Developing ‘once-and-done’ gene editing medicines to treat cardiovascular disease

Sekar Kathiresan, MD
Co-founder and CEO, Verve Therapeutics

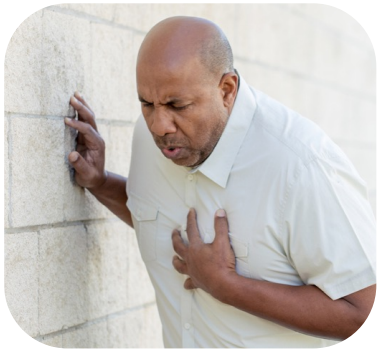
ESC Cardiovascular Round Table
February 1, 2024

Atherosclerotic cardiovascular disease (ASCVD): #1 cause of death worldwide despite available treatments

One person

dies every 34 seconds

from cardiovascular disease in the U.S.[1]



100s of millions

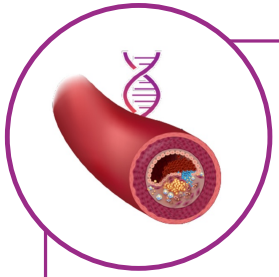
of patients worldwide

~800K heart attacks

per year in the U.S.[2]

1. Centers for Disease Control and Prevention, National Center for Health Statistics. About Multiple Cause of Death, 1999-2020. CDC WONDER Online Database website. Atlanta, GA: , Accessed February 21, 2022.
2. Tsao CW et al. *Circulation.* 2022;145(8):e153–e639

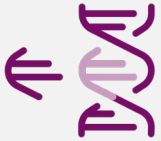
What causes ASCVD?



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

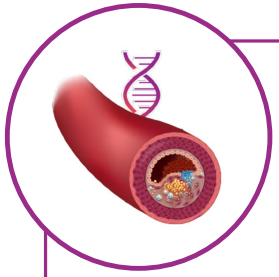
Cholesterol carried in 3 lipoproteins:

Heterozygous familial hypercholesterolemia (FH): a serious, inherited subtype of ASCVD with high LDL-C from birth & heart attack at early ages

American Heart Association Diagnostic Criteria				
High LDL-C + Family history (of high LDL-C or premature ASCVD)	Monogenic or polygenic	≥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

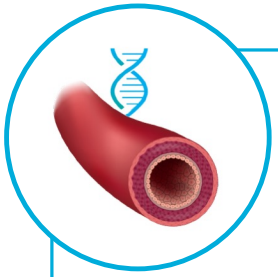
What's a solution to ASCVD?



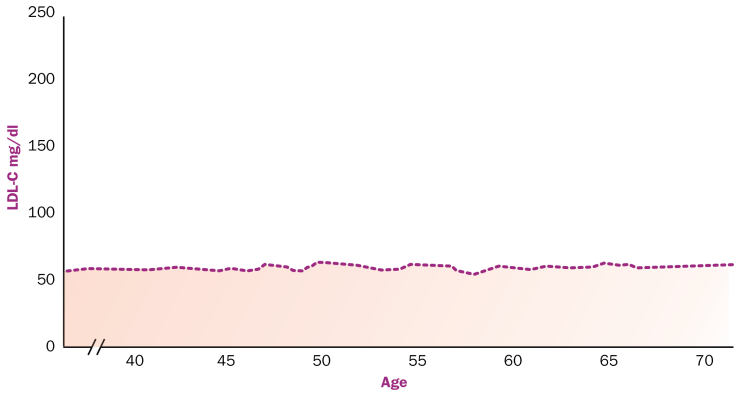
High cumulative life-long exposure to blood cholesterol clogs heart arteries

Cholesterol carried in 3 lipoproteins:

Cholesterol Triglycerides



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



Individuals who naturally lack ANGPTL3 gene: lifelong low blood LDL-C & TG, 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

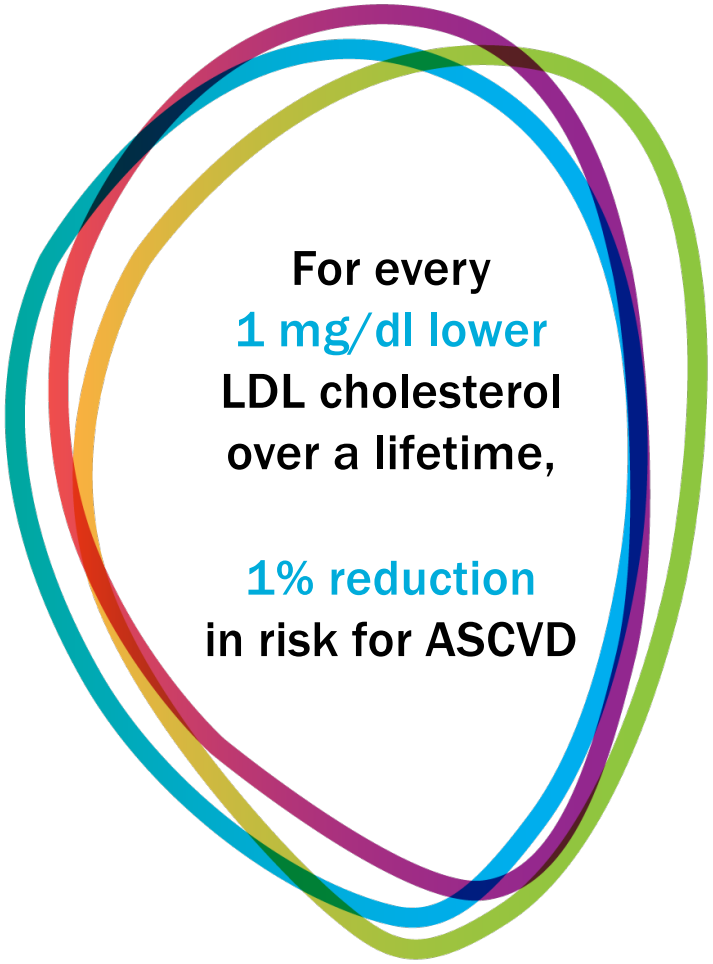
verve THERAPEUTICS

There are people walking around who are naturally resistant to ASCVD, have PCSK9 gene switched off

~50 mg/dl lower LDL cholesterol in blood

~50% lower risk for ASCVD

Healthy


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

What if we developed a medicine that mimicked resistance mutations?

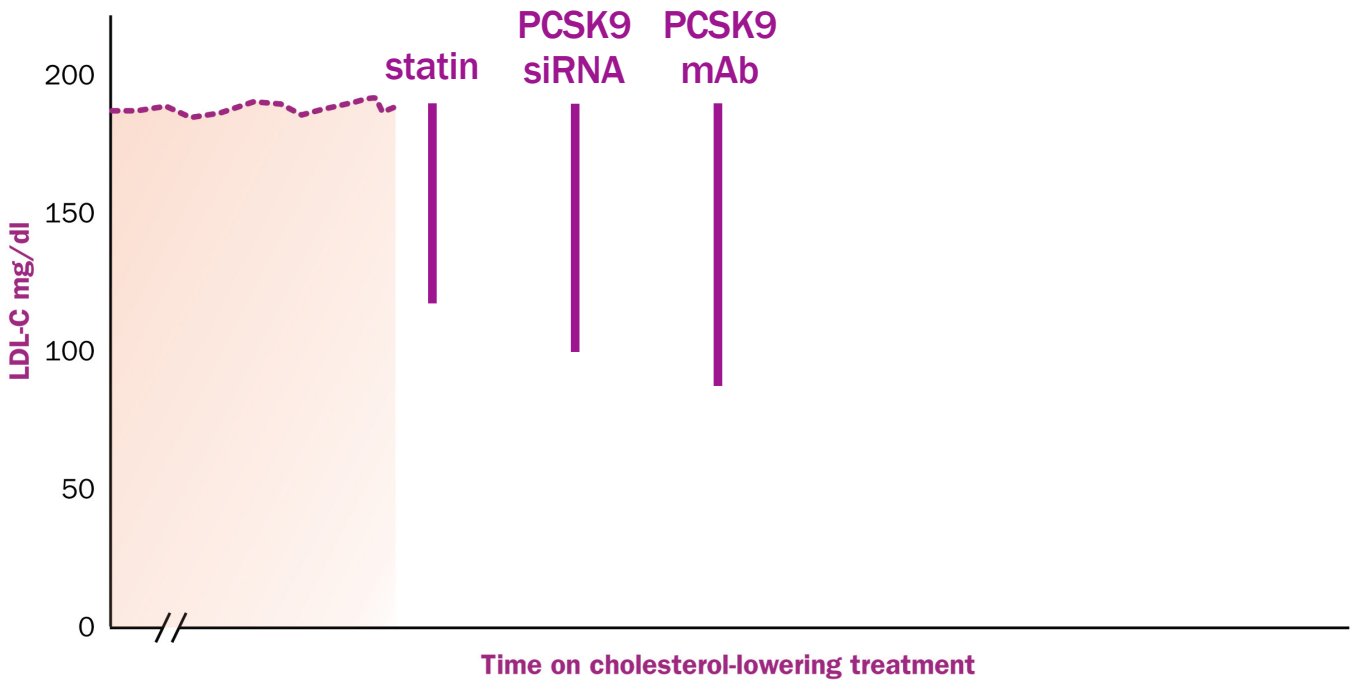
~50 mg/dl lower LDL cholesterol in blood

~50% lower risk for ASCVD

Healthy

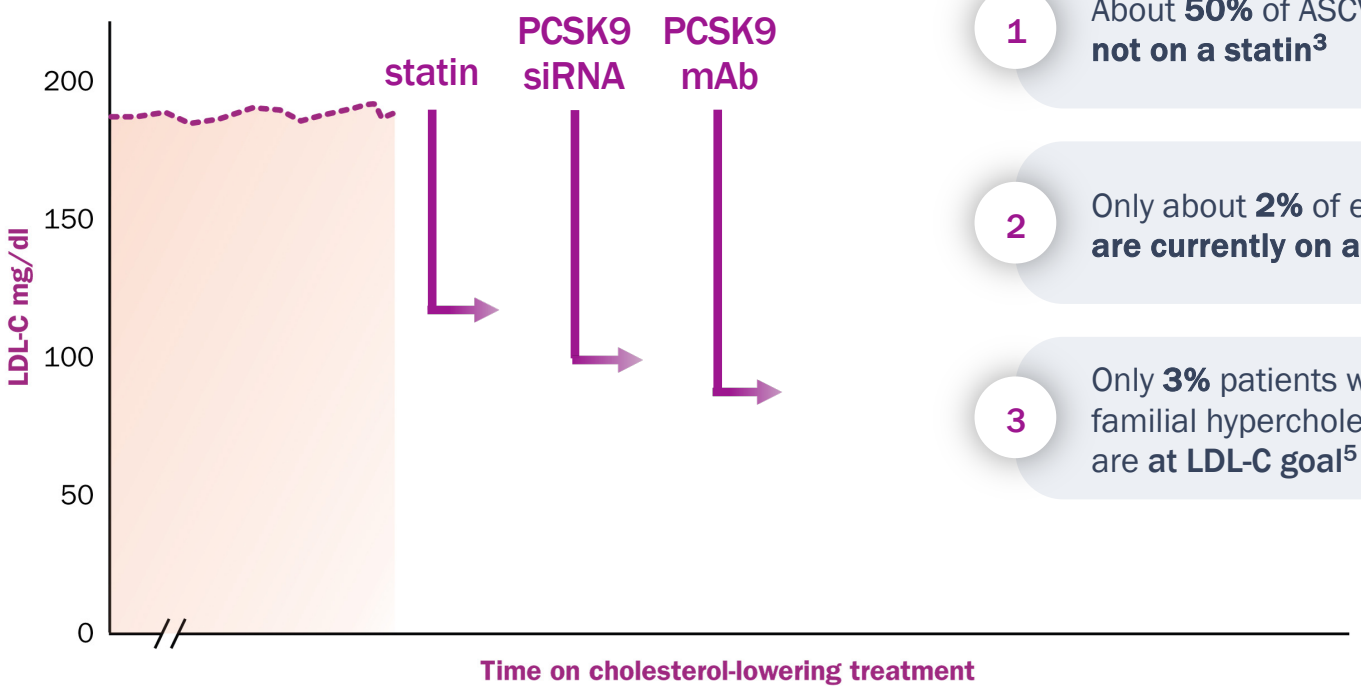
How is ASCVD treated today and is there an unmet need?

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]

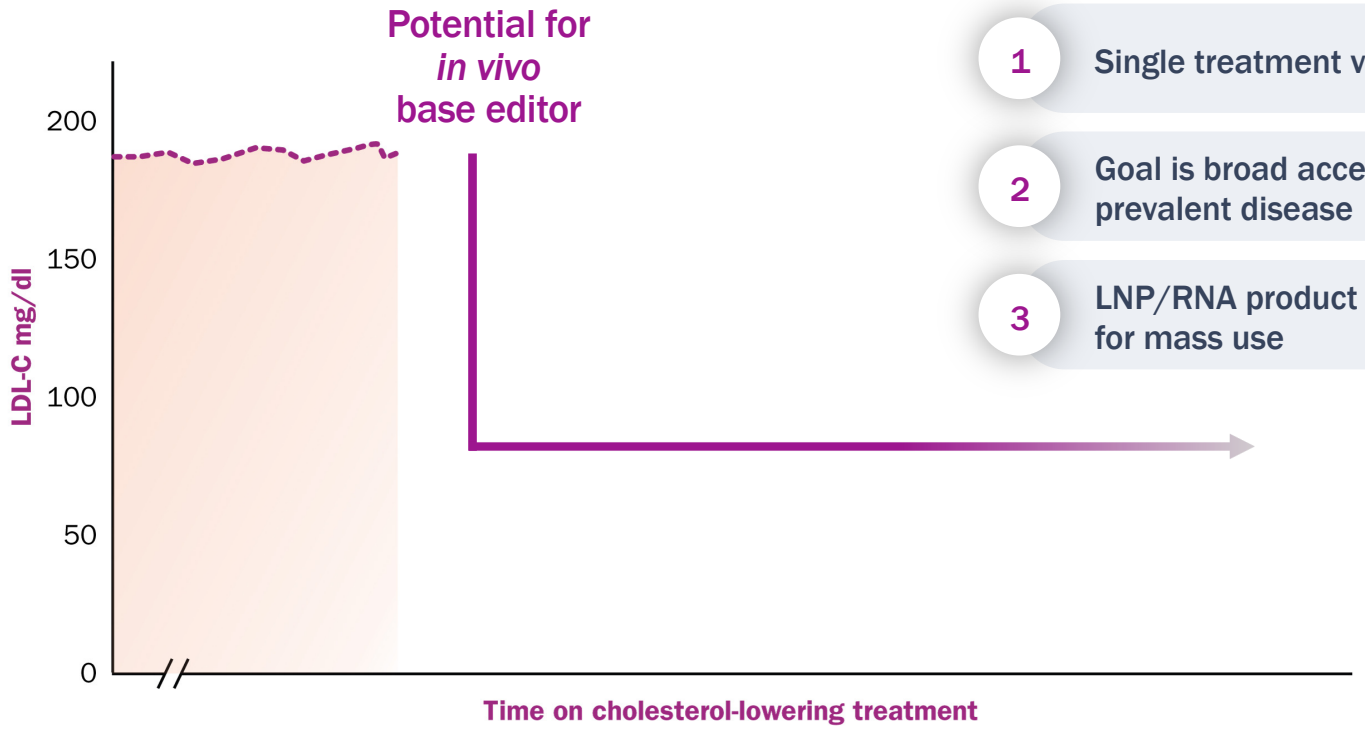
Unmet need: for many, real-world LDL-C lowering is close to zero



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%** 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

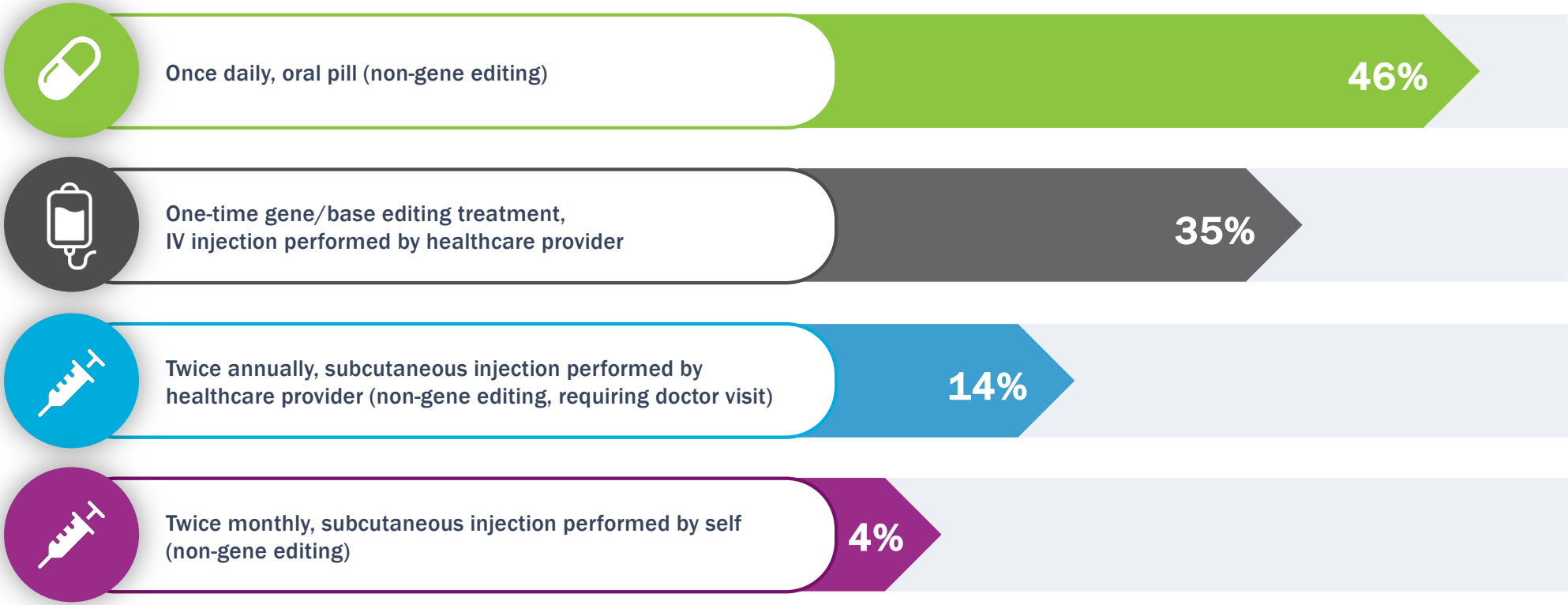


Differentiation:

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

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

Can we transform care of ASCVD from daily pills or intermittent injections over decades to a “one-time procedure”?

