Proof-of-concept for *in vivo* Base Editing to Inactivate the *PCSK9* Gene and Lower LDL-Cholesterol in Humans

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Presented at TIDES USA
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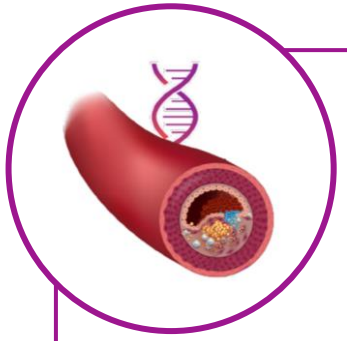
Conflict of Interest Declaration

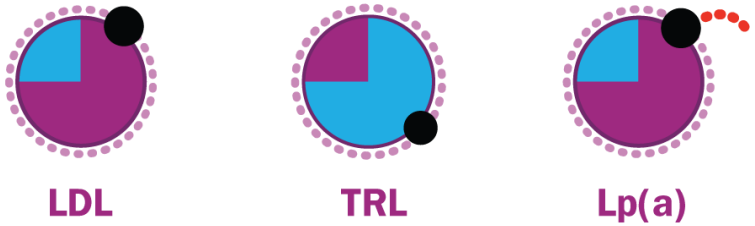
I am an employee of and hold equity in Verve Therapeutics.

What causes atherosclerotic cardiovascular disease (ASCVD) and what's a solution?



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

Cholesterol carried in 3 lipoproteins:



LDL, low-density lipoprotein; TRL, triglyceride-rich lipoprotein; Lp(a), lipoprotein(a)

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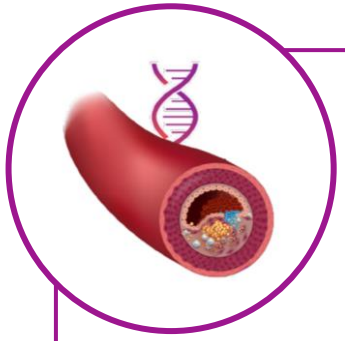

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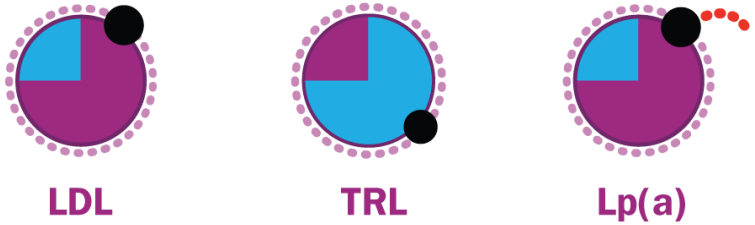
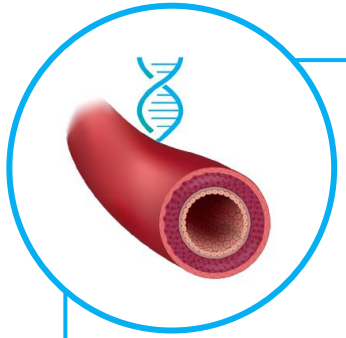
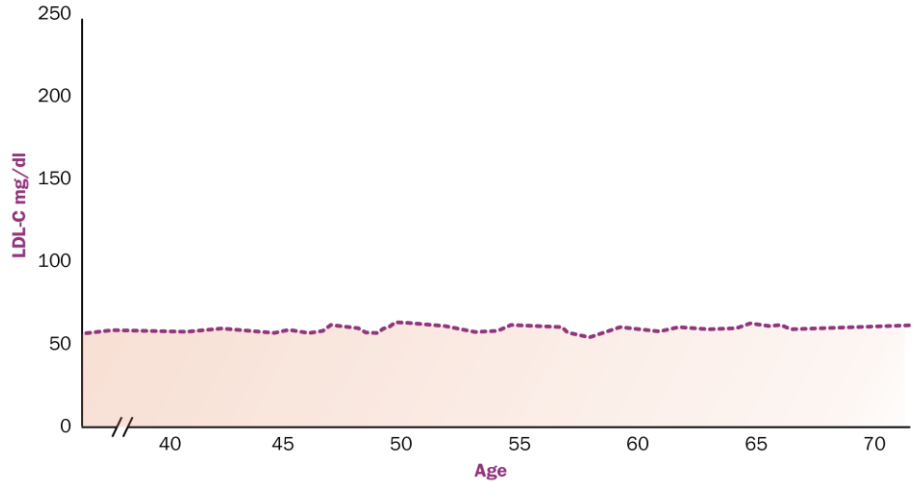


Cholesterol Triglycerides *Apolipoprotein B* *Apolipoprotein(a)*



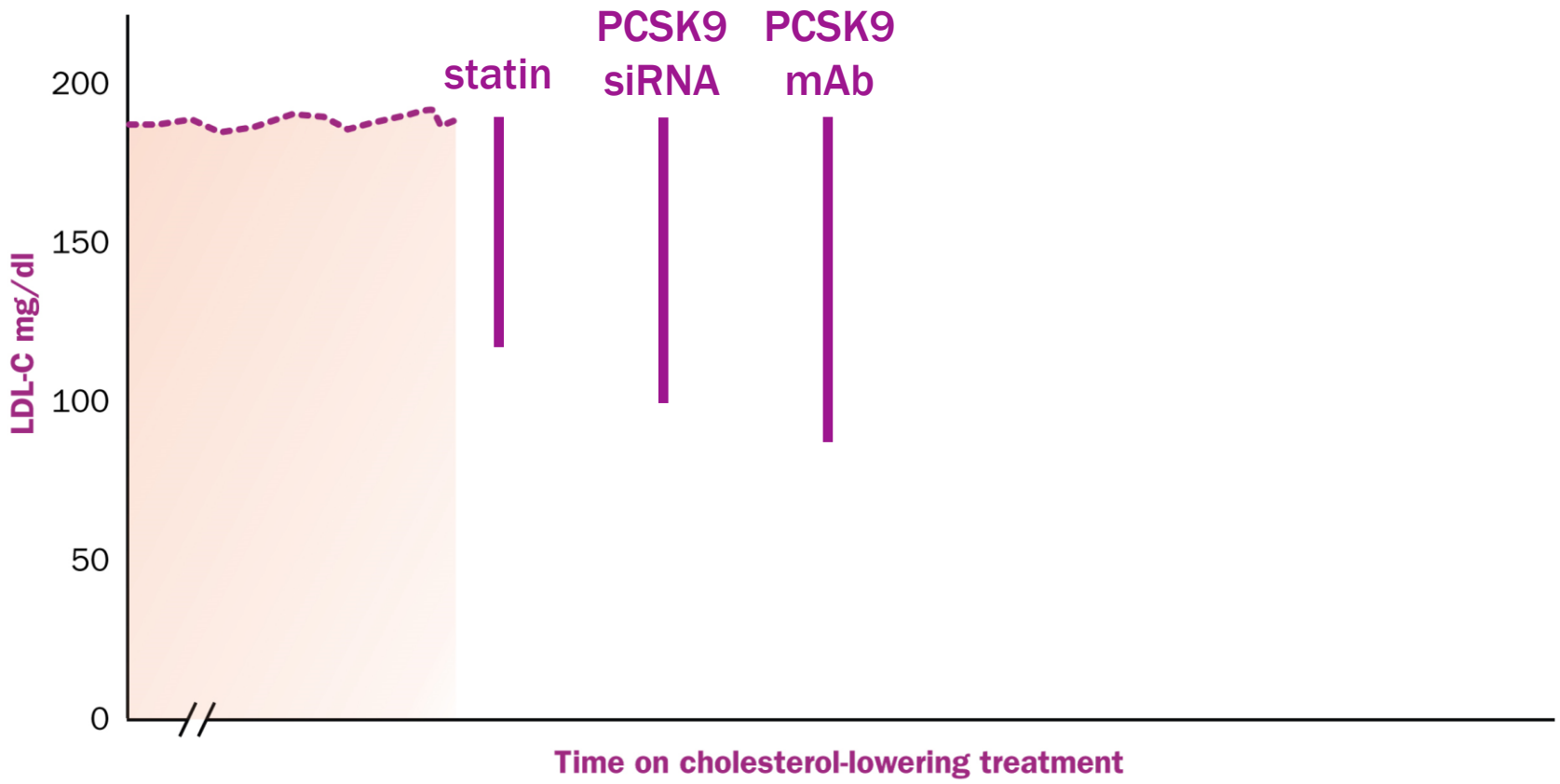
Solution: keep blood cholesterol as low as possible for as long as possible



LDL, low-density lipoprotein; TRL, triglyceride-rich lipoprotein; Lp(a), lipoprotein(a)

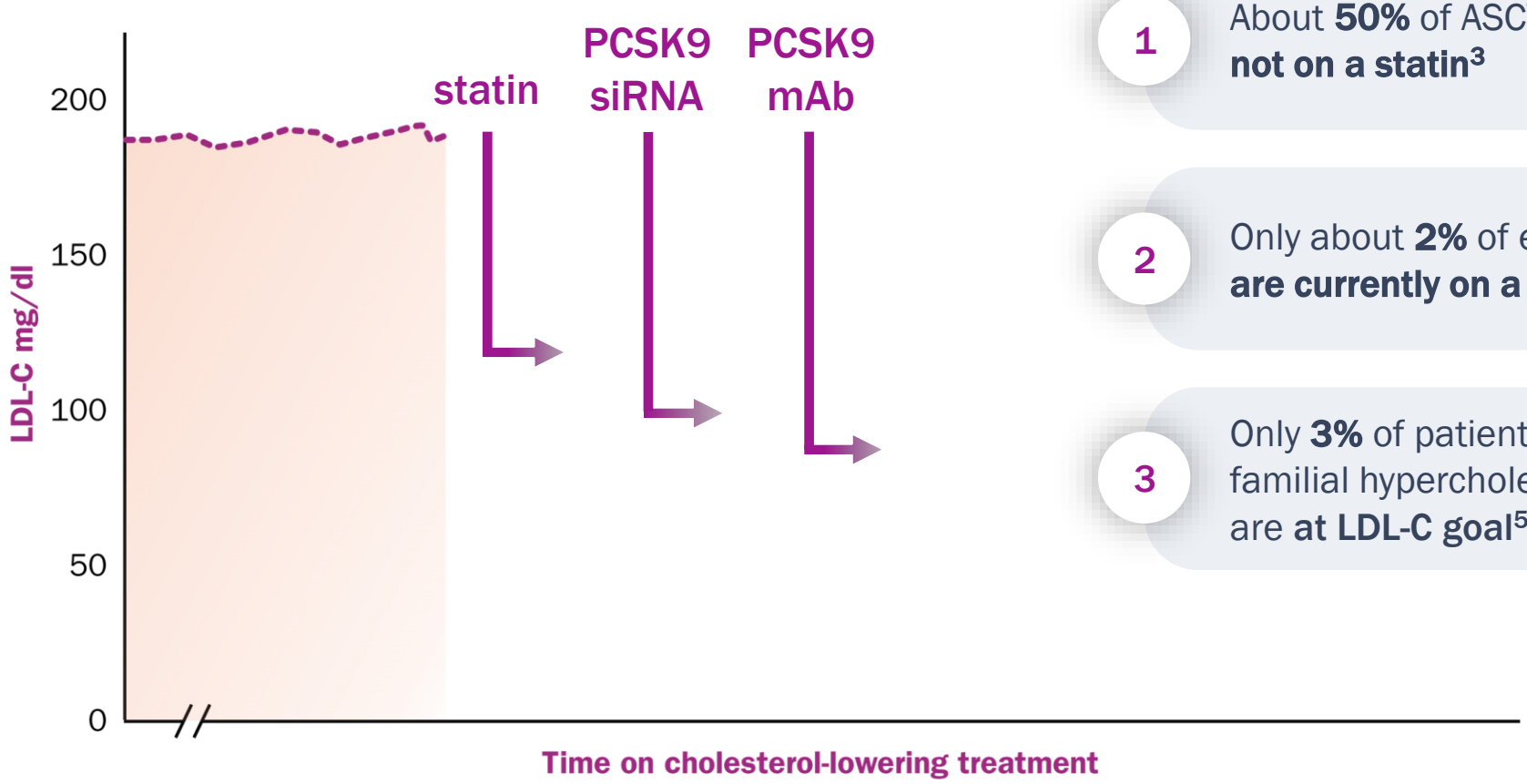
How is ASCVD treated today and is there an unmet need?

