Developing single-course gene editing medicines to treat cardiovascular disease

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

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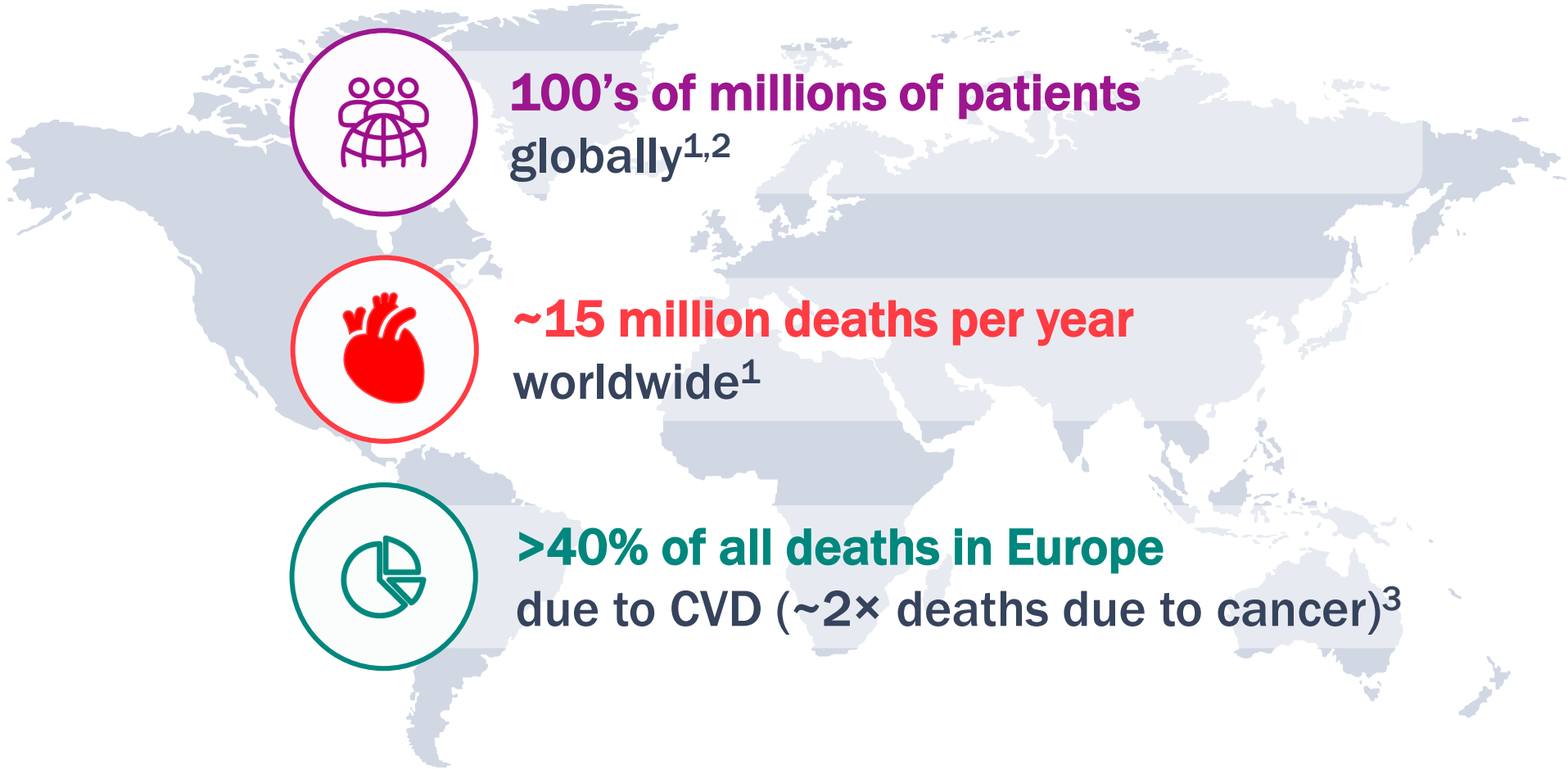
Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of mortality worldwide



100's of millions of patients globally[1,2]

~15 million deaths per year worldwide[1]

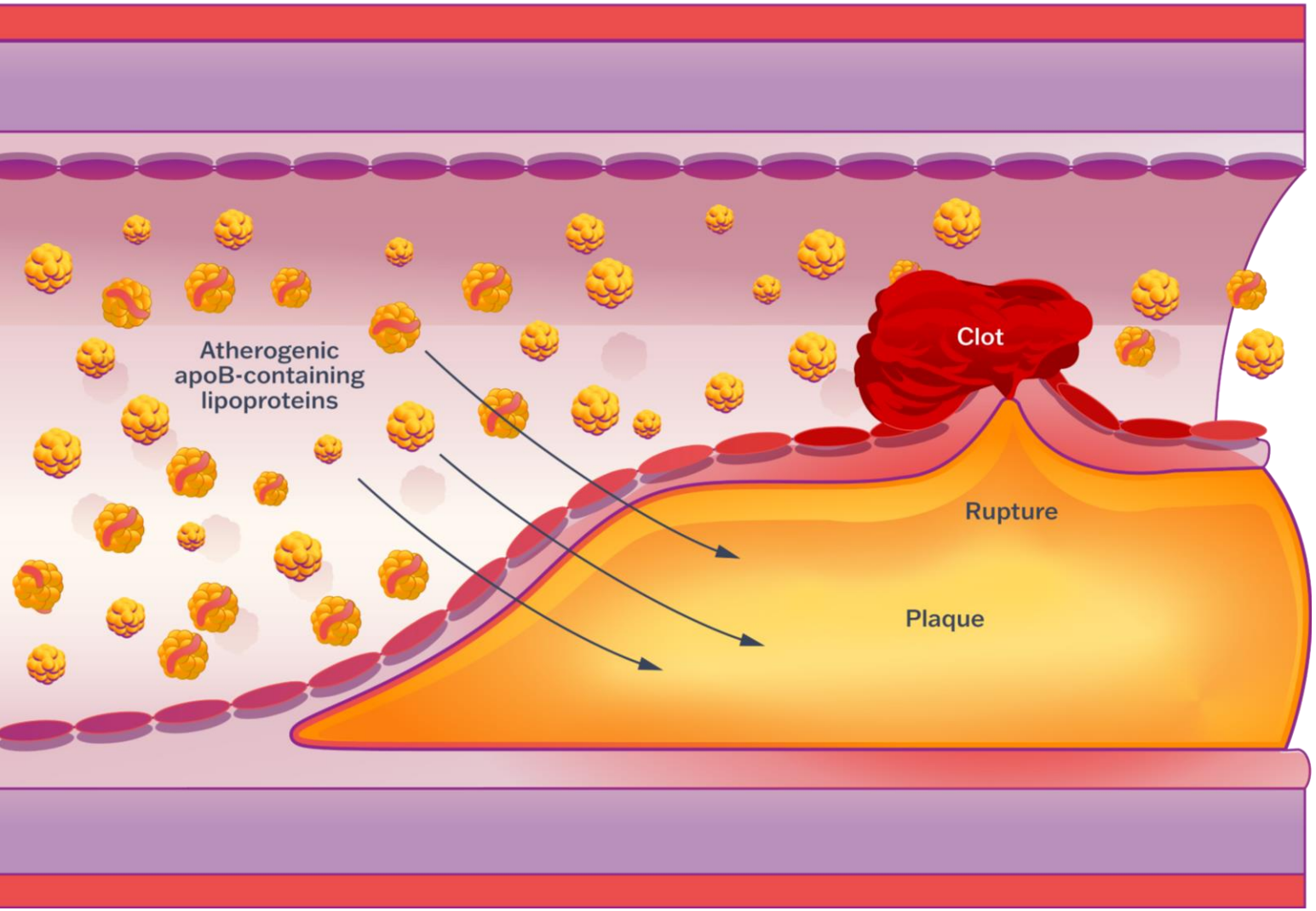
>40% of all deaths in Europe due to CVD (~2× deaths due to cancer)[3]

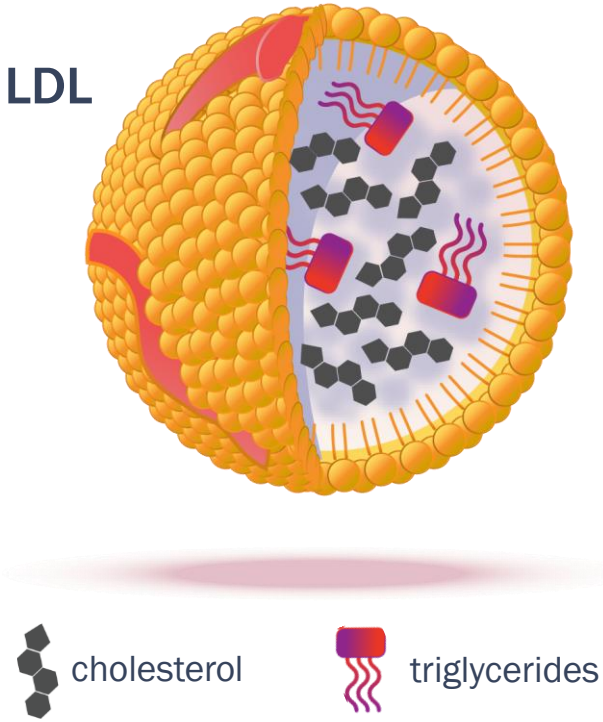
CVD, cardiovascular disease

1. Ray KK et al. *Glob Heart* 2022;17(1):75; 2. Roth GA et al. *J Am Coll Cardiol* 2020;76(25):2982-3021. 3. Timmis A et al. *Eur Heart J*. 2020;41(1):12-85.

What is a cause of ASCVD?

