Verve Therapeutics Reports New Preclinical Data with VERVE-101 Demonstrating Robust, Durable and Precise Editing of the PCSK9 Gene for the Treatment of Cardiovascular Disease

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Treatment of Non-Human Primates with Clinical Candidate, VERVE-101, Led to Durable Reductions of PCSK9 Protein and Low-density Lipoprotein Cholesterol

Comprehensive Off-Target Editing Analysis Using Industry Leading Methods, ONE-seq and Digenome-seq Showed No Off-Target Editing Across 244 Potential Sites in Human Liver Cells

Data Support Continued Advancement of VERVE-101 Toward IND Submission in 2022

CAMBRIDGE, Mass., Sept. 23, 2021 (GLOBE NEWSWIRE) -- Verve Therapeutics, a biotech company pioneering a new approach to the care of cardiovascular disease with single-course gene editing medicines, today reported data from a new preclinical study in 36 non-human primates (NHPs) with its lead clinical candidate, VERVE-101, a potential single-course gene editing treatment for atherosclerotic cardiovascular disease (ASCVD). Findings from that study as well as additional studies in rodents demonstrated potent and durable lowering of blood PCSK9 protein and low-density lipoprotein cholesterol (LDL-C), with no evidence of adverse events or significant off-target editing. The data will be presented today at the TIDES USA Oligonucleotide & Peptide Therapeutics Conference.

VERVE-101 is being developed initially for the treatment of patients with heterozygous familial hypercholesterolemia (HeFH), a potentially fatal genetic heart disease. In patients with HeFH, a genetic mutation in one copy of the LDL receptor (LDLR) gene down-regulates LDLR expression, which limits the ability of liver cells to remove LDL-C from the bloodstream, resulting in extremely high LDL-C levels in the blood. VERVE-101 is designed to inactivate the PCSK9 gene, resulting in sustained reduction in PCSK9 protein levels and increased LDLR expression, leading to lower LDL-C levels and reduced risk for ASCVD.

“Building off our earlier pilot study with a precursor formulation, today’s data are the first presentation from our clinical candidate, VERVE-101, and demonstrate potent whole liver editing and durable reductions in PCSK9 protein and LDL-C in NHPs, with a well-tolerated safety profile,” said Sekar Kathiresan, M.D., co-founder and chief executive officer of Verve. “The precise and predictable nature of base editors combined with the well-established preferential distribution of LNPs to the liver makes for an ideal approach to targeting PCSK9. We believe that studies in NHPs are a powerful predictor of efficacy in humans for LNP delivery to the liver as well as gene editing in the liver. We’re very encouraged by these data and look forward to advancing this potentially life-changing treatment to patients with ASCVD around the world.”

The presentation today describes several new studies with the clinical formulation of VERVE-101, including a long-term durability and safety study in NHPs, a durability challenge study consisting of a partial hepatectomy model in mouse, a germline editing assessment in sexually mature male NHPs, and an expanded off-target analysis. Key findings across the studies include:

- 70% mean editing at the PCSK9 target site in NHPs treated with 1.5 mg/kg VERVE-101 (n=22) as observed in liver biopsies at two weeks, consistent with previously reported data;
- Large, durable reductions in PCSK9 and LDL-C levels after a single dose of VERVE-101 at two different dose levels in NHPs when measured at day 14 and day 180:
    - Approximately 86% mean PCSK9 protein reduction and approximately 62% mean LDL-C reduction observed at day 14 and maintained out to 180 days in NHPs treated with 1.5 mg/kg VERVE-101 (n=22);
    - Approximately 54% mean PCSK9 protein reduction and approximately 38% mean LDL-C reduction observed at day 14, which further improved to 71% and 46%, respectively, at day 180 in NHPs treated with 0.75 mg/kg VERVE-101 (n=4);
- Greater potency with VERVE-101 in primary human hepatocytes than in primary monkey hepatocytes, further supporting the potential for potency in the clinic;
- No evidence of germline editing in an analysis conducted in sexually mature male NHPs receiving a 1.5 mg/kg dose of VERVE-101 (n=6);
- Sustained editing of PCSK9 in regenerated liver lobes at 95 days post-treatment, as demonstrated in a partial hepatectomy mouse model to determine durability of PCSK9 base editing in the liver;
- Demonstration that VERVE-101 introduced a precise A to G edit at the on-target site in PCSK9 with no evidence of any bystander edits;
- No significant off-target editing observed in human liver cells among 244 candidate sites, as evaluated through a comprehensive off-target analysis in primary human hepatocytes using a highly sensitive hybrid capture assay;
- No significant off-target editing at the same 244 candidate sites following an extended analysis to primary human splenic cells; and
- A generally well-tolerated profile with VERVE-101 in NHPs at all doses evaluated, with only reversible, mild transient ALT elevations observed and no impact on glucose levels.

In addition, Verve provided an update from its pilot study in NHPs initiated in 2020 using a precursor formulation (ABE-PCSK9). At 15 months following a single gene-editing treatment, the company observed persistent lowering of both blood PCSK9 protein and LDL-C levels of approximately 90% and 60%, respectively.

Andrew Bellinger, M.D., Ph.D., chief scientific officer of Verve added, “Critical to the field of gene editing is minimizing the potential for off-target editing, which we assess using comprehensive, sensitive and state-of-the-art methods, including ONE-seq and Digenome-seq. Analysis of VERVE-101 with these methods continued to demonstrate excellent safety, with no off-target editing at 244 potential sites evaluated in human liver cells. Further, no evidence of germline editing in NHPs has been observed. These findings, combined with the potent and durable reductions in LDL-C, support the continued advancement of VERVE-101 as we prepare to submit our IND and begin human trials in 2022.”

Presentation Details

Title: *In vivo* CRISPR Base Editing of PCSK9 Durably Lowers Cholesterol in Primates
Track: mRNA and Genome Editing TRACK: Genome Editing Advances from Preclinical to the Clinic
Date/Time: Thursday, September 23, 2021, 9:30 a.m. - 10:00 a.m. ET

About Verve Therapeutics
Verve Therapeutics, Inc. (Nasdaq: VERV) is a genetic medicines company pioneering a new approach to the care of cardiovascular disease, transforming treatment from chronic management to single-course gene editing medicines. The company's initial two programs target PCSK9 and ANGPTL3, genes that have been extensively validated as targets for lowering blood lipids such as low-density lipoprotein cholesterol, a root cause of cardiovascular disease. Verve's lead product candidate, VERVE-101, is designed to turn off the PCSK9 gene in the liver in order to disrupt blood PCSK9 protein production and thereby reduce blood LDL-C levels, with the goal of reducing a patient's risk for cardiovascular disease. VERVE-101, currently in IND-enabling studies, is being developed initially for the treatment of patients with heterozygous familial hypercholesterolemia, a potentially fatal genetic heart disease. 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 initiation, and timing, of the Company's planned IND submission and future clinical trials and its research and development plans. 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, and obtain and maintain regulatory approvals for, its product candidates; continue to advance its product candidates in clinical trials; initiate and enroll 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 its other product candidates; 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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