From Reading the Genome for Risk to Rewriting It for Cardiovascular Health

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Verve Therapeutics

Presented at the American Society of Nephrology Kidney Week
State of the Art Lecture, October 25, 2024

Speaker disclosure, forward looking statements, and disclaimers

Dr. Kathiresan is an employee and equity holder of Verve Therapeutics

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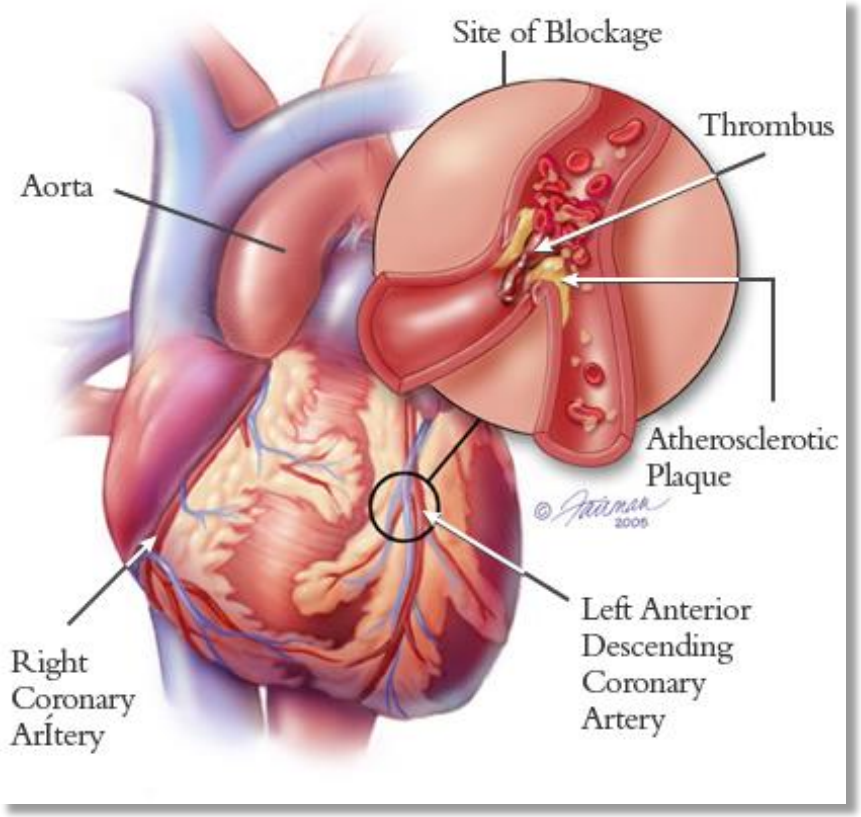
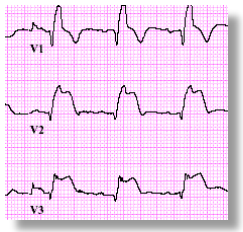
Myocardial infarction (MI) & Atherosclerotic Cardiovascular Disease (ASCVD)



Symptoms

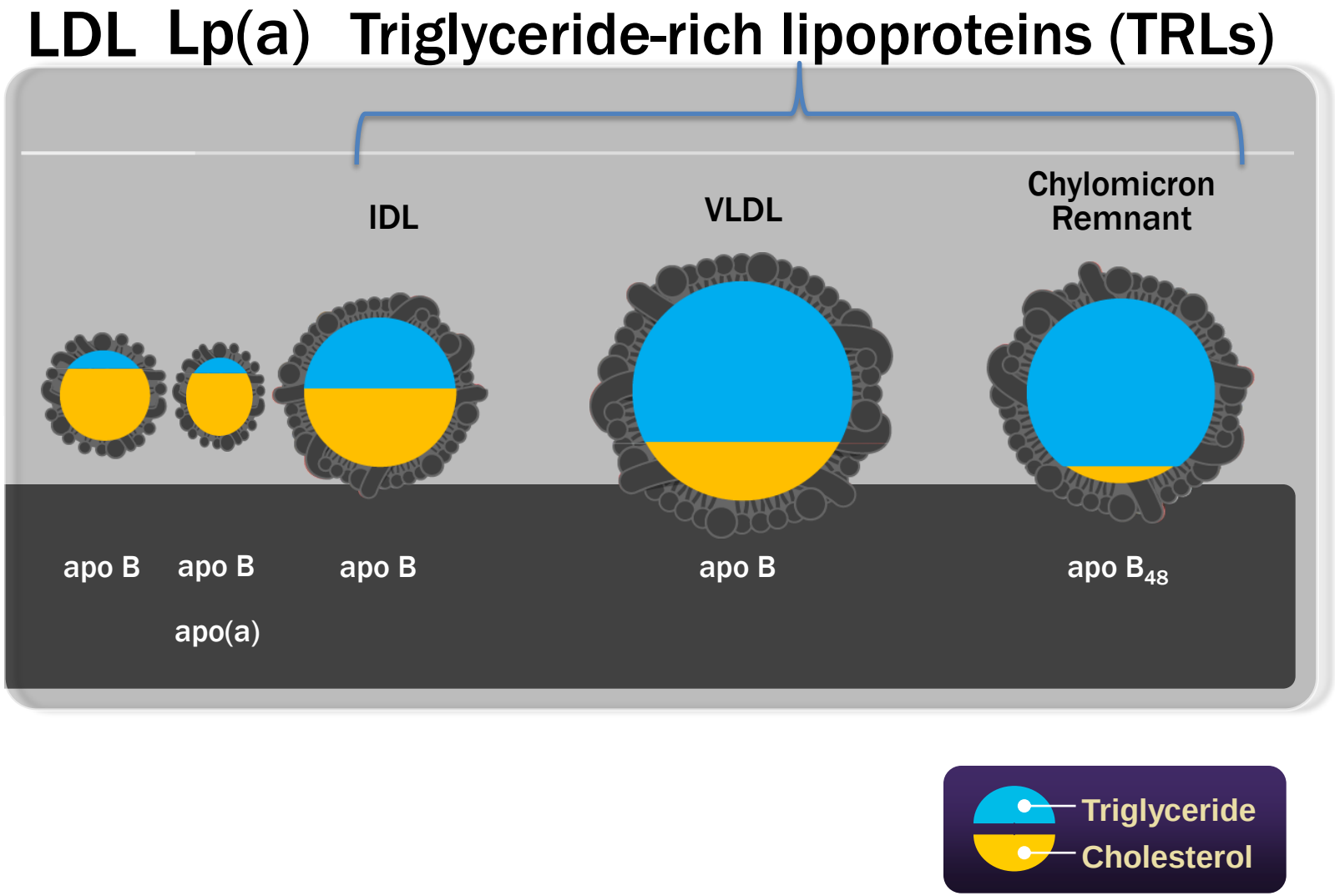


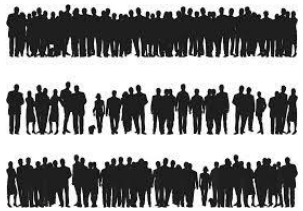
EKG change

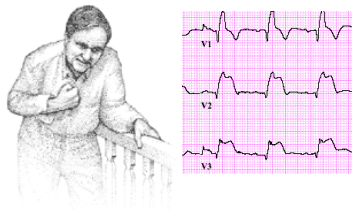
Elevation in cardiac biomarkers

- Remains leading cause of death worldwide despite available treatments

apoB-containing lipoproteins: key drivers for atherosclerosis







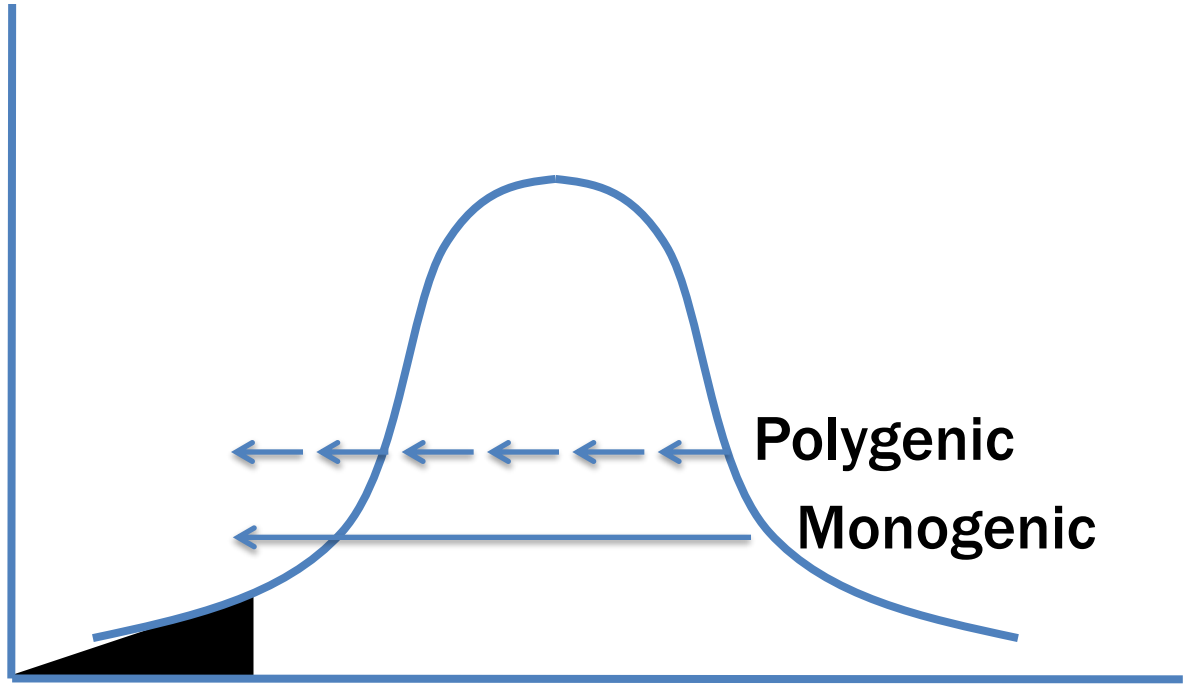
Average
MI risk

What is genetic basis for higher risk?

What is genetic basis for resistance?

Can we rewrite genome to treat or prevent?

Two inherited paths to MI risk



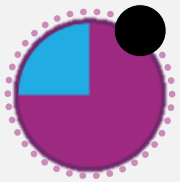
Several genes where coding mutations confer large effects on MI risk

Gene	Carrier frequency	Blood biomarker	Clinical Effect
Low-density lipoprotein receptor (LDLR)	1 in 250	 LDL	4-fold
ATP-binding cassette transporter G5 (ABCG5)	1 in 1000	 LDL	2-fold
Lipoprotein lipase (LPL)	1 in 500	 TRL	2-fold
Apolipoprotein A5 (APOA5)	1 in 3000		4-fold
Apolipoprotein(a) (LPA)	1 in 100	 Lp(a)	3-fold

Other genes: PCSK9, APOB, LDLRAP1

Goldstein, Cell (2015)
Do*, Stitziel* et al., Nature (2015)
Khera*, Won* et al., JAMA (2017)
Clarke et al., N Engl J Med (2009)

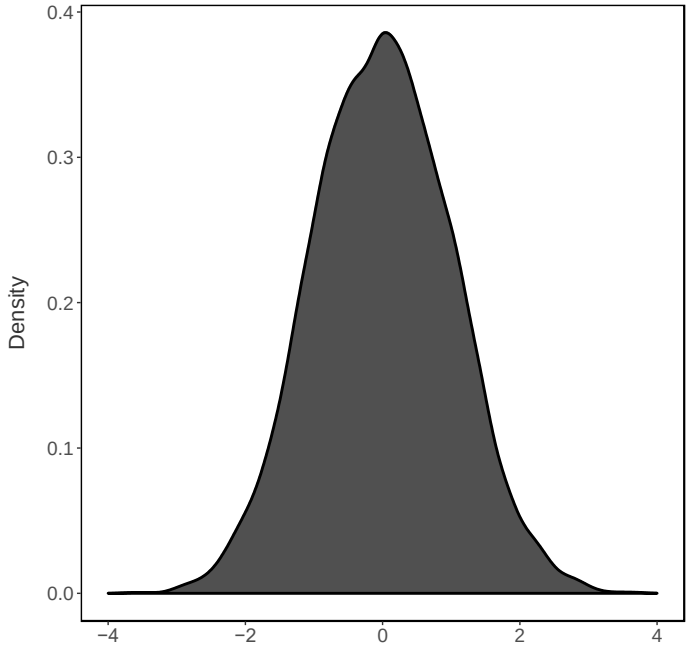
Heterozygous familial hypercholesterolemia (HeFH): a serious, inherited disease with high cholesterol from birth & MI at early ages