Current treatment options lower LDL-C by about 40% to 60% & intended to be taken lifelong



But, up to 50% of patients discontinue CVD medications within 12 months[1,2]

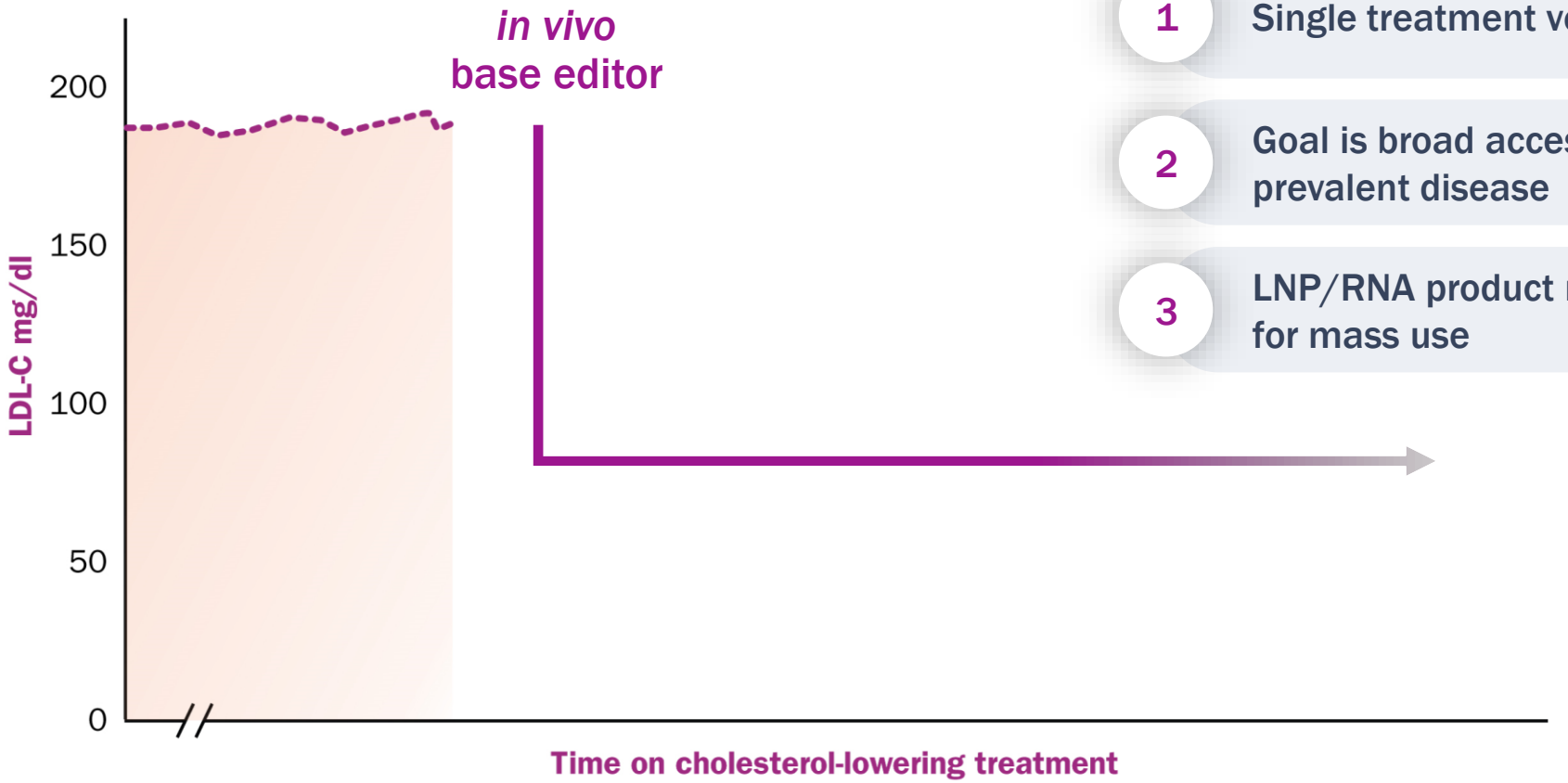
Unmet need: for many, real-world LDL-C lowering is close to zero



1. About **50%** of ASCVD patients **not on a statin**[3]
2. Only about **2%** of eligible patients **are currently on a PCSK9 agent**[4]
3. Only **3%** of patients with heterozygous familial hypercholesterolemia are **at LDL-C goal**[5]

1. Nelson A et al., *Nature Reviews Cardiology* 2024. https://doi.org/10.1038/s41569-023-00972-1; 2. Naderi SH et al., *Am J Med.* 2012;125, 882–887.e1; 3. Nelson AJ et al., *J Am Coll Card.* 2022;79(18):1802–13; 4. Dayoub EJ et al., *J Am Heart Assoc.* 2021 May 4; 10(9): e019331; 5. EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). *Lancet*. 2021;398(10312):1713-1725

How might we address this unmet need?
A new treatment option: one-time procedure, lifelong cholesterol lowering



Differentiation:

1. Single treatment versus chronic care
2. Goal is broad access for highly prevalent disease
3. LNP/RNA product now precedented for mass use

Verve is advancing a pipeline of *in vivo* gene editing programs designed to lower cholesterol lifelong after a single treatment

TARGET	INDICATION	TECHNOLOGY	DEVELOPMENT STATUS			RIGHTS
			Research	IND-enabling	Clinical	
PCSK9 (VERVE-101)	Heterozygous familial hypercholesterolemia / ASCVD	Base Editor				verve, Lilly
PCSK9 (VERVE-102)	Heterozygous familial hypercholesterolemia / ASCVD	Base Editor				verve, Lilly
ANGPTL3 (VERVE-201)	Homozygous familial hypercholesterolemia / Refractory hypercholesterolemia	Base Editor				verve, Lilly
LPA	ASCVD patients with high blood Lp(a)	Novel Editor				verve, Lilly
Undisclosed	Undisclosed ASCVD	Base Editor				verve, Lilly
Undisclosed	Undisclosed liver disease	Novel Editor				verve, VERTEX

Rationale for permanent gene inactivation of *PCSK9*, *ANGPTL3*, and *LPA*

Human Genetics

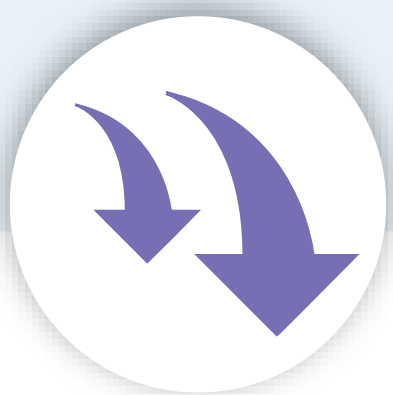
People with naturally occurring loss of function variants are protected from cardiovascular disease and otherwise healthy[1,2,3,4]

✓ *PCSK9* ✓ *ANGPTL3* ✓ *LPA*

Pharmacological Validation

Potent target inhibition and cholesterol lowering appears safe in real-world use and/or third party clinical trials[5,6,7]

✓ *PCSK9* ✓ *ANGPTL3* ✓ *LPA*



1. Zhao Z, et al. *Am J Hum Genet*. 2006; 2. Musunuru K, et al. *NEJM*. 2010; 3. Stitziel NO, et al. *JACC*. 2017; 4. Lim ET, et al. *PLOS Genet*. 2014; 5. O'Donoghue ML et al. *Circulation*. 2022; 6. Raal FJ, et al. *NEJM*. 2020; 7. O'Donoghue ML, *NEJM*. 2022.

What are the expected attributes for a successful *in vivo* gene editing medicine?

1 Potency

Sufficient editing to produce a clinically meaningful response

2 Durability

Sustained pharmacodynamic effect

3 Acute Safety

Well-tolerated during infusion and immediate post-treatment period

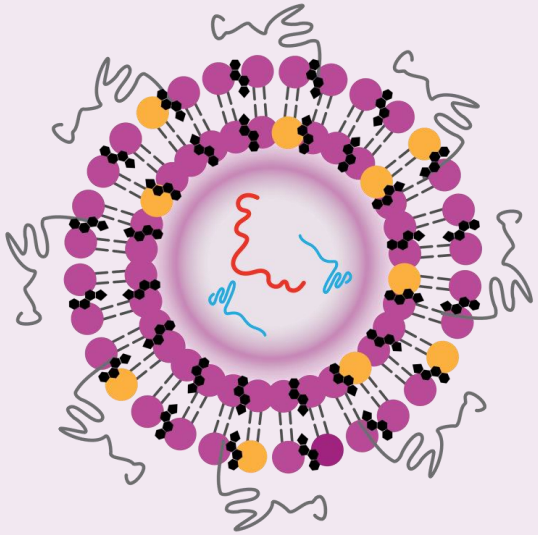
4 Long-term Safety

No evidence for emergent adverse effects months-to-years after treatment

PCSK9 Program

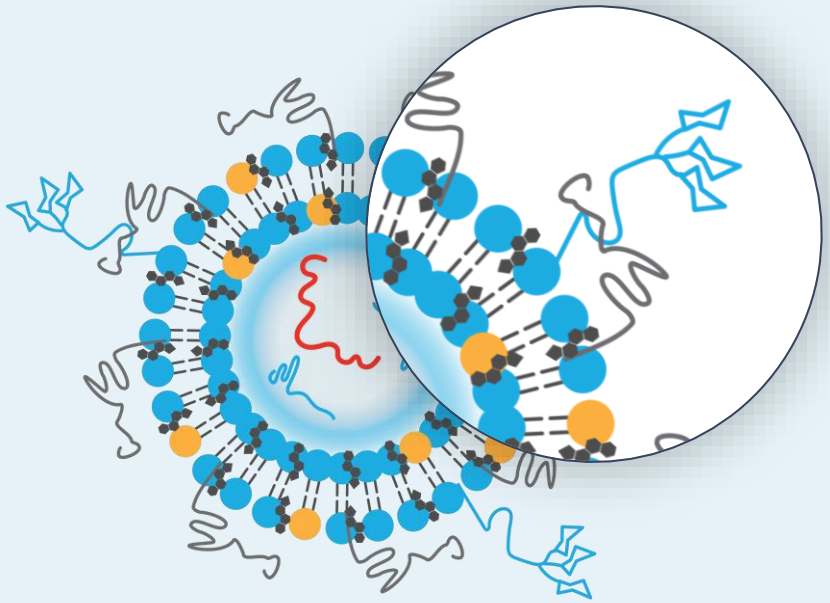
Verve has two *in vivo* base editing product candidates that target *PCSK9* with an identical base editor and guide RNA but different lipid nanoparticle delivery systems

