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

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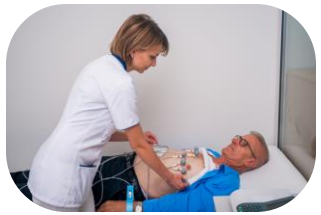
91st EAS Congress

Forward looking statements

This presentation contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995 that involve substantial risks and uncertainties, including statements regarding the timing and availability of clinical data from the Company's heart-1 clinical trial, the timing of initiation of clinical trials of VERVE-201, the Company's research and development plans, the potential advantages and therapeutic potential of the Company’s programs, including VERVE-101 and VERVE-201, and the period over which the Company believes that its existing, cash, cash equivalents and marketable securities will be sufficient to fund its operating expenses. All statements, other than statements of historical facts, contained in this presentation, including statements regarding the Company’s strategy, future operations, future financial position, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “should,” “target,” “will,” “would” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements are based on management’s current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in, or implied by, such forward-looking statements. These risks and uncertainties include, but are not limited to, risks associated with the Company’s limited operating history; the timing of and the Company’s ability to submit applications for its product candidates; continue to advance its product candidates in clinical trials; initiate and enroll patients in its ongoing and future clinical trials on the timeline expected or at all; correctly estimate the potential patient population and/or market for the Company’s product candidates; replicate in clinical trials positive results found in preclinical studies and/or earlier-stage clinical trials of VERVE-101 and VERVE-201; advance the development of its product candidates under the timelines it anticipates in current and future clinical trials; obtain, maintain or protect intellectual property rights related to its product candidates; manage expenses; and raise the substantial additional capital needed to achieve its business objectives. For a discussion of other risks and uncertainties, and other important factors, any of which could cause the Company’s actual results to differ from those contained in the forward-looking statements, see the “Risk Factors” section, as well as discussions of potential risks, uncertainties and other important factors, in the Company’s most recent filings with the Securities and Exchange Commission and in other filing that the Company makes with the Securities and Exchange Commission in the future. In addition, the forward-looking statements included in this presentation represent the Company’s views as of the date hereof and should not be relied upon as representing the Company’s views as of any date subsequent to the date hereof. The Company anticipates that subsequent events and developments will cause the Company’s views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, the Company specifically disclaims any obligation to do so.

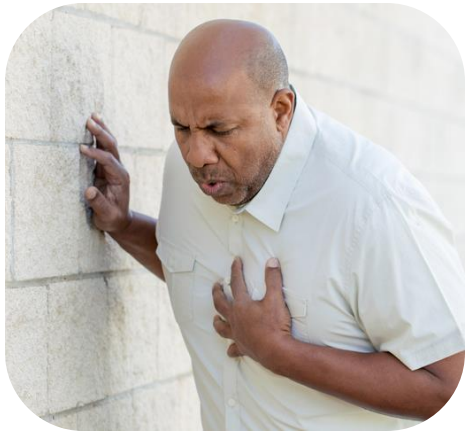
Atherosclerotic cardiovascular disease (ASCVD): #1 cause of death worldwide despite available treatments



One person

dies every 34 seconds

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



100s of millions

of patients worldwide

~800K heart attacks

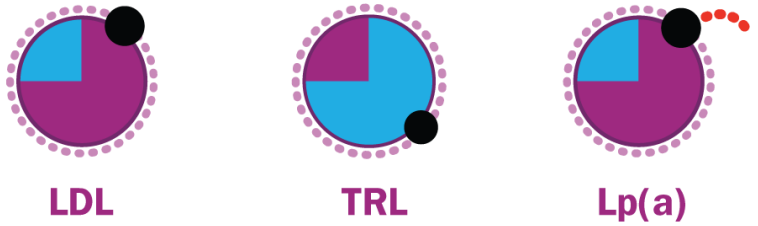
per year in the U.S.[2]

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:



Familial hypercholesterolemia (FH): a genetic subtype of ASCVD, sky-high LDL cholesterol from birth leading to ASCVD at young ages

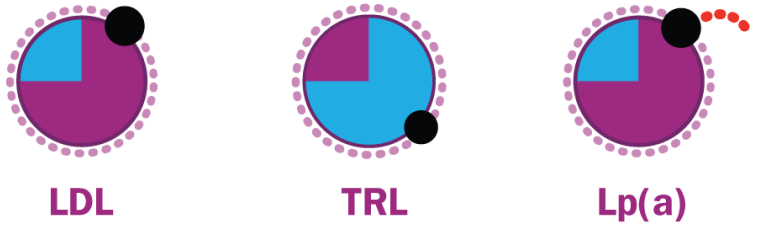
					
Heterozygous FH (HeFH)	*LDLR* mutation in single copy	>190 mg/dl	30-60 years	>95% patients worldwide not at LDL-C goal	~3M patients in US/Europe
Homozygous FH (HoFH)	*LDLR* mutation in both gene copies	>400 mg/dl	Childhood	Despite 4 or 5 meds, almost all not at LDL-C goal	~3,000 patients in US/Europe

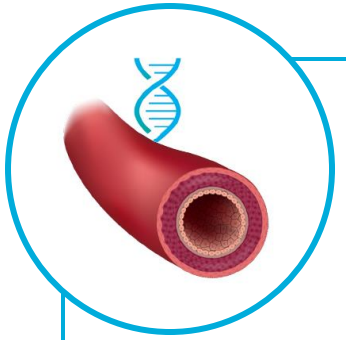
Adapted from Family Heart Foundation; https://familyheart.org/familial-hypercholesterolemia/homozygous-familial-hypercholesterolemia

What's a solution to ASCVD?

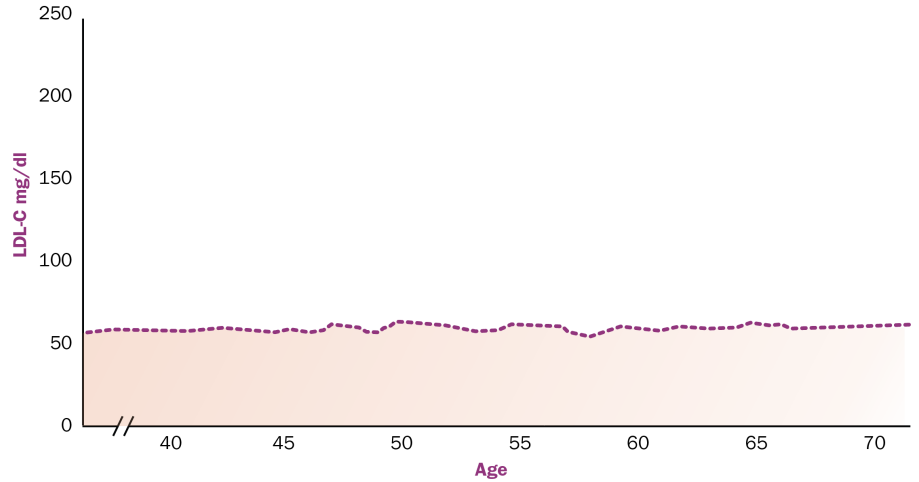
High cumulative life-long exposure to blood cholesterol clogs heart arteries

Cholesterol carried in 3 lipoproteins:





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

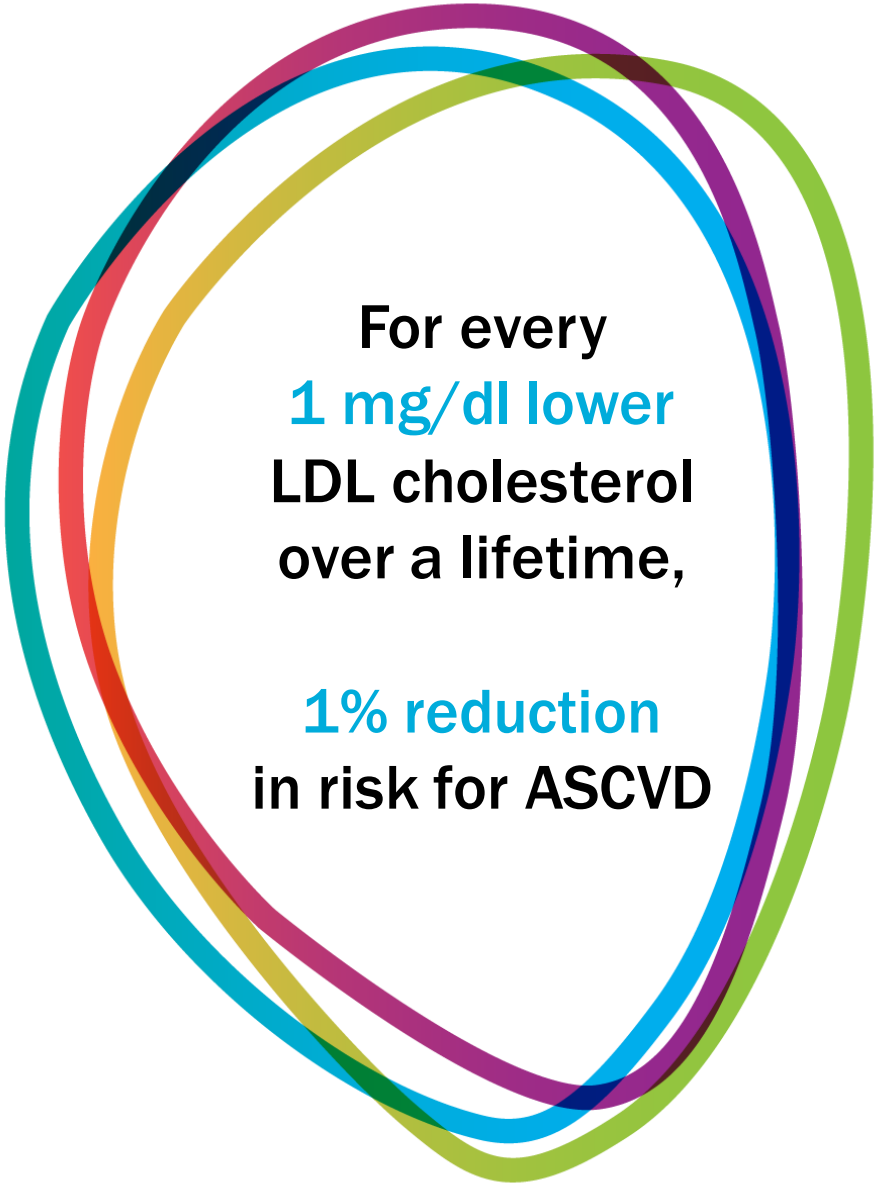
Resistant to ASCVD

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

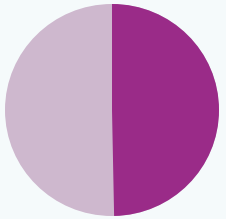
~50% lower risk
for heart disease

Healthy

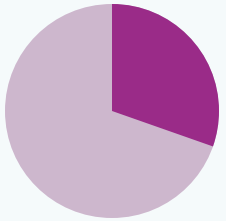
We have 3 pills & 3 injections available now to lower cholesterol What's the unmet need?

ASCVD

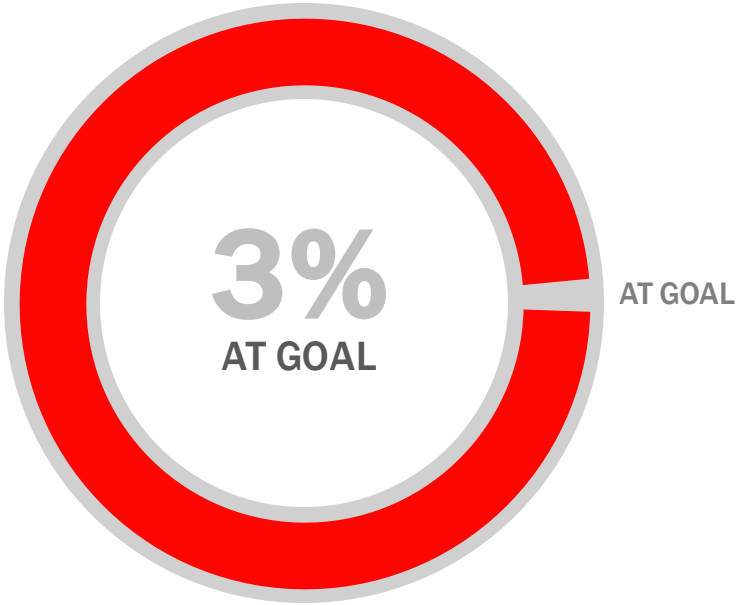
Only 50% ASCVD patients in U.S. on statin[1]



Only 27% ASCVD patients in U.S. at LDL-C goal[2]



FH



In a global registry of HeFH patients,
3% attain
LDL-C < 70 in current chronic care model

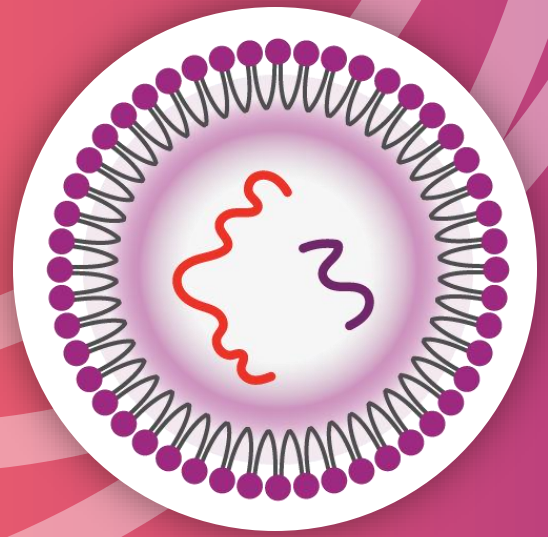
Chronic care model to treat chronic disease is broken

**Daily pills/intermittent injections,
administered often over decades,
places a heavy treatment burden
on patients, providers, and healthcare system**

Can we transform care of ASCVD from daily pills/intermittent injections to a “One Time Procedure”?