American Heart Association Diagnostic Criteria				
High LDL-C + Family history (of high LDL-C or premature ASCVD)	Mutations in LDLR, PCSK9, or APOB	≥190 mg/dl	30-60 years	>3M adults in US/Europe >20M adults globally

Adapted from Family Heart Foundation; https://familyheart.org/familial-hypercholesterolemia/homozygous-familial-hypercholesterolemia

Polygenic score, a quantitative risk factor for MI: a single number which can capture genetic liability

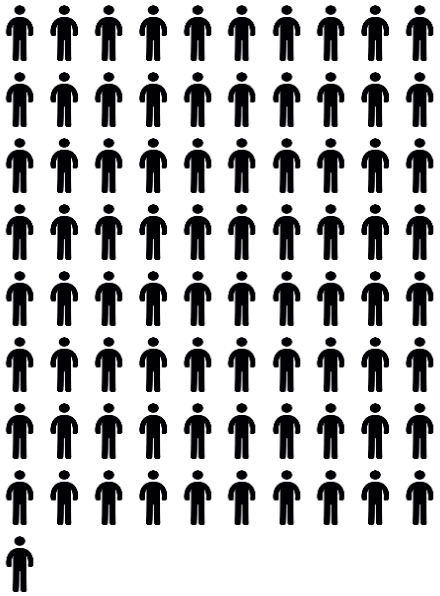
Polygenic score of 6.6 million common variants



Khera*, Chaffin* et al., Nat Genet (2018)

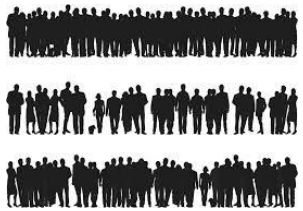
Contributions of two genetic models to early MI

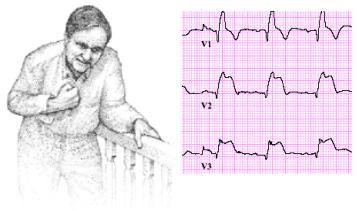
100 patients with early MI



	↑ Risk
Monogenic	3.8-fold
High polygenic	3.7-fold

Khera*, Chaffin* et al., Nat Genet (2018)





Average
MI risk

What is genetic basis for higher risk?

What is genetic basis for resistance?

Can we rewrite genome to reduce risk?

There are people walking around who are naturally resistant to ASCVD, have a cholesterol-raising gene (*PCSK9*) naturally switched off

~50 mg/dl lower
LDL cholesterol in blood

~50% lower risk
for ASCVD

Healthy

Abifadel et al., Nat Genet (2003); Cohen et al., N Engl J Med (2006)

Individuals who naturally lack ANGPTL3 gene: lifelong low blood LDL-C & triglycerides, healthy, and resistant to ASCVD

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.
Jess T. Dugan for The New York Times

What if you carried a genetic mutation that left you nearly impervious to heart disease? What if scientists could bottle that miracle and use it to treat everyone else?

In a series of studies, the most recent published on Wednesday, scientists have described two rare genetic mutations that reduce levels of triglycerides, a type of blood fat, far below normal. People carrying these genes seem invulnerable to heart disease, even if they have other risk factors.

Drugs that mimic the effects of these mutations are already on the way, and many experts believe that one day they will become the next blockbuster heart treatments. Tens

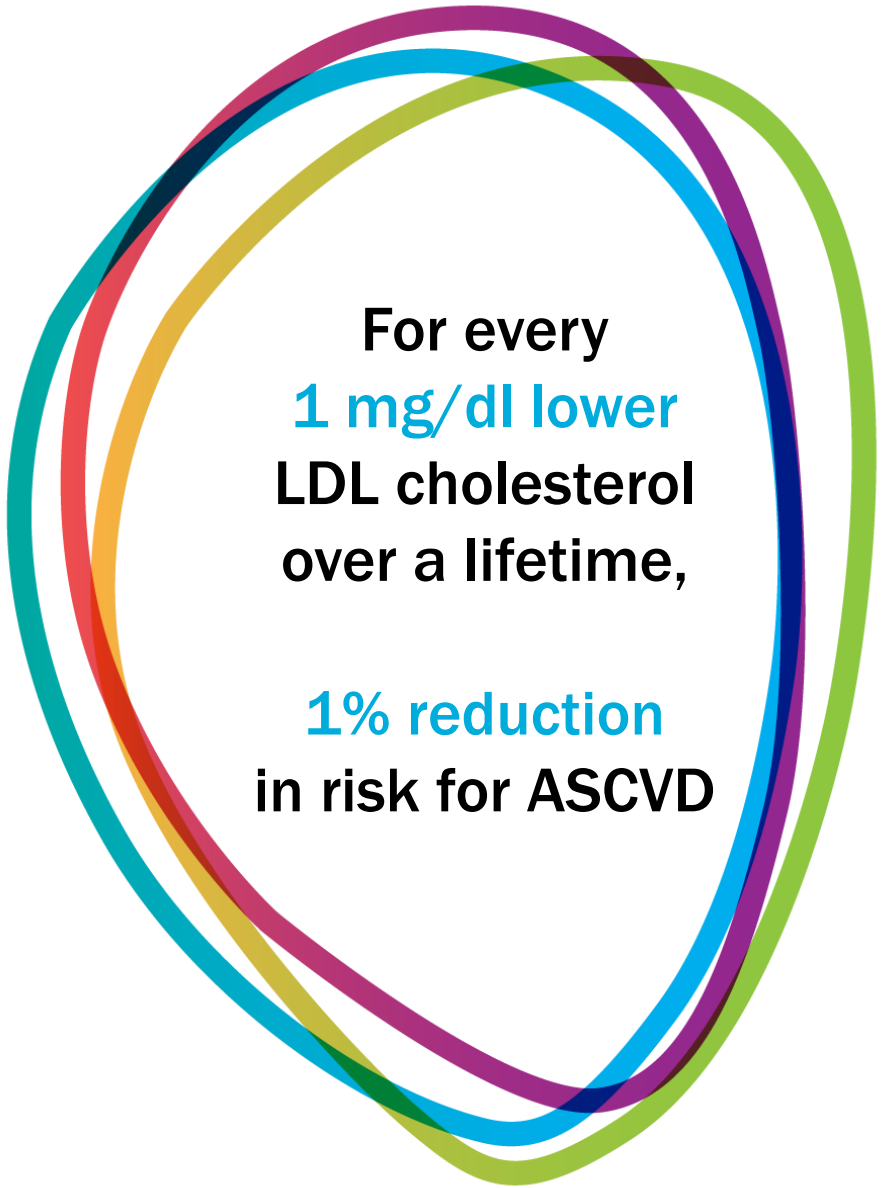
Human knockout:
Extremely low LDL-C & TG
37 mg/dL / 19 mg/dL

Heterozygous deficiency:
Low lipids
Resistant to ASCVD

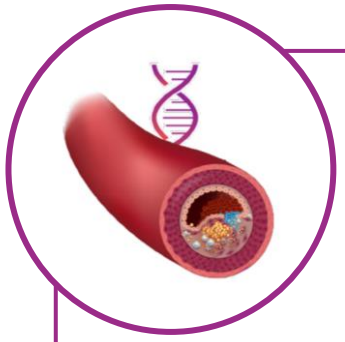
Musunuru et al., N Engl J Med (2010)

Eight genes where MI resistance mutations reside;
Highlight 3 pathways for resistance: LDL, TRL, and Lp(a)

PCSK9	NPC1L1	LPA	APOC3	ANGPTL3	ANGPTL4	ASGR1	APOB
1 in 40	1 in 650	1 in 71	1 in 150	1 in 300	1 in 360	1 in 120	1 in 1035
LDL	LDL	Lp(a)	TRL	TRL LDL	TRL	TRL	LDL, TRL
80% lower risk	53% lower risk	24% lower risk	40% lower risk	34% lower risk	53% lower risk	34% lower risk	78% lower risk

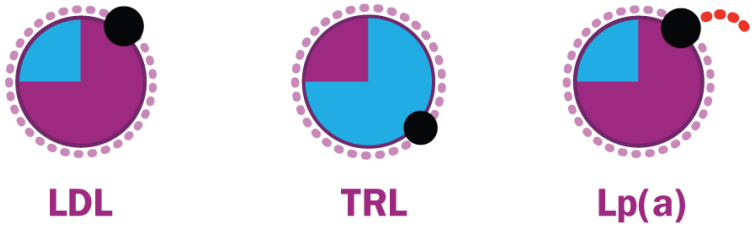

For every
1 mg/dl lower
LDL cholesterol
over a lifetime,
1% reduction
in risk for ASCVD

What causes ASCVD?

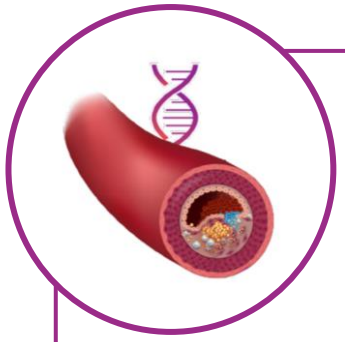


High cumulative life-long exposure to blood cholesterol clogs heart arteries

Cholesterol carried in 3 lipoproteins:



What's a solution to ASCVD?



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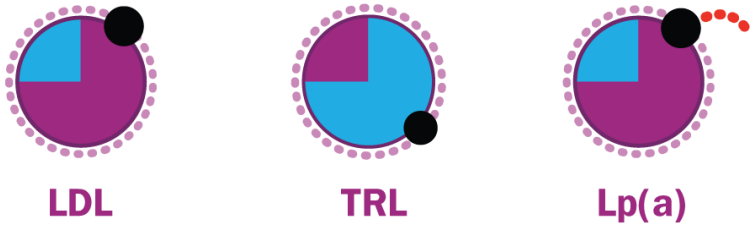
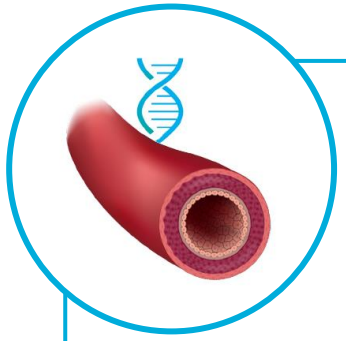
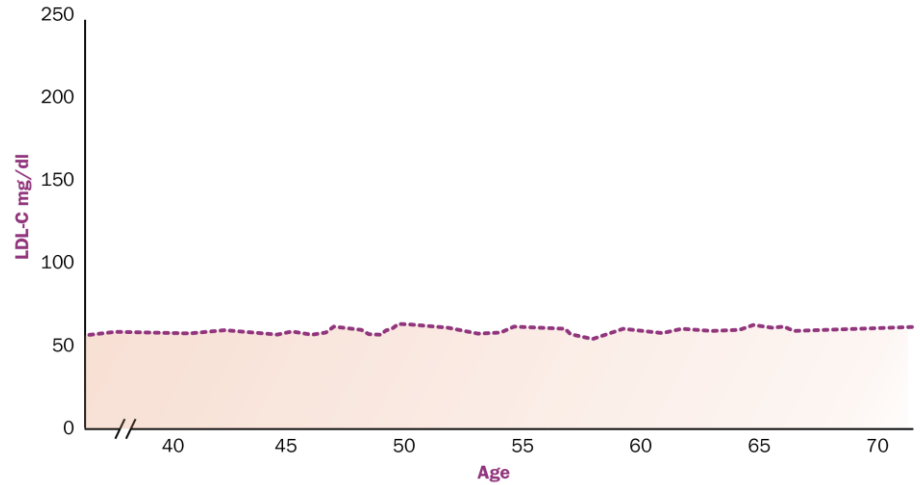




