Verve Therapeutics Announces Positive Initial Data from the Heart-2 Phase 1b Clinical Trial of VERVE-102, an In Vivo Base Editing Medicine Targeting PCSK9

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Single infusion of VERVE-102 led to dose-dependent decreases in blood PCSK9 and LDL-C, with mean reduction in LDL-C of 53% and a maximum reduction of 69% observed in the 0.6 mg/kg dose cohort

VERVE-102 was well-tolerated with no treatment-related serious adverse events and no clinically significant changes in ALT or platelets observed at any dose level among 14 participants

VERVE-102 utilizes a proprietary GalNAc-LNP which has demonstrated a potentially best-in-class safety profile

In the second half of 2025, Verve expects to report final Heart-2 dose escalation data, dose the first patient in a Phase 2 clinical trial for VERVE-102, and receive a decision from Eli Lilly and Company for the PCSK9 opt-in

Company to host conference call and webcast today, Monday, April 14, 2025, at 8 a.m. ET

BOSTON, April 14, 2025 (GLOBE NEWSWIRE) -- Verve Therapeutics, a clinical-stage company developing a new class of genetic medicines for cardiovascular disease, today announced positive initial data from the Heart-2 Phase 1b clinical trial of VERVE-102. The Heart-2 Phase 1b clinical trial is evaluating patients with heterozygous familial hypercholesterolemia (HeFH) and/or premature coronary artery disease (CAD), two populations that require deep and durable reductions of low-density lipoprotein cholesterol (LDL-C) levels in the blood. Among 14 participants across three dose levels, VERVE-102 was well-tolerated, with no treatment-related serious adverse events (SAEs) and no clinically significant laboratory abnormalities observed. A single infusion of VERVE-102 led to dose-dependent decreases in blood PCSK9 protein levels and LDL-C, with a mean reduction in blood LDL-C of 53% and a maximum LDL-C reduction of 69% observed among four participants in the 0.6 mg/kg dose cohort.

“These initial Heart-2 data are promising with respect to both safety and efficacy and suggest the potential for a new era of cardiovascular disease treatment where a single dose might lead to lifelong control of LDL-C,” said Eugene Braunwald, M.D., Distinguished Hersey Professor of Medicine at Harvard Medical School and Founding Chairman, TIMI Study Group, Brigham and Women’s Hospital. “Despite existing treatments to lower LDL-C, atherosclerotic cardiovascular disease (ASCVD) remains the most frequent cause of death worldwide. The reduction of ASCVD risk depends on both the magnitude of LDL-C reduction as well as the duration. With existing treatments, approximately half of patients discontinue their prescribed lipid lowering therapy within one year, resulting in poor real-world control of LDL-C. VERVE-102 holds great promise to transform the care of ASCVD and move that care from daily pills or intermittent injections over decades to a one dose future for sustained LDL-C lowering.”

VERVE-102
VERVE-102 is a novel, *in vivo*, investigational base editing medicine designed to be a single-course treatment that permanently turns off the *PCSK9* gene in the liver and durably reduces disease-driving LDL-C. VERVE-102 consists of an adenine base editor and a guide RNA (gRNA) targeting the *PCSK9* gene. Both are encapsulated in a lipid nanoparticle (LNP) and administered as a single intravenous infusion over two to four hours. VERVE-102 uses Verve’s proprietary GalNAc-LNP delivery technology, which is designed to allow the LNP to access liver cells using either the low-density lipoprotein receptor (LDLR) or the asialoglycoprotein receptor (ASGPR).

Heart-2 Clinical Trial Design
The Heart-2 clinical trial is an open-label Phase 1b clinical trial designed to evaluate the safety and tolerability of VERVE-102 administration in adult patients with HeFH and/or premature CAD who require additional lowering of LDL-C. The trial is a single-ascending dose study and endpoints include pharmacokinetics and changes in blood LDL-C and PCSK9 protein levels. HeFH is diagnosed based on high LDL-C levels, a personal or family history of ASCVD, physical exam features, and/or mutations identified in certain genes. Premature CAD is defined as evidence of CAD (heart attack, coronary revascularization procedure, or coronary atherosclerosis on imaging) occurring in men ≤ 55 years old or women ≤ 65 years old.

