Design of Heart-2

A Phase 1b clinical trial of VERVE-102, an *in vivo* base editing medicine delivered by a GalNAc-LNP and targeting *PCSK9* to durably lower LDL cholesterol

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Speaker Disclosure

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

Investigational Product

VERVE-102 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-102, the Company’s timing and ability to enroll patients in its ongoing Heart-2 trial, the timing and availability of initial data from the Heart- 2 trial, the Company's research and development plans, and the potential advantages and therapeutic potential of the Company’s programs, including its PCSK9 program. 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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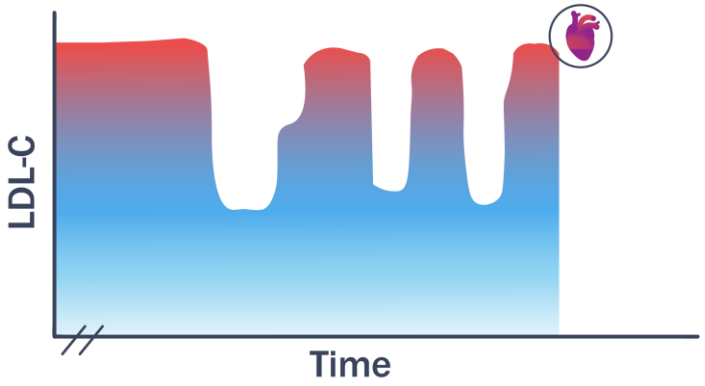
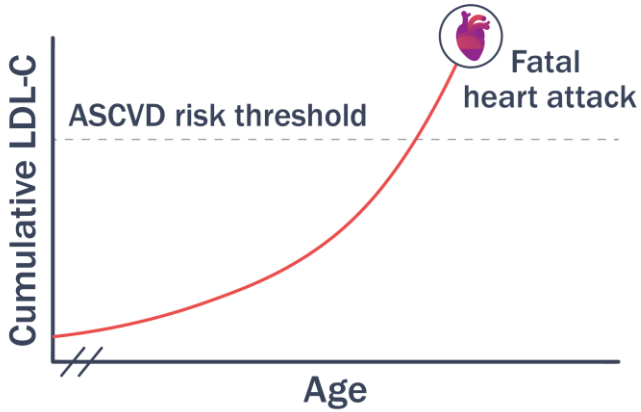
How might single-course base editing medicines address the limitations of the chronic care model for ASCVD?

Chronic care model

- About **50%** of ASCVD patients are **not on a statin**[1]
- Only about **2%** of eligible patients are **currently on a PCSK9 agent**[2]
- Up to **50%** of patients **discontinue** CVD medications **within 12 months**[3,4]

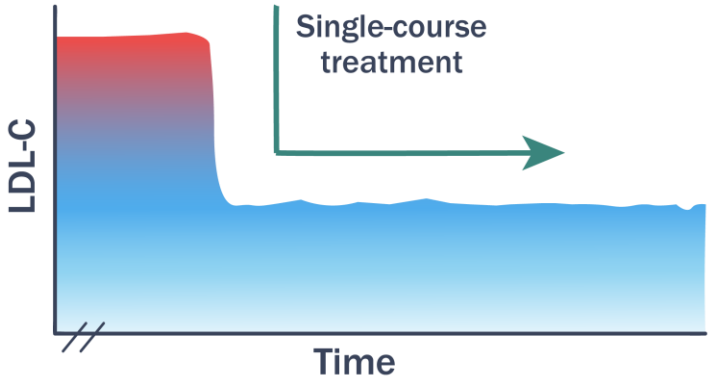
Poor LDL-C control increases the risk for major CV events

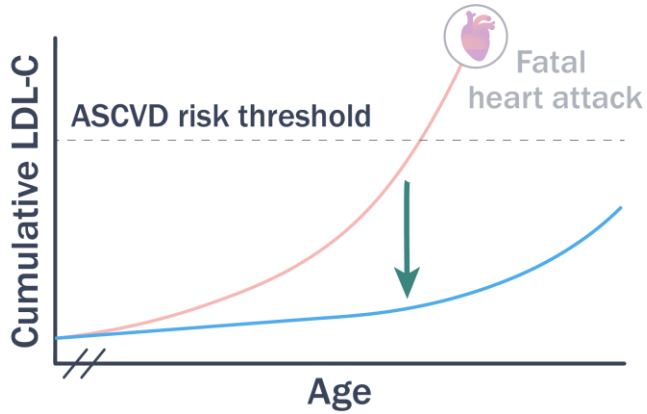




Potential solution: single-course base editing medicine to inactivate cholesterol-raising genes leading to lifelong LDL-C lowering

