

Verve Therapeutics: Revolutionizing Cardiovascular Health Via Gene Therapy

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Contra Biotech Review

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Ticker VERV	Analyst rating BUY	Price at publication \$12.41	Last price \$15.14	Change since publication 22.00%	S&P 500 change since publication 9.87%
Days since publication 86					

Summary

Verve Therapeutics is a biotechnology company focused on developing single-course gene editing medicines for cardiovascular disease (CVD), particularly atherosclerotic cardiovascular disease (ASCVD).

The company has advanced its first cardiovascular disease base editor, VERVE101, into a global Phase 1b clinical trial, demonstrating significant progress in gene editing for CVD.

Verve's proprietary lipid nanoparticle delivery technology, GalNAcLNP, is central to their leading drug candidates, including VERVE101 and VERVE102 targeting PCSK9, and VERVE201 targeting ANGPTL3.

The company aims to transform CVD treatment from chronic care to a once-and-done therapy, potentially reducing the burden on patients and healthcare systems.

Verve Therapeutics has secured strategic partnerships and funding, including a \$60 million capital infusion from Eli Lilly, providing financial stability into 2026.



byakkaya

Summary

Verve Therapeutics (NASDAQ:[VERV](#)) is a clinical-stage biotechnology company focused on developing single-course gene editing treatments for cardiovascular diseases.

The company's proprietary technology, GalNAcLNP, aims to enhance the delivery and potency of gene editing tools, with its lead candidate, VERVE101, targeting a heart-disease gene, PCSK9.

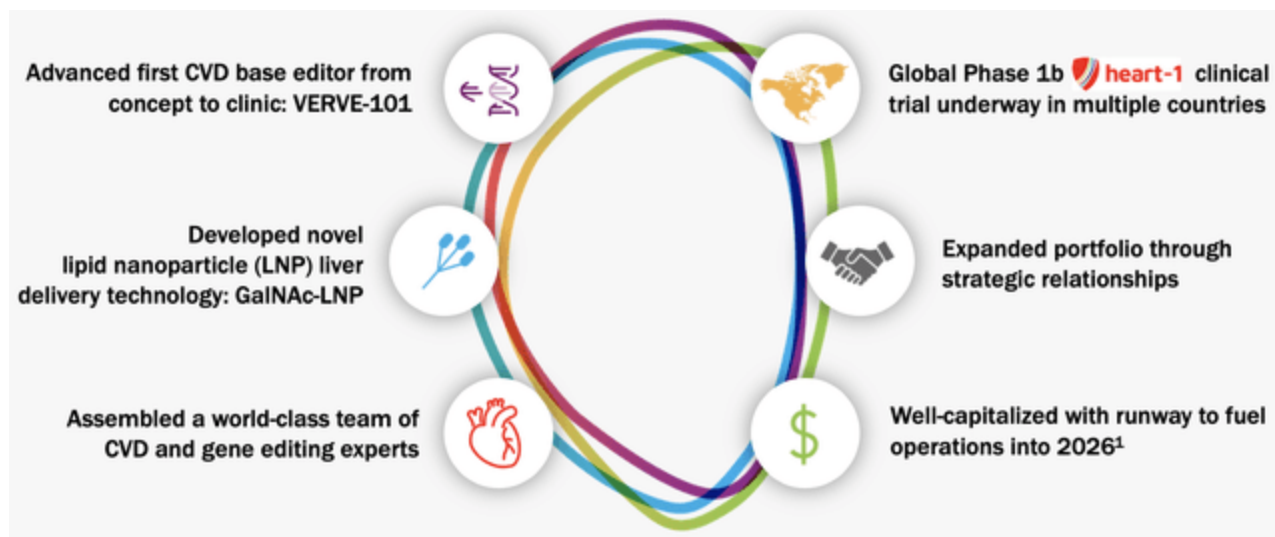
Verve faces substantial risks including the ability to replicate preclinical results in clinical trials, receive regulatory approvals, and manage expenses while raising additional capital.

Strategic relationships, such as the collaboration with Eli Lilly, provide financial support and industry confidence, extending Verve's operational runway into 2026.

In summary, the author projects Verve Therapeutics as a "hold" at a 2-year price target at an optimistic scenario of \$20/share.

