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Nonclinical data demonstrate potent and precise inactivation of liver *PCSK9 in vivo* with clinical stage GalNAc base editing medicine, VERVE-102

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Disclosure Slide

	No, nothing to disclose
X	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Verve Therapeutics					X	X	X	

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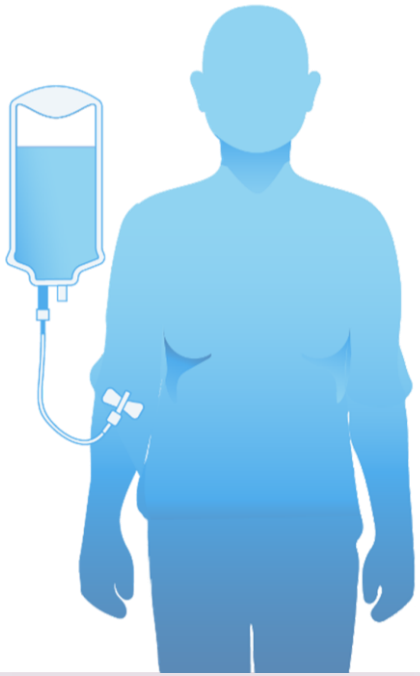
Scott B Vafai, MD, is an employee and equity holder of Verve Therapeutics

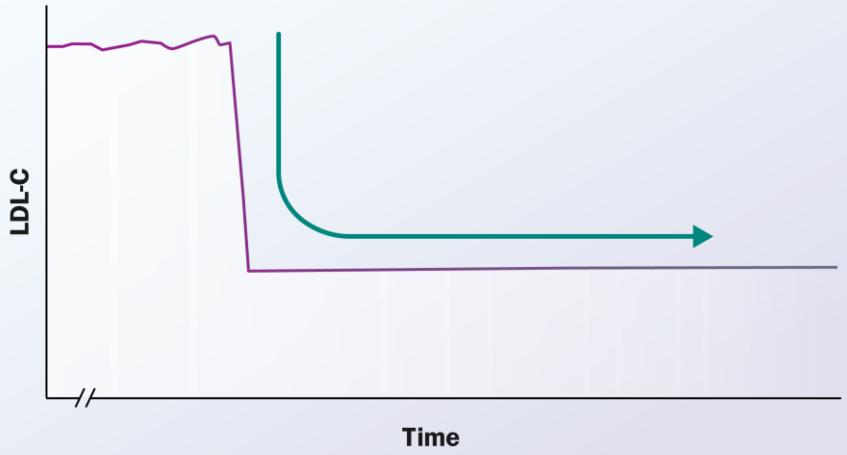
This presentation contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995 that involve substantial risks and uncertainties, including statements regarding the Company’s ongoing Heart-2 clinical trial; the Company’s strategic plans and prospects; and the potential advantages and therapeutic potential of the Company’s programs. 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 Company’s ability to timely submit and receive approvals of regulatory applications for its product candidates; advance its product candidates in preclinical studies and clinical trials; initiate, enroll and complete 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, VERVE-102 and VERVE-201; advance the development of its product candidates under the timelines it anticipates in preclinical studies and 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 filings 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.

Verve's vision: a one dose future to address chronic disease

Single IV Infusion of Verve Product



Lifelong Blood Cholesterol Reduction



VERVE MISSION

Deliver enduring efficacy to patients living with ASCVD

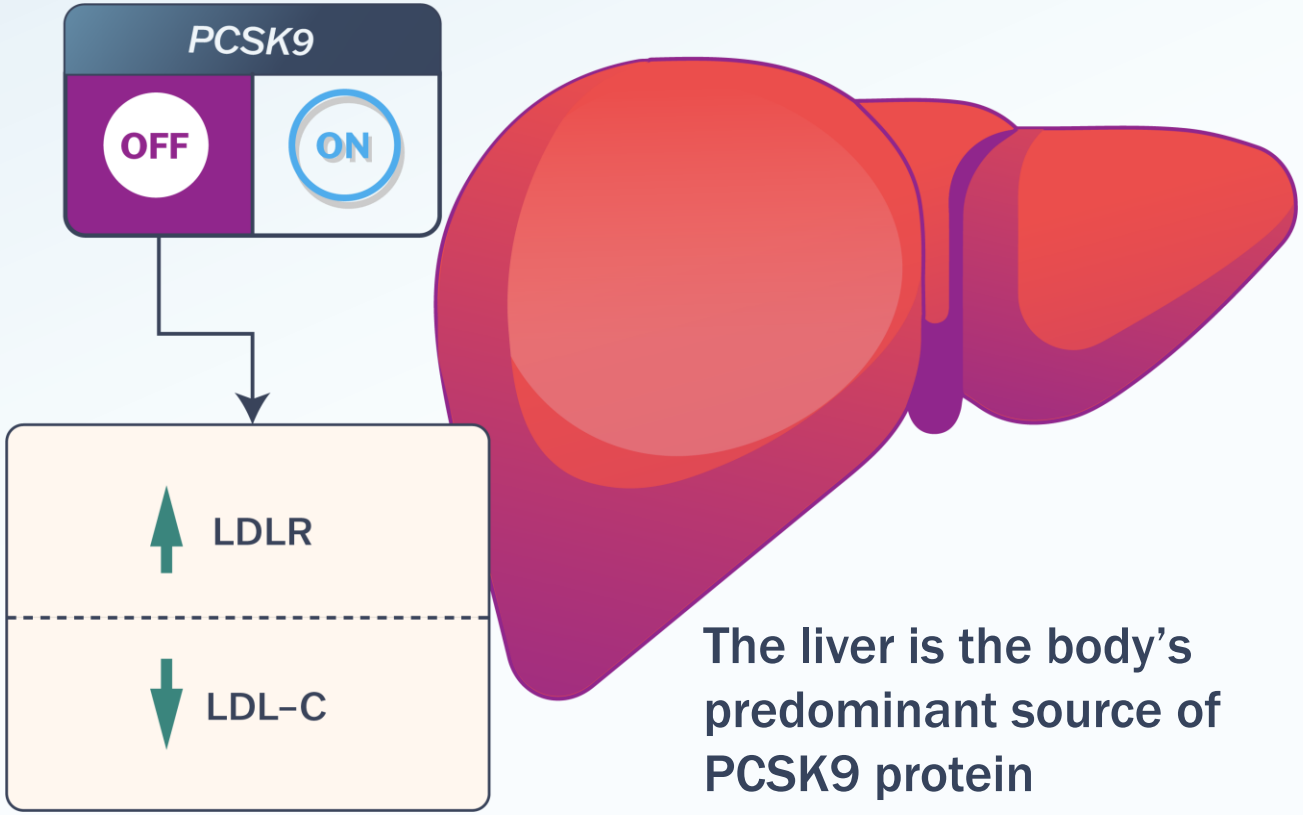
ASCVD, atherosclerotic cardiovascular disease; IV, intravenous; LDL-C, low-density lipoprotein cholesterol

Can we develop a single-course base editing treatment that mimics natural *PCSK9* variants to generate enduring efficacy?

