LNP technology: potential best-in-class for delivery of genetic medicines to liver

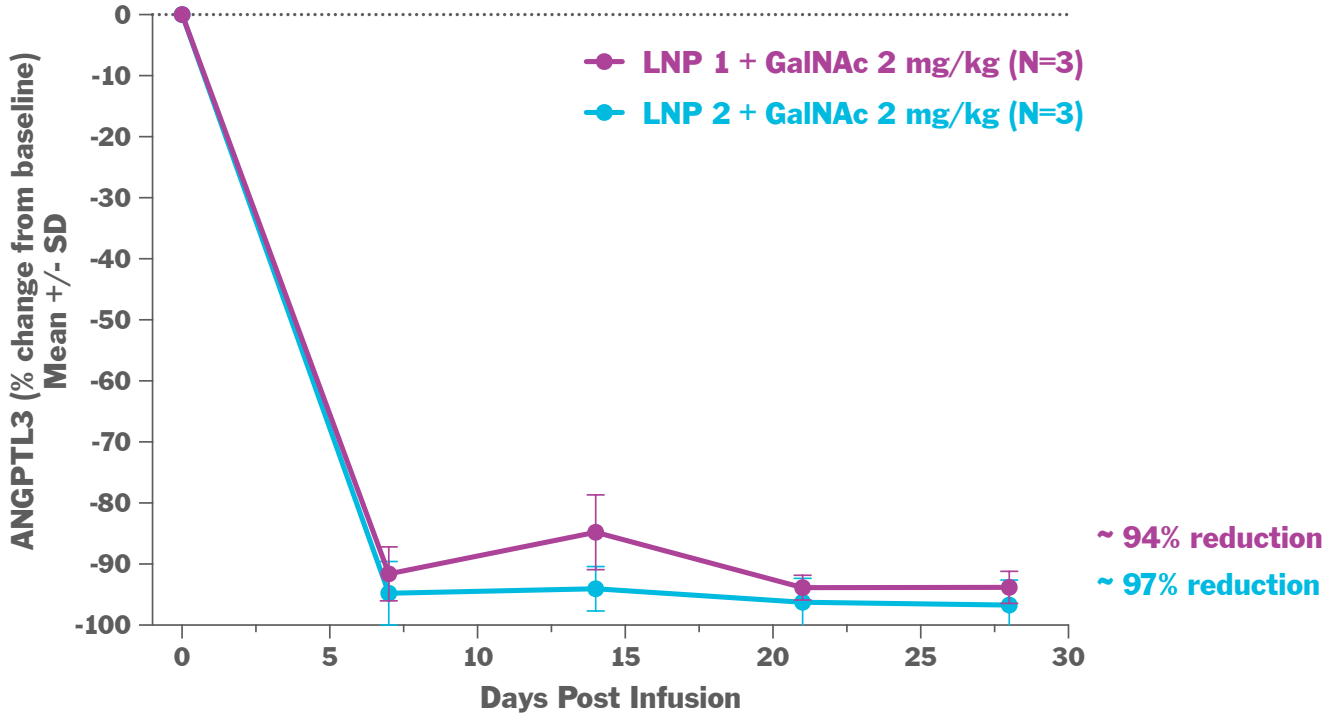


United States Patent
Rajeev et al.
Patent No.: US 11,207,416 B2
Date of Patent: Dec. 28, 2021



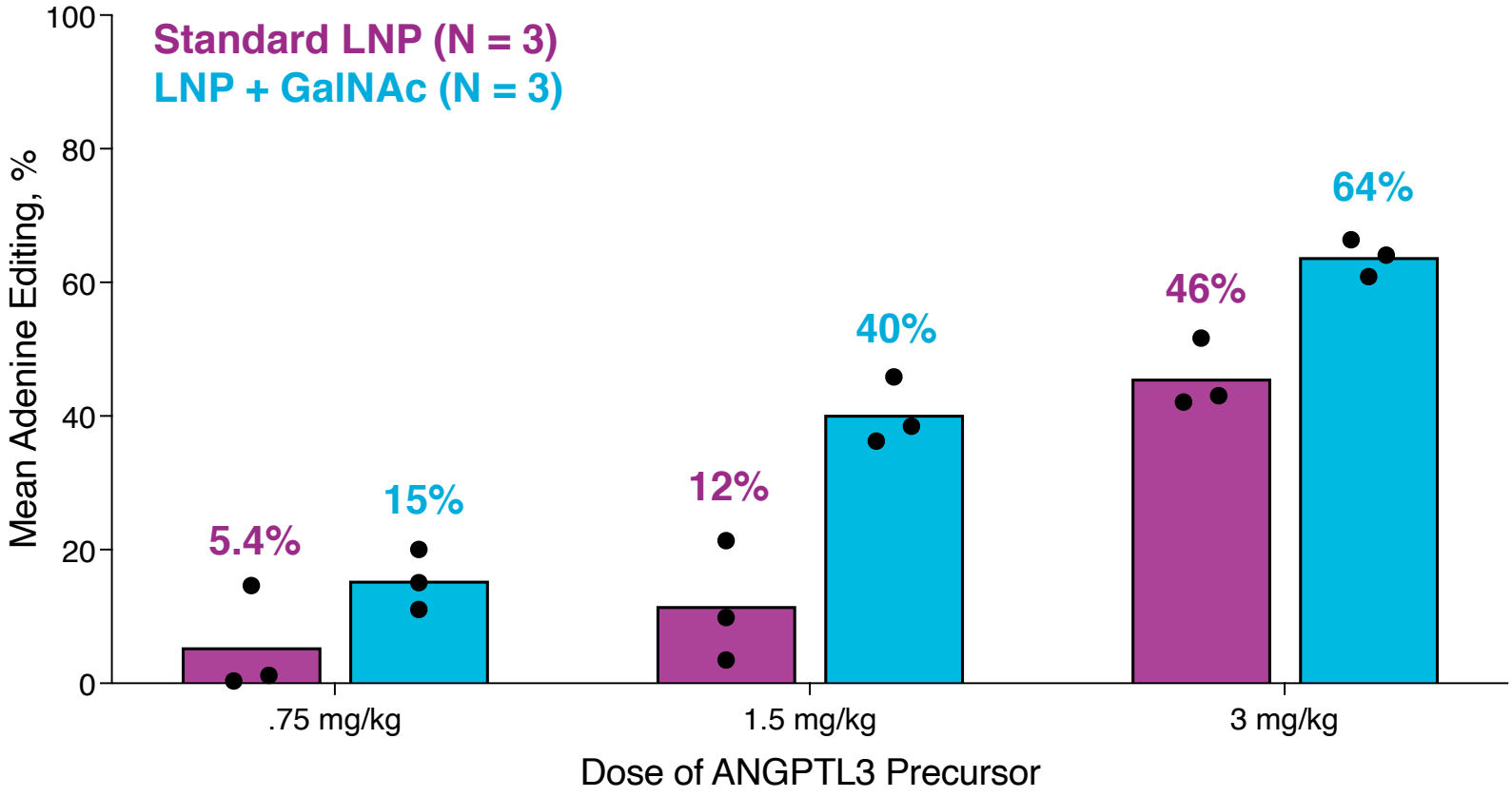
Base editing of ANGPTL3 via GalNAc-LNPs reduces blood ANGPTL3 by 94% - 97% in NHP model of HoFH