1/9: Overview

Verve Therapeutics is making a name for itself in the biotech field with its focus on gene editing therapies aimed at treating cardiovascular disease ("CVD"). The company is pioneering treatments that could replace the need for ongoing medication with a single-course gene therapy. VERVE-101, their leading candidate, has begun clinical trials, which is a crucial step toward testing its efficacy in humans. With a strategic partnership with Eli Lilly, Verve is financially positioned to continue its operations until at least 2026. The company's proprietary GalNAc-LNP delivery system could offer more precise and effective treatments, setting it apart from competitors. However, Verve must navigate the challenges faced by many clinical-stage biotech companies, including proving the safety and efficacy of its gene editing treatments in a strict regulatory environment.





















Verve Investor Presentation (2023)

The competitive landscape for CVD treatments and the high costs associated with drug development may require Verve to secure additional funding and manage its finances strategically. From an investment perspective, Verve represents the high-risk, high-reward nature of the biotech sector. The company's innovative approach has the potential to revolutionize CVD treatment. However, investors should weigh the company's transformative potential against the complex and competitive process of developing and marketing new treatments. The success of Verve will depend on its ability to successfully conduct clinical trials and navigate market and regulatory hurdles, making it an intriguing option for those interested in investing in advanced medical therapies.

2/9: Core technology

Verve Therapeutics is at the forefront of developing gene editing treatments for cardiovascular diseases, specifically targeting conditions like atherosclerotic cardiovascular disease ("ASCVD") and familial hypercholesterolemia ("FH"). Their innovative in vivo base editing technology aims to make precise DNA changes in liver cells, which could lead to a lasting reduction in harmful low-density lipoprotein cholesterol ("LDL-C") levels. The potential to replace long-term medication with a one-time treatment could revolutionize the management of CVD. Verve's drug candidates are in various stages of development, each designed to address different aspects of CVD using novel delivery methods such as lipid nanoparticles. The company's collaboration with Eli Lilly and strong financial footing until 2026 position it well for continued research and development. However, Verve must navigate the complexities of clinical trials, regulatory landscapes, long-term safety concerns, and the competitive CVD treatment market to achieve commercial success.

TARGET	INDICATION	TECHNOLOGY	DEVELOPMENT STATUS			RIGHTS
			Research	IND-enabling	Clinical	
PCSK9 (VERVE-101)	Heterozygous familial hypercholesterolemia ASCVD	Base Editor				 
PCSK9 (VERVE-102)	Heterozygous familial hypercholesterolemia ASCVD	Base Editor				 
ANGPTL3 (VERVE-201)	Homozygous familial hypercholesterolemia Refractory Hypercholesterolemia	Base Editor				 
LPA	ASCVD patients with high blood Lp(a)	Novel Editor				 
Undisclosed	Undisclosed ASCVD	Base Editor				 
Undisclosed	Undisclosed liver disease	Novel Editor				 

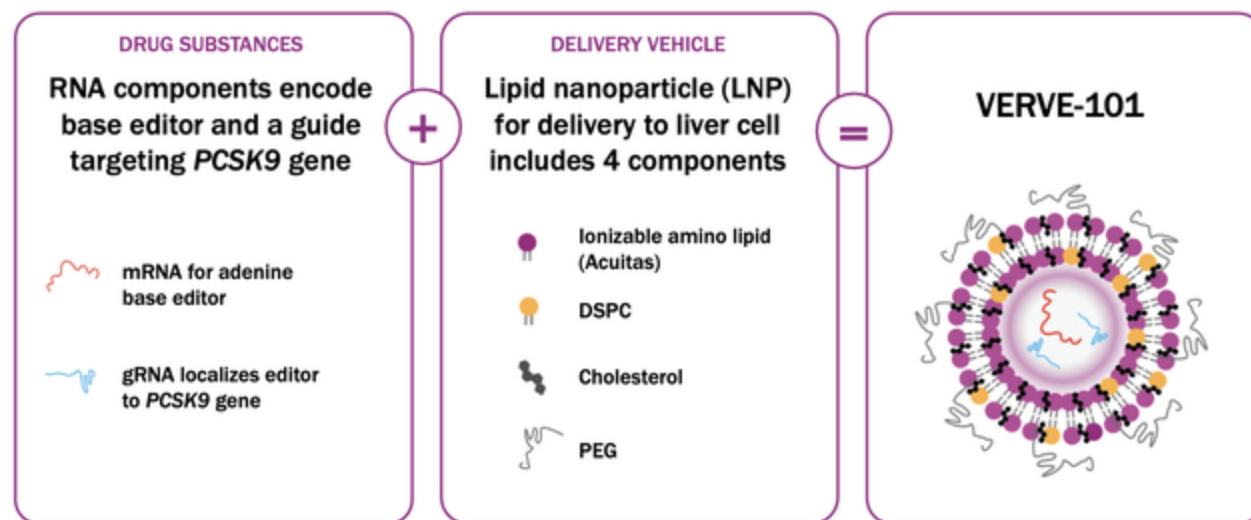
Verve Investor Presentation (2023)