The Heart-2 clinical trial is expected to include four dose cohorts, each comprised of three to nine participants with HeFH and/or premature CAD. Initial data reported today are from 14 participants across the first three cohorts (weight-based cohorts of 0.3 mg/kg, 0.45 mg/kg, and 0.6 mg/kg) with at least 28 days of follow-up for each participant as of a data cutoff date of March 13, 2025.

Heart-2 Safety and Tolerability
VERVE-102 has been well-tolerated, with no treatment-related SAEs, no dose-limiting toxicities, and no cardiovascular events observed. Across all 14 participants, there was one infusion related reaction (Grade 2) which involved transient symptoms that resolved with acetaminophen. No clinically significant changes in alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, or platelets were observed at any dose level. There were no dose-dependent trends in any of these laboratory measurements.

Heart-2 Efficacy Analysis
Following a single infusion of VERVE-102, dose-dependent reductions in two pharmacodynamic (PD) measures were observed: blood LDL-C and PCSK9 protein levels. Of note, in this patient population, LDL-C is a validated surrogate endpoint for clinical benefit accepted by the U.S. Food and Drug Administration (FDA) and other regulatory agencies.

Mean blood LDL-C and PCSK9 protein reductions from baseline, using a time-averaged percent change from day 28 through the last available follow-up, were as follows:

- Cohort 1; 0.3 mg/kg (n=4): LDL-C reduction was 21% and PCSK9 reduction was 46%.
- Cohort 2; 0.45 mg/kg (n=6): LDL-C reduction was 41% and PCSK9 reduction was 53%.
- Cohort 3; 0.6 mg/kg (n=4): LDL-C reduction was 53% and PCSK9 reduction was 60%.

Among the 14 participants, a maximum LDL-C reduction of 69% was achieved in a participant in the 0.6 mg/kg cohort.

For LNP-delivered *in vivo* gene editing medicines, total RNA dose administered is emerging as a key driver of PD. As such, Verve also evaluated the Heart-2 PD data by total RNA dose. The analysis includes the 14 participants in the Heart-2 clinical trial grouped into three ranges of total RNA dose administered: < 25 mg (n=4), 25 – < 50 mg (n=7), and 50 – < 60 mg (n=3).

Mean LDL-C reductions from baseline, using a time-averaged percent change from day 28 through the last available follow-up, were as follows:

VERVE-102 total RNA dose range	**< 25 mg**	**25 – < 50 mg**	**50 – < 60 mg**
Participants, n	4	7	3
Mean total RNA dose	20 mg	37 mg	55 mg
Mean LDL-C % reduction from baseline	-21%	-41%	-59%

Across all 14 participants, VERVE-102 demonstrated a strong dose-dependent response between the amount of total RNA administered and LDL-C reductions. Three participants received a total RNA dose between 50 and 60 mg, with an average dose received of 55 mg of total RNA. In this dose group, VERVE-102 demonstrated a time-averaged LDL-C mean reduction of 59%. Each of the three participants who received a dose ≥ 50 mg achieved a > 50% time-averaged reduction of LDL-C from baseline.

"Verve was founded seven years ago with a vision of one treatment dose potentially leading to a lifetime of LDL-C lowering. The data presented today suggest that this game-changing, one dose future is possible," said Sekar Kathiresan, M.D., co-founder and chief executive officer of Verve Therapeutics. "We are pleased by the safety VERVE-102 has demonstrated so far, and our proprietary GalNAc-LNP delivery technology is showing a potentially best-in-class safety profile. The initial efficacy data suggest that VERVE-102 has the potential to match or exceed the LDL-C reduction provided by currently available PCSK9-targeting therapies. Among participants who received a dose greater than 50 mg total RNA, we observed a mean LDL-C reduction of 59% and a maximum LDL-C reduction of 69%. Furthermore, VERVE-101 has continued to show excellent durability for the base editing mechanism out to nearly two years, with follow-up ongoing."

