Verve Therapeutics Reports New Preclinical Data Demonstrating Potent and Durable Editing of ANGPTL3 Gene with VERVE-201 in Wild-type and LDLR-deficient Non-Human Primates

March 3, 2023

VERVE-201 Preclinical Data Supports Advancement of Drug Candidate Toward Clinical Development for Homozygous Familial Hypercholesterolemia, with Initiation of Clinical Trial Anticipated in 2024

Data to be Presented During an Oral Presentation at the 2023 American College of Cardiology's Annual Scientific Sessions Meeting

BOSTON, March 03, 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 reported new preclinical data in non-human primates (NHPs) demonstrating potent, durable and well-tolerated editing of the *ANGPTL3* gene following administration of VERVE-201.

The VERVE-201 development candidate is composed of messenger RNA for an adenine base editor and a guide RNA designed to target the *ANGPTL3* gene packaged in Verve's proprietary lipid nanoparticle (LNP) technology, GalNAc-LNP. Delivered via a one-time intravenous infusion, VERVE-201 is designed to permanently inactivate the *ANGPTL3* gene in liver cells, turn off liver production of blood ANGPTL3, and thereby durably reduce blood levels of disease-driving low-density lipoprotein cholesterol (LDL-C) and triglyceride-rich lipoproteins (TRLs). VERVE-201 is initially being developed for the treatment of homozygous familial hypercholesterolemia (HoFH), a rare and often fatal genetic subtype of premature atherosclerotic cardiovascular disease (ASCVD) characterized by extremely high blood LDL-C. VERVE-201 aims to reduce the heavy treatment burden associated with available therapies for HoFH including the requirement for multiple oral, injectable, and intravenous infusions in each patient, often administered over decades. Ultimately, beyond HoFH, Verve may develop VERVE-201 for a broader population of patients with refractory hypercholesterolemia, defined as ASCVD patients with LDL-C that is refractory to treatment with available oral and injectable options for LDL-C lowering, such as PCSK9 inhibitors.

"We are highly encouraged by the data that continue to emerge for our second program, VERVE-201, which aims to address multiple ASCVD indications through inactivation of the *ANGPTL3* gene," said Andrew Bellinger, M.D., Ph.D., chief medical and scientific officer of Verve. "ASCVD is not only a devastating but also a challenging group of indications to treat, requiring multiple treatment options for patients. Targeting the *ANGPTL3* gene is a key component of our strategy to address ASCVD broadly by designing medicines to reduce each of the three known causal drivers of ASCVD – LDL-C, TRLs and lipoprotein(a). With VERVE-201, further supported by today's data, we believe we may be able to impact two of these pathways —LDL-C and TRLs—by creating a precise edit in the *ANGPTL3* gene without making a double-stranded DNA break. With these findings, we continue to progress VERVE-201 toward clinical development, with plans to initiate a first-in-human clinical trial in 2024 in people with HoFH, so that we may ultimately offer these patients a potential safe and effective, once-and-done treatment option for their disease."

To support advancement of VERVE-201 toward clinical development, Verve is evaluating the candidate in numerous preclinical studies and today, reported preclinical data in NHPs. VERVE-201cyn, the NHP surrogate of VERVE-201, was studied in 34 wild-type NHPs, across three groups: control (n=12), 1.5 mg/kg dose (n=6) and 3.0 mg/kg dose (n=16). Key results showed:

- Mean whole liver DNA editing at the *ANGPTL3* gene of 55% and 63% and mean blood ANGPTL3 protein reduction from baseline of 89% and 96%, at 1.5mg/kg (n=6) and 3.0mg/kg doses (n=16), respectively, with durable effects observed out to six months following treatment
- Decreased liver triglyceride mass, a nonclinical surrogate for hepatic fat accumulation, in NHPs treated with either 1.5 mg/kg or 3.0 mg/kg of VERVE-201cyn as compared to vehicle control, when assessed six months following treatment
- VERVE-201cyn was well-tolerated with only transient impacts on alanine aminotransferase (ALT) and aspartate aminotransferase (AST) that resolved by day 14 and there was no observed impact on total bilirubin levels
- On-target *ANGPTL3* editing was detected primarily in the liver, with a lower degree of *ANGPTL3* editing in adrenal and spleen tissues and minimal *ANGPTL3* editing elsewhere, consistent with the biodistribution of LNPs

In an additional study, Verve evaluated VERVE-201's potential in an LDL receptor (LDLR)-deficient NHP model designed to mimic the physiology of patients with HoFH. Patients with HoFH have severe or complete LDLR deficiency, which limits the ability of traditional LNPs to deliver base editing medicines to the liver. Verve has developed its proprietary GalNAc-LNP to allow for uptake via an additional receptor, the asialoglycoprotein receptor (ASGPR), which is expected to enable delivery independent of LDLR. Verve first developed LDLR-deficient NHPs (n=4), resulting in an increase in mean LDL-C from 55 to 458 mg/dL. Subsequent treatment in these NHPs with VERVE-201cyn at a dose of 3.0 mg/kg led to:

- Mean whole liver DNA editing at the *ANGPTL3* gene of 60% and a mean 84% reduction in blood ANGPTL3 protein
- Mean 46% decrease in LDL-C (from 458 to 247 mg/dL) and a mean 54% decrease in circulating triglycerides

Verve also reported preclinical findings in *Ldlr*-knockout mice fed a high-fat Western diet, in which administration of VERVE-201mu, as compared to control, led to a 97% reduction in blood ANGPTL3 protein, a 47% reduction in LDL-C and a 72% reduction in triglycerides.

Presentation Details

- **Presentation Title:** Preclinical Data Supporting Potential Efficacy of Verve-201 - An Investigational CRISPR Base Editing Medicine Targeting *ANGPTL3* - In Primary Human Cells, Mice, And Non-Human Primates
- **Session Title:** Highlighted Original Research: Ischemic Heart Disease and the Year in Review
- **Date & Time:** Sunday, March 5, 2023, from 10:47am - 10:57am CST
- **Location:** Ernest N. Morial Convention Center, Room 219

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 two programs – VERVE-101 and VERVE-201 – target genes that have been extensively validated as targets for lowering low-density lipoprotein cholesterol (LDL-C), a root cause of cardiovascular disease, in order to durably reduce blood LDL-C levels. VERVE-101 is designed to permanently turn off the *PCSK9* gene in the liver and is being developed initially for heterozygous familial hypercholesterolemia (HeFH) and ultimately to treat atherosclerotic cardiovascular disease (ASCVD) patients not at goal on oral therapy. VERVE-201 is designed to permanently turn off the *ANGPTL3* gene in the liver and is initially being developed in homozygous familial hypercholesterolemia (HoFH) and ultimately to treat patients with refractory hypercholesterolemia. For more information, please visit www.VerveTx.com

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 expected timing of initiating a clinical trial of VERVE-201; its research and development plans; and the potential advantages and therapeutic potential of the company's programs, including VERVE-201. 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 timing of and the company's ability to submit 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 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.

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