Advancing a pipeline of single-course *in vivo* gene editing programs

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



VERVE-101 targeting PCSK9: Enrolling in a Phase 1b clinical trial

VERVE-101: adenine base editor mRNA + gRNA packaged in an LNP; edit designed to turn off *PCSK9*

DRUG SUBSTANCES

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

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

+

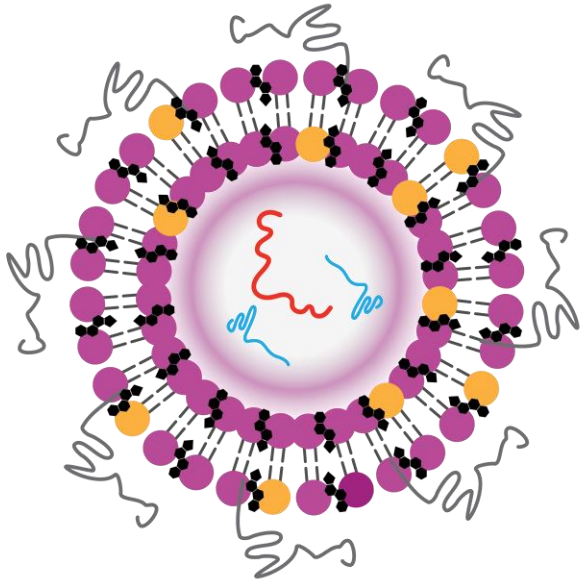
DELIVERY VEHICLE

Lipid nanoparticle (LNP) for delivery to liver cell includes 4 components

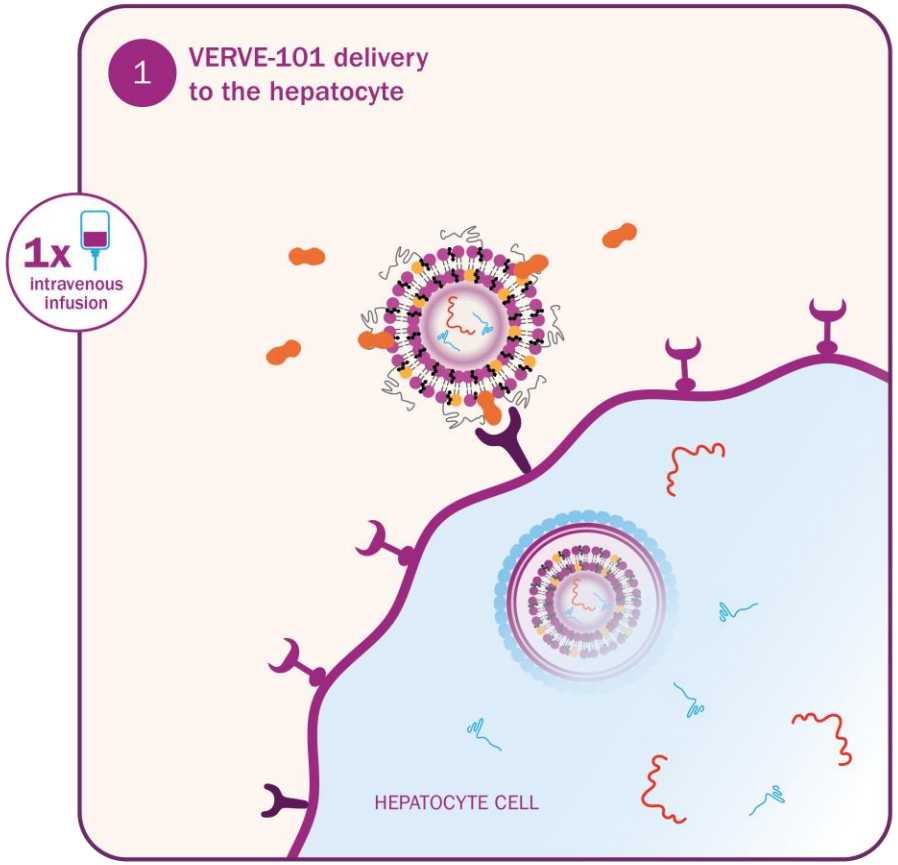
- Ionizable amino lipid
- DSPC
- Cholesterol
- PEG

=

VERVE-101

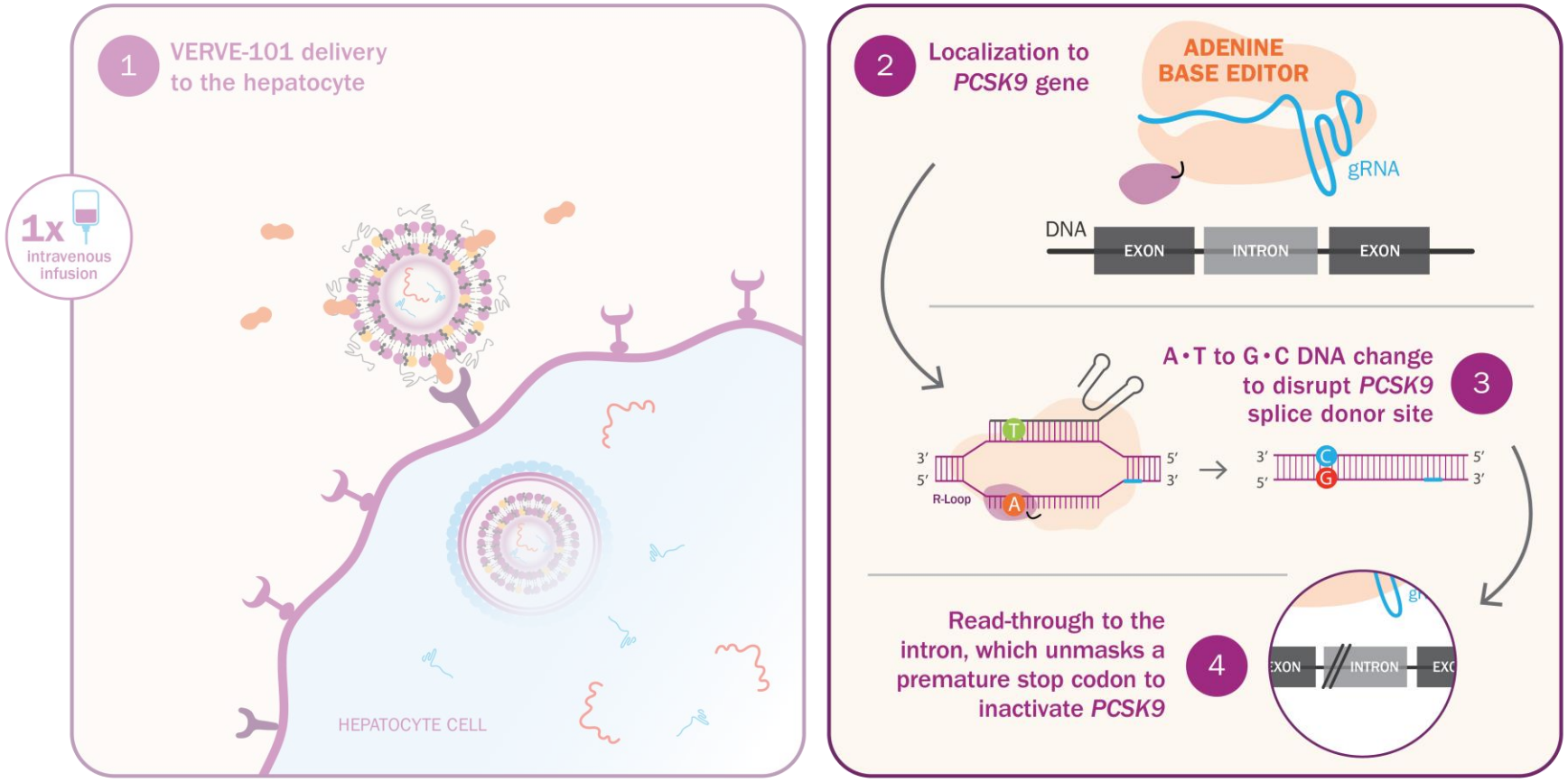


VERVE-101: base editing medicine designed to inactivate hepatic *PCSK9* and lower LDL-C



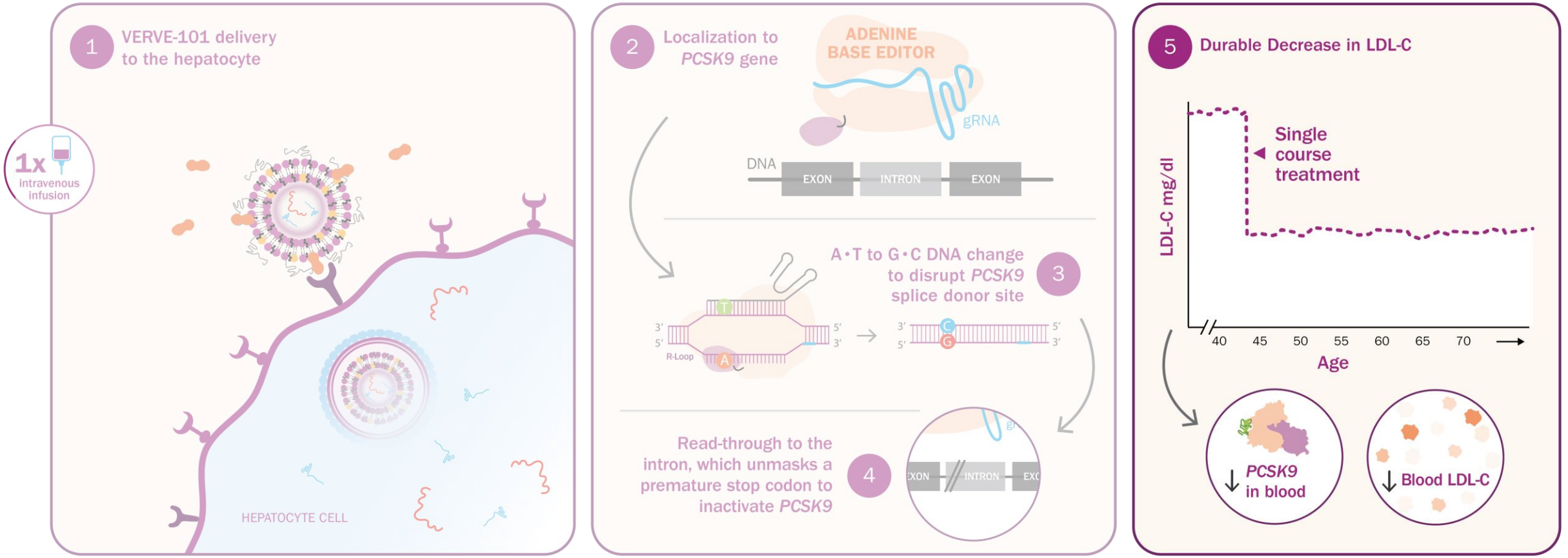
Lipid nanoparticle
Ionizable amino lipid
DSPC
LDL receptor (LDLR)
apoE
mRNA
gRNA
PEG Lipid
Cholesterol

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

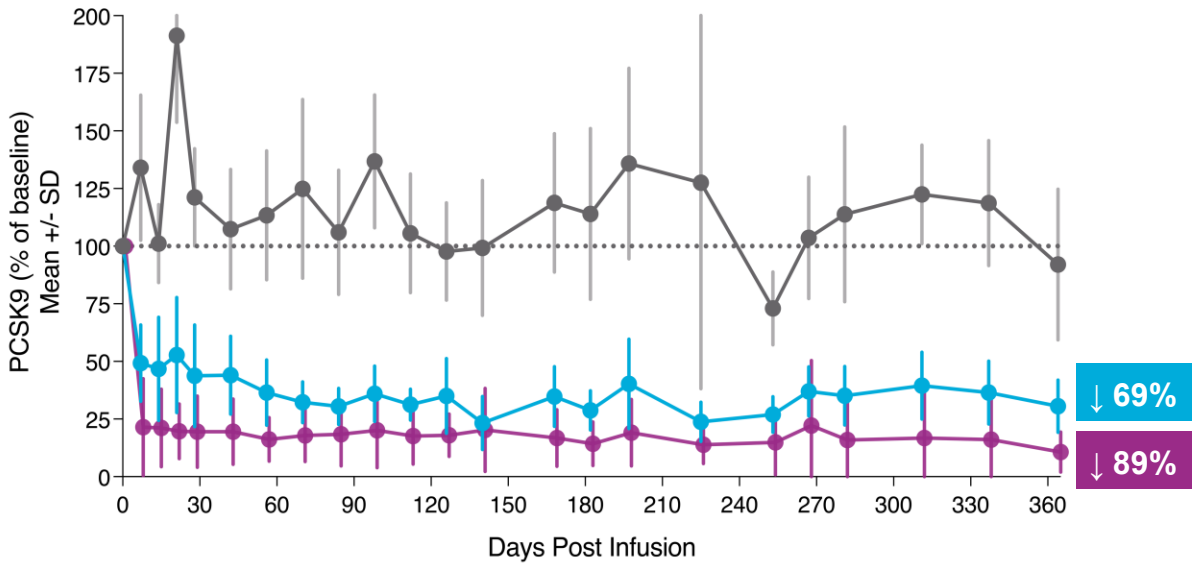
VERVE-101: base editing medicine designed to inactivate hepatic *PCSK9* and lower LDL-C



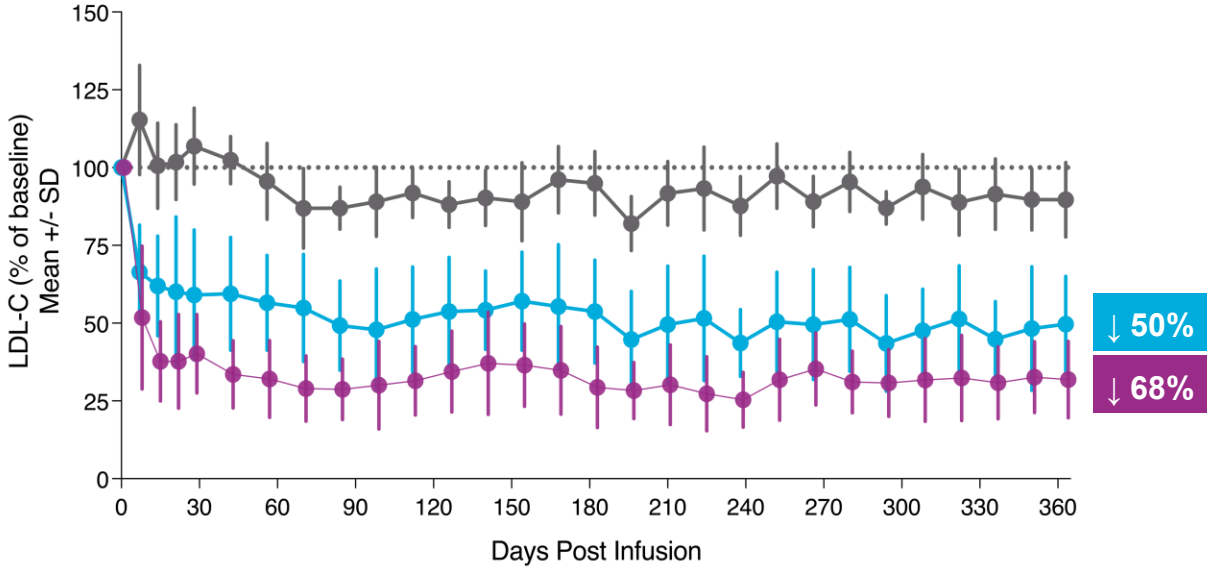
Lipid nanoparticle · Ionizable amino lipid · DSPC · LDL receptor (LDLR) · apoE · mRNA · gRNA · PEG Lipid · Cholesterol

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)

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

entire human genome

identification techniques

Experimental: ABE-digenome-seq

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

Experimental: ONE-Seq

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

Bioinformatics:

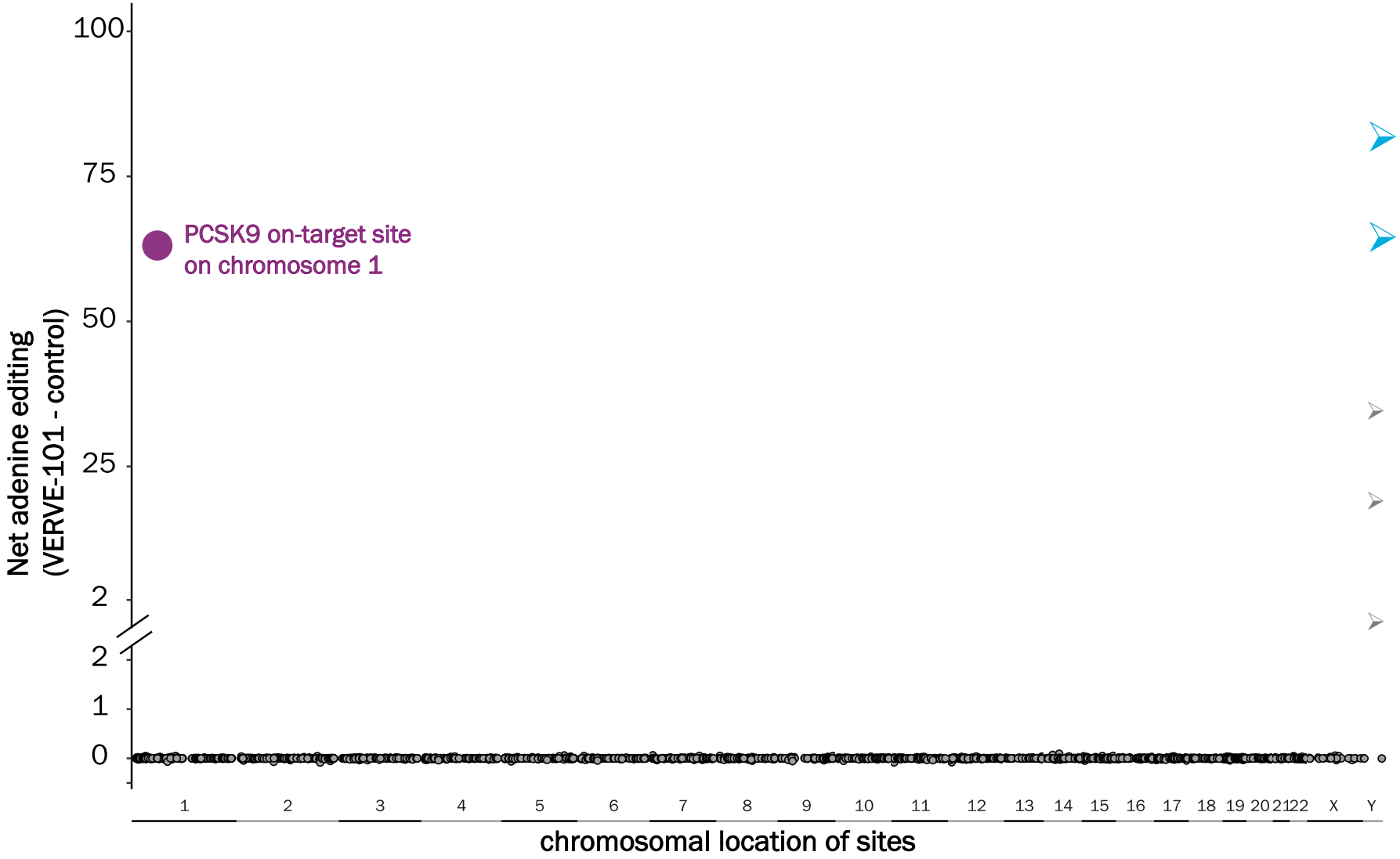
sites of greatest sequence homology

panel of candidates

3166 sites

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

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



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

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

Initial safety and efficacy data from single ascending dose portion of Phase 1b heart-1 study expected in 2H23

heart-1

SINGLE ASCENDING DOSE

Starting dose ····· Low dose ····· Intermediate dose ····· High dose

3-6 participants per group with staggering and sentinel dosing

GLOBAL REGULATORY STRATEGY

- Regulatory clearances in New Zealand and the U.K.

Working to resolve Investigational New Drug (IND) application hold and start trial in the U.S.

STUDY ENROLLMENT

- Recruitment ongoing in New Zealand and the U.K.

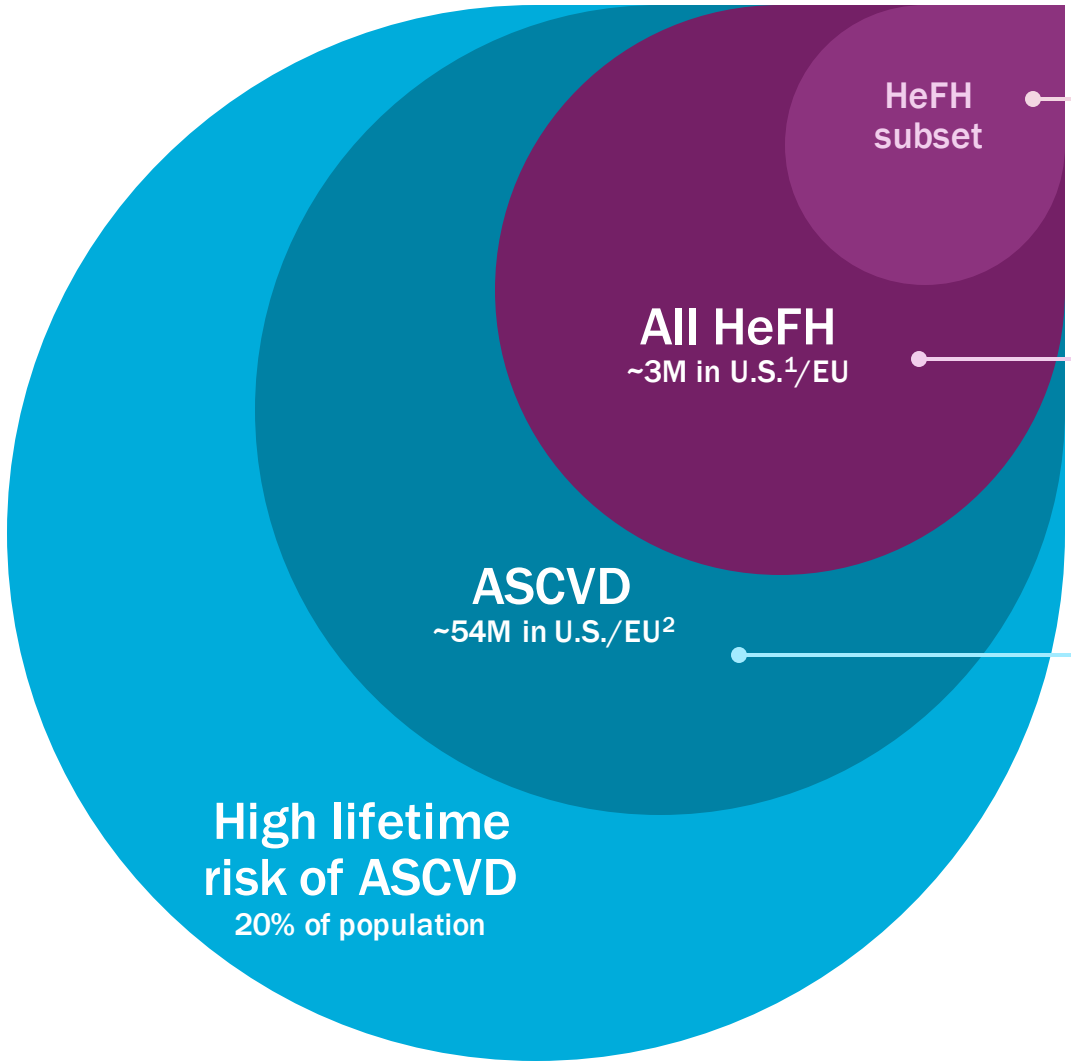
Enrolling high risk HeFH patients with established ASCVD and LDL not at goal

INITIAL DATA IN 2H23

- Data from dose escalation portion of the study

Safety parameters, blood PCSK9, and blood LDL-C

Stepwise clinical development strategy for VERVE-101 starting with HeFH and potential to expand to broader populations with ASCVD



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

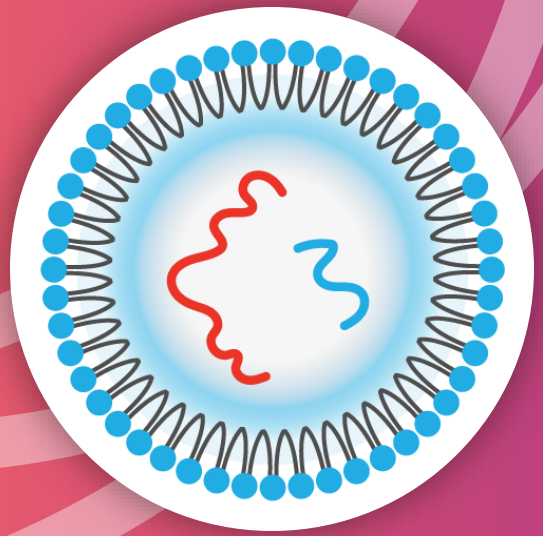
- Phase 2 in all HeFH
- Pivotal Phase 3 in all HeFH (LDL-C endpoint)

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

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

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.



VERVE-201 targeting ANGPTL3:

First patient dosing anticipated in 2024

Homozygous FH (HoFH): severe, morbid disease

HEALTH

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

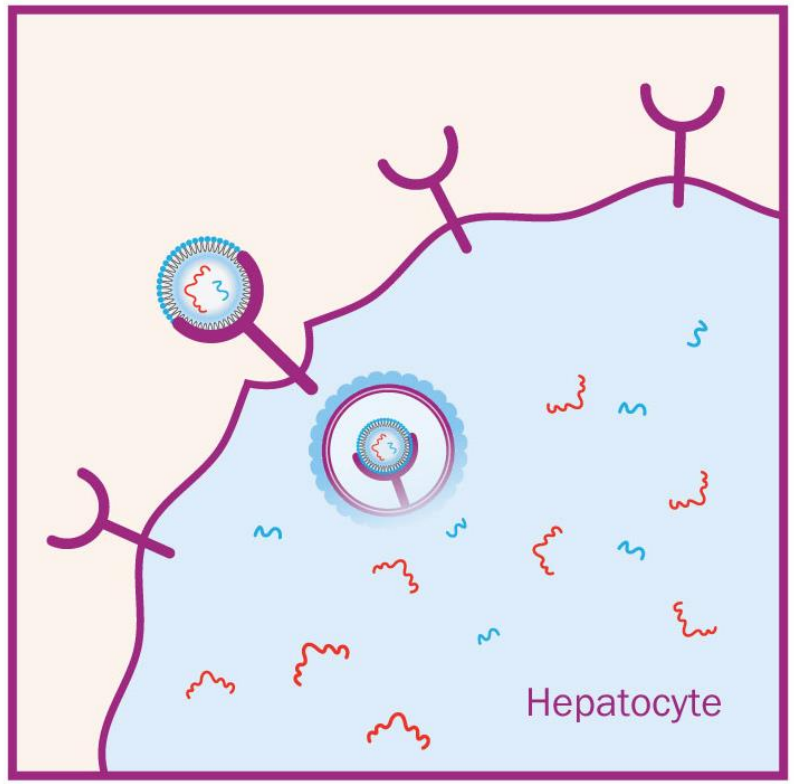
Verve Therapeutics is considering a half-dozen candidate genes that could be edited with the CRISPR technique in order to sharply reduce a patient's levels of cholesterol or triglycerides.

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**

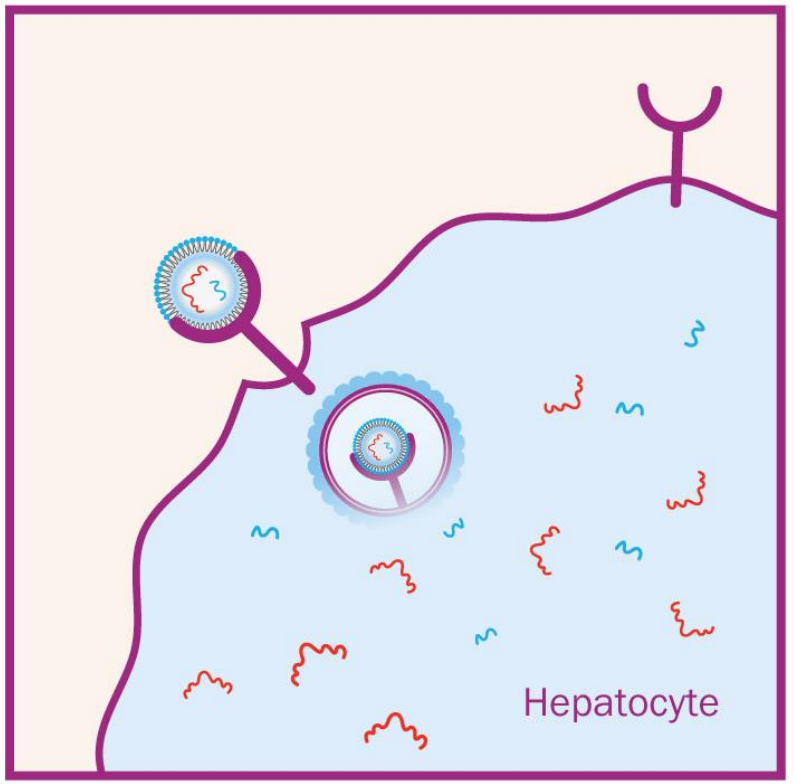
Leslie Barbaro

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

Normal liver



Heterozygous FH (HeFH)



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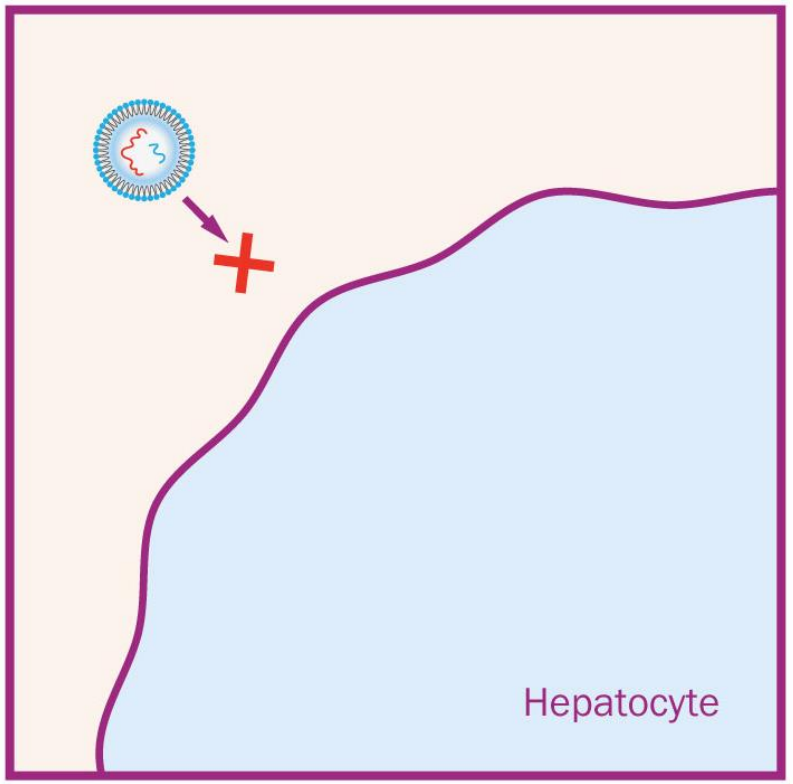
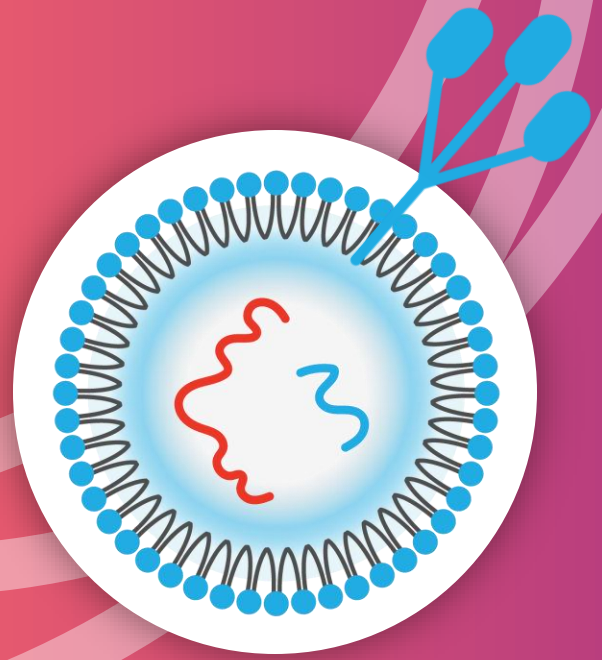
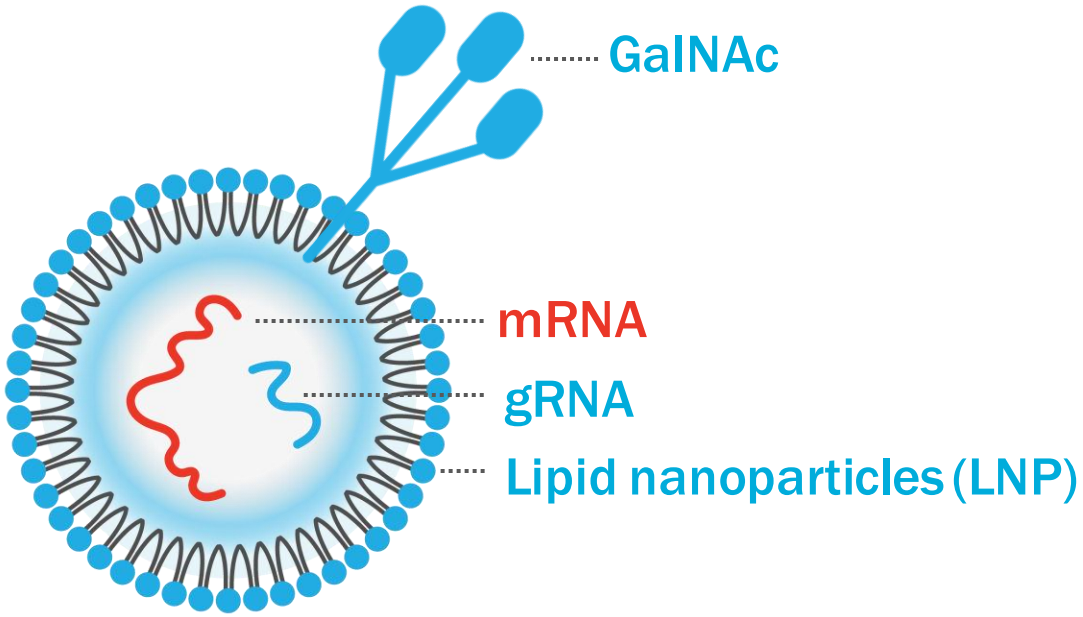