verve™ THERAPEUTICS

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

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

DRUG SUBSTANCES

RNA components encode base editor and a guide targeting *PCSK9* gene

- mRNA for adenine base editor
- gRNA localizes editor to *PCSK9* gene

+

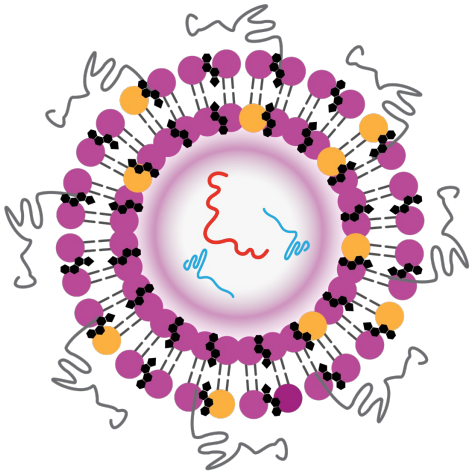
DELIVERY VEHICLE

LNP for delivery to liver cell includes 4 components

- Ionizable amino lipid (Acuitas)
- DSPC
- Cholesterol
- PEG

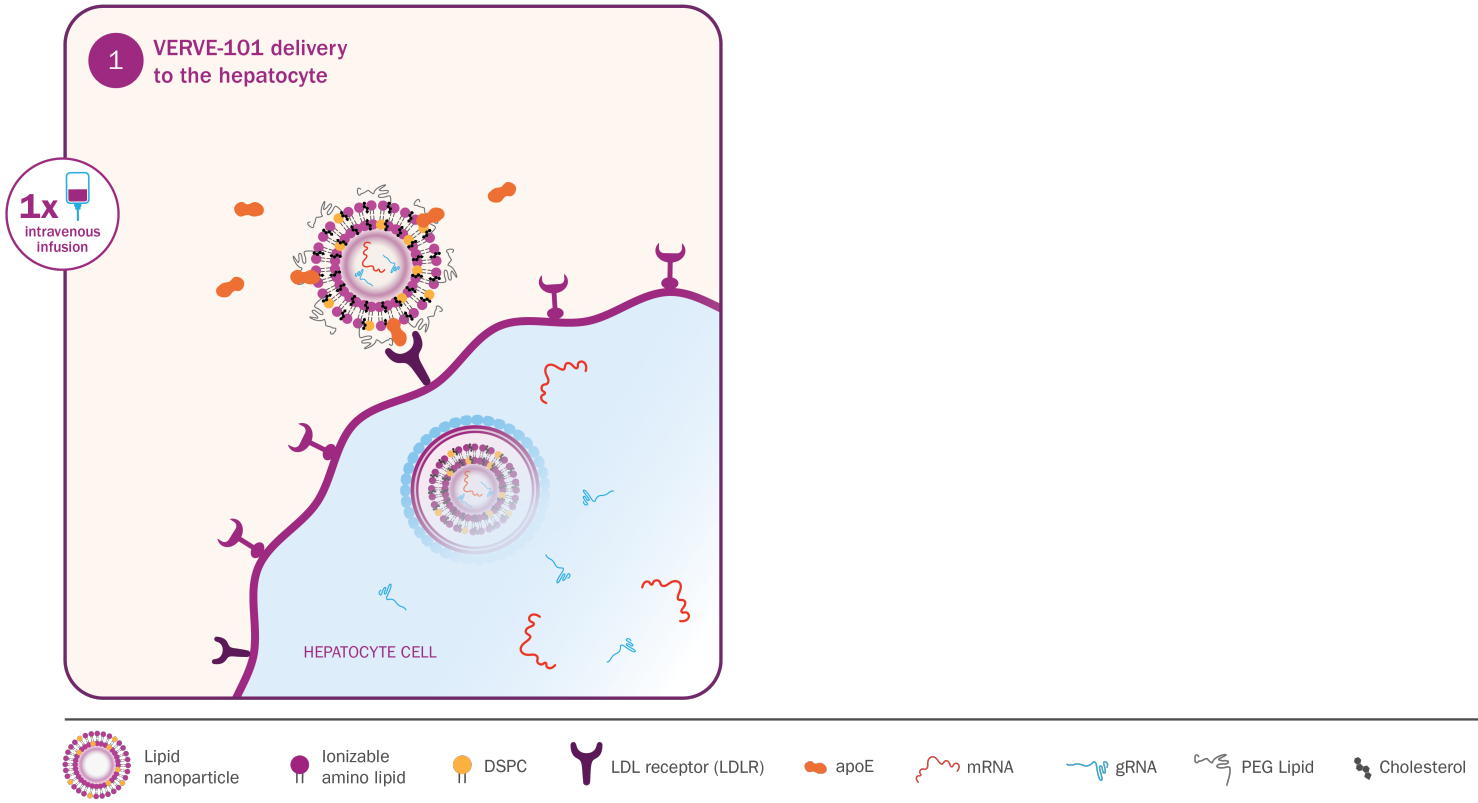
=

VERVE-101

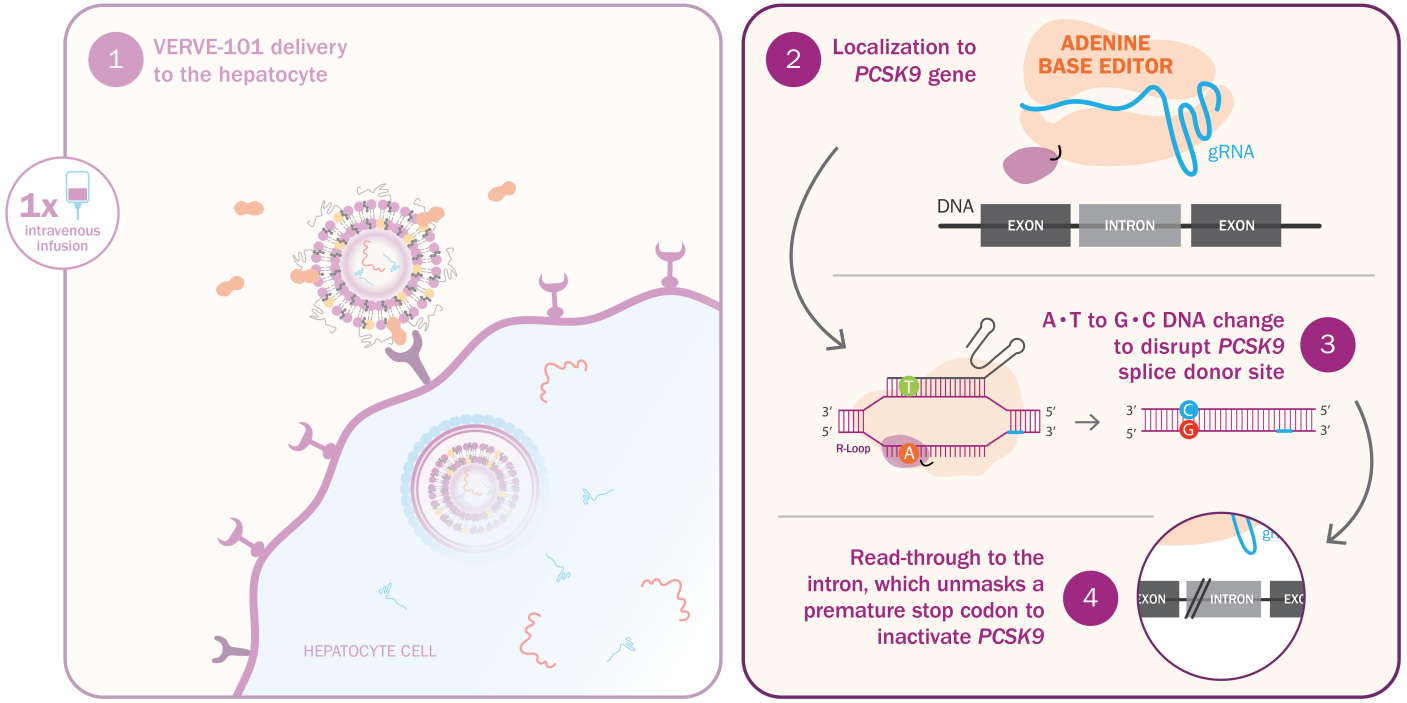


PCSK9, proprotein convertase subtilisin/kexin type 9; LDL-C, low-density lipoprotein cholesterol; RNA, ribonucleic acid; mRNA, messenger RNA; gRNA, guide RNA; LNP, lipid nanoparticle; DSPC, distearoyl-sn-glycerol-3-phosphocholine; PEG, polyethylene glycol

VERVE-101: base editing medicine designed to inactivate hepatic *PCSK9* and lower LDL-C

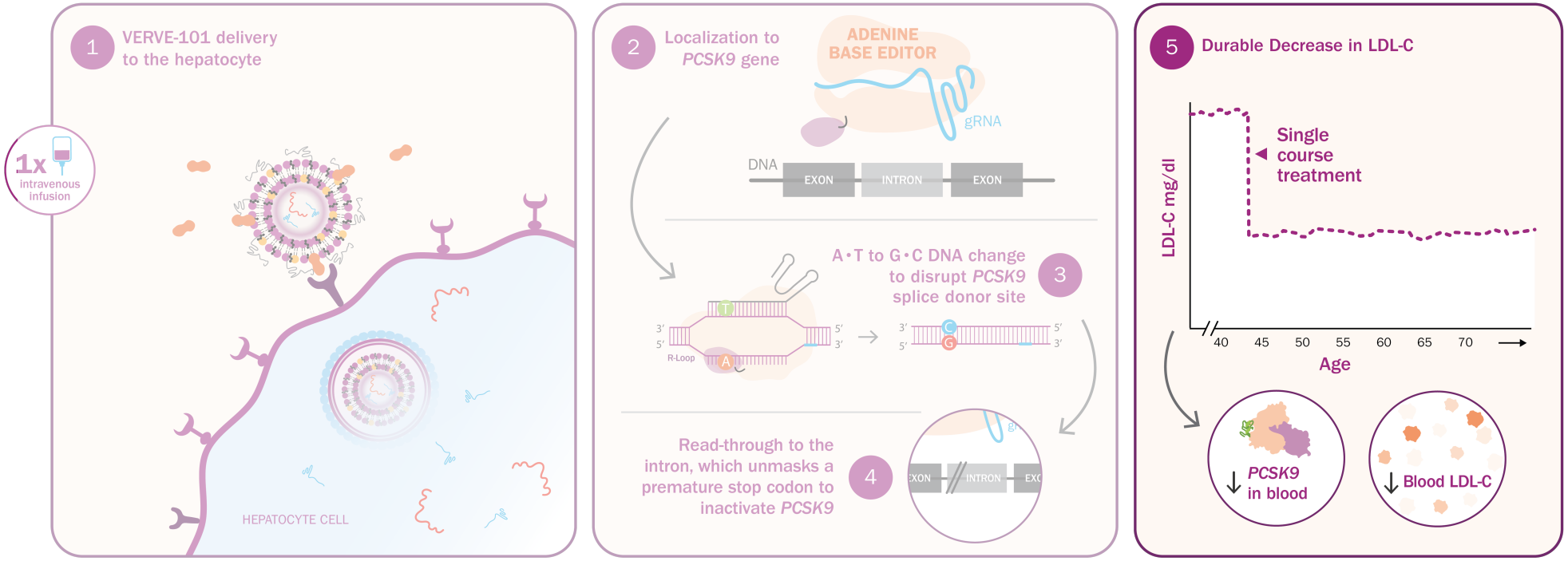


VERVE-101: base editing medicine designed to inactivate hepatic *PCSK9* and lower LDL-C



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

VERVE-101: base editing medicine designed to inactivate hepatic *PCSK9* and lower LDL-C



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

nature

Nature | Vol 593 | 20 May 2021 |

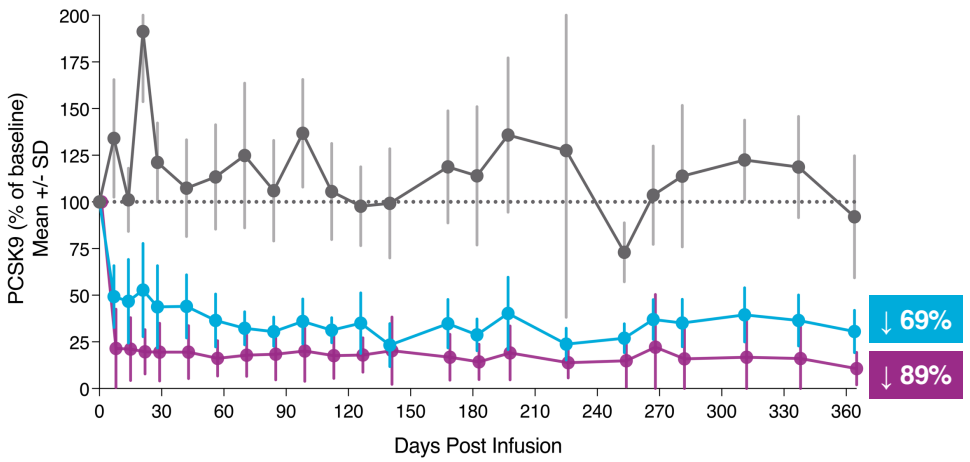
Article

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

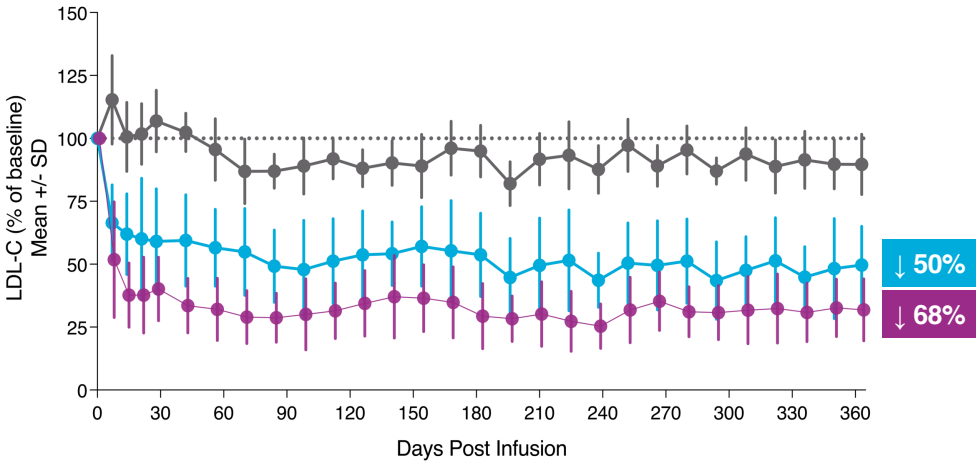
Gene-editing technologies, which include the CRISPR–Cas nucleases[1–3] and CRISPR base editors[4,5], have the potential to permanently modify disease-causing genes in patients[6]. The demonstration of durable editing in target organs of nonhuman primates is a key step before in vivo administration of 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.

In non-human primates (NHPs), single infusion of VERVE-101 durably lowers blood PCSK9 and LDL-C

Reductions in blood PCSK9 level



Reductions in blood LDL-C level



Vehicle control (N = 10) VERVE-101 0.75 mg/kg (N = 4) VERVE-101 1.5 mg/kg (N = 22)

Lee RG et al. *Circulation*. 2022; doi: 10.1161/CIRCULATIONAHA.122.062132. Epub ahead of print.

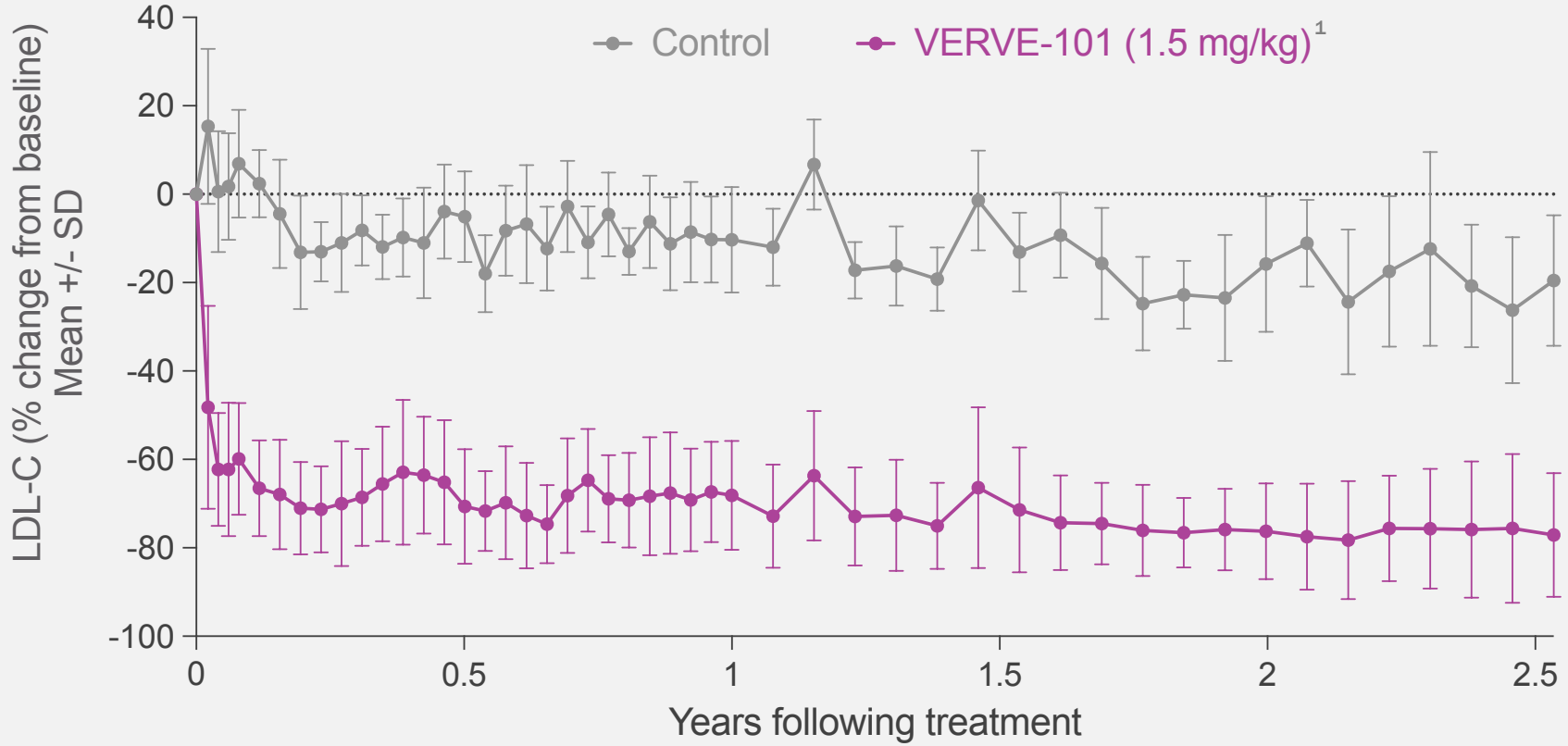
Extensive preclinical evaluation of VERVE-101 in non-human primates & human cells

1. Durability

2. Liver-specific biodistribution

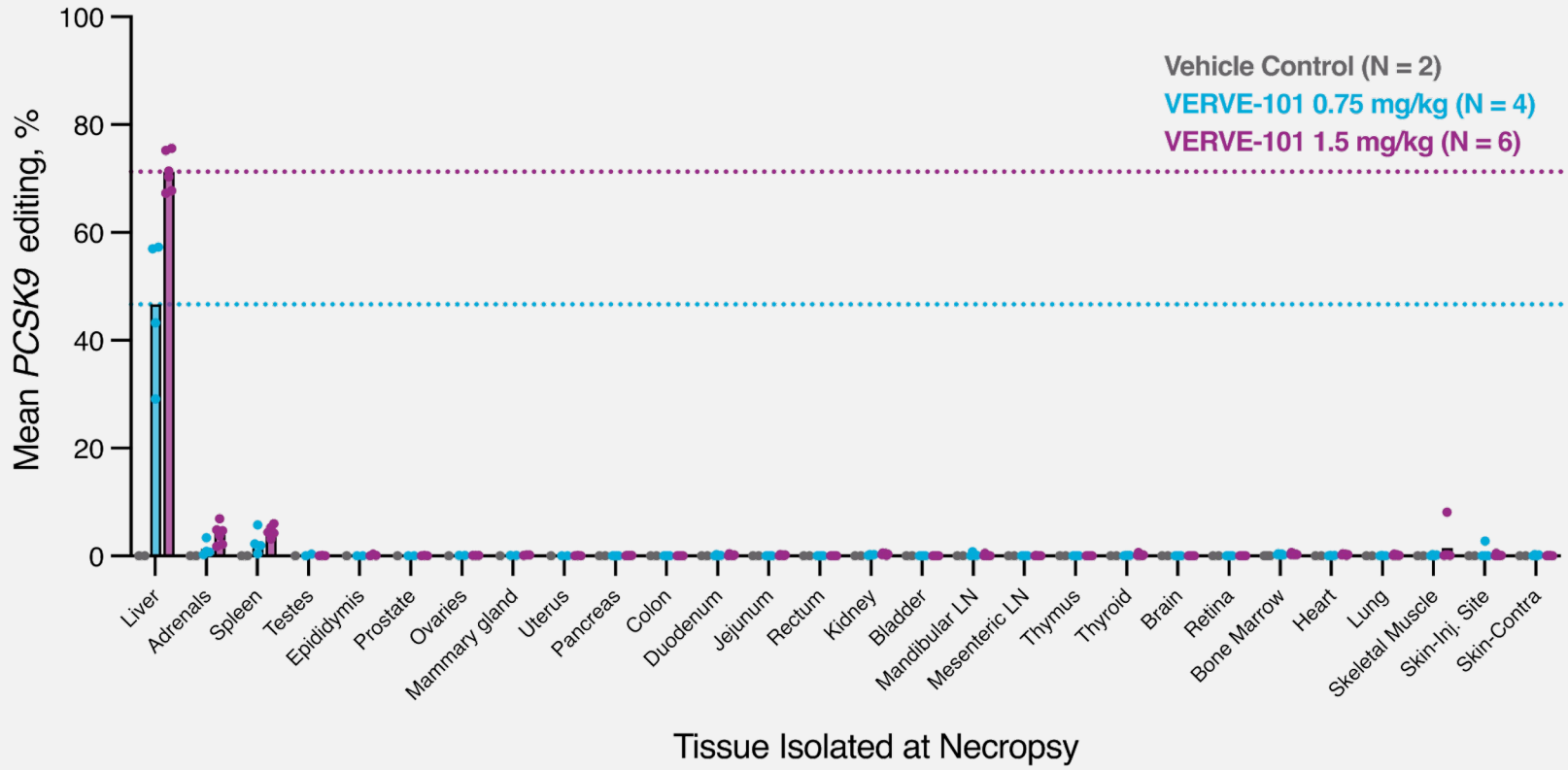
3. No significant off-target editing

Durability out to 2.5 years observed after a single dose of VERVE-101 in non-human primates



1. 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

Liver-specific biodistribution observed in non-human primates treated with VERVE-101



Multiple orthogonal techniques have been used to nominate ~6000 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:

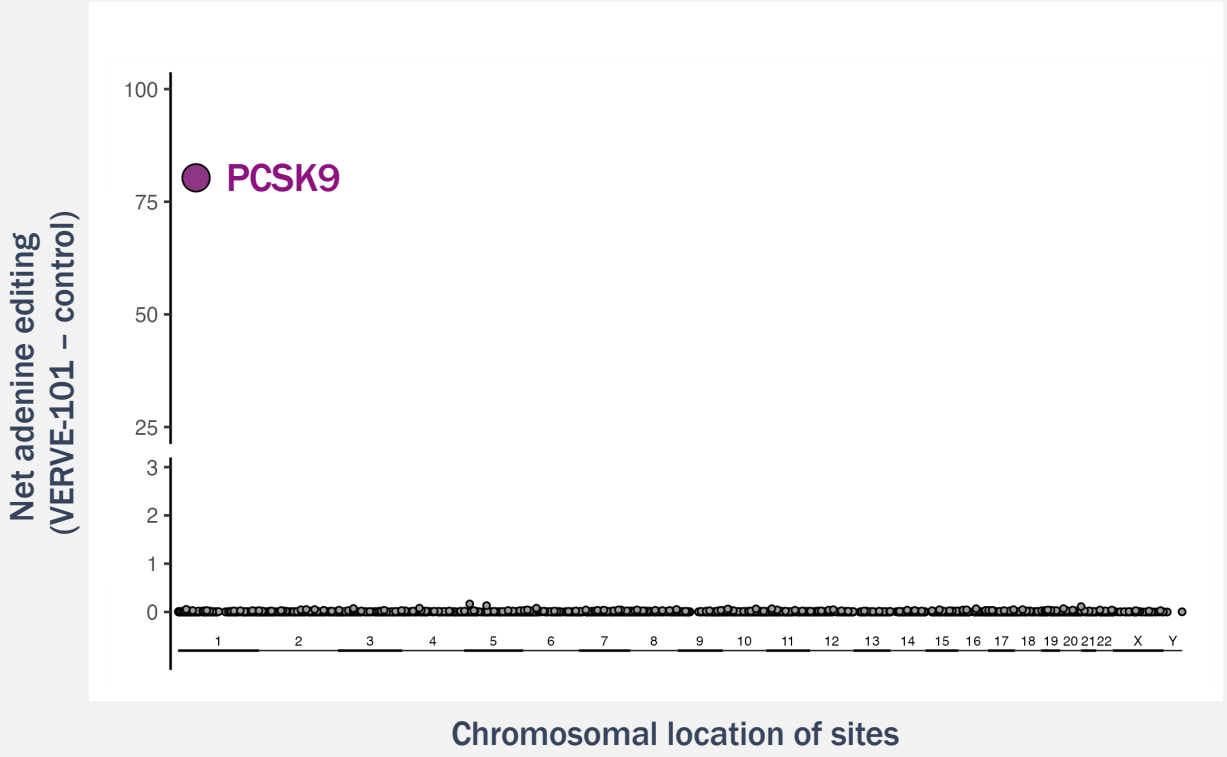
sites of greatest sequence homology

panel of candidates

~6000 sites

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

In human liver cells treated with VERVE-101, no evidence for off-target editing



- Donor primary human hepatocytes treated with saturating dose of VERVE-101 LNPs
- 'Manhattan-style' plot of ~6000 candidate sites
- No candidate sites show statistically significant net editing