Lifelong exposure to elevated blood cholesterol carried in lipoproteins



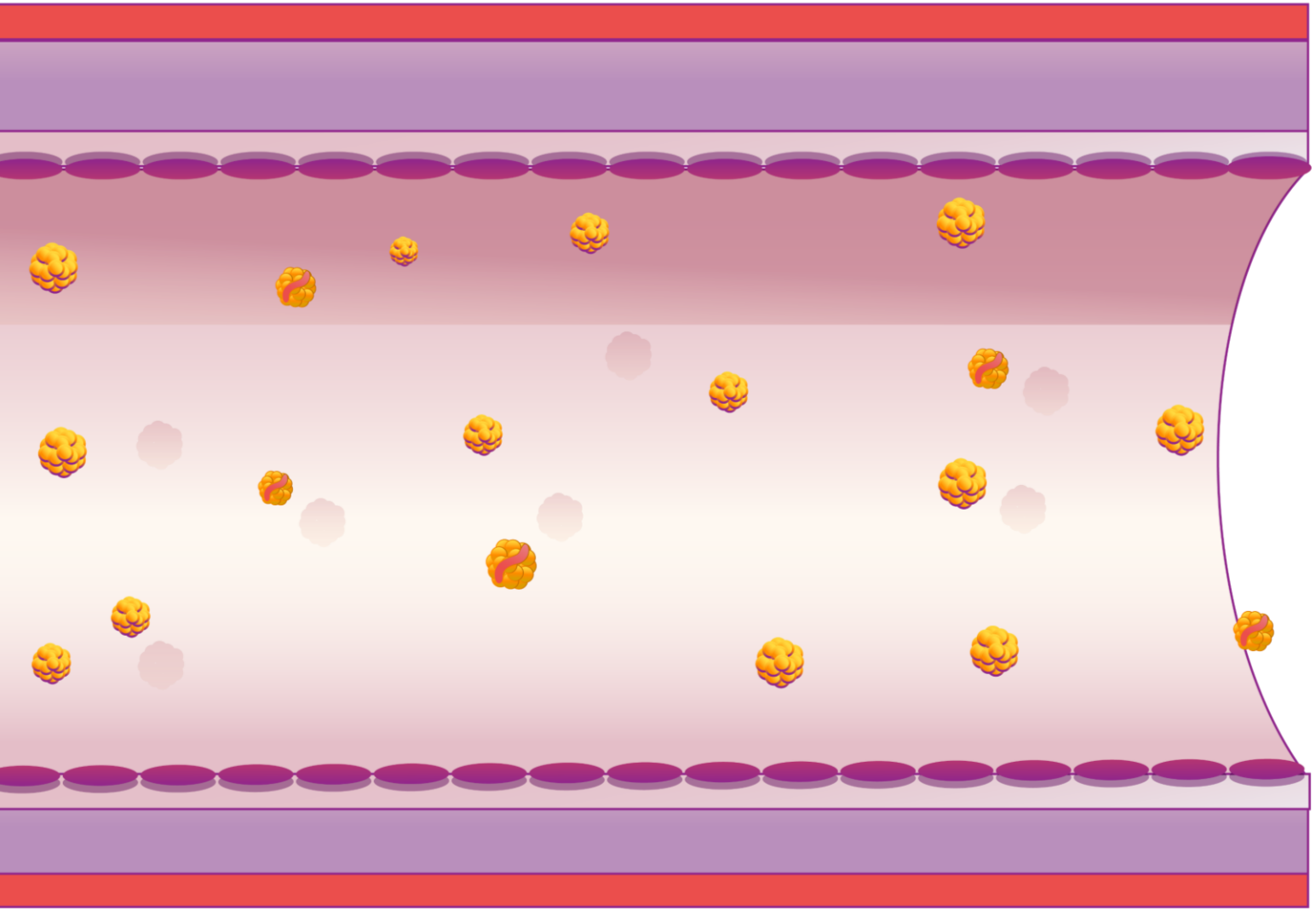


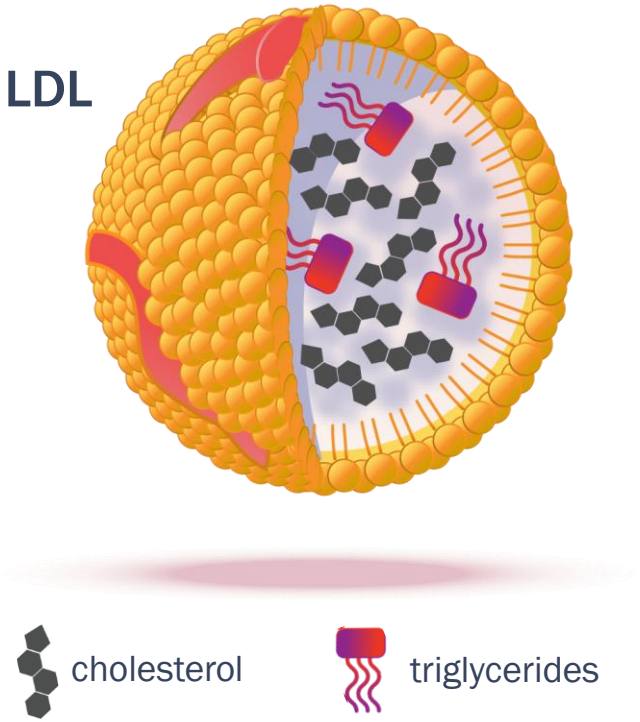
Elevated low-density lipoprotein cholesterol (LDL-C) is a primary cause of ASCVD

apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; LDL, low-density lipoprotein

What is a potential solution to ASCVD?

Keep blood cholesterol as low as possible for as long as possible



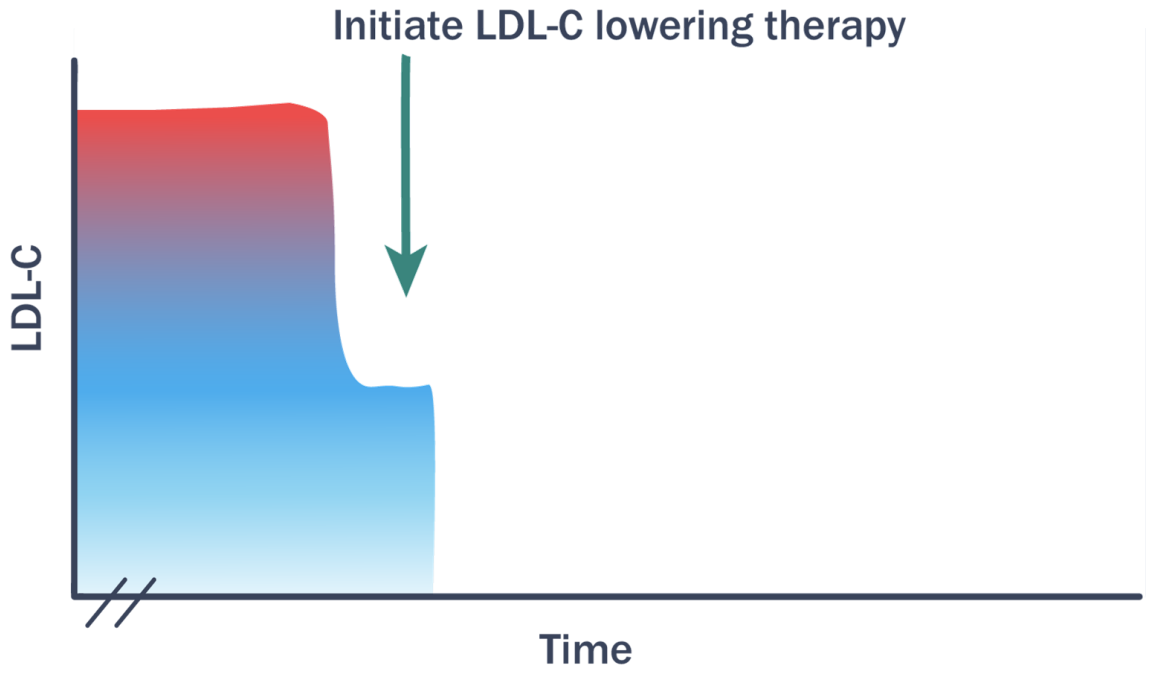


Elevated low-density lipoprotein cholesterol (LDL-C) is a primary cause of ASCVD

ASCVD, atherosclerotic cardiovascular disease; LDL, low-density lipoprotein

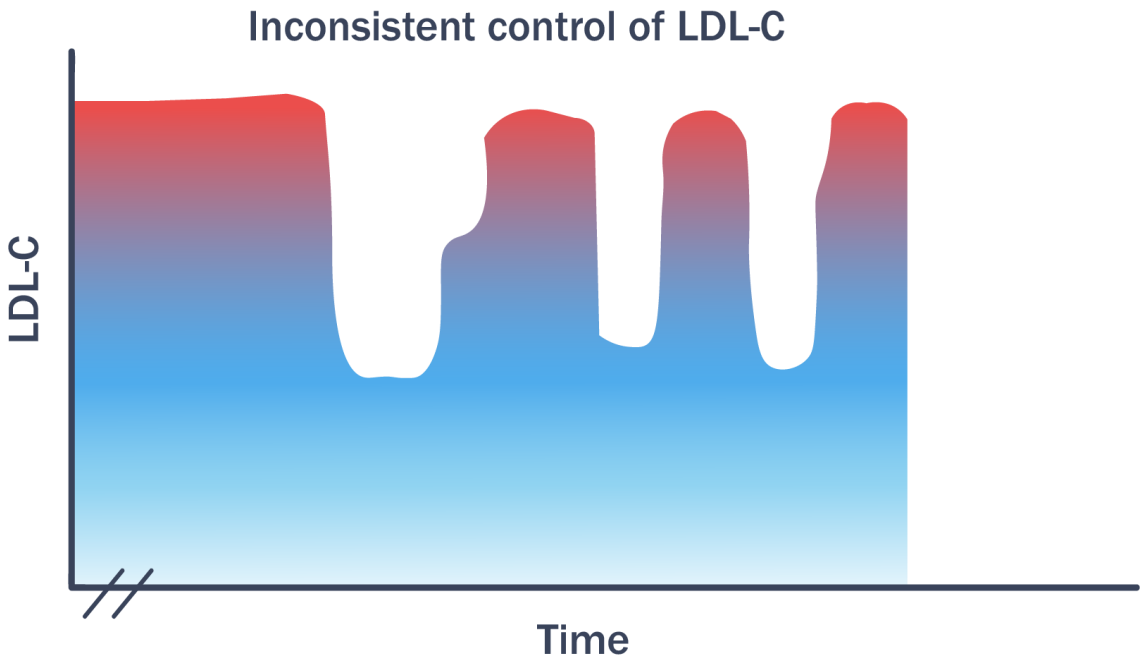
What is the unmet medical need?

Current treatments lower LDL-C by 40–60% but need to be taken lifelong



What is the unmet medical need?

The requirement for decades of chronic therapy leads to very poor real-world LDL-C control



About **50%** of ASCVD patients are **not on a statin**[1]

Only about **2%** of eligible patients are **currently on a PCSK9 agent**[2]

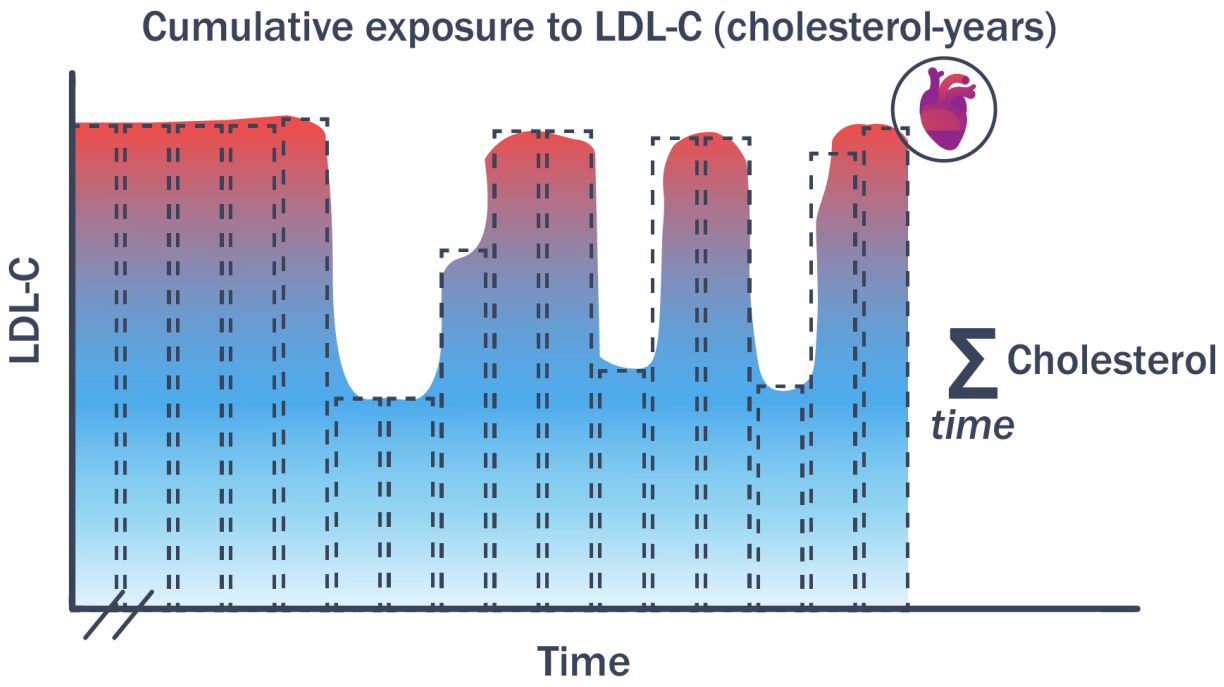
Up to **50%** of patients **discontinue** CVD medications **within 12 months**[3,4]

