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# Verve Therapeutics: 礼来公司的经验是体内基因治疗计划的一个受欢迎的补充

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## About this article

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S&P 500 change since publication 11.18%		Days since publication 97			

## 概括

Verve Therapeutics 专注于开发针对心血管疾病的体内基因编辑疗法。

该公司旨在通过针对与动脉粥样硬化性心血管疾病相关的基因来破坏心血管疾病的慢性护理模式。

Verve 1b 期临床试验的中期数据显示，在降低 LDL-C 方面具有良好的功效，但安全问题导致其股票遭到抛售。

Beam Therapeutics 最近将其 Verve 主导项目的权利出售给礼来公司，以换取 2.5 亿美元的预付款和 3.5 亿美元的潜在里程碑付款。

有了礼来公司的加入，如果潜在的安全问题能够得到充分的管理，Verve 可能已经找到了推进其发展的理想合作伙伴。

我是 Edmund Ingham，一名生物技术顾问和 CFA。我经营着Haggerston BioHealth投资集团，该集团提供对波动最大的生物健康股票的独家分析。



安迪

## 投资概况

Verve Therapeutics, Inc. (纳斯达克股票代码: [VERV](#)) 是一家总部位于马萨诸塞州波士顿的生物技术公司, 于 2021 年 6 月[首次公开募股](#), 通过发行 1610 万股每股 19 美元的股票筹集了约 3.07 亿美元资金。

Verve 的重点是心血管疾病 ( "CVD" ), 该公司在最近提交的第三季度季度报告/第十季度报告中称, 心血管疾病是 "全球主要死亡原因" 。10Q 概述了 Verve 的 "使命" 如下:

我们的目标是通过提供一种新的单疗程体内基因编辑治疗方法来颠覆 CVD 的慢性护理模式, 重点解决这种高度流行且危及生命的疾病的根本原因。

我们正在开发一系列基因编辑程序, 针对导致动脉粥样硬化性心血管疾病 ( "ASCVD" ) 的三种脂蛋白途径: 低密度脂蛋白 ( "LDL" )、富含甘油三酯的脂蛋白和脂蛋白 (a) ( "Lp(a)" ) " ) 。我们最初的项目针对 PCSK9 和 ANGPTL3, 这些基因已被广泛验证为降低血脂 (例如低密度脂蛋白胆固醇或 LDL-C) 的靶标。

我们相信, 编辑这些基因可以在患有动脉粥样硬化性心血管疾病 (ASCVD, 最常见的 CVD 形式) 或有风险的患者的一生中有效且持久地降低 LDL-C。

To accomplish its goal of creating an *in vivo* gene therapy to treat cardiovascular disease, Verve employs some cutting-edge technologies, including lipid nanoparticle delivery technology - LNP's were used in the successful messenger RNA COVID vaccines developed by Pfizer Inc. ([PFE](#)) / BioNTech SE ([BNTX](#)) and Moderna, Inc. ([MRNA](#)), and prevent delicate drug payloads being broken up by the immune system before reaching their target - and a form of gene editing known as "base editing" pioneered by another Massachusetts-based biotech, Beam Therapeutics Inc. ([BEAM](#)).

As I wrote in a recent [note for Seeking Alpha](#) on Beam Therapeutics:

Base editing is more like using a pencil to erase a single letter, or "point mutation" - one of the four bases found in DNA which are adenine ("A"), cytosine ("C"), guanine ("G"), or thymine ("T") - and rewriting a different letter in its place.

The technique may be used to overcome many of the limitations affecting the use of Crispr, Beam's management believes, which include the unpredictability of the repairing of cuts made by Crispr - so-called "Non-homologous end joining ("NHEJ"), toxicities associated with double-stranded breaks e.g., cell disruption or death, the delivery and positioning of a replacement DNA template, and the inability to correct genes in non-dividing cells.