Interim results from the heart-1 clinical trial of VERVE-101

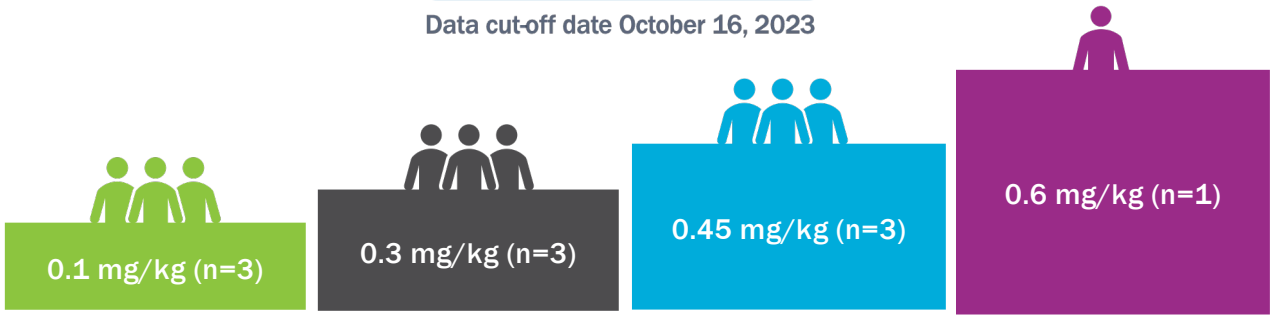
heart-1 is a first-in-human Phase 1b trial designed to evaluate the safety and tolerability of VERVE-101

heart-1

Open-label, single ascending dose design with flexible, adaptive dose levels and n=3 to 6 per cohort

Interim update:
10 participants treated across 4 dose cohorts[1]

Data cut-off date October 16, 2023



Clinical trial registration: NCT05398029; 1. 10 participants included in the safety analysis, but only 9 participants included in the pharmacodynamic analyses as the 10th participant had not reached the 28-day follow-up as of the data cut-off date. Single participant dosed at 0.6 mg/kg prior to initiation of 0.45 mg/kg cohort.

verve THERAPEUTICS

FDA draft guidance on human genome editing products: study population

Subjects with severe or advanced disease may be more willing to accept the risks of an investigational human GE product. However, these subjects may be predisposed to experiencing more AEs or be receiving concomitant treatments, which could make the safety or effectiveness data difficult to interpret. Therefore, in some instances, subjects with less advanced or more moderate disease may be appropriate for inclusion in first-in-human clinical studies.

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-gene-therapy-products-incorporating-human-genome-editing

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

STUDY POPULATION SUMMARY

- Males and females[2] (age 18 to 75)
- HeFH
- Established ASCVD
- Uncontrolled LDL-C[3]
- On maximally-tolerated oral lipid-lowering therapy[4]

DRUG ADMINISTRATION

- Pre-medication with dexamethasone and antihistamines
- VERVE-101 delivered as single infusion via a peripheral IV[5]

TRIAL ENDPOINTS

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

Clinical trial registration: NCT05398029

1. 10 participants included in the safety analysis, but only 9 participants included in the pharmacodynamic analyses as the 10th participant had not reached the 28-day follow-up as of the data cut-off date; 2. Women of childbearing potential are excluded from the study; 3. LDL-C threshold for inclusion value varies by country-specific protocol; 4. maximum tolerated statin and/or ezetimibe (statin intolerant allowed) 5. dosing based on weight for participants ≤ 100 kg; participants > 100 kg are dosed on an assumed 100 kg weight; single participant dosed at 0.6 mg/kg prior to initiation of 0.45 mg/kg cohort.

Participants enrolled to date have severe, advanced ASCVD and high risk for cardiovascular events (near-term and lifetime)

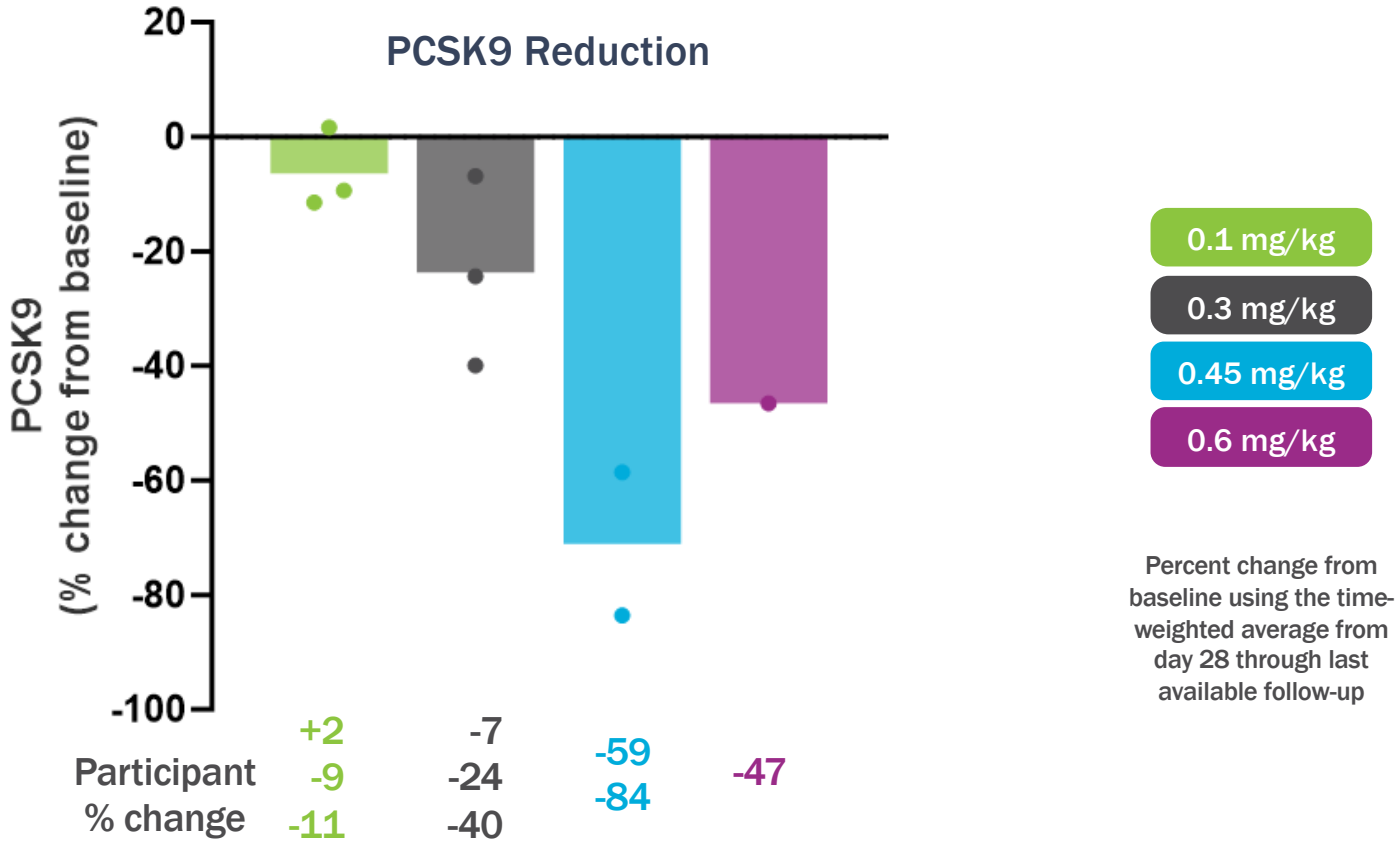
Characteristic	Total (n=10)
Mean age, years (min, max)	54 (29, 69)
Sex, male, n	8
Mean screening LDL-C, mg/dL (min, max)	193 (107, 373)
Mutation in *LDLR* detected, n[1]	9
Cardiovascular Risk Profile	
Prior coronary revascularization, n	9
Prior coronary artery bypass grafting, n	3
≥ 1 prior percutaneous coronary intervention, n	7
≥ 1 prior myocardial infarction, n	4
Prior cardiac arrest, n	1
Concomitant and Prior Lipid-Lowering Therapy	
On statin therapy, n	8
Prior use of PCSK9-targeted therapy, n	2

4.95 mmol/L

As of October 16, 2023. Data are from an ongoing study with an open database and have not been fully cleaned

1. One participant diagnosed based on clinical criteria

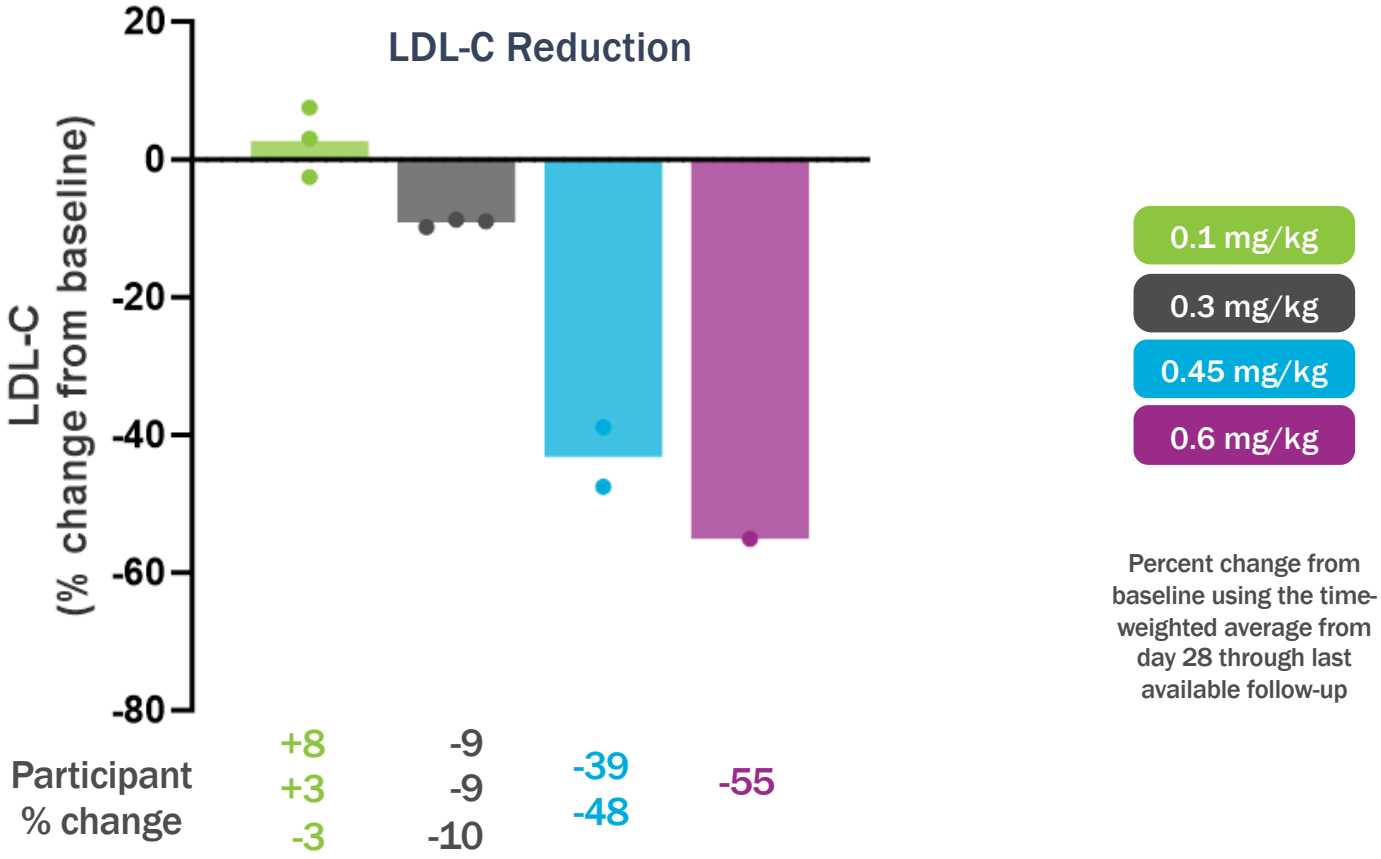
Reductions in blood PCSK9 protein level of 47%, 59% and 84% observed in the two higher dose cohorts following VERVE-101 administration



As of October 16, 2023. Data are from an ongoing study with an open database and have not been fully cleaned

Day 28 value was used for time-weighted average in participants where day 28 was latest timepoint. One participant who has not reached day 28 excluded from analysis. Observations in 2 participants in 0.1 mg/kg cohort censored from analysis after changes in lipid lowering treatment (both >90 days after VERVE-101 infusion).

Reductions in blood LDL-C of 39%, 48% and 55% observed in the two higher dose cohorts following VERVE-101 administration

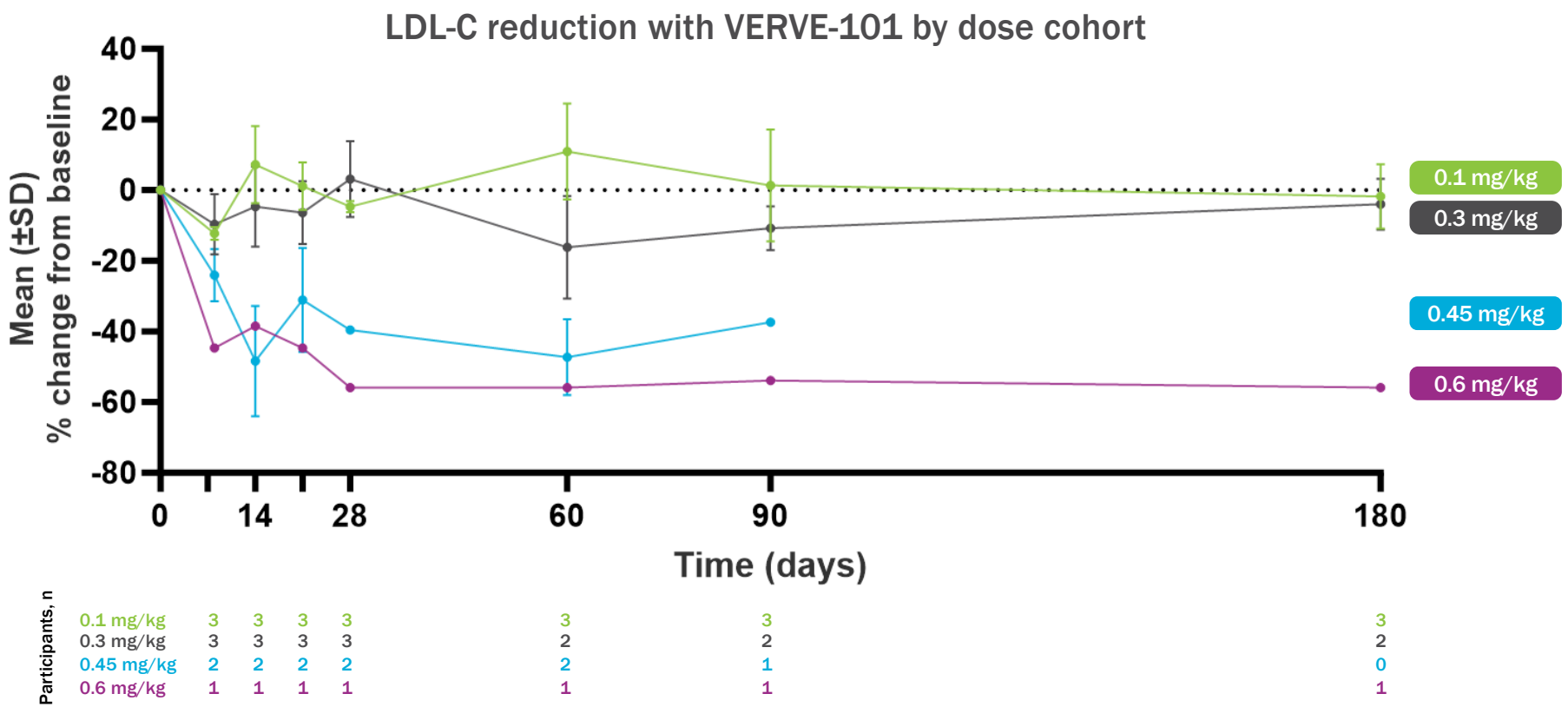


Percent change from baseline using the time-weighted average from day 28 through last available follow-up

As of October 16, 2023. Data are from an ongoing study with an open database and have not been fully cleaned

Day 28 value was used for time-weighted average in participants where day 28 was latest timepoint. One participant who has not reached day 28 excluded from analysis. Observations in 2 participants in 0.1 mg/kg cohort censored from analysis after changes in lipid lowering treatment (both >90 days after VERVE-101 infusion).

Durable 55% reduction in LDL-C extending up to 180 days in the single participant in the highest dose cohort



As of October 16, 2023. Data are from an ongoing study with an open database and have not been fully cleaned
SD, standard deviation

Interim safety summary: observed adverse events (AEs) consistent with a severe, advanced ASCVD patient population

Infusion-related reactions at doses ≥ 0.45 mg/kg

Transient, reversible increases in liver function tests

CV SAEs occurred in 2 participants:

- fatal cardiac arrest (dose 0.3 mg/kg) deemed unrelated to treatment
- myocardial infarction (MI) and non-sustained ventricular tachycardia (NSVT) (dose 0.45 mg/kg) in participant with unstable angina symptoms (unreported) prior to treatment with VERVE-101
  - MI deemed to be potentially related to treatment due to proximity to dosing
  - NSVT deemed unrelated to treatment

All safety events were reviewed with the independent DSMB who recommended continuation of trial enrollment with no protocol changes required

As of an October 16, 2023 interim data cut. SAE, serious adverse event; DSMB, data and safety monitoring board

Initial results of heart-1 trial demonstrated first proof-of-concept for *in vivo* DNA base editing in humans

1. Dose-dependent reductions in blood PCSK9 protein & LDL-C levels following VERVE-101 infusion

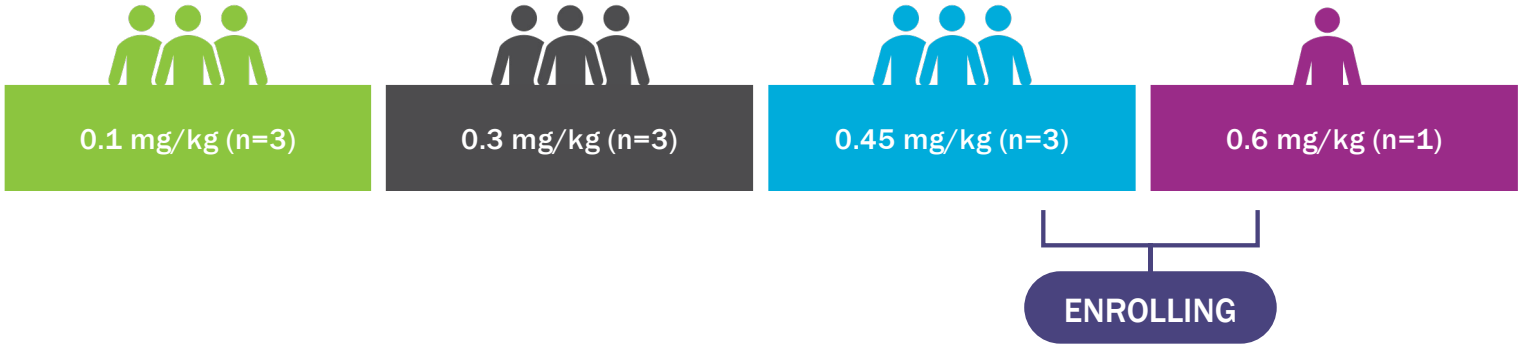
2. LDL-C reductions of 39%, 48%, & 55% among participants in the two highest dose cohorts

3. Durability extending to 6 months in the single participant in the highest dose cohort

4. Safety profile supports continued development of VERVE-101

As of an October 16, 2023 interim data cut.

