Safety and Pharmacodynamic Effects of VERVE-101

An Investigational DNA Base Editing Medicine Designed to Durably Inactivate the *PCSK9* Gene and Lower LDL Cholesterol – Interim Results of the Phase 1b heart-1 Trial

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Speaker Disclosure

Andrew M Bellinger is an employee and equity holder of Verve Therapeutics.

Investigational Product

VERVE-101 is an investigational agent that is not approved for commercial use in any jurisdiction.

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 safety, tolerability, and potential benefits of VERVE-101, the company’s timing and ability to enroll patients in its ongoing heart-1 trial, the timing of initiation of a clinical trial of VERVE-102, the Company's research and development plans, and the potential advantages and therapeutic potential of the Company’s programs, including VERVE-101 and VERVE-102. 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 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 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.

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Heterozygous familial hypercholesterolemia (HeFH): serious, inherited disease where few patients at LDL-C goal

HeFH is a morbid disease

- Lifelong severe elevations in LDL-C[1]
- Accelerated atherosclerotic cardiovascular disease (ASCVD)
- Estimated three million adult patients in US/Europe[2]

Chronic care model for patients living with HeFH

- Daily pills/intermittent injections, over decades
- Heavy treatment burden on patients, providers, & healthcare system

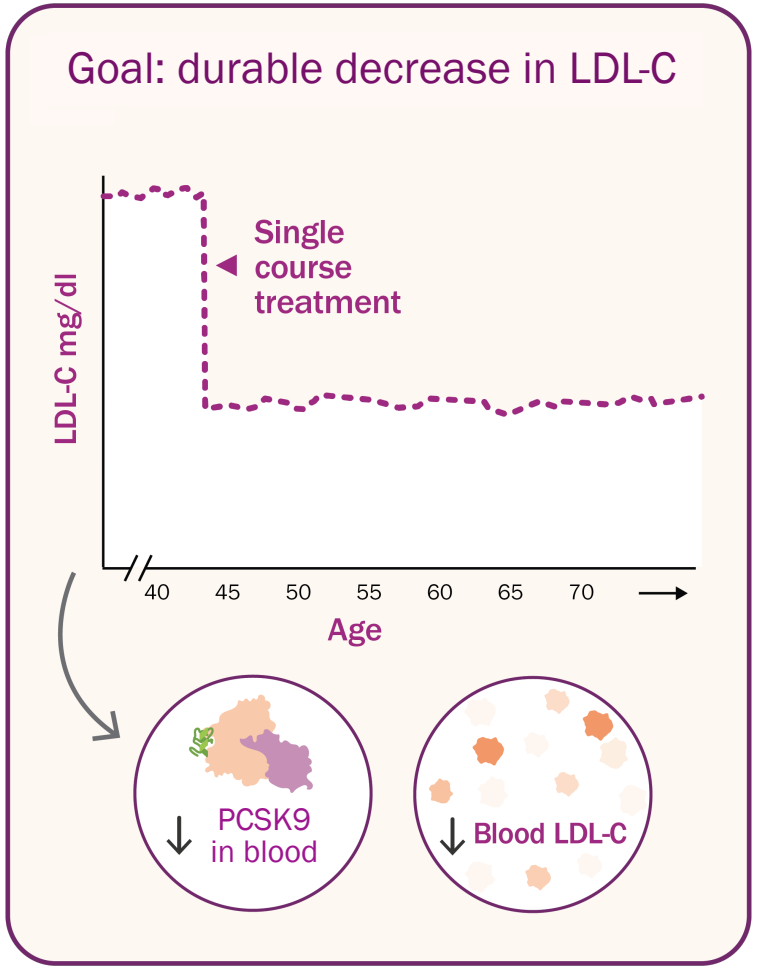
1. Gidding SS, et al. Circulation. 2015;132:2167-2192; 2. de Ferranti SD, et al. Circulation. 2016;133:1067-1072; 3. Duell PB, et al. Atherosclerosis. 2019;289:85-93; 4. Vallejo-Vaz AJ, et al. Lancet. 2021;398(10312):1713-1725.
ASCVD, atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol

Human genetics suggests a potential solution: turning off the cholesterol-raising gene *PCSK9* in the liver to durably lower LDL-C

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

- Lifelong LDL-C lowering
- Protection against ASCVD
- No apparent deleterious effects[1,2,3]