Although base editing is an exciting technology that's regarded as having significant promise, Beam's progress in the clinic has been measured relative to some of its gene editing rivals. For example, on Dec. 8 CRISPR Therapeutics AG ([CRSP](#)) and Vertex Pharmaceuticals Incorporated ([VRTX](#)) Sickle Cell Disease ("SCD") therapy Exa-Cel may be approved by the Food and Drug Agency ("FDA") for commercial use.

This therapy uses CRISPR/Cas9, *ex vivo* cell engineering to "functionally cure" patients, with a safety profile that was recently given an [endorsement](#) by an FDA Advisory Committee. Beam's lead candidate, BEAM-101, also targets SCD, but has only recently entered a Phase 1/2 clinical study, meaning that commercial approval remains years away, with many clinical and regulatory hurdles still to overcome.

Beam's other candidates - other than a T-cell therapy targeting CD7, which also is in a Phase 1/2 study, remain at the preclinical stage, which is the reason why I gave Beam stock a "sell" rating in my Seeking Alpha note earlier this month.

Although the company is cash rich, reporting >\$1bn in cash as of Q3 2023, Beam has racked up an accumulated deficit of >\$1.3bn, and while it continues to burn shareholder cash, the prospect of a near or medium-term drug approval look remote.

## Pharma Giant Lilly Successfully Bids For Verve Partnered Programs

Beam and Verve had been engaged in a collaboration and license agreement over Verve's lead assets, VERVE-101, and VERVE-102, targeting PCSK9, and indicated for Heterozygous familial hypercholesterolemia (HeFH"), plus a third asset, VERVE-201, targeting ANGPTL3, and also indicated for HeFH, plus refractory hypercholesterolemia.

At the end of October, however, Beam [agreed](#) to sell these rights to the pharma giant Eli Lilly and Company ([LLY](#)), in exchange for a \$200m upfront payment, and \$50m equity investment, with potentially up to \$350m also payable by Lilly to Beam based on certain development and commercial milestones.

My initial take - outlined in my note on Beam - was that Beam had made a false move by agreeing to this sale. Given the company has a lengthy funding runway in place, why agree to sell the rights to three promising in-vivo gene editing programs that could, if successful, open up a breakthrough commercial opportunity?

With that said, it's well known that, as promising an area of research as *in vivo* gene editing is, there are major hurdles to overcome in the clinic before commercialization becomes a realistic prospect.

The advantages over an *ex vivo* cell therapy are obvious - no painful preconditioning regimes so that patients' cells can be extracted, no waiting for cells to be engineered to be in a lab, and no danger of a patient's immune system rejecting engineered cells when re-infused. From an efficacy, safety, and cost perspective, *in vivo* gene therapy, theoretically at least, ought to be the superior therapeutic option.

To date, however, there are no approved *in vivo* gene therapies, and many challenges are still to be overcome. While Verve forms part of a vanguard of companies pioneering in-vivo gene therapy, alongside e.g., CRISPR Therapeutics AG, Intellia Therapeutics, Inc. ([NTLA](#)), Exuma Biotech, Umoja Biopharma, Vector BioPharma, Capstan Therapeutics, and Sana Biotechnology, Inc. ([SANA](#)), the company's progress has been far from trouble-free.

## Verve's *in vivo* Data Worries Market - Sends Stock Sliding

My belief is that Lilly and Verve will ultimately benefit more than Beam from the sale of Verve's in vivo assets - with Lilly providing the financial clout and R&D resources, and Verve the engineering expertise to potentially gain an historic first approval for an in-vivo gene therapy in a major disease indication - was tested almost as soon as the deal was announced.

A few days after the deal concluded, Verve shared interim data from its ongoing heart-1 phase 1b clinical trial of VERVE-101. From an efficacy perspective, the data seemed encouraging - as per a Verve [press release](#):

In the interim dataset, six patients were treated at sub-therapeutic doses (0.1 mg/kg and 0.3 mg/kg), and three patients were treated at potentially therapeutic doses (0.45 mg/kg and 0.6 mg/kg).

