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

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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
- Accelerated atherosclerotic cardiovascular disease (ASCVD)
- Estimated three million adult patients in US/Europe

Chronic care model for patients living with HeFH

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

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\(^1,2,3\)

Goal: durable decrease in LDL-C

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


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

1. VERVE-101 delivery to the hepatocyte
2. Localization to PCSK9 gene
3. A to G “spelling” change in DNA to turn off gene

Lipid nanoparticle  Ionizable amino lipid  DSPC  LDL receptor (LDLR)  apol E  mRNA  mRNA  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

**Net adenine editing (VERVE-101 – control) vs Chromosomal location of sites**

- PCSK9
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

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.

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

Data cutoff date October 16, 2023

Interim update: 10 participants treated across 4 dose cohorts

STUDY POPULATION SUMMARY
- Males and females1 (age 18 to 75)
- HeFH
- Established ASCVD
- Uncontrolled hypercholesterolemia2
- On maximally-tolerated oral lipid-lowering therapy3

DRUG ADMINISTRATION
- Pre-medication with dexamethasone and antihistamines
- VERVE-101 delivered as single infusion via a peripheral intravenous4

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=10)</th>
</tr>
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<tbody>
<tr>
<td>Mean age, years (min, max)</td>
<td>54 (29, 69)</td>
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<tr>
<td>Sex, male, n</td>
<td>8</td>
</tr>
<tr>
<td>Mean screening LDL-C, mg/dL (min, max)</td>
<td>193 (107, 373)</td>
</tr>
<tr>
<td>Mutation in LDLR detected, n^1</td>
<td>9</td>
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</tbody>
</table>

**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. 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.
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.

LDL-C reduction with VERVE-101 by dose cohort.

- Mean (±SD) change from baseline
- % change from baseline
- 0.1 mg/kg
- 0.3 mg/kg
- 0.45 mg/kg
- 0.6 mg/kg

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

Participants, n:
- 0.1 mg/kg: 3
- 0.3 mg/kg: 3
- 0.45 mg/kg: 2
- 0.6 mg/kg: 1
## Interim safety summary

<table>
<thead>
<tr>
<th>Number of participants experiencing:</th>
<th>0.1 mg/kg (n=3)</th>
<th>0.3 mg/kg (n=3)</th>
<th>0.45 mg/kg (n=3)</th>
<th>0.6 mg/kg (n=1)</th>
<th>Total (n=10)</th>
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<tbody>
<tr>
<td>AE occurring in more than 1 participant</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>6</td>
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<tr>
<td>Infusion-related reaction, n</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>4</td>
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<td>Upper respiratory infection and COVID-19, n</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
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<td>Any serious AE</td>
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<td>1</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Cardiovascular events, n</td>
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<td>Non-cardiovascular events, n</td>
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<td>Any treatment-related AE grade 3 or higher</td>
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<tr>
<td>Cardiovascular events, n</td>
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<td>0</td>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>1</td>
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<tr>
<td>Increased liver transaminases, n</td>
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<td>0</td>
<td>0</td>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1</td>
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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.

<sup>a</sup> 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

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 \textit{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

\textit{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}
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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