VERVE-101



First-in-human program

VERVE-102

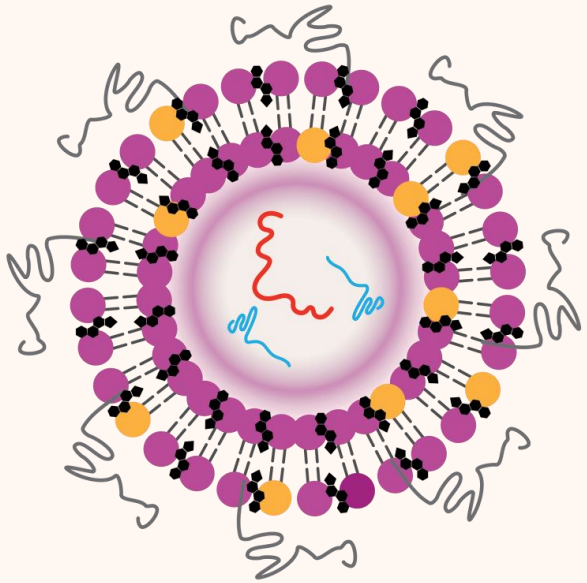


Dosing ongoing

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

VERVE-101: designed to inactivate liver *PCSK9* and lower LDL-C with a single DNA base pair change

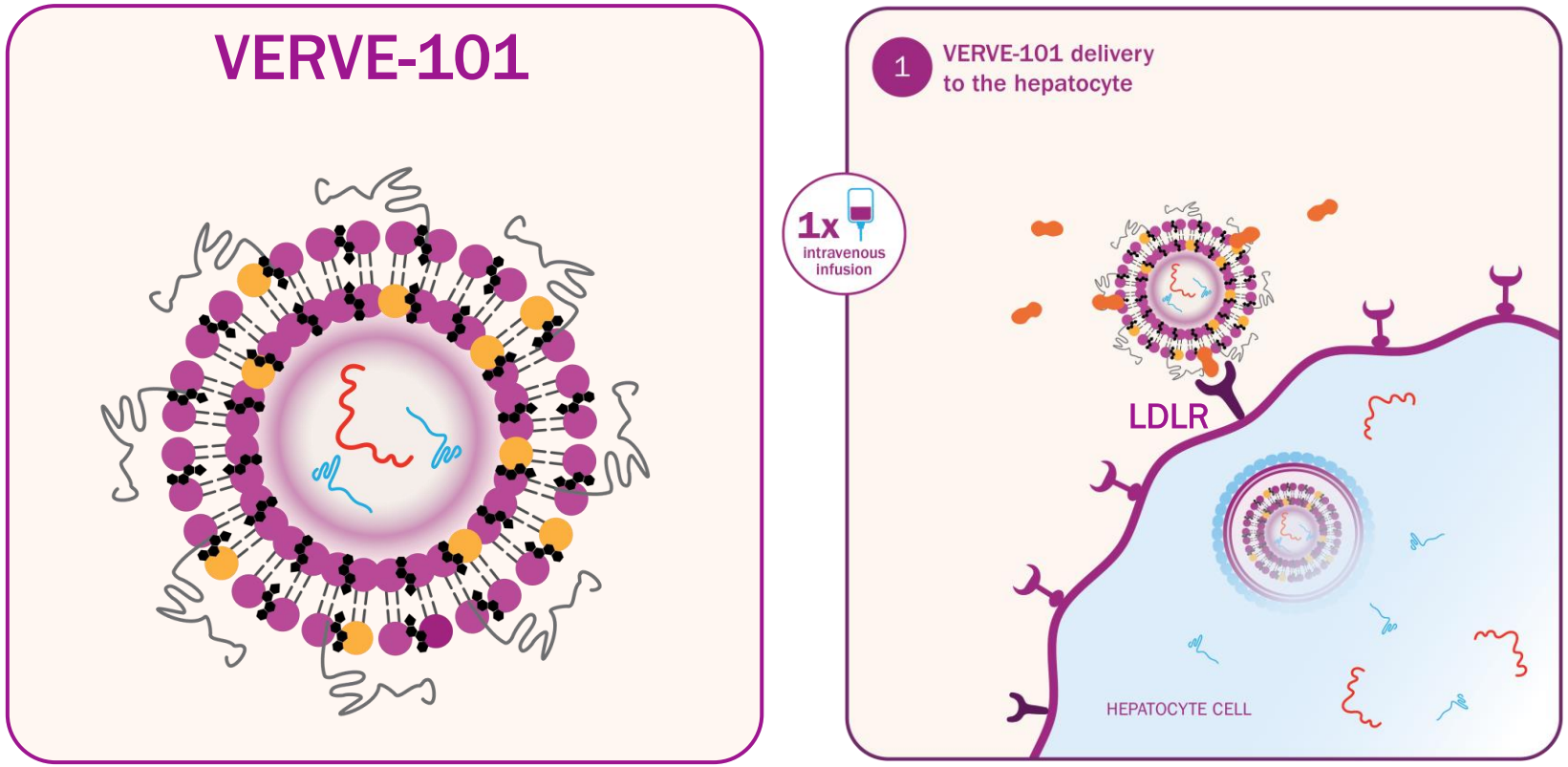
VERVE-101



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

DSPC, distearoyl-sn-glycerol-3-phosphocholine; gRNA, guide RNA; LNP, lipid nanoparticle; mRNA, messenger RNA; RNA, ribonucleic acid

VERVE-101: designed to inactivate liver *PCSK9* and lower LDL-C with a single DNA base pair change



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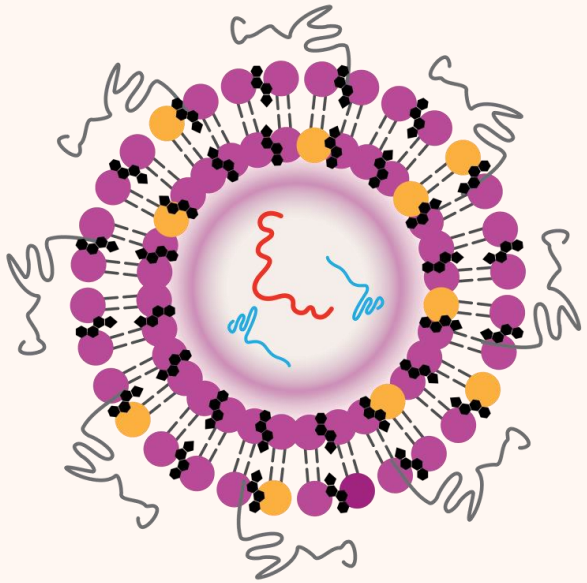
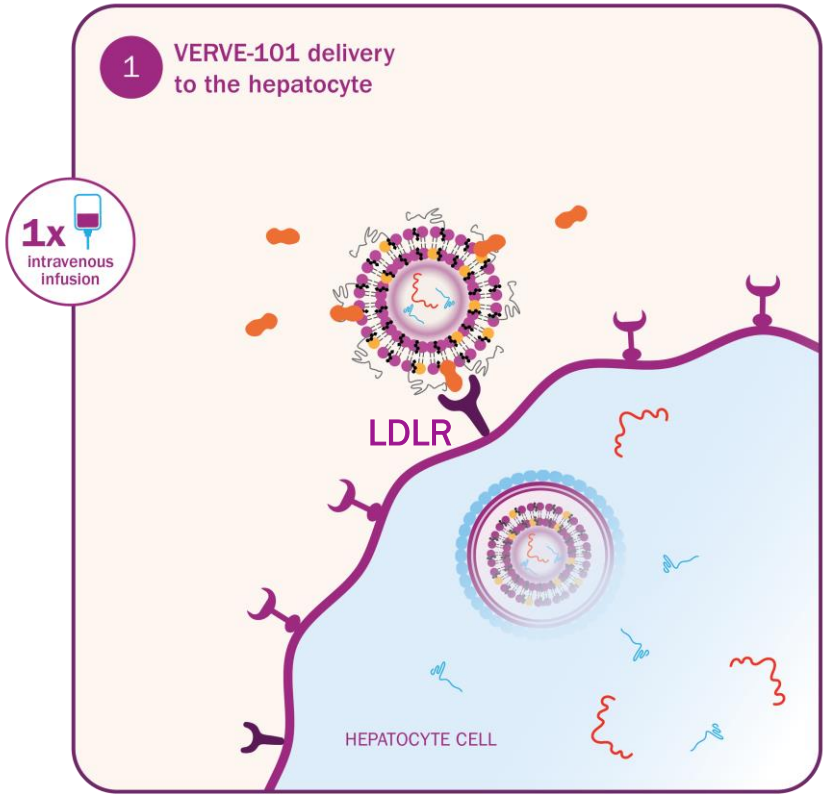
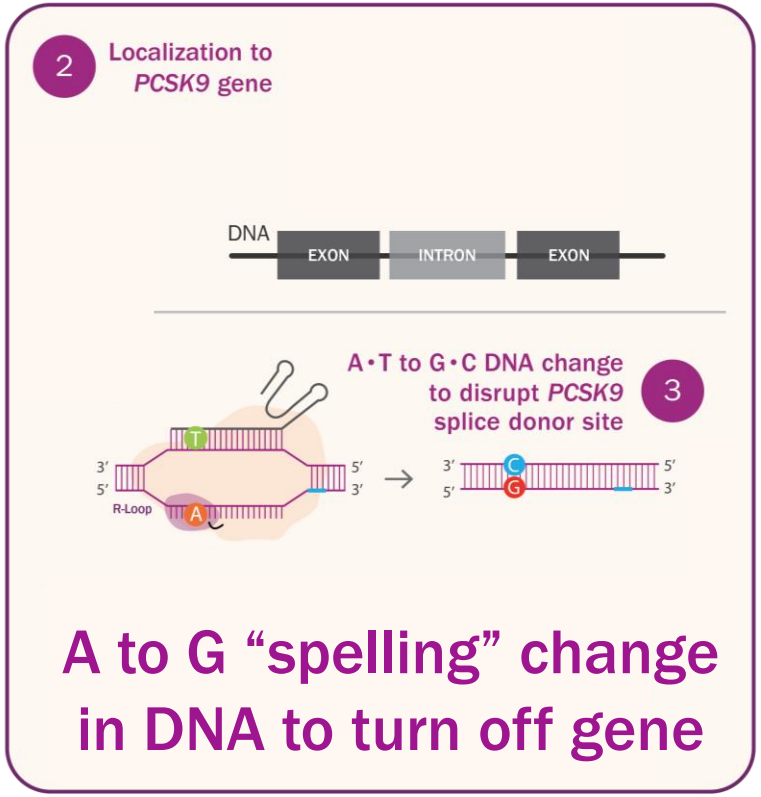