Pharmacologic validation of target

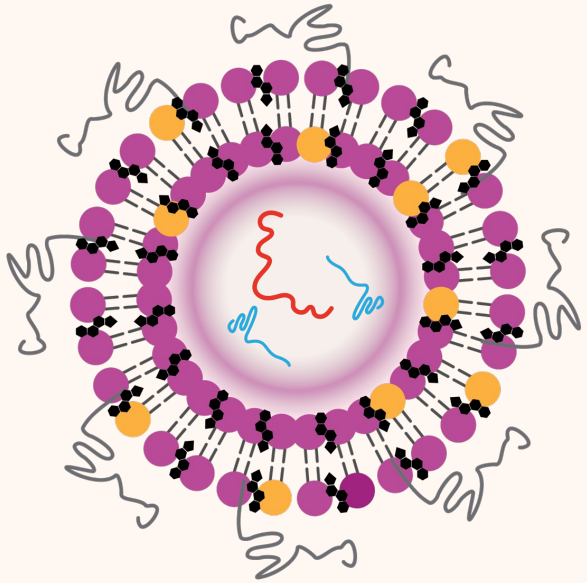


Can we develop a single-course treatment that mimics natural PCSK9 variants which protect against ASCVD?

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

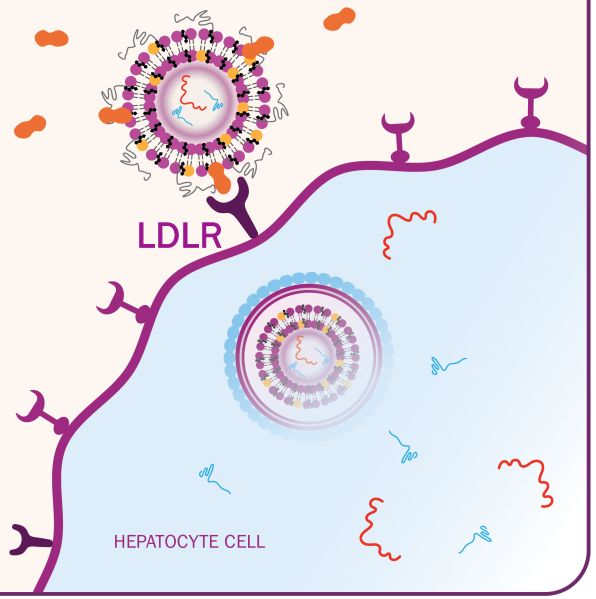
VERVE-101: novel CRISPR base editing medicine designed to inactivate hepatic *PCSK9* and lower LDL-C with a single DNA base pair change