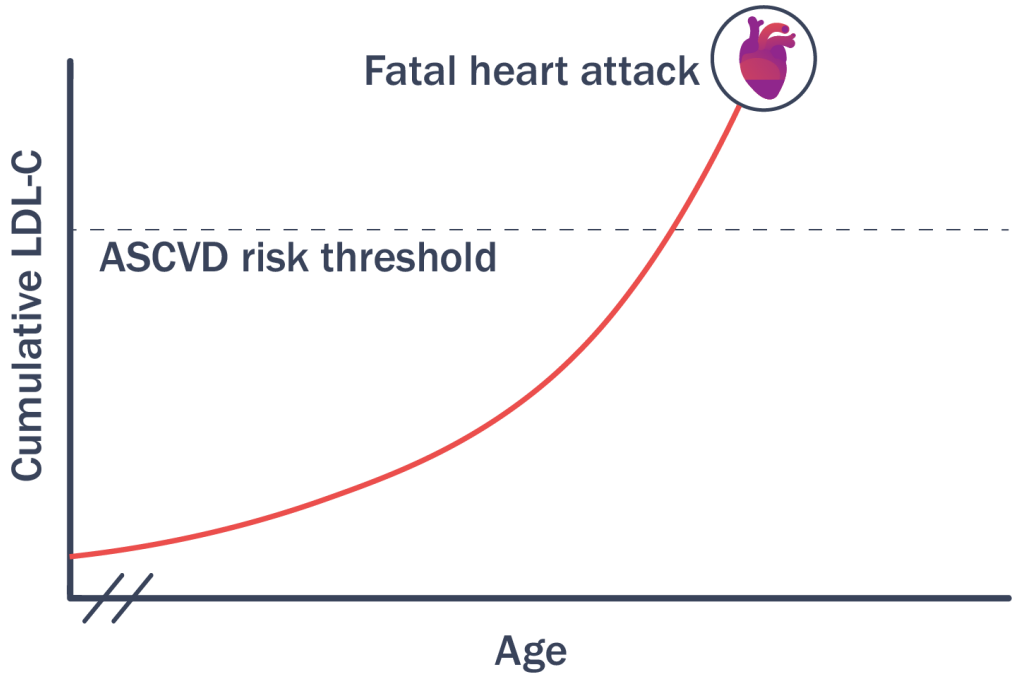
Only **20%** of high & very-high risk European patients **at LDL-C goal**[5]

1. Nelson AJ et al., J Am Coll Card. 2022;79(18):1802–13; 2. Dayoub EJ et al., J Am Heart Assoc. 2021 May 4; 10(9): e019331; 3. Nelson A et al., Nature Reviews Cardiology 2024. https://doi.org/10.1038/s41569-023-00972-1; 4. Naderi SH et al., Am J Med. 2012;125, 882–887.e1; 5. Ray KK et al., The Lancet Regional Health – Europe, Volume 29, 100624.

What is the unmet medical need?

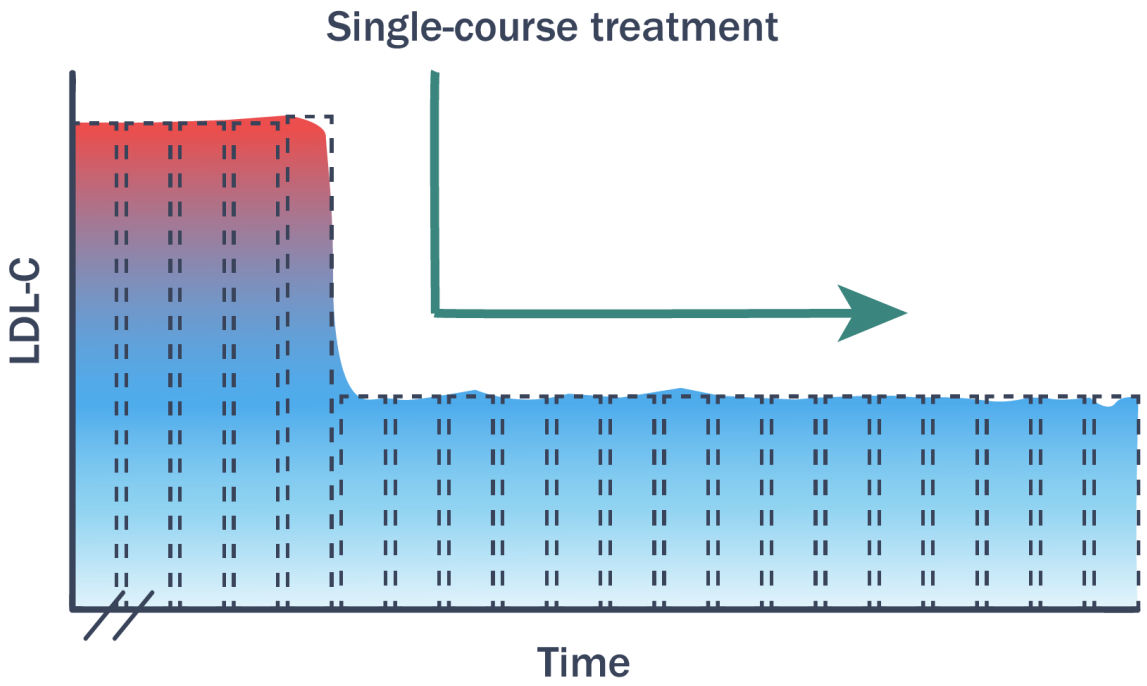
Years of exposure to elevated LDL-C increases the risk for major cardiovascular events

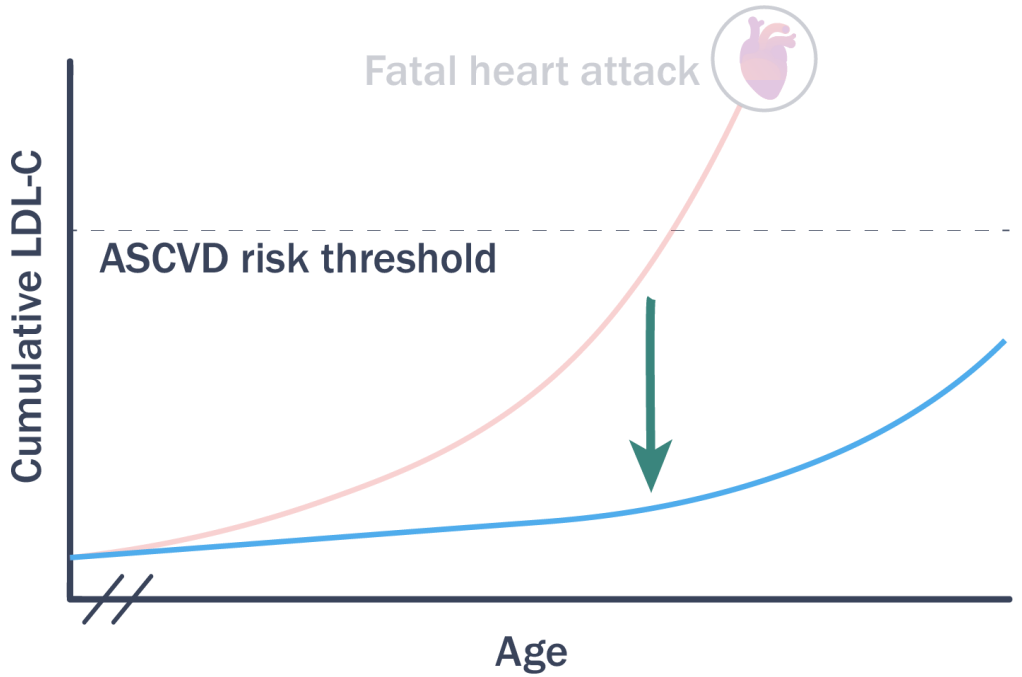




How might we address this unmet need?

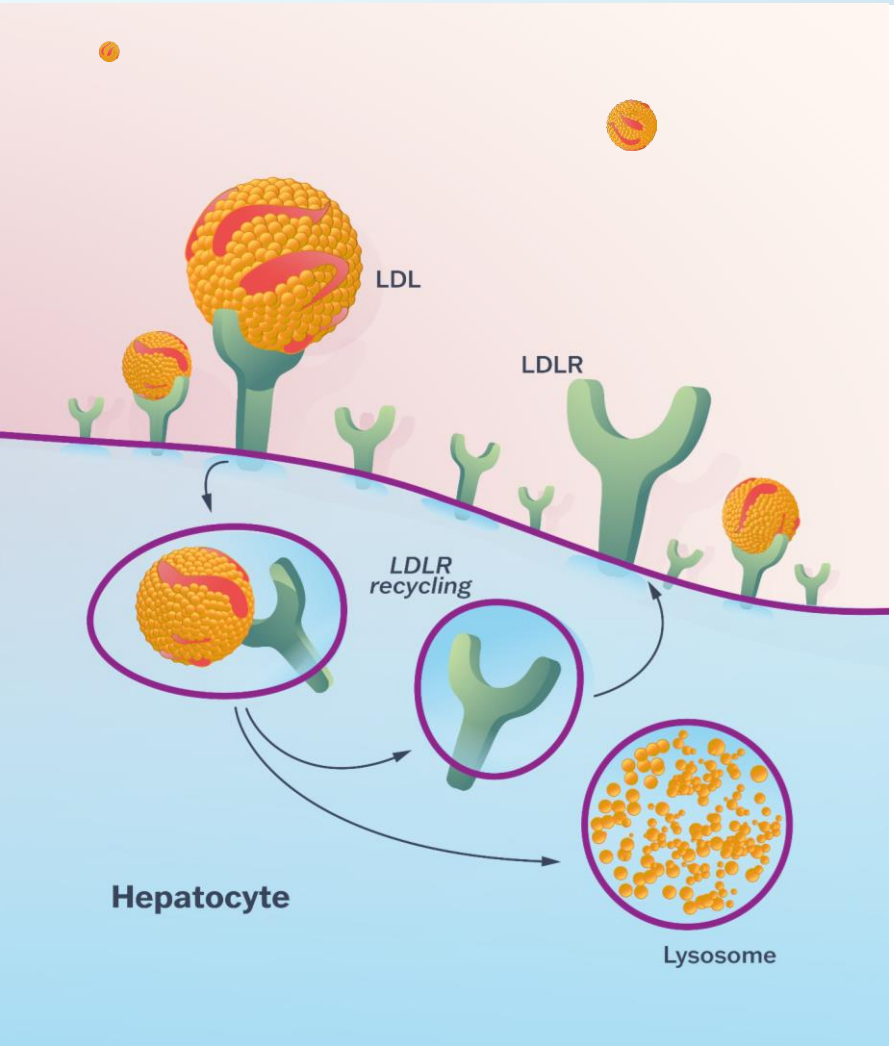
A new treatment approach: one-time procedure, lifelong cholesterol lowering