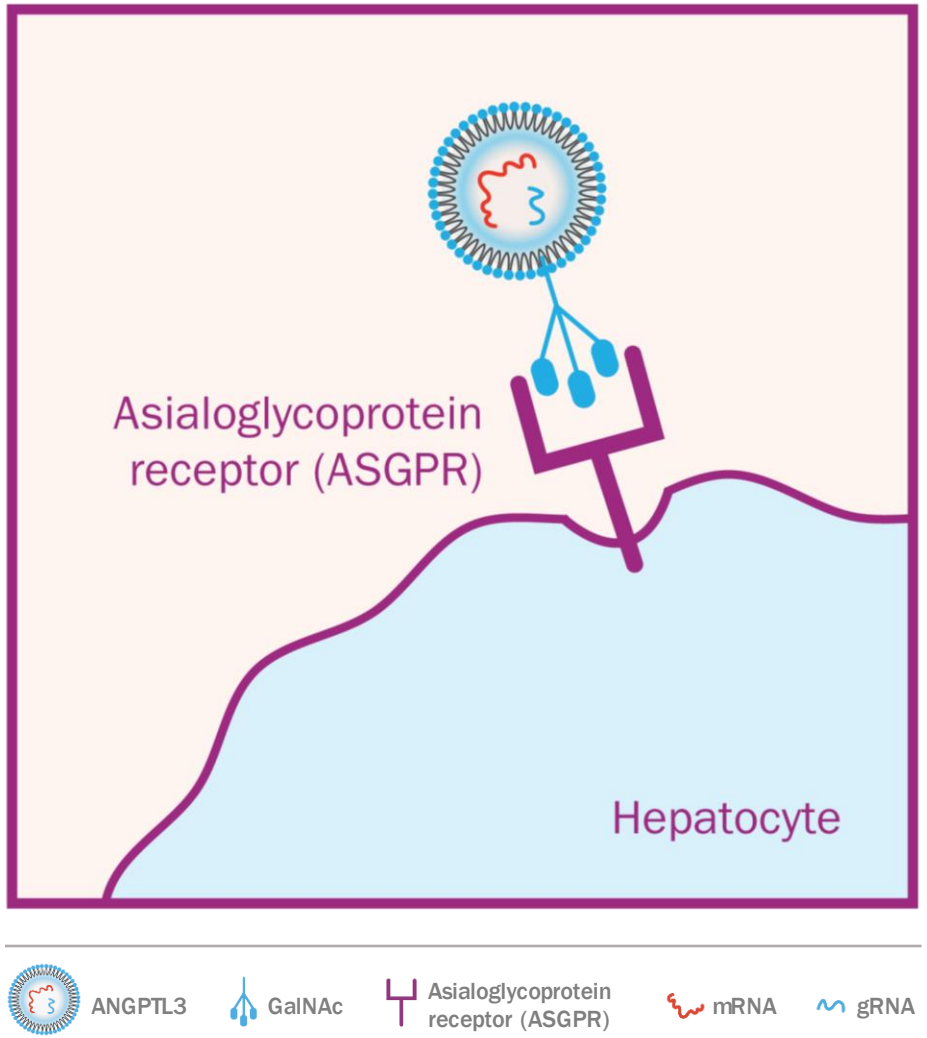
LDL Receptor Lipid nanoparticle (LNP) mRNA gRNA



Novel liver delivery platform: GalNAc-LNP

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





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

+

=

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DELIVERY VEHICLE

Lipid nanoparticle for delivery to liver cell includes 5 components

Ionizable amino lipid

DSPC

Cholesterol

GalNAc

PEG

=

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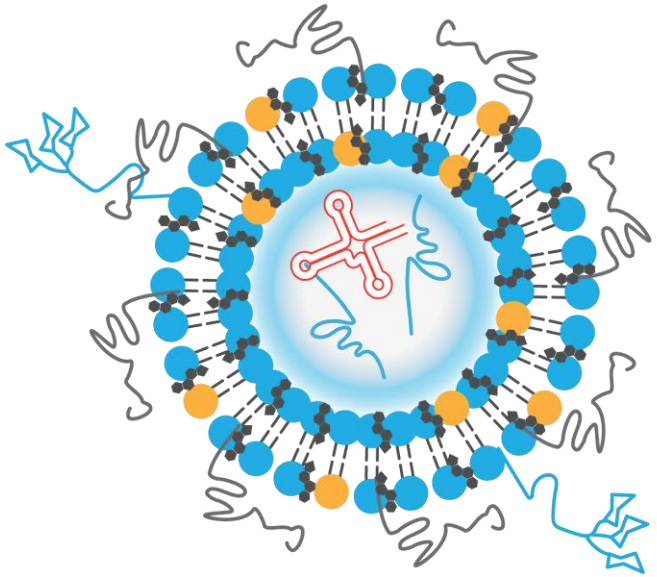
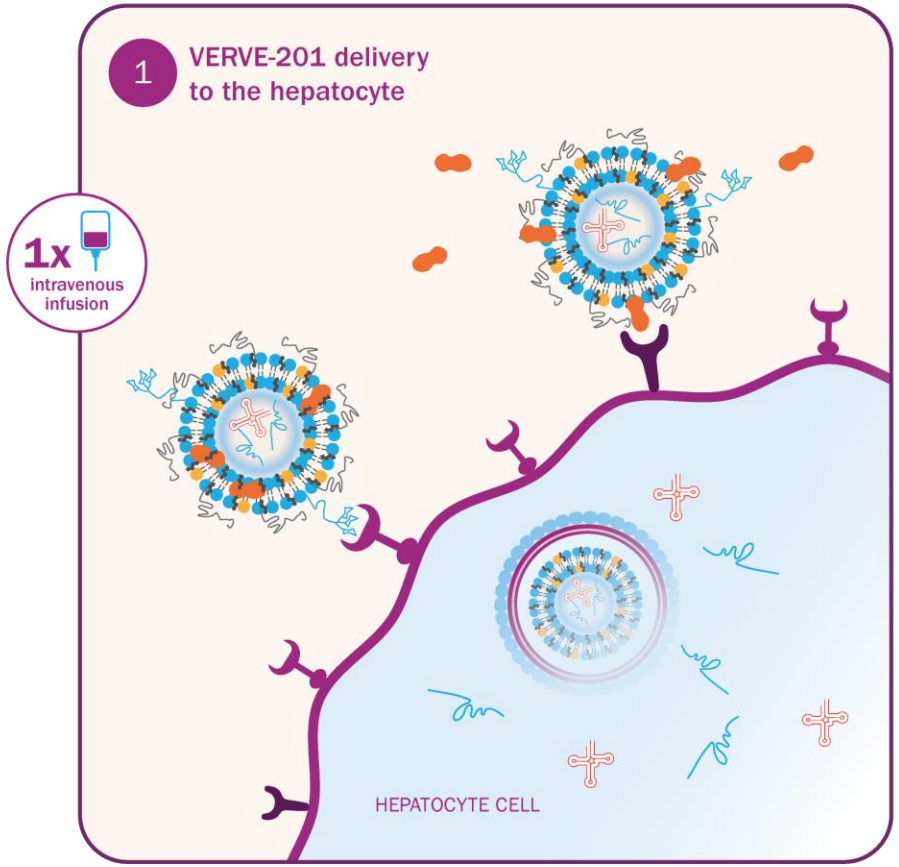
VERVE-201



VERVE-201: base editing medicine designed to inactivate hepatic ANGPTL3 and lower LDL-C and TG



Lipid nanoparticle
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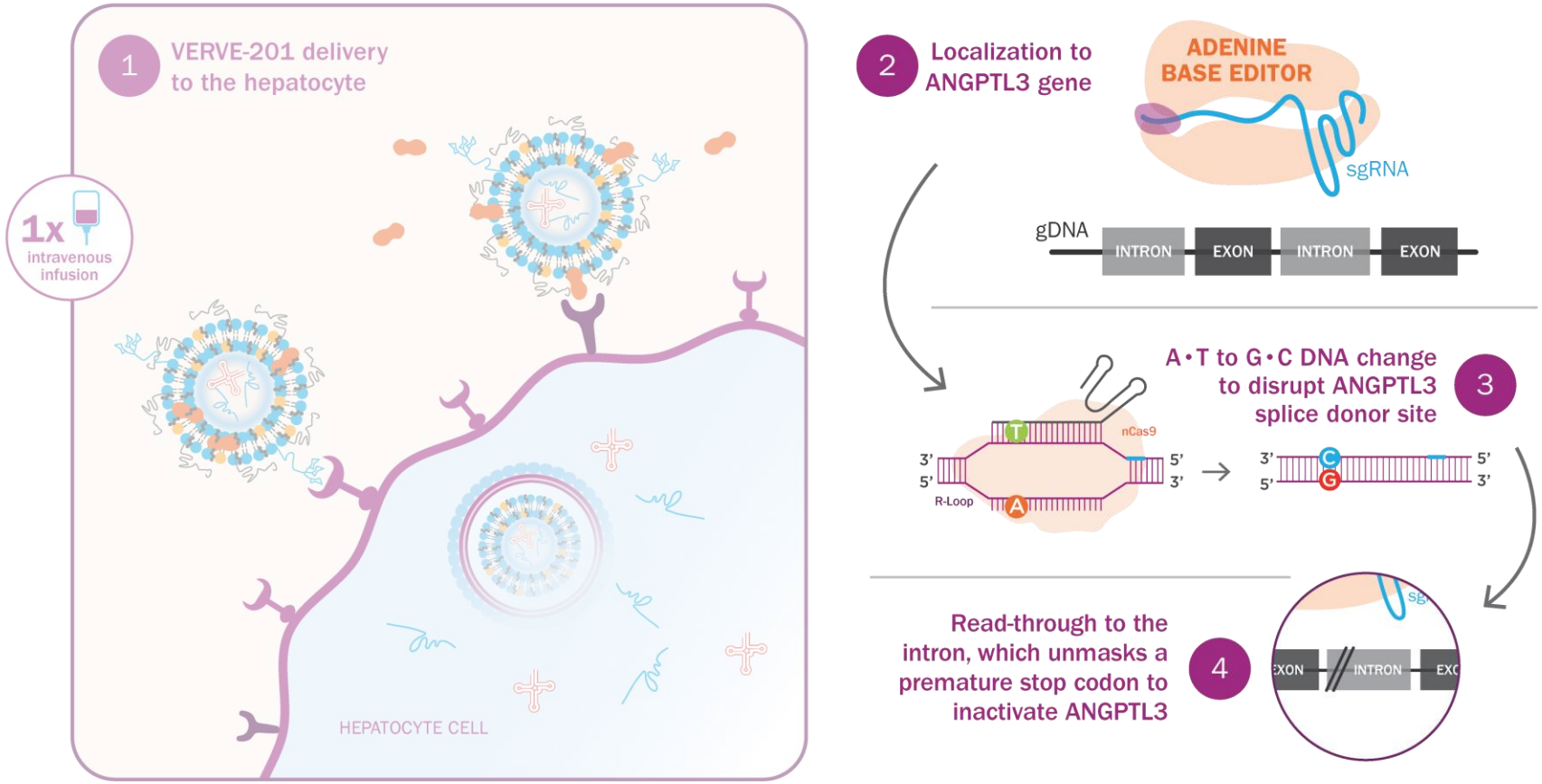
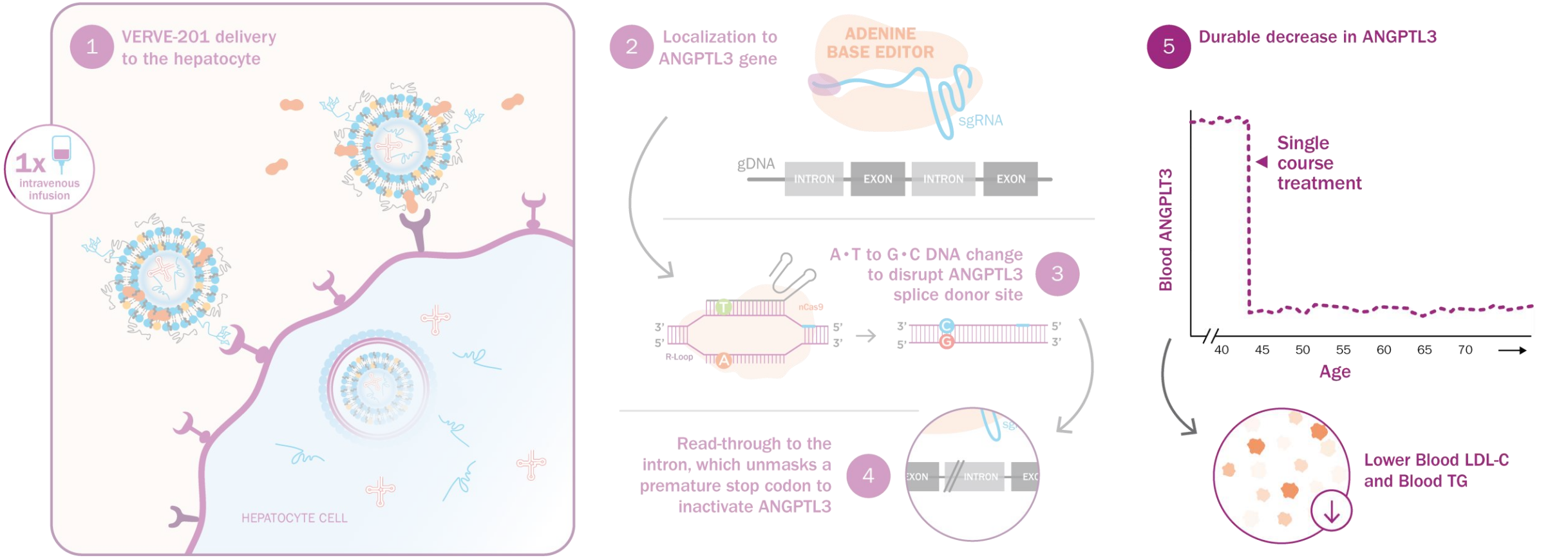
VERVE-201: base editing medicine designed to inactivate hepatic ANGPTL3 and lower LDL-C and TG



