Verve Therapeutics Reports Preclinical Data Demonstrating Potent Editing of ANGPTL3 Gene Using Proprietary GalNAc-LNP Delivery Technology in Non-Human Primates

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ANGPTL3 Base Editor Delivered via Internally Developed GalNAc-LNPs Potently Reduced Blood ANGPTL3 Protein by 94-97% in a Novel NHP Model of Homozygous Familial Hypercholesterolemia

GalNAc-LNP Delivery of ANGPTL3 Base Editor Led to Potent Editing in both LDLR-Deficient and Normal NHP Livers, Supporting Potential Broad Applicability

CAMBRIDGE, Mass., Nov. 09, 2021 (GLOBE NEWSWIRE) -- <u>Verve Therapeutics</u>, a biotech company pioneering a new approach to the care of cardiovascular disease with single-course gene editing medicines, today announced new preclinical data highlighting the ability of its internally developed GalNAc-lipid nanoparticle (LNP) technology to deliver a base editor targeting ANGPTL3 to the livers of non-human primates (NHPs). The data demonstrate that delivery of Verve's ANGPTL3 base editor via its proprietary GalNAc-LNP led to potent reductions in blood ANGPTL3 protein levels and disease-driving low-density lipoprotein cholesterol (LDL-C) in a novel NHP model of homozygous familial hypercholesterolemia (HoFH). HoFH is a rare genetic subtype of atherosclerotic cardiovascular disease (ASCVD) characterized by extremely high blood LDL-C. The full data will be published in a manuscript on bioRxiv.org.

Verve is advancing its *in vivo* ANGPTL3 base editing program for the treatment of ASCVD indications, including HoFH. In HoFH patients, delivery of base editors to the liver with standard LNPs is challenging due to deficiency of LDL receptor (LDLR) protein, which is known to mediate LNP uptake. To address this challenge, Verve has developed proprietary LNPs with the addition of a GalNAc ligand. These GalNAc-LNPs are designed to bind to asialoglycoprotein receptors (ASGPRs), which bypass LDLR, thereby enabling uptake into the liver in HoFH patients. Today's data build upon <u>previously reported</u> findings from an HoFH mouse model showing efficient and safe delivery of base editors leveraging the company's GalNAc-LNPs and now demonstrate the effectiveness of this delivery technology in NHPs that lack LDLR.

"The ANGPTL3 gene is a well-validated genetic target for lowering blood lipids, such as LDL-C, a key driver of ASCVD. Base editing of ANGPTL3 has the potential to offer a new treatment approach that could benefit patients across multiple different cardiovascular indications," said Andrew Bellinger, M.D., Ph.D., chief scientific officer and chief medical officer of Verve. "Leveraging our innovation in GalNAc-LNPs, we have generated evidence supporting application of our ANGPTL3 base editing program in a patient population for which standard LNP delivery is not possible, expanding the potential reach of our single-course gene editing therapies. These NHP data increase our confidence in the translation of therapeutic impact to patients with HoFH and support the potential of our approach to treat a broad range of ASCVD indications."

To evaluate the company's ANGPTL3 program for HoFH using its GalNAc-LNP approach for delivery, Verve implemented a multi-step strategy assessing delivery capabilities, editing potential and addressable disease states. The process and findings include:

- **Development of a Novel NHP Disease Model of HoFH with LDLR Deficiency:** Verve created an NHP model of HoFH by editing the LDLR gene and eliminating its expression in the livers of NHPs, leveraging Cas9 and a dual guide RNA (gRNA) strategy encapsulated in standard LNPs that deliver to the liver.
    - Administration of the spCas9-dual gRNA LNP efficiently disrupted the LDLR gene, leading to nearly 70% whole liver DNA editing at the LDLR gene, resulting in an approximately 94% reduction in LDLR protein in the liver and a substantial rise in blood LDL-C.
- **Precise Editing of ANGPTL3 via Base Editor Delivered with a GalNAc-LNP:** Verve then evaluated its ANGPTL3-targeted base editor delivered via its GalNAc-LNPs in its NHP model of HoFH.
    - Following administration of two different internally developed GalNAc-LNP formulations, Verve observed approximately 94% (n=3) and 97% (n=3) reductions in blood ANGPTL3 protein, and substantial reductions in LDL-C of nearly 100mg/dL, which was an approximately 35% reduction from baseline.
- **Application of GalNAc-LNP Delivery to Both LDLR-deficient and Normal Livers:** Finally, to assess the potential broad utility of its GalNAc-LNP for delivery of an ANGPTL3-targeted base editor, Verve conducted a study evaluating delivery efficiency of its ANGPTL3 base editor using both a GalNAc-LNP and a standard LNP without GalNAc in wild-type NHPs with normal livers.
    - Verve's GalNAc-LNP led to an approximately 89% reduction in ANGPTL3 protein in wild-type NHPs compared with an approximately 74% reduction with a standard LNP, which suggests that GalNAc-LNP delivery may be utilized in indications where LDLR is present.

Verve is conducting additional preclinical studies with its GalNAc-LNP technology and plans to select a development candidate for its ANGPTL3 program and initiate investigational new drug-enabling studies in 2022.

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 initiation, and timing, of the Company's planned regulatory submissions, including an investigational new drug application, and future clinical trials, its 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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