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

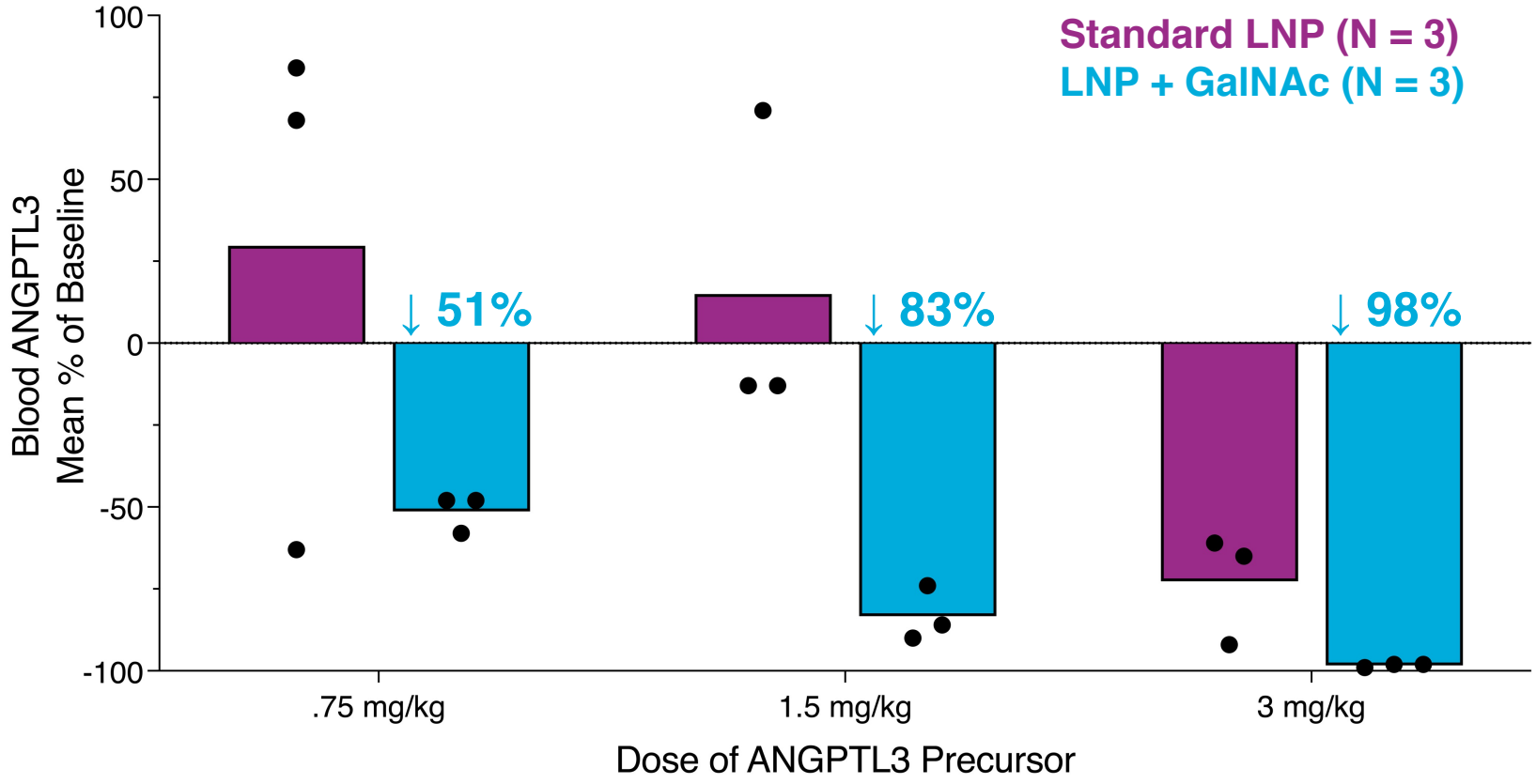


Hypothesis: In wild-type NHPs, GalNAc-LNP is more potent when compared with standard LNP

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



In wild-type NHPs, GalNAc-LNP leads up to 98% reduction in blood ANGPTL3, reflecting improved consistency compared with standard LNP

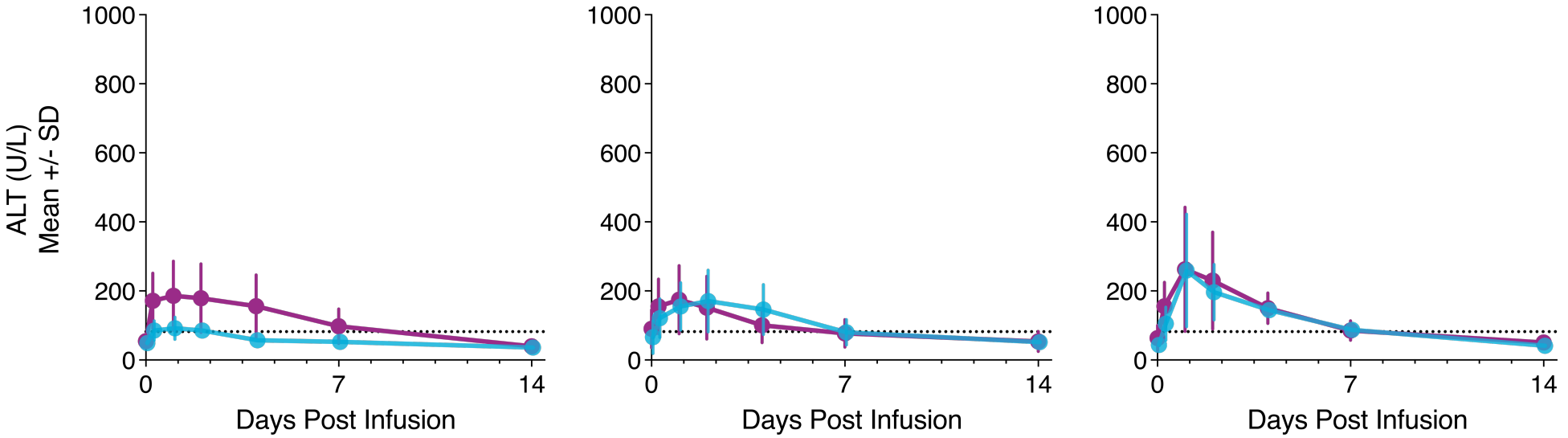


Addition of GalNAc to LNP did not alter safety profile: transient impact on alanine aminotransferase