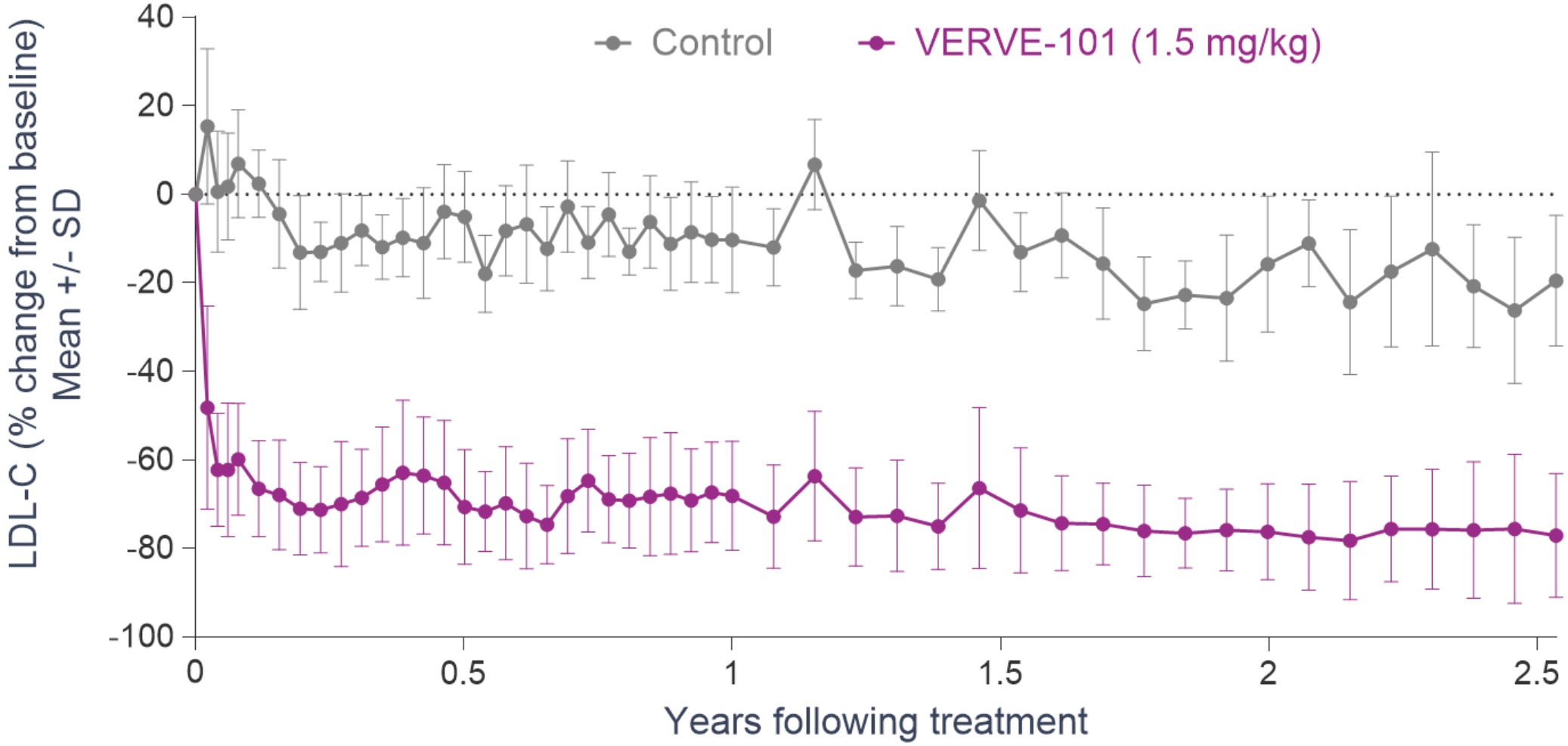


A to G "spelling" change in DNA to turn off gene

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

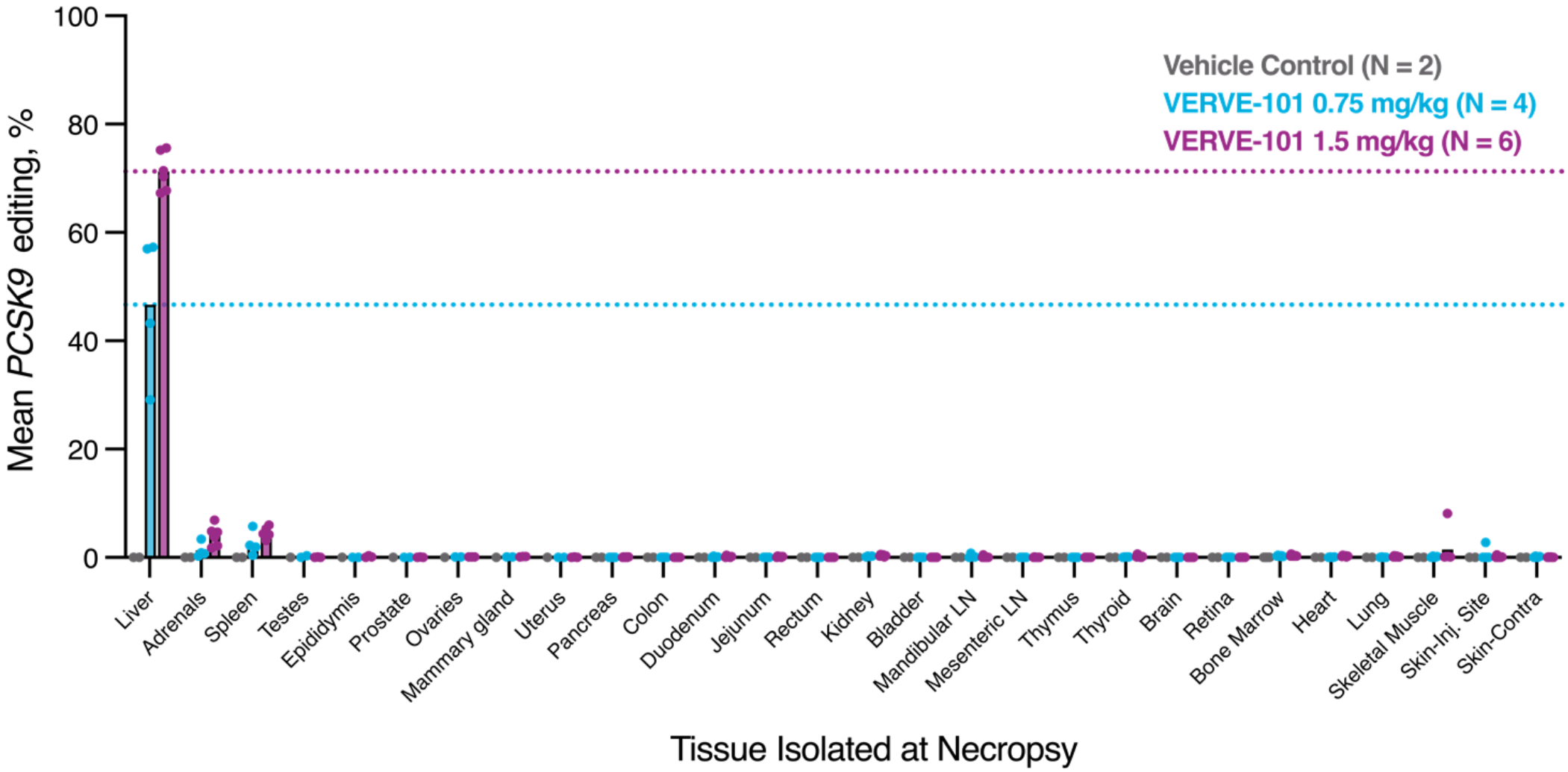
DSPC, distearoyl-sn-glycerol-3-phosphocholine; gRNA, guide RNA; LNP, lipid nanoparticle; mRNA, messenger RNA; RNA, ribonucleic acid

In non-human primates, blood LDL-C observed to be durably lowered for 2.5 years following single infusion of VERVE-101



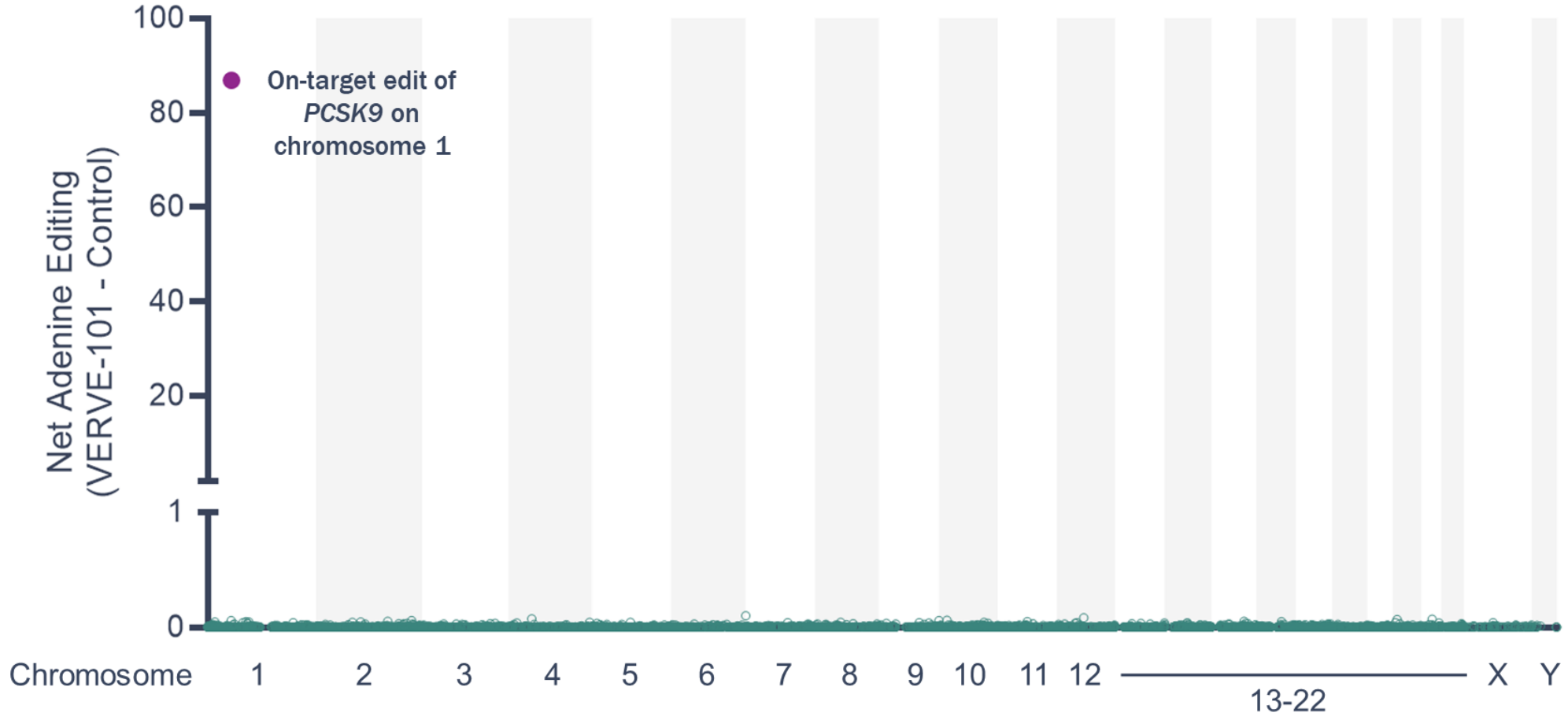
Data represents mean +/- SD for cohorts which included N=10 in control and N=22 in VERVE-101 at the earliest time points and N=7 and N=16, respectively, at the last time point.

