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Vectoring In On Verve Therapeutics

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About this article

Ticker	Analyst rating	Price at publication	Last price	Change since publication	S&P 500 change since publication
VERV	HOLD	$12.50	$15.14	21.12%	6.42%

Days since publication
52

Summary

Verve Therapeutics aims to revolutionize treatment for cardiovascular disease through in vivo gene therapy using base editing technology.

Their lead candidate, VERVE-101, has shown promising results in reducing LDL-C levels in preclinical studies.

Verve has partnerships with Beam Therapeutics, Eli Lilly, and Vertex Pharmaceuticals, and analysts have a positive outlook on the company.

A full investment analysis around Verve Therapeutics stock is presented in the paragraphs below.

I am Bret Jensen, an analyst with years of experience in the biotech sector. I lead the investing group The Biotech Forum where we focus on proprietary, breaking research on biotech and biopharma stocks.

Mohammed Haneefa Nizamudeen

Pursue what catches your heart, not what catches your eyes."— Roy T. Bennett

Today, we put **Verve Therapeutics (NASDAQ:VERV)** in the spotlight. Verve aims to revolutionize treatment through in vivo gene therapy using base editing technology, with its lead candidate VERVE-101 showing promising results in reducing LDL-C levels. An analysis follows below.

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Company Overview

Verve Therapeutics, Inc. is a Boston based early clinical-stage genetic medicines concern focused on the development of single-course editing modalities to treat cardiovascular disease [CVD]. The company as one program in the clinic and two more undergoing IND-enabling studies. Verve commenced operations in 2018 and went public in June 2021, raising net proceeds of $281.6 million at $19 per share. After a hot IPO - that opened at $30 and reached $73.80 nine trading sessions later - its stock trades just under $14.00 a share, translating to a market cap of $1.05 billion.

Cardiovascular Disease

The company's primary target in its attempt to reduce CVD is low density lipoprotein-cholesterol (LDL-C), a compound whose facilitation is heavily influenced by binding to the PCSK9 protein. LDL-C is believed to promote atherosclerotic plaque that can progress to hardened arteries, the primary trait of atherosclerotic CVD (ASCVD), which manifests as coronary heart disease, ischemic stroke, and peripheral vascular disease. This believed correlation is buttressed by studies showing a lowering of LDL-C by 39mg/dL for five years with established ASCVD reduces the risk of another event by 21%. That same LDL-C reduction over the lifetime of an individual, cuts the risk of a first ASCVD event by 88%.

Company Website

The current paradigm for lowering LDL-C involves (first and foremost) daily ingestion of statin drugs, which according to Dr. Perlmutter in his book *Grain Brain*, ups the risk for Alzheimer's disease by 50%. Two monoclonal antibodies designed to bind to the PSCK9 protein have been approved - **Amgen's (AMGN)** Repatha (evolocumab) and **Regeneron's (REGN)** Praluent (alirocumab) - but they require twice monthly injections. Also, **Novartis' (NVS)** Leqvio (inclisiran) is a twice yearly small interfering RNA subcutaneous injection that likewise targets PCSK9. Across three studies, Leqvio demonstrated an LDL-C reduction of 47.4% at day 510. Blunt force workarounds include the insertion of stents and bypass surgery. Despite these 'advancements' in care, four out of five patients do not achieve their LDL-C goals and CVD remains the leading cause of death worldwide, with approximately one in three succumbing to the malady. Furthermore, according to the CDC, CVD saps over $350 billion annually out of American wallets (over $1,000 per citizen) in healthcare outlays and lost productivity.

Verve's Solution(s)

Verve aims to turn the current treatment paradigm on its head through single administration (*in vivo*) gene therapy that employs base editing technology. To further illustrate the company's approach, the currently en vouge CRISPR-Cas gene editing technology involves splicing the double-stranded DNA with the consequent self-repair designed to knockout the gene. By contrast, Verve's base editing strategy is akin to a pencil that erases and rewrites one letter in the gene. This is accomplished through a compound consisting of a lipid nanoparticle that encapsulates both the mRNA encoding for the gene (or base) editor and a guide RNA targeting the gene of interest. In theory, this more tailored and precise approach should lead to fewer unwanted DNA modifications or off-target editing effects. Although in its early stage, Verve is the only company advancing an *in vivo* CVD gene therapy in the clinic, giving it potential first-mover advantage.

VERVE-101

That candidate, VERVE-101, is designed to permanently disable the PCSK9 gene in the liver in order to knockout the production of PCSK9 protein. Through its reduction, the liver can more easily clear LDL-C from the blood. VERVE-101 is undergoing evaluation for the treatment of heterozygous familial hypercholesterolemia (HeFH), a genetic disorder characterized by LDL-C levels between 200 and 400mg/dL (normal/good: 70 to 130mg/dL) that afflicts ~1.3 million Americans. This is not to be confused with homozygous familial hypercholesterolemia (HoFH), which is characterized by two mutant alleles of the LDLR gene - HeFH has one mutated allele - and LDL-C levels north of 500mg/dL that afflicts ~1,300 Americans.

In the preclinic, a single one to two hour infusion of VERVE-101 was shown to reduce LDL-C levels by 50% (0.75mg/kg) and 68% (1.5mg/kg) in non-human primates at one-year post-treatment, which set that stage for a Phase 1b clinical trial (heart-1) that dosed its first of ~40 HeFH patients with established ASCVD in July 2022. However, the trial was only given a green light in New Zealand and the UK, as the FDA placed a hold on Verve's IND in December 2022, requesting various information, including available clinical data from heart-1, as well as a request to modify its trial protocol in the U.S. to (amongst other measures) increase the length of the staggering interval between dosing of participants.