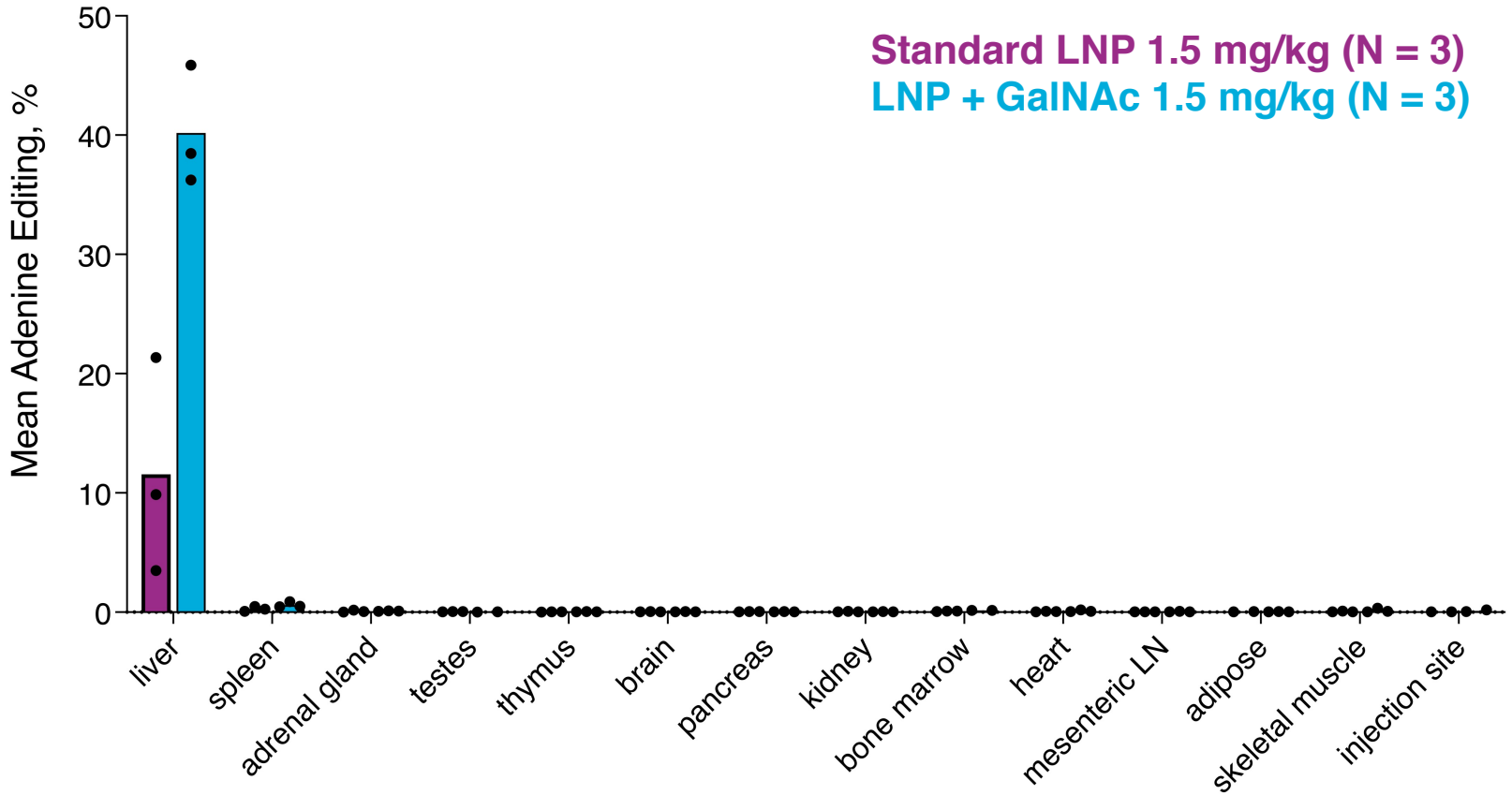
Standard LNP 0.75 mg/kg (N = 3)
LNP + GalNAc 0.75 mg/kg (N = 3)