Verve Therapeutics is a clinical-stage biotechnology company focused on developing gene editing treatments for cardiovascular disease. Their approach involves using base editing technology to make precise DNA modifications within liver cells. The goal is to achieve a sustained decrease in LDL-C levels, which play a significant role in the progression of CVD. The company has several drug candidates in its pipeline:

VERVE-101 is a base editor designed to address heterozygous familial hypercholesterolemia ("HeFH") and ASCVD, delivered via lipid nanoparticles ("LNPs").

VERVE-102, similar to VERVE-101, is a base editor targeting HeFH and ASCVD but utilizes a GalNAc-LNP delivery system, which may enhance liver targeting and efficacy.

VERVE-201 is another base editor, this time focusing on homozygous familial hypercholesterolemia ("HoFH") and refractory hypercholesterolemia, also using a GalNAc-LNP delivery vehicle. The Lp(a) program is developing a novel editor to help ASCVD patients with high levels of lipoprotein(a) in their blood. The delivery method for this program has not been disclosed.

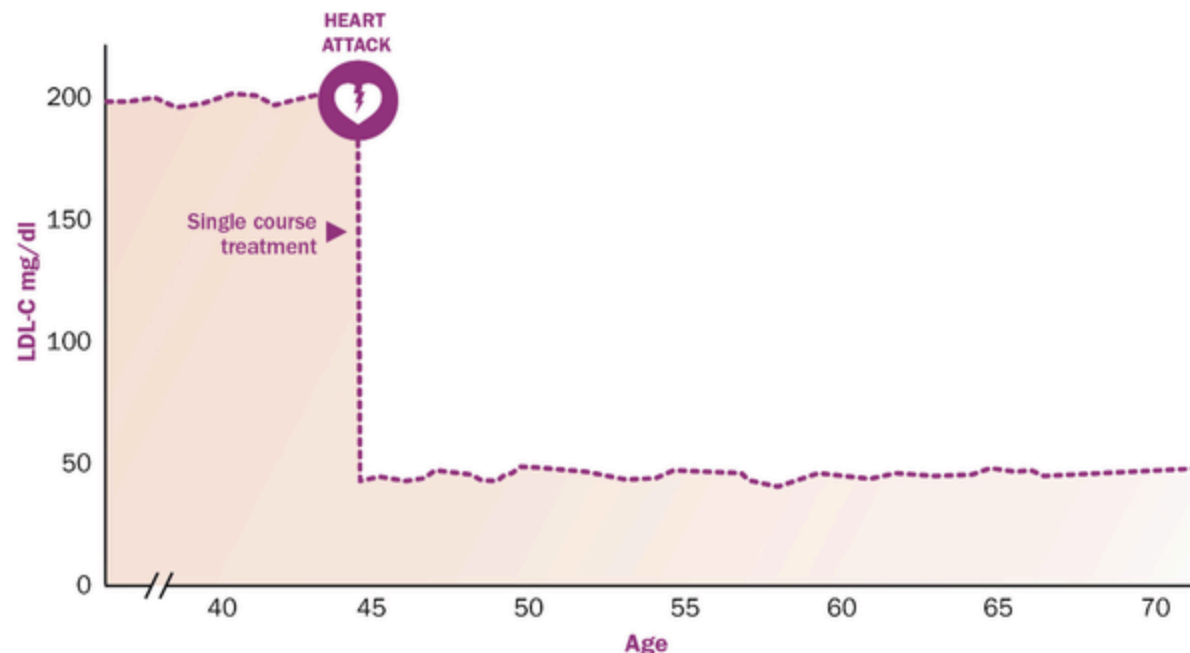


Verve Investor Presentation (2023)

The advantages of Verve's technology include the potential to replace lifelong CVD medication with a single-course therapy and the use of a proprietary delivery system that may improve the delivery and efficacy of gene editing tools. The company's partnership with Eli Lilly provides financial support and credibility, and Verve's financial runway into 2026 allows for ongoing R&D without immediate additional funding needs. However, Verve faces challenges as a clinical-stage company. These include the risks associated with clinical trials, regulatory hurdles, safety concerns, and the uncertainty surrounding the long-term effects and potential off-target consequences of their gene editing technology. Furthermore, they will likely need additional capital for commercialization and must carefully manage costs and secure further funding. Competition in the CVD treatment market is intense, and Verve will need to establish a strong presence for its gene editing therapies to succeed. In conclusion, Verve Therapeutics is positioned to potentially transform the treatment landscape for CVD with its gene-editing platform. While the company has a strong partnership and financial stability, it will have to carefully navigate the inherent risks and challenges of bringing novel treatments to market. Success will depend on the company's ability to execute its clinical development strategies efficiently and effectively.