VERVE-101



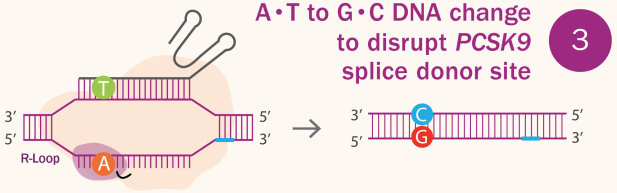
1 VERVE-101 delivery to the hepatocyte

1x intravenous infusion



2 Localization to *PCSK9* gene

A•T to G•C DNA change to disrupt *PCSK9* splice donor site 3

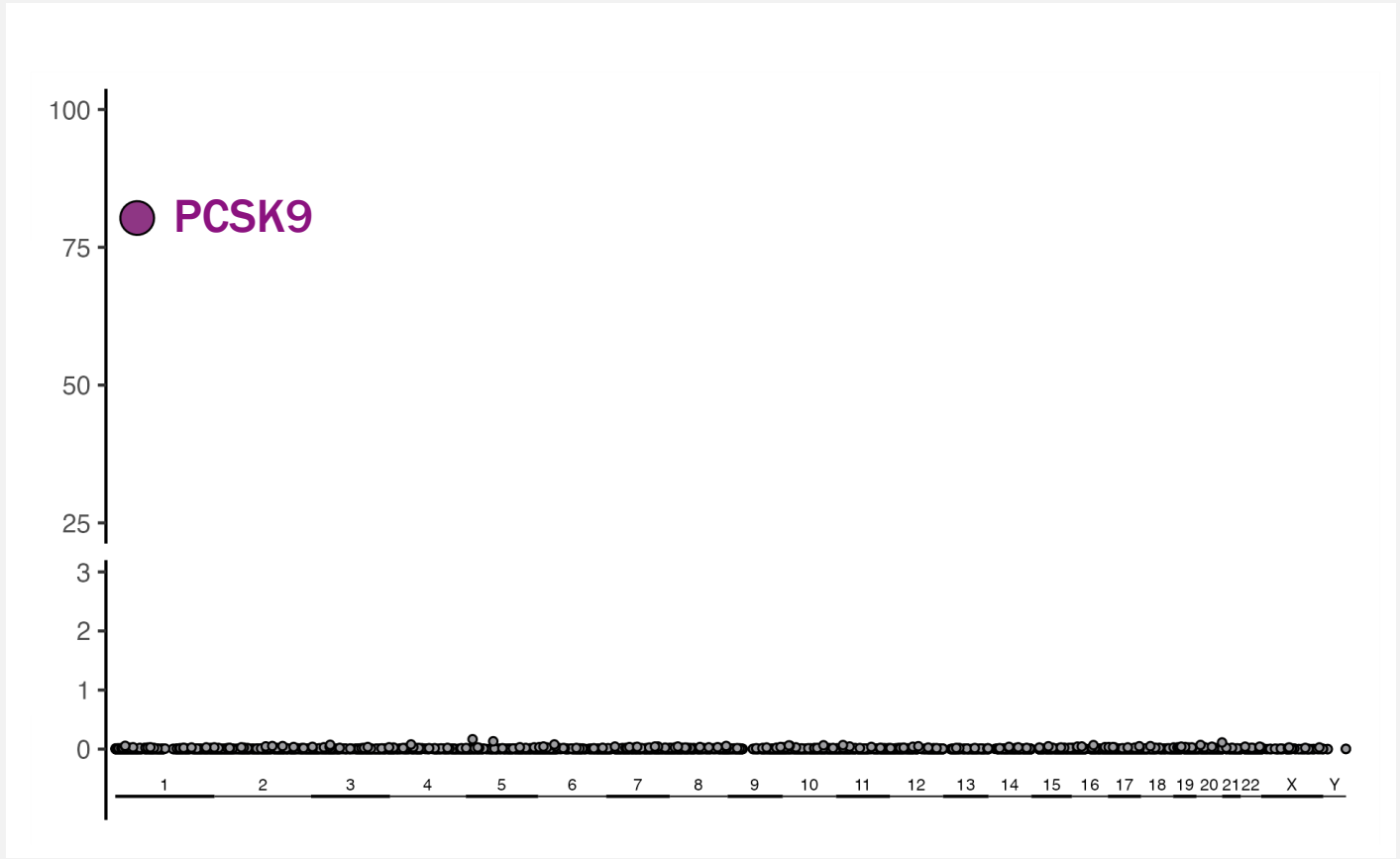


A to G "spelling" change in DNA to turn off gene

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

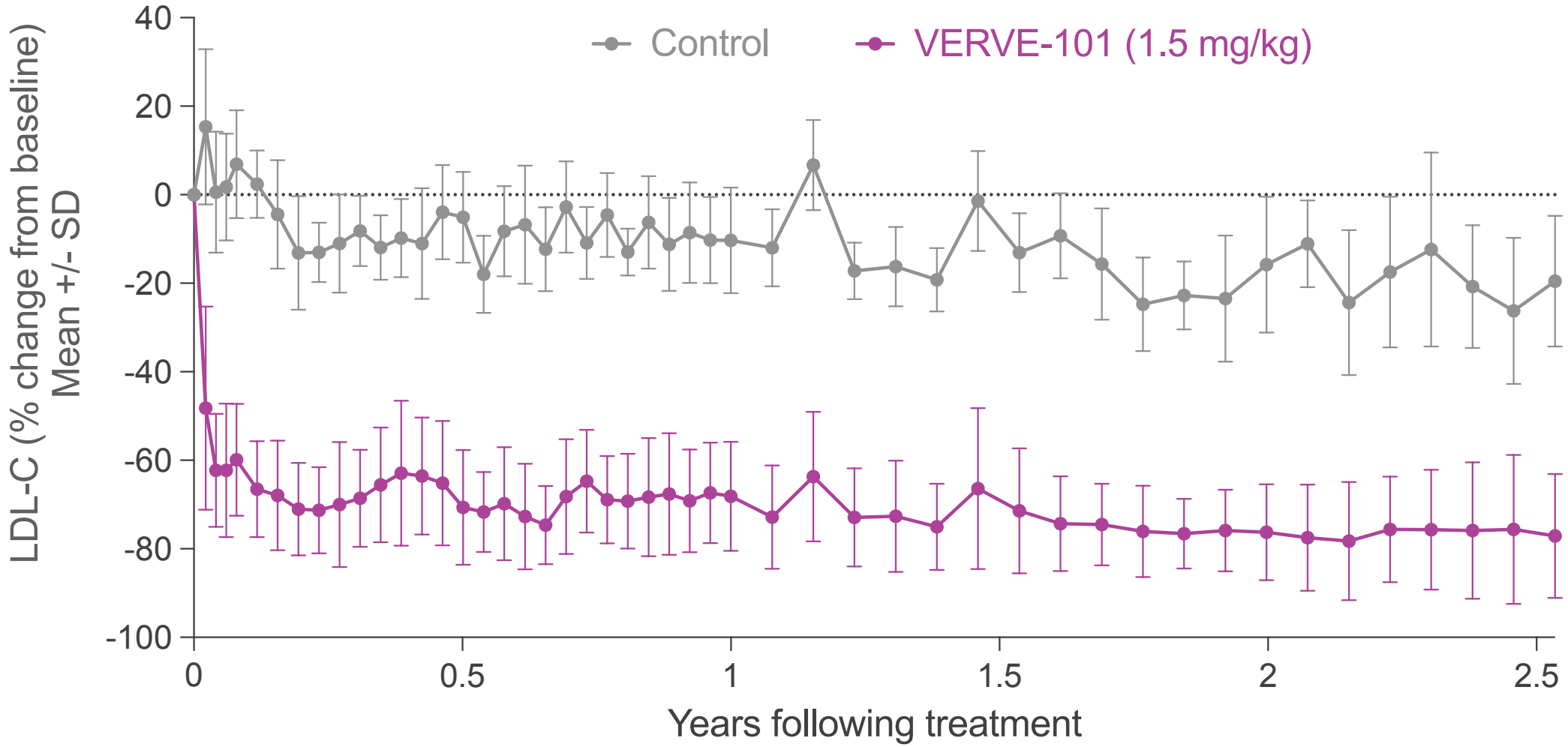
DSPC, distearoyl-sn-glycerol-3-phosphocholine; gRNA, guide RNA; LNP, lipid nanoparticle; mRNA, messenger RNA; RNA, ribonucleic acid