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

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

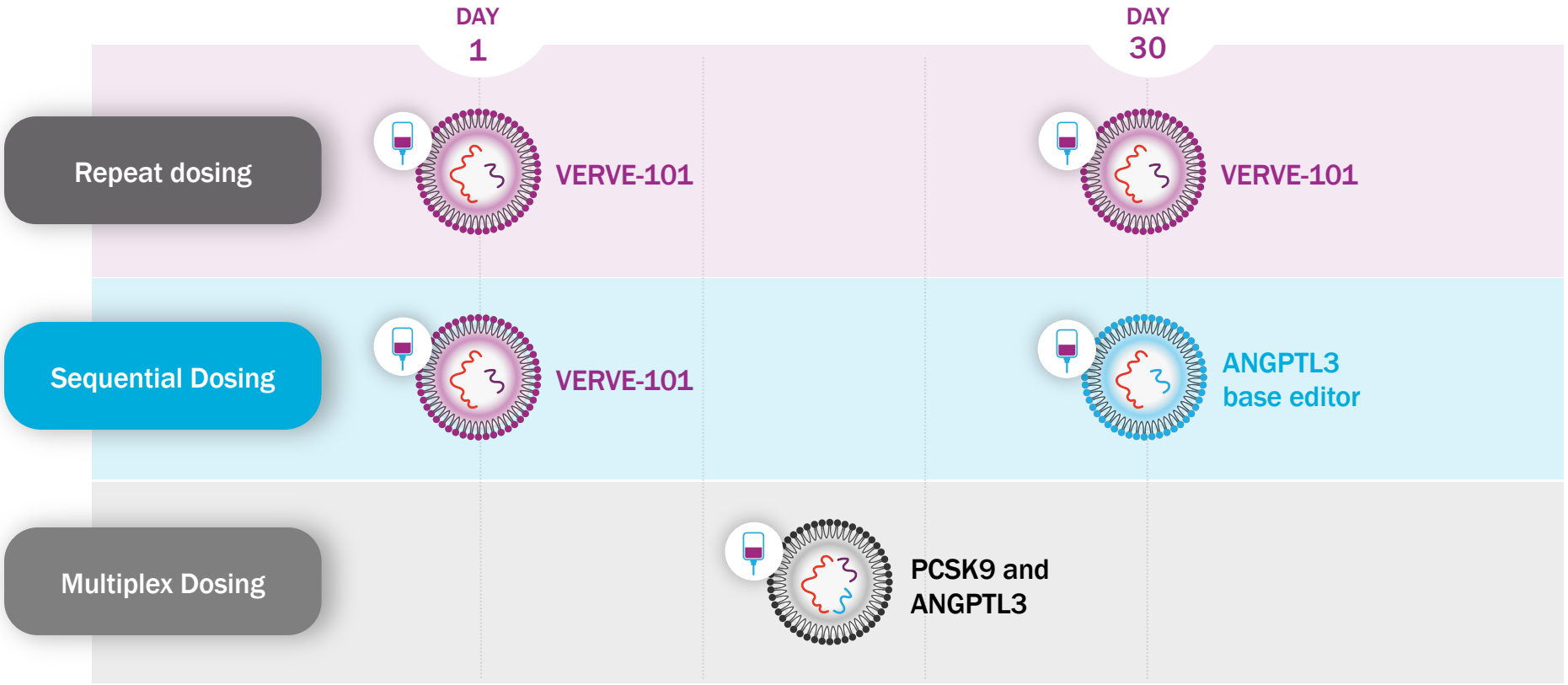


Specific delivery to the liver with GalNAc-LNP

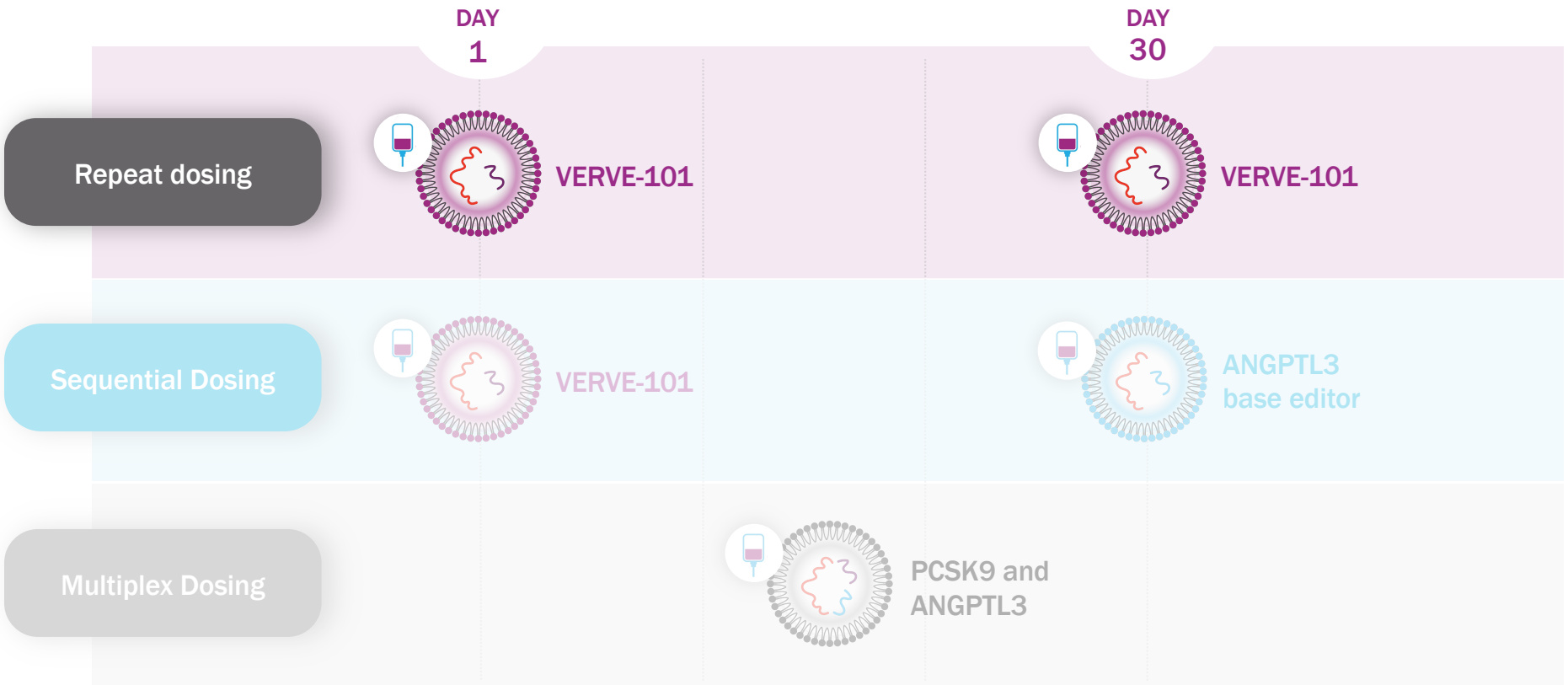


Future dosing options

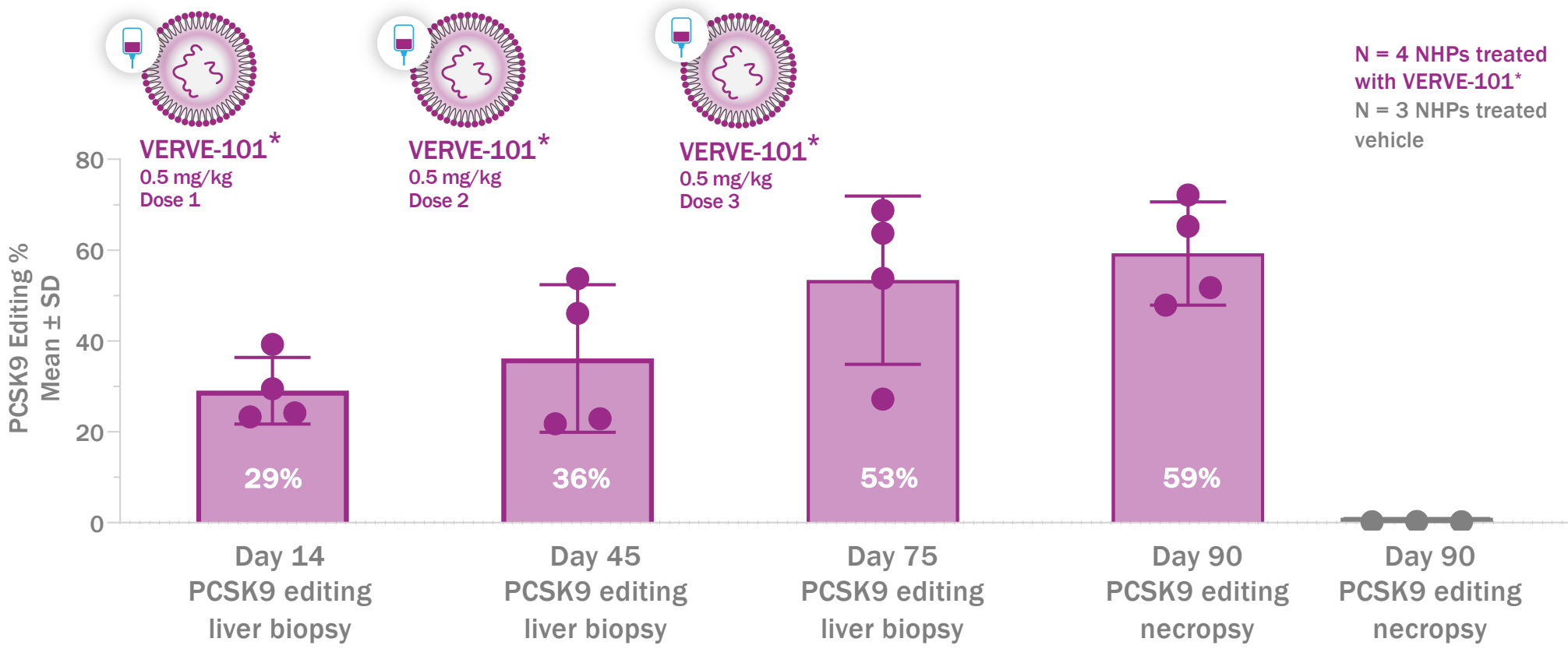
Several dosing options explored in NHPs



Repeat dosing of VERVE-101 – uniquely possible with LNP delivery



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



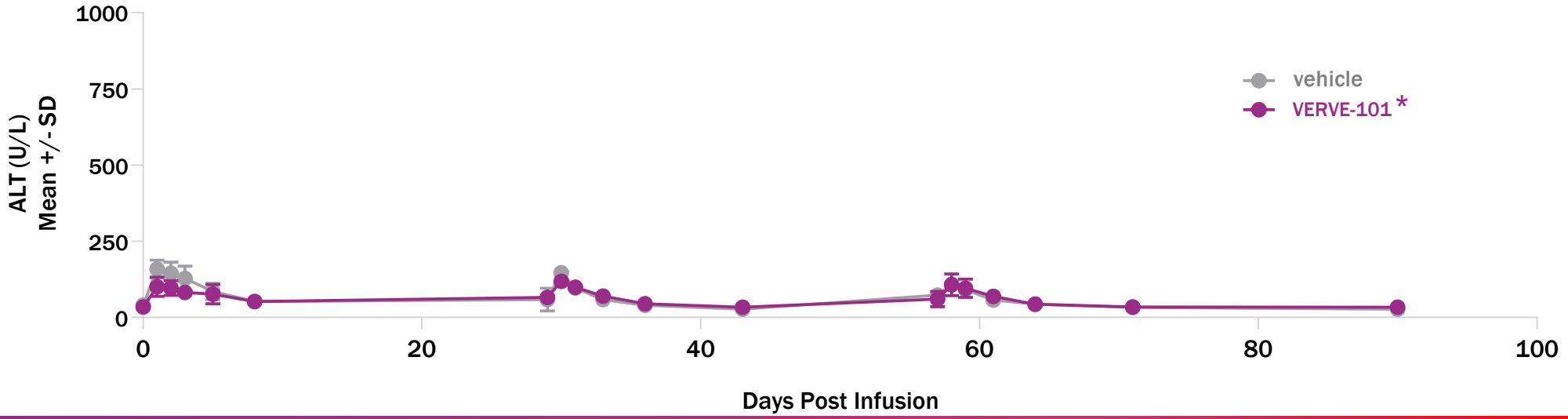