Solution: keep blood cholesterol as low as possible for as long as possible

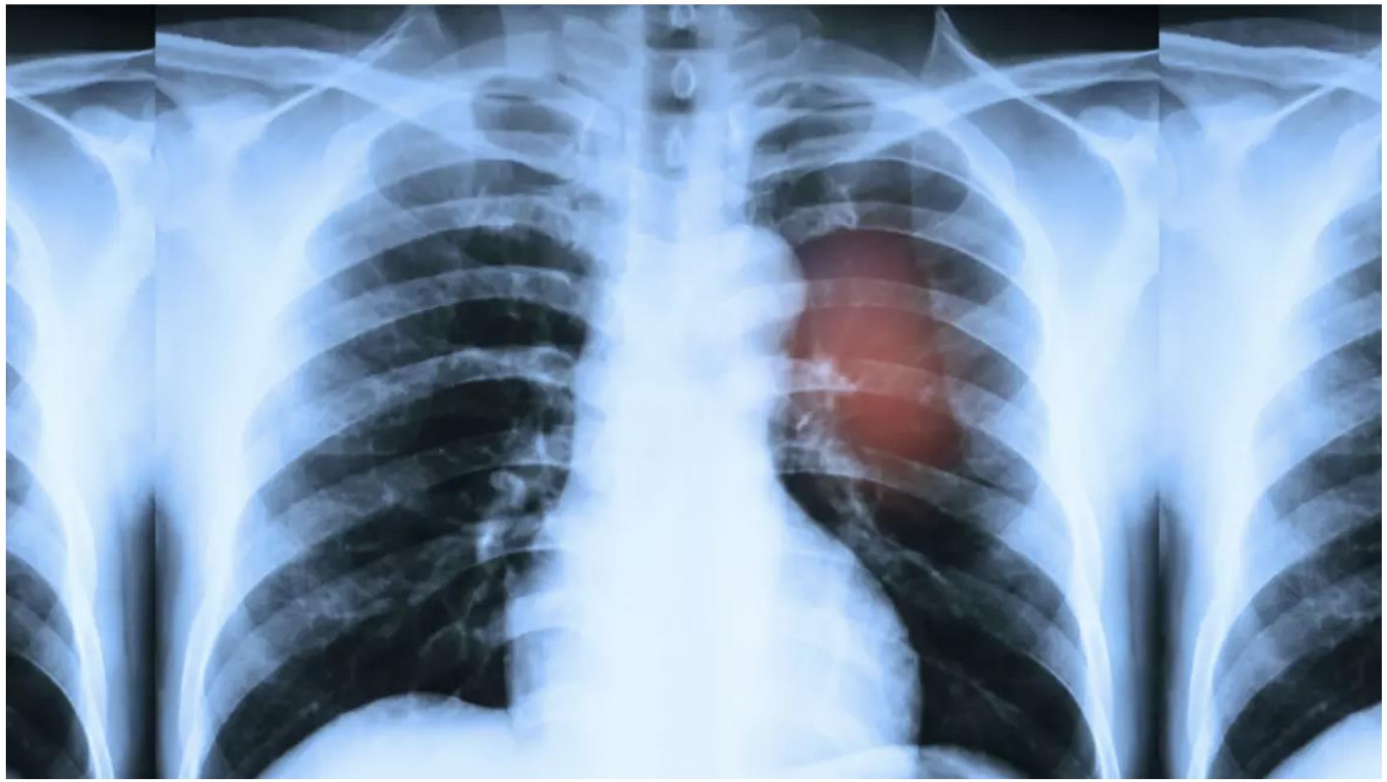


American Heart Association “One Brave Idea” competition: 2016

01-14-16

AHA, Alphabet Set Aside $75 Million To Cure Coronary Heart Disease

The disease kills more than 370,000 Americans each year.



[PHOTO: JES2U.PHOTO VIA SHUTTERSTOCK]

What if we developed a medicine that mimicked resistance mutations?

~50 mg/dl lower
LDL cholesterol in blood

~50% lower risk
for ASCVD

Healthy

Our proposal from 2016

The End of Coronary Heart Disease: 'OneShot', One Cure

Executive Summary:

Coronary heart disease (CHD) is a worldwide epidemic. The efficacy of available treatments is limited by expense, side effects and poor adherence. We need a curative therapy.

Rare genetic mutations can confer lifelong resistance to the development of CHD (**Table**)[1-7]. For some exceptional individuals, this inborn protection is ***nearly complete*** (i.e., **~90% reduction in CHD risk**) and without detectable toxicity. A therapeutic that extended the remarkable properties of these mutations into the general population could effectively 'cure' CHD in this century.

Our 'Brave Idea' is to perform gene editing in adult humans to introduce mutations *protective* against disease. CRISPR-Cpf1 is a RNA-guided endonuclease, analogous to CRISPR-Cas9, which can be easily programmed to cleave specific sequences in the human genome.[8] This breakthrough discovery offers the remarkable opportunity to precisely edit the human genome and introduce protective mutations into adults.

We propose to develop an injectable therapeutic administered once in life (OneShot) that will edit the genome and confer resistance to CHD. OneShot will combine the CRISPR-Cpf1 protein and guide RNA with liposome-mediated delivery to *permanently* inactivate a gene in the somatic liver tissue of adult humans. For initial development, we have prioritized two genes: proprotein convertase subtilisin/kexin type 9 (*PCSK9,* OneShot^{PCSK9}) and apolipoprotein C3 (*APOC3*, OneShot^{APOC3}).

BIOTECH

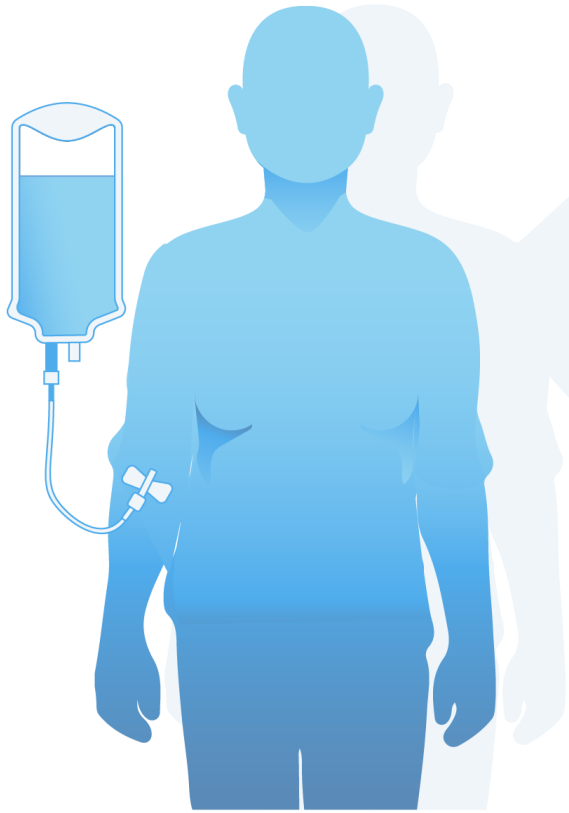
GV leads $58.5M round for Verve, a startup looking to pit gene editing against heart attacks

By **Amirah Al Idrus** • May 7, 2019 06:00am

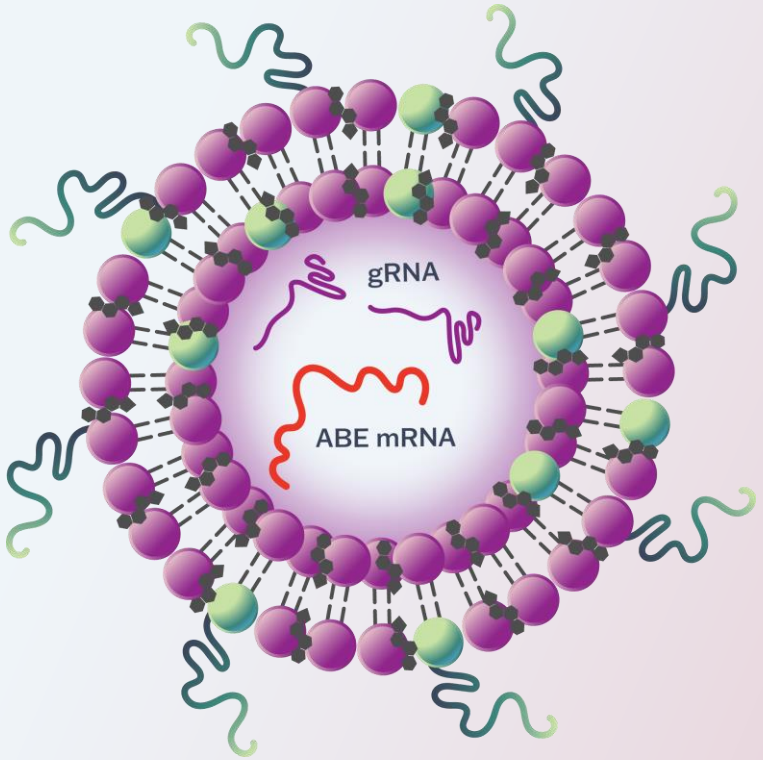
Can we transform care of ASCVD from daily pills/intermittent injections to “once-and-done”?

Product concept: mRNA encoding an adenine base editor and guide RNA carried in a lipid nanoparticle (LNP) delivery vehicle
Goal: turn off a cholesterol-raising in the liver

IV infusion of LNP



LNP Cross Section

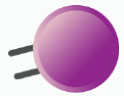


RNA Components

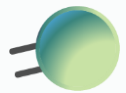
mRNA encoding adenine base editor

Guide RNA targeting *PCSK9*

LNP Components



Ionizable lipid



DSPC

PEG

Cholesterol

ABE, adenine base editor; DSPC, 1,2-distearoyl-sn-glycero-3-phosphocholine; gRNA, guide RNA; mRNA, messenger RNA; PEG, polyethylene glycol

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

TARGET	INDICATION	TECHNOLOGY	RESEARCH	IND-ENABLING	CLINICAL	RIGHTS
PCSK9 (VERVE-102)	Heterozygous familial hypercholesterolemia ASCVD	Base Editor (novel GalNAc-LNP)				verve / Lilly
PCSK9 (VERVE-101)[1]	Heterozygous familial hypercholesterolemia ASCVD	Base Editor				verve / Lilly
ANGPTL3 (VERVE-201)	Homozygous familial hypercholesterolemia Refractory hypercholesterolemia	Base Editor (novel GalNAc-LNP)				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

1. As of April 2, 2024, Verve has paused enrollment of the Heart-1 Phase 1b trial of VERVE-101 and is prioritizing clinical development of VERVE-102.

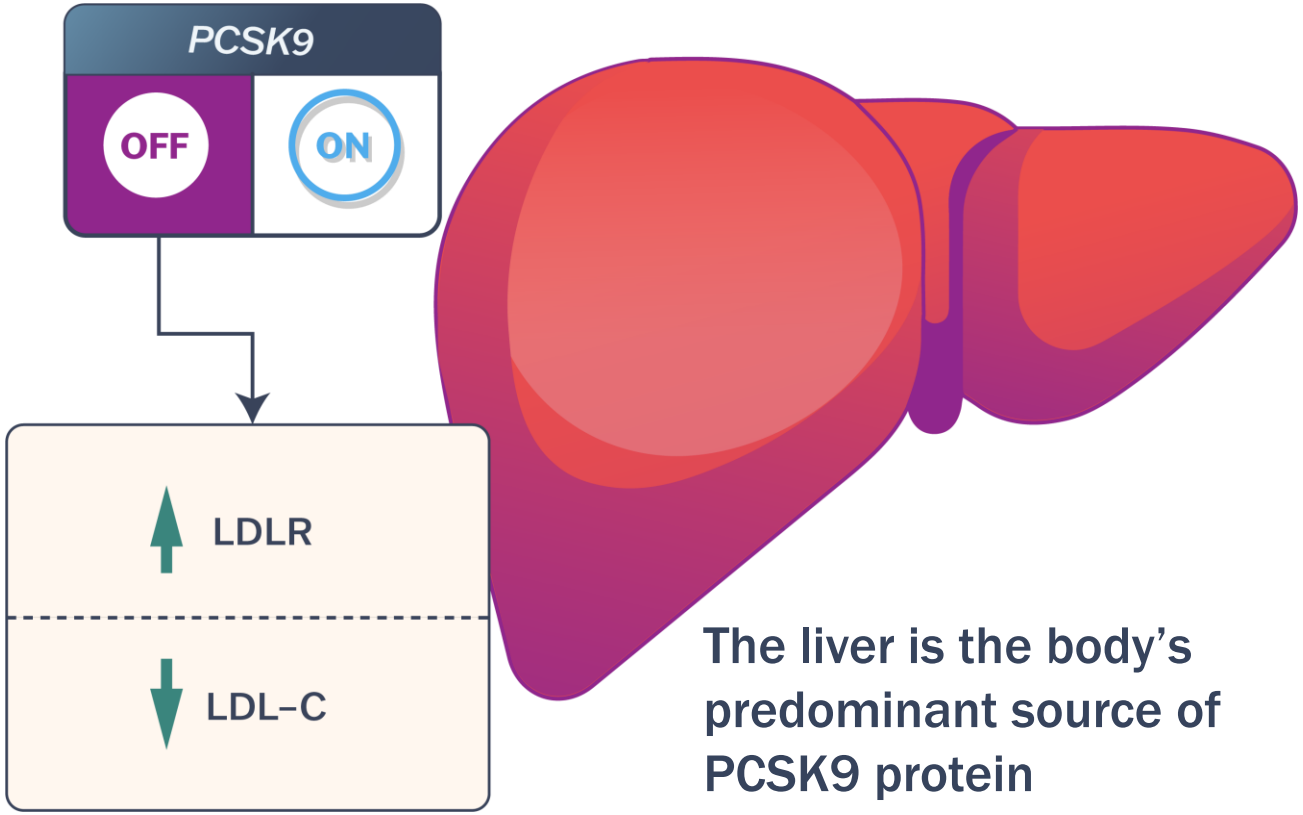
PCSK9 Program

Human genetics suggests turning off the *PCSK9* gene in the liver may enable permanent LDL-C lowering