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

In non-human primates, blood LDL-C observed to be durably lowered for 2.5 years following single infusion of VERVE-101



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.

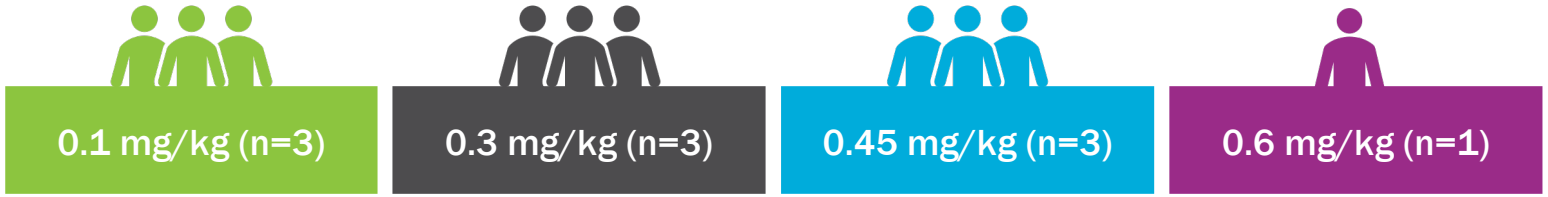
heart-1 is a first-in-human Phase 1b trial designed to evaluate the safety and tolerability of VERVE-101

heart-1

First-in-human, open-label, single ascending dose study in patients with HeFH and high risk for cardiovascular events

Interim update:
10 participants treated across 4 dose cohorts[5]

Data cut-off date October 16, 2023



STUDY POPULATION SUMMARY

- Males and females[1] (age 18 to 75)
- HeFH
- Established ASCVD
- Uncontrolled hypercholesterolemia[2]
- On maximally-tolerated oral lipid-lowering therapy[3]

DRUG ADMINISTRATION

- Pre-medication with dexamethasone and antihistamines
- VERVE-101 delivered as single infusion via a peripheral intravenous[4]

TRIAL ENDPOINTS

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

Clinical trial registration: NCT05398029; 1. Women of childbearing potential are excluded from the study; 2. LDL-C threshold for inclusion value varies by country-specific protocol; 3. maximum tolerated statin and/or ezetimibe (statin intolerant allowed). 4. dosing based on weight for participants ≤ 100 kg; participants > 100 kg are dosed on an assumed 100 kg weight; 5. 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.