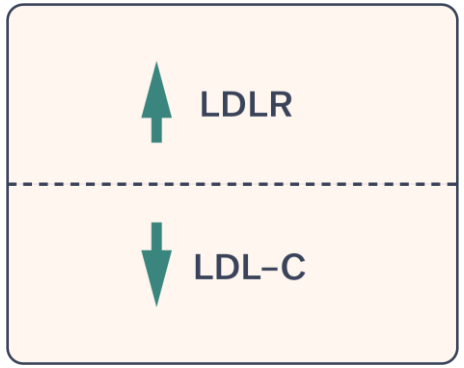




PCSK9 Program

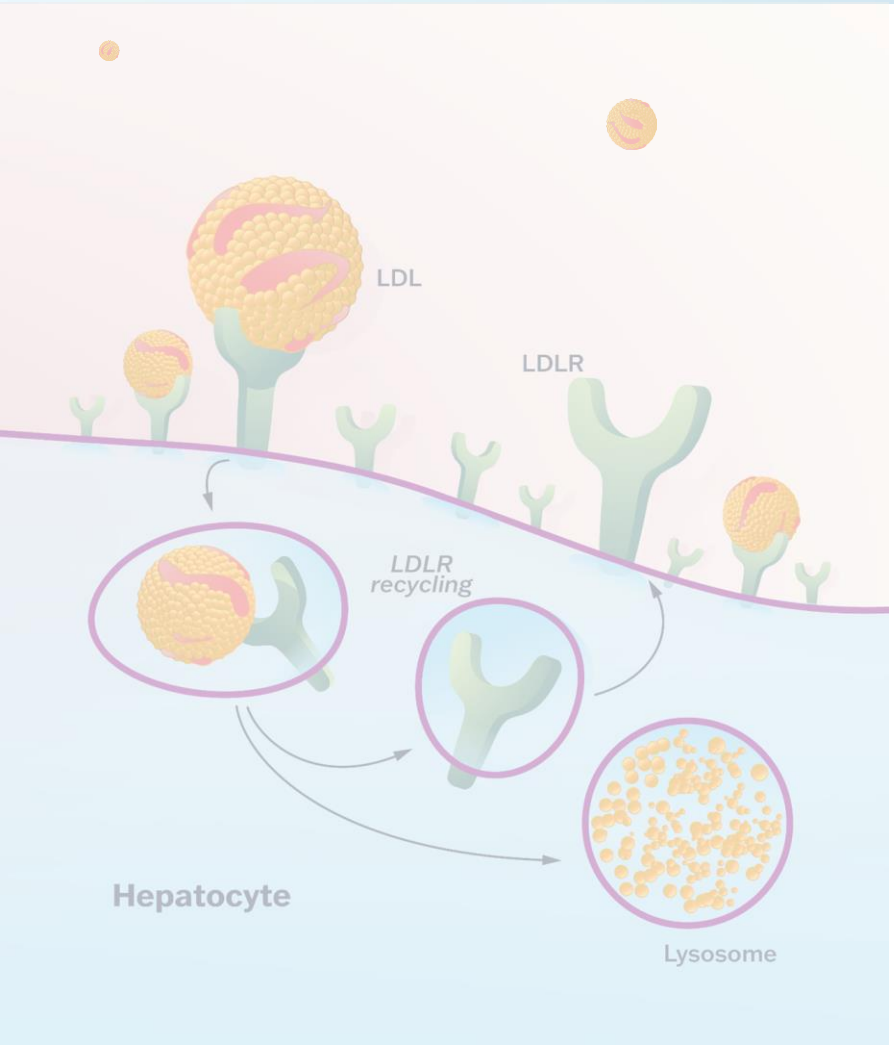
The low-density lipoprotein receptor (LDLR) on the surface of hepatocytes clears LDL-C from circulation

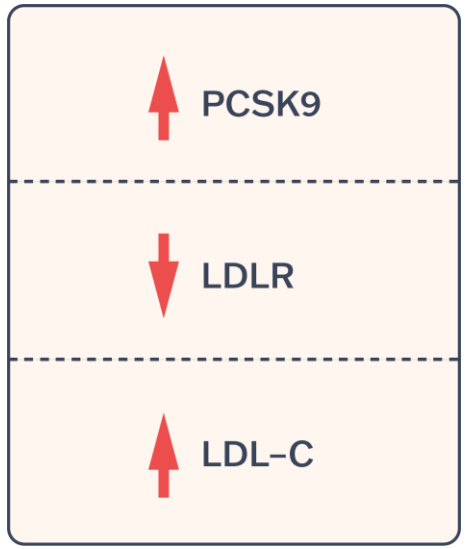




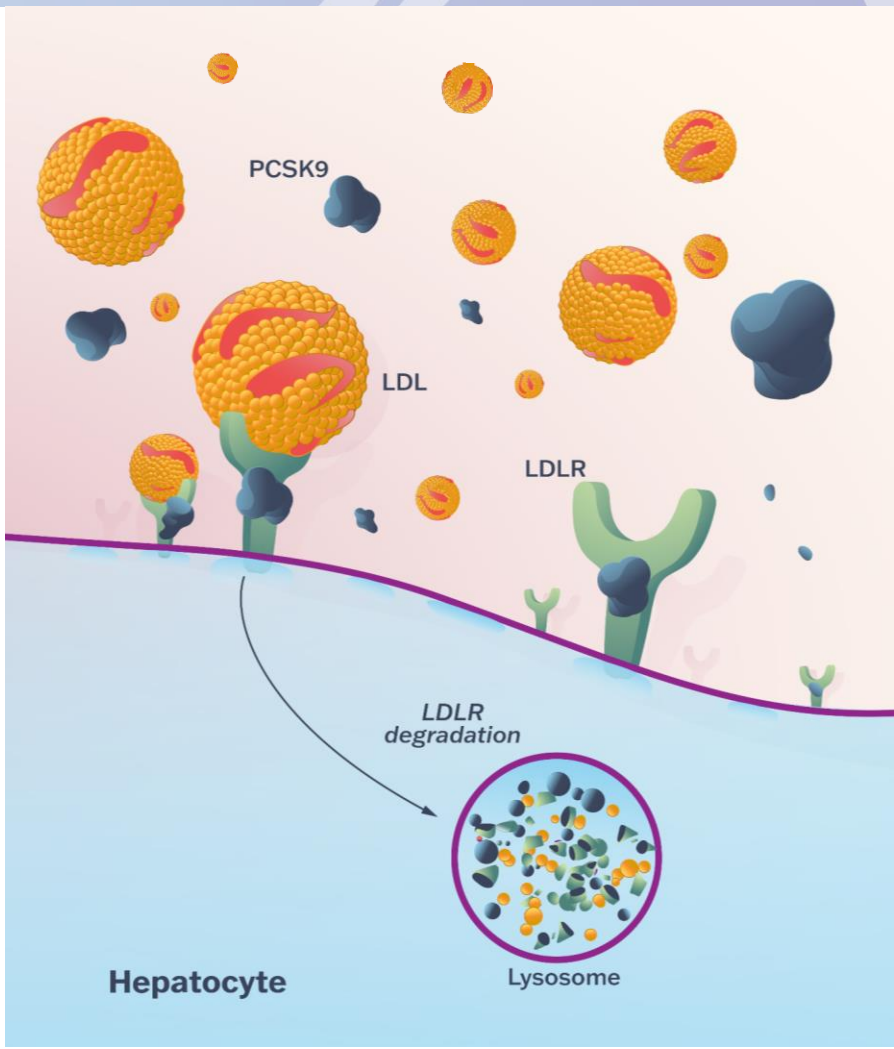
LDLR transports LDL to the lysosome for degradation and can then be recycled to the cell surface

PCSK9 is a protein that promotes LDLR degradation leading to increased levels of LDL-C in the blood





PCSK9 ends the LDLR lifecycle and leads to increased blood LDL-C



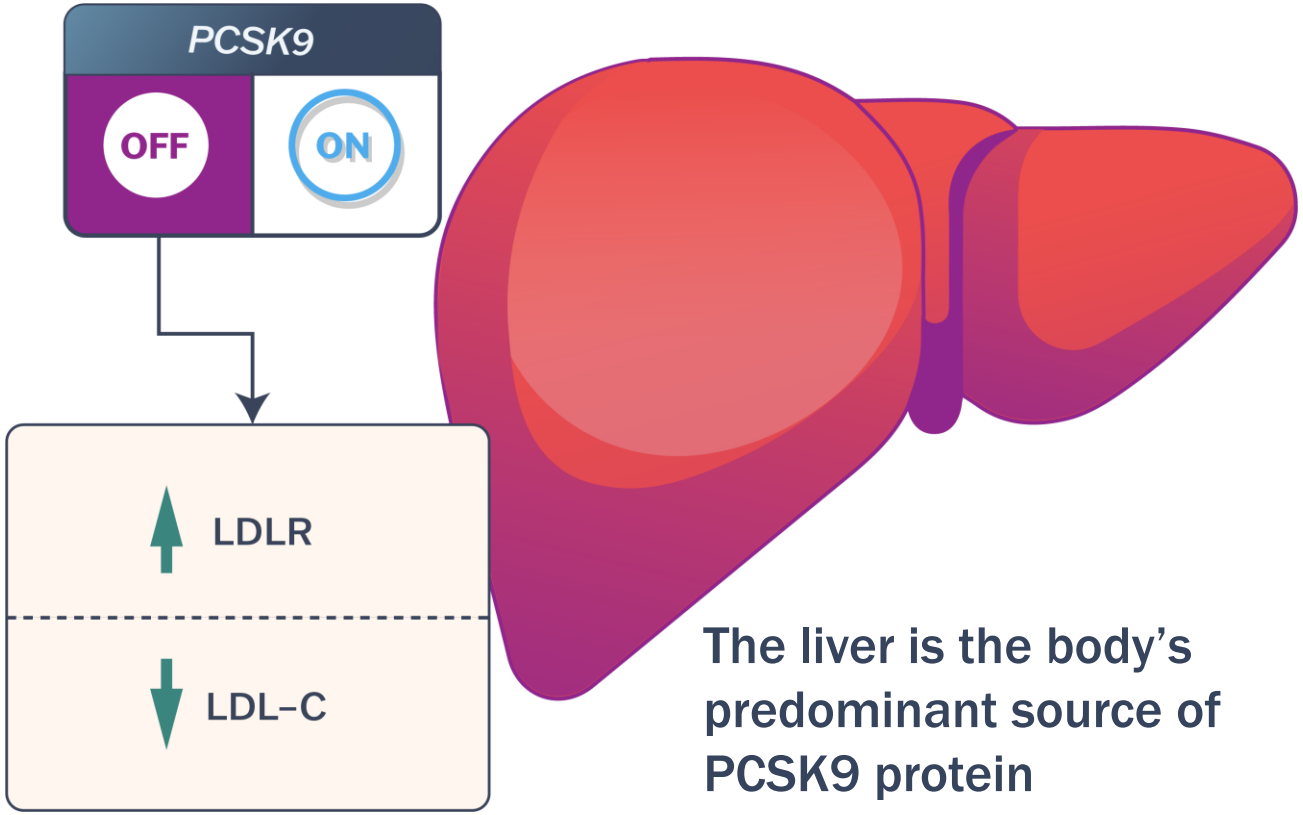
PCSK9, proprotein convertase subtilisin/kexin type 9

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.
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Pharmacologic validation of target