Naturally occurring gene variants that turn off *PCSK9* result in:

- Lifelong LDL-C lowering
- Protection against ASCVD
- No apparent deleterious effects[1–3]

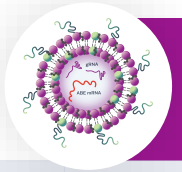
Pharmacologic validation of target

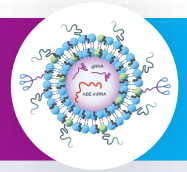


The liver is the body's predominant source of PCSK9 protein

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.
PCSK9, proprotein convertase subtilisin/kexin type 9

Verve's PCSK9 program has two product candidates with different lipid nanoparticle (LNP) formulations: VERVE-101 and VERVE-102

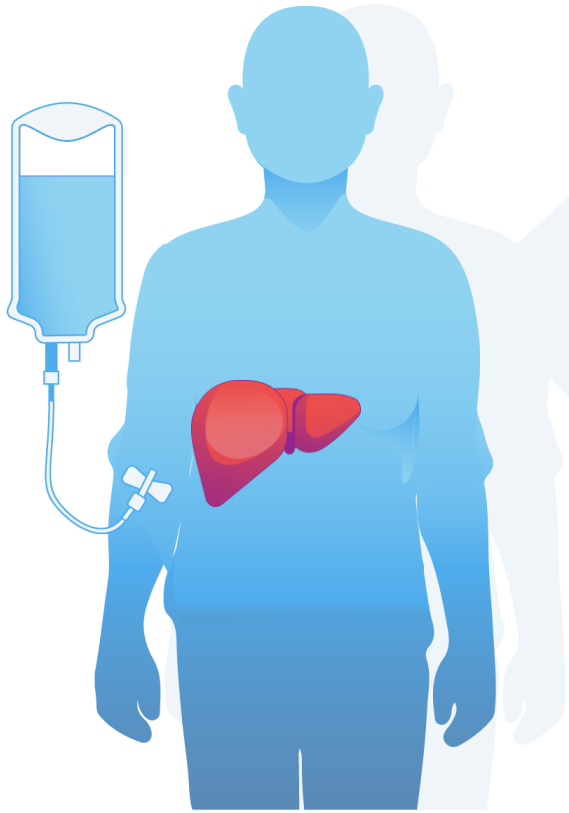




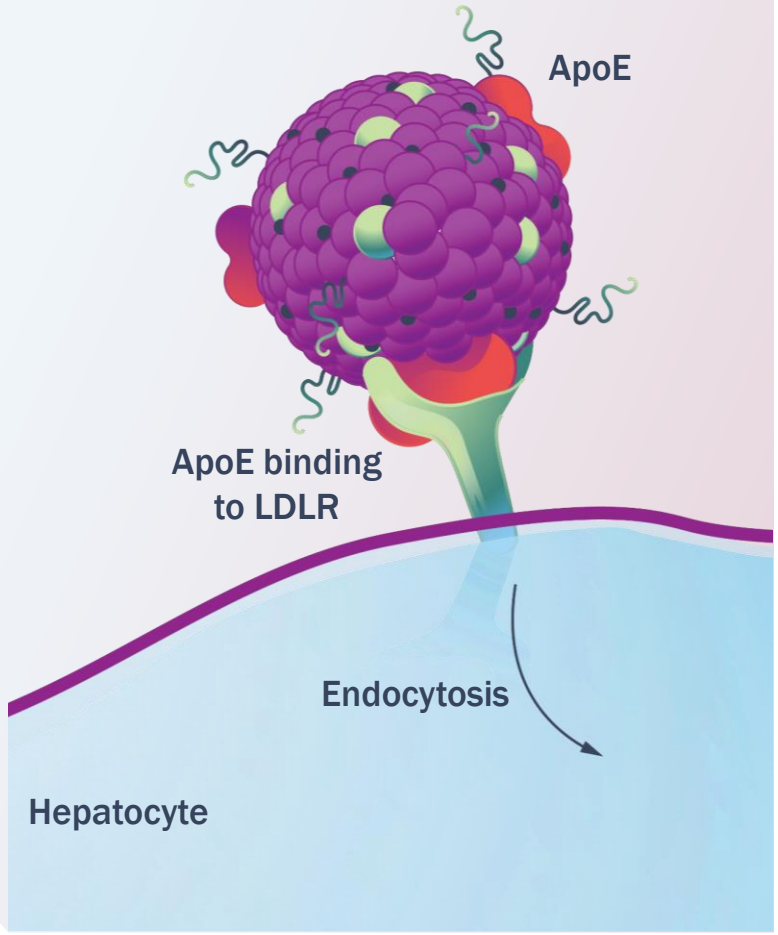
	VERVE-101	VERVE-102
TARGET	*PCSK9* gene	
ADENINE BASE EDITOR (ABE)	Same adenine base editor (ABE) used in both product candidates	
GUIDE RNA	Same guide RNA (gRNA) targeting *PCSK9*	
IONIZABLE LIPID	ALC-0307	LP000001
PEG LIPID	ALC-0159	DMG-PEG$_{2000}$
LIVER-TARGETING LIGAND	—	GalNAc

Uptake of the VERVE-101 LNP into hepatocytes occurs primarily by endocytosis through LDLR

IV infusion of LNP



VERVE-101 LNP Uptake



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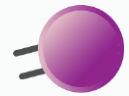
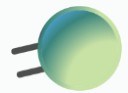
Guide RNA targeting *PCSK9*

LNP Components



Ionizable lipid



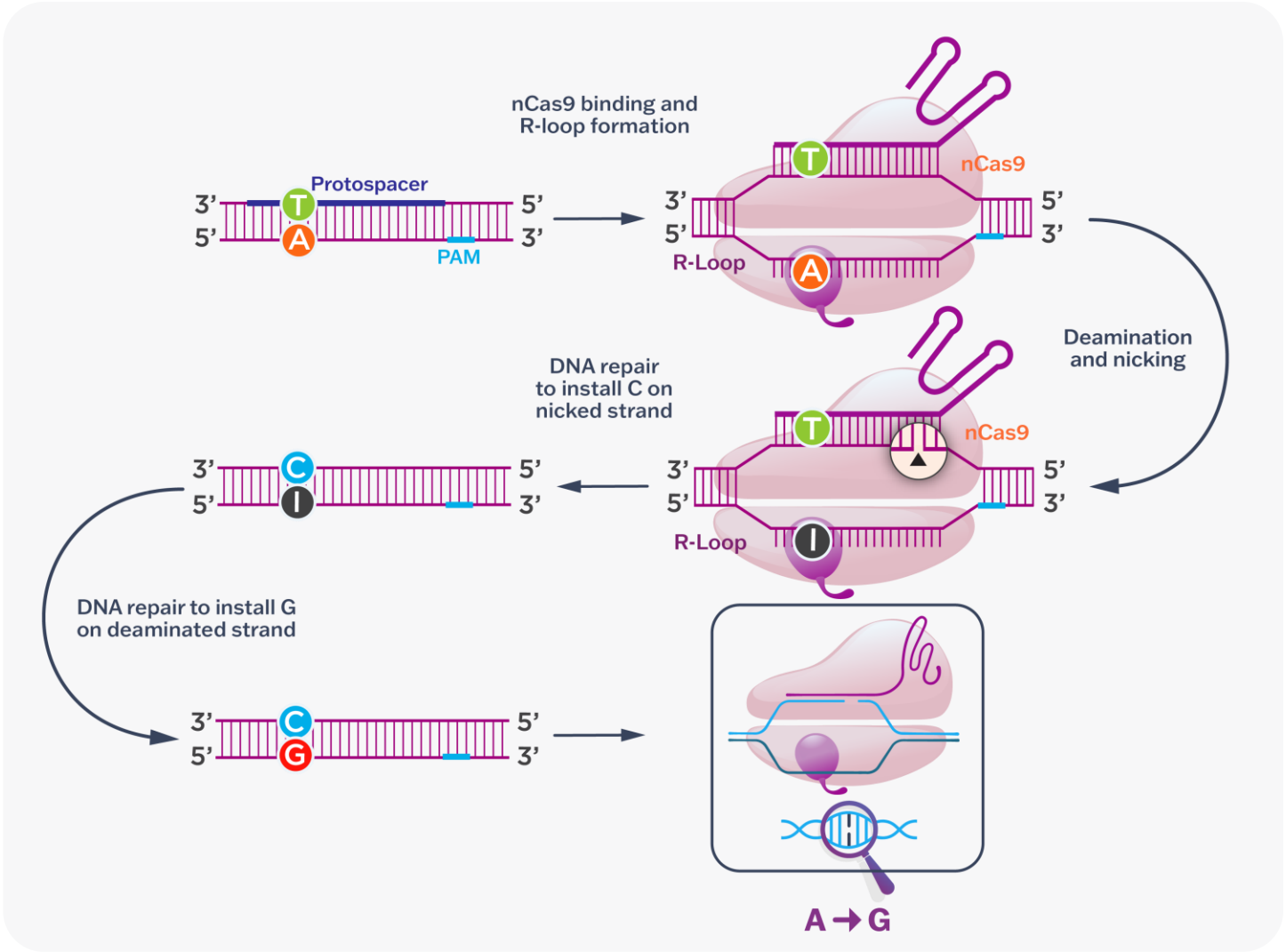
DSPC

PEG

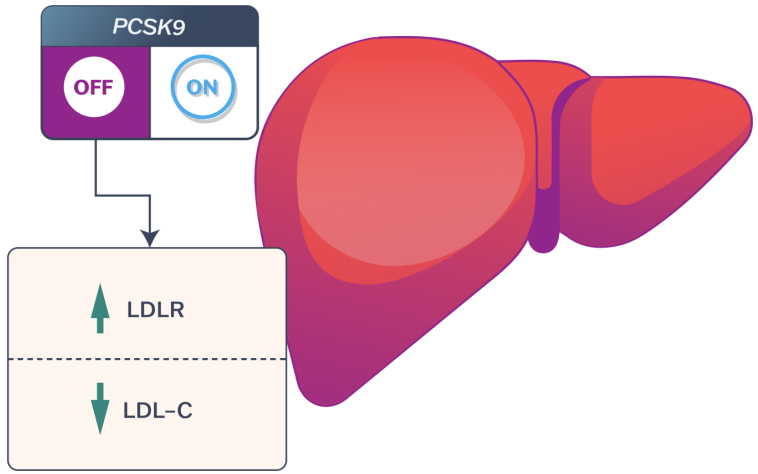
Cholesterol

ApoE, apolipoprotein E

In the hepatocyte, the mRNA is translated to ABE protein which pairs with the gRNA to ultimately make a single spelling change in the PCSK9 DNA sequence to turn it off: think pencil and eraser