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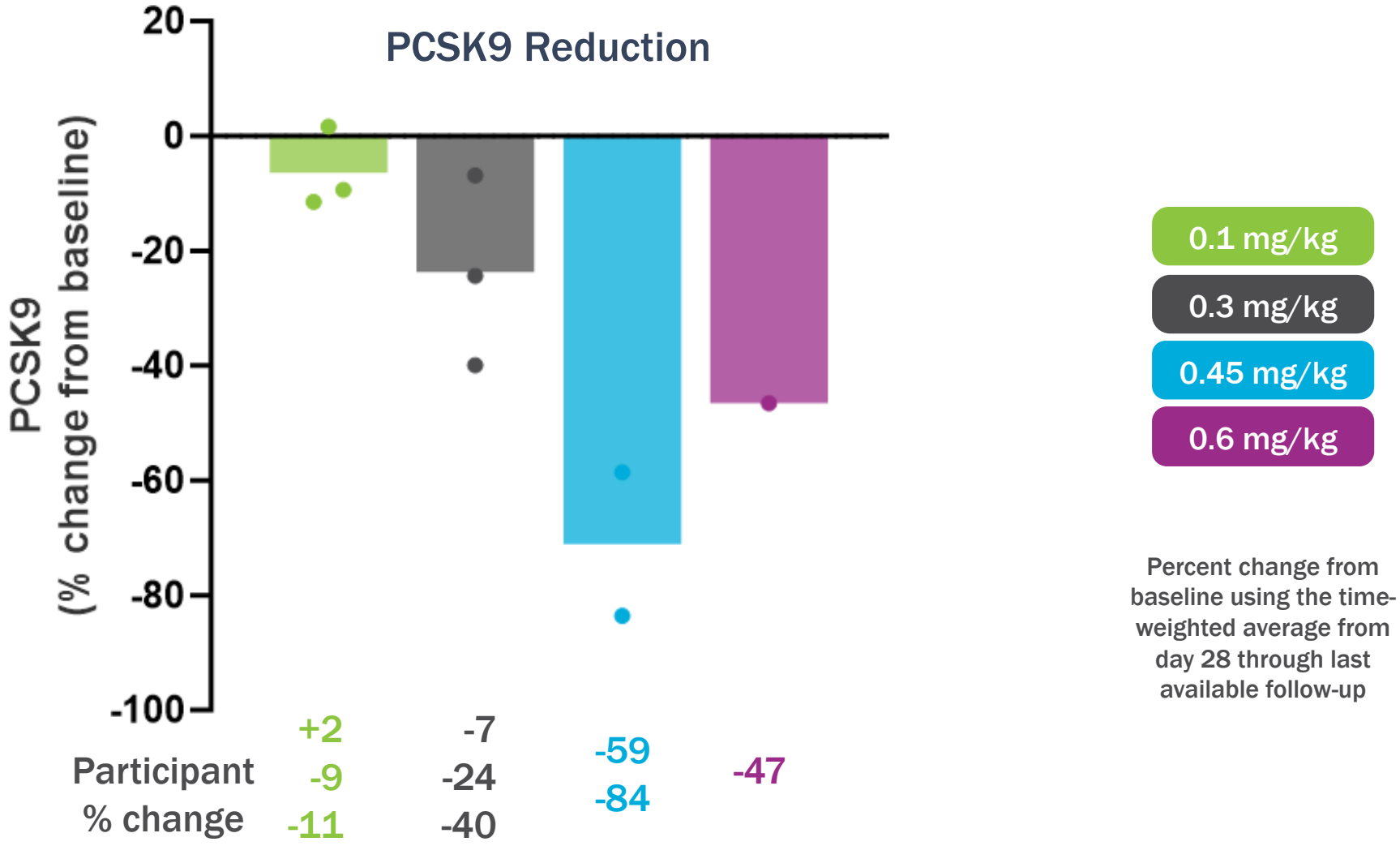
Participants enrolled to date have severe, advanced ASCVD and high risk for cardiovascular events (near-term and lifetime)

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. 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