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

VERVE-201: base editing medicine designed to inactivate hepatic ANGPTL3 and lower LDL-C and TG

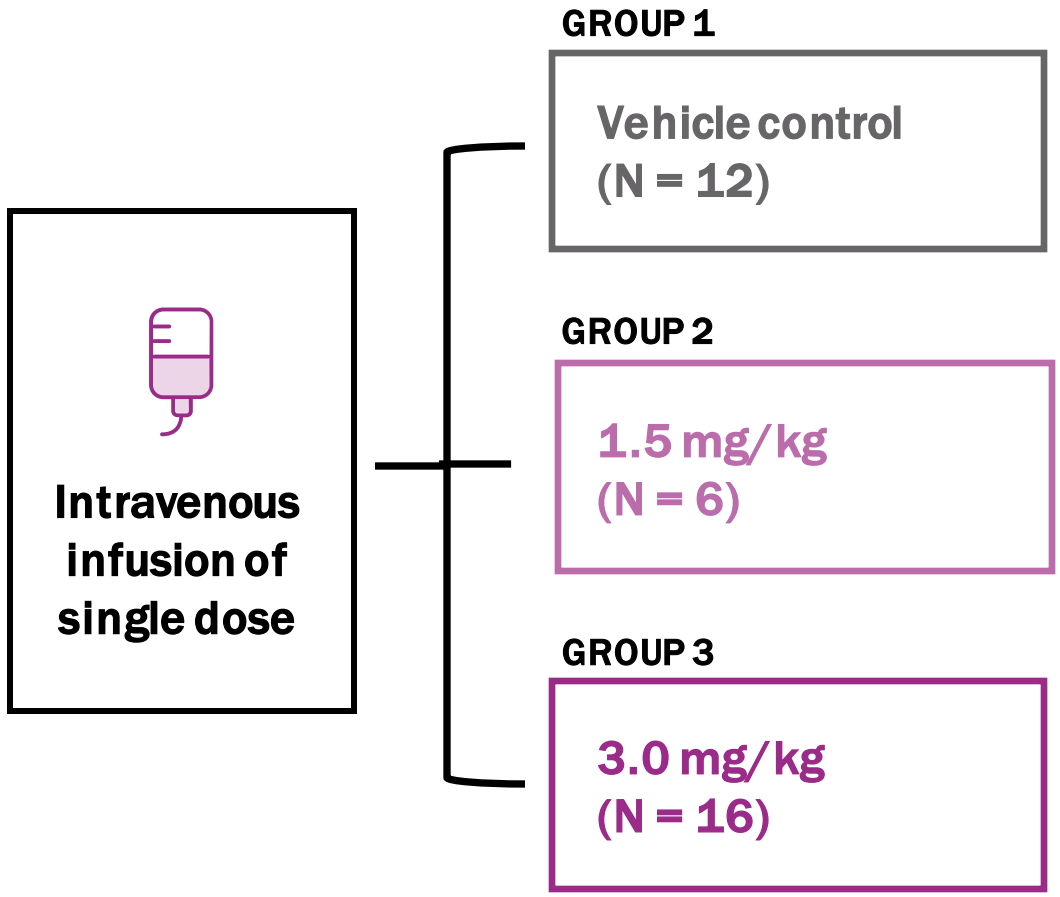


Lipid nanoparticle | Ionizable amino lipid | DSPC | Asialoglycoprotein receptor (ASGPR) | LDL receptor (LDLR) | GalNAc | apoE | mRNA | gRNA | PEG Lipid | Cholesterol

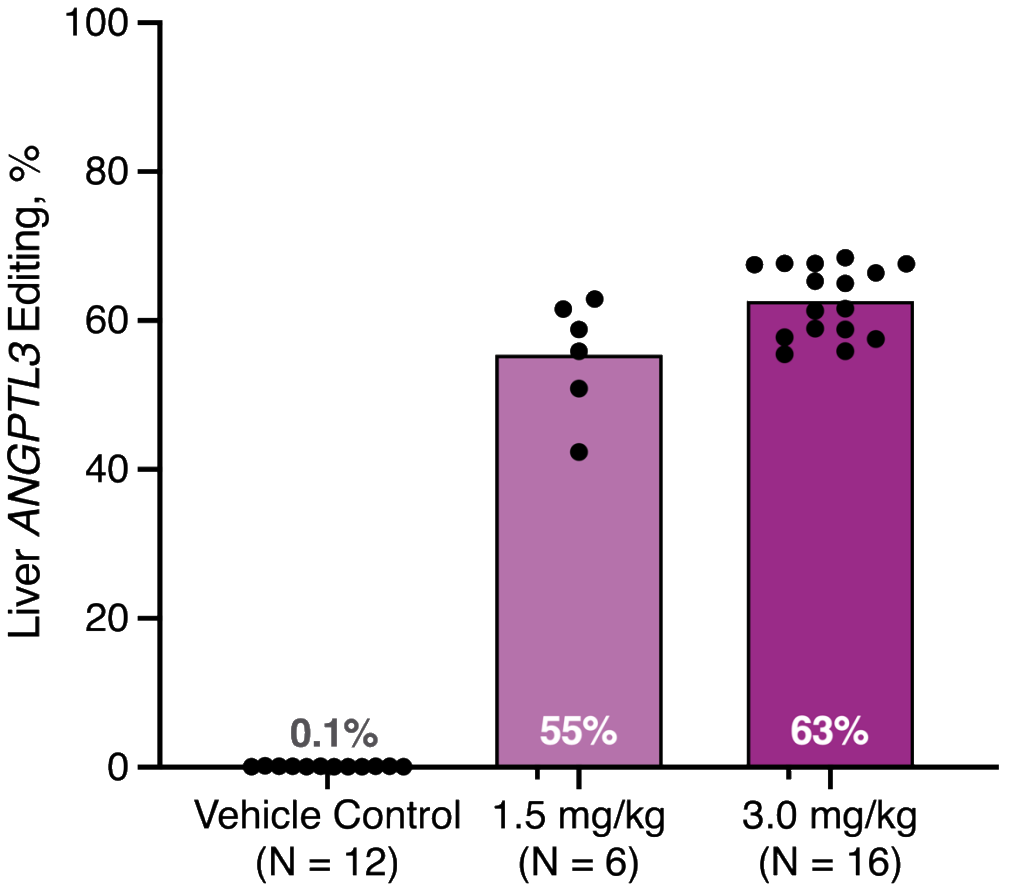
Pharmacology study of VERVE-201cyn in wildtype non-human primates

In non-human primates, VERVE-201cyn achieved mean liver *ANGPTL3* editing of 63% at higher dose

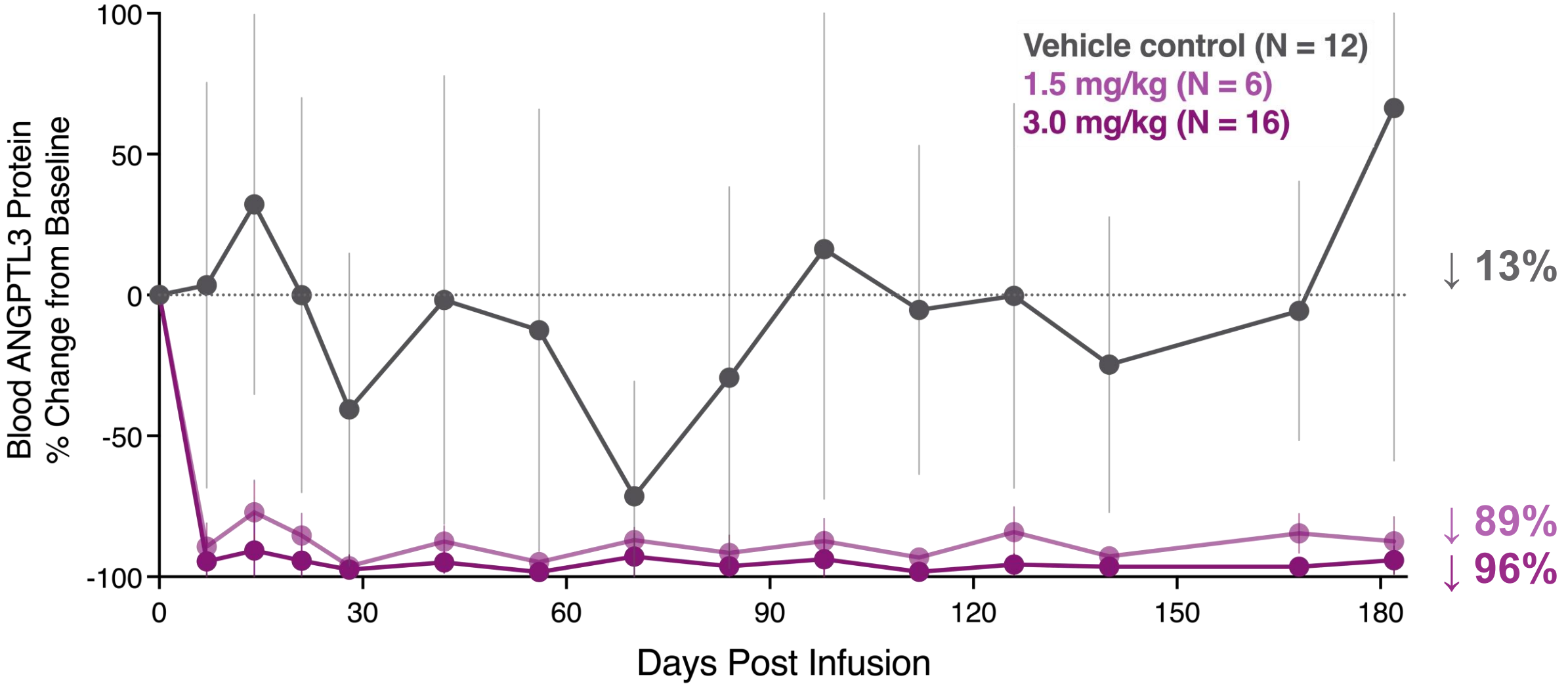
Study of 34 Non-human Primates



Liver *ANGPTL3* editing

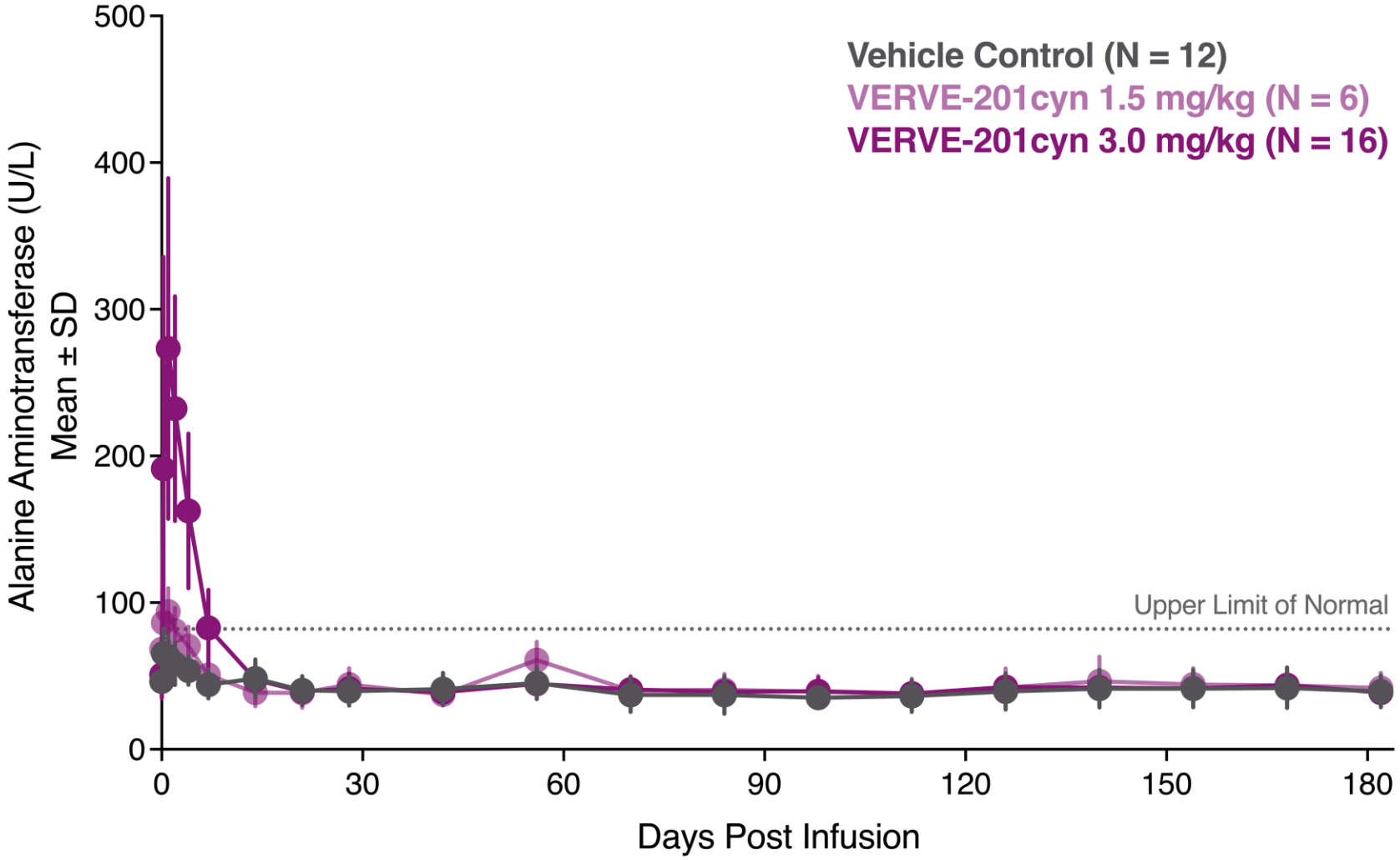


In non-human primates, VERVE-201cyn achieved mean 96% reduction* in blood ANGPTL3 protein at higher dose



* Measured as time-weighted average % change from baseline from days 28 to 182 following dosing.