A-to-G change disrupts a splice donor site and inactivates the *PCSK9* gene



nature

Nature | Vol 593 | 20 May 2021 |

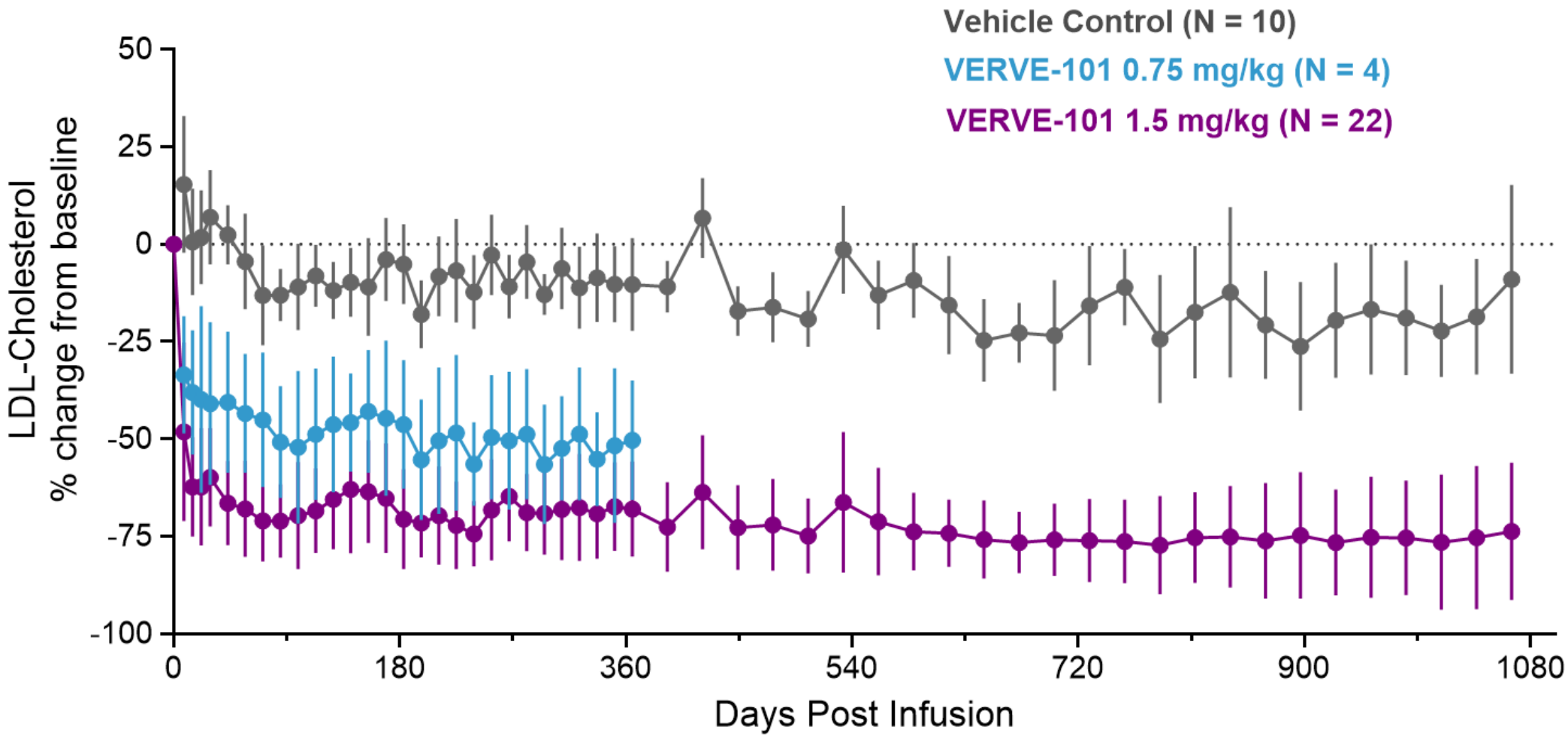
Article

In vivo CRISPR base editing of *PCSK9* durably lowers cholesterol in primates

Gene-editing technologies, which include the CRISPR–Cas nucleases[1–3] and CRISPR base editors[4,5], have the potential to permanently modify disease-causing genes in patients[6]. The demonstration of durable editing in target organs of nonhuman primates is a key step before in vivo administration of gene editors to patients in clinical trials. Here we demonstrate that CRISPR base editors that are delivered in vivo using lipid nanoparticles can efficiently and precisely modify disease-related genes in living cynomolgus monkeys (*Macaca fascicularis*). We observed a near-complete knockdown of *PCSK9* in the liver after a single infusion of lipid nanoparticles, with concomitant reductions in blood levels of PCSK9 and low-density lipoprotein cholesterol of approximately 90% and about 60%, respectively; all of these changes remained stable for at least 8 months after a single-dose treatment. In addition to supporting a 'once-and-done' approach to the reduction of low-density lipoprotein cholesterol and the treatment of atherosclerotic cardiovascular disease (the leading cause of death worldwide[7]), our results provide a proof-of-concept for how CRISPR base editors can be productively applied to make precise single-nucleotide changes in therapeutic target genes in the liver, and potentially in other organs.

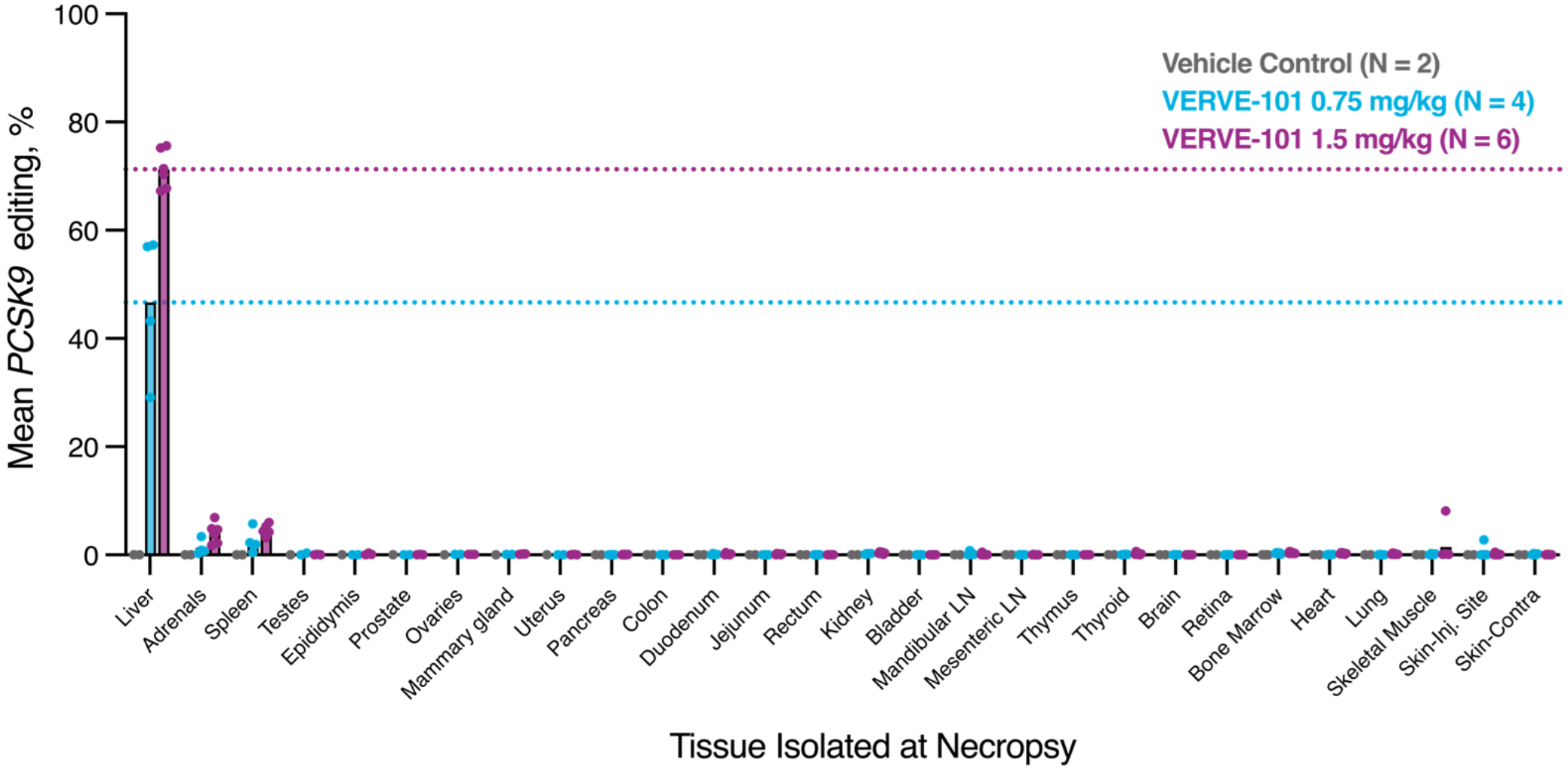
verve THERAPEUTICS

Durability in non-human primates: a single infusion of VERVE-101 reduced blood LDL-C for 3 years

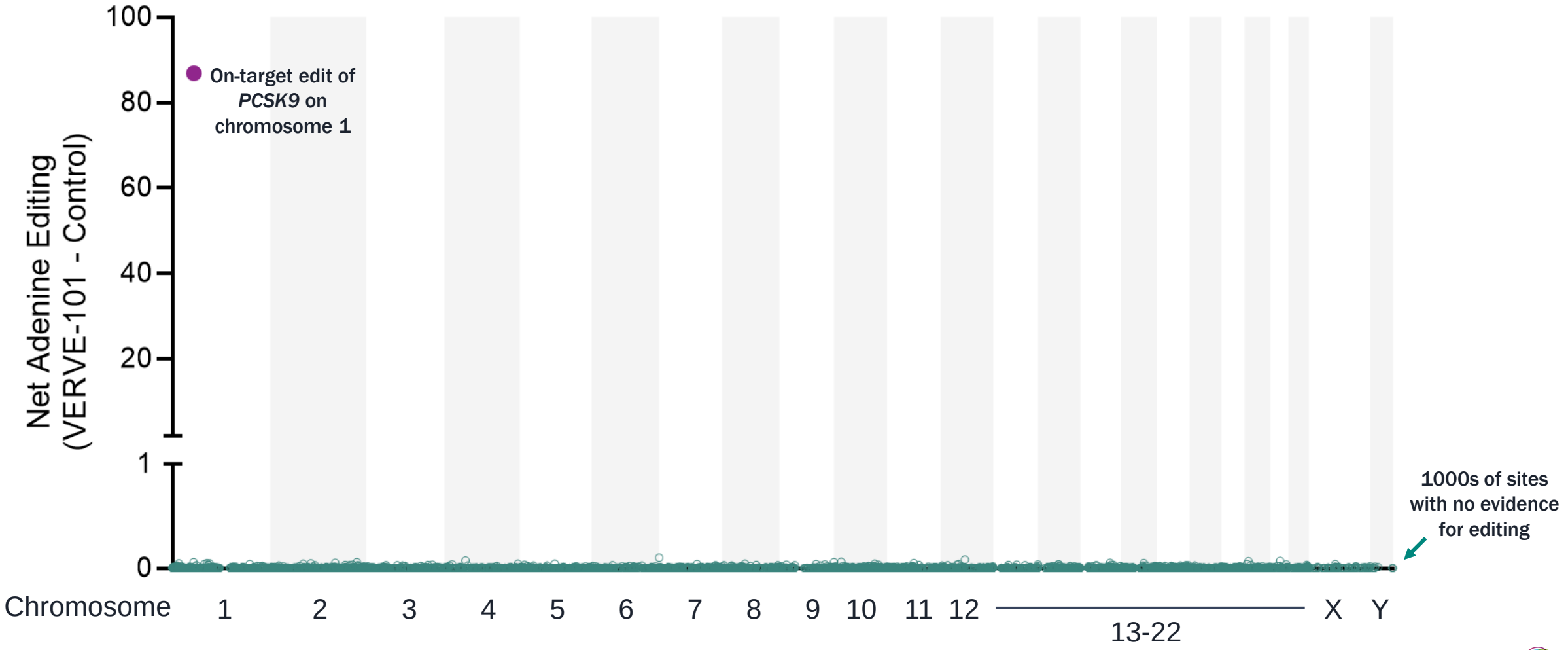


NHP, non-human primate
Data represents mean +/- SD for cohorts which included N=10 in control and N=22 in VERVE-101 at the earliest time points and N=7 and N=16, respectively, at the last time point
Reductions are time-weighted average change from baseline

NHP data demonstrate that VERVE-101 is predominantly taken up by the liver



No off-target editing was observed with VERVE-101 in analysis of ~6000 candidate sites in primary human hepatocytes *in vitro*



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

13 patients dosed

STUDY POPULATION SUMMARY

- Males and females (age 18 to 75)
- HeFH and established ASCVD
- High cholesterol despite treatment

TREATMENT

- Pre-medication with dexamethasone and antihistamines
- VERVE-101 delivered by single IV infusion

HeFH Heterozygous familial hypercholesterolemia

- Serious, inherited form of high cholesterol
- Lifelong elevations in LDL-C and premature ASCVD
- Estimated three million adult patients in EU/US[1]

Data as of Oct. 3, 2024; Clinical trial registration: NCT05398029
Women of childbearing potential are excluded from the study. LDL-C threshold for inclusion value varies by country-specific protocol.
Ongoing treatment for high cholesterol for participants consists of maximum tolerated statin and/or ezetimibe (statin intolerant allowed).
Dosing based on weight for participants ≤ 100 kg; participants > 100 kg are dosed on an assumed 100 kg weight.
EU, European Union; US, United States
1. de Ferranti SD, et al. *Circulation*. 2016;133;1067-1072; 2. Vallejo-Vaz AJ, et al. *Lancet*. 2021;398(10312):1713-1725.