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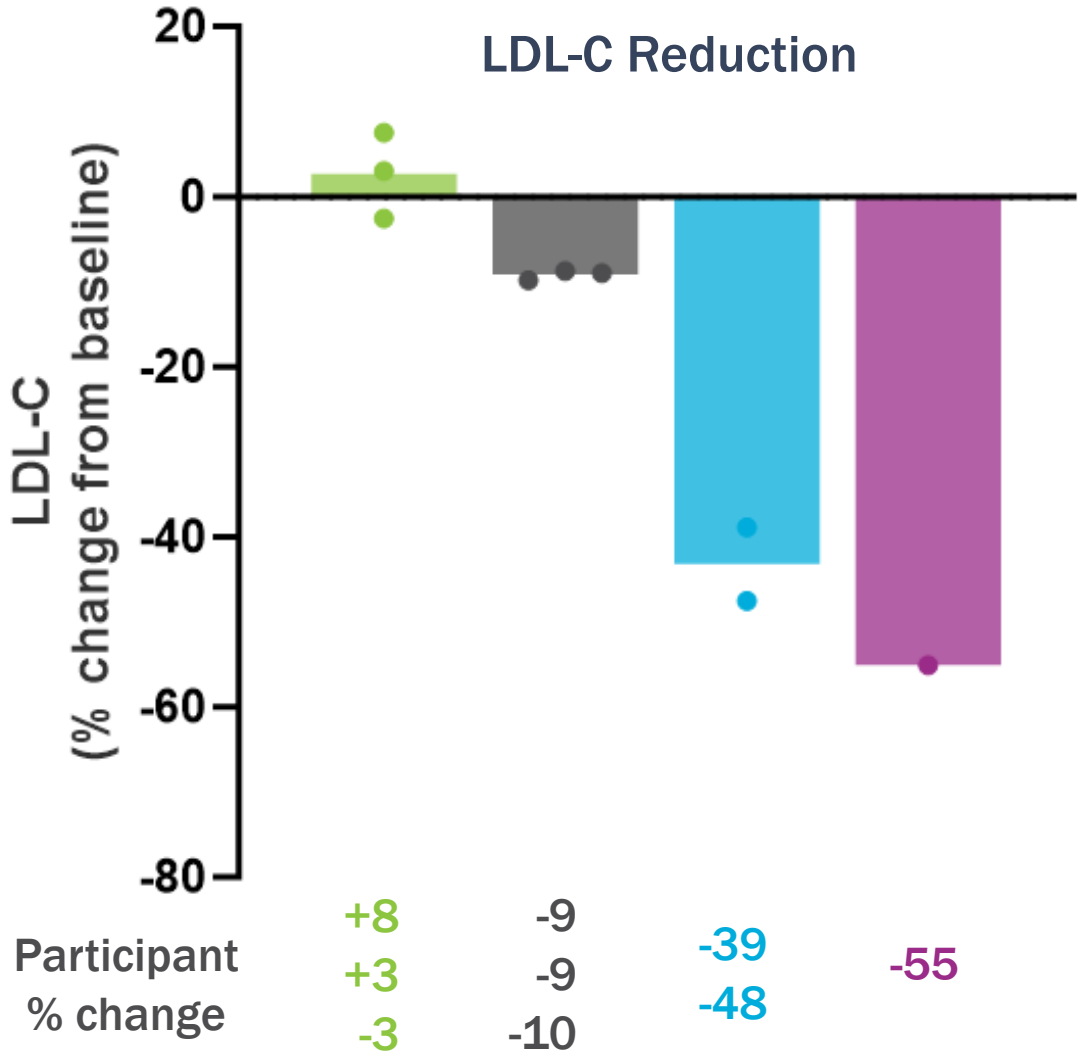
Day 28 value was used for time-weighted average in participants where day 28 was latest timepoint. One participant who has not reached day 28 excluded from analysis. Observations in 2 participants in 0.1 mg/kg cohort censored from analysis after changes in lipid lowering treatment (both >90 days after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

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



0.1 mg/kg

0.3 mg/kg

0.45 mg/kg

0.6 mg/kg

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

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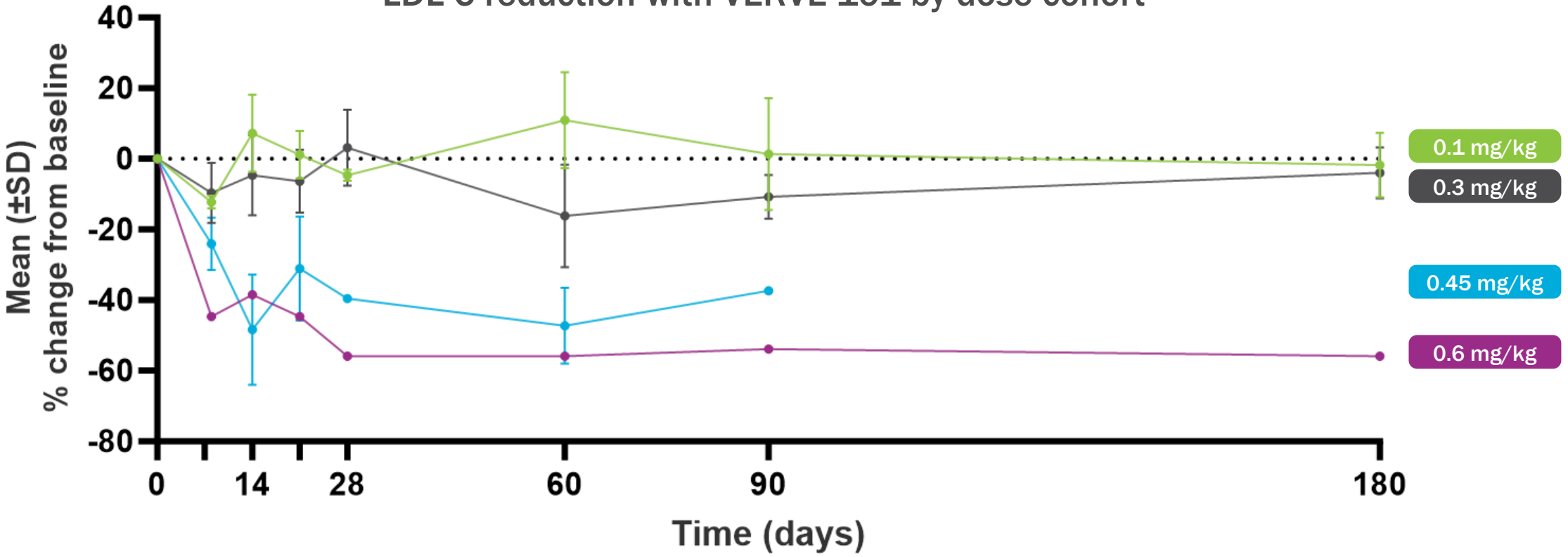
Durable 55% reduction in LDL-C extending up to 180 days in the single participant in the highest dose cohort

