Verve Therapeutics Announces Interim Data for VERVE-101 Demonstrating First Human Proof-of-Concept for In Vivo Base Editing with Dose-Dependent Reductions in LDL-C and Blood PCSK9 Protein in Patients with Heterozygous Familial Hypercholesterolemia

November 12, 2023 8:30 PM EST

LDL-C Reductions Up to 55% and Blood PCSK9 Protein Reductions Up to 84% Observed After a Single Infusion of VERVE-101 at Potentially Therapeutic Doses

Safety Profile Supports Continued Development of VERVE-101

Enrollment Ongoing in the 0.45 mg/kg and 0.6 mg/kg Cohorts with Plans to Initiate Expansion Cohort in 2024

Company to Host Conference Call and Webcast Today at 6:30 p.m. ET

BOSTON, Nov. 12, 2023 (GLOBE NEWSWIRE) -- Verve Therapeutics, Inc., a clinical-stage biotechnology company pioneering a new approach to the care of cardiovascular disease with single-course gene editing medicines, today announced first human proof-of-concept data for *in vivo* base editing from the ongoing heart-1 phase 1b clinical trial of VERVE-101. Treatment with VERVE-101 led to dose-dependent reductions of disease-causing low-density lipoprotein cholesterol (LDL-C) in people living with heterozygous familial hypercholesterolemia (HeFH), a life-threatening inherited disease characterized by lifelong elevations in blood LDL-C and accelerated atherosclerotic cardiovascular disease (ASCVD). VERVE-101 is an investigational, *in vivo* base editing medicine designed to be a single-course treatment that inactivates the *PCSK9* gene in the liver to durably lower blood LDL-C.

“Of the more than three million people with HeFH in the U.S. and Europe, very few are currently at LDL-C goal, due in part to a care model that requires lifetime therapies. This model puts a strain on the healthcare system and is failing our patients,” said Deepak L. Bhatt, M.D., M.P.H., Director of the Mount Sinai Fuster Heart Hospital and the Dr. Valentin Fuster Professor of Cardiovascular Medicine at the Icahn School of Medicine in New York. “I am very encouraged by the initial data from the heart-1 trial that demonstrated the potential for single-course gene editing as a new approach to treat patients with HeFH. The data showed that VERVE-101 could meaningfully and durably lower LDL-C in these patients. This trial enrolled patients with advanced coronary disease, and the cardiovascular adverse events were consistent with what might be expected in this patient population. We’re at an exciting moment for cardiovascular prevention where the management of ASCVD may fundamentally change.”

heart-1 Clinical Trial Design
heart-1 is an open-label, phase 1b clinical trial in patients living with HeFH, established ASCVD and uncontrolled hypercholesterolemia. The trial is designed to evaluate the safety and tolerability of VERVE-101, with additional analyses for pharmacokinetics and pharmacodynamic reductions in blood PCSK9 protein and LDL-C. Single doses of 0.1 mg/kg (n=3), 0.3 mg/kg (n=3), 0.45 mg/kg (n=3), and 0.6 mg/kg (n=1) of VERVE-101 have been administered via intravenous infusion. Initial safety data reported are from all ten patients enrolled as of a data cut-off date of October 16, 2023. One patient who received a 0.45 mg/kg dose had not reached day 28 as of the data cut-off date and is not included in the efficacy analysis.

Patients included in both the safety and efficacy analyses have had a high burden of coronary artery disease, consistent with the 2022 U.S. Food and Drug Administration (FDA) draft guidance for human genome editing products[1] that suggests a first-in-human trial include patients with severe, advanced disease. Nine patients have had prior coronary revascularizations with either coronary artery bypass grafting or coronary stenting procedures and four have had prior myocardial infarctions. With a mean screening LDL-C of 193 mg/dL, none of the patients were at LDL-C goal on maximally tolerated oral lipid-lowering therapy.

heart-1 Efficacy Analysis
Following a single infusion of VERVE-101, dose-dependent reductions in pharmacodynamic measures of blood PCSK9 protein levels were observed, suggesting successful editing at the intended genomic target. Dose-dependent LDL-C reductions, a validated measure of clinical efficacy for this patient population, were observed one month after treatment.

In the interim dataset, six patients were treated at sub-therapeutic doses (0.1 mg/kg and 0.3 mg/kg) and three patients were treated at potentially therapeutic doses (0.45 mg/kg and 0.6 mg/kg). The two patients treated with 0.45 mg/kg of VERVE-101 had a time-averaged blood PCSK9 protein reduction of 59% and 84%. The patient treated with 0.6 mg/kg of VERVE-101 had a time-averaged blood PCSK9 protein reduction of 47%.

The two patients treated with 0.45 mg/kg of VERVE-101 had a time-averaged LDL-C reduction of 39% and 48%. The patient treated with 0.6 mg/kg of VERVE-101 had a time-averaged LDL-C reduction of 55%. In this single participant in the highest dose cohort, the 55% reduction in LDL-C was durable out to 180 days, with follow-up ongoing.

Blood PCSK9 protein and LDL-C reductions are quantified as percent change from baseline using the time-weighted average from day 28 through last available follow-up.

heart-1 Safety and Tolerability
The safety profile observed in the heart-1 trial supports continued development of VERVE-101, and the adverse events have been consistent with the severe, advanced ASCVD patient population enrolled.

VERVE-101 was well-tolerated in the two lower dose cohorts, with no treatment-related adverse events observed. In the two higher dose cohorts, treatment-related adverse events were observed, including transient, mild or moderate infusion reactions and transient, asymptomatic increases in liver transaminases with mean bilirubin levels below the upper limit of normal. All infusion reactions and liver transaminase elevations resolved without clinical sequelae.