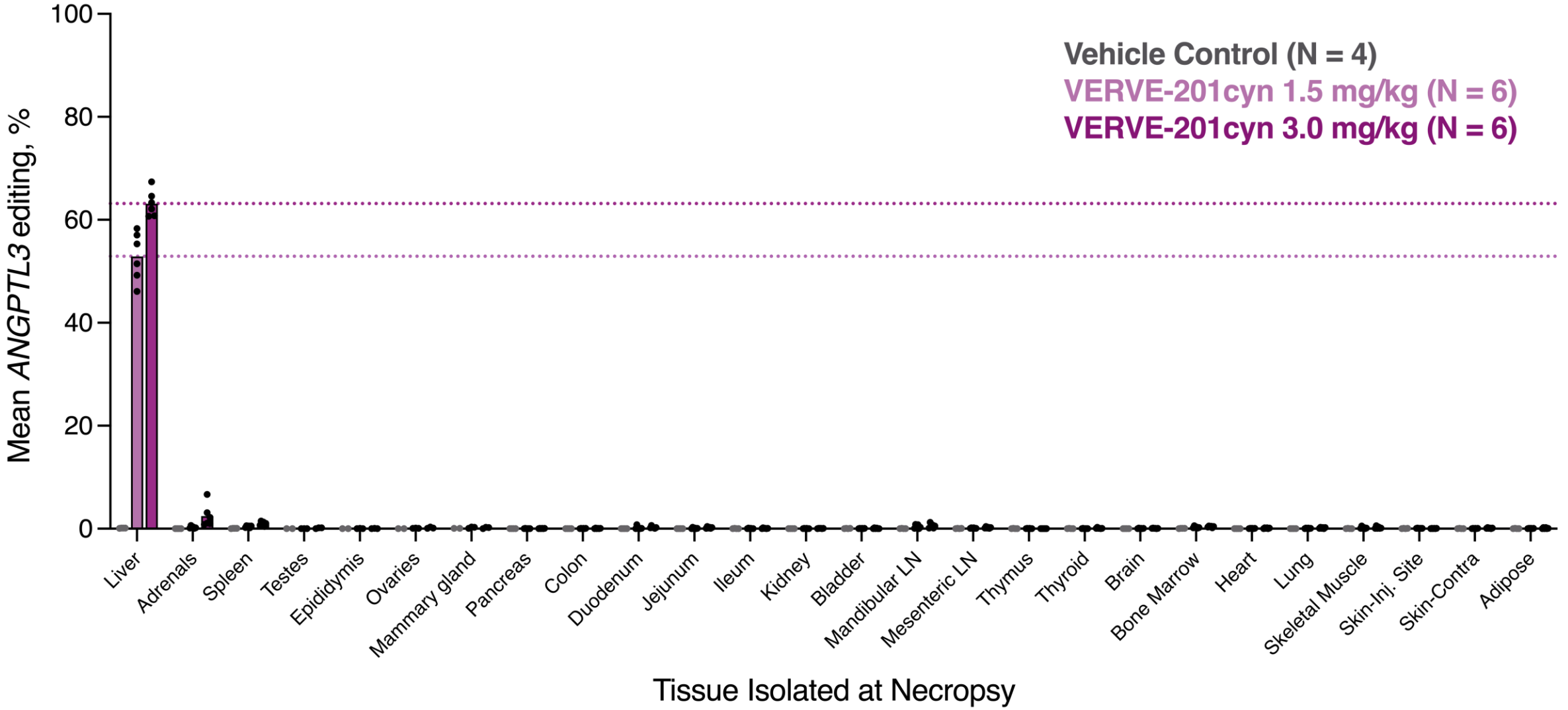
In non-human primates, VERVE-201cyn was well-tolerated with only transient impact on ALT



Liver safety monitoring

- Maximal ALT and AST concentrations noted 24 hours after dosing, normalized by day 14
- Normal total bilirubin observed with no change from baseline

In non-human primates dosed with VERVE-201cyn, on-target *ANGPTL3* editing occurred mostly in the liver*

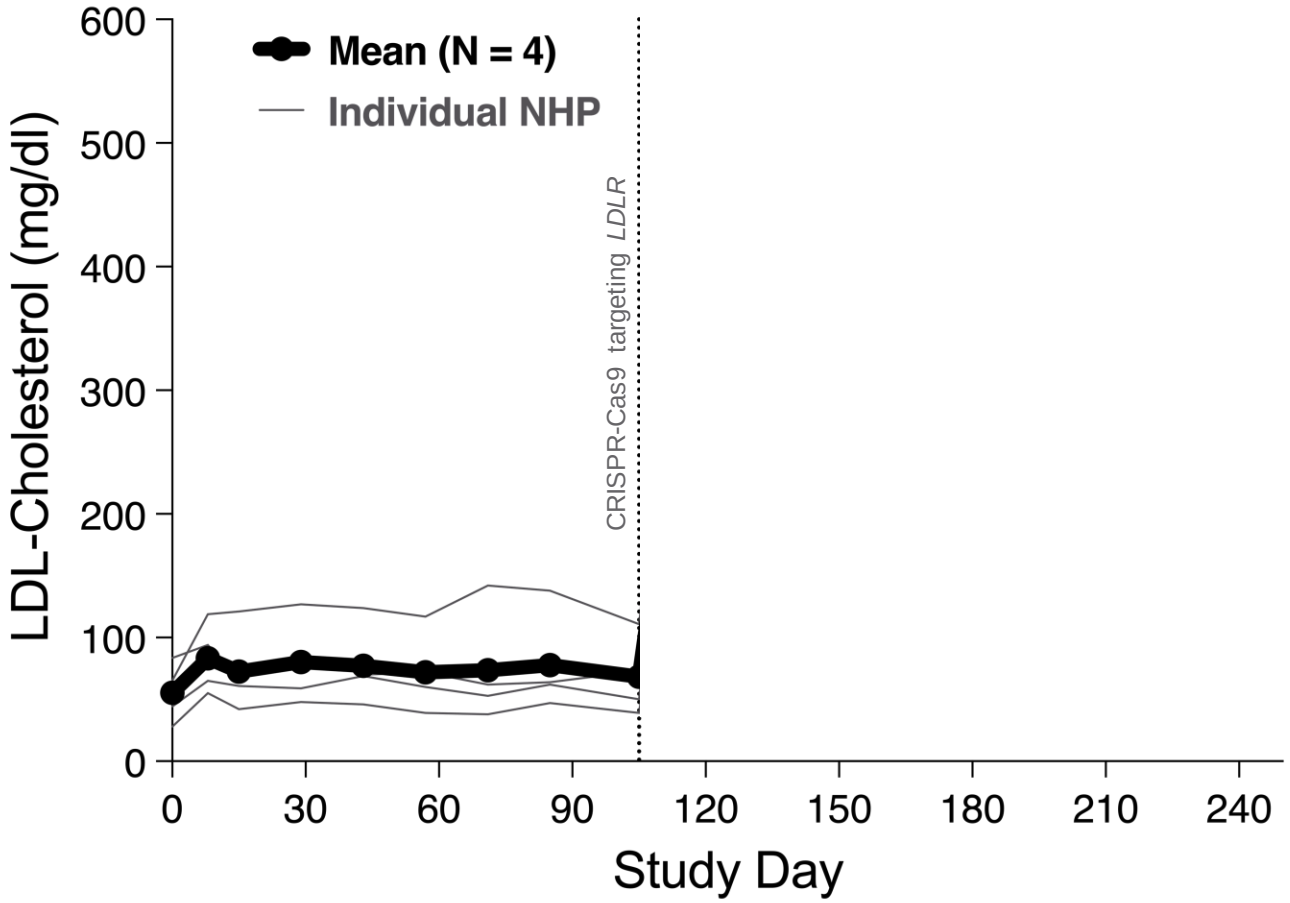


* *ANGPTL3* editing assessed using targeted amplicon sequencing in tissues isolated at scheduled necropsy 6 months after dosing