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

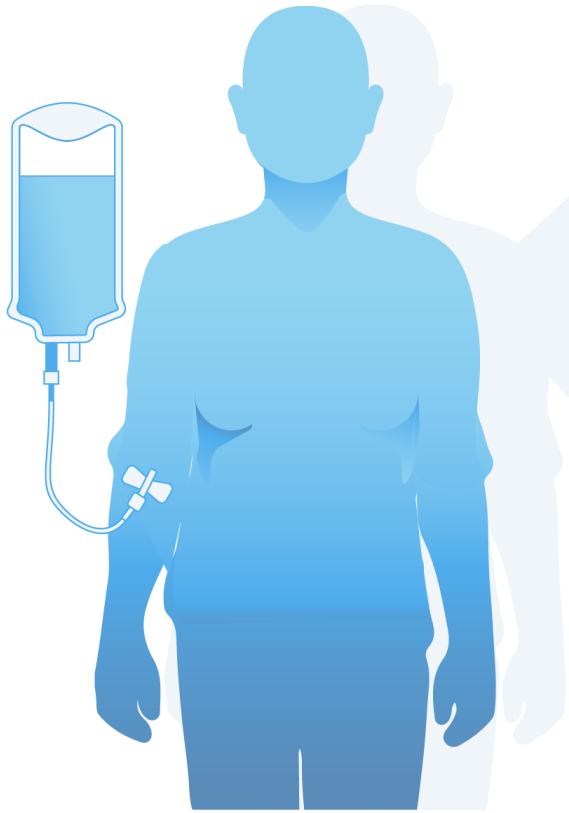
1. Zhao Z, et al. Am J Hum Genet. 2006;79:514-523; 2. Cohen JC, et al. N Eng J Med. 2006;354:1264-1272; 3. Rao AS, et al. Circ Genom Prec Med. 2018;11(7):e002162.
PCSK9, proprotein convertase subtilisin/kexin type 9

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

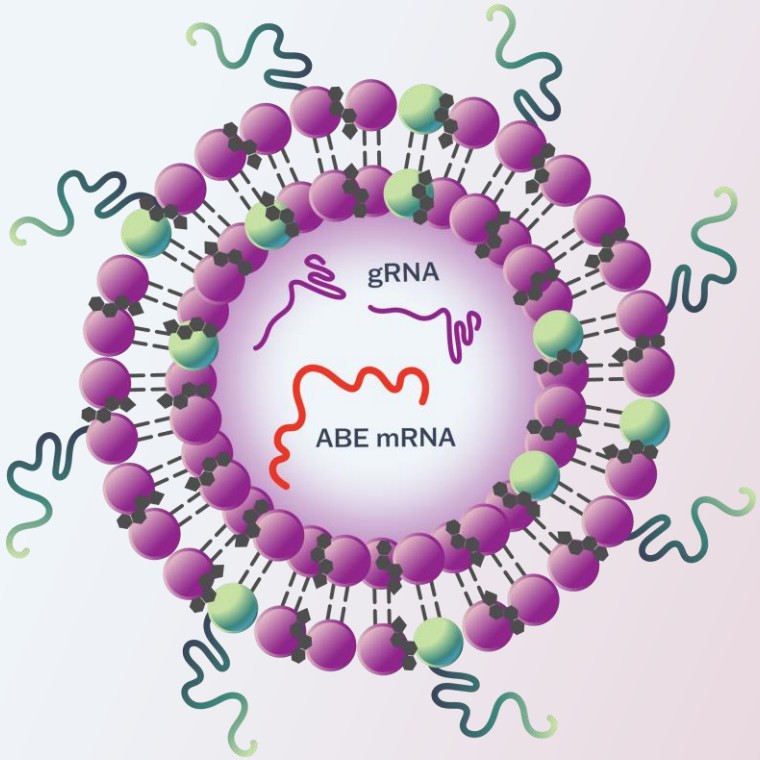
	VERVE-101	VERVE-102
TARGET	*PCSK9* gene	
ADENINE BASE EDITOR (ABE)	Same adenine base editor (ABE) used in both product candidates	
GUIDE RNA	Same guide RNA (gRNA) targeting *PCSK9*	
IONIZABLE LIPID	ALC-0307	LP000001
PEG LIPID	ALC-0159	DMG-PEG$_{2000}$
LIVER-TARGETING LIGAND	—	GalNAc

VERVE-101 consists of an mRNA encoding an adenine base editor and guide RNA targeting *PCSK9* carried in a lipid nanoparticle (LNP)

IV infusion of LNP



VERVE-101 LNP Cross Section

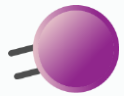


RNA Components

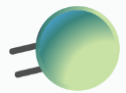
mRNA encoding adenine base editor

Guide RNA targeting *PCSK9*

LNP Components



Ionizable lipid



DSPC

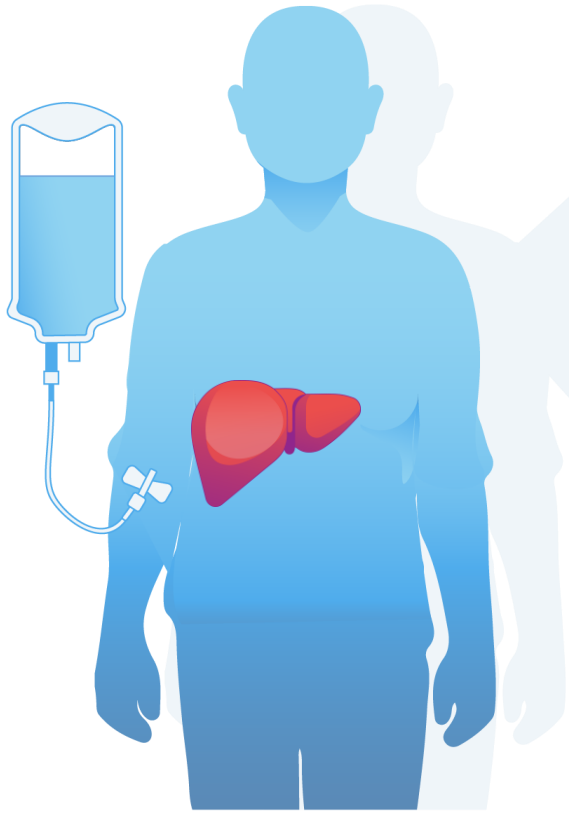
PEG

Cholesterol

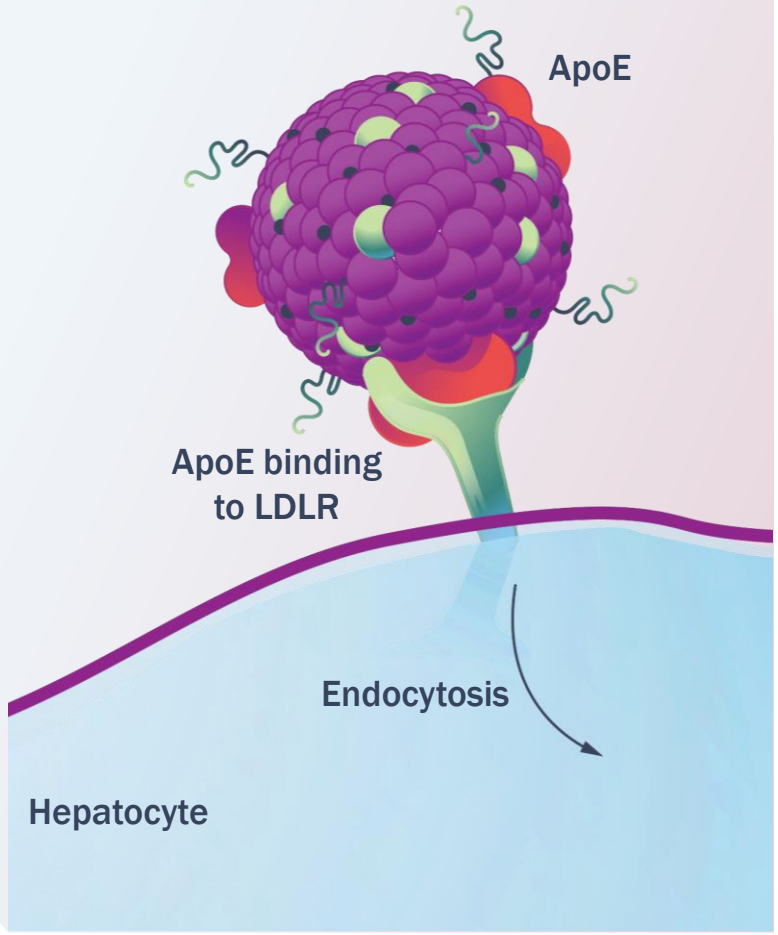
ABE, adenine base editor; DSPC, 1,2-distearoyl-sn-glycero-3-phosphocholine; gRNA, guide RNA; mRNA, messenger RNA; PEG, polyethylene glycol