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

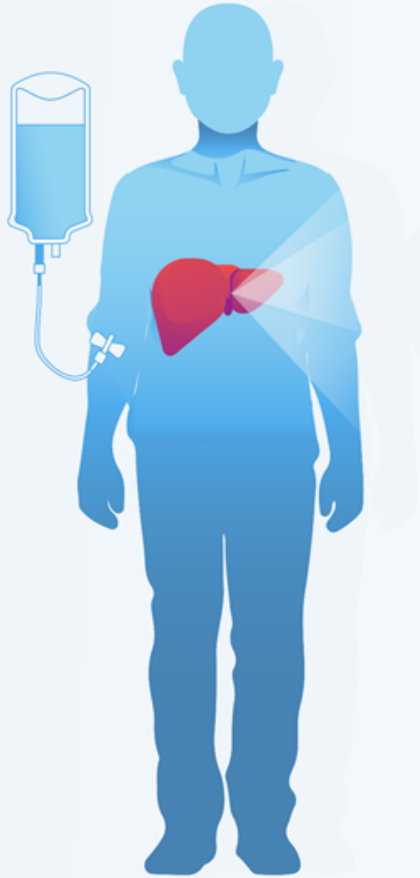


The liver is the body's predominant source of PCSK9 protein

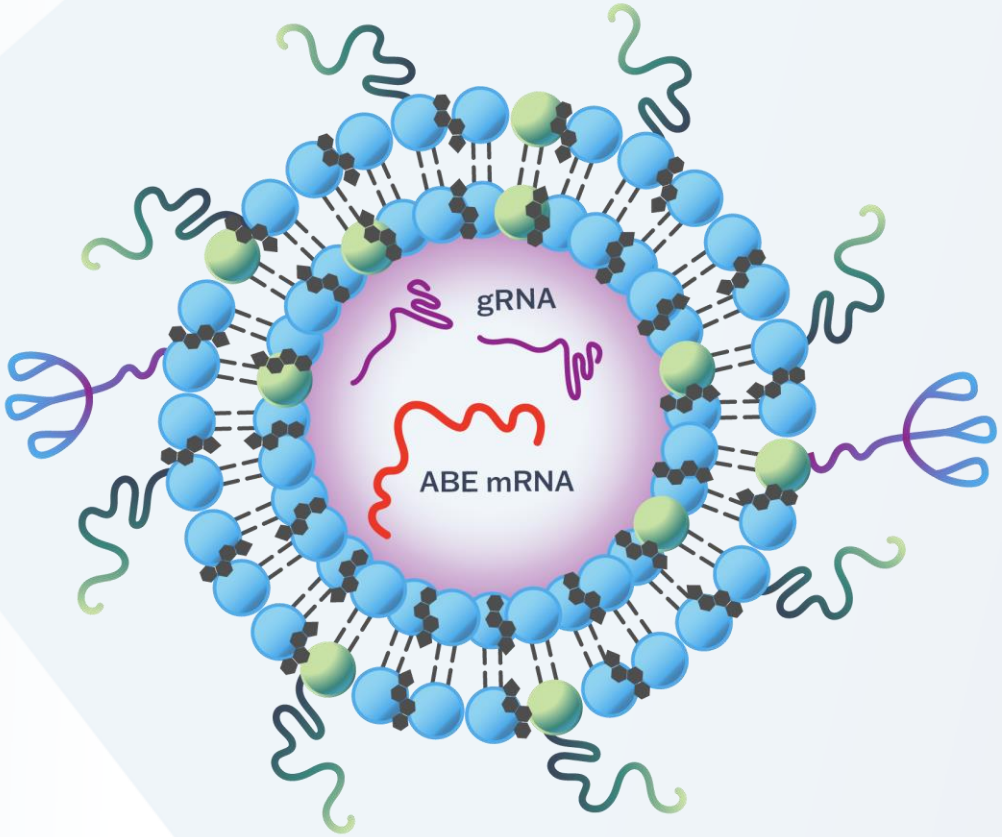
1. Zhao Z, et al. Am J Hum Genet. 2006;79:514-523; 2. Cohen JC, et al. N Eng J Med. 2006;354:1264-1272; 3. Rao AS, et al. Circ Genom Prec Med. 2018;11(7):e002162.
ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9

VERVE-102 concept: mRNA encoding an adenine base editor (ABE) and guide RNA carried in a GalNAc-LNP delivery vehicle
Goal: turn off *PCSK9* gene in the liver

IV infusion of VERVE-102

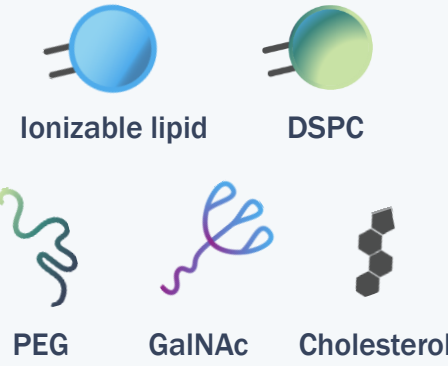


VERVE-102 GalNAc-LNP



RNA components

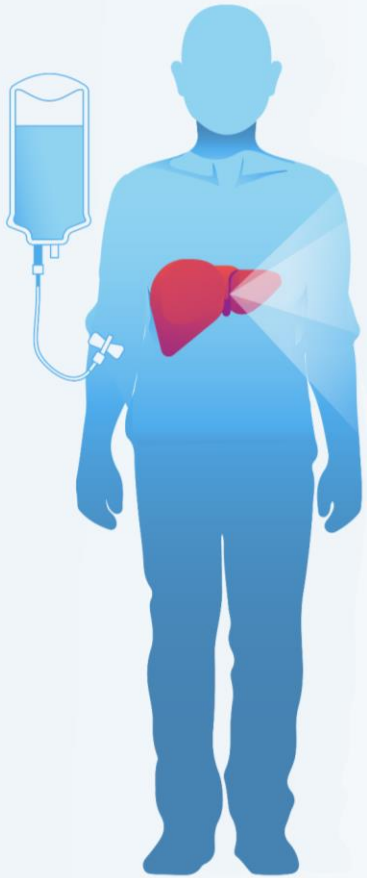
LNP components



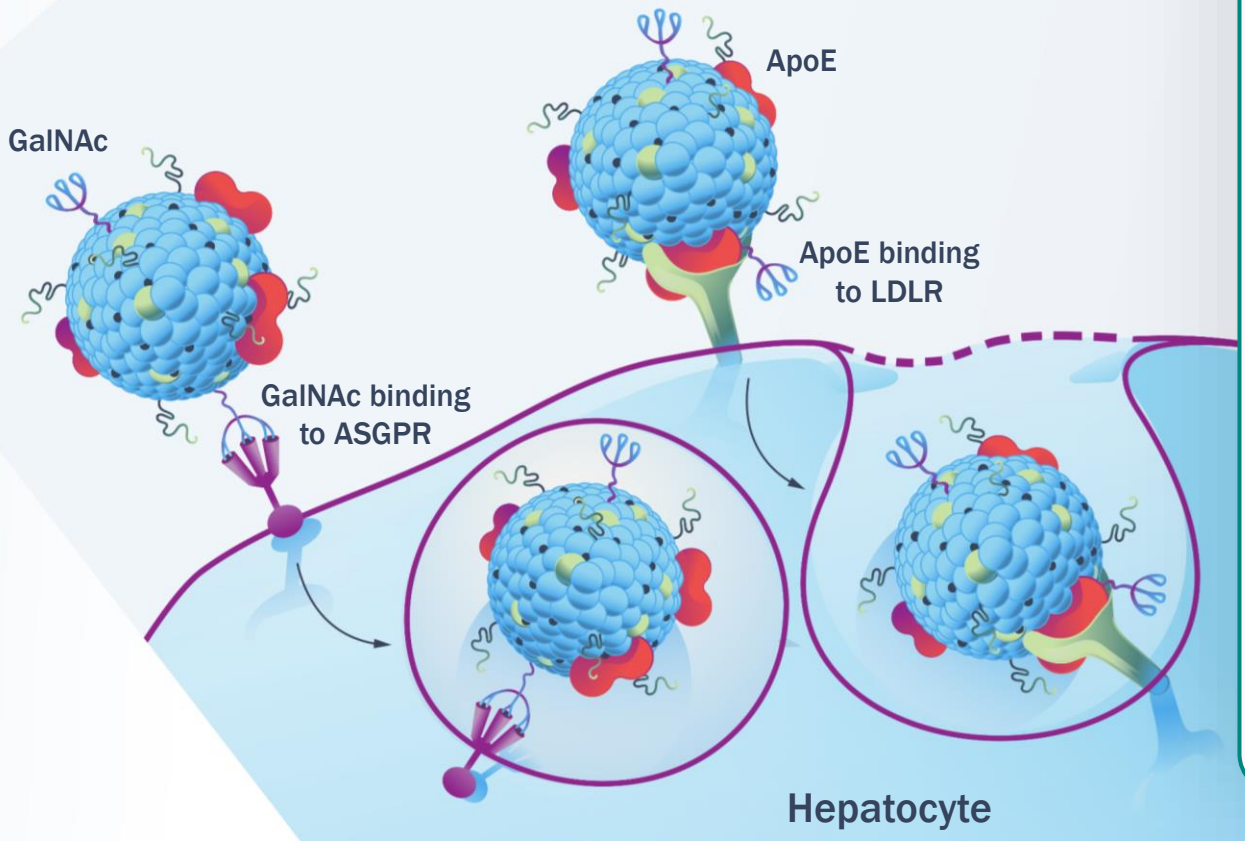
DSPC, 1,2-distearoyl-sn-glycero-3-phosphocholine; IV, intravenous; LNP, lipid nanoparticle; mRNA, messenger RNA; PEG, polyethylene glycol