3/9: Diseases being targeted

Atherosclerotic Cardiovascular Disease (ASCVD) and familial hypercholesterolemias, such as Heterozygous Familial Hypercholesterolemia (HeFH) and Homozygous Familial Hypercholesterolemia (HoFH), represent significant health challenges due to the buildup of cholesterol in arterial walls, leading to heart attacks, strokes, and peripheral vascular disease.

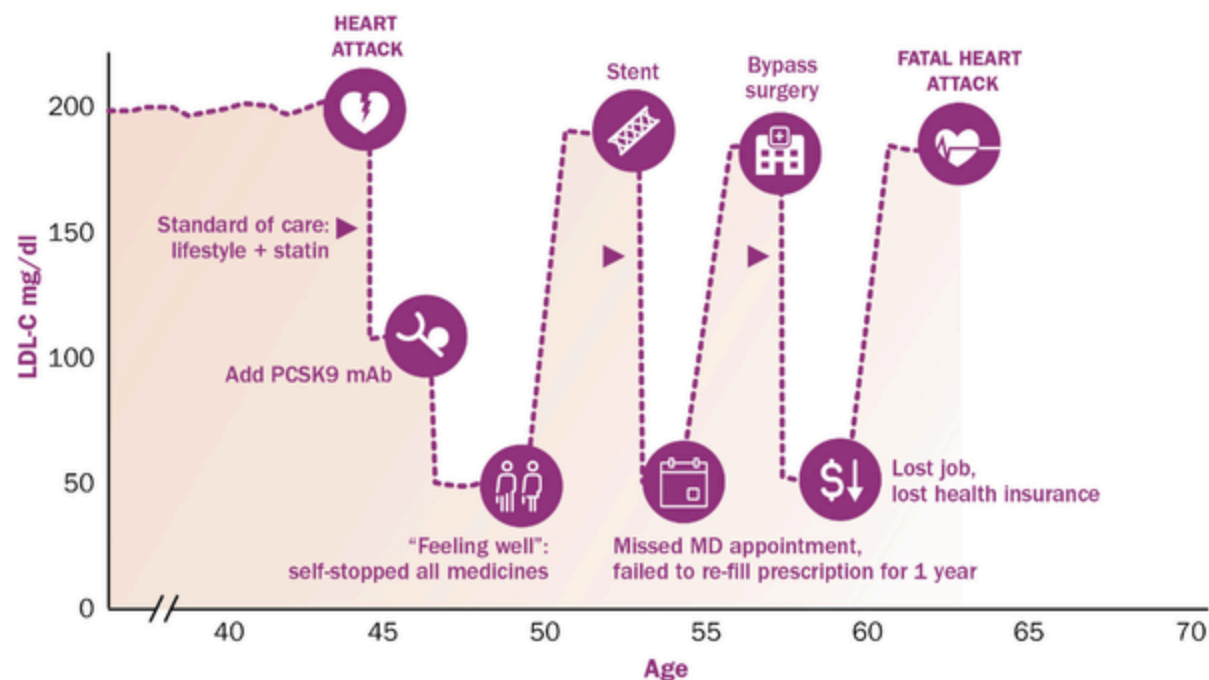


Verve Investor Presentation (2023)

These conditions are the leading causes of death globally. Despite standard treatments like lifestyle changes and statins, many patients fail to reach their low-density lipoprotein cholesterol (LDL-C) targets, signaling a need for more effective therapies.

1. ASCVD is marked by cholesterol plaque accumulation in arteries, increasing heart attack, stroke, and peripheral vascular disease risks. Current treatments include lifestyle modifications, statins, ezetimibe, and PCSK9 inhibitors, but a significant patient subset remains at high cardiovascular risk despite these.
2. HeFH, a genetic disorder, results in lifelong high LDL-C levels and an elevated risk of early ASCVD due to mutations in the LDL receptor gene or related genes. High-intensity statin therapy, combined with other lipid-lowering agents, is the standard care, but many patients still do not achieve LDL-C goals, indicating the necessity for new treatments.