Durable LDL-C lowering reduces CV risk





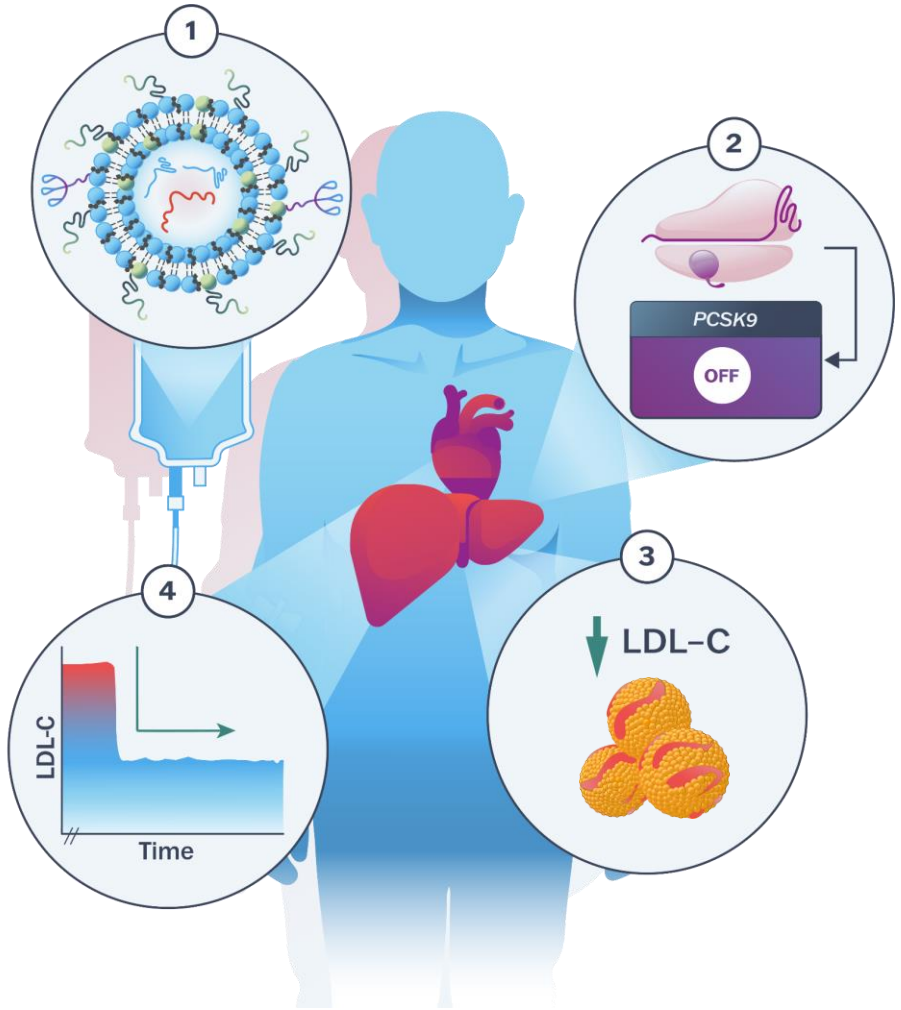
ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; LDL-C low-density lipoprotein cholesterol; 1. Nelson AJ et al., J Am Coll Card. 2022;79(18):1802–13; 2. Dayoub EJ et al., J Am Heart Assoc. 2021 May 4; 10(9): e019331; 3. Nelson A et al., Nature Reviews Cardiology 2024. https://doi.org/10.1038/s41569-023-00972-1; 4. Naderi SH et al., Am J Med. 2012;125, 882–887.e1

Can we use *in vivo* base editing medicines to mimic naturally occurring loss-of-function variants in *PCSK9* that protect against ASCVD?