Next steps in the heart-1 trial of VERVE-101



- Enroll in 0.45 & 0.6 mg/kg cohorts to complete dose escalation phase
- Transition to patients with less advanced, more moderate disease
- Open U.S. trial sites for additional patient enrollment
- Complete enrollment in 2024, with additional data release planned in 2H 2024

VERVE-102: adenine base editor mRNA + gRNA packaged in a GalNAc-LNP; edit designed to turn off *PCSK9*

DRUG SUBSTANCES

RNA components encode base editor and a guide targeting *PCSK9* gene

(same construct as VERVE-101)

- mRNA for adenine base editor
- gRNA localizes editor to *PCSK9* gene

+

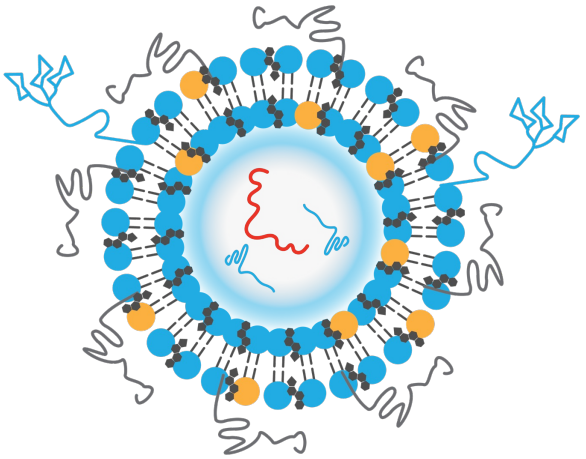
DELIVERY VEHICLE

LNP for delivery to liver cells includes 5 components

- Ionizable amino lipid (Novartis)
- DSPC
- Cholesterol
- GalNAc
- PEG

=

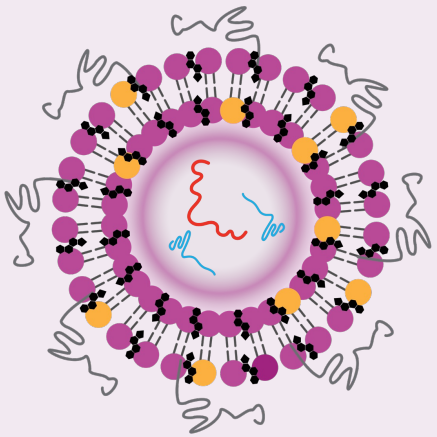
VERVE-102



mRNA, messenger RNA; gRNA, guide RNA; GalNAc, N-acetylgalactosamine; LNP, lipid nanoparticle; PCSK9, proprotein convertase subtilisin/kexin type 9; RNA, ribonucleic acid; DSPC, distearoyl-sn-glycerol-3-phosphocholine; PEG, polyethylene glycol

VERVE-102 is differentiated from VERVE-101, with potential for improved potency

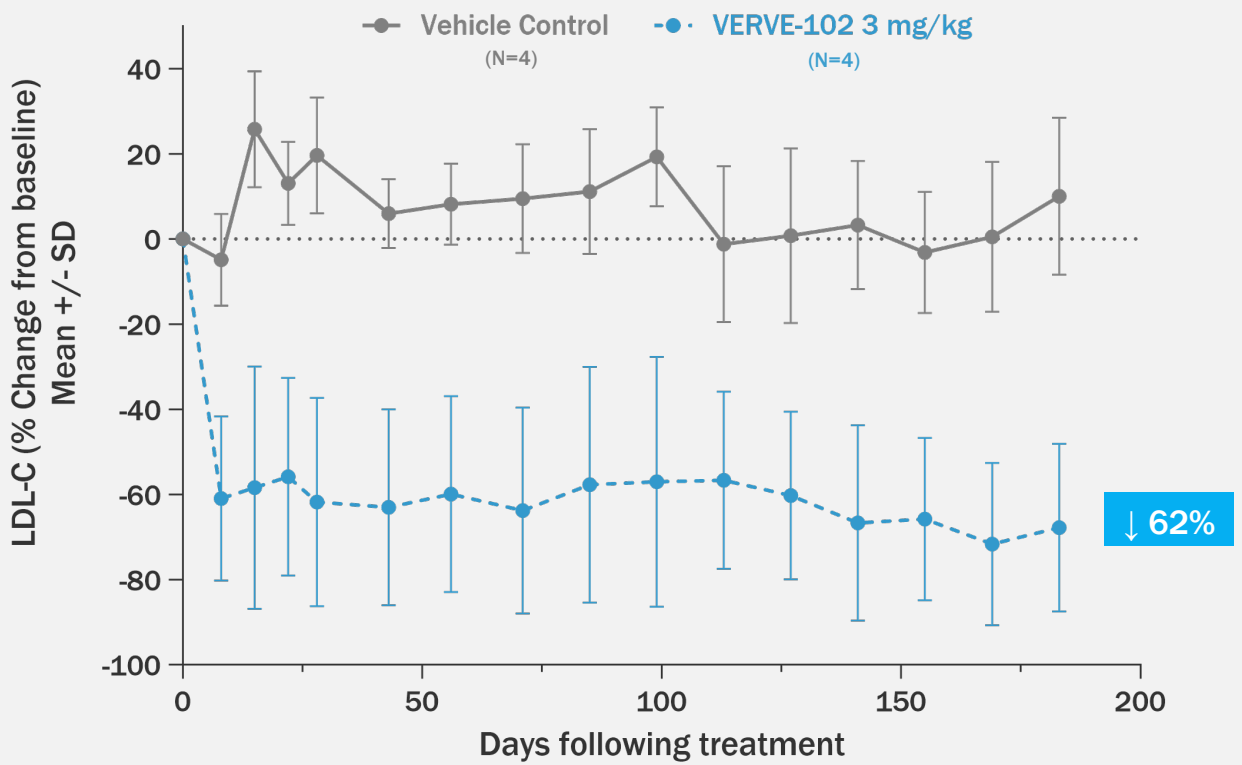
VERVE-101



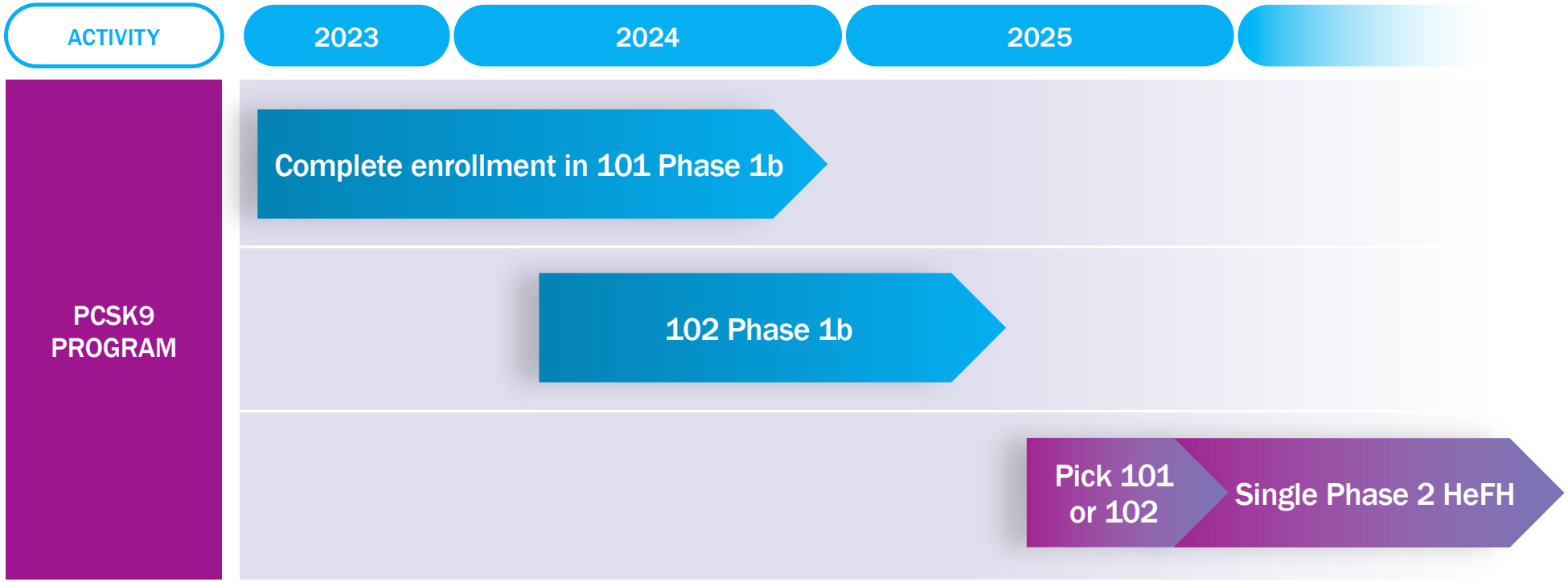
VERVE-102

- Different ionizable lipid, licensed from Novartis
- Addition of GalNAc targeting ligand - allowing for entry into hepatocytes by any of two receptors (LDLR or ASGPR)

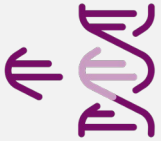
VERVE-102 has demonstrated durable LDL-C reduction in non-human primates out to 6 months



Simultaneous development of VERVE-101 and VERVE-102, followed by selection of one product candidate to take to Phase 2

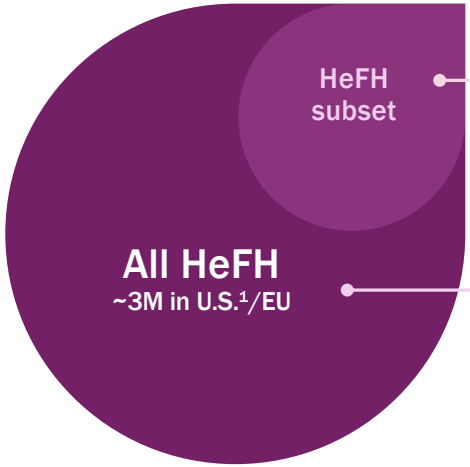


Heterozygous familial hypercholesterolemia (FH): a serious, inherited subtype of ASCVD with high LDL-C from birth & heart attack at early ages

American Heart Association Diagnostic Criteria				
High LDL-C + Family history (of high LDL-C or premature ASCVD)	Monogenic or polygenic	≥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

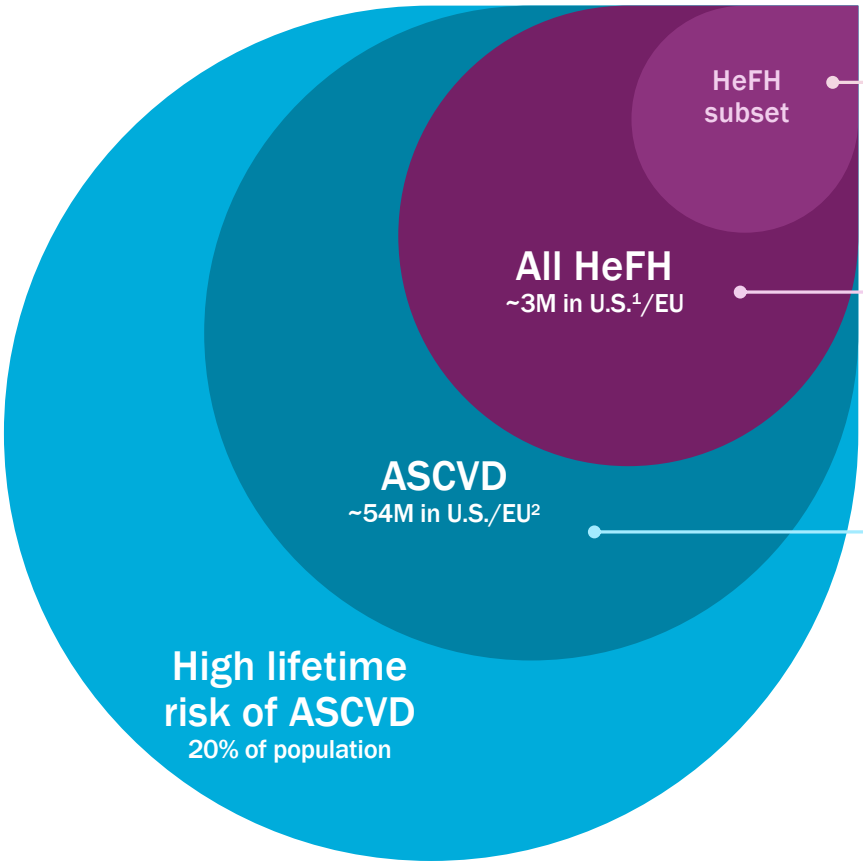
Stepwise clinical development strategy for VERVE-101 starting with HeFH (3M patients in US/Europe) and LDL-C endpoint



- Phase 1b proof-of-concept in high-risk HeFH

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

Potential to expand to ASCVD with LDL-C endpoint for approval but likely also CVOT for market adoption



- Phase 1b proof-of-concept in high-risk HeFH

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

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

Clinical development strategy subject to alignment with regulators

1. Tsao CW et al., Heart Disease and Stroke Statistics – 2022 Update: A Report from the American Heart Association. *Circulation.* 2022;145(8):e153–e639.
2. Gu J et al., *Am J Prev Cardiol. 2022*;10:100336.

ANGPTL3 Program

Homozygous FH (HoFH): severe, orphan disease

HEALTH

10-year-old's cholesterol was over 800. Can CRISPR fix the problem?

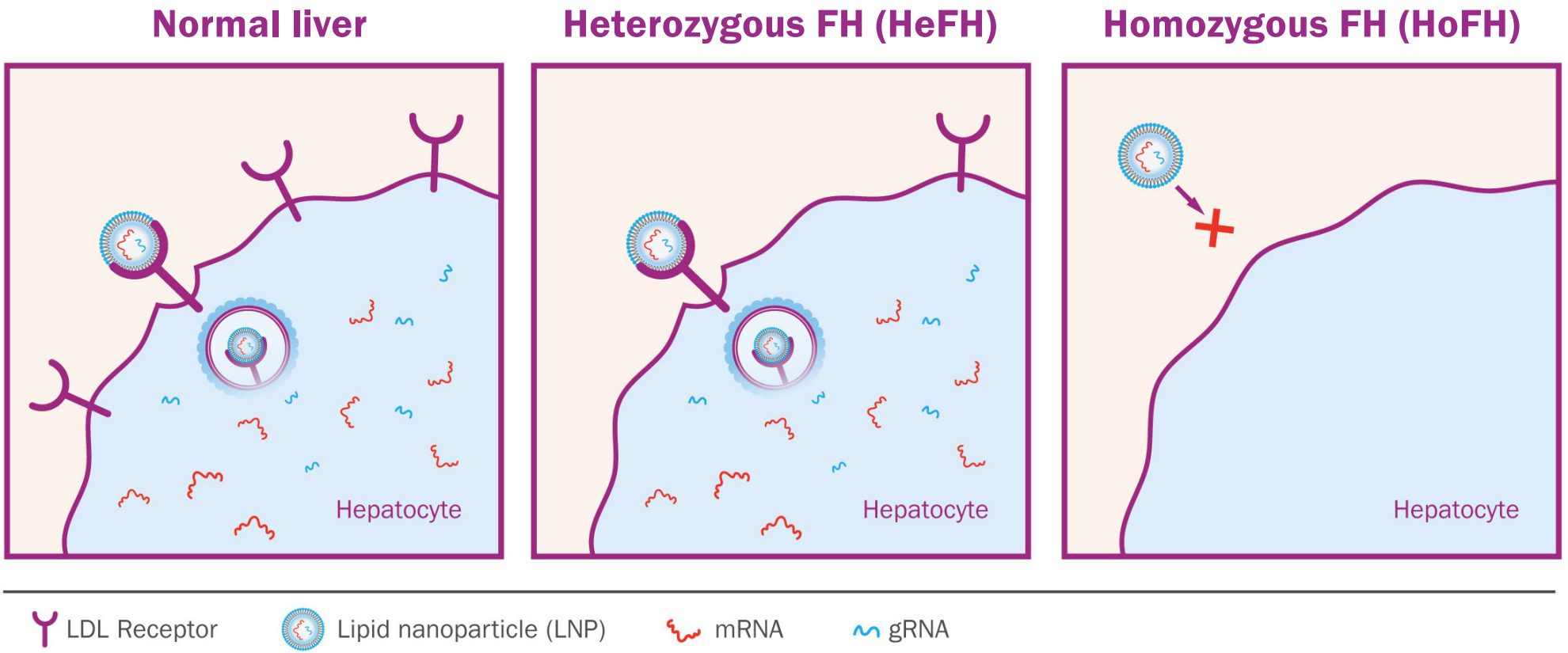
Verve Therapeutics is considering a half-dozen candidate genes that could be edited with the CRISPR technique in order to sharply reduce a patient's levels of cholesterol or triglycerides.

Due to a genetic condition that causes high cholesterol, 10-year-old Avery Watts, of Hagerstown, Md., undergoes treatment twice a month at Nemours / Alfred I. duPont Hospital for ... **Read more**

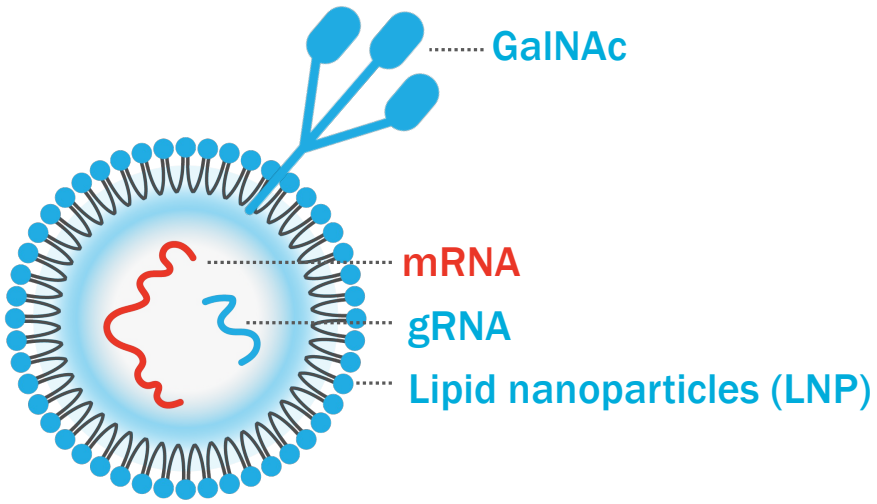
Leslie Barbaro

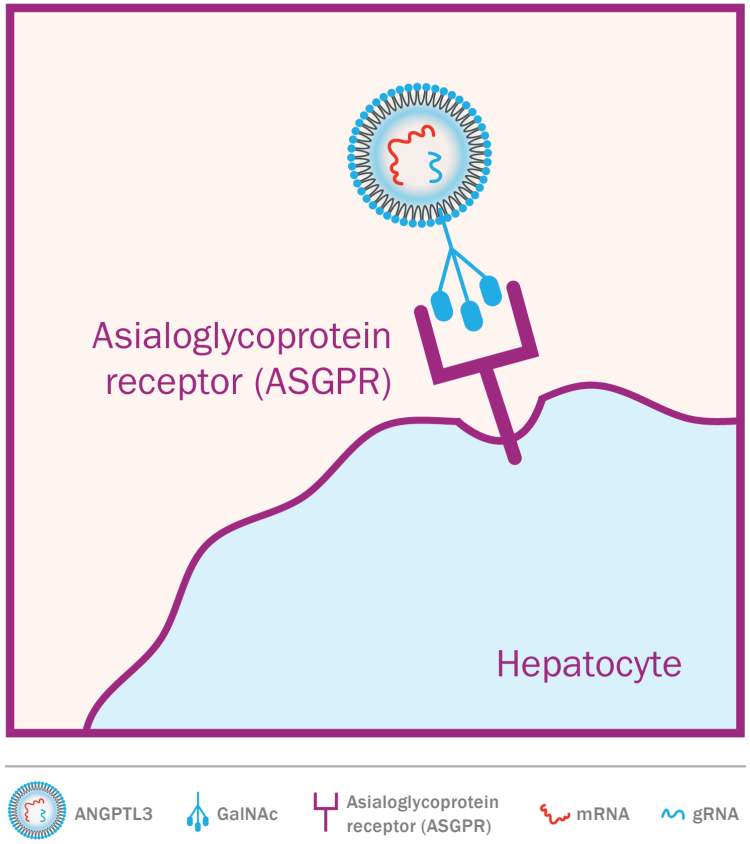
Philadelphia Inquirer, June 10, 2019

Delivery challenge: HoFH patients lack LDL receptor; in this setting, delivery with standard LNP does not work



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





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

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-201 medicine candidate: adenine base editor mRNA + gRNA packaged in a GalNAc-LNP; edit designed to turn off *ANGPTL3*