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

IV infusion of LNP



VERVE-101 LNP Uptake

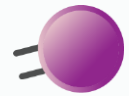


RNA Components

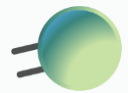
mRNA encoding adenine base editor

Guide RNA targeting *PCSK9*

LNP Components



Ionizable lipid



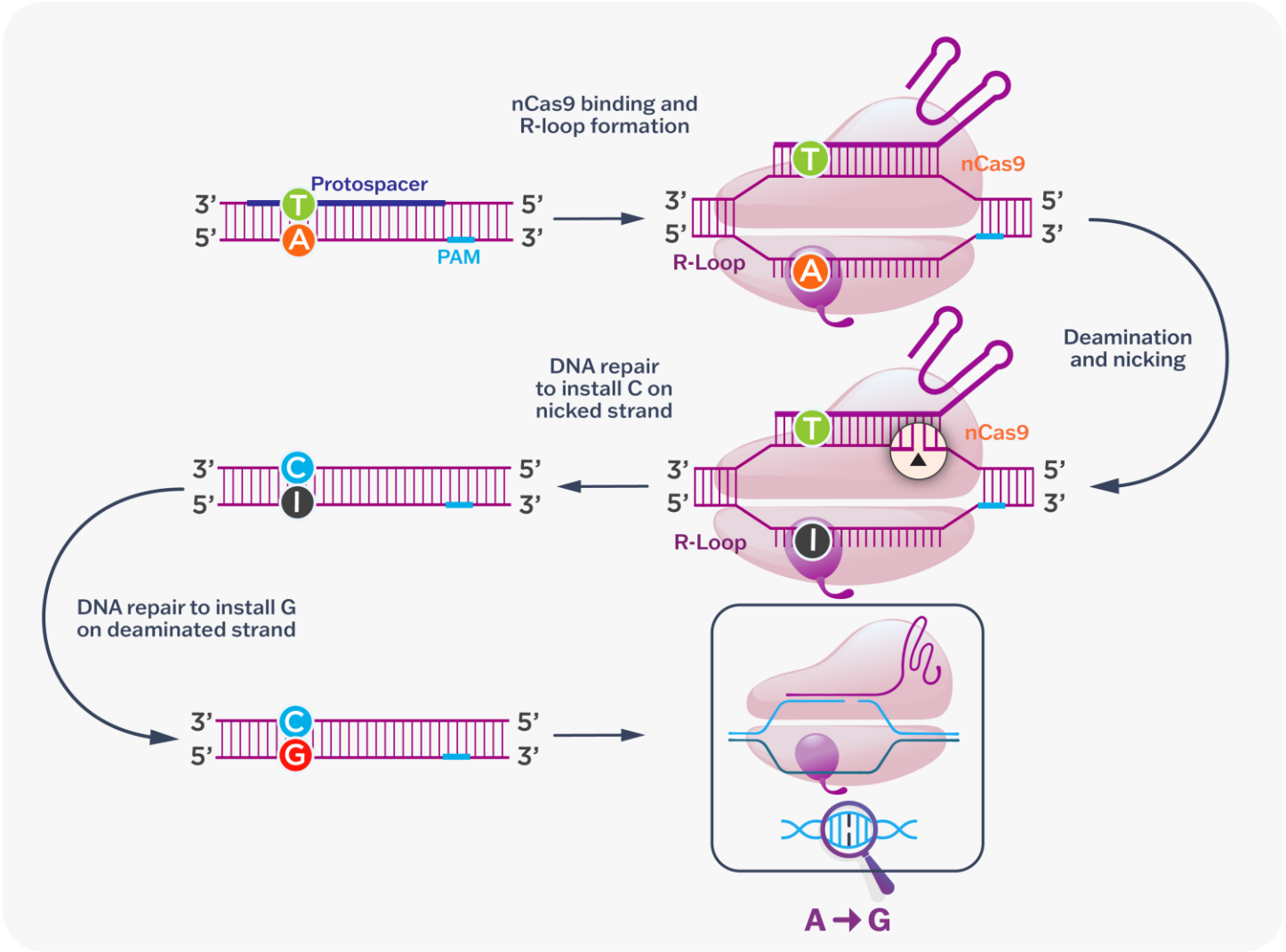
DSPC

PEG

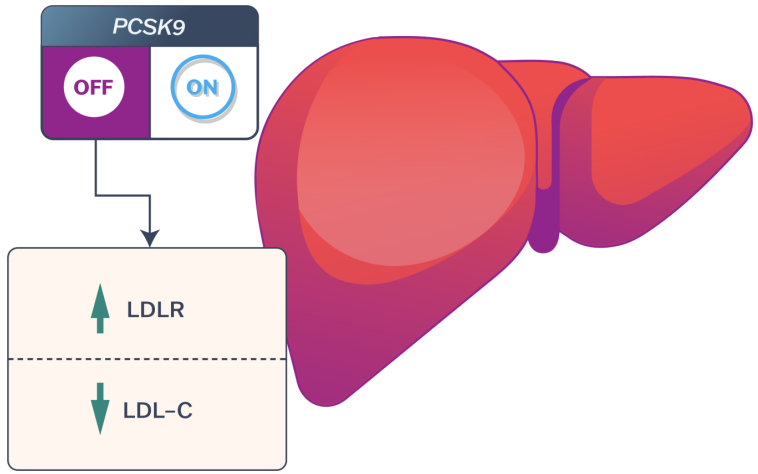
Cholesterol

ApoE, apolipoprotein E

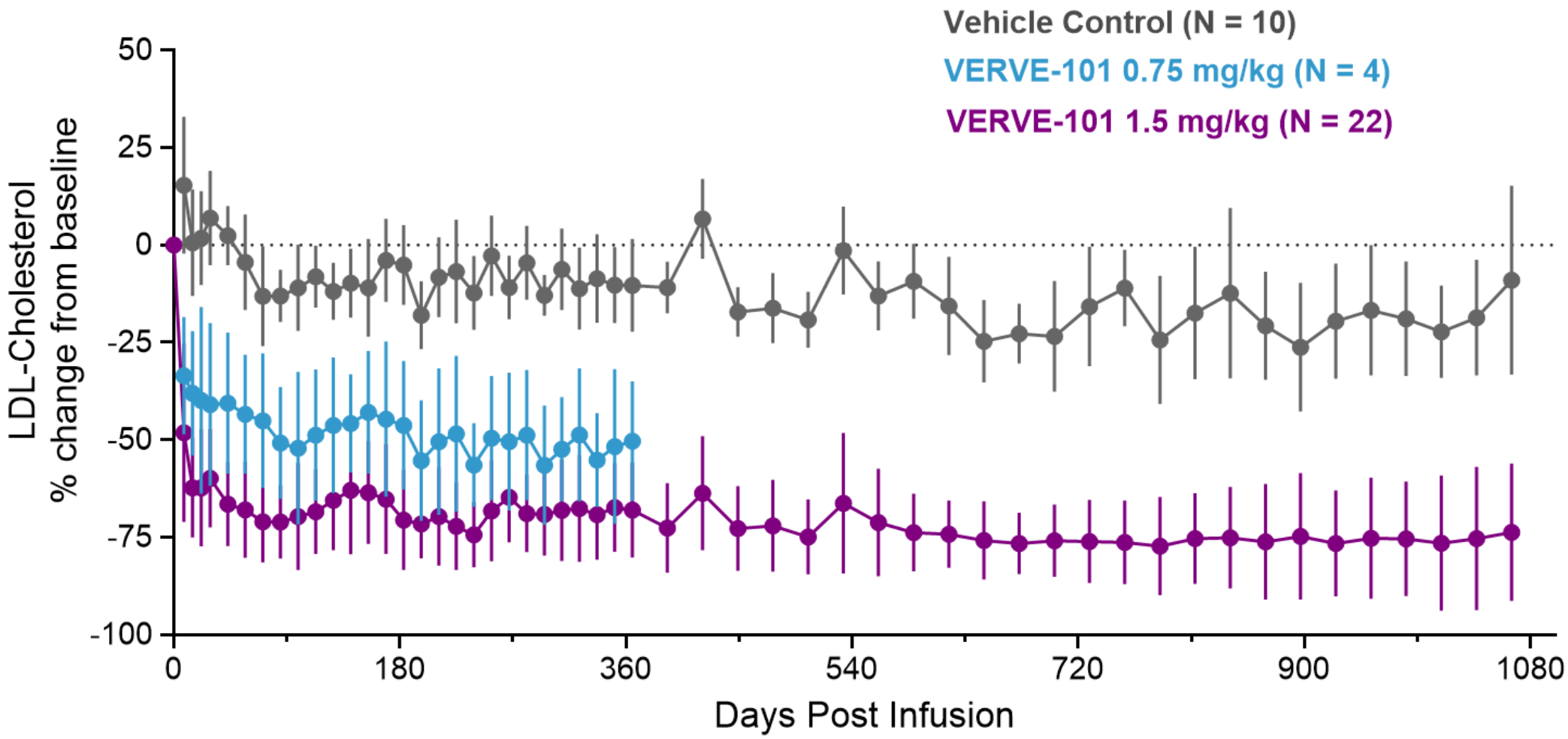
In the hepatocyte the translated ABE pairs with the gRNA to inactivate *PCSK9* with a single base pair change and no double-strand breaks