* VERVE-101 precursor

No evidence of liver injury observed following repeat dosing in NHPs

VERVE-101 *
0.5 mg/kg
Dose 1

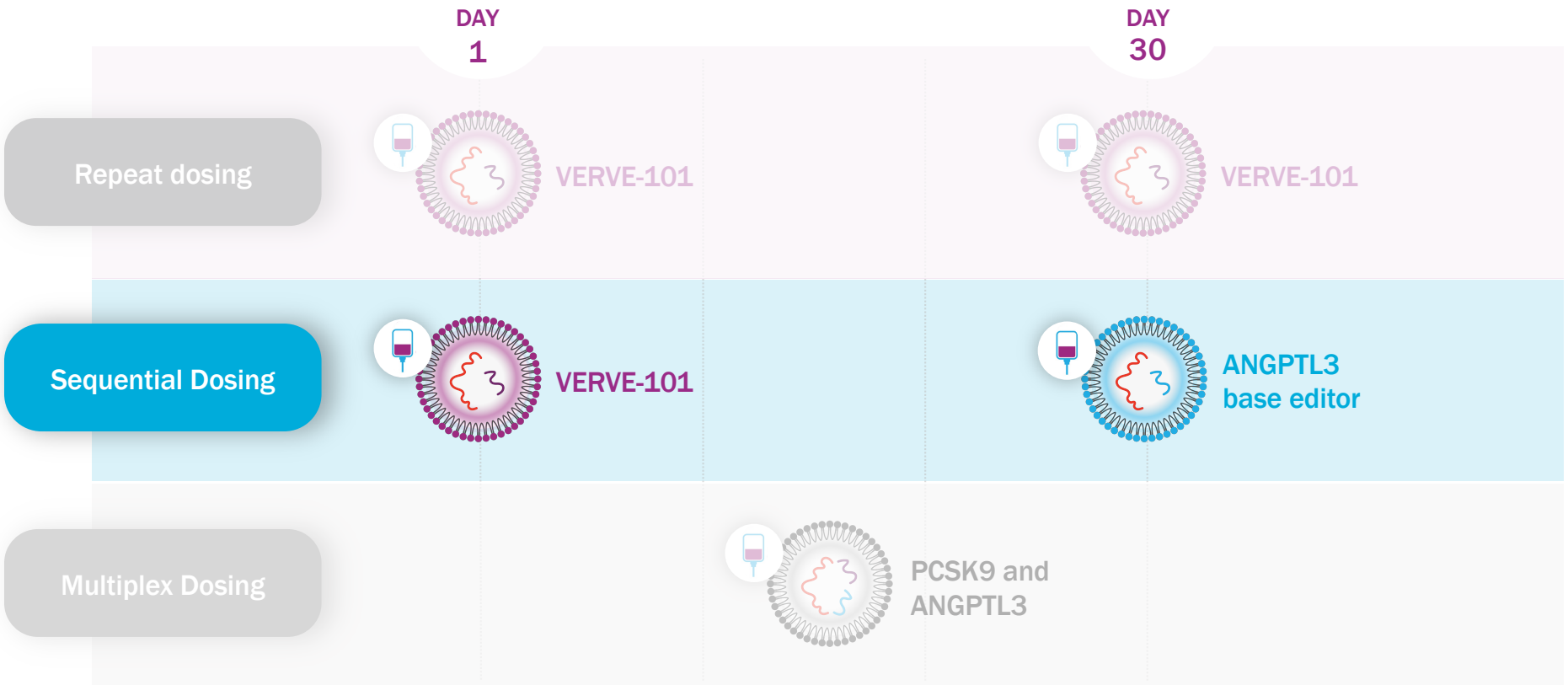
VERVE-101 *
0.5 mg/kg
Dose 2

VERVE-101 *
0.5 mg/kg
Dose 3

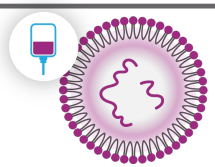


* VERVE-101 precursor with modestly reduced potency

Sequential dosing of VERVE-101 followed by ANGPTL3 base editor



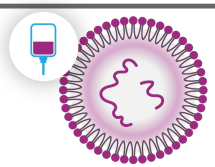
Sequential dosing of VERVE-101



		Biopsy Day 15 PCSK9 editing
Treatment	VERVE-101 1.0 mg/kg	
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%

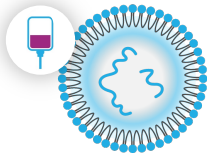
* biopsy error, initial biopsy 16%, repeat 69%

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



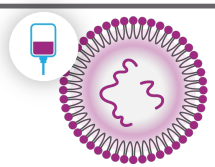
ANGPTL3
1.0 mg/kg

Biopsy
Day 45
ANGPTL3 editing

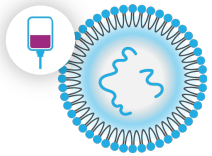
Treatment	NHP 1	70%	59%
	NHP 2	67%	50%
	NHP 3	79%	54%
	NHP 4	69%*	44%
	average	71 ± 5%	52 ± 6%
Control	NHP 1	0.1%	0.2%
	NHP 2	0.3%	0.2%
	NHP 3	0.2%	0.2%

