# Verve Therapeutics Presents Comprehensive Analyses of Off-target Editing Risk for VERVE-101 at Precision Genome Engineering Keystone Symposia

April 26, 2022

*Extensive Analyses in Multiple Human Cell Types Demonstrate Minimal to No Off-target Editing Following VERVE-101 Treatment, Supporting its Planned Clinical Initiation in 2022*

*Whole Genome Sequencing at 500X Coverage of Primary Human Liver Cells Treated with VERVE-101 Demonstrated No Increased Frequency of Adenine Editing Compared to Untreated Controls*

CAMBRIDGE, Mass., April 26, 2022 (GLOBE NEWSWIRE) -- Verve Therapeutics, a biotechnology company pioneering a new approach to the care of cardiovascular disease with single-course gene editing medicines, announced new findings from a comprehensive off-target assessment of its lead product candidate, VERVE-101, demonstrating minimal to no off-target editing and supporting the favorable tolerability profile observed across multiple non-human primate studies conducted to date. The data will be presented at the Precision Genome Engineering Keystone Symposia in Keystone, Colorado on April 29.

VERVE-101 is designed to precisely edit a single base pair in the *PCSK9* gene without creating double-stranded DNA breaks, and permanently turn off the gene in the liver, the target tissue, to reduce disease-driving low density lipoprotein cholesterol (LDL-C). Verve plans to investigate VERVE-101 initially as a treatment for heterozygous familial hypercholesterolemia (HeFH), a genetic form of atherosclerotic cardiovascular disease (ASCVD).

Consistent with recent industry guidance from the U.S. Food and Drug Administration (FDA), Verve researchers employed multiple orthogonal methods, including a sensitive biochemical method called ONE-seq, an unbiased genome-wide analysis called ABE-digenome-seq, and an *in silico* method, to identify more than 3,000 potential sites of off-target editing across the genome, i.e., those with the greatest experimental or bioinformatic similarity to the on-target site. Verve researchers then applied a highly sensitive and customized next-generation sequencing assay to verify *bona fide* off-target editing at those 3,000 potential sites in primary human liver cells from multiple donors. After treatment with the VERVE-101 batch made under Good Manufacturing Practices (GMP), no sites were observed to have statistically significant off-target editing.

Extensive additional evaluation in non-target cells (spleen cells, adrenal cells, and hematopoietic stem cells) and in other cellular contexts (pediatric human liver cells and human liver cell lines) identified only two potential sites with statistically significant editing above untreated controls in any cell type and with any batch. The two instances of off-target editing occurred at doses greater than those expected to achieve saturation for on-target editing. Based on these data, Verve believes that VERVE-101 has a low risk of off-target genomic modifications that would be expected to have an associated clinical adverse effect.

In addition, in order to assess for potential guide-independent off-target effects on a genome-wide scale, a whole genome sequencing analysis of human liver cells treated with VERVE-101 was performed at a very high coverage depth of 500 sequencing reads per base. This analysis demonstrated no increase in adenine editing compared to untreated controls. Finally, in order to assess for genomic integrity, including chromosomal rearrangements and large insertions or deletions, Verve researchers performed whole genome optical mapping in primary human liver cells and observed no additional structural variants after VERVE-101 treatment when compared with untreated controls.

“Based on our interactions with regulatory agencies and as part of our clinical development path for VERVE-101, we have conducted rigorous analyses to ensure that we are advancing a therapy predicted to be both effective and safe,” said Andrew Bellinger, M.D., Ph.D., chief scientific and medical officer of Verve. “These updated findings, leveraging industry-leading and highly sensitive off-target analysis tools, continue to demonstrate minimal to no off-target editing and support our plans to initiate global clinical development with VERVE-101 for later this year.”

**Precision Genome Engineering Keystone Symposia Presentation Details**
**Title:** Comprehensive approach to evaluate off-target editing for an in vivo liver base editing medicine targeting the PCSK9 gene
**Presented by:** Hari Jayaram, Ph.D., Vice President, Editing and Discovery, Verve
**Track:** Workshop 2: Therapeutic Applications (Joint) Session
**Date/Time:** April 29, 2022, 2:30 – 2:45 p.m. MT (4:30 – 4:45 p.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 (LDL-C), a root cause of cardiovascular disease. Verve’s lead product candidate, VERVE-101, is designed to permanently turn off the PCSK9 gene in the liver in order to disrupt blood PCSK9 protein production and thereby durably 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 implications of preclinical data, the initiation, and timing, of the research and development plans and the potential advantages and therapeutic potential of the Company’s programs. 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 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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