3. HoFH is an even more severe familial hypercholesterolemia form, with both copies of the LDLR gene mutated, leading to extremely high LDL-C levels from a very young age and a high risk of early cardiovascular events. Treatment includes a combination of lipid-lowering therapies and potentially lipoprotein apheresis or newer agents like evinacumab, yet achieving LDL-C targets remains challenging for many.
4. Refractory hypercholesterolemia refers to the condition where patients' LDL-C levels remain high despite using maximally tolerated lipid-lowering therapies. These patients may need additional treatments like evinacumab and other novel agents, as their cardiovascular risk is high.
5. Lipoprotein(a) [Lp(a)] is a variant lipoprotein that is an independent risk factor for ASCVD. Genetic factors mainly determine Lp(a) levels, and they are not significantly altered by lifestyle or statins. Niacin and PCSK9 inhibitors may have some effect, but there are no specific approved treatments to lower Lp(a) levels, making this an active research area.



Verve Investor Presentation (2023)

Verve Therapeutics is developing gene-editing therapies aimed at providing single-course treatments for these diseases by targeting genes like PCSK9, ANGPTL3, and LPA. These therapies are in various preclinical and clinical development stages and could revolutionize the treatment paradigm for patients with ASCVD and familial hypercholesterolemia. However, the technology is still early in development and carries significant risks and uncertainties regarding clinical success, regulatory approval, and commercialization.

4/9: Platform competitiveness

In evaluating the potential of Verve Therapeutics' drug candidates to surpass the current standard of care for cardiovascular diseases and familial hypercholesterolemia, it is essential to analyze both the safety and efficacy data of similar gene editing modalities and to weigh the pros and cons of such treatments. Gene editing therapies, particularly those utilizing CRISPR/Cas9 and base editing, are in the nascent stages with ongoing accumulation of long-term safety and efficacy data. Insights are primarily derived from clinical trials of gene therapies for various conditions, which have demonstrated potential but also raised safety concerns including immune reactions, off-target effects, and other long-term unknowns.

Verve Therapeutics' modality presents several advantages. It offers the possibility of a one-off treatment with sustained results, a significant improvement over the lifetime medication regimens currently prescribed. The precision of base editing could minimize off-target effects, and the targeted delivery systems, such as LNPs and GalNAc-LNP, promise enhanced efficacy and fewer systemic side effects. Additionally, Verve's therapies may fulfill the unmet needs of patients who are non-responsive or intolerant to existing treatments.

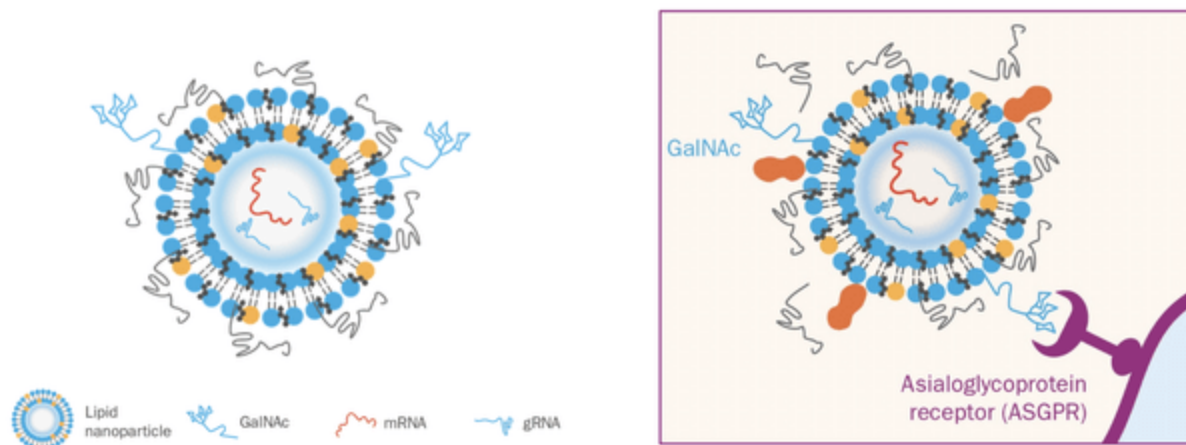
Conversely, there are notable disadvantages and challenges. The novelty of gene editing brings a lack of long-term safety data and the possibility of unexpected side effects. The regulatory landscape for gene therapies is complex and may impede timely access to treatments. Patient and physician apprehension about the new technology, ethical concerns, and cost could affect market acceptance. Moreover, the anticipated high cost of such therapies may restrict accessibility and uptake, particularly if not covered by insurance.