* 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

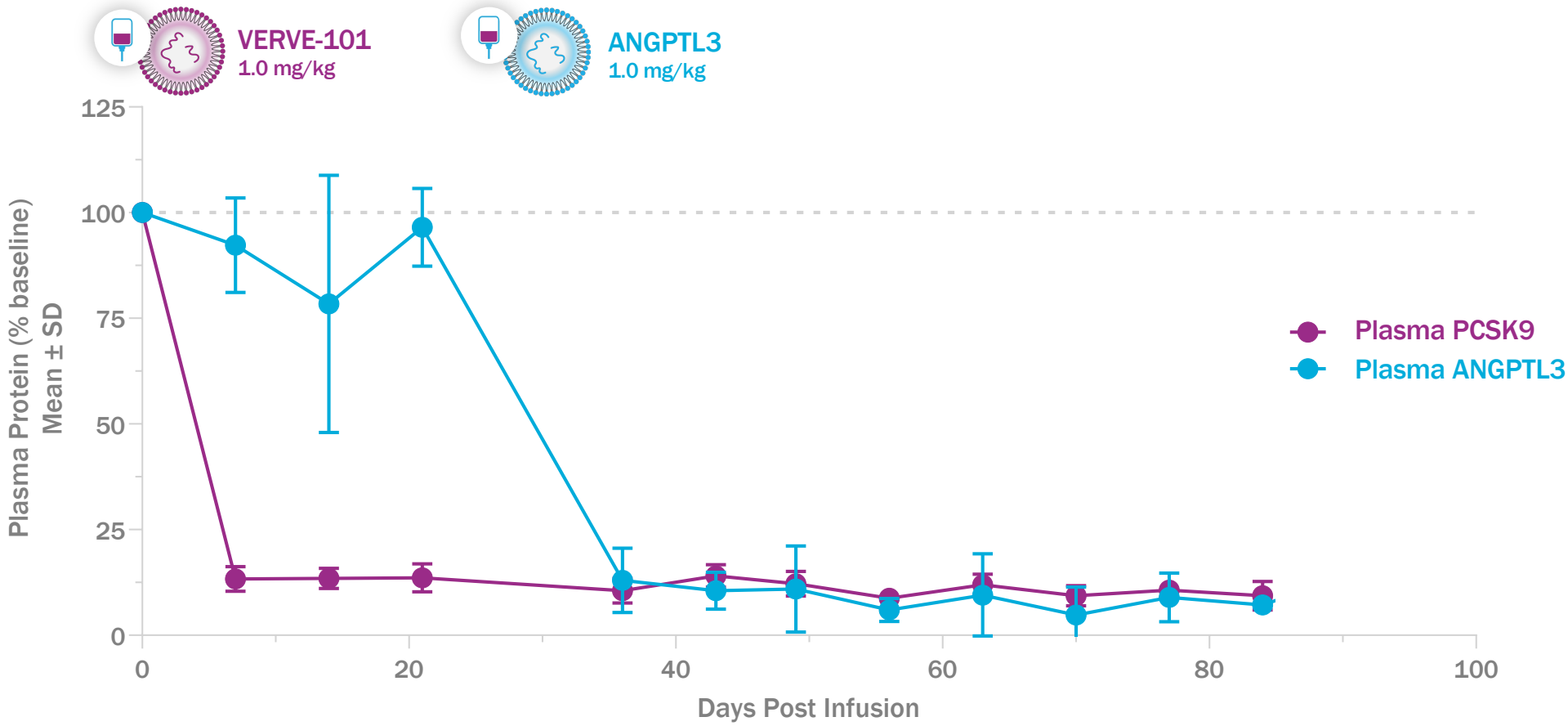


ANGPTL3
1.0 mg/kg

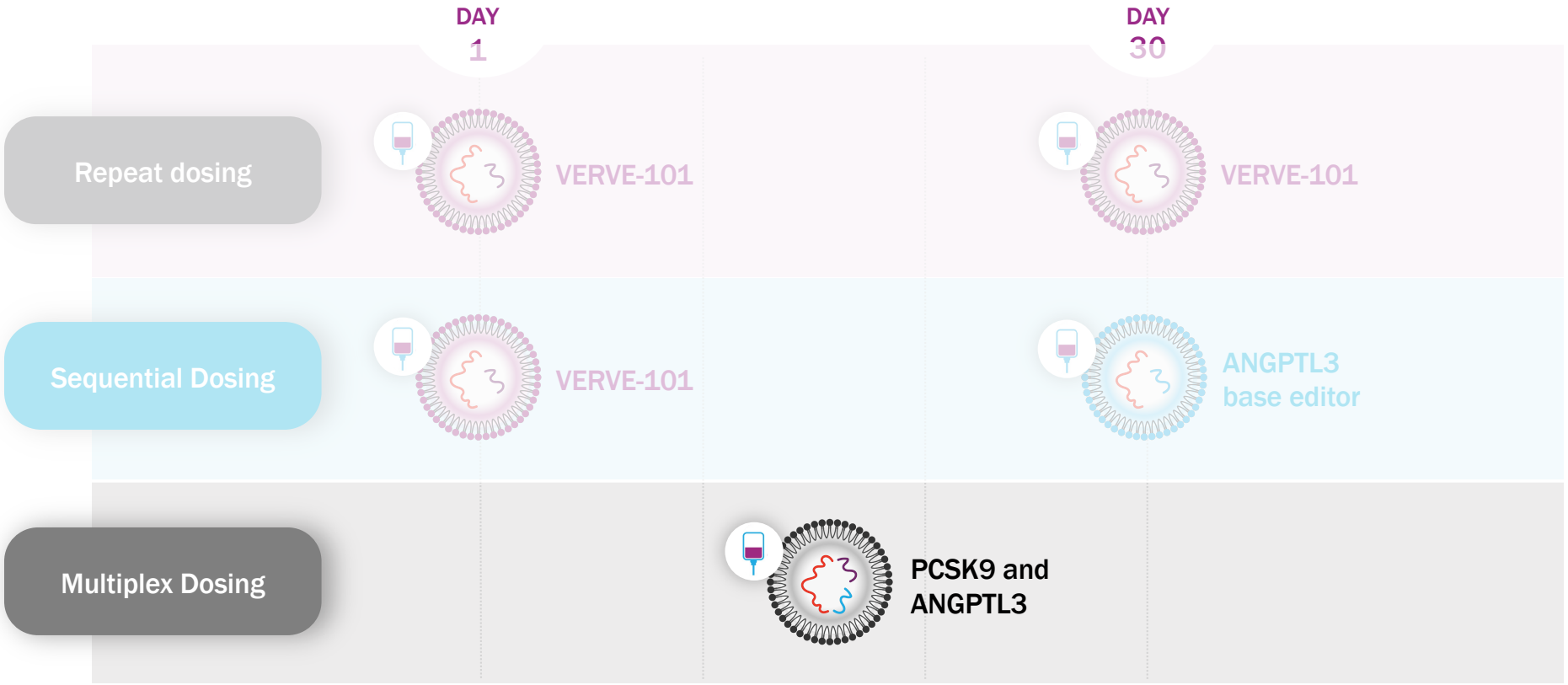
		Biopsy Day 15 PCSK9 editing	Biopsy Day 45 ANGPTL3 editing	Necropsy Day 90
Treatment	NHP 1	70%	59%	68% PCSK9 63% ANGPTL3
	NHP 2	67%	50%	69% PCSK9 62% ANGPTL3
	NHP 3	79%	54%	70% PCSK9 62% ANGPTL3
	NHP 4	69%*	44%	70% PCSK9 63% ANGPTL3
	average	71 ± 5%	52 ± 6%	69 ± 1% PCSK9 63 ± 1% ANGPTL3
Control	NHP 1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

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

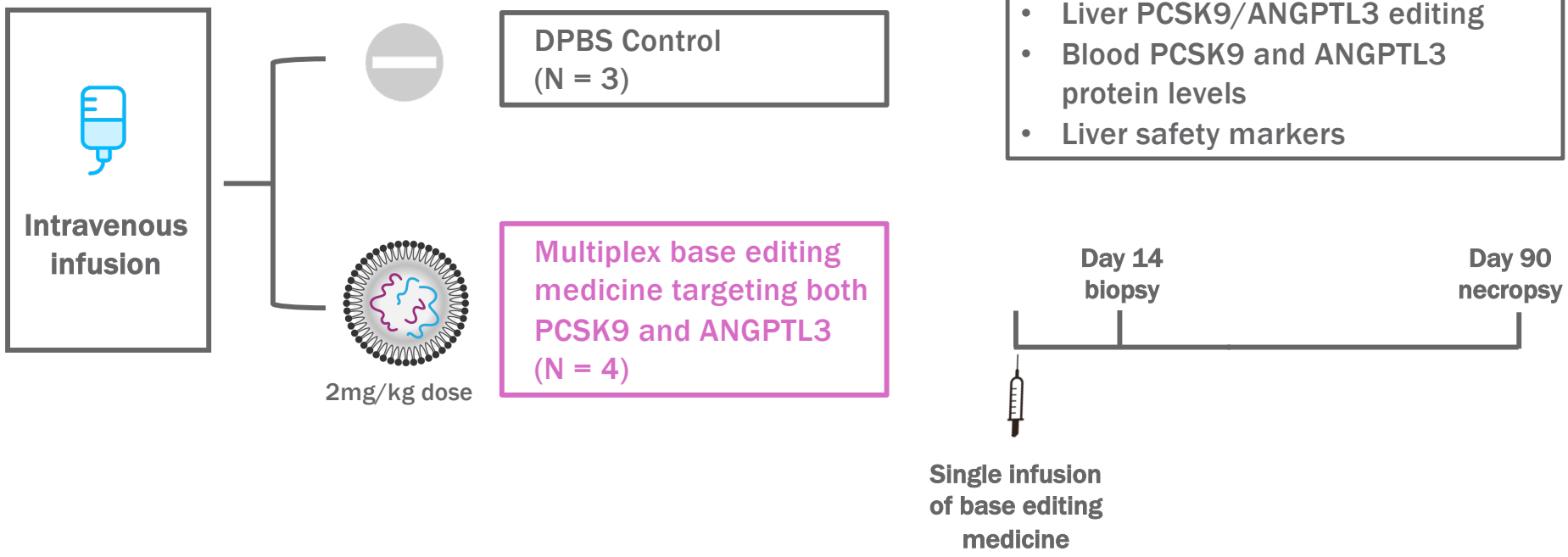
Sequential dosing in NHPs: >90% reduction of plasma PCSK9 protein followed by >90% reduction observed of plasma ANGPTL3 protein



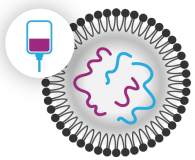
New data today: a single drug product to edit 2 genes!