VERVE-102: in the hepatocyte the translated ABE pairs with the guide RNA and turns off *PCSK9* with a single A•T to G•C DNA change

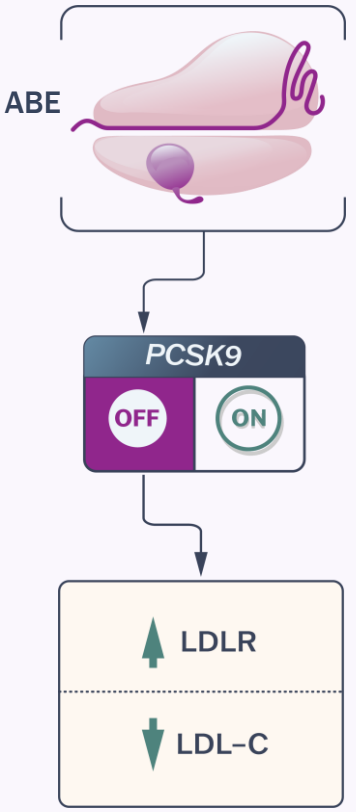
IV infusion of VERVE-102



GalNAc-LNP uptake

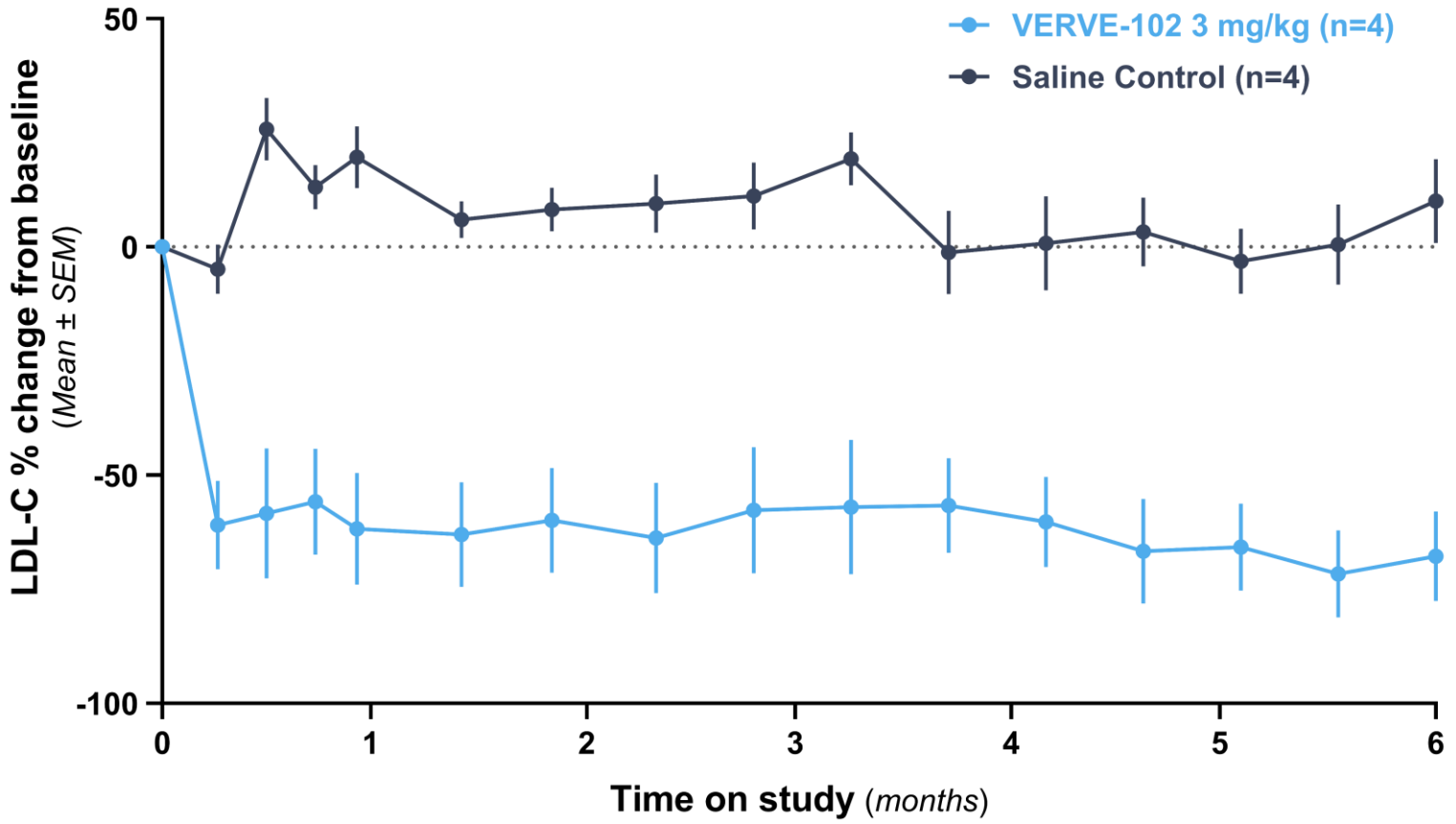


PCSK9 inactivation



ApoE, apolipoprotein E; ASGPR, asialoglycoprotein receptor; IV, intravenous; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LNP, lipid nanoparticle

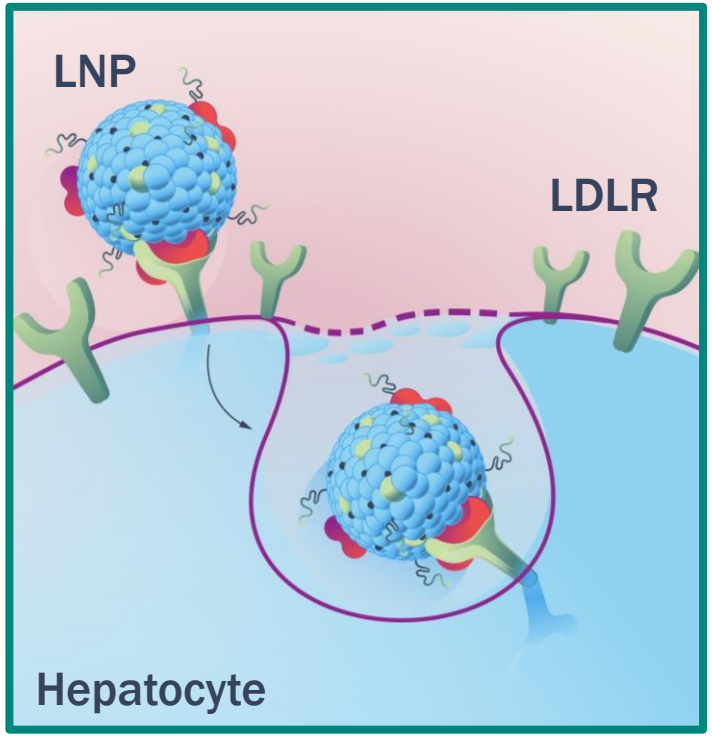
Single infusion of VERVE-102 durably lowered LDL-C by 62% in non-human primates



LDL-C lowering is based on time-averaged LDL-C change from baseline from day 28 through study completion at month 6.
SEM, standard error of the mean

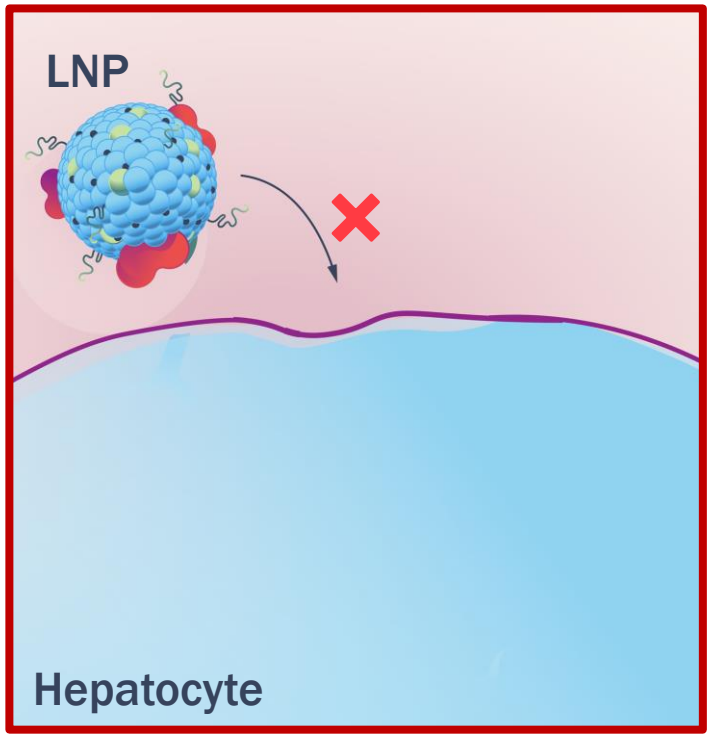
Can addition of GalNAc enable LNP uptake in the setting of LDLR deficiency that may be present in familial hypercholesterolemia?