LDL-C reduction with VERVE-101 by dose cohort



Participants, n								
0.1 mg/kg	3	3	3	3	3	3	3
0.3 mg/kg	3	3	3	3	2	2	2
0.45 mg/kg	2	2	2	2	2	1	0
0.6 mg/kg	1	1	1	1	1	1	1

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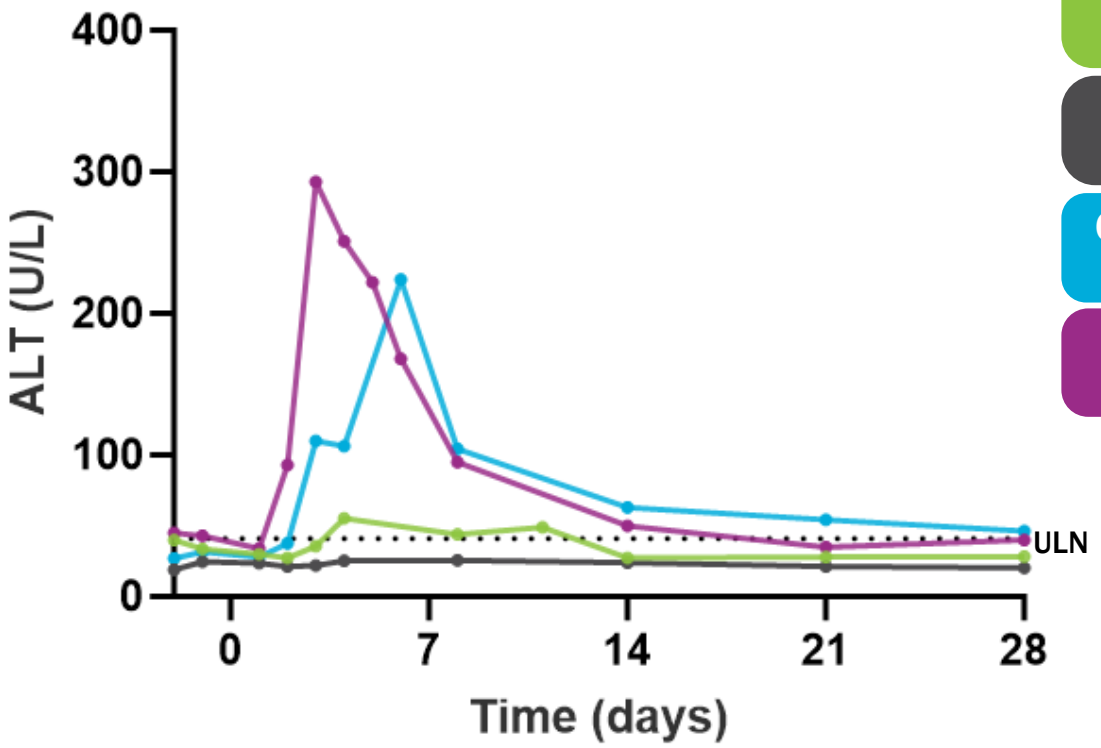
SD, standard deviation

Interim safety summary

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. Data are from an ongoing study with an open database and have not been fully cleaned. AEs are treatment emergent adverse events.
a. Myocardial infarction assessed as potentially related to treatment; b. transient, asymptomatic increase in liver transaminases with changes in bilirubin 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