DRUG SUBSTANCES

RNA components encode base editor and a guide targeting *ANGPTL3* gene

- mRNA for adenine base editor
- gRNA localizes editor to *ANGPTL3* gene

+

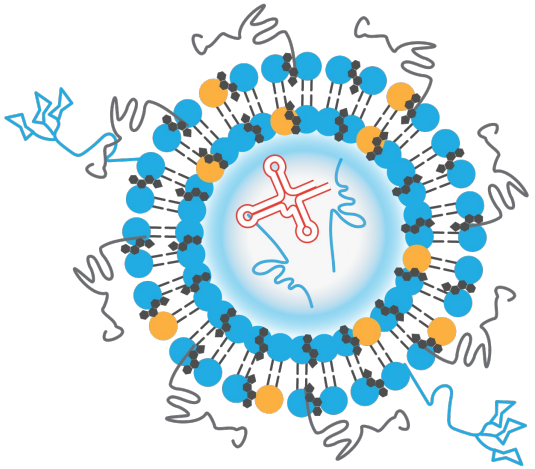
DELIVERY VEHICLE

Lipid nanoparticle for delivery to liver cell includes 5 components

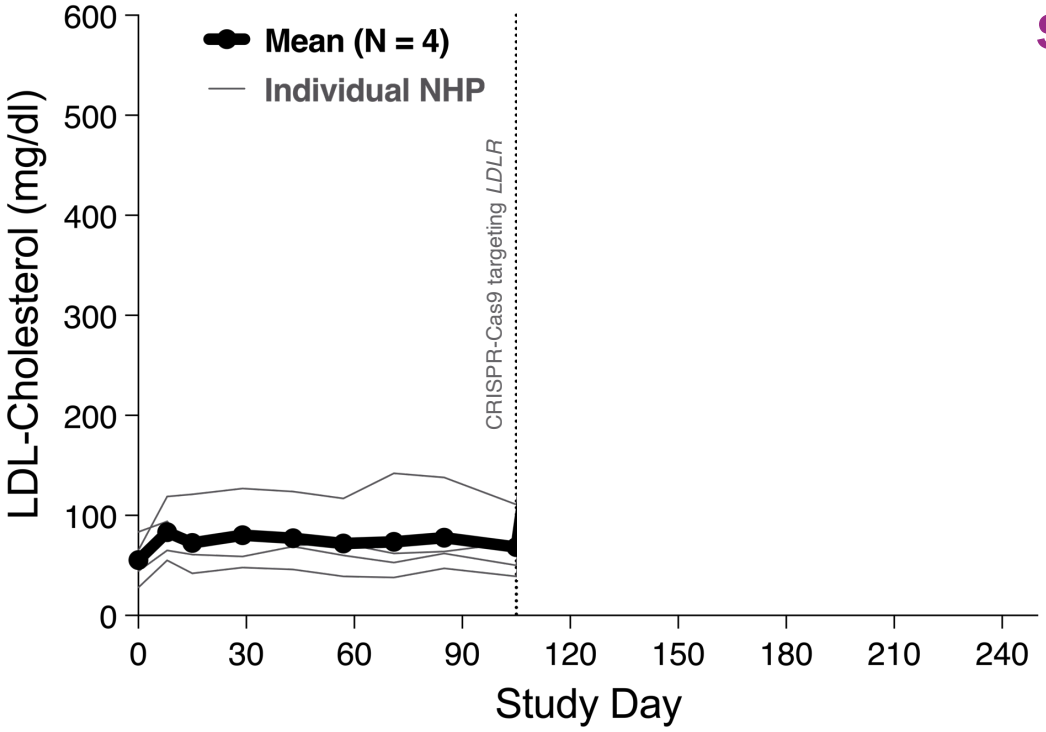
- Ionizable amino lipid
- DSPC
- Cholesterol
- GalNAc
- PEG

=

VERVE-201



To model homozygous FH physiology, Verve developed LDLR-deficient non-human primates

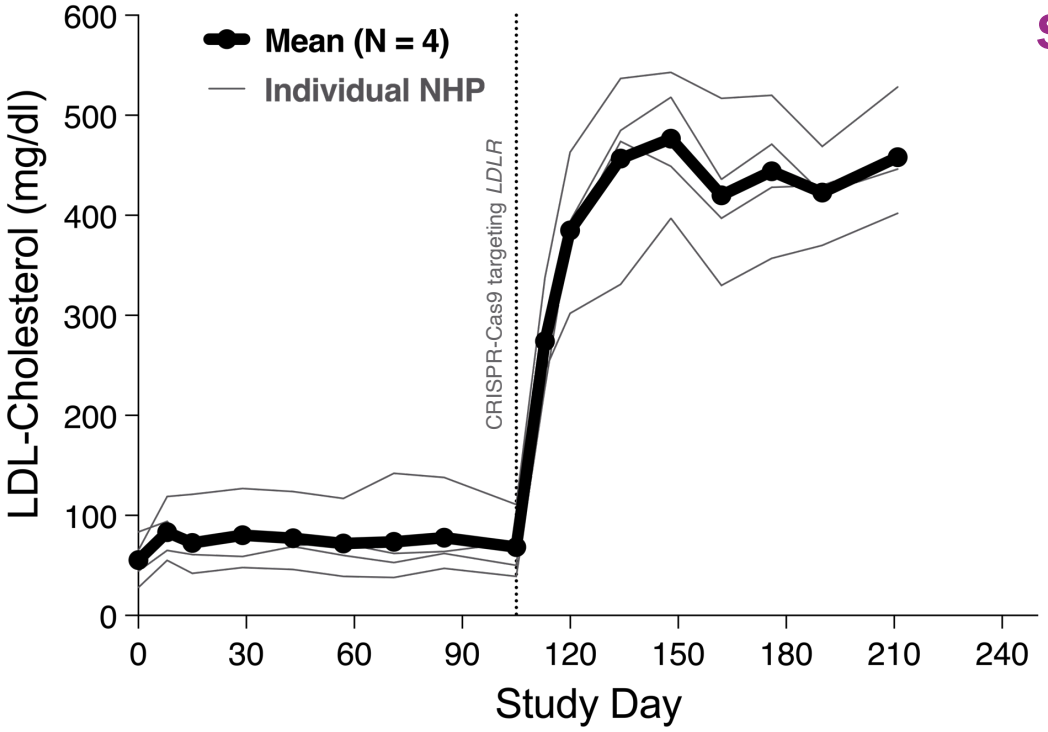


Step #1: Develop LDLR-deficient NHPs

- NHP model of LDLR-deficiency not readily available
- Treated 4 NHPs with CRISPR-Cas9 to inactivate ***LDLR*** in the liver.[1]

1. Method previously described in Kasiewicz et al. biorXiv, 2021

LDL-C goes up > 8-fold in the LDLR-deficient NHPs

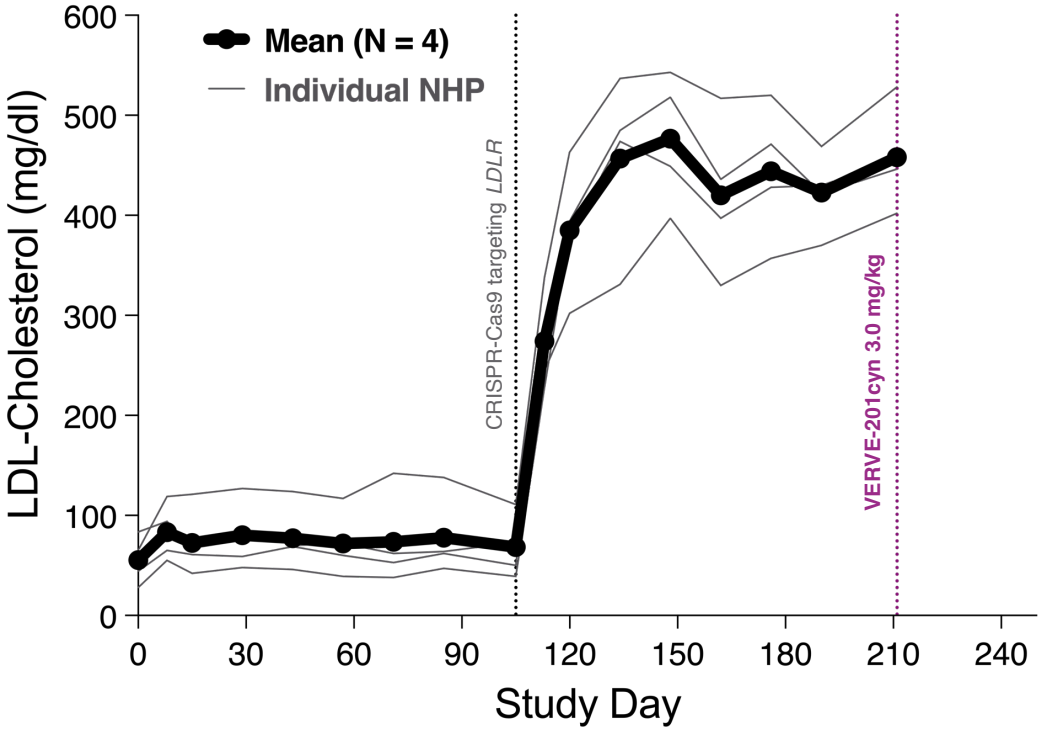


Step #1: Develop LDLR-deficient NHPs

- NHP model of LDLR-deficiency not readily available
- Treated 4 NHPs with CRISPR-Cas9 to inactivate ***LDLR*** in the liver:[1]
  - 64% mean ***LDLR*** editing
  - >80% lower hepatic LDLR protein versus control NHPs
  - Mean LDL-C increased from baseline of 55 to 458 mg/dL

1. Method previously described in Kasiewicz et al. biorXiv, 2021

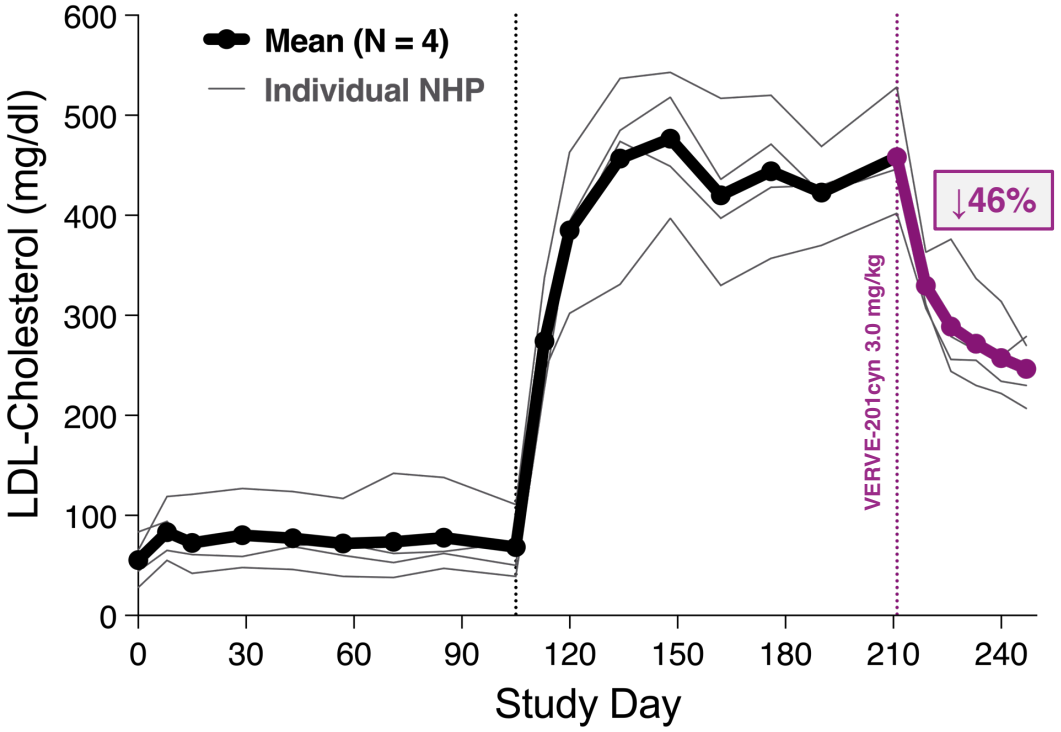
Treat with VERVE-201cyn – 84% reduction in blood ANGPTL3



Step #2: Treat with VERVE-201cyn

- Treated 4 NHPs with VERVE-201cyn at a dose of 3.0 mg/kg.
- At time of necropsy 5 weeks following dosing:
  - 60% mean *ANGPTL3* liver editing
  - 84% mean reduction from baseline in blood ANGPTL3

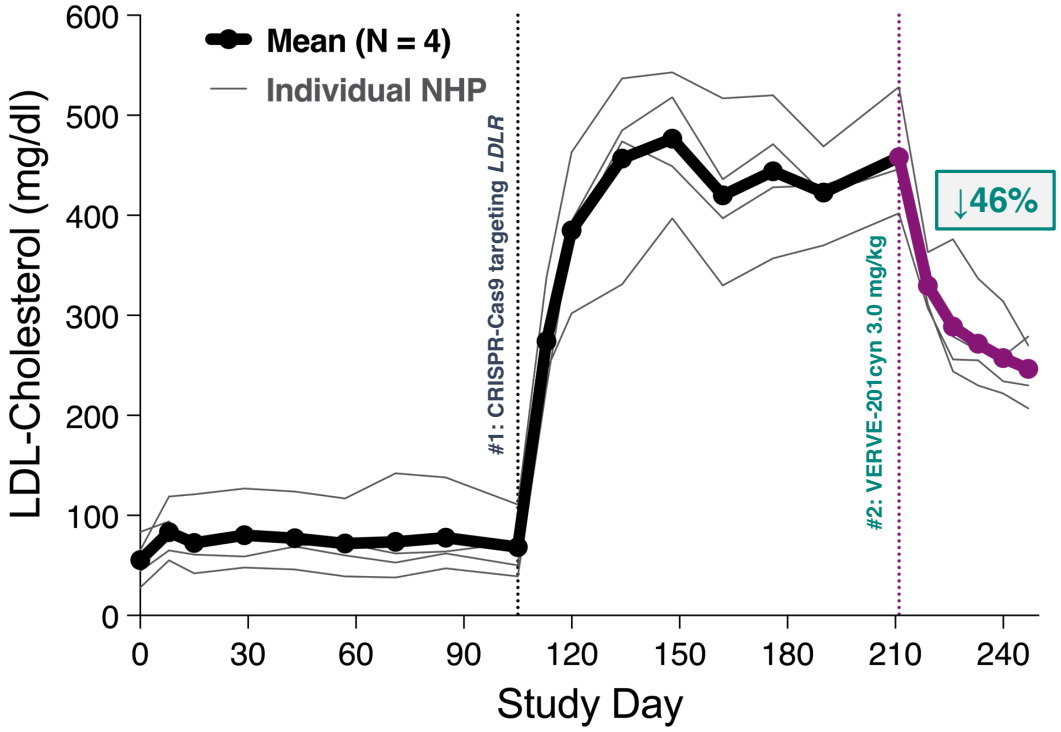
In LDLR-deficient NHPs treated with VERVE-201cyn, 46% mean decrease in LDL-C observed (458 to 247 mg/dL)



Step #2: Treat with VERVE-201cyn

- Mean LDL-C decreased from 458 to 247 mg/dL
- VERVE-201cyn in NHPs:
  - 46% decrease in LDL-C
  - 54% decrease in TG

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



Clinical trial initiation in 2H 2024

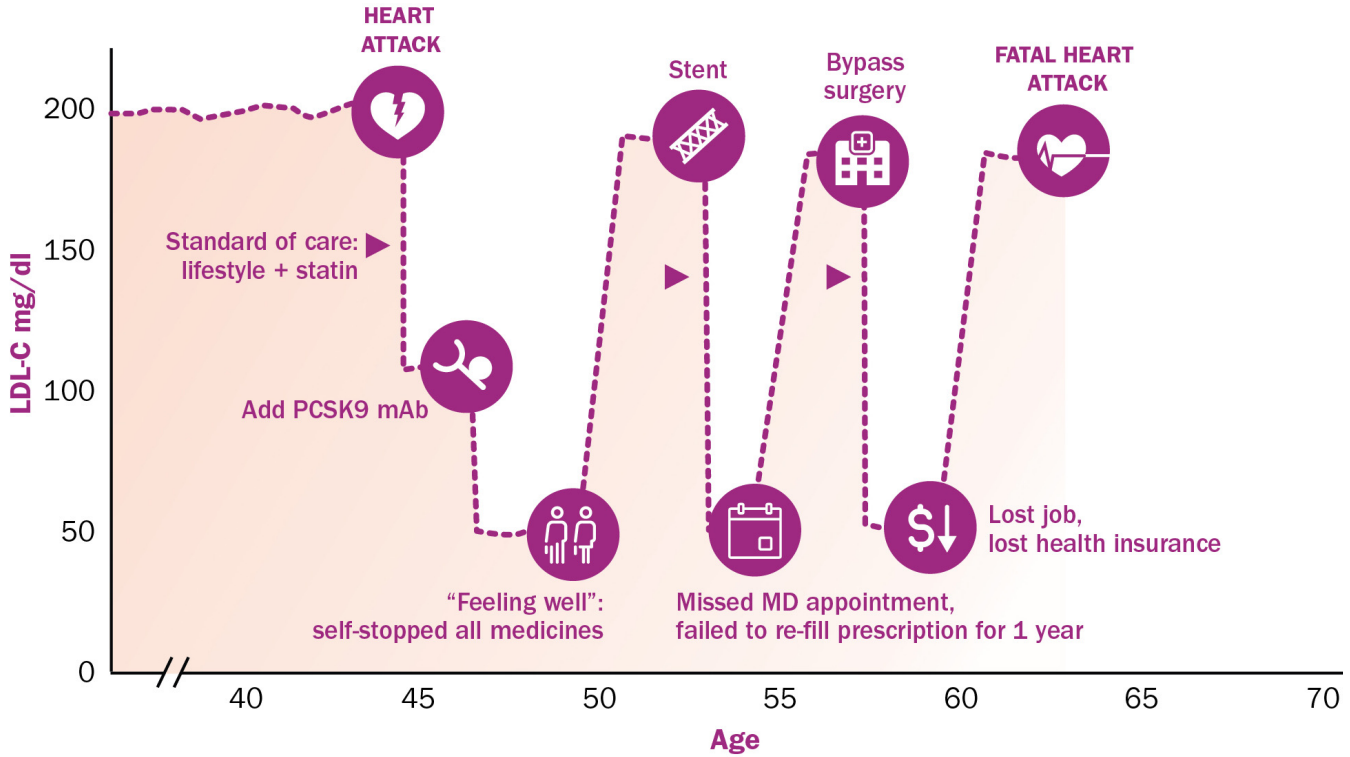
Subject to regulatory clearance

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

In 2024, we will have three *in vivo* gene editing programs at clinical stage & this is our focus

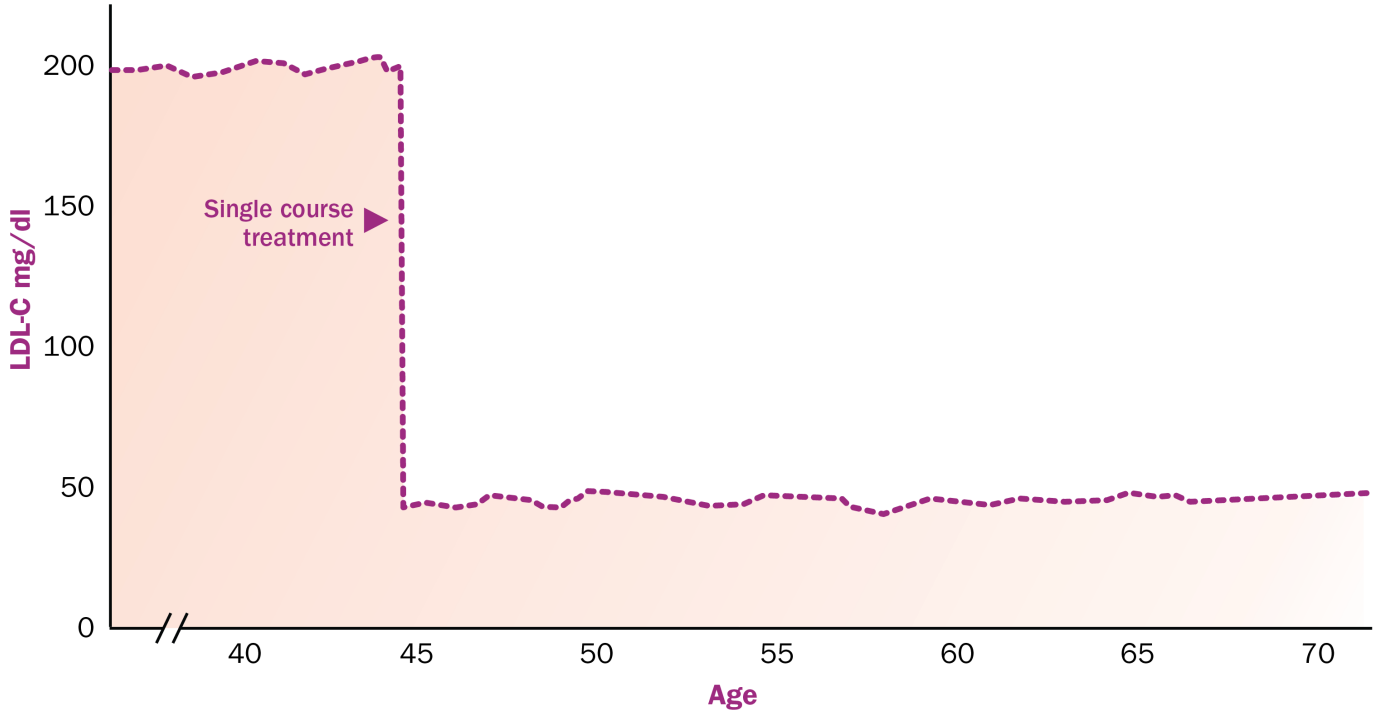
TARGET	INDICATION	TECHNOLOGY	DEVELOPMENT STATUS			RIGHTS
			Research	IND-enabling	Clinical	
PCSK9 (VERVE-101)	Heterozygous familial hypercholesterolemia / ASCVD	Base Editor				verve, Lilly
PCSK9 (VERVE-102)	Heterozygous familial hypercholesterolemia / ASCVD	Base Editor				verve, Lilly
ANGPTL3 (VERVE-201)	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

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



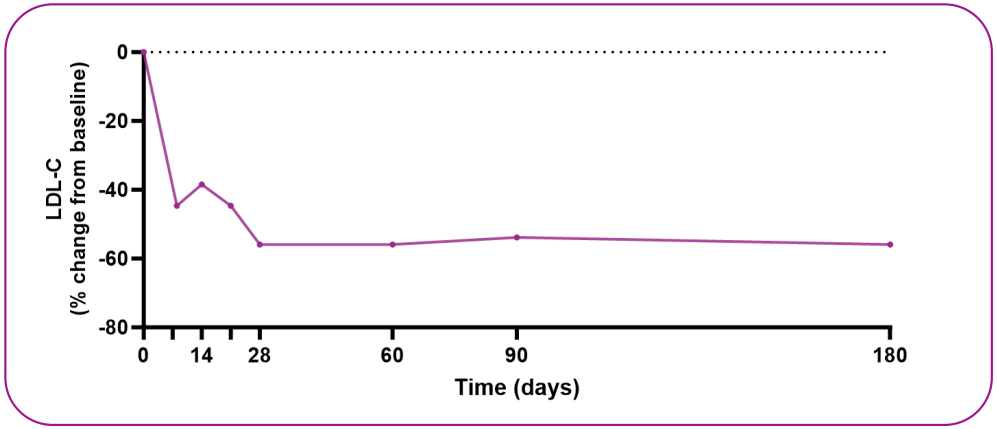
Illustrative graphic depicts the journey of a hypothetical patient with familial hypercholesterolemia who began standard-of-care treatment after suffering a heart attack at age 44

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



Where could gene editing fit into the LDL-C treatment landscape?