Lipid nanoparticle without GalNAc



LDLR wild type

LDLR $^{+/+}$



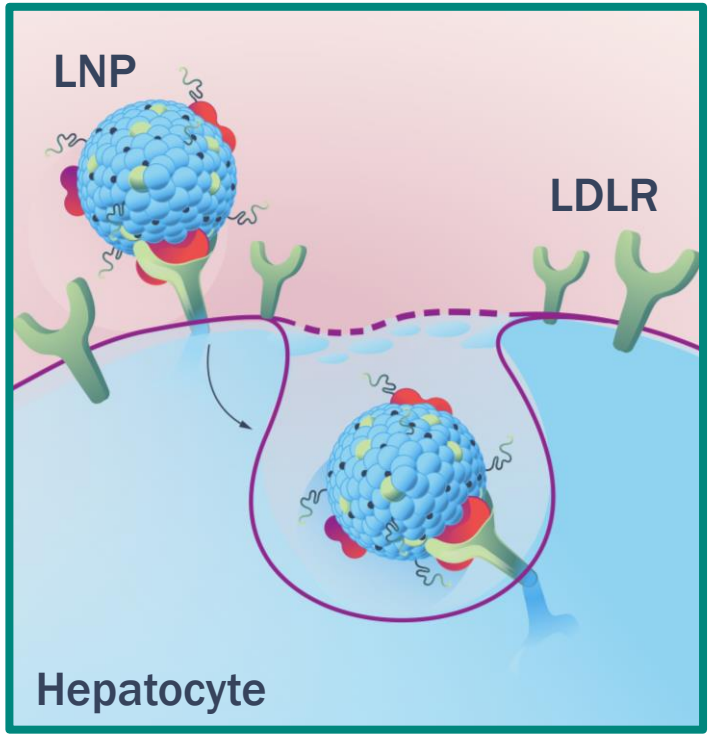
LDLR null

LDLR $^{-/-}$

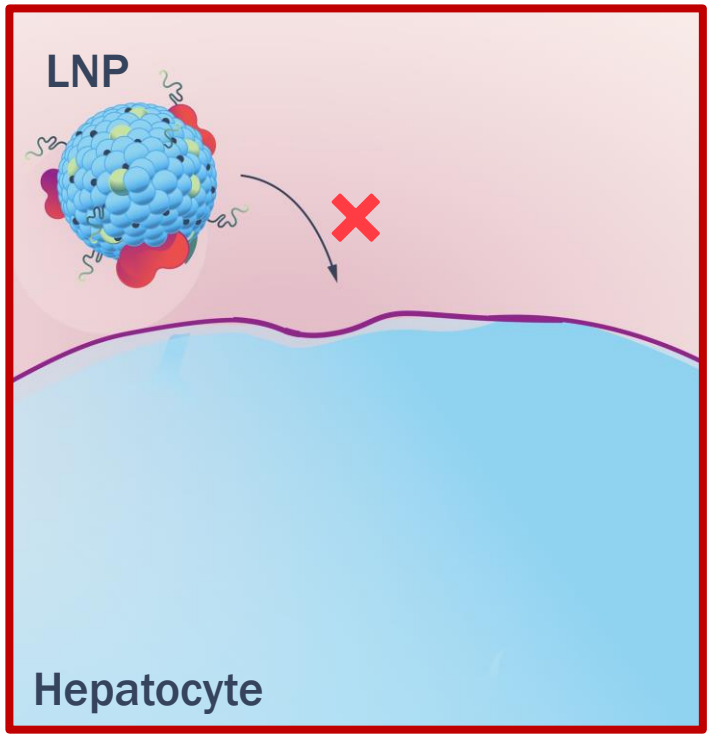
ASGPR, asialoglycoprotein receptor; LDLR, low-density lipoprotein receptor; LNP, lipid nanoparticle

Can addition of GalNAc enable LNP uptake in the setting of LDLR deficiency that may be present in familial hypercholesterolemia?