Biodistribution studies in non-human primates treated with VERVE-101 demonstrate editing occurs predominantly in the liver



No off-target editing observed in primary human hepatocytes treated with VERVE-101 *in vitro*

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

Off-target risk assessment for VERVE-101 shows a low risk for clinically relevant off-target edits

Analysis of ~6000 candidate sites in multiple cellular settings

Two potential sites with low frequency A→G changes identified in a subset of cell types

Site characterization

- Off-target editing unlikely to occur at pharmacological doses *in vivo*
- Sites not in protein coding regions
- Sites not in or near genes associated with cancer
- Sites not likely to impact nearby gene expression

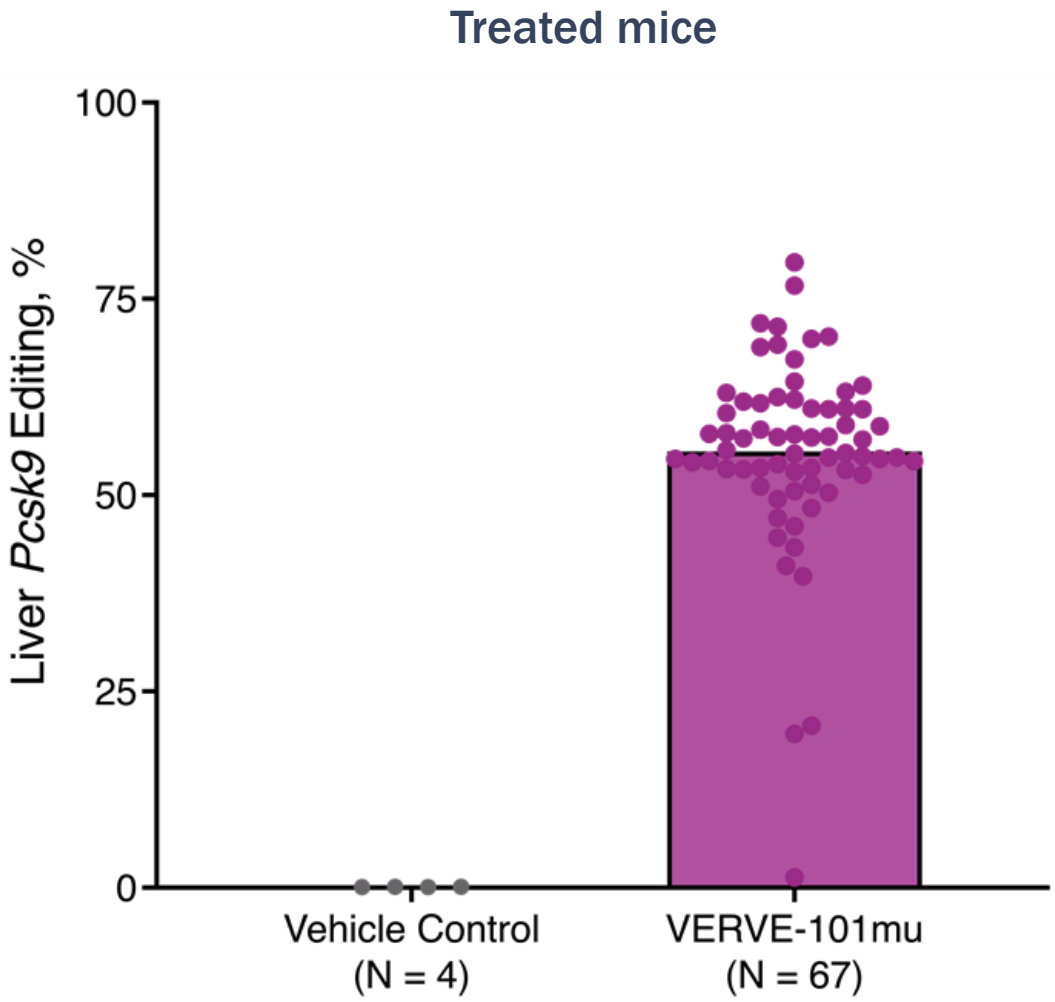
Clinical relevance conclusions

Low risk of off-target genomic modifications expected to have an associated clinical adverse effect

Germline editing: F1 progeny study of VERVE-101mu treated female mice

Objective

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



VERVE-101mu, VERVE-101 mouse surrogate; Data from 67 out of 90 females that became pregnant

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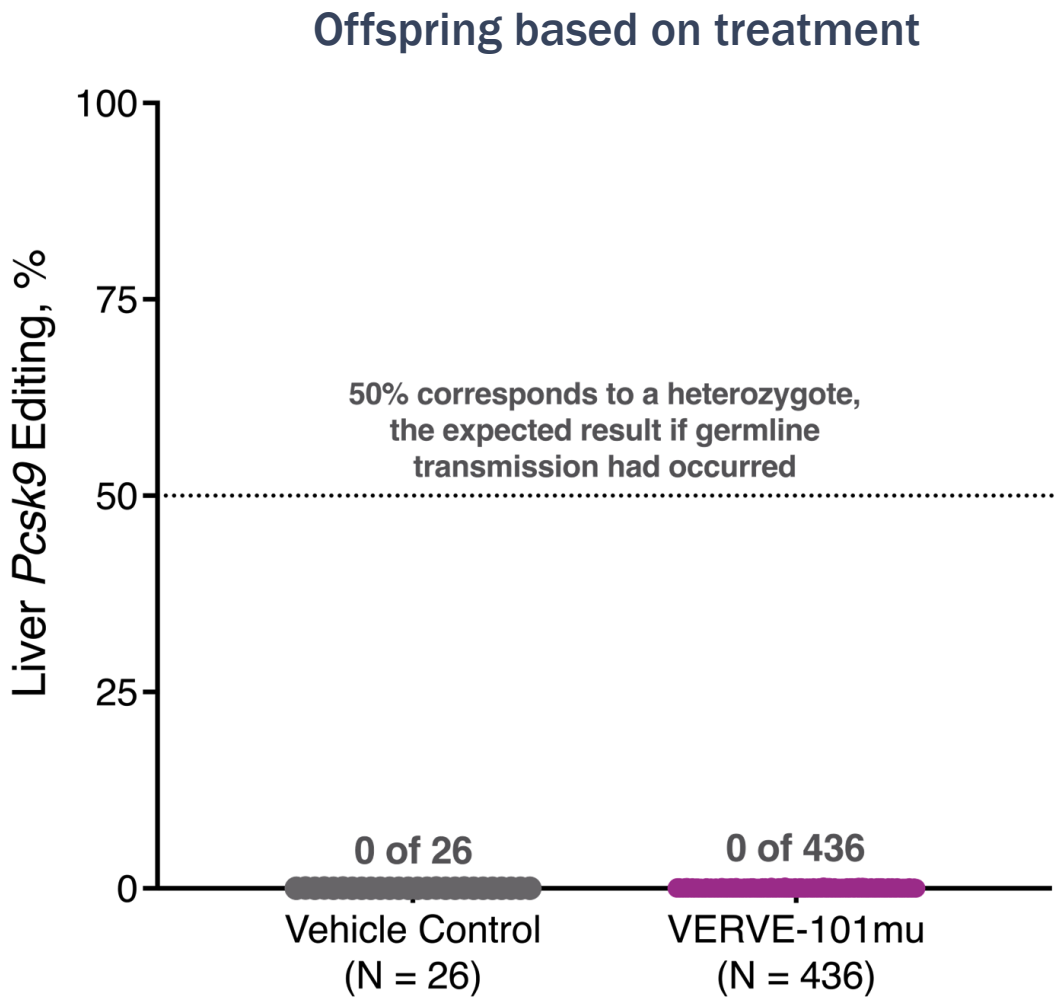
Results

No detectable germline transmission in 436 offspring of treated females



VERVE-101mu, VERVE-101 mouse surrogate; Data from 67 out of 90 females that became pregnant

Heart-1 is a first-in-human Phase 1b trial designed to evaluate the safety and tolerability of VERVE-101

heart-1

First-in-human, open-label, single ascending dose study in patients with HeFH and high risk for cardiovascular events

Enrollment update:
13 participants treated across 4 dose cohorts

Data cut-off date March 18, 2024

STUDY POPULATION SUMMARY

- Males and females[1] (age 18 to 75)
- HeFH
- Established ASCVD
- Uncontrolled hypercholesterolemia[2]
- On maximally-tolerated oral lipid-lowering therapy[3]

DRUG ADMINISTRATION

- Pre-medication with dexamethasone and antihistamines
- VERVE-101 delivered as single infusion via a peripheral intravenous[4]

TRIAL ENDPOINTS

- Primary: Safety and tolerability
- Additional endpoints:
  - Pharmacokinetics of VERVE-101
  - Blood PCSK9 and LDL-C, quantified as percent change from baseline, time averaged from day 28 onward
- Study duration 1 year with long-term follow-up required by FDA for another 14 years

Clinical trial registration: NCT05398029; 1. Women of childbearing potential are excluded from the study; 2. LDL-C threshold for inclusion value varies by country-specific protocol; 3. maximum tolerated statin and/or ezetimibe (statin intolerant allowed). 4. dosing based on weight for participants ≤ 100 kg; participants > 100 kg are dosed on an assumed 100 kg weight

verve THERAPEUTICS

Heart-1 provides human proof of concept for *in vivo* base editing of the *PCSK9* gene with VERVE-101