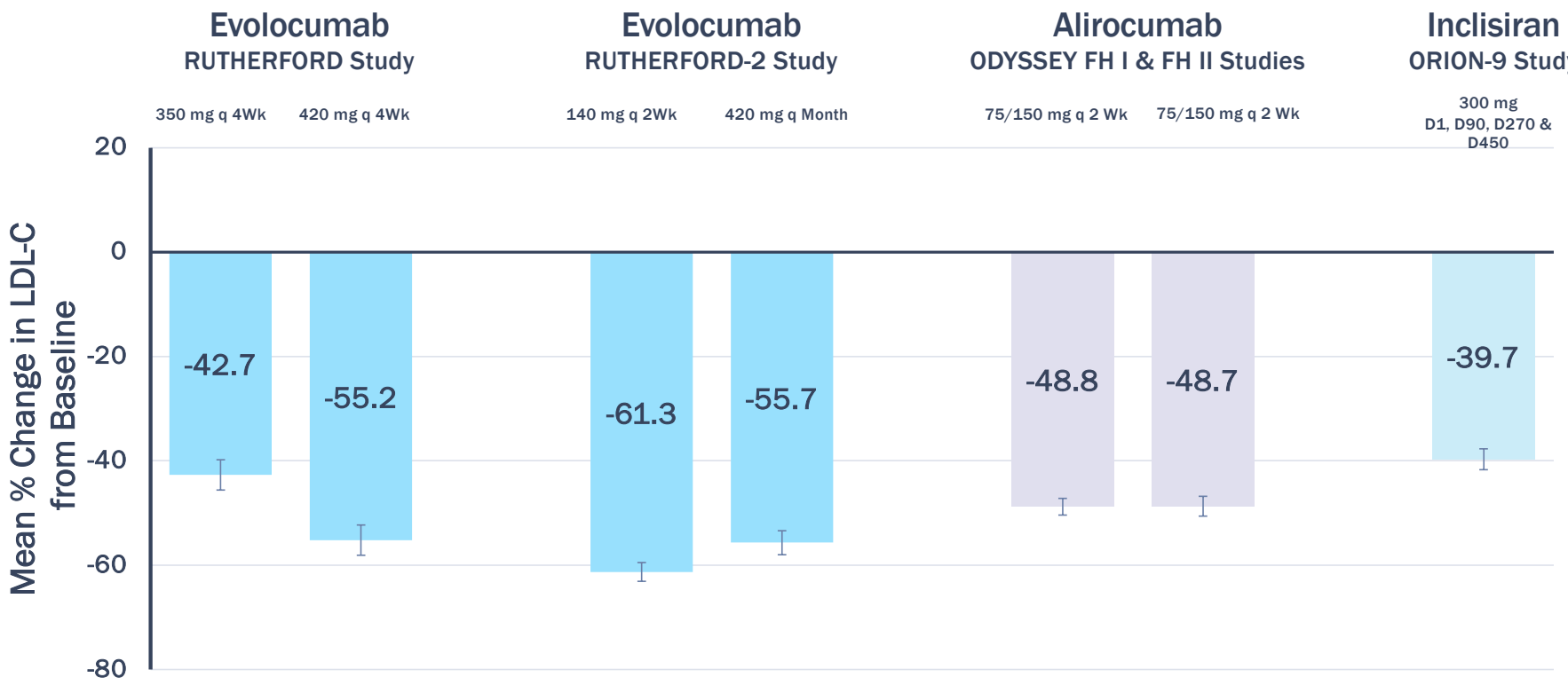
In patients who require deep LDL-C lowering over decades, single-course gene editing medicines may emerge as an option to overcome limitations of the chronic care model



Our team

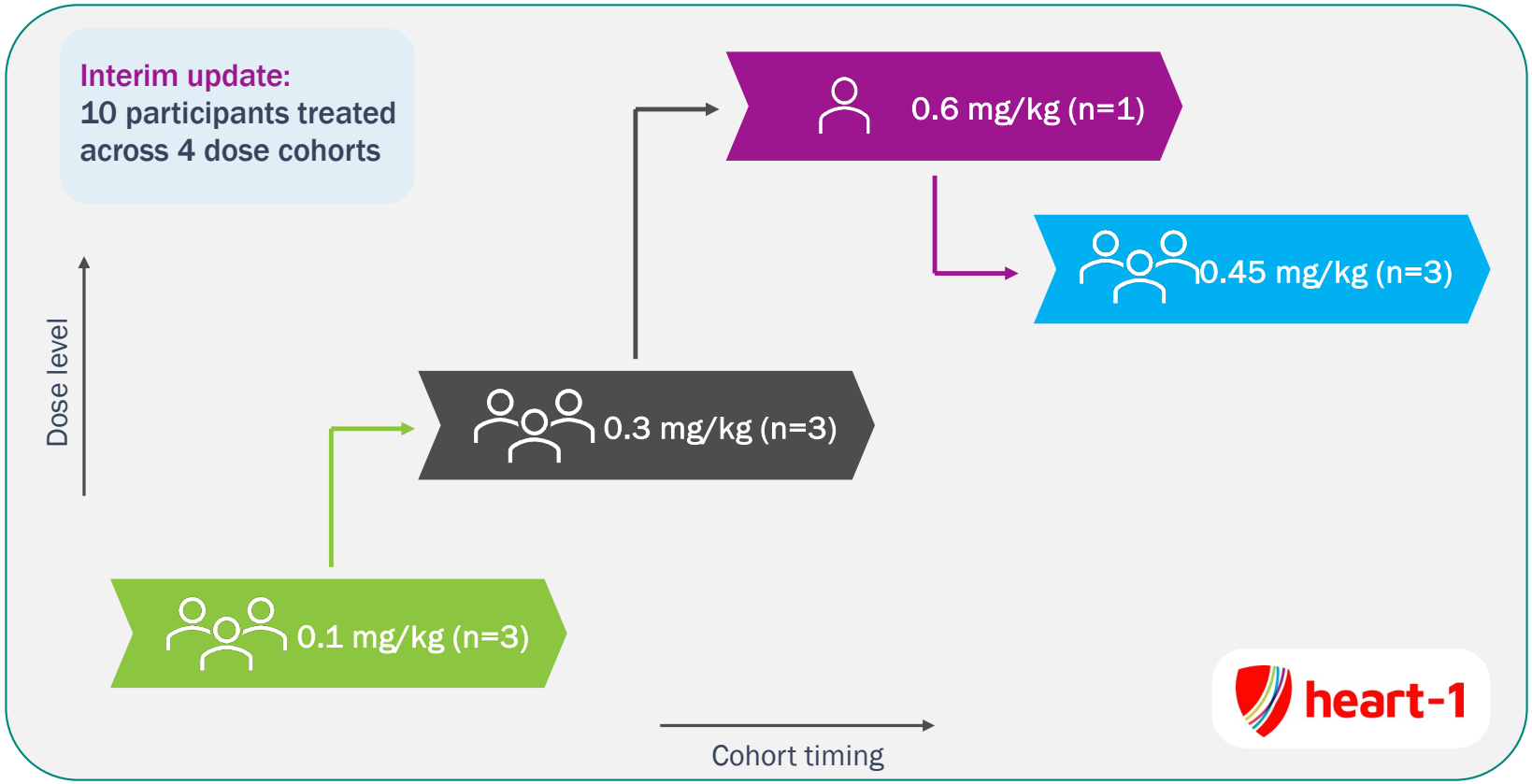
Back up

Effect of prior PCSK9 therapies in HeFH patient population: ~40-60% reduction in LDL-C



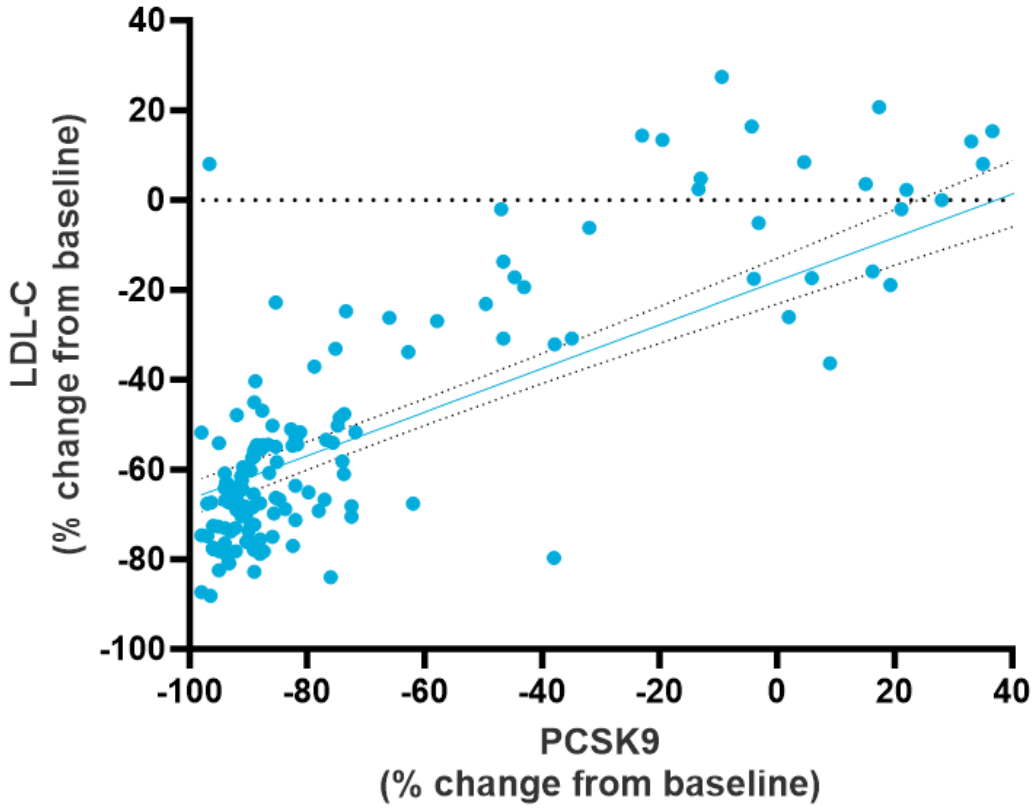
Results are presented from different published clinical studies at different points in time with differences in study design. No head-to-head studies have been conducted among all the results shown.

heart-1 designed as a single ascending dose study with up to 6 flexible dose cohorts, each with 3-6 participants



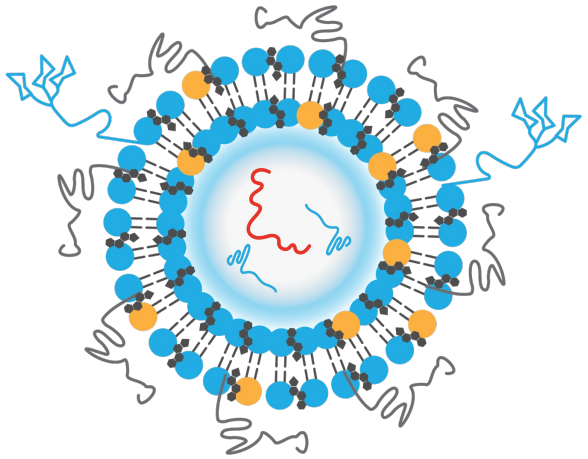
As of October 16, 2023 interim data cut.

Aggregated NHP data shows strong pattern of correlation between PCSK9 reduction and LDL reduction, but variability was common



Aggregated NHP studies on VERVE-101 at various doses showed pattern of correlation

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

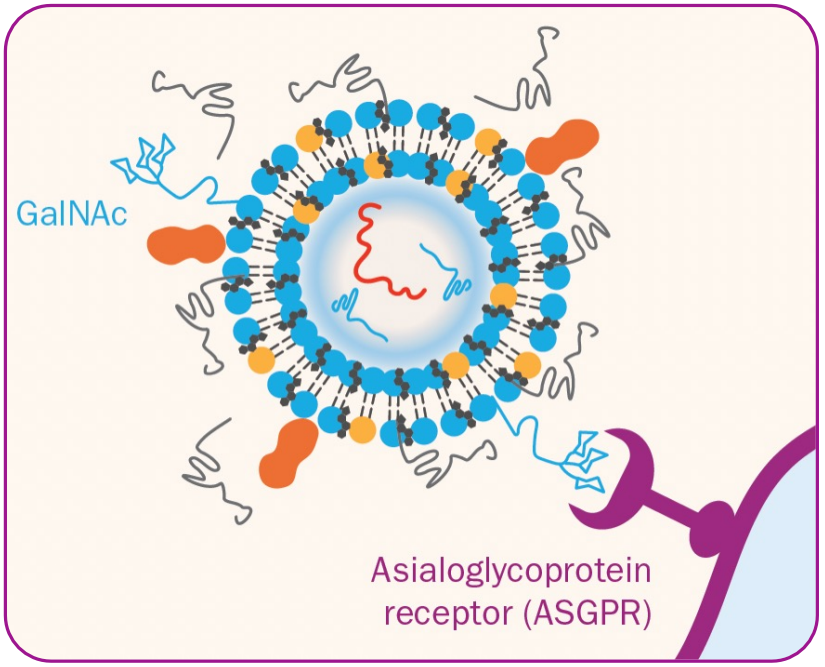


Lipid nanoparticle

GalNAc

mRNA

gRNA

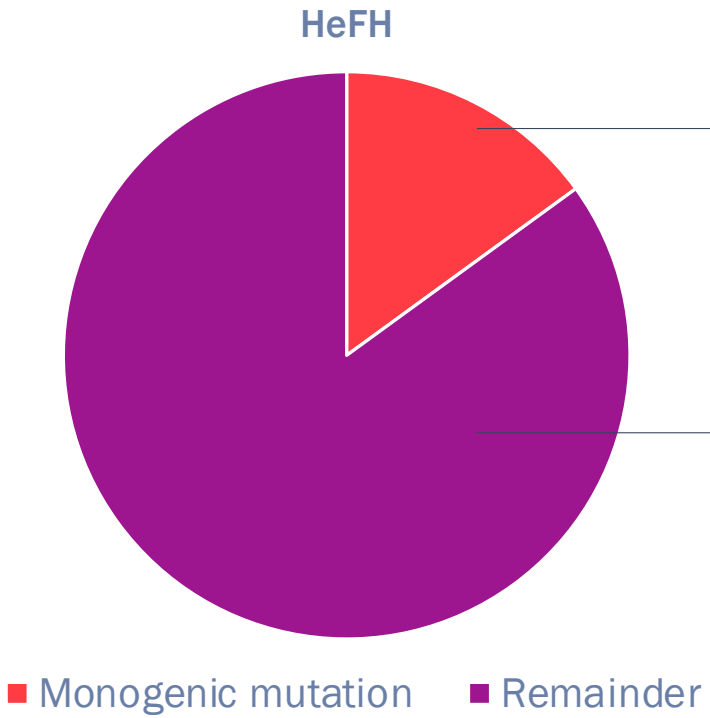


Effect of prior PCSK9 therapies in HeFH patient population: ~40-60% reduction in LDL-C

	Study	N	Dose	Mean Baseline LDL-C (mg/dl)	Mean % Change from Baseline*	Timepoint
Evolocumab	Rutherford	55 HeFH	350 mg q 4Wk	162 159 (in 350 mg group) 151 (in 420 mg group)	-42.7 ± 2.9	12 weeks
		56 HeFH	420 mg q 4Wk		-55.2 ± 2.9	12 weeks
	Rutherford-2	110 HeFH	140mg q 2Wk	156 (per USPI) 162 (in 140 mg group) 155 (in 420 mg group)	-61.3 ± 1.8	12 weeks
		110 HeFH	420 mg q month		-55.7 ± 2.3	12 weeks
Alirocumab	ODYSSEY – FH I	322 HeFH	75/150 mg q 2 Wk	144.7	-48.8 ±1.6	24 weeks
	ODYSSEY – FH II	166 HeFH	75/150 mg q 2 Wk	134.6	-48.7 ±1.9	24 weeks
Inclisiran	ORION-9	242 HeFH	300 mg D1, D90, D270 and D450	151.4	-39.7% ± 2	Day 510

Mean +/- SE

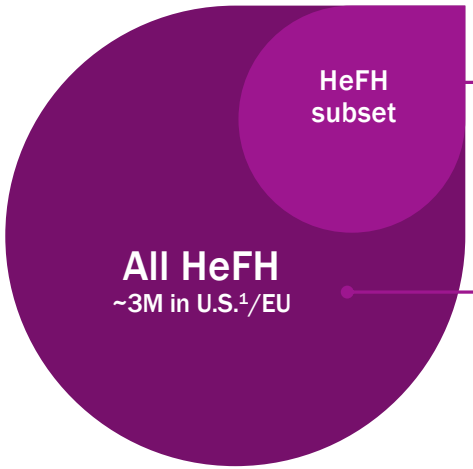
Roughly 15% of patients with diagnosis of HeFH carry a monogenic mutation in LDLR, PCSK9, or APOB



15% of HeFH patients: monogenic mutation in LDLR, PCSK9, or APOB

85% of HeFH patients: Polygenic inheritance or more complex models

Stepwise clinical development strategy for VERVE-PCSK9 starting with HeFH

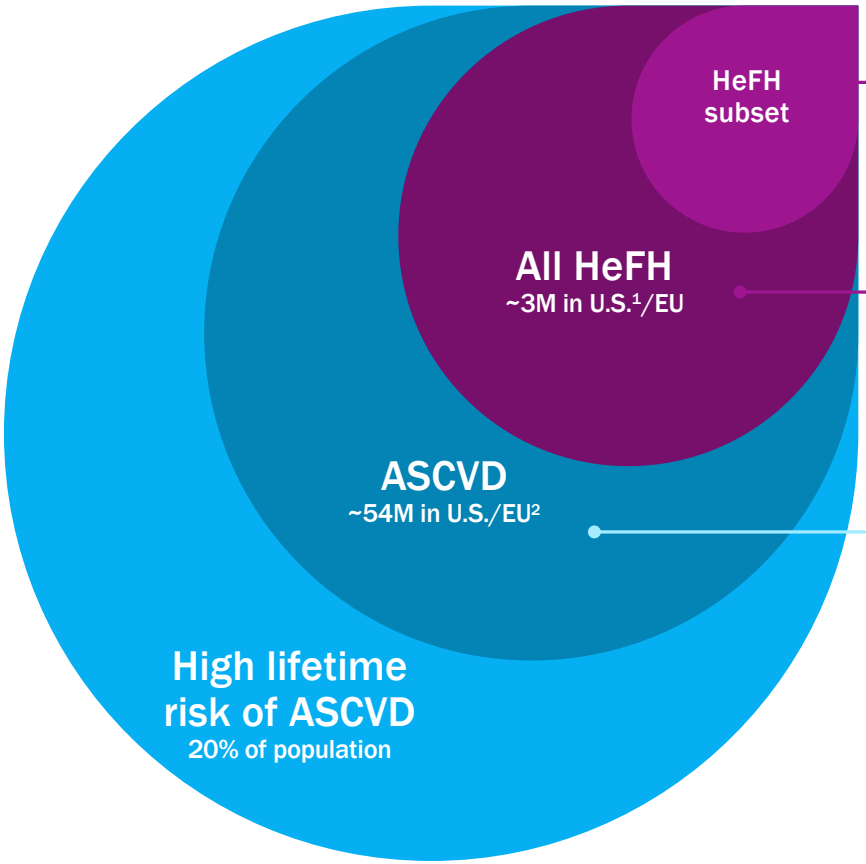


- Phase 1b proof-of-concept in high-risk HeFH
- Phase 2 in all HeFH
- Pivotal Phase 3 in all HeFH (LDL-C endpoint)

Clinical development strategy subject to alignment with regulators

1. Tsao CW et al., Heart Disease and Stroke Statistics – 2022 Update: A Report from the American Heart Association. *Circulation.* 2022;145(8):e153–e639.