Lipid nanoparticle without GalNAc

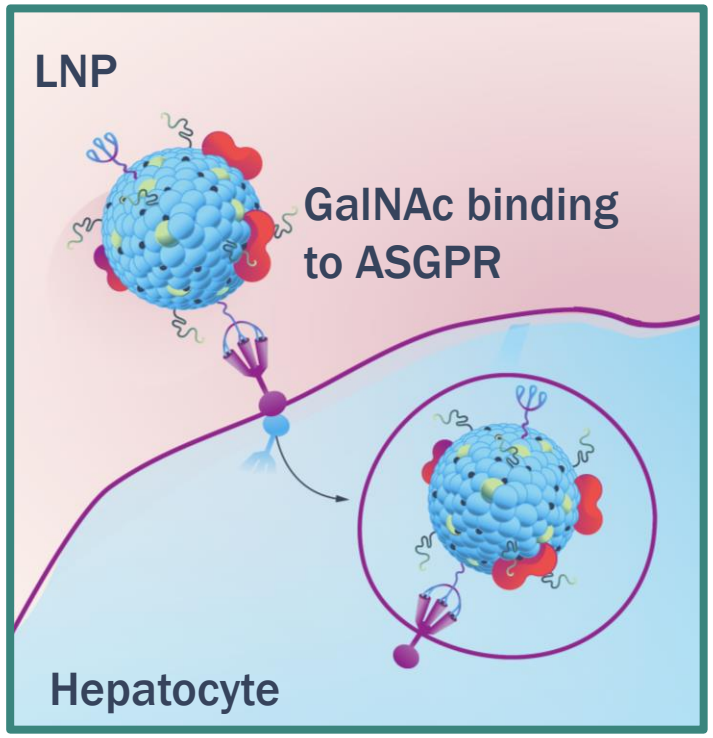


LDLR wild type
LDLR $^{+/+}$



LDLR null
LDLR $^{-/-}$

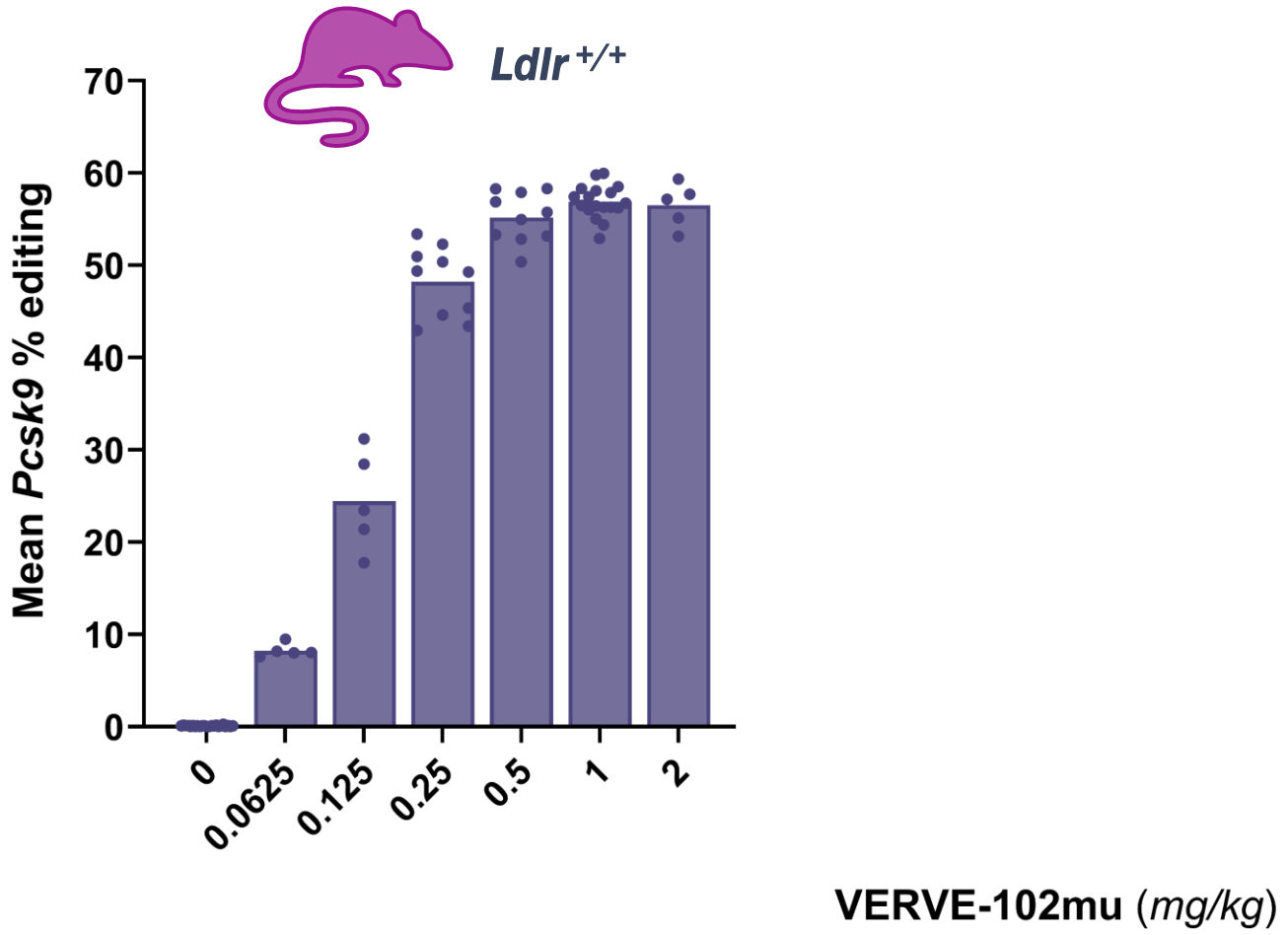
GalNAc-LNP



LDLR null
LDLR $^{-/-}$

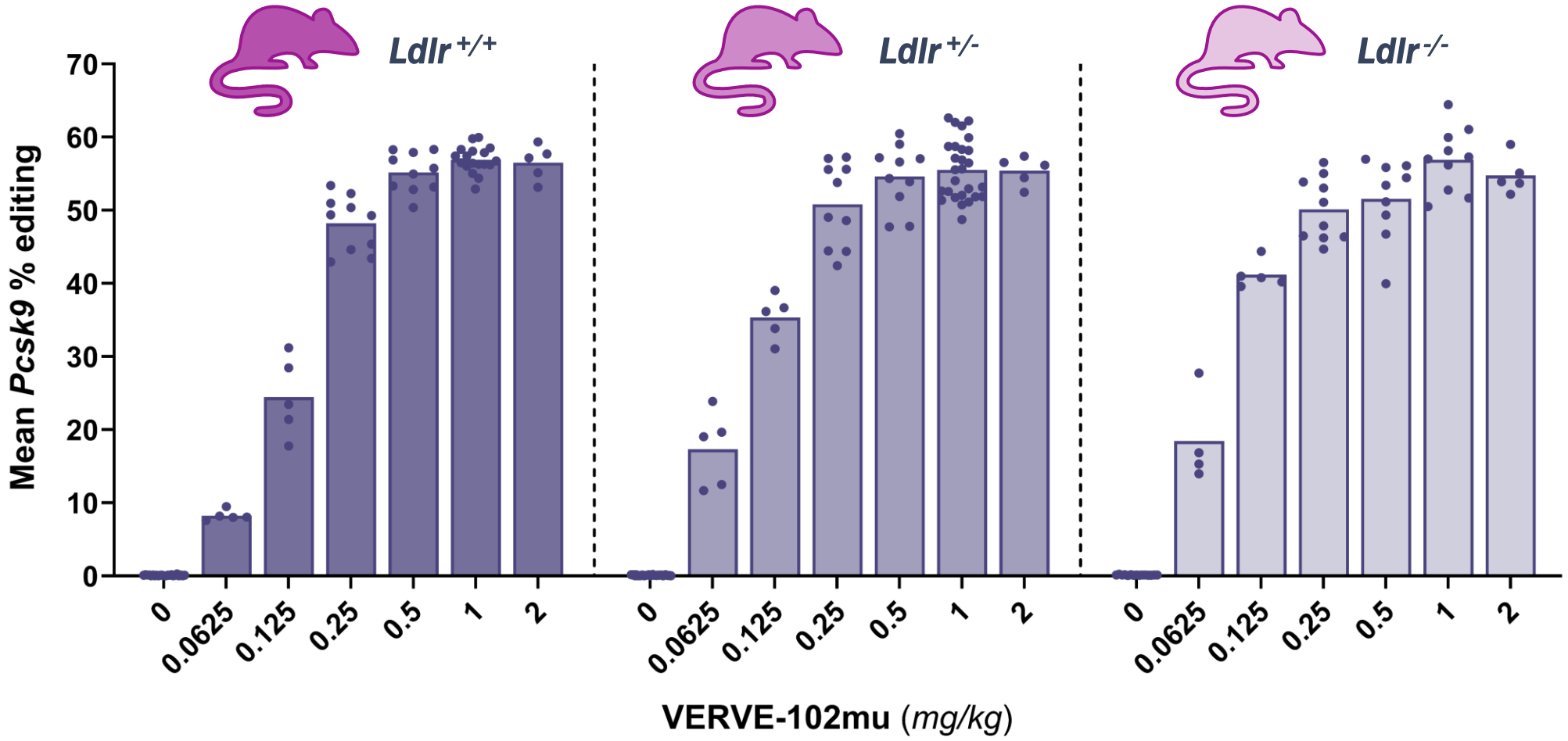
ASGPR, asialoglycoprotein receptor; LDLR, low-density lipoprotein receptor; LNP, lipid nanoparticle

Potent and dose-dependent editing of *Pcsk9* in *Ldlr* wild type mice with VERVE-102mu



Ldlr, low-density lipoprotein receptor; Pcsk9, proprotein convertase subtilisin/kexin type 9; VERVE-102mu, murine surrogate of VERVE-102

In mouse models of familial hypercholesterolemia, GalNAc-LNP equalizes editing efficiency between wild type, *Ldlr* $^{+/-}$, and *Ldlr* $^{-/-}$ *mice*



Ldlr, low-density lipoprotein receptor; Pcsk9, proprotein convertase subtilisin/kexin type 9; VERVE-102mu, murine surrogate of VERVE-102