- Dose-dependent reductions in blood PCSK9 protein & LDL-C
- Mean LDL-C reductions of 46% at 0.45 mg/kg (n=5; range 21-73%)[1]
- Durability extending to 9 months in first patients dosed at 0.45 and 0.6 mg/kg

1. As of data cut off date of March 18, 2024. Mean is based on time-averaged reduction in LDL-C from day 28 through follow up; One participant dosed at 0.45 mg/kg had not yet reached day 28 and is not included in mean estimate.
ALT, alanine aminotransferase; ASCVD, atherosclerotic cardiovascular disease; SAE, serious adverse event

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- Mild-to-moderate infusion reactions and transient, asymptomatic ALT increases
- Cardiovascular events consistent with severe ASCVD population
- Participant in 0.45 mg/kg cohort experienced grade 3 drug-induced ALT increase and grade 3 SAE of drug-induced thrombocytopenia without bleeding or clinical symptoms that fully resolved

Enrollment paused pending investigation of laboratory abnormalities to determine next steps

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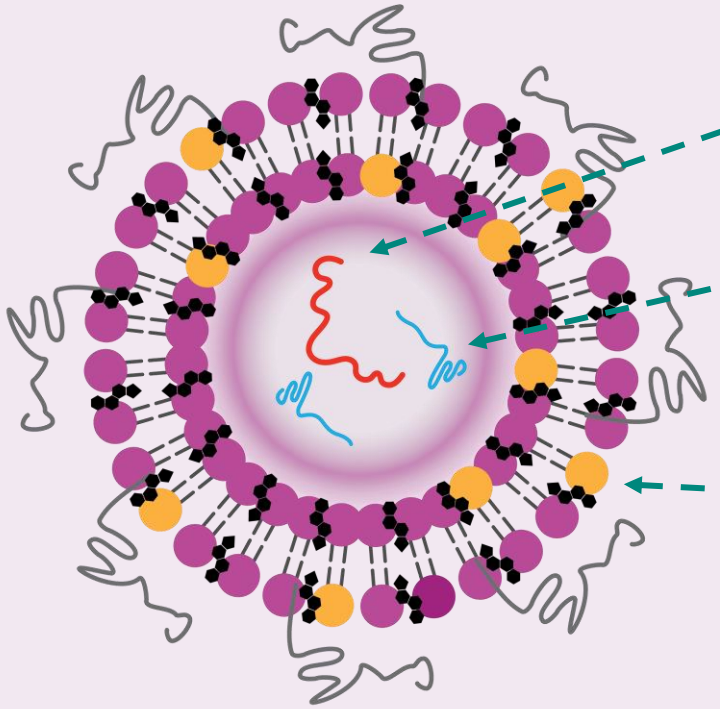
Assessing the three components of VERVE-101 based on Heart-1 experience

VERVE-101 Components



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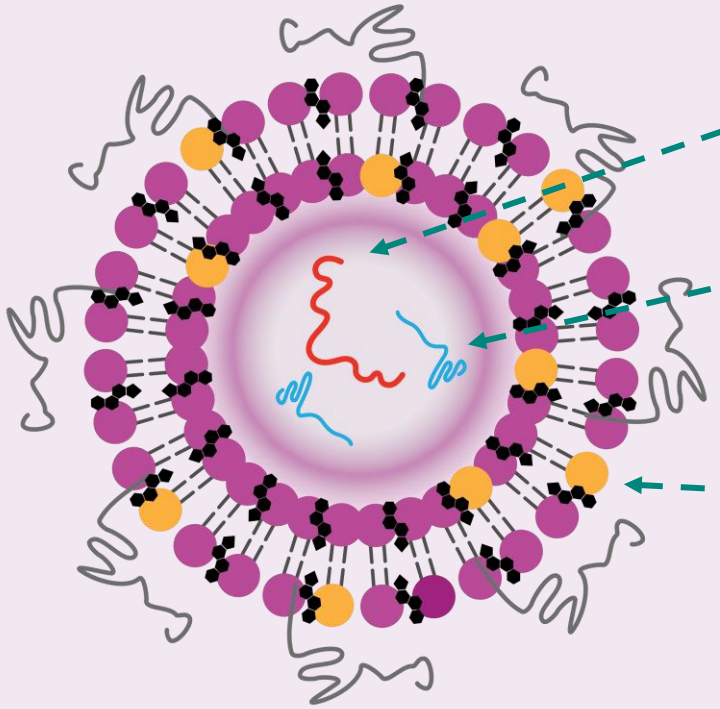

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ABE and gRNA edit *PCSK9 in vivo* and lower LDL-C

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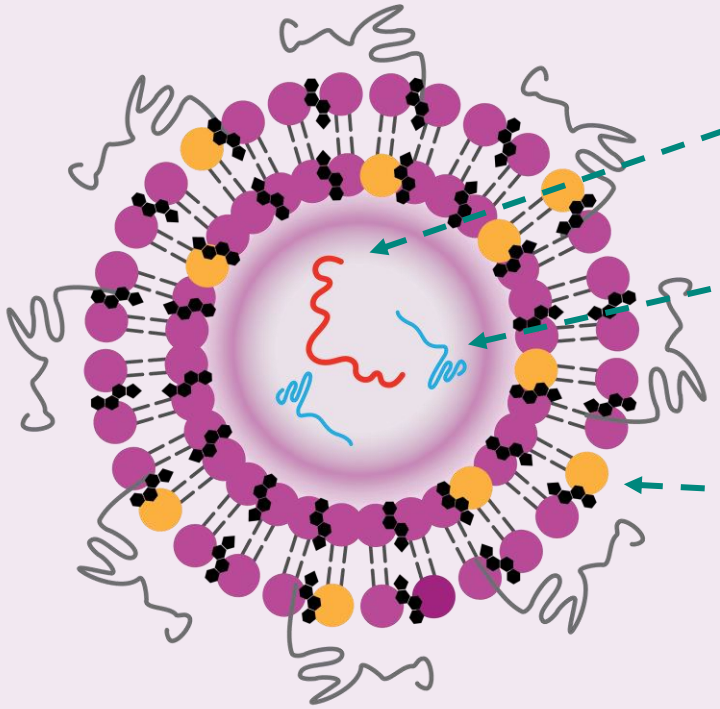
VERVE-101 Components



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1 2

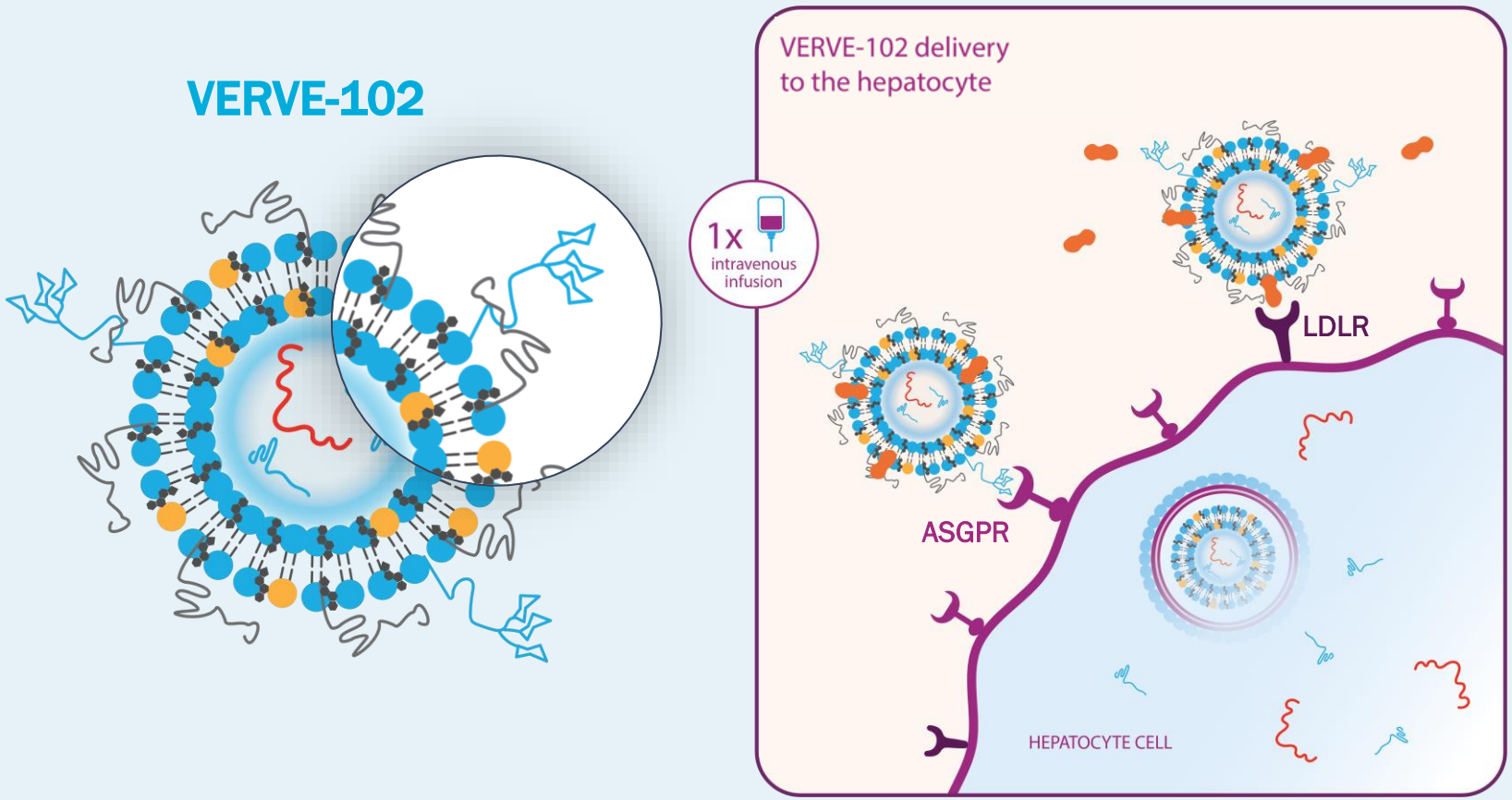
ABE and gRNA edit *PCSK9 in vivo* and lower LDL-C ✓

3

LNP suspected to contribute to laboratory abnormalities[1] ?