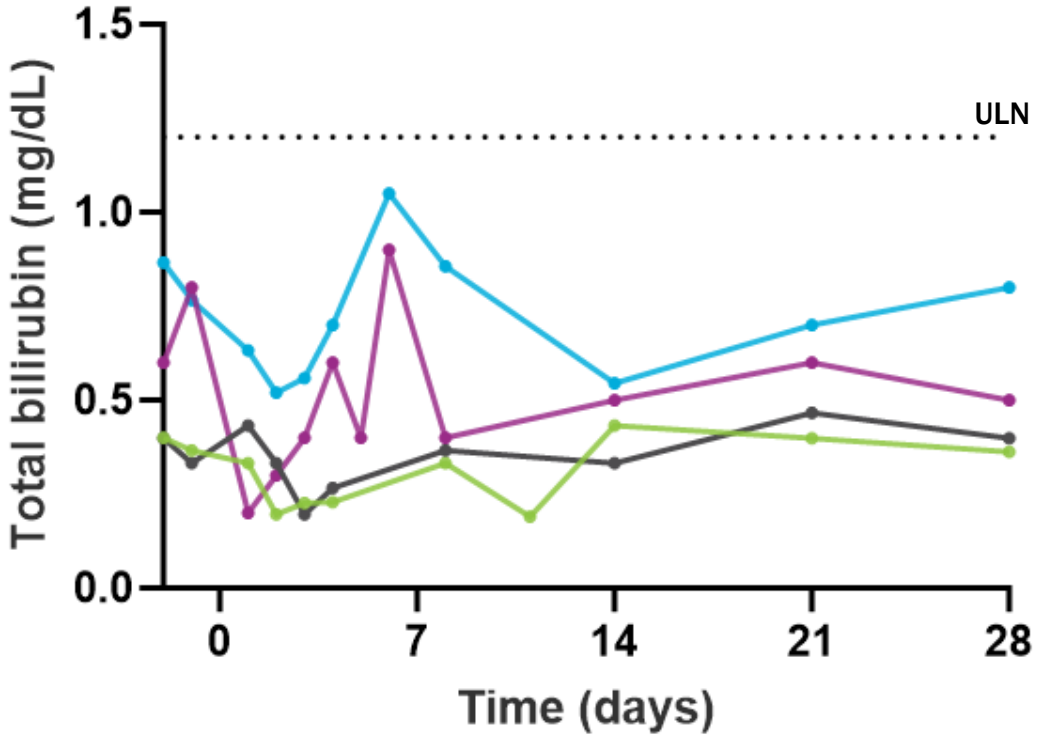


0.1 mg/kg (n=3)

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. Data are from an ongoing study with an open database and have not been fully cleaned; 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

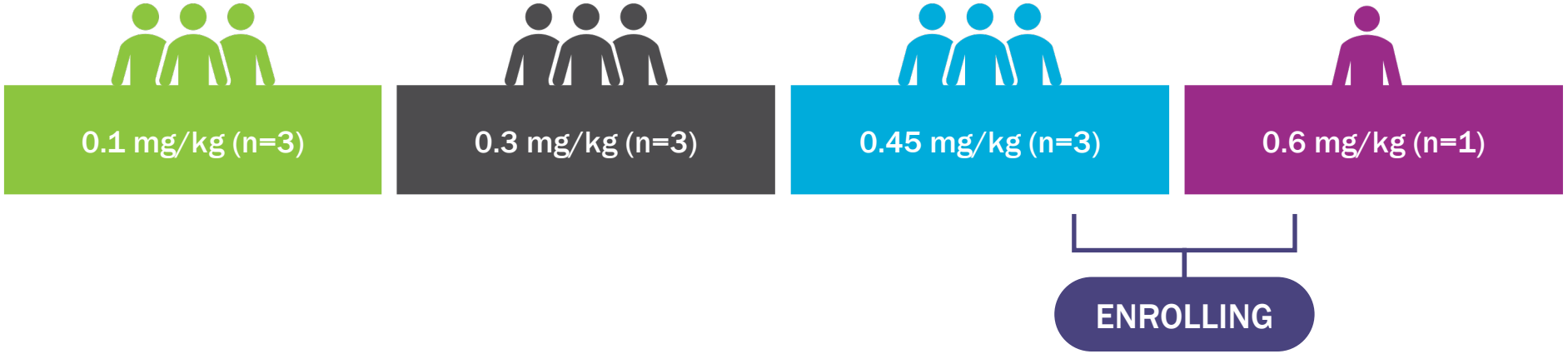
(3 events in total, of which 2 were determined to be unrelated)

- 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. Data are from an ongoing study with an open database and have not been fully cleaned
SAE, serious adverse event; CAD, coronary artery disease; MI, myocardial infarction

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



- Enrolling in 0.45 & 0.6 mg/kg cohorts to complete dose escalation phase
- Plan to enroll an expansion cohort in 2024
- For PCSK9 program, plan to initiate a randomized and placebo-controlled phase 2 trial in 2025

Conclusions: 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

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

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heart-1

Thank you to the patients and families, investigators and study staff, our partners, and the independent DSMB for their participation in the heart-1 trial.

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