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

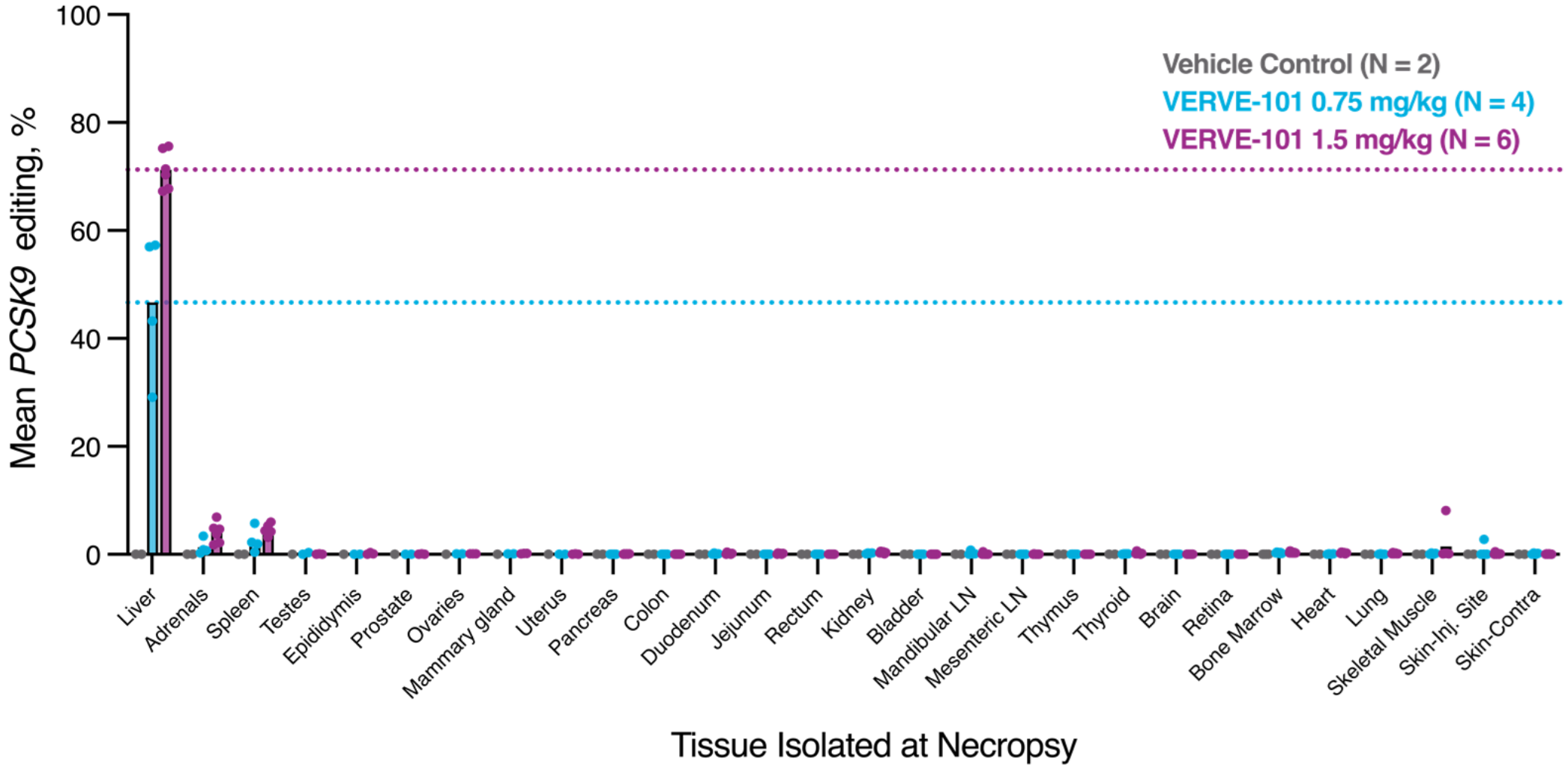


A single infusion of VERVE-101 reduced blood LDL-C for 3 years in NHPs

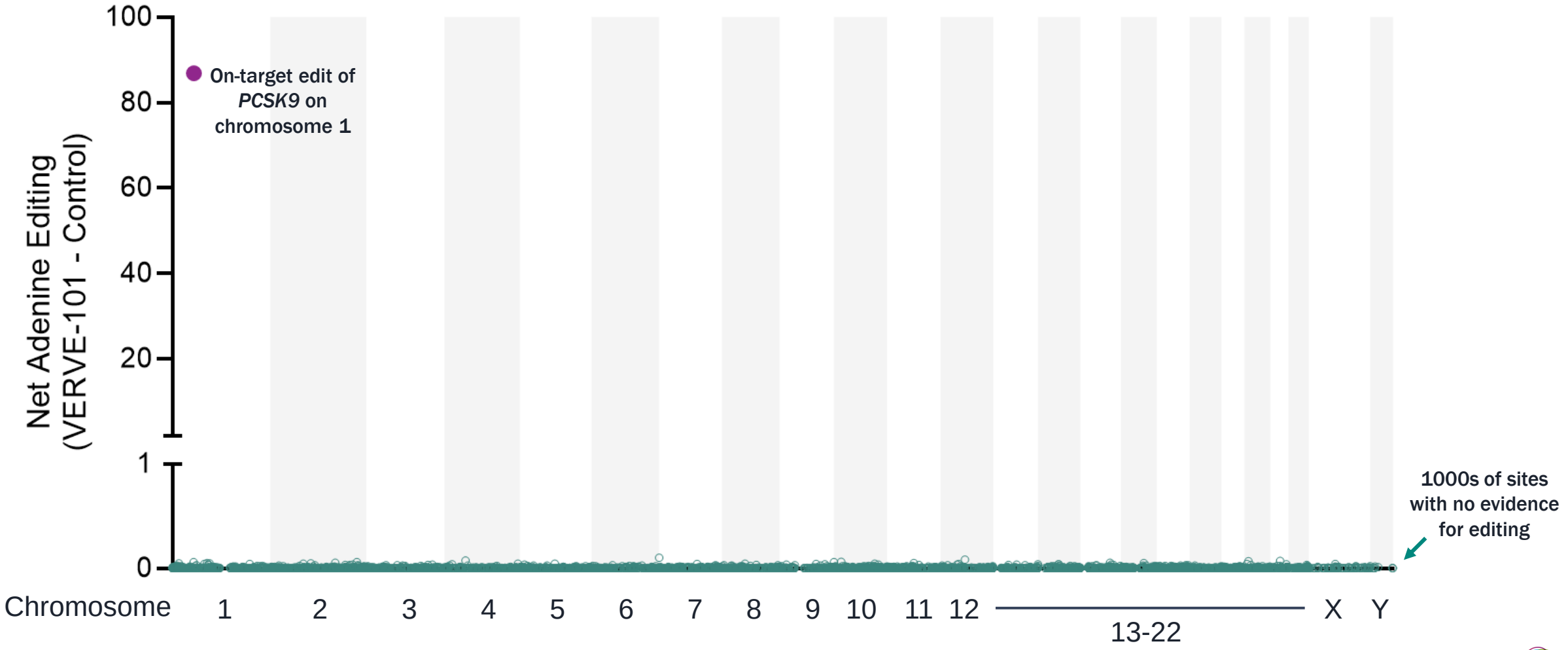


NHP, non-human primate
Data represents mean +/- SD for cohorts which included N=10 in control and N=22 in VERVE-101 at the earliest time points and N=7 and N=16, respectively, at the last time point
Reductions are time-weighted average change from baseline

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.

verve THERAPEUTICS

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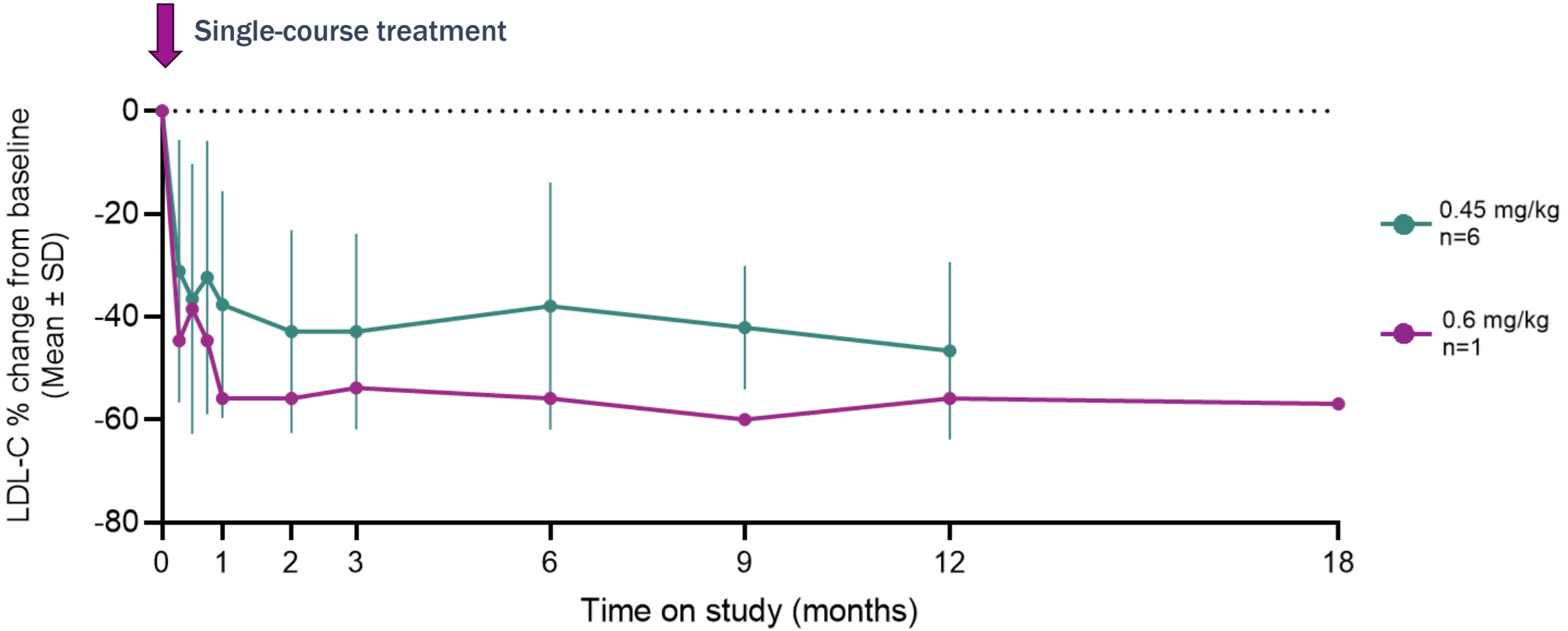
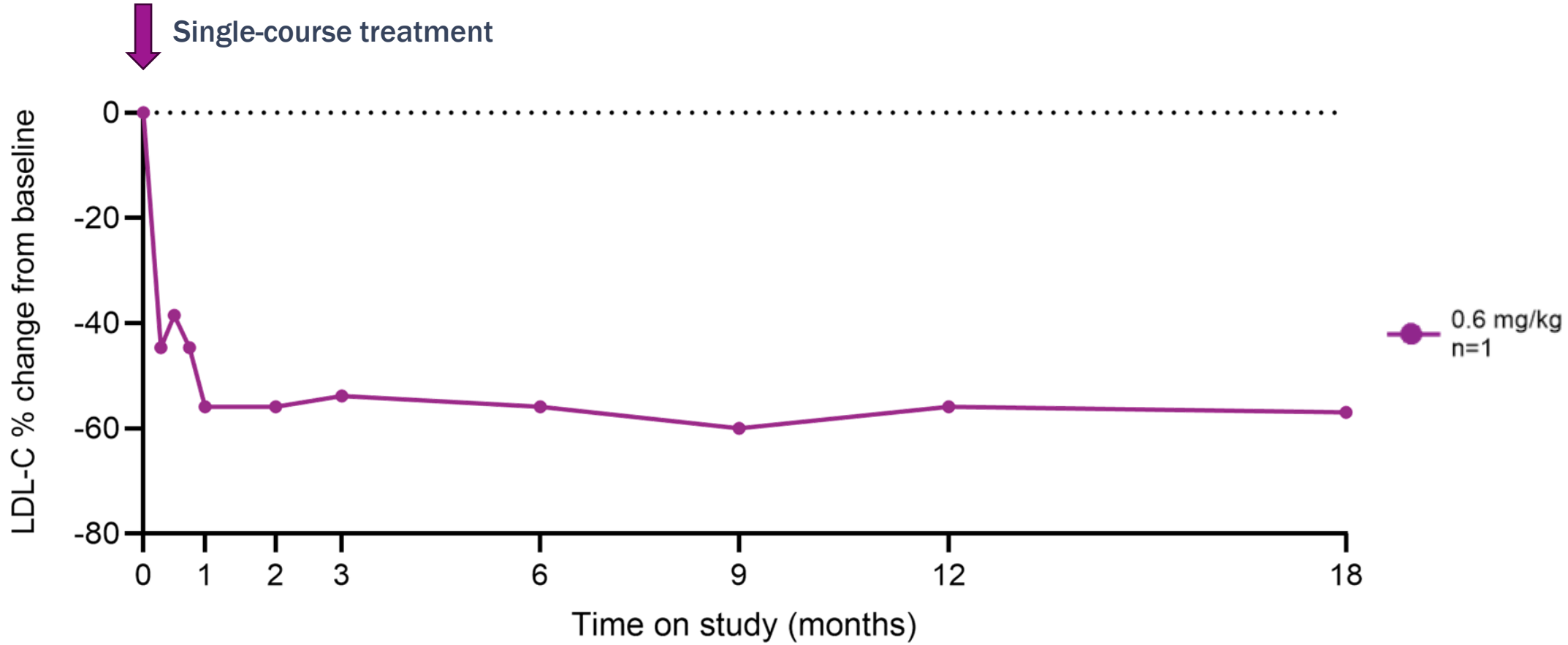
Durability: Evidence for sustained LDL-C reduction following single-course VERVE-101 treatment in two higher dose cohorts



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

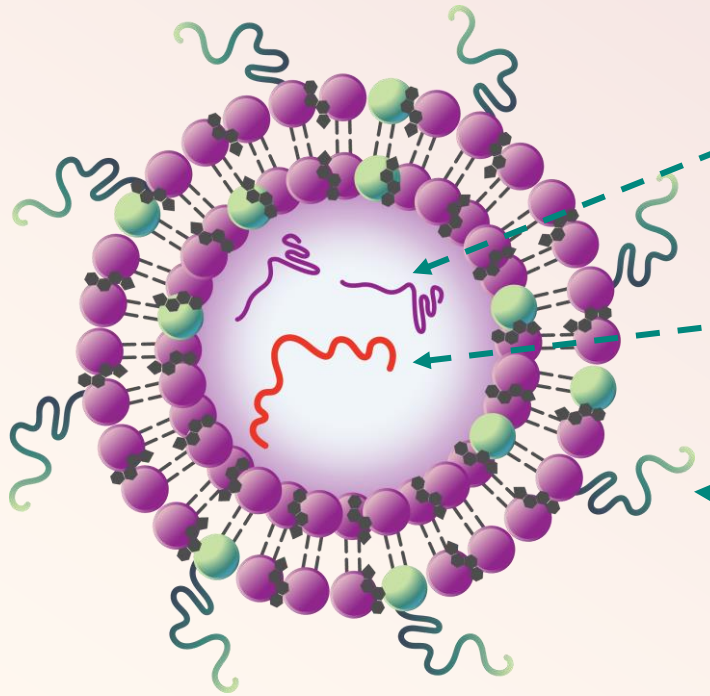
Durability: Proof-of-concept for LDL-C lowering extends to 18 months in participant dosed at 0.6 mg/kg



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 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

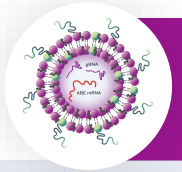
ABE and gRNA edit *PCSK9 in vivo* and durably lower LDL-C