When compared to the current standard of care, which includes statins, ezetimibe, PCSK9 inhibitors, and lifestyle modifications, Verve's therapies could represent a transformative leap. Current treatments necessitate ongoing compliance and may not be effective or tolerable for all patients. Notably, no specific treatments currently exist for reducing Lp(a) levels, an area Verve's Lp(a) program could potentially address. If Verve's therapies can demonstrate superior safety and efficacy, they could revolutionize treatment by offering a lasting solution without the need for continuous medication. However, they must establish themselves as markedly better in terms of efficacy, safety, and cost-effectiveness to displace existing treatments.

In summary, Verve Therapeutics' drug candidates hold the promise of significantly improving upon the current standard of care for cardiovascular diseases and familial hypercholesterolemia, particularly for those with unmet medical needs. The success of these therapies hinges on clinical trial results, regulatory approval, market reception, and affordability. While it remains uncertain if they will be 10x better, they have the potential to fundamentally change the treatment landscape.

5/9: Technology competitiveness

Verve Therapeutics stands out in the gene editing and cardiovascular disease treatment landscape with its proprietary technology and innovative approach to therapy. The company's unique lipid nanoparticle delivery system and ambition to develop single-course treatments position it well in the market. However, it faces significant competition and must overcome challenges related to its newness, clinical trial progression, and financial sustainability.



Verve Investor Presentation (2023)

Verve's proprietary GalNAc-LNP delivery system is designed to target the liver, potentially increasing the success of their gene therapies while minimizing side effects. This technology could be particularly advantageous for liver-related diseases. Additionally, the company's focus on creating single-course treatments for cardiovascular diseases is a bold strategy that could lead to improved patient outcomes and compliance, as well as lower healthcare costs. The preclinical success of their lead candidate, VERVE-101, is encouraging. It aims to reduce LDL-C by targeting PCSK9, a novel approach that could be highly effective in treating hypercholesterolemia. On the flip side, Verve's limited operating history presents risks, as the company has yet to prove its ability to navigate the challenges of clinical development and regulatory approval. Replicating the positive results from preclinical studies in human trials is another significant hurdle, as success in animal models does not always predict clinical success in humans. Financially, the company must manage its expenses and secure funding to sustain operations until it can generate its own revenue-a common challenge in the biotech industry.

Verve Therapeutics must be evaluated against a backdrop of competitors with varying technological strengths and clinical development stages, including Beam Therapeutics, Editas Medicine, CRISPR Therapeutics, Intellia Therapeutics, Sangamo Therapeutics, and Alnylam Pharmaceuticals. The company's ability to overcome early-stage development risks and financial challenges will be crucial for its success. Innovating and advancing its pipeline will be key to distinguishing itself from these competitors and achieving a leading position in the market.

6/9: Competitors

In the biotech industry, various companies are pioneering the development of gene therapies and genetic medicines, each with its unique technological approaches and strategic focuses. Beam Therapeutics ([BEAM](#)) specializes in base editing, a form of genome editing that offers precision with potentially fewer off-target effects. Editas Medicine ([EDIT](#)) and CRISPR Therapeutics ([CRSP](#)) are utilizing CRISPR/Cas9 technology to address a range of genetic disorders, with Editas also employing CRISPR/Cas12a. Intellia Therapeutics ([NTLA](#)) is advancing in vivo CRISPR/Cas9 treatments, while Sangamo Therapeutics ([SGMO](#)) works with zinc finger nuclease ("ZFN") technology. Alnylam Pharmaceuticals ([ALNY](#)) stands out with its focus on RNA interference ("RNAI")) therapeutics, which silence specific genes without permanently modifying them. Each company's progress, potential market reach, and therapeutic impact are balanced against the challenges and risks associated with developing and commercializing gene therapies, such as regulatory hurdles, technological limitations, and the need for clinical validation.

Deeper dive into competitors

Beam Therapeutics' approach to precision genetic medicine involves base editing, which allows for precise DNA base conversions without the double-strand breaks associated with CRISPR/Cas9. This could lead to safer gene editing with fewer unintended modifications. Their pipeline targets a variety of genetic conditions, including sickle cell disease and beta-thalassemia. However, the technology is still preclinical, and the regulatory landscape remains uncertain due to its novelty.