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



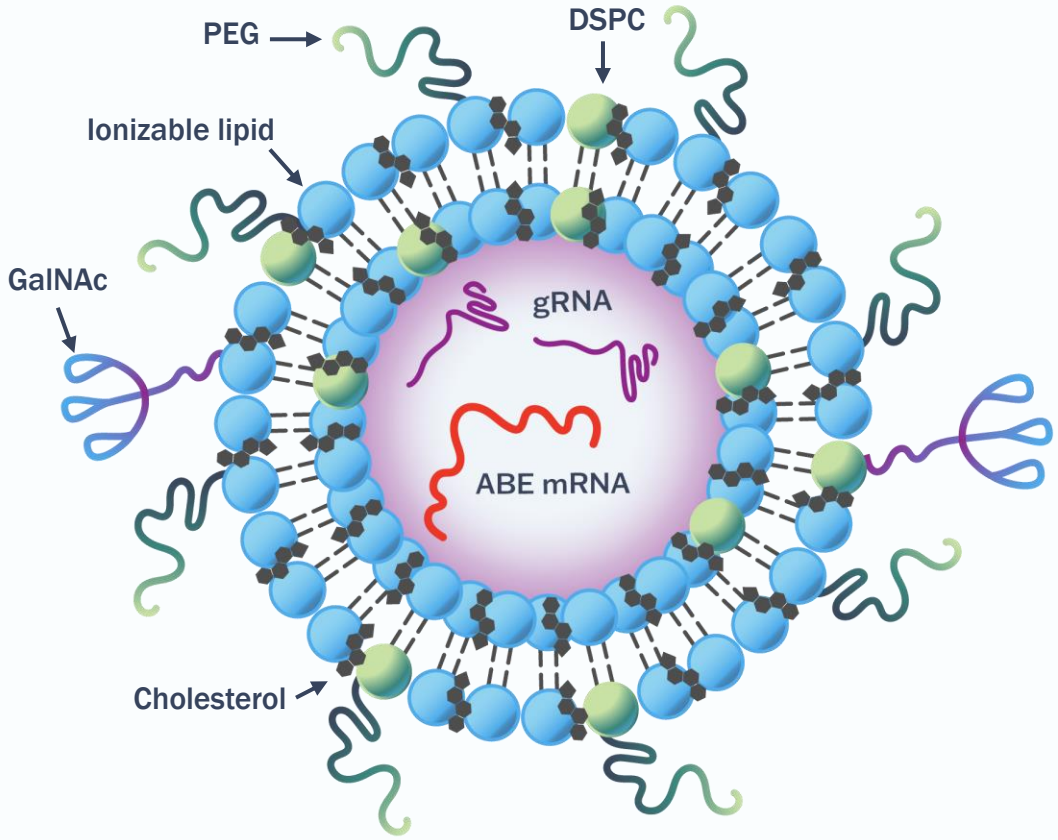
Proposed approach to liver *PCSK9* inactivation using *in vivo* base editing

1) IV infusion of lipid nanoparticle (LNP) carrying base editing components
2) Base editor delivered to liver inactivates *PCSK9* with a single DNA base pair change
3) Reduction in PCSK9 protein leads to lower LDL-C
4) Potentially durable LDL-C response based on permanent *PCSK9* inactivation

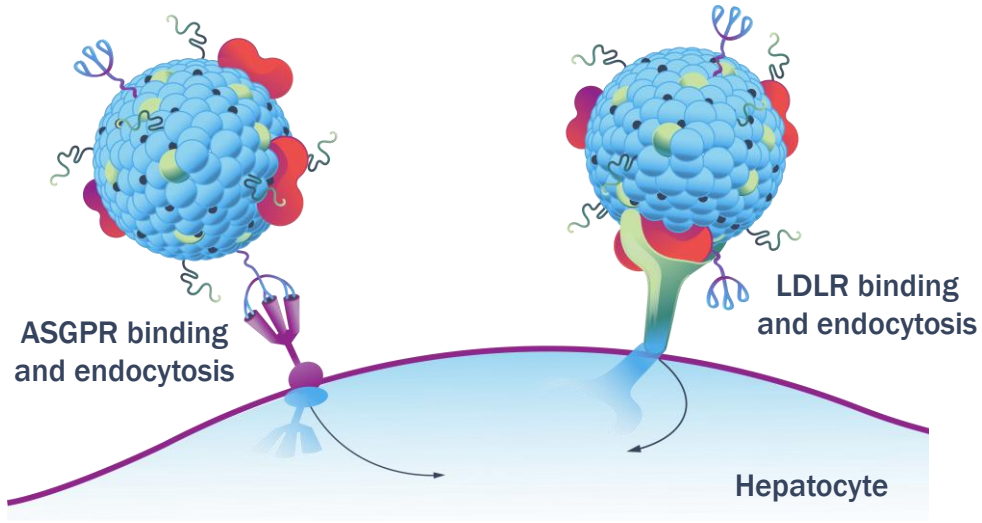
1. Zhao Z, et al. Am J Hum Genet. 2006;79:514-523; 2. Cohen JC, et al. N Eng J Med. 2006;354:1264-1272; 3. Rao AS, et al. Circ Genom Prec Med. 2018;11(7):e002162.
IV, intravenous; PCSK9, proprotein convertase subtilisin/kexin type 9

VERVE-102 is an investigational *in vivo* base editing medicine that is delivered by a GalNAc-LNP and inactivates *PCSK9* with a single A-to-G DNA change

VERVE-102 LNP



After IV infusion of the GalNac-LNP, VERVE-102 enters hepatocytes through LDLR or ASGPR



The translated adenine base editor (ABE) pairs with the gRNA to target and inactivate *PCSK9* with precise DNA edit

ABE, adenine base editor; ASGPR, asialoglycoprotein receptor; DSPC, 1,2-distearoyl-sn-glycero-3-phosphocholine; gRNA, guide RNA; LDLR, low-density lipoprotein receptor; mRNA, messenger RNA; PEG, polyethylene glycol