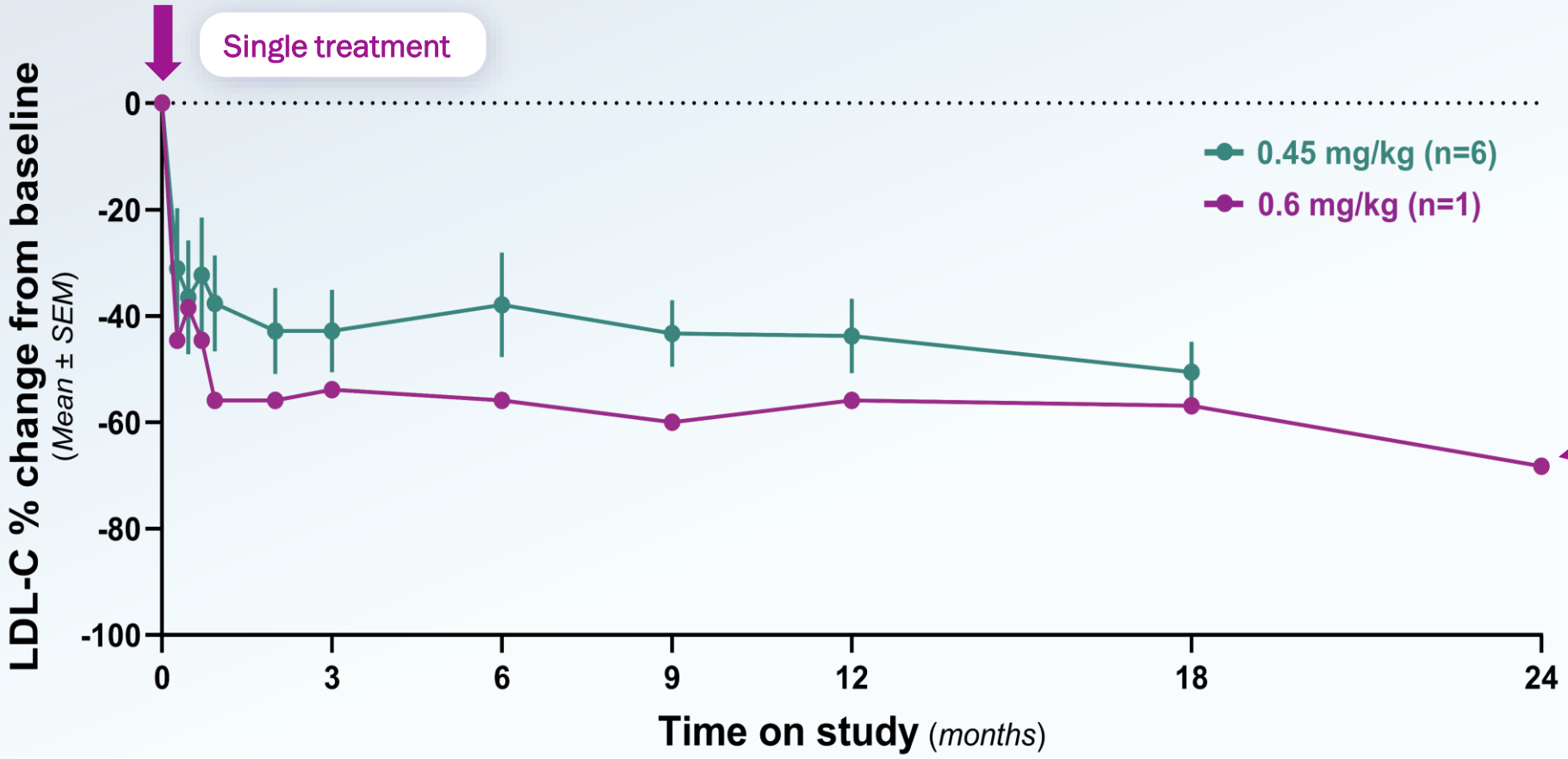
PCSK9 program clinical update

Verve has developed two PCSK9 product candidates: VERVE-102 has same editing mechanism but improved delivery platform vs. VERVE-101

	VERVE-101 (Heart-1 Clinical Trial)	VERVE-102 (Heart-2 Clinical Trial)
TARGET	*PCSK9* gene	
ADENINE BASE EDITOR (ABE)	Same ABE used in both product candidates	
GUIDE RNA (gRNA)	Same gRNA targeting *PCSK9*	
IONIZABLE LIPID	ALC-0307	LP000001
PEG LIPID	ALC-0159	DMG-PEG$_{2000}$
TARGETING LIGAND	-	GalNAc

PCSK9, proprotein convertase subtilisin/kexin type 9

VERVE-101 data provides proof-of-concept that base editing mechanism may deliver enduring efficacy: 2 years after treatment, time-averaged LDL-C reduction of 58% for single participant

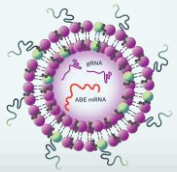


Patient diagnosed with HeFH who had suffered heart attack before age 30

Post VERVE-101 treatment, has been at LDL-C goal for 2 years

Data from parent Heart-1 study as of February 27, 2025. Data from long-term follow-up study as of March 26, 2025. Data have not been fully cleaned. Participants in 0.45 mg/kg cohort have variable duration of follow up, with n=2 at 18 months and n=4 at 12 months. Select time points were impacted for two participants in the 0.45 mg/kg cohort due to changes in background lipid-lowering therapy.
HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; SEM, standard error of the mean

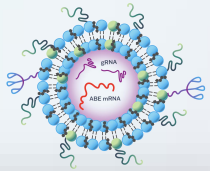
LNP-driven, transient laboratory abnormalities (ALT, platelets) with VERVE-101 motivated prioritization of VERVE-102



VERVE-101

Transient laboratory abnormalities (ALT, platelets) in clinic

Nonclinical studies conducted in 2024 confirmed LNP as source of laboratory abnormalities



VERVE-102

Nonclinical data indicate that with novel GalNAc-LNP, VERVE-102 is better tolerated at higher doses than VERVE-101

LNP, lipid nanoparticle; ALT, alanine aminotransferase

Heart-2: Phase 1b clinical trial designed to evaluate safety and tolerability of VERVE-102 (PCSK9)

Population: HeFH and/or premature coronary artery disease patients who require additional LDL-C lowering

heart-2

Intervention:
Single dose administered as a 2- to 4-hour peripheral intravenous infusion[1]

Phase 1b
Single ascending dose, n = 3 – 9 per cohort

- 0.3 mg/kg
- 0.45 mg/kg
- 0.6 mg/kg
- 0.7 mg/kg

Phase 2*
Expect first patient dosed H2 2025

Doses selected based on findings from Phase 1

Objectives:

- Primary: evaluate safety and tolerability
- Secondary: measure changes in blood PCSK9 and LDL-C levels

* Subject to regulatory clearance. [1]Pre-medication with dexamethasone and antihistamines.
HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9. NCT06164730

Initial update: safety and pharmacodynamic data from 14 participants across first three cohorts of Heart-2 trial

Population: HeFH and/or premature coronary artery disease patients who require additional LDL-C lowering

heart-2

Intervention:
Single dose administered as a 2- to 4-hour peripheral intravenous infusion[1]

Phase 1b
Single ascending dose, n = 3 – 9 per cohort

- 0.3 mg/kg (n=4)
- 0.45 mg/kg (n=6)
- 0.6 mg/kg (n=4)
- 0.7 mg/kg

Initial data from first 14 participants dosed across first three cohorts with ≥ 28 days of follow up

Phase 2*
Expect first patient dosed H2 2025

Doses selected based on findings from Phase 1

Objectives:

- Primary: evaluate safety and tolerability
- Secondary: measure changes in blood PCSK9 and LDL-C levels

As of March 13, 2025, data cut off date
*Subject to regulatory clearance. [1]Pre-medication with dexamethasone and antihistamines.
HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9. NCT06164730