Non-human primate model of homozygous FH physiology

Study of VERVE-201cyn

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

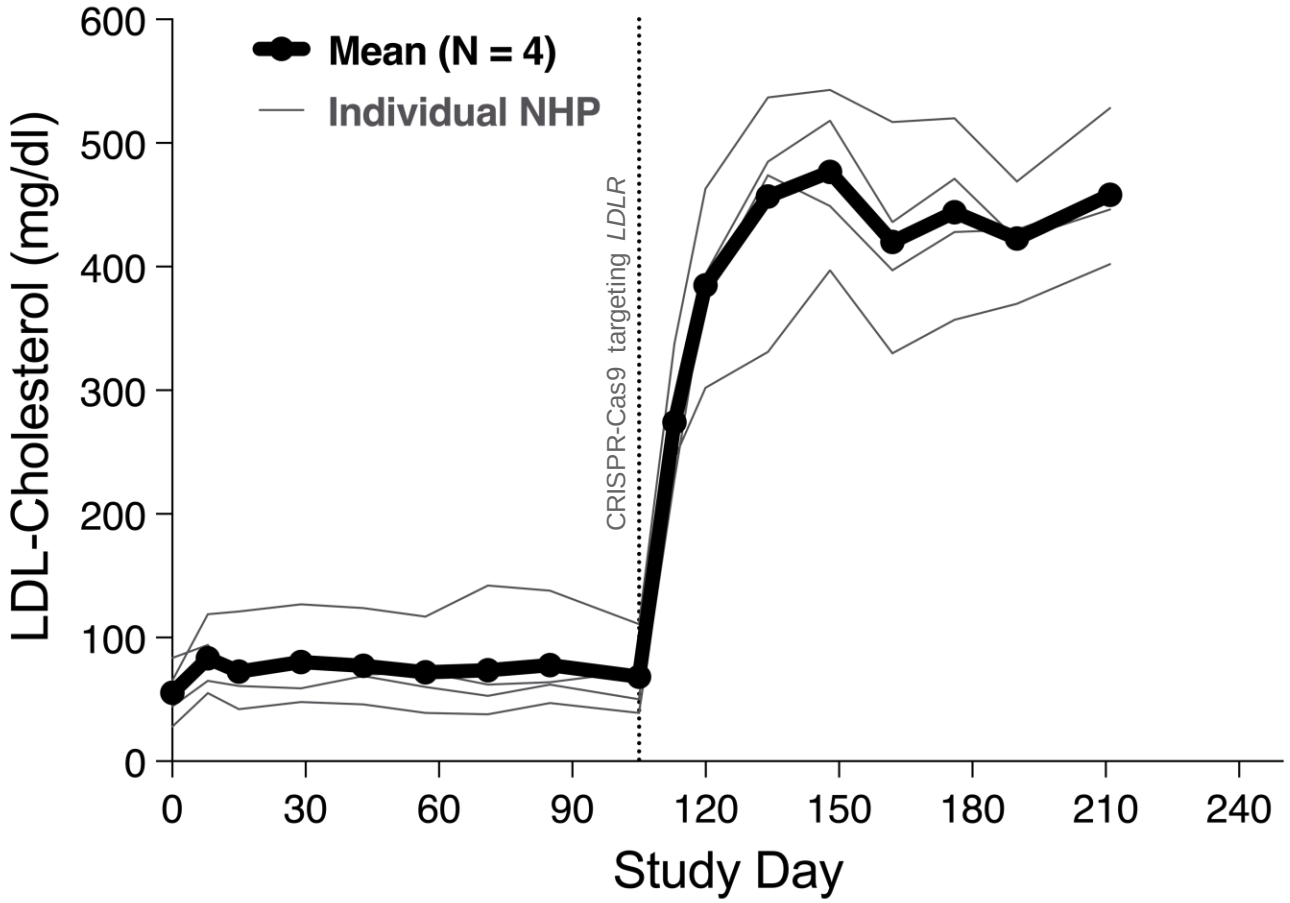


Step #1: Develop LDLR-deficient NHPs

- 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

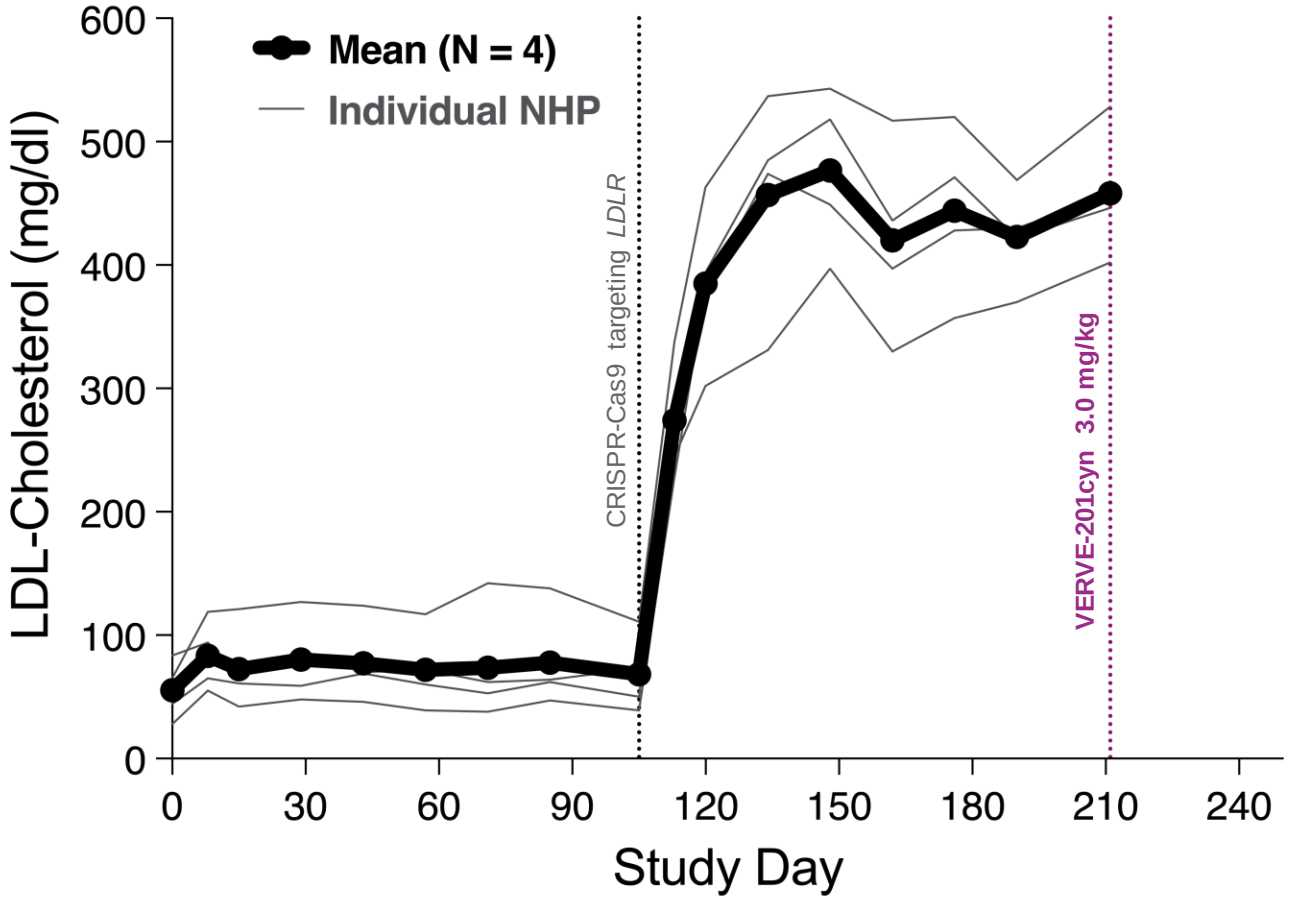


Step #1: Develop LDLR-deficient NHPs

- 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

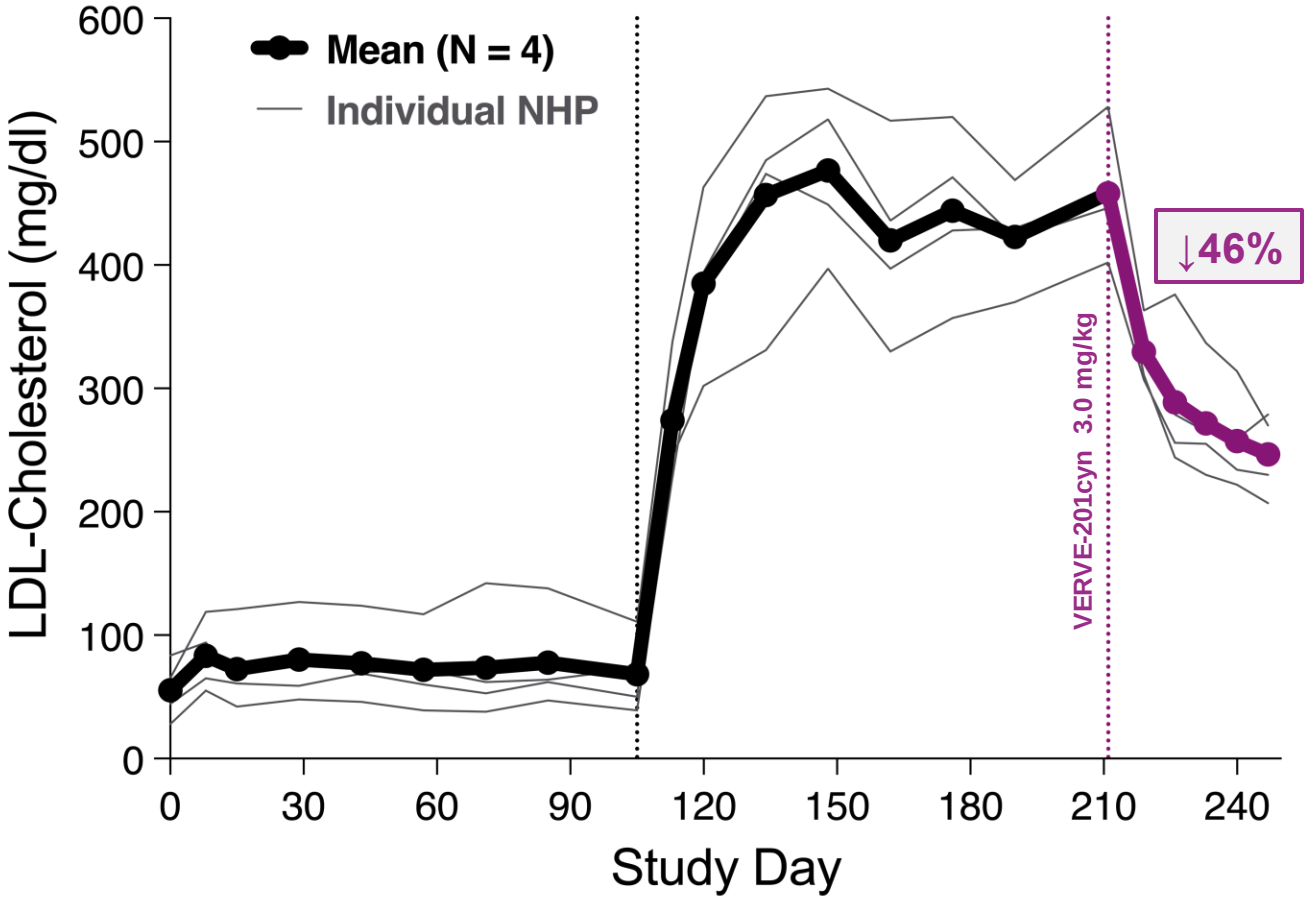
Treat with VERVE-201cyn – 84% reduction in blood ANGPTL3



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)



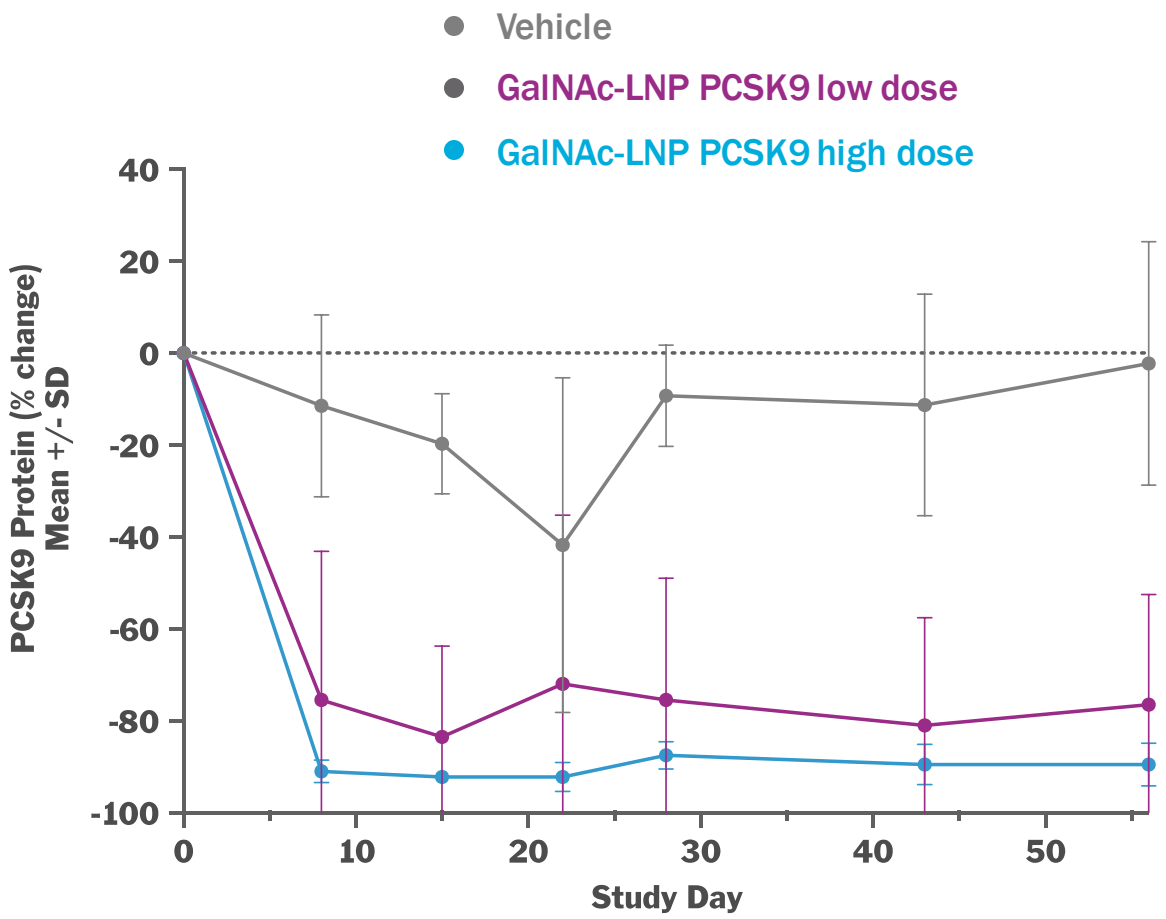
Step #2: Treat with VERVE-201cyn

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

Executing on the development strategy for VERVE-201

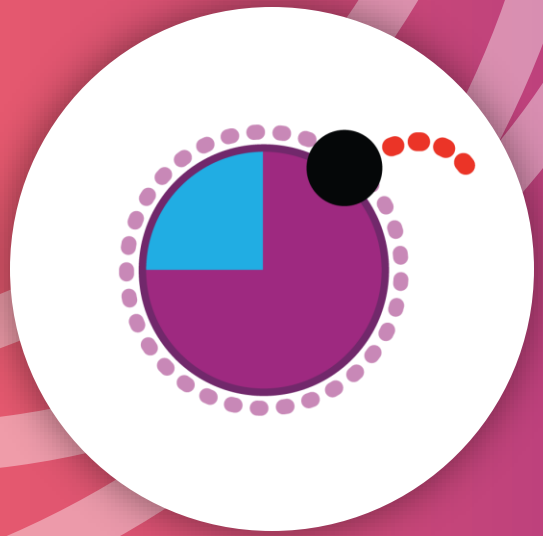
VERVE-102: targets PCSK9 but using GalNAc-LNP delivery system

GalNAc-LNP PCSK9



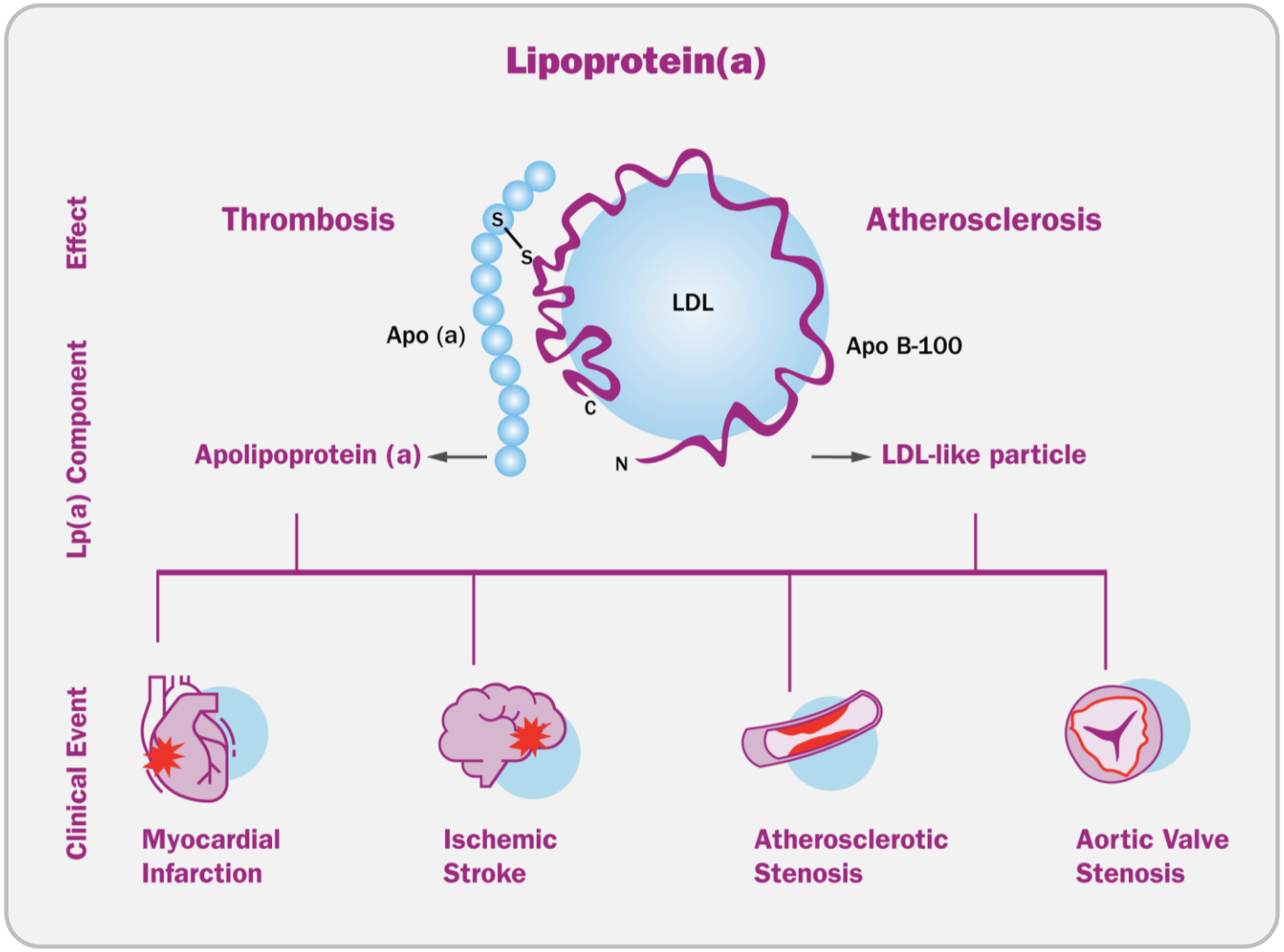
Advancing a pipeline of single-course *in vivo* gene editing programs

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



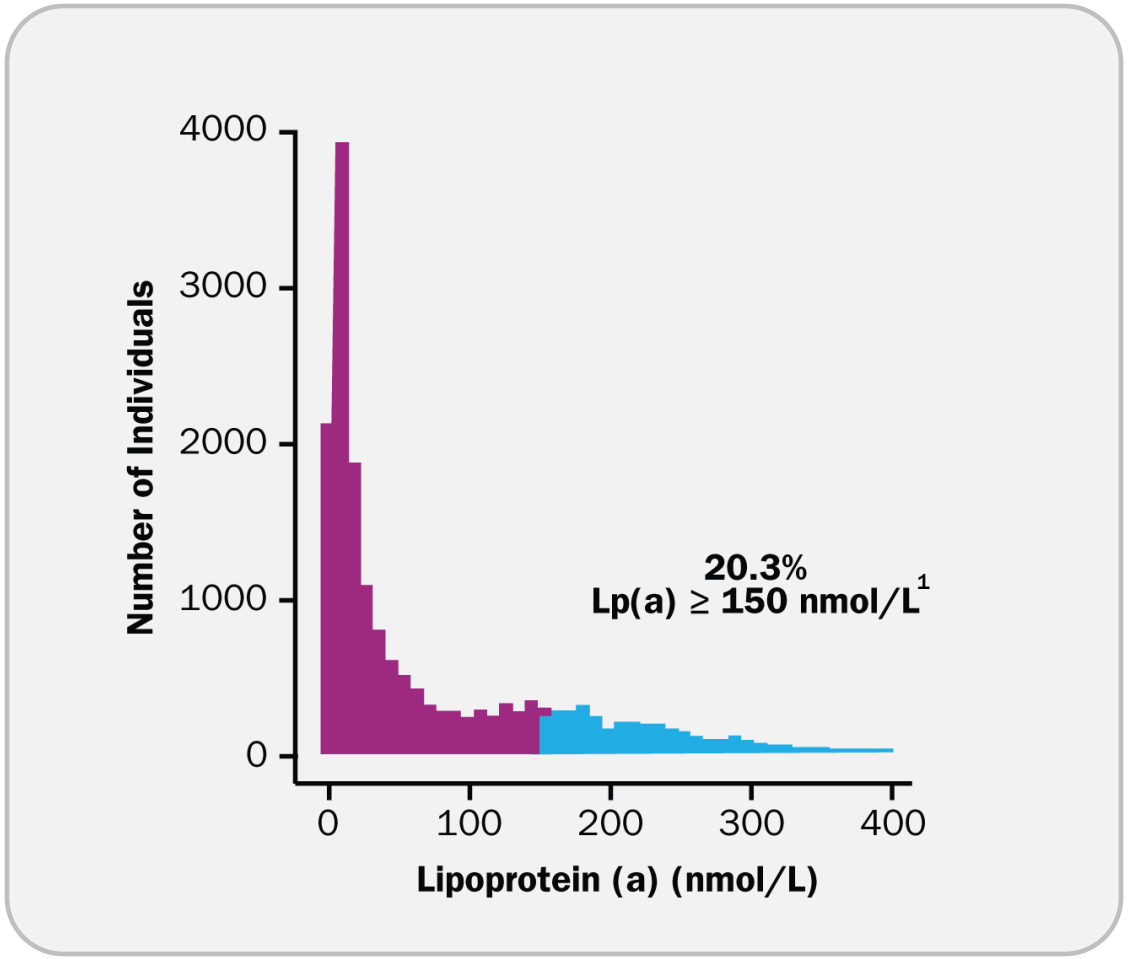
Targeting third pillar of lipoprotein risk: Discovery efforts on Lp(a)

High blood levels of lipoprotein(a) contribute to risk for ASCVD



- Liver-derived, circulates in blood
- Associated with higher risk for ASCVD endpoints including myocardial infarction and ischemic stroke

High Lp(a) is large addressable market, distinct ASCVD subset from patients with high LDL-C



- Large addressable market
  - ~11M in the U.S./EU
- 20% of ASCVD patients with Lp(a) > 150 nmol/L (~ 70 mg/dL)[1]
- Distinct patients from those with high LDL-C; correlation coefficient between blood LDL-C and Lp(a) is low (r^2=0.01)[2]

1. Patel AP et al., *Arterioscler Thromb Vasc Biol.* 2021;41(1):465-474.
2. Welsh P et al., *Eur J Prev Cardiol.* 2022;28(18):1991-2000.

Why once-and-done gene editing medicine for Lp(a)?