Heart-2 is a Phase 1b, first-in-human, open-label trial of VERVE-102 in adults with HeFH or premature coronary artery disease (CAD)

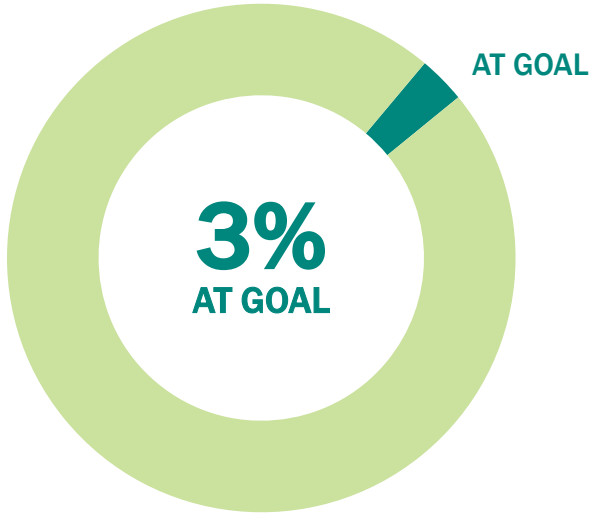
heart-2

Study population summary

- Males and females (age 18 to 70)
- HeFH or premature CAD
- Require additional lipid lowering
- On maximally tolerated oral lipid-lowering therapy
- Not currently taking a PCSK9 inhibitor

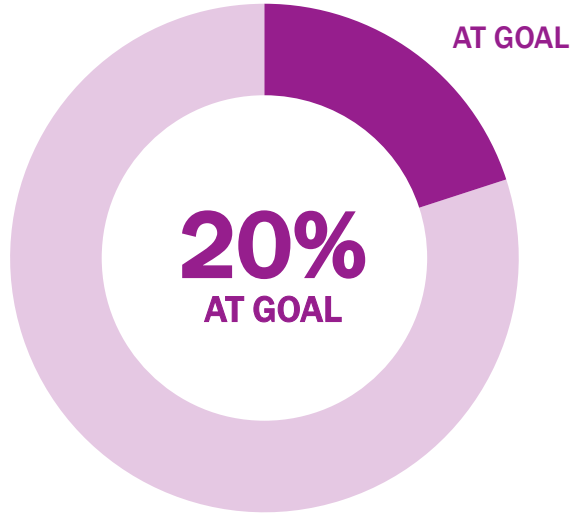
Majority of people with HeFH and CAD are not at LDL-C target levels

HeFH



In a global registry of HeFH patients, 3% attain LDL-C < 70 mg/dL (1.8 mmol/L)[1]

CAD



In a cross-sectional study across 18 European countries, only 20% of patients with CAD had a guideline-directed LDL-C of < 55 mg/dL (1.4 mmol/L)[2]

Clinical trial registration: NCT06164730; Women of childbearing potential are excluded from the study; HeFH, heterozygous familial hypercholesterolemia

1. EAS Familial Hypercholesterolemia Studies Collaboration (FHSC). Lancet. 2021; 2. Ray KK, et al. Eu J Prev Cardiol. 2021.

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Heart-2: single ascending dose design to evaluate the safety, pharmacokinetics and pharmacodynamics of VERVE-102

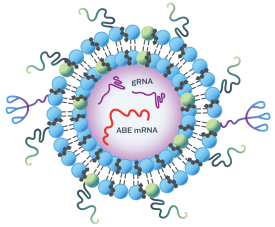
heart-2

Trial Endpoints

- Primary: Safety and tolerability
- Pharmacokinetics of VERVE-102
- Changes in blood PCSK9 and LDL-C

Study duration 1 year with long-term follow-up for another 14 years in a separate trial

Single ascending dose design[1]



- Each participant receives a single IV infusion of VERVE-102
- Decisions to dose escalate are made in consultation with the independent data and safety monitoring board (DSMB)

1. The number of dosing cohorts may be adjusted.

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Heart-2 is a first-in-human study to assess the safety and LDL-C lowering potential of VERVE-102

heart-2 Update

Data cut-off date Oct 29, 2024

- Dosing complete in 7 participants in first two dose cohorts, 0.3 mg/kg and 0.45 mg/kg
- VERVE-102 has been well-tolerated; no serious adverse events and no clinically significant laboratory abnormalities
- Dosing ongoing with regulatory clearances in UK, Canada, Australia, New Zealand, and Israel

Conclusions

1. The chronic care model for LDL-C lowering leads to poor real-world LDL-C control
2. VERVE-102 is designed to inactivate *PCSK9* in the liver to provide durable LDL-C reduction after a single infusion
3. Results from Heart-2 will be used to inform clinical trial dose selection
4. Initial pharmacodynamic data from Heart-2 are expected in the first half of 2025