Editas Medicine is at the forefront of CRISPR technology, with EDIT-101 being developed for a rare genetic eye disorder known as Leber congenital amaurosis 10 ("LCA10")). The company's expertise in complex genetic diseases could provide transformative treatments. Nevertheless, the specificity and efficiency of CRISPR/Cas9 and Cas12a are under close examination, and any negative clinical outcomes could affect the company's value and progress.

CRISPR Therapeutics, in collaboration with Vertex Pharmaceuticals ([VRTX](#)), is developing CTX001 for transfusion-dependent beta-thalassemia and sickle cell disease. The partnership enhances the development and commercialization potential, and early clinical results are promising. Still, there are concerns about off-target effects and immune responses that could impede approval or acceptance.

Intellia Therapeutics focuses on in vivo treatments, such as NTLA-2001 for transthyretin amyloidosis ("ATTR"). Their in vivo method and lipid nanoparticle delivery system could revolutionize treatment delivery and safety. However, the concentration on non-cardiovascular diseases and the unproven nature of the in vivo approach in clinical settings add to the company's uncertainties.

Sangamo Therapeutics utilizes ZFN technology to target a diverse range of diseases. With a relatively advanced pipeline and industry collaborations, Sangamo may enter the market sooner. However, the precision and efficiency of ZFN may not match newer gene editing methods, and the company's broad focus could spread its resources thin, affecting the success of individual programs.

Alnylam Pharmaceuticals has successfully commercialized RNAi therapeutics, which silence genes involved in disease without permanent modification. This has led to multiple approved products and a broad disease target range. However, the need for repeated treatments could increase costs and patient burden, and their RNAi focus may limit their engagement in gene editing ventures. For a biotech venture capitalist, understanding these companies' strengths, limitations, and strategic positions is crucial for making informed investment decisions in the rapidly evolving field of gene therapy. Each company's technology, pipeline, and collaborations must be carefully considered against the backdrop of technological risks and the challenges inherent in bringing gene therapies to market.

7/9: Upside potential

In the volatile landscape of biotech investments, Verve Therapeutics has recently witnessed a significant market downturn following the release of clinical data for its lead program, VERVE-101, targeting heterozygous familial hypercholesterolemia ("HeFH"). The market response raises questions about the future trajectory of the company's stock price. This analysis aims to dissect the key factors influencing Verve Therapeutics' stock and offer insights into potential scenarios.

Safety Concerns and Market Reaction

The recent phase 1b clinical trials of VERVE-101 revealed safety concerns, with incidents of heart attacks leading to a substantial drop in the company's stock. While the fatal heart attack is deemed unrelated to the treatment, the non-fatal heart attack is being cautiously considered as "potentially" related. The market's reaction suggests an immediate and pronounced response to these safety issues, emphasizing the significance of safety data in the biotech sector.

Clinical Context and Investor Perception

Despite the setbacks, the market might be overlooking the broader clinical context. Analysts suggest that the safety concerns, while impactful, may not fully represent the overall potential of VERVE-101. Investors are advised to consider the complexity of clinical data interpretation, recognizing that early-stage trials are designed to identify safety concerns and provide insights for larger trials.

Financial Position and Future Funding

Verve Therapeutics currently boasts \$485 million in cash, equivalents, and investments, with operations funded through the start of 2026. While the company may need additional capital in the future, collaborations with Eli Lilly and Vertex Pharmaceuticals could provide significant funding support. This financial stability tempers immediate concerns about the company's viability.

Likely Scenarios

Considering the safety concerns, analysts suggest that the market's skepticism toward safety factors could persist. The likelihood of another substantial drop in share price remains high, given the uncertainties associated with early-stage pipeline programs. However, as more clinical safety data becomes available, positive developments could lead to a gradual rebuilding of investor confidence and significant upside.

Opinion on Future Share Price

Given the current uncertainties and the market's heightened sensitivity to safety issues, a cautious outlook on Verve Therapeutics' share price is warranted in the short to medium term. While positive clinical data could potentially drive a rebound in investor confidence, the inherent risks associated with early-stage biotech ventures suggest that the road to recovery may be gradual.