Stepwise clinical development strategy for VERVE-PCSK9 starting with HeFH, with potential expansion to ASCVD

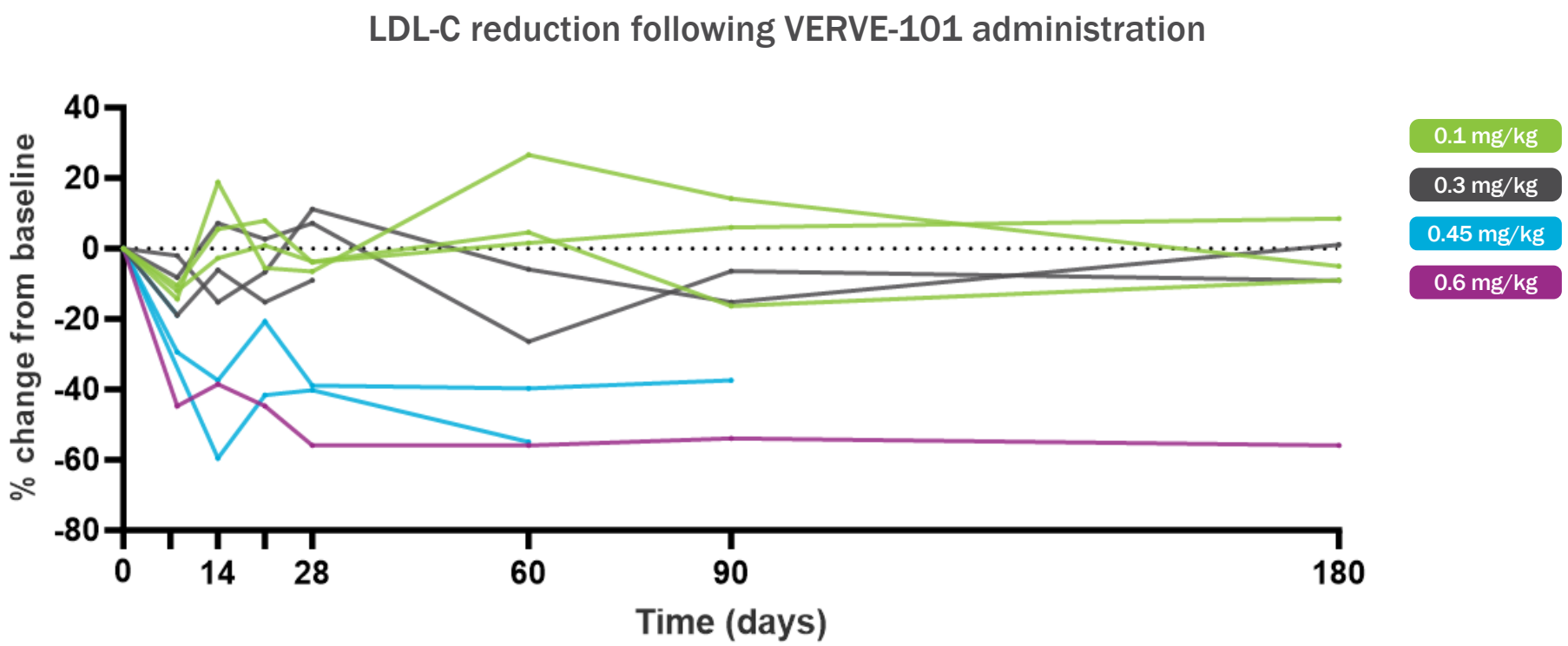


- Phase 1b proof-of-concept in high-risk HeFH
- Phase 2 in all HeFH
- Pivotal Phase 3 in all HeFH (LDL-C endpoint)
- Pivotal Phase 3 in ASCVD (LDL-C endpoint)
- Cardiovascular outcome study in ASCVD

Clinical development strategy subject to alignment with regulators

1. Tsao CW et al., Heart Disease and Stroke Statistics – 2022 Update: A Report from the American Heart Association. *Circulation.* 2022;145(8):e153–e639.
2. Gu J et al., *Am J Prev Cardiol.* 2022;10:100336.

Serial LDL-C by individual participants (n=9)



As of October 16, 2023 interim data cut.

U.S. FDA cleared investigational new drug application (IND) for VERVE-101 in patients with HeFH

Received FDA clearance to initiate heart-1 trial in U.S.

Plan to activate U.S. sites for VERVE-101 development

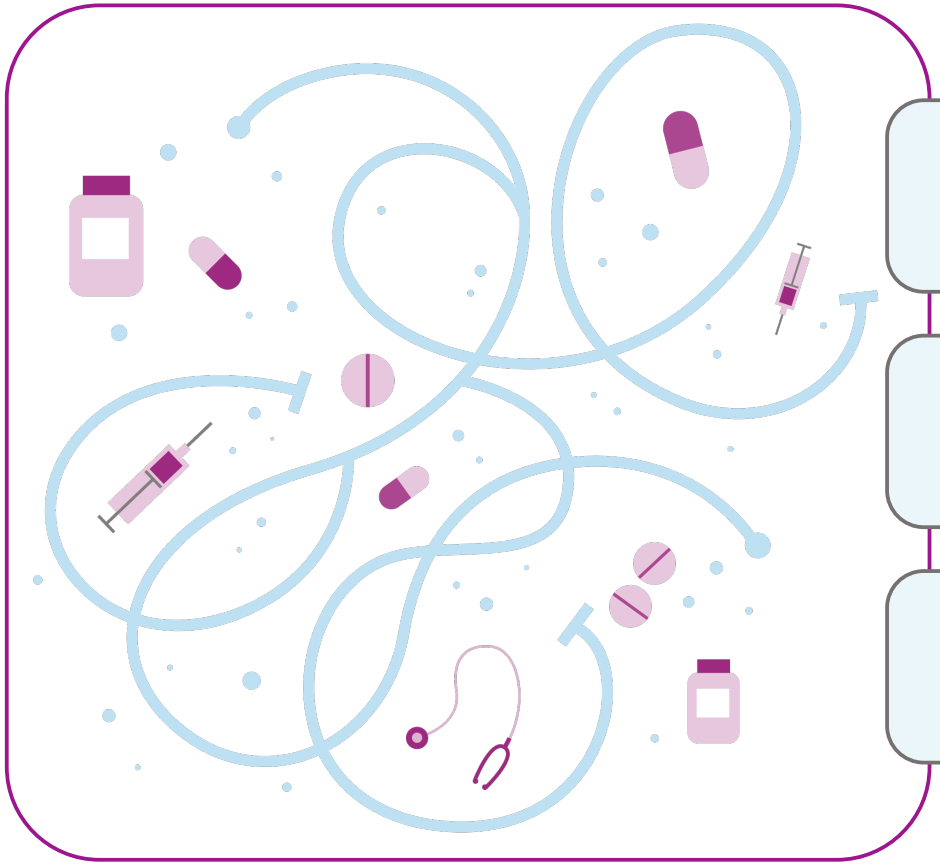
Plan to incorporate learnings from FDA interaction to impact future pipeline (VERVE-102, VERVE-201)

FDA reviewed our complete response which included:

- Comprehensive experiments to address preclinical requests
- heart-1 clinical trial dataset

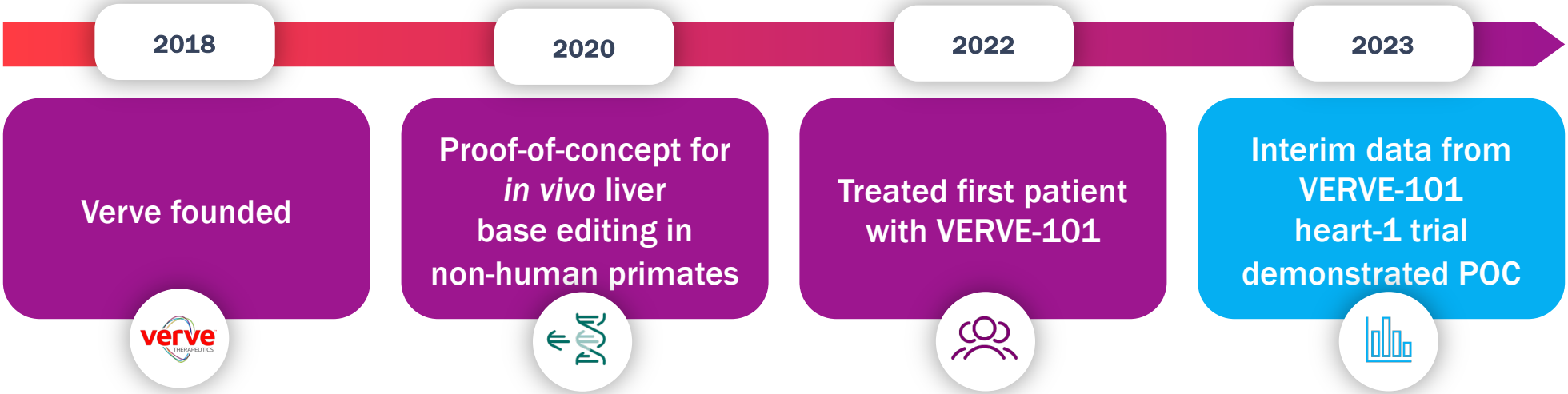
First IND for *in vivo* base editing

Chronic care model to treat HeFH and ASCVD seems broken



- Daily pills or intermittent injections
- Administered often over decades
- Heavy treatment burden on patients, providers, and healthcare system

Significant milestone: interim data has demonstrated proof-of-concept in humans for *in vivo* liver base editing



Adverse events occurring in more than 1 participant

Number of participants experiencing:	0.1 mg/kg (n=3)	0.3 mg/kg (n=3)	0.45 mg/kg (n=3)	0.6 mg/kg (n=1)	Total (n=10)
AE occurring in more than 1 participant	2	0	3	1	6
Infusion-related reaction, n	0	0	3	1	4
Upper respiratory infection and COVID-19, n	2	0	0	1	3
Any serious AE	0	1	1	0	2
Cardiovascular events, n	0	1	1	0	2
Non-cardiovascular events, n	0	0	0	0	0
Any treatment-related AE grade 3 or higher	0	0	1	1	2
Cardiovascular events, n	0	0	1[a]	0	1
Increased liver transaminases, n	0	0	0	1[b]	1

As of October 16, 2023 interim data cut.
a. Myocardial infarction assessed as potentially related to treatment; b. transient, asymptomatic increase in liver transaminases with bilirubin levels below the upper limit of normal

Any serious adverse event

Number of participants experiencing:	0.1 mg/kg (n=3)	0.3 mg/kg (n=3)	0.45 mg/kg (n=3)	0.6 mg/kg (n=1)	Total (n=10)
AE occurring in more than 1 participant	2	0	3	1	6
Infusion-related reaction, n	0	0	3	1	4
Upper respiratory infection and COVID-19, n	2	0	0	1	3
Any serious AE	0	1	1	0	2
Cardiovascular events, n	0	1	1	0	2
Non-cardiovascular events, n	0	0	0	0	0
Any treatment-related AE grade 3 or higher	0	0	1	1	2
Cardiovascular events, n	0	0	1[a]	0	1
Increased liver transaminases, n	0	0	0	1[b]	1

As of October 16, 2023 interim data cut.

a. Myocardial infarction assessed as potentially related to treatment; b. transient, asymptomatic increase in liver transaminases with bilirubin levels below the upper limit of normal

Any treatment-related adverse event, grade 3 or higher

Number of participants experiencing:	0.1 mg/kg (n=3)	0.3 mg/kg (n=3)	0.45 mg/kg (n=3)	0.6 mg/kg (n=1)	Total (n=10)
AE occurring in more than 1 participant	2	0	3	1	6
Infusion-related reaction, n	0	0	3	1	4
Upper respiratory infection and COVID-19, n	2	0	0	1	3
Any serious AE	0	1	1	0	2
Cardiovascular events, n	0	1	1	0	2
Non-cardiovascular events, n	0	0	0	0	0
Any treatment-related AE grade 3 or higher	0	0	1	1	2
Cardiovascular events, n	0	0	1[a]	0	1
Increased liver transaminases, n	0	0	0	1[b]	1

As of October 16, 2023 interim data cut.
a. Myocardial infarction assessed as potentially related to treatment; b. transient, asymptomatic increase in liver transaminases with bilirubin levels below the upper limit of normal

Participants enrolled to date have severe, advanced ASCVD and high risk for cardiovascular events (near-term and lifetime)

Characteristic	Total (n=10)
Mean age, years (min, max)	54 (29, 69)
Sex, male, n	8
Mean screening LDL-C, mg/dL (min, max)	193 (107, 373)
Mutation in *LDLR* detected, n[1]	9
Cardiovascular Risk Profile	
Prior coronary revascularization, n	9
Prior coronary artery bypass grafting, n	3
≥ 1 prior percutaneous coronary intervention, n	7
≥ 1 prior myocardial infarction, n	4
Prior cardiac arrest, n	1
Concomitant and Prior Lipid-Lowering Therapy	
On statin therapy, n	8
Prior use of PCSK9-targeted therapy, n	2

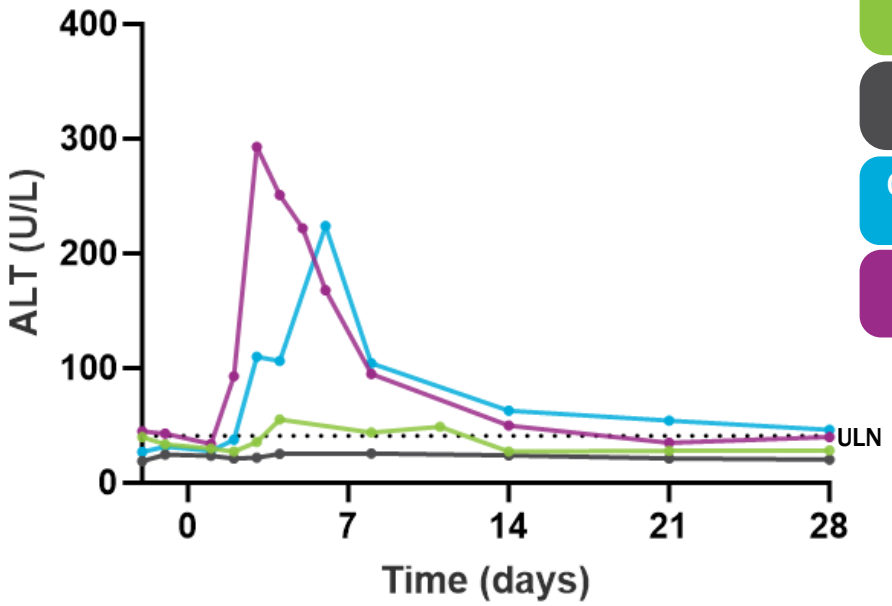
As of October 16, 2023 interim data cut.
1. One participant diagnosed based on clinical criteria

Interim safety summary: observed adverse events (AEs) consistent with a severe, advanced ASCVD patient population

Number of participants experiencing:	0.1 mg/kg (n=3)	0.3 mg/kg (n=3)	0.45 mg/kg (n=3)	0.6 mg/kg (n=1)	Total (n=10)
AE occurring in more than 1 participant	2	0	3	1	6
Infusion-related reaction, n	0	0	3	1	4
Upper respiratory infection and COVID-19, n	2	0	0	1	3
Any serious AE	0	1	1	0	2
Cardiovascular events, n	0	1	1	0	2
Non-cardiovascular events, n	0	0	0	0	0
Any treatment-related AE grade 3 or higher	0	0	1	1	2
Cardiovascular events, n	0	0	1[a]	0	1
Increased liver transaminases, n	0	0	0	1[b]	1

As of October 16, 2023 interim data cut.
a. Myocardial infarction assessed as potentially related to treatment; b. transient, asymptomatic increase in liver transaminases with bilirubin levels below the upper limit of normal

Transient, reversible increases in ALT observed at higher doses with mean bilirubin levels below the upper limit of normal

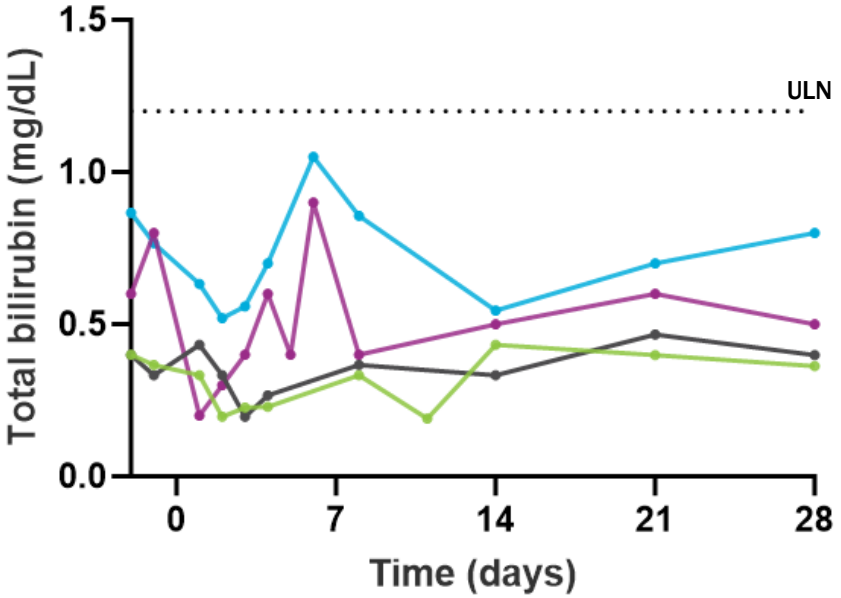


0.1 mg/kg (n=3)

0.3 mg/kg (n=3)

0.45 mg/kg (n=3)

0.6 mg/kg (n=1)



Lines indicate cohort mean values

As of October 16, 2023 interim data cut; values for one patient in 0.45 mg/kg cohort are a mix of central and local laboratory values due to a period of hospitalization; ULNs are from central laboratory; ULN on ALT graph is value for males of 41 U/L, female ULN is 33 U/L

ALT, alanine aminotransferase; U, units; ULN, upper limit of normal

Observed serious adverse events consistent with a severe, advanced ASCVD patient population

Cardiovascular SAEs occurred in 2 participants
(3 events in total, of which 2 were determined to be unrelated)

- Fatal cardiac arrest about 5 weeks after infusion (DOSE 0.3 MG/KG)
  - Ischemic cardiomyopathy at baseline & prior cardiac arrest
  - On autopsy, severe underlying CAD; no evidence of pulmonary embolism, myocardial inflammation, or coronary thrombus
  - Investigators & DSMB determined as unrelated to study treatment
- MI and non-sustained ventricular tachycardia (NSVT) (DOSE 0.45 MG/KG)
  - Unstable chest pain symptoms (unreported to investigators) prior to treatment with VERVE-101
  - MI occurred day after infusion
  - On coronary angiography, critical left-main equivalent CAD (in-stent restenosis lesions involving both LAD and LCx arteries)
  - NSVT occurred >4 weeks after infusion
  - Investigators & DSMB determined MI as potentially related to treatment due to proximity to dosing; NSVT determined to be unrelated

Independent data and safety monitoring board (DSMB) agreed that SAEs were consistent with a severe, advanced ASCVD patient population and recommended continuing dosing

As of October 16, 2023 interim data cut.
SAE, serious adverse event,; CAD, coronary artery disease; MI, myocardial infarction

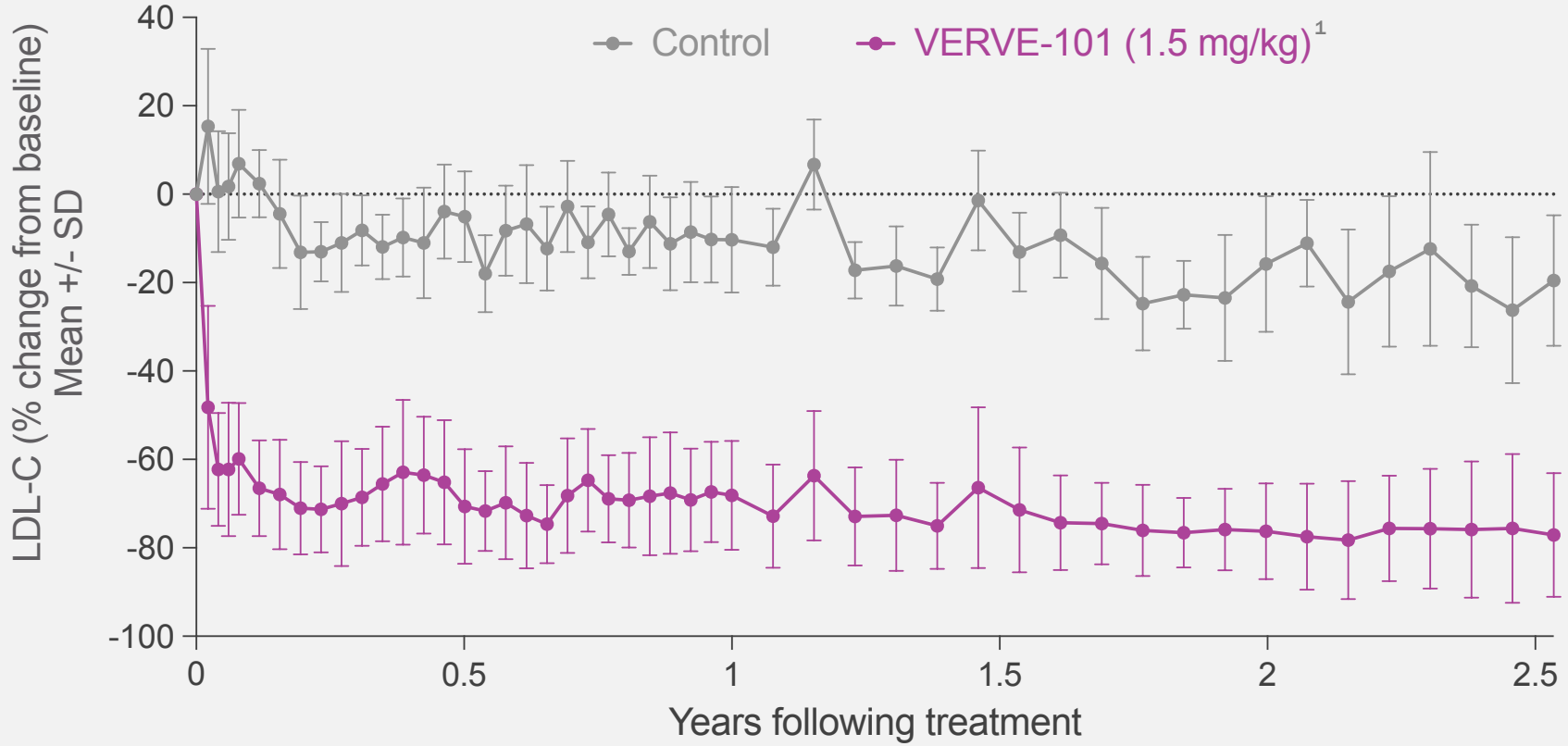
Extensive preclinical evaluation of VERVE-101 in non-human primates & human cells