The two patients treated with 0.45 mg/kg of VERVE-101 had a time-averaged blood PCSK9 protein reduction of 59% and 84%. The patient treated with 0.6 mg/kg of VERVE-101 had a time-averaged blood PCSK9 protein reduction of 47%.

The two patients treated with 0.45 mg/kg of VERVE-101 had a time-averaged LDL-C reduction of 39% and 48%. The patient treated with 0.6 mg/kg of VERVE-101 had a time-averaged LDL-C reduction of 55%. In this single participant in the highest dose cohort, the 55% reduction in LDL-C was durable out to 180 days, with follow-up ongoing.

The fact that Verve-101 was able to successfully target PCSK9 protein, and trigger a reduction in LDL-C is notable - as Verve states in its press release:



High cumulative life-long exposure to LDL-C drives the development of atherosclerotic plaque that results in the hardening of arteries seen in ASCVD. The relationship between lowering of cumulative LDL-C exposure and reduction in the risk of ASCVD is among the best understood relationships in medicine.

For context, analysts at William Blair (source: [FierceBiotech](#)) noted that Leqvio (inclisiran), developed by the RNA-interference specialist Alnylam Pharmaceuticals, Inc. ([ALNY](#)) and partner Novartis AG ([NVS](#)), which also targets PCSK9, and is approved to help reduce LDL-C, achieved a 40% reduction in a less severe HeFH patient population.

Leqvio is considered a potential best-in-class medicine, competing in the marketplace against PCSK9 inhibitors Repatha and Praluent, developed by Amgen Inc. ([AMGN](#)) and Regeneron Pharmaceuticals, Inc. ([REGN](#)) respectively, which are themselves pegged for peak revenues of ~\$3bn later this decade.

Despite the clear promise in terms of both efficacy and commercial opportunity, the market sold off Verve stock on the news, dropping it from ~\$15 to \$8 overnight after identifying [a potential safety concern](#). Two patients in the study experienced serious adverse events, and while one - a fatal cardiac arrest approximately five weeks after treatment - was deemed unrelated to treatment, the second was discussed as follows:

One patient dosed in the 0.45 mg/kg cohort experienced a myocardial infarction (Grade 3) the day after treatment. The event was considered potentially related to treatment due to the proximity to dosing. The event occurred in the setting of unstable chest pain symptoms prior to dosing that were unreported to investigators. Coronary angiography taken after the event showed critical left main equivalent coronary artery disease.



The study is being carried out in the United Kingdom and New Zealand, due to the fact that the FDA had placed Verve's Investigational New Drug ("IND") application for VERVE-101 under a clinical hold, preventing Verve from initiating any in-human studies of the drug in the US - in November 2022. The FDA's reasoning was that the long-term safety implications of *in vivo* base editing had not yet been fully explored.

Ironically, the FDA lifted its clinical hold in October this year, but as Verve notes in its Q3 10Q submission, "We cannot be certain that our IND for VERVE-101 will not be placed on clinical hold again in the future."

## Beam Stock Soars, Verve Stock Sinks - But Will Fortunes Reverse In Time?

As we can see below, at the same time as Verve stock was tanking, Beam stock was climbing rapidly:



3m share price performance Verve vs Beam (TradingView)

Verve stock had initially soared in response to the news that its new partner for its in vivo programs would be Eli Lilly, the world's most valuable Pharmaceutical company, which seemingly has a knack for developing breakthrough drugs e.g. donanemab for Alzheimer's Disease, and tirzepatide, its GLP-1 agonist, to treat Type 2 Diabetes and Obesity.

As soon as the Phase 1 data were released, however, the two companies' stock prices reversed course, suggesting that the market believed Beam was right to take Lilly's cash up front and distance itself from a drug development program fraught with safety concerns.

While the market's reaction was negative, the scientific community appears to have taken a **much more positive** view of Verve's results, with many observers appearing **genuinely enthusiastic** about future prospects for this *in vivo* approach.