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

heart-1

13

patients dosed

- **Dose-dependent reductions in blood PCSK9 protein & LDL-C**
- **Mean PCSK9 protein reductions of >60% for two higher dose cohorts (0.45 and 0.6 mg/kg)**
- **Mean LDL-C reductions of 42% at 0.45 mg/kg (n=6) and 57% at 0.6 mg/kg (n=1)[1]**

As of data cut off date of October 3, 2024. Data are from an ongoing study with an open database and have not been fully cleaned.
1. Means are based on time-averaged reduction in LDL-C and PCSK9 protein from day 28 through last available follow up; observations from one participant dosed at 0.45 mg/kg censored after change in lipid lowering therapy from baseline more than 6 months after VERVE-101 treatment; effective dose for participant at 0.6 mg/kg was ~0.5 mg/kg.

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Safety: Laboratory abnormalities (transient, reversible) after LNP infusion led to pause in enrollment

heart-1

13

patients dosed

- Mild-to-moderate infusion reactions and transient, asymptomatic ALT increases
- Transient laboratory abnormalities in one patient of ALT increase and grade 3 SAE of drug-induced thrombocytopenia
- Cardiovascular events consistent with severe ASCVD population
- No new treatment-related adverse events occurred more than 2 days after treatment

Enrollment paused pending completion of investigation of laboratory abnormalities; preliminary findings support hypothesis that laboratory abnormalities attributable to LNP

As of data cut off date of October 3, 2024. Data are from an ongoing study with an open database and have not been fully cleaned.
AE, adverse event; ALT, alanine aminotransferase; SAE, serious adverse event

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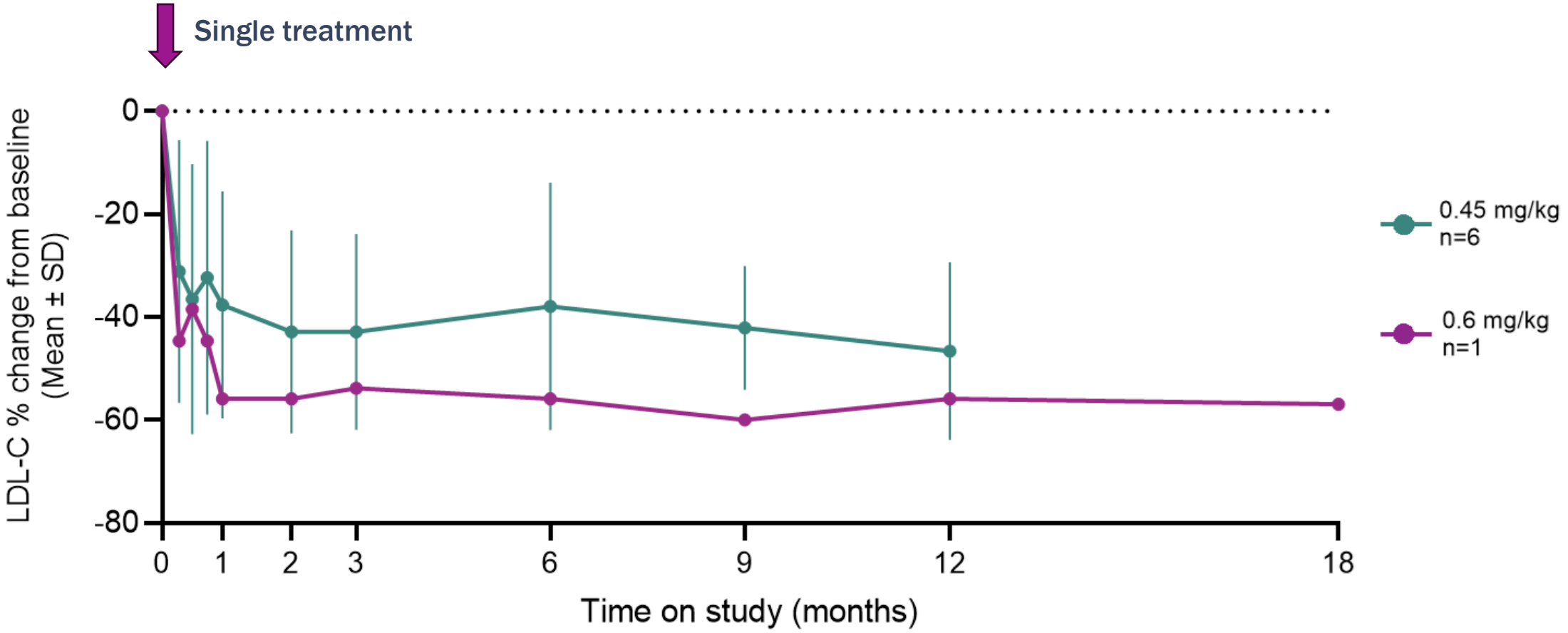
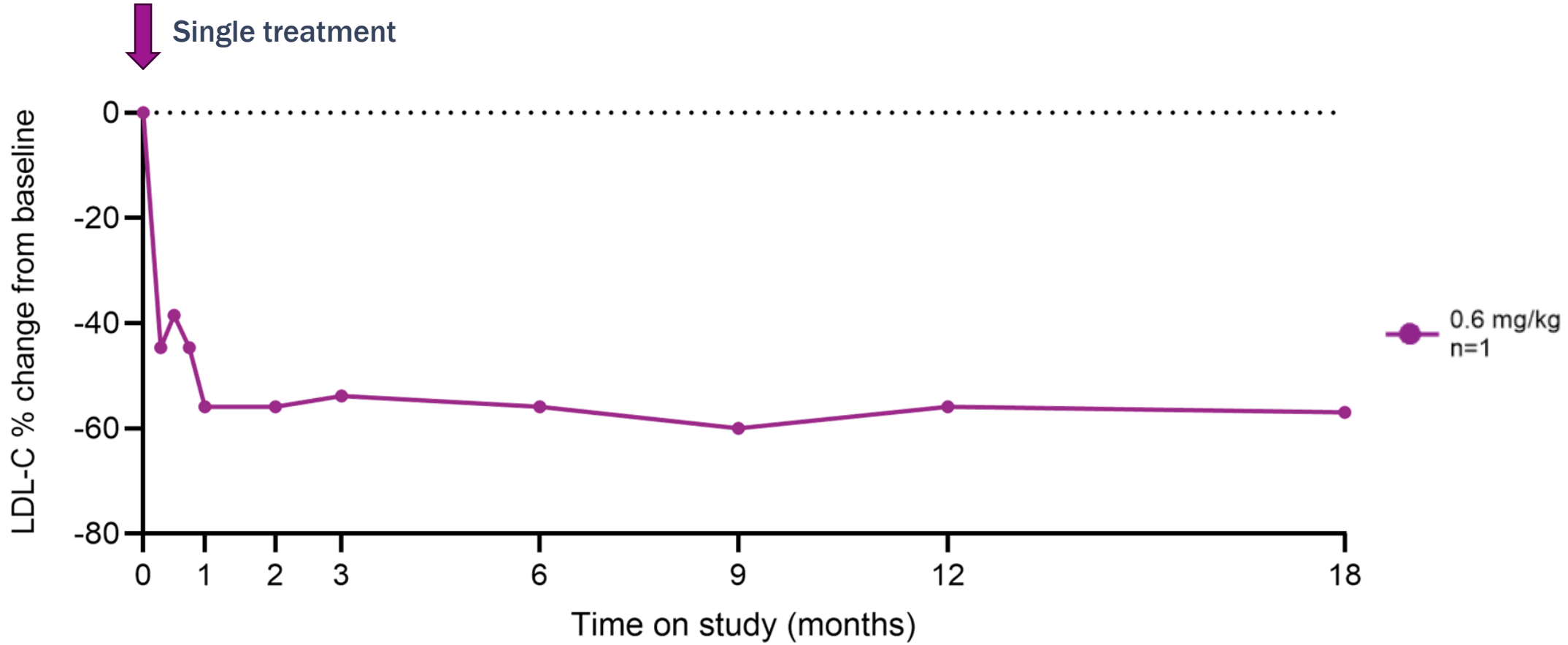
Durability in humans: Evidence for sustained LDL-C reduction following single VERVE-101 treatment in two higher dose cohorts



As of October 3, 2024. Data are from an ongoing study with an open database and have not been fully cleaned. Participants in 0.45 mg/kg cohort have variable duration of follow up, with n=6 at 6 months and n=3 at 9 months and 12 months. One of the six 0.45 mg/kg participants intensified statin therapy from baseline more than 6 months after VERVE-101 treatment.
SD, standard deviation

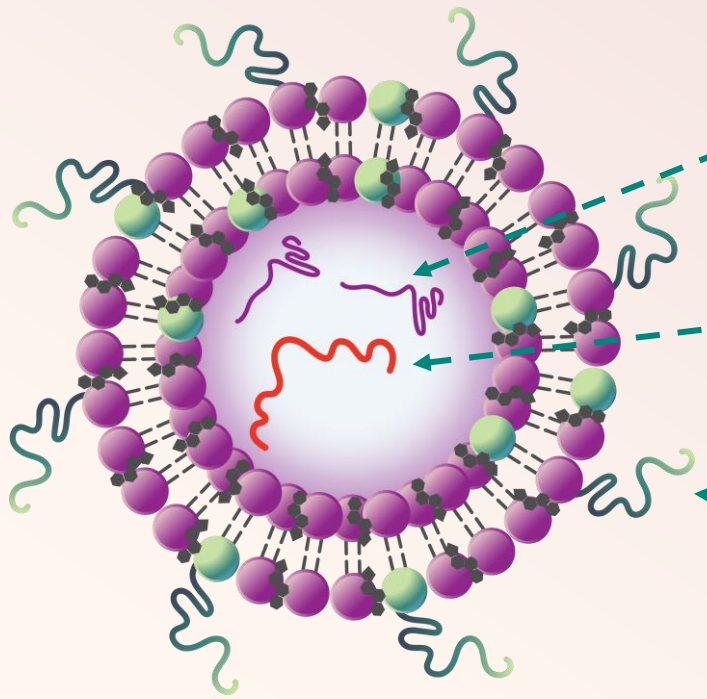
Durability: Proof-of-concept for LDL-C lowering extends to 18 months in participant dosed at 0.6 mg/kg



As of October 3, 2024. Data are from an ongoing study with an open database and have not been fully cleaned.

Heart-1 learnings: ABE editor and guide RNA work as designed, LNP suspected to contribute to acute laboratory abnormalities