1. Durability

2. Liver-specific biodistribution

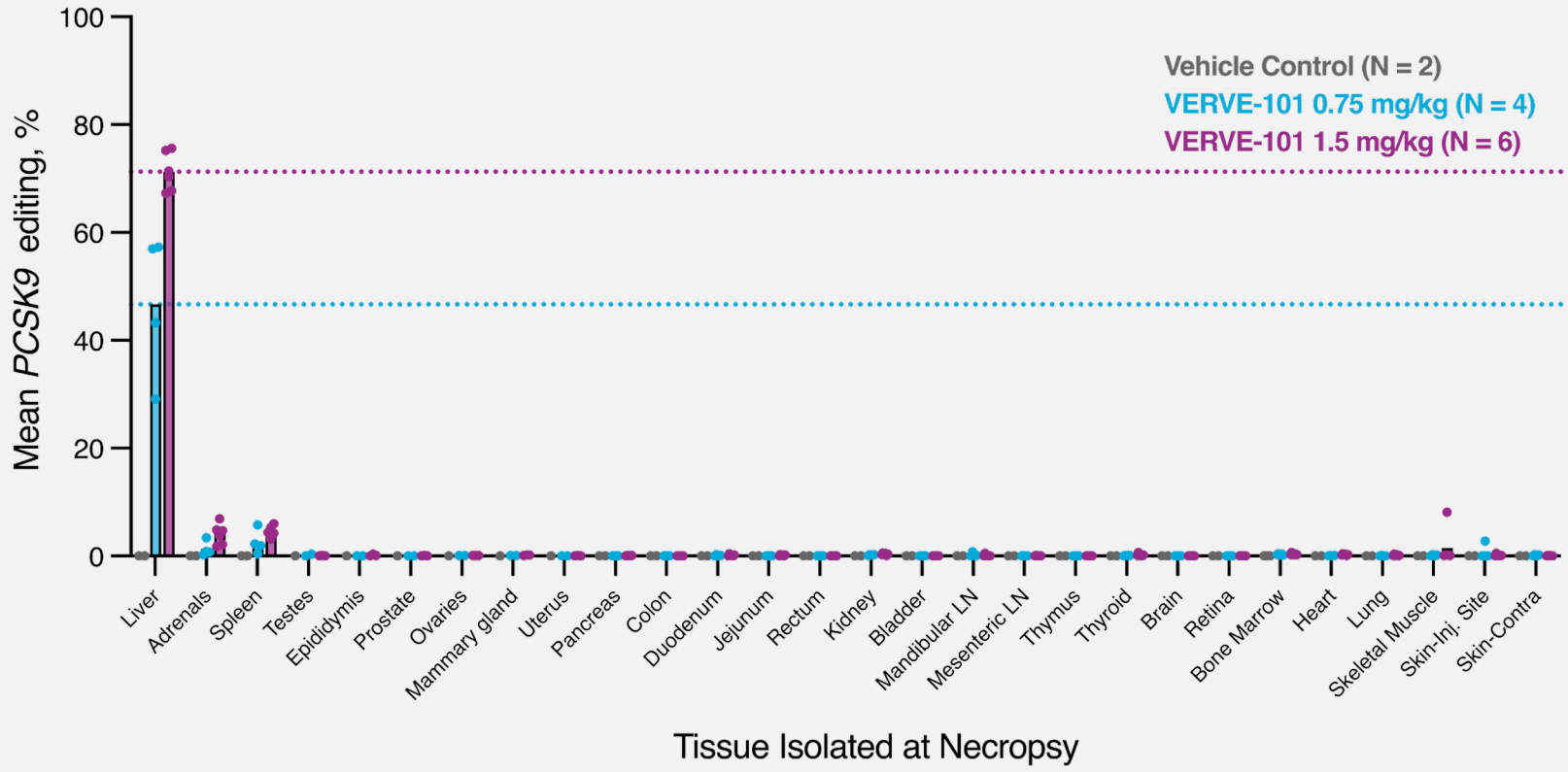
3. No significant off-target editing

Durability out to 2.5 years observed after a single dose of VERVE-101 in non-human primates

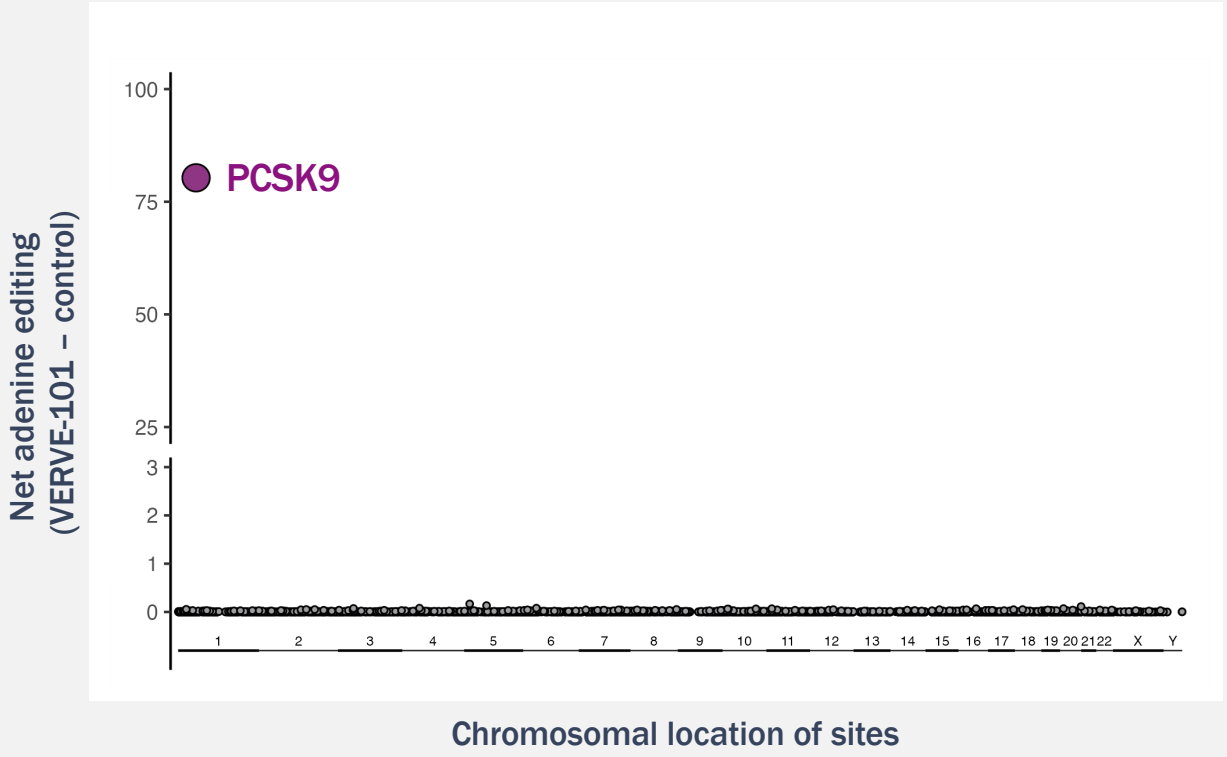


1. Data represents mean +/- SD for cohorts which included N=10 in control and N=22 in VERVE-101 at the earliest time points and N=7 and N=16, respectively, at the last time point

Liver-specific biodistribution observed in non-human primates treated with VERVE-101



In human liver cells treated with VERVE-101, no evidence for off-target editing

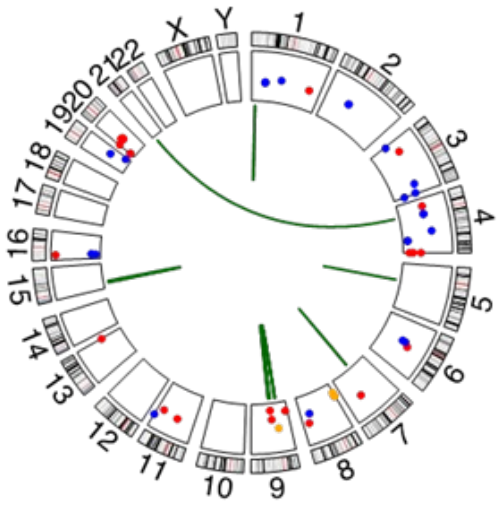


- Donor primary human hepatocytes treated with saturating dose of VERVE-101 LNPs
- 'Manhattan-style' plot of ~6000 candidate sites
- No candidate sites show statistically significant net editing

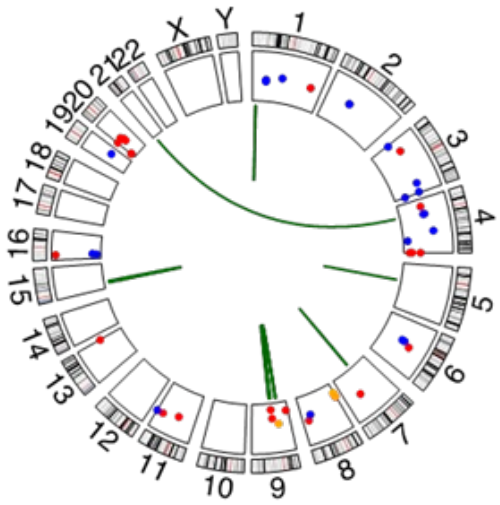
No chromosomal translocations or structural variants identified following treatment of primary human liver cells with VERVE-101

Primary liver cell
Lot 1

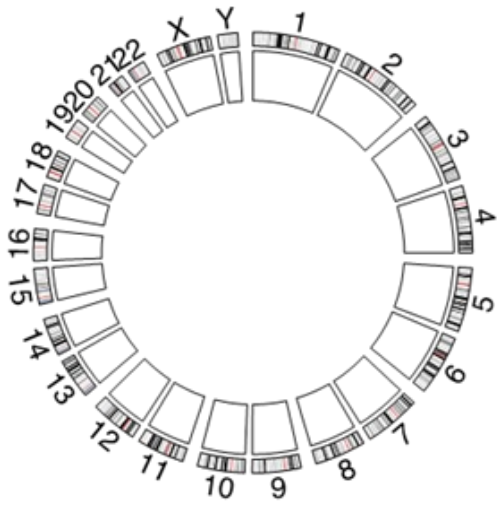
untreated



VERVE-101



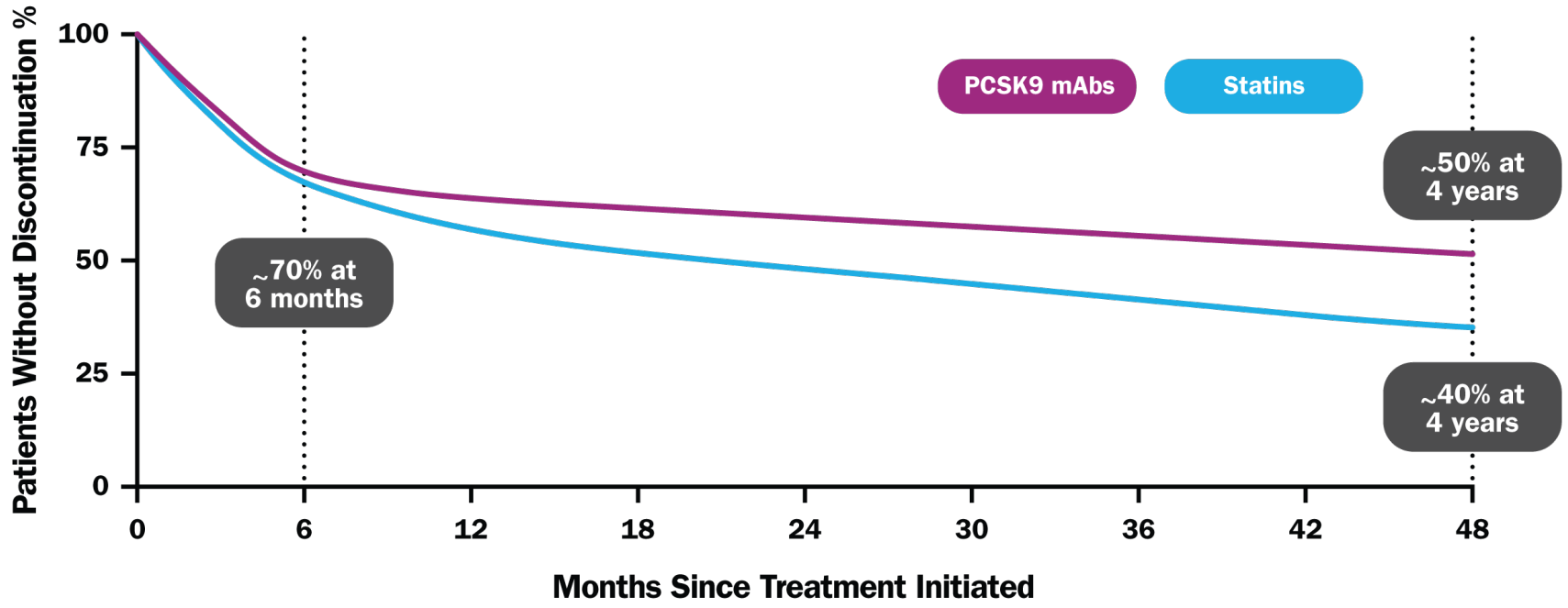
VERVE-101 minus untreated



• insertion • duplication • deletion • inversion — translocation

Current options lower LDL-C but not for long enough.
Unmet need is lifelong LDL-C lowering

At 4y, <50% patients on any cholesterol-lowering medication



Adapted from Zafrir et al., *J Clin Lipidol* 2021:15(1):202-211.e2 and Lin et al., *J Manag Care Spec Pharm* 2016;22(6):685-98.

Verve's core capabilities to develop *in vivo* liver gene editing medicines

Internally developed novel LNPs

mRNA design, purification, and GMP production

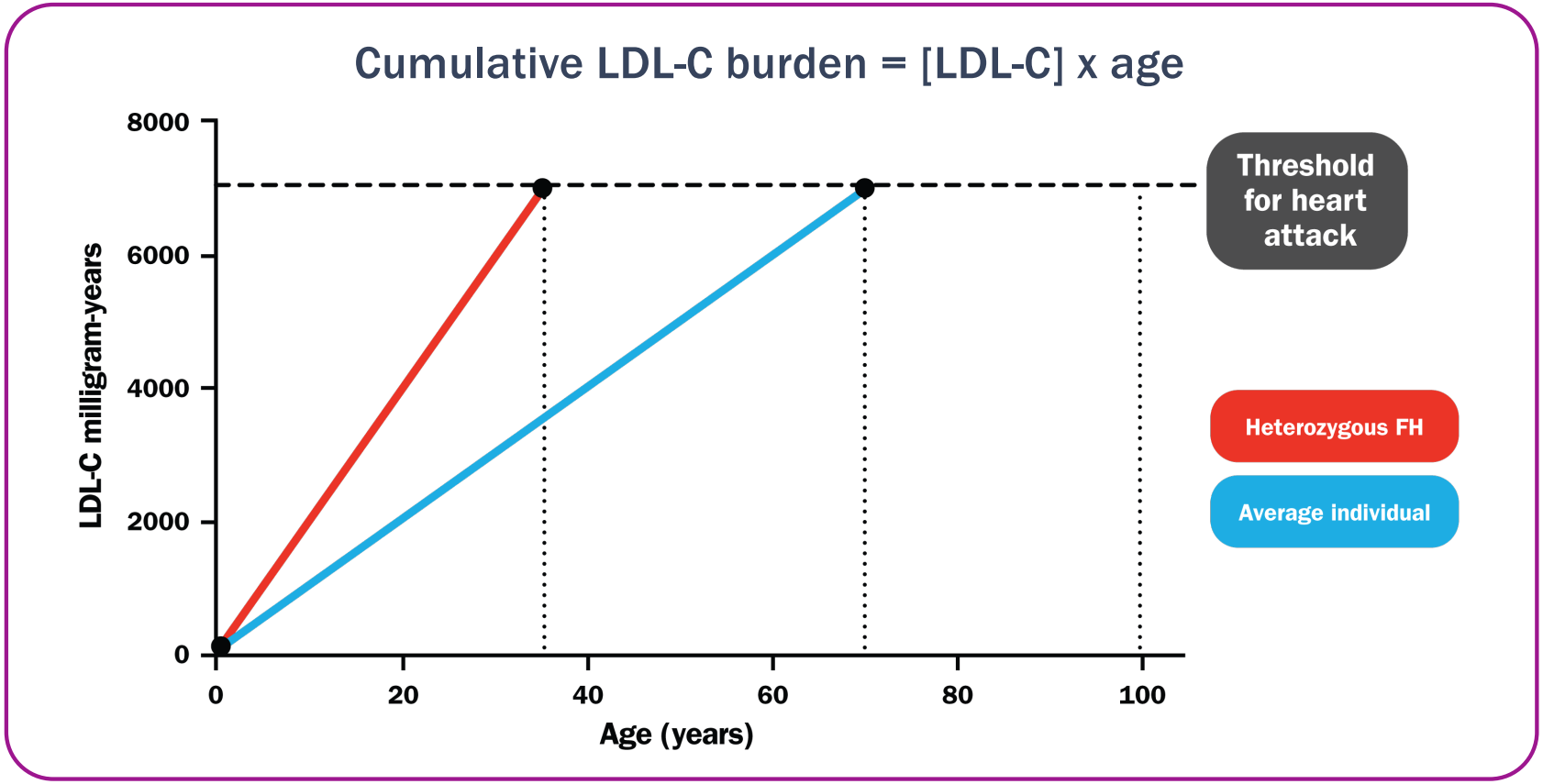
gRNA design and purification

Base editing as well as internally developed new editing approaches

Comprehensive off-target assessment

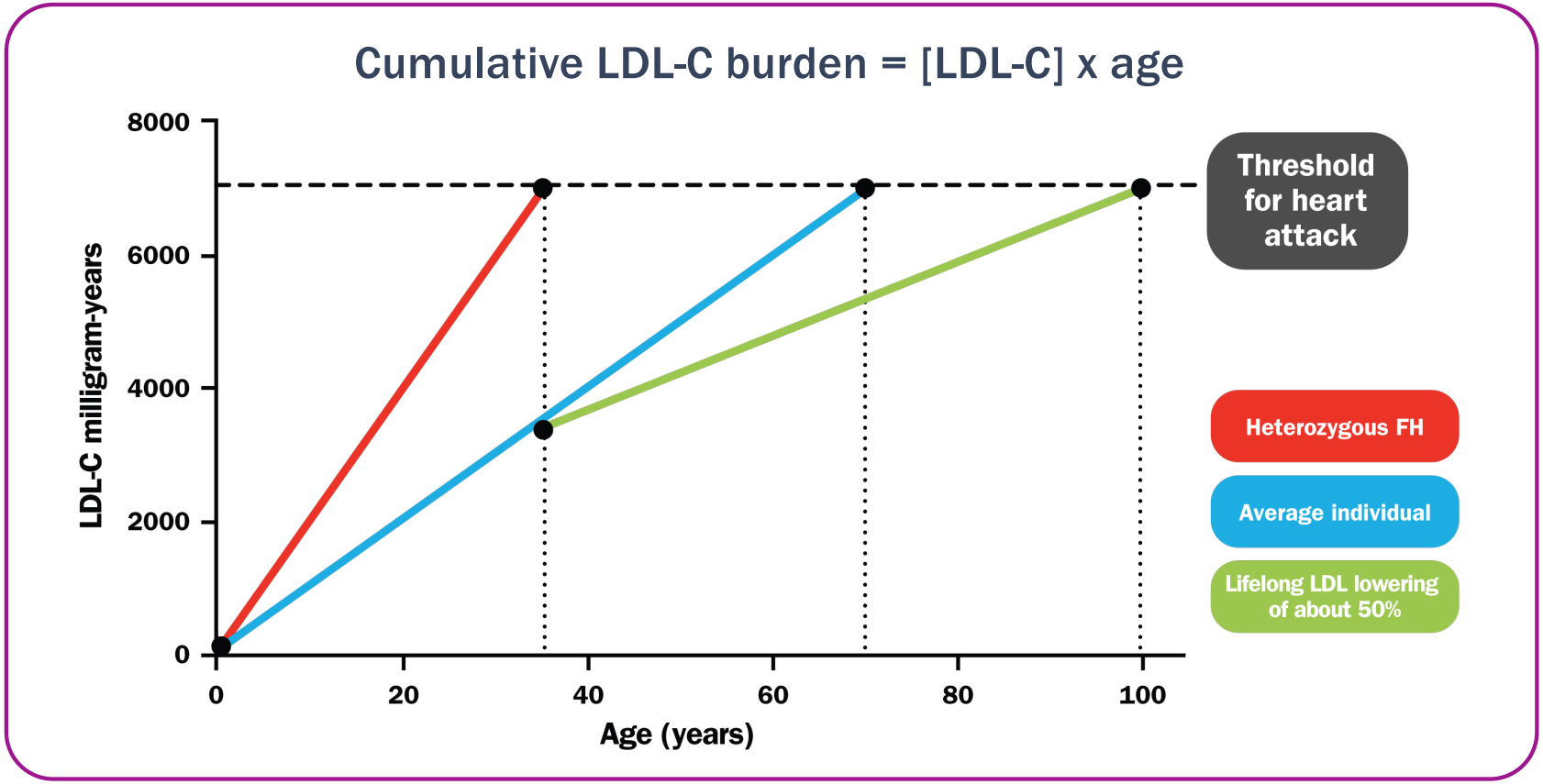
LNP, lipid nanoparticles; GMP, good manufacturing practices; RNA, ribonucleic acid; mRNA, messenger RNA; gRNA, guide RNA

Potential impact of lifelong cholesterol lowering: "cholesterol-years" concept



Braunwald E. *Eur Heart J*. 2022;43:249-50; Horton JD, Cohen JC, Hobbs HH. *J Lipid Res* 2009;50 Suppl:S172–S179.

Potential impact of lifelong LDL lowering: substantially delay onset of heart attack



Braunwald E. *Eur Heart J*. 2022;43:249-50; Horton JD, Cohen JC, Hobbs HH. *J Lipid Res* 2009;50 Suppl:S172–S179.