Humans with genetic Lp(a) deficiency:

- resistant to heart attack & stroke[1]
- no signal for adverse events

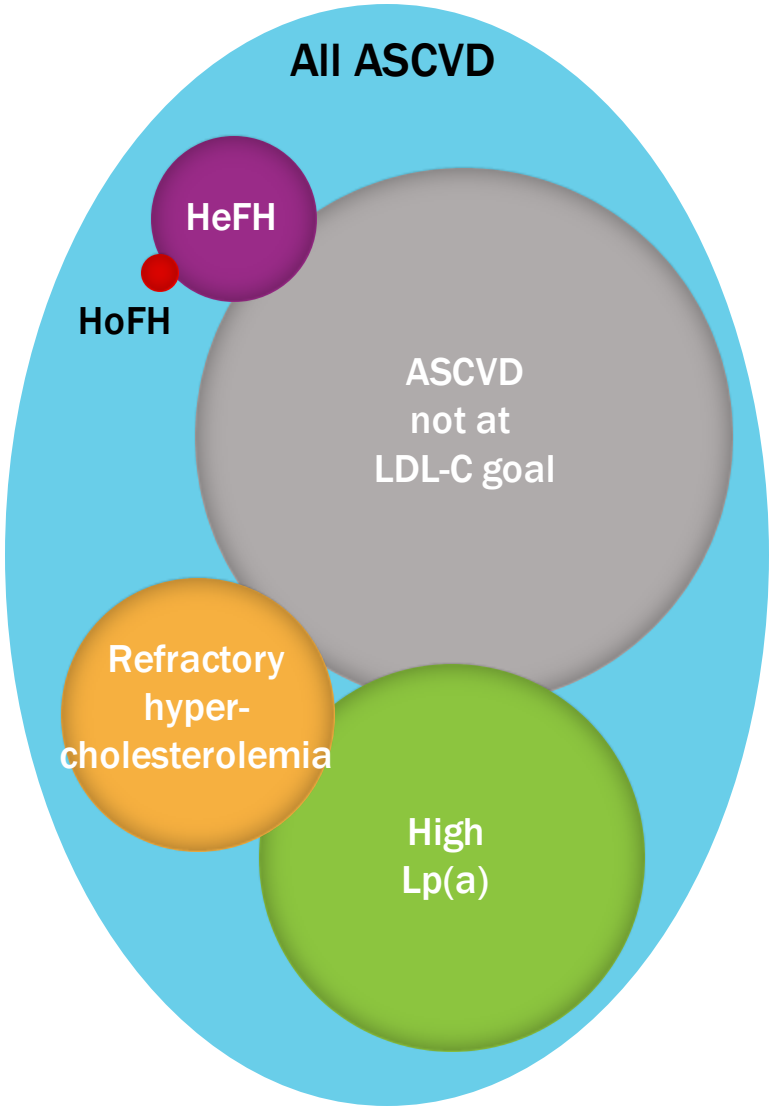
Blood level almost entirely determined by inheritance

Lifestyle factors and statins have minimal to no impact on blood Lp(a)

Research efforts ongoing to develop a bespoke gene editor tailored to target LPA

1. Emdin CA et al. *J Am Coll Cardiol.* 2016;68(25):2761-2772.

Verve's pipeline of gene editing programs address distinct ASCVD subsets



	POPULATION	PROGRAM
All ASCVD	~ 54M in US/EU	
HeFH	~ 3M in US/EU	VERVE-101 (PCSK9)
ASCVD not at LDL-C goal on statin[1,2]	~ 21M in US/EU	VERVE-101 (PCSK9)
HoFH	~ 2,800 in US/EU	VERVE-201 (ANGPTL3)
Refractory Hypercholesterolemia[3] (ASCVD not at LDL-C goal on statin + PCSK9i)	~ 7M in US/EU (~13% ASCVD)	VERVE-201 (ANGPTL3)
Elevated Lp(a)	~ 11M in US/EU (~20% ASCVD)	Lp(a) program

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

Focused on our mission: transform the treatment of cardiovascular disease from chronic management to once-and-done gene editing medicines

2018

Verve founded

2020

Proof-of-concept for *in vivo* liver base editing in NHPs

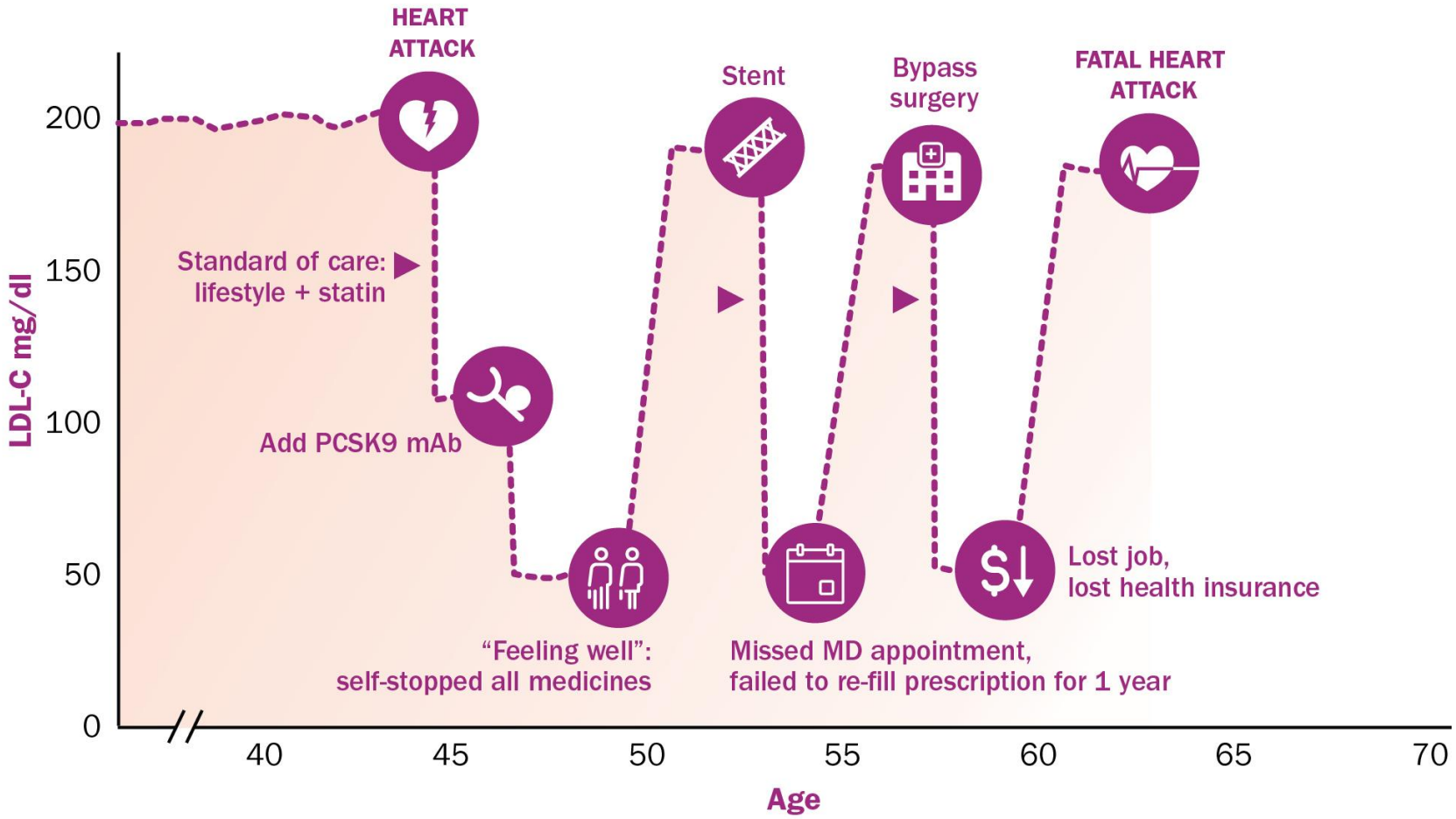
2022

Treated first patient with VERVE-101

2023

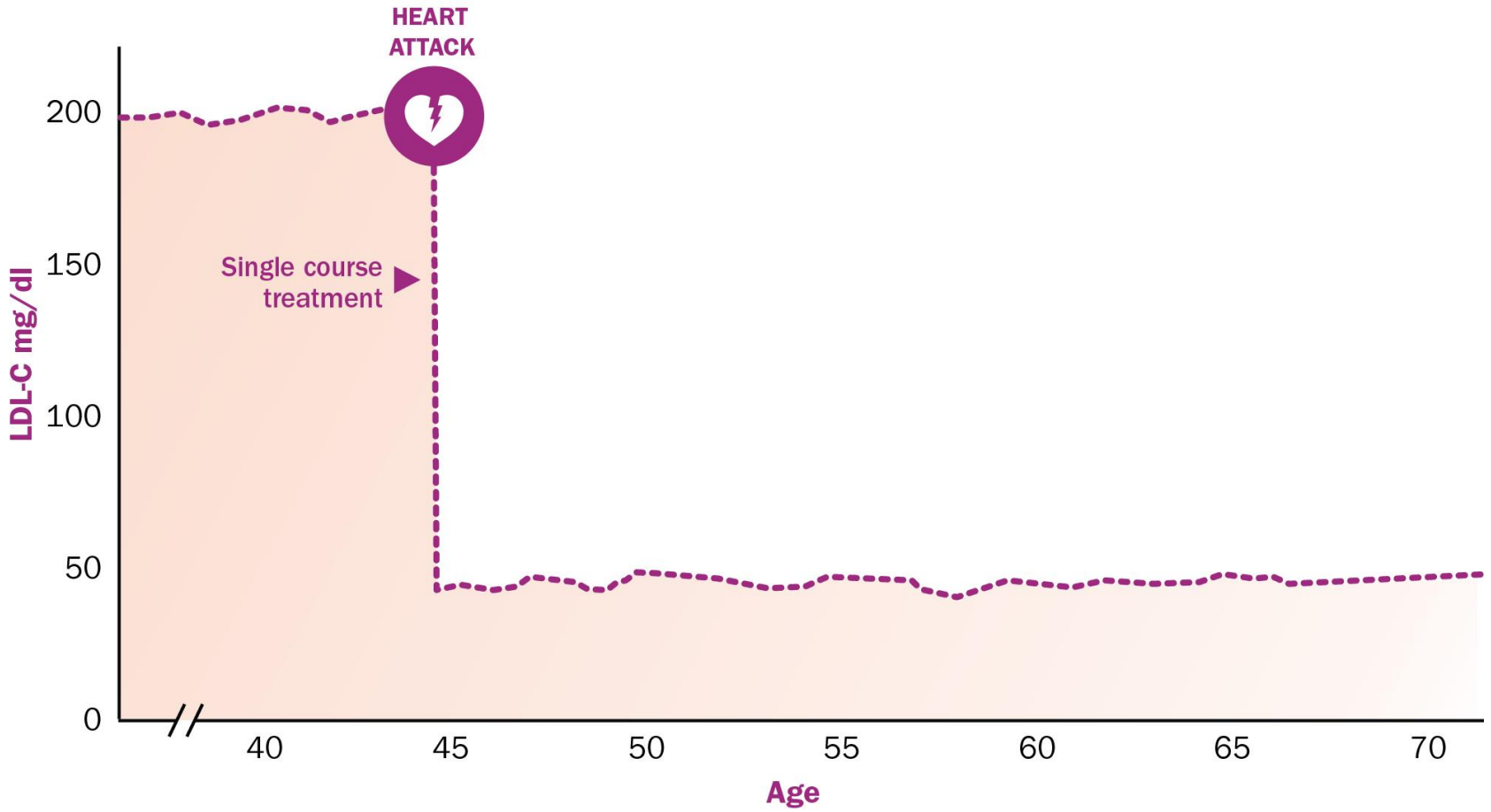
Initial data from VERVE-101 heart-1 trial

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

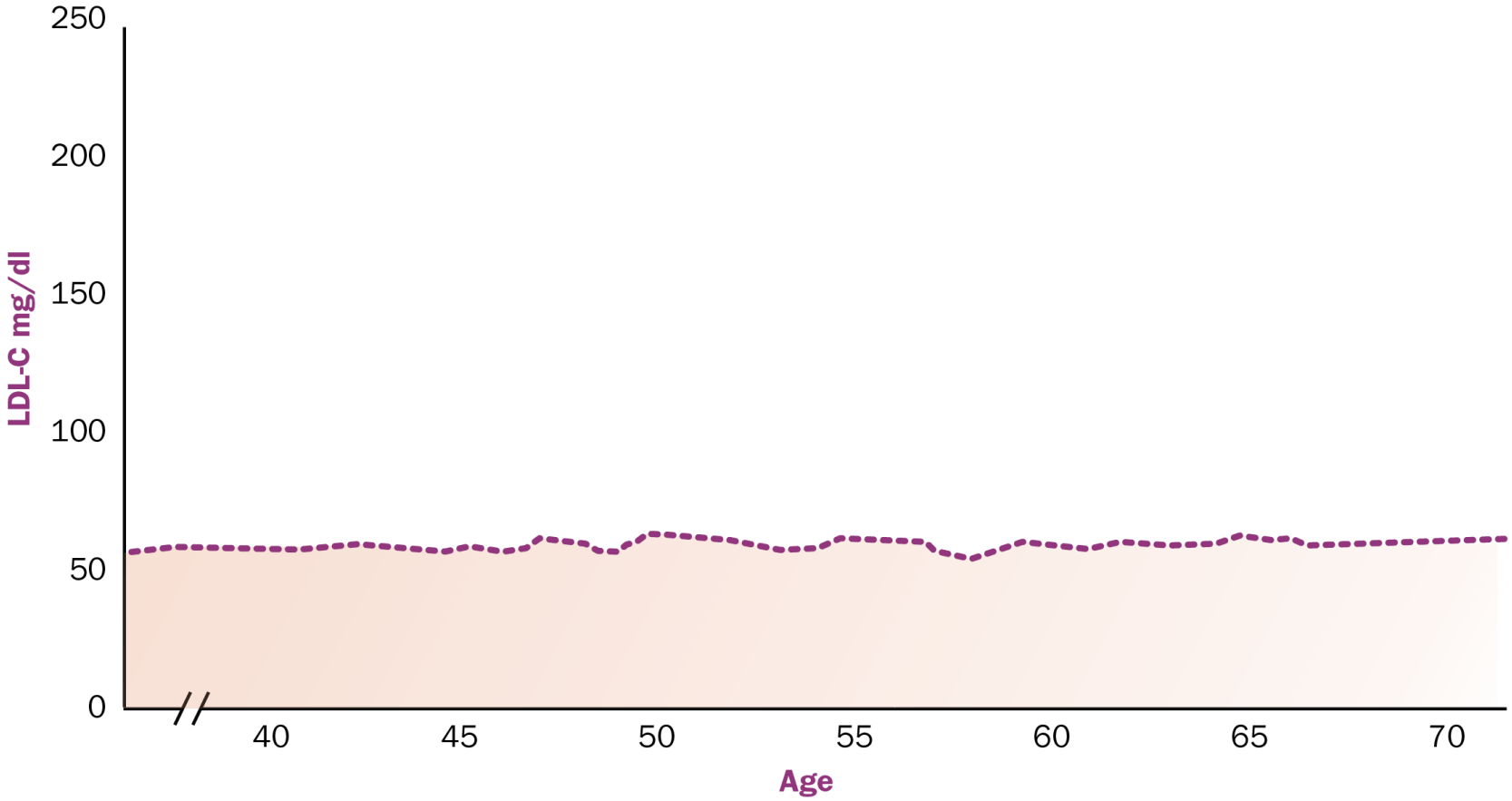


Illustrative graphic depicts the journey of a hypothetical patient with familial hypercholesterolemia who began standard-of-care treatment after suffering a heart attack at age 44

Can we fundamentally change the way chronic disease is treated?



Ultimately, may be useful to prevent heart attack in first place



Our team