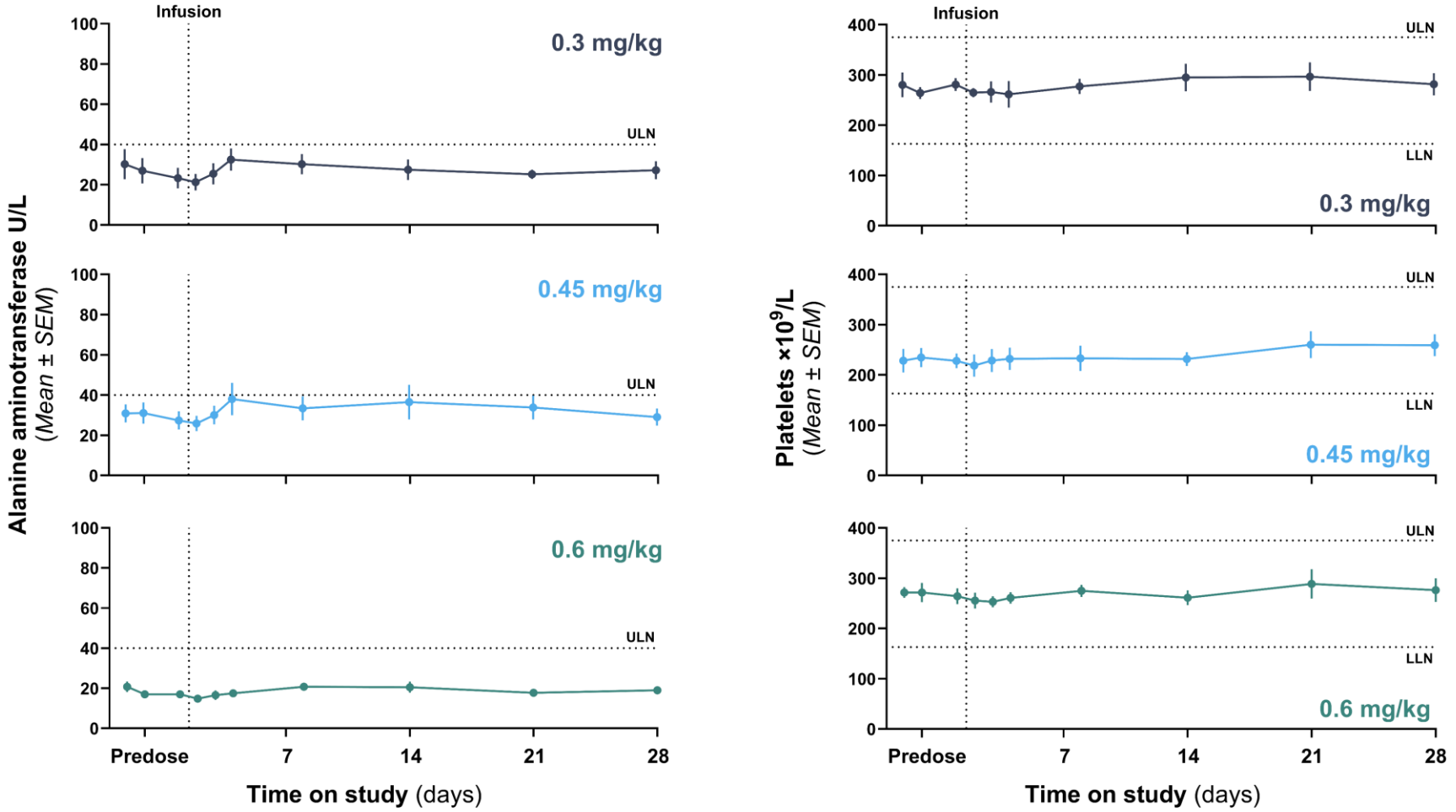
verve THERAPEUTICS

Clinical safety: VERVE-102 was well-tolerated across all dose levels

- No treatment-related SAEs and no DLTs
- No clinically significant laboratory abnormalities
- No cardiovascular events
- Across all 14 participants, there was one infusion-related reaction (IRR)
  - Single Grade 2 IRR in a participant dosed at 0.6 mg/kg (transient symptoms that resolved with acetaminophen)

As of March 13, 2025, data cut off date; data are from an ongoing study with an open database and have not been fully cleaned.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; SAE, serious adverse event; DLT, dose-limiting toxicity

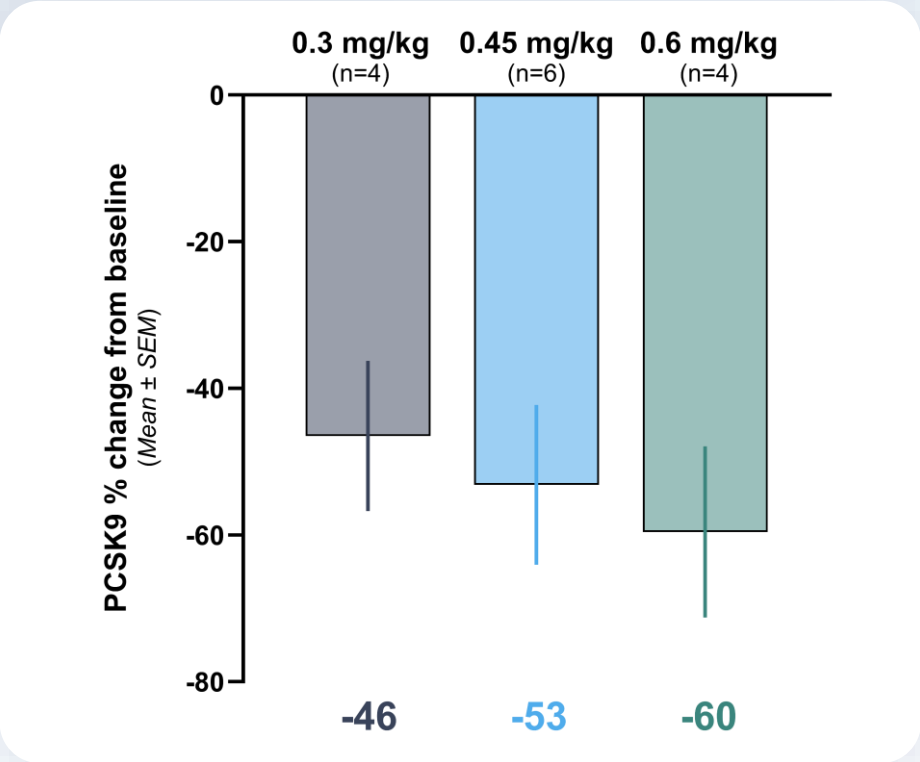
Laboratory assessment: no clinically significant changes in alanine aminotransferase (ALT) or platelets at any dose level following VERVE-102 infusion



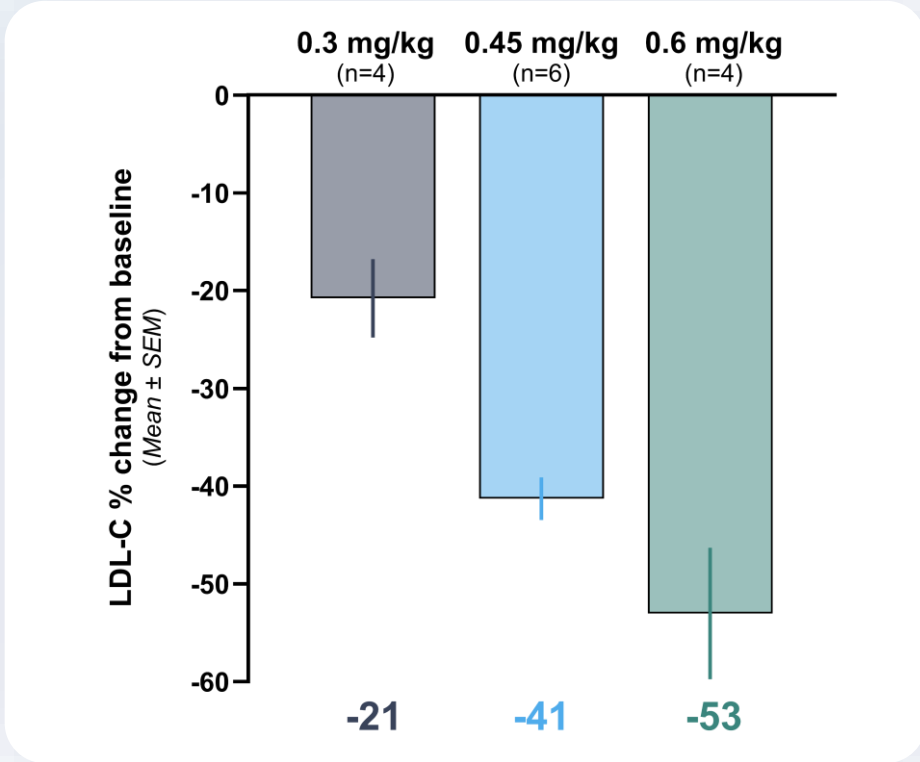
As of March 13, 2025, data cut off date; predose values include screening visits and day of infusion before dosing; ULN indicated for ALT is value for males (female ULN is 33 U/L).
LLN, lower limit of normal; SEM, standard error of the mean; ULN, upper limit of normal

Single infusion of VERVE-102 led to dose-dependent reductions in blood PCSK9 protein and blood LDL-C

PCSK9 protein reduction:
mean reduction of 60% observed in highest weight-based dose group