Multiplex base editing in NHPs targeting both PCSK9 and ANGPTL3: *in vivo* non-human primate study



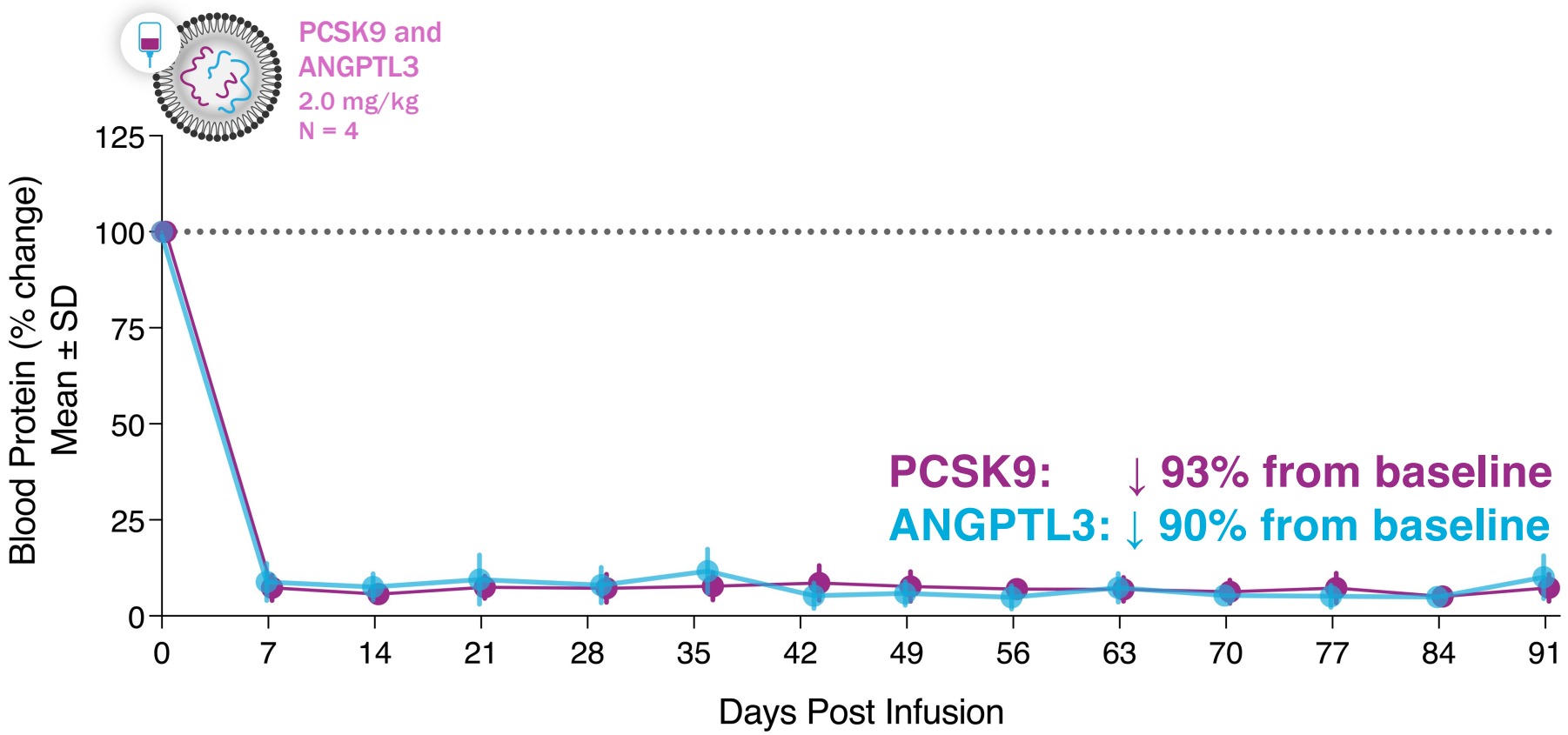
A single infusion of multiplex base editor product in NHPs: potent liver editing of both PCSK9 and ANGPTL3 genes



PCSK9 and ANGPTL3
2.0 mg/kg

		Day 14 biopsy		Day 90 necropsy	
		PCSK9 editing	ANGPTL3 editing	PCSK9 editing	ANGPTL3 editing
Treatment	NHP 1	81.7%	64.0%	73.8%	61.8%
	NHP 2	75.8%	63.1%	75.8%	67.8%
	NHP 3	72.3%	54.6%	68.4%	55.5%
	NHP 4	80.3%	64.0%	81.8%	69.9%
	average +/- SD	77.5 +/- 4.3 %	61.4 +/- 4.6 %	75.0 +/- 5.5 %	63.8 +/- 6.5%
Control	NHP 1	0.1%	0.1%	0.1%	0.1%
	NHP 2	0.3%	0.1%	0.1%	0.2%
	NHP 3	0.2%	0.2%	0.1%	0.2%

Single infusion of a multiplex base editor product in NHPs: ≥ 90% reduction in both PCSK9 and ANGPTL3 proteins in blood!!



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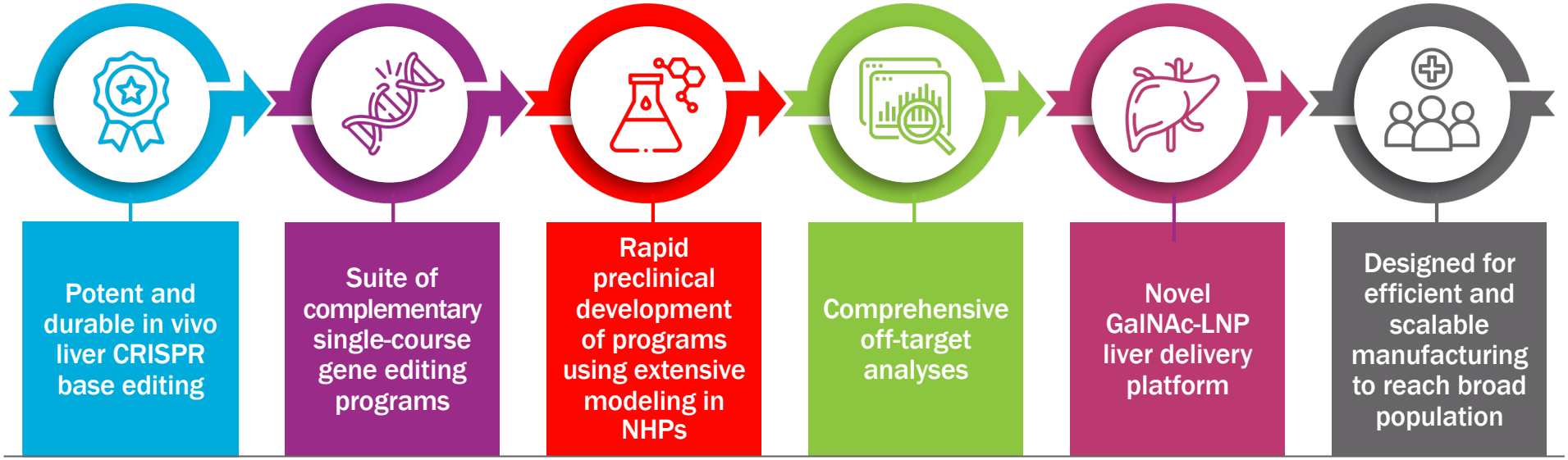

...from chronic management to single-course gene editing medicines