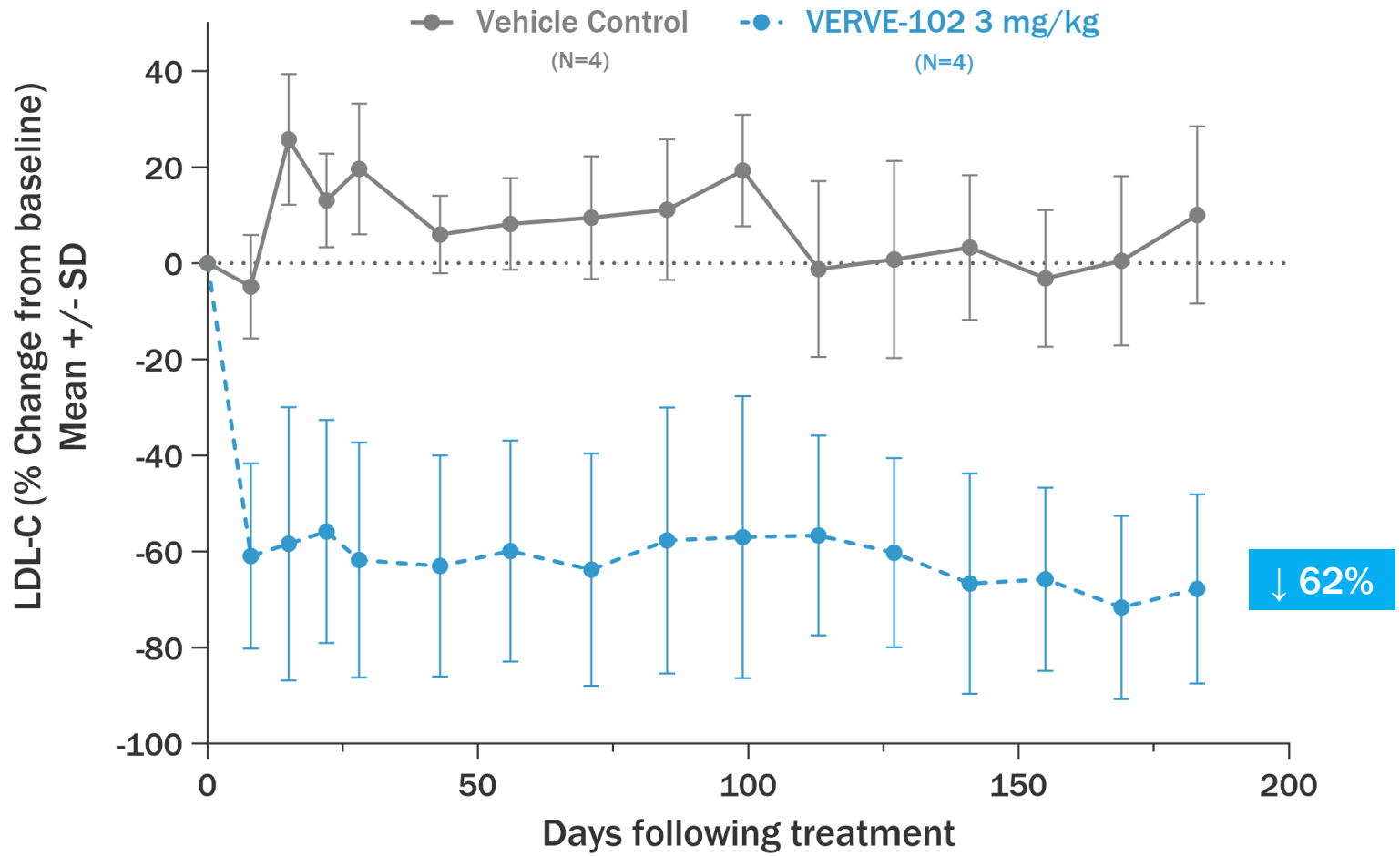
1. Laboratory abnormalities of grade 3 drug-induced ALT increase and serious adverse event of grade 3 drug-induced thrombocytopenia experienced by participant in 0.45 mg/kg dose cohort

For now, prioritizing clinical development of VERVE-102



- Different ionizable lipid
- Addition of GalNAc targeting ligand - allowing for entry into hepatocytes by either of two receptors (LDLR or ASGPR)

VERVE-102 has demonstrated durable LDL-C reduction in non-human primates out to 6 months



Heart-2 is a Phase 1b trial designed to evaluate the safety, pharmacokinetics and pharmacodynamics of VERVE-102

heart-2

First-in-human, open-label trial in adults with heterozygous familial hypercholesterolemia (HeFH) or premature coronary artery disease (CAD)

PART A Single Ascending Dose

Three to nine participants per cohort receive a single dose

PART B Optional Second Dose Cohort

Eligible participants from Part A who received a low dose may be retreated

STUDY POPULATION SUMMARY

- Males and females (age 18 to 65)
- HeFH and/or premature CAD
- Require additional LDL-C lowering despite maximally tolerated oral therapies

TRIAL ENDPOINTS

- Primary: Safety and tolerability
- Pharmacokinetics of VERVE-102
- Changes in blood PCSK9 and LDL-C

CTAs cleared in the U.K. and Canada

Dosing ongoing

CTA, clinical trial application; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9

verve THERAPEUTICS

ANGPTL3 Program

VERVE-201 targets *ANGPTL3* – a compelling target with human genetics & pharmacology validation to lower LDL-C, via a mechanism additive to PCSK9 inhibition

Humans with ANGPTL3 deficiency:

- ✓ Very low LDL-C
- ✓ Very low triglycerides
- ✓ Healthy

EVKEEZA®

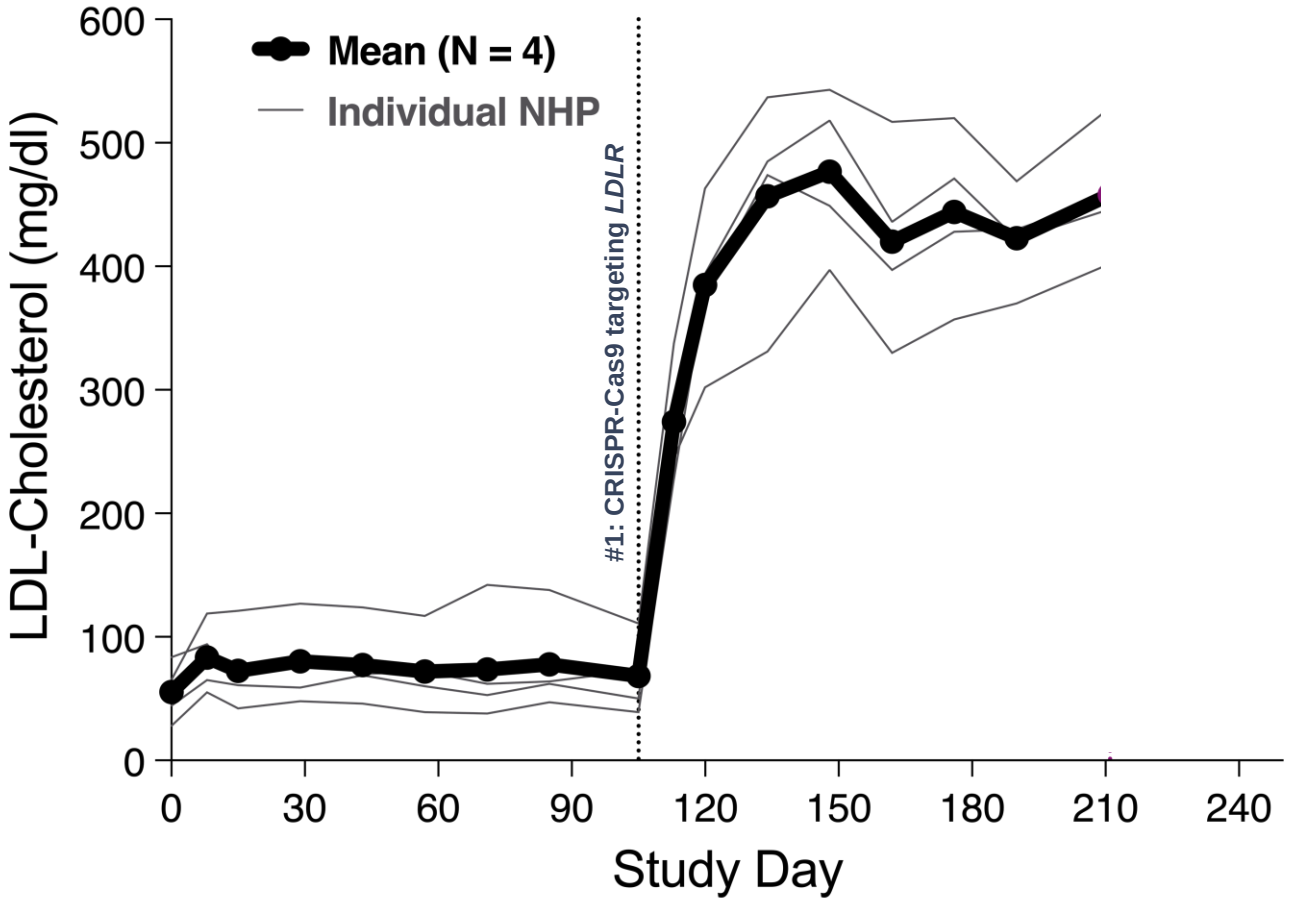
(mAb targeting ANGPTL3)

lowers LDL-C by ~50% in 2 patient populations

1. Homozygous FH (rare, orphan, FDA-approved label indication)
2. Refractory hypercholesterolemia[1] (~7 M people in US/EU)