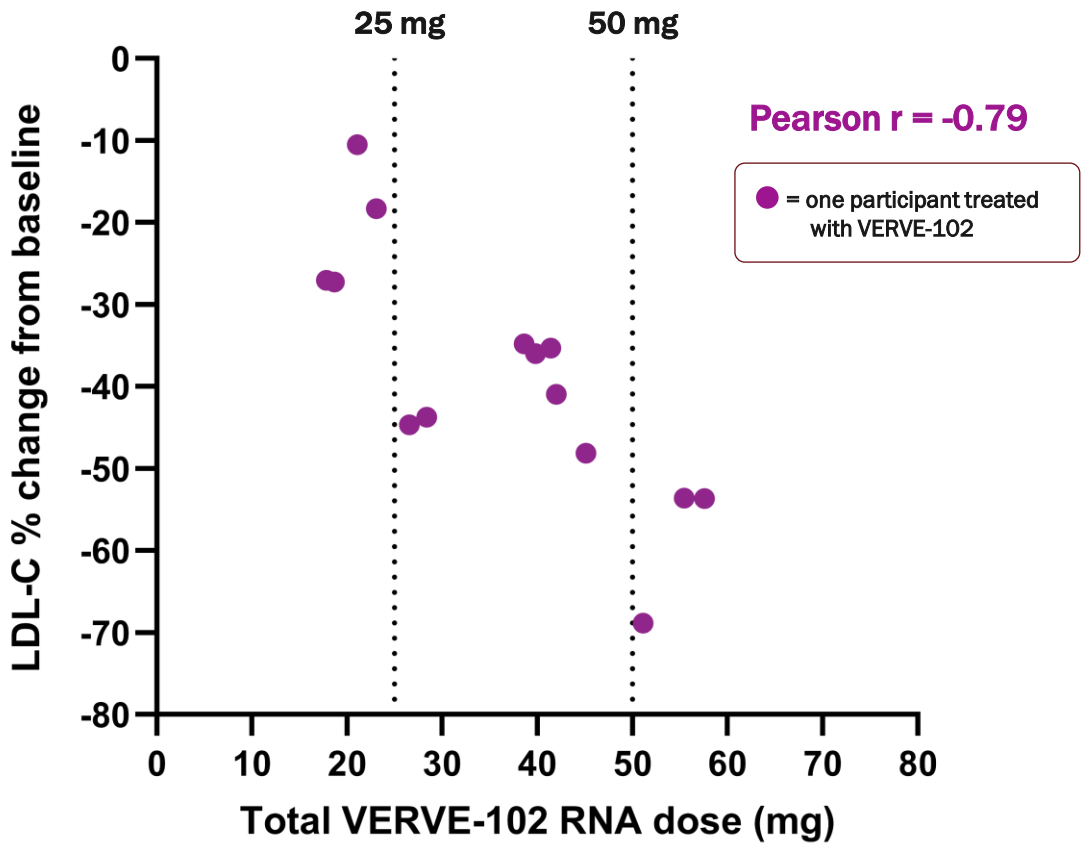
LDL-C reduction:
mean reduction of 53% observed in highest weight-based dose group



As of March 13, 2025. Data are from an ongoing study with an open database and have not been fully cleaned. Percent change from baseline uses time-averaged values from Day 28 through last available follow-up. Day 28 value was used in participants where the Day 28 was the last timepoint. Single observation in 2 participants censored due to changes in background lipid-lowering therapy.
PCSK9, proprotein convertase subtilisin/kexin type 9; SEM, standard error of the mean, LDL-C, low-density lipoprotein cholesterol

LDL-C by total RNA dose, per participant: across 14 participants, strong dose-dependent response observed with near-linear relationship

Maximum LDL-C reduction of 69%



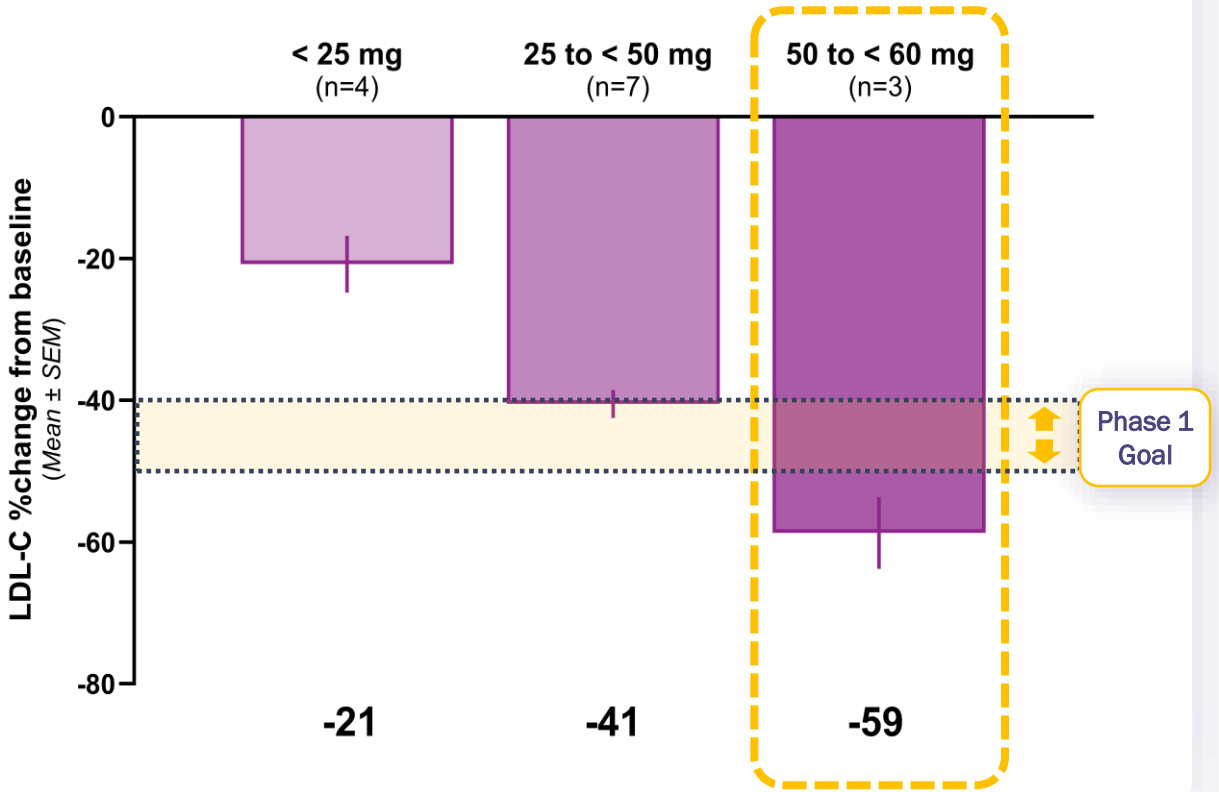
Total RNA Ranges:

- < 25 mg
- 25 – < 50 mg
- 50 – < 60 mg

As of March 13, 2025. Data are from an ongoing study with an open database and have not been fully cleaned. Percent change from baseline uses time-averaged values from Day 28 through last available follow-up. Day 28 value was used in participants where the Day 28 was the last timepoint. Single observation in 2 participants censored due to changes in background lipid-lowering therapy.
RNA, ribonucleic acid, LDL-C, low-density lipoprotein cholesterol

LDL-C: mean reduction of 59% in blood LDL-C observed in highest total RNA dose group of VERVE-102

All participants who received ≥ 50 mg achieved > 50% LDL-C reduction from baseline



VERVE-102 dose range	< 25 mg	25 - < 50 mg	50 - < 60 mg
Participants (n)	4	7	3
Mean total RNA dose	20 mg	37 mg	55 mg
Mean LDL-C % reduction from baseline	-21%	-41%	-59%

As of March 13, 2025. Data are from an ongoing study with an open database and have not been fully cleaned. Percent change from baseline uses time-averaged values from Day 28 through last available follow-up. Day 28 value was used in participants where the Day 28 was the last timepoint. Single observation in 2 participants censored due to changes in background lipid-lowering therapy.
LDL-C, low-density lipoprotein cholesterol; RNA, ribonucleic acid; SEM, standard error of the mean

VERVE-102 is an investigational base editing medicine designed to permanently inactivate *PCSK9* and lower LDL-C

1. Nonclinical data indicate GalNAc-LNP may enable delivery of editing components in the setting of LDLR deficiency

2. Base editing mechanism to inactivate *PCSK9* has been shown to lead to durable LDL-C lowering for up to two years with follow up ongoing[1]

3. Heart-2 safety: VERVE-102 was well-tolerated at all dose levels[2]

4. Heart-2 pharmacodynamics: Strong dose-dependent response with a mean LDL-C reduction of 59% at total RNA doses > 50 mg[2]

1. Data from parent Heart-1 study as of February 27, 2025. Data from long-term follow-up study as of March 26, 2025. Data have not been fully cleaned. 2. As of March 13, 2025, data cut off date; data are from an ongoing study with an open database and have not been fully cleaned. LNP, lipid nanoparticle; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9

Acknowledgments

Thank you to participants and their families

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