Dr. Kathiresan continued, "In sum, VERVE-102 has the potential to solve the urgent need for enduring efficacy in patients living with HeFH or ASCVD. We are incredibly grateful to the patients and healthcare professionals who believe in our mission and participate in our clinical trials. Together, we are striving to revolutionize cardiovascular disease treatment and deliver a one dose future."

Next Steps
The Heart-2 clinical trial is enrolling participants in the fourth dose cohort of 0.7 mg/kg in the United Kingdom, Canada, Israel, Australia, and New Zealand. As of April 7, 2025, Verve has dosed two participants in this cohort. The early laboratory and clinical safety profile is in line with the first three cohorts. Verve expects to announce the final data from the dose escalation portion of the Heart-2 clinical trial, including durability data, in the second half of 2025.

Verve plans to dose the first patient in the Phase 2 clinical trial of VERVE-102 in the second half of 2025, subject to regulatory clearance. With the recent clearance by the U.S. FDA of the investigational new drug (IND) application for VERVE-102, Verve expects to enroll patients at U.S. trial sites in the Phase 2 clinical trial. Verve expects its current capital position to be sufficient to fund its operations into mid-2027, which includes the completion of the Phase 2 clinical trial.

Under the PCSK9 program collaboration agreement with Verve, Eli Lilly and Company (Lilly) holds the right to opt-in to share worldwide development expenses (33% contributed by Lilly) and to jointly commercialize and share profits and expenses related to commercialization in the U.S. on a 50/50 basis. Verve retains control of the development and commercialization of all collaboration products in the U.S., and Verve holds all product rights outside the U.S. Verve expects to deliver the opt-in package for the PCSK9 program and receive a decision from Lilly in the second half of 2025.

Conference Call Information
Verve will host a conference call and webcast today, Monday, April 14, 2025, at 8 a.m. ET to review the initial Heart-2 clinical data. The conference call can be accessed via this link: https://register-conf.media-server.com/register/BI2d0a1d3cccc6461f95e6d7f836157a60. A live webcast will also be available under Events in the Investors section of the company's website at https://ir.vervetx.com/events. The archived webcast will be available on the company's website beginning approximately two hours after the event.

About Verve Therapeutics
Verve Therapeutics, Inc. (Nasdaq: VERV) is a clinical-stage company developing a new class of genetic medicines for cardiovascular disease with the potential to transform treatment from chronic therapies to single-course gene editing medicines. The company's lead programs – VERVE-102, VERVE-201, and VERVE-301 – target the three cholesterol drivers of atherosclerosis: LDL-C, remnant cholesterol, and Lp(a). VERVE-102 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 patients with established atherosclerotic cardiovascular disease (ASCVD) who continue to be impacted by high LDL-C levels. VERVE-201 is designed to permanently turn off the *ANGPTL3* gene in the liver and is initially being developed for refractory hypercholesterolemia, where patients still have high LDL-C despite treatment with maximally tolerated standard of care therapies, and homozygous familial hypercholesterolemia (HoFH). VERVE-301 is designed to permanently turn off the *LPA* gene to reduce Lp(a) levels. Lp(a) is a genetically validated, independent risk factor for ASCVD, ischemic stroke, thrombosis, and aortic stenosis. For more information, please visit www.VerveTx.com.

Cautionary Note Regarding 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 company's ongoing Heart-2 clinical trial; the timing and availability of data for the Heart-2 trial and timing for initiation of the Phase 2 clinical trial for VERVE-102; the timing for delivery of the opt-in package and of Lilly's decision for the PCSK9 program; the potential advantages and therapeutic potential of VERVE-102 and the period over which the company believes that its cash, cash equivalents and marketable securities will be sufficient to fund its operating expenses. 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 company's ability to timely submit and receive approvals of regulatory 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, VERVE-102, 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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