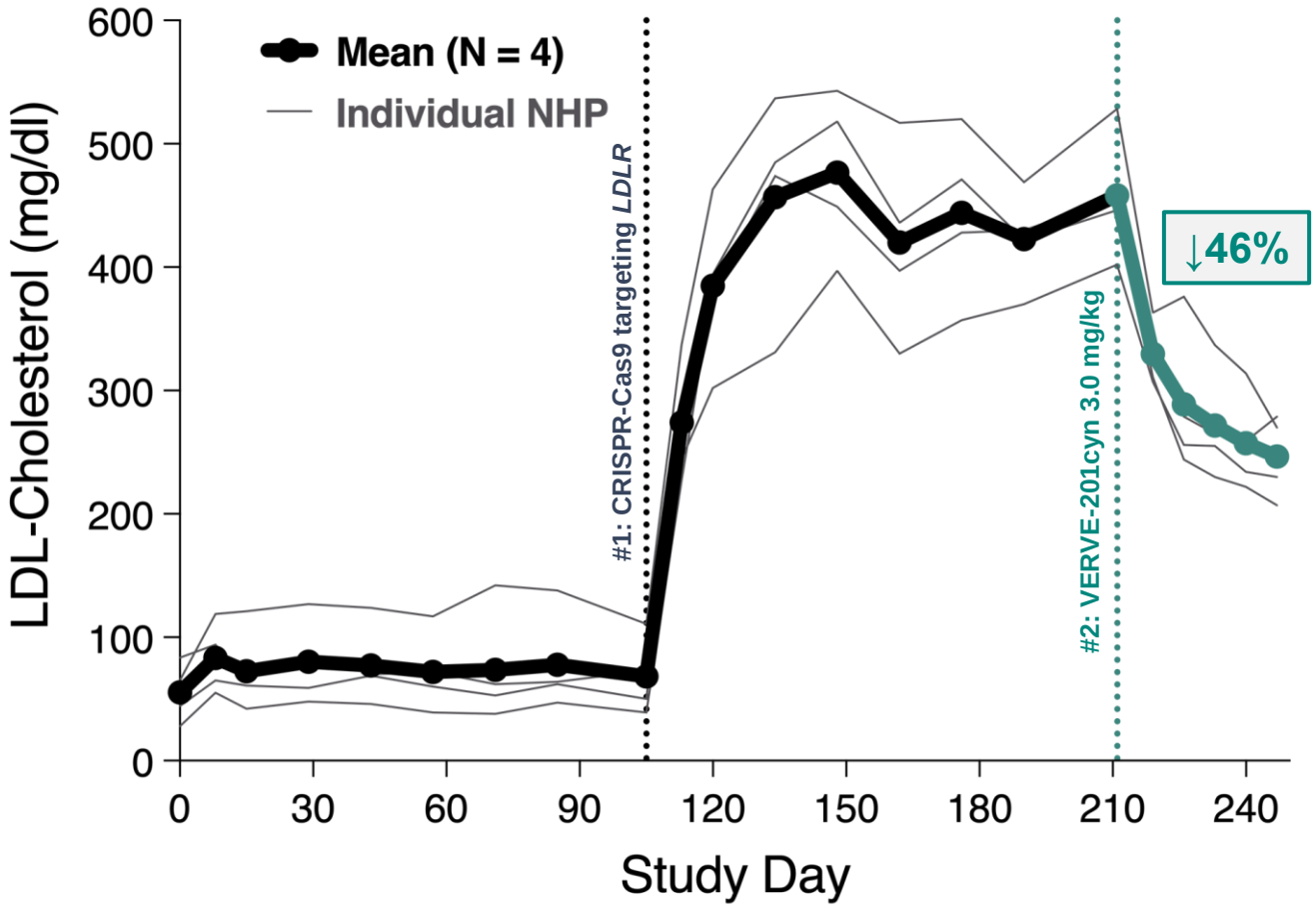
mAb, monoclonal antibody; 1. Rosenson RS et al., *N Engl J Med*. 2020;383(24):2307-2319

Verve developed a non-human primate model of HoFH (LDLR deficiency in liver) where mean blood LDL-C is 458 mg/dl



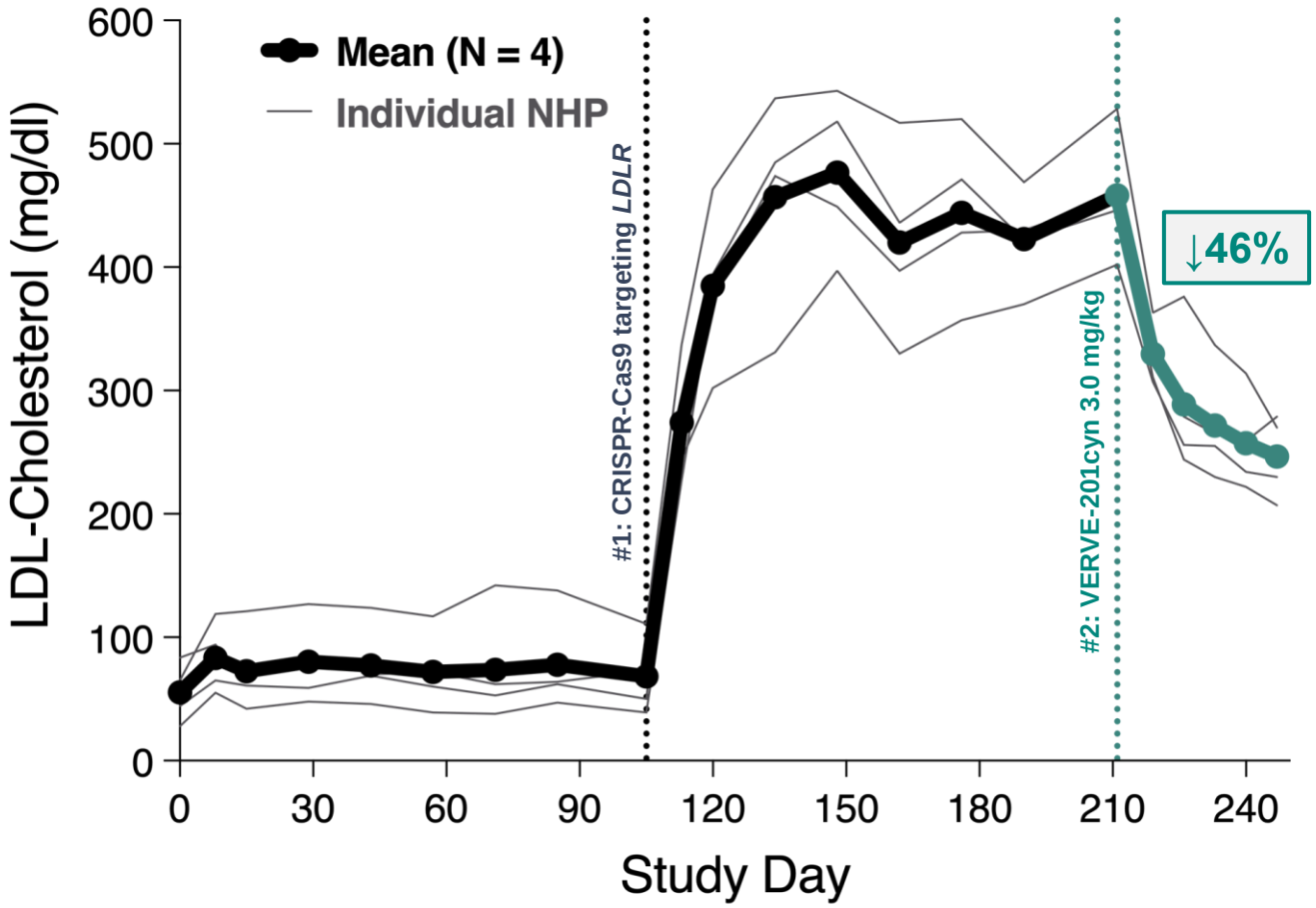
Kasiewicz et al., *Nat Comm* 2023;14(1):2776.

In LDLR-deficient non-human primates treated with VERVE-201cyn targeting ANGPTL3, 46% mean decrease in LDL-C observed (458 to 247 mg/dl)



Kasiewicz et al., *Nat Comm* 2023;14(1):2776.

Clinical trial initiation for VERVE-201 planned in 2H 2024



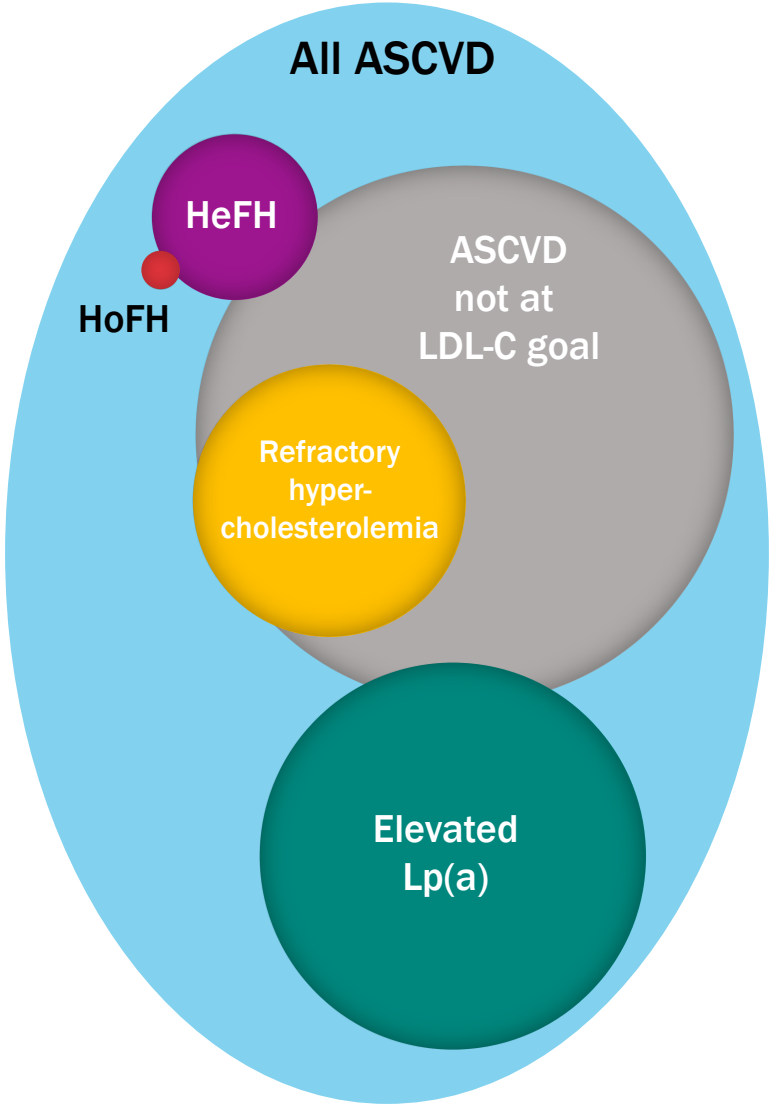
2H 2024

Clinical trial initiation expected in 2H 2024

Subject to regulatory clearance.

Kasiewicz et al., *Nat Comm* 2023;14(1):2776.

Verve's pipeline of gene editing programs designed to address three risk pathways as well as distinct ASCVD subsets



	POPULATION	PROGRAM
All ASCVD	~ 54M in US/EU	
HeFH	~ 3M in US/EU	PCSK9
ASCVD not at LDL-C goal on statin[1,2]	~ 21M in US/EU	PCSK9
HoFH	~ 2,800 in US/EU	ANGPTL3
Refractory hypercholesterolemia[3] (ASCVD not at LDL-C goal on standard of care)	~ 7M in US/EU (~13% ASCVD)	ANGPTL3
Elevated Lp(a)	~ 11M in US/EU (~20% ASCVD)	LPA

1. Gu J et al., *Am J Prev Cardiol.* 2022; 10:100336
2. Ray KK et al., *European Journal of Preventive Cardiology*. 2021; 28(11):1279–1289
3. O'Donoghue ML et al., *Circulation*. 2022; 146(15):1109-1119

Anticipated 2024 and 2025 milestones for Verve

2024

PCSK9 PROGRAM

- Dose first patient in Heart-2 trial (VERVE-102)

ANGPTL3 PROGRAM

- Initiate Phase 1 trial (VERVE-201)[1]

2025

PCSK9 PROGRAM

- Data update for PCSK9 program
- Complete enrollment for VERVE-102 trial
- Select PCSK9 product candidate
- Deliver opt-in package to Lilly
- Initiate randomized, controlled Phase 2

ANGPTL3 PROGRAM

- Data update for VERVE-201

Rest of pipeline: progress pre-clinical collaboration programs with Lilly (*LPA* and undisclosed ASCVD target) and Vertex (undisclosed liver-disease target)

1. Subject to regulatory clearance.