VERVE-101 Components



1. Guide RNA
2. mRNA for ABE
3. Lipid nanoparticle

1 2

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

3

LNP suspected cause of laboratory safety findings

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

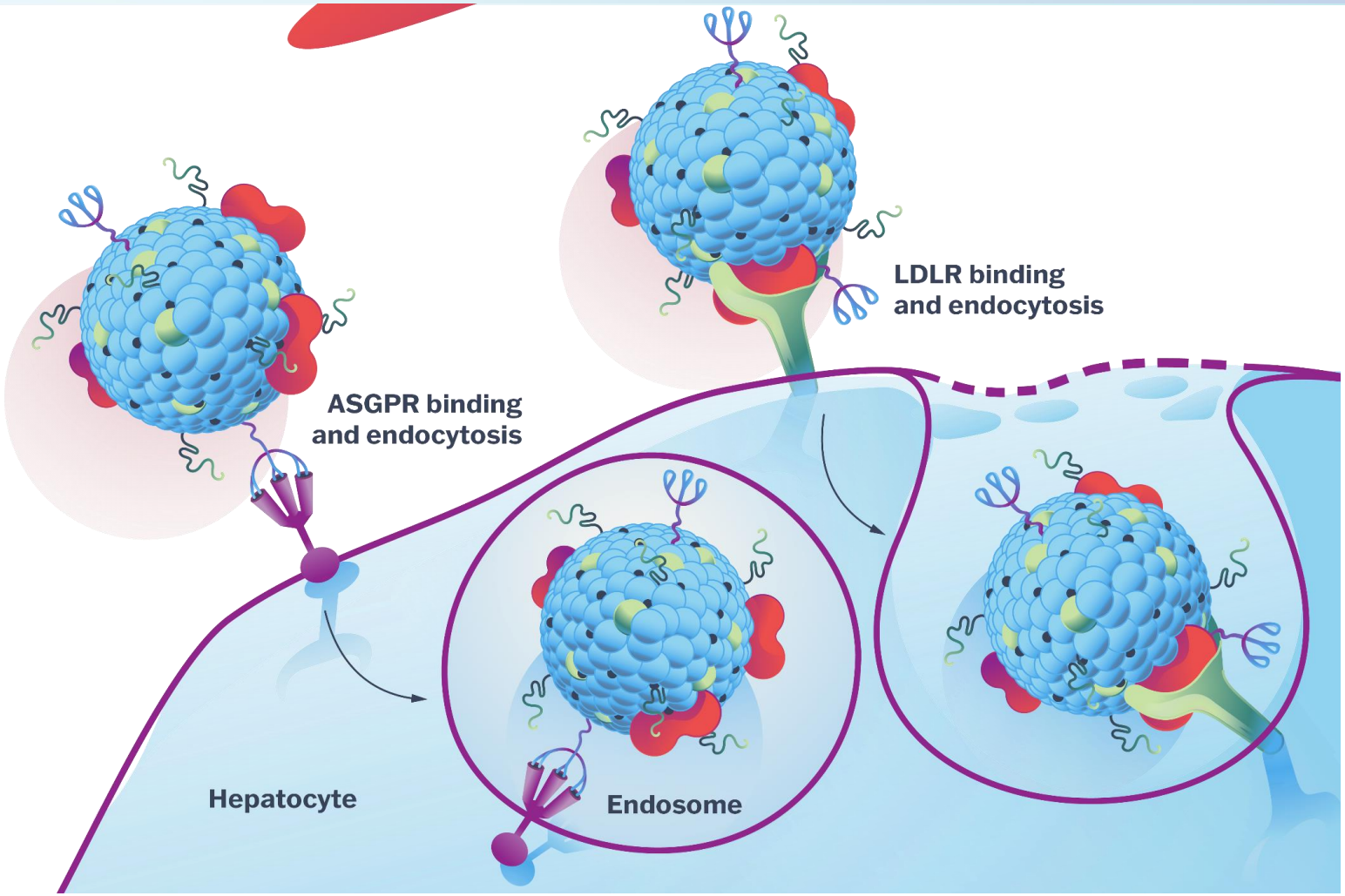
VERVE-102 retains the same ABE mRNA and guide RNA but switches out the LNP formulation and adds a liver-targeting ligand (GalNAc)

	VERVE-101	VERVE-102
TARGET	*PCSK9* gene	
ADENINE BASE EDITOR (ABE)	Same adenine base editor (ABE) used in both product candidates	
GUIDE RNA	Same guide RNA (gRNA) targeting *PCSK9*	
IONIZABLE LIPID	ALC-0307	LP000001
PEG LIPID	ALC-0159	DMG-PEG$_{2000}$
LIVER-TARGETING LIGAND	—	GalNAc

- Ionizable lipid and PEG-lipid in VERVE-102 have been well-tolerated in >80 patients (third-party clinical trials)
- Addition of GalNAc in VERVE-102 allows for LDLR- or ASGPR-mediated uptake into hepatocytes

ASGPR: asialoglycoprotein receptor

VERVE-102 is designed to enter hepatocytes through either ASGPR or LDLR



- GalNAc may enable more robust delivery in setting of LDLR-deficiency, present in some patients with familial hypercholesterolemia
- GalNAc-LNP has shown high specificity for liver in nonclinical biodistribution analysis

Heart-2 is a Phase 1b trial designed to evaluate VERVE-102; clinical data expected in 1st half of 2025

heart-2

First-in-human, open-label trial in adults with HeFH and/or premature coronary artery disease (CAD)

Single Ascending Dose

Three to nine participants per cohort receive a single dose

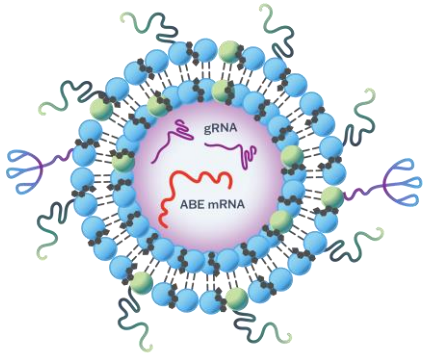
STUDY POPULATION SUMMARY

- 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

VERVE-102



First patient dosed in 2Q 2024

Clinical trial registration: NCT06164730
Women of childbearing potential are excluded from the study.

Prioritizing the clinical development of VERVE-102

Editor and Guide Work

Heart-1 data for VERVE-101 demonstrate that *in vivo* liver editing for *PCSK9* has the potential to meaningfully and durably reduce LDL-C in HeFH patients

Change LNP Delivery System

VERVE-102 uses a different LNP delivery system with a well tolerated ionizable lipid and a GalNAc liver-targeting ligand

Preliminary findings from nonclinical studies support hypothesis that observed laboratory abnormalities attributable to LNP

Current focus on VERVE-102

Regulatory clearances in Australia, Canada, Israel, N.Z., and the U.K.

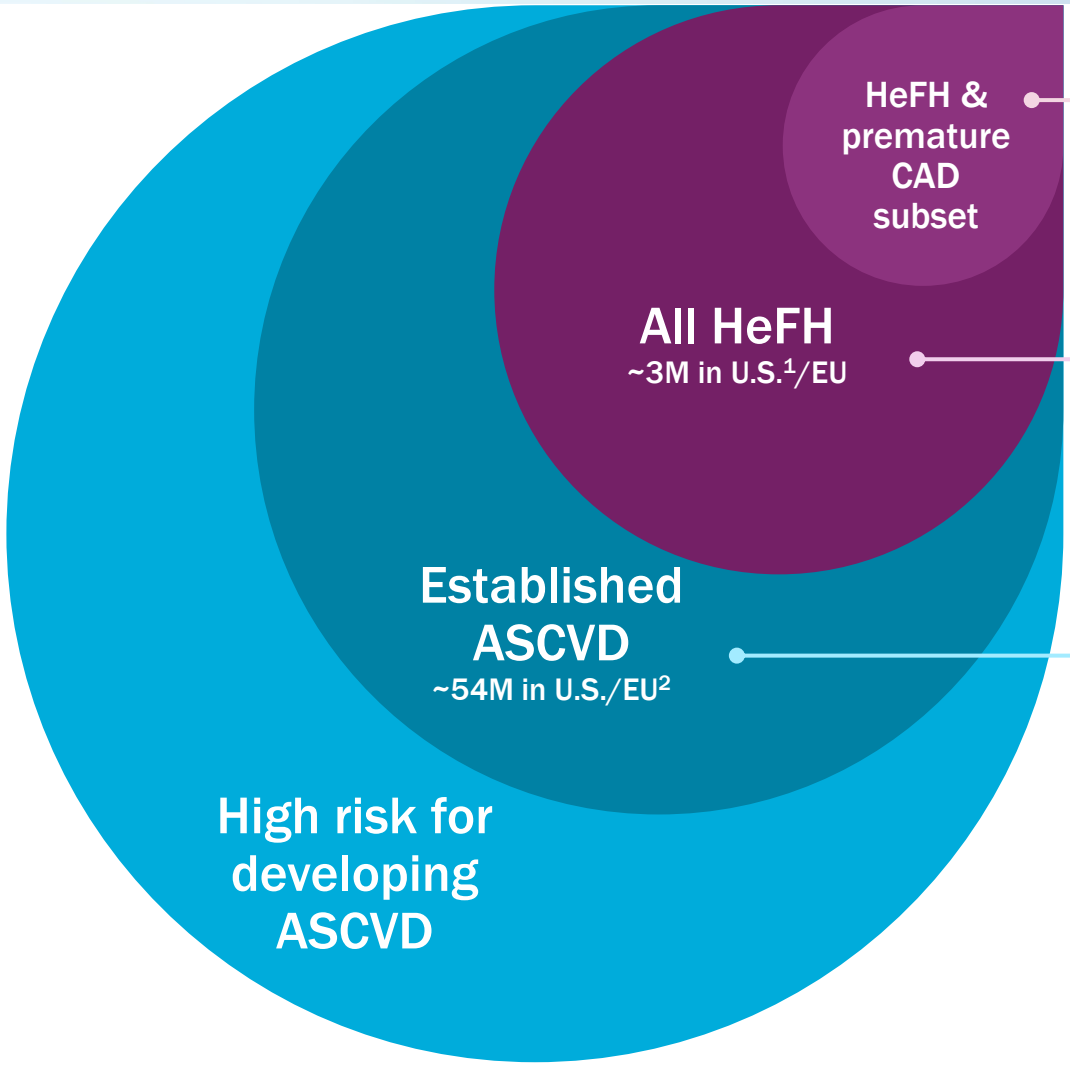
Heart-2 trial currently enrolling patients

Interim Phase 1 data expected in 1H 2025

LNP, lipid nanoparticle

Developing Gene Editing Medicines for Cardiovascular Disease

Possible stepwise approach to clinical development that enables gene editing medicines to address unmet need in increasingly broad patient subsets



- Phase 1b in high-risk patient subset with the highest unmet need and potential to benefit

- Phase 2 in all HeFH
- Pivotal Phase 3 in all HeFH (LDL-C endpoint)

- Pivotal Phase 3 in ASCVD (LDL-C endpoint)
- Potential cardiovascular outcome study in ASCVD

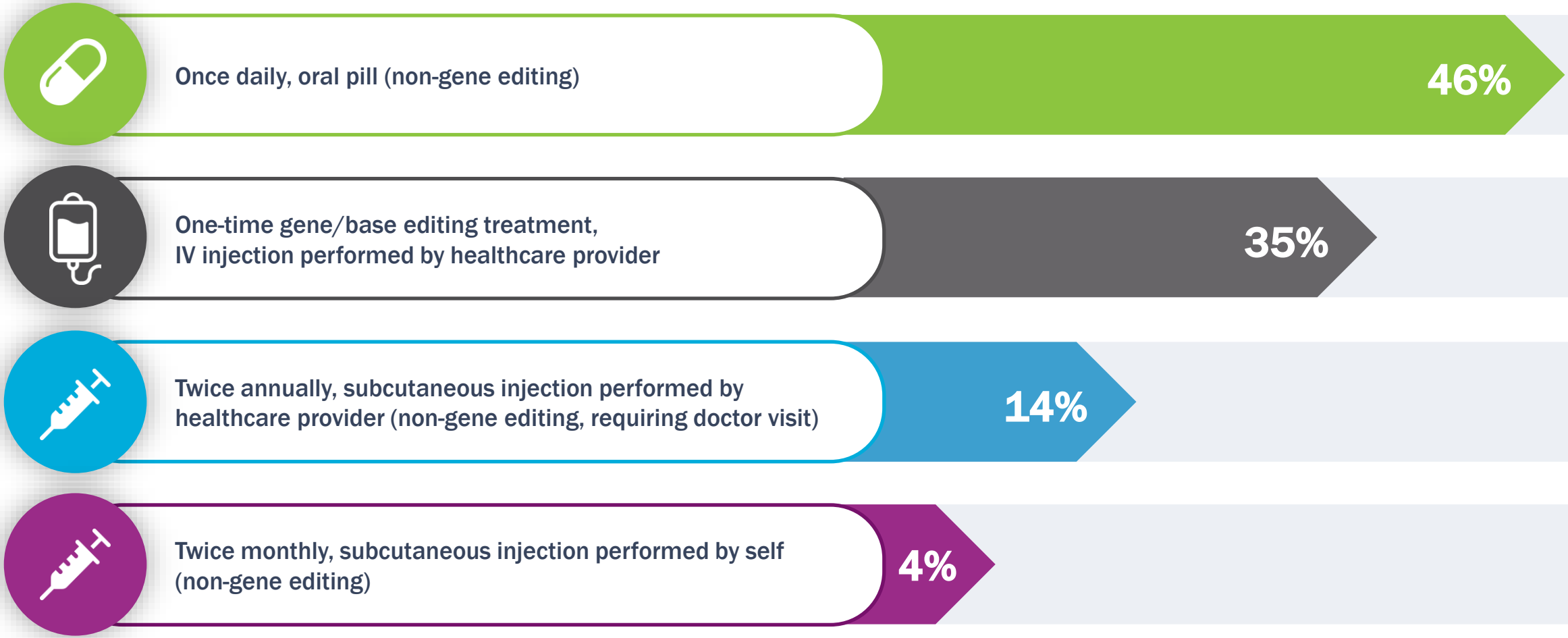
Lowering LDL-C by targeting *PCSK9* remains a large unmet need

1. Tsao CW et al., *Circulation*. 2022;145(8):e153–e639; 2. Gu J et al., *Am J Prev Cardiol*. 2022;10:100336
CAD, coronary artery disease; EU, European Union; HeFH, heterozygous familial hypercholesterolemia