Two patients experienced serious adverse events, which were each cardiovascular events in the context of severe underlying ASCVD. One patient dosed in the 0.3 mg/kg cohort had a fatal cardiac arrest approximately five weeks after treatment due to underlying ischemic heart disease, which was determined by the investigator and independent data and safety monitoring board (DSMB) to be not related to treatment.

One patient dosed in the 0.45 mg/kg cohort experienced a myocardial infarction (Grade 3) the day after treatment. The event was considered potentially related to treatment due to the proximity to dosing. The event occurred in the setting of unstable chest pain symptoms prior to dosing that were unreported to investigators. Coronary angiography taken after the event showed critical left main equivalent coronary artery disease. The same patient also experienced non-sustained ventricular tachycardia (Grade 2) more than four weeks after dosing, which was determined to be unrelated to treatment.

All safety events were reviewed with the independent DSMB who recommended continuation of trial enrollment with no protocol changes required.

"We are excited to have reached this milestone of positive first-in-human data supporting the significant potential for *in vivo* liver gene editing as a treatment for patients with HeFH. VERVE-101 is the first *in vivo* base editor to be evaluated in the clinic," said Sekar Kathiresan, M.D., co-founder and chief executive officer of Verve. "This milestone is only possible because of the incredible patients, families, and physicians who are participating in our study, and the highly talented team at Verve in their steadfast commitment to bringing VERVE-101 forward."

"Our goal is to fundamentally disrupt the chronic care model for cardiovascular disease and provide a new single-course treatment option for patients," said Andrew Bellinger, M.D., Ph.D., chief scientific officer of Verve. "These data confirm our hypothesis that a single-course gene editing medicine has the potential to induce meaningful and durable reductions in LDL-C when administered at therapeutic doses. Based on the favorable initial findings in the heart-1 trial, we are continuing to enroll patients in the potentially therapeutic dose cohorts. And with the recent clearance of the U.S. investigational new drug (IND) application for VERVE-101, we look forward to expanding our clinical trial into the U.S."

Next Steps
The heart-1 trial is enrolling patients in the 0.45 mg/kg and 0.6 mg/kg cohorts in the United Kingdom and New Zealand. With the recent clearance of the IND application by the FDA for VERVE-101, Verve plans to activate and open U.S. sites. In 2024, the company plans to select a single dose from the dose escalation phase, initiate an expansion cohort, and complete this expansion cohort of the heart-1 clinical trial. In the first half of 2024, the company plans to initiate a phase 1 clinical trial of VERVE-102, subject to regulatory clearance. VERVE-102 is an *in vivo* base editing medicine that aims to inactivate the *PCSK9* gene in a similar way to VERVE-101. VERVE-101 and VERVE-102 share an identical guide RNA targeting *PCSK9* as well as similar messenger RNA expressing an adenine base editor; however, VERVE-102 is delivered using the company's proprietary GalNAc-LNP delivery technology. Following completion of the heart-1 trial and the VERVE-102 trial, Verve plans to initiate a randomized, placebo-controlled phase 2 clinical trial of either VERVE-101 or VERVE-102 in 2025.

Conference Call Information
Verve will host a webcast investor event today, November 12 at 6:30 p.m. ET to review the heart-1 clinical trial data. The event can be accessed under Events in the Investors section of the company's website at www.VerveTx.com. The archived webcast will be available on the company's website beginning approximately two hours after the event.

About heart-1 and HeFH
heart-1 is an open-label phase 1b clinical trial designed to enroll adult patients with heterozygous familial hypercholesterolemia (HeFH) who have established atherosclerotic cardiovascular disease (ASCVD) to evaluate the safety and tolerability of VERVE-101 administration, with additional analyses for pharmacokinetics and reductions in blood PCSK9 protein and low-density lipoprotein cholesterol (LDL-C).

HeFH is a prevalent and potentially life-threatening subtype of ASCVD. High cumulative life-long exposure to LDL-C drives the development of atherosclerotic plaque that results in the hardening of arteries seen in ASCVD. The relationship between lowering of cumulative LDL-C exposure and reduction in the risk of ASCVD is among the best understood relationships in medicine.

About Verve Therapeutics
Verve Therapeutics, Inc. (Nasdaq: VERV) is a clinical-stage genetic medicines company pioneering a new approach to the care of cardiovascular disease, potentially transforming treatment from chronic management to single-course gene editing medicines. The company's initial three programs – VERVE-101, VERVE-102, and VERVE-201 – target genes that have been extensively validated as pharmacologic targets for lowering low-density lipoprotein cholesterol (LDL-C), a root cause of cardiovascular disease. VERVE-101 and VERVE-102 are designed to permanently turn off the *PCSK9* gene in the liver and are being developed initially for heterozygous familial hypercholesterolemia (HeFH) and ultimately to treat atherosclerotic cardiovascular disease (ASCVD) patients not at LDL-C goal on oral therapy. VERVE-201 is designed to permanently turn off the *ANGPTL3* gene in the liver and is initially being developed for homozygous familial hypercholesterolemia (HoFH) and ultimately to treat patients with refractory hypercholesterolemia. For more information, please visit www.VerveTx.com.

Cautionary Note Regarding Forward Looking Statements
This press release 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 and activate clinical trial sites in the U.S.; the expected timing of the expansion cohort of VERVE-101; the receipt of regulatory clearances and timing of initiating the phase 1 clinical trial of VERVE-102 and phase 2 clinical trial for the company's *PCSK9* program; and the company's strategic plans and prospects. All statements, other than statements of historical facts, contained in this press release, 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 press release 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.

Investor Contact
Jen Robinson
Verve Therapeutics, Inc.
jrobinson@vervetx.com

Media Contact
Ashlea Kosikowski
1AB
ashlea@1abmedia.com

---

[1] https://www.fda.gov/media/156894/download