Verve Therapeutics Announces Nature Publication Highlighting its Use of Base Editing to Potently and Durably Lower Blood PCSK9 and LDL-C in Non-Human Primates

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Data Support Continued Development of Single-course Gene Editing Therapies for Treatment of Cardiovascular Disease, Led by VERVE-101

CAMBRIDGE, Mass. — May 19, 2021— Verve Therapeutics, a biotech company pioneering a new approach to the care of cardiovascular disease with single-course gene editing medicines, today announced the publication of proof-of-concept data highlighting the company's gene editing approach for the treatment of cardiovascular disease in the journal *Nature*. Data reported included that from an ongoing preclinical study of the administration of a single gene editing treatment in non-human primates (NHPs). In this study, Verve observed potent and durable lowering of both blood PCSK9 protein and low-density lipoprotein cholesterol (LDL-C) levels of approximately 90% and 60%, respectively, following administration of a single gene editing treatment. These data showed durability out to 10 months at the most recent analysis.

Verve's gene editing treatments are designed to make a single DNA spelling change in a target gene, permanently turn off a disease-causing gene in the liver, and stop the production of a specific protein known to drive atherosclerotic cardiovascular disease (ASCVD). The company's initial gene editing programs utilize base editing technology, comprising a messenger RNA encoding for an adenine base editor, as well as a guide RNA packaged in an engineered lipid nanoparticle (LNP). The company's pipeline is led by VERVE-101, which is designed to permanently turn off the PCSK9 gene in the liver. Inhibition of the PCSK9 gene has been shown in third-party human clinical trials to lower blood PCSK9 protein as well as LDL-C levels and reduce the risk for ASCVD. VERVE-101 is being developed initially for the treatment of patients with heterozygous familial hypercholesterolemia, a potentially fatal genetic heart disease.

"Our goal is to disrupt the cardiovascular disease chronic care model by providing a new therapeutic approach with single-course, *in vivo* liver-targeted gene editing treatments aimed at addressing the root causes of this highly prevalent and life-threatening disease," said Sekar Kathiresan, M.D., chief executive officer of Verve. "VERVE-101 brings together multiple breakthroughs in 21 st century biomedicine – human genetic analysis, gene editing, mRNA-based therapies and LNP delivery. We believe that these data showed evidence of our ability to precisely, predictably and durably turn off the PCSK9 gene, resulting in measurably lower LDL-C in NHPs. We believe these findings further validate base editing as a potentially viable approach to providing long-term benefit for patients with or at risk for ASCVD."

The NHP data published in *Nature* are from short-term studies using VERVE-101 and a long-term study using a VERVE-101 precursor formulation. Key observations in the paper include:

- Optimized VERVE-101 formulation, with substantial potency observed at LNP doses as low as 0.5 mg/kg
- At least 50% average whole liver editing in NHPs, and as high as 76% whole liver editing, across dose levels ranging from 0.5 mg/kg to 3.0 mg/kg, observed at two weeks following a single-dose treatment with VERVE-101
- Durable lowering of blood PCSK9 protein of approximately 90% and LDL-C of approximately 60% observed in a long-term study following a single-dose of a VERVE-101 precursor formulation, with reductions observed to be stable at eight months, and which in the most recent analyses, have been maintained out to 10 months
- VERVE-101 was generally well-tolerated in NHPs, with only mild transient elevations of alanine aminotransferase (ALT) observed, consistent with mild acute liver injury, which was resolved to within the normal range within one week of dosing
- VERVE-101 biodistribution indicated that most editing in NHPs was confined primarily to the liver, with lesser rates of editing observed in the spleen and adrenal glands

In addition, in preclinical studies, there has been no observation of off-target editing with VERVE-101 across any of 63 potential off-target sites identified by the ONE-seq and Digenome-seq techniques, as assessed in primary human hepatocytes.

"We believe that *in vivo* liver gene editing has the potential to offer meaningful, long-term treatment options for ASCVD, and these data further support that hypothesis," said Andrew Bellinger, M.D., Ph.D., Verve's chief scientific officer and chief medical officer, and co-senior author of the *Nature* publication. "We are encouraged to see high levels of liver editing at LNP dose levels as low as 0.5 mg/kg in NHPs, which we believe may be a powerful predictor of efficacy in humans for gene editing. These data, along with the evidence of favorable tolerability in NHPs and no observed off-target editing in human liver cells, provide rationale to evaluate the utility of the base editing approach in patients with ASCVD."

About Verve Therapeutics

Verve Therapeutics 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 atherosclerotic 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 atherosclerotic 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.

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