Clinical development strategy subject to alignment with regulators

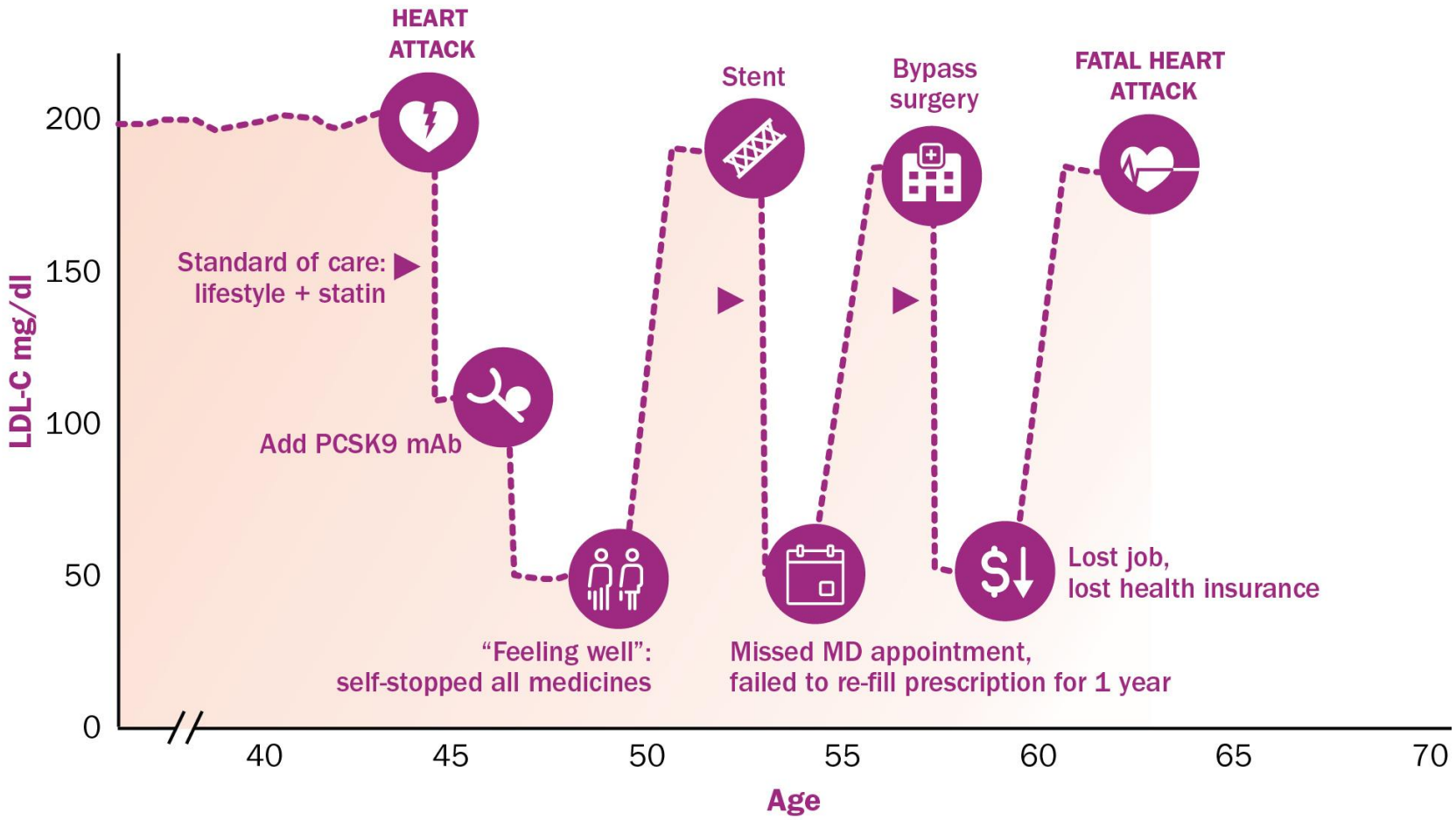
Will patients be open to a one-time gene editing procedure as a solution?
Patient preference surveys show remarkable openness

Assuming you will have lifelong therapy in the treatment of high cholesterol and/or cardiovascular disease, please select the therapeutic option that is most appealing to you (N=484)



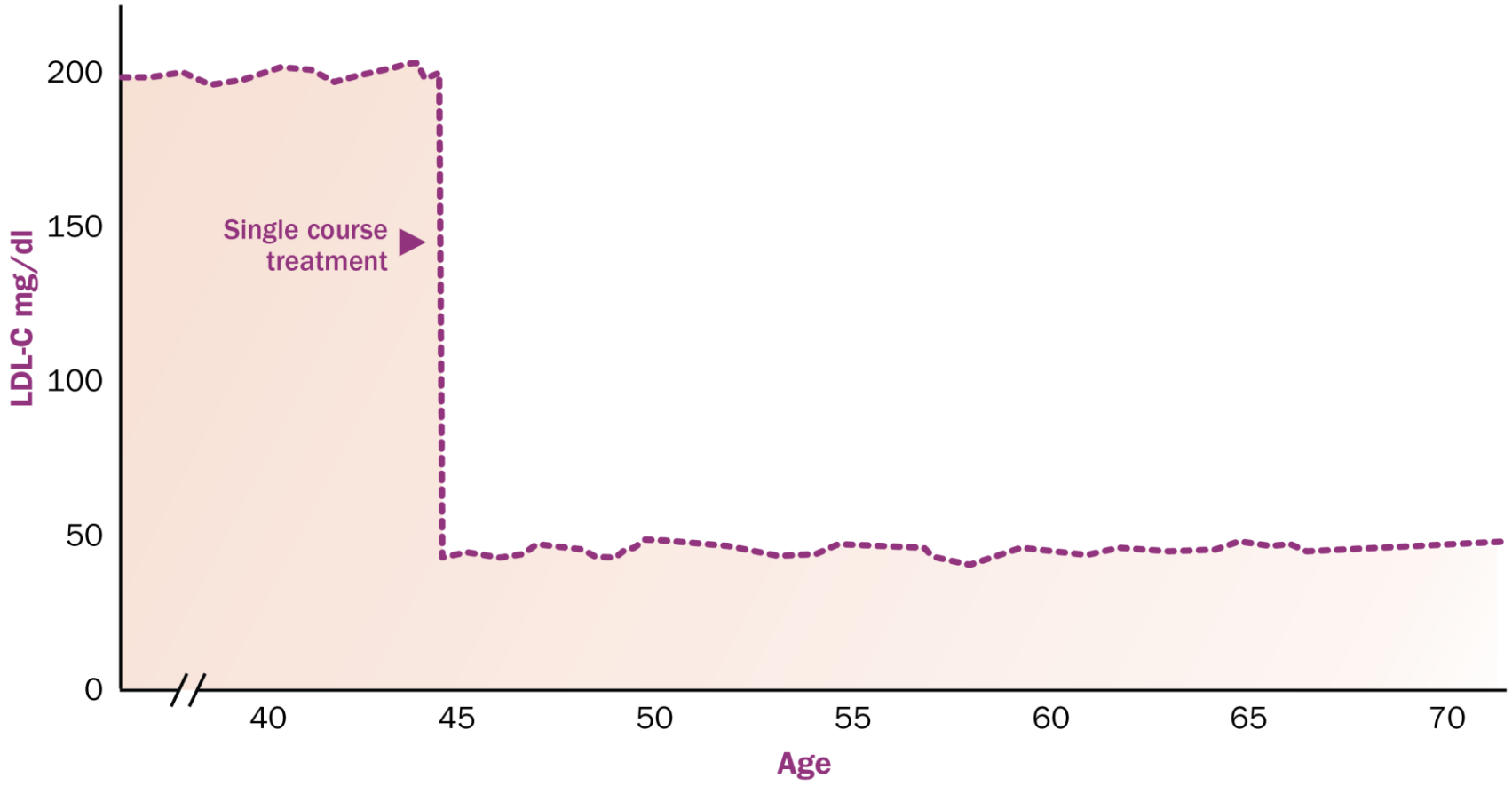
Source: Patient preferences survey conducted by polling firm Morning Consult; LifeSci Capital

Current care model for chronic disease: poor control of LDL-C

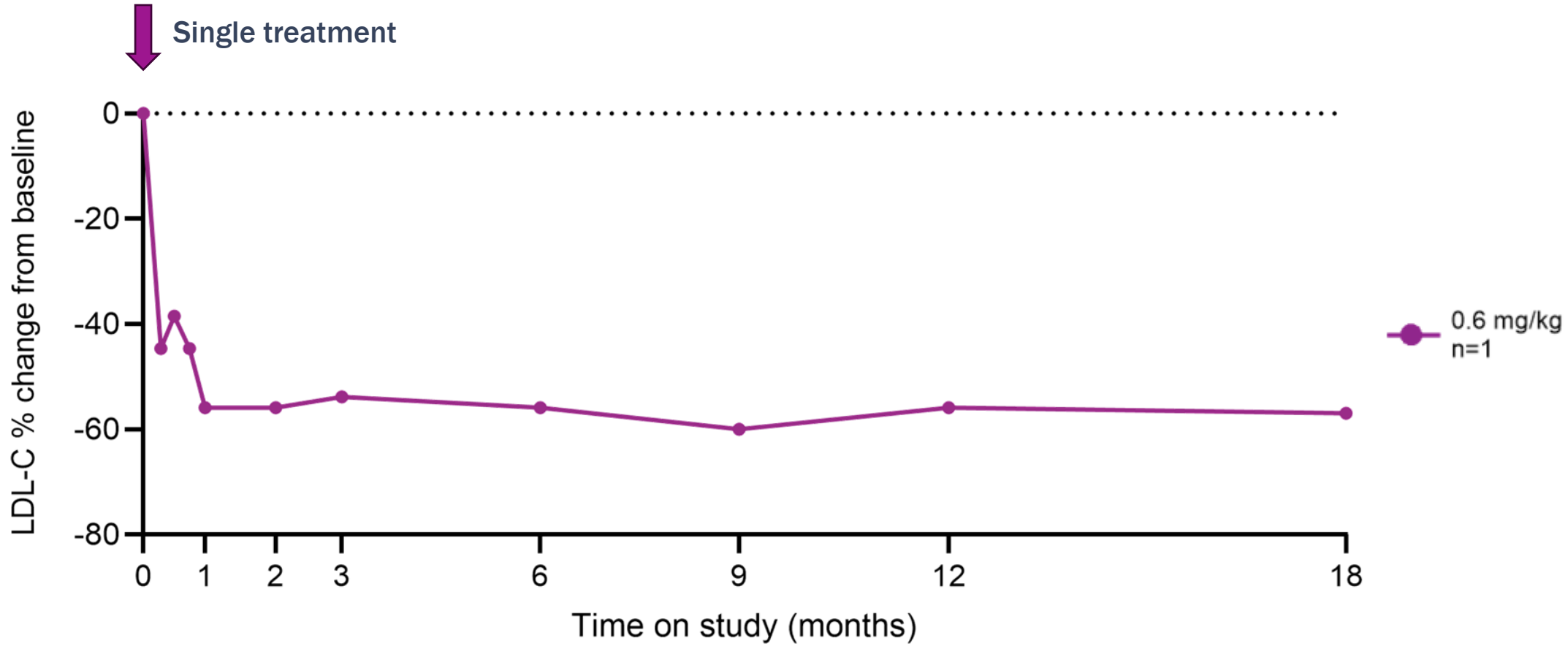


Illustrative graphic depicts the journey of a hypothetical patient with familial hypercholesterolemia who began standard-of-care treatment after suffering a heart attack at age 44

Verve's vision: from chronic care to one-time treatment, lifelong cholesterol lowering



And it all looks possible…



As of October 3, 2024. Data are from an ongoing study with an open database and have not been fully cleaned.

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

TARGET	INDICATION	TECHNOLOGY	RESEARCH	IND-ENABLING	CLINICAL	RIGHTS
PCSK9 (VERVE-102)	Heterozygous familial hypercholesterolemia ASCVD	Base Editor (novel GalNAc-LNP)				verve / Lilly
PCSK9 (VERVE-101)[1]	Heterozygous familial hypercholesterolemia ASCVD	Base Editor				verve / Lilly
ANGPTL3 (VERVE-201)	Homozygous familial hypercholesterolemia Refractory hypercholesterolemia	Base Editor (novel GalNAc-LNP)				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

1. As of April 2, 2024, Verve has paused enrollment of the Heart-1 Phase 1b trial of VERVE-101 and is prioritizing clinical development of VERVE-102.

Thank you