There are undoubtedly many more significant challenges ahead - proving the durability of the therapy, for example, beyond the six months of data available at present. Continuing to show the approach has "best-in-class" potential against the likes of Leqvio, Repatha, and Praluent, and of course, doubling down on safety.

Verve says it plans to open up trial centers in the US, as well as enrolling more patients in the UK and New Zealand and also will move VERVE-102 into clinical studies in the first half of next year.

VERVE-102 has a differentiated delivery mechanism, utilizing a "GalNAc-LNP" (GalNAc being a sugar molecule which binds effectively to cells in the liver) to target two different receptors, LDLR and ASPGR. Verve plans to compare the two candidates and move whichever performs better into a Phase 2 study in 2025.

**Concluding Thoughts - A Rising Tide May Lift All Boats - But Verve Stock May Be A Superior Contrarian Bet For Investors**

To summarize the content of this post, and my thoughts on the investment opportunity in relation to Verve, I believe that while the market was quick to sell off Verve stock after gaining its first look at Verve-101 data, the long-term potential of these programs, as assessed by the scientific community, appears promising, provided Lilly and Verve proceed with caution.

It's clear the market was initially enthusiastic about the Lilly deal, as Verve stock jumped from ~\$9, to ~\$20, when the news was first announced, valuing Verve at ~\$1.2bn. The market's reaction to the data and subsequent sell-off is understandable, although it's an unfortunate fact that adverse safety events are a part and parcel of clinical studies, and most drug trials encounter similar issues from time to time.

Of course, safety is absolutely paramount and the market could be forgiven for concluding "here we go again" as a few weeks after its clinical hold was lifted by the FDA, Verve's data revealed a potential adverse safety event. We also should take into account the fact that major pharmas often opt into smaller biotechs' drug development programs, but that in itself is no guarantee of success.

Verve is a heavily loss-making company just like Beam is, reporting a net loss for the first nine months of 2023 of \$152m, with only ~\$500m current assets, as opposed to Beam's >\$1bn cash. Verve also has plenty of competition in the cardiovascular disease space - some of the competitors listed by the company in its 2022 annual report / 10K submission include Arrowhead Pharmaceuticals, Inc. ([ARWR](#)), already conducting Phase 3 studies of its RNAi candidates in HeFH, an antisense oligonucleotide licensed by Novartis from Ionis Pharmaceuticals, Inc. ([IONS](#)) for lipoprotein reduction, plus PCSK9 targeting drugs in development by Pharma giants Merck & Co., Inc. ([MRK](#)) and AstraZeneca PLC ([AZN](#)).

因此，购买 Verve 股票存在不可否认的风险，但在我看来，基于该公司在为体内碱基编辑疗法生成概念验证数据方面的早期成功，Eli 经验丰富的合作伙伴的参与礼来公司拥有数十年治疗心血管疾病的经验，以及最近的市场抛售，只要以正确的方式进行探索，其碱基编辑程序的前景就很有趣。

早在 2021 年，当 Intellia Therapeutics 证明它可以使用体内 CRISPR/Cas9 编辑来平均降低转甲状腺素蛋白 (ATTR) 淀粉样变性患者的血清 TTR 时，其股价几乎一夜之间从 75 美元飙升至 175 美元，该公司的估值为 > 100 亿美元。如今，Intellia 的价值仍接近 30 亿美元。Verve 凭借最初的 Verve-101 数据实现了类似的壮举，在撰写本文时，其市值仅为 7.15 亿美元，为投资者提供了一个以合理价格买入前景光明的药物开发领域的机会。

这篇文章的作者是



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11.02K 关注者

埃德蒙·英厄姆 (Edmund Ingham) 是一名生物技术顾问。他从事生物技术、医疗保健和制药领域的研究已超过 5 年，并整理了 1,000 多家公司的详细报告。他领导投资集团Haggerston BioHealth。该小组适合新手和经验丰富的生物技术投资者。它为寻找和买卖评级提供了催化剂。它还提供所有大型制药公司的产品销售和预测、预测、综合财务报表、贴现现金流分析和逐个市场分析。[了解更多。](#)

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