The hold was finally lifted in October 2023 with first data from New Zealand and the UK released on November 12, 2023. The good news: the efficacy data was positive with the evaluable patients treated with a therapeutic level of VERVE-101 (0.45mg/kg n=2; 0.60mg/kg n=1) achieving LDL-C reductions of 39%, 48%, and 55% (0.60mg/kg patient) at least one month after infusion.

However, one patient in the low dose cohort (0.30mg/kg n=6) suffered a fatal heart attack (deemed not treatment related) while one patient in the 0.45mg/kg cohort experienced a Grade 3 myocardial infarction that was deemed potentially treatment related due to the proximity to dosing (one day post-treatment). It should be noted that the patient had unstable chest pain symptoms prior to dosing that went unreported to investigators. That same patient also suffered an unrelated Grade 2 non-sustained ventricular tachycardia (rapid heartbeat) four weeks post-treatment. This news sent shares of VERV into a one-day 41% decline to $9.29 a share, immediate squashing potentially positive news regarding its collaboration with **Beam Therapeutics (BEAM)** announced back on October 31, 2023. More on that development shortly.

Pre-Clinical Assets

In addition to VERVE-101, the company has similar functioning assets in the preclinic. One, VERVE-102, is essentially VERVE-101 with a modified delivery vehicle that includes a N-Acetylgalactosamine lipo-nanoparticle that permits introduction through either the LDLR receptor (like VERVE-101) or ASGPR hepatocyte receptor to lower LDL-C. Initiation of a Phase 1b study is expected in 1Q24.

Verve's other asset undergoing IND-enabling studies is VERVE-201, an ANGPTL3 targeting gene therapy for the treatment of HoFH that should enter the clinic in 2H24.

Collaboration News

The base editor technology for VERVE-101, -102, and -201 was in-licensed from Beam under a 2019 agreement that was amended in 2022. For the PCSK9 and ANGPTL3 gene therapies, after the final patient has been dosed in a Phase 1, Beam has the right to opt-in to each program, which constitutes covering 33% of the clinical expenses and a 50/50 share of profits in the U.S. An opt-in to a third gene target by Beam would obligate it to 35% of the development expenses and 35% of the profit share worldwide.

That arrangement was somewhat modified when Eli Lilly entered into an agreement with Beam to obtain certain product rights to all three Verve targets for a consideration of $200 million upfront, a $50 million equity investment in Beam, and potential milestone obligations totaling $350 million.

That news comes on the heels of Verve's own agreement with Lilly in June 2023, under which the latter obtained a license from the former to develop a lipoprotein(a) targeted gene therapy for the treatment of ASCVD for a consideration of $30 million upfront, a $30 million stock investment, potential milestones of $465 million, and high single-digit to low double-digit royalties. Verve has the option to forego the milestones and royalties by opting-in after Phase 1 for an undisclosed fee in return for a 40% of the profit share as well as 40% of the development expenses after Phase 1.

Verve also has a 2022 collaboration agreement with Vertex Pharmaceuticals (VRTX), under which it received a total initial consideration of $60 million ($25 million cash; $35 million equity investment) for one target. Vertex is potentially on the hook for milestones totaling $406 million and single digit royalties.

Balance Sheet & Analyst Commentary

Although the market reacted negatively to the early data on VERVE-101, the company executed secondary offerings on November 28, 2023, raising total net proceeds of $157.7 million at $10 per share, including a private placement purchased by Lilly that accounted for $23.0 million of the total funds raised. That should put cash and investments somewhere in the neighborhood of $610 million with one month remaining in 2023, providing a cash runway into 2026.

Despite the market's unenthusiastic reaction to VERVE-101 data, Street analysts lean positive on Verve. Since third quarter numbers were posted in early November, four analyst firms including RBC Capital and BMO Capital have reissued Buy ratings on the stock. Price targets proffered range from $32 to $56 a share. JP Morgan maintained its Hold rating and $27 price target.

GV 2023 GP, LLC, represented on the board by Krishna Yeshwant, purchased 1.8 million shares on the secondary, raising its ownership interest to 15%.

Verdict:

Net of balance sheet cash, the market values Verve's one-off, *in vivo* eraser-and-pencil approach at ~$450 million. There is little in the way of data, but there is also little in the way of competition for a one-and-done approach. Only **CRISPR Therapeutics (CRSP)** has a one-off *in vivo* asset on the drawing board (CTX330) targeting CVD and that is still in the discovery phase. Although very early in the game, if further safety data on VERVE-101 can validate that the adverse event in the 0.45mg/kg patient was a fluke - meaning higher dose levels are possible - Verve could be off to the races, as the efficacy aspect of its approach does not appear to be much in question.

Admittedly, this is a coin flip. However, a '*heads*' outcome not only produces a significant rise in its share price - shares of VERV traded at $78 shortly after the company's IPO in September 2021 - but also introduces the likelihood of a buyout by Eli Lilly, who is energetically perusing a meaningful stake in the CVD gene therapy arena. A *'tails*' outcome leaves the company with (currently) ~$7.50 a share in cash and two more assets entering the clinic in 2024. As such, for the risk tolerant, Verve is worthy of a small investment pending further developments.

> *When the heart speaks, the mind finds it indecent to object.*"— Milan Kundera

This article was written by

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Bret leads the investing group The Biotech Forum, in which he and his team offer a model portfolio with their favorite 12-20 high upside biotech

stocks, live chat to discuss trade ideas, and weekly research and option trades. The group also provides market commentary and a portfolio update every weekend. Learn more.

Analyst's Disclosure: I/we have a beneficial long position in the shares of VERV either through stock ownership, options, or other derivatives. I wrote this article myself, and it expresses my own opinions. I am not receiving compensation for it (other than from Seeking Alpha). I have no business relationship with any company whose stock is mentioned in this article.

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