Potential Scenarios for 2024:

<i>\$ in actual</i>	FYE 2024		
Scenarios	Pessimistic	Base	Optimistic
Industry Avg. Multiple (Price to earnings)	30.0	30.0	30.0
ASCVD market (in M)	\$67,950	\$67,950	\$67,950
HEFH market (in M)	\$38,990	\$38,990	\$38,990
Total market size in 2030 (in M)	\$87,445	\$87,445	\$87,445
Market penetration	20%	30%	40%
Verve's expected market share (in M)	\$17,489	\$26,234	\$34,978
Expected profit (in M)	\$6,996	\$10,493	\$13,991
EPS Forecast (at approval / E 2030)	\$110	\$165	\$219
Expected valuation of the company in 2030 (in M)	\$3,292	\$4,938	\$6,584
Probability of approval	8%	14%	20%
Expected market cap by Contraview in 2024 (in M)	263	691	1,317
Expected market cap by Wall Street in 2024 (in M)	1,434	2,805	4,271
Shares Outstanding (in M)	64	64	64
Total Debt (+) -Q3 (in M)	\$77	\$77	\$77
Total Cash (-) -Q3 (in M)	\$485	\$485	\$485
Share Price Forecast by Contraview	\$4.1	\$10.8	\$20.7
Share Price Forecast by Wall Street	\$22.5	\$44.0	\$67.0
<i>Current Stock Price</i>	\$11.23	\$11.23	\$11.23
% Change (Wall Street)	100%	292%	497%
 Weighted (Wall Street)	298%		
% Change (Contraview)	-63%	-3%	84%
 Weighted (Contraview)	10%		

Contra Biotech Review

Verve's focus on developing high-impact first-line treatments for Atherosclerotic Cardiovascular Disease ("ASCVD") and Heterozygous Familial Hypercholesterolemia ("HeFH") forms the core of the analysis. Assumptions of an approximate 30x PE industry average multiple sets the stage. Contra believes this is warranted due to the expected impact of their gene therapy if successful and the broad focus on CVD generally. Calculations of market cap, based on market size and penetration assumptions, reveal a 2030 market projection of \$87b. Profit expectations, assuming a 40% margin, range from \$7b to nearly \$14b across scenarios.

EPS forecasts lead to 2030 valuations ranging from \$3.3b to \$6.6b. Adding the probability of drug approval (8% to 20% | [Pharmagellan Guide to Biotech Forecasting, 2017](#)) and considering 2024 market cap scenarios, Contra adopts a conservative stance with estimates of \$263 million, \$691 million, and \$1.3 billion for Pessimistic, Base, and Optimistic scenarios. In contrast, Wall Street's share price forecasts of \$22.5, \$44.0, and \$67.0 paint a more optimistic picture near-term with equivalent market caps of \$1.4b, \$2.8b, and \$4.3b.

The weighted average upside of 298% based on Wall Street offers a nuanced perspective. Notably, Contra's conservative approach highlights a potential discrepancy in Wall Street's expectations. Share prices, according to Contra, stand at \$4.1, \$10.8, and \$20.7 for Pessimistic, Base, and Optimistic scenarios with an average upside of 10% over the next 12 months. This insight underscores the importance of a discerning approach to evaluating Verve Therapeutics' potential valuation, suggesting that share prices may align more closely with the conservative estimates provided by Contra. In the ever-evolving landscape of biotech investments, a balanced and informed strategy is crucial for navigating uncertainties and making sound investment decisions.

9/9: Conclusion

Verve Therapeutics is an attractive investment opportunity within the biotech industry, particularly for its focus on gene editing to treat cardiovascular diseases. The company's innovative single-course treatments are supported by proprietary technology and a robust scientific team. The progression to a global Phase 1b clinical trial for VERVE-101 and a strategic partnership with Eli Lilly both validate the company's potential. Verve's gene editing platform could revolutionize cardiovascular disease treatment by potentially improving patient outcomes and compliance. Its unique GalNAc-LNP delivery system may also provide a competitive advantage in gene therapy. Financially, the company is well-positioned until 2026, reducing some of the inherent risks of early-stage biotech companies. However, Verve faces significant challenges, such as the uncertainties of its limited operating history and the early development stage of its lead candidate. The long-term effects and market acceptance of its novel treatments are unknown, and there may be competition from established therapies. Furthermore, despite its current financial stability, Verve will likely require additional funding for commercialization, and its success will depend on effective cost management and the ability to secure more capital. In summary, Verve Therapeutics offers a promising but risky investment due to the high-stakes nature of early drug development. The company's strategic approach and financial health are positive, but investors should remain aware of the clinical, regulatory, and competitive challenges ahead. Diversification is recommended to manage the risks inherent in biotech investments.

In summary, the author projects Verve Therapeutics as a "hold" at a 2-year price target at an optimistic scenario of \$20/share.

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