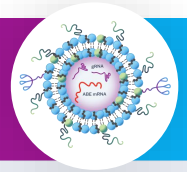
3

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 GalNAc



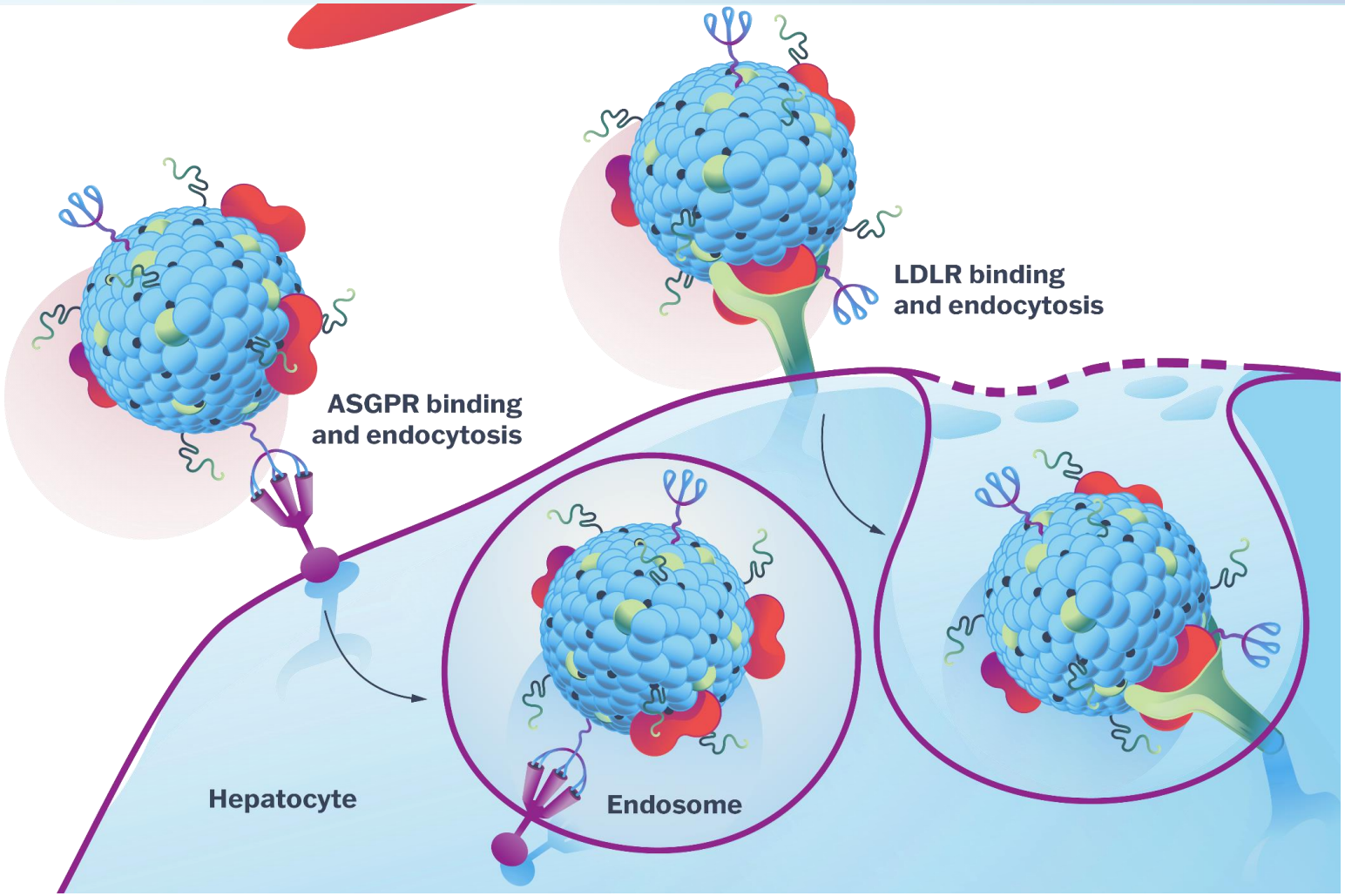


	VERVE-101	VERVE-102
TARGET	*PCSK9* gene	
ADENINE BASE EDITOR (ABE)	Same adenine base editor (ABE) used in both product candidates	
GUIDE RNA	Same guide RNA (gRNA) targeting *PCSK9*	
IONIZABLE LIPID	ALC-0307	LP000001
PEG LIPID	ALC-0159	DMG-PEG$_{2000}$
LIVER-TARGETING LIGAND	—	GalNAc

- 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 the safety, pharmacokinetics and pharmacodynamics of VERVE-102

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

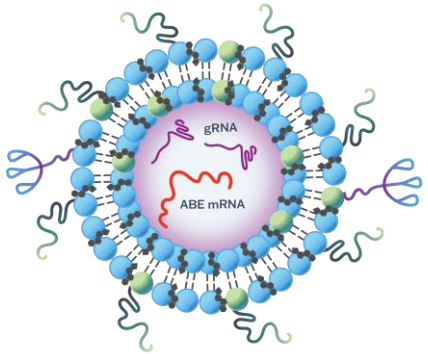
STUDY POPULATION SUMMARY

- 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.

verve THERAPEUTICS

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.

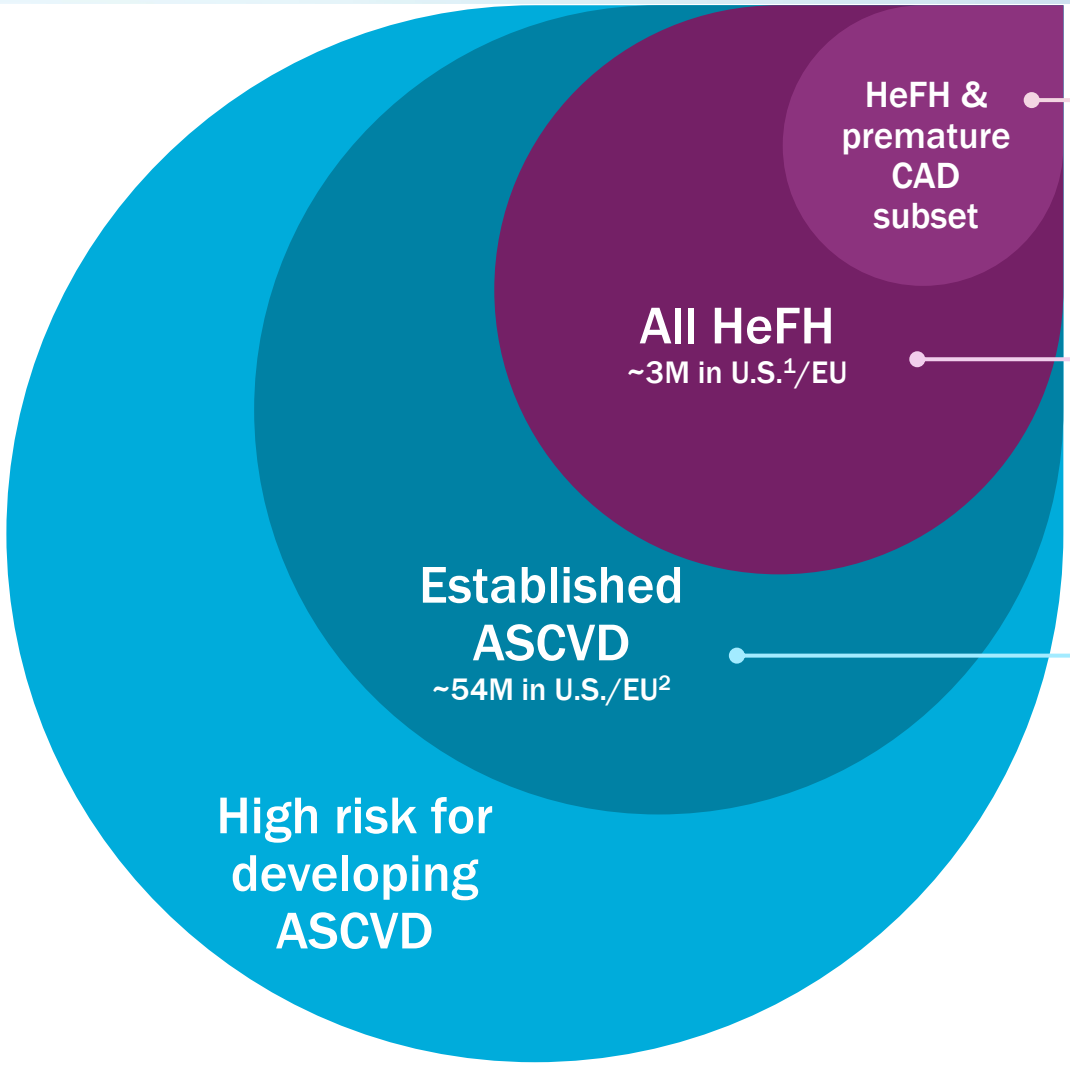
Heart-2 trial currently enrolling patients

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)

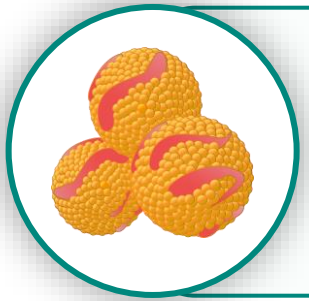
- Pivotal Phase 3 in ASCVD (LDL-C endpoint)
- Potential cardiovascular outcome study in ASCVD

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

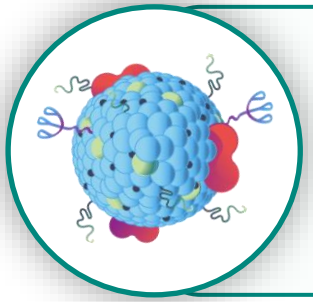
Clinical development strategy subject to alignment with regulators

What factors may support expansion of gene editing technology to larger and larger groups of people with cardiovascular disease?



LDL-C is an accepted surrogate endpoint for improved clinical outcomes

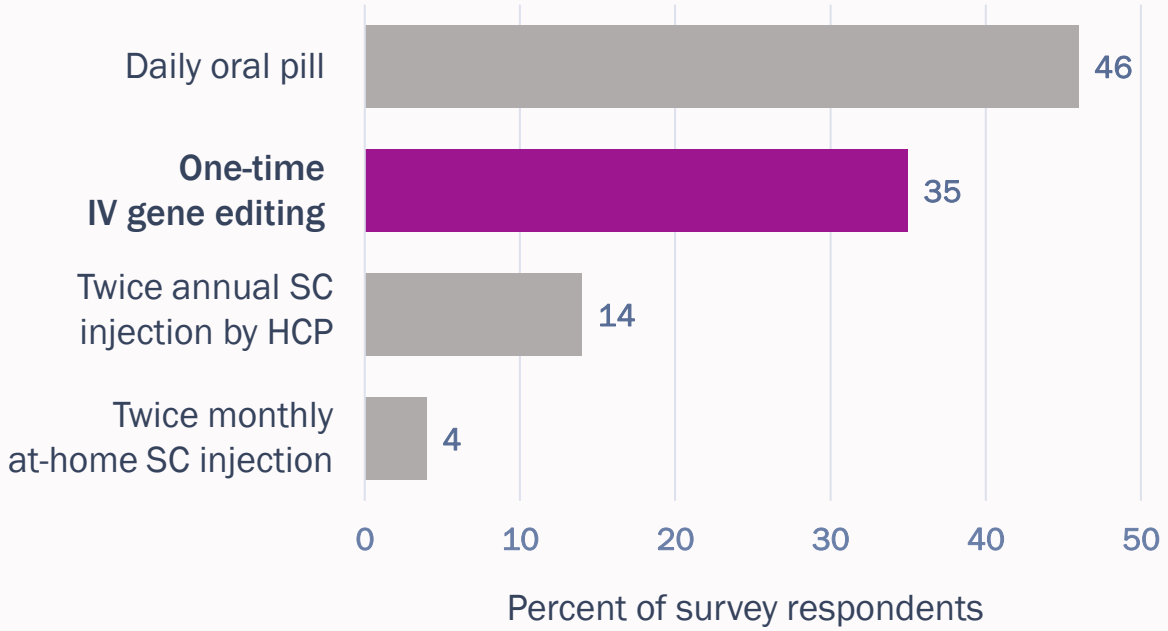
Selection of gene editing targets, such as *PCSK9* and *ANGPTL3*, that have human genetic and pharmacologic validation



Potential to efficiently manufacture LNPs carrying RNA at large scale

Patients are receptive

Which therapeutic approach is most appealing for life-long treatment of high cholesterol or cardiovascular disease?



Source: Morning Consult Poll, April 2023.

HCP, healthcare provider; IV, intravenous; SC, subcutaneous

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